DEVELOPMENT OF AMINE ALPHA-FUNCTIONALIZATIONS INVOLVING

AZOMETHINE YLIDE INTERMEDIATES

by

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ABSTRACT OF THE DISSERTATION

Development of Amine Alpha-Functionalizations Involving Azomethine Ylide

Intermediates

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The α-functionalization of amines is a synthetic challenge of much interest to organic chemists. Common methods involve deprotonation with strong bases or oxidation with stoichiometric oxidants or transition metal catalysts. An alternative redox-neutral azomethine ylide-mediated approach to amine functionalization that harnesses the intrinsic reactivity of simple aldehyde and amine precursors without the need for harsh oxidants or bases will be detailed in this dissertation. The development of non-pericyclic amine annulations yielding aminal, *N,O*-acetal and *N,S*-thioacetal products will be discussed along with joint computational and experimental mechanistic studies on these reactions. The aminals are closely related to several naturally-occurring alkaloids and multiple methods were developed to synthesize these bioactive natural products and analogs. Additionally, two more azomethine ylide-based reactions will be discussed. The first is a variant on the classical Strecker reaction using α-amino acids which decarboxylatively gives rise to cyclic α-amino nitriles. Finally, a redox-neutral 1,5-electrocyclization reaction between secondary amines and α,β-unsaturated carbonyl compounds yielding amine heterocycles will be demonstrated.

ACKNOWLEDGEMENTS

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Chapter 1

Introduction

1.1 Background

The C–H bond, being found in nearly all organic molecules, is an incredibly important functionality in organic chemistry.[1] Due to their general stability, however, most carbon-hydrogen bonds are looked upon by the organic chemist as inert.[2] More often, chemists will look to carbon-heteroatom bonds for the functionalization of a carbon center, ignoring the ubiquitous but stable C–H bond unless activated by a nearby functionality.

Figure 1.1 **C–H Activation of sp³ Bonds**
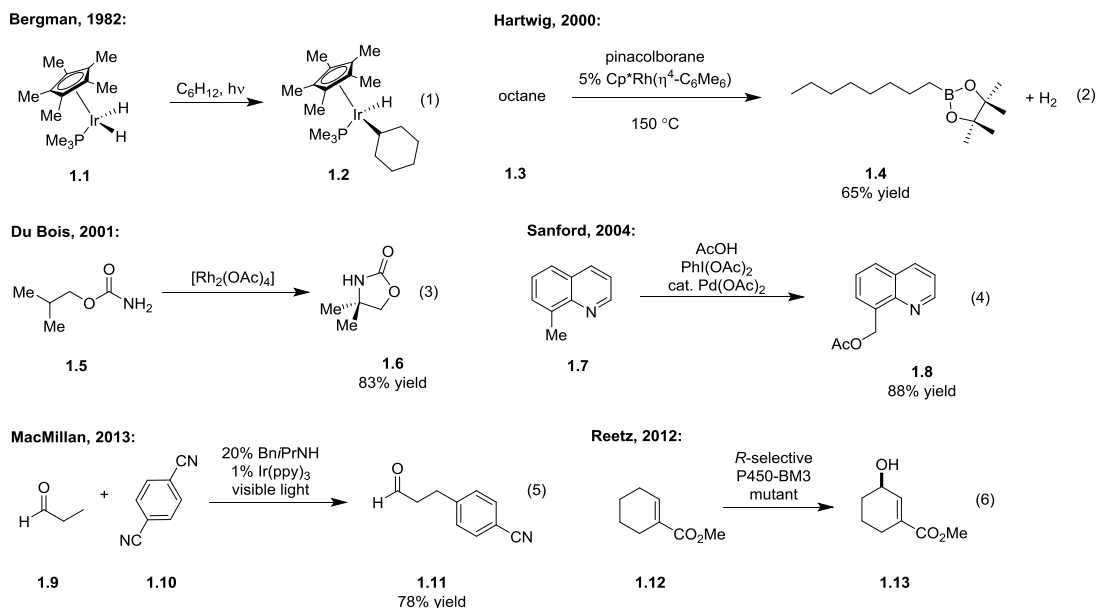
In recent years, however, there has been much interest in the development of new chemical methods for the direct functionalization of unreactive C–H bonds.[3] One of the first reactions generally termed C–H activation comes from Bergman and coworkers in 1982 (Figure 1.1, eq 1).[4] Iridium species **1.1** underwent oxidative addition to the C–H

bond of cyclohexane upon irradiation, resulting in the formation of complex **1.2**. In 2000, Hartwig et al. published a catalytic, regioselective method of transforming simple alkanes, such as octane (**1.3**), to alkylboranes (**1.4**) with a rhodium-based catalyst (Figure 1.1, eq 2).[5] Considering the abundance of simple hydrocarbons and the general utility of boronic esters in organic synthesis, this reaction was an important advance in the development of C−H functionalizations. A method for the intramolecular insertion of nitrenes into sp[3] C−H bonds with a dirhodium catalyst was disclosed by Du Bois and coworkers in 2001, resulting in the formation of oxazolidinone structures (**1.6**, Figure 1, eq 3).[6] The selective, chelation-derived addition of acetic acid to C−H bonds in quinolines using $Pd(OAc)_2$ as catalyst was described by Sanford in 2004 (Figure 1, eq 4).[7] In 2013, MacMillan and coworkers developed a method for the β-C−H functionalization of ketones and aldehydes by combining enamine catalysis with photoredox catalysis (Figure 1, eq 5).[8] While C−H activation reactions have been much studied by chemists for the past 30 years, nature has been able to functionalize C−H bonds enzymatically with high selectivity for some time now.[9] In 2012, Reetz et al. employed a guided evolution approach to oxidizing allylic C−H bonds, preforming selective mutations on cytochrome P450 to create new enzymes capable of yielding either isomer of **1.13** from **1.12** (Figure 1, eq 6).[9]

1.2 Approaches to Amine α-C−H Functionalization

Amines can be found in the majority of medicinal drugs on the market,[10] making methods development for amine functionalization necessary. A number of N−H bond functionalizations have been well developed, including reductive aminations,[11] nucleophilic substitutions[12] and cross-coupling reactions.[13] Making use of the α-C−H bond in aliphatic amines is somewhat more difficult, although a number of different approaches have been developed.[14]

Figure 1.2 **Approaches to Amine α−C−H Functionalization**
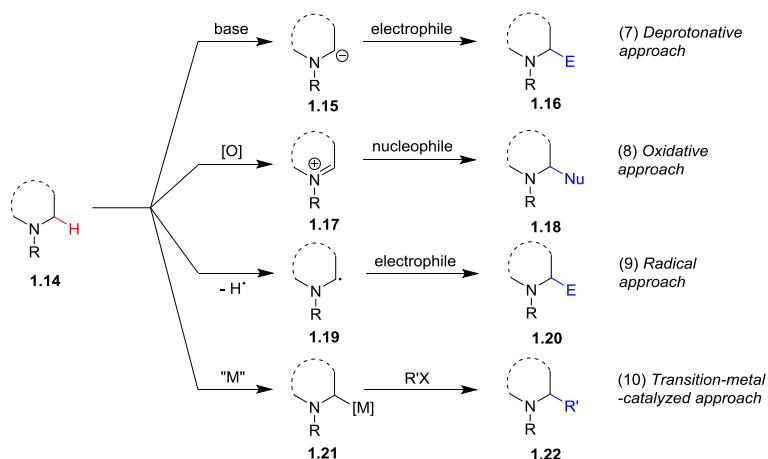
The first class of amine C−H functionalizations can be termed the "deprotonative approach" (Figure 1.2, eq 7). These methods generally involve the use of a strong base to create a carbanion next to nitrogen which can then react with an array of different electrophiles. The next class can be called the "oxidative approach," where the amine is converted to an iminium which is then attacked by a nucleophile (Figure 1.2, eq 8). The iminium can be created using stoichiometric or catalytic oxidants or by hydride shift or prototropy. The "radical approach" involves the formal abstraction of a hydrogen radical, leaving a species of the type **1.19**, which can then attack an electrophile (Figure 1.2, eq 9). Finally, the "transition-metal-catalyzed approach" functionalizes the C−H bond via either an inner sphere or outer sphere mechanism (Figure 1.2, eq 10). There are a number of different subtypes of these four pathways, but most amine C−H functionalizations proceed through one of these approaches.

1.3 Amine C−H Functionalization Through Deprotonation

The deprotonation of a tertiary amine with a strong base can be a very useful method for the synthesis of more complex amines. The use of butyllithium in

conjunction with a diamine ligand helps to stabilize the resulting deprotonated amine for attack on an appropriate electrophile.[14]

Figure 1.3 **Deprotonative Amine Functionalizations**
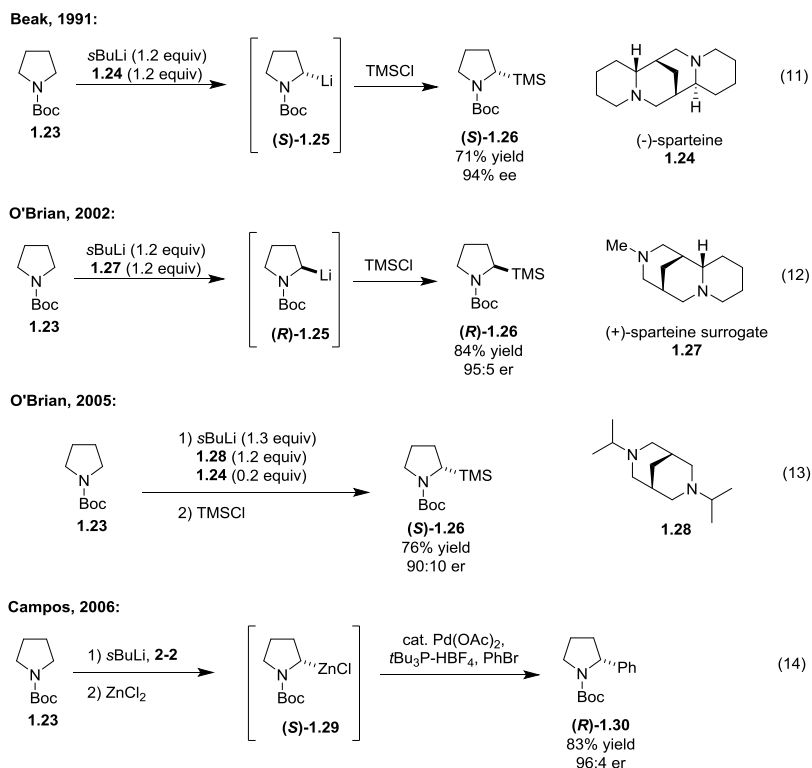
In 1991, Beak et al. demonstrated the use of the natural diamine (-)-sparteine (**1.24**) as a chiral ligand for lithium (Figure 1.3, eq 11).[15] *N*-Boc pyrrolidine (**1.23**) was deprotonated with *sec*-butyllithium in the presence of **1.24** and then exposed to trimethylsilyl chloride (TMSCl) resulting in the formation of **(S)-1.26** with good *ee*. (+)-Sparteine was, however, commercially unavailable and required a long synthetic route to make, which made it difficult to access the other enantiomer in these reactions.[14] To circumvent this, O'Brian and coworkers reported in 2002 an analog of (+)-sparteine (**1.27**) which allowed for the synthesis of **(R)-1.26** with comparable *ee* (Figure 1.3, eq 12).[16] These reactions, while useful for the synthesis of these chiral products, required stoichiometric amounts of chiral diamine – a method that consumes a large amount of

potentially expensive ligand. In 2005, O'Brian and coworkers developed an achiral ligand (**1.28**) that can be used stochiometrically in conjunction with catalytic chiral ligands (Figure 1.3, eq 13).[17] The Li-**1.28** complex is less reactive than the Li-**1.24** complex, allowing ligand exchange to result in enantiomerically enriched products. In 2006, Campos and coworkers greatly extended the utility of these reactions by the transmetalation of organolithium **(S)-1.23** with $ZnCl_2$, preforming a Negishi cross-coupling with resulting organozinc species **(S)-1.29** (Figure 1.3, eq 14).[18] While the deprotonative approach can be quite useful for the functionalization of amines, the scope is limited to substrates stable to butyllithium reagents.

1.4 Oxidative Approaches to C−H Functionalization – Chemical Oxidants

The use of external oxidants to generate iminium ions from amines is quite common.[19] Stoichiometric oxidants, such as molecular iodine, can be used to effectively generate an iminium that can be attacked by a nucleophile, as in the Henry-type reaction demonstrated by Leonard et al. (Figure 1.4, eq 15).[20] Many catalytic approaches have been developed for this type of reaction, usually using either oxygen or peroxides as the terminal oxidant. In 2006 Doyle and coworkers developed a dirhodium/*t*BuOOH-based oxidation thought to proceed through an iminium (Figure 1.4, eq 16).[21] Klussmann and coworkers published a tandem $VO(acac)_2$/proline for an oxidative Mannich-reaction, although any *ee*'s obtained were marginal, potentially due to a retro-Mannich racemization (Figure 1.4, eq 17).[22] The comparatively inexpensive $FeCl_3$ was shown by Kumaraswamy and coworkers to catalyze the oxidation of even somewhat challenging substrates, such as amine **1.38**, yielding cyclic *N,O*-acetal **1.39** (Figure 1.4, eq 18).[23] In 2013, Wang et al. were able to demonstrate a successful enantioselective oxidative Mannich-reaction using phenylalanine as asymmetric organocatalyst and DDQ as stoichiometric oxidant (Figure 1.4, eq 19).[24] Recently, Tokuyama and coworkers

reported a metal-free aza-Henry reaction, using only acetic acid as an additive and molecular oxygen as oxidant (Figure 1.4, eq 20).[25]

Figure 1.4 **Oxidative Methods for Amine Functionalizations**
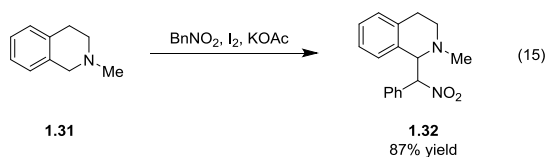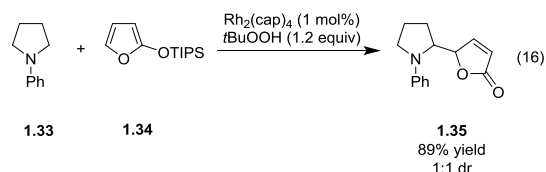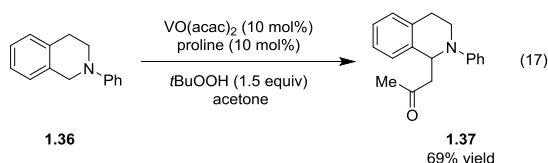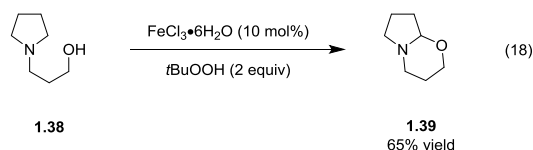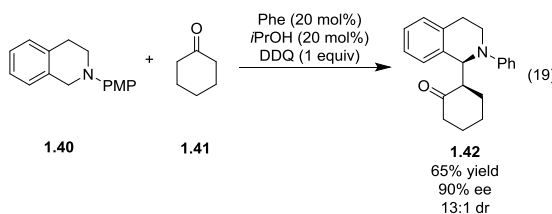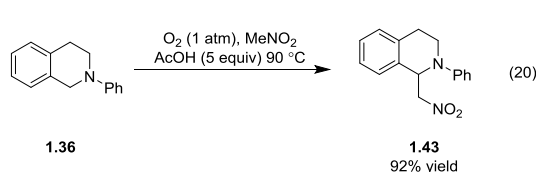
Perhaps the most commonly used metal in this type of oxidative functionalization is copper.[19] This kind of copper oxidation was first demonstrated by Li et al. in 2004, where terminal alkynes were added to amines using catalytic CuBr to in both the oxidation of amine and the activation of alkyne (Figure 1.5, eq 21).[26] This reaction was later made asymmetric by the same group through the use of chiral ligands for copper.[27] In addition to the use of sp carbons as nucleophile, Li and coworkers extended the reaction to include sp[2] nucleophiles such as indole (Figure 1.5, eq 22)[28] and sp[3] nitroalkanes.[29] In 2009, the same group expanded the reaction to include secondary amines, such as **6-5**, preforming coupling reactions with boronic acids (Figure 1.5, eq 23).[30] In the same year, Klussmann and coworkers reported a copper-catalyzed

Mannich-reaction, using silyl enol ethers as the nucleophile (Figure 1.5, eq 24).[31] Simple nucleophilic attack on the resultant iminium ion is not the only potential mode of reaction for copper-based oxidation. In 2011, Miura et al. were able to demonstrate Povarov-reaction between *N,N*-dimethylaniline (**1.44**) and *N*-phenylmaleimide (**1.50**), yielding polycyclic cycloaddition product **1.51**, albeit in low yield (Figure 1.5, eq 25).[32] In 2014, Seidel and coworkers developed an alternative oxidative Povarov-reaction between *N*-aryl 1,2,3,4-tetrahydroisoquinolines (**1.36**) and various dienophiles (Figure 1.5, eq 26).[33]

Figure 1.5 **The Use of Copper Salts as Amine Oxidants**
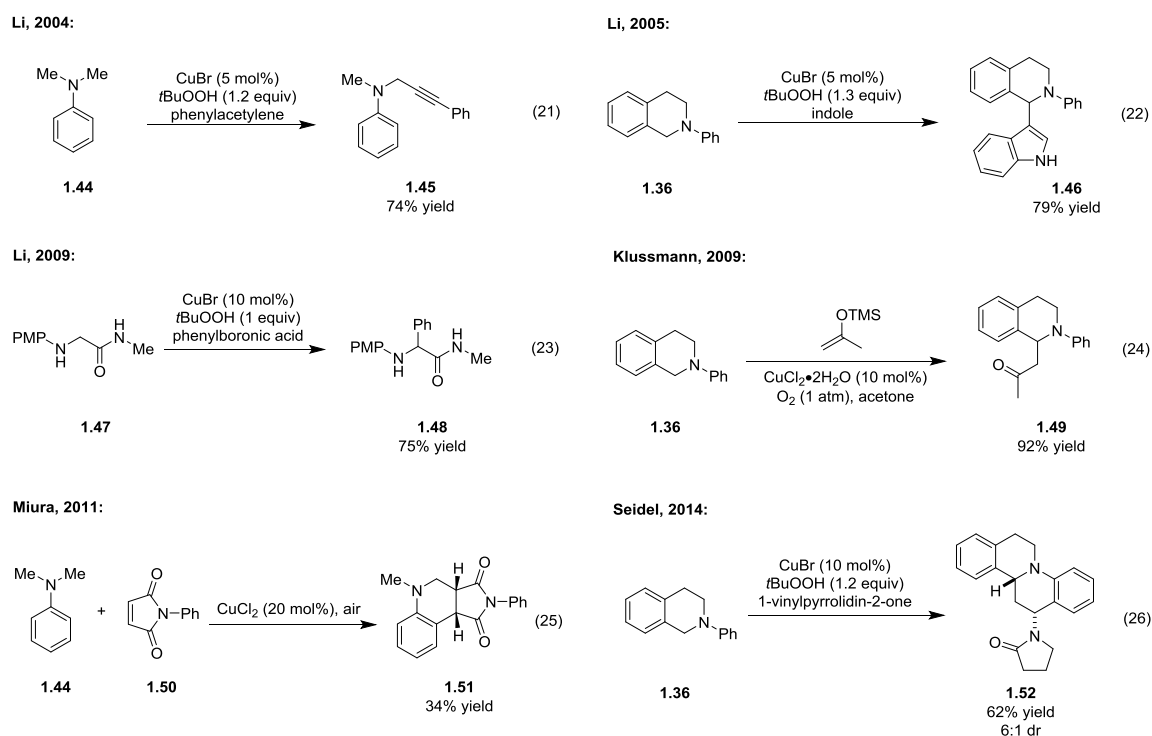
1.5 Photochemical Methods for Amine Functionalization

Within the last few years, photochemical methods for the functionalization of amines have been extensively developed.[34] Before 2010, the few reports of photochemical amine functionalizations tended to have only marginal utility, such as the

addition of benzene to triethylamine upon irradiation with a mercury arc lamp (Figure 1.6, eq 27).[35]   In 2010, Stephenson and coworkers applied an iridium-based photocatalyst to the oxidation of *N*-phenyl tetrahydroisoquinoline (**1.36**), allowing for a high-yielding aza-Henry reaction using visible light to activate the catalyst (Figure 1.6, eq 28).[36] Rueping's group was later able to demonstrate a photocatalyzed Mannich-reaction using Ru(bpy)$_3$$^{2+}$ with proline as enamine catalyst (Figure 1.6, 29).[37]

Figure 1.6 **Photochemical Amine Functionalizations**
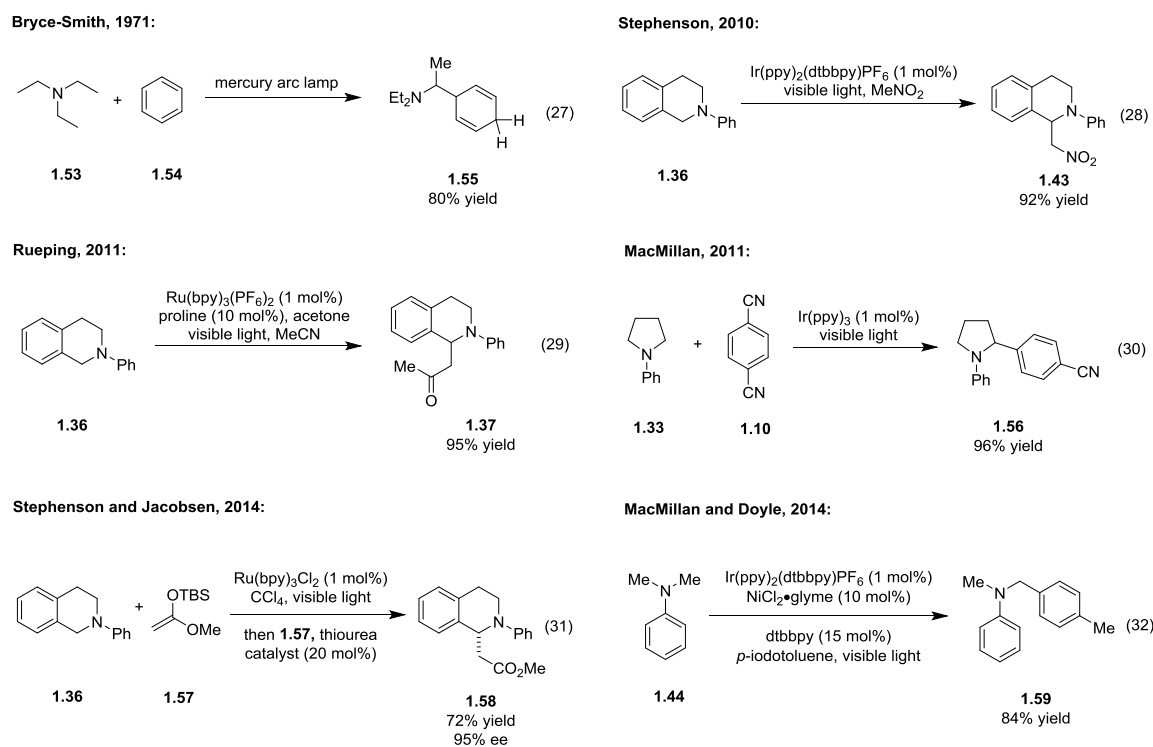
In 2011, MacMillan and coworkers combined high-throughput screening with serendipity to discover a photocatalyzed amino α-C–H arylation reaction using cyanobenzenes (**1.10**) as a radical coupling partner (Figure 1.6, eq 30).[38] In 2014, the groups of Stephenson and Jacobsen reported an asymmetric approach to photochemical oxidation, where first a chloride is installed in the amine α-position, followed by the use of an anion-binding, asymmetric thiourea catalyst to enantioselectively add silyl enol

ethers (Figure 1.6, eq 31).[39]   Recently, the MacMillan and Doyle groups together developed a method to combine photoredox catalysis and transition metal-based cross-coupling, using Ni(II) and aryl halides to functionalize amine α-C–H bonds (Figure 1.6, eq 32).[40]

1.6 Electrochemical Methods for Amine Functionalization

Another method to generate both iminium and radical intermediates for amine C–H bond functionalization is electrochemically via anodic oxidation.[14] One potential advantage of this route is the lack of waste generated from chemical oxidants and the ability to avoid using sometimes expensive transition metal catalysts.

Figure 1.7 **Electrochemical Amine C–H Functionalization**
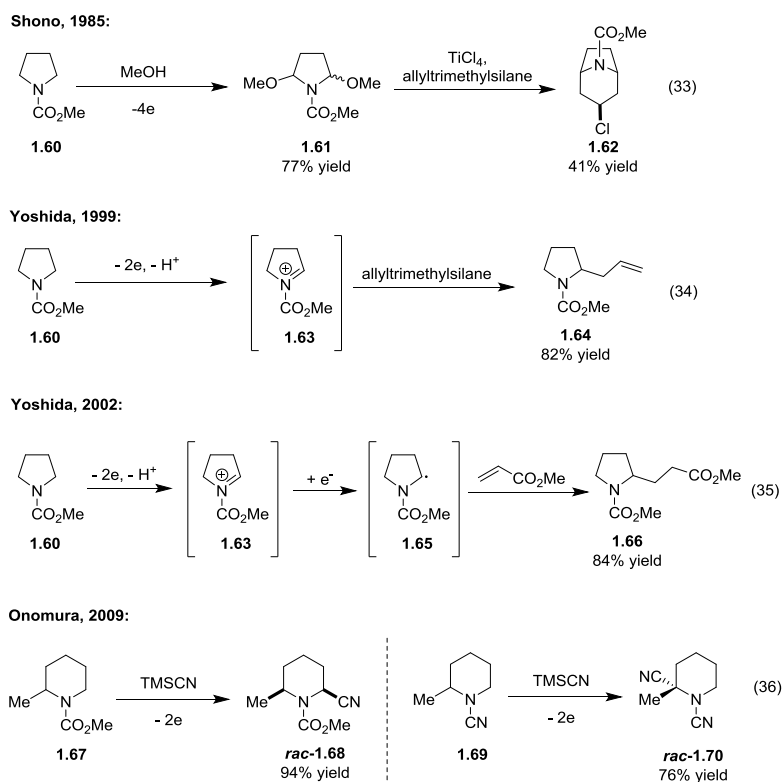
Using a platinum electrode and tetrabutylammonium *p*-toluenesulfonate as electrolyte, Shono and coworkers were able to doubly oxidize protected amine **1.60** to

yield dimethoxy functionalized amine **1.61** (Figure 1.7, eq 33).[41] The unstable nature of the *N,O*-acetal bond allowed for further elaboration with a (3+3) annulation with allyltrimethylsilane and TiCl$_4$, yielding bicycle **1.62**. In 1999, Yoshida and coworkers developed a "cation-pool" method for amine functionalization, where the substrate is aniodically oxidized to build up a large concentration of iminium **1.63**, followed by addition of nucleophile under non-oxidizing conditions, eliminating any unwanted oxidation of the nucleophile (Figure 1.7, eq 34).[42] In 2002, the same group extended the cation-pool method to the radical approach to amine functionalization (Figure 1.7, eq 35).[43] After generation of iminium **1.63**, conditions are applied resulting in electrochemical one electron reduction, giving carbon-centered radical **1.65** which can then react with electrophiles. In 2009, Onomura et al. developed amine protecting groups that resulted in the selective electrochemical cyanation of either side of non-symmetrical amines **1.67** and **1.69** (Figure 1.7, eq 36).[44]

1.7 Radical Methods for Amine Functionalization

Chemically-generated radicals can also be used to add functional groups to amine C–H bonds. In 1990, Snieckus, Curran and coworkers demonstrated the α-functionalization of amide **1.71** by using a well-placed aryl bromide for radical translocation (Figure 1.8, eq 37).[45] When exposed to a radical initiator, aryl radical **1.73** is formed, which undergoes 1,5-hydrogen atom transfer to give the nitrogen α-radical species **1.74**, which can then react with various electrophiles. In 1995, Murakami, Ito et al. published a report on a similar reaction using amine **1.76** and SmI$_2$ as the radical generator (Figure 1.8, eq 38).[46] The 1,5-hydrogen atom transfer resulted in the selective endocylic functionalization of the benzylic pyrrolidine. In 2005, Yoshimitsu, Nagaoka and coworkers disclosed a radical process for amine functionalization not involving pre-

installed aryl halides (Figure 1.8, eq 39).[47] Et$_3$B, in the presence of air, generated the radicals needed to add *p*-methoxybenzaldehyde to triethyamine.

Figure 1.8 **Amine Functionalizations via Radicals**
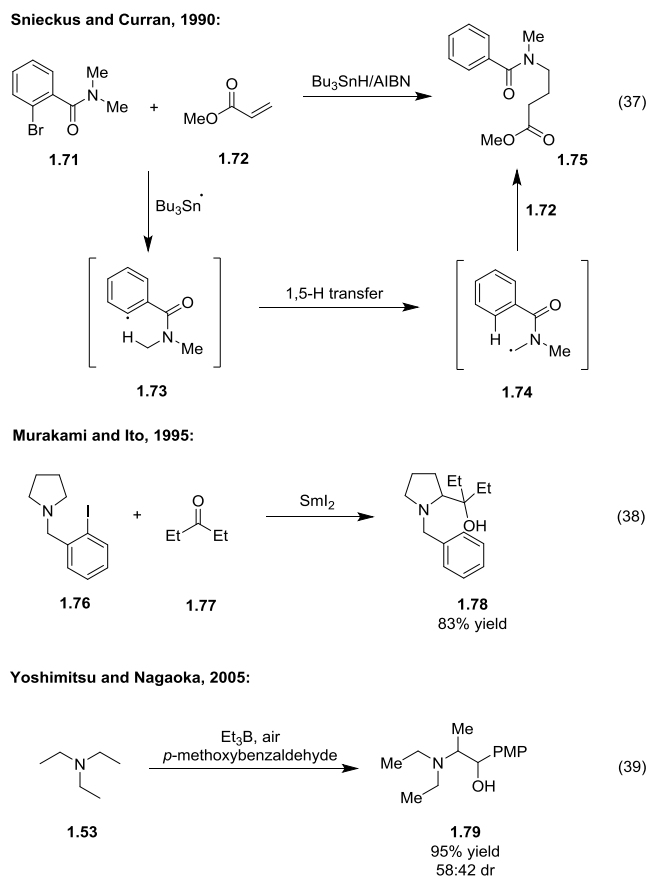
1.8 Transition-Metal-Catalyzed Approaches to C−H Functionalization

In addition to forming the iminium or radical intermediates for amine functionalization, transition-metal catalysts can also be used to functionalize amine C−H bonds through both outer-sphere and inner-sphere mechanisms.[14] The outer-sphere pathway generally involves the use of a dirhodium catalyst to facilitate the insertion of a carbenoid or nitrenoid species into a C−H bond.[48] In 1999, Davies and coworkers developed the C−H insertion of aryldiazoacetate **1.80** into *N*-Boc-pyrrolidine **1.23** using a chiral dirhodium catalyst, yielding product **1.81** with high enantio- and

diastereoselectivity (Figure 1.9, eq 40).[49] Simultaneously, Winkler published a similar route to methylphenidate **1.83** (the children's psychotropic medication Ritalin) with a more modest *ee* that was improved upon recrystallization (Figure 1.9, eq 41).[50] In 2003, the Davies group applied Rh_2(*S*-DOSP)$_4$ to the kinetic resolution of racemic proline ester **rac-1.84**, resulting in reasonable *ee* and *de* (Figure 1.9, eq 42).[51] The addition of a nitrene to an amine α-C–H bond was disclosed by Compain et al. in 2006, where amine **1.86** undergoes an intramolecular annulation to form aminal **1.87** (Figure 1.9, eq 43).[52]

Figure 1.9 **Carbenoid and Nitrenoid Insertions**
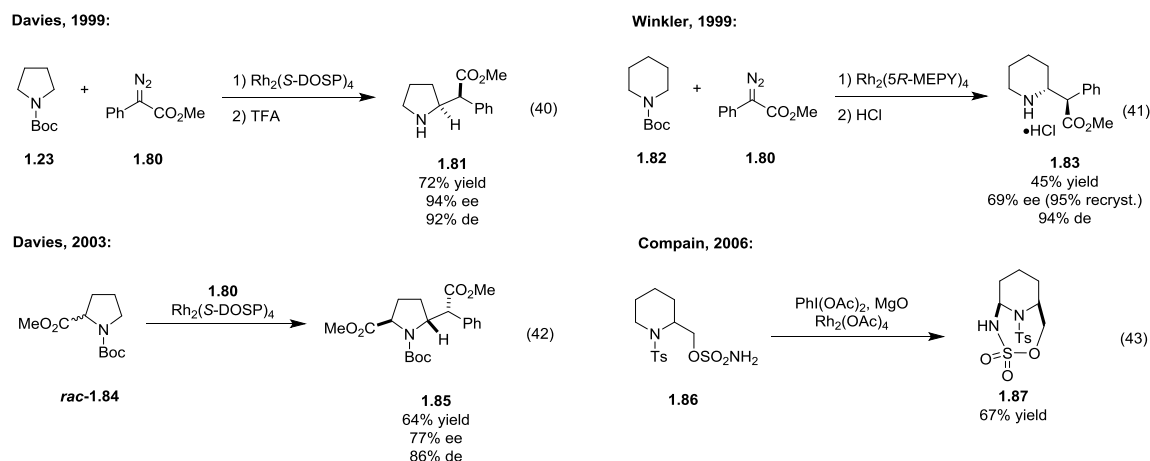
As an alternative to carbene and nitrene insertion reactions, inner-sphere amine functionalizations proceed via the oxidative addition of the C–H bond to the metal complex. Jun and coworkers, in 1998, used $Ru_3(CO)_{12}$ as catalyst to add 1-hexene to benzylic amine **1.88** (Figure 1.10, eq 44).[53] The nitrogen on the pyridinyl group of **1.88** is thought to coordinate with ruthenium and act as a directing group. In 2000, Murai et al. were able to achieve carbonyl insertion into pyrrolidinyl pyridine **1.90** using carbon monoxide, ethylene and a rhodium catalyst (Figure 1.10, eq 45).[54] Again, the nitrogen on the pyridine was crucial as a directing group. In 2004, Yi and coworkers were able to demonstrate the alkylation of cyclic secondary amines such as azepane (**1.92**) with

ethylene and a ruthenium-hydride complex (Figure 1.10, eq 46).[55] Only certain bulky

substrates yielded secondary amine products like **1.93**, with most amines yielding the

imine form like **1.94**. In 2006, the Sames group was able to achieve the α-arylation of

pyrrolidines using $Ru_3(CO)_{12}$ and aryl boronate ester coupling partners (Figure 1.10, eq

47).[56] Once again, the use of nitrogen directing groups was key to this transformation.

Figure 1.10 **Amine Functionalization Through Inner-Sphere Mechanisms**
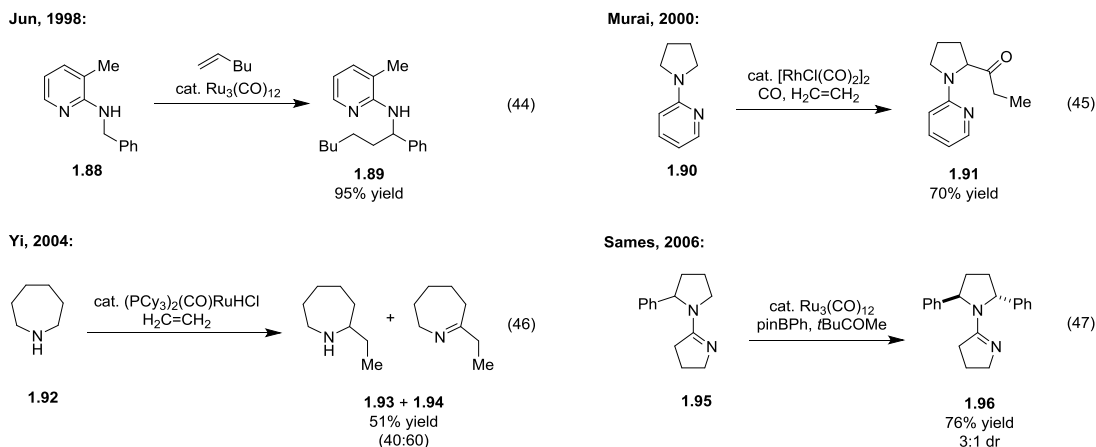
1.9 Redox-Neutral Reactions

In contrast to traditional oxidative or reductive reactions, redox-neutral reactions

present a pathway that can be more atom economical and reduce the waste generated

from external oxidants or reductants.[57] In a redox-neutral reaction, both oxidations and

reductions occur, but the overall change in oxidation state is zero. This means that no

external oxidant or reductant is required. A good example of a redox-neutral process is

the Tishchenko reaction.[58] In it, two molecules of aldehyde (**1.97**) combine to form a

single ester molecule (**1.98**) through the formal oxidation of one aldehyde and the

formal reduction of another (Figure 1.11, eq 48). The Stetter reaction can also be

considered a kind of redox-neutral reaction, where an aldehyde is added to an activated

alkene (Figure 1.11, eq 49).[59] In 1990, Evans and coworkers developed a SmI_2-mediated

variant of the Tishchenko reaction, where a molecule of aldehyde is converted to the ester oxidation state and a ketone is reduced with excellent yield and dr (Figure 1.11, eq 50).[60] In 2012, Krische et al. published a report on a redox-neutral, enantioselective crotylation of benzylic alcohols (**1.103**) with butadiene (**1.104**) using a ruthenium transfer hydrogenation catalyst in conjunction with a chiral phosphoric acid (Figure 1.11, eq 51).[61] This process does not require prefunctionalization of starting materials or result in the formation of any byproducts, making it very efficient. The potential of redox-neutral chemistry is that, if the right starting materials and conditions are selected, costly and wasteful oxidation state adjustments of molecules can be avoided by harnessing the intrinsic reactivity of the molecules.

Figure 1.11 **Some Examples of Redox-Neutral Reactions**
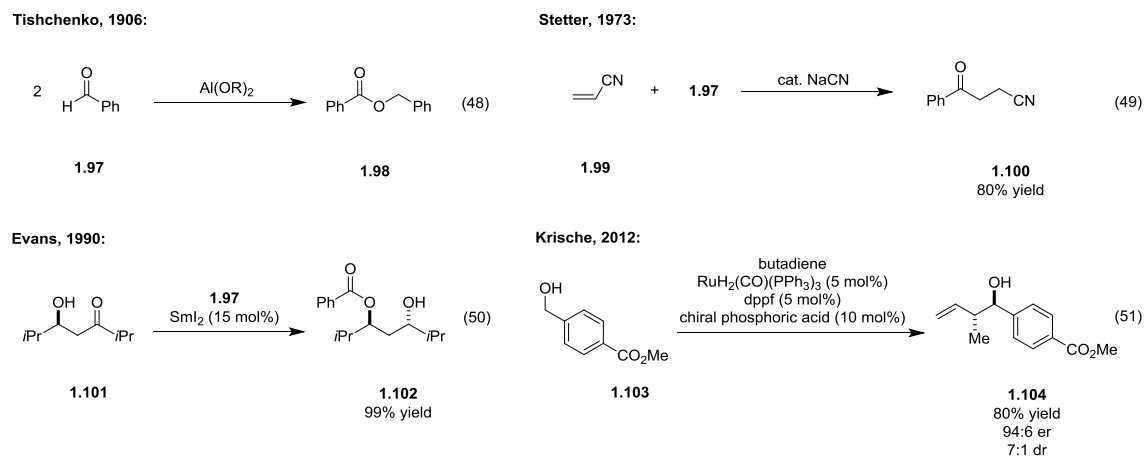
1.10 Redox-Neutral Reactions by Hydride Shift

One powerful method for C–H bond functionalization involves the use of a hydride shift.[62] Both the Tishchenko reaction (eq 48) and Evans' variant on the Tishchenko reaction (eq 50) have the transfer of a hydride as part of their proposed mechanisms. Through the transfer of a hydride to a different part of the molecule and

the subsequent nucleophilic attack on the resultant cation, C–H functionalization can be achieved without the use of external oxidants.

Figure 1.12 **Some Early Examples of Intramolecular Hydride Shifts**
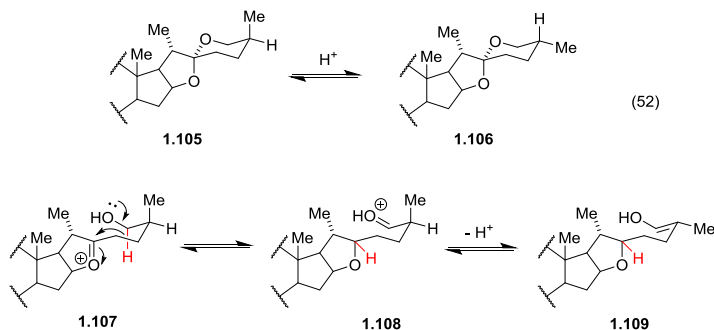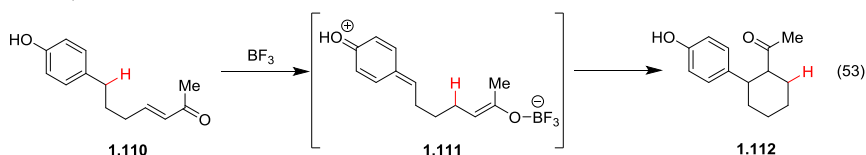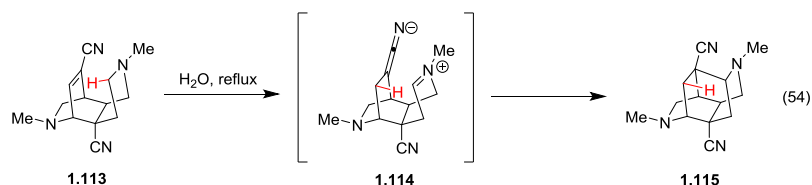
One early proposal for the involvement of a hydride transfer step in an intramolecular process was from Woodward and coworkers in 1958 (Figure 1.12, eq 52).[63] They proposed that the acid-catalyzed epimerization of steroidal sapogenins (**1.105** and **1.106**) proceeded through an equilibrium with an acetal-ring opening, followed by hydride shift and tautomerization. In 1969, Atkinson reported the cyclization of α,β-unsaturated compound **1.110** in the presence of BF$_3$·Et$_2$O (Figure 1.12, eq 53).[64] It was proposed that the Lewis acid activated the ketone towards hydride shift from benzylic site of the phenol, leading to intermediate **1.111**. Subsequent ring closure

yielded product **1.112**. In 1976, Grabowski and coworkers discovered that reduced Diels-Alder adduct **1.113** underwent a hydride shift/ring closure when heated in water to yield symmetrical diazaditwistane **1.115** (Figure 1.12, eq 54).[65] Deuteration studies were used to support the mechanistic proposal of a hydride shift.

Figure 1.13 **Recent Non-Amine-Based Hydride Shift Reactions**
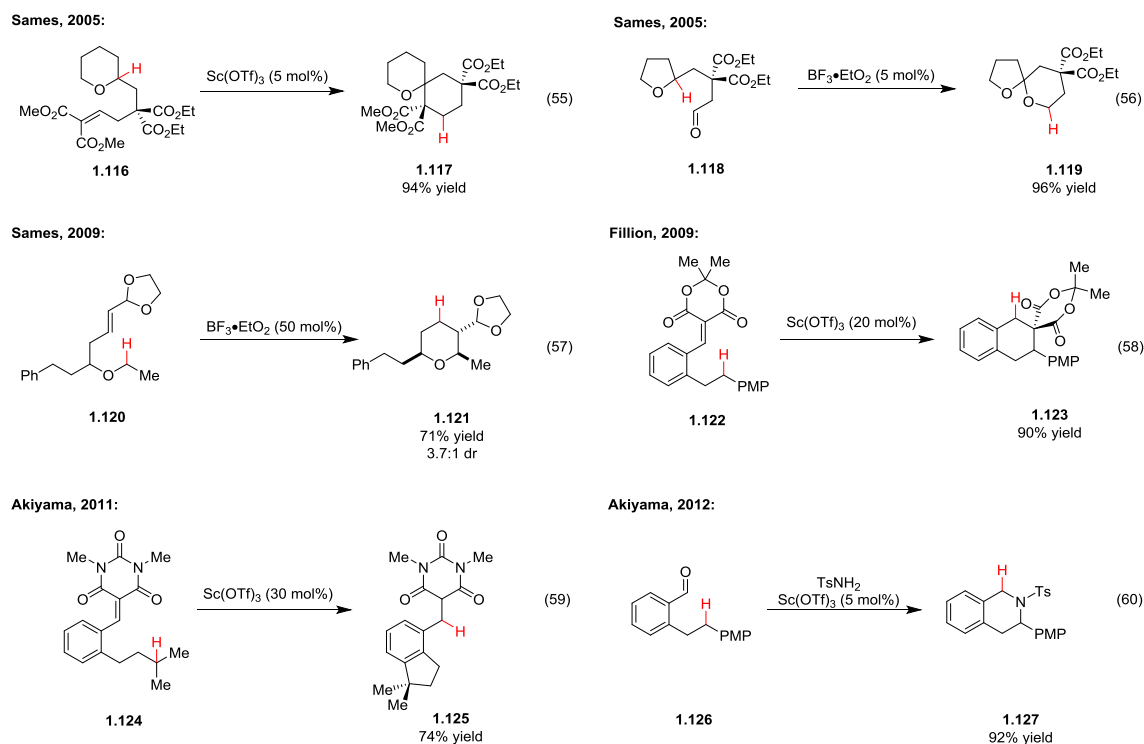
More recently, Sames' group reported the use of Sc(OTf)$_3$ to activate the alkylidenemalonate hydride acceptor moiety in compound **1.116** towards 1,5-hydride transfer from the tetrahydropyran (Figure 1.13, eq 55).[66] Similarly, the same group performed an analogous reaction using aldehydes as the hydride acceptor rather than alkylidenemalonates, resulting in the formation of spiroketals like **1.119** (Figure 1.13, eq 56).[67] In 2009, the Sames group published a report on another ether-based hydride shift, this time using ethylene glycol-protected α,β-unsaturated aldehydes as the hydride acceptor (Figure 1.13, eq 57).[68] The acetal protecting group was shown to lead to rate

acceleration over the unprotected aldehyde. In the same year, Fillion and coworkers were able to demonstrate a Sc(OTf)$_3$-catalyzed 1,5-hydride shift/ring closure from a benzylic carbon not adjacent to a heteroatom (Figure 1.13, eq 58).[69] The benzylidene Meldrum's acid moiety was shown to be an effective hydride acceptor. In 2011, Akiyama and coworkers demonstrated a hydride shift from an even more challenging substrate, an alkyl sp[3] carbon center on substrate **1.124** (Figure 1.13, eq 59).[70] In this reaction, the group was able to achieve the more rare 1,6-hydride shift, followed by an unexpected Friedel-Crafts reaction to yield indane product **1.125**. In 2012, the same group was able to access various tetrahydroisoquinoline structures through the intramolecular hydride shift to an in situ formed imine (Figure 1.13, eq 60).[71] This allowed the group to achieve the formal synthesis of natural product (±)-tetrahydropalmatine in good yield.

Figure 1.14 **Variations on the *tert*-Amino Effect**
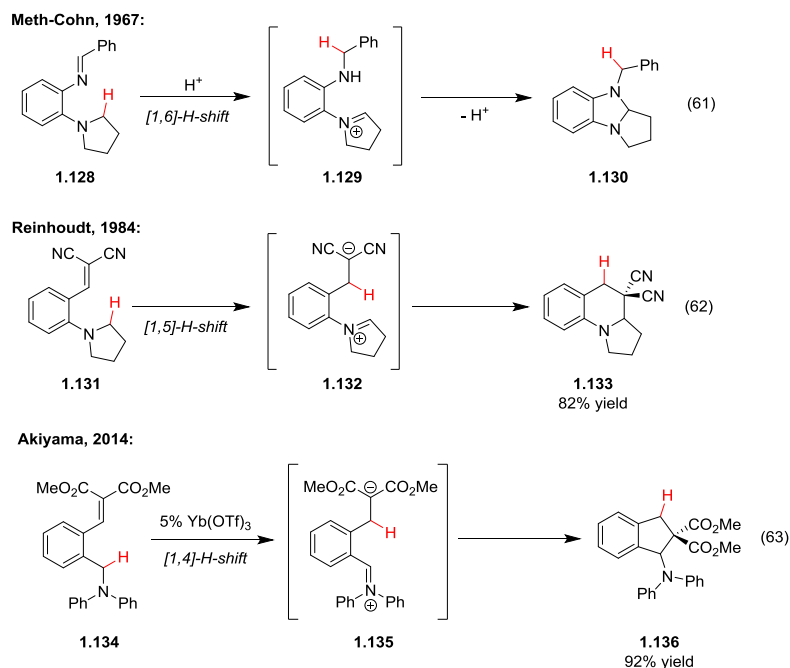
The variety of intramolecular hydride shift/ring closure reaction in which the hydride donor is a tertiary amine is known as the "*tert*-amino effect."[62] An early example

of this reaction was reported by Meth-Cohn and coworker in 1967 (Figure 1.14, eq 61).[72] Proceeding via a 1,6-hydride shift, the hydride is transferred from an aryl pyrrolidine to a pronated imine, leading to iminium **1.129** which, upon ring closure, yields aminal **1.130**. The *tert*-amino effect had been well developed by the Reinhoudt group in the 1980s.[62] In this example of a 1,5-hydride shift from 1984, good yield was achieved in the formation of tetrahydroquinoline **1.133** (Figure 1.14, eq 62).[73] While 1,5-hydride shifts are quite common and 1,6-hydride shifts are not particularly rare in the literature, very few examples of a 1,4-hydride shift exist in the literature. Recently, the Akiyama group achieved a $Yb(OTf)_3$-catalyzed 1,4-hydride shift/cyclization, resulting in the formation aminoindane **1.136** in high yield (Figure 1.14, eq 63).[74]

In 2009, the Akiyama group published a Brønsted acid catalyzed *tert*-amino effect cyclization using tertiary aminobenzaldehydes (**1.137**) and primary amines (Figure 1.15, eq 64).[75] In this reaction, the primary amines condense with aldehydes to form imines, which, when protonated by the acid readily accept the transferred hydride. At the same time, the Seidel group independently discovered the same reaction, mostly developing the reaction with cyclic tertiary aminobenzaldehydes (**1.139**) which yielded tricyclic aminal products(**1.140**) (Figure 1.15, eq 65).[76] Later that year, the same group published a *tert*-amino effect reaction using $Gd(OTf)_3$ as a Lewis acid which greatly increased the rate of the reaction (Figure 1.15, eq 66).[77] Whereas most *tert*-amino effect reactions in the literature required high temperatures for hours, with $Gd(OTf)_3$, most reactions completed in less than an hour at room temperature. Again in 2009, the Seidel group published the first asymmetric variant on the *tert*-amino effect using Mg(II)/DBFox ligand as a Lewis acid able to coordinate with an oxazolidone-based hydride-acceptor moiety (Figure 1.15, eq 67).[78] In 2010, Kim and coworkers successfully developed a combined *tert*-amino effect/asymmetric iminium catalysis reaction using

chiral amine **1.146** to form the iminium intermediate which acts as hydride acceptor (Figure 1.15, eq 68).[79]

Figure 1.15 **Recent Advances in the *tert*-Amino Effect**
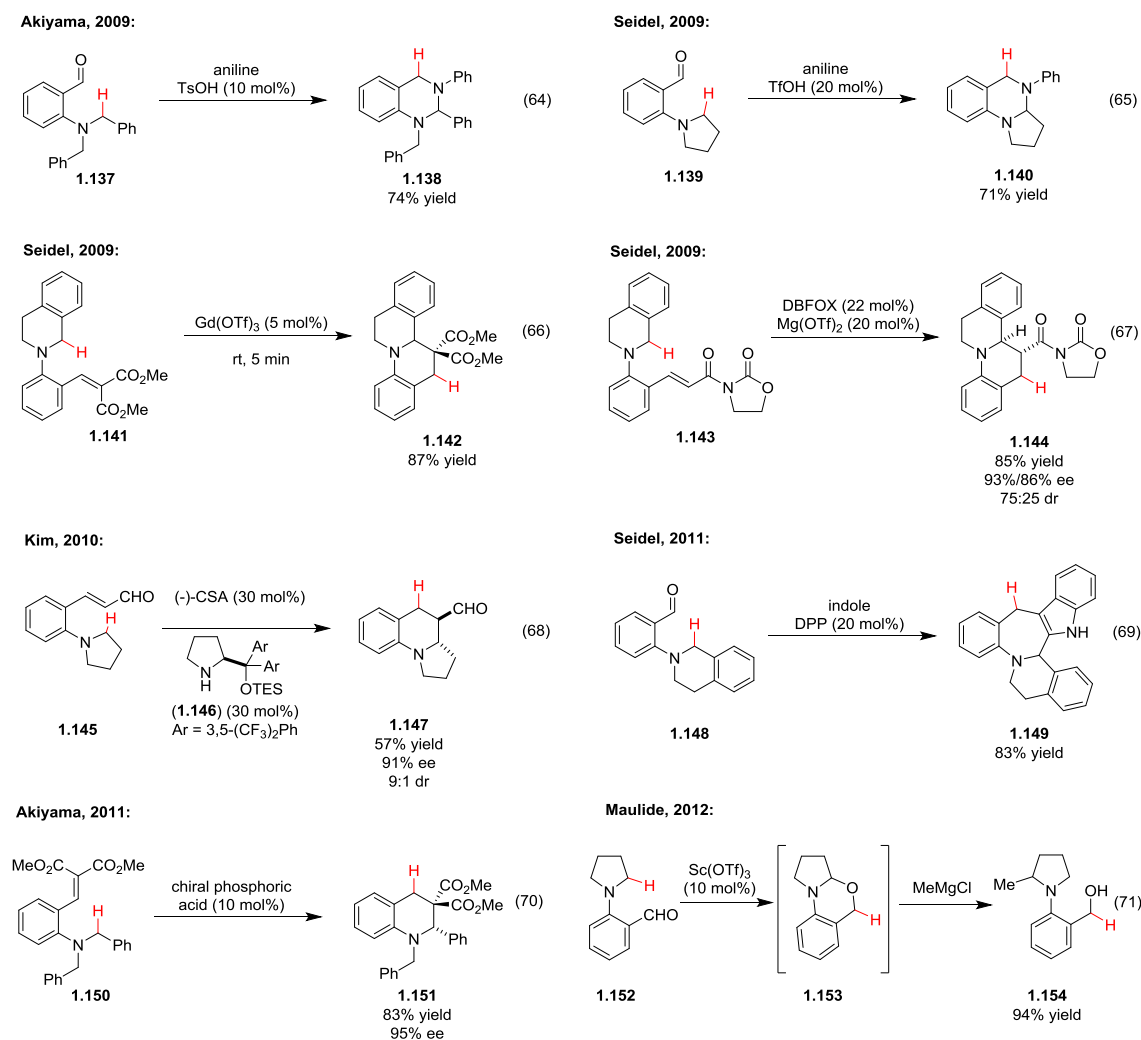
In 2011, Seidel et al. disclosed a hydride shift reaction which led to the formation of a seven-membered ring (**1.149**) (Figure 1.15, eq 69).[80] In the reaction, indole acts as a double nucleophile initially condensing with aldehyde **1.148** and, after the hydride shift, attacking the resultant iminium ion from the 2-position. In 2011, Akiyama and coworkers developed a new asymmetric variant on the *tert*-amino effect, using chiral phosphoric acids to yield products (**1.151**) in high *ee* (Figure 1.15, eq 70).[81] In 2012,

Maulide and coworkers introduced a new version of the *tert*-amino effect reaction, this time using aldehydes as the hydride acceptor, to yield *N,O*-acetal products (**1.153**) (Figure 1.15, eq 71).[82] These intermediate *N,O*-acetals were then exposed to Grignard reagents to produce α-alkylated and -arylated amines.

1.11 Azomethine Ylide Intermediates for Redox-Neutral Functionalization

Another useful method for the redox-neutral α-functionalization of amines involves the intermediacy of azomethine ylide species. Once generated, an azomethine ylide can undergo (3+2) cycloaddition, 1,5- or 1,7-electrocyclization, or be protonated and attacked by a nucleophile (Figure 1.16).[83]

Figure 1.16 **Modes of Azomethine Ylide Functionalization**
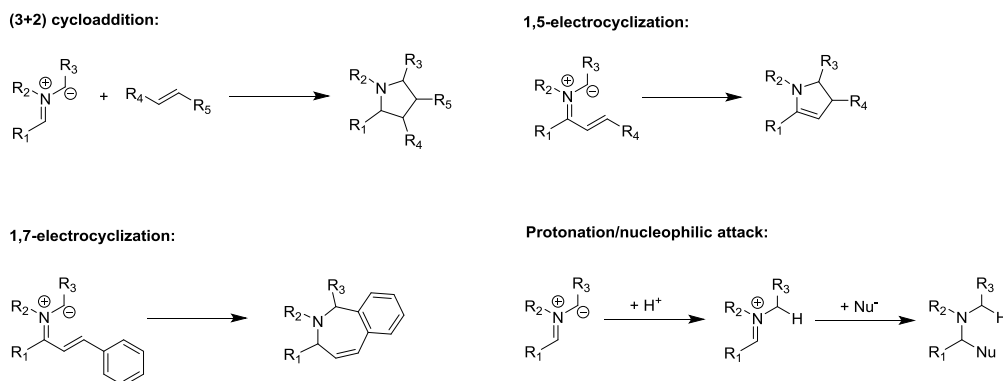
While there are many methods for the generation of azomethine ylide intermediates, most tend to fall within the categories described in Figure 1.17. The deprotonative pathway, as illustrated by an early example by Huisgen et al. (Figure 1.17, eq 72),[84] involves the deprotonation of an iminium ion at an sp[3] carbon α to nitrogen. The iminium can either be pre-formed, as with compound **1.155**, or be generated in situ either by the protonation of an imine or the condensation between a secondary amine and a carbonyl. Another method for azomethine ylide generation proceeds through the ring-opening of a neutral species. Aziridines are common starting materials for this type

of reaction (Figure 1.17, eq 73),[85] but other ring systems have been used.[83c] One last method worth mentioning for its relevance for redox-neutral synthesis is the decarboxylative pathway. First demonstrated by Rizzi and coworkers in 1970 (Figure 1.17, eq 74), the decarboxylative pathway proceeds through the condensation an amino acid with an aldehyde or ketone to form an oxazolidone intermediate (**1.163**) which decarboxylates under heating to form the desired azomethine ylide.[86] Due to the abundance of natural α-amino acids, this pathway can be quite useful for azomethine ylide generation.

Figure 1.17 **Common Methods for Azomethine Ylide Generation**
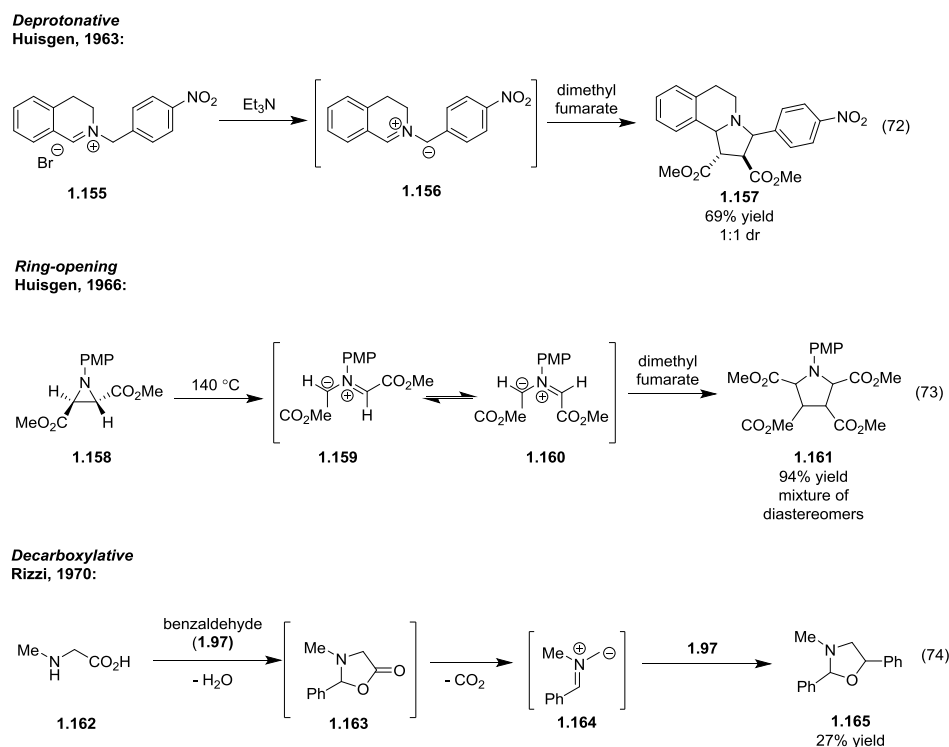
In 1979, Cohen and coworkers discovered that 2-hydroxy-6-methylacetophenones (**1.166**) could condense decarboxylatively with proline to form benzoxazine structrures (**1.167**) via an azomethine protonation/nucleophilic attack pathway (Figure 1.18, eq 75).[87] Substitution at the 6-position was shown to be necessary

for the reaction; with a hydrogen in the 6-position, only starting ketone and pyrrolidine were recovered. It was rationalized that sterics helped to prevent this undesired pathway with 6-methyl substrate **1.166**. In 1983, Confalone et al. demonstrated that α-amino esters could be effective starting materials for the generation of azomethine ylides (Figure 1.18, eq 76).[88] Sarcosine ethyl ester, when allowed to condense with aldehyde **1.168**, forms an iminium which can be deprotonated to form an azomethine ylide due to the activating nature of the ester group. This azomethine ylide then undergoes an intramolecular (3+2) reaction to yield cycloadduct **1.169**.

Figure 1.18 **Early Examples of Redox-Neutral Azomethine Ylide Reactions**
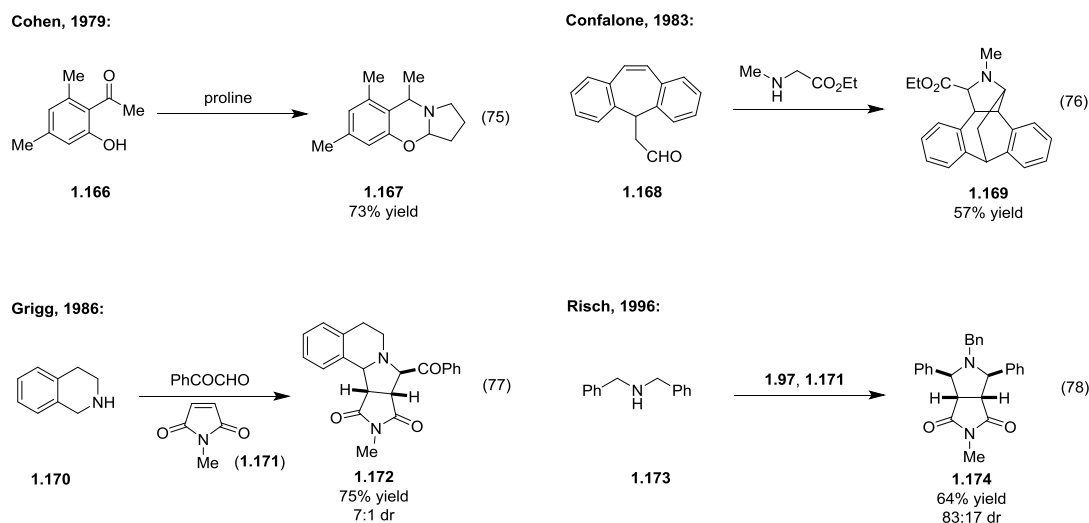
In 1986, Grigg and coworkers demonstrated the efficacy of tetrahydroisoquinoline (**1.170**) for deprotonative azomethine ylide formation (Figure 1.18, eq 77).[89] **1.170** and phenylglyoxal condense to form and azomethine ylide which undergoes (3+2) cycloaddition with *N*-methylmaleimide (**1.171**) to yield **1.172**. The benzylic site on **1.170** likely helps to stabilize the azomethine ylide through resonance, allowing the reaction to proceed. An example of an acyclic secondary amine undergoing deprotonative azomethine ylide formation was published by Risch and coworkers in

1996 (Figure 1.18, eq 78).[90] Dibenzylamine (**1.173**) reacted with benzaldehyde (**1.97**) and dipolarophile **1.171** to yield cycloadduct **1.174**.

Recently, there have been a number of new reports on redox-neutral annulations which proceed through azomethine ylide intermediates. Redox-neutral, asymmetric variants on the (3+2) reaction have been well developed.[91] In 2002, Zhang and coworkers published the first catalytic enantioselective (3+2) cycloaddition in a reaction between activated imines (**1.175**) and dimethyl maleate (**1.176**) (Figure 1.19, eq 79).[92] Enantioselectivity is introduced from binding of the azomethine ylide to a chiral Ag(I)/phosphine ligand complex. In 2008, Seidel and coworkers discovered an amine α-amination reaction which occurs between *o*-aminobenzaldehydes (**1.178**) and cyclic secondary amines (Figure 1.19, eq 80).[93] The condensation, which occurs in refluxing ethanol, was remarkable for the fact that it worked well for unactivated secondary amines, such as pyrrolidine. Formerly, amino acids such as proline were needed to include a pyrrolidine group in an azomethine ylide reaction, but, under these conditions, unfunctionalized, unactivated secondary amines could be used. Concurrently, Dang and Bai discovered a similar amination reaction, using amino acids and esters to yield annulated products (Figure 1.19, eq 81).[94] This reaction was discovered when aldehyde-tethered dipolarophile **1.180** failed to give the desired (3+2) product, instead yielding aminal **1.181**. In 2010, Seidel and coworkers published a microwave-assisted pyrrole formation from secondary amines and 1,3-diketones (Figure 1.19, eq 81).[95] The reaction, which proceeds through a 1,5-electrocyclization, yields pyrrole **1.183** after aromatization from the elimination of water from the initial cyclization product. In 2011, the same group developed a 1,6-annulation by reacting aldehyde-tethered nucluophiles (such as **1.184**) with secondary amines and amino acids (Figure 1.19, eq 83).[96] Like with the amination reaction, this process involved the protonation of the azomethine ylide, followed by the attack of the tethered nucleophile. A number of different polycyclic ring

systems were made using this methodology. Recently, the Hajra group developed a method for redox-neutral (3+2) cycloadditions using pyrrolidine and benzaldehyde to form the azomethine ylide (Figure 1.19, eq 84).[97] The dipolarophile used in this case was a second equivalent of benzaldehyde, yielding cyclic *N,O*-acetal **1.186** as product.

Figure 1.19 **Recent Redox-Neutral Azomethine Ylide-Based Annulations**
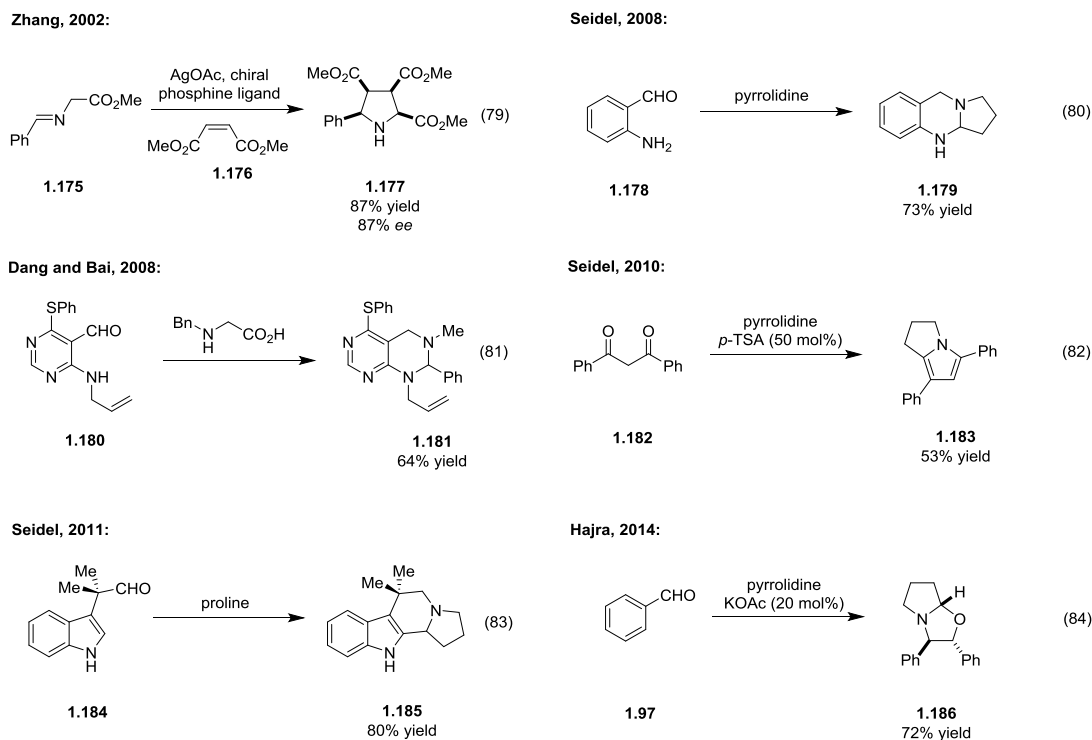
In 2011, the Seidel group developed a new approach to azomethine ylide functionalization related to the α-amination reaction (Figure 1.19, eq 80) reported in 2008. In this variant, however, the nucleophile was not tethered to the aldehyde, leading to an intermolecular nucleophilic attack (Figure 1.20, eq 85).[98] Non-annulated products (e.g. **1.188**) were produced decarboxylatively from amino acids in this process. Later, the same group developed methods for redox-neutral α-functionalization of simple secondary amines with various nucleophiles using iminium isomerization through azomethine ylide intermediates. In 2013, the Seidel group published an amine α-

alkynylation using terminal alkynes as the nucleophiles (Figure 1.20, eq 86).[99] Sterically demanding aldehydes like **1.189** were necessary to avoid the alkyne group adding to the benzylic position rather than endocyclically. Diphenylphosphine oxide (**1.191**) was also demonstrated to be a good nucleophilic partner in redox-neutral amine α-functionalizations, yielding α-aminophosphonates (**1.192**) in a variation on the Kabachnik-Fields reaction (Figure 1.20, eq 87).[100] Unlike with alkynylation, the phosponation reaction did not require bulky aldehydes. Whereas the alkynylation reaction is nearly irreversible, phosphonation at the benzylic site is reversible and can lead to the formation of thermodynamically more stable product **1.192**.

Figure 1.20 **Redox-Neutral Azomethine Ylide Protonation/Functionalization Reactions**
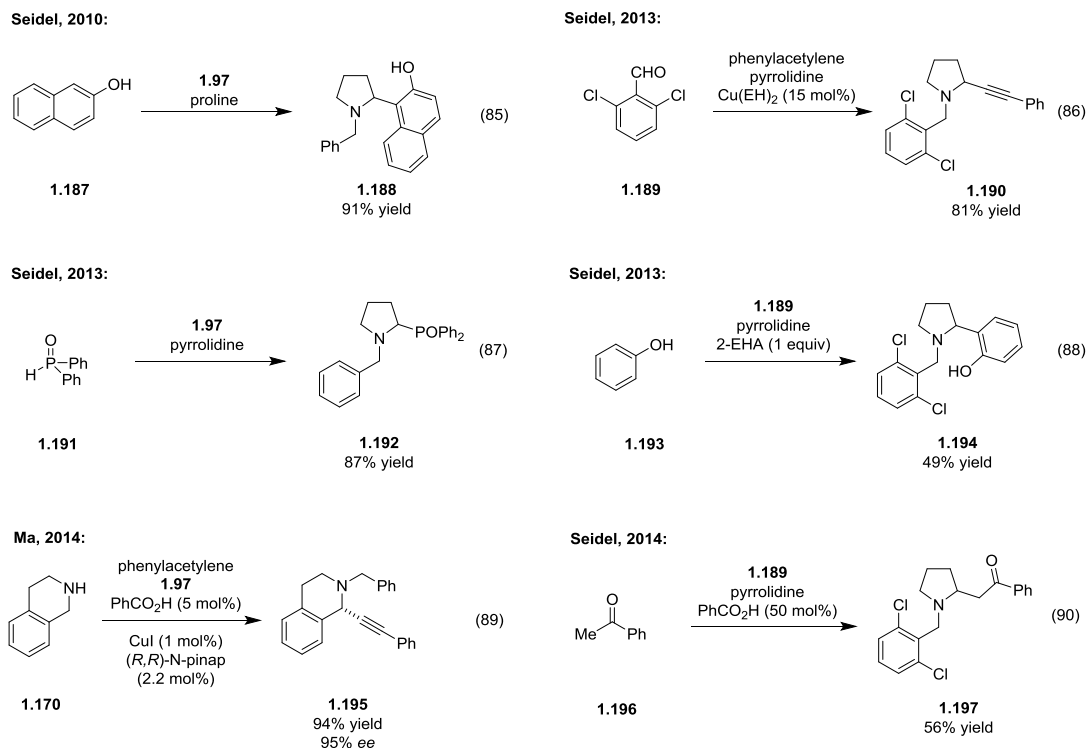
Phenols, naphthols and indoles were later included in the list of nucleophiles that can be used in redox-neutral amine α-functionalization reactions, forming products like

α-aryl amine **1.194** (Figure 1.20, eq 88).[101] Sterically hindered aldehydes like **1.189** were required for this reaction as with the alkynylation. An α-alkylation reaction with tetrahydroisoquinoline (**1.170**) as amine was reported by Yu et al. in 2013[102] and very soon afterwards, Ma and coworkers published an asymmetric variant on this reaction (Figure 1.20, eq 89).[103] When chiral ligand (*R,R*)-*N*-pinap was used with CuI, high *ee*'s were obtained in α-alkynylated amines (**1.195**). In 2014, the Seidel group developed a redox-Mannich reaction using the lessons learned from previously developed α-functionalizations (Figure 1.20, eq 90).[104] While bulky aldehyde **1.189** was needed for the reaction when pyrrolidine was used as the amine, a wide variety of aldehydes could be used with **1.170**.

Figure 1.21 **Redox-Neutral Amine α,β-Difunctionalization**
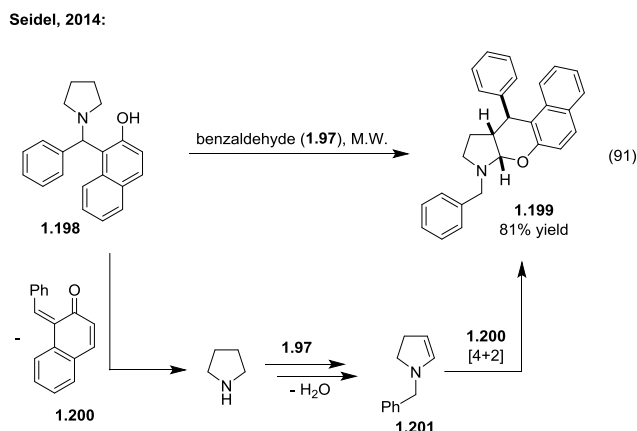
During efforts to develop the amine α-arylation chemistry, the Seidel group discovered that undesired naphthol regioisomer product **1.198** could, when exposed to benzaldehyde under microwave conditions, produce α,β-difunctionalized annulation product **1.199** (Figure 1.21, eq 91).[105] The reaction is thought to proceed via fragmentation of **1.198** to form quinoidal species **1.200** and pyrrolidine. The pyrrolidine can then condense with benzaldehyde and, through an azomethine ylide

intermediate, produce enamine **1.201**, which could undergo a [4+2] reaction with **1.200** to form annulated *N,O*-acetal product **1.199**.

1.12 Alternative Redox-Neutral Amine Functionalizations

Some other redox-neutral amine functionalization reactions are worth noting for their relevance to the previous discussion. Several examples are known of the redox-neutral aromatization of secondary amines through azomethine ylide intermediates. In 2009, Tunge and coworkers demonstrated that 3-pyrroline (**1.202**) can condense with aldehydes and ketones to form *N*-alkylated pyrroles (**1.204**) (Figure 1.22, eq 92).[106] This reaction was later shown by Seidel and coworkers to proceed via an azomethine ylide.[107] The analogous conversion of indoline (**1.205**) to *N*-alkylated indoles (**1.206**) was independently developed by the groups of Pan[108] and Seidel[107] (Figure 1.22, eqs 93 and 94). The two methods were rather similar beside the use of microwave heating by Seidel et al. In 2011, the Seidel group introduced the use of 4-hydroxyproline (**1.207**) as a substitute for unstable 3-pyrroline (**1.202**) in the pyrrole formation reaction (Figure 1.22, eq 95).[109] This route has some advantages with **1.207** being stable and, since found in collagen, readily available, unlike **1.202**.

One last related reaction from the Seidel group involves the use of indole to react with *o*-aminobenzaldehydes (Figure 1.22, eq 96).[110] When heated with indole in the presence of *p*-TSA, *N*-methylaminobenzaldehyde **1.209** yields the annulated natural product neocryptolepine (**1.210**). However, when primary aminobenzaldehyde **1.178** is allowed to react under the same conditions, the product is ring-opened indole product **1.211**. These substituted quinolines can be used in the synthesis of other, related natural products.

Figure 1.22 **Other Examples of Redox-Neutral Amine Functionalization**

Tunge, 2009:

1.202 + **1.203** → **1.204** (92) 88% yield

Pan, 2010:

1.205 → **1.206** (93) 76% yield

Seidel, 2011:

1.205 → **1.206** (94) 77% yield

Seidel, 2011:

1.207 → **1.208** (95) 48% yield

Seidel, 2011:

1.210 77% yield ← **1.209** R = Me / **1.178** R = H → **1.211** (96) 83% yield
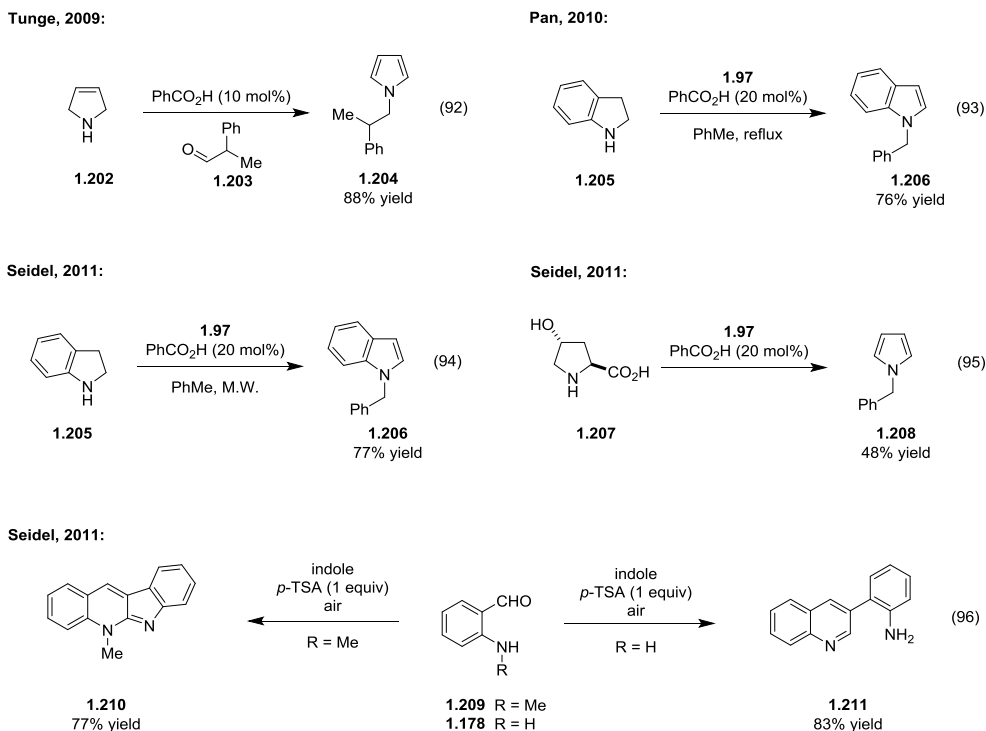
1.13 Objectives

Redox-neutral methods have been shown to be effective tools in amine functionalization, yielding complex products from simple starting materials without the need for external oxidants or reductants. The build-up of complexity can be achieved quickly, with many drug-like structures able to be synthesized in a single step. With azomethine ylide based amine α-functionalizations, secondary amines are doubly functionalized in one step, resulting in a formal reductive amination and oxidative amine α-functionalization, something that would otherwise have two be done in two steps without a redox-neutral approach.

This thesis will focus on the development of azomethine ylide-based redox neutral amine functionalization reactions, especially of the non-pericyclic kind. Chapter 2 will discuss the further development of the Seidel group's α-amination reaction (Figure

1.19, eq 16-a) and include in depth studies on the mechanism both experimentally and computationally, in collaboration with K. N. Houk's group. It will also cover methods developed for the synthesis of related bioactive natural products. Chapter 3 will discuss the development analogous α-oxygenation and α-sulfenylation reactions, again with mechanistic insights provided by Houk's group. Finally, chapter 4 will deal with the development of a decarboxylative version of the Strecker reaction and in chapter 5 a redox-neutral 1,5-electrocylization with secondary amines will be discussed.

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Chapter 2

Studies on a Redox-Neutral α-Amination

2.1 Background

As noted in the introductory chapter, the α-functionalization of C−H bonds in amines is of great synthetic importance. The aminal substructure[1] is present in a number of natural products, which makes simple synthetic procedures to their precursors and analogues important to the organic chemist.[2] A few redox-neutral aminal syntheses are known in the literature, but these reactions are generally rare.

Figure 2.1 **Some Examples of Aminal Syntheses**
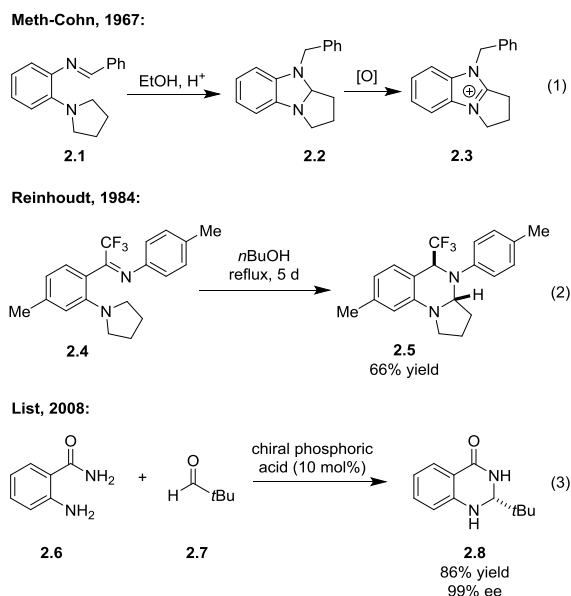
Meth-Cohn and coworkers published an early 1,6-hydride shift reaction which led to aminal product **2.2**, but this product tended to oxidize to **2.3** (Figure 2.1, eq 1).[3] Another *tert*-amino effect reaction leading to an aminal product was described by Reinhoudt in 1984 (Figure 2.1, eq 2).[4a] Activated starting material **2.4** required five days under reflux in *n*-butanol to yield aminal **2.5** in 66%, making this approach not very

synthetically useful. The groups of Akiyama and Seidel independently developed efficient, Brønsted acid-catalyzed variants of this reaction in 2009.[4b,4c] A common method to synthesize aminals is the condensation of aldehydes with diamines. In 2008, List et al. developed a chiral phosphoric acid-catalyzed aminal synthesis, yielding aminals like **2.8** with high *ee* (Figure 2.1, eq 3).[5] The drawback of this pathway is that the products are limited to simple alkyl or aryl groups at the 2-position, making annulated polycyclic aminals such as **2.8** or **2.5** difficult to create.

In 2008, the Seidel group published a report on the synthesis of aminals from *o*-aminobenzaldehydes and cyclic secondary amines.[6] The reaction was discovered serendipitously when pyrrolidine was used as the base in an attempted di-Friedländer condensation between aminobenzaldehyde **2.9a** and diketone **2.10** (Figure 2.2, eq 4).[7] While some monoquinoline **2.11** was obtained, unexpected aminal **2.12a** was isolated in a substantial yield. Following optimization, the same reaction run without the ketone yielded **2.12a** in 95% (Figure 2.2, eq 5). Despite the Friedländer condensation being known for over 100 years,[8] these aminal side products had never been reported.

Figure 2.2 **Discovery of Redox-Neutral α-Amination**
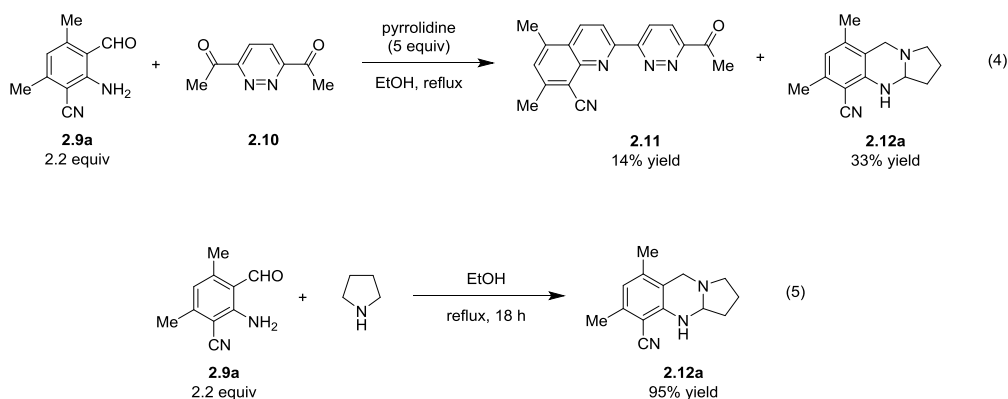
The reaction was shown to tolerate a wide range of functionality on aminobenzaldehyde (Figure 2.3), including electron withdrawing groups (**2.12b**),

electron donating groups (**2.12d**), heteroaromatics (**2.12e**) and even secondary aminobenzaldehydes (**2.12f**). Variation on the secondary amine partner was less well tolerated. Use of piperidine (**2.12g**) or morpholine (**2.12h**) led to decreased yields even at 140 °C in a sealed tube. 1,2,3,4-tetrahydroisoquiniline (THIQ), however, resulted in high yields (**2.12i** and **2.12j**), likely due to activation at the benzylic position. Tryptoline, too, yielded the desired product, but with moderate yield (**2.12k**).

Figure 2.3 **Selected Scope of α-Amination Reaction**
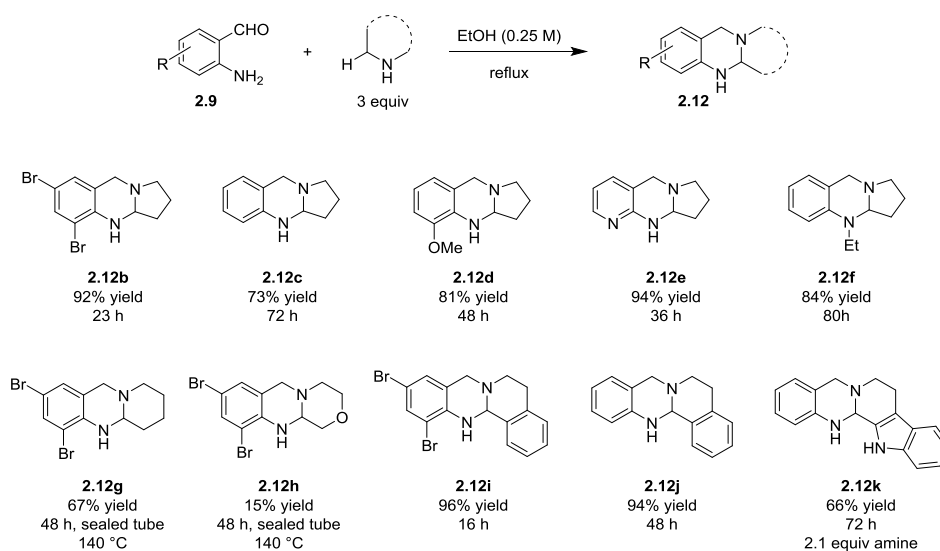
While this redox-neutral method for the α-functionalization of amines was intriguing, the mechanism of the reaction was not clear. It seemed likely that the reaction somehow proceeded via an azomethine ylide intermediate, but a 1,6-hydride shift pathway could not be ruled out. Knowledge of the mechanism of this amination could aid in the understanding of this class of α-functionalization and be useful in the development of new reactions. With this in mind, we undertook a joint experimental and computational study of the mechanism with K. N. Houk's group.[9]

2.2 Mechanistic Study – Potential Pathways

Various potential mechanisms have been considered for these transformations, all of which are in line with experimental conditions. Using the reaction of **2.9c** and pyrrolidine as a prototypical example, a number of potential mechanistic pathways are summarized in Figure 2.4. All start with the formation of hemiaminal **2.13c** that should be formed rapidly upon mixing of the aldehyde and amine. Afterwards, **2.13c** can eliminate hydroxide to form iminium ion **2.14c**, which can undergo a variety of reactions. Deprotonation by an external base either leads to *ortho*-aza-quinone methide **2.15c**,[10] or azomethine ylide **2.16c**.[11,12] Aza-quinone methide **2.15c** can also be obtained by a direct dehydration of hemiaminal **2.13c** (*vide infra*).

Figure 2.4 **Potential Mechanistic Pathways**
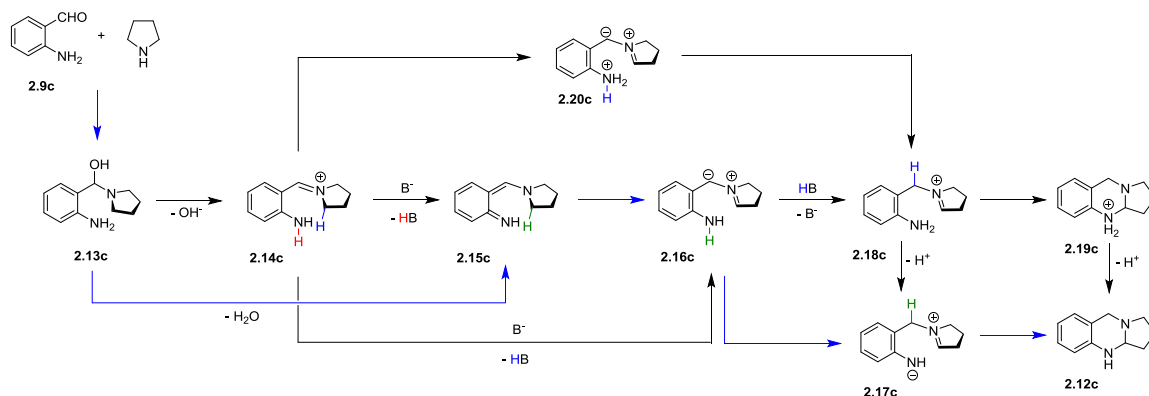
Alternatively, the protonated azomethine ylide **2.20c** can be formed by an internal proton transfer[13] and is likely to undergo another proton transfer resulting in iminium species **2.18c**. In addition to the rather unlikely pathway involving **2.20c** as an intermediate, iminium ion **2.18c** can be obtained from **2.15c** via azomethine ylide **2.16c**. The latter could be formed from **2.15c** either by a 1,6-hydride shift[14] or a 1,6-proton transfer.[13] Subsequent protonation of azomethine ylide **2.16c**, e.g. by solvent molecules, results in **2.18c**. The ring closure can either proceed via iminium ion **2.18c**

or zwitterion **2.17c**. An intramolecular attack of the amino group nitrogen on the iminium moiety in **2.18c** leads to the protonated product **2.19c**, while the formation of **2.17c** by a (solvent-mediated) proton transfer and a subsequent intramolecular attack leads to the neutral product **2.12c**. The direct transformation of **2.14c** to **2.18c** via 1,3-hydride shift was not considered.[15]

Overall, there are several plausible and interconnected mechanisms leading to products **2.12** that differ with respect to the intermediates involved and their protonation states. As a consequence, a purely experimental mechanistic elucidation of this reaction is likely to be extremely challenging. In order to discriminate between the different mechanistic possibilities, we undertook a detailed computational study based on DFT and arrived at a consistent, but partly unexpected mechanism. In addition, new experimental data were obtained on selectivities and reactivities of different substrates, and deuterium-labeling studies were performed that provide evidence that supports the computational results. Further support was obtained by trapping of an azomethine ylide and an azaquinone methide.

2.3 Mechanistic Study – Evidence for an Azaquinone Methide Intermediate

In order to support or rule out the mechanistic pathways presented in Figure 2.4, we designed a number of experiments with the goal to trap some of the proposed intermediates, in particular *ortho*-azaquinone methides (e.g., **2.15c**) and azomethine ylides (e.g., **2.16c**). After a series of failed attempts to trap the proposed quinoidal intermediates via intermolecular hetero-Diels-Alder reactions (Figure 2.5, eq 6), we explored the possibility of tethering a dienophile to one of the reactants. 2-Allyl pyrrolidine **2.23** was allowed to react with aminobenzaldehyde **2.9b**, but desired [4+2] product **2.24** was not observed (Figure 2.5, eq 7). In addition to expected aminals **2.25** and **2.26**, methyl aminal **2.27** and quinoline **2.28** were obtained in nearly equal

amounts, suggesting the possibility of a fragmentation leading to these two products. Potentially, this fragmentation could occur through the formation of dienamine **2.30**. Upon addition of water, **2.30** could fragment to yield enamine **2.32** and acetaldehyde, which can react with a second molecule of **2.9b** to form quinoline **2.28** in a Friedländer condensation. This result, while interesting, did not help to trap an azaquinone methide intermediate.

Figure 2.5 **Initial Attempts at Azaquinone Methide Trapping**
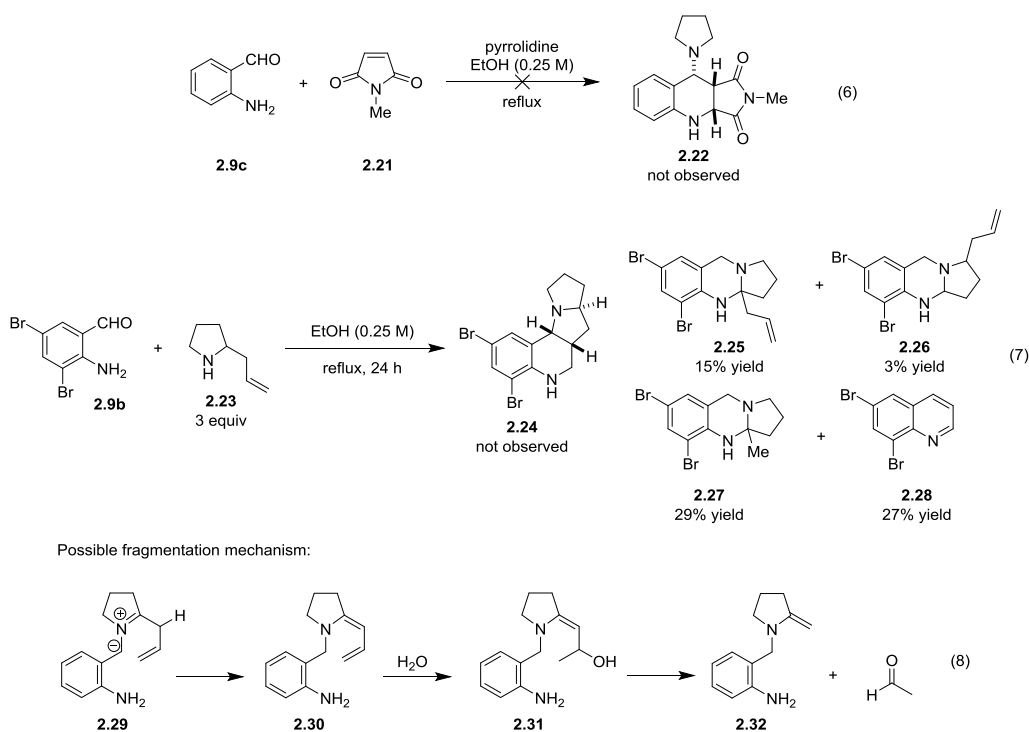
Next, we prepared aminobenzaldehyde **2.33** bearing an α,β-unsaturated ester attached to nitrogen via a four-carbon alkyl chain linker (Figure 2.6). Upon exposure of **2.33** to standard aminal forming conditions with excess pyrrolidine, we recovered compound **2.34** in 7% yield, the apparent product of an endo-selective hetero-Diels-Alder reaction (see structure **2.38**). Another product that was isolated from the reaction mixture is compound **2.35** (7%), possibly formed upon elimination of pyrrolidine from

compound **2.34**. In addition, we obtained conjugate addition product **2.36** (42%), aminal **2.37** (20%),[16] and recovered starting material **2.33** (9%). While these results are consistent with an *ortho*-azaquinone methide intermediate, we needed to rule out alternative reaction pathways for the formation of **2.34** that do not involve a [4+2] cycloaddition.

Figure 2.6 **Trapping the Azaquinone Methide via a [4+2] Cycloaddition**
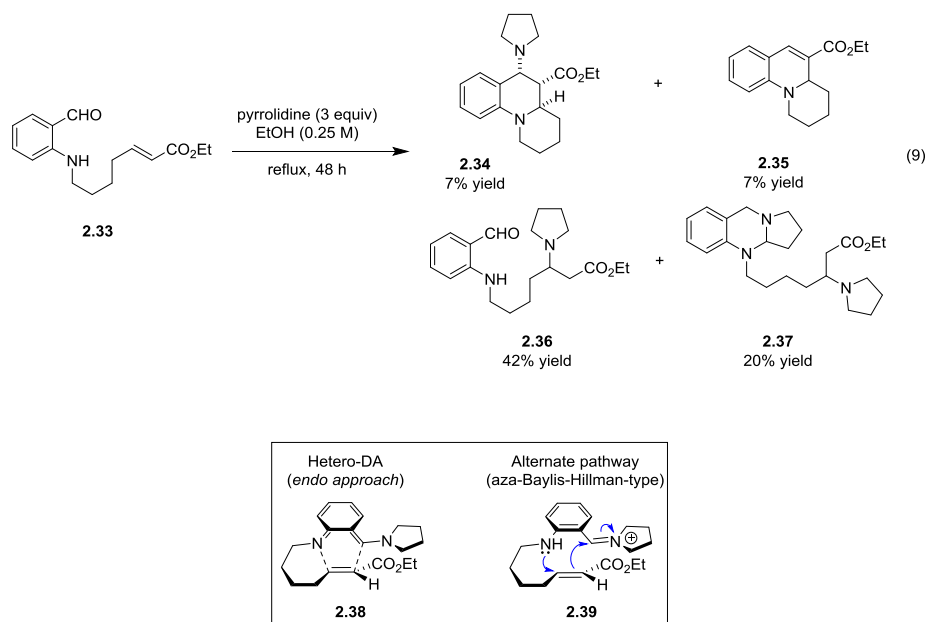
Potentially, tricycle **2.34** could be formed directly in a Baylis-Hillman-like reaction,[17] and a conjugate addition of pyrrolidine to **2.35** could result in the formation of apparent Diels-Alder product **2.34**. We tested for this possibility in a series of experiments (Figure 2.7). Heating **2.33** in the absence of any additives did not lead to formation of **2.35**. Since pyrrolidine could simply act as a base to catalyze cyclization of tethered alkene **2.33** to yield cyclization product product **2.35**, we also performed the reaction in the presence of Hünig's base (similar pK_{aH} to pyrrolidine) and *N*-methylpyrrolidine. No reaction was observed in either case, and starting material **2.33** was recovered quantitatively. Furthermore, to ensure that the apparent Diels-Alder

product **2.34** is not the product of conjugate addition of pyrrolidine to tricycle **2.35**, the latter was exposed to pyrrolidine in refluxing ethanol for 48 hours. No reaction was observed in this instance. This strongly suggests that **2.34** is not a conjugate addition product, but rather that **2.35** results from the elimination of pyrrolidine from **2.34**.

Figure 2.7 **Control Experiments for Azaquinone Methide Trapping**
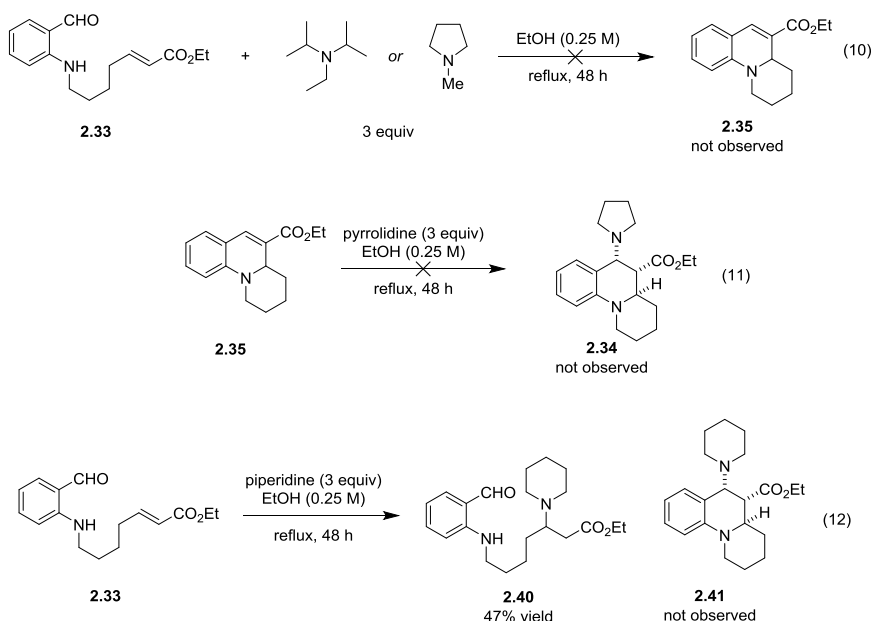
An aza-Baylis-Hillman-type pathway[17] (e.g., structure **2.39** in Figure 2.6) would also account for the formation of **2.34**. However, given the unlikeliness of iminium ion formation under the reaction conditions (see computational results), this pathway was not considered further. The analogous reaction of **2.33** with piperidine only led to conjugate addition product **2.40** in 47% yield, in addition to recovered starting material. The lack of formation of **2.41** or the corresponding aminal product can be attributed to an increased difficulty of accessing the required *ortho*-azaquinone methide or azomethine ylide intermediates. Another possible pathway, namely pyrrolidine acting as a nucleophilic Lewis base catalyst in an intramolecular Baylis-Hillman reaction was

ruled out on the basis that this would require the formation of an intermediate with a ten-membered ring (not shown).

2.4 Mechanistic Study – Evidence for an Azomethine Ylide Intermediate

As noted in the first chapter of this thesis, a common reaction that azomethine ylides undergo is the (3+2) cycloaddition.   In 2011, the Seidel group exploited this reactivity to establish azomethine ylides as intermediates in a redox-neutral pyrrole formation (Figure 2.8, eq 13).[18] Tethered dipolarophile **2.42** yielded (3+2) cycloadduct **2.43** when heated in the microwave with 3-pyrroline. To trap the proposed azomethine ylide intermediates in the α-amination reaction, analogous tethered dipolarophile **2.44** was synthesized and allowed to react with pyrrolidine under standard reaction conditions (Figure 2.8, eq 14). Cycloadduct **2.45**, however, was no obtained as a product in the reaction, but rather quinoline **2.46** was found to be the major product. The exact mechanism of this quinoline formation is not known, but may involve an olefin isomerization followed by an attack on the aldehyde by the resulting enamine.

Figure 2.8 **Unanticipated Quinoline Formation**
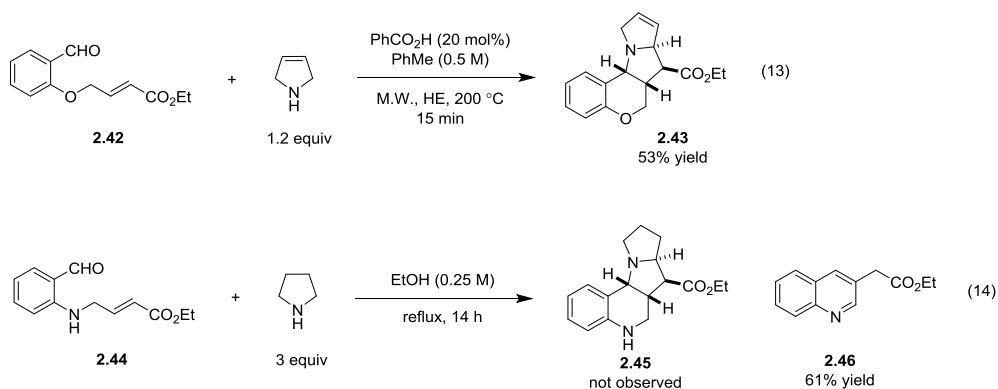
Aldehydes are known to act as potent dipolarophiles in reactions with azomethine ylides.[19]   In order to promote intermolecular (3+2) cycloaddition and hopefully suppress aminal formation, pyrrolidine was allowed to react with two

equivalents of aminobenzaldehyde **2.9b** (Figure 2.9). The reaction was performed in ethanol solution fourfold more concentrated than under standard conditions. A microwave reactor was used to facilitate product formation. Following a reaction time of 30 min at 150 °C, cycloaddition product **2.47** was isolated in 18% yield along with aminal **2.12b** (74%). When toluene was used as the solvent under otherwise identical conditions, the yield of the (3+2) product **2.47** increased to 27%, while aminal **2.12b** was recovered in 58% yield. This increase in yield in an apolar solvent is consistent with a reduced quantity of proton sources available to protonate the azomethine ylide. In both solvents, **2.47** was obtained as a single diastereomer. The relative stereochemistry of **2.47** matches that of the major products previously reported in analogous (3+2) reactions.[19] These observations strongly support the intermediacy of an azomethine ylide.

Figure 2.9 **Azomethine Ylide Trapping via (3+2) Cycloaddition**
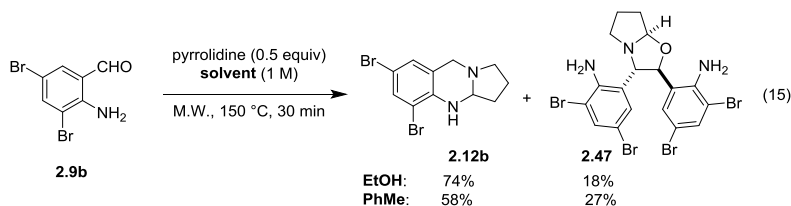
2.5 Mechanistic Study – Deuteration Experiments

A number of deuterium-labeling experiments were performed in order to obtain further insights into the mechanism of the aminal formation. When a reaction of aminobenzaldehyde **2.9b** and pyrrolidine was conducted in EtOD, aminal **2.12b** was obtained with close to 100% incorporation of one deuterium atom, distributed approximately equally over the two diastereotopic benzylic protons (Figure 2.10, eq 16).[20] To confirm that deuteration occurred during aminal formation, non-deuterated **2.12b** was exposed to identical reaction conditions (reflux in EtOD for 48 h in presence

of two equivalents of pyrrolidine). No trace of deuterium incorporation was observed in this case. These results are consistent with an azomethine ylide intermediate related to **2.16b** being protonated by solvent to form an iminium ion of type **2.18b**.

Figure 2.10 **Deuterium Incorporation for Mechanistic Elucidation**
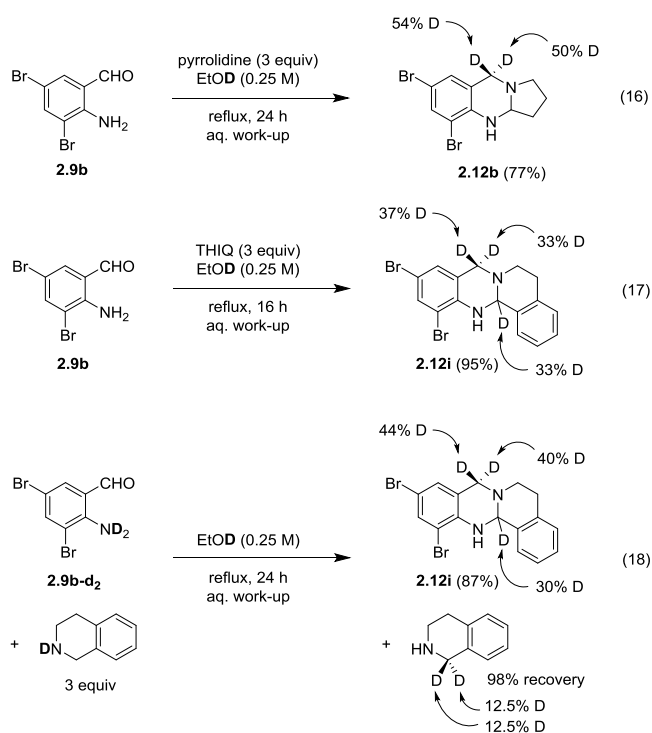
The corresponding experiment was also performed with THIQ (Figure 2.10, eq 17). Interestingly, in this case partial deuterium incorporation was observed for all three benzylic protons with a total deuterium incorporation of ~ 100%. The observation of deuterium incorporation at the aminal carbon likely reflects a difference in charge distributions of the azomethine ylides derived from pyrrolidine vs. THIQ.[21] However, the fact that substantially less than one deuterium atom was incorporated into the two diastereotopic benzylic positions of the dibromoaniline ring seemed at odds with the proposed mechanism. One possible explanation would be that the protonation step exhibits a relatively large kinetic isotope effect. The two starting materials could serve as

a source of protons. In order to minimize the total number of protons available in the system, we repeated this experiment with substrates in which the exchangeable protons had been replaced with deuterium (Figure 2.10, eq 18). Indeed, when the reaction was run, substantially increased deuterium incorporation was observed in the benzylic position of the dibromoaniline ring. Interestingly, the recovered THIQ was found to be partially deuterated, indicating the reversibility of the early reaction steps. Deuteration of the benzylic position of THIQ requires the presence of **2.9b** (i.e., heating of THIQ in EtOD under reflux for 16 h did not lead to any incorporation of deuterium into the benzylic position of THIQ).

Deuterium labeling experiments were also used to potentially gain some insights into the nature of the rate limiting step of the reaction by measuring the kinetic isotope effect (KIE). As the relatively long reaction times and high temperatures required for aminal formation would make spectroscopic monitoring of the progress rather difficult, we chose to measure isotope effects with P_H/P_D values from competition experiments rather than determining K_H/K_D from reaction rates.[22]

Figure 2.11 **KIE Experiments with Isotopically-Labeled Solvent**
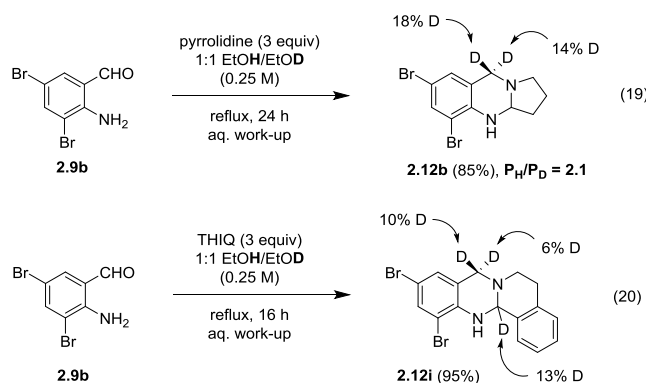
A reaction of aminobenzaldehyde **2.9b** and pyrrolidine was conducted in a 1:1 mixture of EtOH and EtOD (Figure 2.11, eq 19). A P_H/P_D value of 2.1 was observed,

which would be consistent with the protonation step being rate determining. A similar outcome was observed in the corresponding experiment with THIQ (Figure 2.11, eq 20). However, calculation of a meaningful P_H/P_D value is complicated by the above mentioned complexities (see eqs 17 and 18). Regardless, there appears to be a substantial KIE.

*Figure 2.12* **KIE Experiments with Isotopically-Labeled Amines**
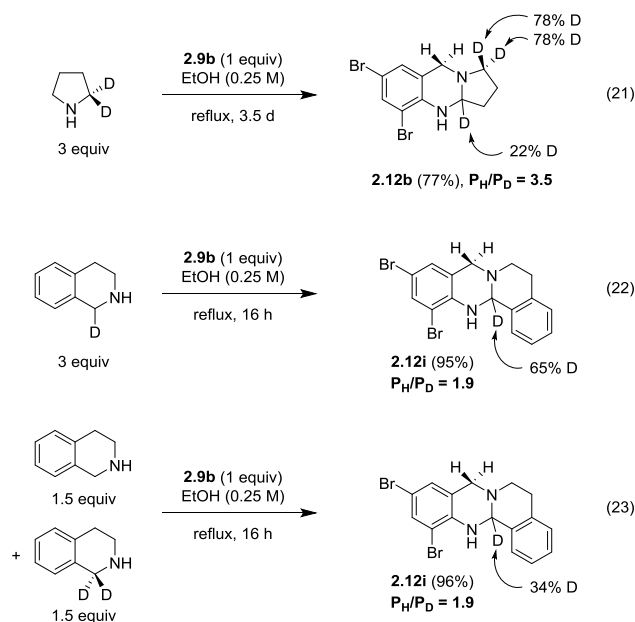
The relative rates of C–H vs. C–D functionalization were probed with partially deuterated amine substrates (Figure 2.12). A reaction of pyrrolidine-2,2-d$_2$ with **2.9b** resulted in the formation of partially deuterated **2.12b** in 77% yield (Figure 2.12, eq 21). The observed P_H/P_D value of 3.5 is consistent with the C–H functionalization step being rate determining. A substantially lower P_H/P_D value of 1.9 was observed in the corresponding reaction with THIQ-1-d (Figure 2.12, eq 22). A related competition experiment with a 1:1 mixture of THIQ and THIQ-1,1-d$_2$ also gave rise to a P_H/P_D value of 1.9 (Figure 2.12, eq 23). The experiments in eqs 21–23 conclusively rule out the intervention of a 1,3-hydride shift, as no measurable amount of deuterium was

incorporated into the benzylic position of the dibromoaniline ring. Overall, the isotopic labeling experiments outlined in eqs 16–23 do not rule out azomethine ylide protonation or C–H functionalization as the rate limiting step.

2.6 Mechanistic Study – Regioselectivity with Non-Symmetrical Amines

Insights into the mechanism of the aminal formation may also be obtained from nonsymmetrical amines that could, at least in principle, give rise to different regioisomeric products. As shown earlier, the reaction of THIQ and aminobenzaldehyde **2.9c** under standard conditions gave rise to product **2.12j** in high yield, resulting from exclusive functionalization of a benzylic C–H bond (Figure 2.3). This outcome is entirely anticipated based on the generally observed greater reactivity of benzylic over aliphatic C–H bonds. We were thus surprised to observe trace amounts of regioisomeric product **2.12l** when this reaction was first conducted under microwave conditions with the initial goal of simply enhancing the reaction rate. Closer inspection revealed that substantial amounts of product **2.12l** can be obtained at higher temperatures (Figure 2.13, eq 24). Specifically, a reaction of **2.9c** and THIQ, conducted under microwave irradiation at 250 °C for 30 min, gave rise to **2.12l** in 16% yield in addition to the expected product **2.12j** which was isolated in 72 % yield. Moreover, extending the reaction time from 30 min to 2 h led to the formation of **2.12l** as the major product in 47% yield, without significantly affecting the combined yield of **2.12j** and **2.12l**. These observations suggest that aminal **2.12j** is in fact the kinetic product of this transformation whereas **2.12l** represents the thermodynamically more stable aminal product. Furthermore, there appears to be a pathway for product isomerization. Similar observations were made with dibromo-analog (Figure 2.13, eq 25), although higher temperatures led to decomposition. Interestingly, 1,2,3,4-tetrahydroquinoline (THQ) did not yield aminal product under a number of different conditions (Figure 2.13, eq 26).

Figure 2.13 **Regioisomeric Products Formed from Non-Symmetrical Amines**
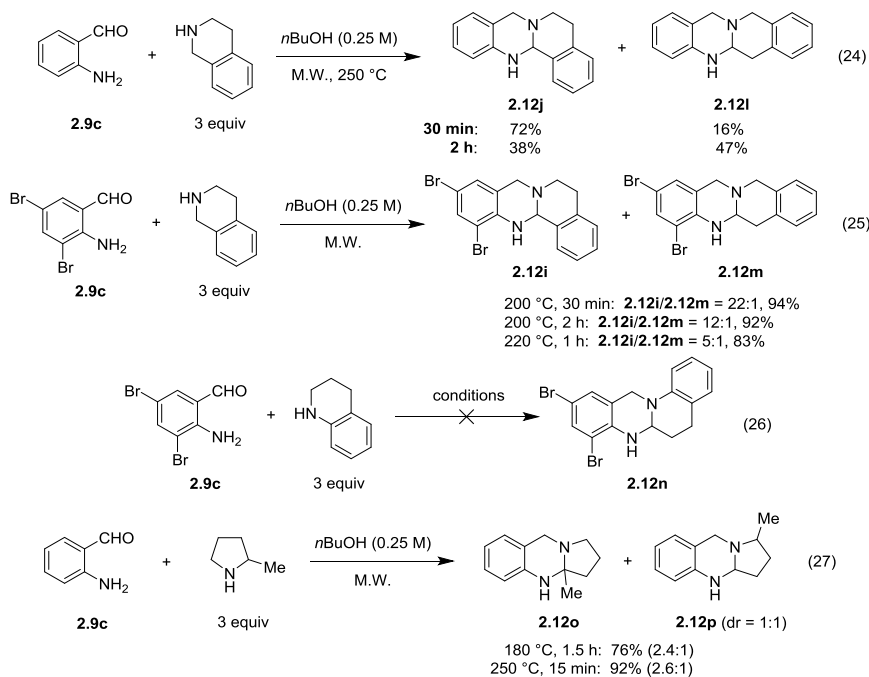
Prompted by the discovery of this isomerization, we decided to investigate the reaction of 2-methylpyrrolidine with aminobenzaldehyde **2.9c** (Figure 2.13, eq 27). Interestingly, for this particular substrate combination, virtually identical product ratios were obtained under a variety of conditions. Aminal **2.12o** was consistently obtained as the major product, illustrating the preferential functionalization of a tertiary over a secondary C–H bond. These results are consistent with our previous findings in a reaction of 2-methylpyrrolidine with **2.9b** which was conducted under reflux.[6]

2.7 Mechanistic Study – Computational Mechanism

At the outset of our computational study we considered all mechanisms depicted in Figure 2.4. In the following, the mechanism that was predicted to be the most favorable is discussed with the prototypic reaction of amino aldehyde **2.9c** and pyrrolidine (Figure 2.14). A matching free energy profile is shown in Figure 2.15.

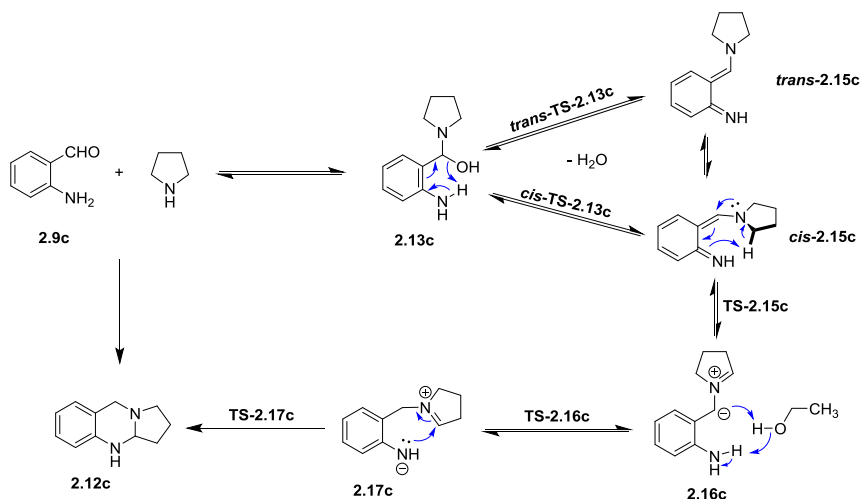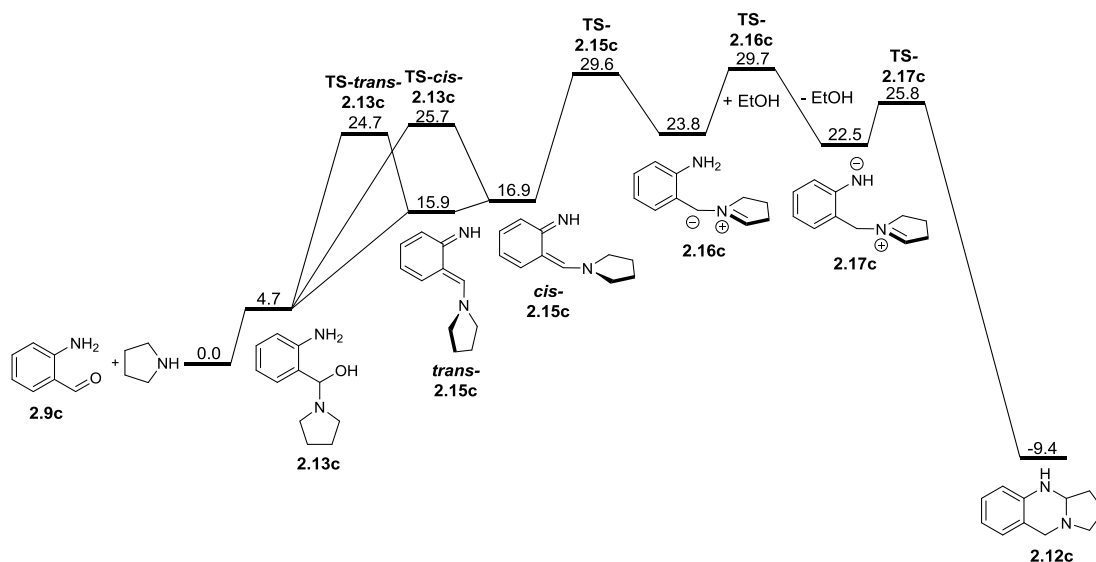*Figure 2.14* **General Mechanism for the α-Amination**

Figure 2.15 **Free Energy Profile for the Formation of Aminal 2.12c (kcal mol⁻¹)**

The first step in the reaction cascade is the formation of hemiaminal **2.13c,** which is exothermic, but endergonic according to our calculations. To obtain an iminium ion as suggested in Figure 2.4, hydroxide needs to be eliminated. Upon elimination, hydroxide spontaneously abstracts the amine hydrogen leading to a set of two quinoidal intermediates, **cis-2.15c** and **trans-2.15c**. We could also locate

transition states ***trans*-TS-2.13c** and ***cis*-TS-2.13c,** directly connecting hemiaminal **2.13c** with ***trans*-2.15c** and ***cis*-2.15c** by a concerted elimination of water (Figures 2.14 and 2.15).

Both transition states are lower in terms of enthalpy and free energy than the corresponding iminium ion, suggesting that ***trans*-2.15c** and ***cis*-2.15c** are formed directly from **2.13c** and not via iminium species **2.14c** as previously assumed. As a consequence, pathways involving the iminium ion do not warrant further consideration.

It must be noted that computed enthalpies and as a consequence free energies are overestimated particularly for **TS-2.13c,** as this transition state benefits greatly from hydrogen bonding of solvent molecules to the leaving water molecule. As a consequence, we consider **TS-2.13c** (24.7 kcal mol^{-1}) to be always lower in enthalpy and free energy than **TS-2.15c** (15.9/16.9 kcal mol^{-1}), which is in perfect agreement with experimental data.

***trans*-TS-2.13c** and ***cis*-TS-2.13c** differ with respect to the geometry of substituents at one exocyclic double bond. While ***cis*-2.15c** allows an abstraction of the α-hydrogens of the heterocycle by the imine nitrogen via **TS-2.15c,** an intramolecular reaction is impossible in ***trans*-2.15c. *trans*-TS-2.13c** and ***trans*-2.15c** are 1 kcal mol^{-1} lower in energy than their corresponding *cis*-isomers due a greater planarity of the resulting exocyclic π-system, corresponding to a reduced A^{1,3}-strain interaction.

A highly negative charge on the primary nitrogen obtained from a natural population analysis in **2.15c** indicates a significant contribution from a zwitterionic resonance-structure involving an iminium ion at the heterocycle, which restores the aromaticity of the system. Although the *trans*-geometry is slightly preferred, the *cis/trans* energy difference is quite small and dihedral scans proved the barrier for

isomerization to be lower than the barrier for intramolecular proton transfer (**TS-2.15c**), so that ***trans*-2.15c** can be directly converted to ***cis*-2.15c.** Furthermore, up to this point all steps are reversible so that ***trans*-2.15c** may be recycled to ***cis*-2.15c.** The transition state for an intramolecular proton transfer **TS-2.15c** has a free energy barrier of 12.7 kcal mol^{-1} relative to ***cis*-2.15c** and is likely to be the rate-determining step. While a 1,6-hydride shift has been considered before, the substantial negative charge on the nitrogen in **2.15c** precludes this mechanistic alternative. The intrinsic reaction coordinate associated with **TS-2.15c** leads to azomethine ylide **2.16c** (Figure 2.14). A natural population analysis of **2.16c** shows the negative charge resides mainly on the exocyclic methine carbon, which is rapidly protonated by ethanol (**TS-2.16c**). Experimental deuterium labeling studies with EtOD show deuterium incorporation at this position, supporting our proposed mechanism (*vide supra*). While the enthalpic barrier of **TS-2.16c** is negative, the free energy barrier calculated for an ethanol concentration of 17.12 mol L^{-1} has a value of 5.9 kcal mol^{-1} with respect to **2.16c.** Although we attempted to correct the free energy for the large excess of solvent molecules, it is still substantially overestimated as the entropic penalty for this step can be assumed to be negligible.

The protonation of **2.16c** is directly followed by deprotonation of the primary amino group by the coordinated ethoxide, which proceeds without a barrier as the resulting zwitterion **2.17c** is resonance-stabilized. Finally, ring-fused aminal **2.12c** is formed from **2.17c** by intramolecular nucleophilic attack on the iminium ion. The free energy barrier for this step is very small (3.3 kcal mol^{-1}), resulting in a very short lifetime of **2.17c.** Product formation is substantially exergonic (−9.4 kcal mol^{-1}) and probably irreversible under the experimental conditions.

Table 2.1 **Free energies (and enthalpies in parentheses) in kcal mol^{-1} for all intermediates and transition states (M06-2X/6-31+G(d,p)/SMD(Ethanol)).**

product 2.12x	2.13x	trans-TS-2.13x	cis-TS-2.13x	trans-2.15x	cis-2.15x	TS-2.15x	2.16x	TS-2.16x	2.17x	TS-2.17x	2.12x
b	3.4	21.9	22.6	11.1	11.8	25.1	18.1	23.9	12.9	17.7	-8.6
	(-9.1)	(10.3)	(11.0)	(8.8)	(9.8)	(21.5)	(15.8)	(13.6)	(11.9)	(14.2)	(-17.0)
c	4.7	24.7	25.7	15.9	16.9	29.6	23.8	28.0	22.5	25.8	-9.4
	(-7.7)	(13.1)	(14.4)	(12.7)	(14.4)	(25.7)	(21.2)	(16.4)	(19.0)	(20.4)	(-13.5)
g	2.9	29.2	29.2	13.3	15.2	32.1	23.5	26.8	15.9	17.2	-7.8
	(-8.4)	(18.2)	(18.8)	(11.3)	(11.3)	(29.9)	(23.5)	(17.9)	(14.9)	(14.3)	(-11.4)
h	2.9	31.4	30.8	16.2	16.8	32.9	26.0	32.1	21.4	21.9	-4.6
	(-8.0)	(20.0)	(20.4)	(14.1)	(15.5)	(30.5)	(24.6)	(22.0)	(19.9)	(19.0)	(-7.8)
i	0.0	25.3	25.5	15.1	16.3	23.1	14.4	28.5	14.0	15.7	-11.0
	(-11.4)	(16.2)	(16.6)	(13.8)	(15.0)	(20.1)	(12.7)	(14.8)	(13.6)	(12.3)	(-15.9)
j	4.7	30.6	31.5	20.3	21.2	27.5	19.0	29.1	22.7	24.1	-6.9
	(-7.3)	(19.2)	(20.2)	(18.7)	(19.6)	(24.1)	(16.9)	(19.1)	(20.7)	(20.4)	(-11.0)
l	4.7	30.6	31.4	20.7	22.3	33.9	28.9	32.8	25.7	27.6	-9.2
	(-7.3)	(19.4)	(20.2)	(19.2)	(20.0)	(30.5)	(26.9)	(23.2)	(24.0)	(24.2)	(-13.4)
m	2.4	25.5	24.2	16.2	17.4	29.8	23.3	32.2	16.4	19.7	-13.8
	(-10.7)	(16.5)	(16.7)	(14.1)	(15.3)	(26.2)	(21.3)	(18.0)	(16.0)	(16.0)	(-17.9)
n	4.6	32.2	34.1	20.1	21.1	35.6	32.5	37.5	25.4	27.4	-9.3
	(-6.7)	(21.4)	(22.6)	(17.1)	(17.9)	(31.2)	(29.4)	(25.3)	(22.7)	(22.8)	(-13.8)

2.8 Mechanistic Study – Calculations for Aliphatic Amines

Inspection of the reactions of pyrrolidine with aldehydes **2.9b** and **2.9c** (Figure 2.3) reveals dibromo-substitution of the aldehyde to give better yields after shorter reaction times. A comparison of the calculated free energies profiles for both reactions (Table 2.1) shows the reaction of **2.9b** and pyrrolidine to proceed via lower lying intermediates and transition states. The phenyl ring of aldehyde **2.9b** is electron-deficient and induces a better charge delocalization into the aromatic system in all intermediates and transition states following **2.13b.** This effect is most pronounced in **2.17b,** which is stabilized by 9.6 kcal mol^{-1} relative to **2.17c.** The formation of hemiaminal **2.13b** is also more favorable by 1.3 kcal mol^{-1} than the formation of **2.13c** owing to the more electrophilic character of the carbonyl group in **2.9b.** The free energy difference between the rate-determining transition states **TS-2.15b** and **TS-2.15c** is 4.5

kcal mol⁻¹, which is exclusively caused by the change in electronic structure and explains the higher yield of the reaction involving aldehyde **2.9b.** Piperidine requires higher reaction temperatures and gives slightly lower yields than pyrrolidine while morpholine gives low yields even at elevated temperatures (Figure 2.3).

Figure 2.16 **An overlay of the geometries of cis-2.15b and cis-2.15g (sticks) with transition states TS-2.15b and TS-2.15g (balls and sticks)**
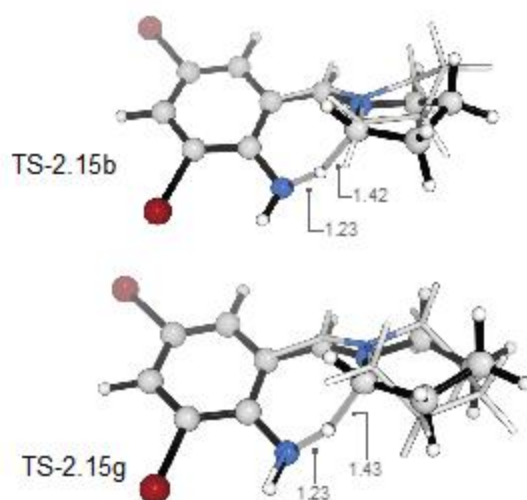

The formation of quinoidal intermediates **2.15g** and **2.15h** is disfavored in comparison to **2.15b. 2.15g** and **2.15h** also partly restore the aromaticity of the aryl-ring by adopting a zwitterionic resonance structure, which involves an exocyclic double bond at the iminium ion. The formation of the latter is less favorable in six-membered than in five-membered rings. Free energies of **TS-2.15g** and **TS-2.15h** are higher than **TS-2.15b,** because **2.15g** and **2.15h** require more distortion to adopt the transition state geometries (Figure 2.16). This does explain the better experimental performance of pyrrolidine; however no significant discrimination can be made between piperidine and morpholine based on the energies of the rate-limiting steps **TS-2.15g** and **TS-2.15h**.

2.9 Mechanistic Study – Calculations for THIQ and THQ

Our experimental results indicate that products **2.12i** and **2.12j** are obtained under kinetic control, while **2.12l** and **2.12m** represent the thermodynamically stable products. Transition state energies for **TS-2.15i** and **TS-2.15j** are lower by 6.7 and 6.4 kcal mol^{-1} than those of **TS-2.15l** and **TS-2.15m,** respectively, confirming the experimental results. This stabilization is caused by the location of the proton to be abstracted in THIQ**,** which allows an effective delocalization of the resulting charge into the aromatic ring in **2.16i** and **2.16j** (Figure 2.17). However, products **2.12i** and **2.12j** are less stable than **2.12l** and **2.12m,** respectively, which explains their isomerization at prolonged reaction times. Furthermore, **2.12j** is predicted to be less stable by 4.1 kcal mol^{-1} than **2.12i** and thus allows a more facile isomerization.

Figure 2.17 **Structures and Carbon Charges of THIQ Azomethine Ylides**
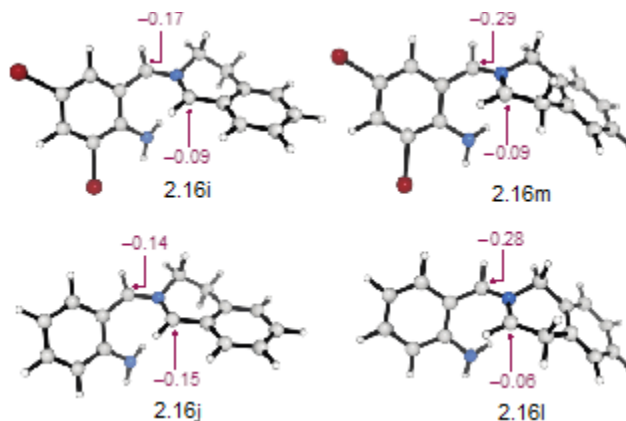
No product could be obtained at all when THQ was used as an amine instead of THIQ**.** The high barrier of **TS-2.15n** is in good agreement with this finding and is partly caused by a substantial distortion required to transform *cis*-**2.15n** to **TS-2.15n.** In addition, the reactions to obtain intermediate *cis*-**2.15n** have a strongly positive reaction free energy (21.1 kcal mol^{-1}) as iminium-like structures involving THQ are

energetically disfavored, probably due to the conjugation of the nitrogen lone pair with the aromatic ring.

2.10 Mechanistic Study – Calculations Related to the (3+2) Cycloaddition

The azomethine ylide **2.16b** could be trapped experimentally by a 1,3-dipolar cycloaddition with aldehyde **2.9b**. Not surprisingly, the cycloaddition of these highly polar reactants involves a stepwise mechanism with a zwitterionic intermediate **2.48** (Figure 2.18).

Figure 2.18   **Transition states TS-2.49 and TS-2.50 and zwitterionic intermediate 2.48 for the (3+2) cycloaddition between 2.9b and 2.16b**
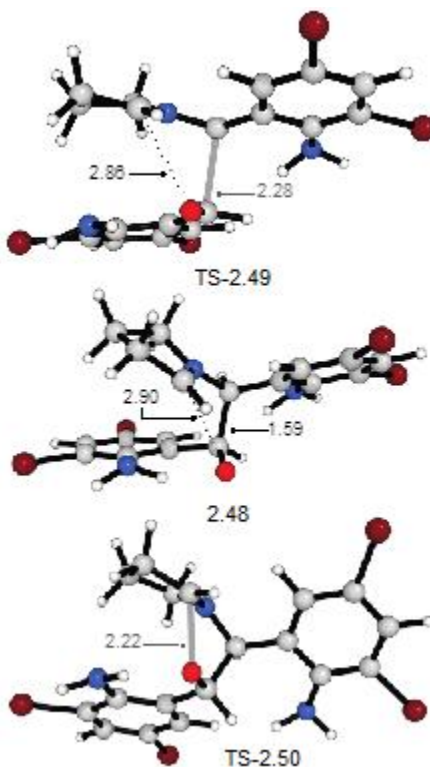
Transition state **TS-2.49** for the first bond formation features a distance of 2.28 Å between the reaction centers while the oxygen and iminium carbon are well separated (2.86 Å). The calculated barrier of 1.6 kcal mol^{-1} is significantly lower than any barrier

for the amination reaction cascade and indicates that this reaction is essentially diffusion-controlled. However, the rate is limited by the low concentration of azomethine ylide **2.16b**, which is readily protonated by ethanol being present in huge excess. The formation of the zwitterionic intermediate **2.48** is exergonic by -8.1 kcal mol^{-1} and followed by a fast intramolecular ring closure via **TS-2.50**. The total cycloaddition reaction is exergonic by -35.6 kcal mol^{-1}.

2.11 Aminal Formation Under Microwave Conditions

After completing this mechanistic study, we looked into expanding the scope of the α-amination reaction.[23] In the course of the previous study we had found dramatic rate acceleration when microwave conditions were employed (Figure 2.13). Additionally, shortly after the original discovery of the reaction, Polshettiwar and Varma published a report on the use of a microwave reactor to perform the α-amination under neat conditions.[24] We found their results, however, to be irreproducible, so we decided to develop our own protocols for microwave-assisted aminal formation.

Despite a number of attempts to reproduce Polshettiwar and Varma's conditions (neat, 130 °C), no more than trace amounts of the desired products were obtained. The use of *n*-butanol as solvent at temperatures of 200-250 °C led to both higher yields and dramatically shorter reaction times than reflux conditions. Considering that protonation by ethanol was invoked in our proposed mechanism (Figure 2.14), it is not entirely surprising that the use of an alcoholic solvent would aid in the reaction.

In the microwave, pyrrolidine underwent the reaction quite readily at 200 °C with both aminoaldehydes **2.9b** and **2.9c**, yielding the desired products in 95% and 89%, respectively (Figure 2.19, eqs 28 and 29). Piperidine, too, readily gave the dibromoaminal product **2.12g** in high yield (93%), but the unsubstituted analog **2.12q**

required more forcing conditions (250 °C) to yield only 67% of desired product (Figure 2.19, eq 30 and 31). The same high temperature and double the reaction time were required to obtain *N*-phenyl- and *N*-methyl-piperazine products **2.12r** and **2.12s** from **2.9b** in moderate yields (Figure 2.19, eqs 32 and 33).

Figure 2.19 **Aminal Formation Under Microwave Conditions**
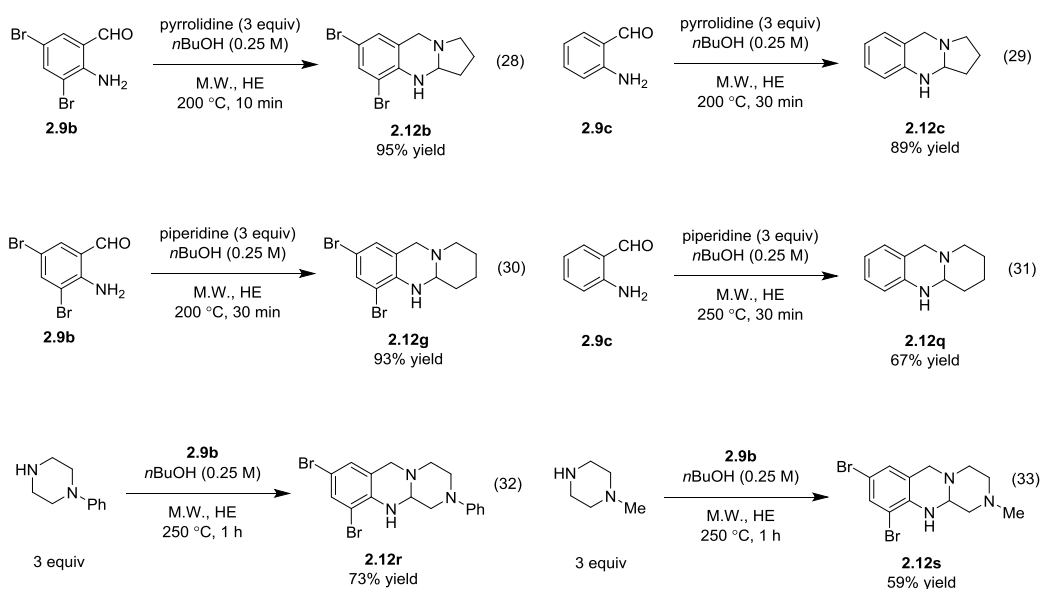
One of the lowest-yielding amines using conventional heating was morpholine, giving on 15% yield of aminal **2.12h** even at 140 °C in a sealed tube (Figure 2.3). We attempted to increase the yield of **2.12h** using microwave conditions, the results of which are summarized in Table 2.2. We first attempted to reproduce Polshettiwar and Varma's conditions,[24] where they reported 65% yield of **2.12h** (entry 1), but no reaction was observed at this temperature. A silicon heating element (HE), which absorbs microwave radiation and releases heat into the reaction vessel, was also used under the same conditions (entry 2), but again, no reaction was observed. An increase of the reaction temperature to 200 and to 250 °C did yield minor amounts of product (entries 3 and 4), but nowhere near the 65% yield reported. Solvents were screened and *n*-butanol

was found work best for the reaction. The rather extreme reaction temperature of 270 °C was found to give the highest yield (49%, entry 14). Higher temperatures may, perhaps, lead to even higher recovery of **2.12h**, however, this was the highest temperature we could obtain in our microwave without vessel rupture.

Table 2.2 **Optimization of the Synthesis of Morpholine Product 2.12h**
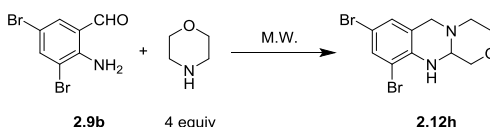
Entry	Solvent (concentration)	HE[a]	Temperature [°C]	Time [min]	Yield (%)
1	-	no	130	45	NR
2	-	yes	130	45	NR
3[b]	-	yes	200	60	16
4	-	yes	250	60	trace[c]
5	EtOH (2.0 M)	no	130	60	NR
6	*n*BuOH (2.0 M)	yes	130	60	NR
7	*n*BuOH (0.5 M)	yes	130	60	NR
8[b]	PhMe (2.0 M)	no	200	45	6
9[b]	*n*BuOH (0.5 M)	yes	200	45	20
10[b]	*n*BuOH (0.25 M)	no	200	45	14
11[b]	*n*BuOH (0.25 M)	yes	200	60	21
12[d]	*n*BuOH (0.25 M)	yes	250	60	29
13	*n*BuOH (0.25 M)	yes	250	60	26
14	*n*BuOH (0.25 M)	yes	270	60	49

[a] HE = silicon carbide heating element; [b] The reaction was incomplete; [c] decomposition was observed; [d] with 3 equiv of morpholine.

Even more challenging was the reaction between parent aminoaldehyde **2.9c** and morpholine. The highest yield obtained for aminal **2.12t** was 12%, alongside a sizable amount of aminobenzaldehyde trimer **2.51a** (Figure 2.20, eq 34). Such trimers have been known to form when aminobenzaldehydes are exposed to amines, although generally primary amines are required.[25] When the solvent of the reaction was changed

from *n*-butanol to toluene, trimer **2.51a** was obtained in 70% yield (Figure 2.20, eq 35). The corresponding pyrrolidine-based trimer (**2.51b**) was found to form at room temperature in ethanol, conditions which did not result in the formation of aminal **2.12c** (Figure 2.20, eq 36). This was first noticed during an NMR experiment where pyrrolidine and **2.9c** were mixed in deuterated methanol; no appreciable difference was observed in the spectra of the two starting materials, but small peaks corresponding to **2.51b** did form over time. The formation of trimer **2.51a** was found to be reversible. When exposed to pyrrolidine under microwave conditions, **2.51a** yielded a small amount of aminal **2.12c** (Figure 2.20, eq 37).

Figure 2.20 **Synthesis of Morpholine Aminal 2.12t and Trimer Formation**
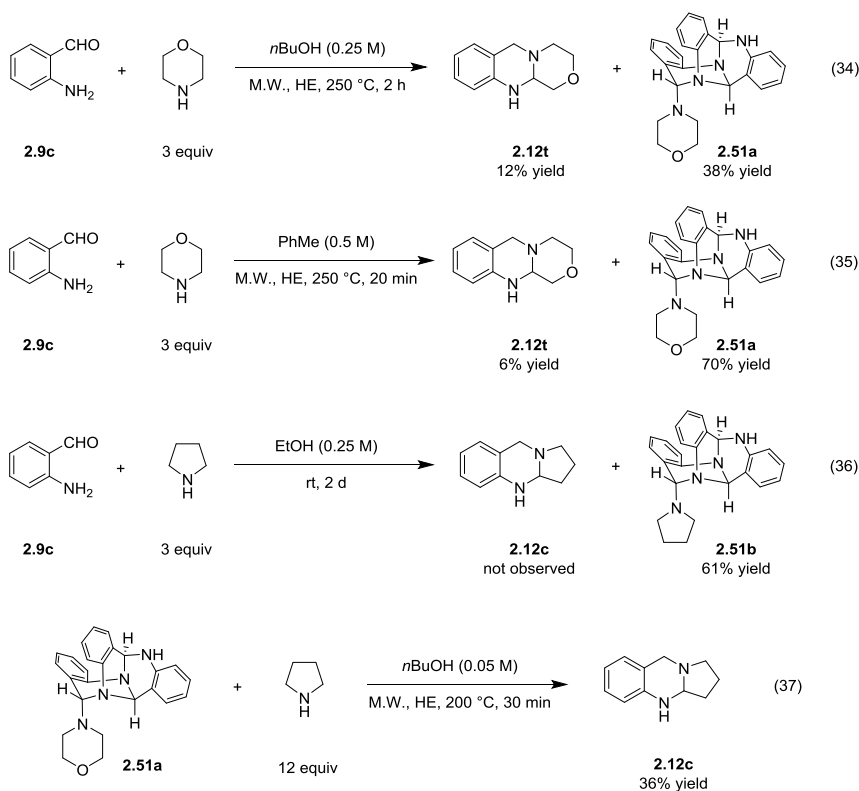
We next investigated the use of potentially more reactive amines featuring benzylic positions (Figure 2.21). Benzoazepine **2.52a**, when allowed to react with **2.9b**

under reflux in *n*-butanol afforded aminal **2.12u** in 79% yield (Figure 2.21, eq 38). Microwave conditions, however, led to increased yield (91%) and shorter reaction time. The same trend could be observed with 1-methyl THIQ **2.52b**, 1-phenyl THIQ derivative **2.52c** and phenyl trytamine **2.52d** (Figure 2.21, eqs 39-41). While microwave conditions tended to work best, conventional heating offered a viable alternative for these benzylic amine substrates.

Figure 2.21 **Alternative Amines Under Microwave and Reflux Conditions**
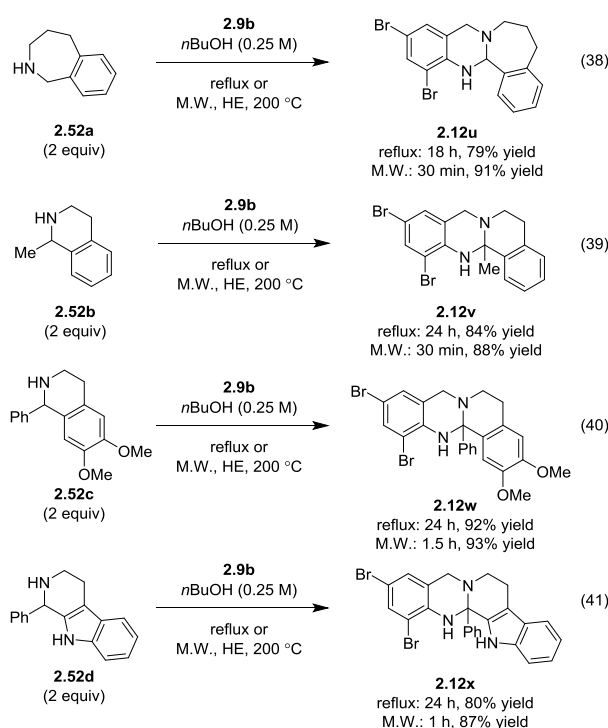
Benzylic amine substrates with various functionalities on the aryl ring were also used to investigate electronic effects. A series of 2-arylpyrrolidines with different substitutents at the *para*-position (-OMe, -H, and $-CF_3$) were synthesized and allowed to react with aminoaldehyde **2.9b** (Figure 2.22, eq 42). In all cases, products with benzylic functionalization (**2.12y**) predominated over regioisomer **2.12z**. However, it can be noted that the more electron donating the *para*-substituent, the more benzylic-

functionalized product **2.12y** was obtained, with total yields of **2.12y** and **2.12z** remaining roughly equivalent. This is perhaps due to an increased likelihood for isomerization from **2.12y** to **2.12z** with electron-poor aryl groups.

Figure 2.22 **Electronic Effects in the α-Amination Reaction**

2.9b + 3 equiv →
*n*BuOH (0.25 M)
M.W., HE, 200 °C
30 min

2.12y + **2.12z** (dr = 1:1)   (42)

R = OMe	**2.12y-a**: 83%	**2.12z-a**: 14%
R = H	**2.12y-b**: 64%	**2.12z-b**: 33%
R = CF$_3$	**2.12y-c**: 58%	**2.12z-c**: 37%

2.9b + 3 equiv →
*n*BuOH (0.25 M)
M.W., HE, 250 °C
30 min

2.12aa   (43)

R = OMe	**2.12aa-a**: 41%
R = H	**2.12aa-b**: 29%
R = CF$_3$	**2.12aa-c**: 20%
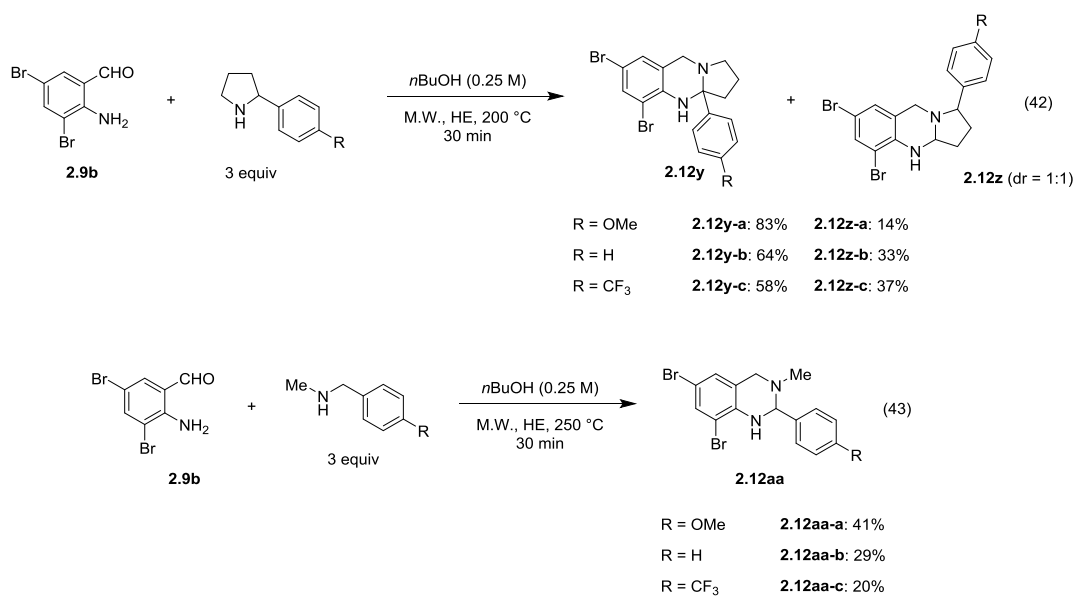
Non-cyclic methyl-benzylamines were also used in the reaction, although yields were generally poor (Figure 2.22, eq 43). There is a trend of increasing yield when increasingly electron-rich aryl groups are used. It cannot be said, however, whether this is due to any more inherent reactivity of the *p*-methoxy amine over the *p*-trifluoromethyl amine, or if the electron-poor products undergo decomposition easier. Hydrolysis of the products was not observed during isolation on silica gel.

One more challenging substrate used under microwave conditions were aminoketones (Figure 2.23). Unlike the aminobenzaldehydes, aminoketones **2.53a** and **2.53b** were far less reactive. Aminobenzophenone **2.53a** and pyrrolidine, at 250 °C under microwave irradiation, gave aminal **2.12ab** in the moderate yield of 53% (Figure

2.23, eq 44). Aminoacetophenone **2.53b**, however, gave less product, with **2.12ac** being isolated in 28% yield (Figure 2.23, eq 45).

Figure 2.23 **Aminoketones in the α-Amination Reaction**
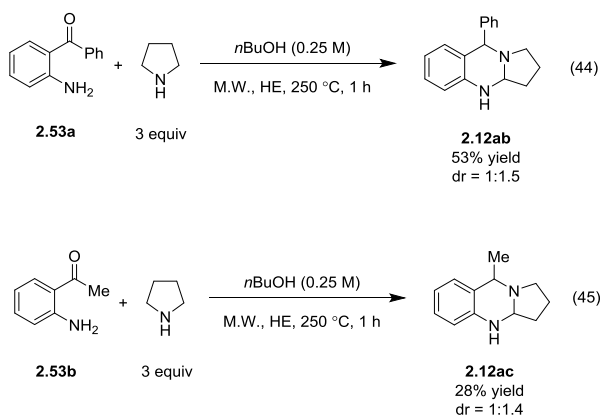
2.12 The Decarboxyaltive Approach to Aminal Synthesis

As noted in the first chapter of this thesis (section 1.11), the condensation of amino acids and aldehydes is a powerful method for the generation of azomethine ylides.[11] The use of proline as a surrogate for pyrrolidine in the α-amination reaction was briefly explored in the initial communication by the Seidel group, although products were obtained in lower yields.[6] Amino acids could prove to be useful starting materials in this reaction, as it may be possible to achieve a regioselectivity not obtainable with non-symmetric amines by using the corresponding amino acid. In order to explore this, we first looked to find useful conditions for aminal formation with simple amino acids (Figure 2.24). *n*-Butanol was found to be an excellent solvent for the decarboxylative variant of the reaction. Both proline and pipecolic acid gave the desired aminal products with aminobenzaldehyde **2.9b** in high yields (Figure 2.24, eqs 46 and 47). Little difference in yield was observed when heterocyclic aminoaldehyde **2.9e** was used with proline (Figure 2.24, eq 48).

Figure 2.24 **Amino Acids as Starting Materials for α-Amination**
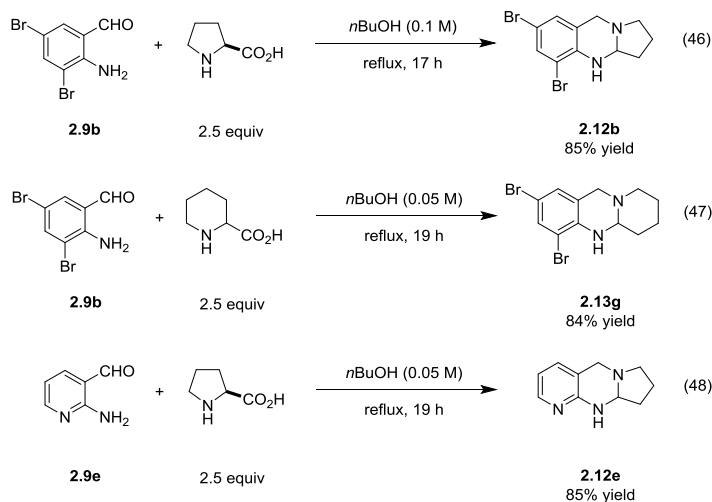
With these conditions in hand, the amino acids of non-symmetrical amines were tested in the reaction. THIQ-3-carboxylic acid was employed in the reaction with **2.9b** (Figure 2.25, eq 49). Expected regioisomer **2.12m** was obtained as the minor product alongside the usual regioisomer **2.12i**. This can be rationalized based on the kind of azomethine ylide formed in the reaction; the azomethine ylide, with two benzylic positions, has little electronic differentiation and exocyclic protonation will yield THIQ and, eventually, product **2.12i**, which is formed under kinetic conditions.

Next, *trans*-4-hydroxyproline and *trans*-3-hydroxyproline were used as starting materials (Figure 2.25, eqs 50 and 51). *trans*-4-Hydroxyproline had been previously used to react with aldehydes to form *N*-alkylated pyrrole products,[26] which made the synthesis of the aminals difficult in this case. Initial reflux conditions in *n*-butanol only led to trace formation of **2.12ad**, so microwave conditions were attempted. At best, only low yields of **2.12ad** and **2.12ae** were obtained (18% and 11%, respectively). Some racemization of the hydroxyl group in **2.12ae** was observed, likely from an acid-catalyzed enamine formation.[7] Aminal **2.12ae**, however, is valuable as being only a single oxidation state away from the plant alkaloid vasicine.[27] In fact, a number of these

aminals are closely related to natural products[27] and in 2008, the Seidel group had published methods for the synthesis of quinazolinone alkaloids from **2.12c** and **2.12k**.[6] Due to the similarity in structure between our products and these bioactive alkaloids, we decided to look into optimizing methods for synthesizing these natural products.

Figure 2.25 **Non-Symmetrical Amino Acids for α-Amination**
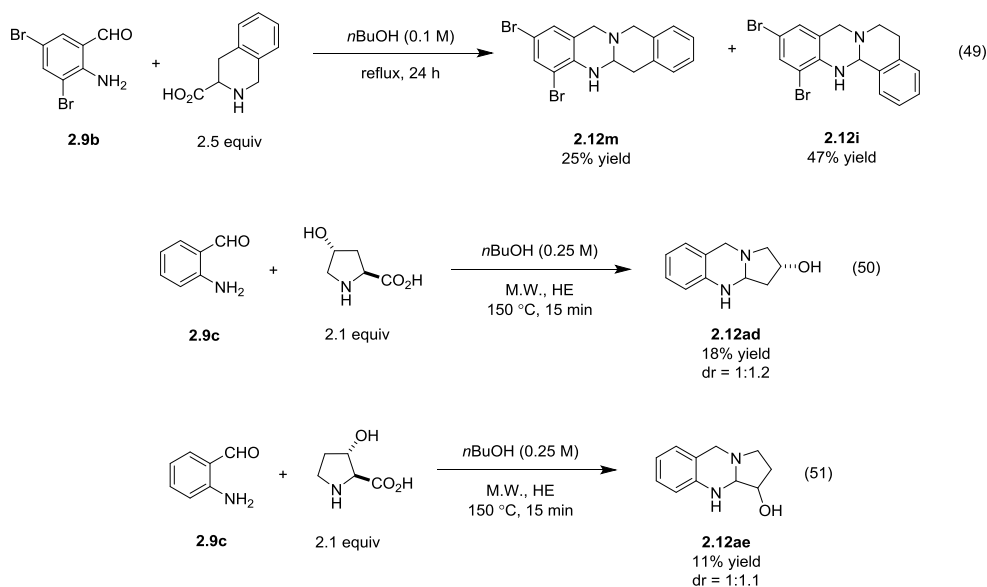
2.13 Quinazoline Alkaloid Synthesis

Quinazoline alkaloids are a class of naturally-occurring compounds with a range of medicinal properties, including use as bronchodilators, vasodilators, anti-inflammatory agents and acetylcholinesterase inhibitors.[28] Many of the plants these products have been isolated from, such as *Adhatoda vasica, Peganum harmala* and *Evodia rutaecarpa*, have been used in folk medicine for centuries.[29] Since the original isolation of vasicine (**2.53a**) in 1888,[30] the biological properties of this class of alkaloids have been extensively studied.

Figure 2.26 **Some Examples of Quinazoline Alkaloids**

vasicine R = OH, **2.53a**
deoxyvasicine R = H, **2.53b**

vasicinone R = OH, **2.54a**
deoxyvasicinone R = H, **2.54b**

mackinazolinone, **2.54c**
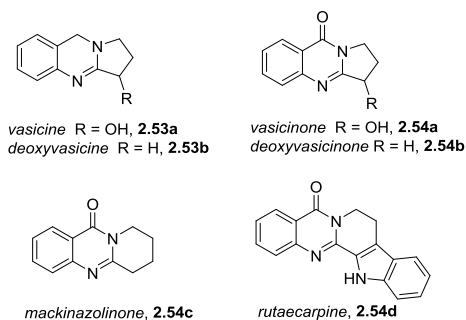
rutaecarpine, **2.54d**

Figure 2.27 **Quinazolinone Alkaloid Synthesis with Stoichiometric Oxidants**
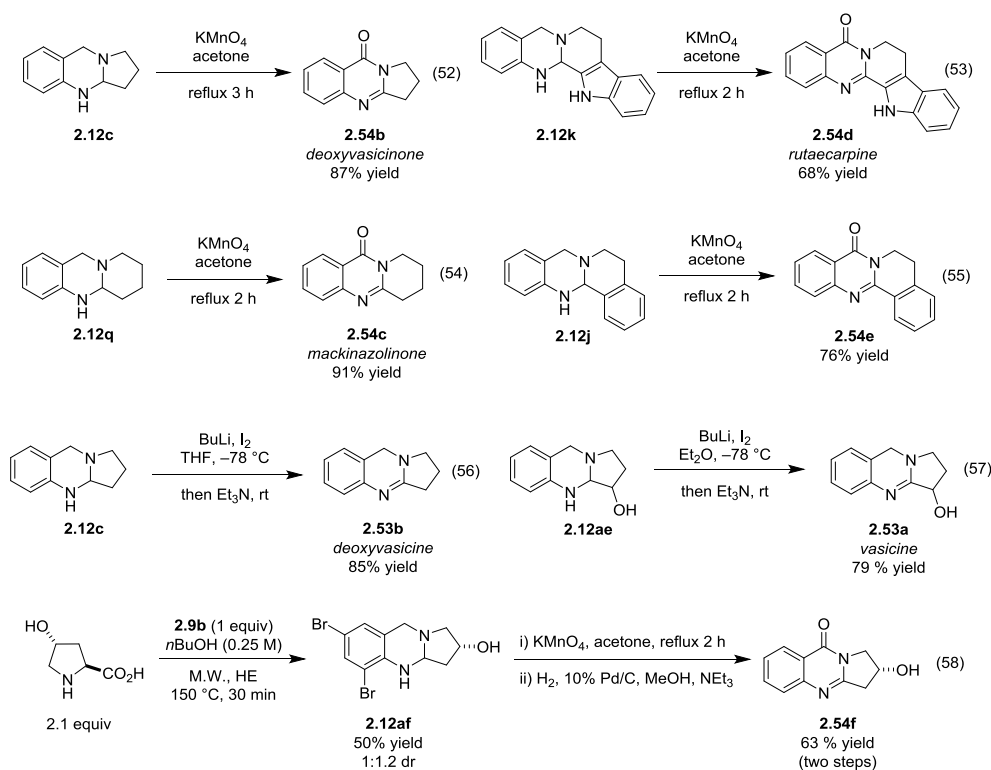
While methods were developed for aminal oxidation using $KMnO_4$ by the Seidel group in 2008 for the syntheses of deoxyvasicinone (**2.54b**) and rutaecarpine (**2.54d**),[6] an improved, multi-gram route to deoxyvasicinone was published by the same group in 2012.[31] We applied these improved conditions to the synthesis of various quinazolinone alkaloids and analogs (Figure 2.27). Deoxyvasicinone and rutaecarpine both gave

slightly improved yields (Figure 2.27, eqs 52 and 53). The alkaloid mackinazolinone (**2.54c**) was also synthesized in good yield (Figure 2.27, eq 54). The unnatural analog **2.54e** was afforded from the oxidation of THIQ aminal **2.12j** (Figure 2.27, eq 55).

While the quinazolinone alkaloids can be made quite easily from aminal starting materials, selective oxidations to give dihydroquinazoline structures such as deoxyvasicine (**2.53b**) could not be obtained by this KMnO$_4$-based methodology. To overcome this, an oxidation using molecular iodine was developed. Using butyllithium and iodine, followed by a deprotonation with triethylamine, aminal **2.12c** was converted to deoxyvasicine in 85% yield (Figure 2.27, eq 56). Hydroxylated aminal **2.12ae** yielded vasicine by this same route (Figure 2.27, eq 57). Despite the low overall yield, this two-step synthesis is, to our knowledge, currently the shortest route to vasicine.[32] An analog of the alkaloid vasicinone was also synthesized using *trans*-4-hydroxyproline and aminobenzaldehyde **2.9b** to give aminal **2.12af** in 50% yield, followed by KMnO$_4$ oxidation and hydrogenolysis of the carbon-bromine bonds, resulting in the isolation of vasicinone regioisomer **2.54f** in 63% yield (Figure 2.27, eq 58).

Many synthetic pathways have been employed in the past to gain access to these quinazoline structures.[33] Perhaps the most commonly employed method involves the condensation of an *ortho*-aminobenzoic ester with a cyclic amide using phosphoryl chloride, known as the Niementowski reaction[34] (Figure 2.28, eq 59). The availability, or lack thereof, of the corresponding amide can determine the length and efficiency of the route. Access to the sometimes more biologically active dihydroquinazolines, such as deoxyvasicine (**2.53b**), from quinazolinones requires a subsequent reduction of the amide. While resulting in good yields and posessing a complimentarity to the Niementowski approach, our oxidation methodologies (Figure 2.27) have the drawback

of requiring large amounts of a strong oxidant for the permanganate oxidation and the necessity of stoichiometric butyllithium for the iodine reaction.

Figure 2.28 **Alternative Routes to Quinazoline Structures**
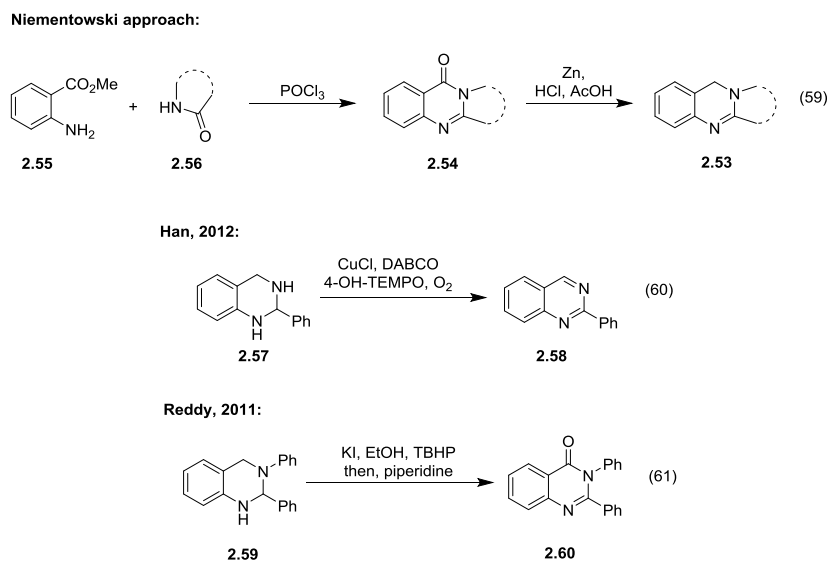
The ability to convert the aminals formed from the condensation of aminobenzaldehydes and secondary amines to the corresponding dihydroquinazoline and quinazolinone structures catalytically and under mild conditions would be preferable to having to use harsh oxidants and strong bases. Han and coworkers have shown the ability of copper salts, in conjunction with oxygen, to catalyze oxidations of 2-substituted tetrahydroquinazoline aminals to quinazolines[35] (Figure 2.28, eq 60). In addition, Reddy and coworkers have developed a catalytic system in which 2,3-substituted tetrahydroquinazoline aminals are converted to quinazolinones using *tert*-butylhydroperoxide (TBHP) and catalytic potassium iodide (Figure 2.28, eq 61).[36] While these examples deal with the oxidation of bicyclic aminals, we wanted to develop methods to create dihydroquinazoline and quinazolinone alkaloids from tricyclic and polycyclic aminals.[37]

Table 2.3 **Optimization of Conditions for Deoxyvasicine (2.53b) Formation**

Entry	Solvent (0.2M)	Catalyst (mol%)	Acid (equiv)	Temp. [°C]	Time [h]	Yield of **2.53b** [%]
1[a]	MeCN	CuCl$_2$•2H$_2$O (100)	-	rt	6	81
2	MeCN	CuCl$_2$•2H$_2$O (20)	-	81	2	trace (14[b], 10[c])
3	MeCN	Cu(OAc)$_2$•H$_2$O (20)	-	81	3	15 (17[b], trace[c])
4	MeCN	Cu(OAc)$_2$•H$_2$O (20)	AcOH (1.1)	81	3	53
5	MeOH	Cu(OAc)$_2$•H$_2$O (20)	AcOH (1.1)	65	4	81
6	MeOH	Cu(OAc)$_2$•H$_2$O (20)	-	65	4	33 (6[b], 24[c])
7	AcOH	Cu(OAc)$_2$•H$_2$O (20)	-	80	24	18[d]
8	DMF	Cu(OAc)$_2$•H$_2$O (20)	AcOH (1.1)	80	4	17 (20[b])
9	MeOH	Cu(2-EH)$_2$ (20)	2-EHA (1.1)	65	12	71
10	MeOH	CuBr (20)	AcOH (1.1)	65	8	72
11	EtOH[e]	Cu(OAc)$_2$•H$_2$O (20)	AcOH (1.1)	78	1.5	73 (trace[c])
12	MeOH	Cu(OAc)$_2$•H$_2$O (10)	AcOH (1.1)	65	18	67 (trace[c])
13	MeOH	Cu(OAc)$_2$•H$_2$O (20)	AcOH (1.1)	40	24	61 (trace[b,c])
14	MeOH	Cu(acac)$_2$ (10)	AcOH (1.1)	65	24	68[d](trace[b,c])

Reactions were performed on a 0.25 mmol scale. Cu(2-EH)$_2$ = copper (II) 2-ethylhexanoate. 2-EHA = 2-ethylhexanoic acid. a) Nitrogen atmosphere; b) Yield of **2.54b**; c)Yield of **2.61**; d) The reaction was incomplete; e) 95% solution.

Copper-catalyzed oxidation reactions have been an area of great interest for chemists in recent years.[38] Han's copper-catalyzed method for the synthesis of aminals to quinazolines results in very high yields,[35] but the process is unselective for the degree of oxidation; dihydroquinazolines are not isolated as products in these reactions. We set out to find a method for the synthesis of dihydroquinazolines without further oxidation of the benzylic position. A factor complicating this effort was that dihydroquinazolines like deoxyvasicine (**2.53b**) are known to readily autoöxidize to their quinazolinone counterparts (**2.54b**) from exposure to air.[39] To begin with, stoichiometric CuCl$_2$ was simply stirred with aminal **2.12c** in acetonitrile under nitrogen atmosphere, leading to

81% yield of **2.53b** (Table 2.3, entry 1). Stoichiometric metal salts are not, however, the most attractive way to form these compounds, so catalytic conditions were tested. When aminal **2.12c** was heated at reflux under an oxygen atmosphere and in the presence of 20 mol% of CuCl$_2$, **2.53b** was only observed in trace amounts (entry 2); deoxyvasicinone (**2.54b**) and peroxide **2.61** were also formed as products. Switching the catalyst to Cu(OAc)$_2$ led to a 15% yield of desired product **2.53b**, but the process was still unselective (entry 3).

It appears that the first oxidation occurs exclusively at the aminal site to form deoxyvasicine (**2.53b**). The presence of the amidine moiety apparently activates the molecule for oxidation at the benzylic position; we have observed that samples of aminal **2.12c** can remain stable in the freezer for years, whereas **2.53b** begins to convert to **2.54b** within a day when exposed to atmospheric oxygen. Considering this, we reasoned that addition of a weak acid to protonate the relatively basic amidine moiety of **2.53b** might deactivate the benzylic position toward oxidation while not interfering with the initial aminal oxidation. Indeed, using 1.1 equivalents of acetic acid as an additive with catalytic Cu(OAc)$_2$ in acetonitrile led to the formation of **2.53b** in 53% yield without formation of **2.54b** and **2.61** (entry 4). A simple change of the solvent from acetonitrile to methanol drastically improved the yield of **2.53b** to 81% (entry 5). A number of different copper salts, solvents and acids were then evaluated, but none of the changes led to a further improvement in yield. It appears that under certain conditions catalyst deactivation via copper oxide formation decreased the catalyst turnover and consequently product yields.

Using the optimized reaction conditions, a range of different aminals were selectively oxidized to the corresponding dihydroquinazolines (Table 2.4). In general, these products were obtained in moderate to good yields. Product **2.53c**, containing a

piperidine ring, required a higher reaction temperature and resulted in a lower yield than the corresponding pyrrolidine and azepane products (**2.53b** and **2.53e**, respectively). While differences in conformation may in part account for the observed differences in reactivity (X-ray crystal structures of aminals containing pyrrolidine and piperidine revealed that the pyrrolidine-containing aminal adopts a bent structure, whereas the piperidine aminal appears relatively strain-free),[23] this finding likely relates to the reduced propensity of six-membered rings to engage in reactions that form exocyclic double bonds.

Table 2.4 **Scope of Cu(OAc)₂-Cayalyzed Dihydroquinazoline Synthesis**
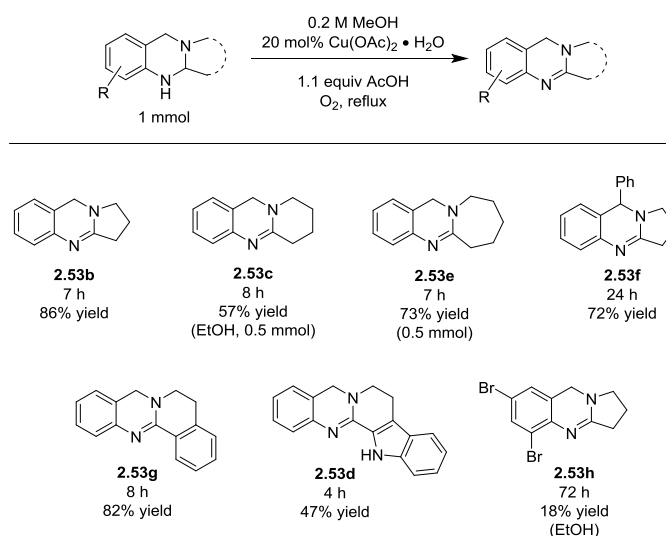
The isolation of azepinoquinazoline **2.53e** in 73% yield was gratifying but somewhat unexpected since Decker reported that samples of the compound completely oxidized to quinazolinone **23** when exposed to air for 24 h.[28b] This demonstrates the need for acetic acid to protonate the amidine, preventing further oxidation. While product **2.53g** was obtained in good yields from tetrahydroisoquinoline-aminal **2.12j**, rutaecarpane-derived product **2.53d** was formed in only 47% yield, apparently due to unidentified side-reactions. The reaction leading to the synthesis of the dibromo-analog

of deoxyvasicine (**2.53h**), even under elevated temperature and extended reaction time, still did not reach completion after 3 days. The attenuated reactivity of aminal **2.12b** is most likely the result of the decreased electron density on the anilinic nitrogen.

Table 2.5 **Optimization of Conditions for Deoxyvasicinone (2.54b) Formation**
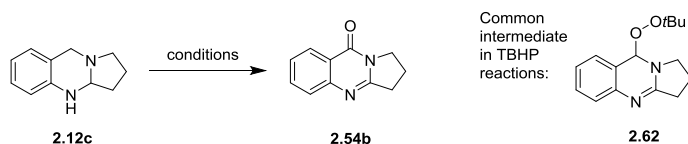
Entry	Solvent (0.2 M)	Catalyst (mol%)	Oxidant (equiv)	Additive (equiv)	Temp. [°C]	Time [h]	Yield of **2.54b** [%]
1	DMSO	CuBr (20)	O_2	-	100	2	21
2	DMSO	CuBr (20)	O_2	DBU (0.4)	100	17	25
3	DMSO	CuBr (20)	O_2	DBU (2.0)	100	3	22
4	DMSO	CuBr (20)	O_2	-	60	3	28
5	MeCN	CuBr(10)	O_2	-	80	24	43
6	DMF	CuBr(10)	O_2	-	80	24	42
7	DMSO	CuI (20)	O_2	-	60	3	29
8	MeCN	$CuCl_2 \cdot 2H_2O$ (20)	O_2	-	50	5	19
9	MeCN	CuCl (10)	O_2	DABCO (0.1), TEMPO (0.05)	80	12	50
10	DMSO	CuCl (10)	O_2	DABCO (0.1), TEMPO (0.05)	100	3	38
11	PhMe	CuBr (20)	TBHP (5)	piperidine[a] (5)	rt	0.5	61
12	EtOH	KI (20)	TBHP (5)	piperidine[a] (5)	rt	36	80

Reactions run on a 0.25 mmol scale. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-Diazabicyclo[2.2.2]octane. TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxy radical. [a] Piperidine was added at end of the reaction and the reaction mixture was heated at 50 °C for 1 h.

Different conditions for the direct catalytic oxidation of aminals to quinazolinones were also explored (Table 2.5). The use of Cu(OAc)$_2$ and methanol, while appropriate for furnishing deoxyvasicine (**2.53b**) from aminal **2.12c**, did not result in satisfactory yields of deoxyvasicinone (**2,54b**). Attempts to use other copper (I) or copper (II) salts and solvents under oxygen without the addition of acid to promote the full oxidation of aminal **2.12c** to deoxyvasicinone (**2.54b**) were met with

disappointment, with yields of **2.54b** for these conditions topping off at around 40% (Table 2.5). In most cases, peroxide **2.61** was observed as a major side product. The Cu/TEMPO/DABCO catalyst system employed by Han et al.[35] for the oxidation of aminals to quinazolines provided an increased yield of 50% (entry 9). The best yields were obtained using the conditions originally developed by Reddy and coworkers,[36] namely the combined use of catalytic amounts of potassium iodide (20 mol%) and excess TBHP (5 equiv), followed by addition of piperidine. In this instance, deoxyvasicinone was isolated in 80% yield (entry 12). In the course of this reaction, the TBHP adduct **2.62** is formed as an intermediate that is subsequently converted to the quinazolinone upon addition of piperidine. A slight modification of Reddy's conditions, in which piperidine was added directly to the solution after 36 hours instead of removing solvent from the intermediate peroxide beforehand, resulted in identical yields.

Table 2.6 **Scope of KI-Cayalyzed Quinazolinone Synthesis**
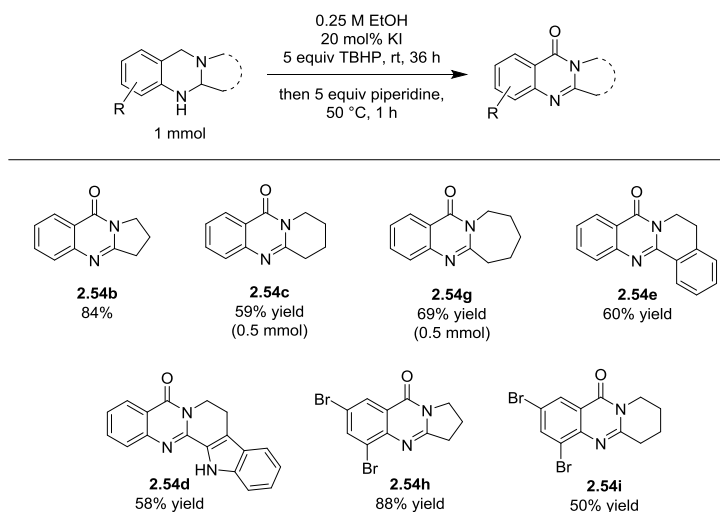
Using the optimized conditions, a range of different quinazolinones were synthesized (Table 2.6). In general, yields were moderate to good for substrates with varying ring sizes. In this manner the natural products deoxyvasicine (**2.54b**), mackinazolinone (**2.54c**) and rutaecarpine (**2.54d**) were prepared, in addition to the

azepinoquinazolone **2.54g**, which has been demonstrated to be a more effective antitussive agent than codeine.[40] Dibromo-deoxyvasicinone analog **2.54h** was obtained in relatively high yield (88%) whereas the corresponding analog of mackinazolinone (**2.54i**) was obtained in only 50% yield.

Interestingly, when quaternary aminal **2.12o** was subjected to oxidative conditions in an attempt to prepare compound **2.63**, deoxyvasicinone (**2.54b**) was obtained as the major product in a process that involved demethylation (Figure 2.29, eq 62). The demethylation of aminals has been previously reported in cases where the product achieves aromaticity,[41] which is presumably the driving force of this transformation. Aminal **2.64**, which contains two tertiary amines and is readily obtainable via an acid-promoted hydride shift process,[42] was also exposed to oxidative conditions (Figure 2.29, eq 63). We had hypothesized that quinazolinone **2.66** might be formed in this reaction via the debenzylation of an intermediate iminium ion. However, the major product from this reaction was identified to be **2.65**, the apparent product of iminium hydrolysis.

Figure 2.29 **Oxidation of Other Aminal Systems**
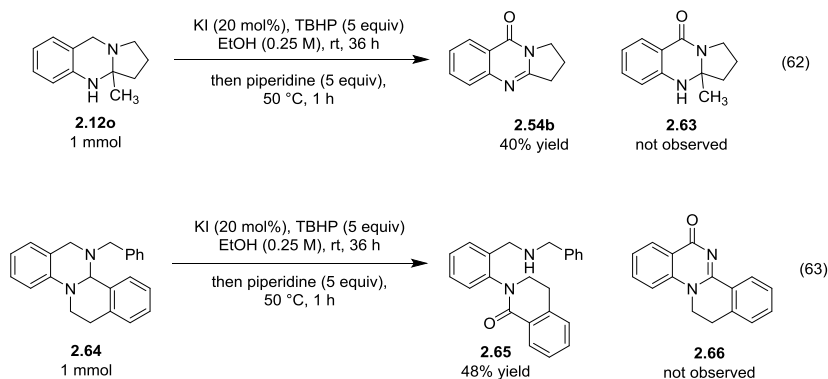
2.14 Conclusion

The redox-neutral amine α-amination reaction first developed by Seidel and coworkers in 2008 has been studied in depth. The mechanism of the reaction was investigated both experimentally and computationally in collaboration with the Houk group. Key findings in this study were that azaquinone methide intermediates likely lead to azomethine ylides in a 1,6-proton transfer step. This was supported by the trapping of key intermediates, deuteration experiments and by calculations.

The scope of the reaction was further expanded by using microwave irradiation instead of conventional heating. The reactivity of various amine, amino acid, aldehyde and ketone partners was explored. Finally, several methods were developed for the synthesis of quinazoline alkaloid natural products. In addition to simple methods using stoichiometric oxidants, catalytic routes were developed.

Experimental Section

General Information: Microwave reactions were carried out in a CEM Discover reactor using sealed 10 mL reaction vessels and temperatures were measured with an infrared temperature sensor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate and Dragendorff-Munier stains followed by heating. Proton nuclear magnetic resonance spectra (^{1}H-NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2CO$ at 2.04 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm).

General Procedure A: A 10 mL round bottom flask was charged with aldehyde (1.0 mmol), solvent (4 mL) and secondary amine. The mixture was stirred at reflux under nitrogen until consumption of the aldehyde as determined by thin-layer chromatography. After this time the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.

General Procedure B: A 10 mL microwave reaction vessel was charged with a 10 x 8 mm SiC passive heating element, aldehyde (1.0 mmol), *n*-BuOH (4 mL) and secondary amine. The reaction tube was sealed with a Teflon-lined snap cap and heated in a

microwave reactor at the appropriate temperature until the aldehyde was consumed as determined by thin-layer chromatography. After cooling with compressed air flow, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.

Aminal 2.12b: Following general procedure A, **2.12b** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and pyrrolidine (3 equiv) in absolute ethanol for 23 h. **2.12b** was recovered as a white solid in 92% yield (0.305 g) (R_f = 0.19 in hexanes/EtOAc 60:40 v/v); mp: 122–124 °C; IR (KBr) 3403, 3052, 2971, 2938, 2907, 2839, 1768, 1692, 1575, 1438, 1349, 1258, 1119, 980, 927, 861, 747, 722, 637 cm-1; ^{1}H NMR (500 MHz, CDCl$_3$) 7.37 (d, J = 1.7 Hz, 1H), 6.99 (d, J = 0.9 Hz, 1H), 4.37 (ddd, J = 5.2, 2.8, 0.8 Hz, 1H), 4.23 (br s, 1H), 4.09 (d, J = 16.2 Hz, 1H), 3.78 (d, J = 16.2 Hz, 1H), 2.82–2.75 (comp, 2H), 2.20–2.11 (m, 1H), 2.04–1.87 (comp, 2H), 1.73 (dddd, J = 12.6, 9.9, 4.2, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.6, 132.5, 129.2, 121.7, 109.0, 108.3, 71.3, 49.9, 49.6, 32.7, 21.7; m/z (ESI–MS) 333.0 [M+H]$^+$.

Aminal 2.12c: Following general procedure A, **2.12c** was obtained from the reaction between 2-aminobenzaldehyde and pyrrolidine (3 equiv) in absolute ethanol for 72 h. **2.12c** was recovered as a white solid in 73% yield (0.127 g) (R_f = 0.25 in EtOAc/MeOH 95:5 v/v); mp: 63–64 °C; IR (KBr) 3246, 2966, 2826, 1608, 1585, 1478, 1383, 1255, 749 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.02 (app t, J = 7.6 Hz, 1H), 6.95 (app d, J = 7.4 Hz, 1H), 6.70 (app dt, J = 7.4, 0.9 Hz, 1H), 6.54 (app d, J = 7.9 Hz, 1H), 4.17–4.13 (m, 1H), 4.04 (d, J = 15.6 Hz, 1H), 3.90 (d, J = 15.6 Hz, 1H), 3.67 (br s, 1H), 3.03 (app dt, J = 8.8, 5.5 Hz, 1H), 2.68 (app dt, J = 8.8, 5.5 Hz, 1H), 2.18–2.09 (m, 1H), 1.97–2.07 (m, 1H), 1.96–1.87 (m, 1H), 1.66 (app tdd, J = 12.3, 10.2, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.6, 133.3, 128.6, 126.0, 125.5, 125.2, 124.3, 120.0, 118.9, 115.2, 72.4, 51.9, 50.9, 31.9, 21.3; m/z (ESI–MS) 175.1 [M+H]$^+$.

Aminal 2.12g: Following general procedure A, **2.12g** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and piperidine (3 equiv) in isopropanol (4 mL) for 48 h in a sealed tube at 140 ºC. **2.12g** was recovered as a white solid in 67% yield (0.232 g) (R$_f$ = 0.28 in Hex/EtOAc 70:30 v/v); mp: 89–92 ºC; IR (KBr) 3405, 2936, 2853, 2771, 1596, 1561, 1486, 1442, 1370, 1351, 1294, 1272, 1190, 1119, 856, 713 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.36 (d, J = 2.1 Hz, 1H), 6.96 (d, J = 1.4 Hz, 1H), 4.22 (s, 1H), 3.79 (br s, 1H), 3.72–3.59 (comp, 2H), 2.96–2.88 (m, 1H), 2.25–2.15 (m, 1H), 1.95–1.87 (m, 1H), 1.76 (app tt, J = 10.1, 4.9 Hz, 1H), 1.71–1.64 (comp, 2H), 1.63–1.54 (m, 1H), 1.50–1.41 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.1, 132.5, 128.7, 122.3, 108.5, 108.3, 70.2, 56.0, 51.5, 31.9, 25.6. 21.3; m/z (ESI–MS) 347.0 [M+H]$^+$.

Aminal 2.12h: Following general procedure A, **2.12h** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and morpholine (3 equiv) in isopropanol (4 mL) for 48 h in a sealed tube at 140 ºC. **2.12h** was recovered as a light brown solid in 15% yield (0.052 g) (R$_f$ = 0.15 in hexanes/EtOAc 80:20 v/v); mp: 156–157 ºC; IR (KBr) 3344, 2982, 2937, 2901, 2855, 1590, 1492, 1464, 1342, 1315, 1280, 1140, 1121, 1079, 1041, 861, 756, 730 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.42 (s, 1H), 7.00 (s, 1H), 4.25 (s, 1H), 4.05 (br s, 1H), 3.97 (app d, J = 15.2 Hz, 1H), 3.91–3.77 (comp, 3H), 3.72–3.61 (comp, 2H), 2.91–2.84 (m, 1H), 2.42–2.36 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.5, 132.5, 128.8, 121.4, 109.3, 108.9, 69.2, 67.0, 66.9, 54.7, 48.3; m/z (ESI–MS) 349.0 [M+H]$^+$.

Aminal 2.12i: Following general procedure A, **2.12i** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (3 equiv) in absolute ethanol for 16 h. **2.12i** was recovered as a white solid in 96% yield (0.378 g) (R$_f$ = 0.43 in hexanes/EtOAc 80:20 v/v); mp: 145–147 ºC; IR (KBr) 3408, 3065, 2934, 2899, 2846, 1590, 1480, 1334, 1280, 1234, 1117, 1006, 991, 865, 772, 735, 721, 685 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43 (d, J = 1.7 Hz, 1H), 7.37–7.27 (comp,

3H), 7.22 (app d, *J* = 7.4 Hz, 1H), 7.07 (s, 1H), 5.28 (d, *J* = 2.3 Hz, 1H), 4.39 (d, *J* = 16.2 Hz, 1H), 4.31 (s, 1H), 3.81 (d, *J* = 16.2 Hz, 1H), 3.19–3.02 (comp, 2H), 2.97–2.86 (m, 1H), 2.77–2.66 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.7, 134.7, 134.5, 132.4, 129.2, 128.8, 128.3, 126.5, 126.4, 121.7, 109.0, 108.7, 69.1, 55.3, 44.5, 29.1; *m/z* (ESI–MS) 395.0 [M+H]$^+$.

Aminal 2.12j: Following general procedure A, **2.12j** was obtained from the reaction between 2-aminobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (3 equiv) in absolute ethanol for 48 h. **2.12j** was recovered as a yellow oil in 96% yield (0.227 g) (R$_f$ = 0.33 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3387, 3024, 2916, 2837, 2791, 2740, 1725, 1606, 1583, 1487, 1424, 1339, 1305, 1249, 1112, 1044, 1021, 936, 749 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) 7.36 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.30–7.23 (comp, 2H), 7.20 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.07 (app t, *J* = 7.6 Hz, 1H), 7.01 (app d, *J* = 7.5 Hz, 1H), 6.77 (app dt, *J* = 7.4, 1.1 Hz, 1H), 6.58 (app d, *J* = 8.0 Hz, 1H), 5.16 (d, *J* = 3.2 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.87 (d, *J* = 15.8 Hz, 1H), 3.86 (br s, 1H), 3.21 (ddd, *J* = 11.4, 8.3, 4.8 Hz, 1H), 3.06 (ddd, *J* = 14.0, 8.3, 5.7 Hz, 1H), 2.98 (app td, *J* = 16.4, 4.8 Hz, 1H), 2.72 (app td, *J* = 10.9, 5.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 142.3, 135.8, 134.9, 129.3, 128.1, 127.5, 127.3, 126.5, 126.4, 119.8, 118.7, 115.6, 69.7, 56.0, 45.5, 29.4; *m/z* (ESI–MS) 237.1 [M+H]$^+$.

Aminal 2.12l: Following general procedure B, **2.12l** was obtained from the reaction between 2-aminobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (2 equiv) in *n*-butanol for 2 h at 250 °C (200 W, 80–120 psi). **2.12l** was recovered as a yellow solid in 47% yield (0.111 g) in addition to **2.12j** (38% yield, 0.089 g). Characterization data for **2.12l**: (R$_f$ = 0.14 in hexanes/EtOAc 80:20 v/v); mp: 151–153 °C; IR (KBr) 3356, 3032, 2894, 2750, 1612, 1591, 1491, 1452, 1437, 1390, 1368, 1270, 1141, 1125, 1093, 1020, 746, 723 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.20–7.11 (comp, 3H), 7.07–7.00 (comp, 2H), 6.98 (app d, *J* = 7.5 Hz, 1H), 6.73 (app dt, *J* = 7.5, 1.1 Hz, 1H), 6.50 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.75–

4.68 (m, 1H), 4.38 (d, J = 16.1 Hz, 1H), 4.03 (d, J = 15.1 Hz, 1H), 3.85 (d, J = 16.1 Hz, 1H), 3.78–3.67 (comp, 2H), 3.33 (dd, J = 16.8, 4.6 Hz, 1H), 2.81 (dd, J = 16.8, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.8, 134.0, 130.4, 128.8, 127.5, 127.2, 126.5, 126.3, 126.0, 118.7, 118.4, 114.8, 65.7, 54.9, 49.6, 34.8; m/z (ESI–MS) 237.1 [M+H]$^+$.

Aminal 2.12m: Following general procedure B, **2.12m** was obtained from the reaction between 2-aminobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (2 equiv) in n-butanol for 1 h at 220 °C (200 W, 80–120 psi). **2.12m** was recovered as a yellow solid in 14% yield (0.0542 g) in addition to **2.12i** (69% yield). Characterization data for **2.12m**: (R$_f$ = 0.20 in hexanes/EtOAc 80:20 v/v); mp: 135–138 °C; IR (KBr) 3384, 3067, 2926, 1701, 1685, 1676, 1589, 1560, 1478, 1342, 1290, 1265, 1128, 1030, 855, 738 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.40 (d, J = 2.0 Hz, 1H), 7.21–7.13 (comp, 3H), 7.07–7.00 (comp, 2H), 4.73–4.69 (m, 1H), 4.29 (d, J = 16.2 Hz, 1H), 4.24 (s, 1H), 3.92 (d, J = 15.0 Hz, 1H), 3.80 (d, J = 16.2 Hz, 1H), 3.69 (d, J = 15.0 Hz, 1H), 3.36 (dd, J = 17.0, 4.8 Hz, 1H), 2.89 (dd, J = 17.0, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.3, 133.4, 132.4, 129.9, 129.1, 128.8, 126.5, 126.4, 126.2, 121.6, 108.9, 108.8, 66.1, 54.7, 49.7, 34.5; m/z (ESI–MS) 395.0 [M+H]$^+$.

Aminal 2.12o: Following general procedure B, **2.12o** was obtained from the reaction between 2-aminobenzaldehyde and 2-methylpyrrolidine (3 equiv) in n-butanol for 15 min at 250 °C (200 W, 100–150 psi). **2.12o** was isolated as a yellow oil in 66% yield (0.124 g) (R$_f$ = 0.27 in EtOAc); IR (KBr) 3397, 2970, 1647, 1609, 1493, 1457, 1414, 1354, 1271, 1215, 1131, 1036, 747 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.01 (app t, J = 7.8 Hz, 1H), 6.95 (app d, J = 7.4 Hz, 1H), 6.64 (app t, J = 7.4 Hz, 1H), 6.43 (app d, J = 7.8 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 3.75 (d, J = 17.0 Hz, 1H), 3.59 (br s, 1H), 3.01 (app td, J = 8.4, 4.4 Hz, 1H), 2.75 (app q, J = 8.4 Hz, 1H), 1.98–1.75 (comp, 4H), 1.41 (s, 3H); ^{13}C NMR

(125 MHz, CDCl$_3$) δ 142.0, 127.4, 127.1, 117.0, 116.6, 114.0, 73.1, 50.8, 45.3, 39.8, 25.5, 19.8; *m/z* (ESI–MS) 189.0 [M+H]$^+$.

In addition, compound **2.12p** was isolated as a yellow oil as a mixture of diastereomers in 26% yield (0.049 g), dr = 54:46 as determined by integration of one set of ^{1}H NMR signals (δ$_{major}$ 1.26 ppm, δ$_{minor}$ 1.16 ppm) (R$_f$ = 0.45 in EtOAc); IR (KBr) 3386, 2961, 2870, 1608, 1494, 1375, 1302, 1262, 1154, 1041, 747 cm^{-1}; ^{1}H NMR of major diastereomer (500 MHz, CDCl$_3$) 7.08–6.98 (comp, 2H), 6.77 (app dt, *J* = 7.4, 1.1 Hz, 1H), 6.70–6.64 (comp, 1H), 4.07 (d, *J* = 13.9 Hz, 1H), 3.99 (br s, 1H), 3.65–3.57 (m, 1H), 3.46 (d, *J* = 13.9 Hz, 1H), 2.49–2.39 (m, 1H), 2.25–1.97 (comp, 2H), 1.74–1.48 (comp, 2H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.1, 143.0, 127.4, 127.1, 127.0, 121.7, 119.2, 117.6, 117.2, 116.8, 113.6, 74.2, 70.8, 58.6, 53.3, 52.6, 45.7, 31.0, 30.7, 29.7, 28.8, 19.5, 18.6; *m/z* (ESI–MS) 189.0 [M+H]$^+$.

Aminal 2.25: Following general procedure A, **2.25** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde (0.5 mmol) and 2-allylpyrrolidine[43] (3 equiv) in absolute ethanol (2 mL) for 24 h. **2.25** and **2.26** were recovered together as a white solid in 15% and 3% yields, respectively. In addition, **2.27** and **2.28** were obtained in 29% and 27% yields. Characterization data of **2.25**: (R$_f$ = 0.13 in hexanes/EtOAc 90:10 v/v); mp: 75–77 °C; IR (KBr) 3414, 2889, 1593, 1490, 1341, 1109, 914, 863 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.38 (d, *J* = 2.1 Hz, 1H), 6.99 (s, 1H), 5.88–5.69 (m, 1H), 5.22–4.97 (comp, 2H), 4.78 (d, *J* = 4.1 Hz, 1H), 4.33–4.11 (comp, 2H), 3.78 (d, *J* = 17.1 Hz, 1H), 2.89–2.78 (m, 1H), 2.56–2.43 (m, 1H), 2.43–2.34 (m, 1H), 2.28–1.95 (comp, 2H), 1.83–1.54 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.5, 135.3, 132.2, 128.8, 120.4, 116.8, 108.0, 107.5, 71.7, 57.6, 46.2, 38.8, 31.2, 27.8; *m/z* (ESI–MS) 373.2 [M+H]$^+$.

Synthesis of aminoaldehyde 2.33: To a 25 mL round bottom flask with fitted with a magnetic stir bar was added 2-aminobenzyl alcohol (0.246 g, 2.00 mmol), methanol (6.25 mL), (*E*)-ethyl 7-oxohept-2-enoate[44] (0.374 g, 2.20 mmol) and acetic acid (0.321 mL, 5.6 mmol). The resulting solution was cooled to 0 °C in an ice bath and sodium cyanoborohydride (0.189 g, 3.00 mmol) was added. The solution was allowed to warm to room temperature and was stirred for 1 h, after which time the reaction was quenched with 5 mL of 5% aq. $KHSO_4$ solution. The product was extracted with EtOAc (2 x 10 mL) and the extract was washed with sat. $NaHCO_3$ (1 x 10 mL) followed by brine (1 x 10 mL). The organic layer was dried over sodium sulfate, filtered and dried *in vacuo*. The crude product was purified by silica gel chromatography and ethyl 7-((2-(hydroxymethyl)phenyl)amino)hept-2-enoate (**2.33'**) was obtained as a colorless oil in 91% yield (0.503 g) as a mixture of stereoisomers; ratio *E/Z* = 3.55:1 (R_f = 0.23 in hexanes/EtOAc 80:20 v/v); Characterization data of the *E* isomer: IR (KBr) 3391, 2931, 1716, 1652, 1607, 1520, 1456, 1312, 1192, 1038, 927, 822, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.21 (app td, *J* = 7.8, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.96 (app dt, *J* = 15.6, 6.9 Hz, 1H), 6.67–6.62 (comp, 2H), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.63 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 2.25 (app qd, *J* = 7.2, 1.4 Hz, 2H), 1.73–1.65 (comp, 2H), 1.64–1.57 (comp, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.7, 147.6, 129.5, 129.0, 124.2, 121.6, 116.2, 110.4, 64.7, 60.2, 43.1, 31.8, 28.8, 25.5, 14.2; *m/z* (ESI–MS) 278.1 [M+H]$^+$.

A 10 mL round bottom flask with a stir bar was charged with **2.33'** (0.277 g, 1 mmol, ratio of stereoisomers (*E/Z*) = 3.55:1), dichloromethane (3.57 mL) and manganese dioxide (0.522 g, 6.00 mmol), and the resulting solution was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of celite and rinsed with dichloromethane (3 x 20 mL). The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography, yielding both *E* and *Z* isomers. Pure

E-isomer **2.33** was obtained as a bright yellow oil in 62% yield (0.198 g) (R_f = 0.31 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3331, 2984, 2745, 1647, 1521, 1457, 1265, 1040, 981, 870, 749 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 9.81 (s, 1H), 8.31 (br s, 1H), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42–7.35 (m, 1H), 6.95 (app dt, *J* = 15.6, 6.9 Hz, 1H), 6.75–6.63 (comp, 2H), 5.87–5.81 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.33–3.19 (m, 2H), 2.36–2.21 (m, 2H), 1.81–1.68 (m, 2H), 1.67–1.56 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 193.9, 166.5, 150.7, 148.3, 136.7, 135.8, 121.8, 118.3, 114.7, 110.7, 60.2, 42.1, 31.8, 28.5, 25.5, 14.2; *m/z* (ESI–MS) 276.3 [M+H]⁺.

Compound 2.34: Following general procedure A, **2.34** was obtained from the reaction between **2.33** (0.25 mmol) and pyrrolidine (3 equiv) in absolute ethanol (1 mL) for 48 h. The residue was purified via silica gel chromatography (hexanes/EtOAc 80:20 v/v – EtOAc/MeOH/NEt₃ 74:25:1 v/v/v). Racemic compound **2.34** was obtained as a tan oil in 7% yield (0.0060 g) (R_f = 0.44 in hexanes/EtOAc 80:20 v/v); Relative stereochemistry was determined using 2D NMR and J–coupling analysis; IR (KBr) 3329, 2933, 1717, 1654, 1577, 1522, 1458, 1338, 1160, 1041, 751 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) 7.08 (app td, *J* = 7.3, 1.7 Hz, 1H), 6.94 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.78 (app d, *J* = 8.2 Hz, 1H), 6.53 (app td, *J* = 7.3, 3.3 Hz, 1H), 4.28–4.20 (m, 1H), 4.15–4.01 (comp, 3H), 3.47 (app td, *J* = 10.7, 2.2 Hz, 1H), 2.87 (app t, *J* = 12.8, 1H), 2.62–2.54 (dd, *J* = 10.7, 4.7 Hz, 1H) 2.54–2.47 (m, 2H), 2.40–2.29 (m, 2H), 1.99–1.93 (m, 1H), 1.87–1.81 (m, 1H), 1.71–1.65 (m, 1H), 1.62–1.46 (comp, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.09–0.99 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 145.5, 130.1, 128.7, 115.3, 111.5, 109.7, 60.2, 59.5, 54.7, 51.8, 50.9, 48.0, 33.5, 25.4, 24.9, 23.4, 14.2; *m/z* (ESI–MS) 327.5 [M–H]⁺.

In addition, compound **2.35** was isolated as a yellow oil in 7% yield (0.0044 g) (R_f = 0.47 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3419, 2360, 2090, 1649, 1559, 1540, 1507, 1457 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.32 (s, 1H), 7.18–7.14 (m, 1H), 7.01 (dd, *J* = 7.4, 1.2

Hz, 1H), 6.65–6.57 (comp, 2H), 4.45 (dd, J = 10.8, 1.9 Hz, 1H), 4.30–4.19 (m, 2H), 3.94 (app d, J = 13.6 Hz, 1H), 3.07–2.97 (m, 1H), 1.85–1.79 (m, 1H), 1.78–1.65 (comp, 3H), 1.54–1.44 (comp, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.6, 145.5, 134.9, 132.1, 130.1, 124.5, 120.6, 116.7, 111.2, 60.4, 58.2, 46.7, 28.9, 25.0, 22.1, 14.3; m/z (ESI–MS) 256.3 [M−H]$^+$.

In addition, compound **2.36** was isolated as a tan oil in 42% yield (0.0370 g) (R_f = 0.20 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3447, 2936, 2870, 2115, 1732, 1652, 1578, 1521, 1459, 1200, 1160, 1039, 751 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 9.80 (s, 1H), 8.29 (br s, 1H), 7.46–7.41 (m, 1H), 7.39–7.33 (m, 1H), 6.69–6.62 (comp, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.29–3.15 (comp, 2H), 3.02–2.93 (m, 1H), 2.64–2.48 (comp, 5H), 2.32 (ddd, J = 14.7, 7.3, 2.3 Hz, 1H), 1.80–1.63 (comp, 6H), 1.63–1.44 (comp, 4H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.8, 172.9, 150.8, 136.7, 135.7, 118.2, 114.5, 110.7, 60.3, 58.6, 49.5, 42.4, 36.4, 32.6, 29.2, 23.5, 23.2, 14.2; m/z (ESI–MS) 347.2 [M+H]$^+$.

In addition, compound **2.37** was isolated as a tan oil in 22% yield (0.0228 g) (R_f = 0.09 in i-PrNH$_2$/MeOH/EtOAc 1:25:74 v/v/v); IR (KBr) 3421, 2931, 1733, 1654, 1497, 1458, 1374, 1033 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (app d, J = 7.3 Hz, 1H), 6.66–6.59 (comp, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.89 (app t, J = 5.7 Hz, 1H), 3.85 (d, J = 14.6 Hz, 1H), 3.79 (d, J = 14.6 Hz, 1H), 3.34–3.26 (m, 1H), 3.14–3.01 (comp, 2H), 2.99–2.92 (m, 1H), 2.61–2.51 (comp, 5H), 2.34 (dd, J = 14.8, 7.3 Hz, 1H), 2.14–2.06 (m, 1H), 1.99–1.80 (comp, 4H), 1.78–1.72 (comp, 4H), 1.66–1.48 (comp, 4H), 1.43–1.33 (comp, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.0, 144.7, 144.6, 127.4, 126.9, 121.0, 120.9, 116.6, 112.0, 60.3, 58.8, 52.3, 51.6, 49.6, 47.6, 47.5, 36.5, 36.4, 32.7, 30.6, 27.4, 27.3, 23.5, 23.4, 20.6, 14.2; m/z (ESI–MS) 400.2 [M+H]$^+$.

Aminoaldehyde 2.40: Following general procedure A, **2.40** was obtained from the reaction between **2.33** (0.25 mmol) and piperidine (3 equiv) in absolute ethanol (1 mL)

for 96 h. The residue was purified via silica gel chromatography (hexanes/EtOAc 80:20 v/v − EtOAc/MeOH/NEt$_3$ 74:25:1 v/v/v). **2.40** was obtained as an orange oil in 47% yield (0.0421 g) (R$_f$ = 0.32 in hexanes/EtOAc 50:50 v/v); IR (KBr) 3328, 2933, 2854, 2740, 1731, 1651, 1610, 1580, 1520, 1462, 1335, 1234, 1159, 1113, 1038, 877, 750, 663 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 9.79 (s, 1H), 8.30 (br s, 1H), 7.44 (app d, J = 7.8 Hz, 1H), 7.36 (app t, J = 7.8 Hz, 1H), 6.75−6.70 (comp, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.21 (dd, J = 12.7, 6.6 Hz, 2H), 3.02−2.91 (m, 1H), 2.52 (dd, J = 14.2, 6.8 Hz, 1H), 2.49−2.43 (comp, 2H), 2.42−2.35 (comp, 2H), 2.15 (dd, J = 14.2, 6.8 Hz, 1H), 1.74−1.63 (comp, 2H), 1.61−1.28 (comp, 10H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.7, 173.3, 150.8, 136.6, 135.7, 118.2, 114.5, 110.7, 61.6, 60.1, 49.4, 42.4, 35.1, 30.7, 28.9, 26.5, 24.9, 24.2, 14.2; m/z (ESI–MS) 361.2 [M+H]$^+$.

Synthesis of aminoaldehyde 2.44: To a 50 mL round bottom flask was added dimethylformamide (10 mL), sodium hydride (0.077 g, 1.934 mmol) and 18-crown-6 (0.025 mL, 0.117 mmol) and the resulting mixture was cooled to 0 °C under nitrogen atmosphere. 2,2,2-trifluoro-N-(2-formylphenyl)acetamide[46] (0.4 g, 1.842 mmol) in dimethylformamide (5 mL) was slowly added to the solution. After 20 min at room temperature (*E*)-ethyl 4-bromobut-2-enoate (0.381 mL, 2.211 mmol) dissolved in dimethylformamide (5 mL) was added dropwise, then the mixture was heated at 60 °C for 4 h. After this time, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 mL). The organic layer was washed with water (1 x 15mL) and brine (1 x 15 mL) and dried over Na$_2$SO$_4$. The solid was removed by filtration, solvent removed under reduced pressure and purified by silica gel chromatography. (*E*)-Ethyl 4-(2,2,2-trifluoro-N-(2-formylphenyl)acetamido)but-2-enoate was isolated in 42% yield (R$_f$ = 0.29 in hexanes/EtOAc 80:20 v/v).

To a 10 mL round bottom flask with stir bar was added (*E*)-Ethyl 4-(2,2,2-trifluoro-N-(2-formylphenyl)acetamido)but-2-enoate (0.050 g, 0.152 mmol) and ethanol (1.5 mL). To this mixture, 1 mL of a 5% w/v aqueous sodium bicarbonate solution was added slowly, resulting in precipitate formation. The mixture was heated at reflux until the solution became homogenous. This solution was cooled to room temperature and stirred for 2 hours. After this, 10 mL of brine was added to the solution and the product was extracted with dichloromethane (3 x 10 mL). The organic layer was washed again with brine (10 mL), dried over sodium sulfate, filtered and the solvent was subsequently removed under reduced pressure. The crude mixture was purified by silica gel chromatography. **2.44** was obtained as a yellow oil in 90% yield (R_f = 0.23 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3334, 2981, 2747, 1717, 1659, 1580, 1520, 1432, 1276, 1180, 1041, 753 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 9.84 (s, 1H), 8.55 (br s, 1H), 7.50 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.42–7.34 (m, 1H), 7.00 (app dt, *J* = 15.7, 4.4 Hz, 1H), 6.78–6.70 (m, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 5.99 (dt, *J* = 15.7, 2.8 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.09–4.05 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.2, 166.0, 150.0, 143.9, 136.7, 135.9, 121.9, 118.7, 115.7, 110.9, 60.4, 43.2, 14.2; *m/z* (ESI–MS) 234.0 [M+H]$^+$.

Quinoline 2.45: Following general procedure A, **2.45** was obtained from the reaction between **2.44** (0.5 mmol) and pyrrolidine (3 equiv) in absolute ethanol (2 mL) for 14 h. Compound **2.45** was obtained as a yellow oil in 61% yield (R_f = 0.19 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3420, 3065, 2982, 2938, 1733, 1571, 1497, 1465, 1368, 1340, 1255, 1158, 1030, 908, 788, 753, 638, 616 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.84 (d, *J* = 2.2 Hz, 1H), 8.08 (app d, *J* = 8.3 Hz, 1H), 8.07–8.05 (m, 1H), 7.77 (app d, *J* = 8.3 Hz, 1H), 7.68 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.52 (app t, *J* = 7.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 1.25 (app td, *J* = 7.1, 0.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6, 151.6,

147.2, 132.7, 129.2, 129.1, 127.8, 127.5, 127.0, 126.8, 61.2, 38.7, 14.2; m/z (ESI–MS) 216.2 [M+H]$^+$.

N,O–Acetal 2.47: Following general procedure B, **2.47** was obtained from the reaction between pyrrolidine (0.5 mmol) and 2-amino-3,5-dibromobenzaldehyde (2 equiv) in toluene for 30 min at 150 °C (200 W, 30–60 psi). Racemic compound **2.47** was obtained as a tan solid in 27% yield (0.0809 g) in addition to **2.12b** (58% yield, 0.0957 g). Characterization data for **2.47**: (R$_f$ = 0.53 in hexanes/EtOAc 60:40 v/v). Relative stereochemistry was determined using 2D NMR and J–coupling analysis; mp: 153–156 °C; IR (KBr) 3438, 3393, 3344, 2961, 1607, 1577, 1570, 1507, 1484, 1458, 1379, 1340, 1286, 1264, 1195, 1170, 1050, 865, 739 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.59 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 5.88 (d, J = 2.1 Hz, 1H), 5.01 (br s, 2H), 4.76 (app d, J = 4.6 Hz, 1H), 4.39 (d, J = 9.8 Hz, 1H), 4.34 (br s, 1H), 4.15 (d, J = 9.8 Hz, 1H), 3.11 (app td, J = 8.8, 3.2 Hz, 1H), 2.69 (app q, J = 8.8 Hz, 1H), 2.28– 2.17 (m, 1H), 2.08–1.94 (comp, 2H), 1.93–1.84 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.6, 137.9, 134.2, 133.2, 132.9, 132.2, 124.5, 117.8, 111.5, 108.5, 108.2, 107.2, 77.3, 64.2, 58.3, 50.0, 33.1, 20.8; m/z (ESI–MS) 611.8 [M+H]$^+$.

Aminal 2.12b-16: Following general procedure A, **2.12b-16** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and pyrrolidine (3 equiv) in ethanol-OD for 24 h. **2.12b-16** was recovered as a white solid in 77% yield (0.257 g) (R$_f$ = 0.33 in hexanes/EtOAc 60:40 v/v); IR (KBr) 3404, 3053, 2971, 2937, 2903, 2839, 1591, 1482, 1333, 1277, 1239, 1222, 1132, 880, 724 cm^{-1}; 1H NMR (500 MHz, CDCl$_3$) 7.39 (d, J = 2.1 Hz, 1H), 7.02–6.99 (m, 1H), 4.47–4.36 (m, 1H), 4.24 (br s, 1H), 4.15–4.06 (comp, 1H, 50% D), 3.84–3.75 (comp, 1H, 54% D), 2.91–2.73 (comp, 2H), 2.24–2.11 (m, 1H), 2.08–1.88 (comp, 2H), 1.81–1.68 (m, 1H); m/z (ESI–MS) 334.1 [M+H]$^+$.

Aminal 2.12i-17:   Following general procedure A, **2.12i-17** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (3 equiv) in ethanol-OD for 16 h.   **2.12i-17** was recovered as a white solid in 95% yield (0.375 g) (R_f = 0.43 in hexanes/EtOAc 80:20 v/v);   IR (KBr) 3408, 3066, 2955, 2911, 2847, 1509, 1480, 1365, 1316, 1281, 1163, 1117, 991, 865, 735, 721 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.44 (d, J = 2.0 Hz, 1H), 7.37–7.25 (comp, 3H), 7.22 (app d, J = 7.4 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 5.32–5.23 (comp, 1H, 33% D), 4.43–4.34 (comp, 1H, 33% D), 4.34–4.28 (comp, 1H), 3.84–3.73 (comp, 1H, 37% D), 3.17–3.02 (comp, 2H), 2.97–2.86 (m, 1H), 2.74–2.64 (m, 1H); m/z (ESI–MS) 395.3 [M+H]$^+$.

Aminal 2.12i-18: *N,N*-dideutero-2-amino-3,5-dibromobenzaldehyde was produced by dissolving 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol) in EtOD (1 mL), heating to reflux, allowing to cool to room temperature, removing solvent *in vacuo* and repeating this process two more times.   1-hydro-2-deutero-3,4-dihydroisoquinoline was produced from 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol) using the same process.   Following general procedure A, **2.12i-18** was obtained from the reaction between *N,N*-dideutero-2-amino-3,5-dibromobenzaldehyde and 1-hydro-2-deutero-3,4-dihydroisoquinoline (3 equiv) in ethanol-OD for 24 h.   **2.12i-18** was isolated as a white solid in 87% yield (0.344 g) (R_f = 0.43 in hexanes/EtOAc 80:20 v/v);   IR (KBr) 3413, 3065, 3023, 2932, 2913, 2868, 2154, 1590, 1475, 1356, 1281, 1013, 1001, 863, 730, 721, 703, 685, 550 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.44 (d, J = 2.0 Hz, 1H), 7.37–7.25 (comp, 3H), 7.22 (app d, J = 7.4 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 5.32–5.23 (comp, 1H, 30% D), 4.43–4.34 (comp, 1H, 40% D), 4.34–4.28 (comp, 1H), 3.84–3.73 (comp, 1H, 44% D), 3.17–3.02 (comp, 2H), 2.97–2.86 (m, 1H), 2.74–2.64 (m, 1H); m/z (ESI–MS) 397.3 [M+H]$^+$.

In addition, partially deuterated THIQ was isolated as a colorless liquid in 98% yield (0.392 g) (R_f = 0.13 in i-PrNH$_2$/MeOH/EtOAc 2:10:78 v/v/v); IR (KBr) 3316, 2922, 2360, 1496, 1454, 1261, 1120, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.17–7.04 (comp, 3H), 7.00 (app t, J = 4.2 Hz, 1H), 4.04–3.95 (comp, 1H, 12.5% D), 3.14 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 1.70 (s, 1H); m/z (ESI–MS) 134.3 [M+H]$^+$.

Aminal 2.12b-19: Following general procedure A, **2.12b-19** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and pyrrolidine (3 equiv) in absolute ethanol (2 mL) and ethanol-OD (2 mL) for 24 h. **2.12b-19** was recovered as a white solid in 85% yield (0.283 g) (R_f = 0.33 in hexanes/EtOAc 60:40 v/v); IR (KBr) 3403, 3054, 2937, 2906, 2839, 1592, 1485, 1347, 1291, 1222, 1148, 1119, 979, 881, 861, 747, 725 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.37 (dd, J = 2.1, 0.6 Hz, 1H), 6.98 (d, J = 0.9 Hz, 1H), 4.37 (ddd, J = 5.0, 2.6, 0.8 Hz, 1H), 4.23 (br s, 1H), 4.12–4.03 (comp, 1H, 14% D), 3.81–3.74 (comp, 1H, 18% D), 2.89–2.71 (comp, 2H), 2.27–2.09 (m, 1H), 2.09–1.84 (comp, 2H), 1.73 (dddd, J = 12.6, 9.8, 4.2, 2.6 Hz, 1H); m/z (ESI–MS) 333.0 [M+H]$^+$.

Aminal 2.12i-20: Following general procedure A, **2.12i-20** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline (3 equiv) in absolute ethanol (2 mL) and ethanol-OD (2 mL) for 16 h. **2.12i-20** was recovered as a white solid in 95% yield (0.377 g) (R_f = 0.43 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3411, 2932, 2345, 1735, 1718, 1654, 1648, 1590, 1480, 1458, 1281, 1162, 1120, 736 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43 (d, J = 1.7 Hz, 1H), 7.37–7.27 (comp, 3H), 7.22 (app d, J = 7.4 Hz, 1H), 7.07 (s, 1H), 5.29–5.26 (comp, 1H, 13% D), 4.42–4.35 (comp, 1H, 6% D), 4.34–4.28 (comp, 1H), 3.84–3.76 (comp, 1H, 10% D), 3.13–3.02 (comp, 2H), 2.97–2.86 (m, 1H), 2.74–2.64 (m, 1H); m/z (ESI–MS) 395.0 [M+H]$^+$.

Aminal 2.12b-21: Following general procedure A, **2.12b-21** was obtained from the reaction between 2-amino-3,5-dibromobenzaldehyde and 2,2-dideuteropyrrolidine[47] (3

equiv) in absolute ethanol for 3.5 d. **2.12b-21** was recovered as a white solid in 77%

yield (0.258 g) (R_f = 0.33 in hexanes/EtOAc 60:40 v/v); IR (KBr) 3404, 3055, 2937,

2902, 2839, 2083, 1592, 1483, 1438, 1348, 1266, 1159, 1123, 963, 866, 741 cm^{-1}; ^{1}H NMR

(500 MHz, CDCl$_3$) 7.39 (dd, J = 2.1, 0.6 Hz, 1H), 7.00 (d, J = 0.9 Hz, 1H), 4.48–4.36

(comp, 1H, 22% D), 4.24 (br s, 1H), 4.12 (d, J = 16.3 Hz, 1H), 3.79 (d, J = 16.3 Hz, 1H),

2.83–2.77 (comp, 2H, 78% D), 2.21–2.12 (m, 1H), 2.06–1.87 (comp, 2H), 1.74 (dddd, J =

12.6, 9.8, 4.2, 2.7 Hz, 1H); m/z (ESI–MS) 335.1 [M+H]$^+$.

Aminal 2.12i-22: Following general procedure A, **2.12i-22** was obtained from the

reaction   between   2-amino-3,5-dibromobenzaldehyde   and   1-deutero-1,2,3,4-

tetrahydroisoquinoline[47] (3 equiv) in absolute ethanol for 16 h. **2.12i-22** was recovered

as a white solid in 96% yield (0.381 g) (R_f = 0.43 in hexanes/EtOAc 80:20 v/v); IR (KBr)

3408, 3066, 2954, 2911, 2846, 2154, 1590, 1474, 1281, 1138, 1117, 1012, 997, 862, 769,

729, 683 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.42 (d, J = 2.1 Hz, 1H), 7.35–7.25 (comp,

3H), 7.21 (app d, J = 7.4 Hz, 1H), 7.06 (d, J = 0.8 Hz, 1H), 5.29–5.25 (comp, 1H, 65% D),

4.42–4.34 (comp, 1H), 4.34–4.26 (comp, 1H), 3.79 (d, J = 16.3 Hz, 1H), 3.18–3.02

(comp, 2H), 2.98–2.85 (m, 1H), 2.76–2.64 (m, 1H); m/z (ESI–MS) 395.0 [M+H]$^+$.

Aminal 2.12i-23: Following general procedure A, **2.12i-23** was obtained from the

reaction between 2-amino-3,5-dibromobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline

(1.5 mmol) and 1,1-dideutero-3,4-dihydro-2H-isoquinoline[48] (1.5 mmol) in absolute

ethanol for 16 h. **2.12i-23** was recovered as a white solid in 96% yield (0.378 g) (R_f =

0.43 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3412, 3064, 2932, 2905, 2867, 1590, 1478,

1338, 1280, 1162, 1121, 1030, 1004, 861, 770, 736, 722, 686 cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$) 7.44 (d, J = 2.1 Hz, 1H), 7.37–7.26 (comp, 3H), 7.22 (app d, J = 7.5 Hz, 1H), 7.07

(d, J = 1.0 Hz, 1H), 5.30–5.24 (comp, 1H, 34% D), 4.42–4.35 (comp, 1H), 4.34–4.29

(comp, 1H), 3.80 (d, J = 16.2 Hz, 1H), 3.17–3.03 (comp, 2H), 2.98–2.85 (m, 1H), 2.76–2.65 (m, 1H); m/z (ESI–MS) 395.9 [M+H]$^+$.

Aminal 2.12r: Following general procedure B, **2.12r** was obtained from 2-amino-3,5-dibromobenzaldehyde and N-phenylpiperazine (3 equiv) after 1 h at 250 °C. **2.12r** was isolated as a tan solid in 73% yield (R_f = 0.31 in hexanes/EtOAc 85:15 v/v); mp: 164–168 °C; IR (KBr) 3317, 2952, 2925, 2830, 2785, 1599, 1491, 1458, 1325, 1267, 1250, 1214, 1145, 930, 844, 771, 757, 691, 608 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43 (app dd, J = 2.3, 0.8 Hz, 1H), 7.33–7.28 (comp, 2H), 7.04 (d, J = 1.4 Hz, 1H), 7.00–6.96 (comp, 2H), 6.98 (app tt, J = 7.3, 1.1 Hz, 1H), 4.31 (br s, 1H), 4.19–4.08 (m, 1H), 3.92 (d, J = 15.5 Hz, 1H), 3.74 (d, J = 15.5 Hz, 1H), 3.52 (dd, J = 11.7, 3.0 Hz, 1H), 3.37–3.26 (comp, 2H), 3.21 (dd, J = 11.8, 6.2 Hz, 1H), 3.04 (ddd, J = 11.5, 6.3, 3.6 Hz, 1H), 2.56 (ddd, J = 11.0, 7.0, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.8, 138.6, 132.6, 129.3, 128.8, 121.9, 120.5, 116.7, 109.6, 109.1, 68.0, 54.8, 53.6, 49.2, 49.1; m/z (ESI–MS) 423.9 [M+H]$^+$.

Aminal 2.12s: Following general procedure B, **2.12s** was obtained from 2-amino-3,5-dibromobenzaldehyde and N-methylpiperazine (3 equiv) after 1 h at 250 °C. **2.12s** was isolated as an off-white solid in 59% yield (R_f = 0.18 in EtOAc/MeOH 90:10 v/v); mp: 116–119 °C; IR (KBr) 3389, 2933, 2842, 2897, 2516, 1594, 1475, 1346, 1323, 1285, 1143, 1079, 900, 856, 706 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.40 (d, J = 1.8 Hz, 1H), 7.00 (s, 1H), 4.27 (br s, 1H), 4.12–3.75 (comp, 2H), 3.68 (d, J = 15.1 Hz, 1H), 2.91 (br s, 1H), 2.78 (br s, 1H), 2.67–2.36 (comp, 4H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.7, 132.5, 128.7, 122.1, 109.4, 108.9, 67.9, 59.1, 54.7, 54.7, 50.0, 45.8; m/z (ESI–MS) 362.0 [M+H]$^+$.

Aminal 2.12t: Following general procedure B, **2.12t** was obtained from 2-aminobenzaldehyde and morpholine (3 equiv) after 2 h at 250 °C. **2.12t** was obtained as a light yellow solid in 12% yield (R_f = 0.36 in EtOAc/MeOH 90:10 v/v); mp: 78–81 °C;

IR (KBr) 3357, 2979, 2852, 1608, 1493, 1456, 1362, 1342, 1290, 1274, 1126, 1045, 1030, 930, 857, 743, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.04 (app td, J = 7.8, 1.6 Hz, 1H), 6.93 (app d, J = 7.5 Hz, 1H), 6.72 (app td, J = 7.5, 1.2 Hz, 1H), 6.58 (dd, J = 7.8, 1.1 Hz, 1H), 4.11–3.73 (comp, 6H), 3.70 (d, J = 15.3 Hz, 1H), 3.58 (dd, J = 11.3, 5.5 Hz, 1H), 3.06–2.87 (m, 1H), 2.52–2.32 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.7, 127.4, 127.0, 119.0, 118.6, 115.3, 69.8, 67.2, 67.1, 55.1, 49.2; m/z (ESI–MS) 189.3 [M+H]$^+$.

Additionally, **2.51a** was obtained as a white solid in 38% yield (R$_f$ = 0.19 in hexanes/EtOAc 70:30 v/v); mp: 251–253 ºC; IR (KBr) 3318, 2024, 2955, 2855, 2807, 1612, 1498, 1479, 1450, 1368, 1308, 1216, 1115, 1094, 1072, 1020, 963, 892, 871, 749 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.30–7.21 (comp, 4H), 7.15–7.02 (comp, 3H), 7.02–6.97 (m, 1H), 6.94–6.81 (comp, 3H), 6.71 (app d, J = 8.0 Hz, 1H), 5.82 (s, 1H), 5.31 (d, J = 3.2 Hz, 1H), 4.84 (br s, 1H), 4.54 (s, 1H), 3.87–3.82 (comp, 4H), 3.45–3.31 (m, 2H), 2.84 (app dt, J = 11.6, 4.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 146.3, 144.4, 140.7, 130.7, 129.1, 129.0, 128.8, 128.7, 128.5, 127.9, 125.3, 124.4, 124.2, 123.7, 123.3, 123.3, 120.00, 117.4, 84.8, 70.4, 67.7, 64.5, 50.5; m/z (ESI–MS) 397.0 [M+H]$^+$.

Trimer 2.51b: Following general procedure A, **2.51b** was obtained from the reaction between 2-aminobenzaldehyde (3 mmol) and pyrrolidine (1 mmol) in absolute ethanol (4 mL) at room temperature for 2. **2.51b** was recovered as a light yellow solid in 61% yield (R$_f$ = 0.26 in hexanes/EtOAc 70:30 v/v); mp: 184–187 ºC; IR (KBr) 3375, 3050, 2967, 2800, 1734, 1610, 1572, 1494, 1480, 1447, 1369, 1334, 1305, 1243, 1218, 1128, 1070, 1007, 963, 952, 873, 792, 742 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.31–7.18 (comp, 3H), 7.14 (app d, J = 7.7 Hz, 1H), 7.11–7.00 (comp, 3H), 7.00–6.93 (comp, 2H), 6.92–6.80 (comp, 2H), 6.71 (app d, J = 7.6 Hz, 1H), 5.95 (s, 1H), 5.29 (d, J = 1.8 Hz, 1H), 4.85 (br s, 1H), 4.50 (s, 1H), 3.37–3.22 (m, 2H), 2.95–2.78 (m, 2H), 2.03–1.82 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 145.9, 144.2, 140.8, 130.2, 129.4, 128.9, 128.5, 128.4, 128.3,

127.8, 127.8, 124.6, 124.2, 123.6, 123.5, 123.1 119.9, 117.4, 83.8, 70.8, 63.8, 51.2, 23.8; *m/z* (ESI–MS) 381.0 [M+H]⁺.

Aminal 2.12u: Following general procedure B, **2.12u** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 2,3,4,5-tetrahydro-1H-benzo[c]azepine (**2.52a**)[49] (2 equiv) at 200 °C for 30 min in *n*-butanol (1 mL). **2.12u** was isolated as a tan solid in 91% yield (R$_f$ = 0.40 in hexanes/EtOAc 70:30 v/v); mp: 124–127 °C; IR (KBr) 3372, 2925, 2849, 1590, 1477, 1451, 1364, 1357, 1292, 1259, 1173, 1061, 946, 880, 749, 635 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$) 7.45 (d, *J* = 2.2 Hz, 1H), 7.33–7.06 (comp, 4H), 6.97 (d, *J* = 2.2 Hz, 1H), 5.50 (d, *J* = 2.5 Hz, 1H), 4.78 (br s, 1H), 4.04 (d, *J* = 15.5 Hz, 1H), 3.63 (d, *J* = 15.5 Hz, 1H), 3.34 (ddd, *J* = 13.5, 7.3, 3.1 Hz, 1H), 3.27–3.02 (comp, 2H), 2.88 (ddd, *J* = 14.7, 9.3, 2.2 Hz, 1H), 1.96–1.82 (m, 1H), 1.82–1.68 (m, 1H); ¹³C NMR (125 MHz, CDCl$_3$) δ 141.7, 139.5, 137.8, 132.2, 130.0, 129.1, 128.9, 128.4, 126.1, 123.3, 109.1, 108.9, 74.4, 54.3, 53.1, 35.2, 26.0; *m/z* (ESI–MS) 409.0 [M+H]⁺.

Aminal 2.12v: Following general procedure B, **2.12v** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (**2.52b**)[50] (2 equiv) at 200 °C for 30 min in *n*-butanol (1 mL). **2.12v** was isolated as a tan solid in 88% yield (R$_f$ = 0.14 in hexanes/EtOAc 93:7 v/v); mp: 121–123 °C; IR (KBr) 3409, 2993, 2920, 2838, 1589, 1478, 1391, 1374, 1294, 1131, 1095, 1038, 933, 884, 753, 725, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$) 7.57 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.38–7.25 (comp, 2H), 7.17 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 4.63 (br s, 1H), 4.55 (d, *J* = 17.0 Hz, 1H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.17–3.06 (m, 1H), 2.92 (app td, *J* = 10.9, 3.5 Hz, 1H), 2.85–2.69 (comp, 2H), 1.73 (s, 3H); ¹³C NMR (125 MHz, CDCl$_3$) δ 139.5, 137.6, 134.1, 132.2, 129.2, 128.6, 127.4, 126.7, 124.7, 120.5, 109.1, 107.9, 69.8, 51.2, 46.3, 29.6, 26.4; *m/z* (ESI–MS) 409.0 [M+H]⁺.

Aminal 2.12w: Following general procedure B, **2.12w** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2.52c**)[51] (2 equiv) at 200 °C for 1 h 30 min in *n*-butanol (1 mL). **2.12w** was isolated as a white solid in 93% yield (R_f = 0.29 in hexanes/EtOAc 70:30 v/v); mp: 73–76 °C; IR (KBr) 3412, 2931, 2831, 1609, 1589, 1515, 1472, 1290, 1251, 1233, 1168, 1140, 1021, 793, 754, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.46 (dd, J = 2.3, 0.7 Hz, 1H), 7.44–7.36 (comp, 2H), 7.31–7.21 (comp, 3H), 6.94 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.20 (s, 1H), 4.77 (br s, 1H), 3.91–3.79 (comp, 4H), 3.60 (s, 3H), 3.45 (d, J = 16.9 Hz, 1H), 3.30 (ddd, J = 16.0, 12.4, 6.1 Hz, 1H), 3.01 (app td, J = 11.7, 3.6 Hz, 1H), 2.82 (ddd, J = 11.7, 6.1, 1.6 Hz, 1H), 2.72 (ddd, J = 16.0, 3.7, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 148.4, 147.7, 145.9, 137.6, 132.3, 132.2, 128.8, 128.3, 127.5, 127.4, 126.4, 121.4, 111.0, 110.7, 108.2, 108.1, 75.9, 56.0, 55.8, 51.7, 45.9, 29.3; *m/z* (ESI–MS) 530.9 [M+H]$^+$.

Compound 2.12x: Following general procedure B, **2.12x** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**2.52d**)[52] (2 equiv) at 200 °C for 1 h in *n*-butanol (1 mL). **2.12x** was obtained as a colorless oil in 87% yield (R_f = 0.35 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3398, 3056, 2903, 2841, 1589, 1463, 1298, 1171, 1106, 1028, 1016, 979, 932, 858, 743, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.58 (app d, J = 7.7 Hz, 1H), 7.55–7.46 (comp, 3H), 7.38–7.28 (comp, 4H), 7.27–7.22 (comp, 2H), 7.17 (app dtd, J = 20.1, 7.1, 1.2 Hz, 2H), 6.99 (br s, 1H), 4.93 (br s, 1H), 3.93 (d, J = 16.8 Hz, 1H), 3.56 (d, J = 16.8 Hz, 1H), 3.26–3.05 (comp, 2H), 3.03–2.92 (m, 1H), 2.92–2.79 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.9, 137.1, 136.5, 135.6, 132.5, 129.0, 128.8, 128.7, 128.4, 127.4, 126.7, 122.6, 121.9, 120.0, 119.1, 111.4, 109.3, 108.8, 73.3, 50.7, 46.8, 21.8; *m/z* (ESI–MS) 510.0 [M+H]$^+$.

Aminal 2.12y-a: Following general procedure B, **2.12y-a** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 2-(4-methoxyphenyl)pyrrolidine (3 equiv)[53] at 200 °C for 30 min in *n*-butanol (1 mL). **2.12y-a** was isolated as a colorless oil in 83% yield. Additionally, **2.12z-a** was obtained as a white semi-solid in 14% yield (1:1 mixture of diastereomers). Characterization data for **2.12y-a**: (R_f = 0.23 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2856, 2360, 2342, 1734, 1700, 1507, 1473, 1457, 1247, 1172, 830, 668 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.43 (d, *J* = 1.8 Hz, 1H), 7.40–7.31 (m, 2H), 6.91 (s, 1H), 6.88–6.81 (m, 2H), 4.75 (br s, 1H), 3.78 (s, 3H), 3.68 (d, *J* = 17.0 Hz, 1H), 3.56 (d, *J* = 17.0 Hz, 1H), 3.16 (app td, *J* = 8.7, 3.1 Hz, 1H), 2.77–2.68 (m, 1H), 2.29–2.14 (m, 1H), 2.13–1.95 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.2, 138.5, 136.1, 132.3, 129.3, 127.8, 121.3, 114.1, 108.4, 107.9, 79.3, 55.5, 50.2, 45.7, 43.4, 21.1; *m/z* (ESI–MS) 438.9 [M+H]⁺.

Aminal 2.12y-b: Following general procedure B, **2.12y-b** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 2-phenylpyrrolidine (3 equiv)[53] at 200 °C for 30 min in *n*-butanol (1 mL). **2.12y-b** was isolated as a colorless oil in 64% yield. Additionally, **2.12z-b** was obtained as a white semi-solid in 33% yield (1:1 mixture of diastereomers). Characterization data for **2.12y-b**: (R_f = 0.32 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3410, 2954, 1593, 1475, 1445, 1285, 1178, 1149, 1121, 993, 756, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.54–7.38 (comp, 3H), 7.38–7.29 (comp, 2H), 7.29–7.21 (m, 1H), 6.91 (s, 1H), 4.79 (br s, 1H), 3.68 (d, *J* = 17.0 Hz, 1H), 3.58 (d, *J* = 17.0 Hz, 1H), 3.19 (app td, *J* = 8.7, 3.5 Hz, 1H), 2.84–2.67 (m, 1H), 2.31–2.20 (m, 1H), 2.14–1.96 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.0, 138.2, 132.08, 129.1, 128.5, 127.5, 126.3, 121.0, 108.2, 107.7, 79.3, 50.2, 45.5, 43.4, 21.1; *m/z* (ESI–MS) 409.0 [M+H]⁺.

Aminal 2.12y-c: Following general procedure B, **2.12y-c** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and 2-(4-trifluoromethylphenyl)pyrrolidine (3

equiv)[53] at 200 °C for 30 min in *n*-butanol (1 mL). **2.12y-c** was isolated as a colorless oil in 58% yield. In addition, **2.12z-c** was obtained as a white semi-solid in 37% yield (1:1 mixture of diasteromers). Characterization data for **2.12y-c**: (R_f = 0.34 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3414, 2955, 1593, 1475, 1406, 1325, 1164, 1126, 1071, 1017, 840 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.61–7.57 (comp, 4H), 7.45 (d, *J* = 2.0 Hz, 1H), 6.93 (s, 1H), 4.77 (br s, 1H), 3.73–3.53 (comp, 2H), 3.20 (app td, *J* = 8.7, 3.3 Hz, 1H), 2.86–2.67 (m, 1H), 2.31–2.15 (m, 1H), 2.15–1.95 (comp, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 148.4, 137.8, 132.3, 129.9, 129.7, 129.2, 127.0, 125.6 (q, J_{C-F} = 3.6 Hz), 120.8, 108.4, 108.3, 79.1, 50.2, 45.4, 43.6, 21.2; *m/z* (ESI–MS) 477.0 [M+H]$^+$.

Aminal 2.12aa-a: Following general procedure B, **2.12aa-a** was obtained from 2-amino-3,5-dibromobenzaldehyde and N-methyl-p-methoxybenzylamine (3 equiv)[54] at 250 °C for 30 min. **2.12aa-a** was obtained as a colorless oil in 41% yield (R_f = 0.36 in hexanes/EtOAc/Et$_3$N 69:30:1 v/v/v); IR (KBr) 3409, 2950, 2835, 1611, 1595, 1510, 1484, 1346, 1301, 1247, 1170, 1126, 1035, 957, 805 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.44 (d, *J* = 2.2 Hz, 1H), 7.38–7.33 (comp, 2H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.94–6.88 (comp, 2H), 4.90 (d, *J* = 2.2 Hz, 1H), 4.75 (br s, 1H), 3.81 (s, 3H), 3.77 (d, *J* = 15.9 Hz, 1H), 3.64 (d, *J* = 15.9 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.0, 139.0, 132.8, 132.6, 129.1, 128.8, 122.2, 114.2, 108.5, 108.4, 75.3, 55.6, 53.2, 40.2; *m/z* (ESI–MS) 412.9 [M+H]$^+$.

Aminal 2.12aa-b: Following general procedure B, **2.12aa-b** was obtained from 2-amino-3,5-dibromobenzaldehyde and N-methylbenzylamine (3 equiv) at 250 °C for 30 min. **2.12aa-b** was obtained as a light yellow solid in 29% yield (R_f = 0.38 in hexanes/EtOAc/Et$_3$N 69:30:1 v/v/v); mp: 108–112 °C; IR (KBr) 3058, 2937, 1684, 1594, 1485, 1447, 1339, 1275, 1158, 1103, 1040, 1013, 983, 864, 742, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.48–7.41 (comp, 3H), 7.41–7.31 (comp, 3H), 7.00 (d, *J* = 1.0 Hz, 1H),

5.01 (d, J = 2.3 Hz, 1H), 4.79 (br s, 1H), 3.77 (d, J = 15.9 Hz, 1H), 3.65 (d, J = 15.9 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.5, 138.6, 132.4, 129.0, 128.7, 128.5, 127.2, 121.8, 108.3, 108.2, 75.2, 52.5, 40.3; m/z (ESI−MS) 383.0 [M+H]$^+$.

Aminal 2.12aa-c: Following general procedure B, **2.12aa-c** was obtained from 2-amino-3,5-dibromobenzaldehyde and N-methyl-p-trifluoromethylbenzylamine (3 equiv)[55] at 250 °C for 30 min. **2.12aa-c** was obtained as a colorless oil in 20% yield (R$_f$ = 0.37 in hexanes/EtOAc/Et$_3$N 69:30:1 v/v/v); IR (KBr) 3399, 2945, 1618, 1595, 1486, 1411, 1325, 1273, 1161, 1125, 1125, 1067, 1014, 856, 823, 739 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.63 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 5.09 (d, J = 2.1 Hz, 1H), 4.84 (br s, 1H), 3.71 (d, J = 16.3 Hz, 1H), 3.58 (d, J = 16.3 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.8, 137.9, 132.5, 130.6 (q, J_{C-F} = 31.4 Hz), 129.1, 127.6, 125.6 (q, J_{C-F} = 3.8 Hz), 123.9 (q, J_{C-F} = 272.3 Hz), 121.6, 108.7, 108.5, 74.3, 51.4, 40.6; m/z (ESI−MS) 451.1 [M+H]$^+$.

Aminal 2.12ab: Following general procedure B, **2.12ab** was obtained from 2-aminobenzophenone (0.5 mmol) and pyrrolidine (3 equiv) at 250 °C for 1 h. **2.12ab** was isolated as a yellow semi-solid in 53% yield (1:1.5 mixture of diastereomers) (R$_f$ = 0.36 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3219, 2956, 2871, 2368, 2602, 1473, 1364, 1300, 1248, 1152, 1089, 1029, 1007, 940, 923, 756, 703 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.39−7.27 (comp, 7H), 7.24−7.19 (comp, 3H), 7.08 (app td, J = 8.4, 1.6 Hz, 1H), 7.02 (app td, J = 7.5, 1.5 Hz, 1H), 6.91 (dd, J = 7.5, 1.6 Hz, 1H), 6.73−6.60 (comp, 3H), 6.58−6.53 (comp, 2H), 4.92 (s, 1H), 4.58 (s, 1H), 4.37 (d, J = 4.3 Hz, 1H), 4.11 (br s, 1H), 3.89−3.84 (m, 1H), 3.75 (br s, 1H), 3.05 (app td, J = 8.5, 3.7 Hz, 1H), 2.90 (app td, J = 8.9, 2.2 Hz, 1H), 2.86−2.77 (m, 1H), 2.24−2.12 (comp, 2H), 2.10−1.85 (comp, 4H), 1.85−1.72 (comp, 2H), 1.66−1.58 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.2, 143.6, 143.0, 129.6, 129.4, 128.8,

128.6, 128.3, 128.1, 127.6, 127.5, 127.1, 126.8, 126.6, 119.2, 118.6, 117.1, 116.6, 113.9, 104.7, 73.7, 69.9, 65.0, 61.0, 50.8, 50.0, 32.7, 30.4, 21.3, 20.0; m/z (ESI–MS) 251.1 [M+H]$^+$.

Aminal 2.12ac: Following general procedure B, **2.12ac** was obtained from 2-aminoacetophenone (0.5 mmol) and pyrrolidine (3 equiv) at 250 °C for 1 h. **2.12ac** was isolated as a tan oil in 28% (1:1.4 mixture of diastereomers) (R_f = 0.25 in EtOAc/MeOH 95:5 v/v); IR (KBr) 3330, 2965, 2874, 1633, 1609, 1496, 1445, 1372, 1342, 1266, 1188, 1101, 1035, 938, 753 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.12–7.06 (m, 1H), 7.06–6.93 (comp, 3H), 6.79–6.71 (m, 1H), 6.69–6.61 (m, 1H), 6.58–6.54 (m, 1H), 6.48–6.42 (m, 1H), 4.70 (app t, J = 4.5 Hz, 1H), 4.07–4.02 (m, 1H), 3.96–3.90 (m, 1H), 3.90–3.83 (m, 1H), 3.64 (br s, 1H), 3.13 (app td, J = 9.0, 4.3 Hz, 1H), 2.97 (app td, J = 8.3, 4.3 Hz, 1H), 2.72–2.61 (m, 1H), 2.52–2.42 (m, 1H), 2.20–1.80 (comp, 7H), 1.75–1.63 (comp, 2H), 1.52–147 (comp, 3H), 1.46–1.42 (comp, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.1, 141.6, 128.0, 127.0(6), 127.0(5), 126.1, 125.3, 122.6, 118.5, 117.0, 115.5, 113.8, 72.6, 64.2, 56.2, 52.4, 49.6, 47.9, 32.9, 31.2, 24.9, 21.0, 20.4, 19.1; m/z (ESI–MS) 189.1 [M+H]$^+$.

Aminal 2.12ad: Following general procedure B, **2.12ad** was obtained from 2-aminobenzaldehyde (0.25 mmol) and *trans*-4-hydroxy-L-proline (2.1 equiv) at 150 °C for 15 min in *n*-butanol (1 mL). **2.12ad** was obtained as a white solid in 18% yield (1:1.2 mixture of diasteromers) (R_f = 0.17 in EtOAc/MeOH 90:10 v/v); mp: 126–129 °C; IR (KBr) 3284, 2922, 2806, 2361, 1610, 1491, 1379, 1267, 1152, 1091, 1018, 822, 746 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.07–6.92 (comp, 4H), 6.77 (app t, J = 7.6 Hz, 1H), 6.70 (app t, J = 7.3 Hz, 1H), 6.60 (app d, J = 7.8 Hz, 1H), 6.51 (app d, J = 8.0 Hz, 1H), 4.56 (br s, 1H), 4.52–4.47 (m, 1H), 4.47–4.40 (m, 1H), 4.23–4.15 (comp, 2H), 4.07 (d, J = 15.8 Hz, 1H), 3.88 (d, J = 15.8 Hz, 1H), 3.83 (d, J = 16.0 Hz, 1H), 3.30 (dd, J = 9.7, 5.9 Hz, 1H), 3.17 (dd, J = 10.4, 6.2 Hz, 1H), 2.96 (app d, J = 10.4 Hz, 1H), 2.73 (app d, J = 9.7 Hz, 1H), 2.50–2.39 (comp, 2H), 2.20–2.00 (comp, 3H), 1.76 (app d, J = 13.8 Hz, 1H); ^{13}C NMR

(125 MHz, CDCl$_3$) 142.7, 142.6, 127.4, 127.3, 119.7, 119.3, 118.6, 118.4, 116.0, 114.7, 104.8, 103.0, 70.9, 70.8, 70.4, 69.9, 60.8, 59.6, 50.1, 49.3, 44.1, 43.3; *m/z* (ESI–MS) 191.2 [M+H]$^+$.

Aminal 2.12ae: Following general procedure B, **2.12ae** was obtained from 2-aminobenzaldehyde (0.25 mmol) and *trans*-4-hydroxy-L-proline (2.1 equiv) at 150 °C for 15 min in *n*-butanol (1 mL). **2.12ae** was obtained as a white solid in 11% yield (1:1.1 mixture of diasteromers) (R$_f$ = 0.21 in EtOAc/MeOH 90:10 v/v); mp: 128–130 °C; IR (KBr) 3271, 2924, 2841, 2784, 1609, 1493, 1451, 1378, 1303, 1263, 1151, 1132, 1087, 1037, 992, 843, 752 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.06 (app t, *J* = 7.7 Hz, 1H), 7.04–6.98 (m, 1H), 6.99–6.91 (comp, 2H), 6.75 (app t, *J* = 7.4 Hz, 1H), 6.72–6.66 (comp, 2H), 6.50 (app d, *J* = 8.0 Hz, 1H), 4.35 (app dt, *J* = 7.6, 3.8 Hz, 1H), 4.27 (br s, 1H), 4.21 (d, *J* = 16.2 Hz, 1H), 4.09–4.05 (m, 1H), 3.90 (d, *J* = 15.0 Hz, 1H), 3.87–3.79 (comp, 3H), 3.21 (app td, *J* = 9.3, 4.0 Hz, 1H), 2.99 (app td, *J* = 9.0, 4.6 Hz, 1H), 2.91 (app td, *J* = 9.2, 6.0 Hz, 1H), 2.53–2.41 (comp, 2H), 2.42–2.27 (comp, 2H), 1.93–1.73 (comp, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.5, 142.4, 127.4(2), 127.4(0), 127.3, 127.2, 120.4, 118.8, 118.3, 114.6, 104.8, 104.3, 77.2, 76.9, 73.8, 71.6, 52.0, 49.3, 49.0, 48.5, 33.0, 32.0; *m/z* (ESI–MS) 191.1 [M+H]$^+$.

Aminal 2.12af: Following general procedure B, **2.12af** was obtained from 2-amino-3,5-dibromobenzaldehyde (0.25 mmol) and *trans*-4-hydroxy-L-proline (2.1 equiv) at 150 °C for 30 min in *n*-butanol (1 mL*). **2.12af** was isolated as a tan solid in 50% yield (1:1.2 mixture of diasteromers) (R$_f$ = 0.19 in EtOAc/MeOH 95:5 v/v); mp: 122–125 °C; IR (KBr) 3302, 2940, 2819, 2360, 2342, 1596, 1483, 1375, 1285, 1258, 1152, 1023, 862, 683 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 4.63 (dd, *J* = 5.4, 2.2 Hz, 1H), 4.58–4.52 (m, 1H), 4.52–4.45 (m, 1H), 4.38 (br s, 1H), 4.34–4.29 (m, 1H), 4.22 (d, *J* = 16.6 Hz, 1H), 4.17 (br s, 1H), 4.07 (d,

J = 15.7 Hz, 1H), 3.84–3.72 (comp, 2H), 3.22 (dd, J = 10.2, 6.4 Hz, 1H), 3.07 (dd, J = 10.0, 5.6 Hz, 1H), 2.83–2.73 (comp, 2H), 2.48 (ddd, J = 13.7, 7.6, 5.1 Hz, 1H), 2.23 (ddd, J = 14.0, 7.3, 2.3 Hz, 1H), 2.15 (ddd, J = 14.0, 5.3, 2.8 Hz, 1H), 1.88–1.79 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.1(3), 139.1(0), 132.5, 132.3, 129.1, 129.0, 122.0, 121.0, 109.9, 109.4, 108.6, 108.4, 70.9, 70.7, 70.5, 69.9, 60.0, 59.0, 49.4, 48.4, 44.5, 43.3; m/z (ESI–MS) 349.2 [M+H]$^+$.

Quinazolinone 2.54f: Aminal **2.12af** (0.05 g, 0.144 mmol) was added to a 10 mL round bottom flask with acetone (4 mL) and potassium permanganate (0.068 g, 0.431 mmol). The resulting solution was heated at reflux for 2 h, cooled to room temperature and filtered through celite. The filtrate was washed with acetone (10 mL) and methanol (10 mL) and solvent was removed under reduced pressure. The residue was purified by silica gel chromatography, resulting in the isolation of (*R*)-5,7-dibromo-2-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one as a tan solid in 64% yield (R$_f$ = 0.28 in EtOAc).

(*R*)-5,7-dibromo-2-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (0.0073 g, 0.02 mmol) was added to a 10 mL round bottom flask with methanol (1 mL), 10% Pd/C (2.158 mg, 0.1 equiv) and triethylamine (8.48 µL, 3 equiv). Hydrogen gas was used to replace the atmosphere using a vacuum. The solution was stirred for 2 h and was filtered through a pad of celite. The filtrate was washed with methanol (15 mL) and the solvent was removed under reduced pressure. **2.54f** was obtained as a white solid in 98% yield (R$_f$ = 0.16 in EtOAc/MeOH v/v); mp: 168–171 ºC; $[\alpha]_D^{25}$ −35.0 (c 0.167, CHCl$_3$); IR (KBr) 3395, 2917, 2849, 2357, 1682, 1633, 1607, 1454, 1392, 1277, 773 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.21 (app d, J = 8.0 Hz, 1H), 7.75–7.67 (m, 1H), 7.61 (app d, J = 8.2 Hz, 1H), 7.43 (app t, J = 7.5 Hz, 1H), 4.87–4.77 (m, 1H), 4.32 (app d, J = 13.2 Hz, 1H), 4.21 (dd, J = 13.2, 4.8 Hz, 1H), 3.40 (dd, J = 17.5, 5.7 Hz, 1H), 3.18 (app d, J = 17.5 Hz,

1H), 2.92 (br s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.9, 157.5, 148.8, 134.3, 126.7, 126.5, 126.4, 120.5, 65.8, 55.2, 42.3; *m/z* (ESI–MS) 203.0 [M+H]$^+$.

General Copper-Oxidation Procedure: A round bottom flask was charged with a magnetic stir bar, aminal (1 mmol), MeOH (5 mL, 0.2 M), acetic acid (1.1 equiv) and Cu(OAc)$_2$•H$_2$O (0.2 equiv). A septum was placed over the flask and the contents of an oxygen-filled balloon were flushed through the flask. A second balloon was placed on top of a reflux condenser, which was placed on top of the flask, and the mixture was heated at reflux until the starting material was consumed as determined by TLC. Solvent was then removed *in vacuo* and the residue was loaded onto a column in celite and purified by silica gel chromatography. The product was then subjected to silica gel chromatography a second time to remove residual colored impurities.

General TBHP-Oxidation Procedure: To a round bottom flask charged with a magnetic stir bar, aminal (1 mmol), absolute EtOH (4 mL, 0.25 M), KI (0.2 equiv) was added *tert*-butylhydroperoxide solution in decane (5.4 M, 5 equiv) dropwise. The mixture was stirred under nitrogen at room temperature for 36 hours. After this time, piperidine (5 equiv) was added and the solution was heated at 50 °C for 1 h, followed by cooling to room temperature. The solvent was removed *in vacuo* and the product was purified by silica gel chromatography.

Compound 2.61: Following the general copper-oxidation procedure but without addition of acetic acid, **2.61** was obtained from aminal **2.12c** (0.25 mmol scale) after 4 h. **2.61** was isolated as a tan solid in 24% yield, in addition to **2.53b** (33%) and **2.54b** (6%). Characterization data for **2.61**: (R$_f$ = 0.35 in EtOAc/MeOH 80:20 v/v); ^{1}H NMR (500 MHz, CDCl$_3$) 7.41 (app d, *J* = 7.6 Hz, 1H), 7.29 (app t, *J* = 7.4 Hz, 1H), 7.14 (app t, *J* = 7.4 Hz, 1H), 7.10 (app d, *J* = 7.9 Hz, 1H), 5.89 (s, 1H), 3.99 (app q, *J* = 8.7 Hz, 1H), 3.39 (app td, *J* = 9.7, 3.1, 1H), 2.08 (ddd, *J* = 17.0, 9.4, 3.4 Hz, 1H), 1.83–1.58 (comp, 2H),

0.90 (app dt, J = 16.5, 9.7, Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 162.3, 142.2, 128.7, 128.6, 124.1, 123.2, 122.9, 76.6, 48.3, 30.0, 18.4; m/z (ESI–MS) 203.2 [M–H]$^+$, 171.3 [M–O$_2$H]$^+$.

Compound 2.53c: Following the general copper-oxidation procedure but using absolute ethanol instead of methanol, **2.53c** was obtained from aminal **2.12q** (0.5 mmol scale) after 8 h. **2.53c** was isolated as a tan solid in 57% yield (0.0534 g) (R$_f$ = 0.10 in EtOAc/MeOH/Et$_3$N 89:10:1 v/v/v); mp: 89–92 °C; IR (KBr) 3041, 2945, 2830, 2360, 2343, 1587, 1560, 1496, 1319, 1160, 1095, 1027, 779, 764, 722, 681 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.12 (app t, J = 7.6 Hz, 1H), 7.01 (app d, J = 8.0 Hz, 1H), 6.92 (app td, J = 7.4, 1.3 Hz, 1H), 6.83 (app d, J = 7.4 Hz, 1H), 4.42 (s, 2H), 3.07 (app t, J = 6.1 Hz, 2H), 2.53 (app t, J = 6.5 Hz, 2H), 1.92–1.80 (comp, 2H), 1.80–1.69 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.7, 142.1, 128.2, 124.8, 123.6, 122.8, 120.2, 51.1, 50.1, 31.5, 23.2, 20.4; m/z (ESI–MS) 187.2 [M+H]$^+$.

Compound 2.53e: Following the general copper-oxidation procedure, **2.53e** was obtained from the corresponding aminal[38] (0.5 mmol scale) after 7 h. **2.53e** was isolated as a tan solid in 73% yield (0.0730 g) (R$_f$ = 0.13 in EtOAc/MeOH/Et$_3$N 89:10:1 v/v/v); mp: 80–83 °C; IR (KBr) 2923, 2854, 1586, 1563, 1493, 1455, 1441, 1342, 1274, 1194, 1142, 1085, 981, 765 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.13 (app td, J = 7.7, 1.5 Hz, 1H), 7.02 (dd, J = 7.8, 1.2 Hz, 1H), 6.94 (app td, J = 7.4, 1.3 Hz, 1H), 6.82 (app d, J = 7.4 Hz, 1H), 4.59 (s, 2H), 3.39–3.25 (comp, 2H), 2.65–2.51 (comp, 2H), 1.86–1.60 (comp, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 163.0, 142.7, 128.2, 124.8, 123.9, 123.3, 121.2, 52.6, 51.5, 36.6, 29.8, 26.9, 25.3; m/z (ESI–MS) 201.3 [M+H]$^+$.

Compound 2.53f: Following the general copper-oxidation procedure, **2.53f** was obtained from aminal **2.12ab** after 24 h. **2.53f** was isolated as a tan solid in 72% yield (0.1788 g) (R$_f$ = 0.17 in EtOAc/MeOH/Et$_3$N 89:10:1 v/v/v); mp: 153–157 °C; IR (KBr)

3061, 3023, 2919, 2859, 1620, 1590, 1567, 1479, 1454, 1432, 1299, 1285, 1196, 1031, 939, 878, 764, 737, 699, 602 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43–7.25 (comp, 5H), 7.23–7.10 (comp, 2H), 6.91 (ddd, J = 8.2, 6.0, 2.6 Hz, 1H), 6.73 (app d, J = 7.6 Hz, 1H), 5.65 (s, 1H), 3.25–3.17 (m, 1H), 3.17–3.09 (m, 1H), 2.84–2.69 (comp, 2H), 2.10–1.88 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 161.4, 142.7, 142.3, 128.8, 128.3, 128.0, 127.5, 127.1, 124.1, 123.8, 123.2, 61.6, 49.2, 31.8, 18.9; m/z (ESI–MS) 249.2 [M+H]$^+$.

Compound 2.53h: Following the general copper-oxidation procedure, using absolute ethanol instead of methanol, **2.53h** was obtained from aminal **2.12b** after 72 h. **2.53h** was isolated as a tan solid in 18% yield (0.0578 g) (R$_f$ = 0.25 in EtOAc/MeOH 90:10 v/v); mp: 164–167 ºC; IR (KBr) 2960, 2865, 1612, 1572, 1498, 1440, 1426, 1395, 1289, 1191, 1160, 855, 750, 734 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.53 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 4.51 (s, 2H), 3.33 (app t, J = 6.9 Hz, 2H), 2.72 (app t, J = 7.9 Hz, 2H), 2.04 (app p, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.5, 141.1, 134.4, 127.9, 122.5, 119.9, 115.4, 51.4, 46.6, 31.7, 18.8; m/z (ESI–MS) 331.1 [M+H]$^+$.

Compound 2.54i: Following the general TBHP-oxidation procedure, **2.54i** was obtained from aminal **2.12g**. **2.54i** was isolated as a tan solid in 50% yield (0.1775 g) (R$_f$ = 0.21 in hexanes/EtOAc 80:20 v/v); mp: 171–173 ºC; IR (KBr) 3071, 2961, 1662, 1582, 1447, 1404, 1324, 1168, 1109, 993, 952, 878, 791, 754, 677 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.25 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 4.02 (app t, J = 6.1 Hz, 2H), 3.01 (app t, J = 6.6 Hz, 2H), 2.08–1.84 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.3, 156.3, 144.0, 139.9, 128.6, 122.4, 122.3, 118.7, 42.7, 32.1, 21.8, 19.0; m/z (ESI–MS) 359.1 [M+H]$^+$.

Compound 2.65: Following the general TBHP-oxidation procedure, **2.65** was obtained from aminal **2.64**. **2.65** was isolated as a tan oil in 48% yield (0.1626 g) (R$_f$ = 0.29 in EtOAc/MeOH 98:2 v/v); IR (KBr) 3307, 3060, 3027, 2892, 2850, 2359, 2341,

1652, 1602, 1577, 1492, 1473, 1453, 1415, 1328, 1228, 1172, 1123, 1032, 742, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.14 (app d, J = 7.7 Hz, 1H), 7.58 (dd, J = 5.7, 3.5 Hz, 1H), 7.49 (app td, J = 7.4, 1.4 Hz, 1H), 7.45–7.31 (comp, 3H), 7.31–7.19 (comp, 4H), 7.19–7.09 (comp, 3H), 3.94 (ddd, J = 12.2, 10.7, 4.7 Hz, 1H), 3.89–3.60 (comp, 5H), 3.10–2.88 (comp, 2H), 2.05 (br s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.5, 141.9, 140.0, 138.5, 137.2, 131.9, 130.4, 129.4, 128.5, 128.4, 128.2, 128.1, 127.9, 127.0, 126.9, 126.8, 126.7, 53.6, 49.8, 49.1, 28.4; m/z (ESI–MS) 343.5 [M+H]$^+$.

Computational Methods: Geometry optimizations were performed with the meta-hybrid density functional M06-2X[57] and a 6-31+G(d,p) basis set. Solvation by ethanol was taken into account by the SMD solvent model,[58] which was applied to both optimizations as well as frequency calculations. It was recently shown that the presence of a polarizable continuum model does not have a great impact on frequencies, while it might be mandatory to locate certain transition states that only exist in polar media.[59] Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L^{-1} (17.12 mol L^{-1} for ethanol) and 298.15 K, as the experimental conditions of refluxing ethanol and high pressure in sealed tubes cannot be reproduced. The resulting free energies refer to Gibbs free energies. Free energies as well as enthalpies are corrected for zero-point vibrational energy. All stationary points were characterized and confirmed by vibrational analysis. An ultrafine grid corresponding to 99 radial shells and 590 angular points was used throughout this study for numerical integration of the density. Natural population analyses[60] used the NBO program (version 3.1) as implemented in *Gaussian 09*. All calculations were performed with *Gaussian 09*.[61]

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Chapter 3

Redox-Neutral α-Oxygenation and Sulfenylation

3.1 Background

As drug discovery programs have come to rely on high-throughput screenings of diverse chemical libraries, the ability to rapidly construct complex, heterocyclic small molecules from simple starting materials is of great importance.[1] The *N,O*-acetal moiety can be found in a diverse set of natural products[2] and useful synthetic intermediates.[3] Benzoxazines in particular have been studied as non-steroidal progesterone receptor agonists,[4] as antibacterial agents[5] and as non-nucleoside reverse transcriptase inhibitors for the treatment of HIV[6] as well as for a wide array of other applications.[7] For example, benzo[*e*][1,3]oxazines such as PD 102 807 (**3.2a**) have been identified as potent, selective inhibitors of the m4 muscarinic receptor, which have made such compounds important leads in Parkinson's disease reaserch.[8]

Figure 3.1 **N,O-Acetal Synthesis Precedent and Related Aminal Synthesis**
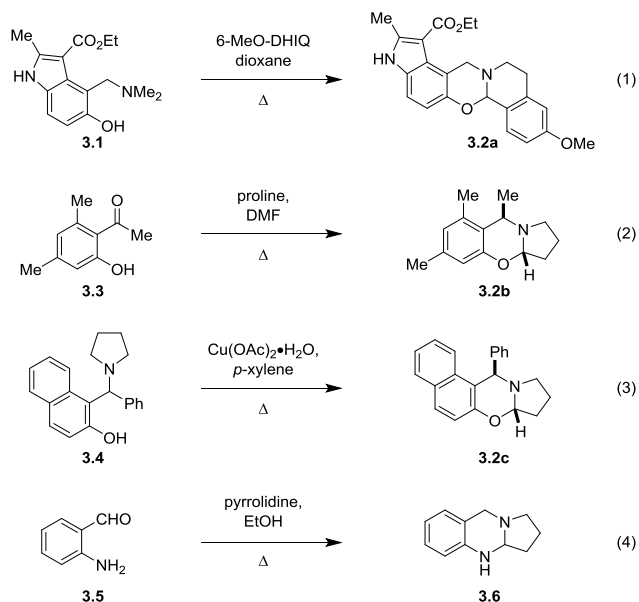
A number of methods for the synthesis of benzo[*e*][1,3]oxazines have been reported.[3i,3l,3o,3q,3v,9] One early approach to polycyclic benzoxazines such as *N,O*-acetal **3.2a** involves the addition of a substituted 3,4-dihydroisoquinoline (DHIQ) to a phenolic Mannich base (e.g., **3.1**), proceeding via an *o*-quinone methide intermediate and generally resulting in low to moderate yields (eq. 1).[8,9g,9o-q,10] An intriguing and unanticipated entry to the *N,O*-acetal motif was reported by Cohen et al. in 1979 (eq. 2).[9h] Proline was found to react with 2-hydroxy-acetophenones (e.g., **3.3**) via a decarboxylative process to yield products such as **3.2b**. Unfortunately, this method exhibited a rather narrow substrate scope. The presence of a methyl group in the *ortho*-position of the ketone was reported to be crucial; replacement with a hydrogen substituent led to the recovery of **3.3** and pyrrolidine (from the decarboxylation of proline). The use of pipecolic acid (piperidine-2-carboxylic acid) in place of proline resulted in the formation of only trace amounts of the corresponding product. Recently, Maycock et al. reported an oxidative, copper(II) acetate catalyzed synthesis of benzoxazines such as **3.2c** from *ortho*-aminomethylnaphthols (e.g., **3.4**) and -phenols (eq. 3).[9r] This report was closely followed by an independent publication by Jana and coworkers in which the same transformation was described using superstoichiometric amounts of Ag_2O as the oxidant.[9t] All previous methods for benzo[*e*][1,3]oxazine synthesis involve either a prefunctionalized amine moiety (an amino acid or imine), an external oxidant and/or a metal catalyst.[11] As discussed in the previous chapter, our group has developed the synthesis of aminals such as **3.6** from *o*-aminobenzaldehydes (e.g., **3.5**) and unactivated secondary amines such as pyrrolidine (eq. 4).[12] These reactions feature a combined reductive *N*-alkylation/oxidative α-amination and function most efficiently in alcoholic solvents in the absence of any additives.[13] The overall redox-neutral nature of this reaction distinguishes it from oxidative approaches to the C−H functionalization of amines which continue to dominate most of the research efforts

conducted in this area.[14] The Seidel group has worked extensively on developing redox-neutral methods for the α-functionalization of amines,[15] many of which involve iminium isomerization through azomethine ylide intermediates.[16,17] The mechanistic study of the amination reaction (eq. 4) revealed some interesting mechanistic features.[12c] Simple iminium ions do not appear to play a role in this reaction and the rate-determining step most likely involves a 1,6-proton transfer event. Based on the ability of *o*-aminobenzaldehydes to undergo these condensations with amines, we decided to explore the analogous reaction with salicylaldehydes in an effort to gain access to the *N,O*-acetal functionality in a facile, redox-neutral fashion.

3.2 Development of Amine α-Oxygenation

To facilitate reaction development, we began our investigation using microwave conditions, which had proven successful in the analogous aminal formation.[12d] Surprisingly, a reaction of pyrrolidine with salicylaldehyde (**3.7**) in *n*-butanol solvent (optimized conditions for aminal formation) did not lead to desired *N,O*-acetal product **3.2d**. Instead, the substituted 2-hydroxy-benzylamine **3.8d**, the apparent product of a reductive amination, was isolated in 92% yield (eq. 5). Similar observations were made in the corresponding reactions of morpholine (eq. 6) and 1,2,3,4-tetrahydroisoquinoline (THIQ) (eq. 7). In the case of THIQ, 3,4-dihydroisoquinoline (DHIQ) was isolated as a second product in 65% yield. This indicates that THIQ functions as the reductant in the formation of **3.8f**. In order to avoid the formation of undesired product **3.8f**, milder conditions were employed and the amount of THIQ was reduced. Heating a 1 : 1.1 mixture of **3.9** and THIQ under reflux in ethanol did, indeed, lead to isolation of *N,O*-acetal **3.2f**, albeit in only 10% yield alongside a substantial amount of **3.8f** and DHIQ (eq. 8). When an otherwise identical reaction was performed under reflux in *n*-butanol

(eq. 9), a trace amount of *N,O*-acetal was observed alongside **3.8f** (37%) and DHIQ (33%). In addition, *n*-butylether **3.9** was isolated in 19% yield.

Figure 3.2 **Reductive Amination of Secondary Amines with Salicylaldehyde**
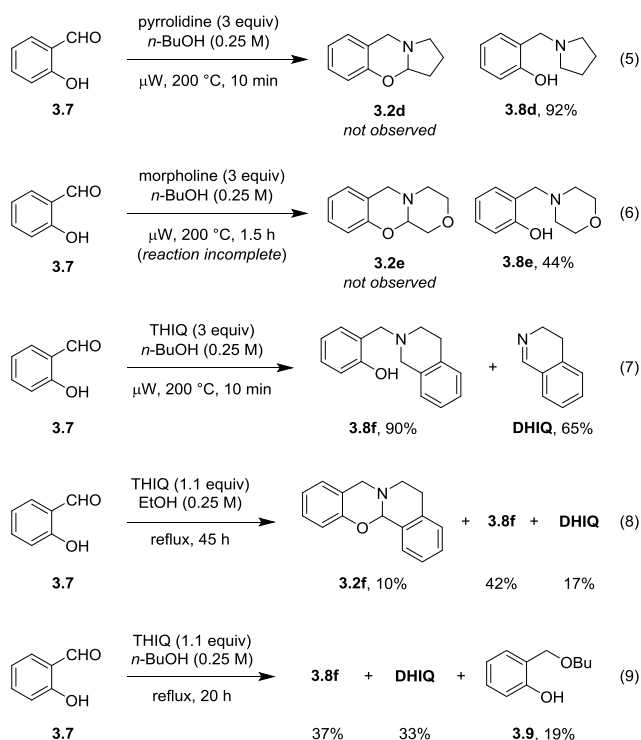
There are a number of different mechanistic scenarios that could account for the formation of the reduced product **3.8f** (Figure 3.3). Firstly, **3.8f** could be formed from the desired product **3.2f**. Fragmentation of **3.2f**, either via a retro [4+2] reaction or a stepwise pathway via zwitterion **3.10f**, would result in the formation of *o*-quinone methide **3.11f** and DHIQ. Reaction of the highly reactive **3.11f** with THIQ would be expected to readily form **3.8f**.[18] Alternatively, the formation of **3.8f** and DHIQ could be explained by reduction of **3.10f** (or the regioisomeric zwitterion from the condensation of **3.7** and THIQ) via intermolecular hydride transfer from THIQ with concurrent oxidation of the latter to DHIQ (not shown). The formation of **3.9** (eq. 9) is consistent with the intermediacy of **3.11f** but not with the hydride transfer pathway. To obtain

further insights into the course of the reaction, benzoxazine **3.2f** was subjected to high temperatures in the presence of an excess of pyrrolidine (Figure 3.3). From this reaction *o*-hydroxybenzyl pyrrolidine **3.8d** and DHIQ were isolated in good yields, providing additional support for the fragmentation pathway.

Figure 3.3 **Potential Reaction Pathways and Experimental Support**
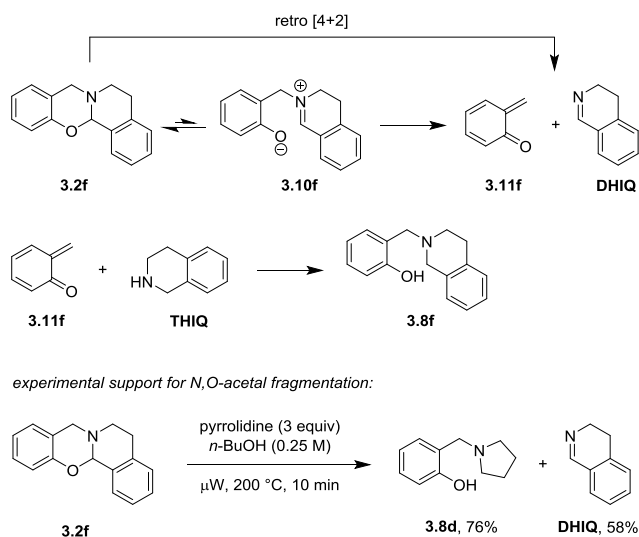
Due to the formation of undesired side-products at higher temperatures and with nucleophilic solvents, we decided to evaluate the reaction under milder conditions (Table 3.1). Toluene, a solvent that had previously been shown to be optimal for other redox-isomerization reactions,[15h-j,l-,o] was selected as the reaction medium. To further facilitate product formation, molecular sieves were added to sequester the water released during the condensation. The desired reaction was found to proceed at room temperature in the absence of any acid additives to provide *N,O*-acetal **3.2f** in 35% isolated yield (entry 1). In addition, the apparent (3+2) product **3.12** was formed in 36% yield, suggesting the intermediacy of an azomethine ylide.[12c,19] Addition of catalytic amounts of benzoic acid dramatically accelerated the rate of the reaction while increasing the yield of both **3.2f** and **3.12** (entry 2). Reduction of the amount of salicylaldehyde (**3.7**) led to a more

favorable product ratio with partial suppression of the (3+2) product **3.12** (entry 3). 2-Ethylhexanoic acid (2-EHA) and acetic acid performed slightly better than benzoic acid and with a reduction in solvent concentration, product **3.12** was no longer observed. Several protic and aprotic solvents were evaluated as potential alternatives to toluene but none resulted in better yields (entries 5–8). Elevating the temperature to 60 °C and using acetic acid in stoichiometric amounts led to the best result and allowed for the isolation of **3.2f** in 98% yield following a reaction time of three hours (entry 16).

Table 3.1: **Optimization of *N,O*-acetal forming reaction between salicylaldehyde and THIQ.**

entry	mmol 7	mmol THIQ	additive (equiv)	solvent (M)	T [°C]	t [h]	yield **2f** [%]	yield **12** [%]
1	2	1	-	PhMe (0.25)	rt	48[a]	35	36
2	2	1	PhCO$_2$H (0.2)	PhMe (0.25)	rt	18	38	48
3	1.1	1	PhCO$_2$H (0.2)	PhMe (0.25)	rt	24	54	25
4	1.1	1	2-EHA (0.2)	PhMe (0.25)	rt	24	62	21
5	1	1.1	2-EHA (0.2)	PhMe (0.25)	rt	48[a]	38	trace
6	1	1.1	2-EHA (0.2)	DMF (0.25)	rt	48[a]	23	trace
7	1	1.1	2-EHA (0.2)	EtOH (0.25)	rt	48[a]	22	31
8	1	1.1	2-EHA (0.2)	MeCN (0.25)	rt	48[a]	62	32
9	1	1.1	2-EHA (1.3)	PhMe (0.25)	rt	48[a]	75	trace
10	1	1.3	2-EHA (1.3)	PhMe (0.25)	rt	48	94	trace
11	1	1.3	2-EHA (1.3)	PhMe (0.25)	60	1.5	95	trace
12	1	1.3	2-EHA (1.3)	PhMe (0.1)	60	3	97	-
13[b]	1	1.3	2-EHA (1.3)	PhMe (0.1)	60	6[a]	64	-
14	1	1.3	AcOH (1.3)	PhMe (0.1)	60	3	98	-
15	1	1.3	AcOH (0.2)	PhMe (0.1)	60	3	59	-
16	1	1.3	AcOH (1.0)	PhMe (0.1)	60	3	98	-

2-EHA = 2-ethylhexanoic acid; [a] Reaction incomplete; [b] No molecular sieves

3.3 Scope of Amine α-Oxygenation

The optimized conditions were employed to evaluate the scope of the α-oxygenation with a number of different salicylaldehydes and related *o*-hydroxy ketones (Figure 3.4).

Figure 3.4 **Variation of the Salicylaldehyde Moiety[a]**

3.2g, 99%
80 °C, 2 h

3.2h, 91%
80 °C, 5 h

3.2i, 90%
60 °C, 3 h

3.2j, 93%
60 °C, 45 min

3.2k, 90%
60 °C, 45 min

3.2l, 84%
60 °C, 30 min

3.2m, 70%
60 °C, 30 min

3.2n, 85%
80 °C, 10 min

3.2o, 96%
80 °C, 15 min

3.2p, 80%
60 °C, 3 h

3.2q, 29%[b]
reflux, 3 h

3.2r, 53%
reflux, 24 h
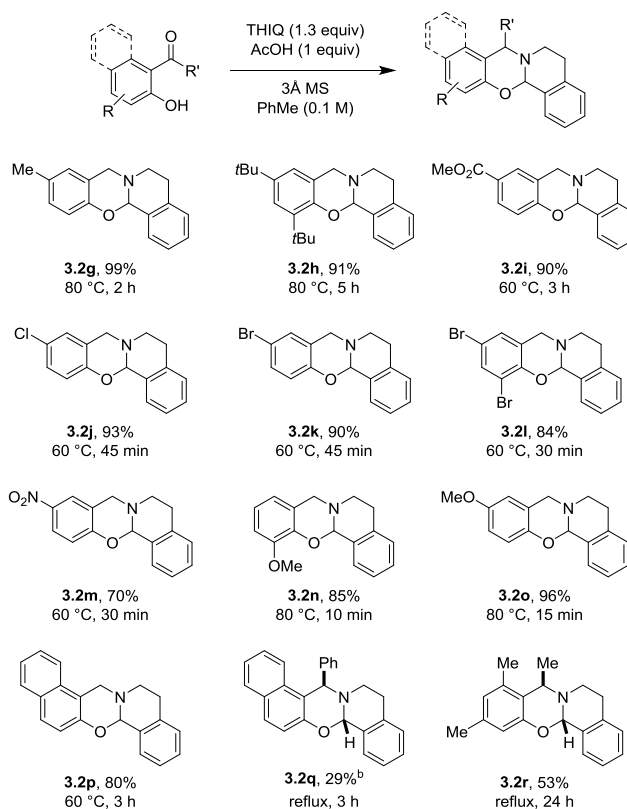
[a] All reactions were performed on a 1 mmol scale.
[b] 1 mmol amine, 2 equiv ketone, xylenes (0.1 M).

Salicylaldehydes with simple alkyl groups appended to the ring provided the corresponding products in good yields, but required a higher temperature of 80 °C to achieve reasonable reaction rates (**3.2g** and **3.2h**). Both electron withdrawing and electron-donating groups were tolerated, although more electron-deficient salicylaldehydes such as 3,5-dibromo- (**3.2l**) and 5-nitrosalicylaldehyde (**3.2m**)

provided products with slightly decreased yields. *o*-Hydroxyketones required higher temperatures and afford *N,O*-acetal products in relatively low yields but as single diastereomers (**3.2q** and **3.2r**).

While ketones with some steric demand in the 6-position did yield the desired products, neither 2-hydroxyacetophenone nor 2-hydroxybenzophenone underwent the formation of *N,O*-acetals with THIQ under a variety of conditions, an observation that is in line with Cohen's findings on the related decarboxylative process.[9h]

Figure 3.5 **Variation of the Secondary Amine[a]**

3.2s, 98%
60 °C, 5 h

3.2t, 99%
60 °C, 5 h

3.2u, 72%
80 °C, 18 h

3.2v, 50%
reflux, 1 h

3.2w, 69%
80 °C, 24 h

3.2x, 55%
reflux, 24 h

3.2c, 71%[b]
reflux, 30 min

3.2y, 40%[b]
reflux, 1.5 h

3.2z, 54%[b]
reflux, 2 h

3.2b, 15%
reflux, 24 h

3.2aa, 29%, dr = 2.5:1[b]
reflux, 1 h

3.2ab, 18%[b]
reflux, 45 min
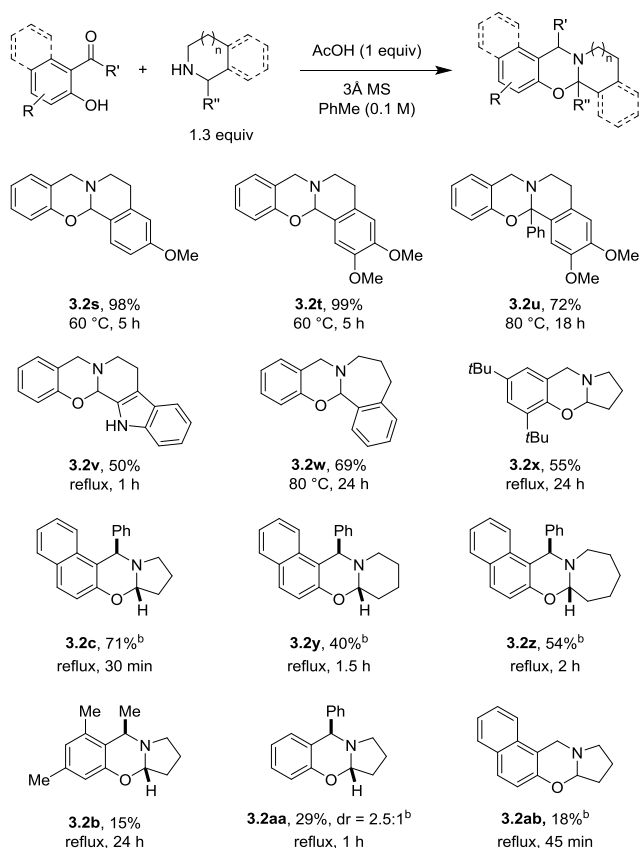
[a] All reactions were performed on a 1 mmol scale.
[b] 1 mmol amine, 2 equiv aldehyde or ketone, xylenes (0.1 M).

The scope of the reaction with regard to other amines was evaluated next (Figure 3.5). Not surprisingly, cyclic secondary amines with benzylic protons in α-position to

nitrogen proved to be the most reactive substrates. Tetrahydroisoquinolines with methoxy-groups appended to the aryl ring, upon reaction with **3.7**, resulted in the formation of products in excellent yields (**3.2s** and **3.2t**). A THIQ derivative with a phenyl-group at the 1-position required more forcing conditions in order to form the corresponding *N,O*-acetal **3.2u**. Nevertheless, this highly substituted product was obtained in 72% yield. *N,O*-Acetal products could also be obtained with pyrrolidine, piperidine, and azepane. However, acyclic amines such as methylbenzyl amine failed to undergo the title reaction. Interestingly, attempted reactions with pyrrolidine and parent salicylaldehyde (**3.7**) did not yield *N,O*-acetal **3.2d** under a variety of conditions. Despite different experimental and computational attempts, this result could so far not be rationalized. Pyrrolidine underwent reaction with 3,5-di-*t*-butylsalicylaldehyde to form the corresponding *N,O*-acetal **3.2x** in 55% yield. Formation of product **3.2c** from pyrrolidine and 2-hydroxy-1-benzoylnaphthalene proceeded in 71% yield but required more forcing conditions (reflux in xylenes). Maycock and coworkers[9r] did not observe benzoxazine **3.2c** as a product with the same starting materials in an experiment conducted at 130°C in xylenes. This failure to obtain product **3.2c** is likely due to the fact that neither acidic additives nor molecular sieves were employed. While products **3.2c**, **3.2y**, **3.2z**, and **3.2b** were all isolated as single diastereomers, product **3.2aa**, which is different in that it lacks a substituent in the 6-position of the aryl ring, was formed as a 2.5:1 mixture of diastereomers.

Interestingly, when 1-methyl THIQ was subjected to the reaction conditions, the desired *N,O*-acetal **3.2ac** was not obtained. Instead, the spirobenzopyran **3.13** was obtained in essentially quantitative yield (Figure 3.6). In this case, *N,O*-acetal **3.2ac** or the corresponding zwitterion (not shown) could exist in equilibrium with enamine **3.14**. The latter can engage a second molecule of salicylaldehyde to give **3.13**. Reactions of structurally related enamines with salicylaldehydes have been previously reported.[20]

Figure 3.6 **Reaction of Salicylaldehyde with 1-Methyl Tetrahydroisoquinoline**
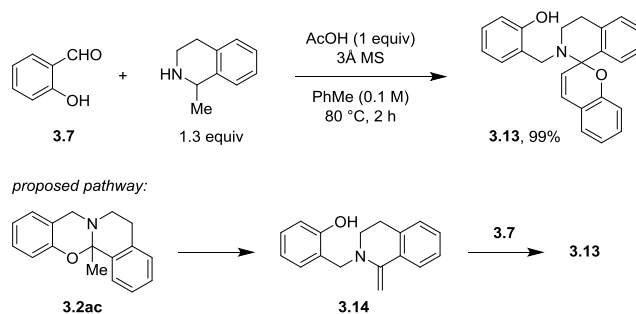
To demonstrate that the redox-neutral synthesis of *N,O*-acetals is amenable to scale-up, the reaction of salicylaldehyde (**3.7**) and THIQ was performed on a 1-g scale in benzene as the solvent (Figure 3.7). In the absence of molecular sieves, heating of the reaction mixture under reflux for a period of 24 h resulted in an incomplete reaction and furnished the expected *N,O*-acetal **3.2f** in only 52% yield. An otherwise identical reaction performed in the presence of a Dean–Stark apparatus (for water removal) was completed after only 1 h and provided **3.2f** in nearly quantitative yield (98%, Figure 3.7). These experiments illustrate not only the ease with which this reaction can be performed under optimized conditions but also the importance of removing water from the reaction mixture.

Figure 3.7 **The Effect of Water on the Condensation Reaction**
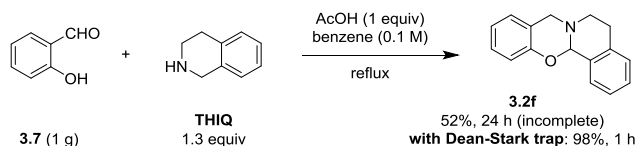
3.4 Mechanistic Conciderations for *N,O*-Acetal Formation

A network of interrelated pathways presented itself when we considered possible mechanisms that would account for the formation of all observed products from the reaction of salicylaldehyde (**3.7**) and THIQ (Figure 3.8). Based on the isolation of

apparent (3+2) product **3.12**, it appears highly likely that the overall transformation involves the intermediacy of azomethine ylide **3.19f**. The reaction most likely begins with the addition of THIQ to salicylaldehyde (**3.7**) to form *N,O*-acetal **3.15f**, a step that may be facilitated by the presence of acetic acid. Subsequent elimination of water could occur either with the assistance of acetic acid, yielding iminium **3.16f**, or in a concerted intramolecular fashion to give zwitterion/quinoidal species **3.17f**. Due to the presence of acetic acid, **3.16f** and **3.17f** may exist in equilibrium. Azomethine ylide **3.19f** could be formed from **3.17f** via a 1,6-proton transfer; an analogous step was established in the formation of the corresponding aminals.[12c]

Figure 3.8 **Potential Mechanistic Pathways for the Formation of 3.2f**
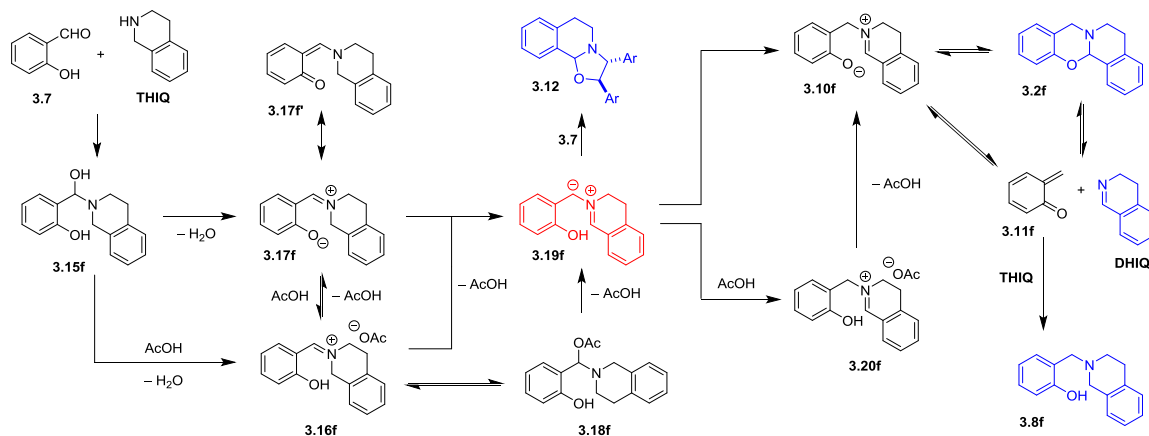
Another pathway to **3.19f** would involve deprotonation of **3.16f**. Alternatively, **3.18f**, which could exist in equilibrium with **3.16f**, could suffer concerted loss of acetic acid to generate azomethine ylide **3.19f**, consistent with a proposal by Yu and coworkers[21] for a related process. Azomethine ylide **3.19f** would then progress to zwitterion **3.10f** either by a stepwise protonation/deprotonation pathway via **3.20f** or by direct proton transfer. Ring closure finally leads to *N,O*-acetal product **3.2f**. *N,O*-Acetal **3.2f** can undergo further transformation to "reduced" product **3.8f** via the addition of THIQ to *o*-quinone methide **3.11f**, formed in a formal retro-[4+2] reaction

that also generates DHIQ. It should be noted that the retro-[4+2] step may occur in a stepwise manner via zwitterion **3.10f**. Facile ring-opening of benzoxazines and the potential existence of an equilibrium between **3.2f** and **3.10f** is supported by an observation about the appearance of benzoxazine **3.2f**. While **3.2f** is a white solid in pure form, solutions of **3.2f** turn bright yellow in the presence of an acid (e.g., acetic acid or silica gel), suggesting the formation of a new species.

Figure 3.9 **Temperature-Dependent ^{1}H NMR Spectra of 3.2l in CDCl$_3$ (400 MHz)**
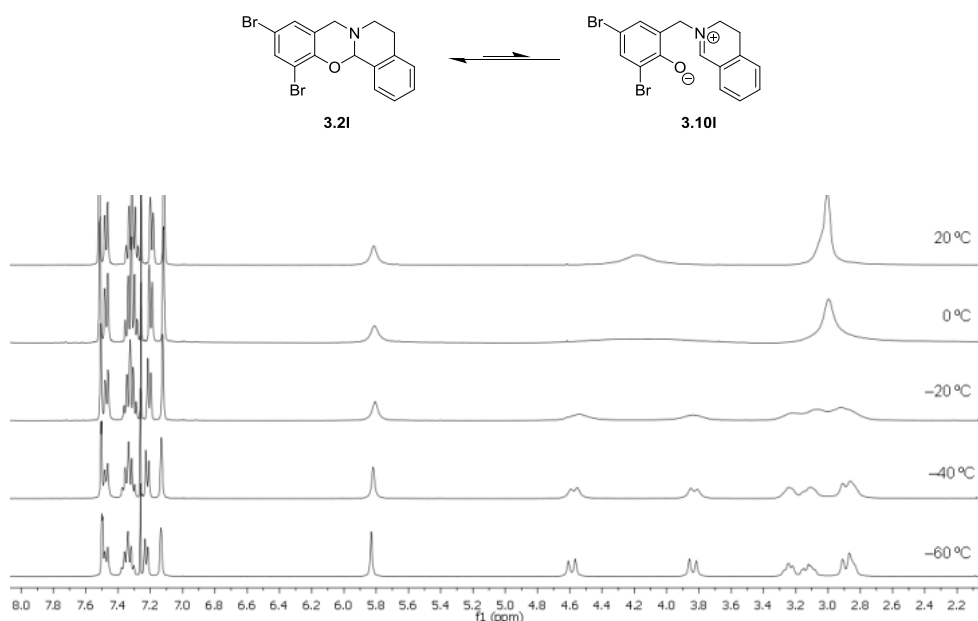
Another observation consistent with the existence of zwitterions in equilibrium with benzoxazines is that benzoxazine products with an electron-deficient phenolic ring (i.e., **3.2i**, **3.2l**, and **3.2m**) exhibit broadened peaks in their ^{1}H NMR spectra (see Supporting Information). Presumably, the electron-withdrawing groups stabilize the phenoxide, allowing the *N,O*-acetal to rapidly equilibrate with zwitterionic form **3.10**. This process is suppressed or slowed down at lower temperatures, as illustrated by a

series of ^{1}H NMR spectra of product **3.2l** that were recorded at temperatures between 20 and −60 °C (Figure 1).

With regard to the above-mentioned oxidative *N,O*-acetal syntheses reported by Maycock and coworkers[9r] (eq 3) and Jana and coworkers,[9t] different mechanisms were proposed by the two groups. Jana and coworkers proposed an initial oxidation of **3.4** at the benzylic position and deprotonation of the resulting iminium ion, followed by a pathway that is based on our previously established mechanism for the corresponding aminal formation, namely, 1,6-proton abstraction to generate an azomethine ylide and subsequent proton transfer and ring closure (not shown). Interestingly, Maycock's mechanistic proposal is radically different (Scheme 9). It involves oxidation of amine **3.4** at the seemingly less activated endocyclic position rather than the benzylic position to give intermediate **3.10c**.

Figure 3.10 **Maycock and Coworkers' Proposed Mechanism for the Oxidative N,O-Acetal Formation**
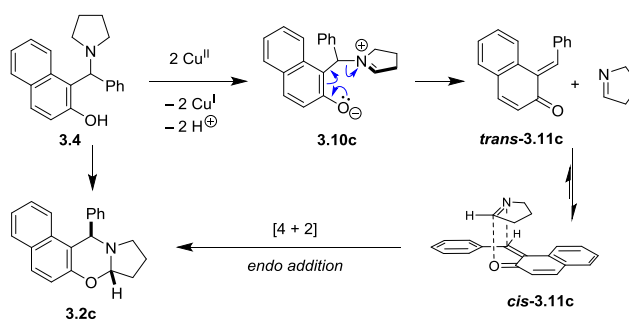
While **3.10c** may undergo direct ring closure to product **3.2c**, the observed diastereoselectivity was rationalized via a different pathway. According to Maycock and coworkers, intermediate **3.10c** undergoes fragmentation to *o*-quinone methides ***trans-3.11c*** and ***cis-3.11c*** and 1-pyrroline. The isomer ***cis-3.11c*** is proposed to engage in an endo-[4+2] cycloaddition with 1-pyrroline to selectively form **3.2c** in the observed

relative configuration. An alternative and perhaps more likely explanation that accounts for the essentially exclusive formation of **3.2c** over its other diastereomer is based on equilibration between the two possible diastereomers via zwitterion **3.10c**. In fact, the equilibration of diastereomers of closely related benzoxazines was studied in detail by Fülöp, Kleinpeter, and coworkers,[9q] who concluded that the diastereomer corresponding to **3.2c** is the thermodynamically more stable product.

3.5 Calculations on the Mechanism of the α-Oxygenation

In order to investigate the underlying mechanism and to identify the most important pathways for the formation of benzoxazines under these conditions, we have employed density functional theory calculations [M06-2X-D3/def2-TZVPP/IEFPCM//TPSS-D2/6-31+G(d,p)/IEFPCM]. The mechanisms for the uncatalyzed and acetic-acid-catalyzed reaction using the model system salicylaldehyde (**3.7**) and THIQ will first be discussed before the influence of substituents at the carbonyl and variation of the amine as well as potential side reactions are analyzed.

Although the uncatalyzed reaction between the aldehyde and the amine results in low yields of the corresponding benzoxazines (Table 3.1), this background reaction is important for the acid-catalyzed reaction as well. Therefore, we first carefully analyzed the mechanism for the prototypic reaction between salicylaldehyde (**3.7**) and tetrahydroisoquinoline (THIQ) in toluene solution in the absence of any catalyst (cf. Figure 3.8). The calculated free energy profile is depicted in Figure 3.11 and selected calculated structures are discussed in Figures 3.12–3.14.

Figure 3.11 **Free Energy Profile (in kcal mol⁻¹) for the Transformation of 3.7 and THIQ to 3.2f in Toluene**
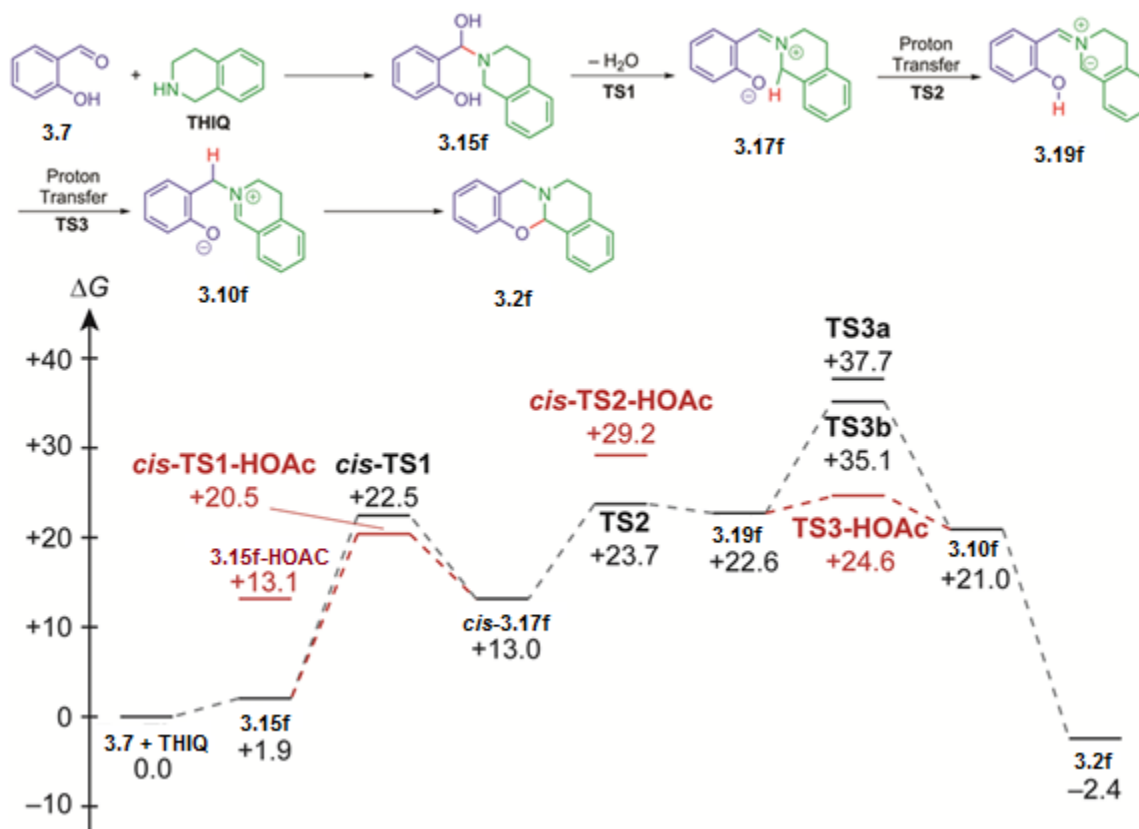
In the first step of this transformation, the aldehyde **3.7** and THIQ form the hemiaminal **3.15f** in a slightly endergonic reaction (ΔG = +1.9 kcal·mol−1). Next, water is eliminated from the hemiaminal, yielding the zwitterionic intermediate **3.17f**. This reaction could occur either in a concerted mechanism ($\Delta G^{\ddagger}$ = +22.5 kcal·mol−1, via ***cis-TS1***, Figure 3.12) or in a stepwise reaction through an iminium ion. In line with previous investigations of the synthesis of tetrahydroquinazolines,[12c] the putative iminium ion obtained from the elimination of a hydroxy group was located 38 kcal·mol−1 above ***cis-TS1*** and is not shown in Figure 3.11. As a consequence, the concerted elimination is also preferred over the stepwise elimination of hydroxide and subsequent deprotonation in these transformations. In principle, both eliminations to the *cis* and the *trans*

zwitterions **3.17f** are possible (Figure 3.12). Our calculations predict **cis-TS1** to be significantly favored over **trans-TS1** ($\Delta \Delta G\ddagger$ = 3.2 kcal·mol−1), while the product **cis-3.17f** is essentially isoenergetic to its isomer **trans-3.17f**. The slight thermodynamic preference for the *trans* conformer can be rationalized by the greater planarity of the exocyclic π-system (as reflected by the dihedral angle θ in Figure 3.12). Analysis of the charge distribution [e.g, natural bond orbital (NBO) or ChelpG] in **3.17f** as well as of smaller model systems revealed that the zwitterionic and neutral resonance structures should be equally important. The next step of the mechanism requires abstraction of one of the α-hydrogens of the heterocycle, which, in an intramolecular reaction, is possible only from the *cis* conformation of **3.17f**. However, previous calculations on the corresponding aminobenzaldehyde-derived intermediates have shown that **cis-** and **trans-3.17f** can be directly interconverted with small barriers.[12c]

Figure 3.12 **Calculated Structures and Relative Free Energies (in kcal mol−1) for TS1 and 3.17f**

cis-TS1
$\Delta\Delta G\ddagger$ = 2.0 kcal mol−1

cis-3.17f
$\Delta\Delta G$ = 0.0 kcal mol−1

trans-TS1
$\Delta\Delta G\ddagger$ = +5.2 kcal mol−1

trans-3.17f
$\Delta\Delta G$ = −0.3 kcal mol−1

cis-TS1-HOAc
$\Delta\Delta G\ddagger$ = 0.0 kcal mol−1
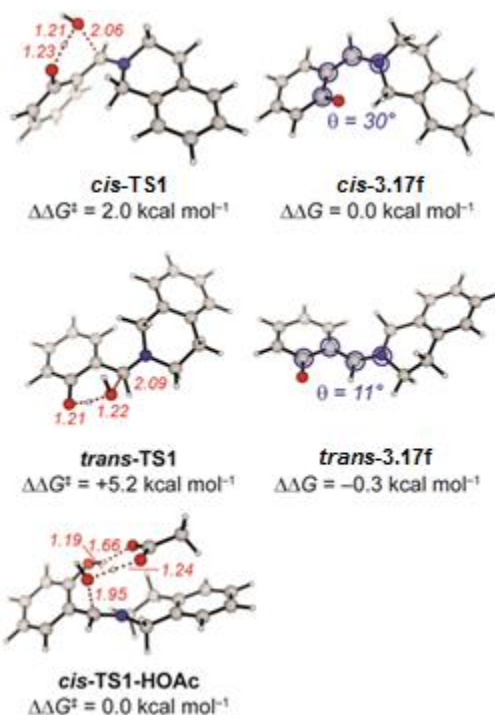
A subsequent proton transfer via **TS2** leads to the azomethine ylide **3.19f** in another endergonic transformation (Figure 3.13). The endergonicity of this step is also reflected in the short O–H bond length of the late transition state **TS2**. This reaction could proceed via either a 1,6-hydride shift or a 1,6-proton transfer, and our charge calculations (NBO or ChelpG) indicate that the latter is more likely due to a significant positive charge on the transferred hydrogen atom.

Figure 3.13 **Calculated Structures and Relative Free Energies (in kcal mol⁻¹ for the Transition States TS2**

Figure 3.13 **Calculated Structures and Relative Free Energies (in kcal mol^{-1} for the Transition States TS2**

TS2
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol^{-1}

TS2-HOAc
$\Delta\Delta G^{\ddagger}$ = +5.5 kcal mol^{-1}
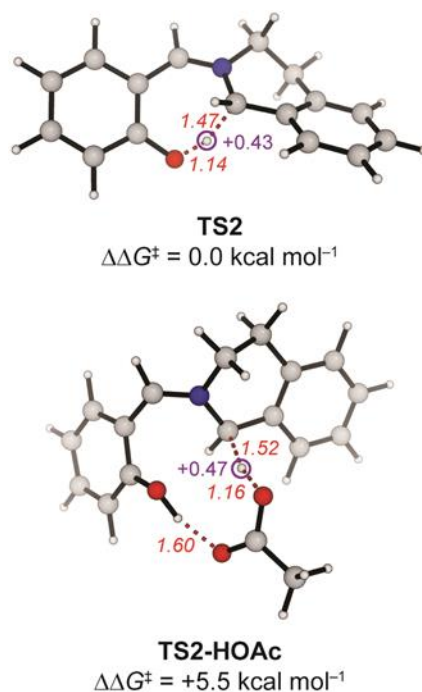
The azomethine ylide **3.19f** then undergoes another, rate-limiting proton transfer yielding the zwitterion **3.10f**. This transformation can either occur in an intramolecular reaction (**TS3**, Figure 3.14) or in a salicylaldehyde-mediated reaction (**TS3-Sali**, Figure 3.14). The entropic penalty ($-T\Delta S$) for the intermolecular reaction through **TS3-Sali** involving a second molecule of salicylaldehyde **3.7** is compensated by the very favorable activation enthalpy rendering **TS3-Sali** the preferred pathway. The

oxazinane **3.2f** is subsequently obtained by a barrierless cyclization of the zwitterionic intermediate **3.10f** in an overall exergonic reaction (ΔG = −2.4 kcal·mol−1).

Figure 3.14 **Calculated Structures and Relative Free Energies (in kcal mol⁻¹) for the Transition States TS3**

TS3a	**TS3b**	**TS3-HOAc**
ΔΔG‡ = +13.1 kcal mol⁻¹	ΔΔG‡ = +10.5 kcal mol⁻¹	ΔΔG‡ = +0.0 kcal mol⁻¹
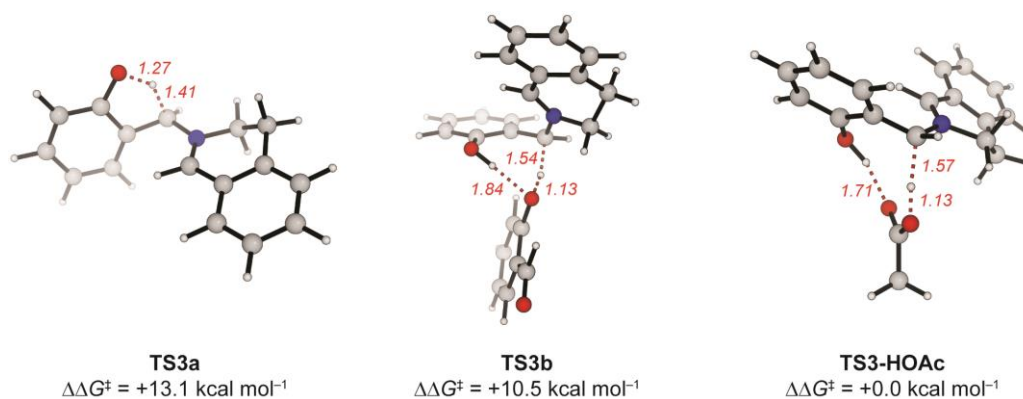
As an alternative pathway, azomethine ylide **3.19f** may be trapped via the reaction with excess salicylaldehyde **3.7**, affording the (3+2) adduct **3.12** (Figure 3.8, Figure 3.15). As the relative stereochemistry of the experimentally isolated adduct has not been determined, we have investigated all four possible stereoisomers and their corresponding transition states. Our calculations indicate that **RSS-3.12** is the most stable stereoisomer of the four [$\Delta\Delta$G(**RRR-3.12**) = +2.2, $\Delta\Delta$G(**RSR-3.12**) = +2.9, and $\Delta\Delta$G(**RRS-3.12**) = +3.6 kcal·mol−1] and only **RSS-3.12** is formed in an exergonic reaction (ΔG = −1.5 kcal·mol−1, Figure 3.15). The lowest-energy transition states were calculated to be **RRR-TS4** (ΔG‡ = 32.6 kcal·mol−1) and **RSS-TS4** (ΔG‡ = 33.0 kcal·mol−1). As the formation of **RRR-3.12** is endergonic, the computational data predict the formation of **RSS-3.12** to be the preferred (3+2) pathway (Figure 6). Both pathways leading to the benzoxazine **3.2f** and the alternate product **RSS-3.12** are similar in both activation and reaction free energies. While formation of the (3+2)

adduct has a slightly smaller activation free energy (kinetic preference), the benzoxazine is preferred thermodynamically. This also explains why the (3+2) cycloaddition is facilitated when the aldehyde is present in large concentrations and used in excess over the amine (e.g., entries 1 and 2 in Table 3.1).

Figure 3.15 **Different Pathways Involving the Azomethine Ylide 3.19f and Transition State TS4**
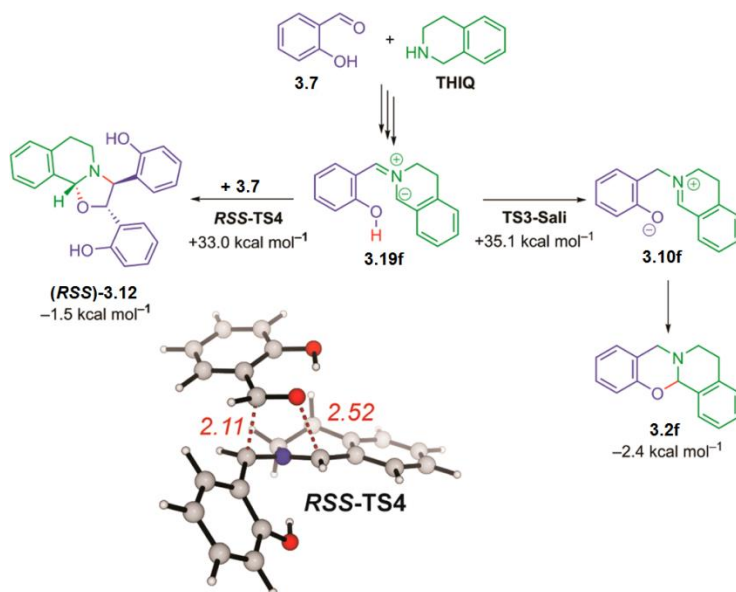
As the rate-limiting step for the uncatalyzed reaction was calculated to be rather high and significant accelerations could be observed in the experiments with acetic acid as a catalyst, we subsequently investigated how acetic acid can catalyze the synthesis of benzoxazinanes (Figures 3.12–3.14). Previous calculations on similar redox isomerizations by Yu and coworkers,[21] employing MP2/6-31+G(d)//B3LYP/6-31+G(d)/CPCM, have already highlighted the crucial role of acetic acid in these transformations and are possibly important for the transformations under investigation.

In a first step, we analyzed whether the acetylated hemiaminal **3.18f** could eliminate acetic acid with formation of the azomethine ylide **3.19f** as proposed by Yu

and coworkers (Scheme 10).[21] However, according to our calculations, the formation of hemiaminal **3.18f** is significantly endergonic (ΔG = +11.2 kcal·mol−1) and the transition state for the elimination of acetic acid **TS5** (ΔG‡ = +35.3 kcal·mol−1) was found to be comparable in energy to the uncatalyzed reaction [ΔG‡(**TS3-Sali**)= +33.2 kcal·mol−1]. Based on these results, this mode of activation by acetic acid does not explain the rate acceleration and has to be rejected for these transformations.

Figure 3.16 **Proposed Acceleration of Acetic Acid as Proposed by Yu and Coworkers**
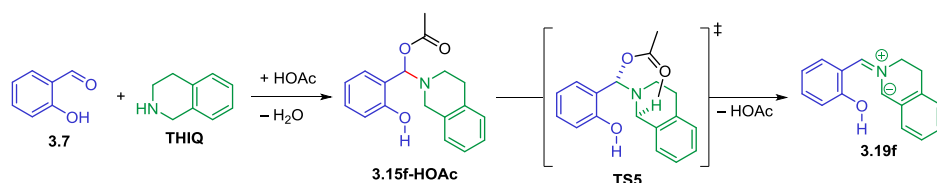
Next, we investigated whether acetic acid can act as a proton shuttle within the transition states **TS1–3** and thereby lower the activation energy of each step. The activation free energies for the acetic-acid-catalyzed reactions are summarized in Figure 3.11 and the optimized structures are depicted in Figures 3.12 to 3.14.

The dehydration of the hemiaminal **3.15f** is slightly facilitated by acetic acid acting as proton shuttle (***cis*-TS1-HOAc** versus ***cis*-TS1**, Figure 3), while the proton transfer yielding the azomethine ylide (**TS2** and **TS2-HOAc**, Figure 4) is actually destabilized by acetic acid. As the barrier for the uncatalyzed reaction is already very small (with respect to **3.19f**), the additional entropy penalty (−TΔS) cannot be compensated by the more favorable enthalpy. As a consequence, the intramolecular proton transfer is preferred over the intermolecular process for this step. In contrast, a large stabilization has been calculated for the rate-limiting proton transfer **TS3** in **TS3-**

HOAc (Figure 3.14), indicating a substantial stabilization of the transition state. In summary, this large difference in free energy for **TS3** (Δ ΔG‡ = 8.6 kcal·mol−1) is also the origin of the favorable acetic acid catalysis. This role of acetic acid in *N,O*-acetal formation has a parallel in the corresponding synthesis of aminals. In the latter case, the solvent, ethanol, has been shown to serve as the proton shuttle.[12c] To better understand the observed reactivities, we next analyzed selected carbonyl-amine combinations including electron-rich and -poor carbonyls and two different amines.

Table 3.2 **Calculated Free Energies for Different Carbonyl-Amine Combinations in Toluene (kcal mol−1)[a]**

	3.2f	3.2ad	3.2r	3.2l	3.2o	3.2d	3.2x
3.15	+1.9	+6.4	+5.6	−0.7	+2.1	−0.2	+1.8
3.15-HOAc	+13.1	+22.8	+20.8	+11.0	+4.1	+2.6	+15.5
cis-**TS1**	+22.5	+27.9	+24.8	+19.5	+24.0	+18.4	+21.6
cis-**TS1-HOAc**	+20.5	+25.9	+25.4	+20.2	+20.6	+15.4	+18.0
cis-**3.17**	+13.0	+20.4	+16.6	+9.5	+15.9	+7.5	+9.8
TS2	+23.7	+30.3	+26.3	+21.4	+23.7	−−−[b]	−−−[b]
TS2-HOAc	+29.2	+24.8	+28.2	+24.5	+29.6	−−−[b]	−−−[b]
3.19	+22.6	+29.3	+22.8	+20.7	+22.3	+26.1	+31.7
TS3	+37.7	+45.5	+38.9	+32.7	+39.3	+36.7	+38.1
TS3-Sali	+35.1	+46.8	+39.6	+32.3	+34.8	+34.3	+42.9
TS3-HOAC	+24.6	+31.9	+31.5	+21.6	+23.7	+22.9	+25.8
3.10	+21.0	+28.0	+22.5	+13.2	+24.9	+22.1	+24.5
3.2	−2.1	+2.4	−3.1	−4.5	−2.6	−5.4	−3.1

[a]Energies are given in kcal·mol−1, M06-2X-D3/def2-TZVPP/IEFPCM//TPSS-D2/6-31+G(d,p)/IEFPCM.
[b]All attempts to locate a transition state for these reactions failed, and potential energy surface scans indicate a barrierless reaction.

Independent of the combinations of carbonyl and amine, the overall reaction free energies are all found within a relatively small range ($-5.4 <$ $\Delta G <$ $+2.4$ kcal·mol^{-1}, Table 3.2), indicating that the substituents on the carbonyl and the choice of amine are less important for the thermodynamics of the overall reaction. The fact that some intermediates (e.g., for **3.19ad** or **3.19d**) are higher in energy than the corresponding acetic-acid-catalyzed transition states indicate that acetic acid can coordinate to the intermediates, which leads to a further stabilization. While the combination of hydroxyacetophenone and THIQ resulted in an endergonic reaction ($\rightarrow$ **3.2ad**) and no detectable product formation, the dimethyl analogue yields the corresponding benzoxazine **3.2r** in an exergonic reaction in line with an isolated yield of 53% (Figure 3.4). Employing truncated model systems, we could show that this difference may be attributed to a relief of 1,3-strain present in the reactant **3.3** but not in the corresponding oxazine.

A pronounced substituent effect is observed, however, for the zwitterionic intermediates **3.10**, as already indicated by the broad NMR peaks (Figure 3.9) for the dibromo compound **3.2l**. The electron-withdrawing bromo substituents in **3.10l** result in a stabilization of 7.8 kcal·mol^{-1} compared to **3.10f**, while the electron-donating methoxy group leads to a destabilization in **3.10o** ($\Delta \Delta G = +3.9$ kcal·mol^{-1}). The additional benzene ring of tetrahydroisoquinoline compared to pyrrolidine only translates to a small difference in free energy (cf. **3.10f** and **3.10d** in Table 3.2) indicating that the interaction with the negatively charged alcoholate is more important for the stability than an interaction with the iminium substructure.

For very bulky substrates (e.g., leading to **3.2r** or **3.2x**), the additional steric interactions in the transition states ***cis*-TS1-HOAc** and **TS3-Sali** completely

compensate any stabilization and render them higher in energy than **cis-TS1** and **TS3**, respectively.

Figure 3.17 **Calculated Transition State TS6 (in kcal mol⁻¹) for the Intermolecular Reduction of Intermediate Zwitterion 3.10f by THIQ**
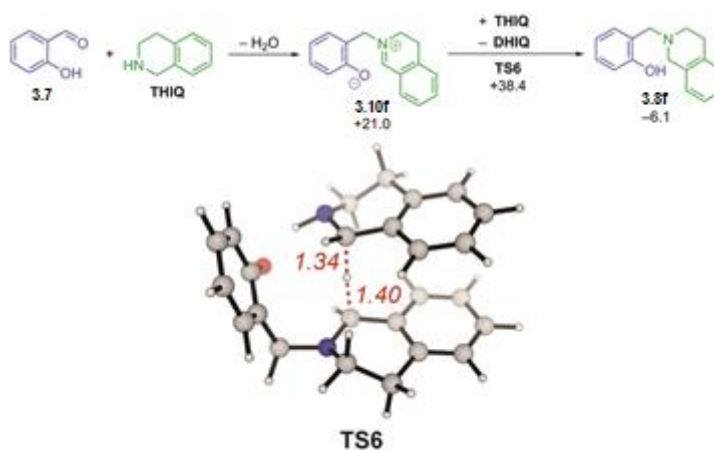
Table 3.3 **Calculated Free Energies for the Intermediates of the Reductive Isomerization in Toluene (kcal mol⁻¹)ᵃ**

	3.2f	3.2ad	3.2r	3.2l	3.2o	3.2d	3.2x
3.10	+21.0	+28.0	+22.5	+13.2	+24.9	+22.1	+24.5
3.2	−2.1	+2.4	−3.1	−4.5	−2.6	−5.4	−3.1
3.11	+22.8	+25.4	+21.0	+21.3	+19.5	+23.8	+20.8
3.23	+24.4	---	---	+17.3	+23.5	+19.5	+21.4
3.8	−6.1	+1.2	−3.9	−8.8	−5.8	−6.8	−4.8

ᵃEnergies are given in kcal·mol−1, M06-2X-D3/def2-TZVPP/IEFPCM//TPSS-D2/6-31+G(d,p)/IEFPCM.

Among the possible pathways for side reactions, we first analyzed the feasibility of an intermolecular reduction of the intermediate zwitterion **3.10f** by excess THIQ (Figure 3.17). The high activation free energy for the hydride transfer ($\Delta G^{\ddagger} = 38.4$

kcal·mol−1) renders this pathway unlikely under the reaction conditions employed (Table 3.1). However, a large excess of the amine would favor this reaction and could slightly reduce the activation free energy.

Figure 3.18 **Calculated Potential Energy Surface Scan for the Retro-Hetero-Diels-Alder Reaction Involving 3.2f**
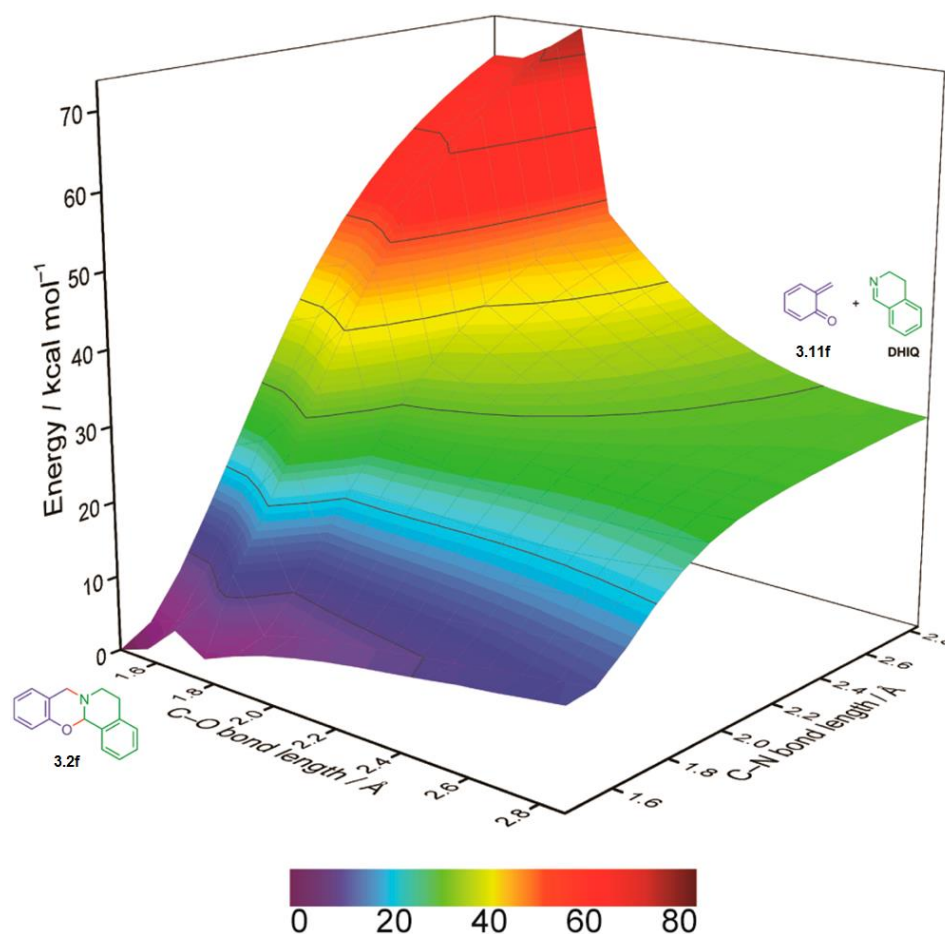
Another possibility, which is also in line with the experimental isolation of dihydroquinoline (DHIQ), is a retro-Diels–Alder reaction followed by a nucleophilic attack of the amine on the formed quinone methide. The energies of all intermediates for these transformations are summarized in Table 3.3. In all cases under investigation,

the alternate product **3.8** is thermodynamically more stable than the corresponding cyclic *N,O*-acetal **3.2** (0.8 < $\Delta\Delta G$ < 4.3 kcal·mol−1) and the intermediates of the putative retro-[4+2] reaction, **3.11** and the corresponding imine, are 20−25 kcal·mol−1 higher in energy. Table 3.3 further shows that the reduced amines dihydroquinoline and pyrroline are comparable in stability ($\Delta\Delta G$ = 1.0 kcal·mol−1). However, we were not able to locate any transition states for any of these transformations. Therefore, we investigated the potential energy landscape around the hemiaminals **3.2** by performing two-dimensional relaxed potential energy surface scans at the TPSS-D2/6-31G(d)/IEFPCM level of theory (Figure 3.18).

Regardless of the proposed mechanism (e.g., stepwise versus concerted cycloaddition), these scans result in a barrierless combination of the quinone methide **3.11f** and the imine DHIQ, yielding the experimentally observed *N,O*-acetal **3.2f**. From these results, we have to conclude that both a putative retro-[4+2] reaction and the subsequent nucleophilic attack would proceed without significant barriers. These results are in agreement with previous kinetic studies by the groups of Freccero, Kresge, Richard, Rokita, Mayr, and others.[22] As a consequence, none of the pathways considered can account for the unusual reactivity of pyrrolidine and salicylaldehyde, and a different reason has to be responsible for the experimental observations.

3.6 *N,S*-Thioacetals

After completing the study on the α-oxygenation of secondary amines, we decided to extend the methodology to the analogous α-sulfenylation. We recognized that an analogous α-sulfenylation of secondary amines with thiosalicylaldehydes would provide a practical entry to ring-fused *N,S*-acetals not easily accessible by other means. Based on the greater nucleophilicity of thiols compared to alcohols, we speculated that α-

sulfenylation might occur with a wider range of substrates. The *N,S*-acetal motif is common in nature and present as a key functional group in pharmacologically active compounds (Figure 3.19).[25] *N,S*-acetals have been investigated as sedatives (e.g., **3.24** and **3.25**),[25a] antibacterials (e.g., **2.26**),[25d] and cell growth inhibitors (e.g., **3.27**).[25c] Penicillins such as amoxicillin (**3.28**) are widely used as antibacterial medicines.[25i]

Figure 3.19 **Examples of Bioactive *N,S*-Acetals**
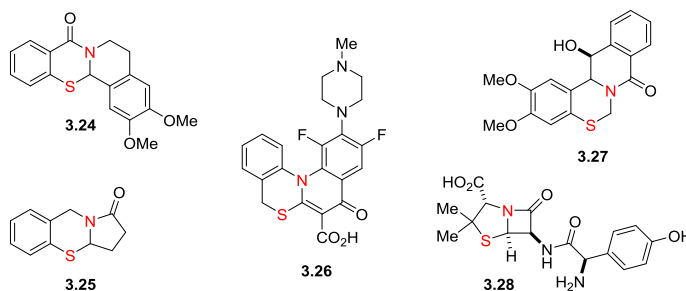
Figure 3.20 **Selected Approaches to *N,S*-Acetals**
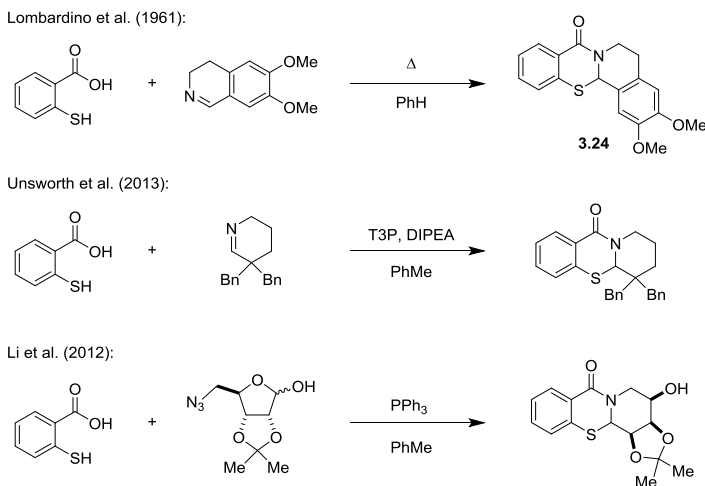
Traditional synthetic approaches to ring-fused *N,S*-acetals include the condensation of preformed imines with thiosalicylic acid, often requiring the addition of a coupling reagent (e.g., Figure 3.20).[25a,26,27] Here we report a new approach to *N,S*-acetals starting from thiosalicylaldehydes and secondary amines. The key feature of this

process is a redox-neutral amine α-C–H bond functionalization with concurrent *N*-alkylation/α-sulfenylation.

The title reaction was evaluated using thiosalicylaldehyde and 1,2,3,4-tetrahydroisoquinoline (THIQ) as the model substrates. Starting from conditions that were found ideal for the formation of the corresponding aminal and *N,O*-acetal analogues, a brief optimization survey was conducted (Table 3.4). Remarkably, the reaction of thiosalicylaldehyde (**3.7–S**) and THIQ was found to proceed in the absence of any additive at room temperature in ethanol solution to provide product **3.29a** in 40% yield (entry 1). In toluene as the solvent, an increased yield of 51% was observed (entry 2). While higher temperatures served to improve the yield further (entries 3 & 4), the addition of acetic acid was found to have a more dramatic effect. With 10 mol% of acetic acid, **3.29a** was obtained in 90% yield following a reaction time of just two hours at room temperature (entry 6).

Table 3.4 **Evaluation of Reaction Conditions for α-Sulfenylation of THIQ with Thiosalicylaldehyde (3.7–S)[a]**
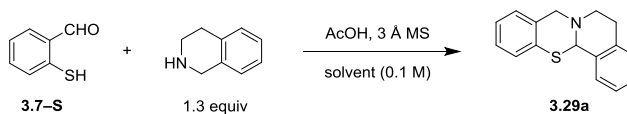
entry	AcOH (equiv)	solvent	T [°C]	time (h)	yield (%)
1	-	EtOH	rt	9	40
2	-	PhMe	rt	18	51
3	-	PhMe	60	0.5	66
4	-	PhMe	120[b]	0.17	60
5	0.1	PhMe	rt	2	90
6	0.1	PhMe	60	0.5	93
7[c]	0.1	PhMe	60	1	46
8	1.0	PhMe	rt	36	trace
9	1.0	PhMe	60	1.5	18

[a] Reactions were conducted on a 1 mmol scale. Yields correspond to isolated yields of chromatographically purified product. [b] Microwave irradiation in sealed vial. [c] Without molecular sieves.

Raising the reaction temperature to 60 °C in an otherwise identical experiment led to full conversion in only 30 min while allowing for the isolation of **3.29a** in 93%, the highest yield observed (entry 6). As previously noted in the corresponding *N,O*-acetal formation, removal of water from the reaction mixture was crucial in order to achieve rapid conversion. A reaction conducted under otherwise optimal conditions but in the absence of molecular sieves led to the formation of **3.29a** in only 46% after one hour (entry 7). Interestingly, increasing the amount of acetic acid to one equivalent had a detrimental effect on conversion and product yield while leading to an increased formation of unidentified byproducts (entries 8-9). This observation is in contrast to what was seen for *N,O*-acetal formation where an increase in the amount of acid proved highly beneficial.

Figure 3.21 **Substrate Scope for the α-Sulfenylation**[a]
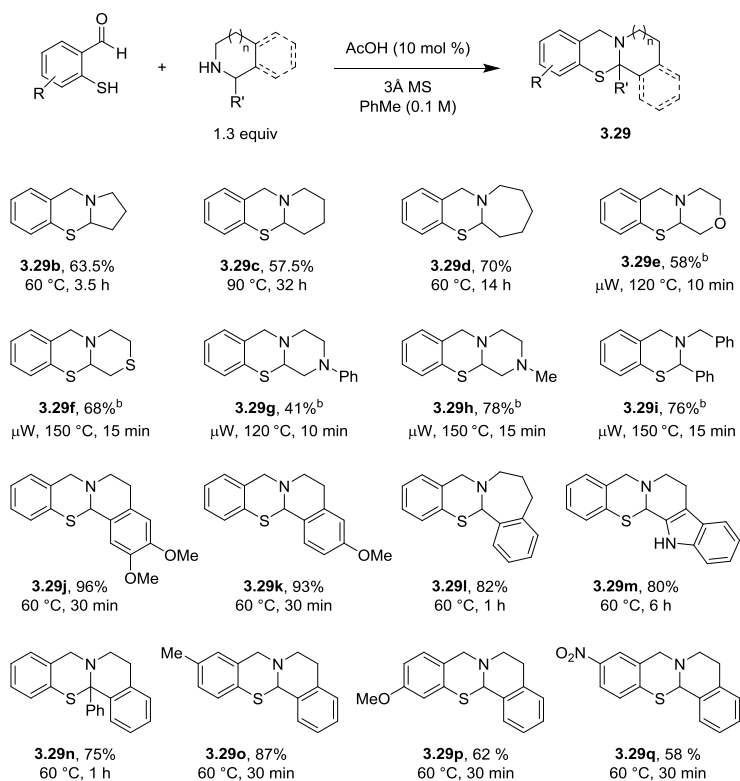
a) Reactions were performed on a 1 mmol scale.
b) with 3 equivalents of amine.

The α-sulfenylation with thiosalicylaldehyde was evaluated with a broad range of secondary amines (Figure 3.21). A number of cyclic amines such as pyrrolidine, piperidine and azepane underwent reaction with thiosalicylaldehyde at moderate temperatures to give product in generally good yields. Relatively electron-deficient amines such as morpholine and *N*-phenyl piperazine, substrates that are typically rather reluctant to undergo α-C–H bond functionalization, furnished the corresponding products at elevated temperatures (microwave irradiation at 120–150 °C). Initial attempts to synthesize these *N,S*-acetals at 60–90 °C required longer reaction times to reach complete consumption of the starting materials. In addition, it was found that for these substrates, oxidative dimerization of thiosalicylaldehyde to the corresponding disulfide was a competing process. This undesirable reaction pathway was reduced at elevated temperatures and further minimized by using a larger excess of the amine (3 equivalents). Under these conditions, dibenzylamine, a representative open-chain substrate, generated the corresponding product **3.29i** in good yield. Several other cyclic amines with benzylic α-C–H bonds, including the sterically demanding 1-phenyl-THIQ, underwent *N,S*-acetal formation under mild conditions. Finally, ring-substitution of thiosalicylaldehyde with either electron-donating or -withdrawing groups was well tolerated.

Figure 3.22 **Regioselectivity of the α-Sulfenylation[a]**
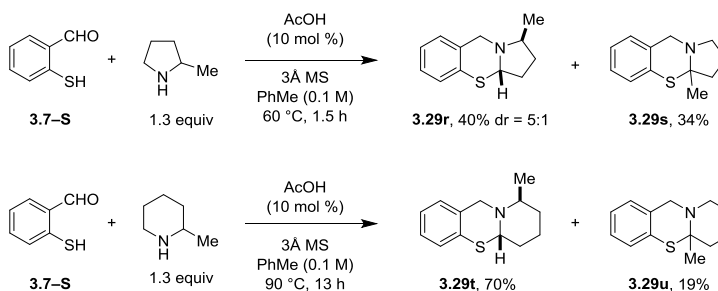
[a] Reactions were performed on a 1 mmol scale.

In order to explore the regioselectivity of the *N,S*-acetal formation for substrates with electronically similar α-C–H bonds, **3.7–S** was allowed to react with 1-methyl pyrrolidine and 1-methyl piperidine (Figure 3.22). Interestingly, in both cases the product distribution reflects a preference for functionalization of a secondary over an electronically favorable tertiary C–H bond. Apparently, steric issues appear to outweigh electronic effects in these instances. This is in stark contrast to the corresponding aminal formation with 1-methyl pyrrolidine and 1-methyl piperidine that exhibit a pronounced preference for tertiary C–H bond functionalization.[12]

Figure 3.23 **Free Energy Profile (kcal·mol⁻¹) for Uncatalyzed Transformation of 3.7–O and 3.7–S and THIQ in Toluene**
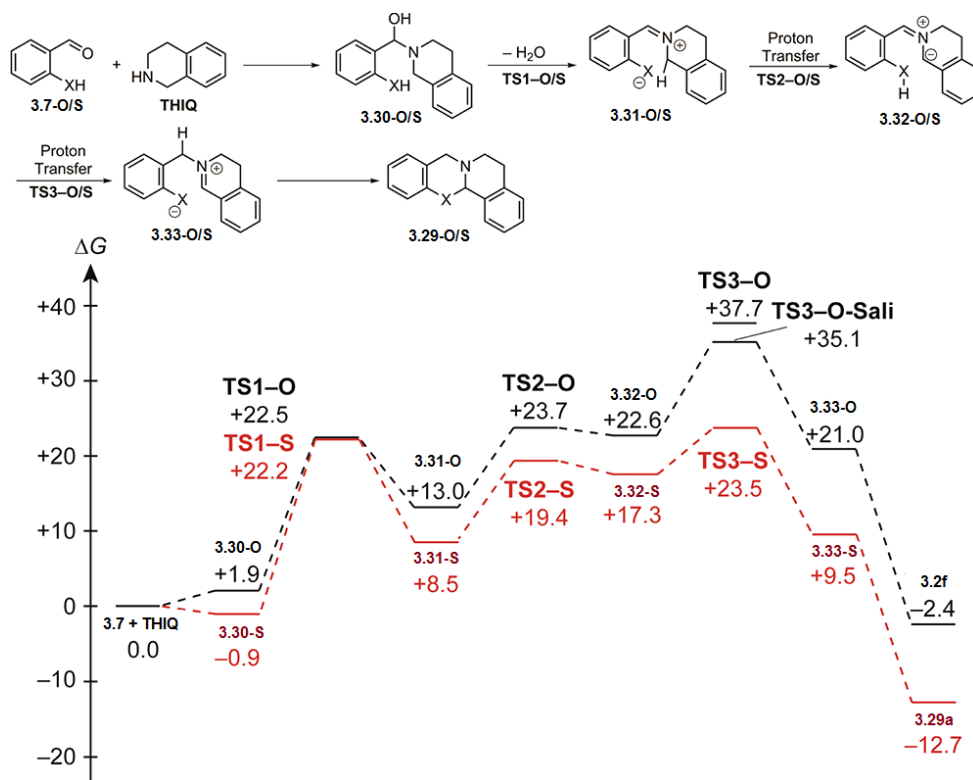
To rationalize the enhanced reactivities in the *N,S*-acetal series compared to the corresponding *N,O*-acetals, we analyzed the model reaction between thiosalicylaldehyde

(**3.7−S**) and THIQ by the same computational method described previously (M06-2X-D3/def2-TZVPP/IEFPCM(toluene)//TPSS-D2/6-31+G(d,p)/IEFPCM(toluene).

For the uncatalyzed reactions without acetic acid, the calculated free energy profiles for the oxo- and thio pathways are summarized in Figure 3.23. The hemiaminals **3.30−O** and **3.30−S** as well as the transition states for the dehydration (**TS1−O/S**) are very similar for both systems. In contrast, a substantial difference was calculated for all other intermediates and transition states. While the sulfur-compound of **3.31**, **TS2**, and **3.32** is 4–5 kcal mol^{-1} more stable than the oxygen analog, differences of more than 10 kcal mol^{-1} were calculated for **TS3**, **3.33**, and **3.29a**. This stability difference can also be rationalized with the higher acidity of thiophenol compared to phenol in both DMSO ($\Delta pK_a \approx 8$) and aqueous solution ($\Delta pK_a \approx 3$).[28] This difference in acidity might also be responsible for the fact that no thiosalicylaldehyde-mediated proton transfer (e.g., the thio-analogue of **TS3-O-Sali**) could be located.

Next, we analyzed whether acetic acid has the same catalytic effect for the synthesis of *N,S*-acetals as previously described for the corresponding *N,O*-acetals. Figure 3.24 summarizes the calculated transition states for the uncatalyzed and acetic-acid-catalyzed *N,S*-acetal formation. Similar to the formation of *N,O*-acetals, acetic acid stabilizes the transition states **TS1−S** ($\Delta\Delta G^{\ddagger} = -1.5$ kcal mol^{-1}) and **TS3−S** ($\Delta\Delta G^{\ddagger} = -2.6$ kcal mol^{-1}). As previously reported for the formation of *N,O*-acetals, transition state **TS2−S** for the endergonic transformation of **3.31−S** to **3.32−S** is actually destabilized by acetic acid ($\Delta\Delta G^{\ddagger} = +10.9$ kcal mol^{-1}). Again, a small barrier (with respect to **3.32−S**) and the entropic penalty ($-T\Delta S$) render **TS2−S-HOAc** less favorable than **TS2−S** and are responsible for the preference of the intramolecular proton transfer over the intermolecular process for this step.

Figure 3.24 **Calculated Transition State Structures and Relative Free Energies (in kcal·mol⁻¹) for the Uncatalyzed and Acetic-Acid-Catalyzed Transformation of 3.7–S and THIQ**

TS1–S
$\Delta\Delta G^{\ddagger}$ = +1.5 kcal mol⁻¹

TS1–S-HOAc
$\Delta\Delta G$ = 0.0 kcal mol⁻¹

TS2–S
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol⁻¹

TS2–S-HOAc
$\Delta\Delta G$ = +10.9 kcal mol⁻¹

TS3–S
$\Delta\Delta G^{\ddagger}$ = +2.6 kcal mol⁻¹

TS3–S-HOAc
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol⁻¹
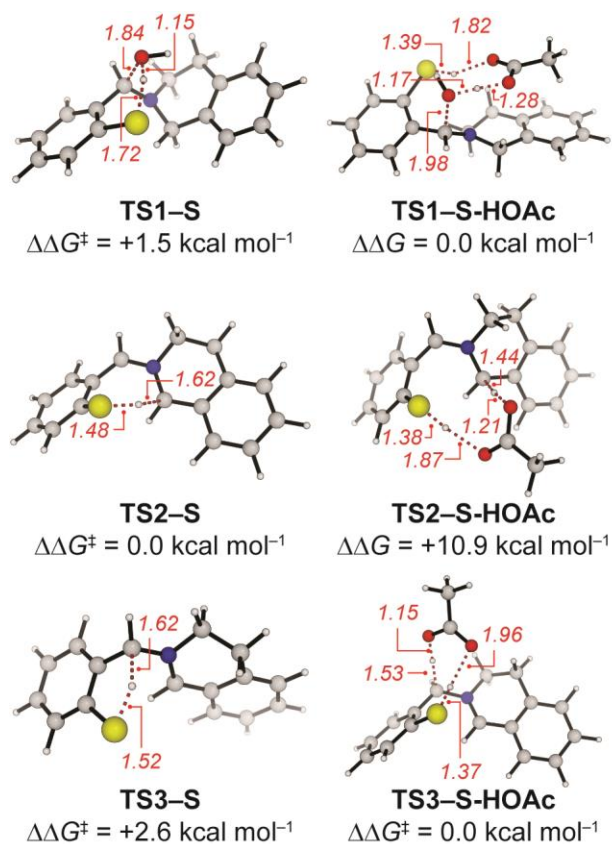
Due to the higher acidities of thiols, the rate-determining step (**TS3–S**) is lowered to a much smaller extent than in the *N,O*-acetal series. These computational findings are also reflected in the experimental data of Table 3.4, as acetic acid is not necessarily required for the formation of *N,S*-acetals but is ultimately needed in the *N,O*-acetal series.

3.7 Conclusion

We have developed new redox-neutral amine α-oxygenation and α-sulfenylation reactions. These processes, while analogous to the amine α-amination described in the previous chapter, required different, milder conditions. Key to the reaction is the removal of water by molecular sieves and the use of acetic acid as catalyst. The mechanisms of these two reactions were studied computationally, identifying a concerted proton transfer aided by acetic acid as important to the reaction. A diverse number of potentially medicinally relevant structures were synthesized by these methods.

Experimental Section

General Information: Salicylaldehydes were purchased from commercial sources unless otherwise stated and were used as received. Secondary amines were purchased from commercial sources unless otherwise stated and were distilled prior to use. Glacial acetic acid was purchased from EMD and was used as received. 3Å powdered molecular sieves were purchased from Alfa Aesar and were activated before use by heating in a furnace to 300 °C for 2 h and were stored in a desiccator. Reagent grade toluene was purchased from Sigma-Aldrich and distilled over sodium. Microwave reactions were carried out in a CEM Discover S reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate and Dragendorff-Munier stains followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using chloroform as the internal standard (7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using chloroform as the internal standard (77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General Procedure A: 2-hydroxy-aldehyde or ketone (1 mmol) was added to a 25 mL round bottom flask containing a stir bar. The flask was charged with toluene (10 mL), 3 Å molecular sieves (200 mg), acetic acid (0.057 mL, 1 mmol) and secondary amine (1.3 mmol). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to the appropriate temperature until the aldehyde or ketone was consumed. Once cooled to room temperature, the mixture was filtered through a pad of celite and rinsed with CH_2Cl_2 (10 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo and the resulting residue was purified via silica gel chromatography.

General Procedure B: 2-hydroxy-aldehyde or ketone (2 mmol) was added to a 25 mL round bottom flask containing a stir bar. The flask was charged with xylenes (10 mL), 3 Å molecular sieves (200 mg), acetic acid (0.057 mL, 1 mmol) and secondary amine (1 mmol). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath at reflux until the amine was consumed. Once cooled to room temperature, the mixture was filtered through a pad of celite and rinsed with CH_2Cl_2 (10 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo and the resulting residue was purified via silica gel chromatography.

General Procedure C: To a solution of aldehyde (1.0 mmol) in toluene (10 mL) was added 3 Å molecular sieves (200 mg), amine (1.3 mmol) and glacial acetic acid (0.1 mmol). The mixture was heated to 60 °C until the aldehyde was consumed. Subsequently, the reaction mixture was cooled to room temperature, filtered through a

plug of celite and washed with 50 mL dichloromethane. The crude product was concentrated in vacuo and purified by silica gel chromatography.

General Procedure D: A solution of aldehyde (1.0 mmol) in toluene (10 mL) was added to a 35 mL microwave vial equipped with a magnetic stir bar and 3 Å molecular sieves (200 mg). To the solution was added amine (3.0 mmol) and glacial acetic acid (0.1 mmol). The mixture was irradiated in the microwave until the aldehyde was consumed. Subsequently, the reaction mixture was cooled to room temperature, filtered through a plug of celite and washed with 50 mL dichloromethane. The crude product was concentrated in vacuo and purified by silica gel chromatography.

Cycloadduct 3.12 (±): Salicylaldehyde (0.213 mL, 2 mmol) was added to a 10 mL round bottom flask containing a stir bar. The flask was charged with toluene (4 mL), 3 Å molecular sieves (200 mg), benzoic acid (0.024 g, 0.2 mmol) and THIQ (0.127 mL, 1 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 18 h, after which time the mixture was filtered through a pad of celite and rinsed with CH_2Cl_2 (10 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo and the resulting residue was purified via silica gel chromatography in 80:20 hexanes/EtOAc, resulting in the isolation of **3.2f** (yield 38%). In addition, 174 mg of **3.12** were obtained as a white solid in a 1:1 diastereomeric ratio (48% yield). Epimerization, indicated by exchange peaks in the NOESY spectrum, complicated the assignment of the relative stereochemistry. (R_f = 0.09 in hexanes/EtOAc 90:10 v/v; mp: 75–79 °C; IR (KBr) 3388, 3038, 2926, 1609, 1586, 1490, 1458, 1388, 1243, 1130, 1034, 1020, 933, 752 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 11.58 (br s, 1H), 8.58 (br s, 1H), 7.57–7.49 (m, 1H), 7.49–7.41 (comp, 2H), 7.41–7.32 (comp, 4H), 7.32–7.17 (comp, 4H), 7.16–7.08 (m, 1H), 6.99

(dd, *J* = 8.1, 1.2 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.89–82 (comp, 2H), 6.81–6.73 (comp, 2H), 6.73–6.59 (comp, 4H), 6.42 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.00–5.90 (comp, 3H), 5.10 (d, *J* = 9.1 Hz, 1H), 4.95 (s, 1H), 4.86 (d, *J* = 9.2 Hz, 1H), 4.27 (d, *J* = 9.1 Hz, 1H), 3.98 (d, *J* = 9.2 Hz, 1H), 3.41 (app td, *J* = 11.8, 11.4, 3.7 Hz, 1H), 3.36–3.25 (comp, 2H), 3.11–2.81 (comp, 5H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 135.0, 134.6, 130.8, 130.3, 130.0, 129.9, 129.8, 129.4, 129.0, 128.9, 128.8, 128.5, 128.0, 127.4, 126.6, 120.0, 119.9, 119.4, 119.1, 118.5, 117.5, 117.4, 117.2, 116.6, 88.3, 85.6, 80.8, 77.6, 72.6, 65.0, 46.1, 44.9, 29.1, 26.5; *m/z* (ESI–MS) 360.1 [M+H]$^+$.

Structural Assignment of 3.12:

3.12
30 mg

3.S1
96%
single diastereomer
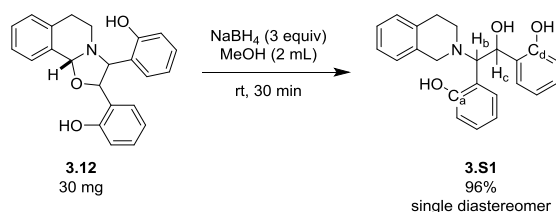
In order to determine the regio- and stereochemistry of **3.12**, this compound was reduced with NaBH$_4$. Compound **3.12** (30 mg) was dissolved in MeOH (2 mL) and to this stirring solution was added NaBH$_4$ (9.47 mg, 3 equiv). The mixture was allowed to stir for 30 minutes, after which time water (20 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine and dried over sodium sulfate. Following filtration and concentration under reduced pressure, the crude product was purified by column chromatography with 70:30 hexanes/EtOAc to yield 29.1 mg of **3.S1** as a white solid (96%). Only a single diastereomer was observed, indicating that the hemiaminal was the site of epimerization. Characterization data for **3.S1**: (R$_f$ = 0.09 in hexanes/EtOAc 70:30 v/v); mp: 71–73 °C; IR (KBr) 3065, 2923, 2836, 1589, 1490, 1457, 1374, 1244, 1085, 1039, 933, 909, 752 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.91 (br s, 2H), 7.21–6.92 (comp, 7H), 6.81–6.66 (comp,

4H), 6.59 (td, J = 7.4, 1.2 Hz, 1H), 5.31 (d, J = 6.4 Hz, 1H), 4.32 (d, J = 6.4 Hz, 1H), 4.02 (d, J = 15.1 Hz, 1H), 3.95 (d, J = 15.1 Hz, 1H), 3.20 (app dt, J = 11.3, 5.4 Hz, 1H), 3.06–2.76 (comp, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.8, 155.4, 133.7, 133.3, 130.8, 129.2, 129.2, 128.8, 128.5, 126.7, 126.4, 126.0, 125.8, 121.6, 119.4, 119.3, 117.3, 116.6, 76.2, 71.1, 53.5, 48.6, 28.9; m/z (ESI–MS) 362.1 [M+H]$^+$. GHMBC NMR spectroscopy revealed a correlation between C$_a$ (155.8 ppm) and H$_b$ (4.32 ppm) and a correlation between C$_d$ (155.4 ppm) and H$_c$ (5.31 ppm). As H$_b$ and H$_c$ couple with each other it can be inferred that the two phenolic aryl rings are situated vicinally on the opened alkyl chain of **3.S1**.

***N,O*-Acetal 3.2g:** Following general procedure A, compound **3.2g** was obtained from the reaction between 5-methylsalicylaldehyde and THIQ at 80 °C for 2 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 248.7 mg of **3.2g** as a white solid (99% yield) (R$_f$ = 0.32 in hexanes/EtOAc 60:40 v/v); mp: 135–136 °C; IR (KBr) 3026, 2991, 2930, 2893, 2872, 1494, 1458, 1399, 1336, 1251, 1217, 1123, 928, 887, 857, 833, 743 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44–7.40 (m, 1H), 7.34–7.25 (comp, 2H), 7.22–7.17 (m, 1H), 6.96–6.92 (m, 1H), 6.86–6.82 (m, 1H), 6.73 (d, J = 8.3 Hz, 1H), 5.71 (s, 1H), 4.56 (d, J = 16.6 Hz, 1H), 3.80 (d, J = 16.6 Hz, 1H), 3.36 (app td, J = 11.0, 4.3 Hz, 1H), 3.11 (ddd, J = 16.8, 10.8, 6.2 Hz, 1H), 2.91 (app dt, J = 16.4, 3.8 Hz, 1H), 2.82 (ddd, J = 11.3, 6.3, 2.9 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.7, 134.7, 133.2, 129.7, 128.7, 128.6, 128.3, 127.1, 126.2, 118.9, 116.4, 104.8, 86.8, 53.6, 44.5, 29.0, 20.6; m/z (ESI–MS) 252.1 [M+H]$^+$.

***N,O*-Acetal 3.2h:** Following general procedure A, compound **3.2h** was obtained from the reaction between 3,5-di-*t*-butylsalicylaldehyde and THIQ at 80 °C for 5 h. The reaction mixture was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 318.8 mg of **3.2h** as a white solid (91%

yield) (R$_f$ = 0.31 in hexanes/EtOAc 90:10 v/v); mp: 57–60 ºC; IR (KBr) 2956, 2865, 1477, 1396, 1362, 1334, 1264, 1223, 1122, 918, 901, 739, 729 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46–7.43 (m, 1H), 7.34–7.24 (comp, 2H), 7.23–7.16 (comp, 2H), 6.91–6.88 (m, 1H), 5.66 (s, 1H), 4.55 (d, J = 16.3 Hz, 1H), 3.85 (d, J = 16.3 Hz, 1H), 3.34 (app td, J = 10.5, 4.3 Hz, 1H), 3.08 (ddd, J = 15.9, 9.9, 5.8 Hz, 1H), 2.94 (app dt, J = 16.4, 4.2 Hz, 1H), 2.82 (ddd, J = 11.4, 5.7, 3.8 Hz, 1H), 1.36 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.3, 142.1, 136.8, 134.9, 133.7, 128.5, 128.3, 128.3, 126.0, 121.9, 121.3, 118.5, 86.6, 54.3, 45.3, 34.8, 34.3, 31.6, 29.7, 29.1; m/z (ESI–MS) 350.2 [M+H]$^+$.

N,O-Acetal 3.2i: Following general procedure A, compound **3.2i** was obtained from the reaction between methyl 3-formyl-4-hydroxybenzoate[29] and THIQ at 60 ºC for 3 h. The reaction mixture was purified via silica gel chromatography in 59:40:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 266.1 mg of **3.2i** as a white solid (90% yield) (R$_f$ = 0.18 in hexanes/EtOAc 60:40 v/v); mp: 118–120 ºC; IR (KBr) 3031, 2951, 2850, 1706, 1161, 1577, 1491, 1439, 1294, 1246, 1221, 1178, 1120, 1097, 986, 917, 868, 839, 767, 737, 704 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85–7.79 (m, 1H), 7.79–7.74 (m, 1H), 7.42 (dd, J = 7.4, 1.4 Hz, 1H), 7.38–7.27 (comp, 2H), 7.21 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.81–4.08 (comp, 2H), 3.88 (s, 3H), 3.01 (br s, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.9, 158.2, 134.6, 132.4, 129.7, 129.1, 129.0, 128.7, 128.4, 126.3, 122.1, 118.7, 116.5, 87.8, 53.3, 51.8, 44.3, 28.8; m/z (ESI–MS) 296.1 [M+H]$^+$.

N,O-Acetal 3.2j: Following general procedure A, compound **3.2j** was obtained from the reaction between 5-chlorosalicylaldehyde and THIQ at 60 ºC for 45 min. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 252.3 mg of **3.2j** as a white solid (93% yield) (R$_f$ = 0.36 in hexanes/EtOAc 60:40 v/v); mp: 140−141 ºC; IR (KBr) 3074, 3049, 2891, 2831, 1477, 1398, 1336, 1248, 1218, 984, 888, 850, 832, 789, 737 cm^{-1}; ^{1}H NMR

(500 MHz, CDCl$_3$) δ 7.40 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.37–7.27 (comp, 2H), 7.20 (app d, *J* = 7.5 Hz, 1H), 7.11–7.05 (m, 1H), 7.05–6.99 (m, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 5.74 (s, 1H), 4.56 (d, *J* = 16.8 Hz, 1H), 3.80 (d, *J* = 16.8 Hz, 1H), 3.39–3.21 (m, 1H), 3.21–3.04 (m, 1H), 3.00–2.74 (comp, 2H); ¹³C NMR (125 MHz, CDCl$_3$) δ 152.6, 134.6, 132.7, 128.9, 128.7, 128.3, 127.8, 126.6, 126.3, 125.0, 120.6, 118.0, 87.2, 53.2, 44.4, 28.9; *m/z* (ESI–MS) 272.2 [M+H]⁺.

***N,O*-Acetal 3.2k:** Following general procedure A, compound **3.2k** was obtained from the reaction between 5-bromosalicylaldehyde and THIQ at 60 °C for 45 min. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 284.9 mg of **3.2k** as a white solid (90% yield) (R$_f$ = 0.36 in hexanes/EtOAc 60:40 v/v); mp: 131–133 °C; IR (KBr) 3073, 2927, 2888, 1576, 1475, 1440, 1396, 1335, 1247, 1265, 1183, 1125, 908, 886, 849, 803, 744, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$) δ 7.40 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.36–7.26 (comp, 2H), 7.24–7.18 (comp, 2H), 7.18–7.13 (m, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 5.74 (s, 1H), 4.56 (d, *J* = 16.9 Hz, 1H), 3.79 (d, *J* = 16.9 Hz, 1H), 3.39–3.22 (m, 1H), 3.22–3.03 (m, 1H), 3.01–2.71 (comp, 2H); ¹³C NMR (125 MHz, CDCl$_3$) δ 153.1, 134.5, 132.6, 130.7, 129.5, 129.0, 128.7, 128.3, 126.3, 121.1, 118.5, 112.3, 87.1, 53.1, 44.3, 28.9; *m/z* (ESI–MS) 316.1 [M+H]⁺.

***N,O*-Acetal 3.2l:** Following general procedure A, compound **3.2l** was obtained from the reaction between 3,5-dibromosalicylaldehyde and THIQ at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 329.9 mg of **3.2l** as a white solid (84% yield) (R$_f$ = 0.39 in hexanes/EtOAc 60:40 v/v); mp: 149–150 °C; IR (KBr) 3049, 2958, 2919, 2895, 2857, 2345, 1559, 1451, 1402, 1300, 1220, 1132, 1100, 984, 852, 765, 753, 878, 649 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$) δ 7.55–7.50 (m, 1H), 7.47 (dd, *J* = 7.5, 1.4 Hz,

1H), 7.37–7.27 (comp, 2H), 7.19 (d, J = 7.2 Hz, 1H), 7.14–7.09 (m, 1H), 5.77 (s, 1H), 4.16 (br s, 2H), 3.20–2.81 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.4, 134.8, 133.7, 132.4, 129.2, 128.8(5), 128.8(3), 126.6, 122.7, 112.3, 111.6, 88.6, 53.4, 44.9, 29.1; m/z (ESI–MS) 396.0 [M+H]$^+$.

***N,O*-Acetal 3.2m:** Following general procedure A, compound **3.2m** was obtained from the reaction between 5-nitrosalicylaldehyde and THIQ at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 69:30:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 198.1 mg of **3.2m** as a yellow solid (70% yield) (R$_f$ = 0.11 in hexanes/EtOAc 60:40 v/v); mp: 150–151 °C; IR (KBr) 3066, 2963, 2927, 2855, 1611, 1580, 1510, 1483, 1440, 1405, 1332, 1319, 1242, 1227, 1134, 1085, 924, 835, 813, 786, 748, 732, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (dd, J = 9.0, 2.8 Hz, 1H), 8.02–7.99 (m, 1H), 7.42 (dd, J = 7.4, 1.6 Hz, 1H), 7.39–7.27 (comp, 2H), 7.22 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 5.93 (s, 1H), 4.28 (br s, 2H), 3.13–2.96 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.8, 134.5, 131.8, 129.3, 128.8, 128.5, 126.4, 124.2, 123.4, 119.0, 117.0, 88.7, 53.1, 44.2, 28.8; m/z (ESI–MS) 283.1 [M+H]$^+$.

***N,O*-Acetal 3.2n:** Following general procedure A, compound **3.2n** was obtained from the reaction between 3-methoxysalicylaldehyde and THIQ at 80 °C for 10 min. The reaction mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 226.5 mg of **3.2n** as a white solid (85% yield) (R$_f$ = 0.10 in hexanes/EtOAc 90:10 v/v); mp: 147–148 °C; IR (KBr) 3037, 2931, 2881, 2838, 1584, 1485, 1401, 1329, 1215, 1189, 1126, 1076, 987, 879, 885, 867, 764, 732 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48 (dd, J = 7.2, 1.8 Hz, 1H), 7.31–7.23 (comp, 2H), 7.18–7.14 (m, 1H), 6.85 (app t, J = 7.9 Hz, 1H), 6.77–6.73 (m, 1H), 6.67–6.63 (m, 1H), 5.77 (s, 1H), 4.61 (d, J = 16.7 Hz, 1H), 3.89–3.77 (comp, 4H), 3.48–3.33 (m, 1H), 3.19–3.05 (m, 1H), 2.96–2.76 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 147.9, 143.7,

134.8, 132.9, 128.7(3), 128.7(2), 128.6, 126.2, 120.0, 119.9, 118.7, 109.8, 87.2, 55.9, 53.4, 44.5, 29.0; m/z (ESI–MS) 268.1 [M+H]$^+$.

N,O-Acetal 3.2o: Following general procedure A, compound **3.2o** was obtained from the reaction between 5-methoxysalicylaldehyde and THIQ at 80 °C for 15 min. The reaction mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 257.5 mg of **3.2o** as a white solid (96% yield) (R_f = 0.34 in hexanes/EtOAc 60:40 v/v); mp: 133–134 °C; IR (KBr) 2999, 2929, 2873, 2832, 1492, 1461, 1399, 1336, 1246, 1209, 1126, 1044, 926, 885, 859, 821, 794, 750 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (dd, J = 7.4, 1.7 Hz, 1H), 7.33–7.24 (comp, 2H), 7.19 (app d, J = 7.8 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 6.71 (dd, J = 8.9, 2.8 Hz, 1H), 6.58 (d, J = 2.8 Hz, 1H), 5.67 (s, 1H), 4.57 (d, J = 16.6 Hz, 1H), 3.81 (d, J = 16.6 Hz, 1H), 3.77 (s, 3H), 3.36 (app td, J = 11.0, 4.4 Hz, 1H), 3.12 (ddd, J = 16.8, 10.8, 6.1 Hz, 1H), 2.91 (app dt, J = 16.4, 3.8 Hz, 1H), 2.83 (ddd, J = 11.3, 6.2, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.5, 147.9, 134.6, 133.2, 128.7, 128.3, 126.2, 119.8, 117.3, 113.7, 111.4, 104.8, 86.7, 55.7, 53.8, 44.6, 29.0; m/z (ESI–MS) 268.1 [M+H]$^+$.

N,O-Acetal 3.2r (±): Following general procedure A, compound **3.2r** was obtained from the reaction between 1-(2-hydroxy-4,6-dimethylphenyl)ethanone[30] and THIQ at reflux for 24 h. The reaction mixture was purified via silica gel chromatography in 92:7:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 148.4 mg of **3.2r** as a white solid (53% yield). The relative stereochemistry was determined by GCOSY and NOESY NMR. (R_f = 0.62 in hexanes/EtOAc 60:40 v/v); mp: 150–151 °C; IR (KBr) 3023, 2968, 2927, 2831, 1617, 1578, 1494, 1442, 1397, 1331, 1314, 1230, 1139, 1062, 1033, 881, 845, 831, 771, 746 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42 (dd, J = 7.3, 1.8 Hz, 1H), 7.35–7.27 (comp, 2H), 7.18 (app d, J = 7.6 Hz, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 5.89 (s, 1H), 3.89 (q, J = 6.9 Hz, 1H), 3.27–3.09 (comp, 2H), 2.87–2.71 (comp, 2H), 2.26 (s, 3H), 2.23 (s, 3H), 1.54 (d, J =

6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.1, 137.4, 135.6, 135.3, 133.6, 129.1, 129.0(3), 129.0(1), 126.4, 123.6, 119.5, 115.1, 81.3, 55.3, 45.2, 29.4, 22.2, 21.3, 18.7; *m/z* (ESI–MS) 280.0 [M+H]$^+$.

N,O-Acetal 3.2s: Following general procedure A, compound **3.2s** was obtained from the reaction between salicylaldehyde and 6-methoxy-1,2,3,4-tetrahydro-isoquinoline[31] at 60 °C for 5 h. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 263.0 mg of **3.2s** as a white solid (98% yield) (R$_f$ = 0.11 in EtOAc); mp: 88−91 °C; IR (KBr) 3003, 2889, 2833, 1608, 1582, 1507, 1488, 1455, 1344, 1334, 1268, 1222, 1126, 1037, 910, 951, 866, 804, 755, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.13 (app td, *J* = 8.3, 1.8 Hz, 1H), 7.05–7.00 (m, 1H), 6.89 (app td, *J* = 7.4, 1.2 Hz, 1H), 6.86–6.80 (comp, 2H), 6.72 (d, *J* = 2.6 Hz, 1H), 5.73 (s, 1H), 4.73–4.48 (m, 1H), 3.89–3.74 (comp, 4H), 3.45–3.24 (m, 1H), 3.21–3.00 (m, 1H), 3.00–2.74 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.8, 154.1, 136.2, 129.5, 127.7, 126.8, 125.8, 120.4, 119.2, 116.6, 113.3, 112.4, 86.7, 55.3, 53.6, 44.3, 29.3; *m/z* (ESI–MS) 268.1 [M+H]$^+$.

N,O-Acetal 3.2t: Following general procedure A, compound **3.2t** was obtained from the reaction between salicylaldehyde and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[32] at 60 °C for 5 h. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 295.2 mg of **3.2t** as a white solid (99% yield) (R$_f$ = 0.07 in hexanes/EtOAc 60:40 v/v); mp: 140−142 °C; IR (KBr) 3038, 2993, 2938, 2831, 1611, 1584, 1523, 1486, 1455, 1426, 1388, 1351, 1273, 1221, 1126, 1096, 1032, 1002, 895, 879, 852, 832, 749 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13 (app t, *J* = 7.9 Hz, 1H), 7.02 (app d, *J* = 7.5 Hz, 1H), 6.95–6.86 (comp, 2H), 6.83 (app d, *J* = 8.3 Hz, 1H), 6.67 (s, 1H), 5.68 (s, 1H), 4.57 (d, *J* = 16.6 Hz, 1H), 4.00–3.71 (comp, 7H), 3.45–3.22 (m, 1H), 3.13–2.94 (m, 1H), 2.93–2.71 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$)

127.1, 126.3, 122.7, 120.8, 119.9, 119.7, 119.0, 116.5, 111.4, 111.2, 83.4, 53.2, 47.0, 21.7; m/z (ESI–MS) 277.1 [M+H]$^+$.

N,O-Acetal 3.2w: Following general procedure A, compound **3.2w** was obtained from the reaction between salicylaldehyde and 2,3,4,5-tetrahydro-1H-benzo[c]azepine[34] at reflux for 24 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 172.1 mg of **3.2w** as a white solid (69% yield) (R_f = 0.52 in hexanes/EtOAc 60:40 v/v); mp: 70–72 °C; IR (KBr) 3024, 2930, 2837, 1604, 1583, 1486, 1455, 1342, 1305, 1275, 1223, 1107, 1033, 991, 902, 872, 840, 748, 727, 693, 602 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.21 (comp, 2H), 7.22–7.11 (comp, 3H), 7.02–6.97 (m, 1H), 6.94–6.86 (comp, 2H), 5.93 (s, 1H), 4.39 (d, J = 15.8 Hz, 1H), 3.73 (d, J = 15.8 Hz, 1H), 3.48–3.35 (m, 1H), 3.24–3.13 (m, 1H), 3.13–3.02 (m, 1H), 2.91–2.78 (m, 1H), 2.04–1.91 (m, 1H), 1.91–1.77 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.6, 141.4, 136.2, 129.9, 129.8, 128.8, 127.7, 127.4, 126.1, 120.7, 120.6, 116.5, 94.1, 54.3, 52.6, 34.8, 27.0; m/z (ESI–MS) 252.1 [M+H]$^+$.

N,O-Acetal 3.2x: Following general procedure A, compound **3.2x** was obtained from the reaction between 3,5-di-t-butylsalicylaldehyde and pyrrolidine at reflux for 24 h. The reaction mixture was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 159.2 mg of **3.2x** as a tan oil (55% yield) (R_f = 0.46 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2954, 2865, 1651, 1478, 1445, 1389, 1360, 1223, 1173, 1123, 947, 886 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15 (d, J = 2.3 Hz, 1H), 6.83 (d, J = 2.3 Hz, 1H), 5.06–5.02 (m, 1H), 4.41 (d, J = 16.7 Hz, 1H), 3.82 (d, J = 16.7 Hz, 1H), 3.05 (app td, J = 8.5, 3.4 Hz, 1H), 2.90 (app q, J = 8.4 Hz, 1H), 2.20–2.07 (comp, 2H), 2.06–1.87 (comp, 2H), 1.37 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.3, 141.7, 136.6, 121.8, 121.5, 117.8, 89.9, 49.5, 47.2, 34.9, 34.2, 32.3, 31.6, 29.7, 21.4; m/z (ESI–MS) 288.2 [M+H]$^+$.

N,O*-Acetal (±): Following general procedure B, compound **3.2z** was obtained from the reaction between (2-hydroxynaphthalen-1-yl)(phenyl)methanone[35] and azepane at reflux for 2 h. The reaction mixture was purified via silica gel chromatography in 97:2:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 177.1 mg of **3.2z** as a white solid (54% yield). The relative stereochemistry was determined by GCOSY and NOESY NMR. (R$_f$ = 0.40 in hexanes/EtOAc 97:3 v/v); mp: 59–61 °C; IR (KBr) 3059, 2934, 2852, 1621, 1598, 1514, 1464, 1410, 1342, 1232, 1168, 1088, 1071, 956, 904, 891, 810, 744, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80–7.75 (m, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.37–7.32 (m, 1H), 7.33–7.17 (comp, 7H), 7.11 (d, *J* = 8.9 Hz, 1H), 5.30 (s, 1H), 4.87 (app t, *J* = 7.2 Hz, 1H), 3.32–3.19 (m, 1H), 2.77–2.64 (m, 1H), 2.21 (app dt, *J* = 15.0, 7.7 Hz, 1H), 1.97–1.61 (comp, 5H), 1.56–1.33 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 152.9, 143.2, 132.5, 129.2, 128.9, 128.5, 128.4, 128.0, 127.0, 126.4, 122.9, 122.6, 119.0, 112.6, 85.2, 64.6, 49.9, 34.0, 30.5, 30.2, 21.8; *m/z* (ESI–MS) 330.1 [M+H]$^+$.

N,O*-Acetal 3.2b (±): Following general procedure A, compound **3.2b** was obtained from the reaction between 1-(2-hydroxy-4,6-dimethylphenyl)ethanone[30] and pyrrolidine at reflux for 24 h. The reaction mixture was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 32.1 mg of **3.2b** as a colorless oil (15% yield). The relative stereochemistry was determined by GCOSY and NOESY NMR. (R$_f$ = 0.50 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2969, 2854, 1617, 1578, 1454, 1371, 1309, 1285, 1180, 1130, 1084, 1047, 975, 959, 836 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.54 (s, 1H), 6.44 (s, 1H), 5.34–5.26 (m, 1H), 3.91 (app q, *J* = 6.9 Hz, 1H), 3.09–2.99 (m, 1H), 2.67 (app q, *J* = 8.6 Hz, 1H), 2.23 (s, 3H), 2.21 (s, 3H), 2.14–2.04 (comp, 2H), 1.98–1.88 (comp, 2H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 152.6, 137.0, 135.7, 122.9, 118.6, 114.5, 85.1, 49.6, 48.2, 32.3, 22.4, 21.0, 20.6, 18.3; *m/z* (ESI–MS) 218.0 [M+H]$^+$.

Benzopyran 3.13: Following general procedure A, compound **3.13** was obtained from the reaction between salicylaldehyde and 1-methyl-1,2,3,4-tetrahydroisoquinoline[12] at 80 °C for 2 h. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 176.5 mg of **3.13** as a yellow solid (99% yield) (R_f = 0.41 in hexanes/EtOAc 90:10 v/v); mp: 138−140 °C; IR (KBr) 3025, 2954, 2858, 1620, 1588, 1487, 1454, 1389, 1311, 1245, 1232, 1154, 947, 935, 824, 760, 732 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.80 (br s, 1H), 7.38 (dd, J = 7.8, 1.5 Hz, 1H), 7.29–7.12 (comp, 6H), 6.98–6.87 (comp, 3H), 6.88–6.79 (comp, 2H), 6.77 (app td, J = 7.4, 1.2 Hz, 1H), 5.66 (d, J = 9.9 Hz, 1H), 4.55 (d, J = 14.4 Hz, 1H), 3.51 (d, J = 14.4 Hz, 1H), 3.36 (app td, J = 11.9, 3.6 Hz, 1H), 3.07 (ddd, J = 17.3, 12.3, 5.7 Hz, 1H), 2.99 (ddd, J = 11.6, 5.7, 1.8 Hz, 1H), 2.83–2.75 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 157.5, 153.2, 137.7, 133.3, 130.2, 129.6, 129.4, 128.7, 128.5, 128.4, 127.3, 127.2, 126.6, 123.1, 121.4, 120.7, 119.5, 118.3, 116.2, 115.2, 90.4, 52.7, 41.4, 29.0; m/z (ESI−MS) 356.2 [M+H]$^+$.

N,S-Acetal 3.29a: Following general procedure C, compound **3.29a** was obtained from the reaction between thiosalicylaldehyde[37] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 236 mg of **3.29a** as a tan solid (93% yield) (R_f = 0.34 in hexanes/EtOAc 90:10 v/v); mp: 175-176 °C; IR (KBr) 2980, 2841, 2407, 1948, 1917, 1587, 1567, 1470, 1431, 1263, 1221, 1175, 1138, 933, 774, 754 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26–7.15 (comp., 4H), 7.12–6.96 (comp., 4H), 6.16 (s, 1H), 4.55 (d, J = 16.6 Hz, 1H), 3.94 (d, J = 16.6 Hz, 1H), 3.31–3.15 (comp., 2H), 2.90–2.77 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.9, 134.8, 133.1, 129.2, 128.0, 127.9, 127.0, 126.6, 126.4, 126.2, 126.1, 124.2, 67.1, 57.8, 43.7, 28.8; m/z (ESI−MS) 254.2 [M+H]$^+$.

N,S-Acetal 3.29b: Following general procedure C, compound **3.29b** was obtained from the reaction between thiosalicylaldehyde[37] and pyrrolidine at 60 °C for 3.5 h. The

reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 122 mg of **3.29b** as an orange solid (64% yield) (R$_f$ = 0.38 in hexanes/EtOAc 85:15 v/v); mp: IR (KBr) 3289, 3958, 2929, 2838, 1586, 1566, 1468, 1468, 1432, 1344, 1259, 1230, 1135, 1063, 991, 919, 873, 742, 609 cm^{-1}; 51-53 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20–6.91 (comp, 4H), 5.10–4.84 (m, 1H), 4.27 (d, J = 15.9 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 2.97–2.86 (m, 1H), 2.78 (app q, J = 8.4 Hz, 1H), 2.39–2.26 (m, 1H), 2.16–2.00 (m, 1H), 2.00–1.86 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.8, 128.1, 127.5, 126.8, 124.1, 67.2, 51.6, 49.1, 32.5, 21.8; m/z (ESI–MS) 192.0 [M+H]$^+$.

***N,S*-Acetal 3.29c:** Following general procedure C, compound **3.29c** was obtained from the reaction between thiosalicylaldehyde[37] and piperidine at 90 °C for 32 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 118 mg of **3.29c** as a yellow solid (58% yield) (R$_f$ = 0.28 in hexanes/EtOAc 90:10 v:v); mp: 106-107 °C; IR (KBr) 3269, 2941, 2412, 1586, 1564, 1465, 1431, 1279, 1188, 1123, 1037, 829, 742, 679, 650, 566 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12–6.88 (comp, 4H), 5.29–5.22 (m, 1H), 4.29 (d, J = 16.4 Hz, 1H), 3.74 (d, J = 16.4 Hz, 1H), 2.76 (app td, J = 11.2, 3.9 Hz, 1H), 2.51 (app dt, J = 11.2, 3.7 Hz, 1H), 2.03 (app tt, J = 13.3, 4.1 Hz, 1H), 1.95–1.50 (comp., 5H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.8, 127.9, 127.0, 126.7, 126.4, 123.7, 64.8, 58.4, 45.9, 29.9, 25.2, 18.1; m/z (ESI–MS) 206.2 [M+H]$^+$.

***N,S*-Acetal 3.29d:** Following general procedure C, compound **3.29d** was obtained from the reaction between thiosalicylaldehyde[37] and azepane at 60 °C for 14 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 154 mg of **3.29d** as a brown oil (70% yield) (R$_f$ = 0.51 in hexanes/EtOAc 80:10 v/v); IR (KBr) 3058, 2930, 2850, 1714, 1587,

1566, 1438, 1354, 1260, 1203, 1145, 1085, 955, 745, 673, 581 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14–6.91 (comp, 4H), 5.20 (app t, J = 7.3 Hz, 1H), 4.22 (d, J = 16.2 Hz, 1H), 3.83 (d, J = 16.2 Hz, 1H), 3.04–2.88 (m, 1H), 2.45 (app dt, J = 14.3, 4.0 Hz, 1H), 2.41–2.25 (m, 1H), 1.94–1.83 (m, 1H), 1.83–1.59 (comp, 5H), 1.47–1.27 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.4, 128.1, 127.7, 127.1, 126.7, 123.5, 69.4, 59.6, 47.6, 36.0, 29.6, 29.4, 23.2; m/z (ESI–MS) 220.2 [M+H]$^+$.

N,S-Acetal 3.29e: Following general procedure D, compound **3.29e** was obtained from the reaction between thiosalicylaldehyde[37] and morpholine at 120 ºC for 10 min. The reaction mixture was purified via silica gel chromatography in 74:25:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 120 mg of **3.29e** as a white solid (58% yield) (R$_f$ = 0.14 in hexanes/EtOAc 85:15 v/v); mp: 140-142 ºC; IR (KBr) 3853, 3675, 3649, 3628, 2889, 2849, 2360, 2340, 1558, 1540, 1521, 1506, 1456, 1436, 1142, 1122, 1098, 1007, 746, 657 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14–6.93 (comp, 4H), 4.95 (s, 1H), 4.28 (d, J = 16.5 Hz, 1H), 3.98–3.91 (comp, 2H), 3.83–3.65 (comp, 3H), 3.04 (app td, J = 11.3, 3.4 Hz, 1H), 2.43–2.36 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.0, 128.0, 127.2, 127.1, 125.9, 124.2, 68.7, 66.7, 63.1, 57.6, 45.8; m/z (ESI–MS) 207.3 [M+H]$^+$.

N,S-Acetal 3.29f: Following general procedure D, compound **3.29f** was obtained from the reaction between thiosalicylaldehyde[37] and thiomorpholine at 150 ºC for 15 min. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 152 mg of **3.29f** as a white solid (68% yield) (R$_f$ = 0.28 in hexanes/EtOAc 80:20 v/v); mp: 158-159 ºC; IR (KBr) 3267, 3057, 2948, 2841, 2432, 1712, 1588, 1467, 1423, 1377, 1283, 1257, 1228, 1185, 1110, 951, 744, 737, 648 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14–7.04 (comp, 2H), 7.06–6.91 (comp, 2H), 5.33–5.29 (m, 1H), 4.31 (d, J = 16.6 Hz, 1H), 3.71 (d, J = 16.6 Hz, 1H), 3.44–3.34 (m, 1H), 3.17–3.08 (m, 1H), 3.05–2.93 (m, 1H), 2.78–2.70 (m, 1H), 2.67–2.60 (m, 1H), 2.57–

2.50 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.0, 127.9, 127.4, 127.0, 126.1, 124.1, 63.0, 59.5, 46.5, 32.1, 27.7; *m/z* (ESI–MS) 224.9 [M+H]$^+$.

***N,S*-Acetal 3.29g:** Following general procedure D, compound **3.29g** was obtained from the reaction between thiosalicylaldehyde[37] and 1-phenylpiperazine at 120 ℃ for 10 min. The reaction mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 117 mg of **3.29g** as a brown solid (41 % yield) (R$_f$ = 0.25 in hexanes/EtOAc 85:15 v/v); mp: 117–119 ℃; IR (KBr) 3053, 2824, 1597, 1501, 1437, 1247, 1225, 1173, 1074, 1037, 1013, 923, 825, 741, 688, 523, 514 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–7.17 (comp, 2H), 7.16–6.78 (comp, 7H), 5.23–5.15 (m, 1H), 4.36 (d, *J* = 16.5 Hz, 1H), 3.85 (d, *J* = 16.5 Hz, 1H), 3.63–3.58 (comp., 2H), 3.32 (dd, *J* = 12.9, 3.0 Hz, 1H), 3.18 (app td, *J* = 11.0, 3.1 Hz, 1H), 3.05 (app td, *J* = 11.2, 3.1 Hz, 1H), 2.70–2.62 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.7, 133.3, 129.0, 128.8, 127.8, 127.0, 126.8, 125.9, 123.8, 119.8, 116.2, 63.2, 57.3, 52.8, 48.1, 45.9;. *m/z* (ESI–MS) 282.8 [M+H]$^+$.

***N,S*-Acetal 3.29h:** Following general procedure D, compound **3.29h** was obtained from the reaction between thiosalicylaldehyde[37] and *N*-methyl piperazine at 150 ℃ for 15 min. The reaction mixture was purified by silica gel chromatography in 29:70:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 172 mg of **3.29h** as an orange solid (78% yield) (R$_f$ = 0.17 in hexanes/EtOAc 30:70 v/v); mp: 92–93 ℃; IR (KBr) 3854, 3822, 3736, 3651, 3054, 2974, 2935, 2854, 2781, 1712, 1587, 1458, 1437, 1340, 1315, 1279, 1162, 1072, 1018, 658 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.07–6.98 (comp, 2H), 6.97–6.88 (comp, 2H), 5.02 (s, 1H), 4.24 (d, *J* = 16.4 Hz, 1H), 3.73 (d, *J* = 16.4 Hz, 1H), 3.00 (app td, *J* = 11.2, 2.9 Hz, 1H), 2.82–2.72 (comp, 2H), 2.57–2.41 (comp, 2H), 2.35–2.21 (comp, 4H).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.5, 127.7, 127.0, 126.7, 125.9, 123.7, 62.9, 58.1, 57.2, 54.5, 45.9, 45.8; *m/z* (ESI–MS) 222.1 [M+H]$^+$.

***N,S*-Acetal 3.29i:** Following general procedure D, compound **3.29i** was obtained from the reaction between thiosalicylaldehyde[37] and dibenzylamine at 150 °C for 15 min. The reaction mixture was purified by silica gel chromatography in 94:5;1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 242 mg of **3.29i** as a yellow solid (76% yield) (R$_f$ = 0.39 in hexanes/EtOAc 95:5 v/v); mp: 98-100 °C; IR (KBr) 3855, 3753, 3676, 3085, 3028, 2926, 2773, 1948, 1870, 1069, 975, 905, 862, 714, 965 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64 (app d, *J* = 7.6 Hz, 2H), 7.40–7.21 (comp, 9H), 7.20–7.15 (m, 1H), 7.08–7.01 (m, 1H), 6.92 (app d, *J* = 7.3 Hz, 1H), 5.75 (s, 1H), 3.92–3.72 (comp, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.3, 138.3, 133.0, 129.0, 128.5, 128.4, 128.3, 127.9, 127.8, 127.2(7), 127.2(5), 126.9, 124.3, 69.4, 54.6, 50.1; *m/z* (ESI–MS) 318.8 [M+H]$^+$.

***N,S*-Acetal 3.29j:** Following the general procedure C, compound **3.29j** was obtained from the reaction between thiosalicylaldehyde[37] and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[32] at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 78:20:2 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 301.6 mg of **3.29j** as a white solid (96% yield) (R$_f$ = 0.25 in hexanes/EtOAc 60:40 v/v); mp: 163–164 °C; IR (KBr) 3056, 2995, 2926, 2840, 1609, 1519, 1459, 1327, 1271, 1259, 1144, 1100, 1036, 1014, 740, 639 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.09 (app td, J = 7.3, 2.1 Hz, 1H), 7.06–6.97 (comp, 3H), 6.68–6.62 (comp, 2H), 6.09 (s, 1H), 4.68–4.40 (m, 1H), 4.05–3.92 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.35–3.01 (comp, 2H), 2.95–2.60 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 148.7, 147.5, 134.9, 128.0, 127.0, 126.8, 126.6, 126.5, 125.2, 124.1, 111.6, 109.0, 67.1, 57.8, 56.0, 55.9, 43.8, 28.5; *m/z* (ESI–MS) 314.1 [M+H]$^+$.

***N,S*-Acetal 3.29k:** Following the general procedure C, compound **3.29k** was obtained from the reaction between thiosalicylaldehyde[37] and 6-methoxy-1,2,3,4-tetrahydro-isoquinoline[31] at 60 °C for 30 min. The reaction mixture was purified via silica gel

chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 262.9 mg of **3.29k** as a white solid (93% yield) (R$_f$ = 0.29 in hexanes/EtOAc 80:20 v/v); mp: 130–131 ⁰C; IR (KBr) 2999, 2944, 2906, 2850, 1607, 1560, 1502, 1468, 1431, 1383, 1323, 1265, 1249, 1067, 1035, 905, 860, 821, 763, 663 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13–7.05 (comp, 2H), 7.05–6.95 (comp, 3H), 6.74 (dd, J = 8.4, 2.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.12 (s, 1H), 4.74–4.26 (comp, 2H), 3.79 (s, 3H), 3.36–3.04 (comp, 2H), 3.00–2.71 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.89, 134.91, 134.39, 127.78, 127.18, 127.14, 126.75, 126.38, 126.33, 123.90, 113.69, 112.06, 66.77, 57.64, 55.01, 43.38, 28.91.; m/z (ESI–MS) 284.2 [M+H]$^+$.

N,S-Acetal 3.29l: Following general procedure C, compound **3.29l** was obtained from the reaction between thiosalicylaldehyde[37] and 2,3,4,5-tetrahydro-$1H$-benzo[c]azepine[34] at 60 ⁰C for 1 h. The reaction mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 219 mg of **3.29l** as a brown solid (82% yield) (R$_f$ = 0.31 in hexanes/EtOAc 95:15 v/v); mp: 110 – 113 ⁰C; IR (KBr) 3048, 2917, 2846,1587, 1560, 1465, 1316, 1108, 1105, 1068, 1035, 980, 871, 848, 769, 738, 662, 612 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18–6.86 (comp, 8H), 6.06 (s, 1H), 4.55 (d, J = 16.7 Hz, 1H), 3.79 (d, J = 16.7 Hz, 1H), 3.45–3.27 (comp, 2H), 2.91–2.78 (m, 1H), 2.70 (app dd, J = 14.9, 6.9 Hz, 1H), 2.00–1.88 (m, 1H), 1.76 (app q, J = 12.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.78, 136.55, 134.14, 130.26, 130.15, 128.44, 128.30, 127.27, 126.84, 126.59, 126.14, 124.33, 74.55, 61.38, 52.25, 34.73, 28.80; m/z (ESI–MS) 268.8 [M+H]$^+$.

N,S-Acetal 3.29m: Following general procedure C, compound **3.29m** was obtained from the reaction between thiosalicylaldehyde[37] and tryptoline at 60 °C for 6 h. The reaction mixture was purified via silica gel chromatography in 78:20:2 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 234.4 mg of **3.29m** as a yellow solid (80% yield) (R$_f$ = 0.21 in hexanes/EtOAc 80:20 v/v); mp: 197–199 ⁰C; IR (KBr) 3397,

2151, 3056, 2919, 2843, 1478, 1466, 1449, 1437, 1367, 1338, 1319, 1186, 1165, 1109, 1067, 748, 731 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.51 (app d, J = 7.9 Hz, 1H), 7.34 (app d, J = 8.1 Hz, 1H), 7.23–7.17 (m, 1H), 7.16–7.03 (comp, 5H), 6.10 (s, 1H), 4.49 (d, J = 16.2 Hz, 1H), 3.97 (d, J = 16.2 Hz, 1H), 3.26–3.12 (m, 1H), 3.06–2.79 (comp, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.4, 134.4, 131.5, 128.4, 128.2, 127.2, 127.1, 126.6, 124.6, 122.5, 119.8, 118.8, 111.2, 109.1, 62.7, 57.6, 45.5, 21.6; *m/z* (ESI–MS) 293.2 [M+H]$^+$.

***N,S*-Acetal 3.29n:** Following general procedure C, compound **3.29n** was obtained from the reaction between thiosalicylaldehyde[37] and 1-phenyl-1,2,3,4-tetrahydroisoquinoline[38] at 60 °C for 1 h. The reaction mixture was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 242.5 mg of **3.29n** as a white solid (75% yield) (R$_f$ = 0.55 in hexanes/EtOAc 80:20 v/v); mp: 146–148 °C; IR (KBr) 3060, 2948, 2892, 1589, 1569, 1486, 1468, 1431, 1320, 1260, 1194, 1147, 1120, 1068, 1035, 827, 740, 700, 674 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74 (app d, J = 6.8 Hz, 2H), 7.36–7.20 (comp, 3H), 7.20–7.06 (comp, 4H), 7.06–6.95 (comp, 2H), 6.92 (app d, J = 7.4 Hz, 1H), 6.64 (app d, J = 7.8 Hz, 1H), 3.97 (d, J = 17.2 Hz, 1H), 3.61 (d, J = 17.2 Hz, 1H), 3.49–3.36 (comp, 2H), 3.10–2.97 (m, 1H), 2.94–2.82 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 145.3, 140.5, 134.2, 132.2, 129.5, 128.7, 128.1, 127.9, 127.8, 127.6, 127.0, 126.9, 126.8, 126.2, 126.0, 124.0, 80.0, 53.6, 47.1, 29.5; *m/z* (ESI–MS) 330.2 [M+H]$^+$.

***N,S*-Acetal 3.29o:** Following general procedure C, compound **3.29o** was obtained from the reaction between 5-methylthiosalicylaldehyde[39] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc /Et$_3$N, resulting in isolation of 232 mg of **3.29o** as a tan solid (87% yield) (R$_f$ = 0.32 in hexanes/EtOAc 90:10 v/v); mp: 167-169 °C; IR (KBr) 3448, 3034, 2957, 2928, 2887, 2848, 1629, 1483, 1474, 1383, 1321, 1144,

1125, 947, 814, 725, 685, 661, 629, 614 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.12 (comp, 4H), 7.00–6.86 (comp, 3H), 6.14 (s, 1H), 4.53 (d, J = 16.6 Hz, 1H), 3.91 (d, J = 16.6 Hz, 1H), 3.34–3.13 (comp, 2H), 2.85–2.27 (comp., 2H), 2.29 (s, 3H);. ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.9, 133.8, 133.0, 131.1, 129.2, 128.6, 127.9, 127.8, 126.4, 126.2, 126.1, 126.0, 66.9, 57.8, 43.7, 28.8, 20.9; m/z (ESI–MS) 268.6 [M+H]$^+$.

***N,S*-Acetal 3.29p:** Following general procedure C, compound **3.29p** was obtained from the reaction between 4-methoxythiosalicylaldehyde[40] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc /Et$_3$N, resulting in isolation of 175 mg of **3.29p** as a tan solid (62% yield) (R$_f$ = 0.29 in hexanes/EtOAc 90:10 v/v); mp: 145–146 °C; IR (KBr) 2996, 2962, 2929, 2840, 1594, 1488, 1359, 1344, 1263, 1233, 1119, 1006, 836, 814, 747, 659 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29–7.11 (comp, 4H), 6.95 (d, J = 8.3 Hz, 1H), 6.71–6.53 (comp, 2H), 6.15 (s, 1H), 4.55–4.42 (m, 1H), 3.98–3.83 (m, 1H), 3.74 (s, 3H), 3.30–3.10 (comp, 2H), 2.93–2.74 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.3, 135.9, 134.6, 133.1, 129.2, 128.9, 127.9, 126.3, 126.1, 118.4, 111.0, 110.9, 67.2, 57.2, 55.3, 43.6, 28.7; m/z (ESI–MS) 284.7 [M+H]$^+$.

***N,S*-Acetal 3.29q:** Following general procedure C, compound **3.29q** was obtained from the reaction between 5-nitrothiosalicylaldehyde[41] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 84:15:1 hexanes/EtOAc /Et$_3$N, resulting in isolation of 173 mg of **3.29q** as a tan solid (57% yield) (R$_f$ = 0.45 in hexanes/EtOAc 85:15 v/v); mp: 193–195 °C; IR (KBr) 3081, 2953, 2848, 1596, 1571, 1330, 1301, 1128, 954, 936, 911, 862, 808, 756, 743, 718, 655, 537 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98–7.88 (comp, 2H), 7.31–7.07 (comp, 5H), 6.27 (s, 1H), 4.31 (br s, 2H), 2.98 (br s, 4H); ^{13}C NMR (75 MHz, CDCl$_3$)

δ 145.8, 143.95, 133.7, 132.9, 129.3, 128.4, 127.0, 126.5, 126.4, 126.1, 122.9, 122.0, 68.6, 57.6, 43.7, 28.6; m/z (ESI–MS) 299.3 [M+H]$^+$.

N,S-Acetal 3.29r: Following general procedure C, compound **3.29r** was obtained from the reaction between thiosalicylaldehyde[37] and 2-methyl pyrrolidine at 60 °C for 1.5 h. The reaction mixture was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 83 mg of **3.29r** as a yellow oil (40% yield). Relative stereochemistry was determined by GCOSY and NOESY NMR. (R$_f$ = 0.44 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3463, 2962, 1705, 1647, 1439, 1373, 1232, 1136, 1068, 1038, 954, 912, 744, 668, 580, 502 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.19–6.95 (comp, 4H), 5.17 (app d, J = 5.9, 1H), 4.23 (d, J = 16.0 Hz, 1H), 3.83 (d, J = 16.0 Hz, 1H), 2.96–2.83 (m, 1H), 2.39–2.29 (app ddt, m, 1H), 2.26–2.17 (m, 1H), 1.93–1.80 (m, 1H), 1.50 (dddd, J = 12.3, 10.3, 7.3, 4.5 Hz, 1H), 1.14 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.8, 128.4, 128.1, 127.5, 126.9, 124.1, 68.9, 53.7, 49.4, 30.8, 30.7, 18.9; m/z (ESI–MS) 206.4 [M+H]$^+$.

In addition, 70 mg of **3.29s** was isolated as a yellow oil (34% yield) (R$_f$ = 0.32 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3057, 2968, 2925, 2846, 1590, 1567, 1476, 1438, 1371, 1341, 1317, 1188, 1069, 1028, 936, 744, 668, 555 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16–6.92 (comp, 4H), 4.43–4.19 (m, 1H), 4.01–3.79 (m, 1H), 3.08–2.91 (m, 1H), 2.83–2.63 (m, 1H), 2.18–1.97 (comp, 2H), 1.95–1.84 (comp, 2H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.5, 128.1, 127.6, 126.7, 126.4, 123.7, 74.8, 50.7, 47.6, 40.9, 29.2, 19.8; m/z (ESI–MS) 206.8 [M+H]$^+$.

N,S-Acetal 3.29t: Following general procedure C, compound **3.29t** was obtained from the reaction between thiosalicylaldehyde[37] and 2-methyl piperidine at 90 °C for 13 h. The reaction mixture was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of a mixture of 153 mg of **3.29t** (70%

yield) and 42 mg of **3.29u** (19% yield) as a yellow solid. Relative stereochemistry of

3.29t was determined by GCOSY and NOESY NMR. Characterization data for **3.29t**:

(R_f = 0.28 in hexanes/EtOAc 90:10 v/v); mp: 74–77 °C; IR (KBr) 3433, 3068, 2976,

2939, 2837, 1571, 1563, 1432, 1372, 1257, 1207, 1157, 1134, 1083, 1070, 741, 677 cm^{-1}; ^{1}H

NMR (500 MHz, CDCl$_3$) δ 7.13–6.87 (comp, 4H), 5.46–5.39 (m, 1H), 4.15 (d, J = 16.4 Hz,

1H), 4.02 (d, J = 16.5 Hz, 1H), 2.69–2.58 (m, 1H), 2.01 (dddd, J = 26.0, 16.7, 13.1, 9.4 Hz,

2H), 1.81–1.70 (m, 1H), 1.68–1.54 (comp, 2H), 1.41–1.24 (m, 1H), 1.05 (d, J = 6.5, Hz,

3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.5, 127.9, 126.9, 126.8(4), 126.8(2), 126.0, 123.6(9),

123.6(7), 66.7, 54.4, 47.1, 34.1, 31.5, 30.4, 19.8, 19.2, 14.1; m/z (ESI–MS) 220.2 [M+H]$^+$.

Computational Details: The conformational space of all intermediates for the

benzoxazine synthesis was explored using the OPLS-2005[42] force field and a modified

Monte Carlo search routine implemented in macromodel 9.9.[43] An energy cutoff of 20

kcal mol^{-1} was used for the conformational analysis, and structures with heavy atom

RMSD less than 1–2 Å after the initial force field optimization were assumed to be the

same conformer. The remaining structures were subsequently optimized employing the

meta-GGA functional TPSS[44] with Grimme's dispersion-correction D2,[45] and the double-

ζ basis set 6-31+G(d,p). Solvation by toluene (or ethanol) was taken into account by

using the integral equation formalism polarizable continuum model (IEFPCM) for all

calculations (optimizations, frequencies, and single points).[46] It has recently been shown

that the use of a polarizable continuum model does not have a large impact on the

calculated frequencies, but is necessary for the location of transition states in some

cases.[47] Vibrational analysis verified that each structure was a minimum or a transition

state. Following the Intrinsic Reaction Coordinates (IRC) confirmed that all transition

states connected the corresponding reactants and products on the potential energy

surface. Two-dimensional potential energy surface scans were performed using the

TPSS-D2/6-31G(d)/IEFPCM level of theory. Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L^{-1} (17.15 mol L^{-1} for ethanol) and 298.15 K. Entropic contributions to the reported free energies were calculated from partition functions evaluated with Truhlar's quasiharmonic approximation.[48] This method uses the same approximations as the usual harmonic oscillator except that all vibrational frequencies lower than 100 cm^{-1} are set equal to 100 cm^{-1} to correct for the breakdown of the harmonic oscillator approximation for low frequencies. Electronic energies were subsequently obtained from single-point calculations of the TPSS-D2 geometries employing the meta-hybrid M06-2X functional,[49] the large triple-ζ def2-TZVPP basis set,[50] IEFPCM for toluene (or ethanol), and Grimme's dispersion-correction D3 (zero-damping),[51] a level expected to give accurate energies.[52] An ultrafine grid corresponding to 99 radial shells and 590 angular points was used throughout this study for numerical integration of the density.[53] All DFT calculations were performed with gaussian 09[53] and the additional D3 corrections for the single-point calculations were carried out with Grimme's DFT-D3 program.[50]

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Chapter 4

The Decarboxylative Strecker Reaction

4.1 Background

The decarboxylative condensation of amino acids and aldehydes is a powerful method for yielding azomethine ylide intermediates (see chapter 1, section 11). Generally, these azomethine ylides then undergo (3+2) cycloadditions or 1,5- or 1,7-electrocyclizations.[1] Before 2011, a few non-pericyclic 1,6-annulation reactions had been reported using this method,[2] however, the three-component variant with an external nucleophile was first reported by Seidel and Zhang in 2010.[3] In this reaction, decarboxylatively formed azomethine ylides are functionalized by naphthol pronucleophiles, yielding α-arylated teriary amines (e.g. **4.3**, Figure 4.1, eq 1). Trace amounts of undesired regioisomer **4.4** are also obtained in this reaction.

Figure 4.1 **Decarboxylative Three-Component Coupling Reaction**
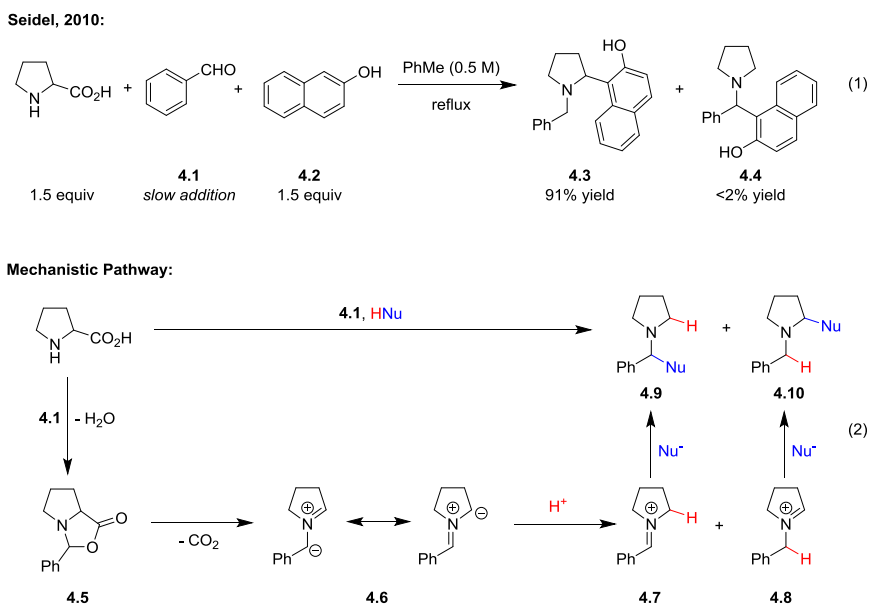
The probable pathway for this type of reaction is shown in eq 2 (Figure 4.1). Condensation of the amino acid with benzaldehyde (**4.1**) results in the formation of oxazolidone **4.5**, which, through decarboxylation, yields azomethine ylide **4.6**. The azomethine ylide, being a 1,3-dipole, can be protonated at one of two sites. Endocyclic protonation leads to iminium **4.7**, which produces undesired regioisomer **4.9** when subjected to nucleophilic attack. Exocyclic protonation leads to iminium **4.8** – inaccessible by conventional amine condensations – resulting in the formation of desired regioisomer **4.10**. The benefit of this chemistry is that these normally inaccessible endocyclic iminium ions can be formed and used in various reactions.

Figure 4.2 **The Strecker Reaction and Uses for α-Amino Nitriles**
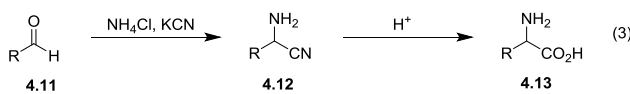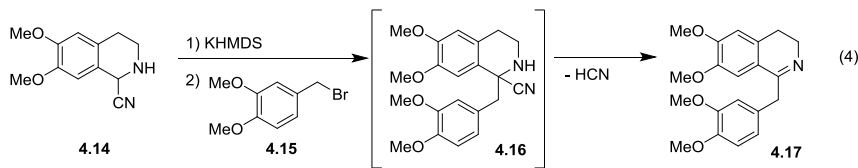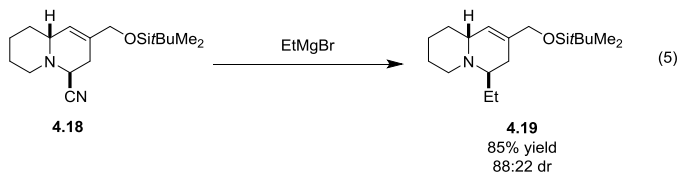
The Strecker Reaction, developed by Adolph Strecker in 1850,[4] is a method to synthesize α-amino nitriles from aldehydes, amines and cyanide (Figure 4.2, eq 3). Since 1850, the reaction has been well developed.[5] Perhaps the most common use of the reaction involves the hydrolysis of the resulting amino nitriles to give α-amino acids. α-

Amino nitriles can be functionalized in other ways, however.[6] Deprotonated amino nitriles readily react with electrophiles.[6e] Noyori and coworkers demonstrated this mode of reactivity in a synthesis of laudanosine (Figure 4.2, eq 4).[7] Alternatively, in a process known as the Bruylants reaction,[8] a Grignard can be added to an α-amino nitrile and – instead of adding to the nitrile – replaces the cyano group on the amine (Figure 4.2, eq 4).[9,10]

While many synthetically useful α-amino nitriles can be made using conventional Strecker methods, ring-functionalized amino nitriles of the type **4.10** required alternative methods of synthesis.[11] We reasoned that, using the decarboxylative three-component methodology previously developed in the group, a facile method for accessing these products could be developed.

4.2 Development of the Decarboxylative Strecker Reaction

We began our investigation by allowing proline and benzaldehyde (**4.1**) to react in the presence of various cyanide sources. Conventional thermal reaction conditions were initially evaluated but quickly abandoned in favor of reactions performed under microwave irradiation, as the latter led to vastly accelerated reaction rates. The results of this survey are summarized in Table 1. The reaction proceeded as anticipated and the desired regioisomer **4.20a** was consistently formed as the predominant product, with only small amounts of **4.21a** being obtained. In favorable cases, the formation of **4.21a** could be suppressed completely. Although various sources of cyanide including simple potassium cyanide enabled product formation, the use of trimethylsilyl cyanide (TMSCN) was found to be most convenient. Under optimized microwave conditions, the reaction of benzaldehyde, 1.3 equiv of proline, and 1.2 equiv of TMSCN in *n*-butanol as the solvent gave rise to product **4.20a** as the only detectable regioisomer in near-quantitative yield (>97%, entry 7). A particularly attractive feature of this reaction is the

brief reaction time, requiring only 10 min for completion. In comparison, an otherwise

identical reaction conducted under reflux in *n*-butanol for 5 h provided **4.20a** in 64%

yield.

Table 4.1 **Evaluation of Reaction Parameters[a]**

entry	proline (equiv)	solvent	XCN (equiv)	ratio **4.20a** : **4.21a**	yield (%)
1	2.0	PhMe	TMSCN (1.2)	**4.20a** only	81
2	1.5	PhMe	TMSCN (1.2)	28 : 1	90
3	1.5	PhMe	TMSCN (1.1)	17 : 1	89
4	1.3	PhMe	TMSCN (1.2)	5 : 1	81
5	1.2	PhMe	TMSCN (1.2)	4 : 1	77
6	1.5	*n*-BuOH	TMSCN (1.2)	**4.20a** only	>97
7	1.3	*n*-BuOH	TMSCN (1.2)	**4.20a** only	>97
8	1.2	*n*-BuOH	TMSCN (1.2)	31 : 1	>97
9	1.5	xylenes	TMSCN (1.2)	17 : 1	>97
10	1.5	*n*-BuOH	CuCN (1.2)	N/A	trace
11	1.5	*n*-BuOH	KCN (1.2)	**4.20a** only	53
12	1.5	*n*-BuOH	$K_3[Fe(CN)_6]$ (1.2)	**4.20a** only	8
13	1.5	*n*-BuOH	EtOCOCN (1.2)	5 : 1	55

[a] Reactions were performed on a 1 mmol scale.

With the optimized reaction conditions in hand, a series of different aldehydes

was evaluated (Figure 4.3). Only one regioisomer was detected in all cases in which no

regioisomeric ratio (rr) is given. Electron-rich and electron-poor aromatic aldehydes

with different substitution patterns provided products in generally excellent yields.

Heteroaromatic aldehydes derived from pyridine, furan, thiophene, and indole were also

viable substrates. Ethyl glyoxylate and enolizable aliphatic aldehydes also engaged in

reactions with proline and TMSCN to give the desired α-amino nitriles. Benzophenone,

although apparently less reactive under these conditions, provided the corresponding

product in moderate yield. Next, we sought to expand the substrate scope to α-amino

acids other than proline (Figure 4.4). The analogous reaction with pipecolic acid as outlined in eq 8 provided the desired product **4.22** as the only detectable regioisomer in near-quantitative yield. The corresponding reaction of tetrahydroisoquinoline-3-carboxylic acid provided the expected product **4.24** in 91% yield (eq 9).

Figure 4.3 **Scope of the Decarboxylative Strecker Reaction with Proline**
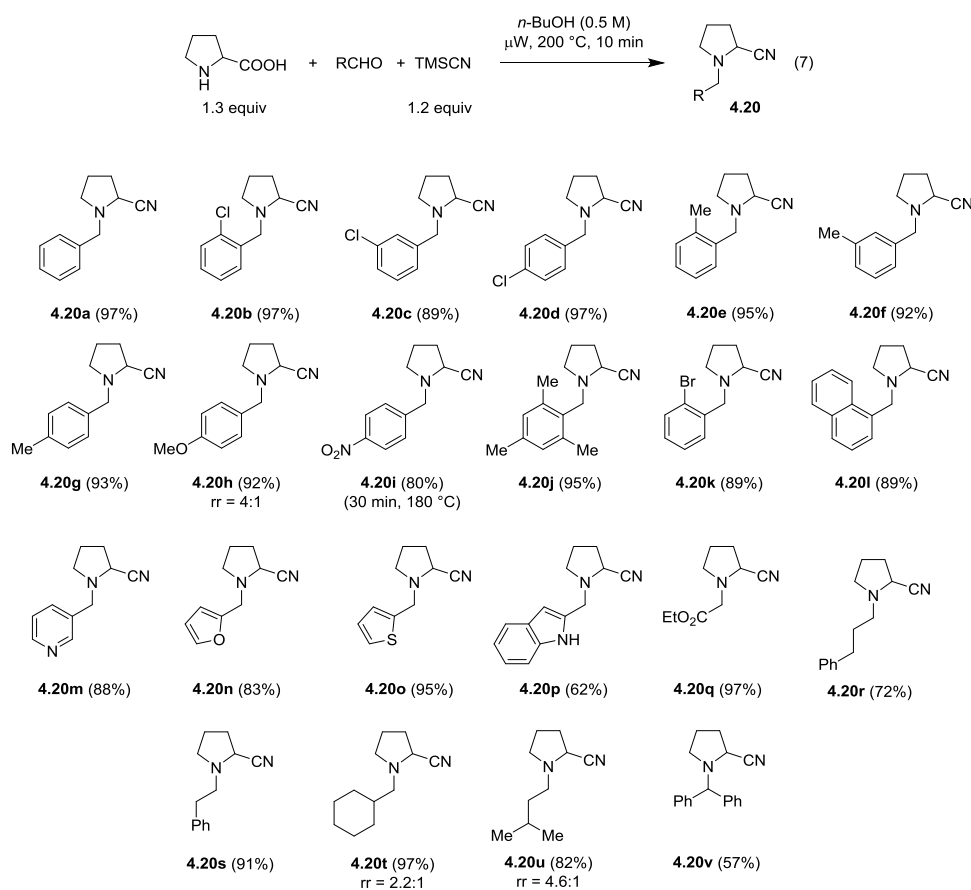
As shown in eqs 10 and 11, single regioisomeric products were also obtained in reactions of N-benzyl glycine and N-methyl glycine (sarcosine). Interestingly, products **4.27** and **4.29** represent the opposite regioisomers to those obtained with cyclic amino acids. This finding most likely reflects the different reactivity of the corresponding azomethine ylides and their individually preferred protonation sites.

Figure 4.4 **α-Amino Acid Scope of the Decarboxylative Strecker Reaction**
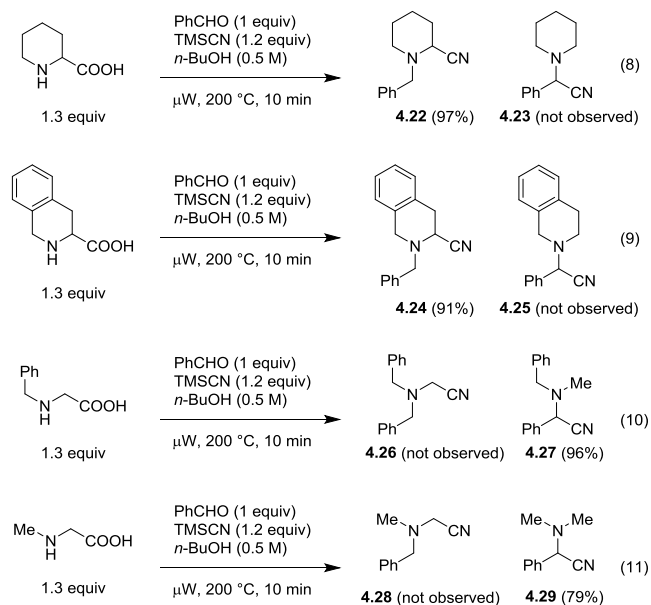
4.3 Mechanistic Insights into the Decarboxylative Strecker

Further analysis of the results displayed in Table 4.1, in particular a comparison of entries 1, 2, 4 and 5, revealed the striking observation that the regioisomeric ratios of **4.20a** and **4.21a** are apparently dependent on the amount of proline used. An increase of the equivalents of proline resulted in a gradual increase of the regioisomeric ratio favoring the desired product **4.20a**, up to the point where **4.21a** could no longer be detected. An attempt to rationalize this finding is provided in Figure 4.5. Under the reaction conditions, regioisomer **4.21a** may be in equilibrium with small amounts of the ion pair **4.21a'**. Interception of **4.21a'** by proline and the associated formation of pyrrolidine could thus be a pathway for regioisomeric enrichment. A sufficient amount of proline could thus lead to complete consumption of undesired **4.21a**.

Figure 4.5 **Proposed Pathway for Regioisomeric Enrichment**
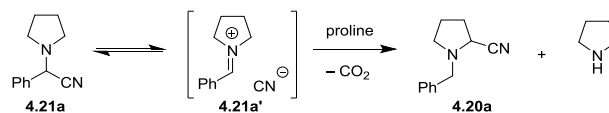
To establish whether the mechanism depicted in Figure 4.5 is indeed operative, a number of control experiments were performed (eqs 12-16). Compound **4.21a** was exposed to a slight excess of proline (1.1 equiv) under the previously established reaction conditions (eq 12). In line with the above considerations, amino nitrile **4.20a** was obtained as the only product in near-quantitative yield.

Figure 4.6 **Mechanistic Studies for the Decarboxylative Strecker**
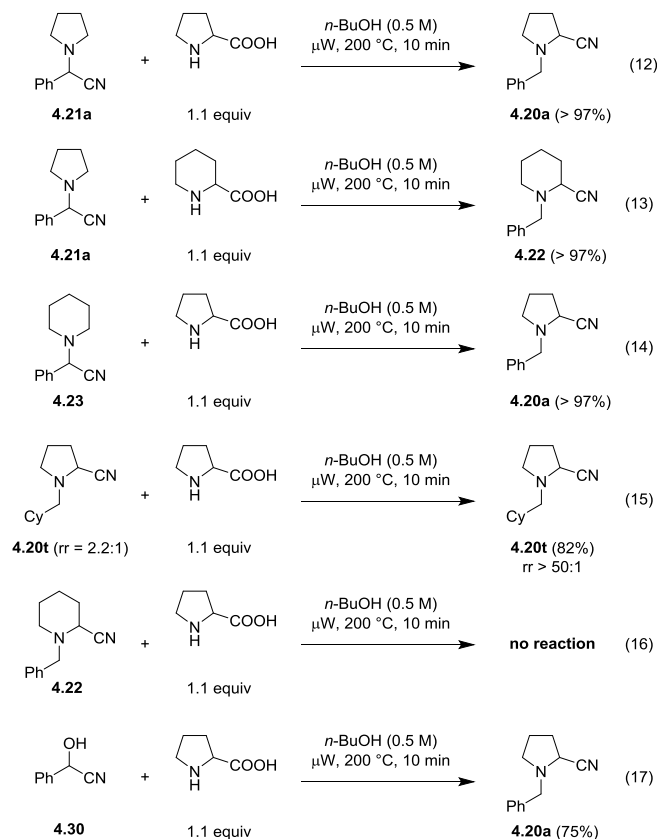
Replacement of proline for pipecolic acid in an otherwise identical experiment led to the exclusive formation of **4.22** (eq 13), establishing the role of the amino acid in

this process. Likewise, starting from **4.23** and proline, **4.20a** was obtained exclusively (eq 14). As implied above, this strategy can be applied to the adjustment of product distribution in reactions that are intrinsically less regioselective. For instance, a 2.2:1 mixture of the cyclohexanecarbaldehyde derived product **4.20t** and its corresponding regioisomer provides regioisomerically pure **4.20t** upon treatment with proline (eq 15). As anticipated, a control experiment in which **4.22** was exposed to an excess of proline led to no reaction (eq 16). In a related process, the reaction of cyanohydrin **4.30** and proline also yielded product **4.20a** in 75%yield (eq 17).

As alluded to earlier, α-amino nitriles are extremely versatile compounds and their use extends beyond the synthesis of amino acids.[6] For instance, compound **4.20a** was used by Rychnovsky et al. as a precursor in an intriguing reductive lithiation/intramolecular carbolithiation process.[12] Another particularly useful transformation specific to α-amino nitriles is the Bruylants reaction, which offers the opportunity to replace the cyano group for aryl or alkyl groups.[8-10] Accordingly, α-amino nitrile **4.20a**, which to our knowledge had not previously been used in Bruylants reactions, readily engaged in reactions with phenyl magnesium bromide or *n*-butyl magnesium bromide to form products **4.31** and **4.32** in good yields (Figure 4.7).

Figure 4.7 **Use of α-Amino Nitrile 4.20a in the Bruylants Reaction**
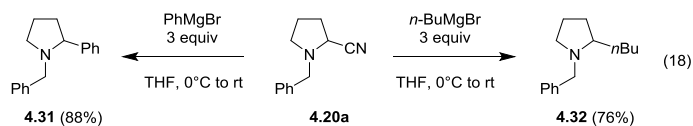
In 2012, Seidel, Ma and Chen followed the publication of the decarboxylative Strecker reaction by synthesizing the same products with unprefunctionalized amines instead of amino acids (Figure 4.8).[13] Undesired regioisomer **4.21a** was demonstrated to isomerize to the endocyclic α-amino nitrile product **4.20a** when exposed to microwave

irradiation and benzoic acid (eq 19). Similarly, cyanohydrin **4.30** underwent the Strecker reaction to yield desired product **4.20a** with high regioisomeric ratio (eq 20). The reversibility of the cyanide addition is thought to be key to these reactions, with **4.20a** being the thermodynamic product.

Figure 4.8 **Redox-Neutral α-Cyanation of Amines**
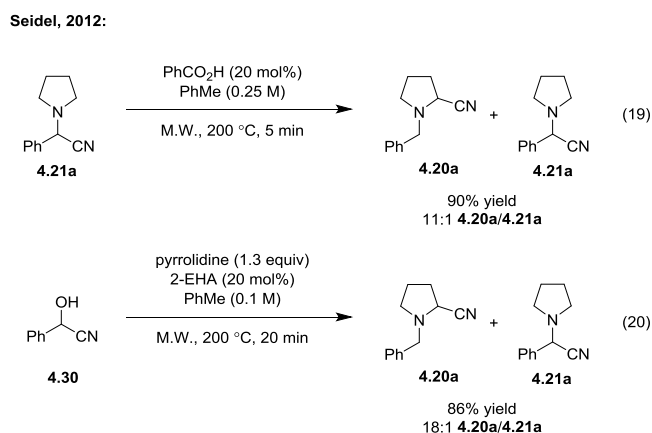
4.4 Conclusion

We have developed a decarboxylative variation on the Strecker reaction where α-amino acids were used to gain access to internal iminium ions which were then functionalized with cyanide, yielding synthetically useful α-amino nitrile products in high yield. This approach is complimentary to classical Strecker chemistry, creating regioisomers generally inaccessible by standard methods. Further functionalization of these products by the Bruylants reaction resulted in α-arylated and alkynylated cyclic amine products.

Experimental Section

General Information: Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230−400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate and Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General Strecker Procedure: A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, amino acid (1.3 mmol), *n*-BuOH (2 mL), aldehyde (1 mmol) and TMSCN (1.2 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70−150 psi) for 10 minutes (Note: SiC passive heating elements must not be used in conjunction with stir bars for they may score glass and cause vessel failure). After cooling with compressed air flow, the reaction mixture was transferred to a round bottom flask and the vessel was

rinsed with EtOAc (4 x 2 mL). Solvent was then removed in vacuo and the reaction mixture was loaded onto a short column and purified by silica gel chromatography. *Note: Due to the use of TMSCN and the potential for HCN formation, all operations should be conducted inside a well-ventilated fume hood.*

Amino Nitrile 4.20b: Following the general Strecker procedure, compound **4.20b** was obtained from *L*-proline and 2-chlorobenzaldehyde as colorless liquid in 97% yield (R_f = 0.17 in 5% EtOAc in Hexanes); IR (KBr) 2960, 2815, 2221, 1572, 1474, 1444, 1376, 1335, 1248, 1138, 1052, 1039, 882, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.43 (app dd, J = 7.2, 2.0 Hz, 1H), 7.38–7.34 (m, 1H), 7.27–7.19 (comp, 2H), 3.98 (d, J = 13.8 Hz, 1H), 3.86 (d, J = 13.8 Hz, 1H), 3.77 (dd, J = 7.4, 2.6 Hz, 1H), 2.95–2.88 (m, 1H), 2.70–2.62 (m, 1H), 2.24–2.09 (comp, 2H), 2.02–1.84 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 135.3, 134.3, 130.5, 129.7, 128.7, 126.7, 118.3, 53.6, 53.5, 51.1, 29.7, 22.0; m/z (ESI-MS) 194.2 [M - CN]$^+$.

Amino Nitrile 4.20c: Following the general Strecker procedure, compound **4.20c** was obtained from *L*-proline and 3-chlorobenzaldehyde as colorless liquid in 89% yield (R_f = 0.14 in 5% EtOAc in Hexanes); IR (KBr) 3062, 2961, 2881, 2820, 2222, 1600, 1576, 1475, 1431, 1373, 1334, 1210, 1144, 1076, 995, 883, 786, 685; ^{1}H NMR (500 MHz, CDCl$_3$) 7.36 (s, 1H), 7.27–7.20 (comp, 3H), 3.87 (d, J = 13.3 Hz, 1H), 3.71 (dd, J = 7.5, 2.4 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 2.92 (ddd, J = 12.7, 8.5, 4.2 Hz, 1H), 2.61–2.52 (m, 1H), 2.23–2.07 (comp, 2H), 2.01–1.87 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.7, 134.3, 129.7, 128.6, 127.6, 126.8, 117.7, 55.8, 53.2, 51.1, 29.4, 21.8; m/z (ESI-MS) 194.1 [M - CN]$^+$.

Amino Nitrile 4.20d: Following the general Strecker procedure, compound **4.20d** was obtained from *L*-proline and 4-chlorobenzaldehyde as a white sticky solid in 97% yield (R_f = 0.13 in 5% EtOAc in Hexanes); IR (KBr) 2960, 2819, 2222, 1644, 1491, 1447,

1409, 1376, 1334, 1124, 1084, 1016, 881, 840 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.29 (app d, J = 1.9 Hz, 4H), 3.87 (app dd, J = 13.2, 1.7 Hz, 1H), 3.67 (dd, J = 7.4, 2.2 Hz, 1H), 3.63 (app dd, J = 13.2, 1.6 Hz, 1H), 2.94–2.86 (m, 1H), 2.59–2.51 (m, 1H), 2.20–2.07 (comp, 2H), 2.00–1.84 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.1, 133.1, 130.0, 128.6, 117.7, 55.7, 53.1, 51.1, 29.4, 21.8; m/z (ESI-MS) 194.1 [M - CN]$^+$.

Amino Nitrile 4.20e: Following the general Strecker procedure, compound **4.20e** was obtained from *L*-proline and *o*-tolualdehyde as colorless liquid in 95% yield (R$_f$ = 0.21 in 5% EtOAc in Hexanes); IR (KBr) 3018, 2957, 2882, 2813, 2221, 1693, 1494, 1460, 1375, 1334, 1286, 1184, 1125, 1051, 882, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.33 (app d, J = 7.4 Hz, 1H), 7.23–7.15 (comp, 3H), 3.93 (d, J = 13.0 Hz, 1H), 3.67 (d, J = 12.9 Hz, 1H), 3.69–3.66 (m, 1H), 2.91 (ddd, J = 12.7, 8.4, 4.3 Hz, 1H), 2.65–2.58 (m, 1H), 2.40 (s, 3H), 2.21–2.08 (comp, 2H), 2.01–1.85 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.3, 135.6, 130.3, 129.3, 127.4, 125.7, 118.1, 54.4, 53.2, 51.0, 29.5, 21.8, 18.9; m/z (ESI-MS) 174.1 [M - CN]$^+$.

Amino Nitrile 4.20f: Following the general Strecker procedure, compound **4.20f** was obtained from *L*-proline and *m*-tolualdehyde as colorless liquid in 95% yield (R$_f$ = 0.14 in 5% EtOAc in Hexanes); IR (KBr) 2959, 2922, 2881, 2814, 2221, 1610, 1487, 1460, 1378, 1334, 1160, 1124, 1089, 886, 789, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.23 (app t, J = 7.5 Hz, 1H), 7.20–7.15 (comp, 2H), 7.10 (app d, J = 7.4 Hz, 1H), 3.90 (d, J = 12.9 Hz, 1H), 3.71 (app dd, J = 7.4, 2.4 Hz, 1H), 3.64 (d, J = 12.9 Hz, 1H), 2.95 (ddd, J = 12.7, 8.5, 4.2 Hz, 1H), 2.63–2.56 (m, 1H), 2.36 (s, 3H), 2.25–2.07 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.0, 137.4, 129.4, 128.2, 128.1, 125.8, 117.8, 56.4, 53.1, 51.1, 29.4, 21.7, 21.2; m/z (ESI-MS) 174.1 [M - CN]$^+$.

Amino Nitrile 4.20g: Following the general Strecker procedure, compound **4.20g** was obtained from *L*-proline and *p*-tolualdehyde as colorless liquid in 93% yield (R$_f$ =

0.14 in 5% EtOAc in Hexanes); IR (KBr) 2960, 2815, 2220, 1633, 1573, 1473, 1445, 1376, 1132, 1052, 1039, 755, 683 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.26 (app d, J = 8.0 Hz, 2H), 7.15 (app d, J = 7.8 Hz, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.69 (app dd, J = 7.4, 2.6 Hz, 1H), 3.64 (d, J = 12.9 Hz, 1H), 2.94 (ddd, J = 12.5, 8.4, 4.2 Hz, 1H), 2.62–2.55 (m, 1H), 2.35 (s, 3H), 2.21–2.07 (comp, 2H), 2.01–1.85 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.0, 134.4, 129.1, 128.7, 117.9, 56.1, 53.0, 51.1, 29.4, 21.8, 21.0; m/z (ESI-MS) 174.1 [M - CN]$^+$.

Amino Nitrile 4.20h: Following the general Strecker procedure, compound **4.20h** was obtained from *L*-proline and *p*-anisaldehyde as colorless liquid in 92% yield, rr = 4:1 (R$_f$ = 0.19 in 10% EtOAc in Hexanes); Characterization data of the major regioisomer: IR (KBr) 2958, 2816, 2222, 1612, 1513, 1462, 1377, 1301, 1245, 1174, 10393, 821 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.27 (app d, J = 8.6 Hz, 2H), 6.86 (app d, J = 8.6 Hz, 2H), 3.85 (d, J = 12.9 Hz, 1H), 3.79 (s, 3H), 3.68–3.64 (m, 1H), 3.59 (d, J = 12.8 Hz, 1H), 2.91 (ddd, J = 12.5, 8.5, 4.2 Hz, 1H), 2.59–2.52 (m, 1H), 2.20–2.06 (comp, 2H), 2.00–1.82 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.9, 129.9, 129.6, 117.9, 113.7, 55.7, 55.1, 52.9, 51.0, 29.3, 21.7; m/z (ESI-MS) 190.0 [M - CN]$^+$.

Amino Nitrile 4.20i: Following the general Strecker procedure, but performing the reaction at 180 ^{o}C for 30 min, compound **4.20i** was obtained from *L*-proline and 4-nitrobenzaldehyde as an off-white solid in 80% yield (R$_f$ = 0.24 in 20% EtOAc in Hexanes); mp: 80–83 ^{o}C; IR (KBr) 2961, 2820, 2220, 1606, 1518, 1346, 1108, 1015, 853, 806, 739 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.17 (app d, J = 8.4 Hz, 2H), 7.53 (app d, J = 8.4 Hz, 2H), 3.98 (d, J = 13.8 Hz, 1H), 3.80 (d, J = 13.9 Hz, 1H), 3.72 (app d, J = 7.6, 2.5 Hz, 1H), 2.91 (ddd, J = 12.7, 8.4, 4.3 Hz, 1H), 2.63–2.56 (m, 1H), 2.26–2.10 (comp, 2H), 2.03–1.87 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 147.3, 145.2, 129.3, 123.7, 117.6, 55.8, 53.4, 51.3, 29.5, 21.9; m/z (ESI-MS) 205.2 [M - CN]$^+$.

Amino Nitrile 4.20j: Following the general Strecker procedure, compound **4.20j** was obtained from *L*-proline and mesitaldehyde as colorless liquid in 95% yield (R_f = 0.16 in 3% EtOAc in Hexanes); IR (KBr) 2954, 2858, 221, 1613, 1461, 1374, 1332, 1120, 1046, 851, 665 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 6.84 (s, 2H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.70 (app dd, *J* = 7.1, 3.4 Hz, 1H), 2.81–2.74 (m, 1H), 2.66–2.55 (m, 1H), 2.37 (s, 6H), 2.27 (s, 3H), 2.15–2.06 (comp, 2H), 1.95–1.85 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.7, 136.7, 131.2, 129.1, 118.8, 53.5, 50.2, 49.5, 29.7, 22.0, 20.8, 20.0; *m/z* (ESI-MS) 202.0 [M - CN]$^+$.

Amino Nitrile 4.20k: Following the general Strecker procedure, compound **4.20k** was obtained from *L*-proline and 2-bromobenzaldehyde as colorless liquid in 89% yield (R_f = 0.19 in 7% EtOAc in Hexanes); IR (KBr) 3059, 2959, 2814, 221, 1567, 1468, 1439, 1375, 1335, 1246, 1134, 1028, 994, 882, 754, 660 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.55 (app dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (app dd, *J* = 7.6, 1.6 Hz, 1H), 7.28 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (app td, *J* = 7.7, 1.7 Hz, 1H), 3.95 (d, *J* = 13.8 Hz, 1H), 3.85 (d, *J* =13.8 Hz, 1H), 3.77 (app dd, *J* = 7.5, 2.7 Hz, 1H), 2.92 (ddd, *J* = 12.8, 8.4, 4.5 Hz, 1H), 2.66 (m, 1H), 2.40 (s, 3H), 2.23–2.09 (comp, 2H), 2.01–1.84 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.8, 132.9, 130.5, 128.8, 127.3, 124.4, 118.2, 55.9, 53.4, 51.0, 29.6, 22.0; *m/z* (ESI-MS) 239.2 [M - CN]$^+$.

Amino Nitrile 4.20l: Following the general Strecker procedure, compound **4.20l** was obtained from *L*-proline and 1-naphthaldehyde as colorless liquid in 89% yield (R_f = 0.27 in 5% EtOAc in Hexanes); IR (KBr) 2957, 2817, 2221, 1597, 1509, 1460, 1379, 1331, 1234, 1142, 1019, 880, 779 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.26 (app d, *J* = 8.5 Hz, 1H), 7.88 (app dd, *J* = 7.8, 1.5 Hz, 1H), 7.83 (app d, *J* = 8.2 Hz, 1H), 7.58–7.49 (comp, 3H), 7.44 (app dd, *J* = 8.1, 1.1 Hz, 1H), 4.45 (d, *J* = 12.8, Hz, 1H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.64 (app t, *J* = 4.9 Hz, 1H), 3.02 (ddd, *J* = 12.7, 8.5, 4.2, 1H), 2.72–2.63 (comp, 1H), 2.15–

2.06 (comp, 2H), 2.02–1.85 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 133.8, 133.3, 132.1, 128.4(2), 128.4(0), 127.2, 125.9, 125.7, 125.2, 124.3, 118.1, 54.7, 53.2, 51.1, 29.5, 21.8; m/z (ESI-MS) 210.1 [M - CN]$^+$.

Amino Nitrile 4.20m: Following the general Strecker procedure, compound **4.20m** was obtained from L-proline and 3-pyridinecarboxaldehyde as colorless liquid in 88% yield (R$_f$ = 0.19 in 50% EtOAc in Hexanes); IR (KBr) 2962, 2822, 2222, 1656, 1579, 1479, 1427, 1378, 1330, 1187, 1124, 1029, 799, 714 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.54 (s, 1H), 8.47 (app d, J = 4.1 Hz, 1H), 7.63 (app d, J = 7.9 Hz, 1H), 7.22 (app dd, J = 7.8, 4.8 Hz, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 3.67–3.64 (m, 1H), 2.84 (ddd, J = 12.4, 8.4, 4.4 Hz, 1H), 2.56–2.49 (comp, 1H), 2.18–2.03 (comp, 2H), 1.96–1.79 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.9, 148.7, 136.3, 133.0, 123.3, 117.6, 53.7, 53.1, 51.0, 29.4, 21.8; m/z (ESI-MS) 188.1 [M + H]$^+$, 161.2 [M - CN]$^+$.

Amino Nitrile 4.20n: Following the general Strecker procedure, compound **4.20n** was obtained from L-proline and furfural as colorless liquid in 83% yield (R$_f$ = 0.16 in 10% EtOAc in Hexanes); IR (KBr) 2962, 2882, 2818, 2222, 1601, 1505, 1445, 1372, 1335, 1224, 1149, 1014, 916, 739, cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.40 (app dd, J = 1.8, 0.7 Hz, 1H), 6.33 (app dd, J = 3.1, 1.8 Hz, 1H), 6.29 (app d, J = 3.1 Hz, 1H), 3.88 (d, J = 13.8 Hz, 1H), 3.76 (d, J = 13.9 Hz, 1H), 3.73 (app dd, J = 7.8, 2.8 Hz, 1H), 2.96 (ddd, J = 12.8, 8.4, 4.4 Hz, 1H), 2.66–2.59 (m, 1H), 2.24–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.2, 142.8, 118.0, 110.5, 109.1, 53.2, 51.4, 48.7, 29.8, 22.2; m/z (ESI-MS) 150.1 [M - CN]$^+$.

Amino Nitrile 4.20o: Following the general Strecker procedure, compound **4.20o** was obtained from L-proline and 2-thiophenecarboxaldehyde as colorless liquid in 95% yield (R$_f$ = 0.24 in 10% EtOAc in Hexanes); IR (KBr) 2959, 2808, 2222, 1645, 1444, 1377, 1329, 1223, 1117, 951, 851, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.25 (app dd, J =

5.2, 1.2 Hz, 1H), 7.00 (app dd, J = 3.4, 1.0 Hz, 1H), 6.94 (app dd, J = 5.1, 1.6 Hz, 1H), 4.07 (d, J = 13.8 Hz, 1H), 3.93 (d, J = 13.8 Hz, 1H), 3.77 (app dd, J = 7.6, 2.5 Hz, 1H), 3.01 (ddd, J = 12.5, 8.3, 4.2 Hz, 1H), 2.64–2.56 (m, 1H), 2.22–2.08 (comp, 2H), 2.02– 1.86 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.6, 126.5, 126.3, 125.4, 117.7, 52.8, 51.0, 50.7, 29.4, 21.8; m/z (ESI-MS) 166.0 [M - CN]$^+$.

Amino Nitrile 4.20p: Following the general Strecker procedure, compound **4.20p** was obtained from *L*-proline and indole-2-carboxaldehyde as colorless liquid in 62% yield (R$_f$ = 0.25 in 80% CH$_2$Cl$_2$ in Hexanes); IR (KBr) 3056, 2961, 2881, 2821, 2224, 1619, 1456, 1421, 1378, 1329, 1289, 1231, 1141, 1087, 995, 927, 879, 791, 750 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.32 (br s, 1H), 7.59 (app d, J = 7.8 Hz, 1H), 7.34 (app dd, J = 8.1, 0.7 Hz, 1H), 7.19 (app dt, J = 7.2, 1.1 Hz, 1H), 7.11 (app dt, J = 7.1, 0.9 Hz, 1H), 6.47 (s, 1H), 4.08 (d, J = 13.6 Hz, 1H), 3.86 (d, J = 13.7 Hz, 1H), 3.72 (dd, J = 7.2, 3.0 Hz, 1H), 2.95 (ddd, J = 12.7, 8.4, 4.3 Hz, 1H), 2.69–2.61 (m, 1H), 2.23 (comp, 2H), 2.05–1.88 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.2, 134.7, 128.2, 121.9, 120.4, 119.8, 117.8, 110.7, 101.8, 53.2, 51.3, 49.5, 29.5, 22.0; m/z (ESI-MS) 199.0 [M - CN]$^+$.

Amino Nitrile 4.20q: Following the general Strecker procedure, compound **4.20q** was obtained from *L*-proline and ethyl glyoxalate solution (~50% in toluene) as colorless liquid in 97% yield (R$_f$ = 0.26 in 20% EtOAc in Hexanes); IR (KBr) 2982, 2822, 2220, 1743, 1464, 1428, 1384, 1200, 1160, 1028, 863 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 4.13 (t, J = 4.1 Hz, 2H), 4.08 (app dd, J = 7.8, 4.1 Hz, 1H), 3.51–3.40 (comp, 2H), 3.00 (ddd, J = 13.0, 8.8, 5.1 Hz, 1H), 2.66–2.58 (m, 1H), 2.26–2.16 (m, 1H), 2.12–2.14 (m, 1H), 1.95– 1.84 (comp, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.7, 118.0, 60.7, 52.8, 52.4, 51.3, 29.8, 22.1, 13.9; m/z (ESI-MS) 156.1 [M - CN]$^+$.

Amino Nitrile 4.20r: Following the general Strecker procedure, compound **4.20r** was obtained from *L*-proline and hydrocinnamaldehyde as colorless liquid in 72% yield

(R_f = 0.16 in 10% EtOAc in Hexanes); IR (KBr) 3026, 2942, 2813, 2220, 1602, 1496, 1454, 1386, 1318, 1182, 1145, 1123, 1079, 1030, 966, 882, 747, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.33–7.27 (comp, 2H), 7.23–7.18 (comp, 3H), 3.76 (app dd, J = 7.6, 2.8 Hz, 1H), 2.89 (ddd, J = 12.9, 8.4, 4.6 Hz, 1H), 2.73 (m, 1H), 2.69 (t, J = 7.6 Hz, 2H), 2.64–2.52 (comp, 2H), 2.23–2.08 (comp, 2H), 2.01–1.82 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.7, 128.3, 128.2, 125.8, 118.1, 53.6, 51.8, 51.0, 33.3, 30.0, 29.5, 21.8; m/z (ESI-MS) 188.3 [M - CN]$^+$.

Amino Nitrile 4.20s: Following the general Strecker procedure, compound **4.20s** was obtained from *L*-proline and phenylacetaldehyde as colorless liquid in 91% yield (R_f = 0.24 in 15% EtOAc in Hexanes); IR (KBr) 3027, 2949, 2815, 2220, 1603, 1497, 1454, 1383, 1342, 1181, 1146, 1122, 1079, 1030, 884, 751, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.33–7.27 (comp, 2H), 7.25–7.18 (comp, 3H), 3.84 (dd, J = 7.4, 2.6 Hz, 1H), 3.01–2.91 (comp, 2H), 2.88–2.78 (comp, 3H), 2.63–2.57 (m, 1H), 2.23–2.09 (comp, 2H), 2.01–1.85 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.5, 128.6, 128.4, 126.2, 118.0, 54.2, 53.7, 51.3, 35.1, 29.6, 21.9; m/z (ESI-MS) 174.2 [M - CN]$^+$.

Amino Nitrile 4.20t: Following the general Strecker procedure, compound **4.20t** was obtained from *L*-proline and cyclohexanecarboxaldehyde as colorless liquid in 97% yield as a mixture of regioisomers; rr = 2.2:1 (R_f = 0.23 in 5% EtOAc in Hexanes); Characterization data of the major regioisomer: IR (KBr) 2923, 2851, 2810, 2221, 1449, 1341, 1244, 1189, 1147, 1114, 1082, 879 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 3.72 (dd, J = 7.5, 2.4 Hz, 1H), 2.83 (app dt, J = 9.1, 4.5 Hz, 1H), 2.54–2.42 (comp, 2H), 2.40–2.33 (m, 1H), 2.19–2.04 (comp, 2H), 1.96–1.81 (comp, 2H), 1.80–1.73 (comp, 2H), 1.73–1.60 (comp, 2H), 1.48–1.37 (m, 1H), 1.31–1.09 (comp, 4H), 0.94–0.74 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 118.3, 59.4, 54.1, 51.4, 36.5, 31.6, 31.5, 29.6, 26.7, 25.9(2), 25.9(1), 21.9; m/z (ESI-MS) 166.2 [M - CN]$^+$.

Amino Nitrile 4.20u: Following the general Strecker procedure, compound **4.20u** was obtained from *L*-proline and isovaleraldehyde as colorless liquid in 82% yield as a mixture of regioisomers; rr = 4.6:1 (R_f = 0.25 in 10% EtOAc in Hexanes); Characterization data of the major regioisomer: IR (KBr) 2956, 2870, 2813, 2220, 1468, 1385, 1367, 1152, 1125, 1097, 885 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 3.75 (dd, *J* = 7.3, 2.7 Hz, 1H), 2.87 (ddd, *J* = 12.8, 8.3, 4.5 Hz, 1H), 2.72–2.62 (m. 1H), 2.57–2.46 (comp, 2H), 2.20–2.05 (comp, 2H), 1.97–1.80 (comp, 2H), 1.67–1.57 (m, 1H), 1.41–1.33 (comp, 2H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 118.1, 53.7, 51.2, 50.8, 37.3, 29.5, 26.2, 22.7, 22.5, 21.8; *m/z* (ESI-MS) 140.1 [M - CN]$^+$.

Amino Nitrile 4.20v: Following the general Strecker procedure, compound **4.20v** was obtained from *L*-proline and 1-naphthaldehyde as a white solid in 57% yield (R_f = 0.22 in 3% EtOAc in Hexanes); mp: 108–111 ^{o}C; IR (KBr) 3061, 3028, 2958, 2821, 2222, 1598, 1491, 1453, 1306, 1186, 1130, 1076, 1028, 927, 887, 748, 706, 628 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.50 (app dd, *J* = 7.7, 1.5 Hz, 4H), 7.30 (app t, *J* = 7.4 Hz, 4H), 7.24–7.19 (comp, 2H), 4.61 (s, 1H), 3.78 (app d, *J* = 7.3 Hz, 1H), 2.98 (ddd, *J* = 11.8, 7.9, 4.2 Hz, 1H), 2.44–2.36 (m, 1H), 2.25–2.14 (m, 1H), 2.13–2.03 (m, 1H), 2.01–1.87 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.5, 142.0, 128.8, 128.6, 127.6, 127.5, 127.3(1), 127.3(0), 117.7, 71.8, 53.1, 49.9, 29.4, 21.8; *m/z* (ESI-MS) 136.0 [M - CN]$^+$.

Amino Nitrile 4.24: Following the general Strecker procedure, compound **4.24** was obtained from (*S*)-(-)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid and benzaldehyde as an off-white solid in 91% yield (R_f = 0.21 in 7% EtOAc in Hexanes); mp: 110–112 ^{o}C; IR (KBr) 2818, 2222, 1644, 1496, 1455, 1357, 1315, 1145, 1091, 1074, 1028, 989, 741, 701 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.42–7.30 (comp, 5H), 7.21–7.15 (comp, 2H), 7.13–7.10 (m, 1H), 7.06 (app t, *J* = 4.3 Hz, 1H), 4.03 (dd, *J* = 6.1, 1.5 Hz, 1H), 3.98 (d, *J* = 15.6 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 3.70 (d, *J* = 13.2 Hz, 1H),

3.31 (dd, J = 16.3, 6.1 Hz, 1H), 2.98 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.4, 132.8, 129.8, 129.0, 128.7(2), 128.7(0), 127.9, 126.7, 126.6, 126.5, 116.3, 60.2, 51.6, 49.3, 32.6; m/z (ESI-MS) 222.2 [M - CN]$^+$.

General Electrocyclization Procedure: α,β–Unsaturated aldehyde or ketone (1 mmol) was added to a 25 mL round bottom flask containing a stir bar. The flask was charged with toluene (10 mL), 3 Å molecular sieves (200 mg), benzoic acid (1 mmol) and secondary amine (5 mmol). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath at reflux until the aldehyde or ketone was consumed. Once cooled to room temperature, the mixture was filtered through a pad of celite and rinsed with EtOAc (50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified via silica gel chromatography.

Pyrroline a2: Following the general electrocyclization procedure, (*E*)-α-methylcinnamaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 1 h. The residue was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 176.6 mg of **a2** as a yellow oil (yield 68%). R$_f$ = 0.12 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3057, 2954, 2925, 2808, 1626, 1493, 1472, 1456, 1393, 1330, 1289, 1260, 1156, 756, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41–7.34 (comp, 2H), 7.31–7.25 (comp, 3H), 7.18 (app d, J = 8.1 Hz, 1H), 7.11 (app d, J = 7.6 Hz, 1H), 7.09–7.04 (m, 1H), 6.82 (app t, J = 7.6 Hz, 1H), 3.48 (app t, J = 8.7 Hz, 1H), 3.21–2.89 (comp, 5H), 2.78 (app t, J = 8.7 Hz, 1H), 1.04 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.58, 138.60, 135.03, 129.77, 128.65, 128.52, 127.20, 126.38, 126.29, 125.44, 120.00, 104.75, 61.52, 48.41, 41.60, 30.43, 17.85; m/z (ESI–MS) 262.3 [M+H]$^+$.

Pyrroline z10a: Following the general electrocyclization procedure, chalcone and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 201.2 mg of

z10a as a colorless oil (yield 77%). R_f = 0.14 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 3024, 2962, 2870, 1625, 1599,1446, 1357, 1246, 1074, 1028, 917, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69–7.62 (comp, 2H), 7.43–7.26 (comp, 8H), 5.18 (d, J = 2.5 Hz, 1H), 4.44 (dd, J = 11.0, 2.5 Hz, 1H), 4.37 (app dt, J = 11.0, 7.6 Hz, 1H), 3.25 (ddd, J = 10.4, 7.0, 4.9 Hz, 1H), 2.92 (app dt, J = 10.5, 7.5 Hz, 1H), 1.70–1.59 (comp, 2H), 1.34–1.25 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.47, 141.60, 134.08, 128.65, 128.22, 128.04, 127.85, 126.97, 126.21, 104.15, 69.03, 51.96, 49.49, 27.53, 25.83; m/z (ESI–MS) 262.3 [M+H]$^+$.

Pyrroline z10b: Following the general electrocyclization procedure, 4-chlorochalcone[28] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 222.8 mg of **z10b** as a colorless oil (yield 75%). R_f = 0.10 in hexanes/EtOAc 70:30 v/v; IR (KBr) 2962, 2870, 1640, 1489, 1445, 1406, 1358, 1245, 1176, 1088, 1014, 751, 695 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65–7.52 (m, 2H), 7.41–7.34 (m, 2H), 7.34–7.28 (comp, 3H), 7.25–7.16 (m, 2H), 5.07 (d, J = 2.0 Hz, 1H), 4.45–4.24 (comp, 2H), 3.28–3.14 (m, 1H), 2.86 (app dt, J = 10.5, 7.5 Hz, 1H), 1.66–1.53 (comp, 2H), 1.32–1.12 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.21, 133.93, 132.01, 130.00, 128.31, 128.23, 128.06, 127.05, 104.76, 103.46, 68.93, 51.95, 48.91, 27.58, 25.88; m/z (ESI–MS) 296.2 [M+H]$^+$.

Pyrroline z10c: Following the general electrocyclization procedure, 4-methoxychalcone[29] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 199.3 mg of **z10c** as a colorless oil (yield 68%). R_f = 0.08 in hexanes/EtOAc 70:30 v/v; IR (KBr) 2968, 2833, 1609, 1509, 1445, 1357, 1245, 1173, 1106, 1035, 833, 761 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66–7.55 (comp, 2H), 7.41–7.34 (comp, 2H), 7.34–7.28 (m, 1H), 7.23–7.15 (comp, 2H), 6.93–6.84 (m, 2H), 5.11 (d, J = 2.4 Hz, 1H), 4.35

(dd, J = 10.9, 2.4 Hz, 1H), 4.29 (ddd, J = 10.9, 7.8, 6.9 Hz, 1H), 3.82 (s, 3H), 3.20 (ddd, J = 10.4, 7.1, 4.9 Hz, 1H), 2.87 (app dt, J = 10.4, 7.4 Hz, 1H), 1.67–1.54 (comp, 2H), 1.33–1.20 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.12, 154.20, 134.17, 133.81, 129.61, 128.26, 127.87, 127.01, 113.49, 104.71, 69.18, 55.26, 52.06, 48.83, 27.58, 25.90; m/z (ESI–MS) 292.3 [M+H]$^+$.

Pyrroline z10d: Following the general electrocyclization procedure, (*E*)-3-mesityl-1-phenylprop-2-en-1-one[30] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 278.6 mg of **z10d** as a colorless oil (yield 92%). R$_f$ = 0.15 in hexanes/EtOAc 70:30 v/v; IR (KBr) 2959, 2916, 1633, 1492, 1478, 1445, 1357, 1258, 1026, 851, 749, 695 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (app d, J = 7.6 Hz, 2H), 7.40 (app t, J = 7.7 Hz, 2H), 7.32 (app t, J = 7.4 Hz, 1H), 6.86 (s, 2H), 5.39 (d, J = 2.7 Hz, 1H), 4.71 (dd, J = 11.3, 2.7 Hz, 1H), 4.45 (ddd, J = 11.4, 8.6, 7.5 Hz, 1H), 3.29 (ddd, J = 10.8, 6.9, 5.1 Hz, 1H), 3.03 (app dt, J = 10.7, 7.3 Hz, 1H), 2.50 (br s, 6H), 2.30 (s, 3H), 1.79–1.63 (comp, 2H), 1.50–1.32 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.37, 137.31, 135.45, 134.42, 133.87, 129.73, 128.26, 127.50, 126.70, 108.90, 67.81, 52.16, 46.67, 28.17, 25.81, 21.63, 20.64.; m/z (ESI–MS) 304.4 [M+H]$^+$.

Pyrroline z10e: Following the general electrocyclization procedure, (*E*)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one[31] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 268.3 mg of **z10e** as a tan oil (yield 86%). R$_f$ = 0.13 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 2962, 2869, 1635, 1596, 1492, 1445, 1359, 1263, 1251, 1090, 1072, 1023, 779, 739, 695 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 6.9 Hz, 2H), 7.60–7.46 (comp, 4H), 7.40 (app t, J = 7.5 Hz, 2H), 7.37–7.30 (m,

1H), 5.26 (d, *J* = 2.5 Hz, 1H), 5.04 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.65 (ddd, *J* = 11.1, 8.3, 7.0 Hz, 1H), 3.24 (ddd, *J* = 10.6, 7.4, 4.4 Hz, 1H), 2.88 (ddd, *J* = 10.5, 8.1, 6.9 Hz, 1H), 1.67–1.47 (comp, 2H), 1.17–1.03 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.20, 138.31, 134.22, 133.70, 132.15, 128.68, 128.32, 127.96, 127.08, 126.92, 126.15, 125.87, 125.51, 125.30, 123.74, 104.04, 68.71, 52.07, 45.59, 27.42, 25.77; *m/z* (ESI–MS) 312.2 [M+H]$^+$.

Pyrroline z10f: Following the general electrocyclization procedure, 4'-chlorochalcone and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 242.1 mg of **z10f** as a colorless oil (yield 82%). R$_f$ = 0.11 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3060, 3025, 2962, 2870, 1621, 1593, 1488, 1451, 1401, 1357, 1246, 1176, 1091, 1012, 835, 762, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.37–7.31 (comp, 4H), 7.28–7.22 (comp, 3H), 5.13 (d, *J* = 2.4 Hz, 1H), 4.38 (dd, *J* = 11.2, 2.5 Hz, 1H), 4.32 (app dt, *J* = 11.0, 7.5 Hz, 1H), 3.18 (ddd, *J* = 11.2, 6.9, 4.9 Hz, 1H), 2.81 (app dt, *J* = 10.4, 7.5 Hz, 1H), 1.69–1.54 (comp, 2H), 1.32–1.16 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.48, 141.41, 133.53, 132.63, 128.68, 128.48, 128.23, 128.13, 126.35, 104.80, 69.10, 51.99, 49.57, 27.60, 25.91; *m/z* (ESI–MS) 296.2 [M+H]$^+$.

Pyrroline z10g: Following the general electrocyclization procedure, 3',4'-dimethoxychalcone[32] and pyrrolidine were heated at reflux for 4 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 182.3 mg of **z10g** as a colorless oil (yield 57%). R$_f$ = 0.09 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 2959, 2834, 1601, 1581, 1514, 1463, 1451, 1417, 1360, 1267, 1136, 1027, 862, 810, 764, 703 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (app t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 4.39 (dd, *J* = 11.1, 2.4 Hz, 1H), 4.32 (app dt, *J* = 10.8, 7.6 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.24–3.16 (m,

1H), 2.88 (app dt, J = 10.2, 7.5 Hz, 1H), 1.67–1.57 (comp, 2H), 1.29–1.20 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.88, 141.78, 128.73, 128.08, 127.14, 126.27, 119.61, 110.92, 110.13, 102.99, 69.10, 55.95, 55.94, 52.17, 49.57, 27.61, 25.93; *m/z* (ESI–MS) 322.2 [M+H]$^+$.

Pyrrole b2: Following the general electrocyclization procedure, 4-nitrochalcone[33] and pyrrolidine were heated at reflux for 2 h. The residue was purified via silica gel chromatography in 90:10 hexanes/EtOAc, resulting in the isolation of 203.0 mg of **b2** as a yellow solid (yield 67%). R_f = 0.26 in hexanes/EtOAc 90:10 v/v; mp = 183–185 °C; IR (KBr) 3066, 2934, 1592, 1560, 1501, 1330, 1246, 1194, 1151, 1107, 1029, 852, 766, 753, 694, 487 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.25–8.16 (comp, 2H), 7.62–7.55 (comp, 2H), 7.54–7.48 (comp, 2H), 7.41 (app t, J = 7.5 Hz, 2H), 7.32–7.25 (comp, 2H), 6.74 (s, 1H), 4.20 (app t, J = 7.1 Hz, 2H), 3.18 (app t, J = 7.3 Hz, 2H), 2.66 (app p, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.39, 143.28, 138.25, 132.60, 130.52, 128.78, 126.60, 125.97, 124.60, 124.33, 114.43, 112.63, 46.80, 27.72, 25.90; *m/z* (ESI–MS) 305.5 [M+H]$^+$.

Pyrroline c2: Following the general electrocyclization procedure, *trans*-cinnamaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 15 min. The residue was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 53.1 mg of **c2** as a yellow oil (yield 21%). R_f = 0.06 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3054, 2935, 2827, 1606, 1493, 1475, 1456, 1333, 1291, 1258, 1155, 1043, 757, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 (app d, J = 8.1 Hz, 1H), 7.40–7.36 (comp, 2H), 7.36–7.31 (comp, 2H), 7.25–7.20 (m, 1H), 7.15–7.07 (comp, 2H), 6.91–6.85 (m, 1H), 3.25 (t, J = 8.8 Hz, 2H), 3.09–2.99 (comp, 4H), 2.84 (t, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.05, 139.46, 135.18, 128.80, 128.76,

128.52, 128.48, 127.45, 126.33, 126.15, 125.44, 114.37, 53.54, 48.35, 36.03, 30.59; *m/z* (ESI–MS) 248.3 [M+H]$^+$.

Pyrroline c3: Following the general electrocyclization procedure, chalcone and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 24 h. The residue was purified via silica gel chromatography in 90:10 hexanes/EtOAc, resulting in the isolation of 257.1 mg of **c3** as a yellow oil (yield 79%). R_f = 0.18 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3025, 2932, 2828, 1951, 1595, 1493, 1455, 1390, 1319, 1262, 1234, 1152, 1129, 1042, 1028, 912, 755, 735, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 (app d, *J* = 7.4 Hz, 3H), 7.47–7.34 (comp, 4H), 7.36–7.27 (comp, 3H), 7.22 (app t, *J* = 7.0 Hz, 1H), 7.18–7.08 (comp, 2H), 6.92 (ddd, *J* = 8.4, 5.9, 2.7 Hz, 1H), 4.28 (dd, *J* = 13.3, 9.7 Hz, 1H), 3.23–3.01 (comp, 3H), 2.93 (dd, *J* = 15.4, 13.2 Hz, 1H), 2.83 (app dt, *J* = 15.6, 3.5 Hz, 1H), 2.74 (app td, *J* = 10.9, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.67, 139.58, 139.11, 135.32, 128.97, 128.73, 128.50, 128.48, 128.46, 127.59, 127.43, 127.32, 126.52, 126.06, 125.47, 111.85, 69.76, 46.19, 46.08, 30.63; *m/z* (ESI–MS) 324.3 [M+H]$^+$.

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Chapter 5

Redox-Neutral 1,5-Electrocyclization

5.1 Background

In the previous sections, we have discussed the functionalization of azomethine ylides though non-pericyclic protonation/nucleophilic attack sequences as well as (3+2) cycloadditions. Another major pathway of azomethine ylide chemistry are 1,5- and 1,7-electrocyclizations.[1] These reactions require conjugated azomethine ylide intermediates that can undergo either 6π- or 8π-cyclizations, producing either five- or seven-member heterocyclic ring products.

The methods for creating these conjugated azomethine ylides for 1,5- and 1,7-dipolar cyclizations are essentially the same as for making azomethine ylides for (3+2) reactions or non-pericyclic functionalizations.[2] Oxidative routes, where an iminium is formed with external oxidant and then deprotonated, are common, as depicted in this example by Grigg (Figure 5.1, eq 1).[3] Another useful method involves the synthesis of an iminium salt (e.g. **5.5**) which, upon exposure to base, leads to a conjugated azomethine ylide (**5.6**) and eventually to cyclization product (**5.7**) (Figure 5.1, eq 2).[4] α-Amino acids are also commonly used, leading to azomethine ylides decarboxylatively (Figure 5.1, eq 3).[5] In this decarboxylative example by Groundwater et al. the products of both 1,5- and 1,7-electrocyclization are obtained.

Figure 5.1 **Common Pathways to Conjugated Azomethine Ylides**
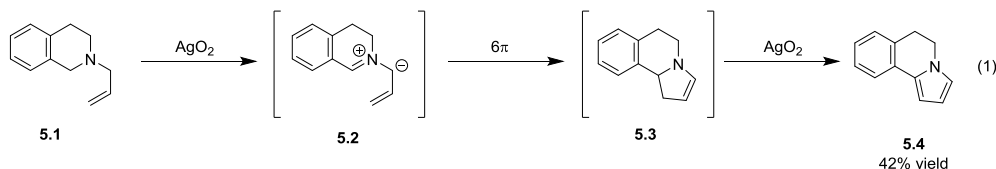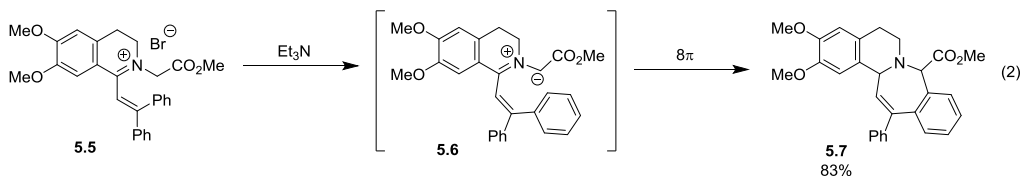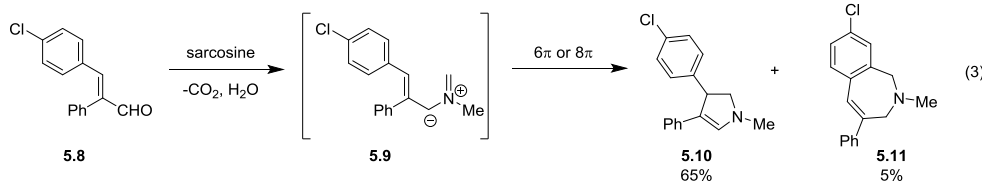
Less common are redox-neutral routes to electrocyclization products. In general, these reactions tend to require either fairly activated protons (benzylic, allylic or α-to a carbonyl) or conjugated amines that can result in intramolecular proton transfer.[1c] In 1976, Reinhoudt and coworkers found that the addition of a 3-amino-thiophene (**5.12**) to dimethylacetylenedicarboxylate (DMAD) led to cyclized product **5.15** (Figure 5.2, eq 4).[6] This reaction likely proceeds via 1,5-dipole **5.14**. Using 1-vinyl THIQ (**5.16**) and electron-poor aldehydes (e.g. **5.17**), Grigg and coworkers demonstrated that azomethine ylides (**5.18**) could be formed and undergo electrocyclization (Figure 5.2, eq 5).[7] The initial cyclization product (**5.19**), however, is able to react with a second equivalent of aldehyde, forming pyrrole **5.20**. Allenamines can also undergo redox-neutral electrocyclizations under thermal conditions.[1c] Maas et al. were able to produce cyclic

product **5.23** via an 8π-electrocyclization of azomethine ylide **5.22** formed prototropically from allenamine **5.21** (Figure 5.2, eq 6).[8]

Figure 5.2 **Redox-Neutral Electrocyclization Reactions**
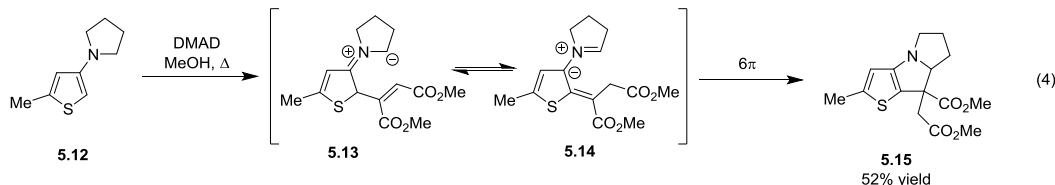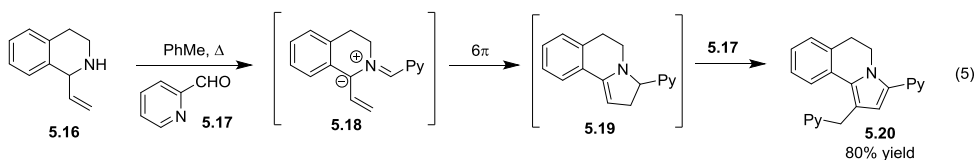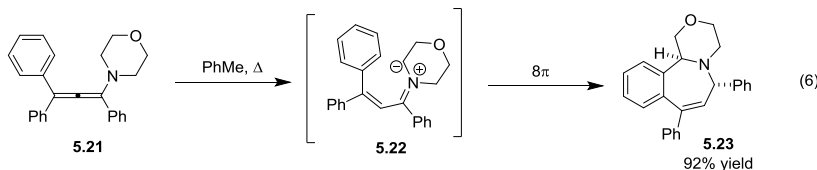
In 2010, the Seidel group published a different approach to redox-neutral 1,5-electrocyclizations that worked with relatively unactivated amines such as pyrrolidine (Figure 5.3, eq 7).[9,10] In this reaction, pyrrolidine condenses with 1,3-diketone **5.24** to give enamine **5.26**. 1,6-Proton transfer results in the formation of conjugated azomethine ylide **5.28** which undergoes 6π-electrocyclization to form dihydropyrrole **5.29**, which upon loss of water yields pyrrole **5.25**. While mechanistically interesting, the reaction required temperatures of 280 °C under microwave irradiation and generally gave moderate yields. Considering that we had further developed conditions for amine α-funtionalization since 2010, we envisioned performing a similar 1,5-electrocyclization using secondary amines and α,β-unsaturated carbonyl compounds (Figure 5.3, eq 8). The products that would be obtained (**5.33**) would be in a different oxidation state than

the pyrroles of the previous project, making this a complimentary approach to amine heterocycles.

Figure 5.3 **Redox-Neutral Pyrrole Formation**
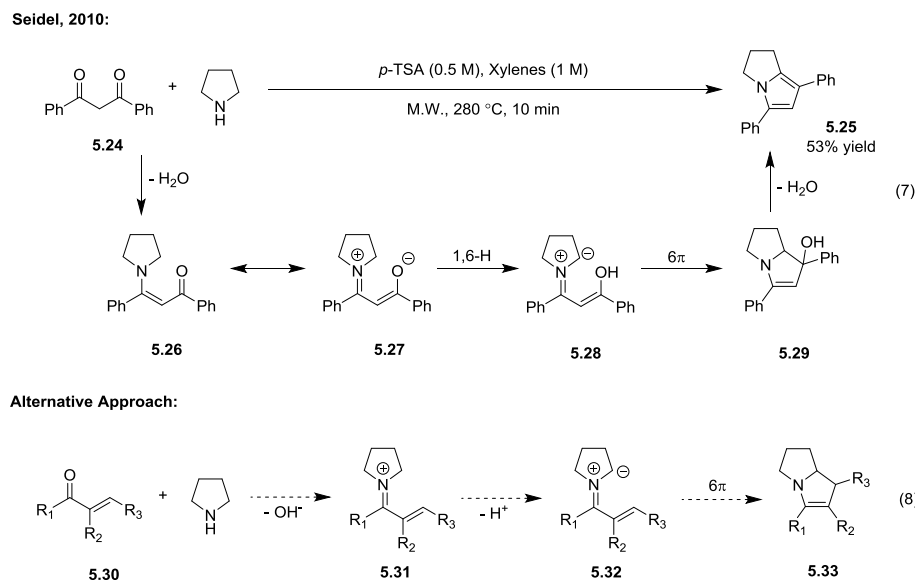
5.2 Reaction Development

We began our investigation using THIQ as the secondary amine, as the benzylic site on the amine makes the formation of the necessary azomethine ylide a more facile process. The reaction partner used was α-methyl cinnamaldehyde (**5.34**). We rationalized that the bulk of the methyl group would help to get the azomethine ylide into a conformation that would result in electrocyclization. After being allowed to react in toluene expected pyrroline **5.37** was not observed in the reaction mixture, but rather isomerized product **5.35a** (Figure 5.4, eq 9). This enamine isomerization presumably proceeds through an azomethine ylide intermediate, assuming the mechanism shown in eq 8 is active. In addition to **5.35a**, oxidized product **5.36** was obtained. The pyrroline products of some 1,5-electrocyclization reactions have been known to autoxidize, so this result was not entirely unanticipated.[11] Microwave conditions were also employed in the

reaction and yielded no oxidized product, but yields of pyrroline **5.35a** were not reproducible (Figure 5.4, eq 10).

Figure 5.4 **Initial Attempts at 1,5-Electrocyclization**
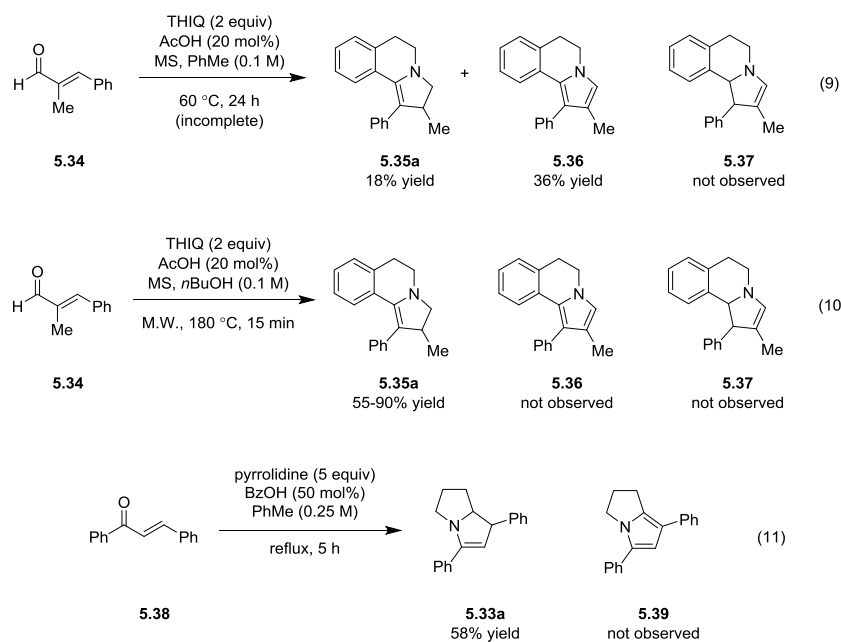
We simultaneously investigated the electrocyclization between chalcone (**5.38**) and pyrrolidine using the optimized conditions from the redox-neutral Mannich reaction previously developed by our group (Figure 5.4, eq 11).[12] This reaction was found to give moderate yields of pyrroline **5.33a** with no observed pyrrole (**5.39**) formation[13] and the reaction was, crucially, reproducible. We decided to proceed by optimizing conditions for this reaction system (Table 4.1).

The use of molecular sieves to sequester the water generated in the condensation increased the yield (entry 2) as did a decrease in solvent concentration (entry 3), presumably decreasing unwanted (3+2) and other side products of intermolecular reactions. A survey of carboxylic acids other than benzoic acid (entries 4-6) led to no increase in yield. Not surprisingly, the use of formic acid resulted in the formation of

reductive amination products (entry 6). A higher loading of benzoic acid led to higher yield (entry 8), while changing the solvent from toluene and decreasing the amount of amine used lowered the yield (entries 9-11). Slow addition of chalcone **5.38** did not appreciably increase the yield (entry 12).

Table 5.1 **Optimization of 1,5-Dipolar Cyclization Between Pyrrolidine and 5.38**

entry	amine (equiv)	solvent (M)	acid (equiv)	time [h]	Yield [%]
1[a]	5	PhMe (0.25)	BzOH (0.5)	5	58
2	5	PhMe (0.25)	BzOH (0.5)	5	65
3	5	PhMe (0.1)	BzOH (0.5)	5	74
4	5	PhMe (0.1)	AcOH (0.5)	5	65
5	5	PhMe (0.1)	2-EHA (0.5)	5	69
6	5	PhMe (0.1)	HCO_2H (0.5)	5	trace
7	5	PhMe (0.1)	BzOH (0.2)	6	68
8	5	PhMe (0.1)	BzOH (1.0)	3	77
9	5	*n*BuOH (0.1)	BzOH (1.0)	5	23
10	5	1,2-DCE (0.1)	BzOH (1.0)	12	trace
11	3	PhMe (0.1)	BzOH (1.0)	3	62
12	5	PhMe (0.1)	BzOH (0.5)	3 + 3[b]	78

Reactions run with 1 mmol chalcone under reflux with 3Å molecular sieves (200 mg). [a] No molecular sieves. [b] Slow addition time plus additional reaction time. Chalcone added in 2.5 mL PhMe.

5.3 Scope of the Electrocyclization Reaction

With optimized conditions in hand, we tested the scope of the reaction with several structurally and electronically different chalcones (Figure 5.5). Chalcones with

bulky substituents on the aryl ring tended to give the highest yields (**5.33d** and **5.33e**). When either aryl group was replaced with a methyl substituent, however, no desired product was detected. Pyrrolidine catalyzed [4+2] cycloaddition is competitive in this case.[14] Electron-donating groups on either ring were tolerated, but led to slightly lower yields (**5.33c** and **5.33g**). Electron-withdrawing chloro-groups worked well (**5.33b** and **5.33f**), however the more electron-poor nitro-chalcone **5.40** did not yield any observable pyrroline product (**5.33h**, Figure 5.6). Even under nitrogen atmosphere, pyrrole **5.41** was isolated as the major product of the reaction. This propensity for electron-poor pyrrolines to autoxidize has been previously observed.[11]

Figure 5.5 **Variation on the α,β-Unsaturated Ketone**
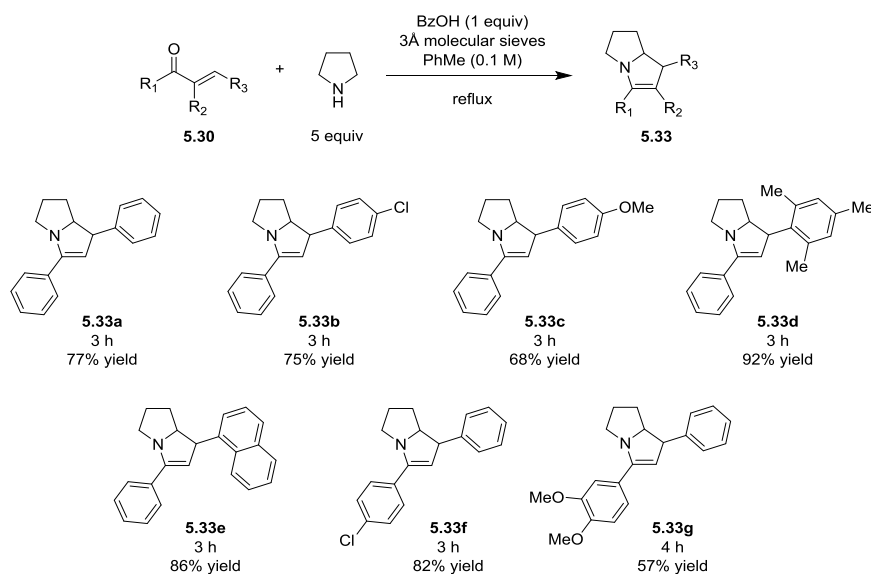
Figure 5.6 **Autoxidation of *p*-Nitrochalcone Product 5.33h**
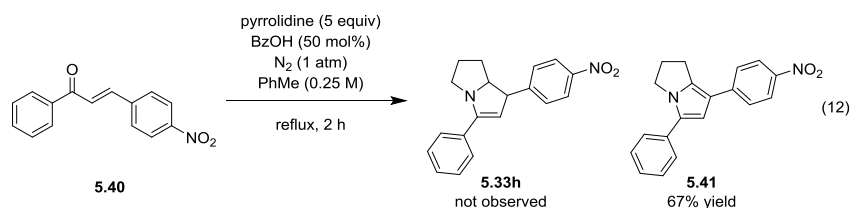
THIQ was also shown to undergo the electrocyclization under these conditions (Figure 5.7). Under the exclusion of oxygen, the desired pyrrolines could be obtained without appreciable pyrrole formation. A trend was observed in that the bulkier substrates required longer reaction times, but also resulted in much higher yields. This may perhaps be due to a lower propensity for the bulkier reactants to undergo undesired intermolecular side-reactions, although an increased α,β-unsaturated carbonyl scope is required to see if this trend holds.

Figure 5.7 **1,5-Electrocyclizations with THIQ**
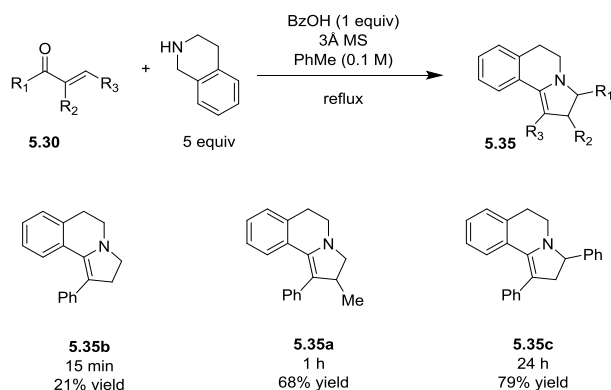
As the products of these reactions tend to autoxidize, we decided to develop conditions to favor the oxidation of these products to pyrroles in situ. While the reaction between secondary amines and 1,3-diketones previously developed in our group can be used to make these products,[9] yields are generally moderate and the temperatures of 280 °C can only be reached by well-maintained microwave reactors. A milder approach could be useful for labs without access to such equipment.

As the autoxidation of pyrroline products **5.33** is presumably a radical reaction,[15] radical catalyst TEMPO was used in the reaction under an air atmosphere (Figure 5.8, eq 13). Pyrrole **5.39** was obtained as the major product in 67% yield. Interestingly chalcone **5.38** is not required as a starting material in the reaction. As a surrogate for

chalcone, benzaldehyde and acetophenone were used, resulting in an identical yield of **5.39** (Figure 5.8, eq 14). As not all chalcones are commercially available, this alternative pathway could be used as a one-step route that avoids the need to synthesize these starting materials. Additionally, the reduction of pyrroline products was explored. When **5.35a** was exposed to palladium on carbon and hydrogen atmosphere, reduced product **5.42** was obtained in good yield (Figure 5.8, eq 15). So far, similar conditions have not been successful for the reduction of pyrrolines **5.33**.

Figure 5.8 **Reaction Between 5.38 and Pyrrolidine Under Oxidative Conditions and Reduction of 3.35a**
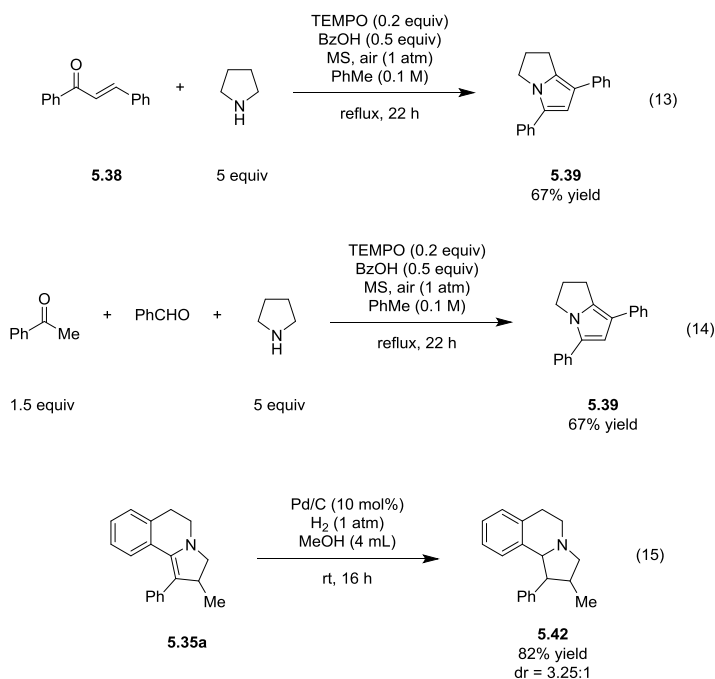
5.4 Conclusion

We have developed a new redox-neutral 1,5-electrocyclization reaction starting from secondary amines and α,β-unsaturated carbonyl compounds. Results are so far promising, but further work is required to develop the reaction in terms of different amines as well as the use of more structural diversity in the aldehydes and ketones.

Further derivatization of the products including the development of a more diastereomerically selective reduction is needed. This 6π-electrocyclization is a simple way to create an array of polycyclic amines through a redox-neutral amine α-functionalization.

Experimental Section

General Information: Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate and Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General Electrocyclization Procedure: α,β–Unsaturated aldehyde or ketone (1 mmol) was added to a 25 mL round bottom flask containing a stir bar. The flask was charged with toluene (10 mL), 3 Å molecular sieves (200 mg), benzoic acid (1 mmol) and secondary amine (5 mmol). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath at reflux until the aldehyde or ketone was consumed. Once cooled to room temperature, the mixture was filtered through a pad of

celite and rinsed with EtOAc (50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified via silica gel chromatography.

Pyrroline 5.35a: Following the general electrocyclization procedure, (*E*)-α-methylcinnamaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 1 h. The residue was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 176.6 mg of **5.35a** as a yellow oil (yield 68%). R$_f$ = 0.12 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3057, 2954, 2925, 2808, 1626, 1493, 1472, 1456, 1393, 1330, 1289, 1260, 1156, 756, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41–7.34 (comp, 2H), 7.31–7.25 (comp, 3H), 7.18 (app d, *J* = 8.1 Hz, 1H), 7.11 (app d, *J* = 7.6 Hz, 1H), 7.09–7.04 (m, 1H), 6.82 (app t, *J* = 7.6 Hz, 1H), 3.48 (app t, *J* = 8.7 Hz, 1H), 3.21–2.89 (comp, 5H), 2.78 (app t, *J* = 8.7 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.58, 138.60, 135.03, 129.77, 128.65, 128.52, 127.20, 126.38, 126.29, 125.44, 120.00, 104.75, 61.52, 48.41, 41.60, 30.43, 17.85; *m/z* (ESI–MS) 262.3 [M+H]$^+$.

Pyrroline 5.33a: Following the general electrocyclization procedure, chalcone and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 201.2 mg of **5.33a** as a colorless oil (yield 77%). R$_f$ = 0.14 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 3024, 2962, 2870, 1625, 1599,1446, 1357, 1246, 1074, 1028, 917, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69–7.62 (comp, 2H), 7.43–7.26 (comp, 8H), 5.18 (d, *J* = 2.5 Hz, 1H), 4.44 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.37 (app dt, *J* = 11.0, 7.6 Hz, 1H), 3.25 (ddd, *J* = 10.4, 7.0, 4.9 Hz, 1H), 2.92 (app dt, *J* = 10.5, 7.5 Hz, 1H), 1.70–1.59 (comp, 2H), 1.34–1.25 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.47, 141.60, 134.08, 128.65, 128.22, 128.04, 127.85, 126.97, 126.21, 104.15, 69.03, 51.96, 49.49, 27.53, 25.83; *m/z* (ESI–MS) 262.3 [M+H]$^+$.

Pyrroline 5.33b: Following the general electrocyclization procedure, 4-chlorochalcone[16] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 222.8 mg of **5.33b** as a colorless oil (yield 75%). R_f = 0.10 in hexanes/EtOAc 70:30 v/v; IR (KBr) 2962, 2870, 1640, 1489, 1445, 1406, 1358, 1245, 1176, 1088, 1014, 751, 695 cm^{-1}; ¹H NMR (500 MHz, CDCl$_3$) δ 7.65–7.52 (m, 2H), 7.41–7.34 (m, 2H), 7.34–7.28 (comp, 3H), 7.25–7.16 (m, 2H), 5.07 (d, J = 2.0 Hz, 1H), 4.45–4.24 (comp, 2H), 3.28–3.14 (m, 1H), 2.86 (app dt, J = 10.5, 7.5 Hz, 1H), 1.66–1.53 (comp, 2H), 1.32–1.12 (comp, 2H); ¹³C NMR (125 MHz, CDCl$_3$) δ 140.21, 133.93, 132.01, 130.00, 128.31, 128.23, 128.06, 127.05, 104.76, 103.46, 68.93, 51.95, 48.91, 27.58, 25.88; *m/z* (ESI–MS) 296.2 [M+H]$^+$.

Pyrroline 5.33c: Following the general electrocyclization procedure, 4-methoxychalcone[17] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 199.3 mg of **5.33c** as a colorless oil (yield 68%). R_f = 0.08 in hexanes/EtOAc 70:30 v/v; IR (KBr) 2968, 2833, 1609, 1509, 1445, 1357, 1245, 1173, 1106, 1035, 833, 761 cm^{-1}; ¹H NMR (500 MHz, CDCl$_3$) δ 7.66–7.55 (comp, 2H), 7.41–7.34 (comp, 2H), 7.34–7.28 (m, 1H), 7.23–7.15 (comp, 2H), 6.93–6.84 (m, 2H), 5.11 (d, J = 2.4 Hz, 1H), 4.35 (dd, J = 10.9, 2.4 Hz, 1H), 4.29 (ddd, J = 10.9, 7.8, 6.9 Hz, 1H), 3.82 (s, 3H), 3.20 (ddd, J = 10.4, 7.1, 4.9 Hz, 1H), 2.87 (app dt, J = 10.4, 7.4 Hz, 1H), 1.67–1.54 (comp, 2H), 1.33–1.20 (comp, 2H); ¹³C NMR (125 MHz, CDCl$_3$) δ 158.12, 154.20, 134.17, 133.81, 129.61, 128.26, 127.87, 127.01, 113.49, 104.71, 69.18, 55.26, 52.06, 48.83, 27.58, 25.90; *m/z* (ESI–MS) 292.3 [M+H]$^+$.

Pyrroline 5.33d: Following the general electrocyclization procedure, (*E*)-3-mesityl-1-phenylprop-2-en-1-one[18] and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the

isolation of 278.6 mg of **5.33d** as a colorless oil (yield 92%). R_f = 0.15 in hexanes/EtOAc

70:30 v/v; IR (KBr) 2959, 2916, 1633, 1492, 1478, 1445, 1357, 1258, 1026, 851, 749, 695

cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (app d, J = 7.6 Hz, 2H), 7.40 (app t, J = 7.7 Hz,

2H), 7.32 (app t, J = 7.4 Hz, 1H), 6.86 (s, 2H), 5.39 (d, J = 2.7 Hz, 1H), 4.71 (dd, J = 11.3,

2.7 Hz, 1H), 4.45 (ddd, J = 11.4, 8.6, 7.5 Hz, 1H), 3.29 (ddd, J = 10.8, 6.9, 5.1 Hz, 1H),

3.03 (app dt, J = 10.7, 7.3 Hz, 1H), 2.50 (br s, 6H), 2.30 (s, 3H), 1.79–1.63 (comp, 2H),

1.50–1.32 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.37, 137.31, 135.45, 134.42,

133.87, 129.73, 128.26, 127.50, 126.70, 108.90, 67.81, 52.16, 46.67, 28.17, 25.81, 21.63,

20.64.; m/z (ESI–MS) 304.4 [M+H]$^+$.

Pyrroline 5.33e: Following the general electrocyclization procedure, (*E*)-3-

(naphthalen-1-yl)-1-phenylprop-2-en-1-one[19] and pyrrolidine were heated at reflux for 3

h. The residue was purified via silica gel chromatography in 94:5:1

hexanes/EtOAc/Et$_3$N, resulting in the isolation of 268.3 mg of **5.33e** as a tan oil (yield

86%). R_f = 0.13 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 2962, 2869, 1635, 1596,

1492, 1445, 1359, 1263, 1251, 1090, 1072, 1023, 779, 739, 695 cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$) δ 8.10 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.68

(d, J = 6.9 Hz, 2H), 7.60–7.46 (comp, 4H), 7.40 (app t, J = 7.5 Hz, 2H), 7.37–7.30 (m,

1H), 5.26 (d, J = 2.5 Hz, 1H), 5.04 (dd, J = 11.1, 2.5 Hz, 1H), 4.65 (ddd, J = 11.1, 8.3, 7.0

Hz, 1H), 3.24 (ddd, J = 10.6, 7.4, 4.4 Hz, 1H), 2.88 (ddd, J = 10.5, 8.1, 6.9 Hz, 1H), 1.67–

1.47 (comp, 2H), 1.17–1.03 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.20, 138.31,

134.22, 133.70, 132.15, 128.68, 128.32, 127.96, 127.08, 126.92, 126.15, 125.87, 125.51,

125.30, 123.74, 104.04, 68.71, 52.07, 45.59, 27.42, 25.77; m/z (ESI–MS) 312.2 [M+H]$^+$.

Pyrroline 5.33f: Following the general electrocyclization procedure, 4'-chlorochalcone

and pyrrolidine were heated at reflux for 3 h. The residue was purified via silica gel

chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 242.1 mg of

5.33f as a colorless oil (yield 82%). R_f = 0.11 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3060, 3025, 2962, 2870, 1621, 1593, 1488, 1451, 1401, 1357, 1246, 1176, 1091, 1012, 835, 762, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.37–7.31 (comp, 4H), 7.28–7.22 (comp, 3H), 5.13 (d, J = 2.4 Hz, 1H), 4.38 (dd, J = 11.2, 2.5 Hz, 1H), 4.32 (app dt, J = 11.0, 7.5 Hz, 1H), 3.18 (ddd, J = 11.2, 6.9, 4.9 Hz, 1H), 2.81 (app dt, J = 10.4, 7.5 Hz, 1H), 1.69–1.54 (comp, 2H), 1.32–1.16 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.48, 141.41, 133.53, 132.63, 128.68, 128.48, 128.23, 128.13, 126.35, 104.80, 69.10, 51.99, 49.57, 27.60, 25.91; m/z (ESI–MS) 296.2 [M+H]$^+$.

Pyrroline 5.33g: Following the general electrocyclization procedure, 3',4'-dimethoxychalcone[20] and pyrrolidine were heated at reflux for 4 h. The residue was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 182.3 mg of **5.33g** as a colorless oil (yield 57%). R_f = 0.09 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3058, 2959, 2834, 1601, 1581, 1514, 1463, 1451, 1417, 1360, 1267, 1136, 1027, 862, 810, 764, 703 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (app t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.4 Hz, 2H), 7.23 (d, J = 7.0 Hz, 1H), 7.18 (dd, J = 8.3, 1.8 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 5.04 (d, J = 2.0 Hz, 1H), 4.39 (dd, J = 11.1, 2.4 Hz, 1H), 4.32 (app dt, J = 10.8, 7.6 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.24–3.16 (m, 1H), 2.88 (app dt, J = 10.2, 7.5 Hz, 1H), 1.67–1.57 (comp, 2H), 1.29–1.20 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.88, 141.78, 128.73, 128.08, 127.14, 126.27, 119.61, 110.92, 110.13, 102.99, 69.10, 55.95, 55.94, 52.17, 49.57, 27.61, 25.93; m/z (ESI–MS) 322.2 [M+H]$^+$.

Pyrrole 5.41: Following the general electrocyclization procedure, 4-nitrochalcone[21] and pyrrolidine were heated at reflux for 2 h. The residue was purified via silica gel chromatography in 90:10 hexanes/EtOAc, resulting in the isolation of 203.0 mg of **5.41** as a yellow solid (yield 67%). R_f = 0.26 in hexanes/EtOAc 90:10 v/v; mp = 183–185 °C;

IR (KBr) 3066, 2934, 1592, 1560, 1501, 1330, 1246, 1194, 1151, 1107, 1029, 852, 766, 753, 694, 487 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.25–8.16 (comp, 2H), 7.62–7.55 (comp, 2H), 7.54–7.48 (comp, 2H), 7.41 (app t, J = 7.5 Hz, 2H), 7.32–7.25 (comp, 2H), 6.74 (s, 1H), 4.20 (app t, J = 7.1 Hz, 2H), 3.18 (app t, J = 7.3 Hz, 2H), 2.66 (app p, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.39, 143.28, 138.25, 132.60, 130.52, 128.78, 126.60, 125.97, 124.60, 124.33, 114.43, 112.63, 46.80, 27.72, 25.90; m/z (ESI–MS) 305.5 [M+H]$^+$.

Pyrroline 5.35b: Following the general electrocyclization procedure, *trans*-cinnamaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 15 min. The residue was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 53.1 mg of **5.35b** as a yellow oil (yield 21%). R$_f$ = 0.06 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3054, 2935, 2827, 1606, 1493, 1475, 1456, 1333, 1291, 1258, 1155, 1043, 757, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 (app d, J = 8.1 Hz, 1H), 7.40–7.36 (comp, 2H), 7.36–7.31 (comp, 2H), 7.25–7.20 (m, 1H), 7.15–7.07 (comp, 2H), 6.91–6.85 (m, 1H), 3.25 (t, J = 8.8 Hz, 2H), 3.09–2.99 (comp, 4H), 2.84 (t, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.05, 139.46, 135.18, 128.80, 128.76, 128.52, 128.48, 127.45, 126.33, 126.15, 125.44, 114.37, 53.54, 48.35, 36.03, 30.59; m/z (ESI–MS) 248.3 [M+H]$^+$.

Pyrroline 5.35c: Following the general electrocyclization procedure, chalcone and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 24 h. The residue was purified via silica gel chromatography in 90:10 hexanes/EtOAc, resulting in the isolation of 257.1 mg of **5.35c** as a yellow oil (yield 79%). R$_f$ = 0.18 in hexanes/EtOAc 70:30 v/v; IR (KBr) 3025, 2932, 2828, 1951, 1595, 1493, 1455, 1390, 1319, 1262, 1234, 1152, 1129, 1042, 1028, 912, 755, 735, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 (app d, J = 7.4 Hz, 3H), 7.47–7.34 (comp, 4H), 7.36–7.27 (comp, 3H), 7.22 (app t, J = 7.0 Hz, 1H), 7.18–7.08 (comp,

2H), 6.92 (ddd, *J* = 8.4, 5.9, 2.7 Hz, 1H), 4.28 (dd, *J* = 13.3, 9.7 Hz, 1H), 3.23−3.01

(comp, 3H), 2.93 (dd, *J* = 15.4, 13.2 Hz, 1H), 2.83 (app dt, *J* = 15.6, 3.5 Hz, 1H), 2.74 (app

td, *J* = 10.9, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.67, 139.58, 139.11, 135.32,

128.97, 128.73, 128.50, 128.48, 128.46, 127.59, 127.43, 127.32, 126.52, 126.06, 125.47,

111.85, 69.76, 46.19, 46.08, 30.63; *m/z* (ESI−MS) 324.3 [M+H]$^+$.

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APPENDIX:

SELECTED NMR SPECTRA
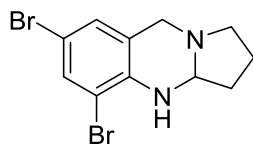
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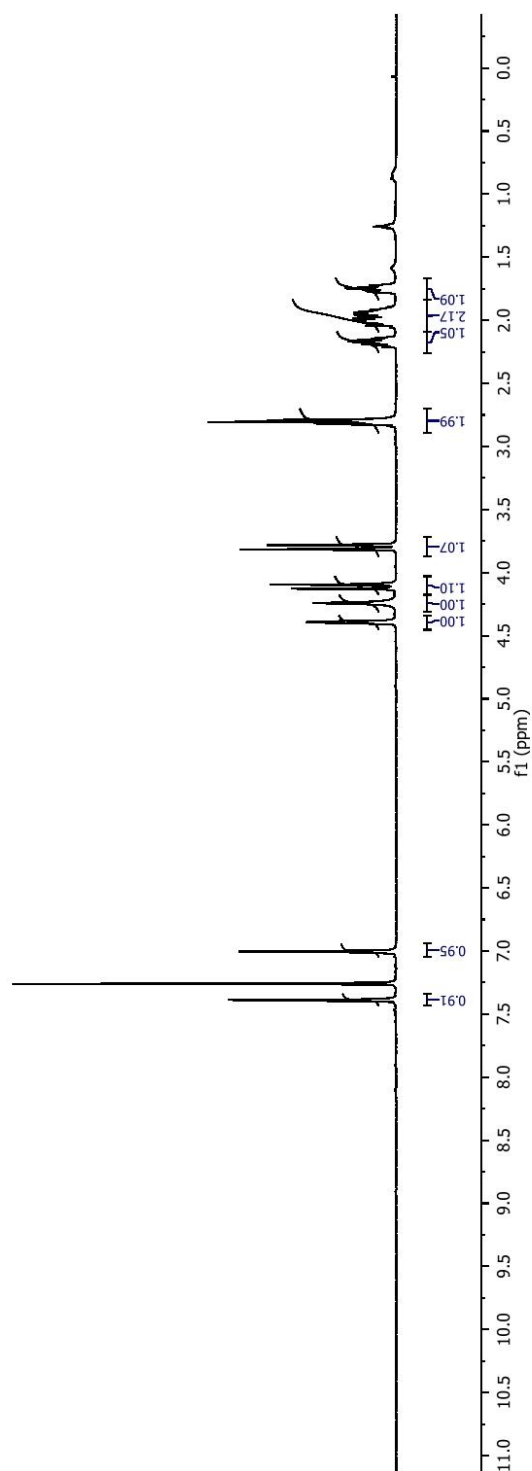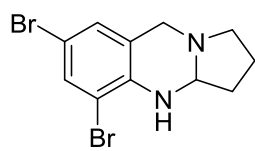
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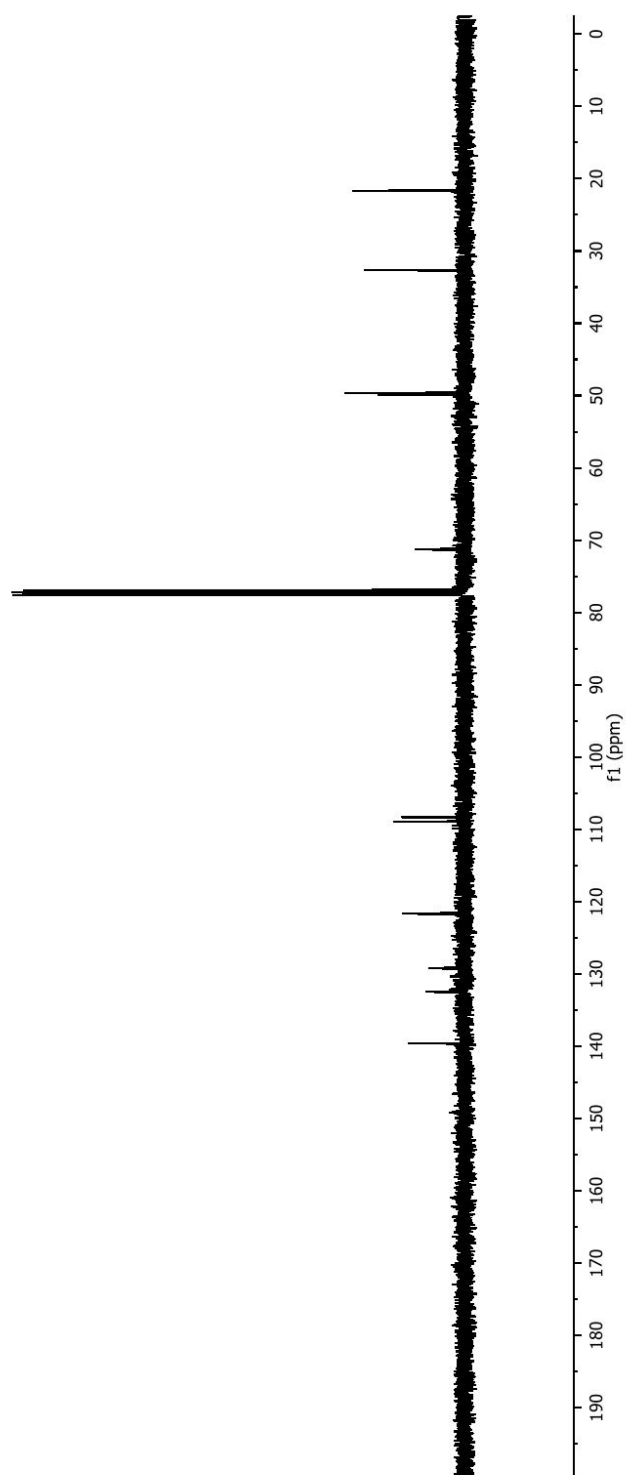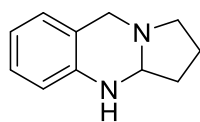
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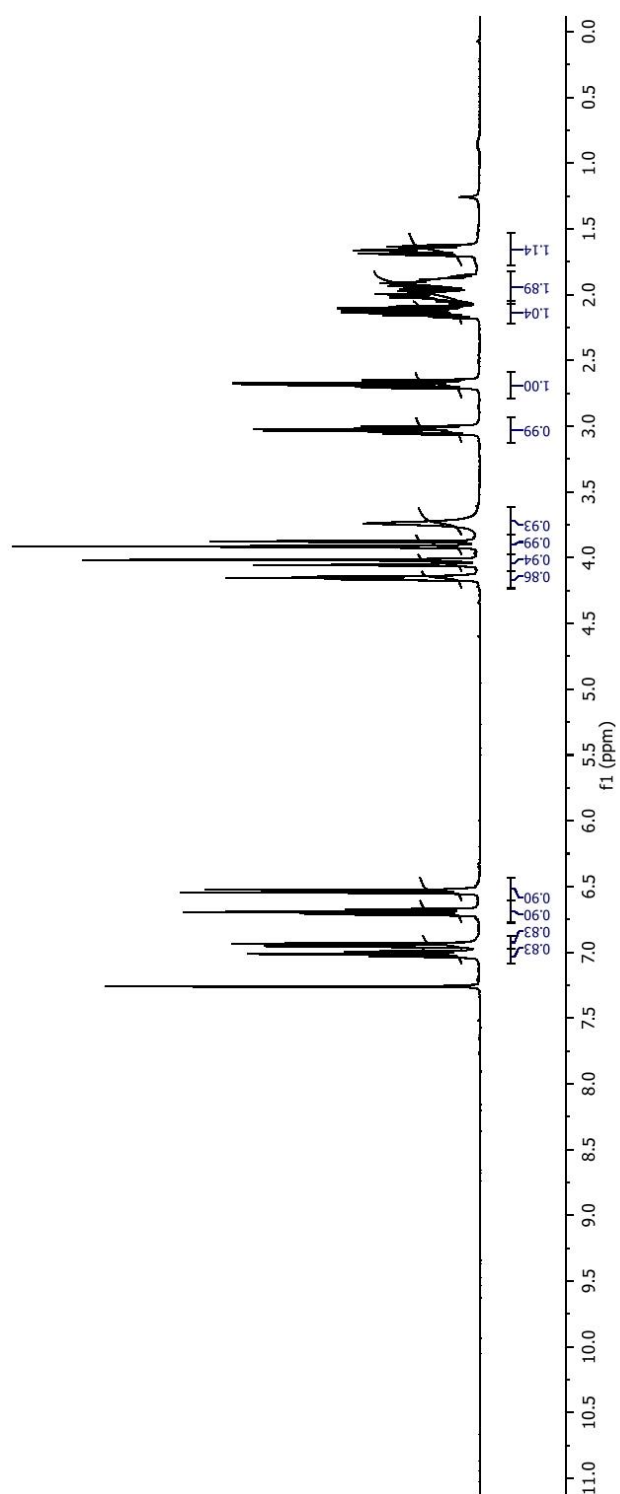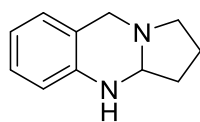
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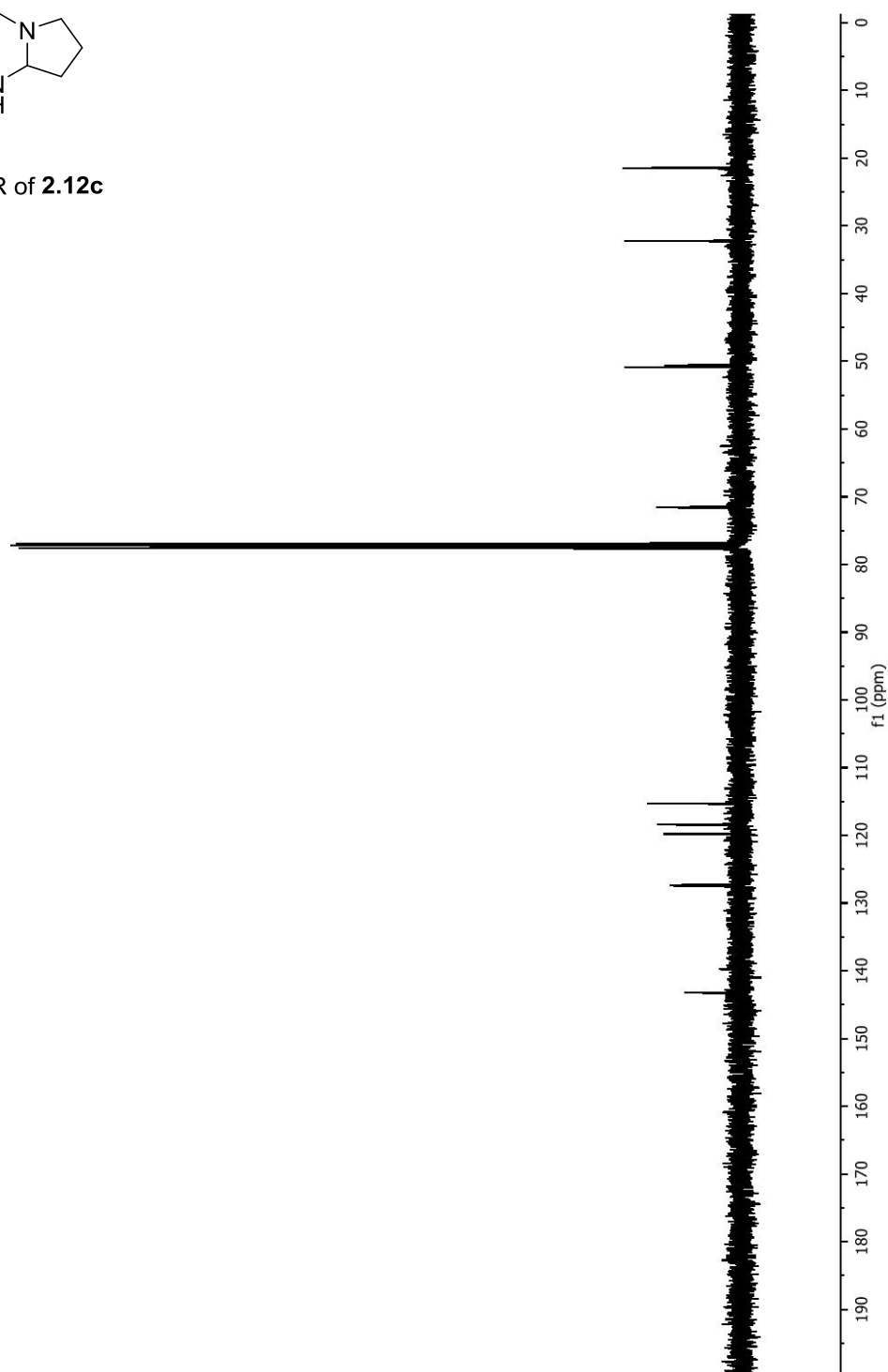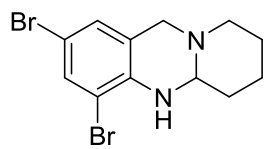
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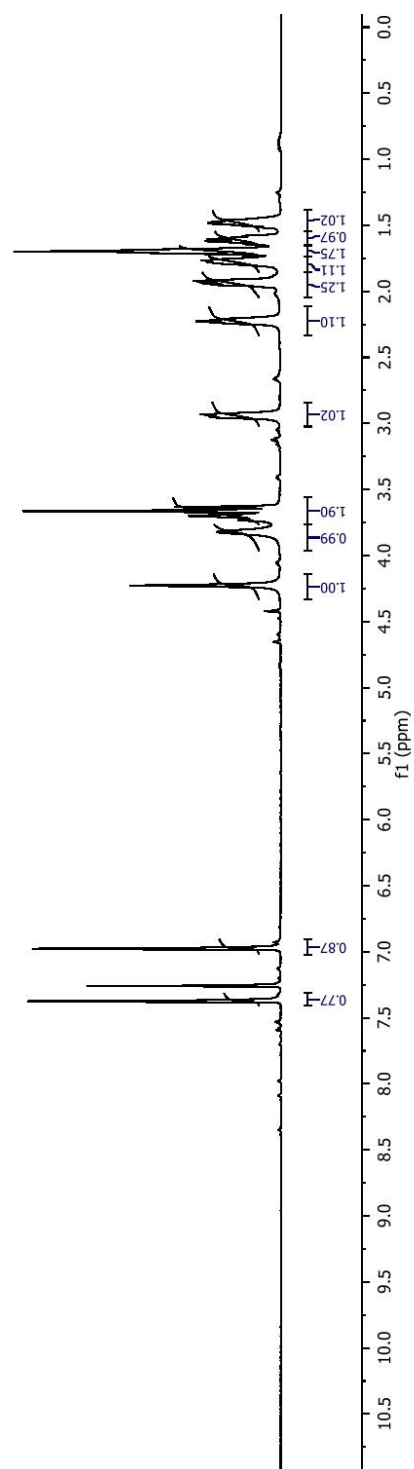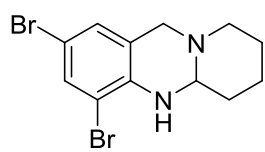
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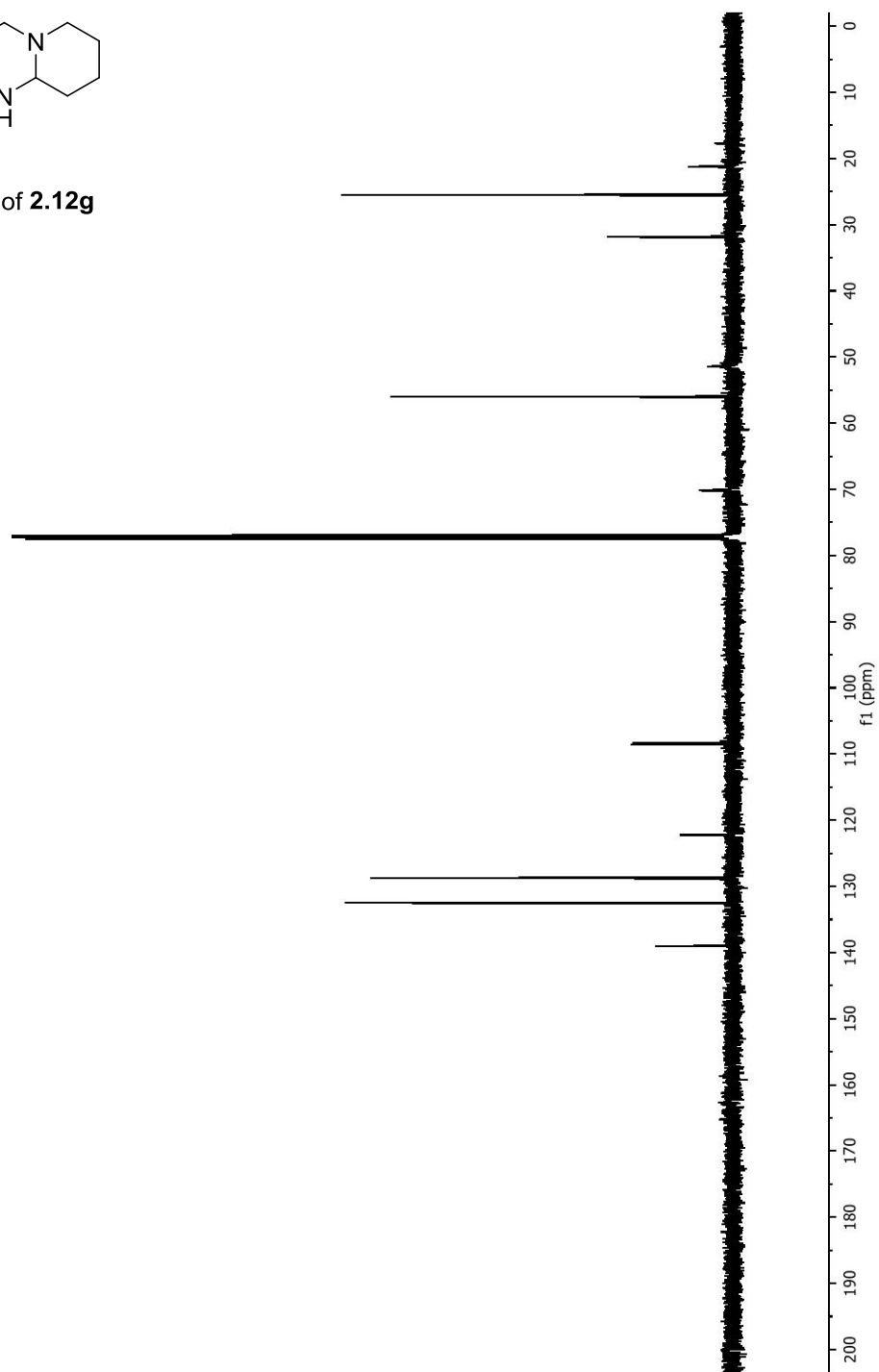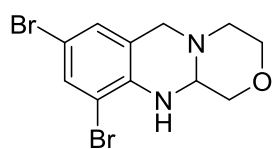
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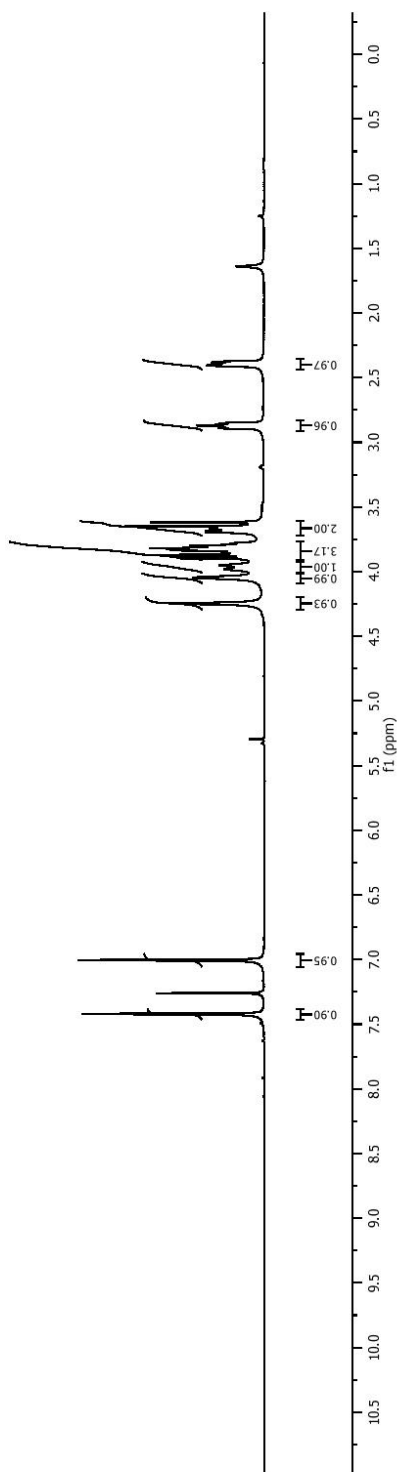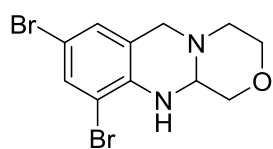
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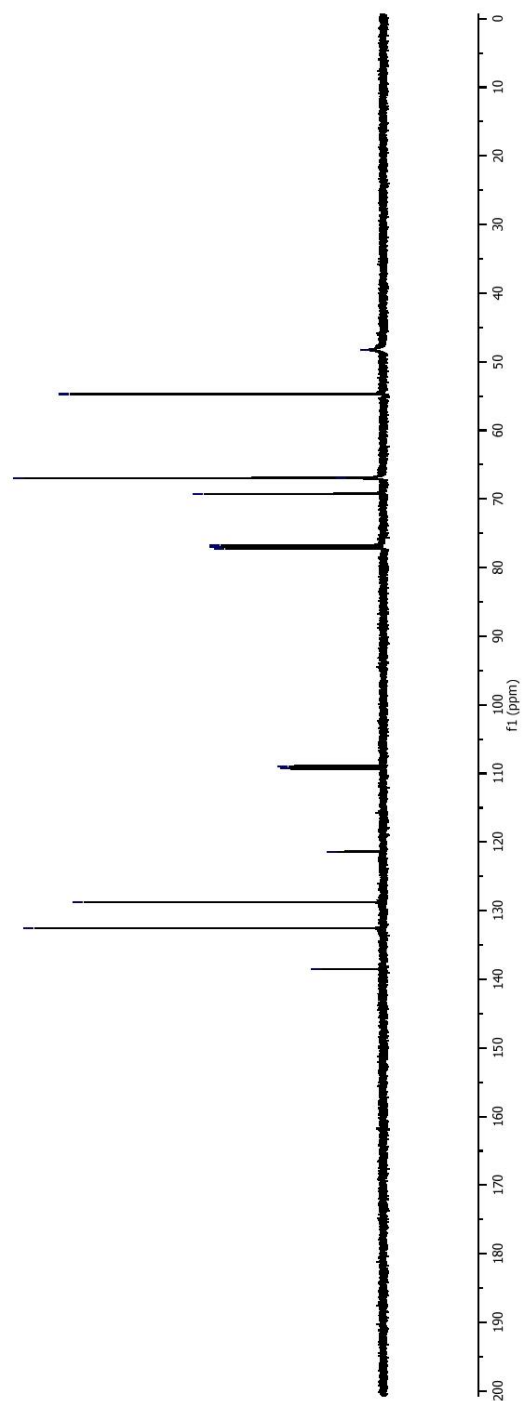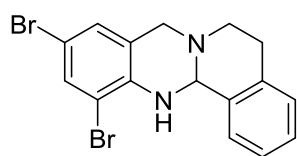
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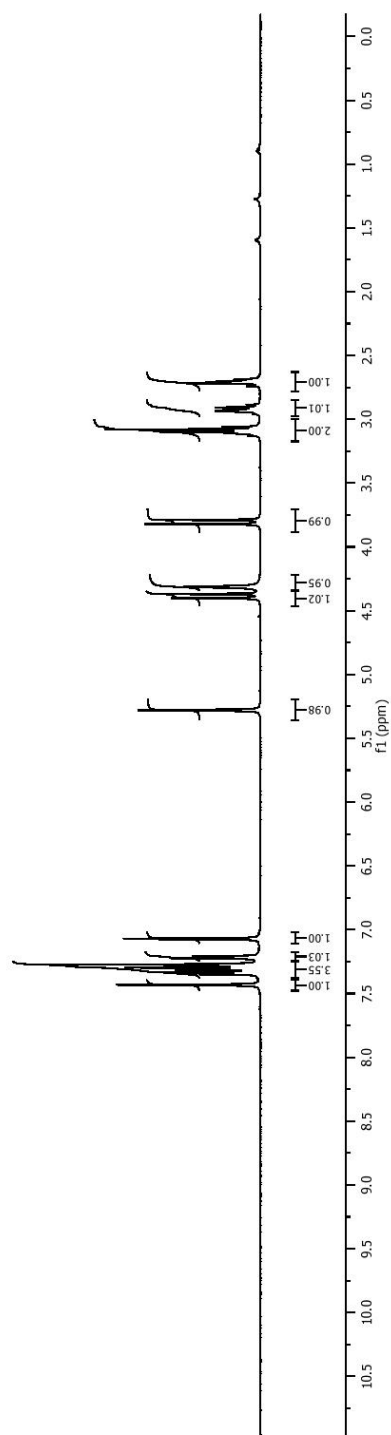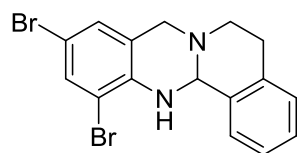
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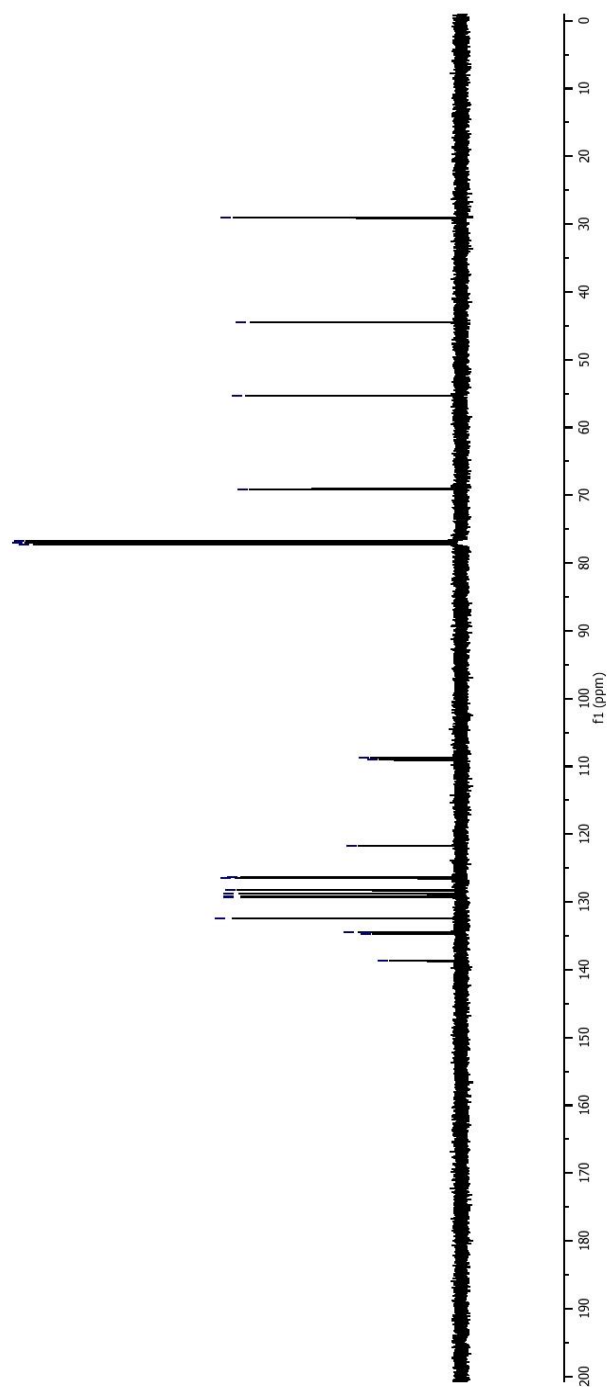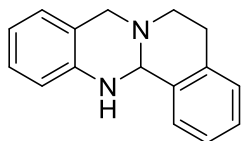
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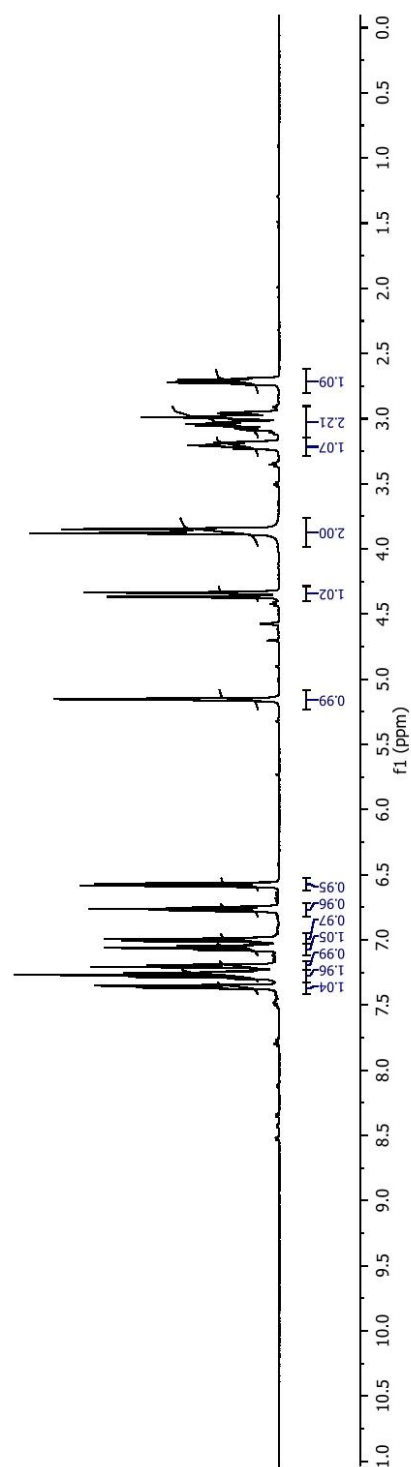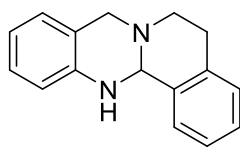
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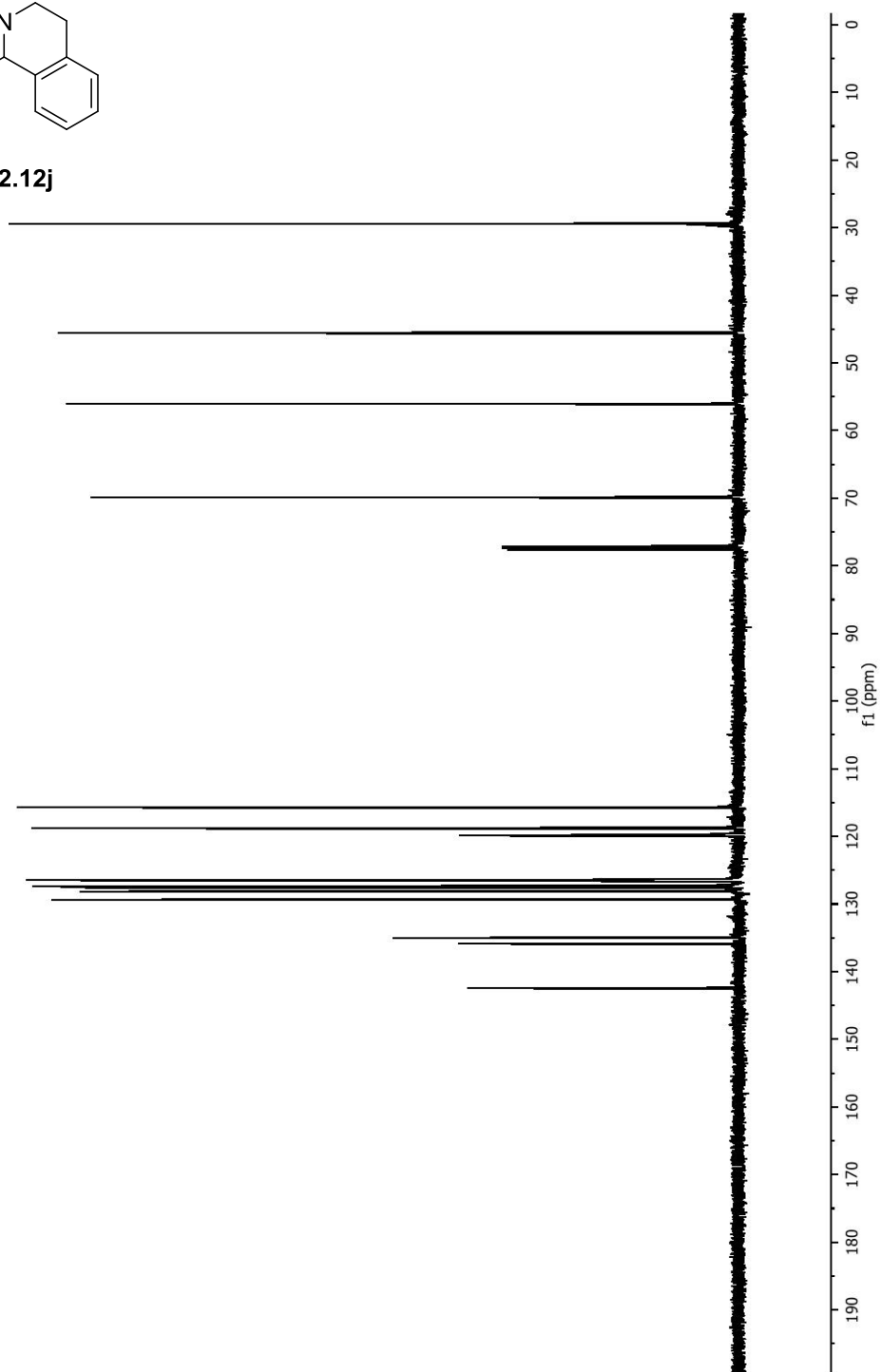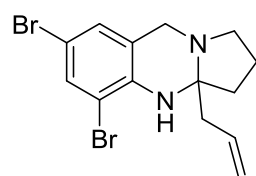
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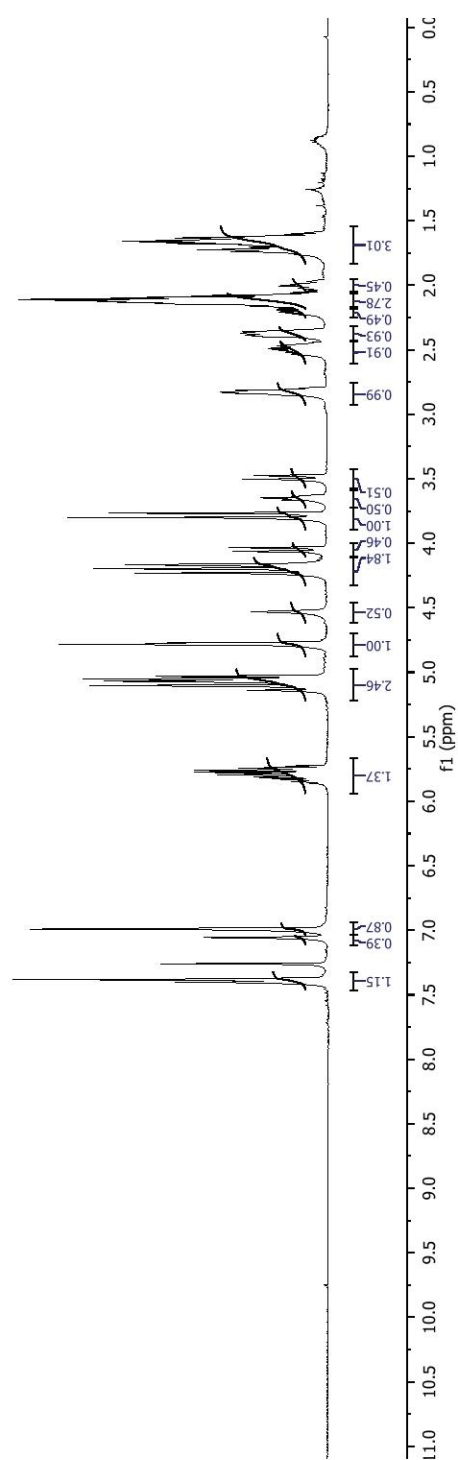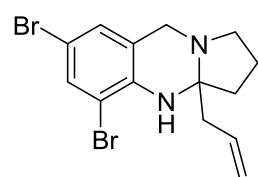
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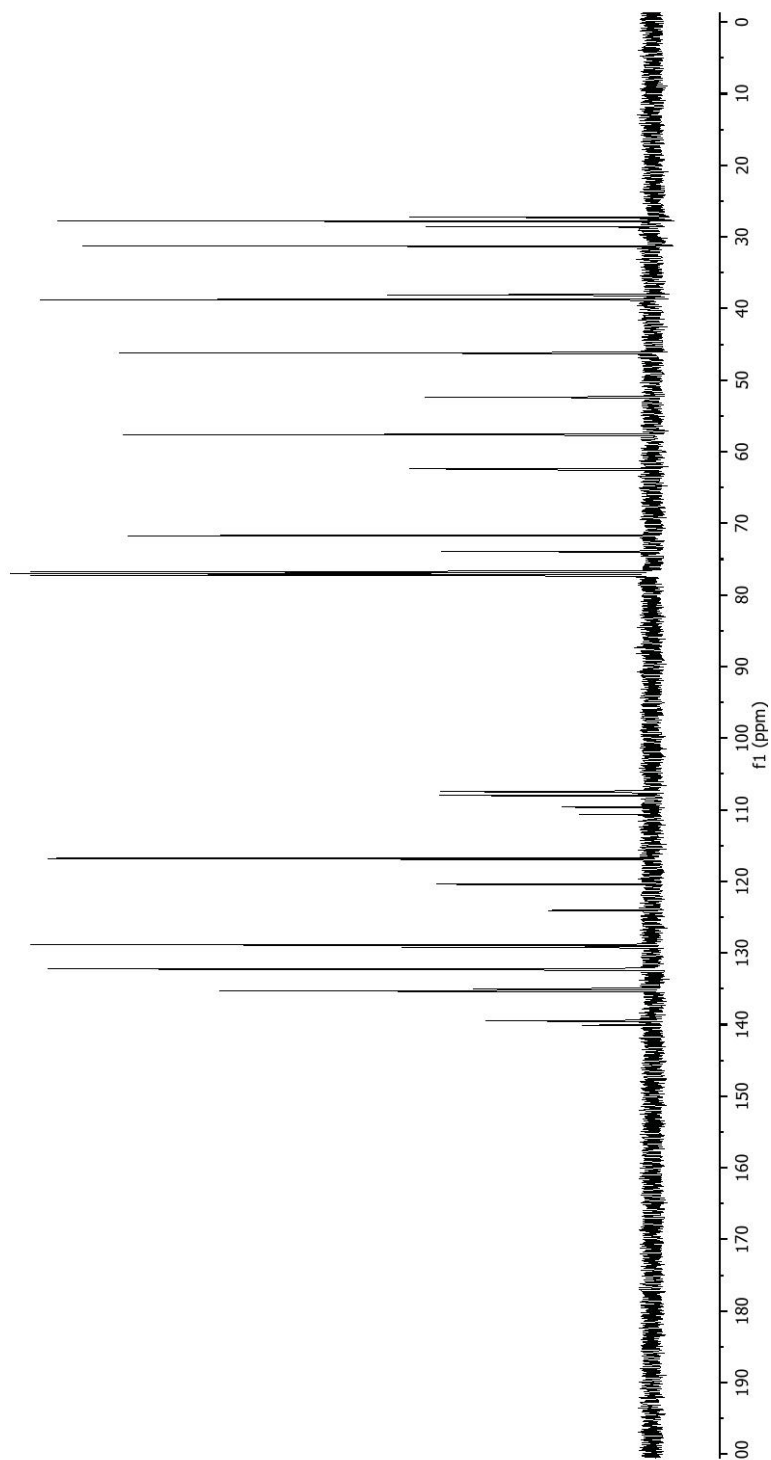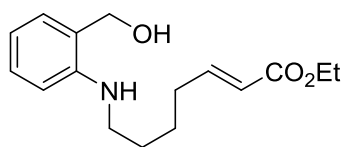
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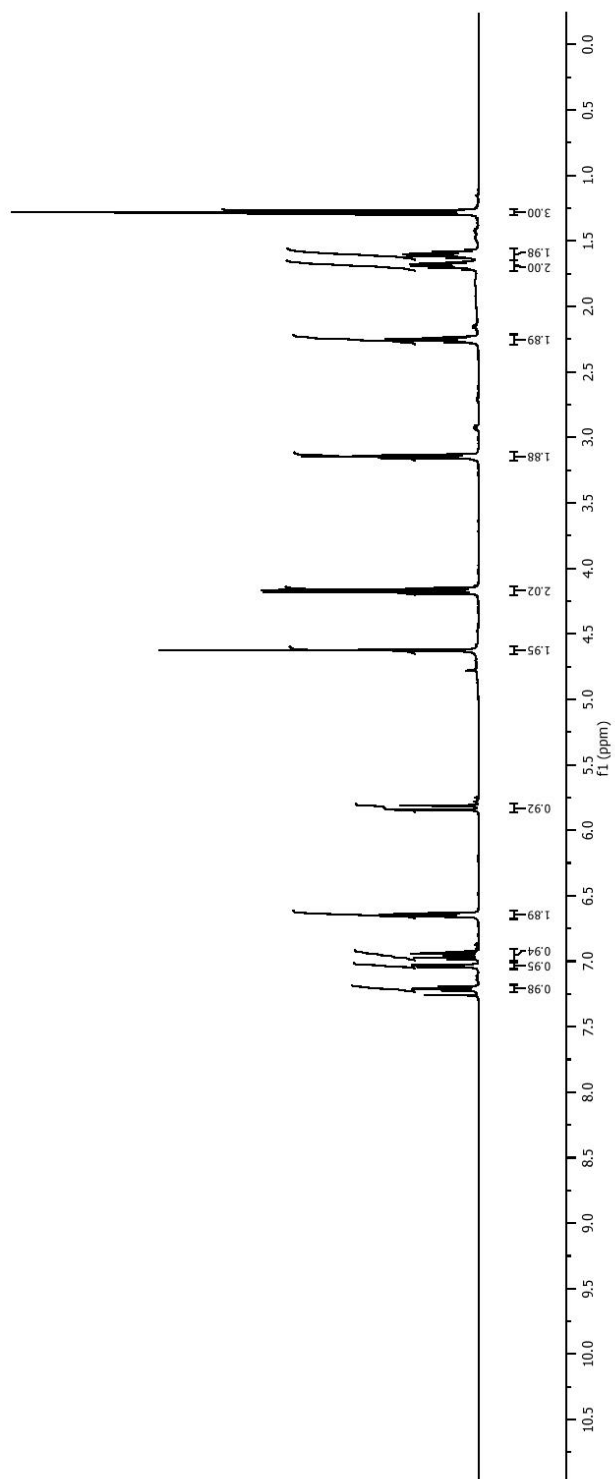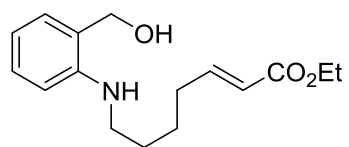
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¹H NMR of **2.33**

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^{13}C NMR of **2.34**

F1 (ppm)

F2 (ppm)
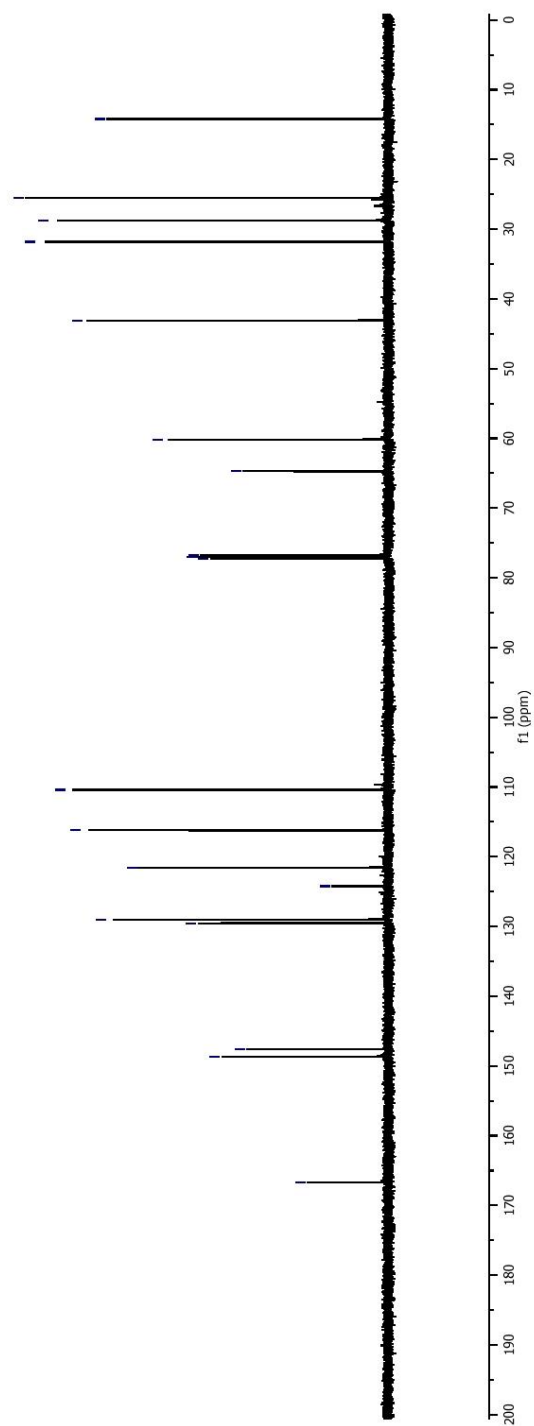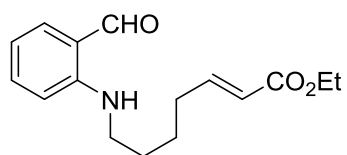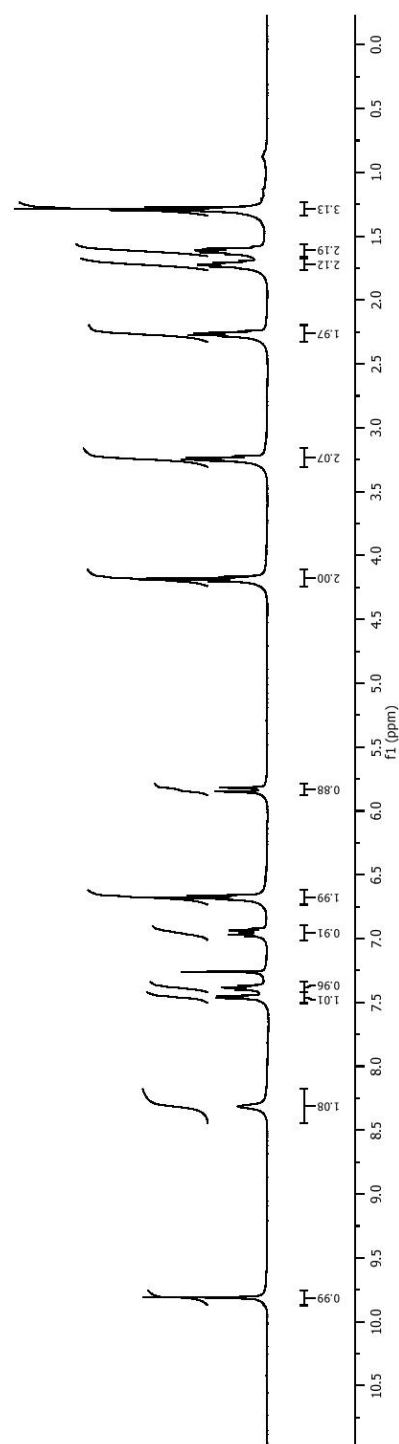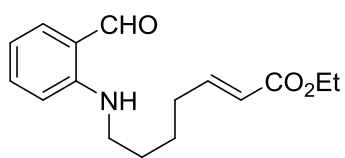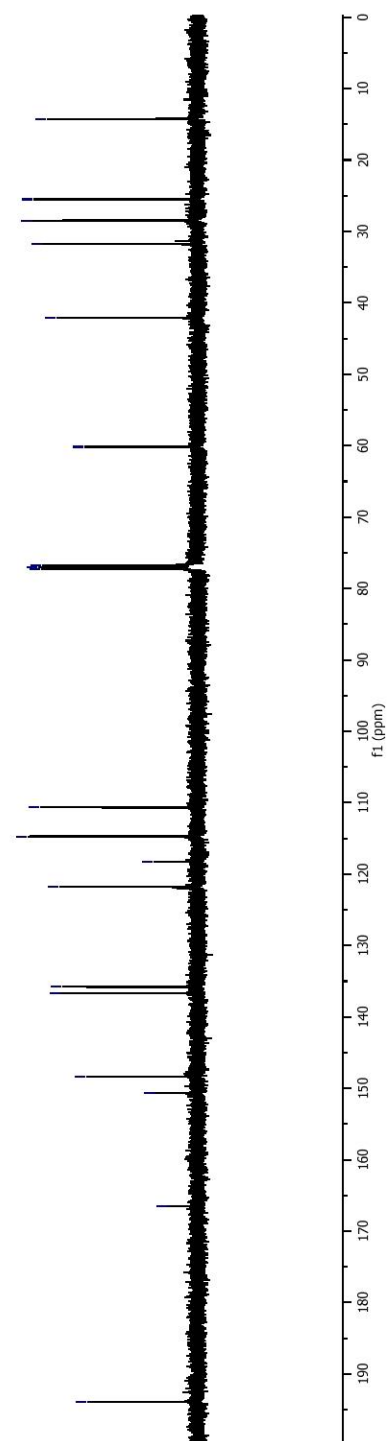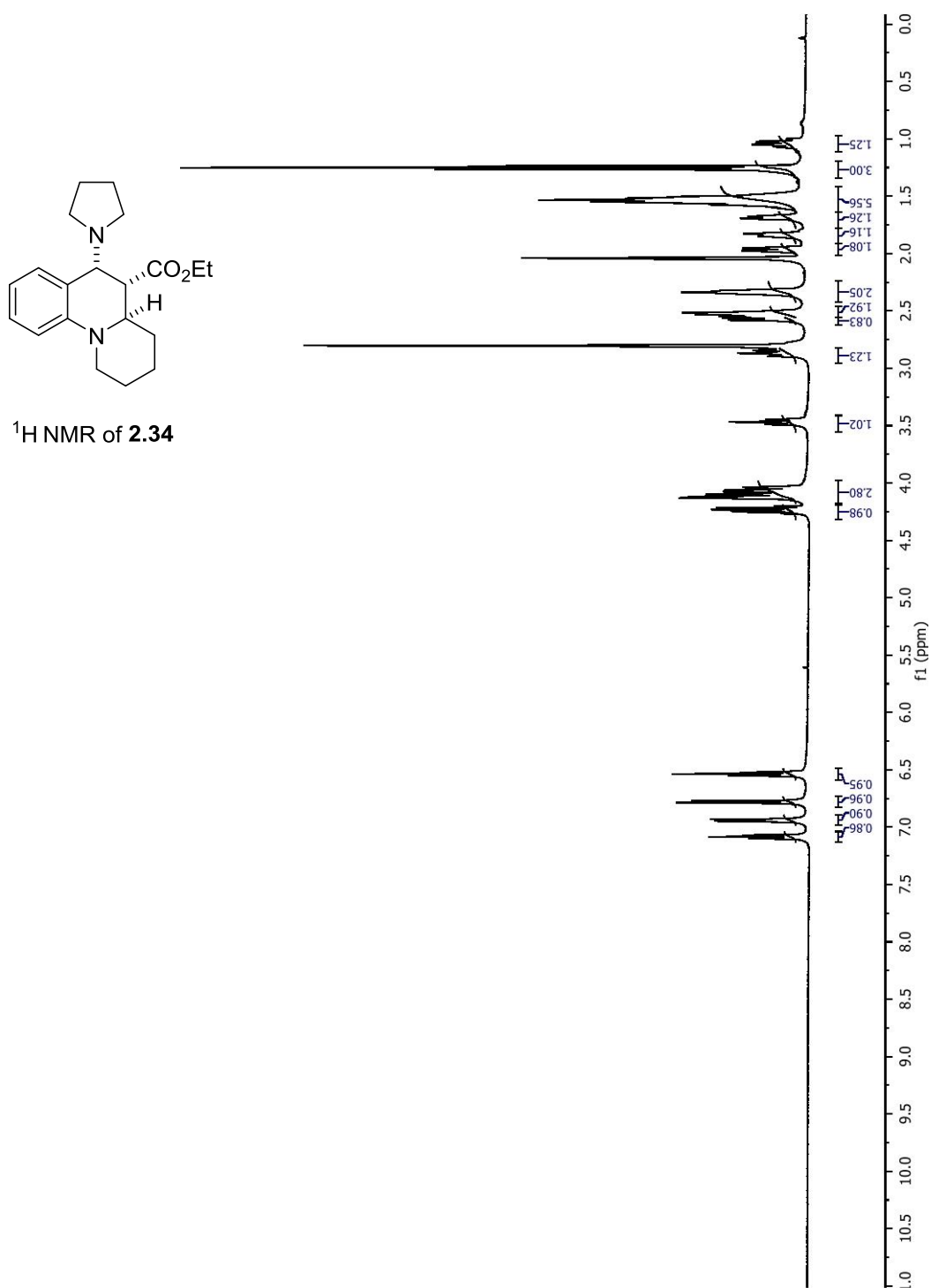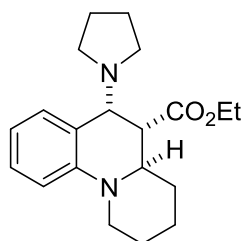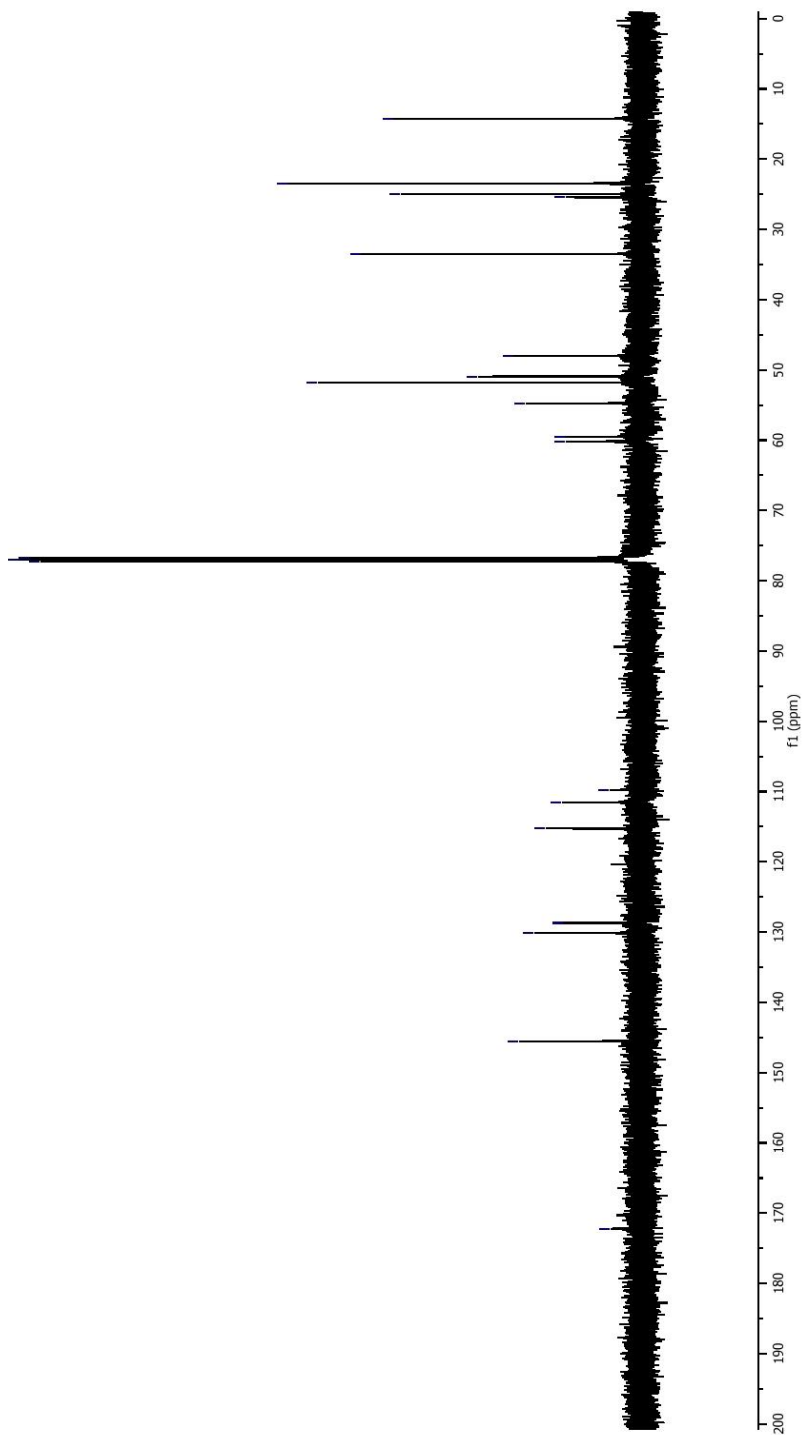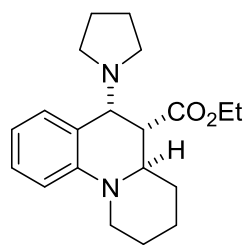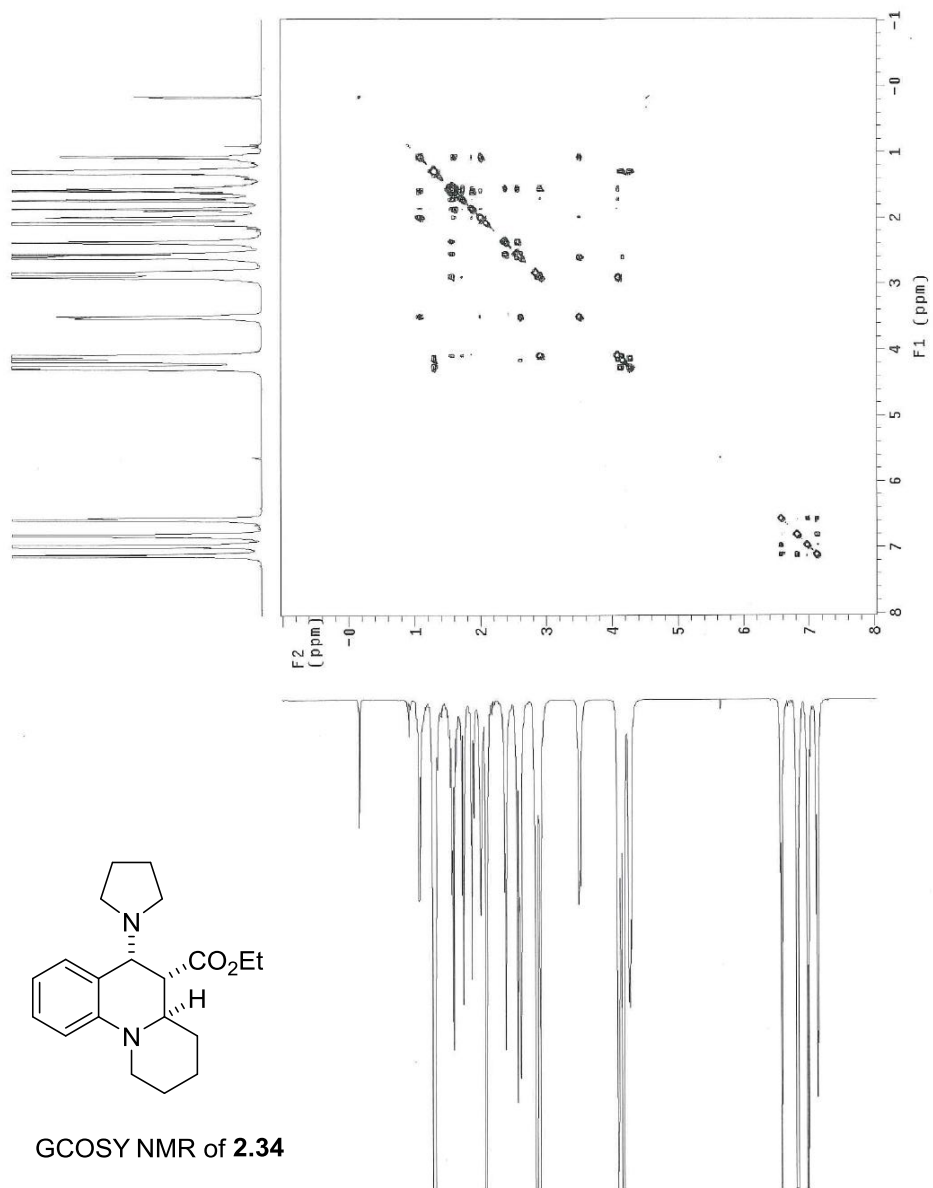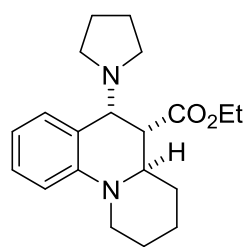
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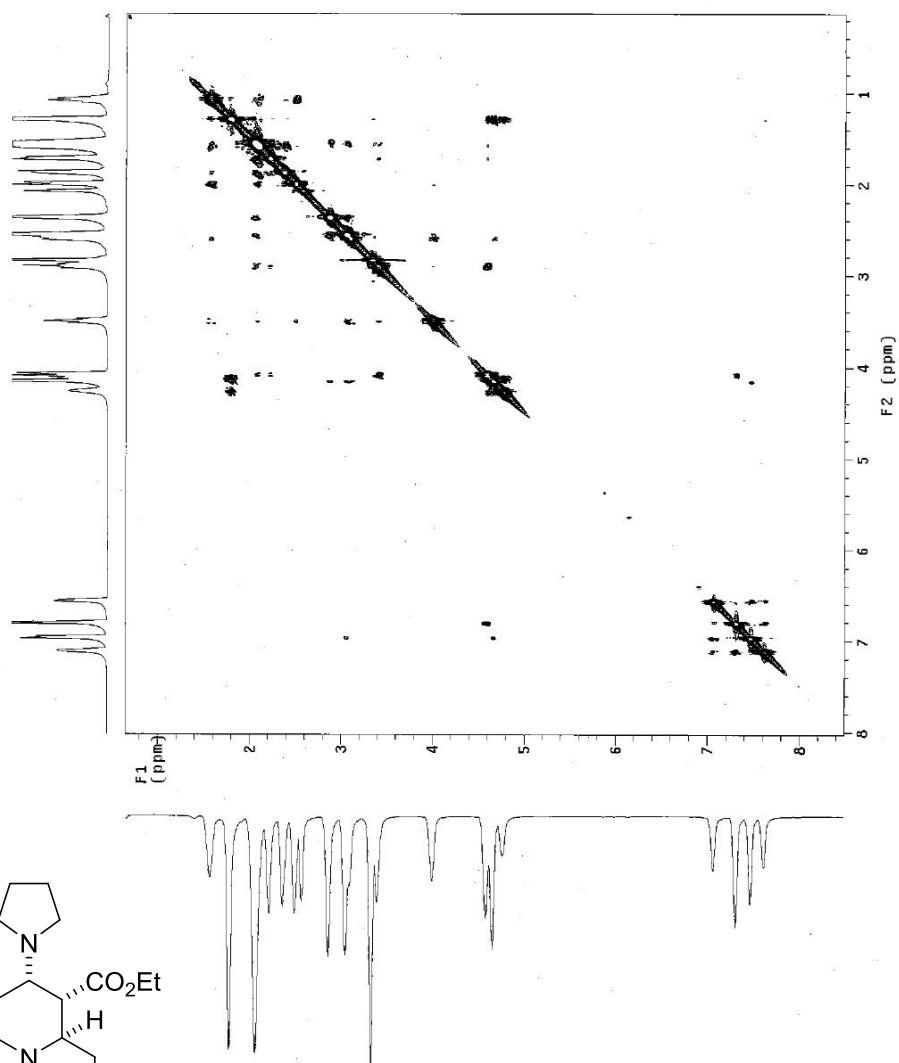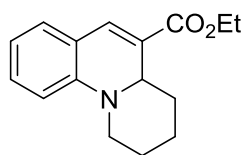
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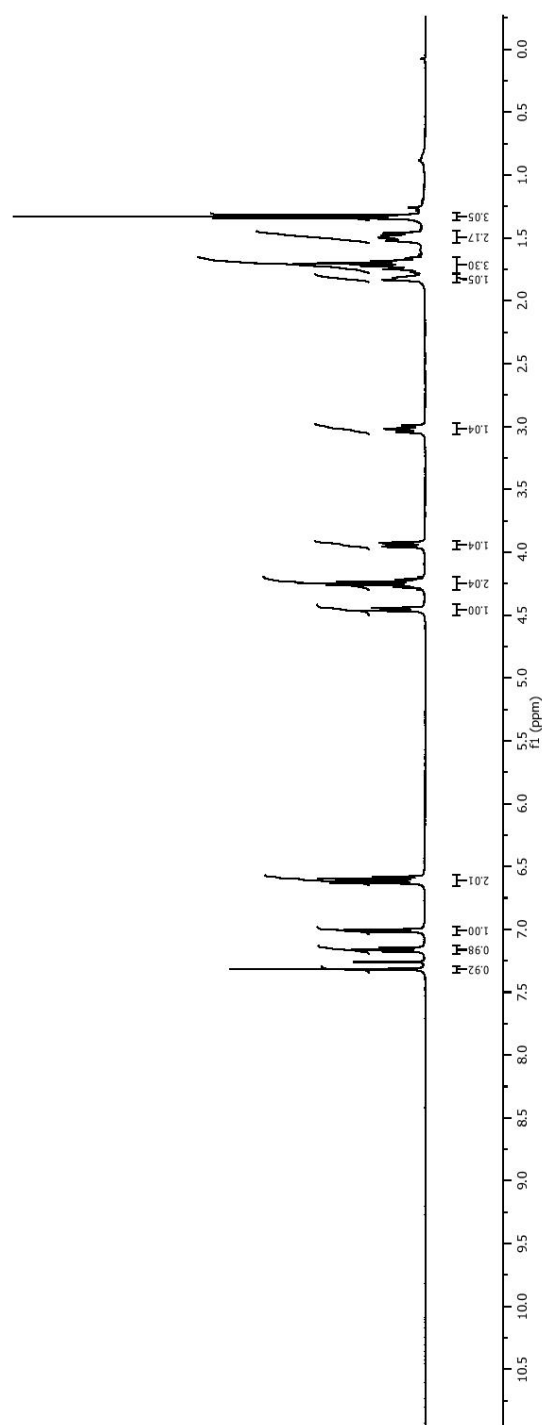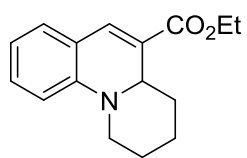
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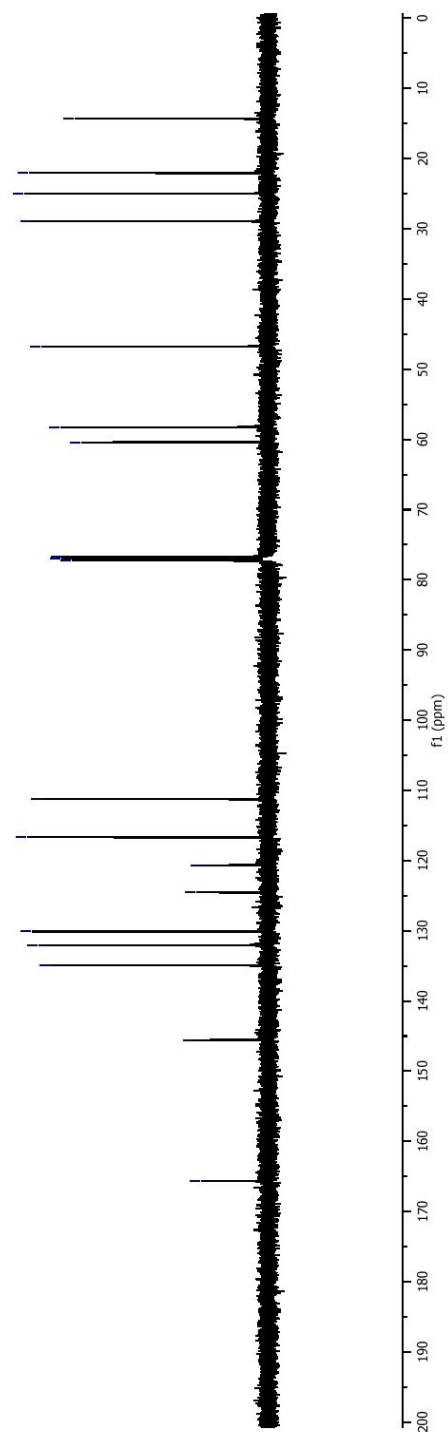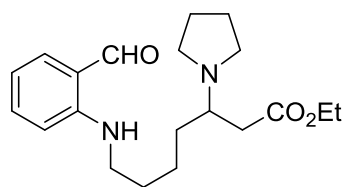
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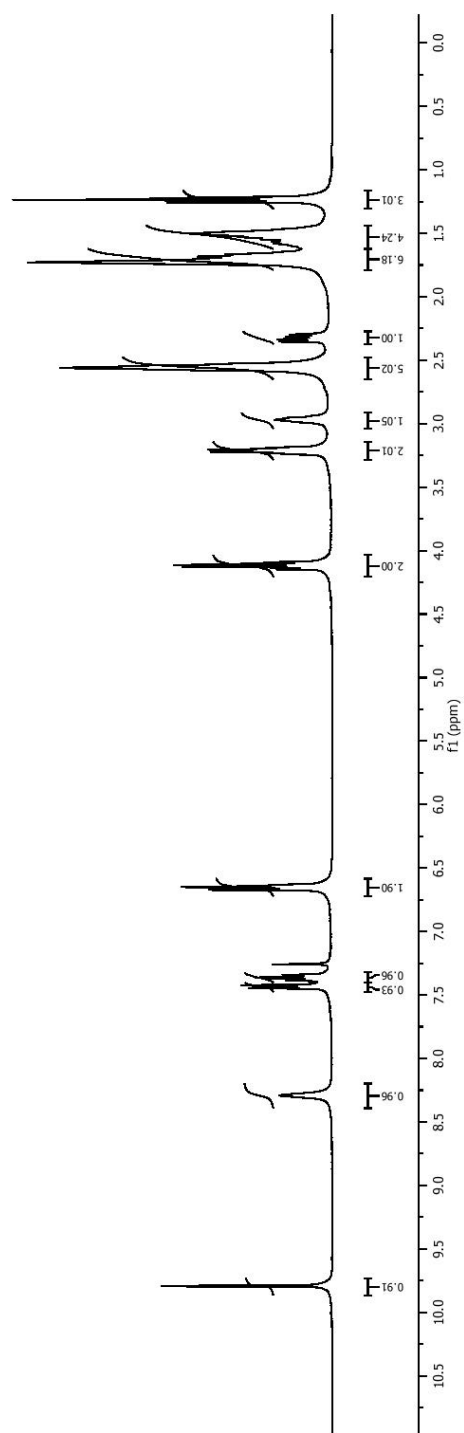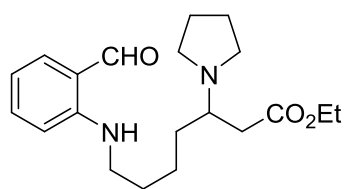
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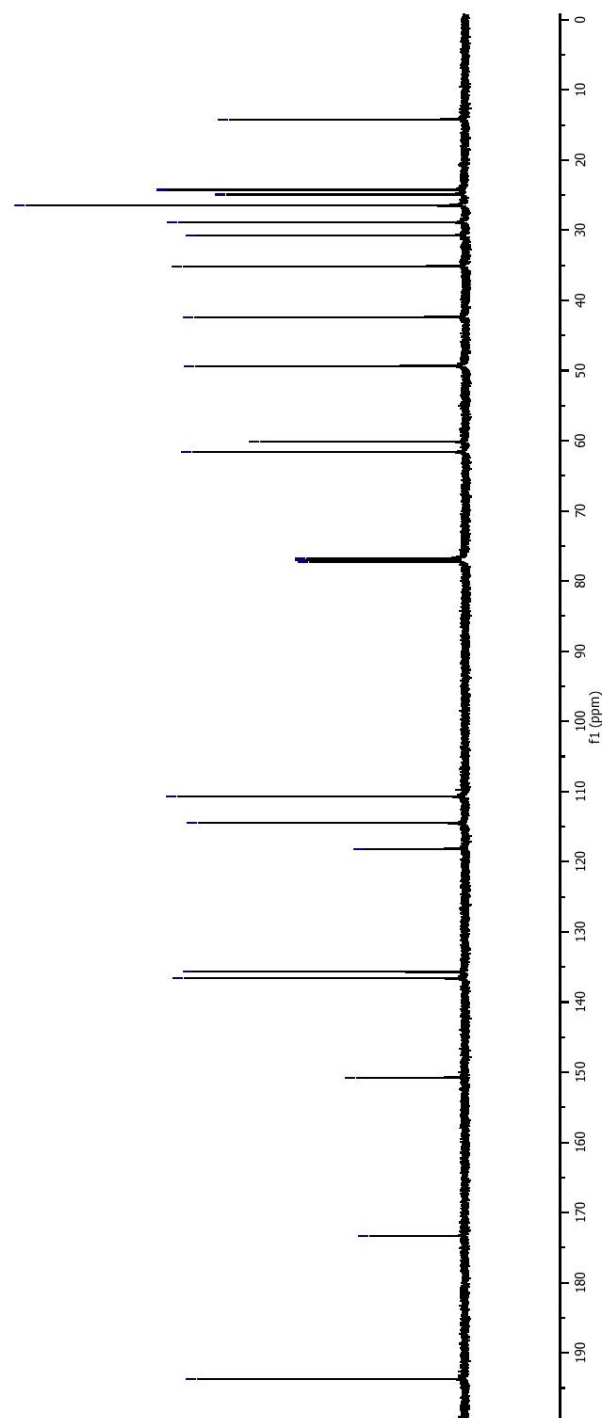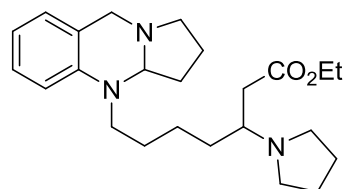
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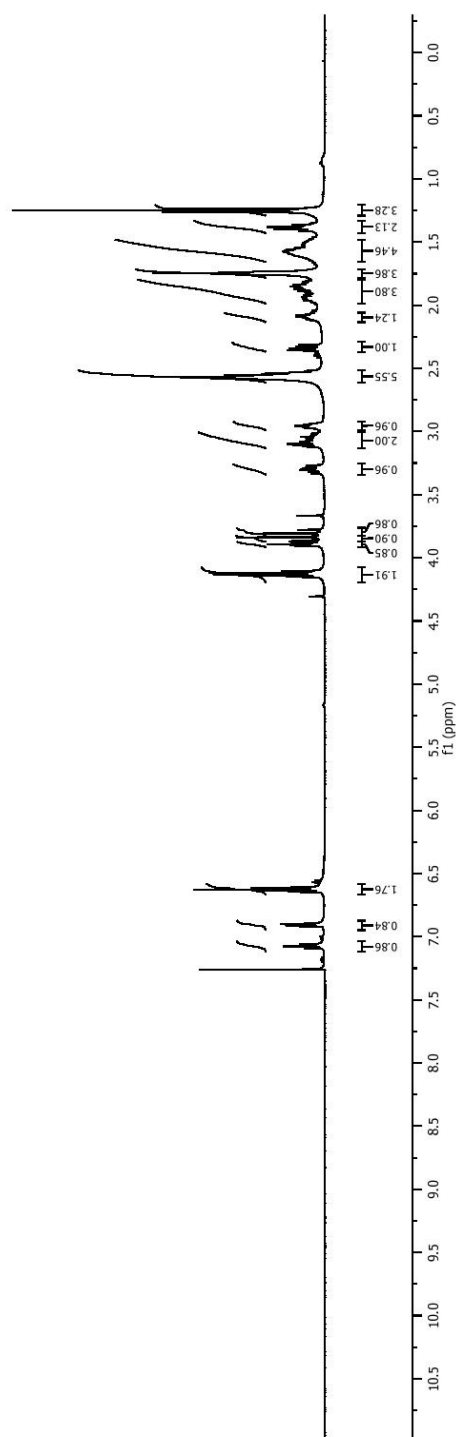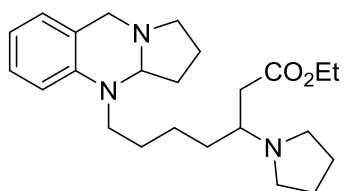
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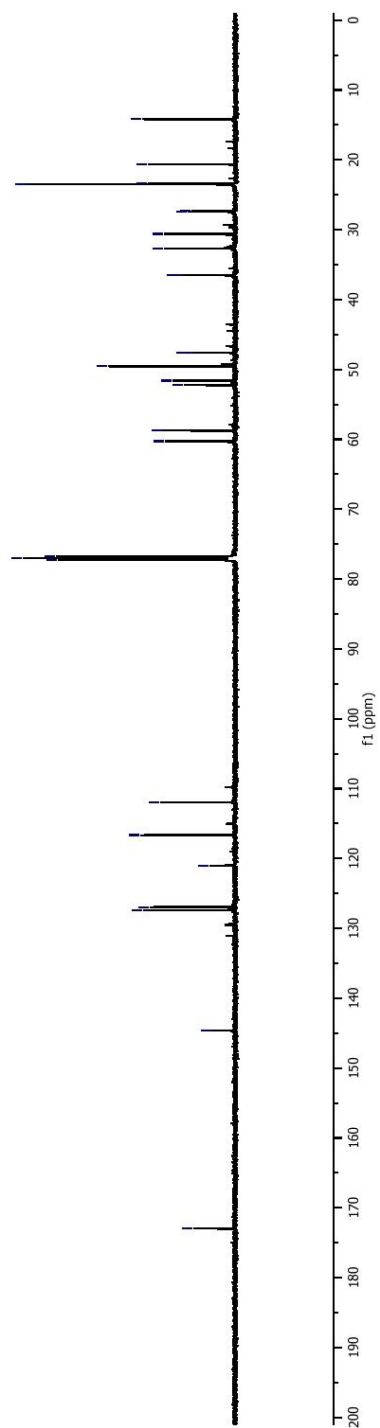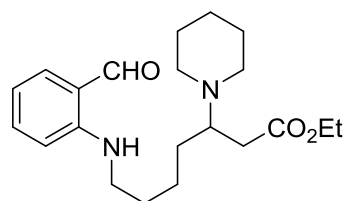
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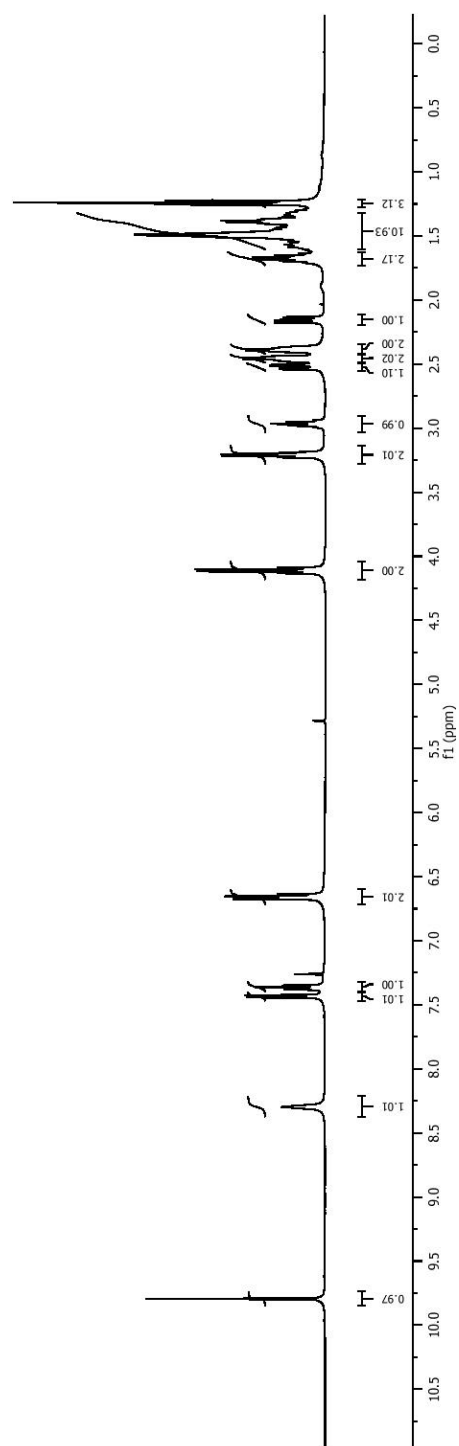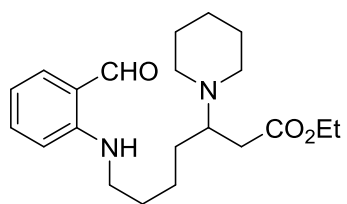
^{13}C NMR of **2.40**
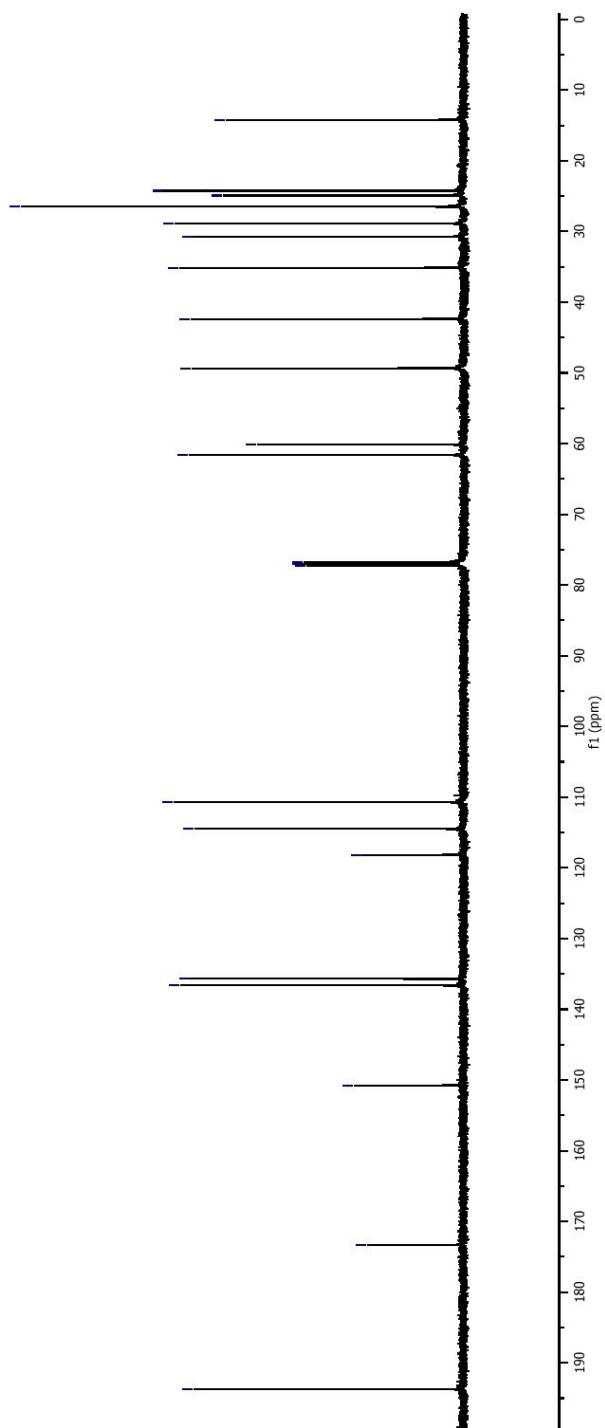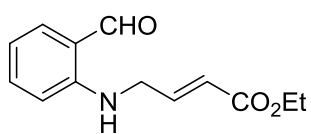
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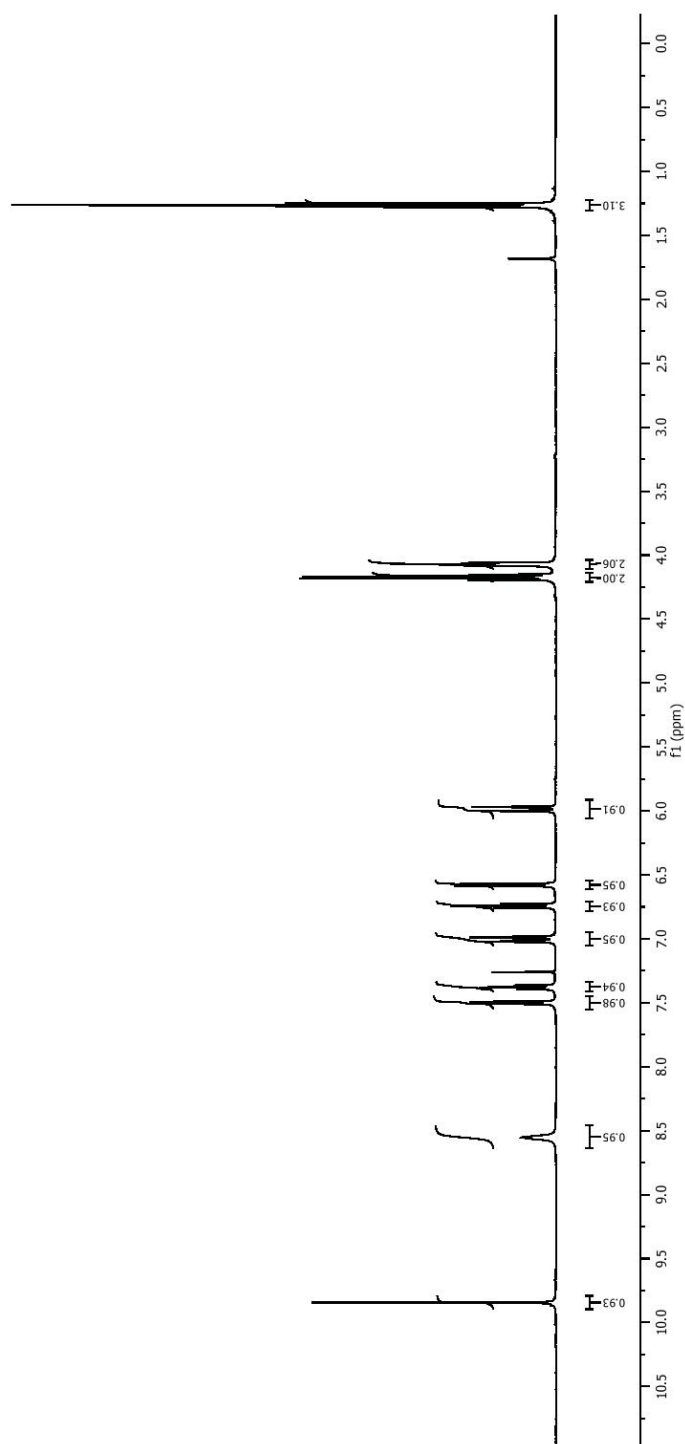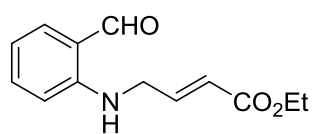
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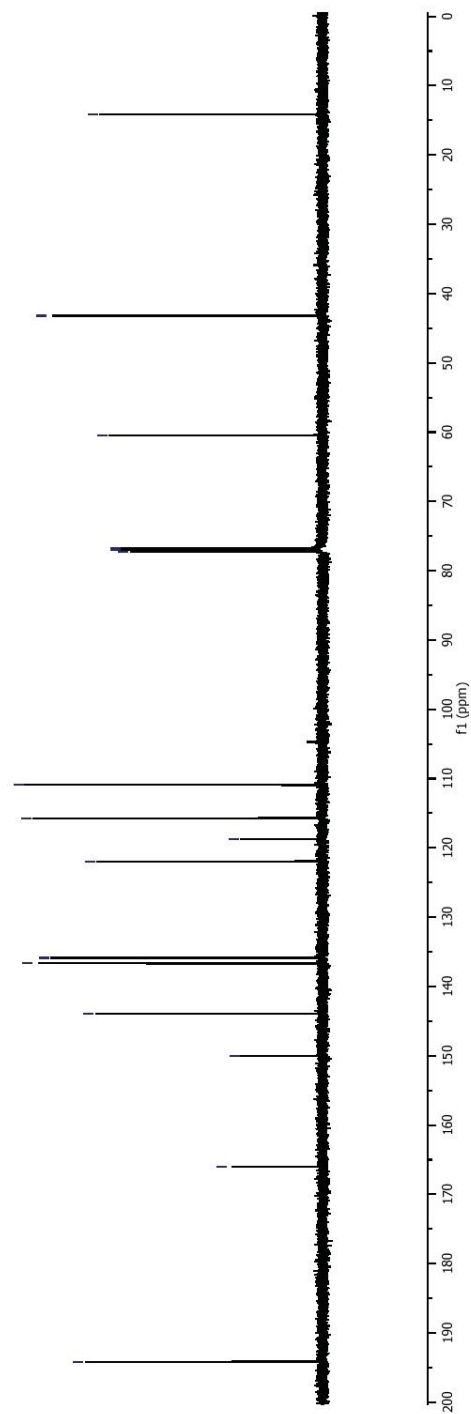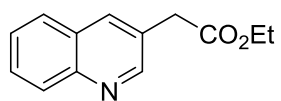
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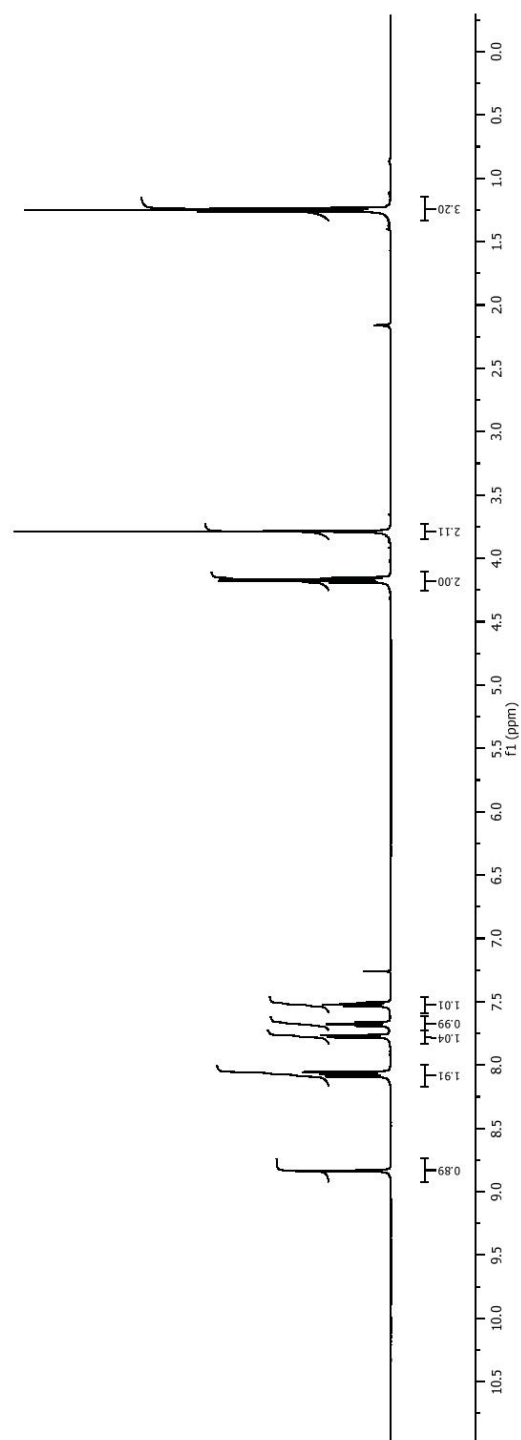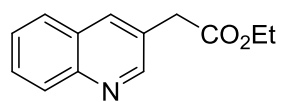
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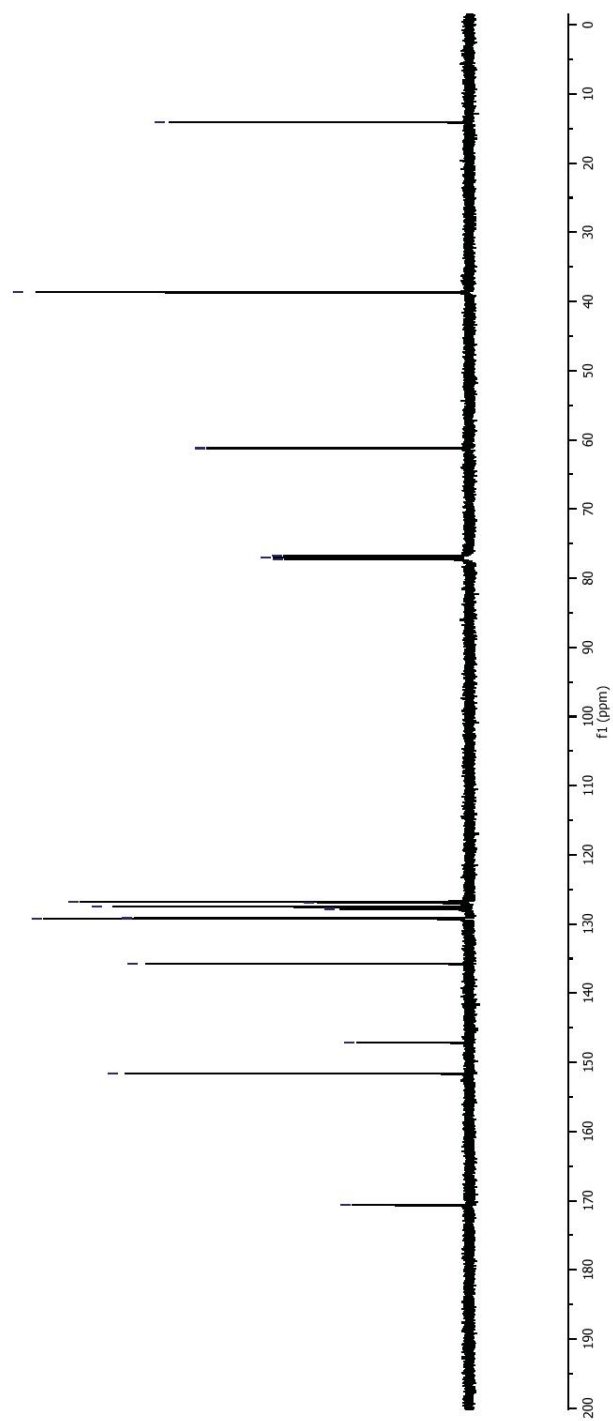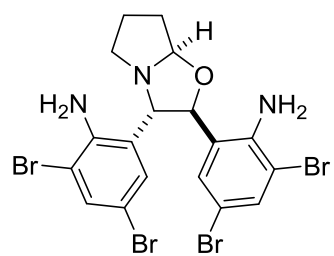
^{1}H NMR of **2.47**

^{13}C NMR of **2.47**

F2 (ppm)

S 40
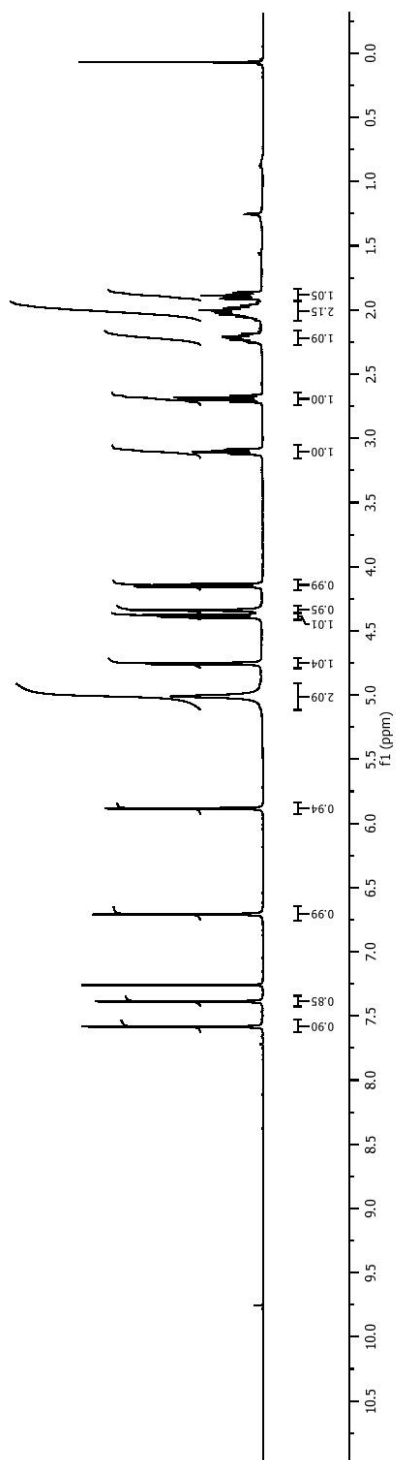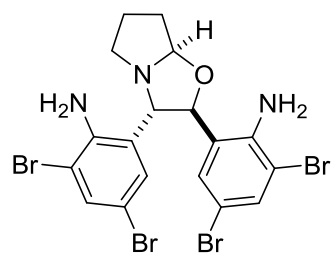
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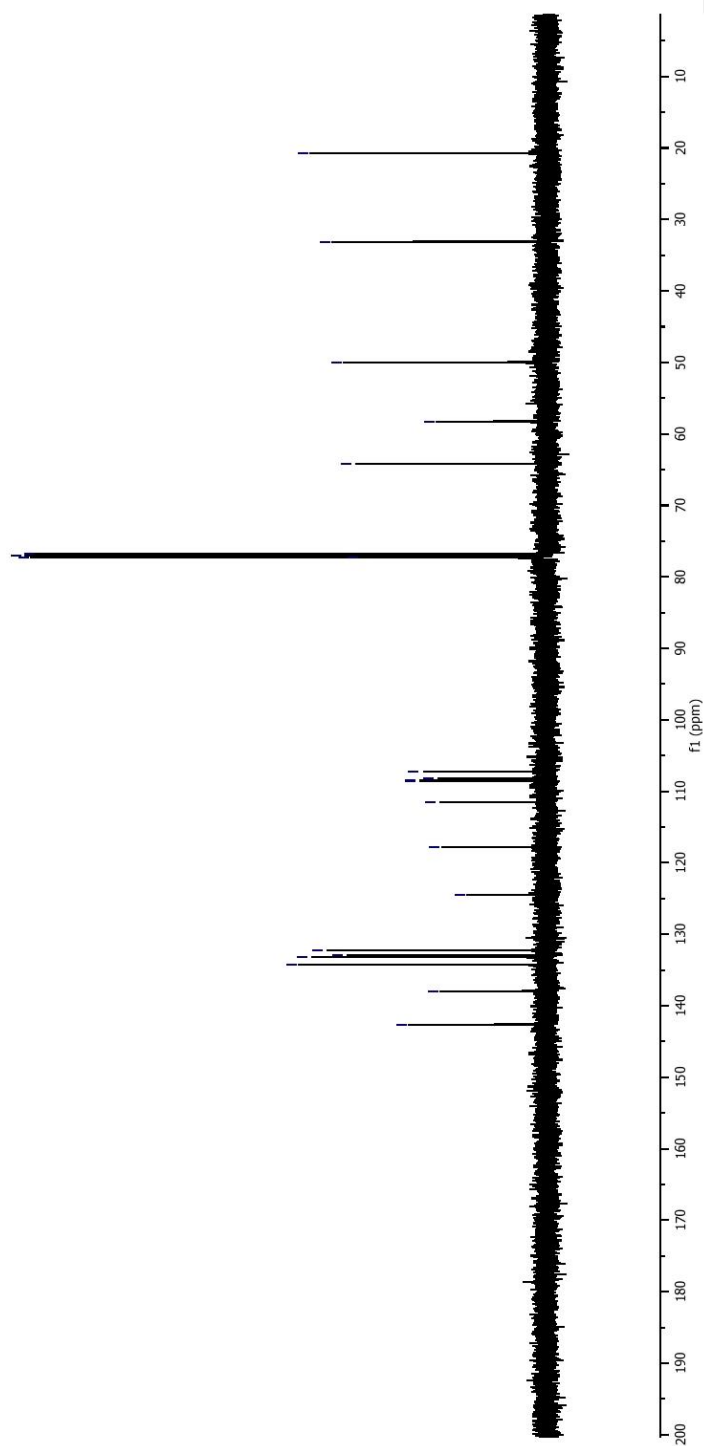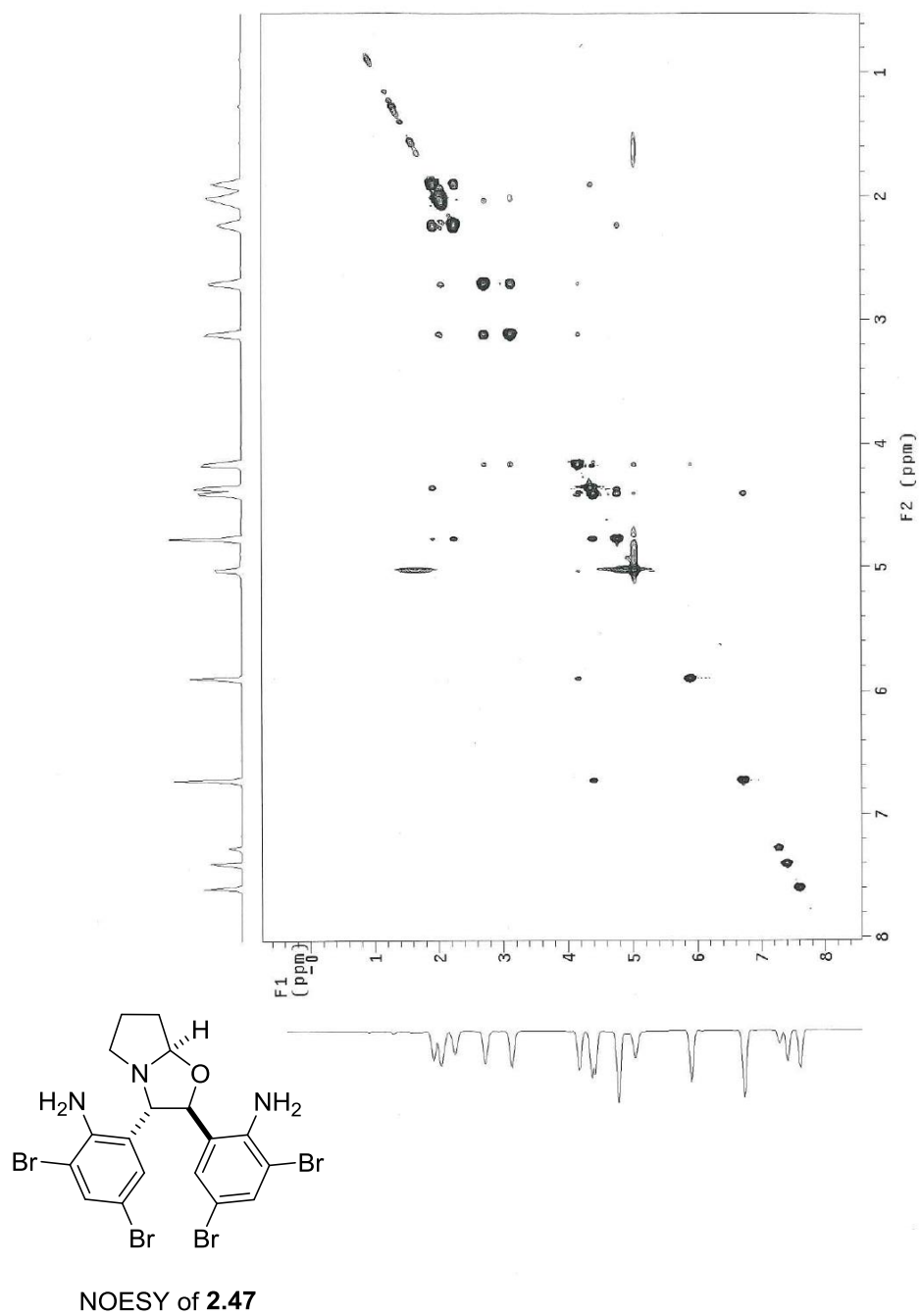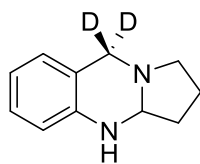
^{1}H NMR of **2.12b (eq 16)**
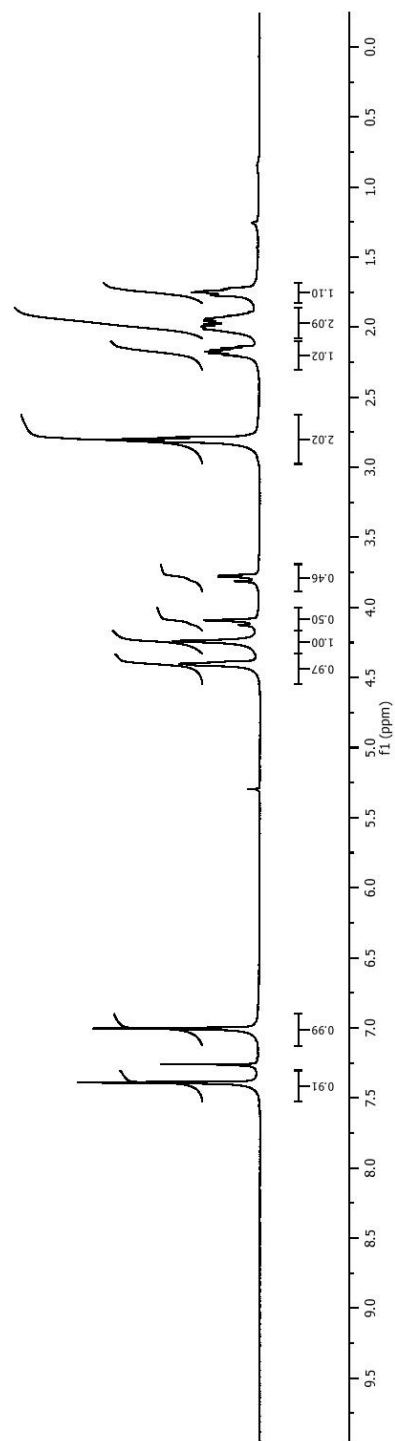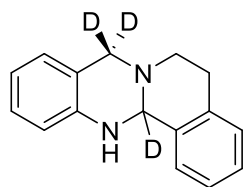
^{1}H NMR of **2.12i (eq 17)**
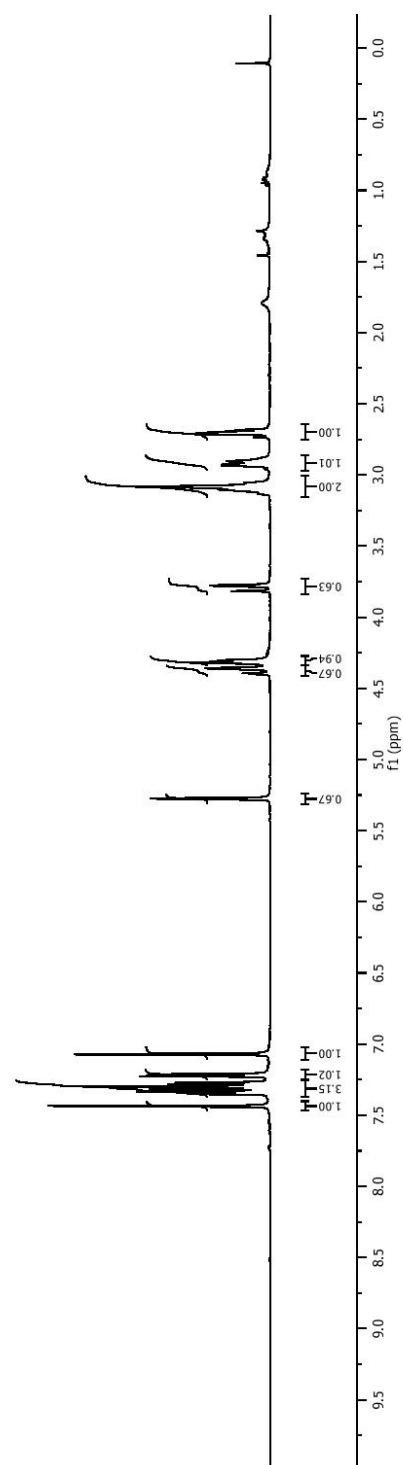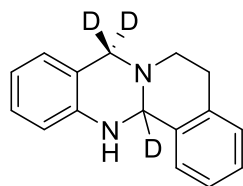
^{1}H NMR of **2.12i (eq 18)**
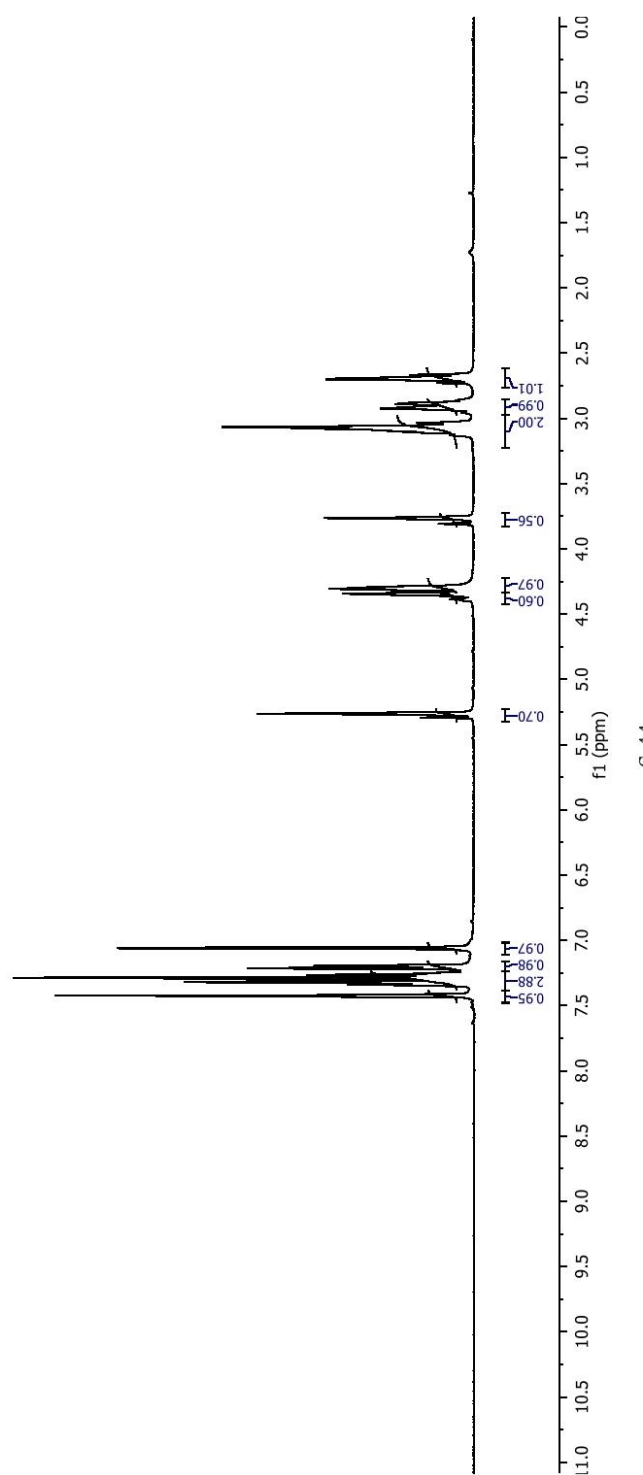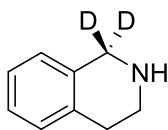
^{1}H NMR of **THIQ (eq 18)**
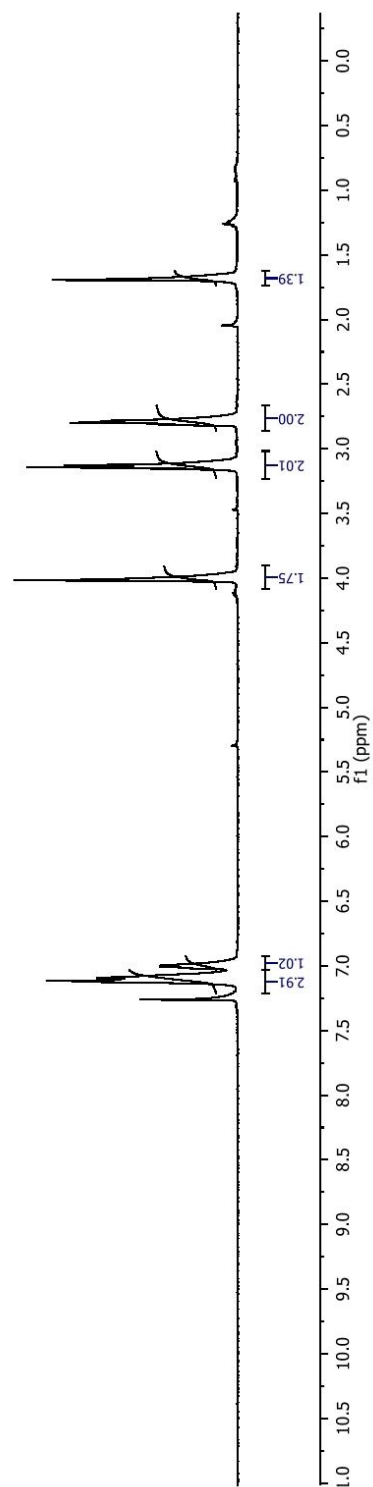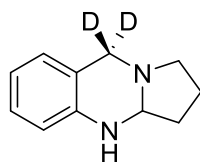
^{1}H NMR of **2.12b (eq 19)**
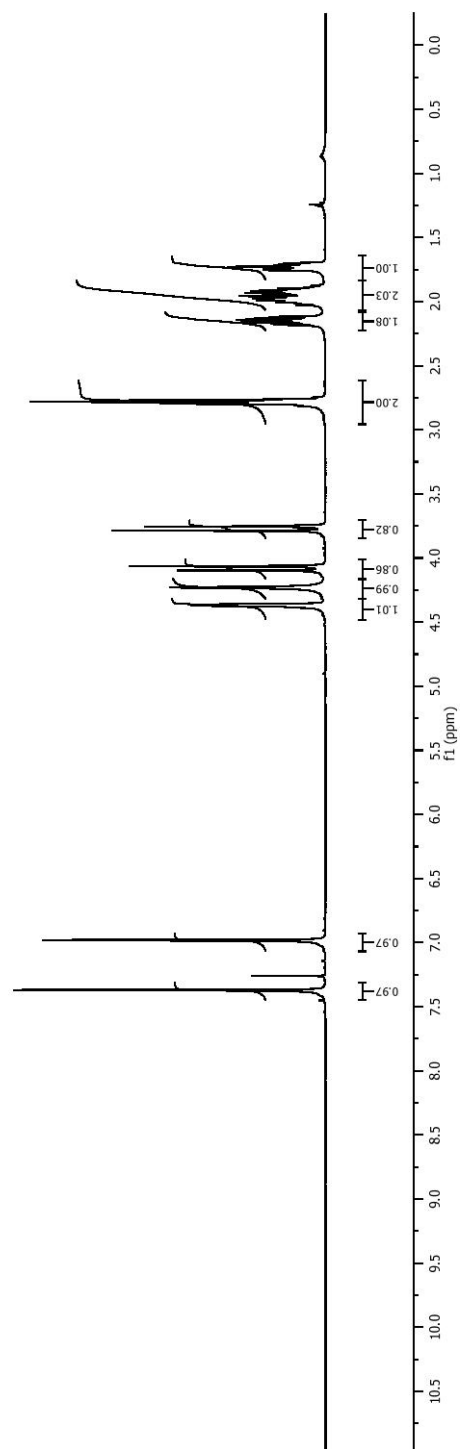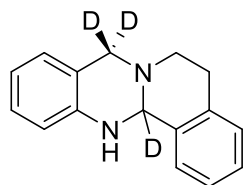
^{1}H NMR of **2.12i (eq 20)**
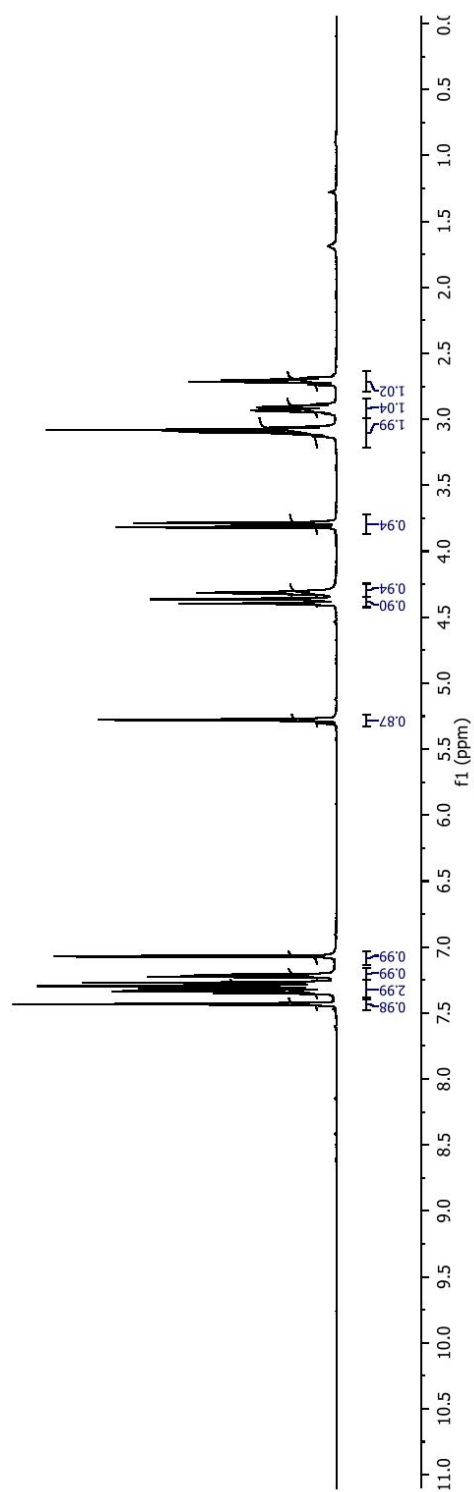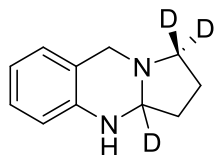
^{1}H NMR of **2.12b (eq 21)**
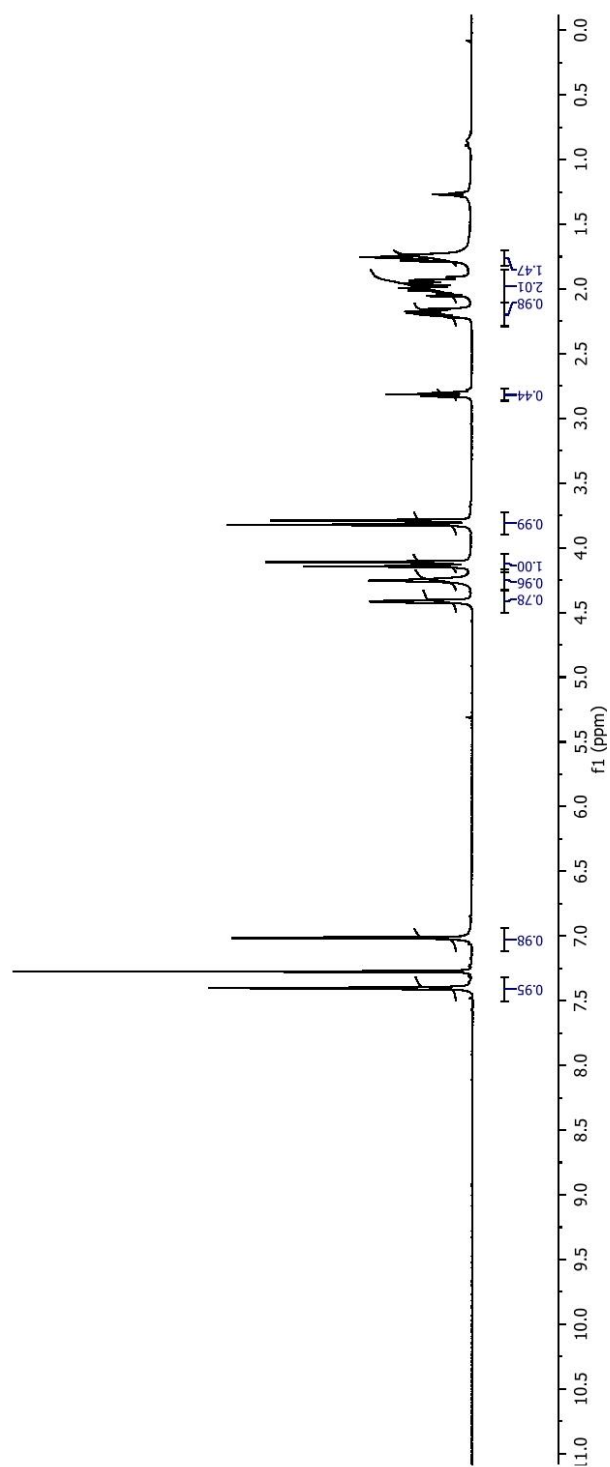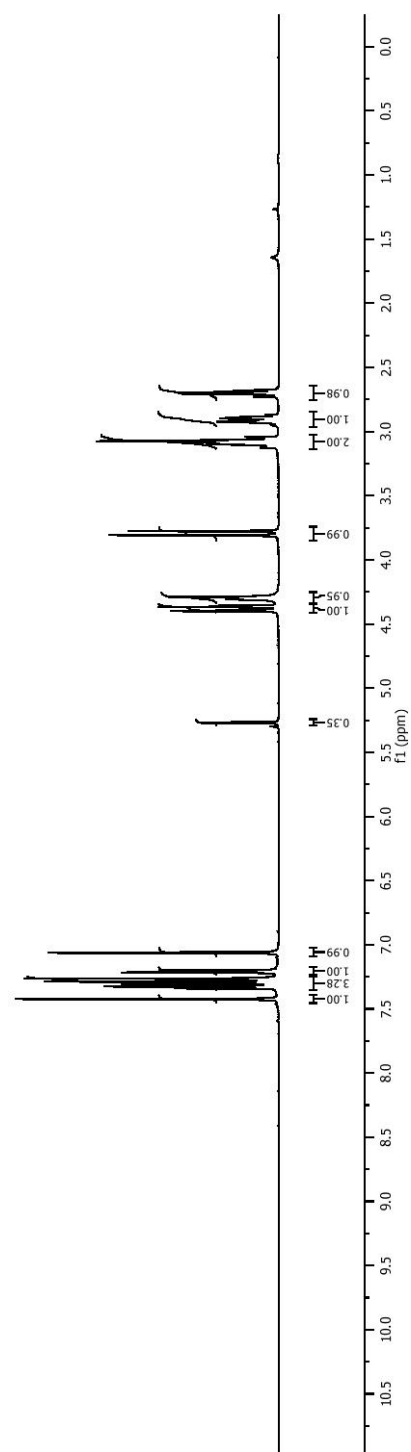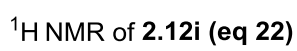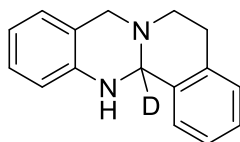
^{1}H NMR of **2.12i (eq 22)**

^{1}H NMR of **2.12i (eq 23)**
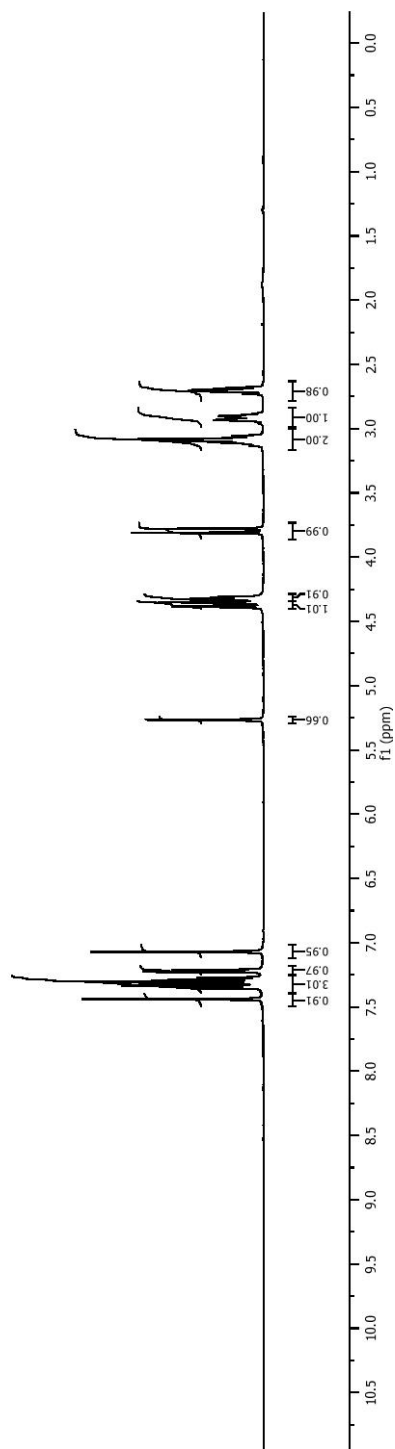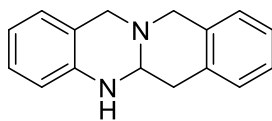
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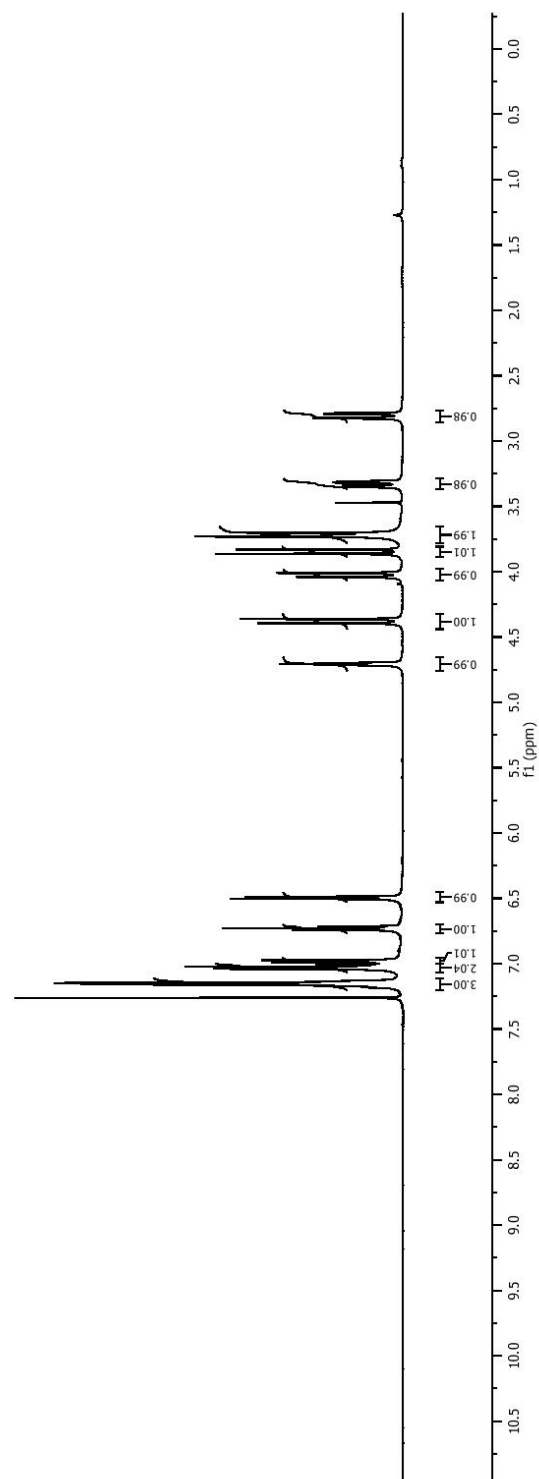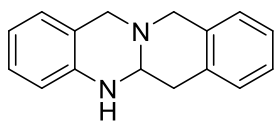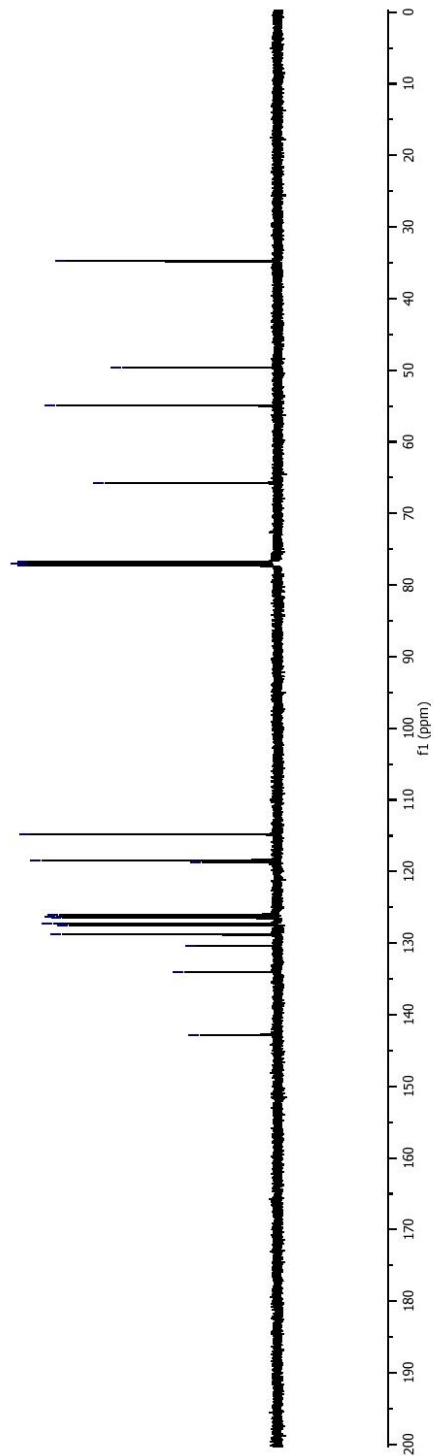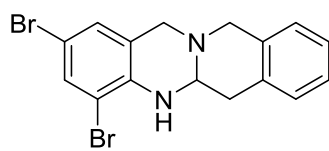
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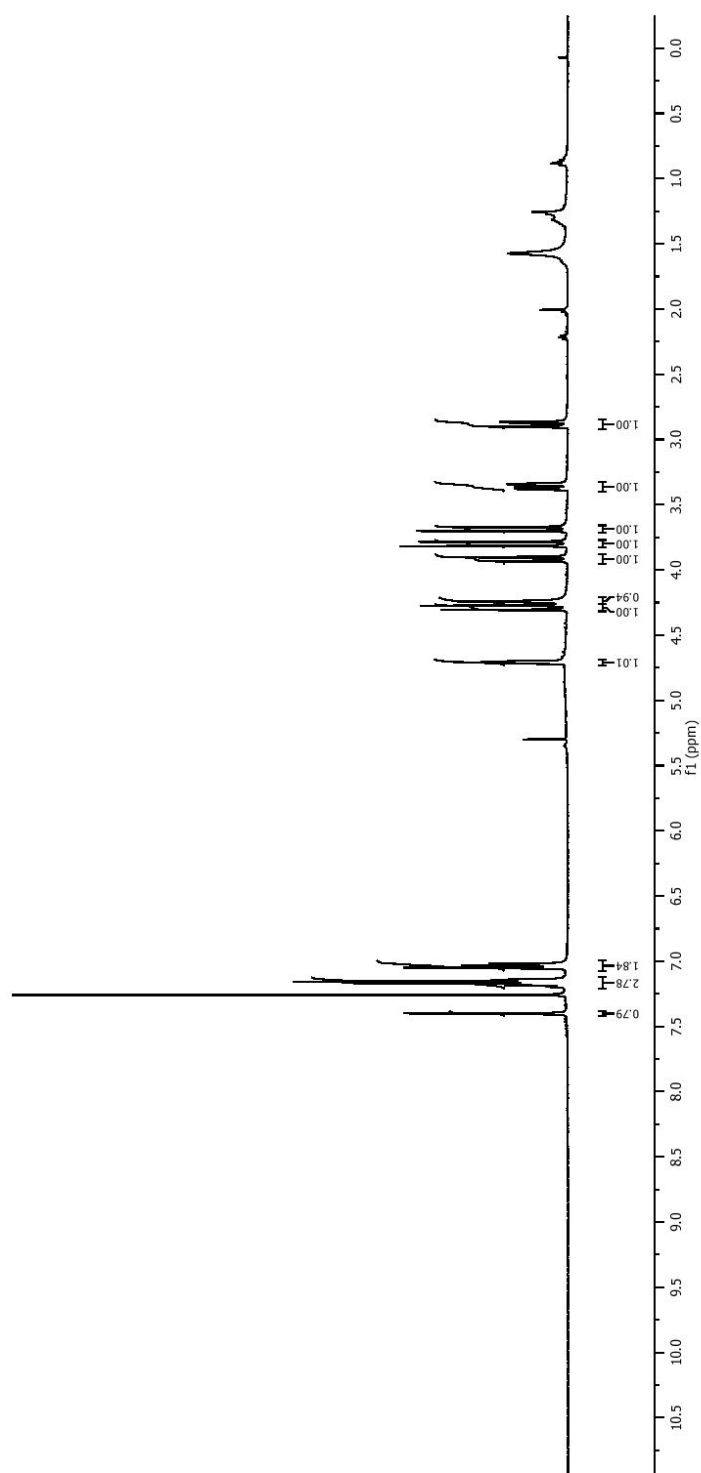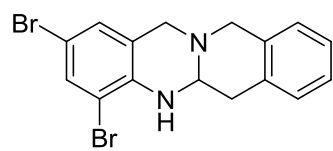
^{1}H NMR of **2.12m**

^{13}C NMR of **2.12m**
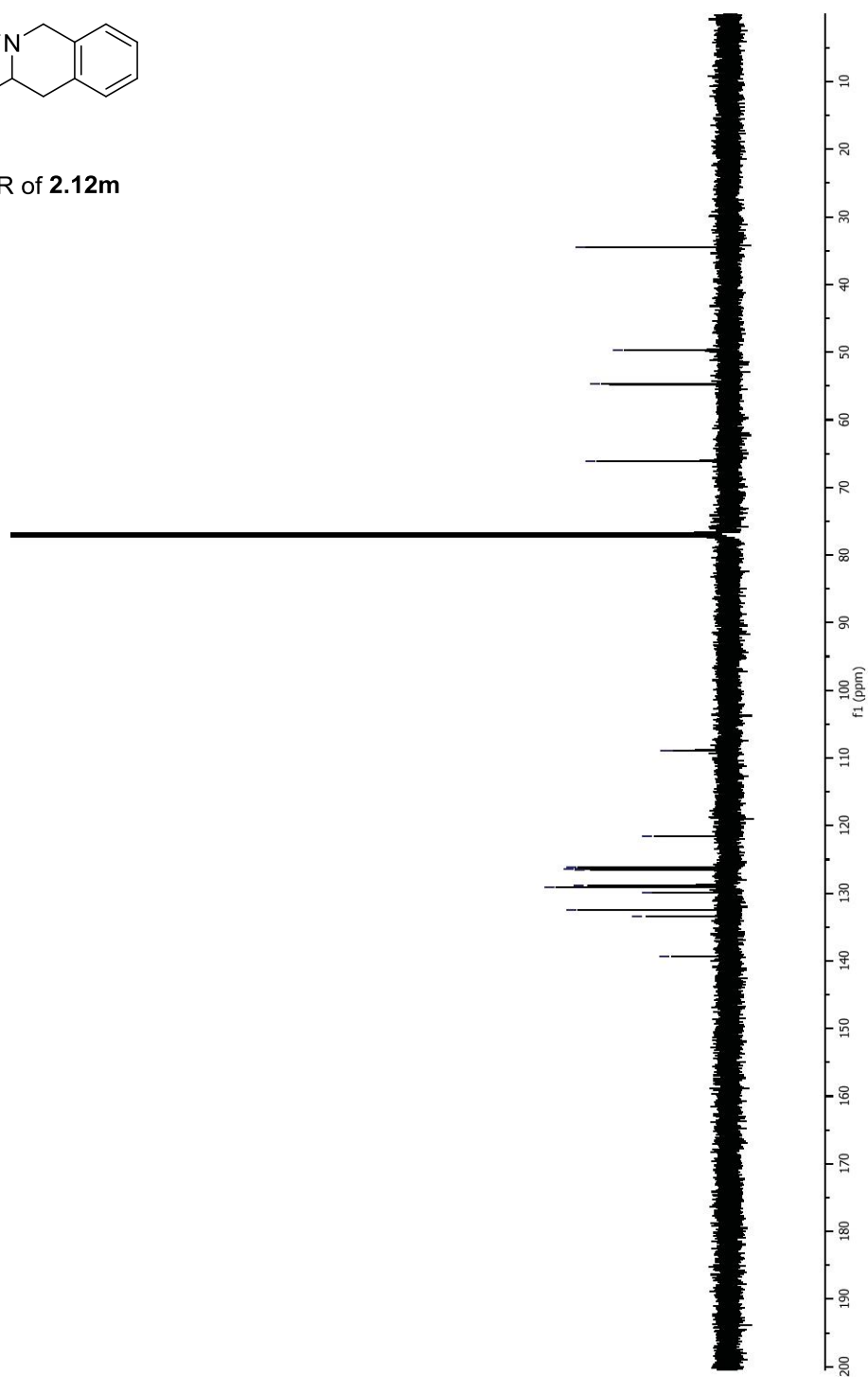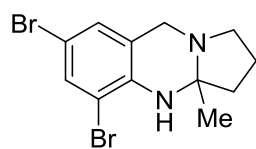
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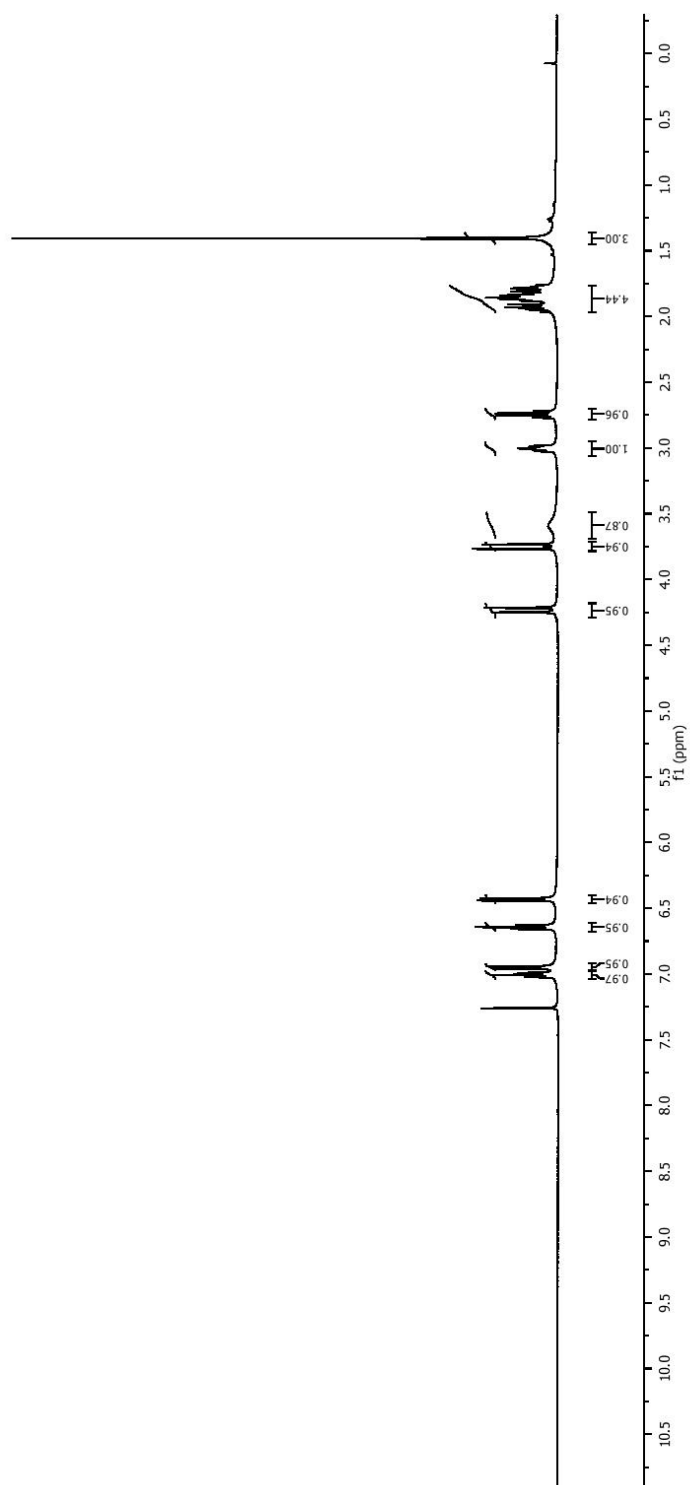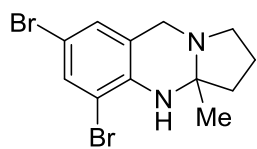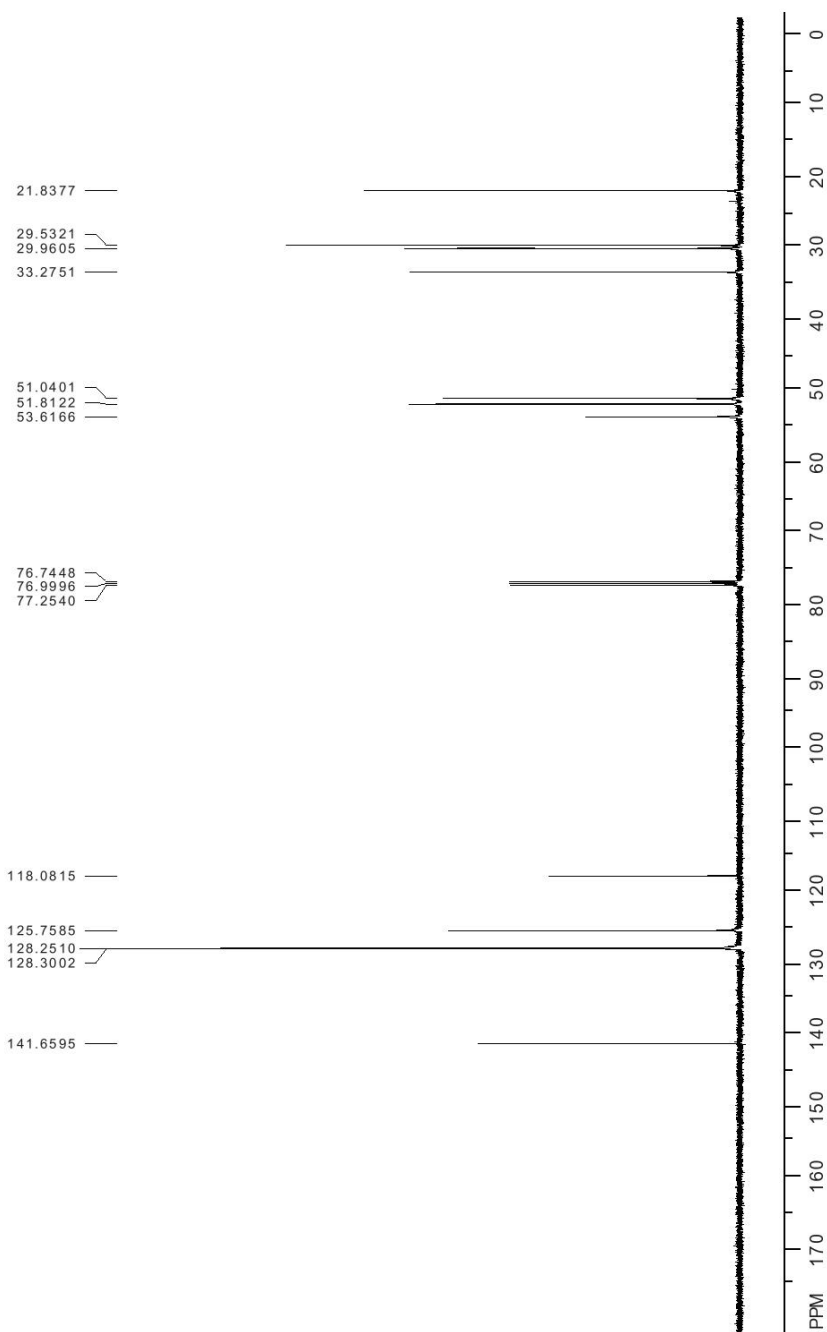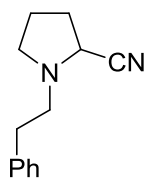
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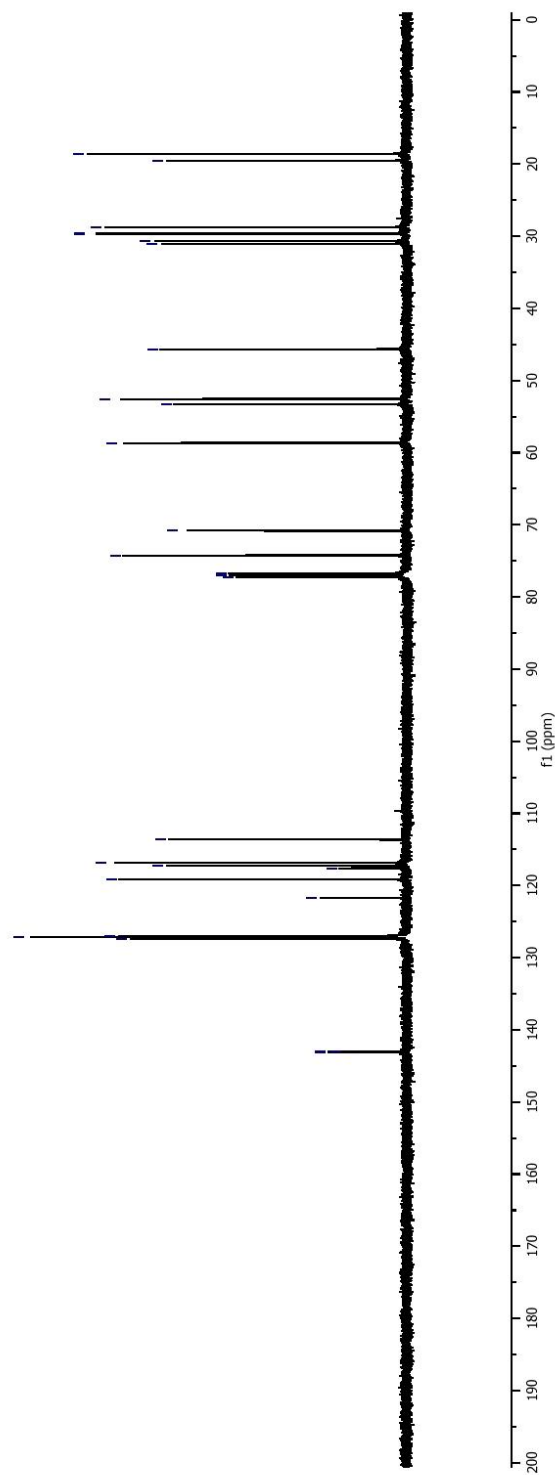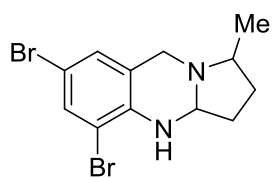
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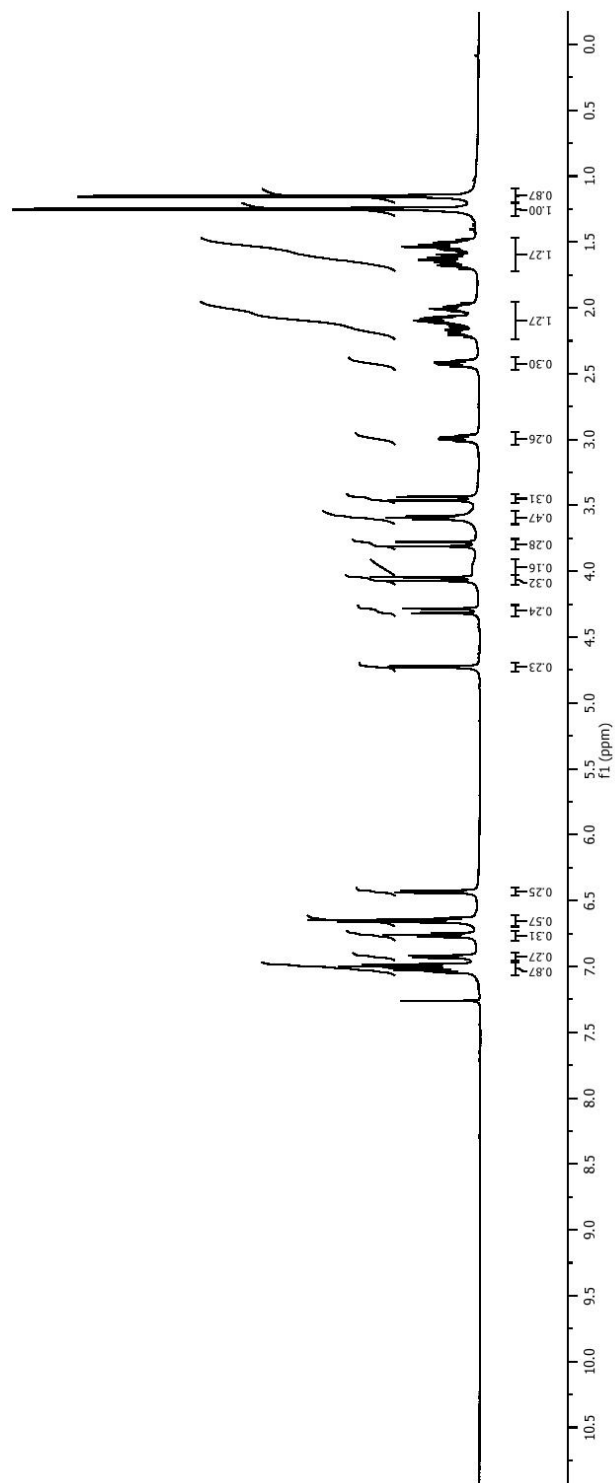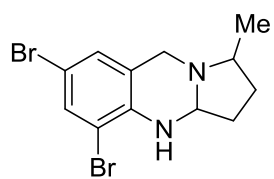
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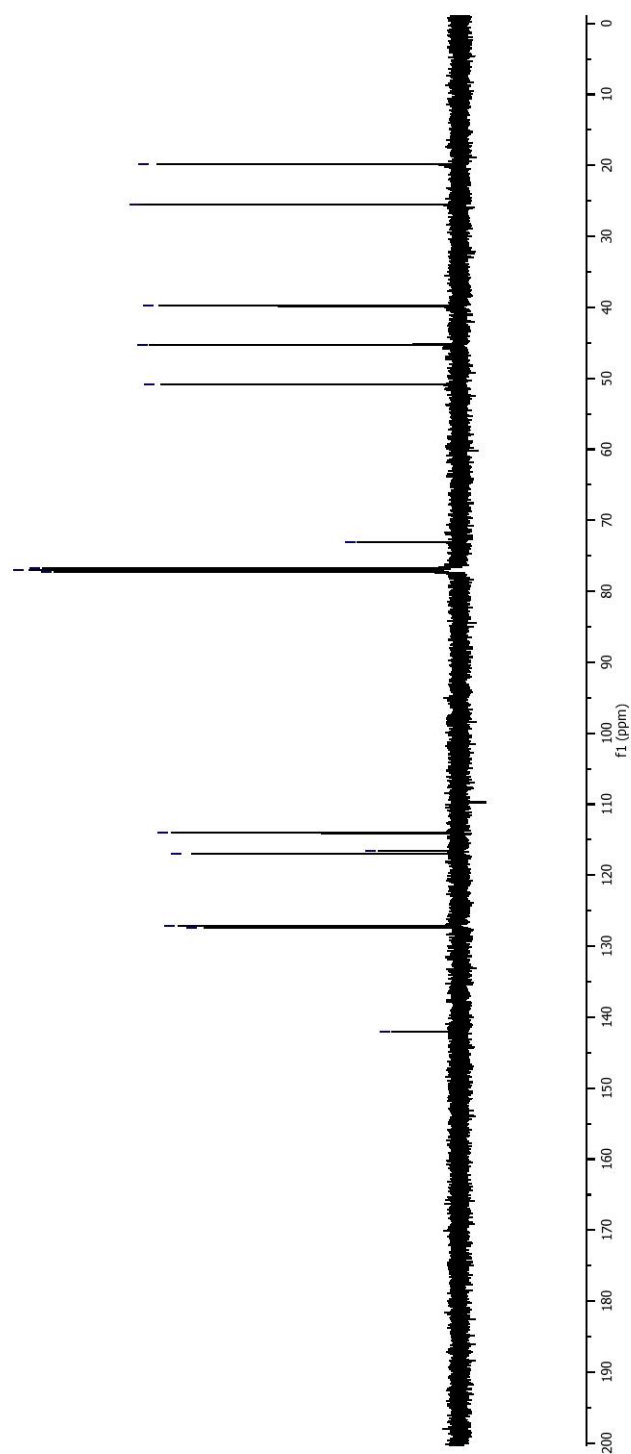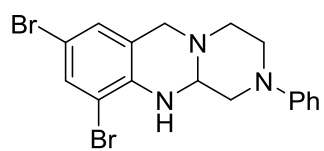
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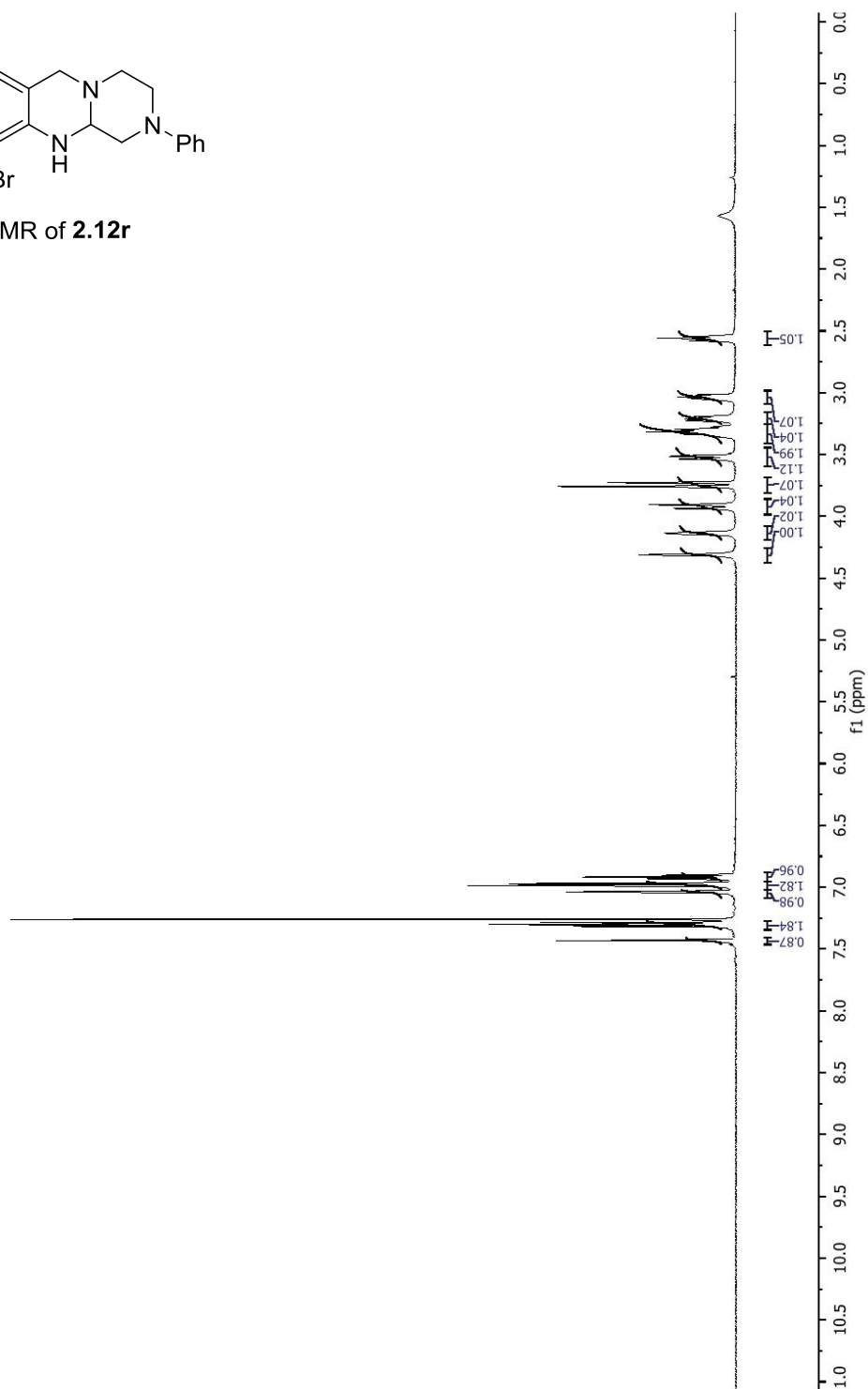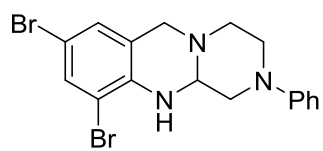
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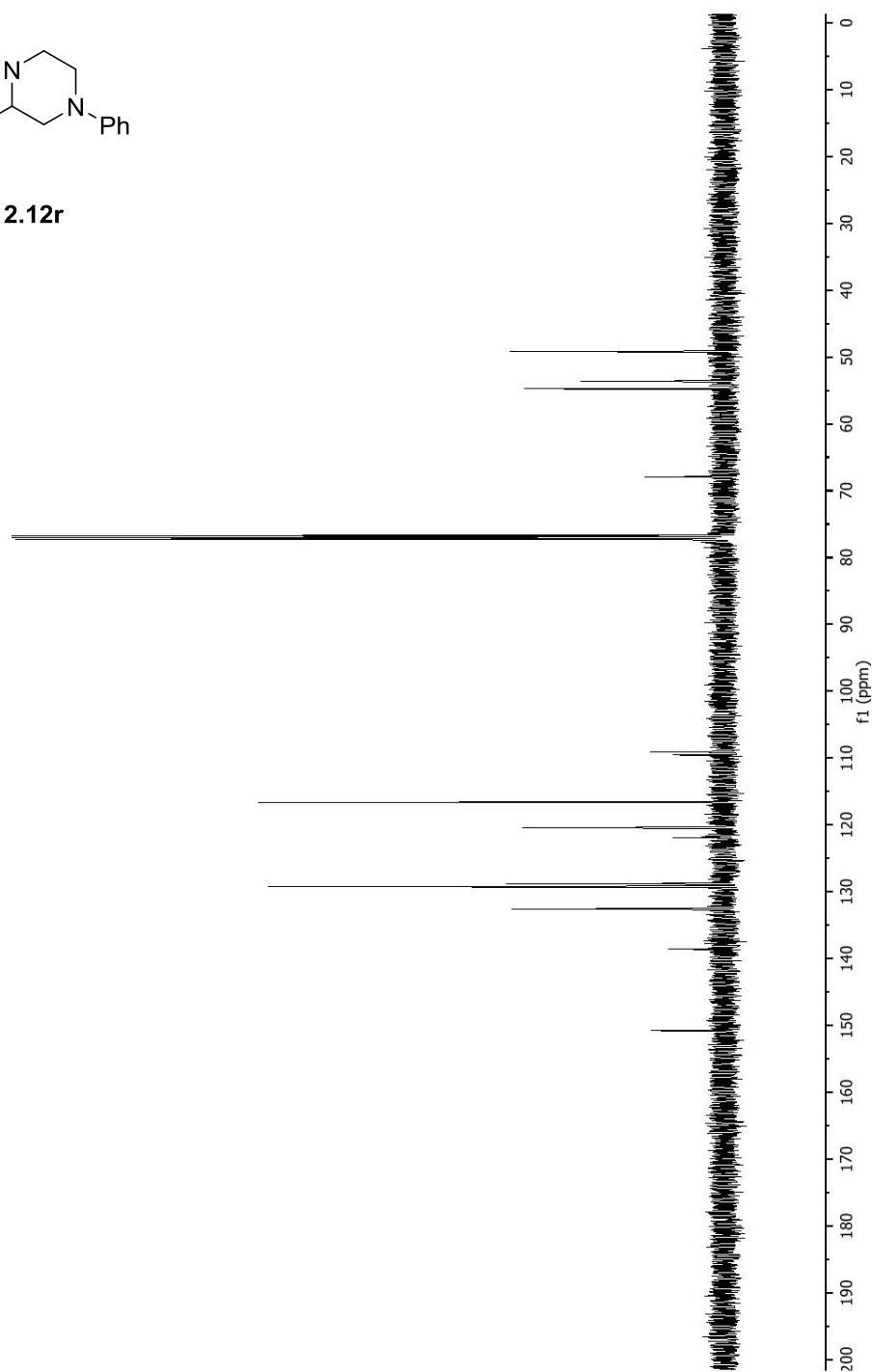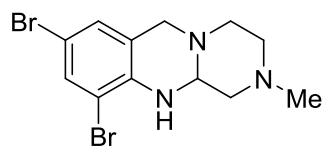
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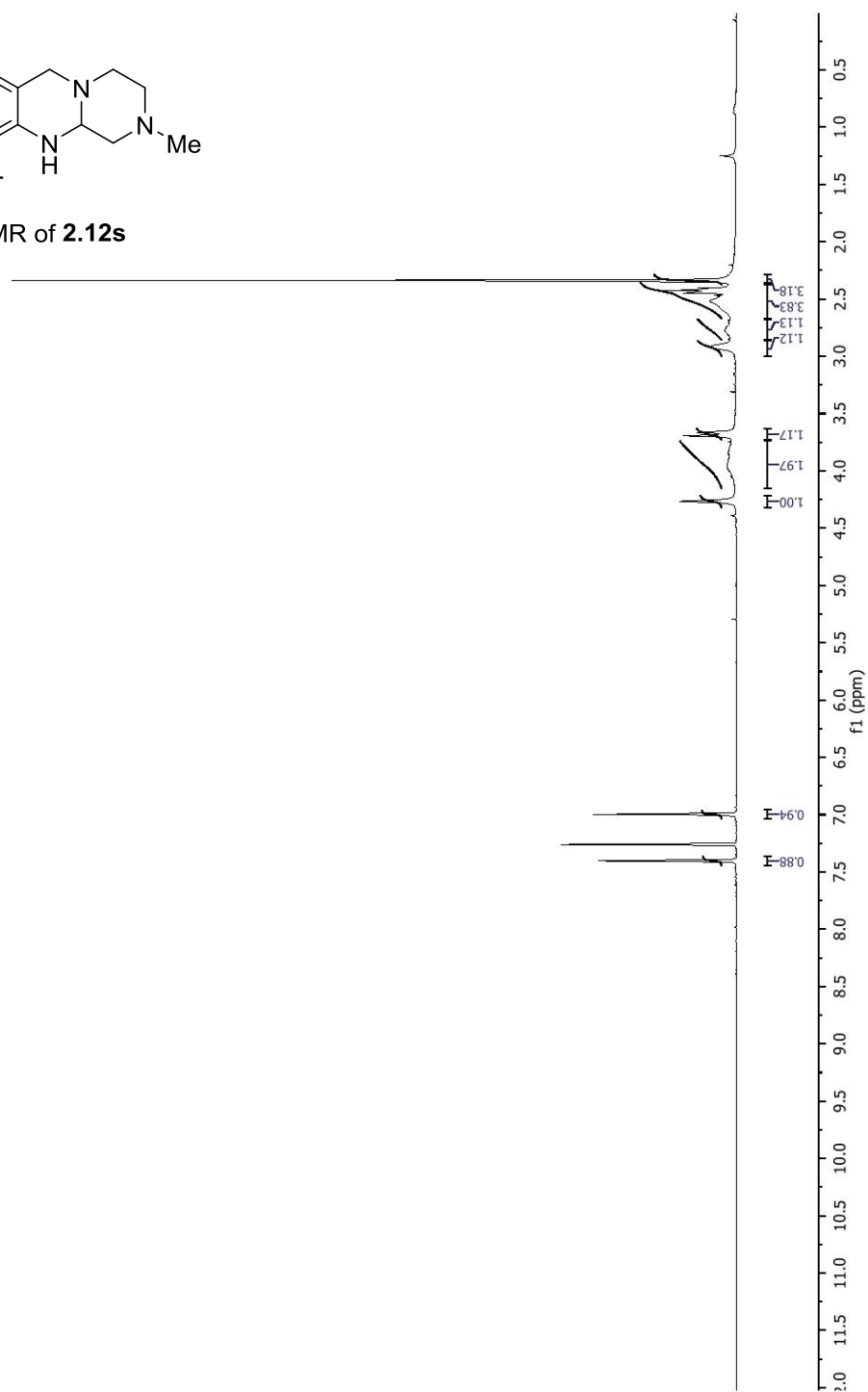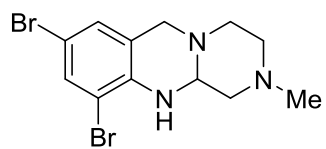
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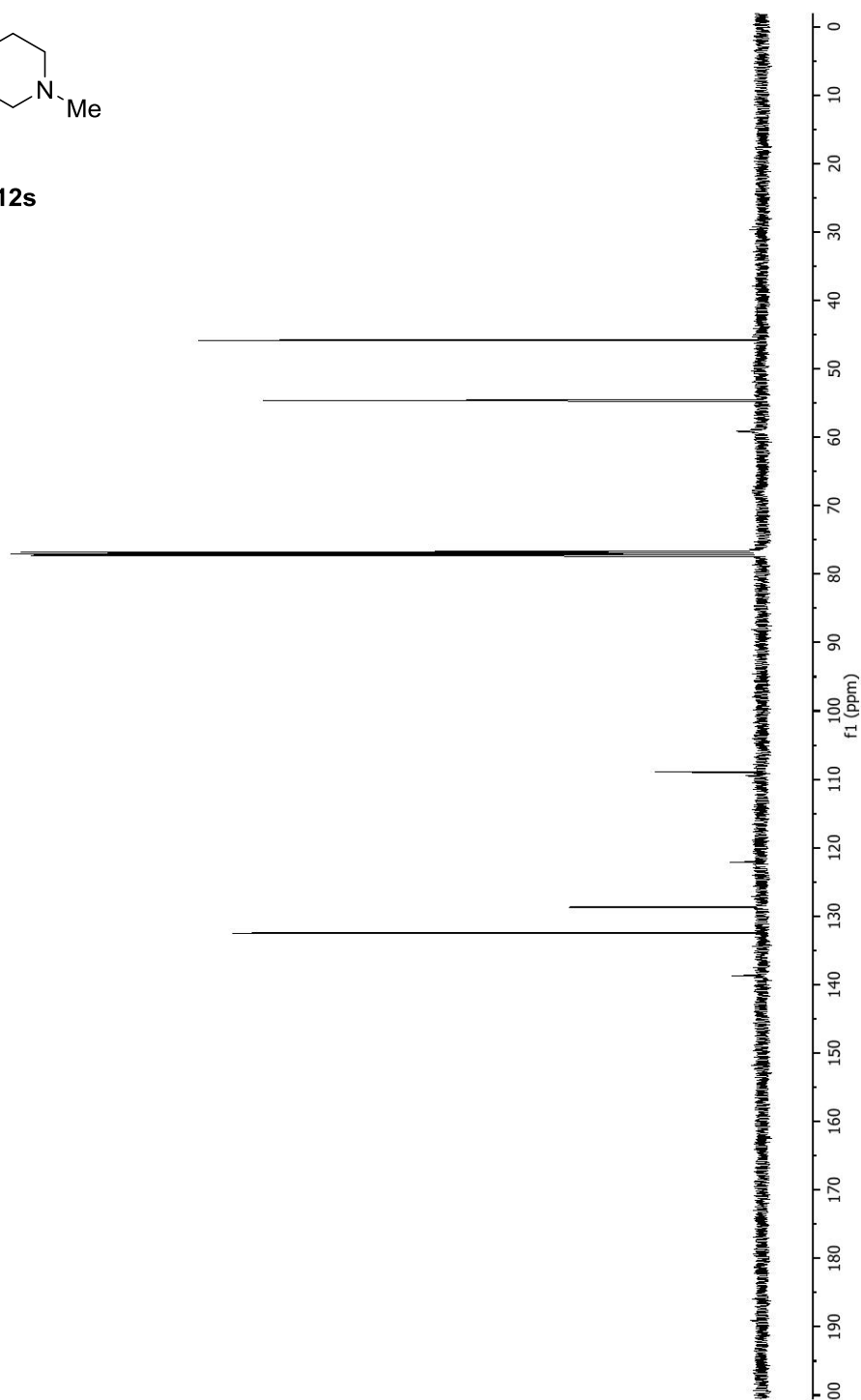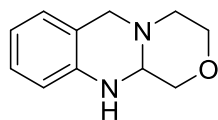
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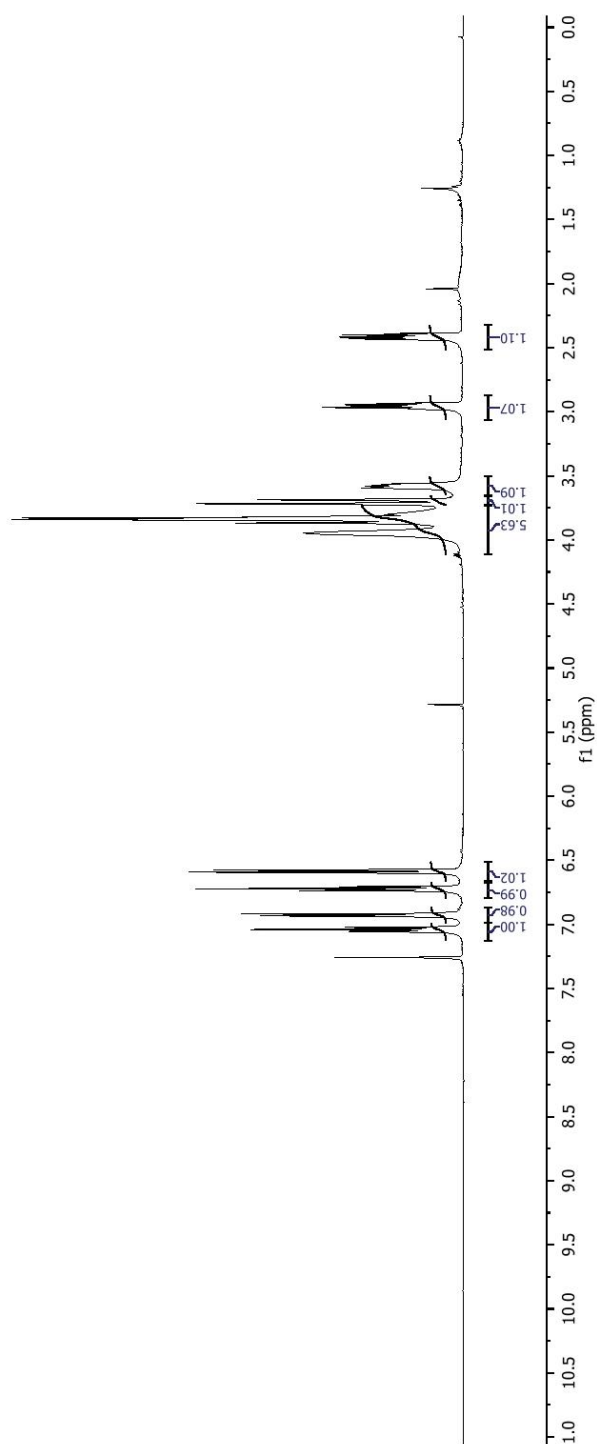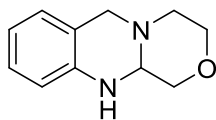
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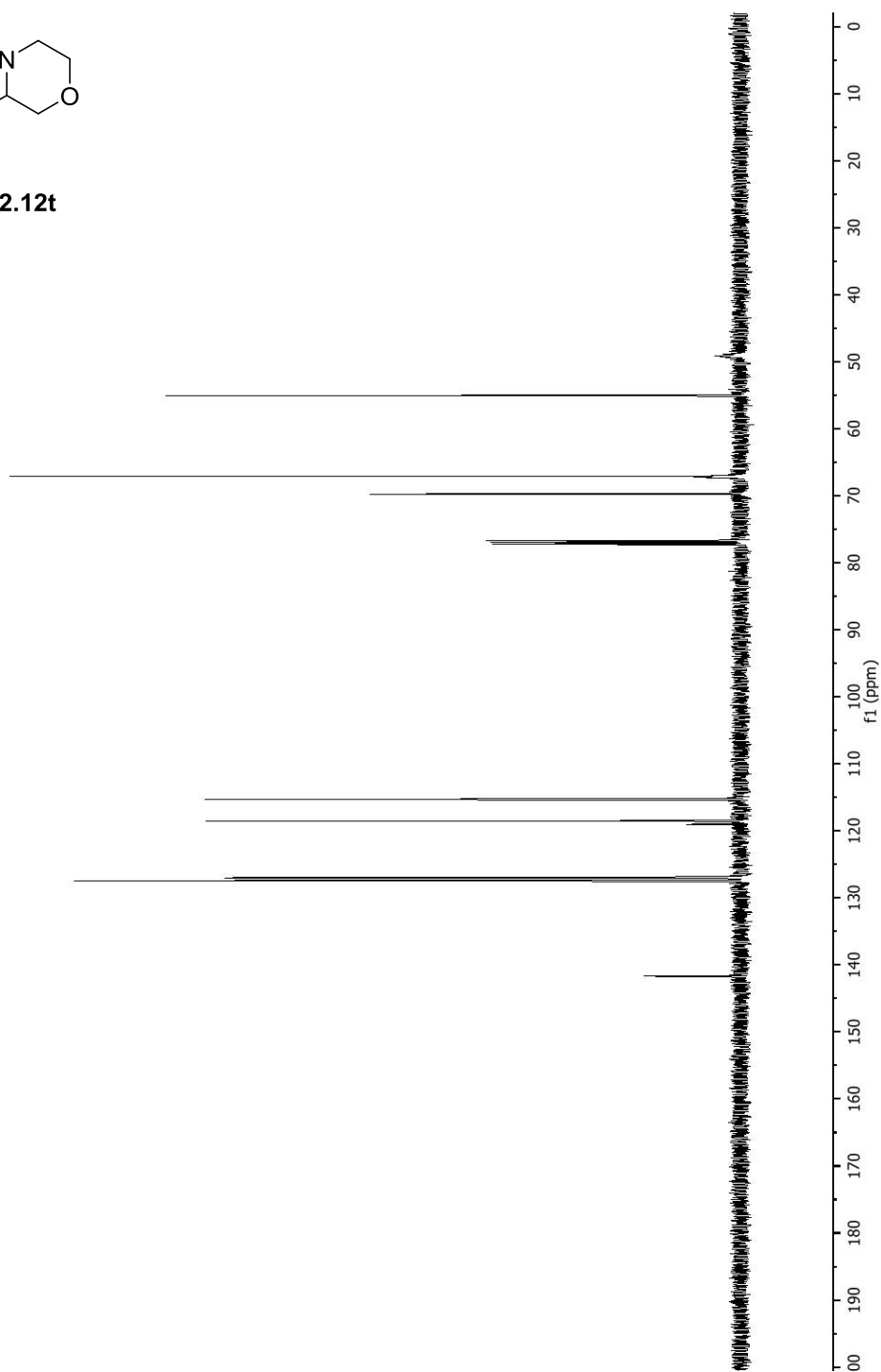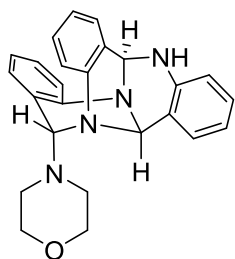
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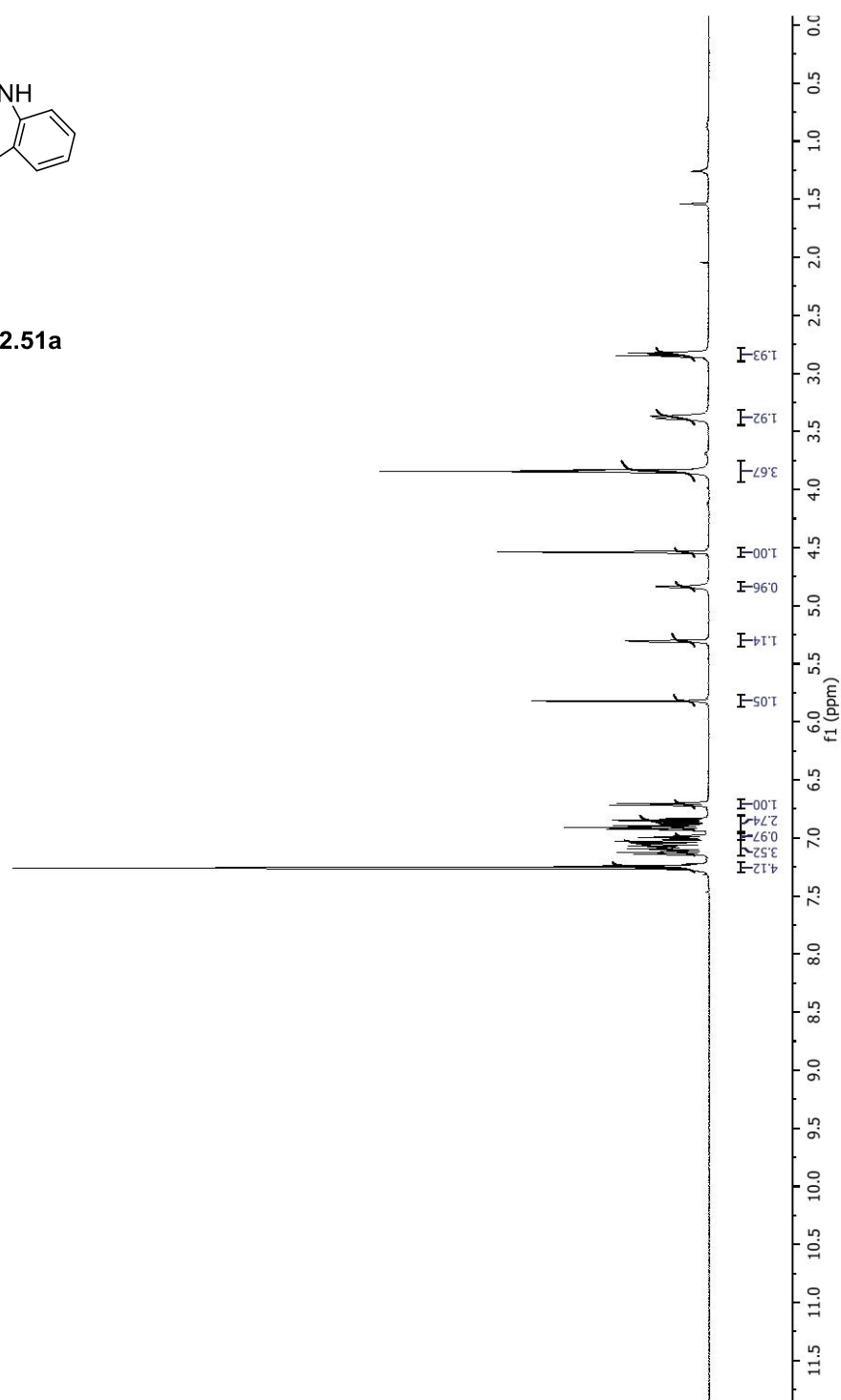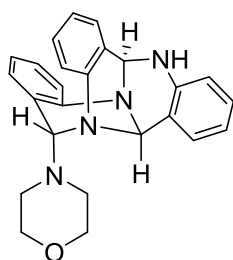
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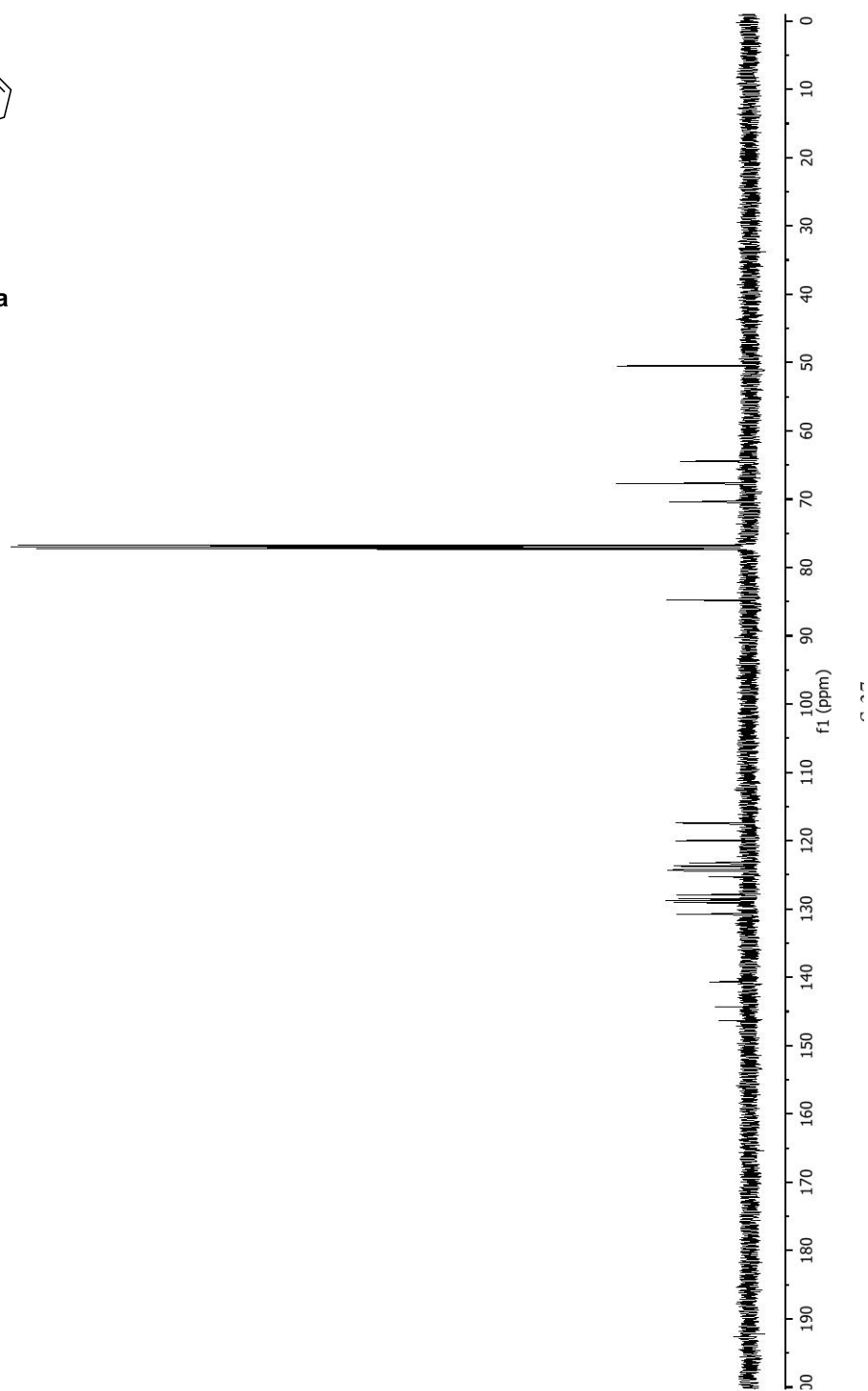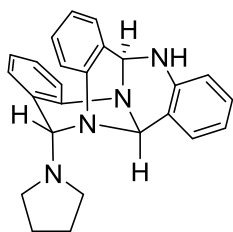
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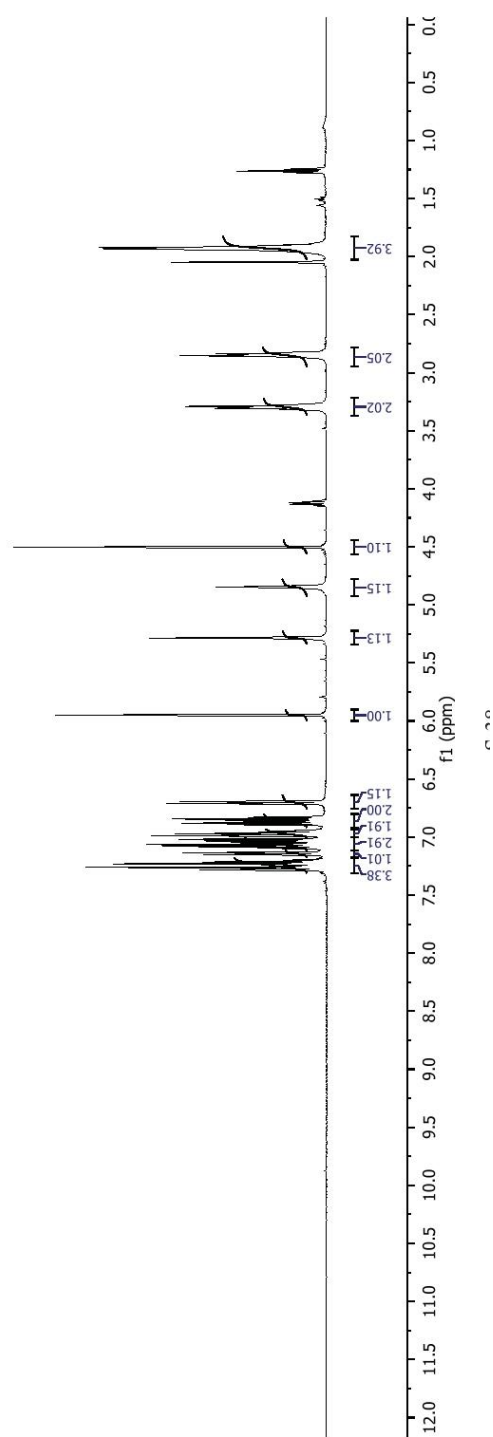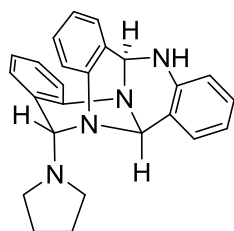
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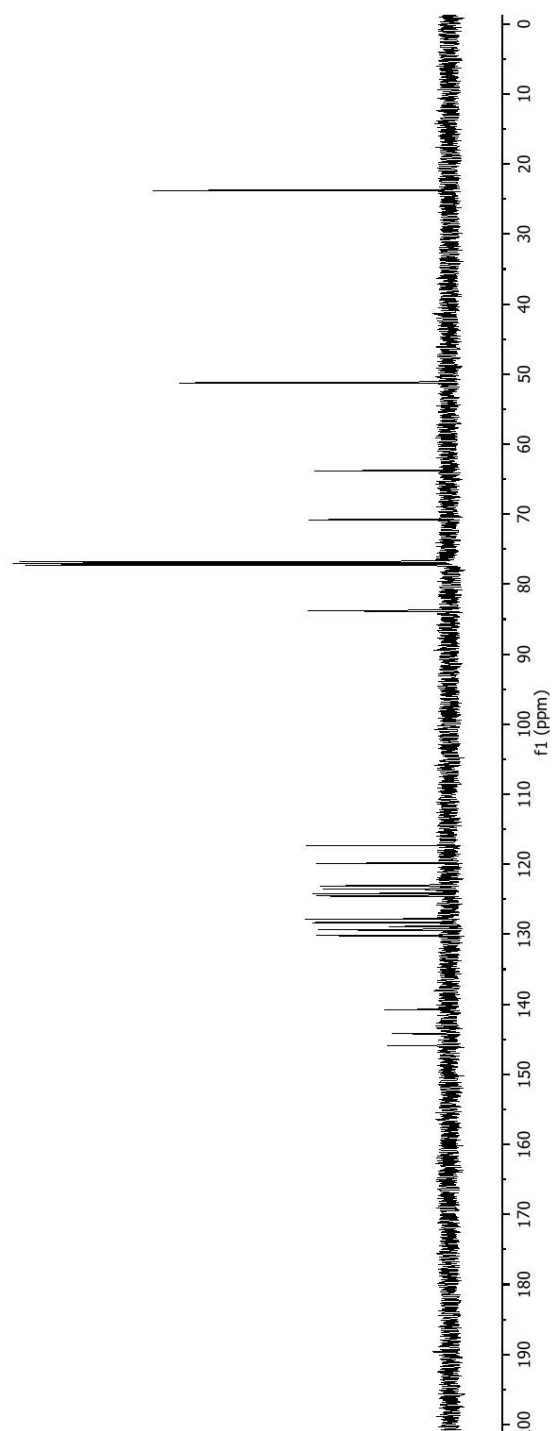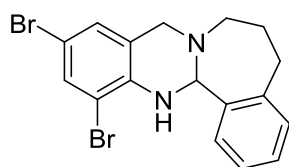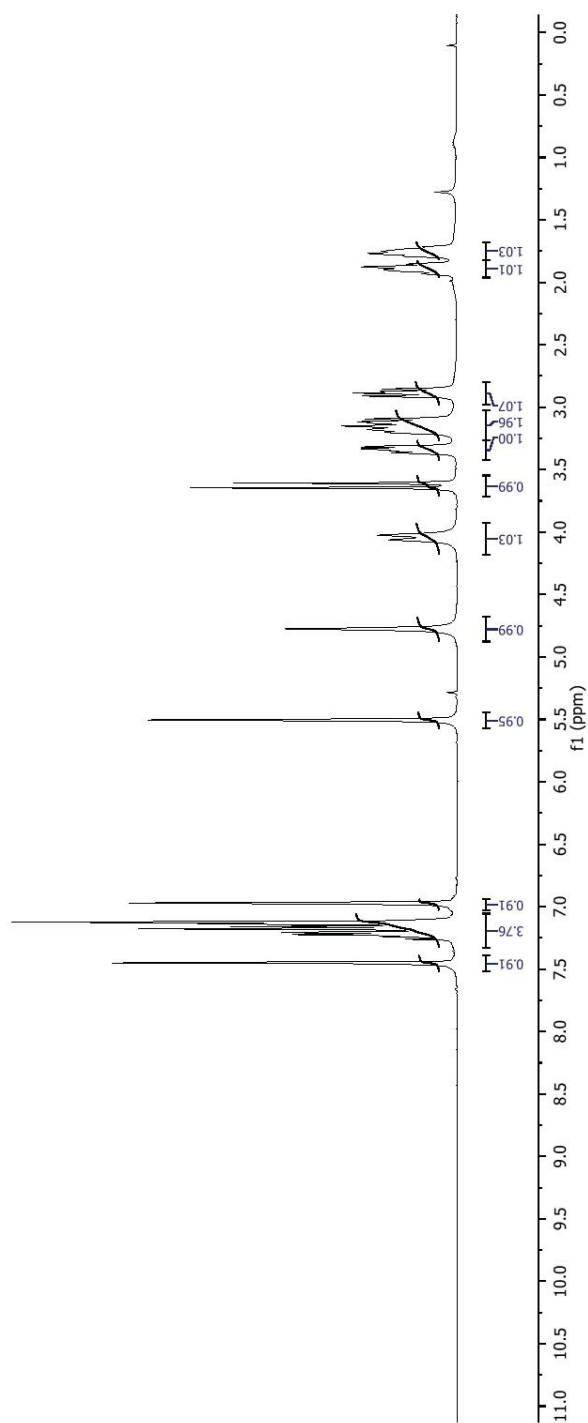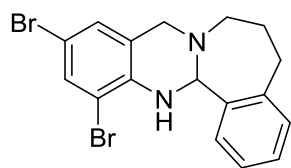
^{1}H NMR of **2.12u**

^{13}C NMR of **2.12u**
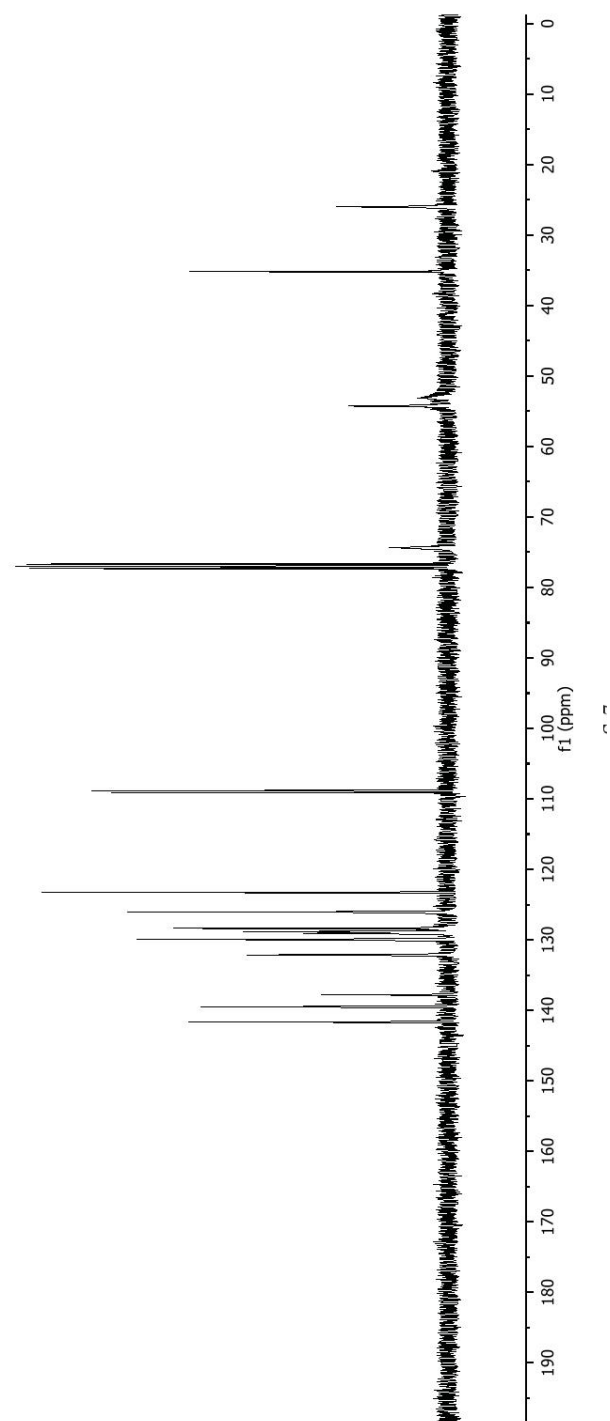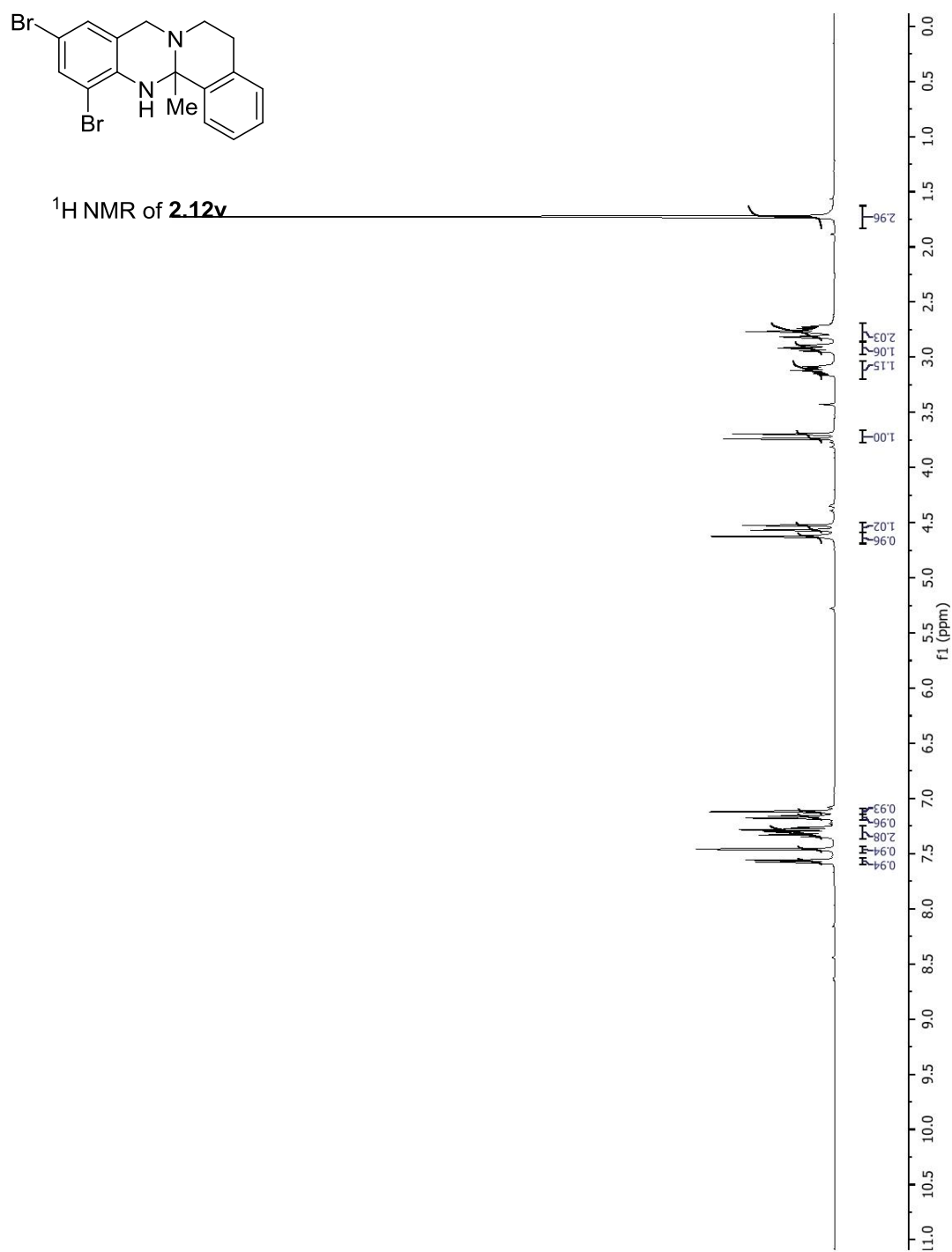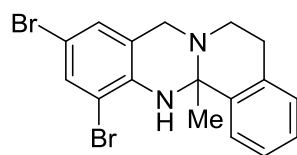
¹H NMR of **2.12v**

^{13}C NMR of **2.12v**
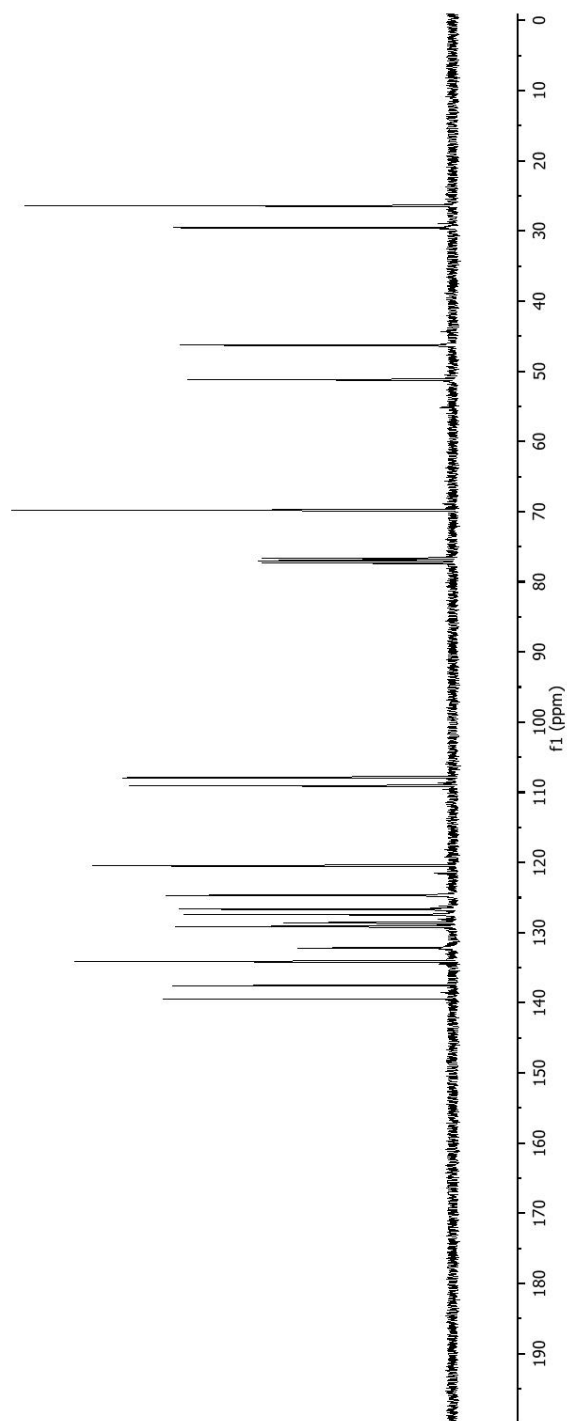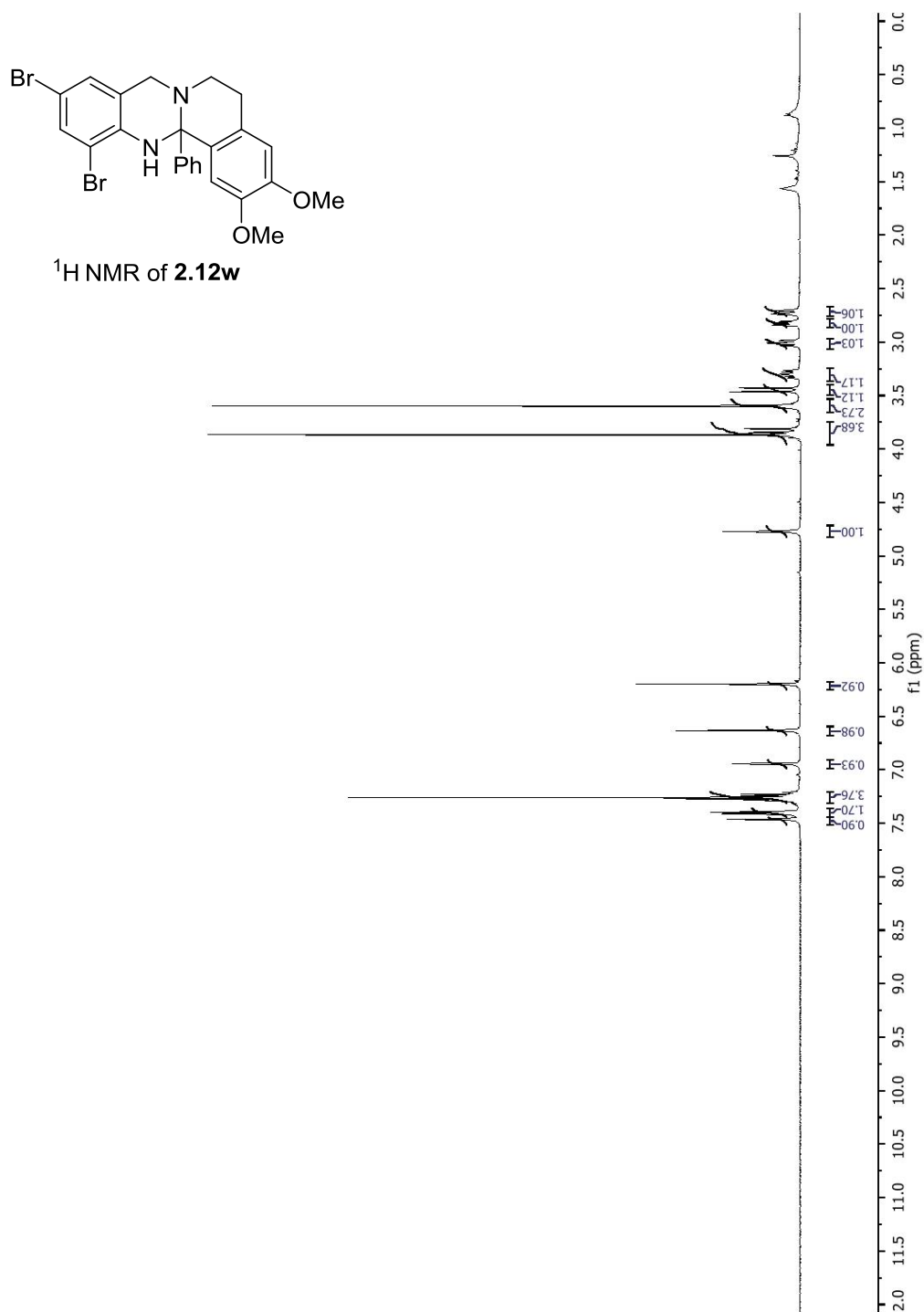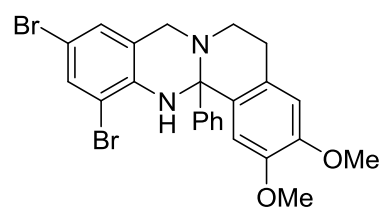
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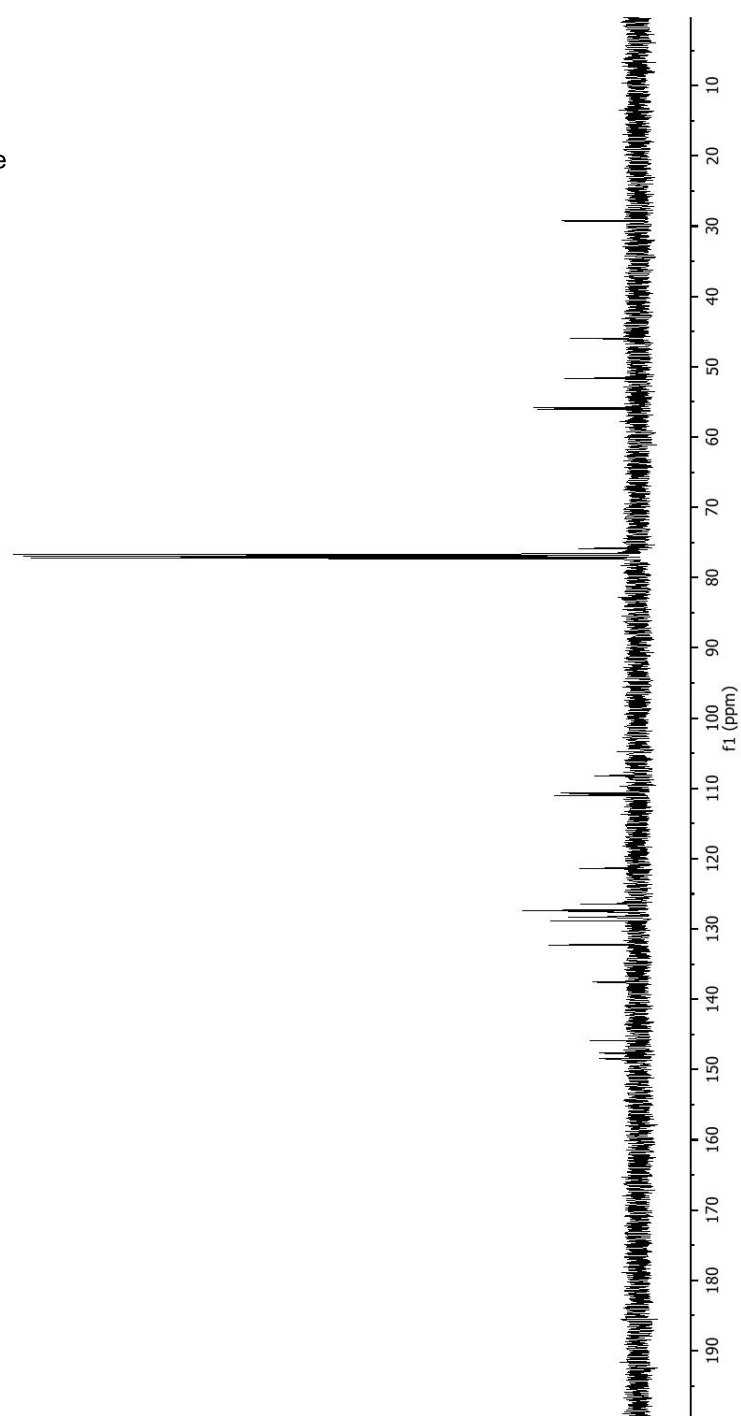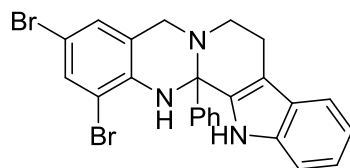
^{13}C NMR of **2.12w**

^{1}H NMR of **2.12x**
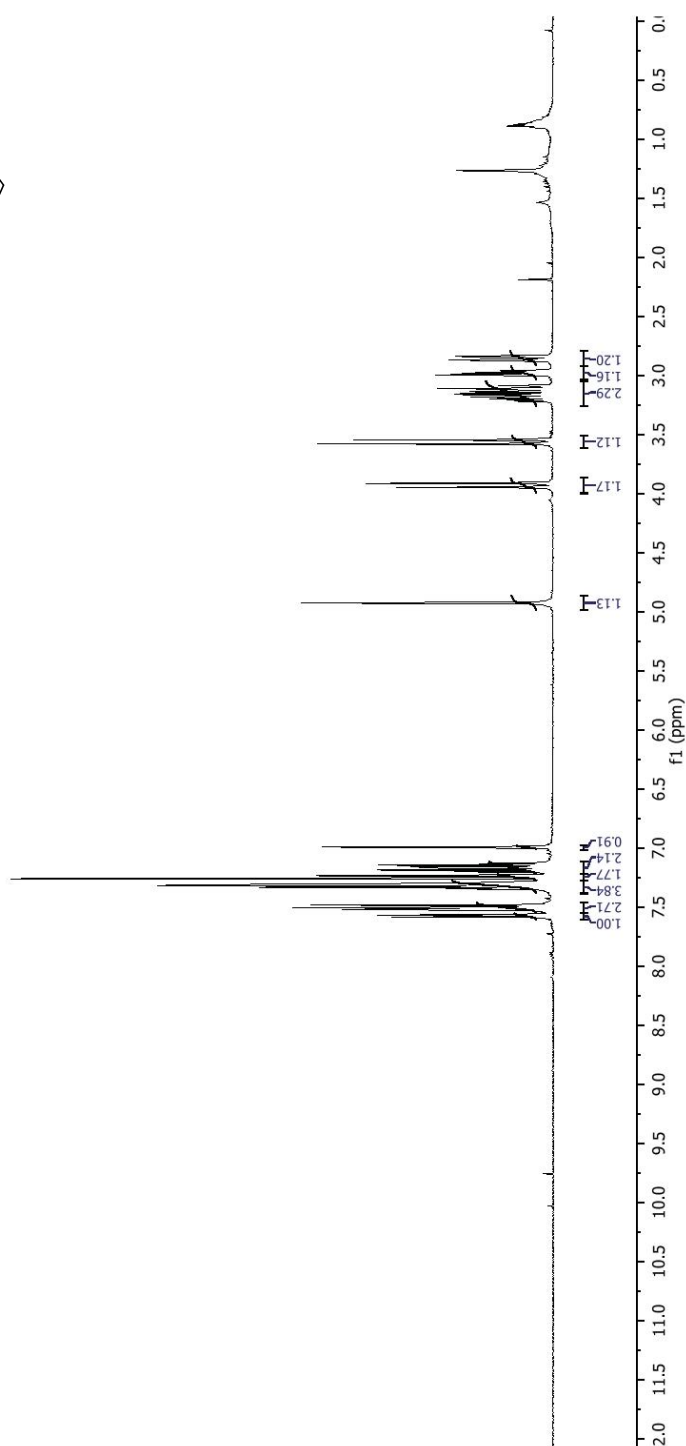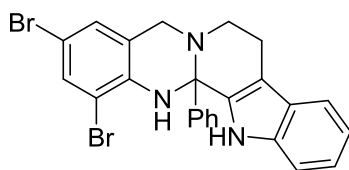
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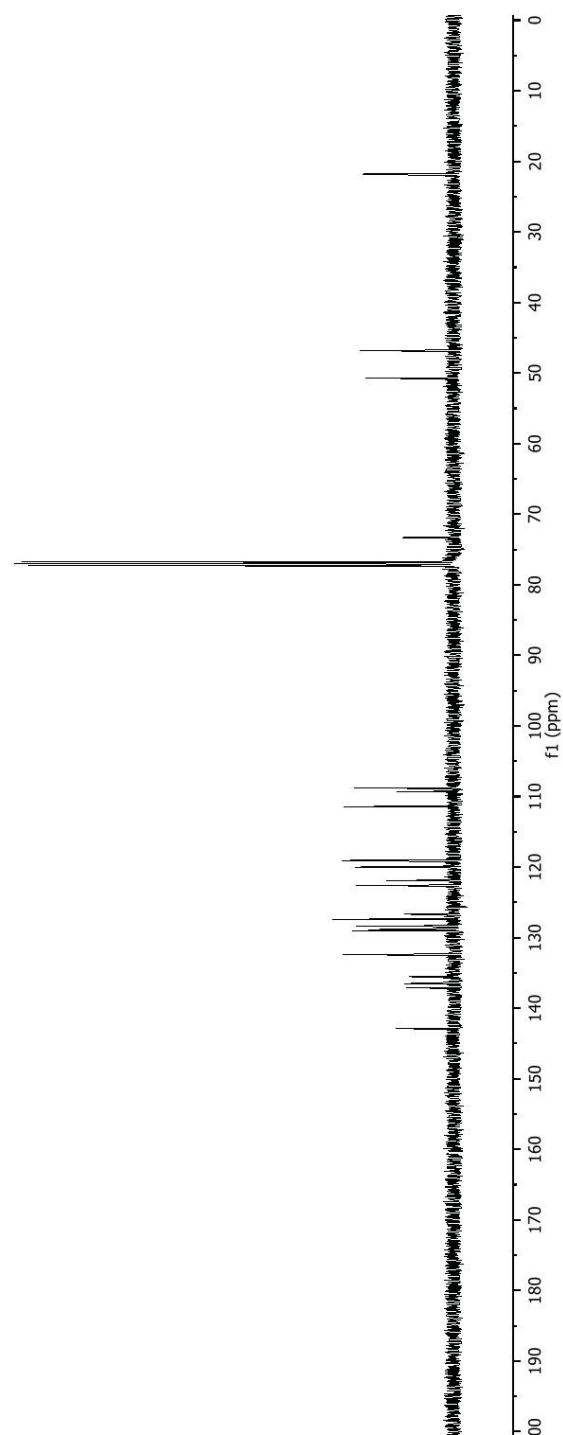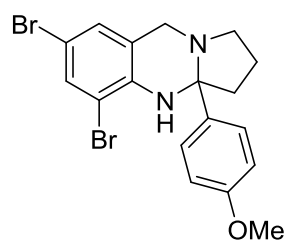
^{1}H NMR of **2.12y-a**
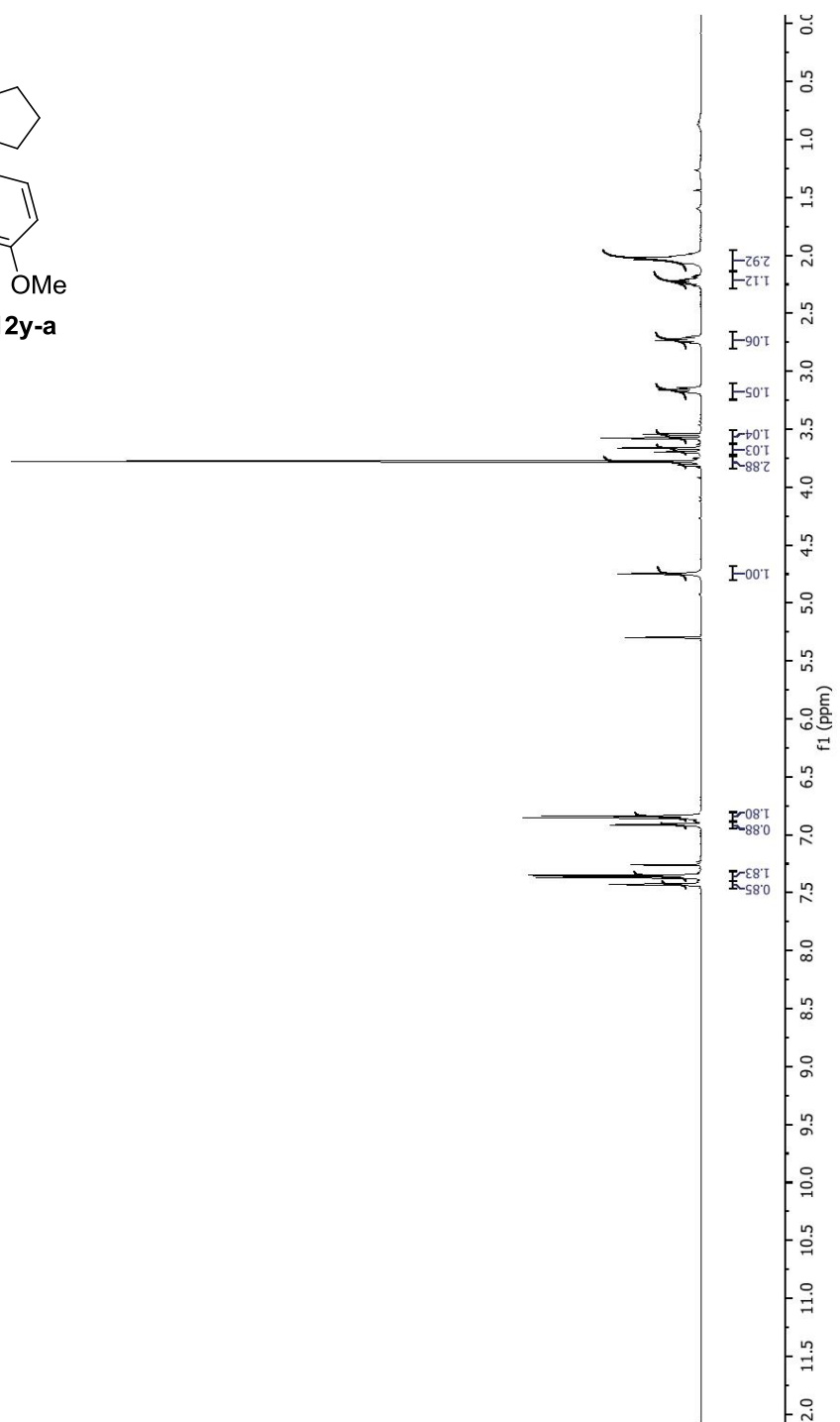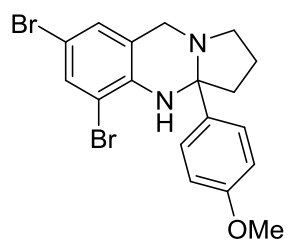
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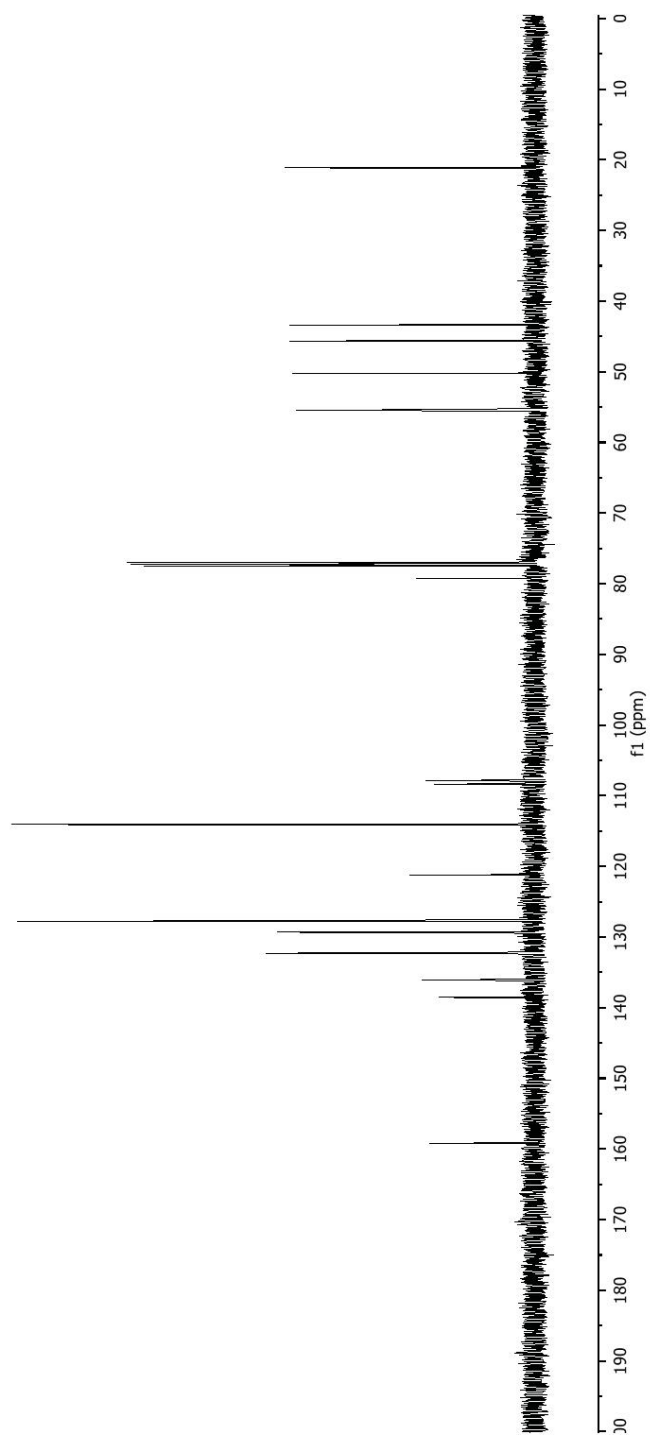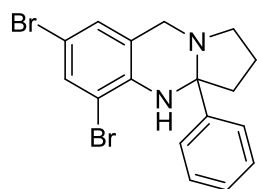
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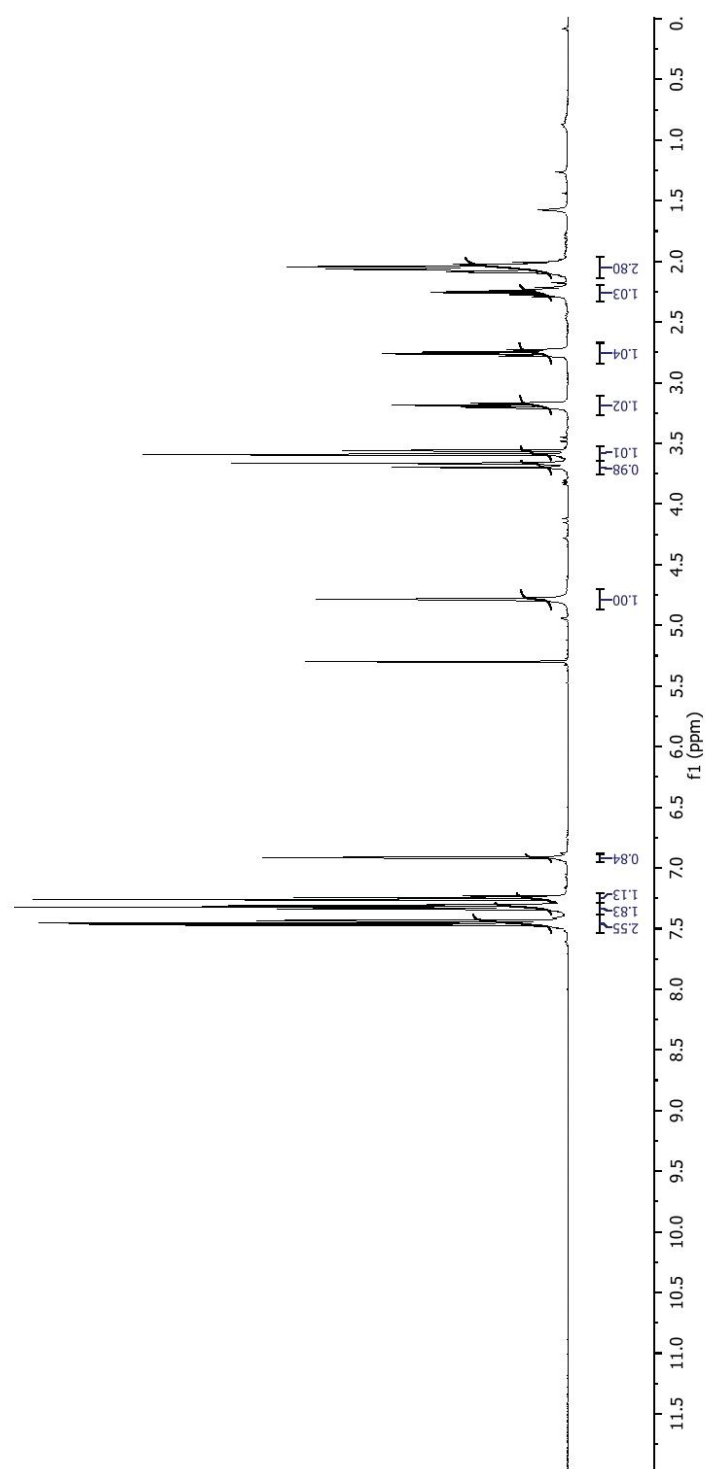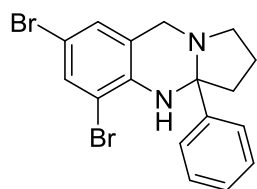
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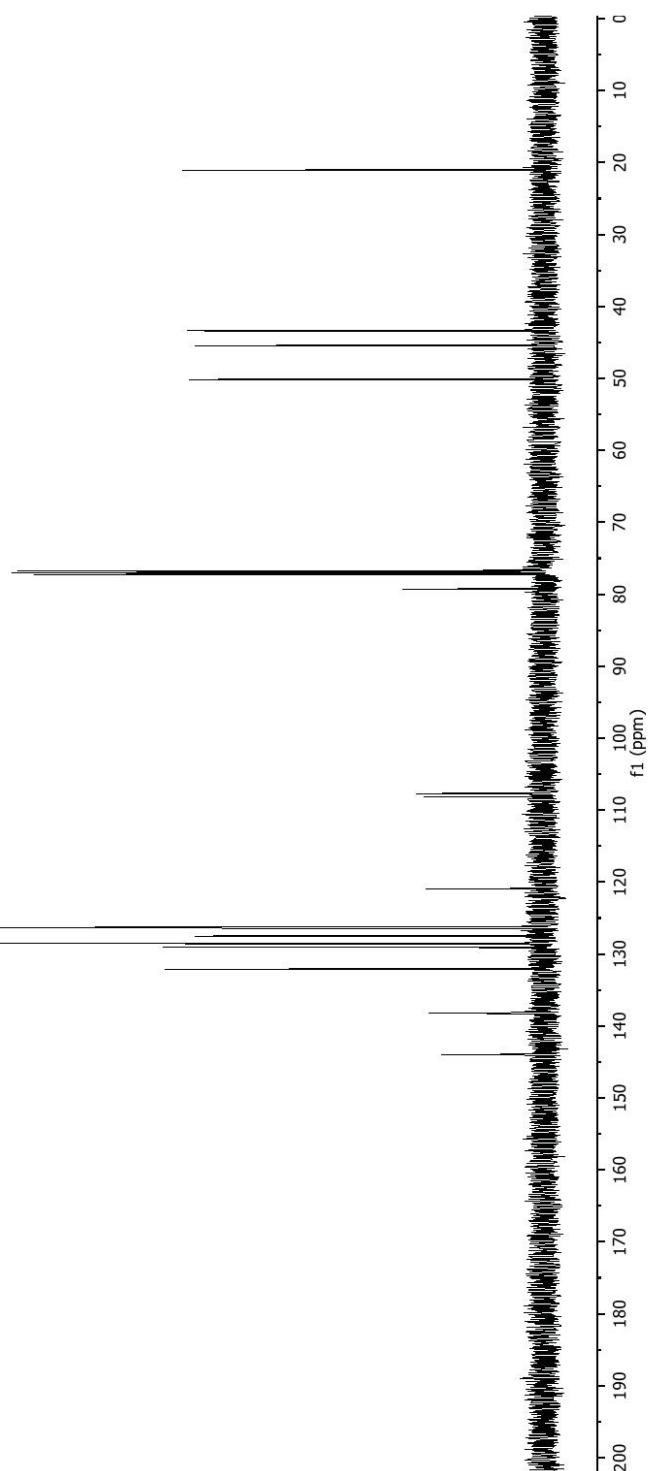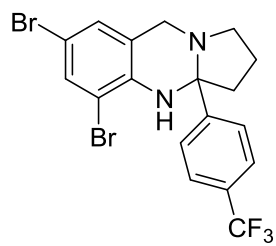
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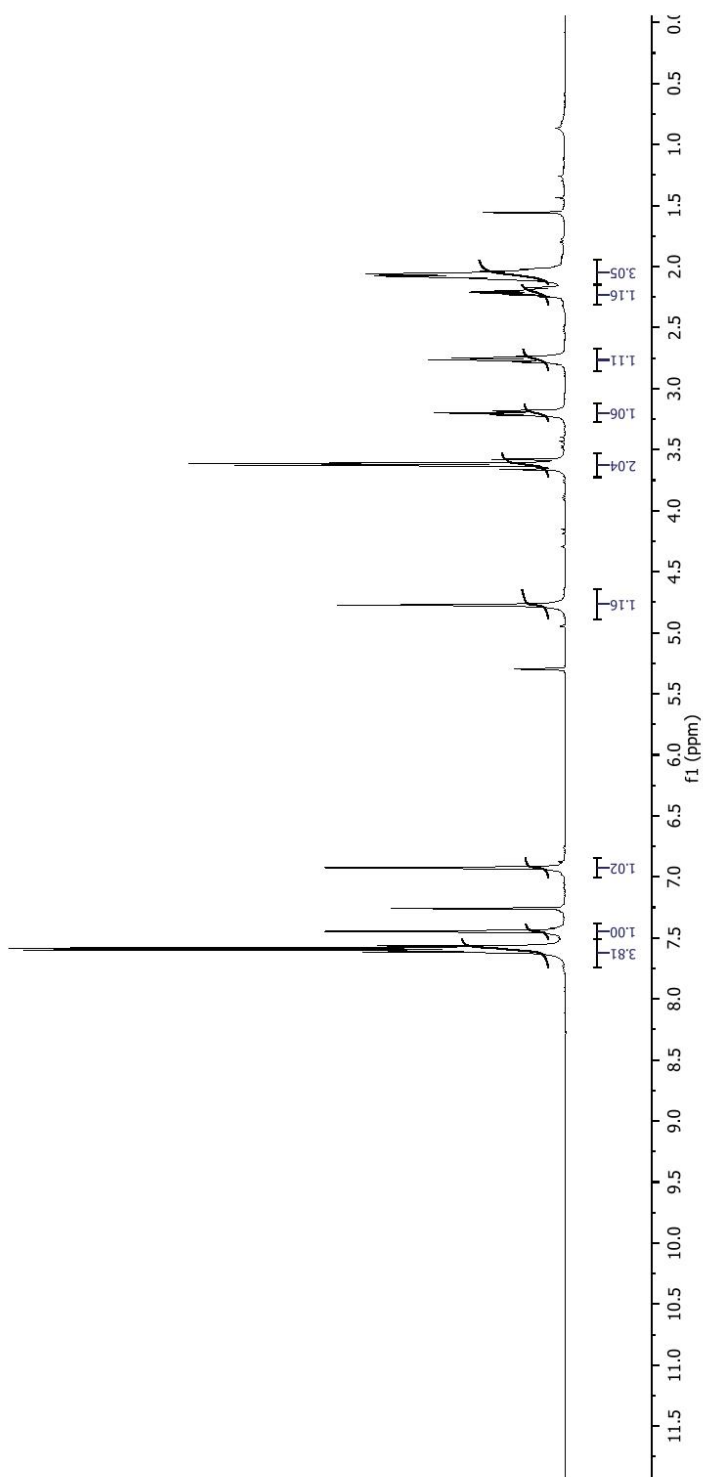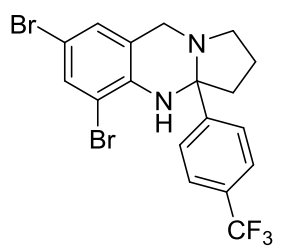
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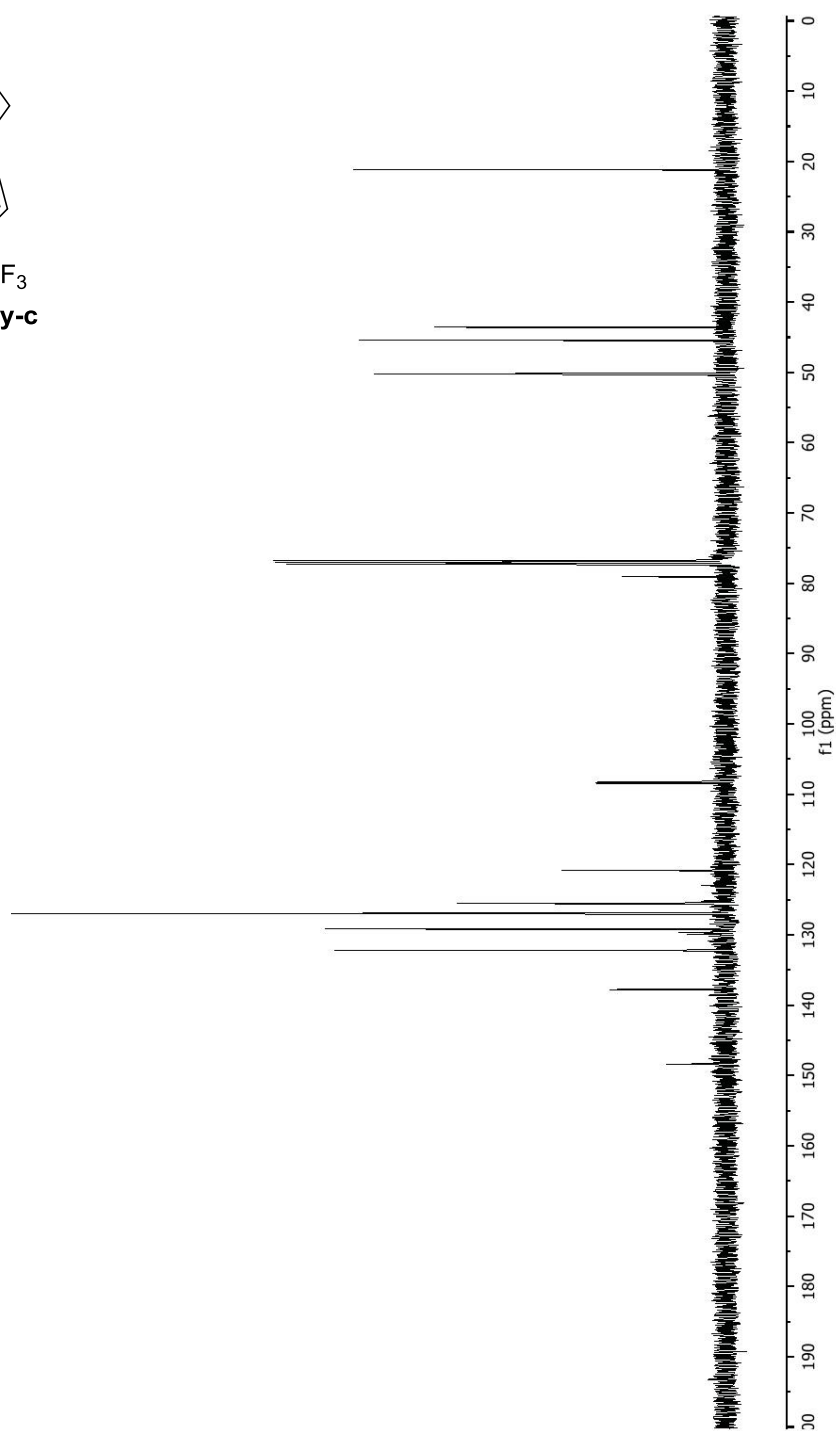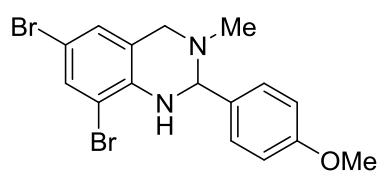
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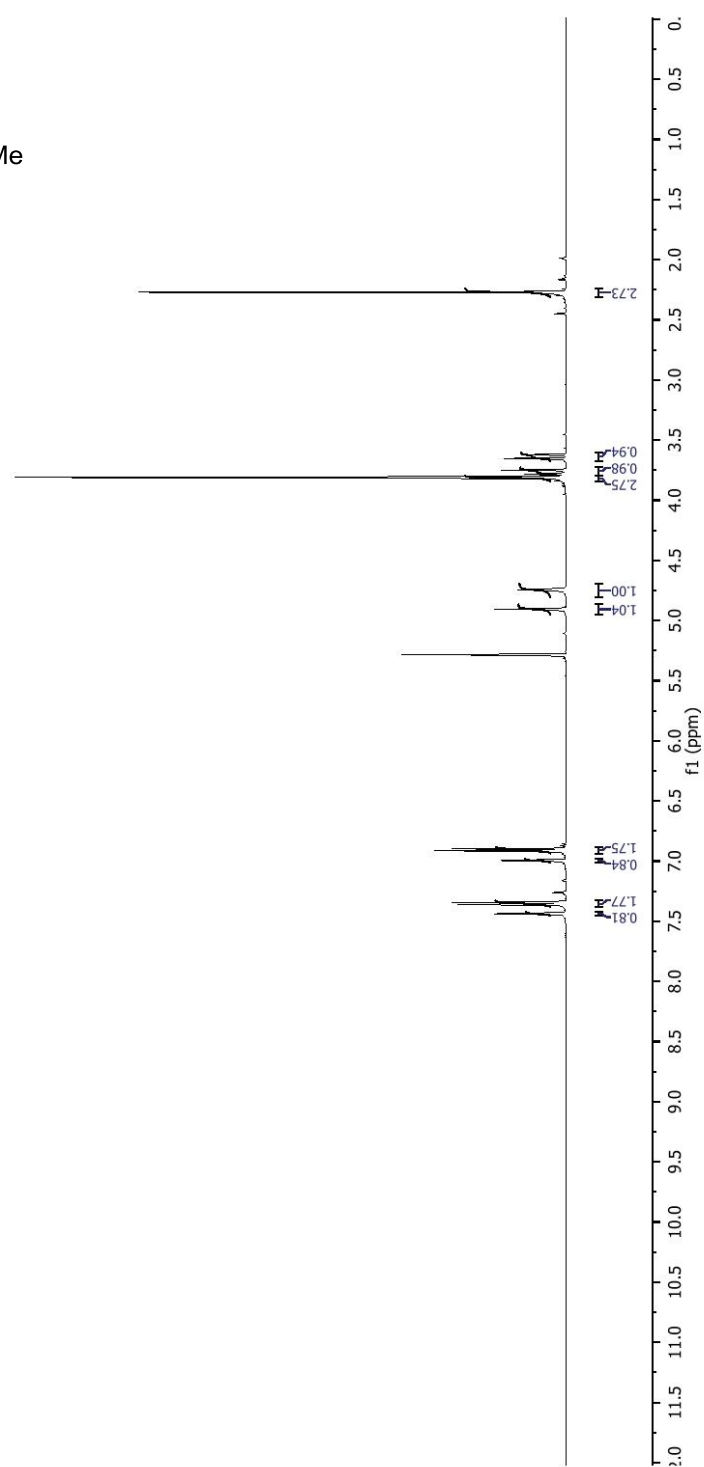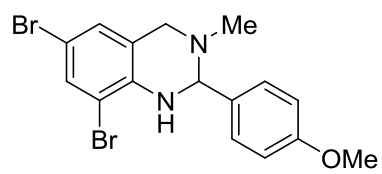
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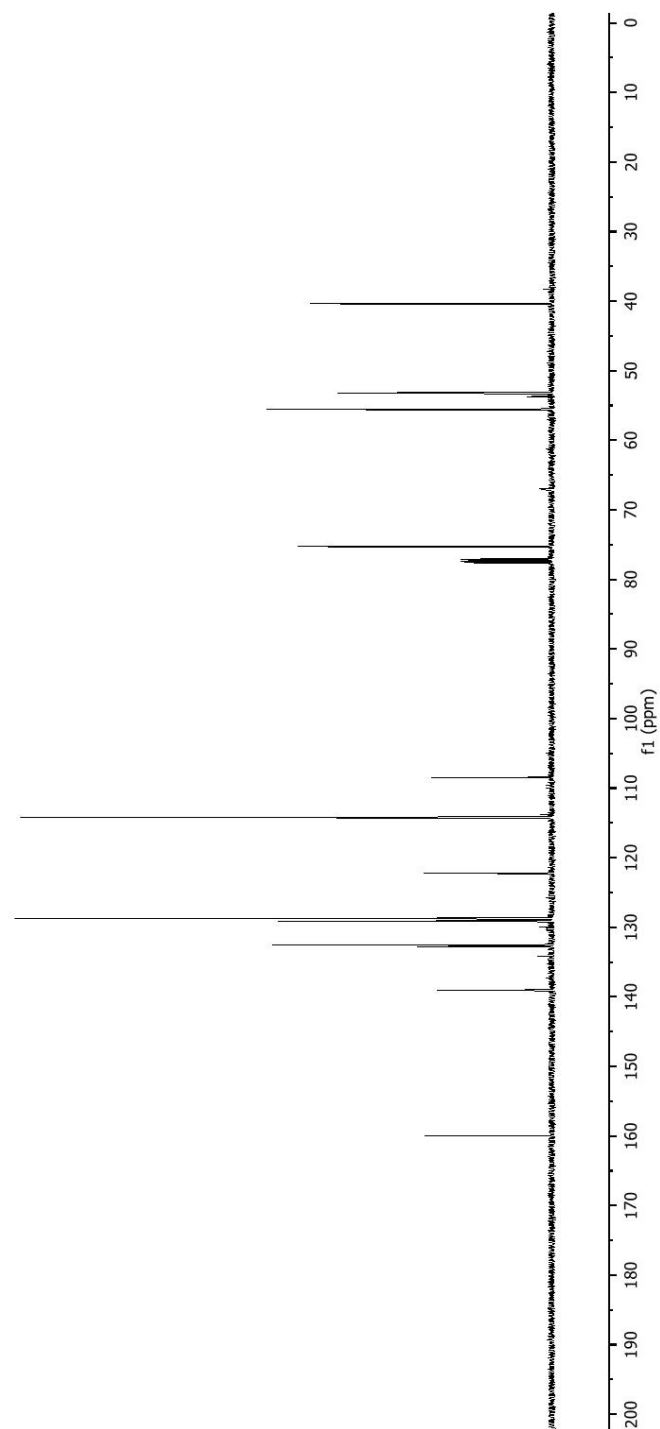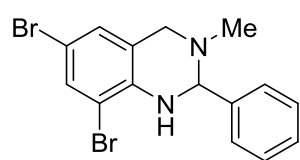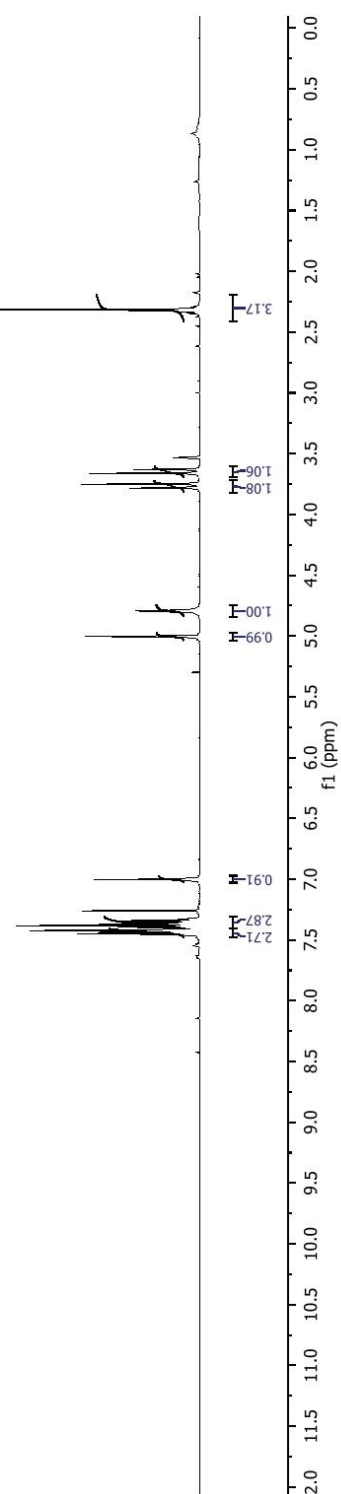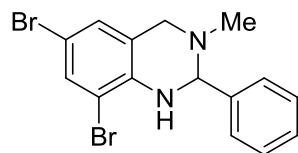
^{1}H NMR of **2.12aa-b**

^{13}C NMR of **2.12aa-b**
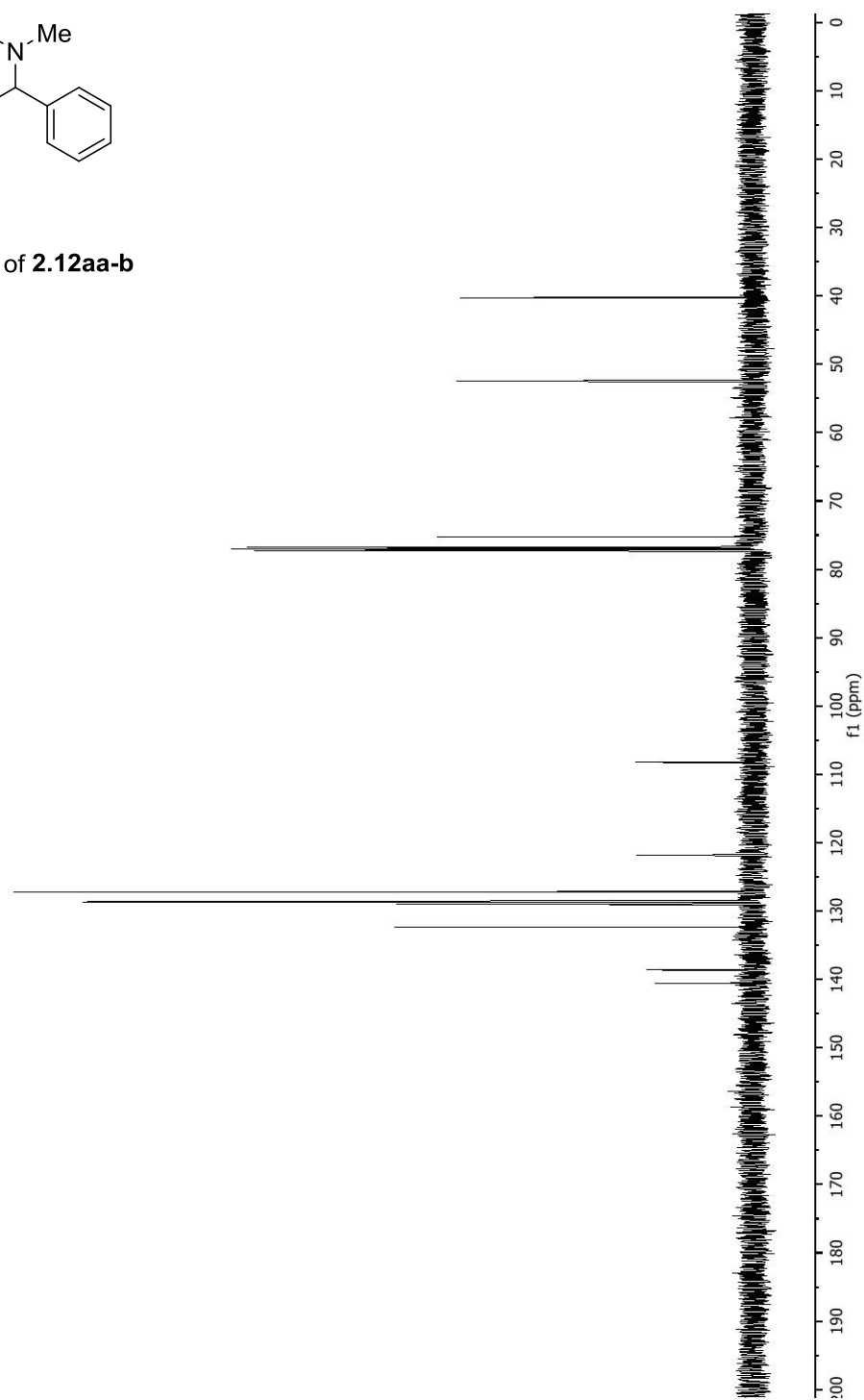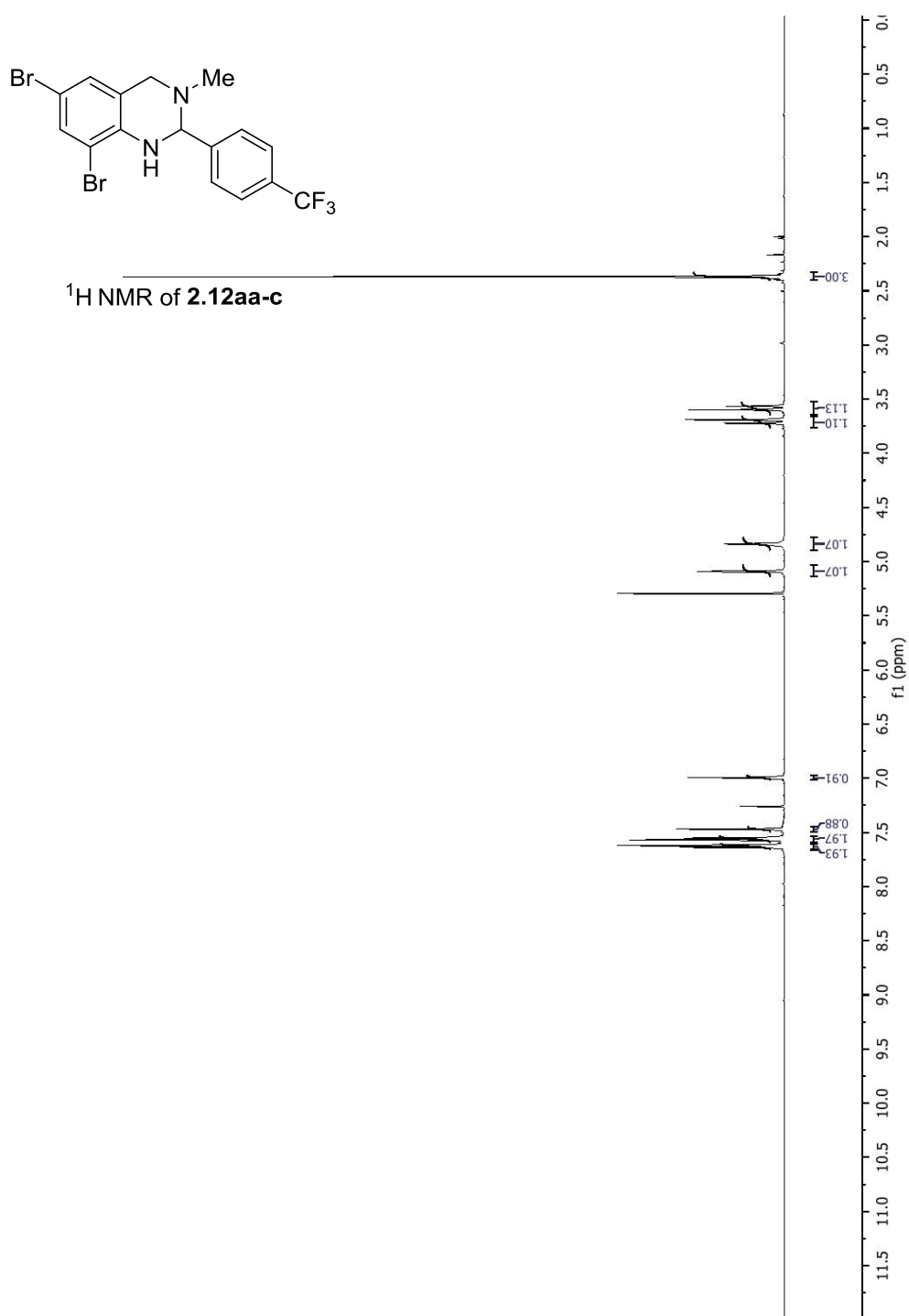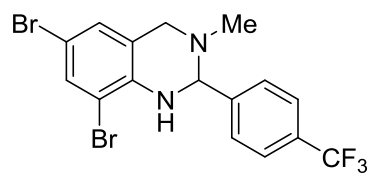
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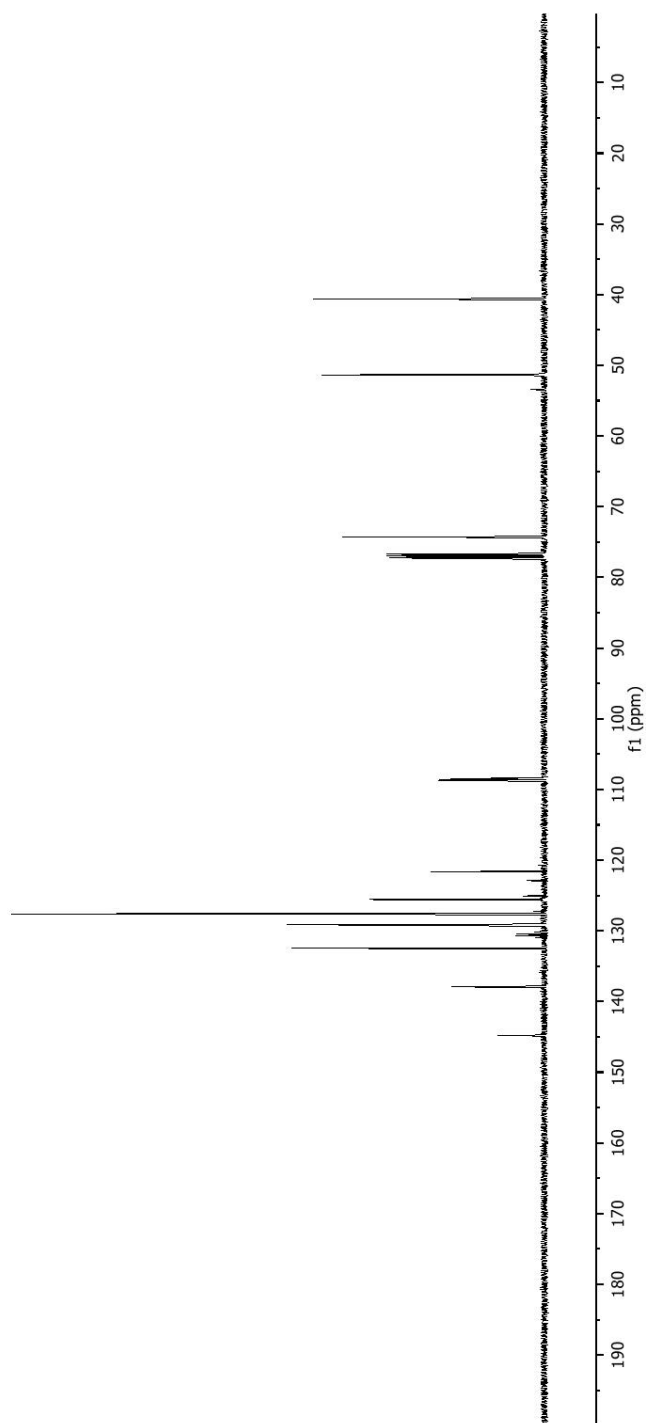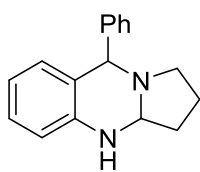
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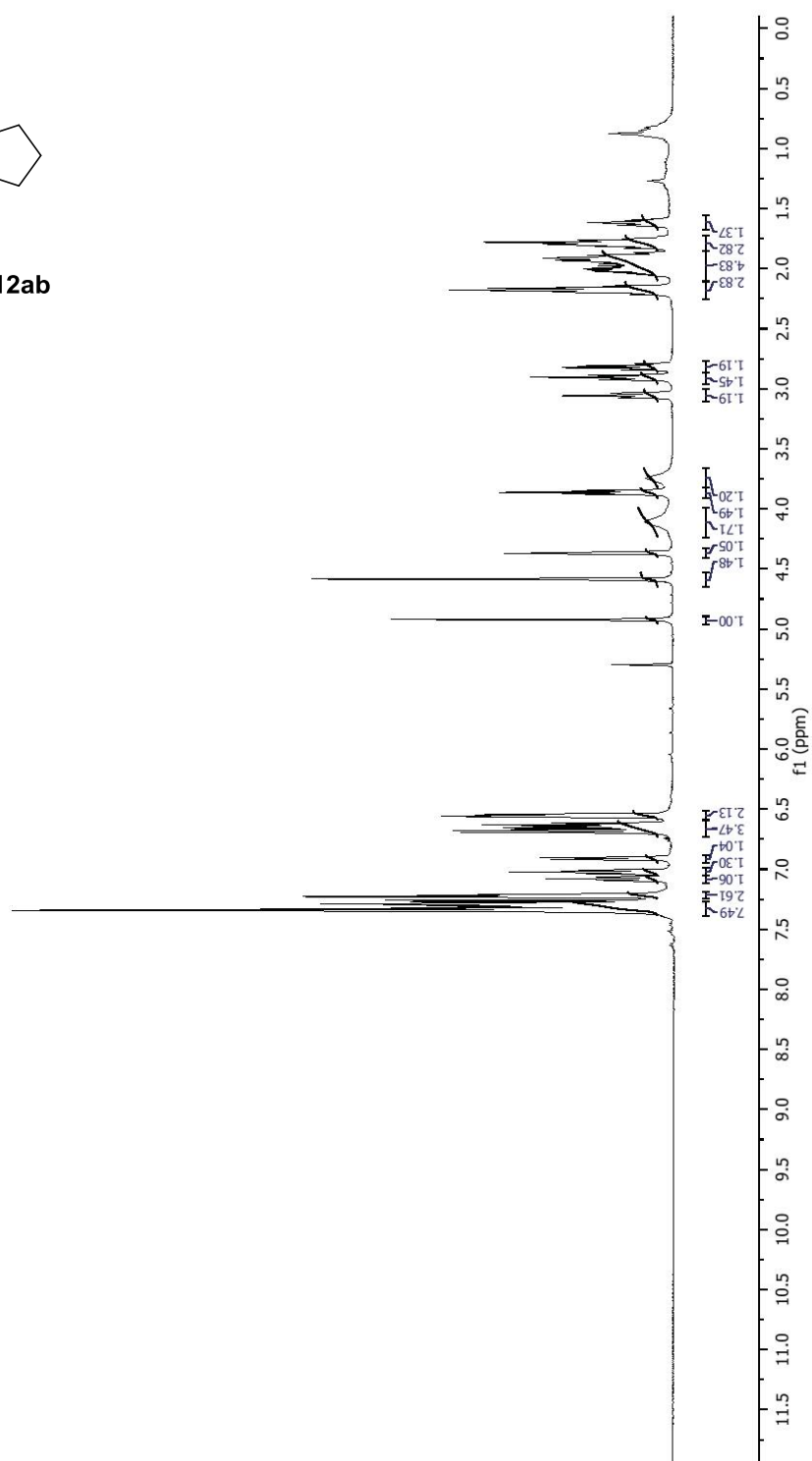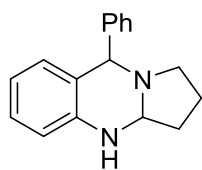
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^{13}C NMR of **2.12ab**
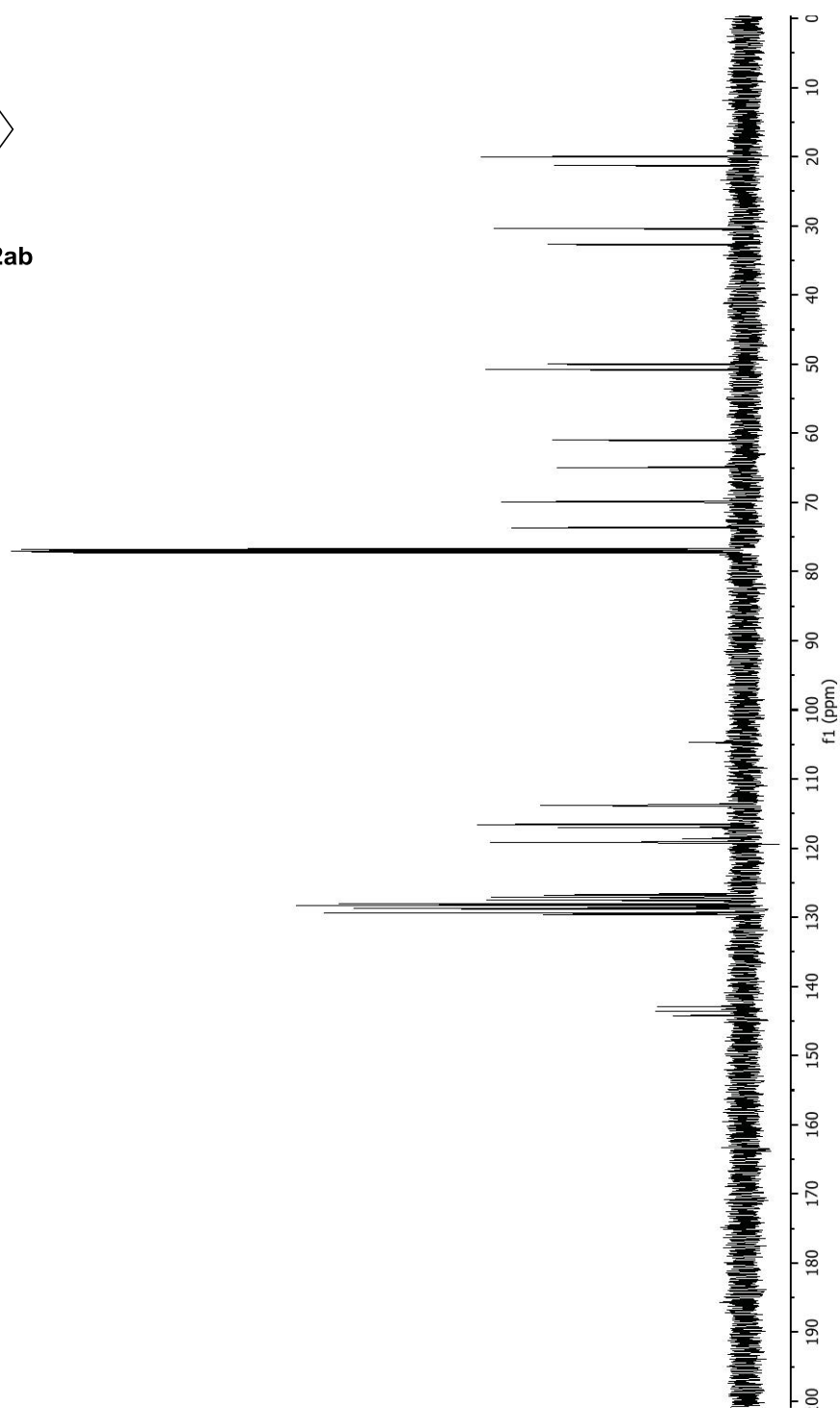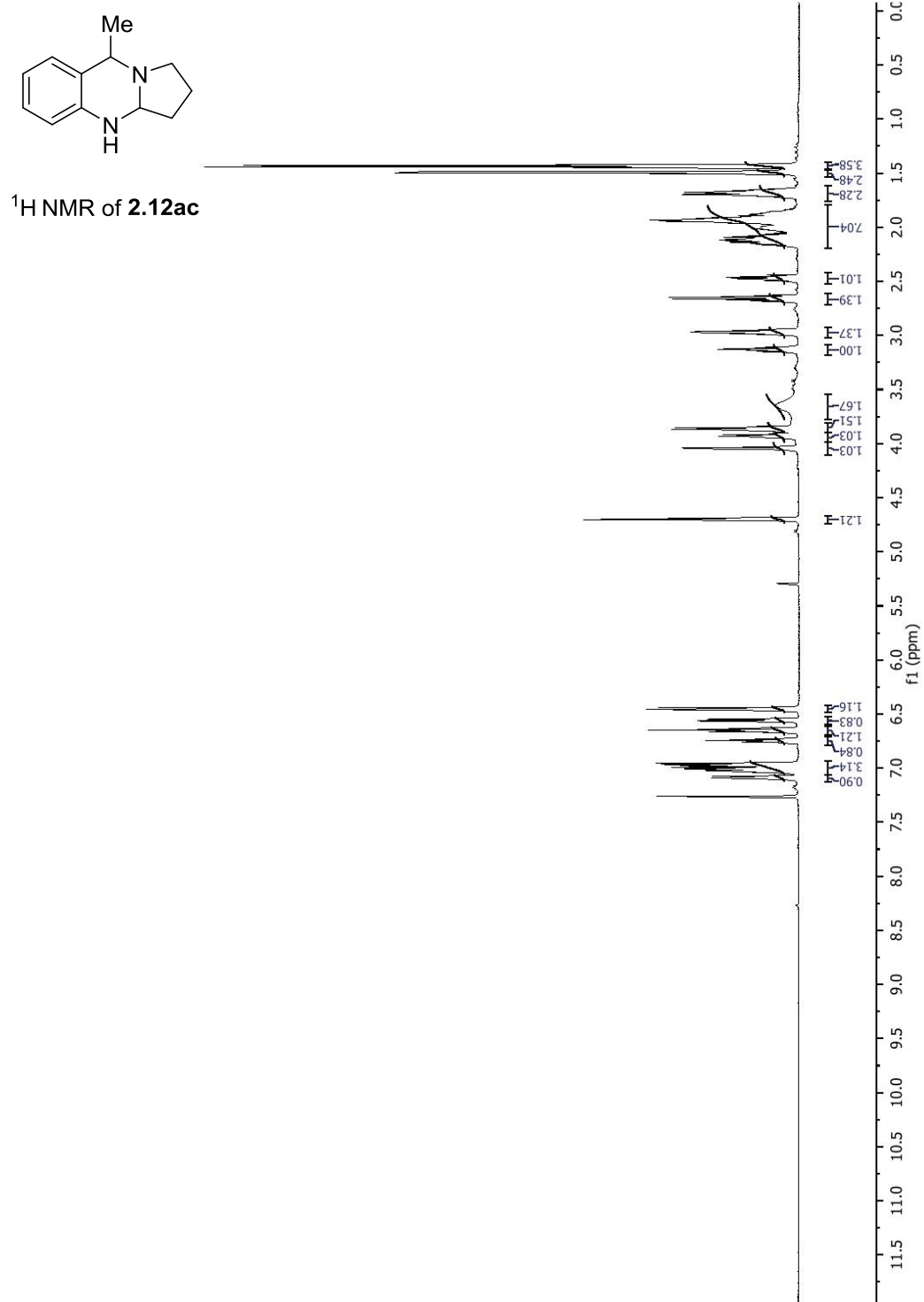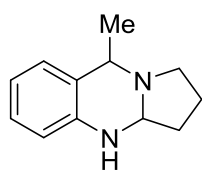
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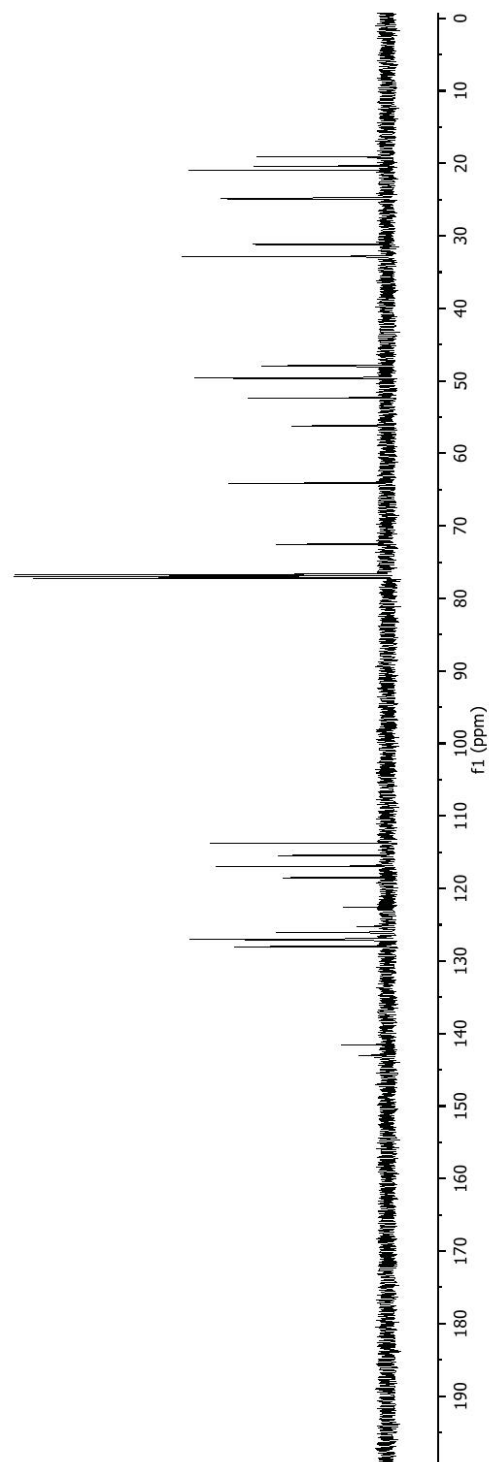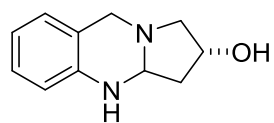
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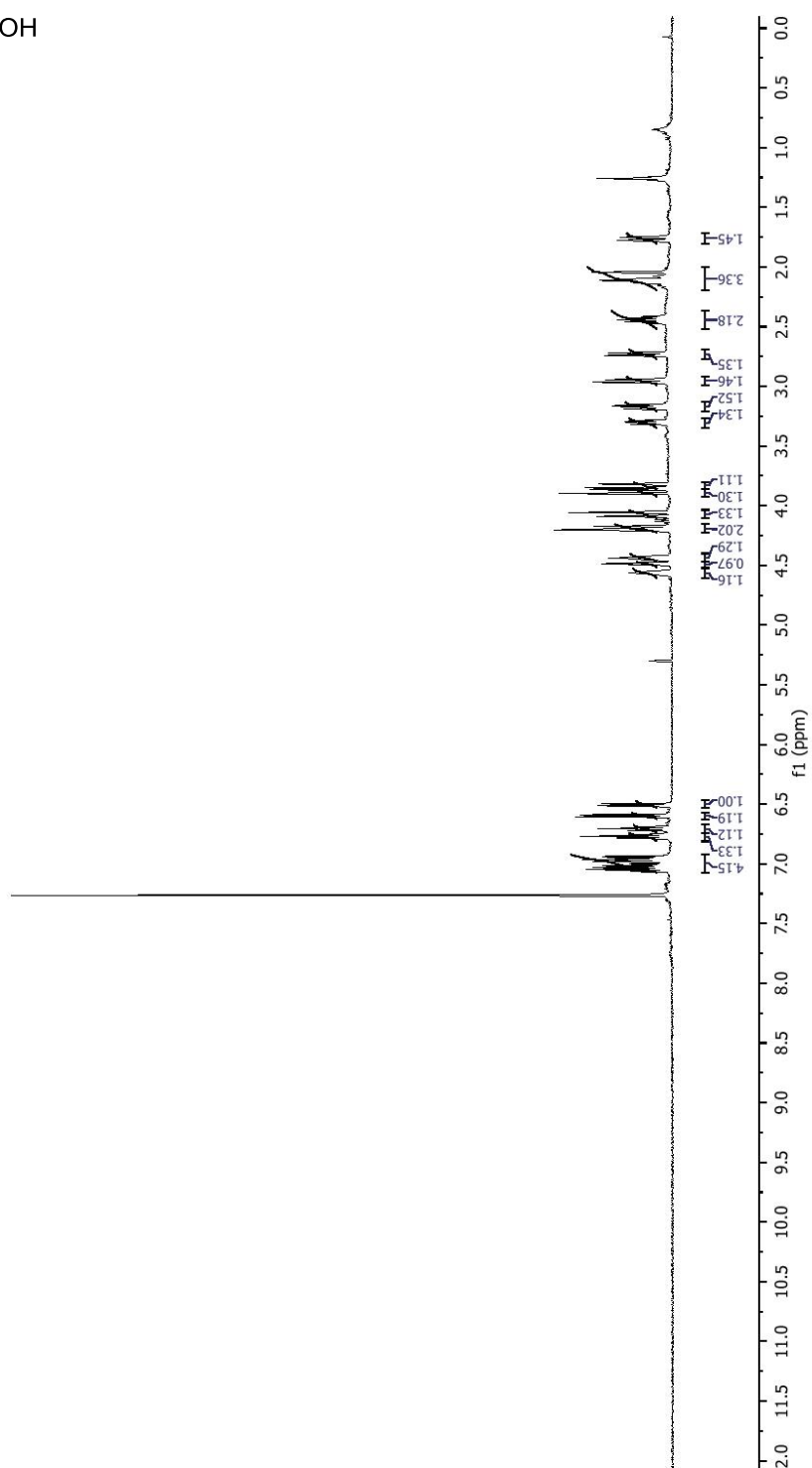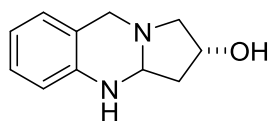
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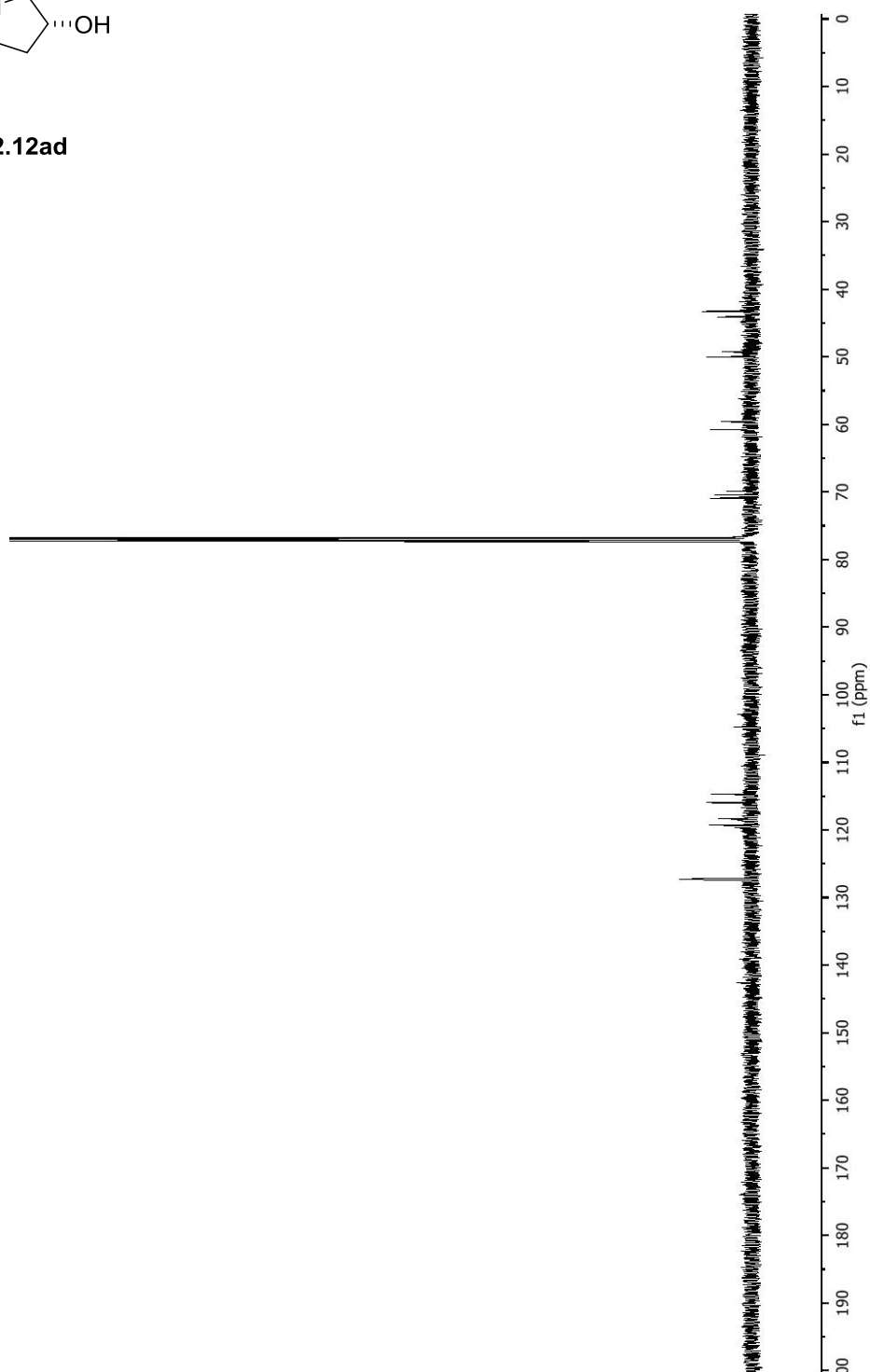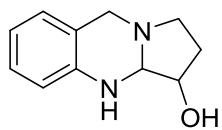
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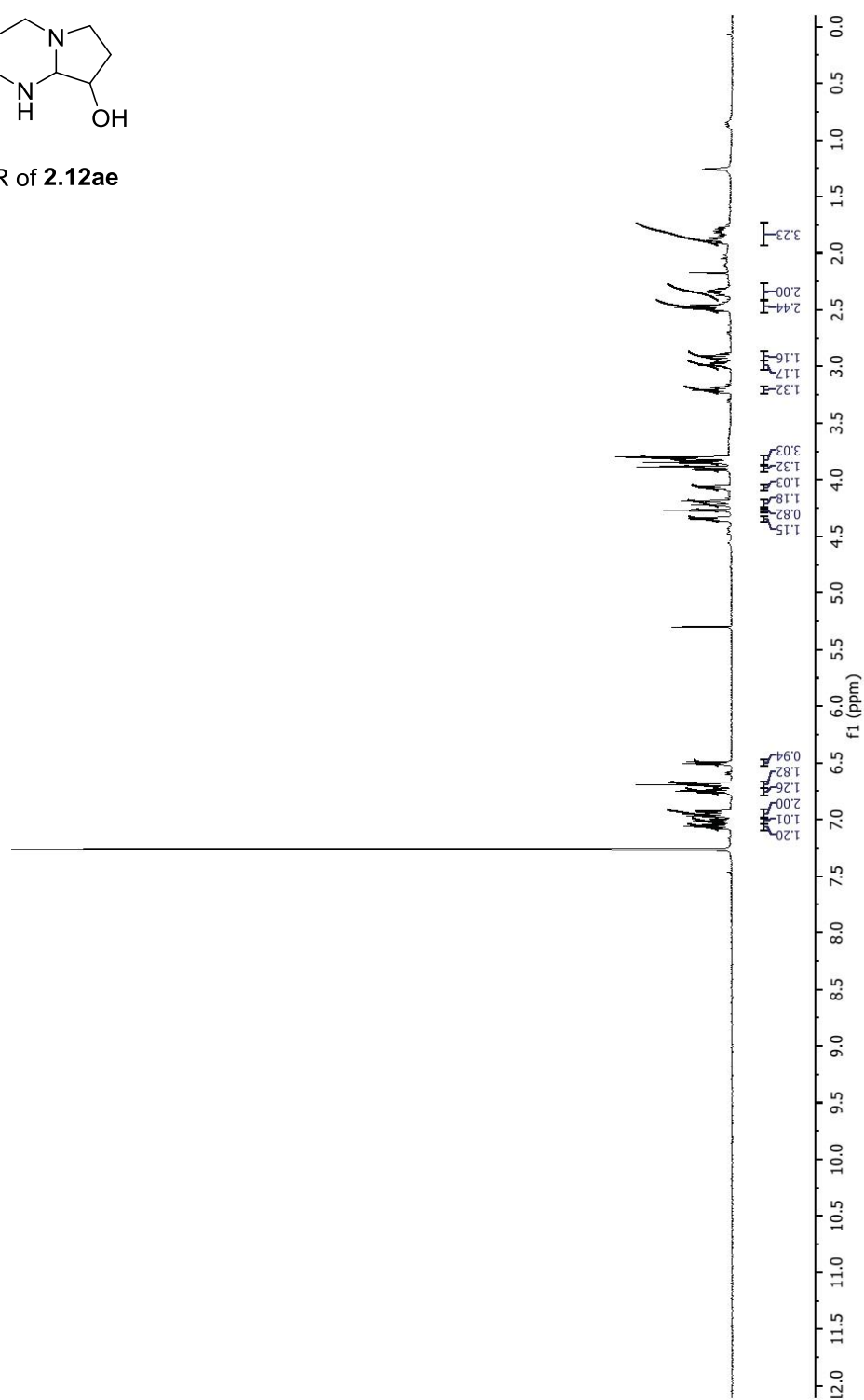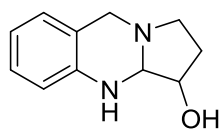
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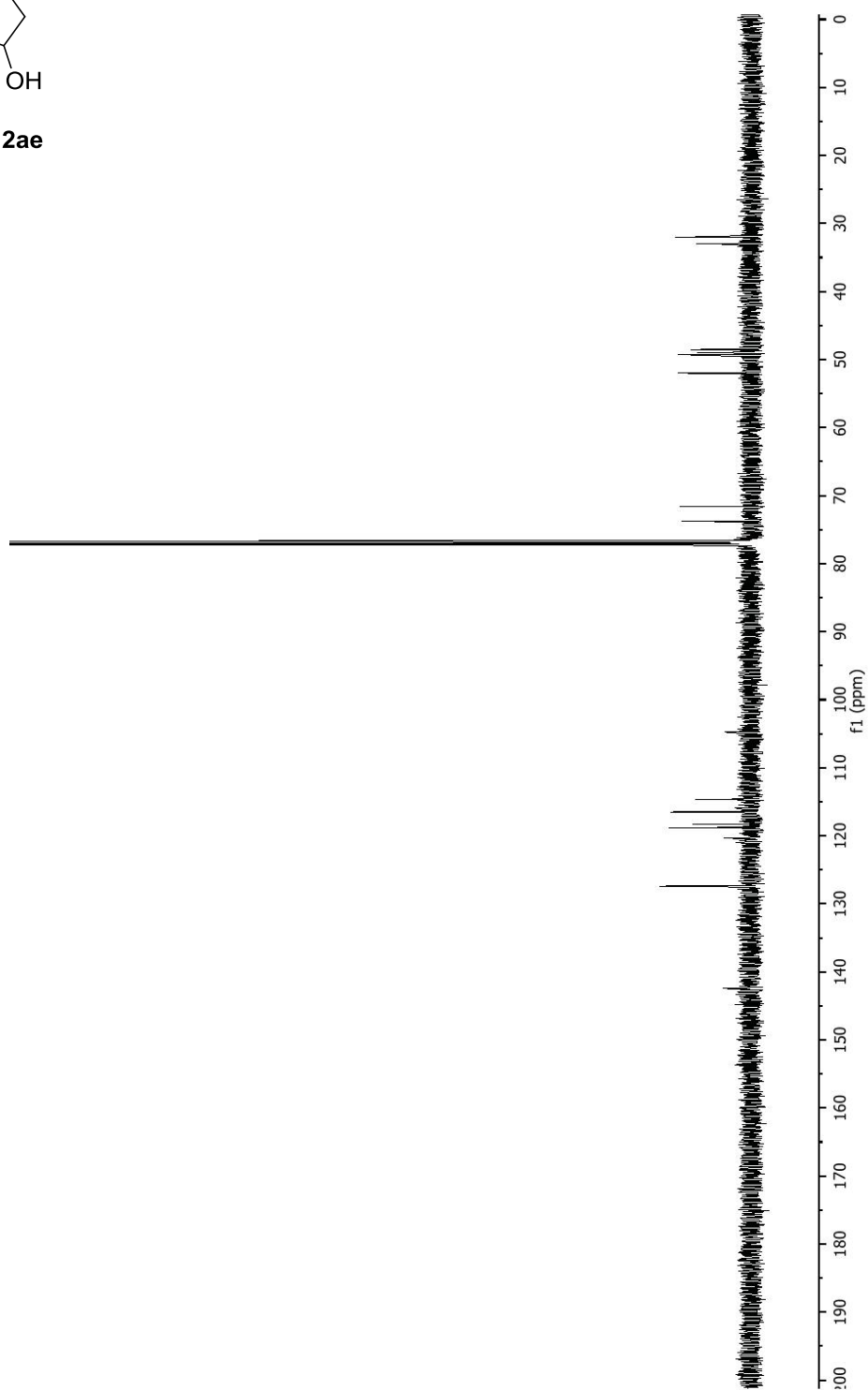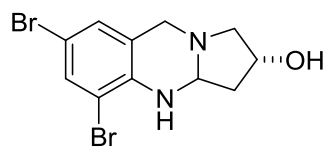
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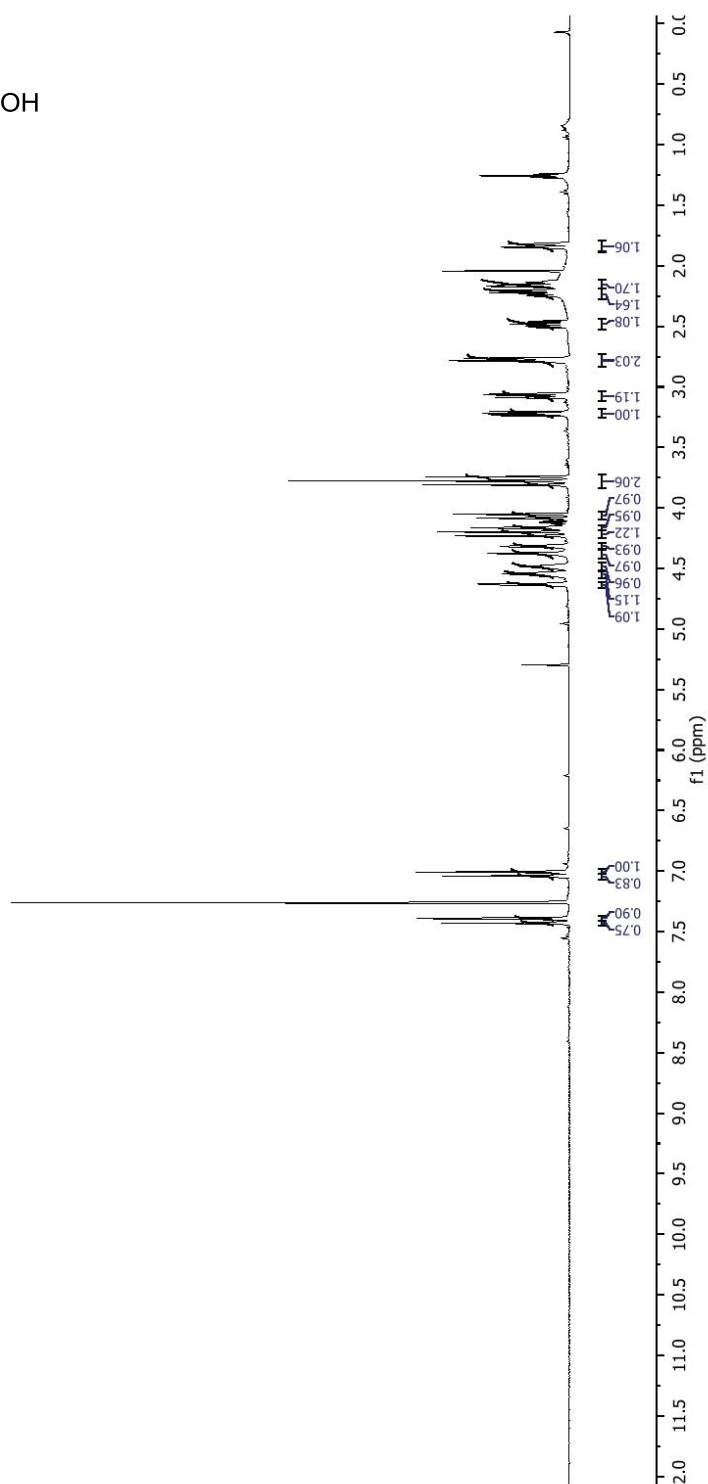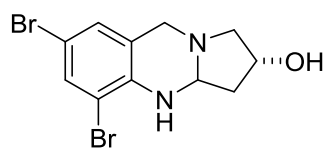
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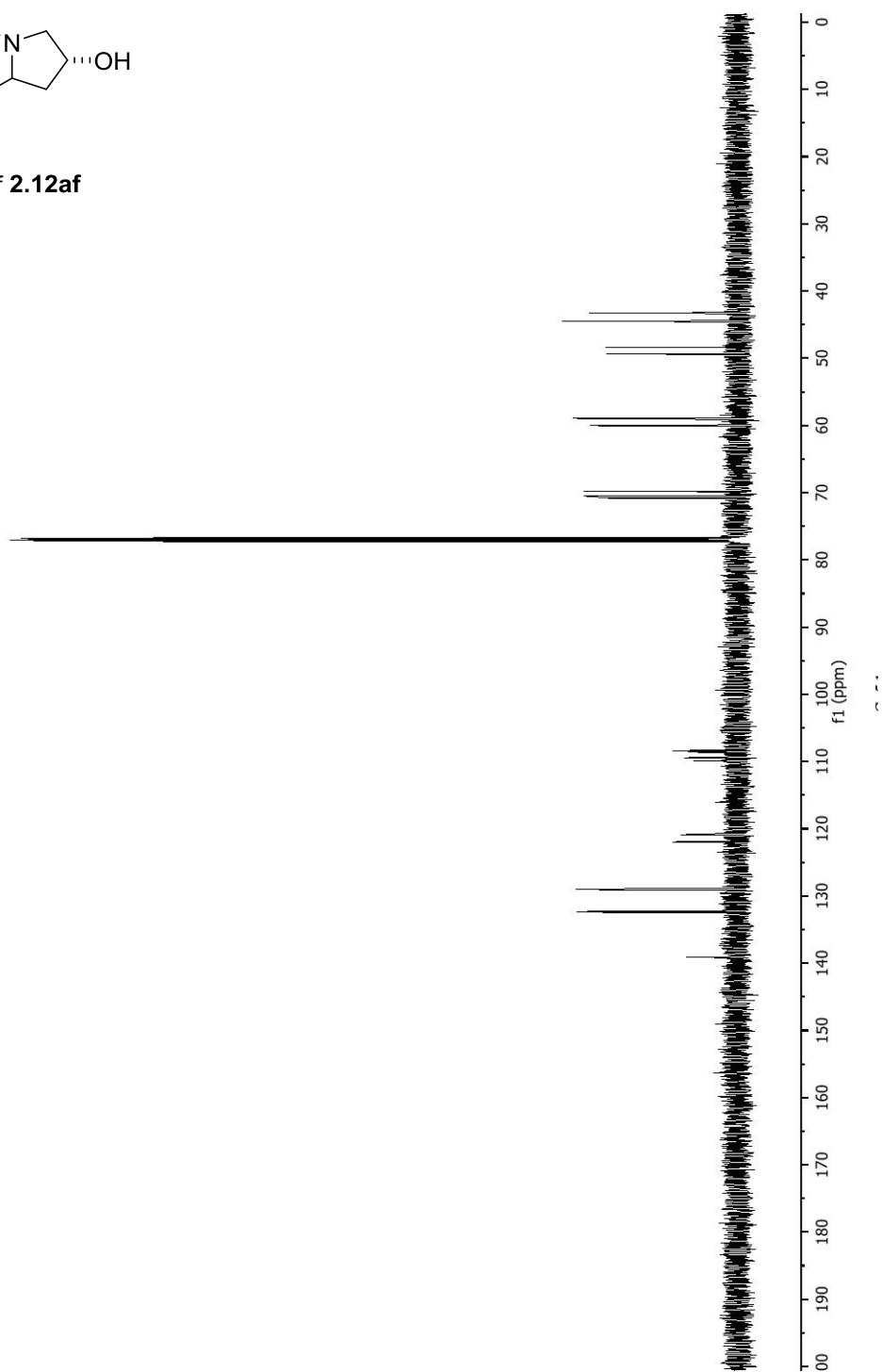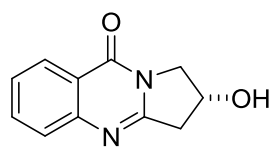
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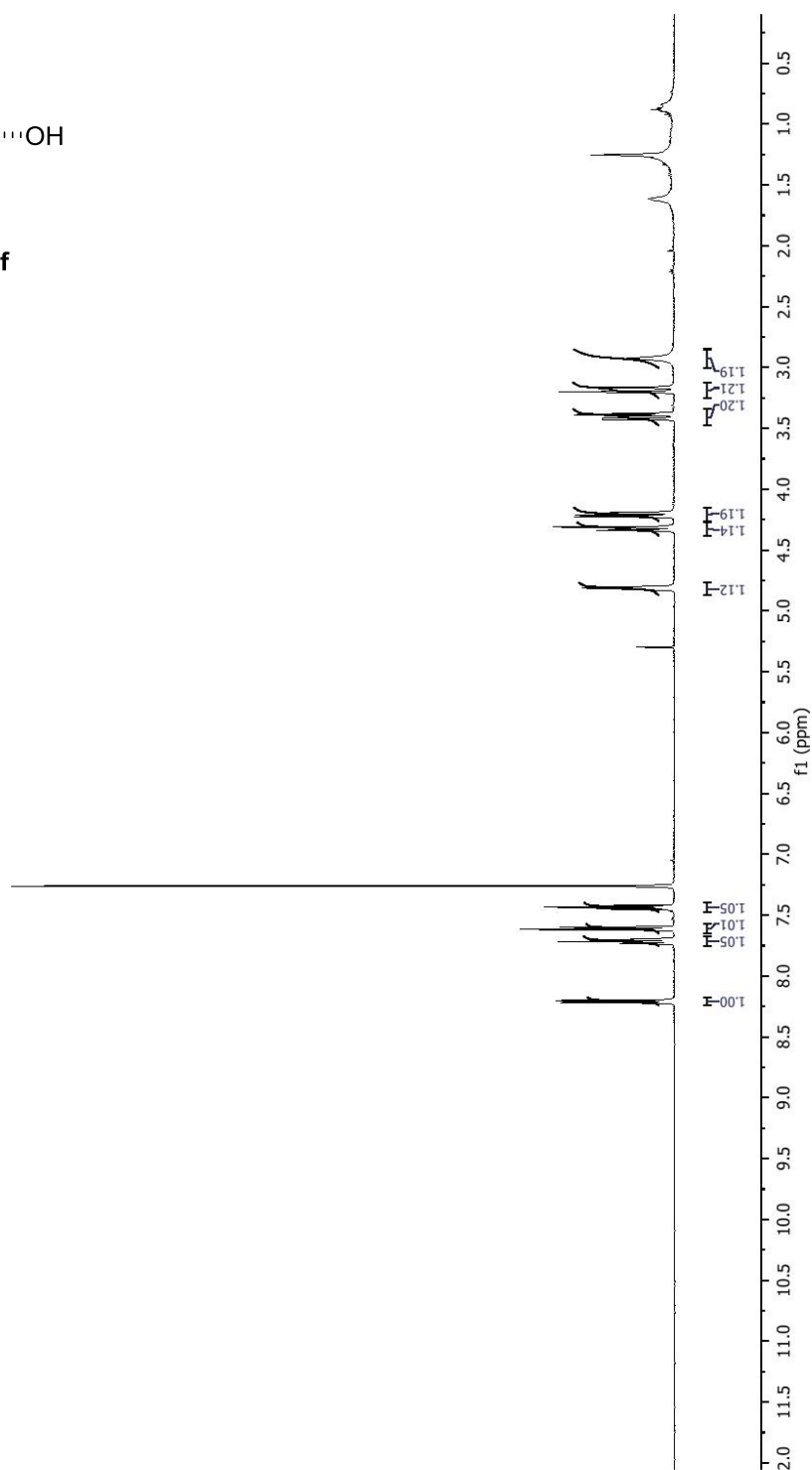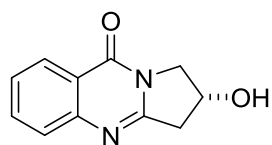
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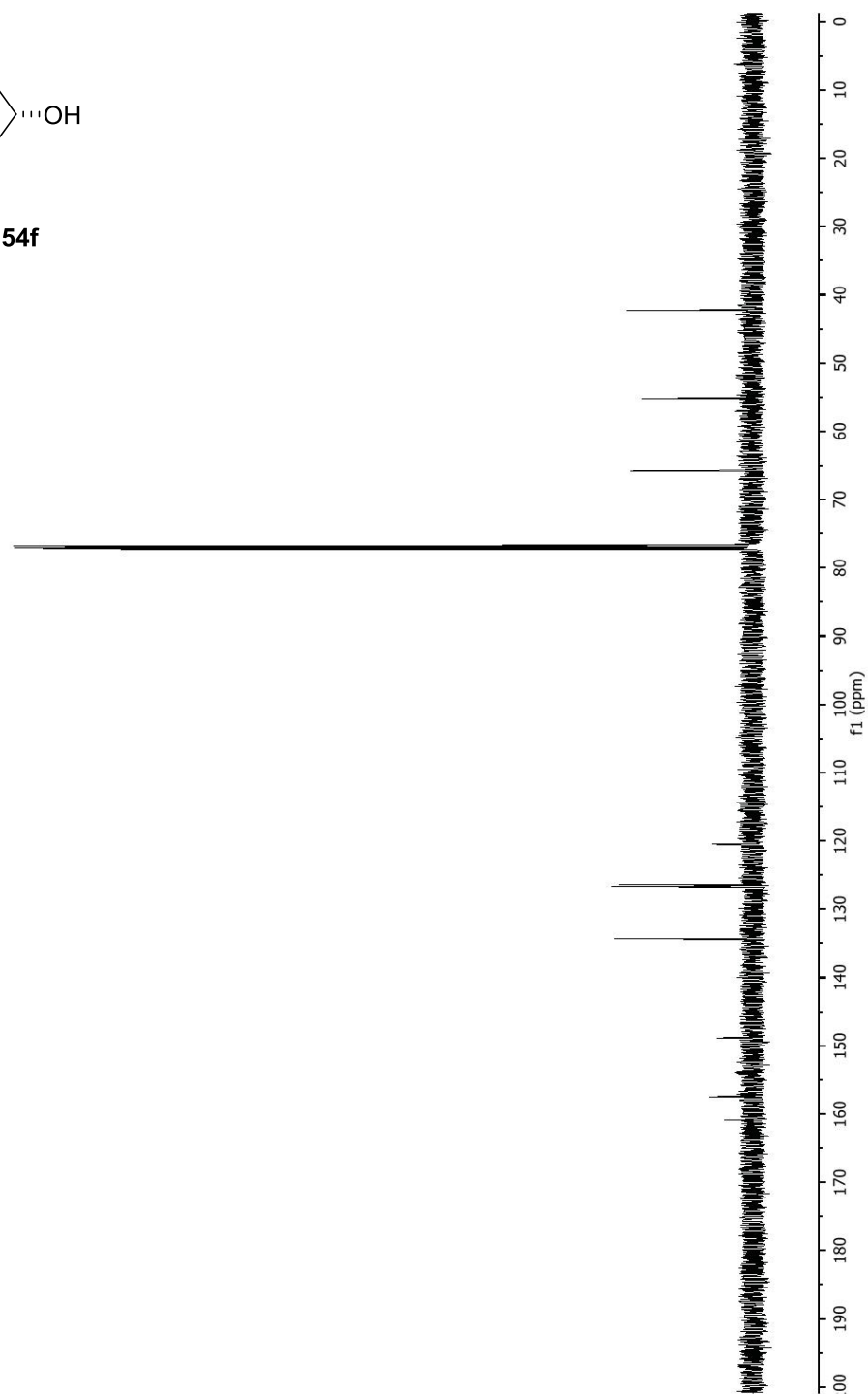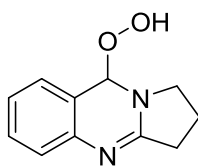
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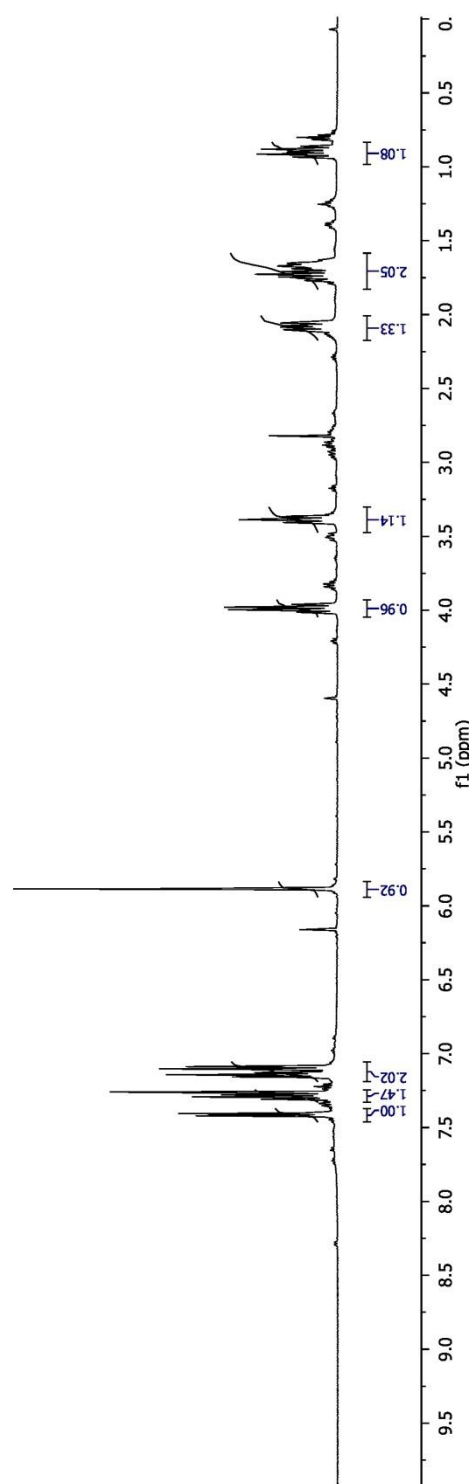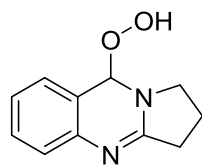
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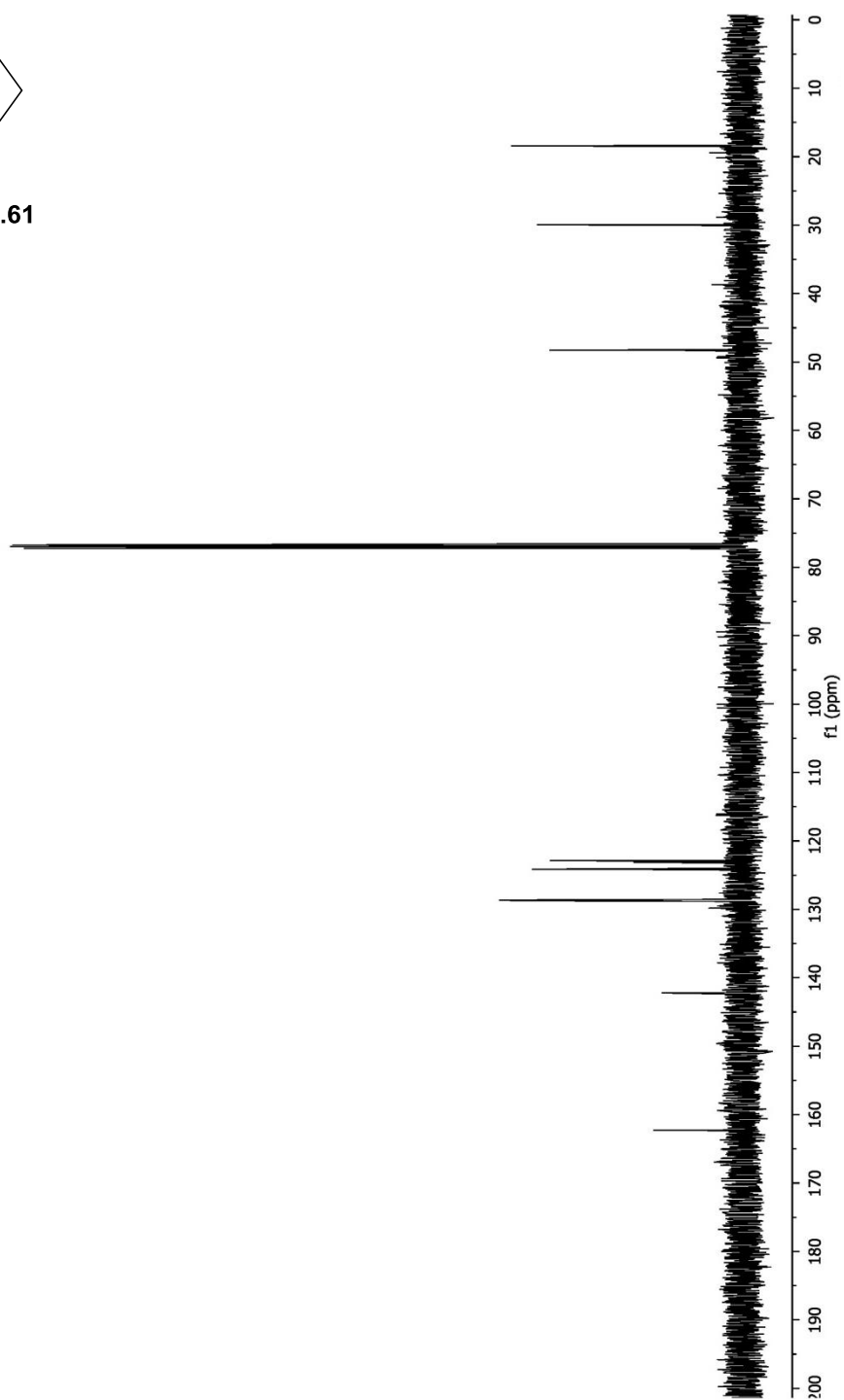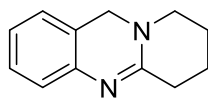
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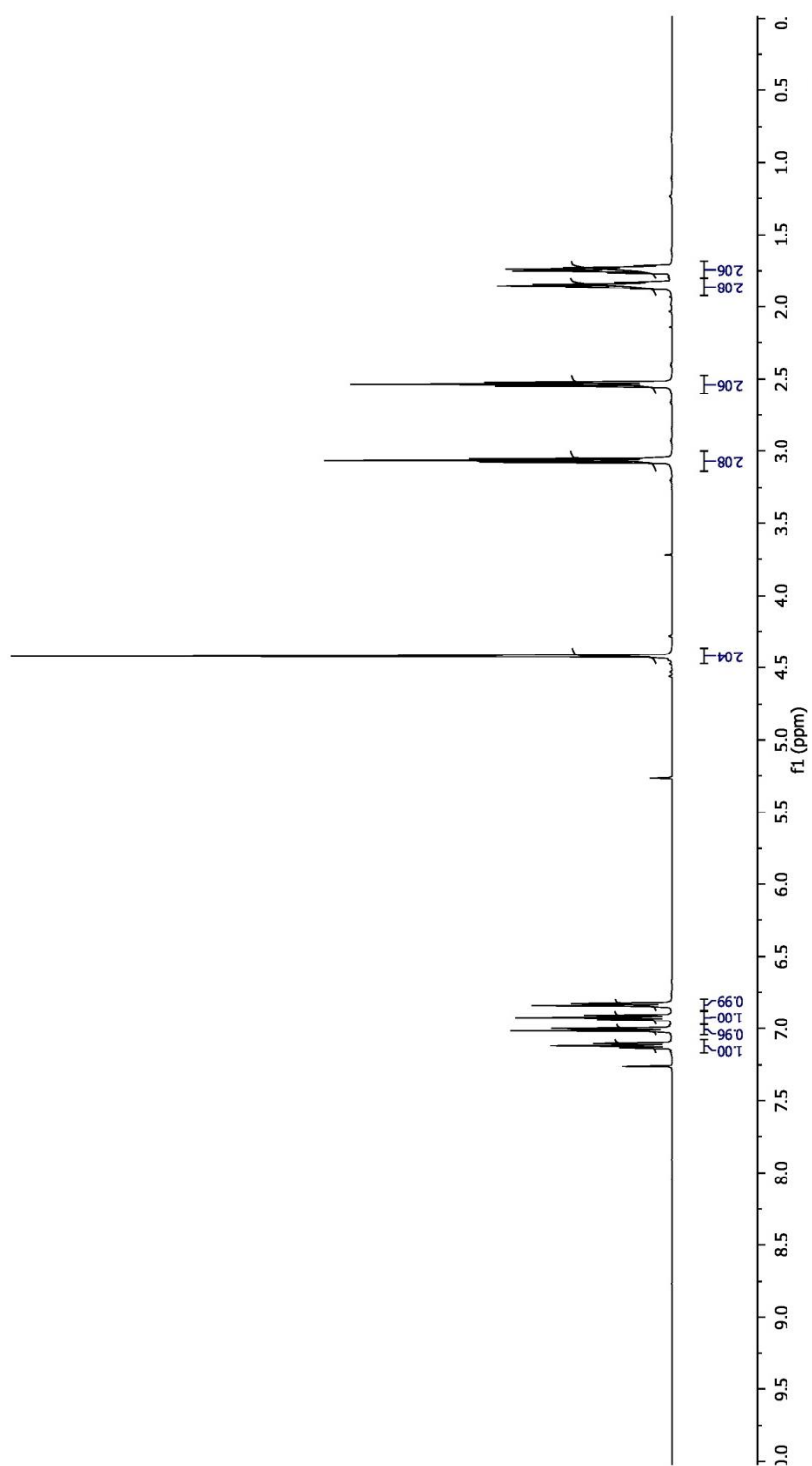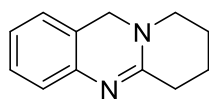
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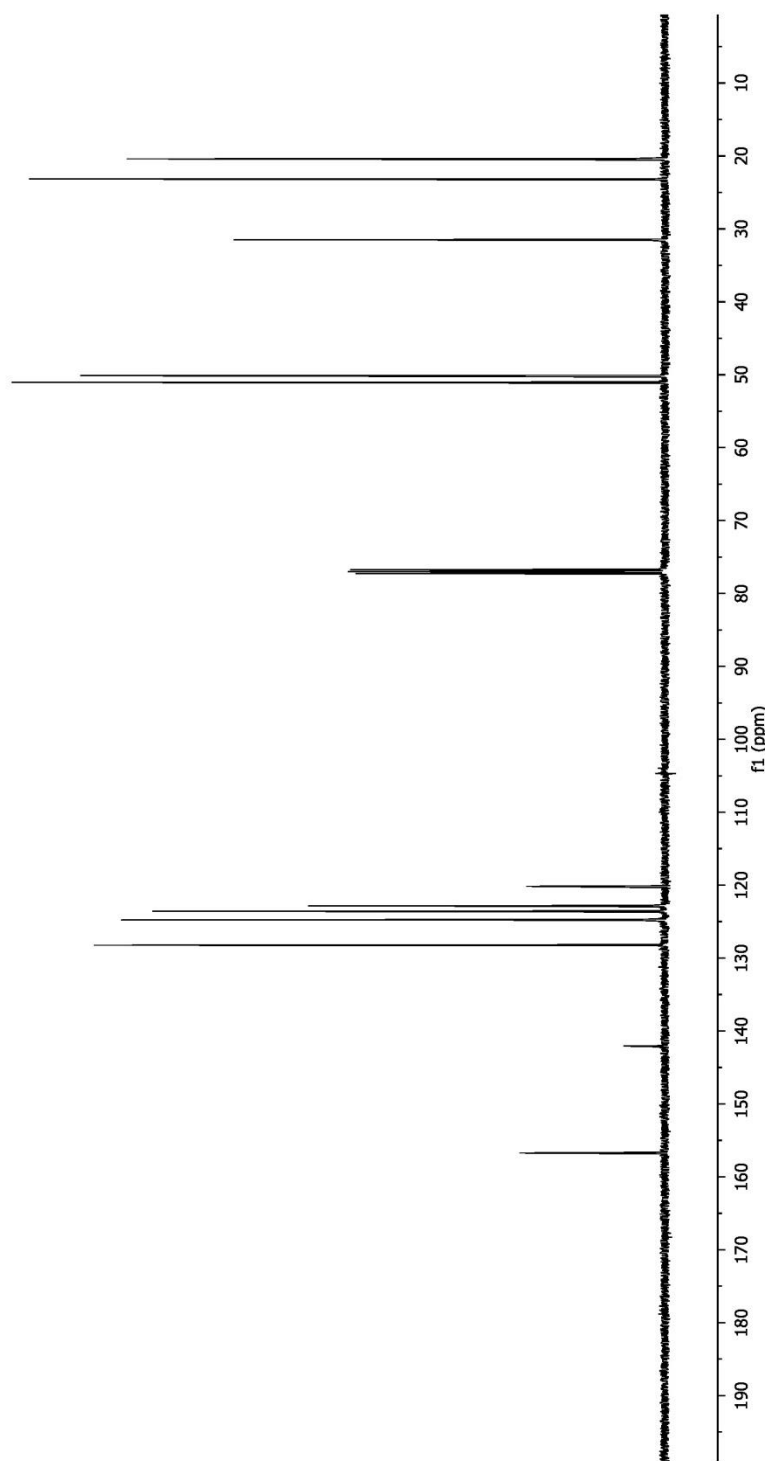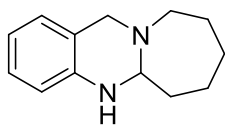
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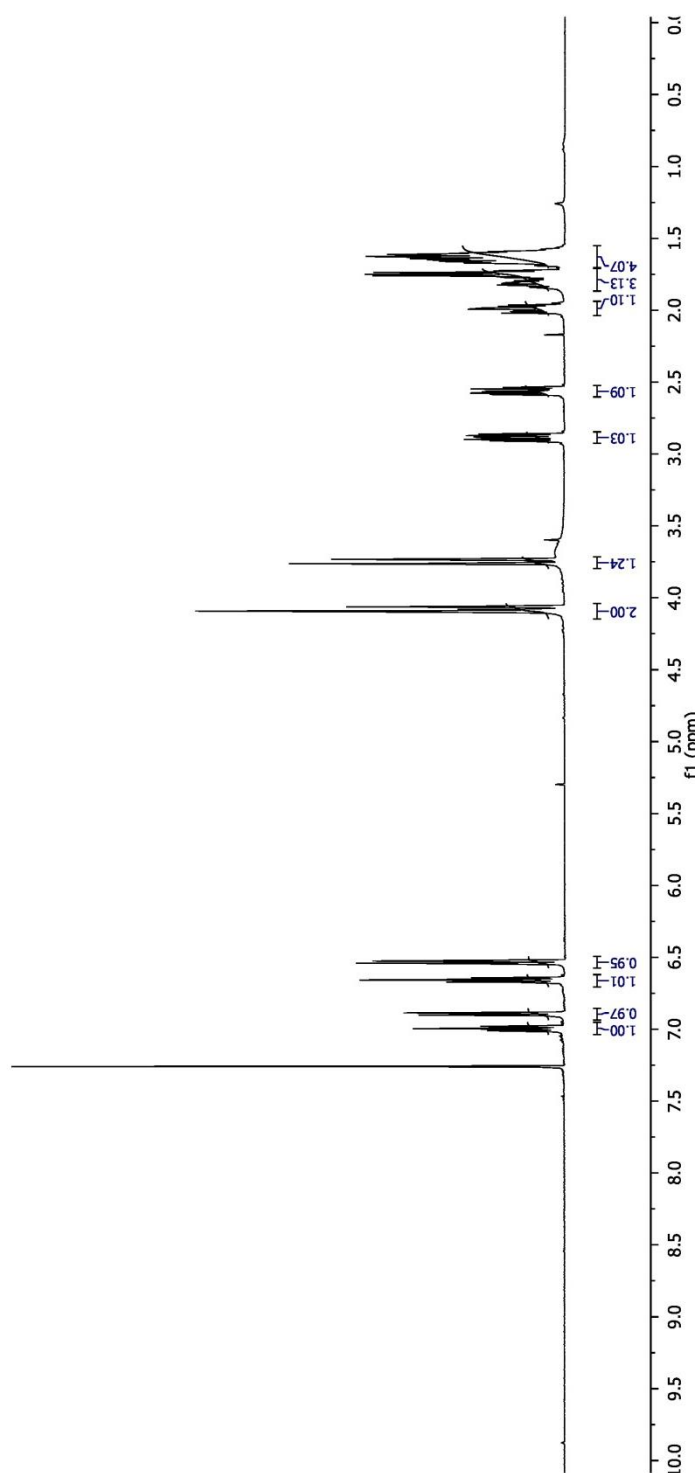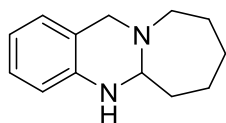
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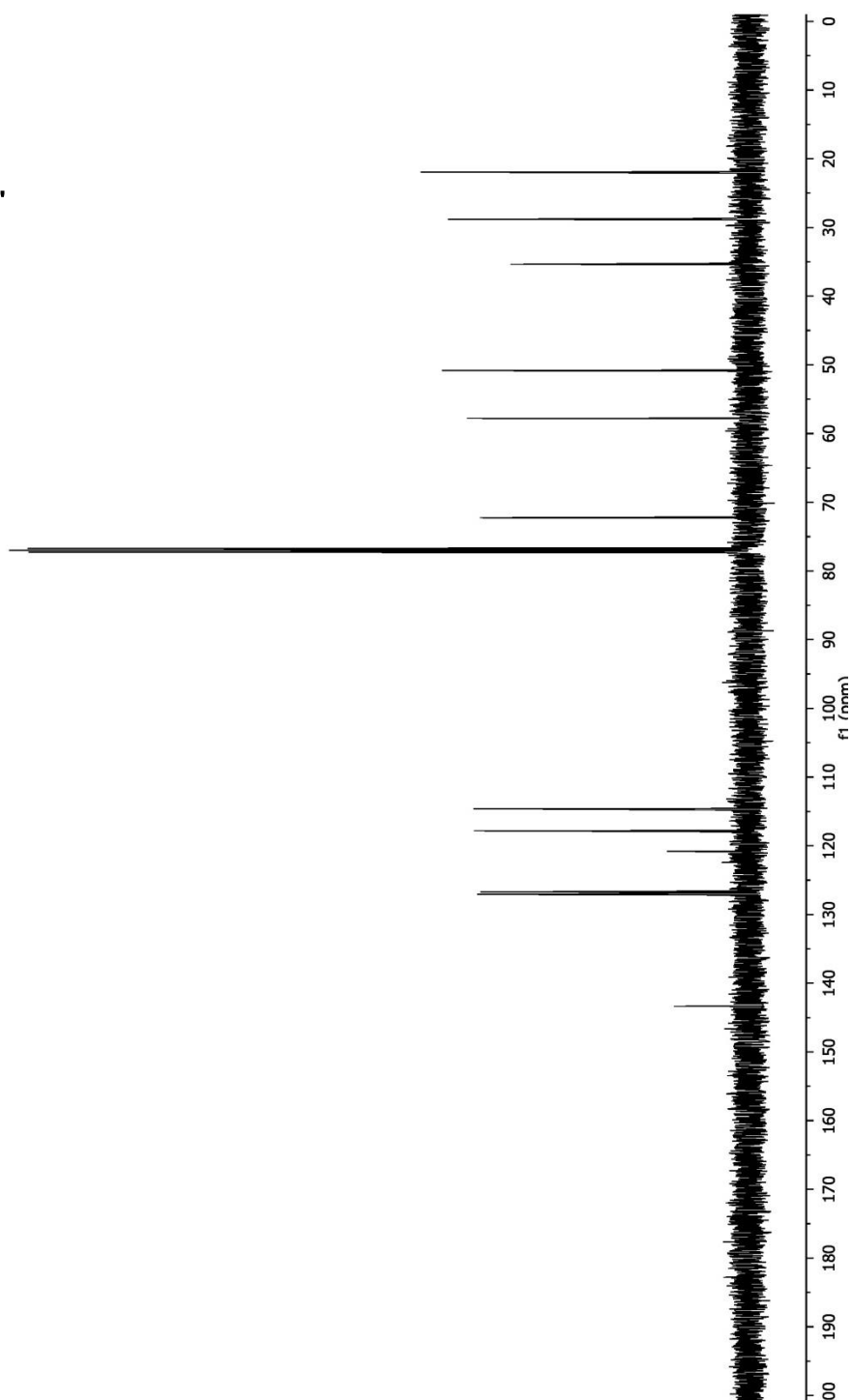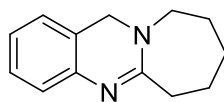
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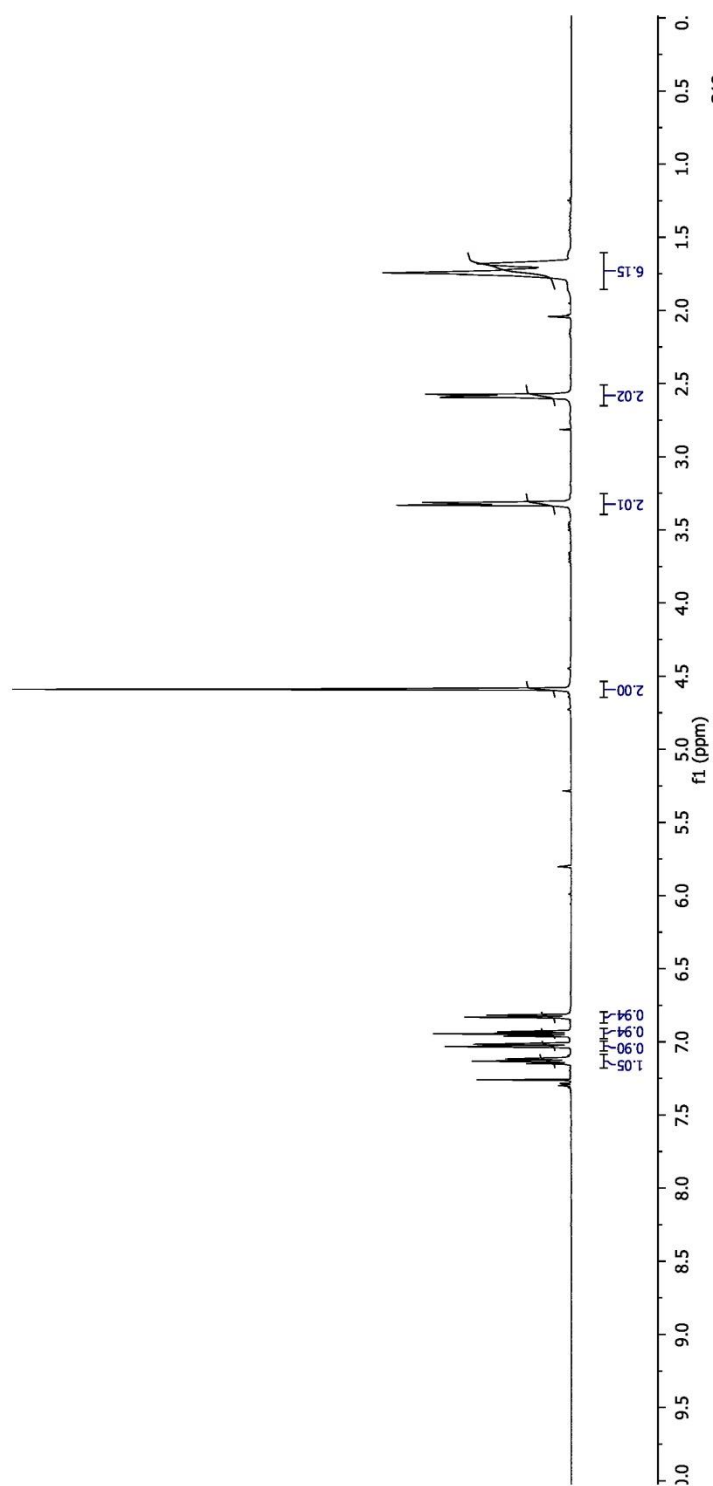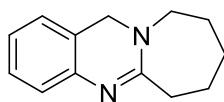
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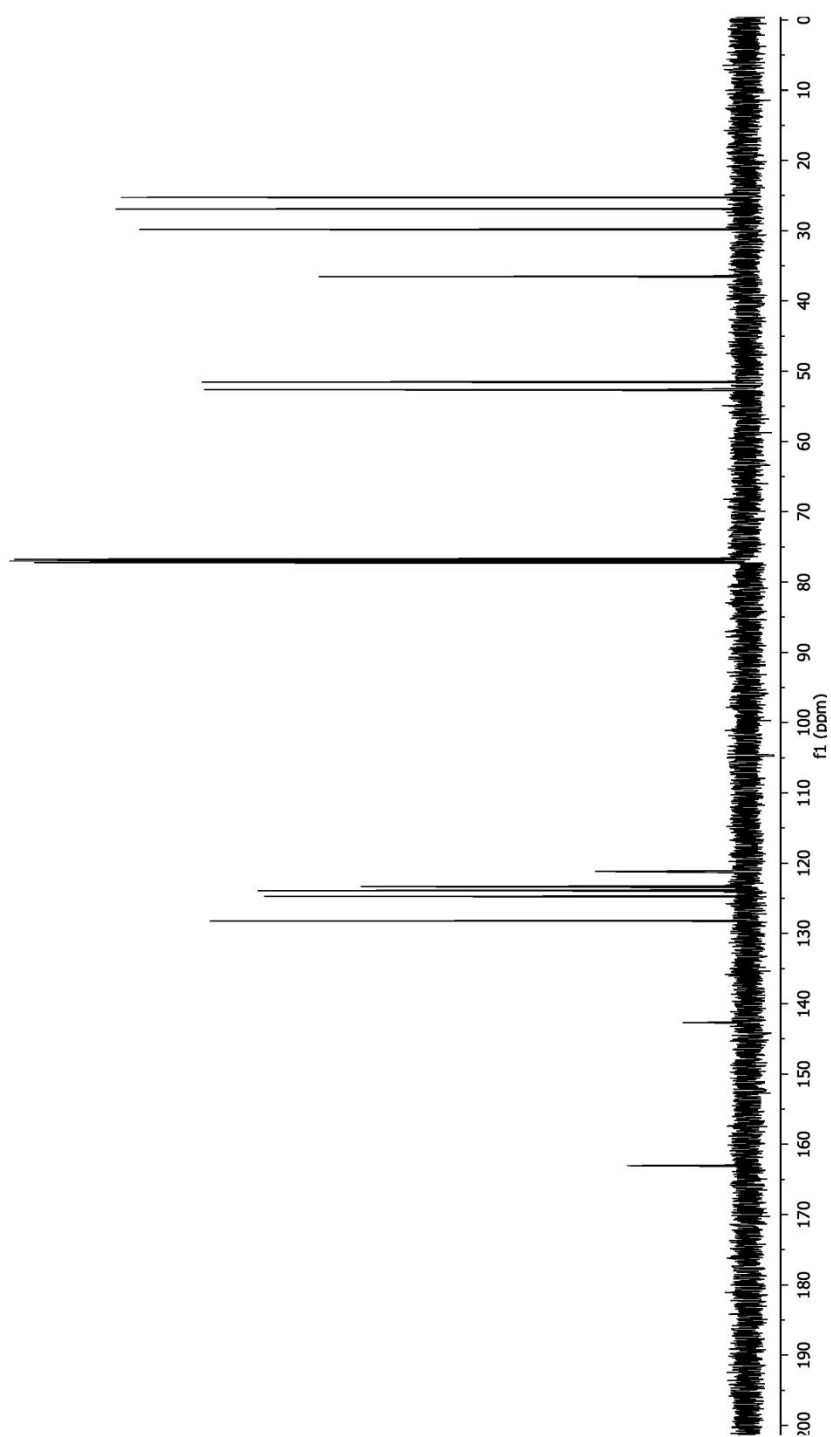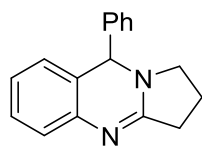
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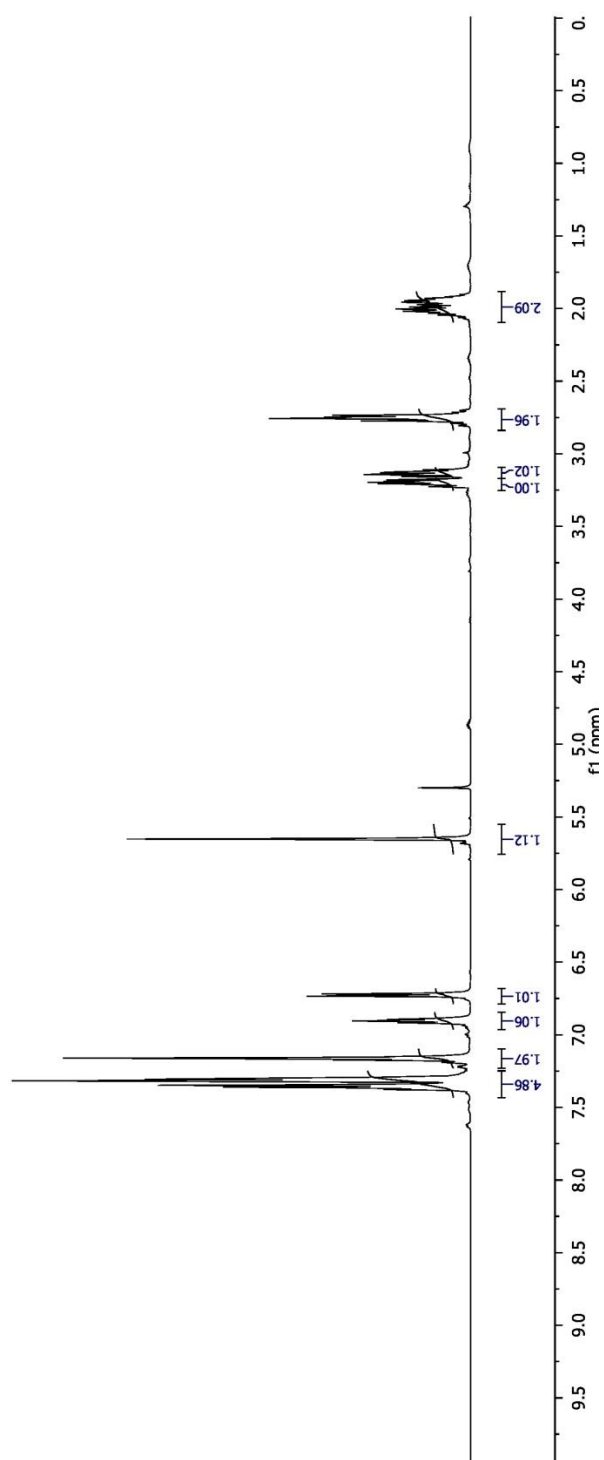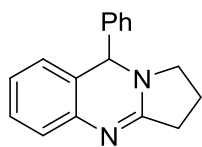
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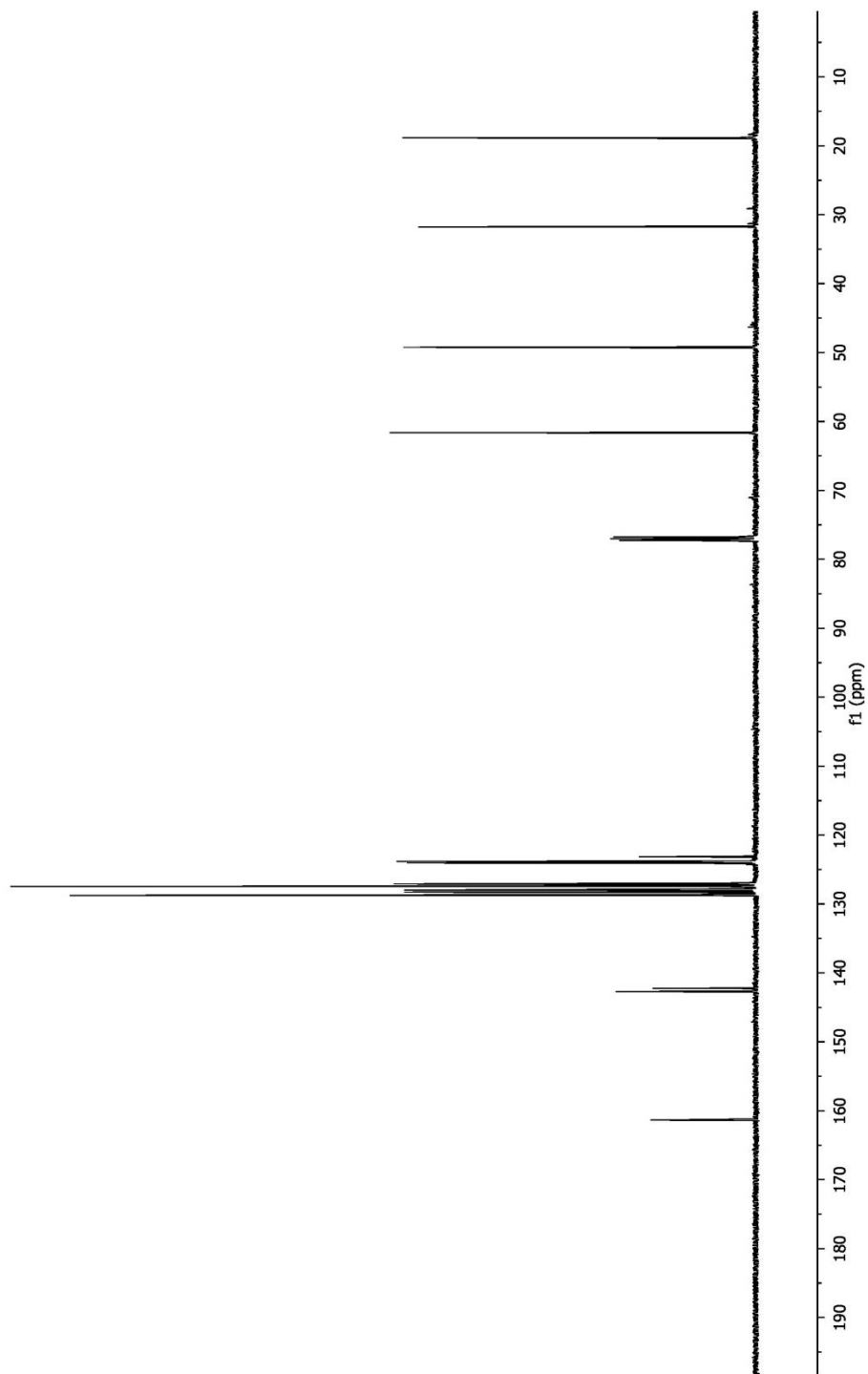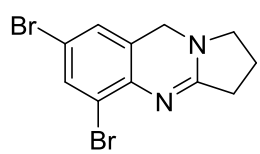
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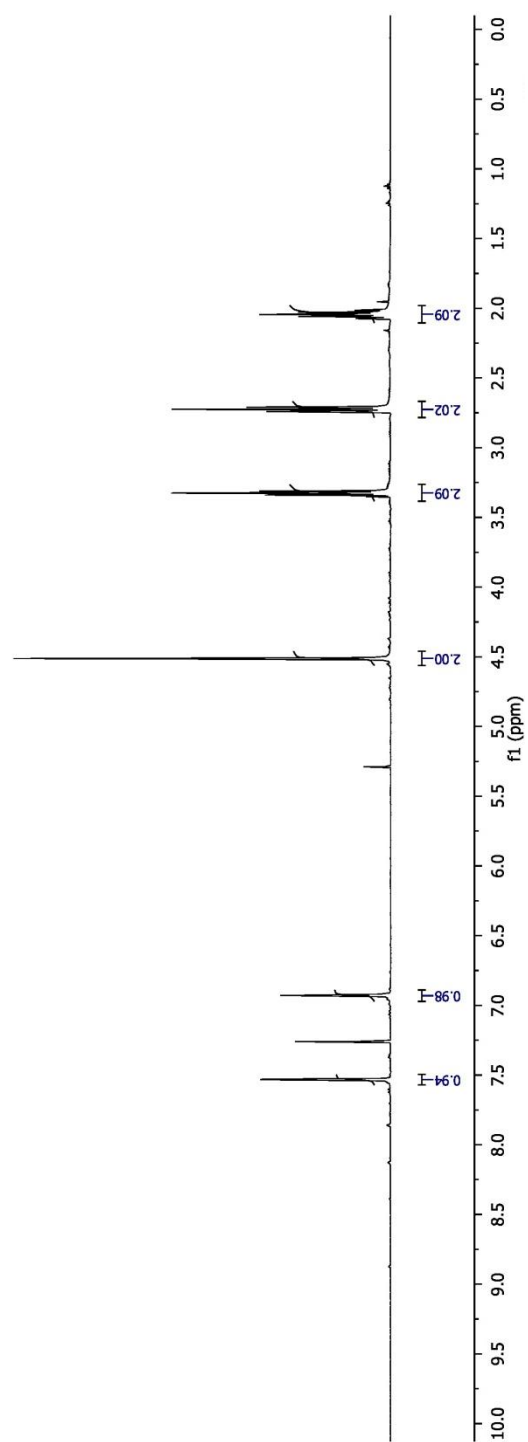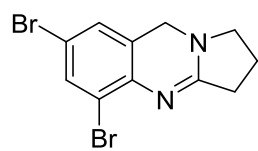
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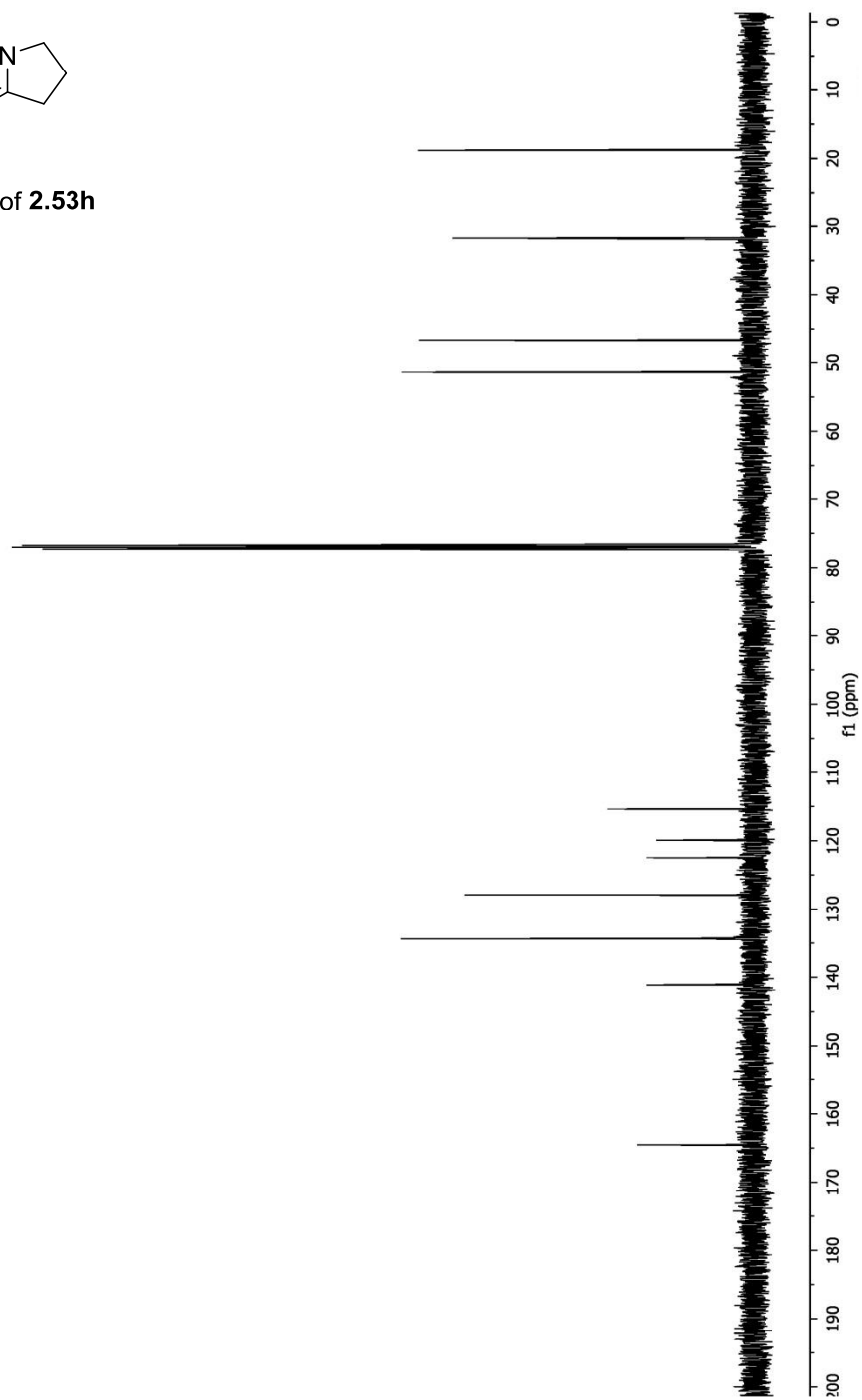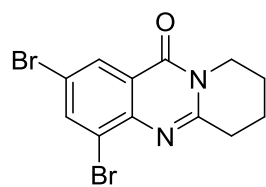
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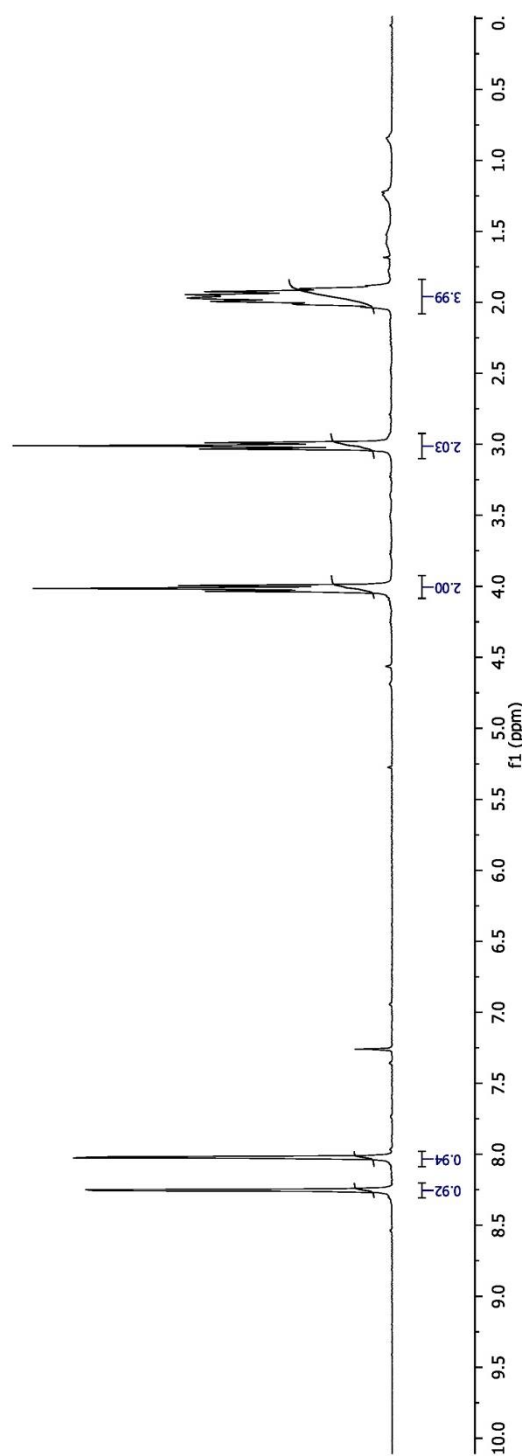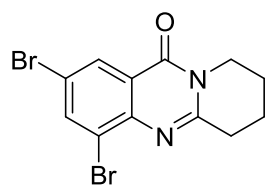
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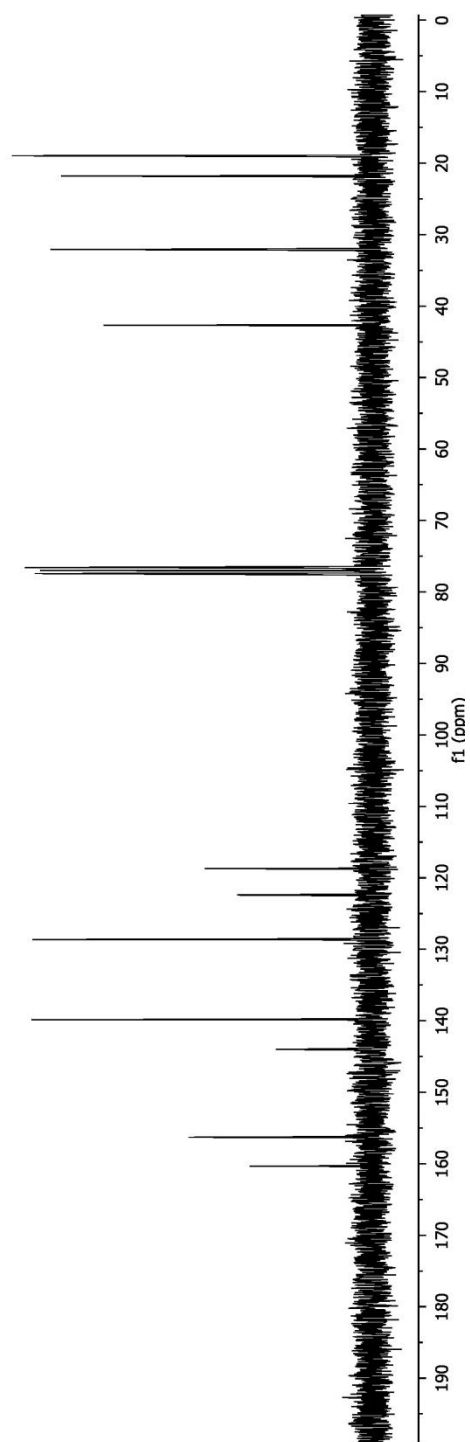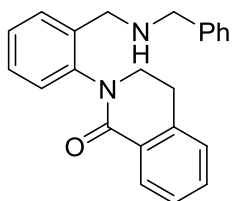
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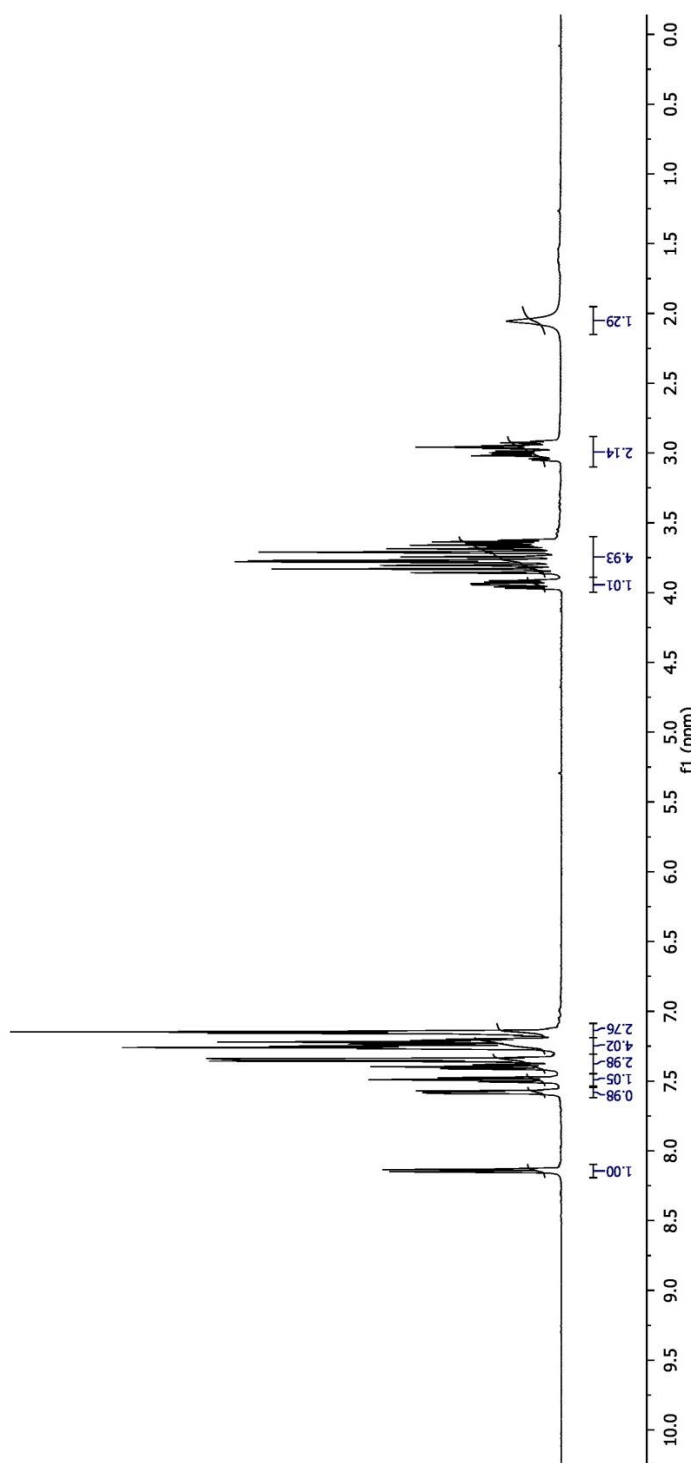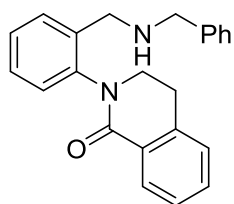
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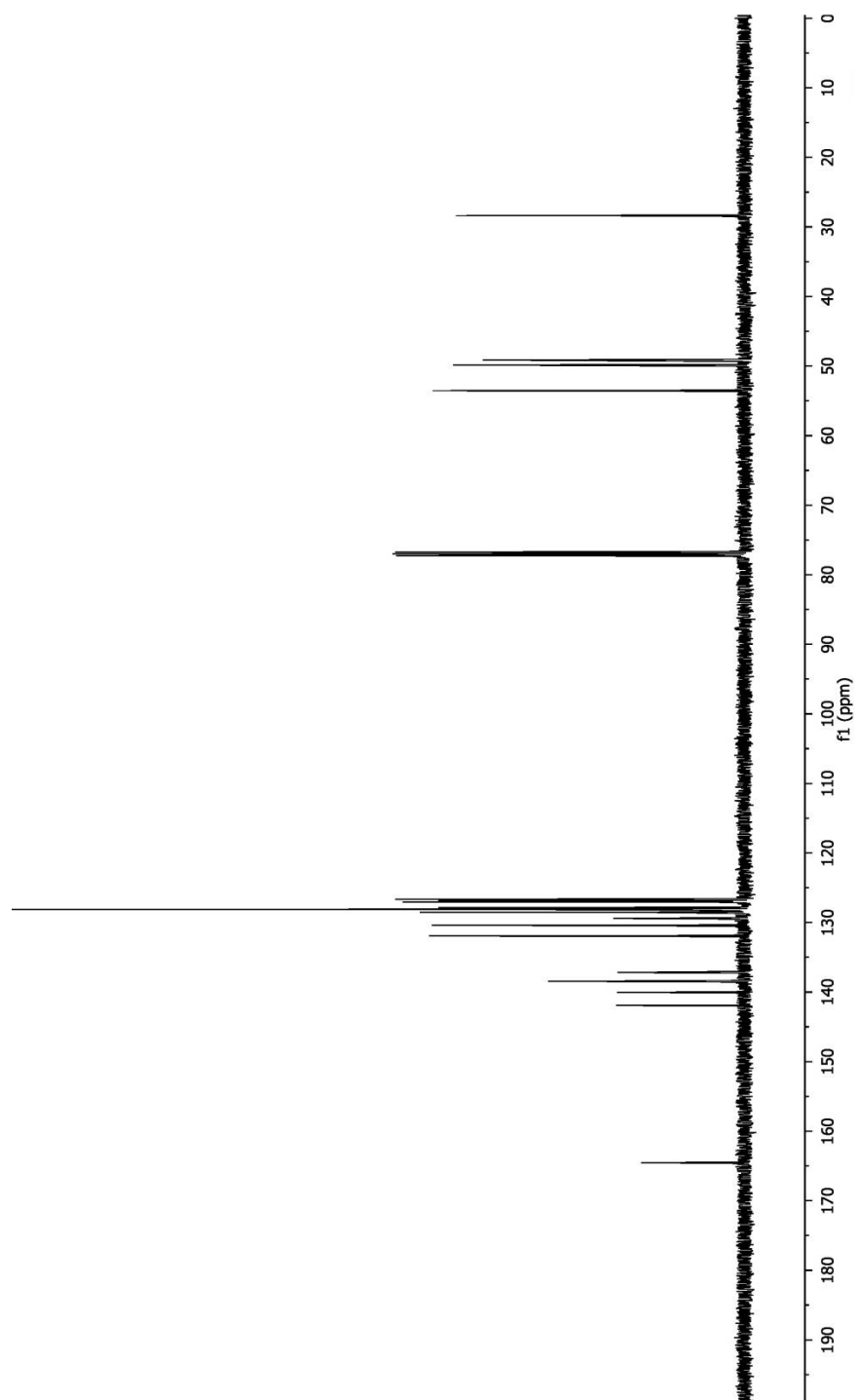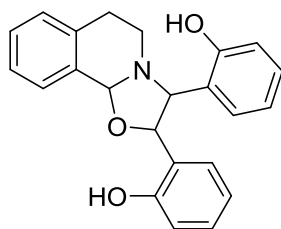
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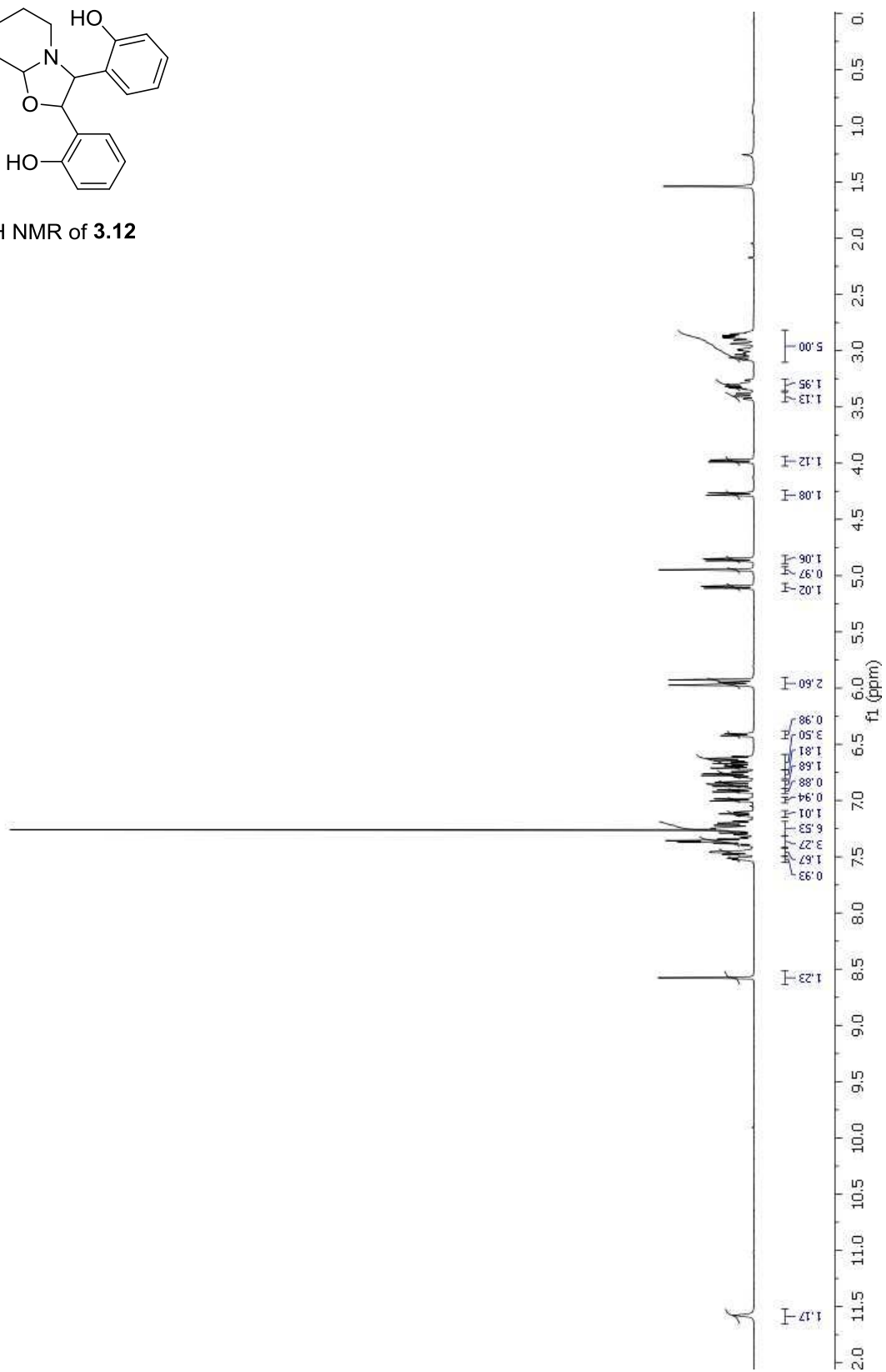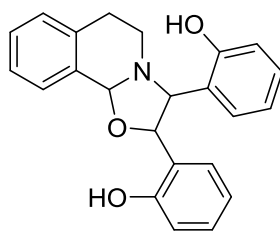
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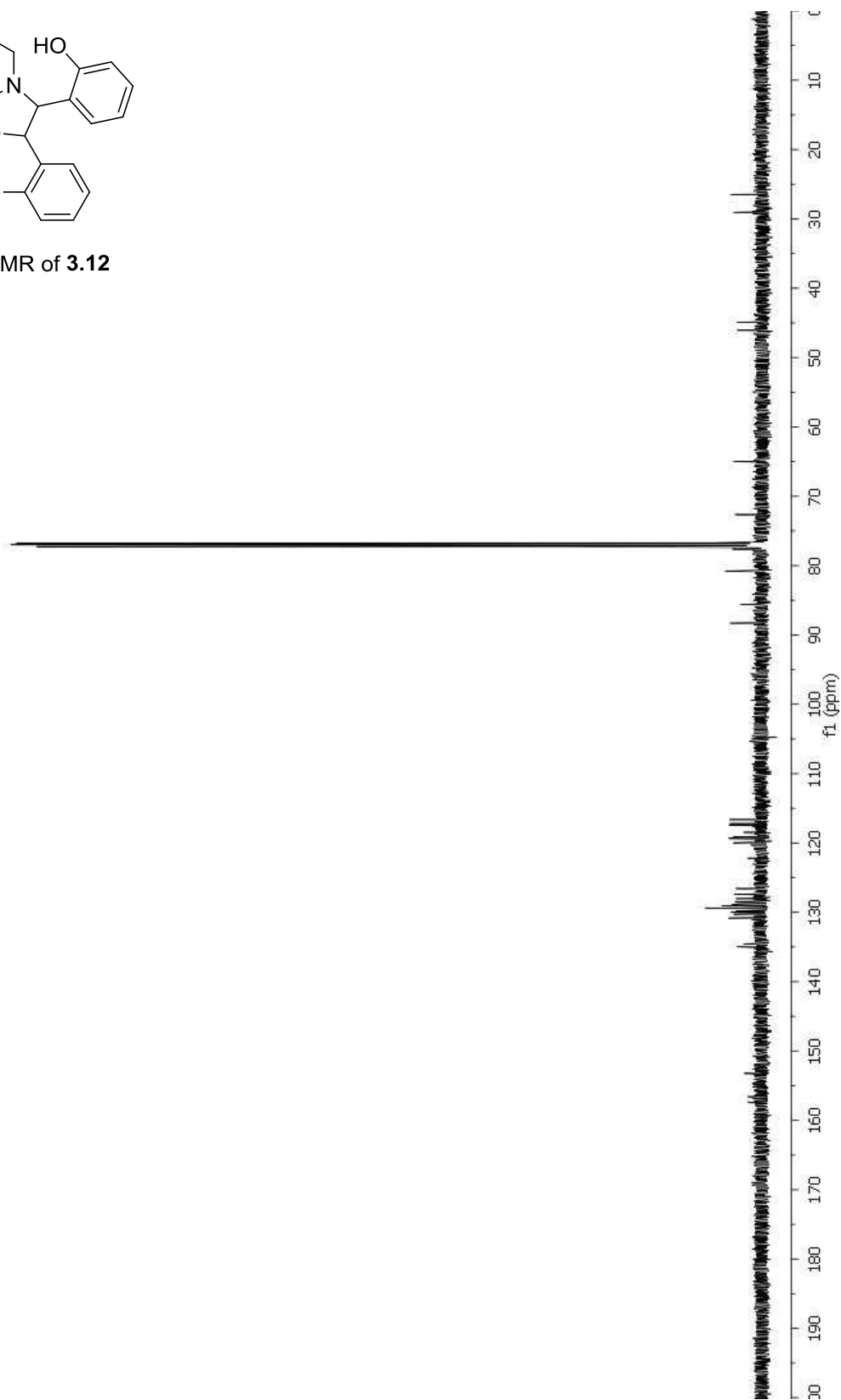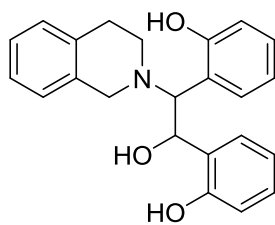
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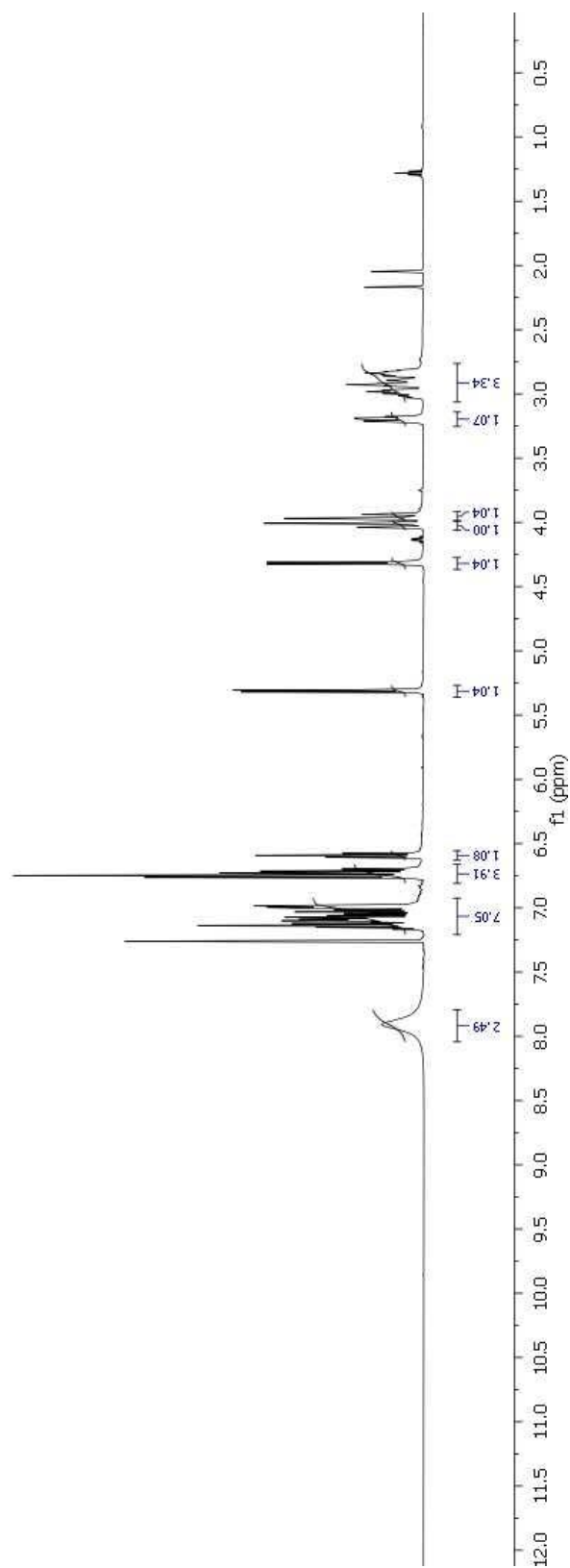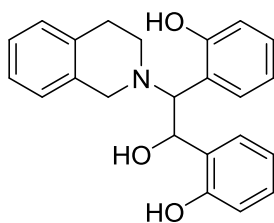
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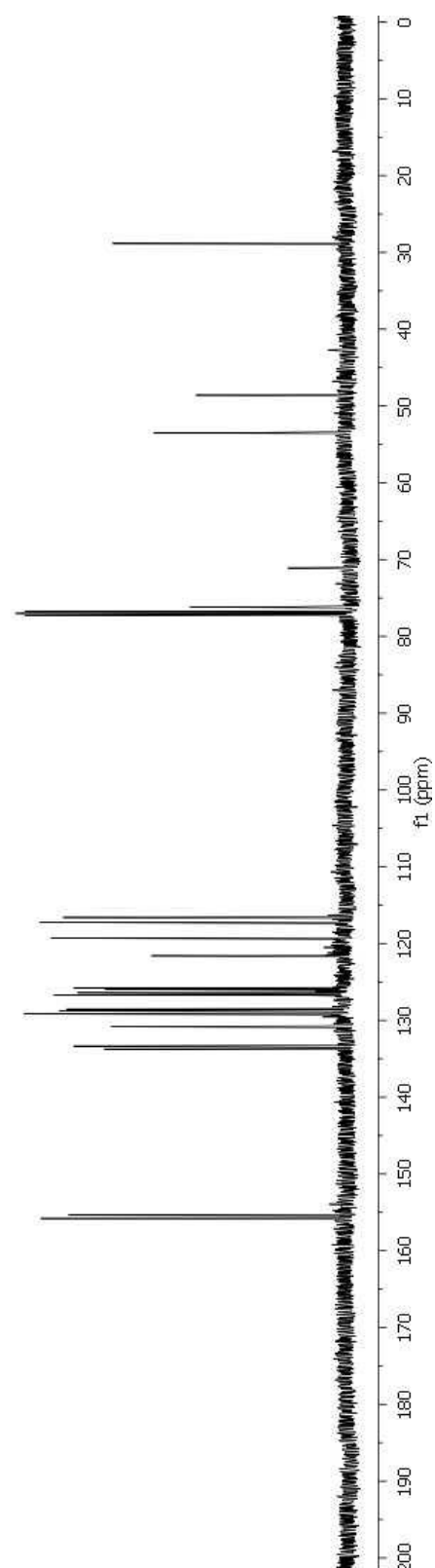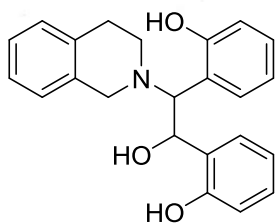
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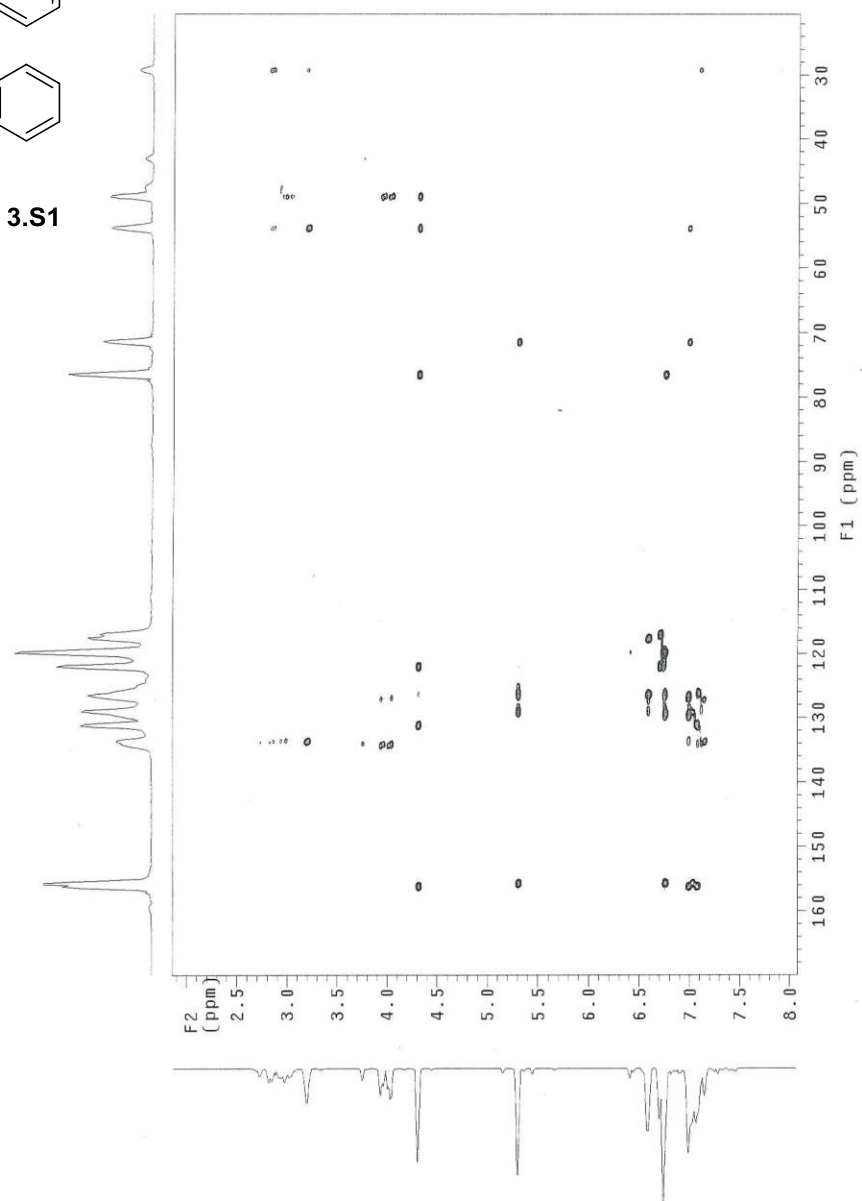
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^{13}C NMR of **3.2g**

*t*Bu

*t*Bu
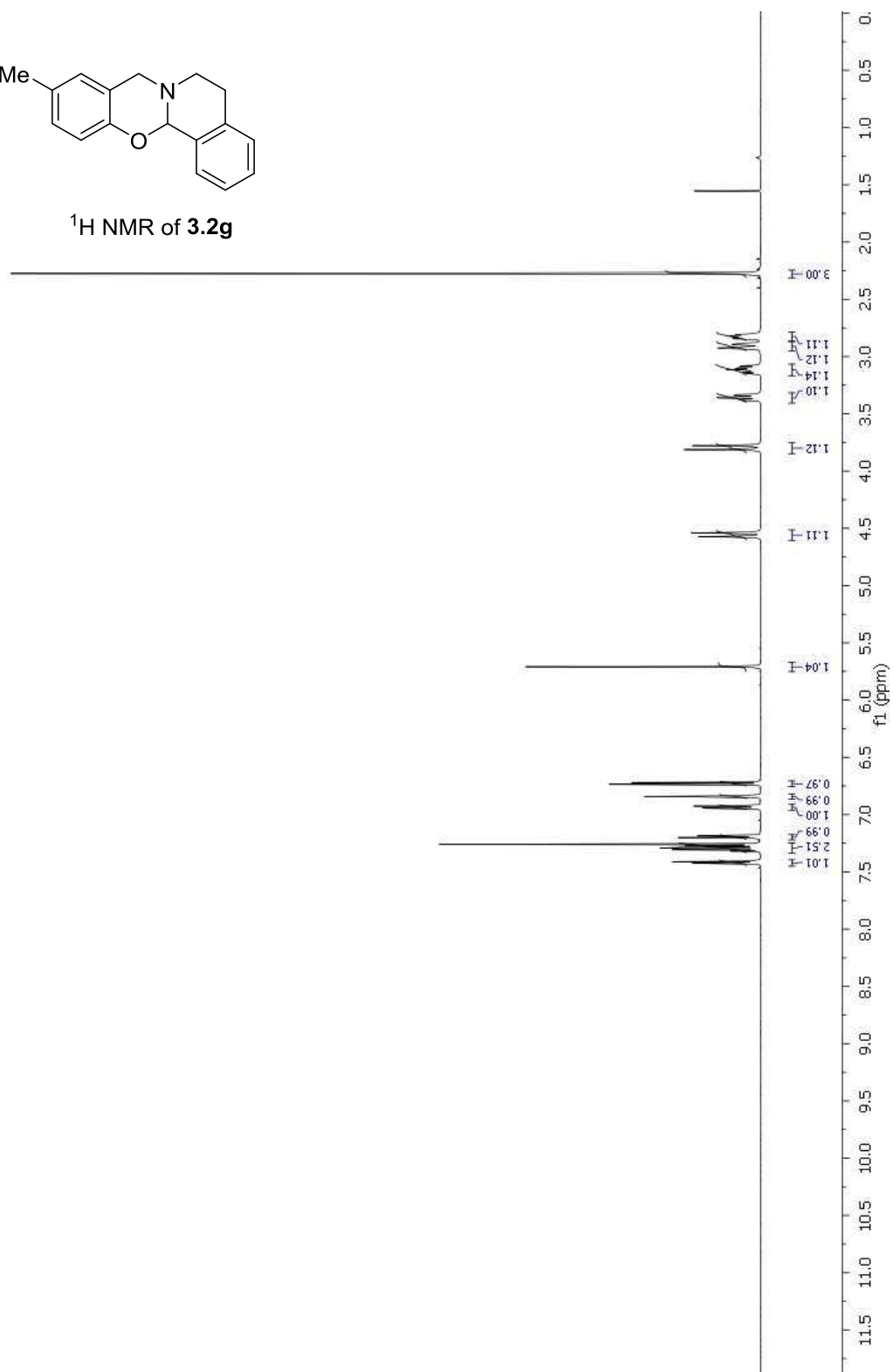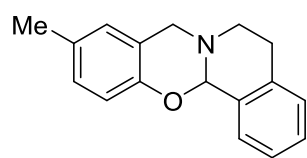
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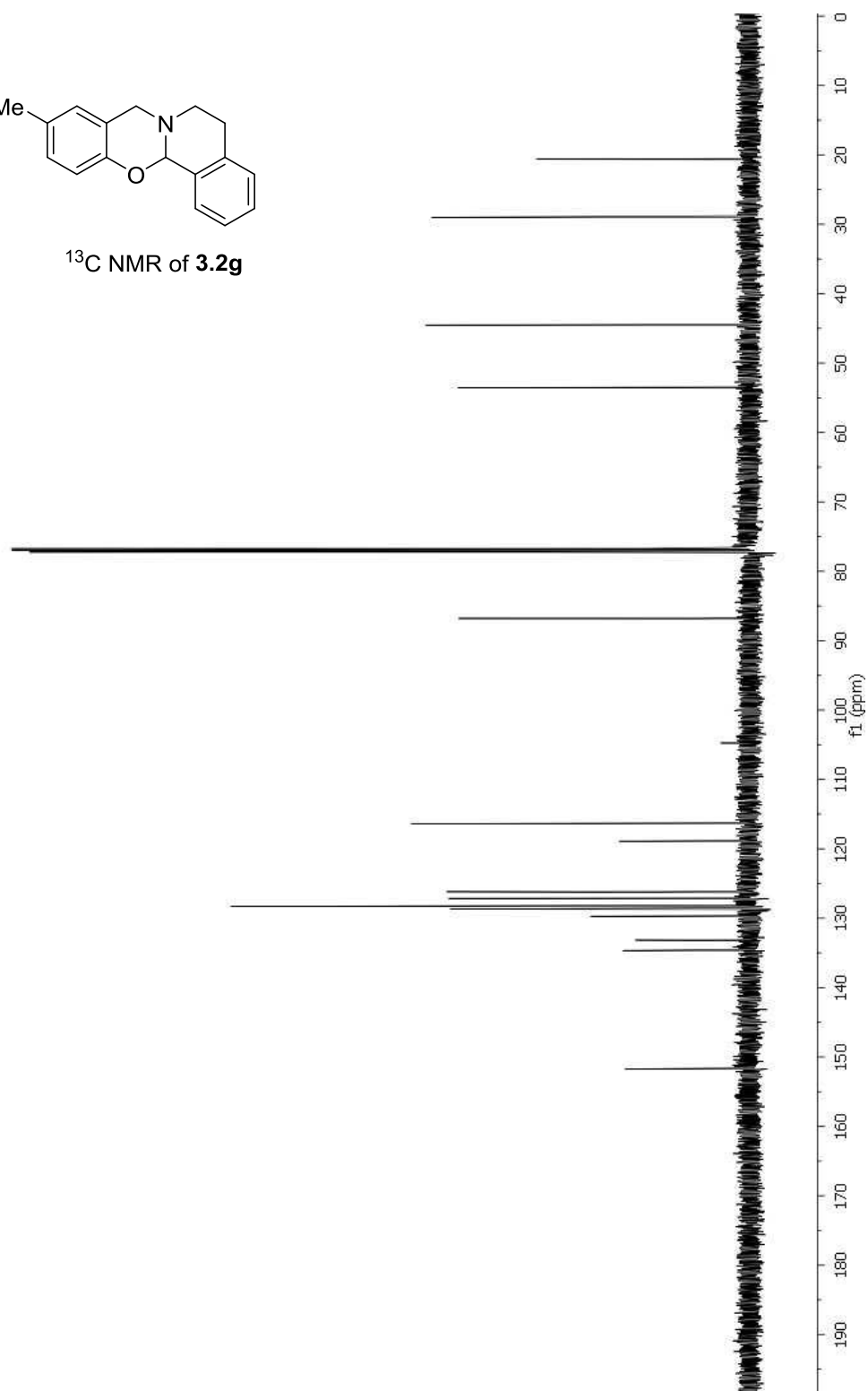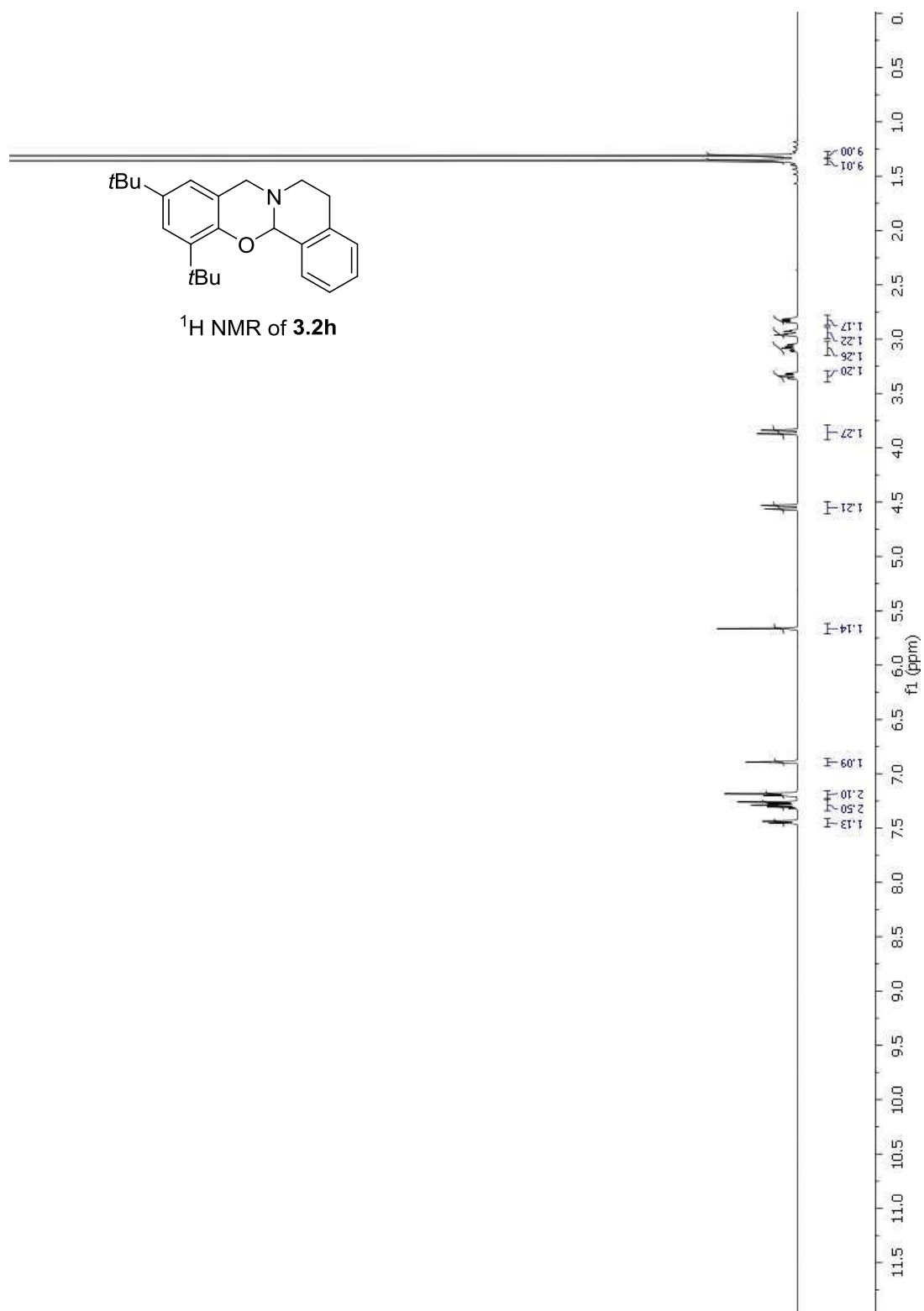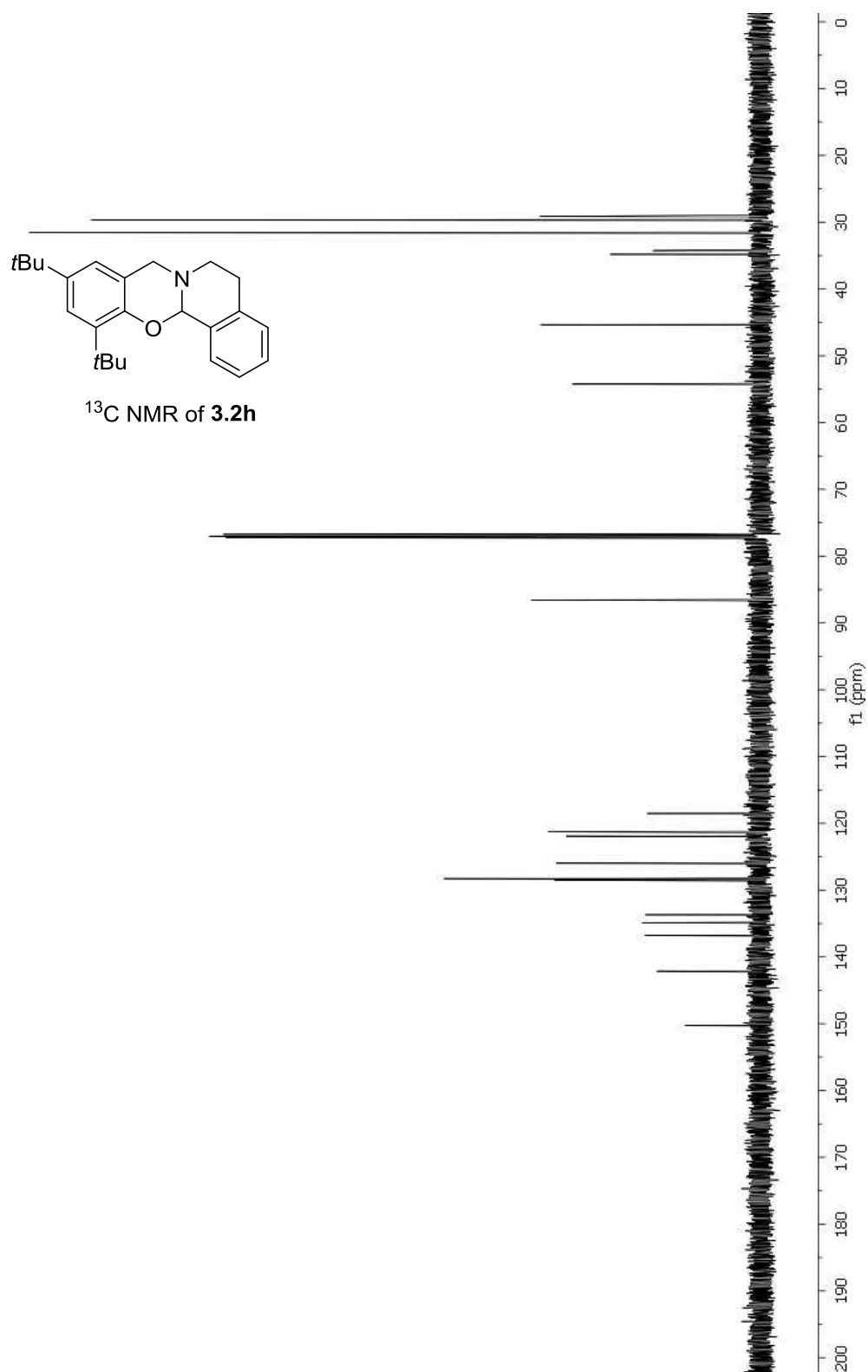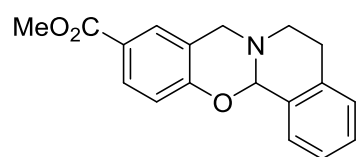
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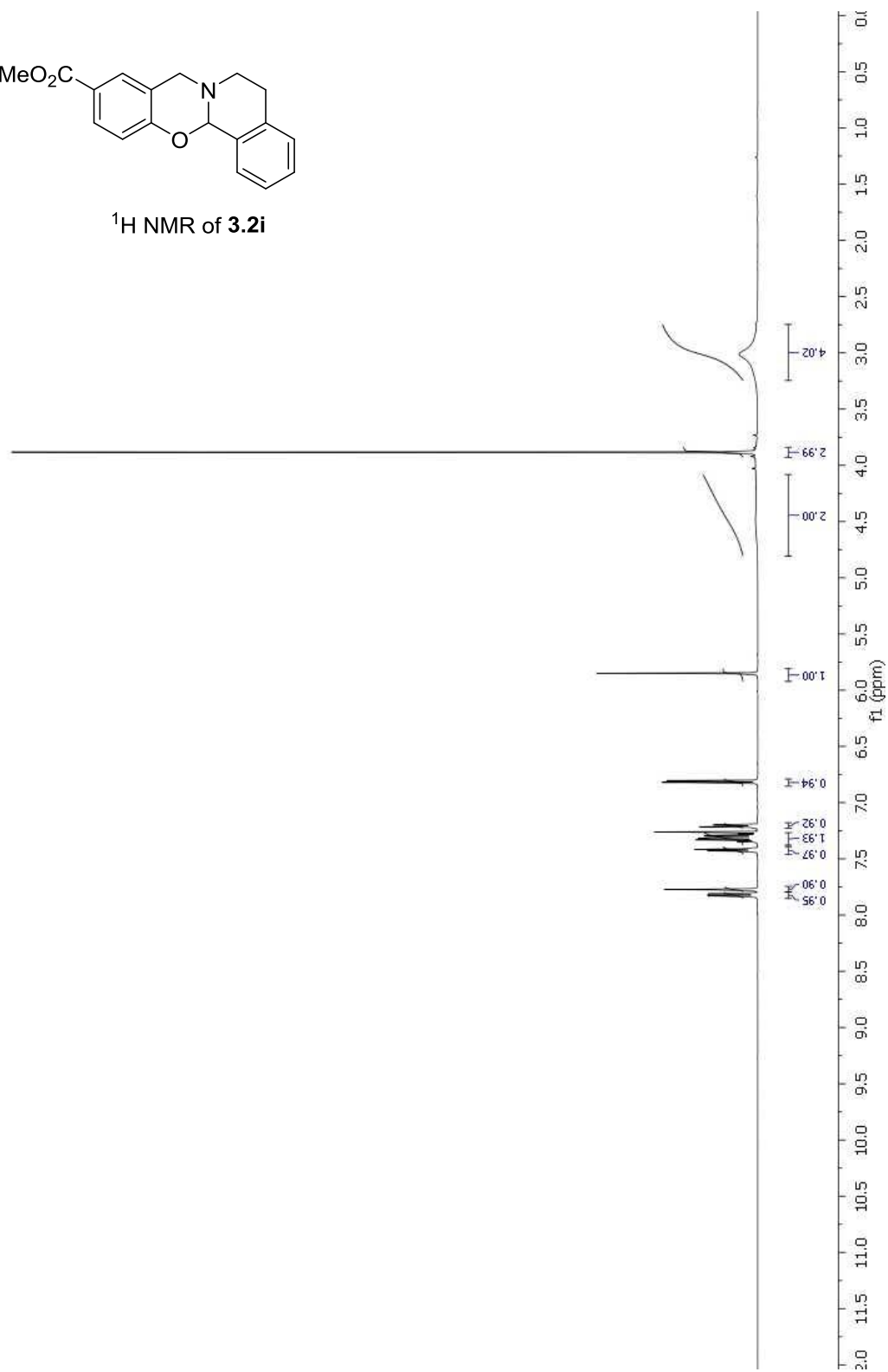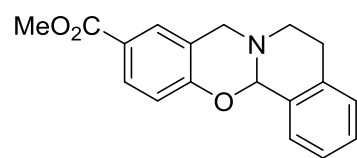
^{1}H NMR of **3.2i**

^{13}C NMR of **3.2i**
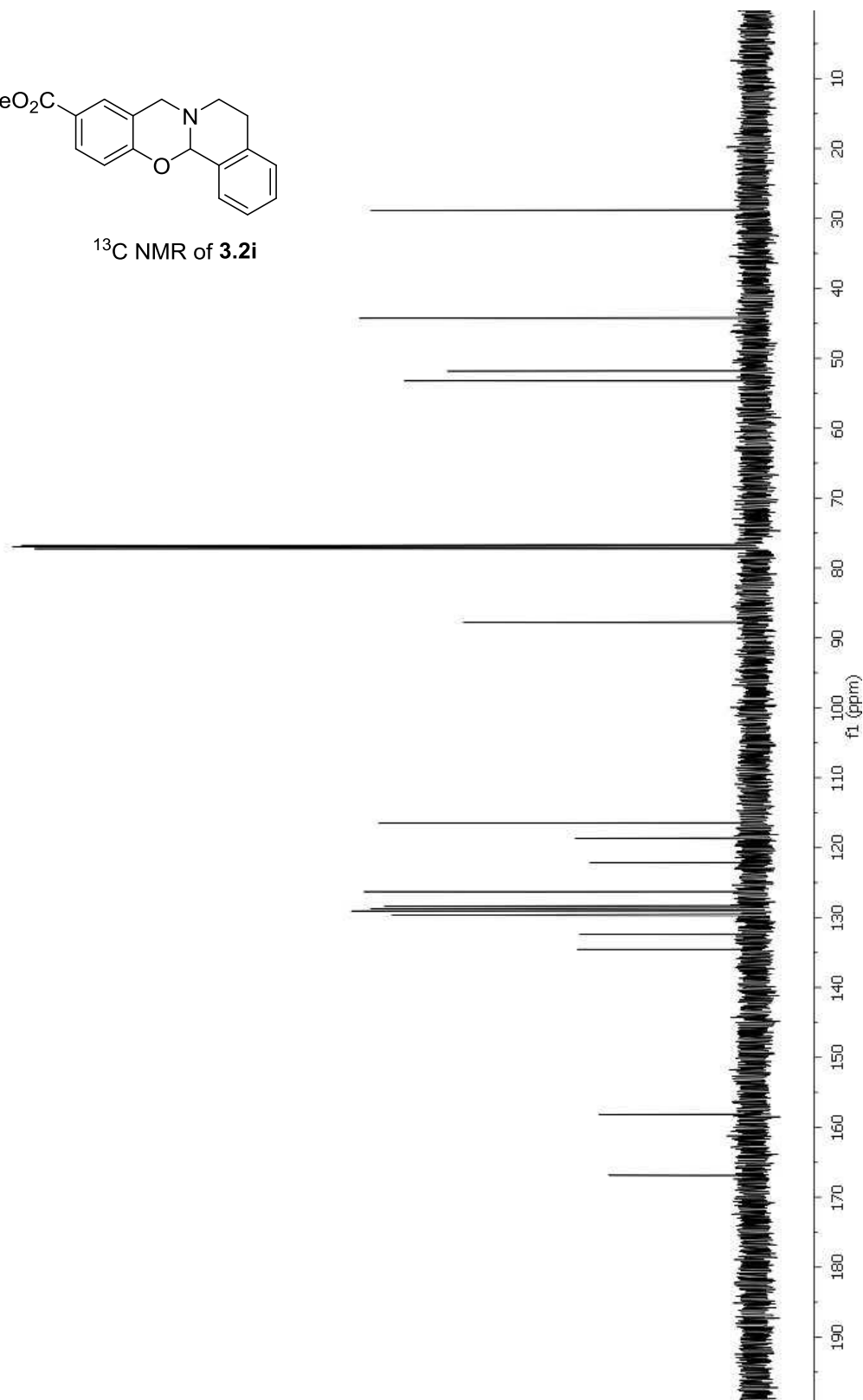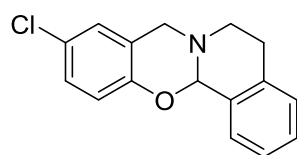
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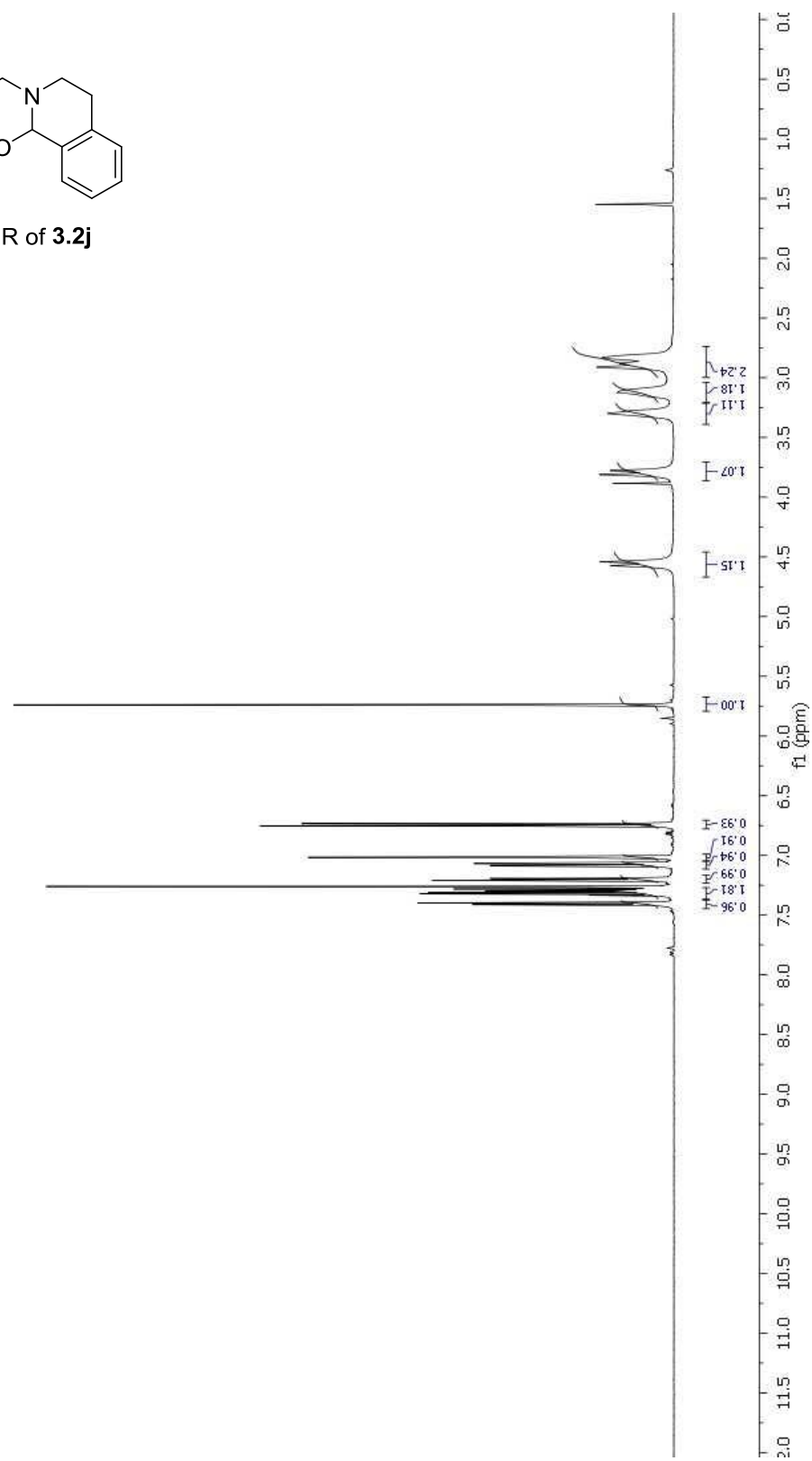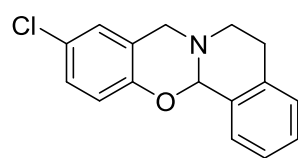
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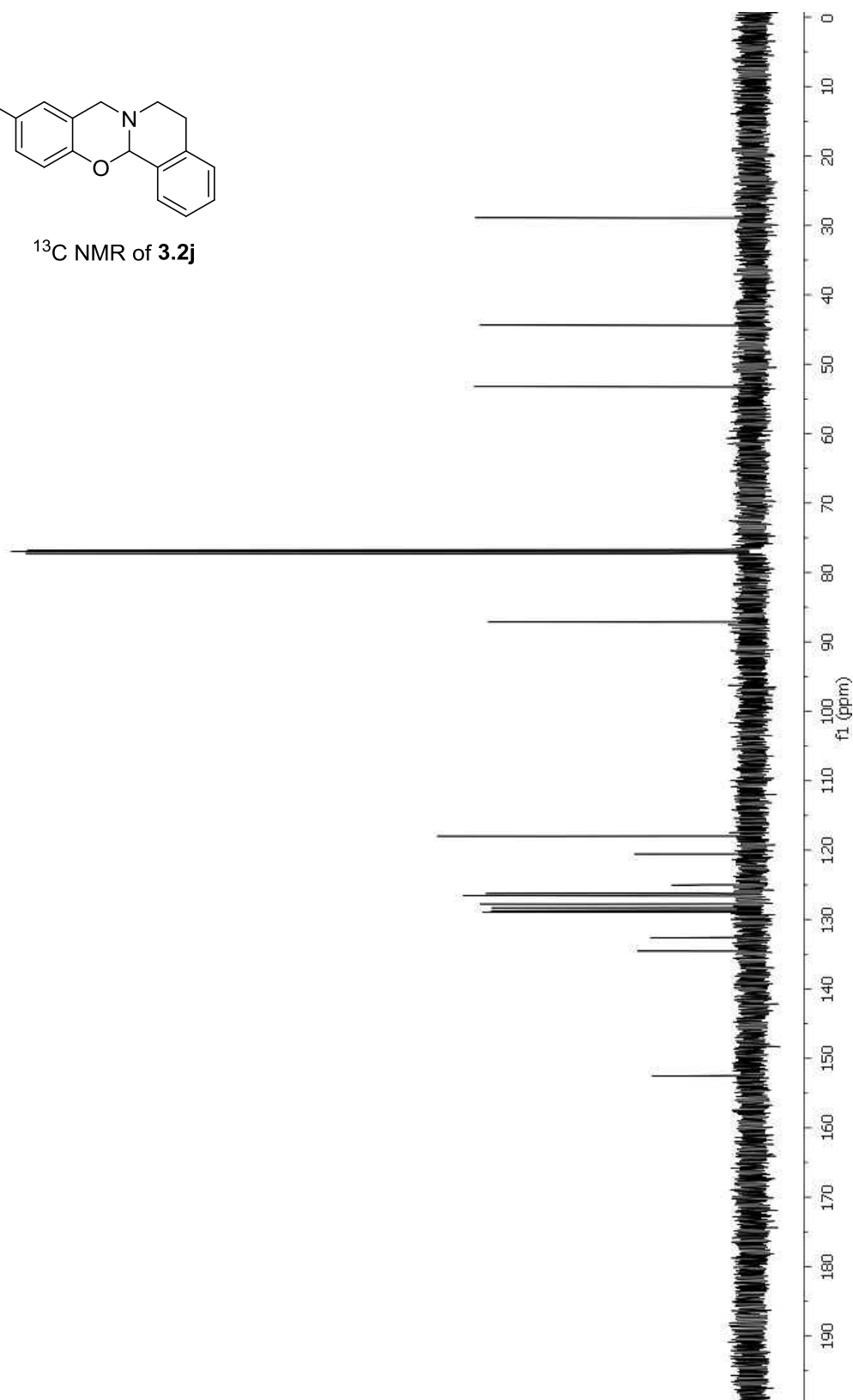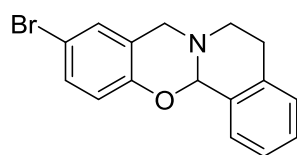
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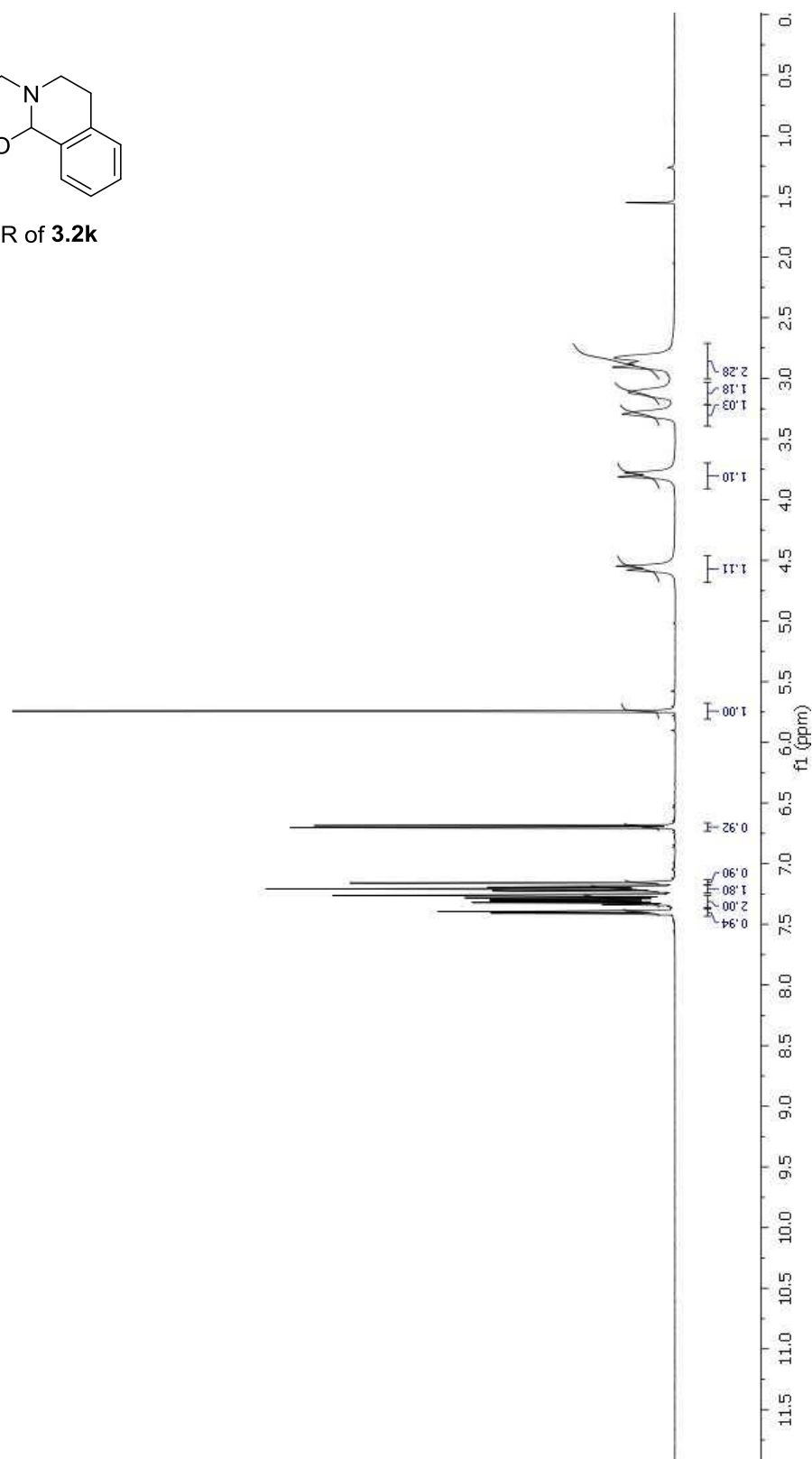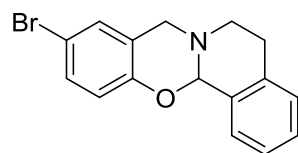
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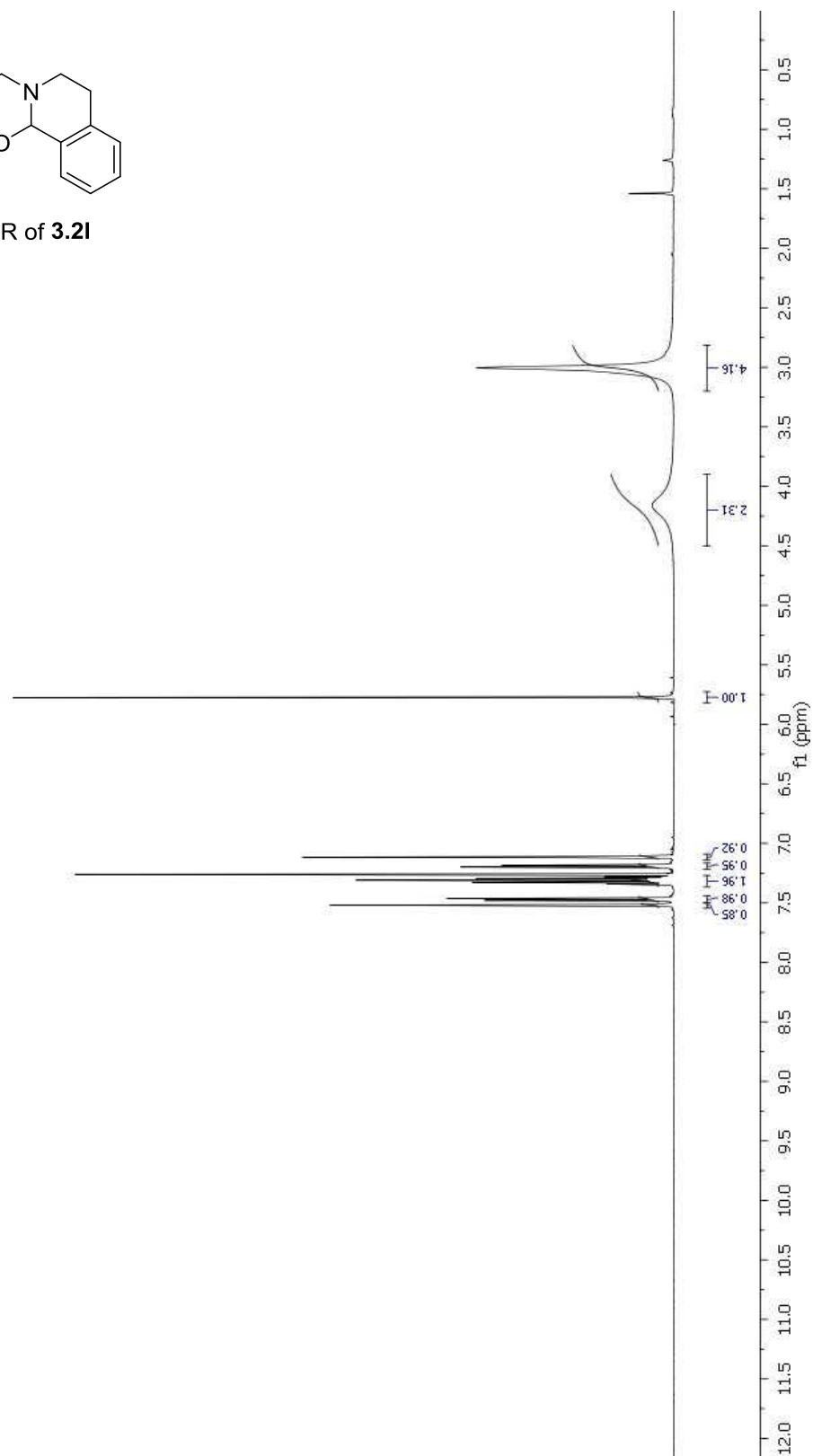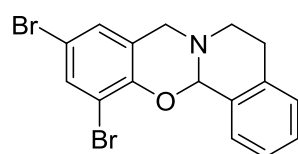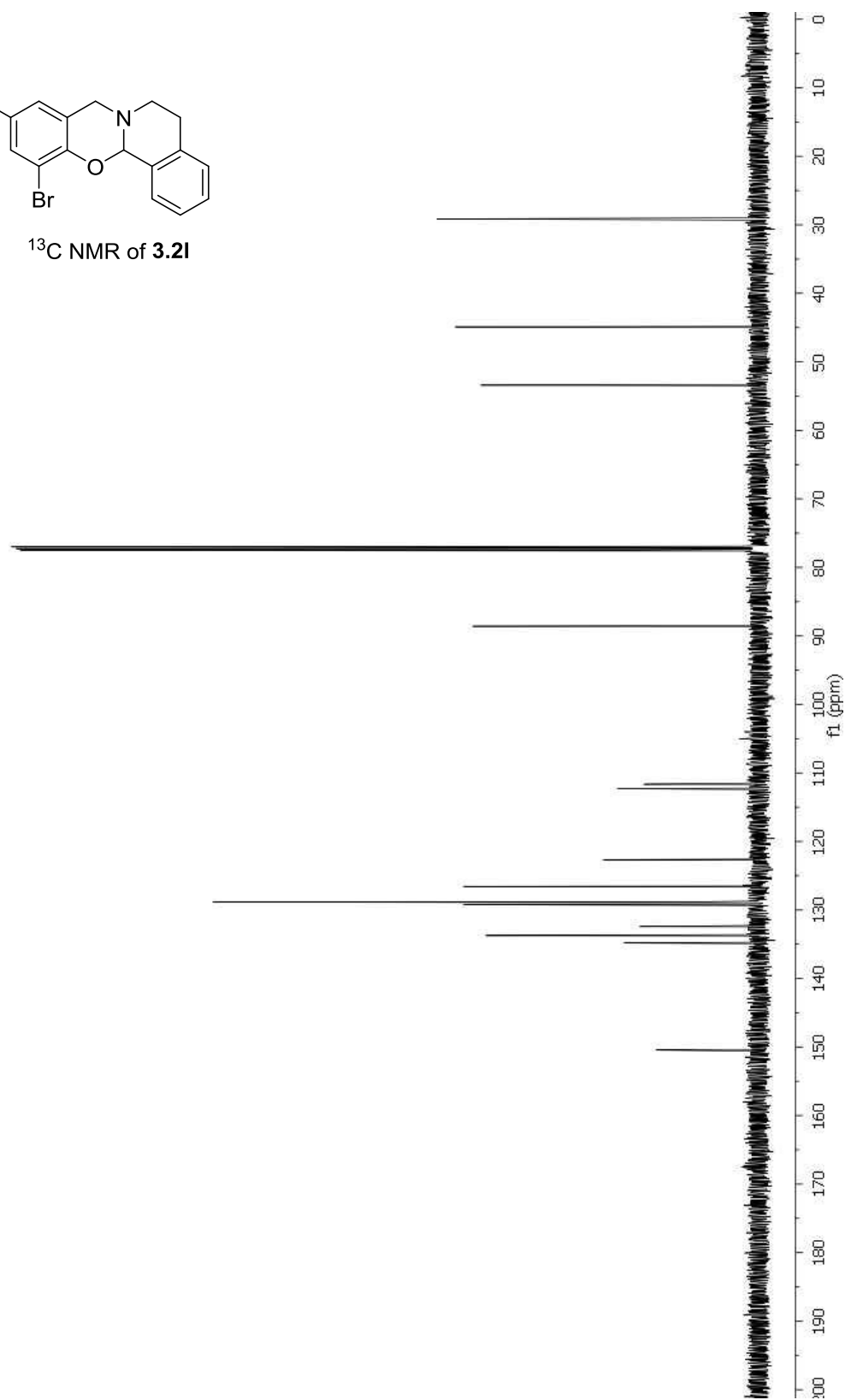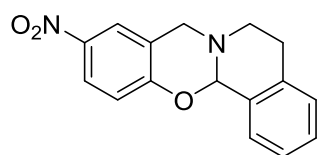
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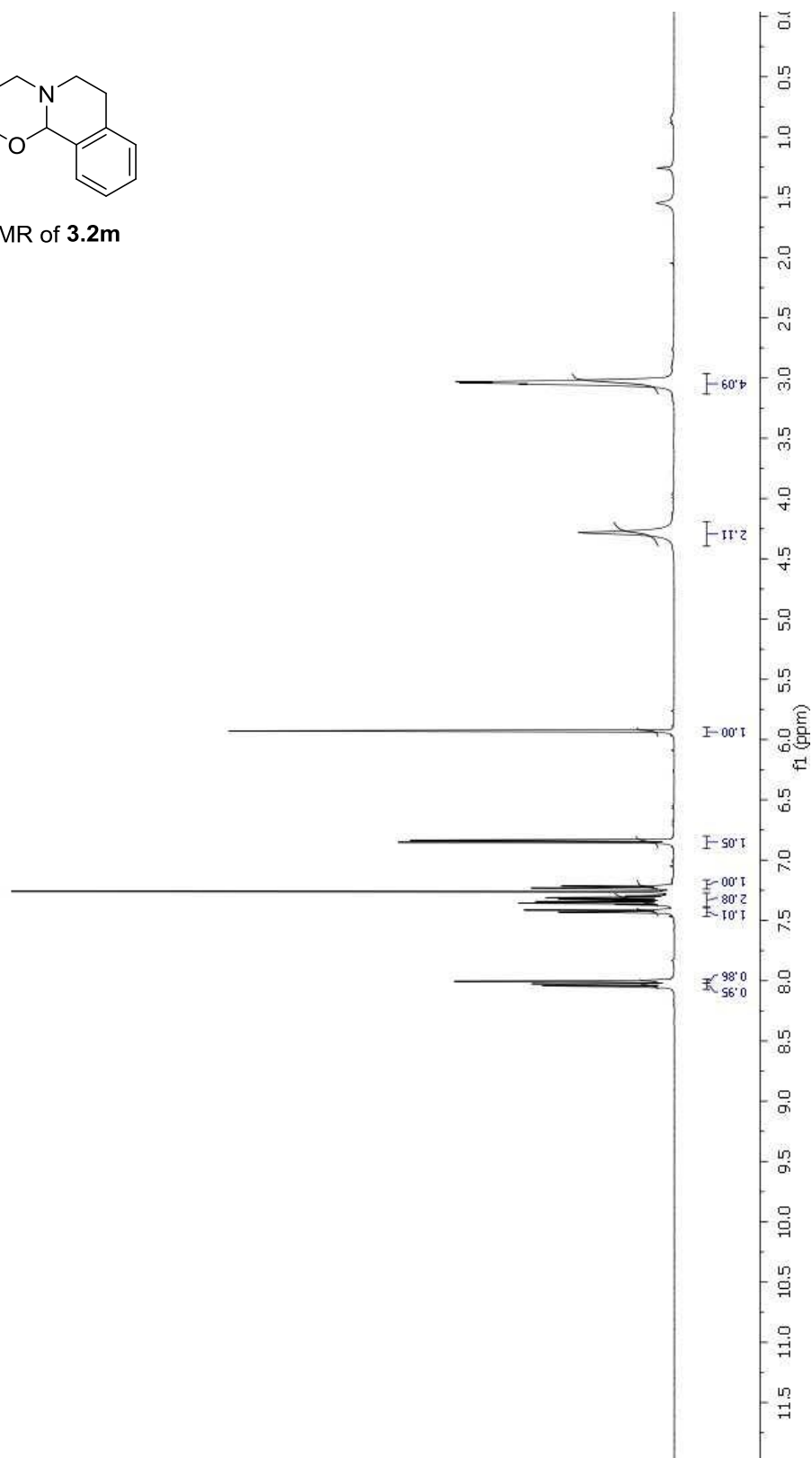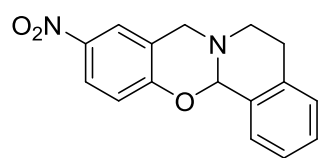
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^{13}C NMR of **3.2m**
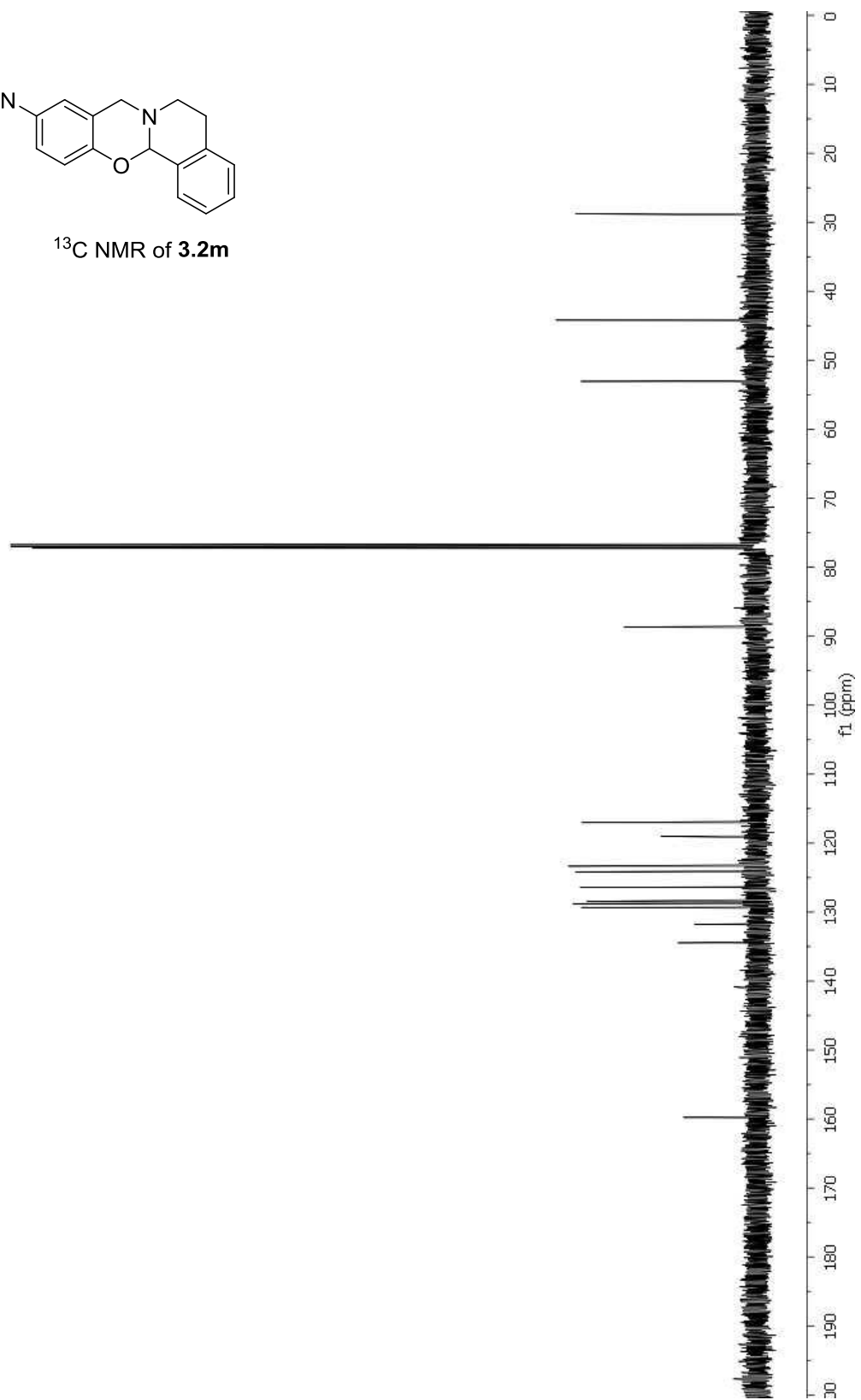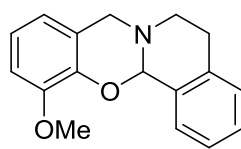
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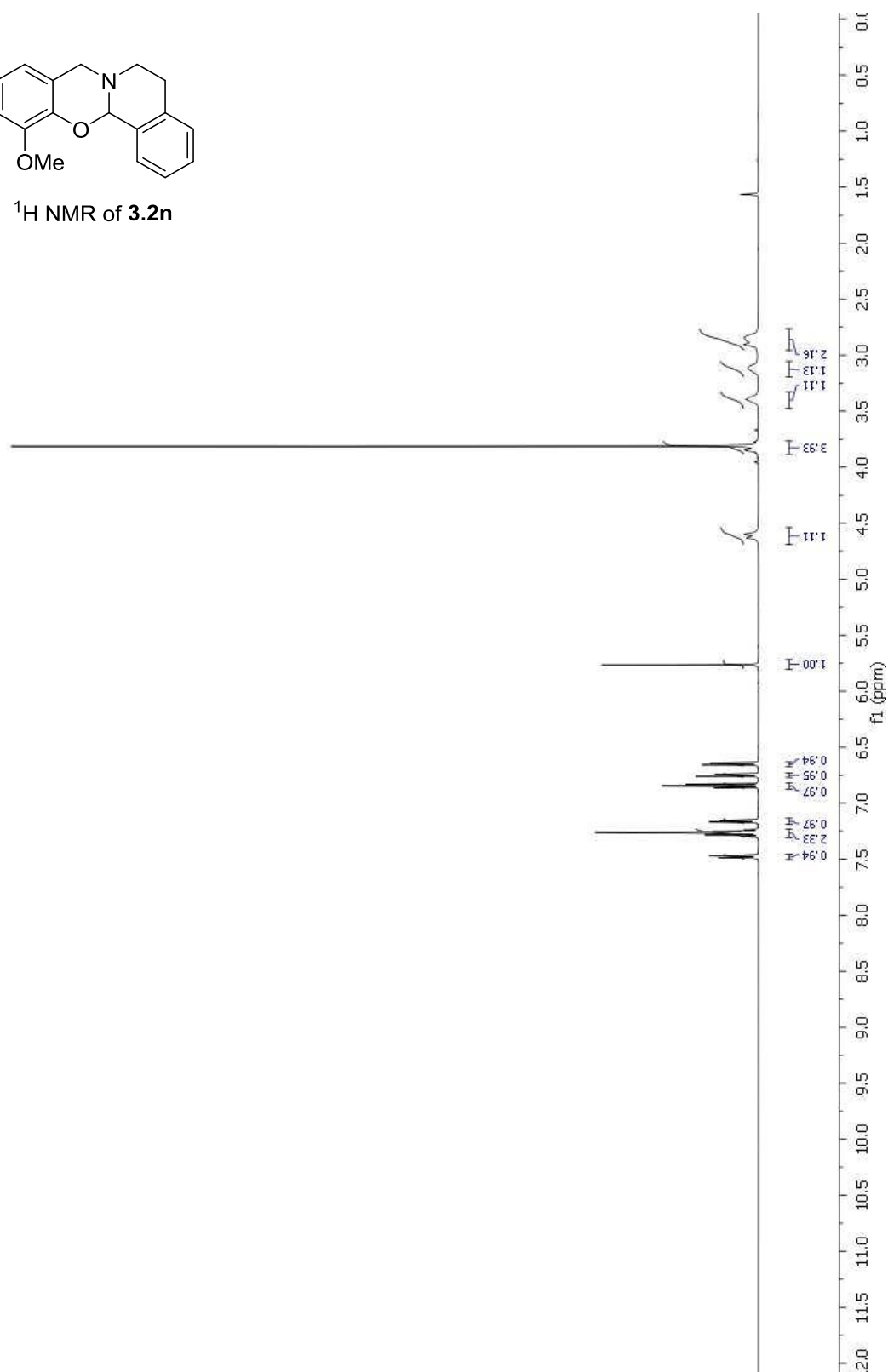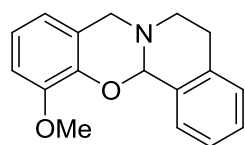
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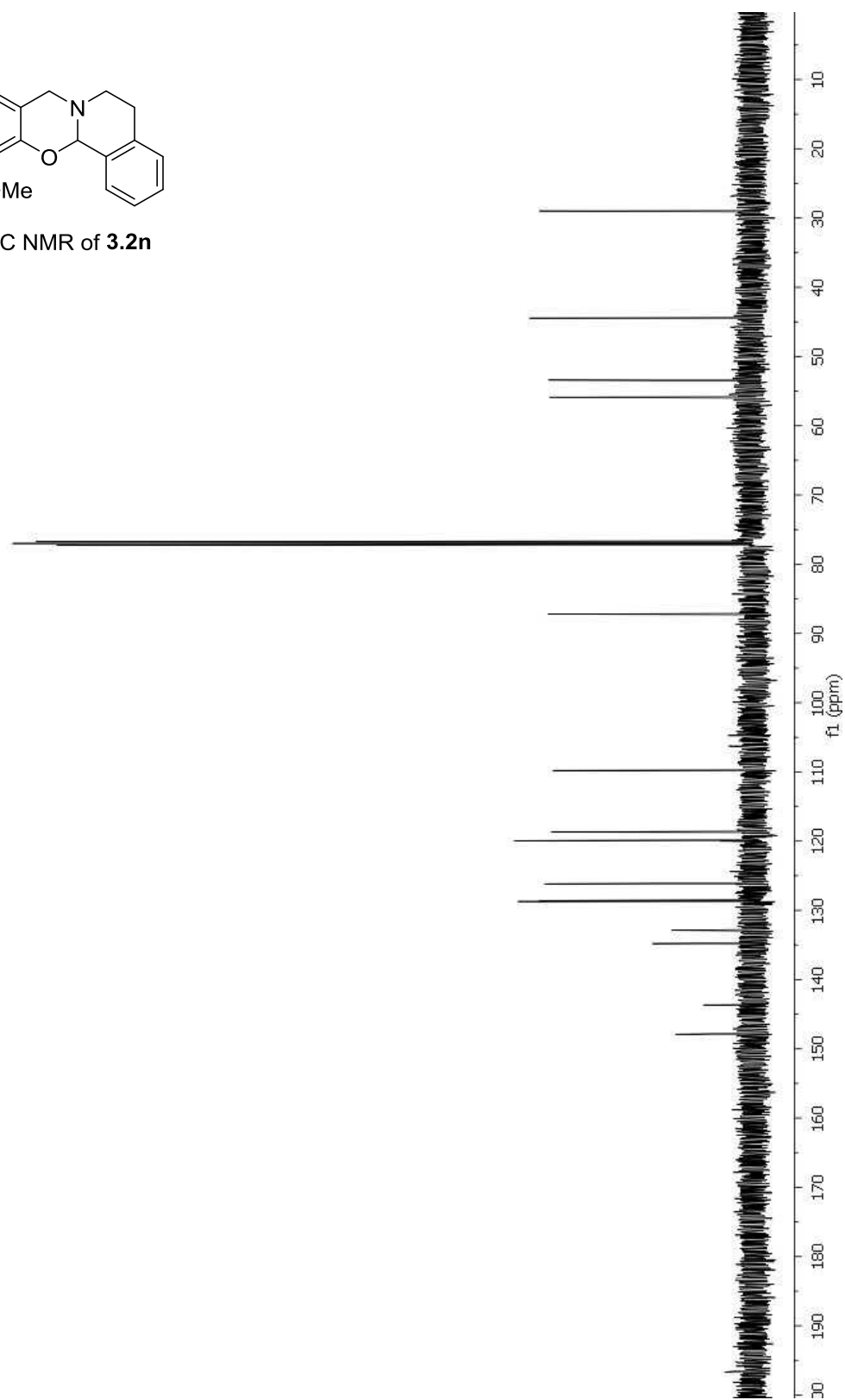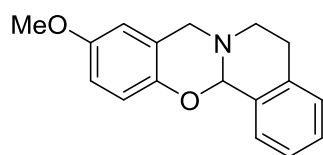
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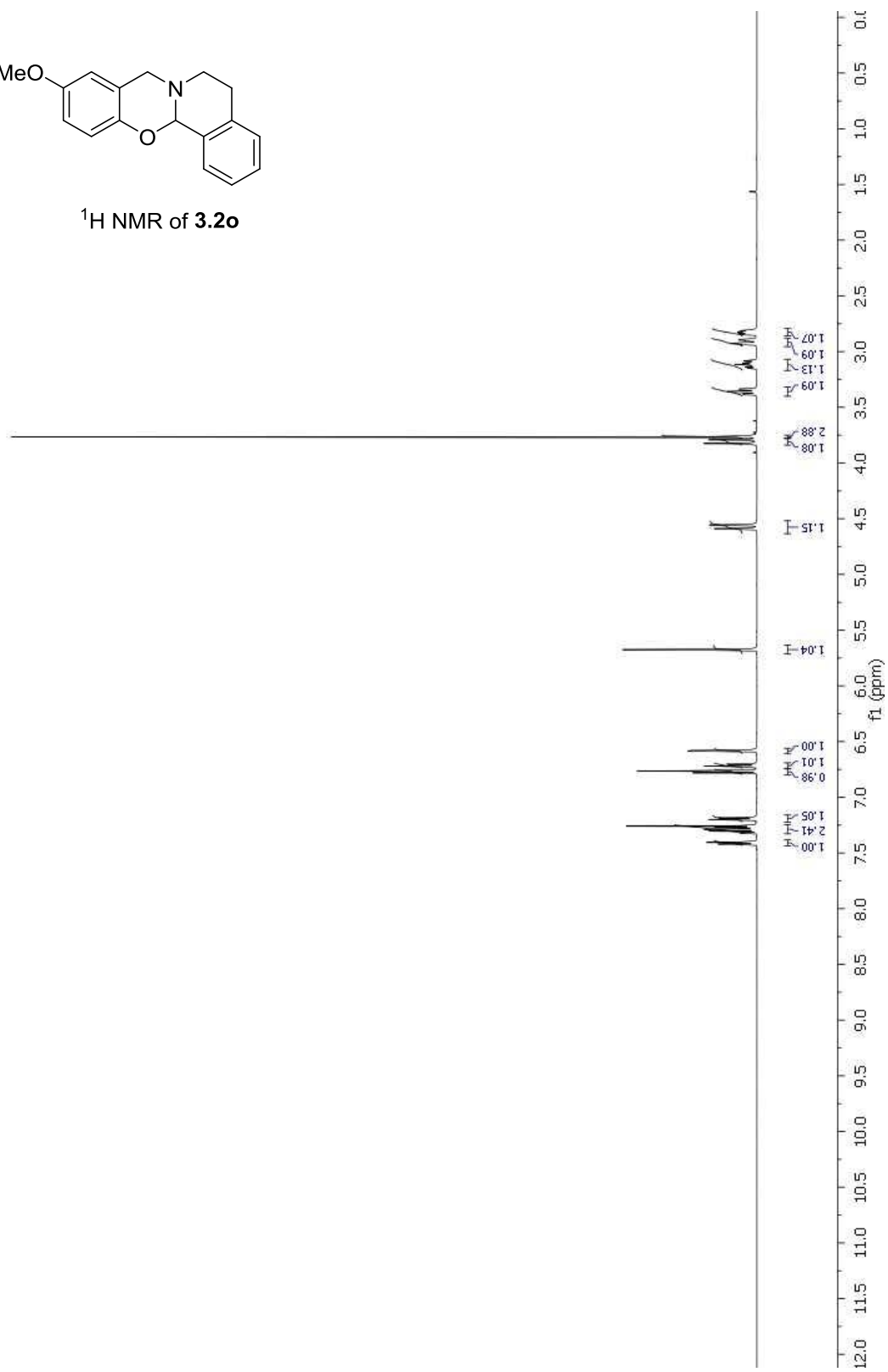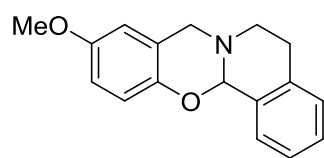
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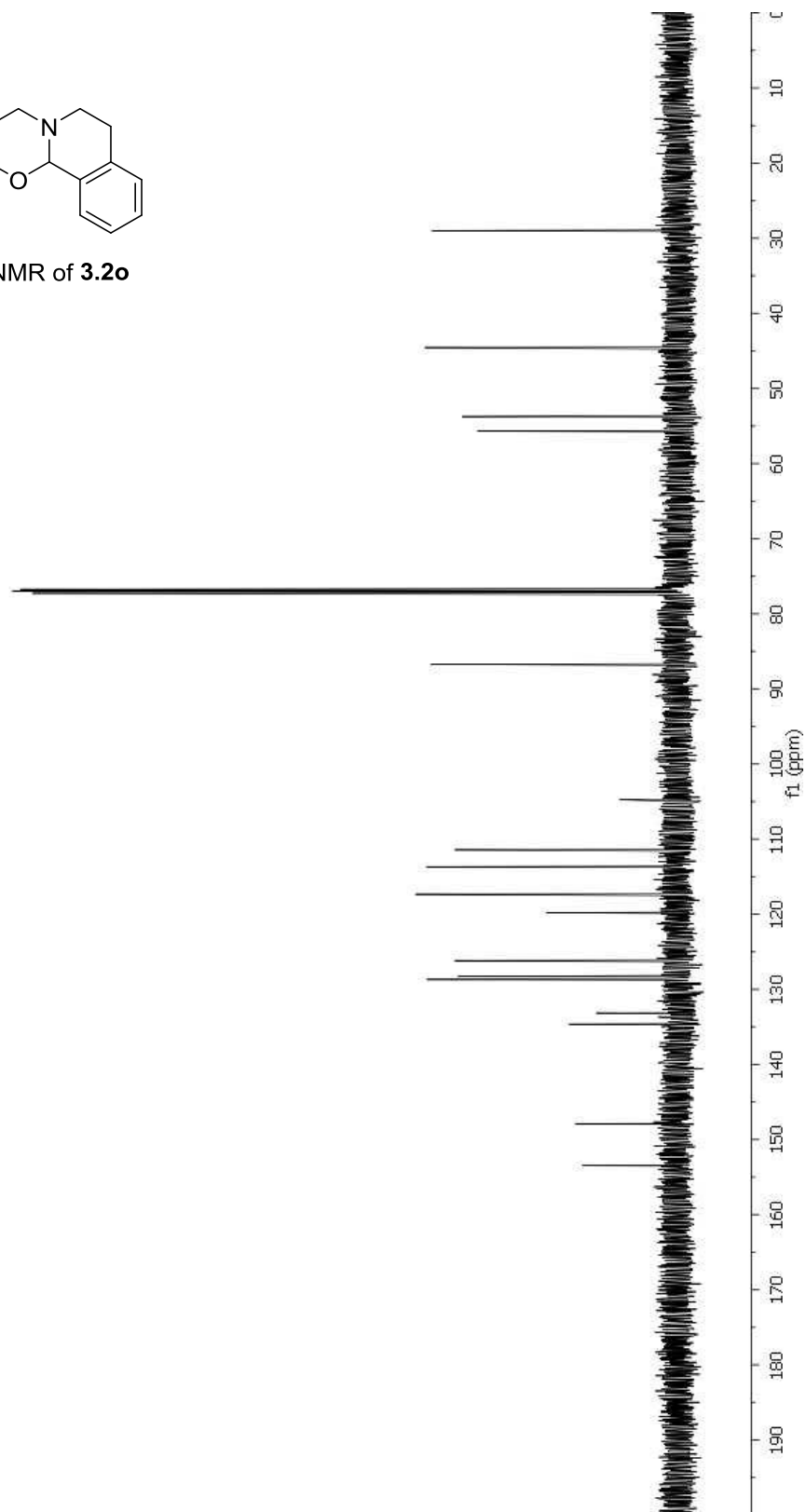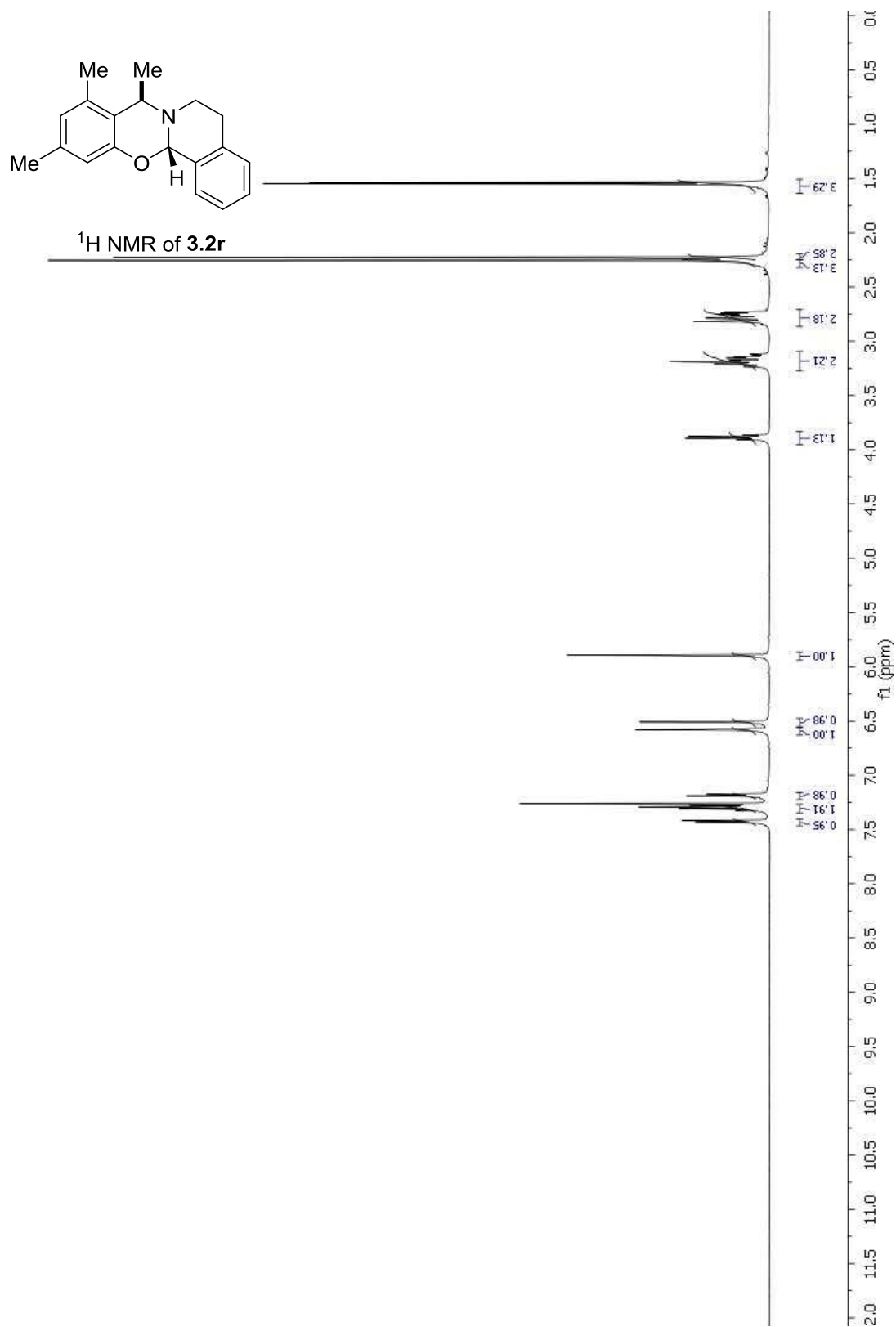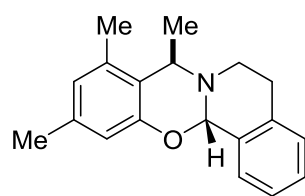
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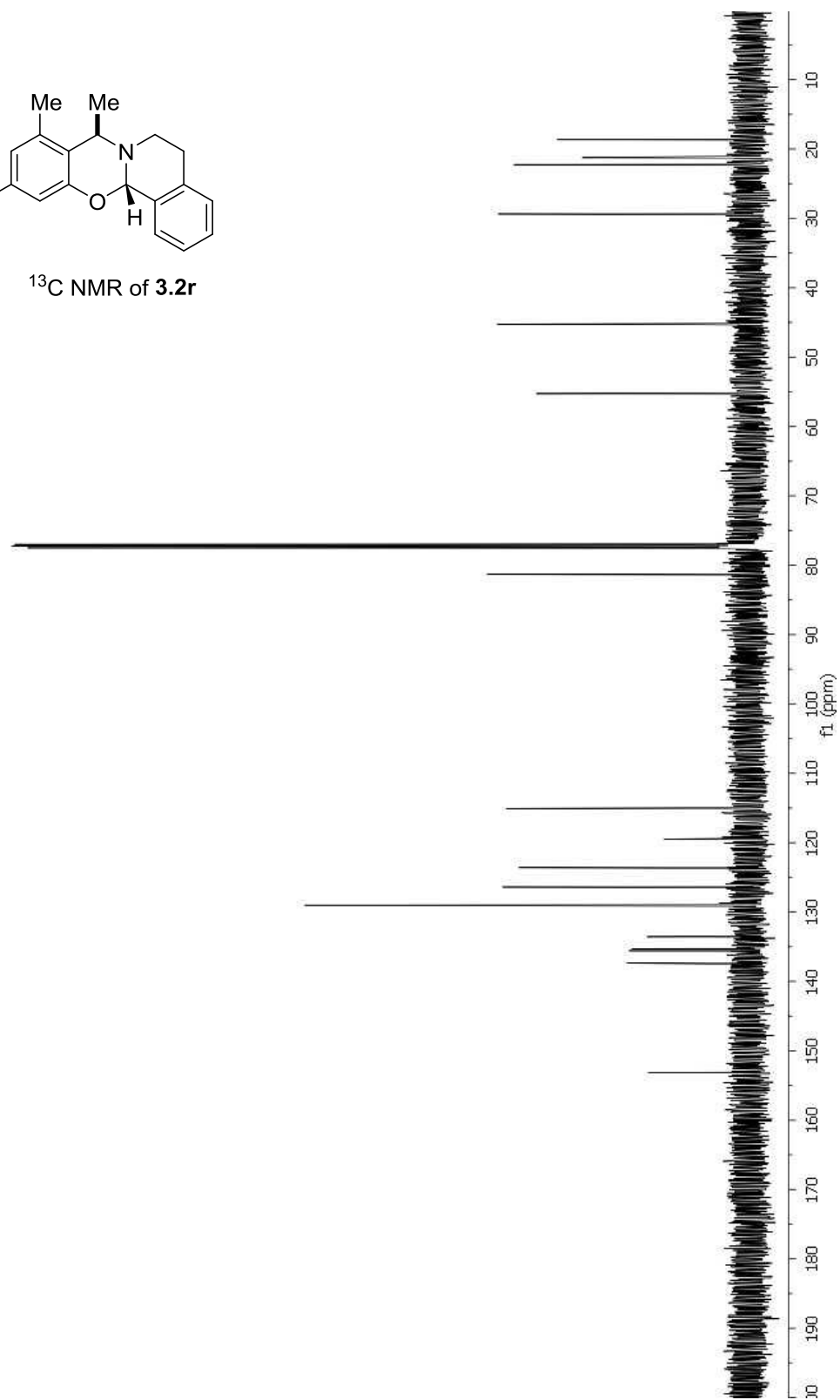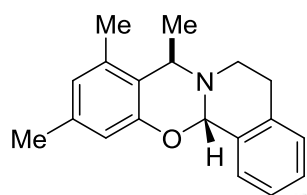
^{13}C NMR of **3.2r**

GCOSY NMR of **3.2r**
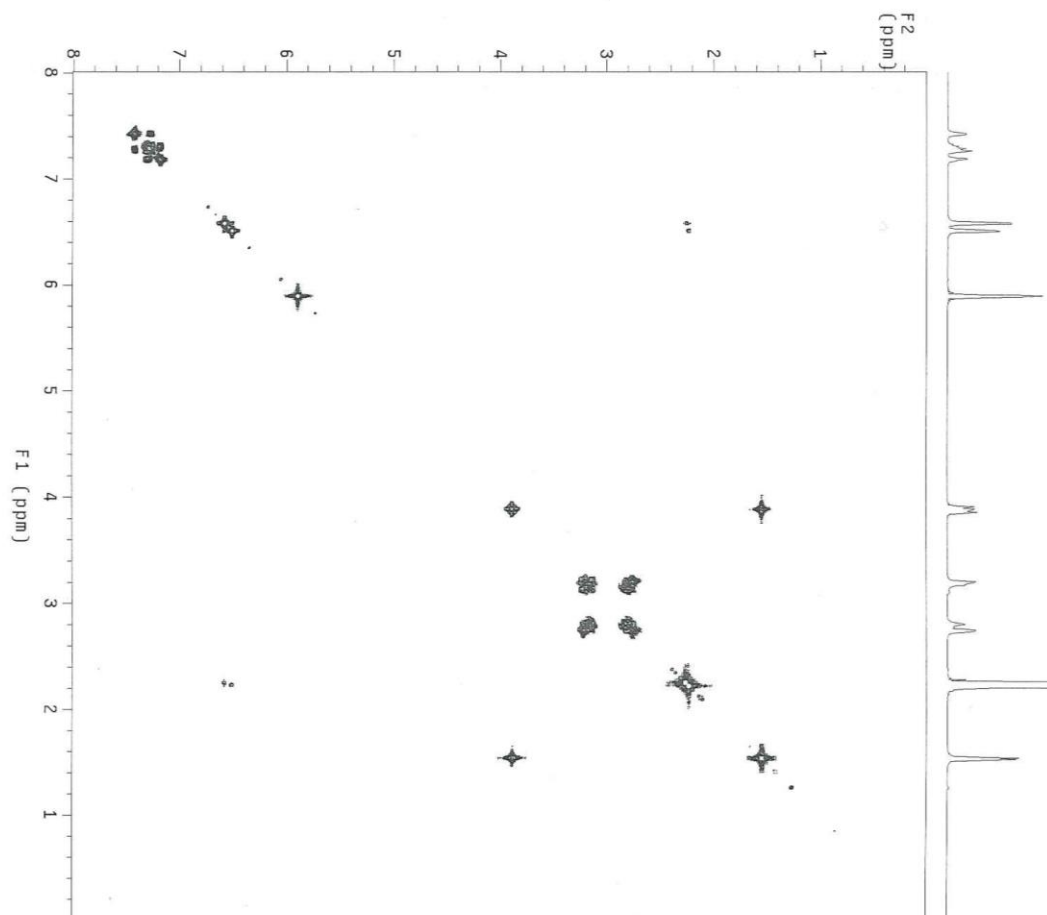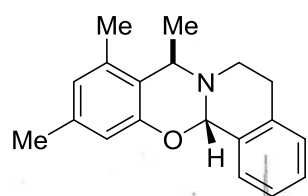
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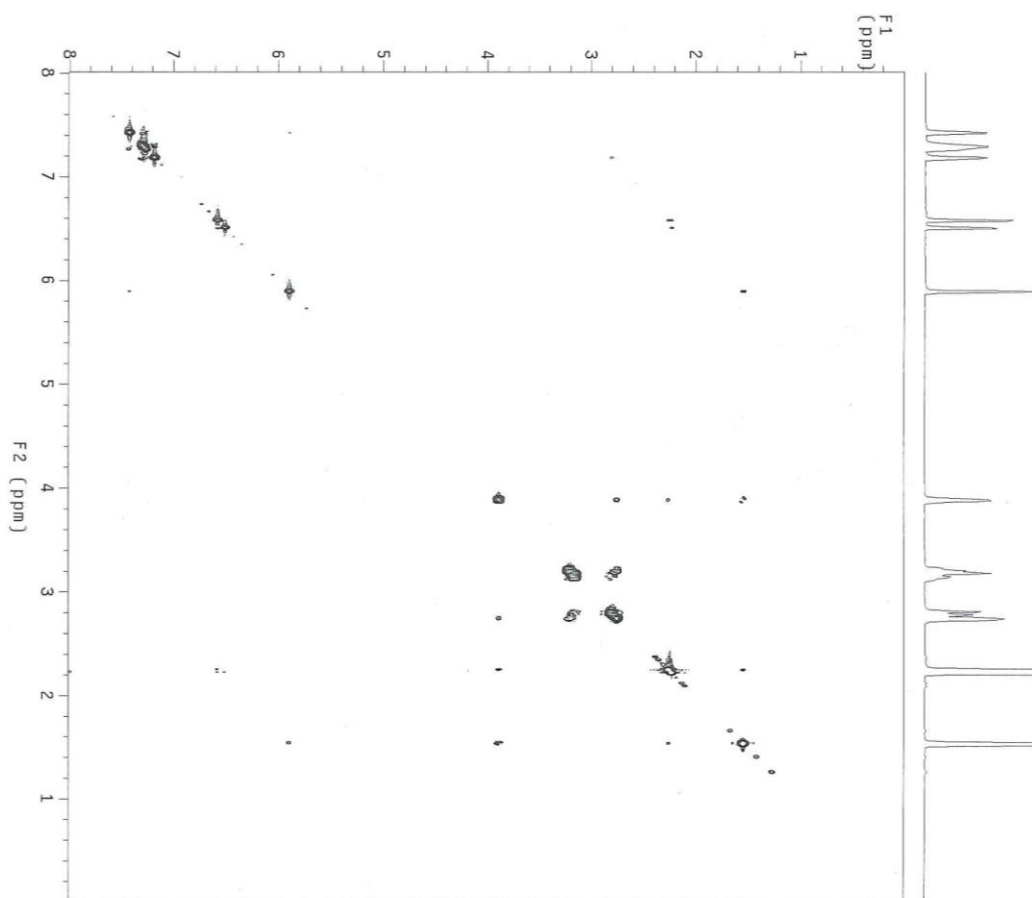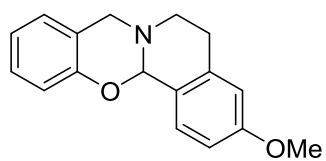
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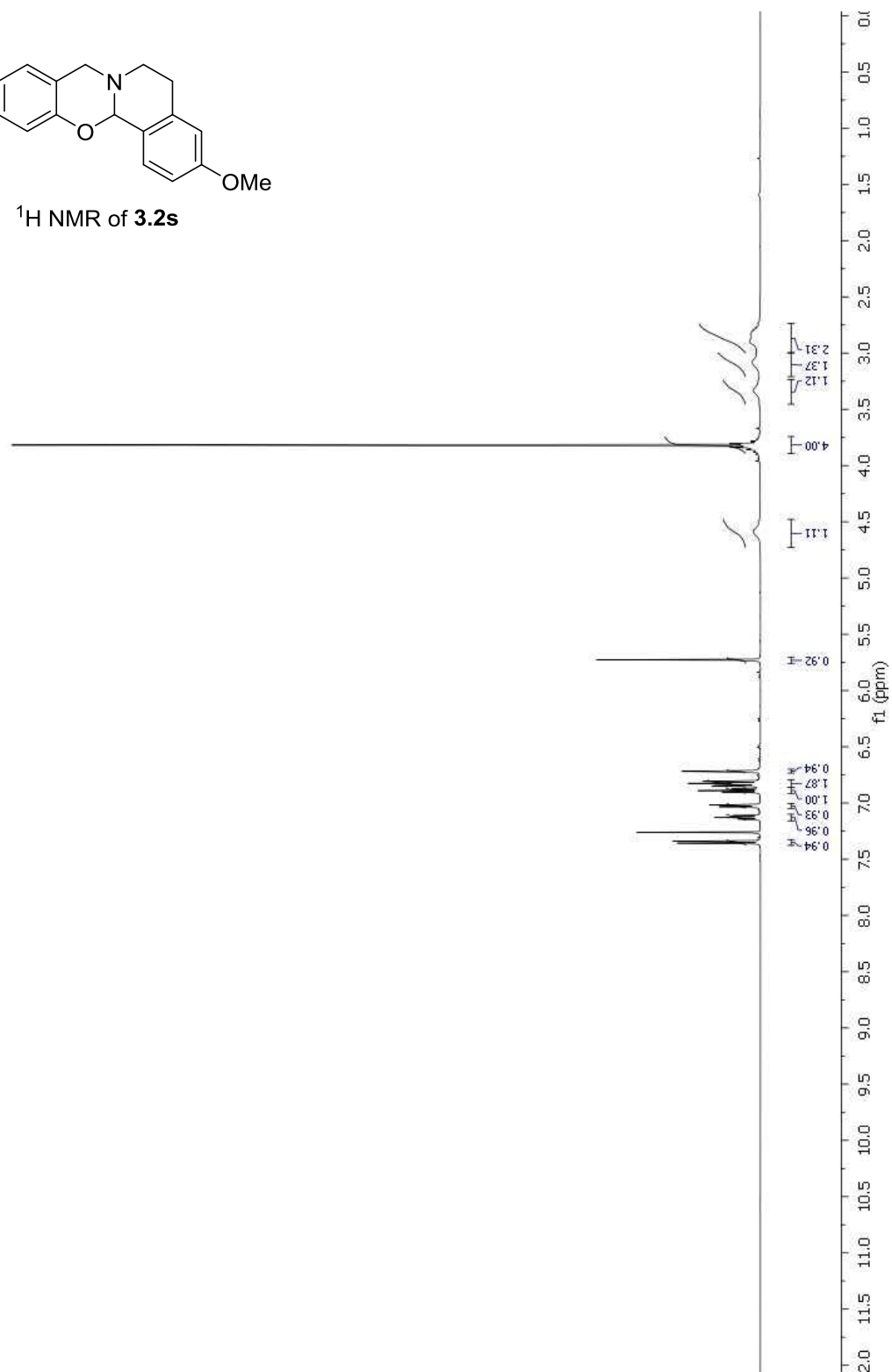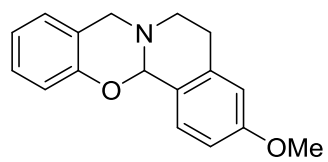
^{13}C NMR of **3.2s**

^{1}H NMR of **3.2t**

^{13}C NMR of **3.2t**

^{1}H NMR of **3.2u**
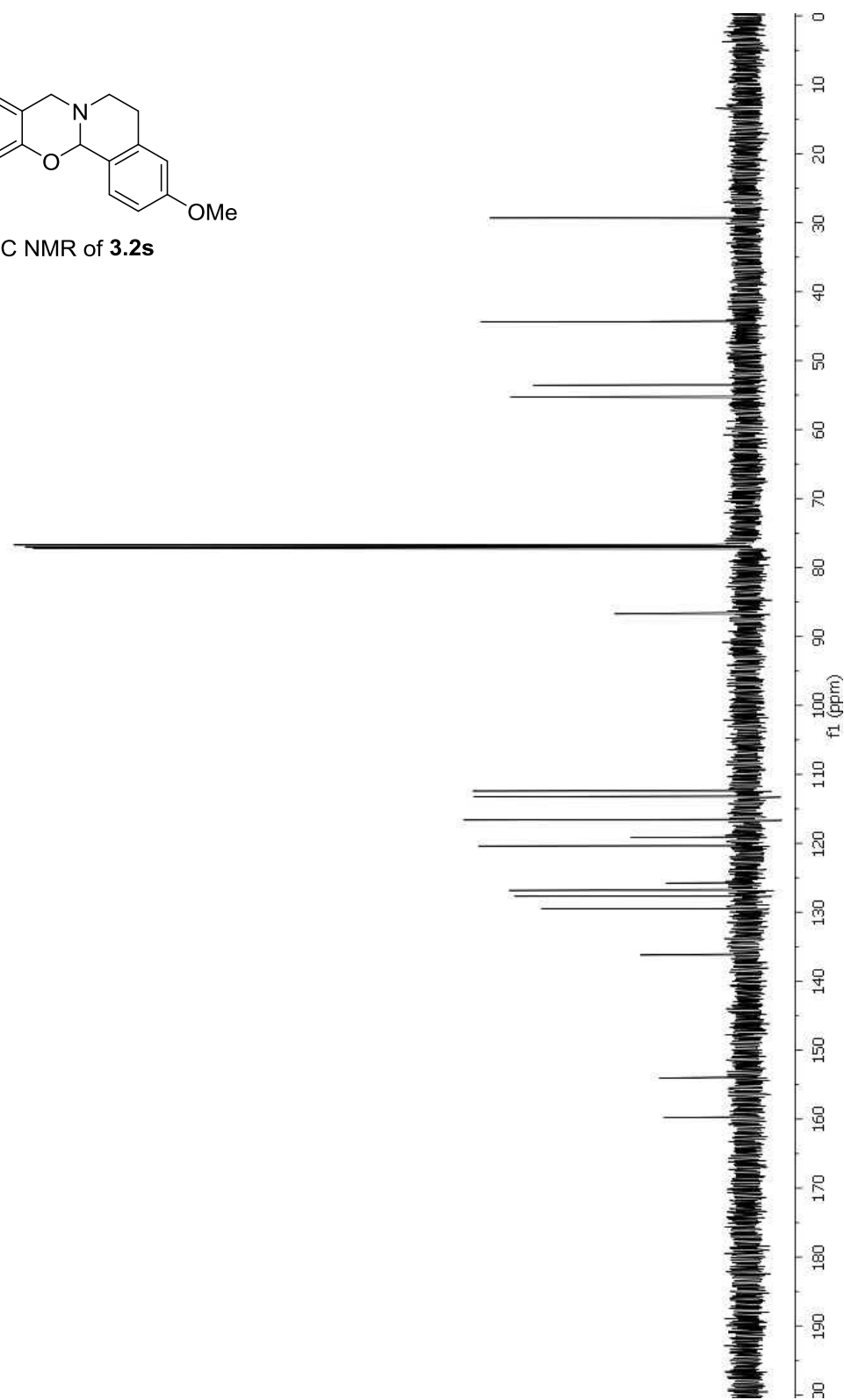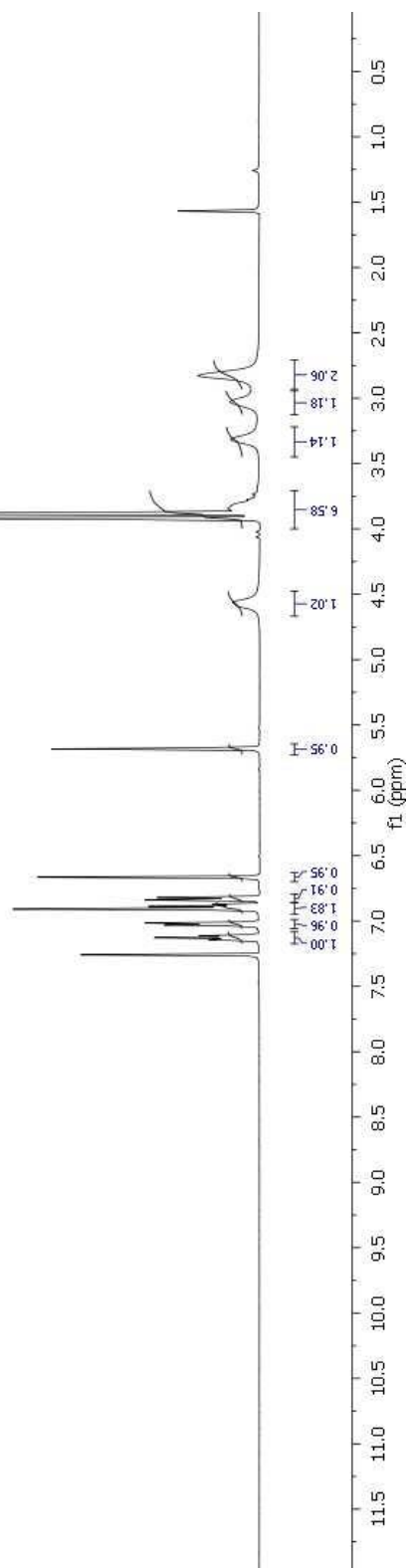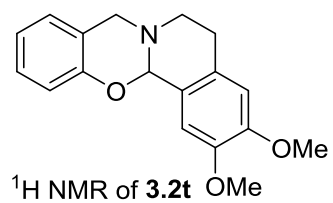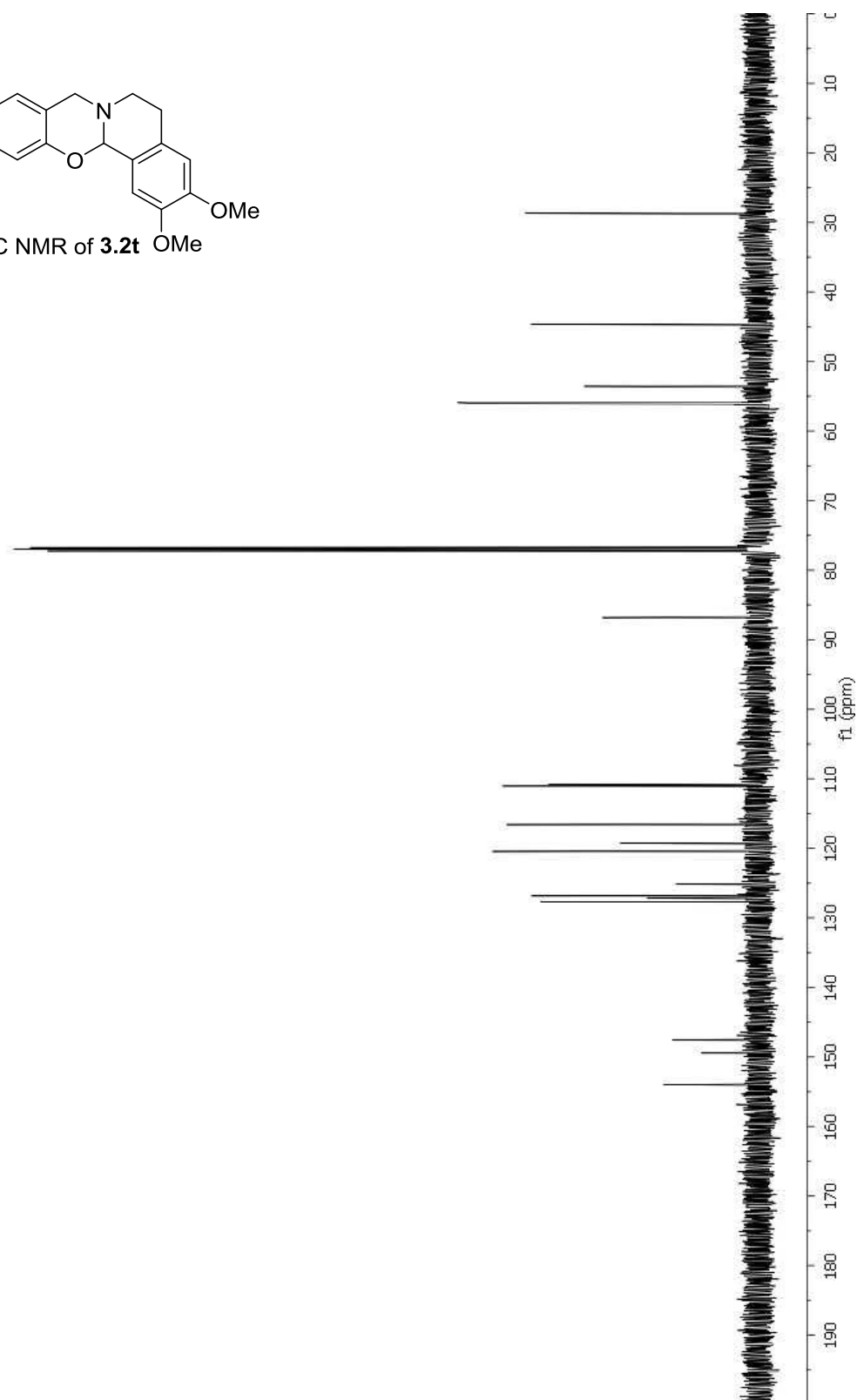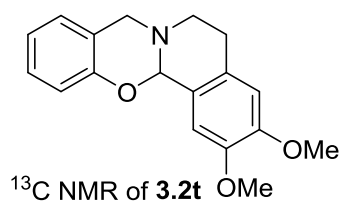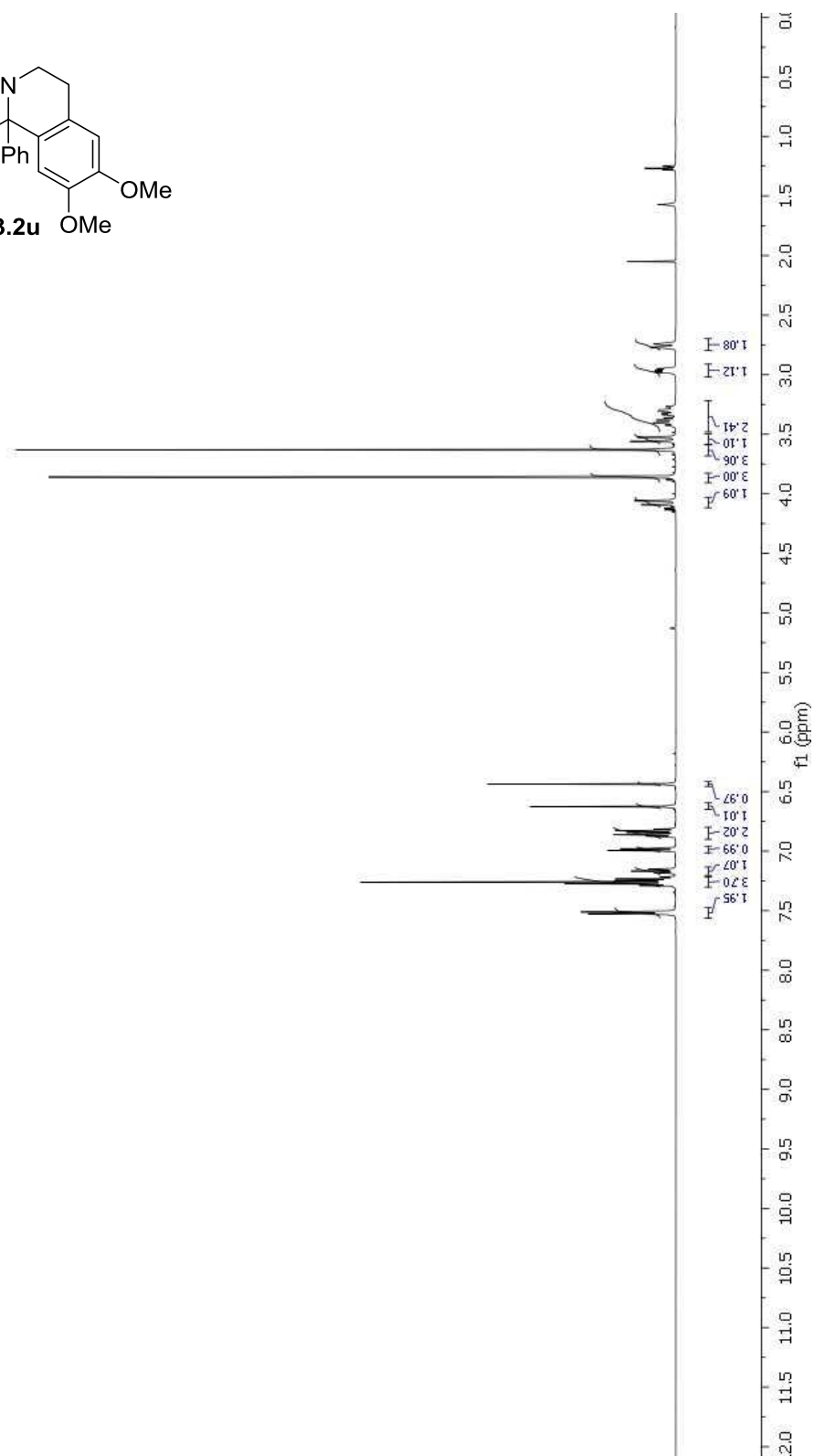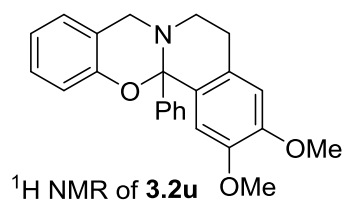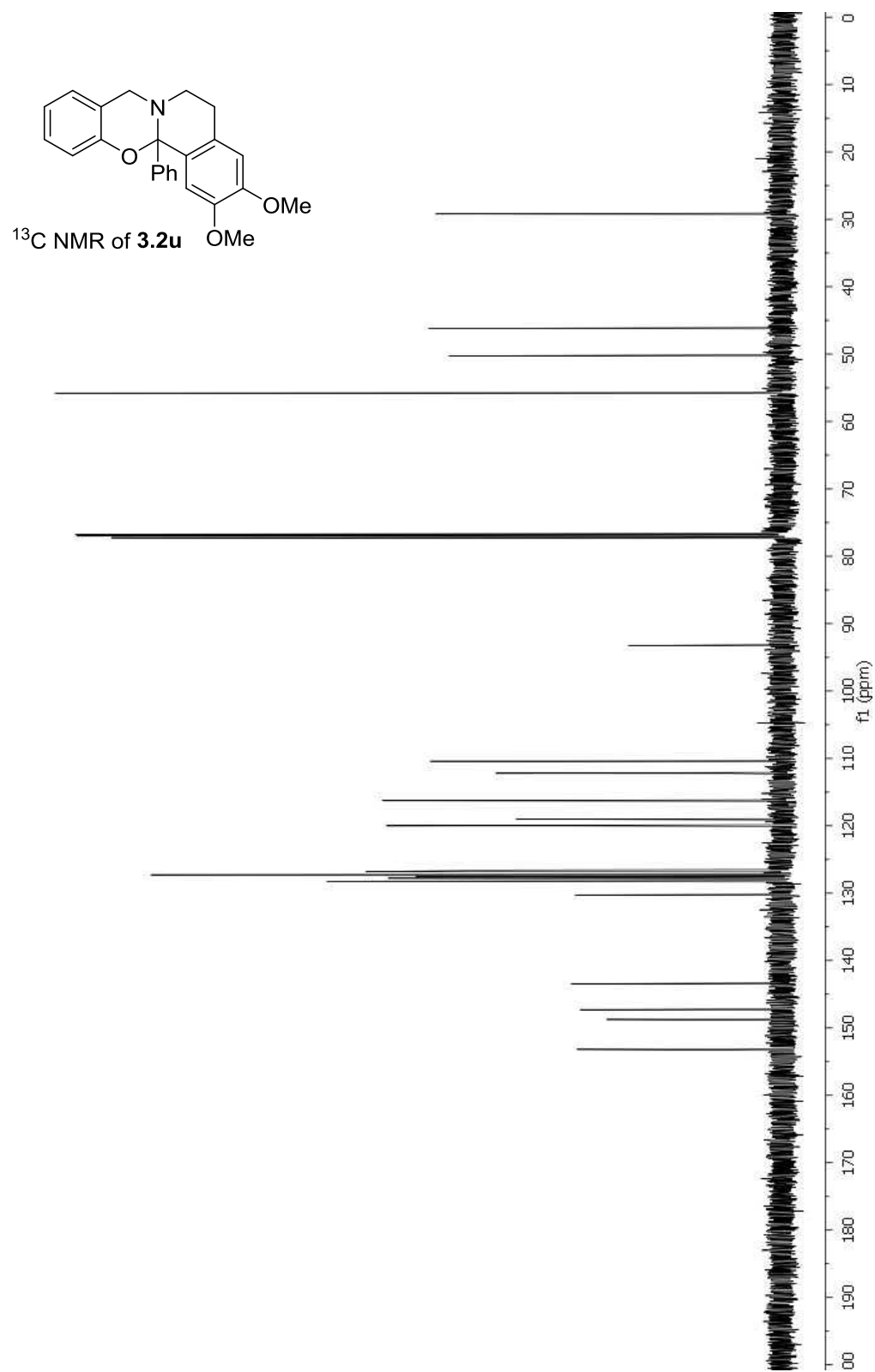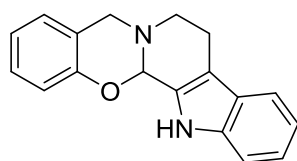
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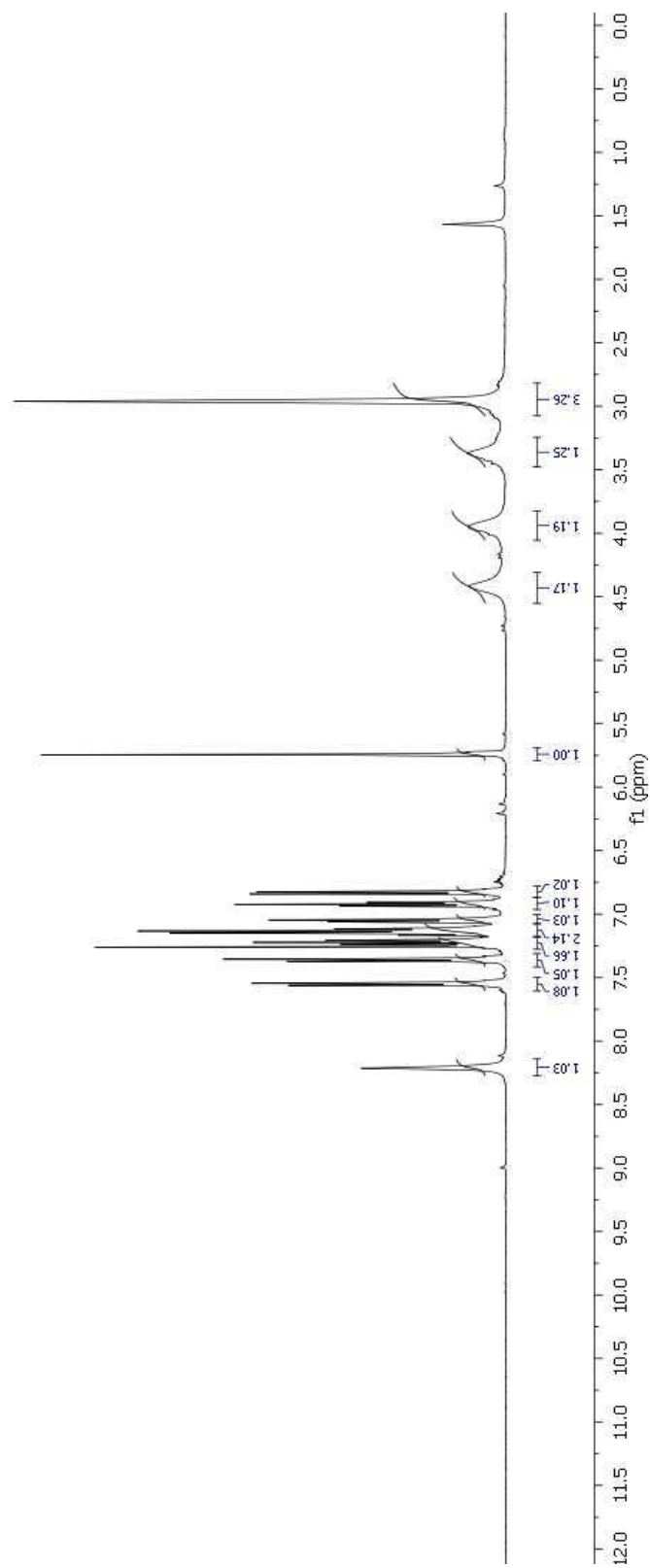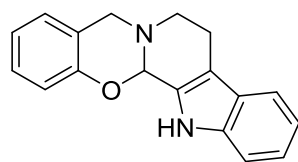
^{1}H NMR of **3.2v**

^{13}C NMR of **3.2v**
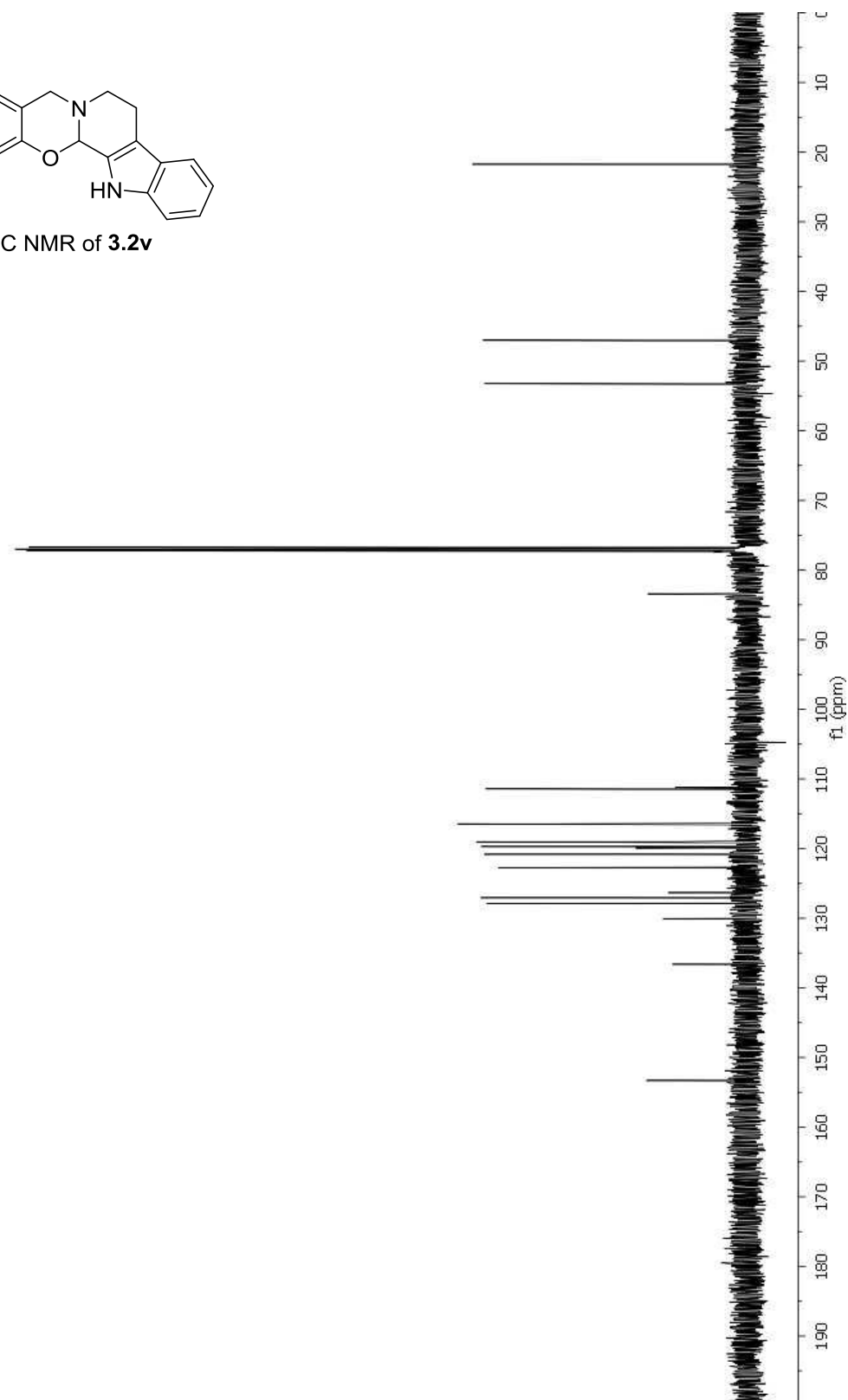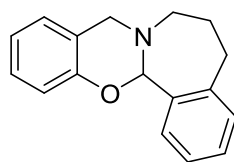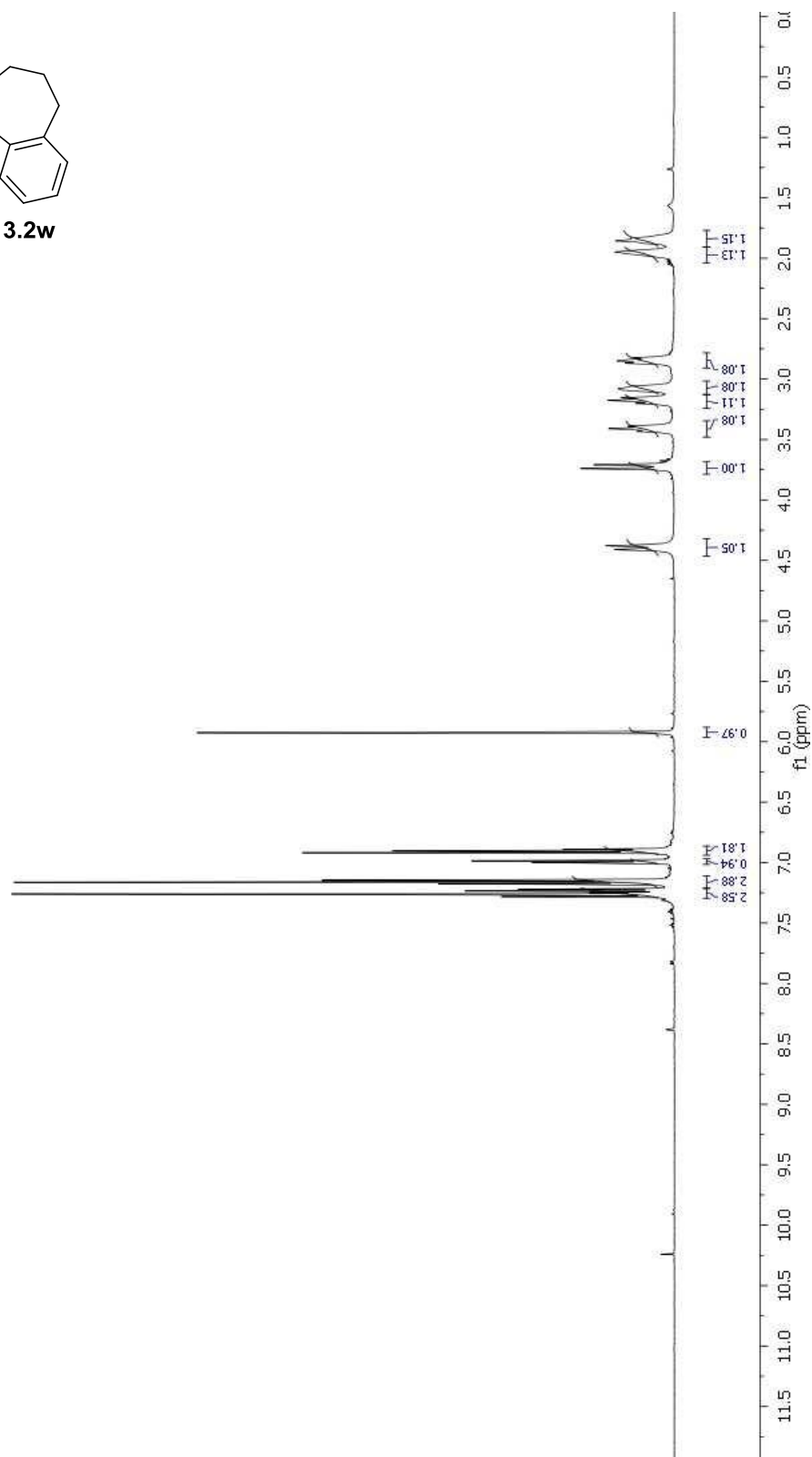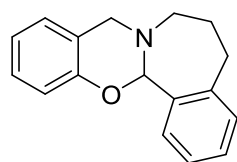
^{1}H NMR of **3.2w**

^{13}C NMR of **3.2w**
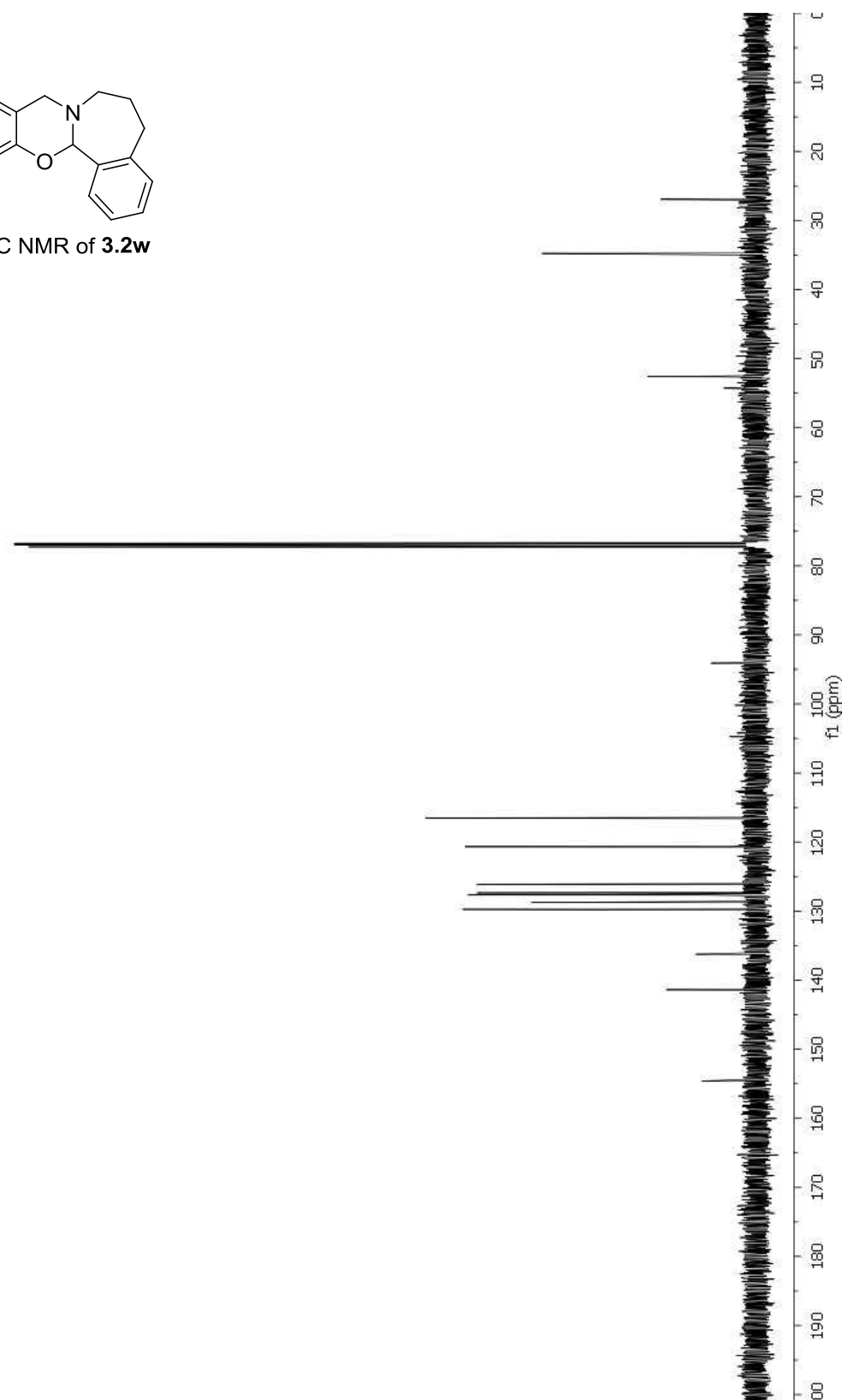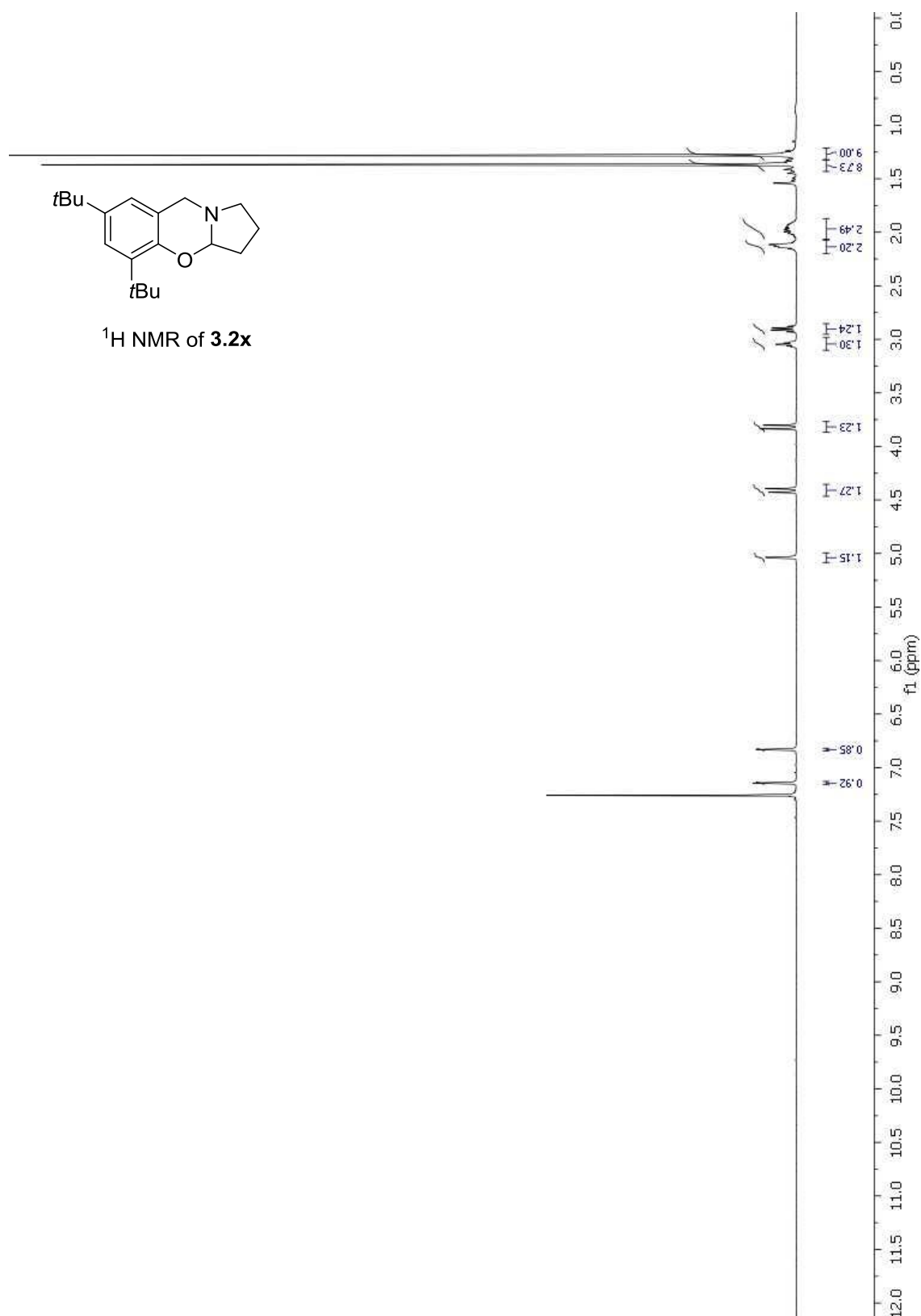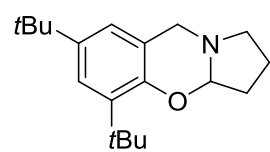
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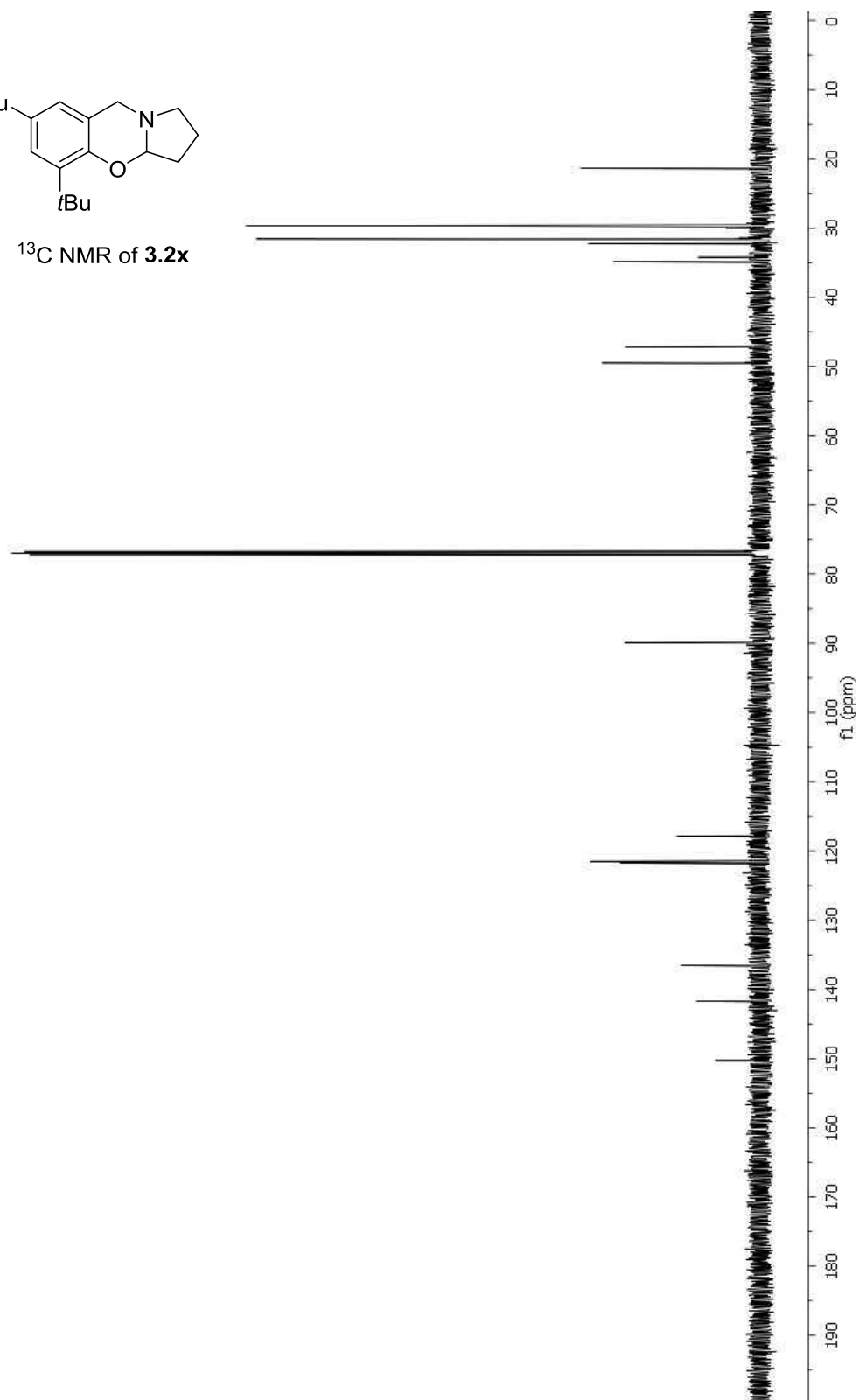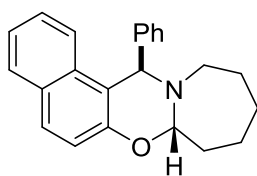
^{13}C NMR of **3.2x**

¹H NMR of **3.2z**
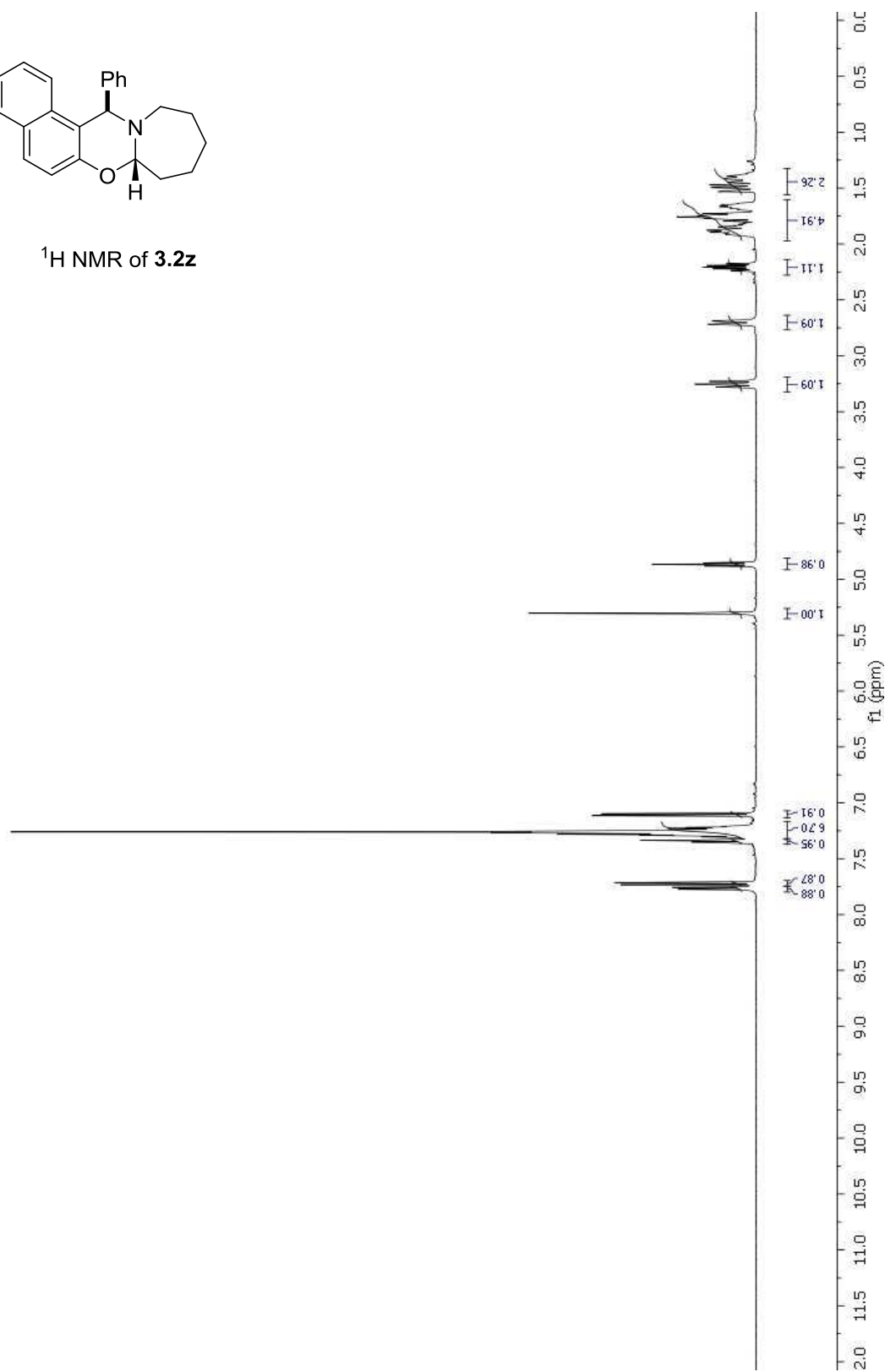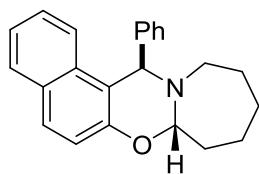
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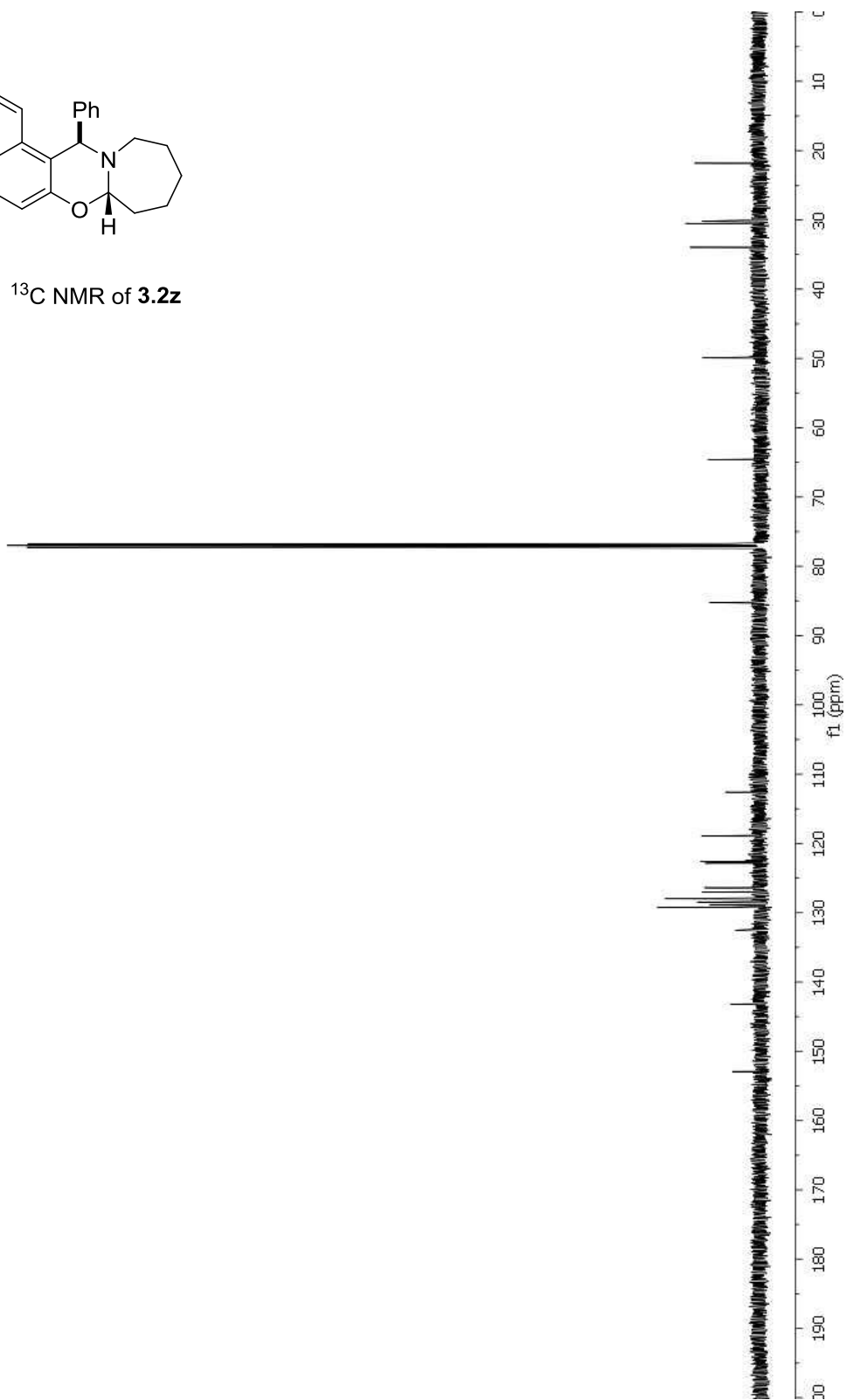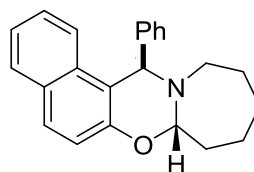
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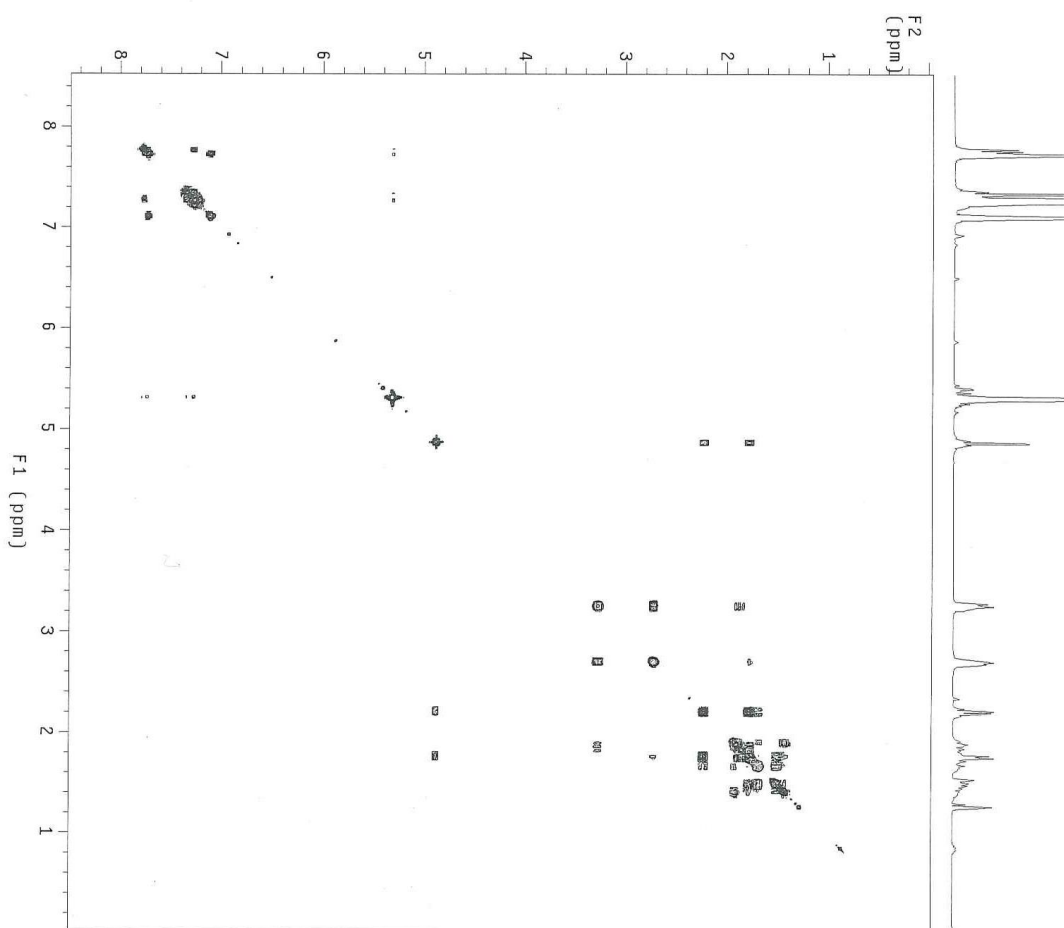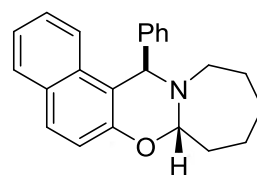
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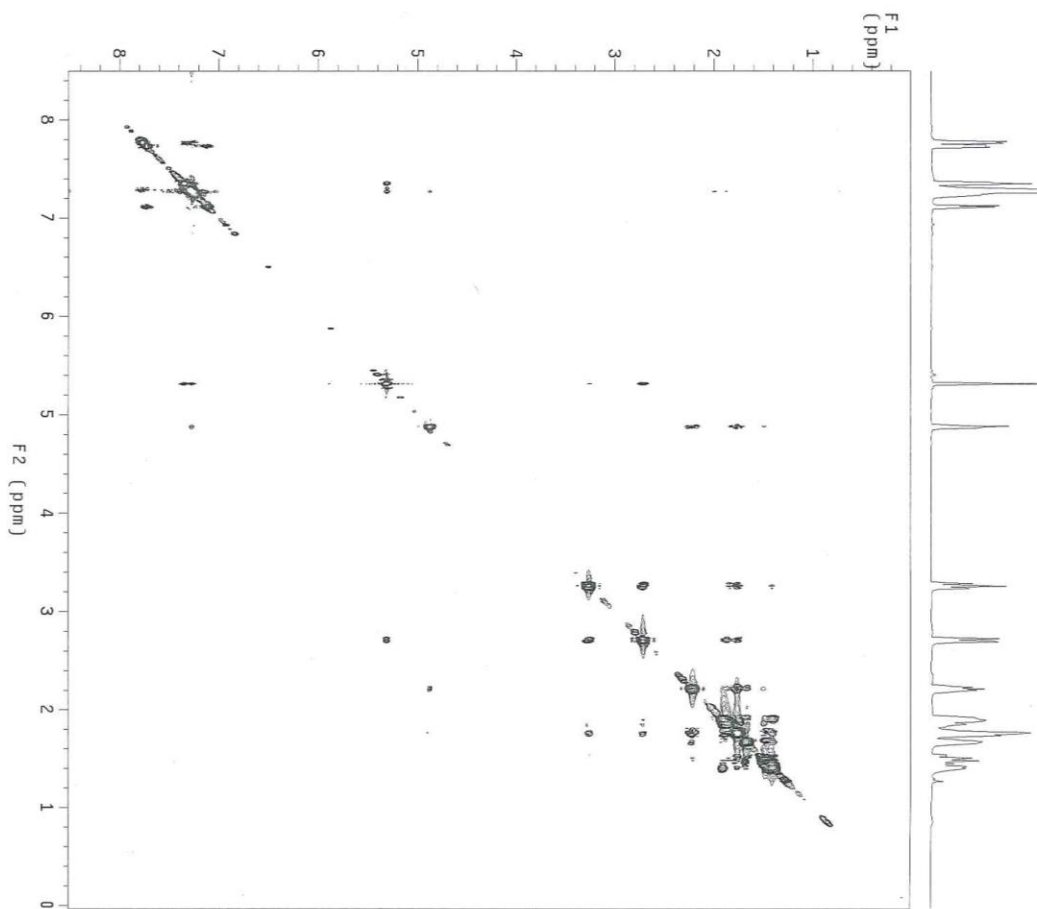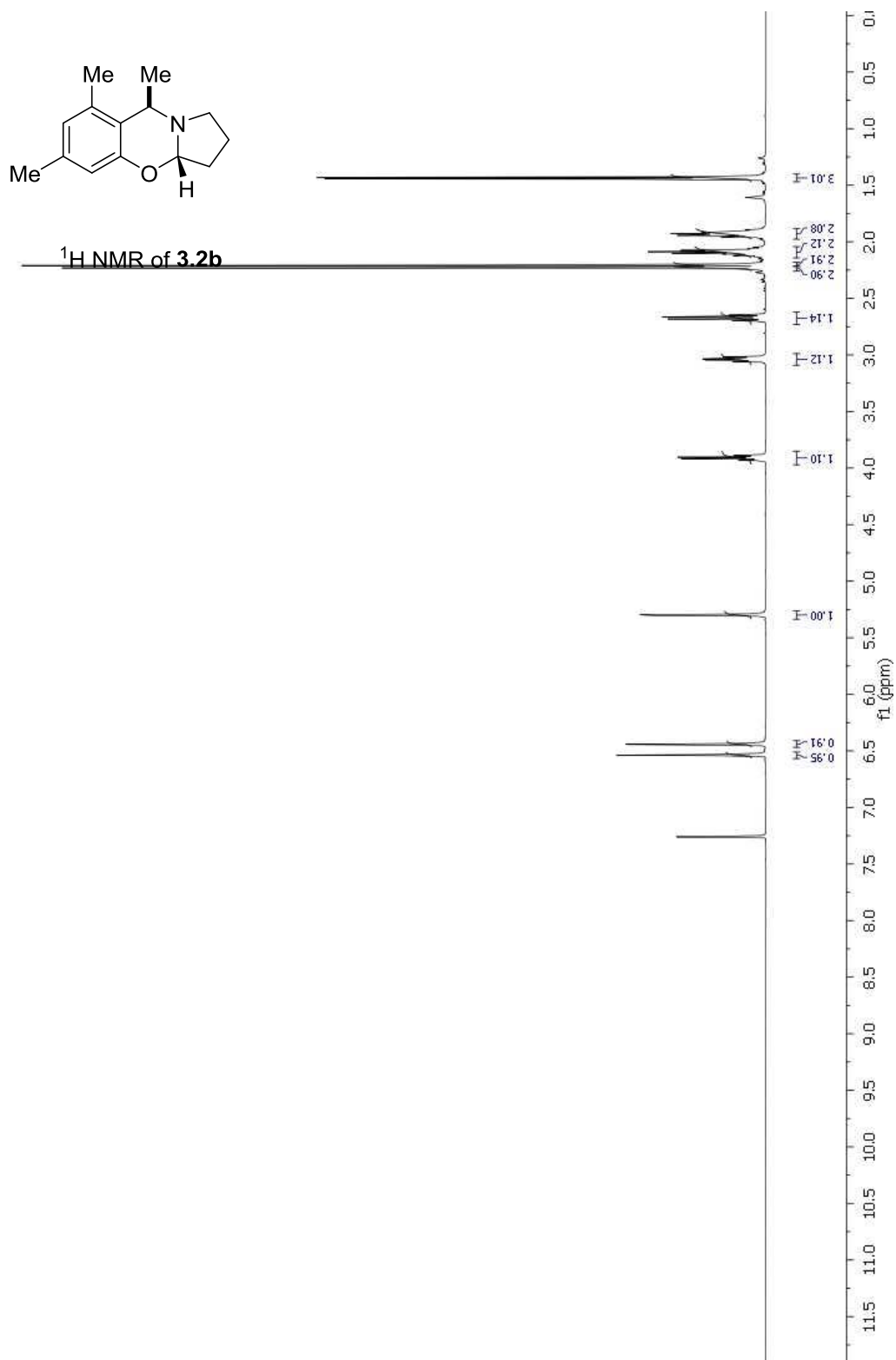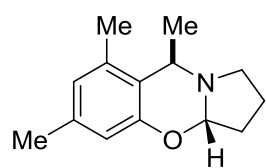
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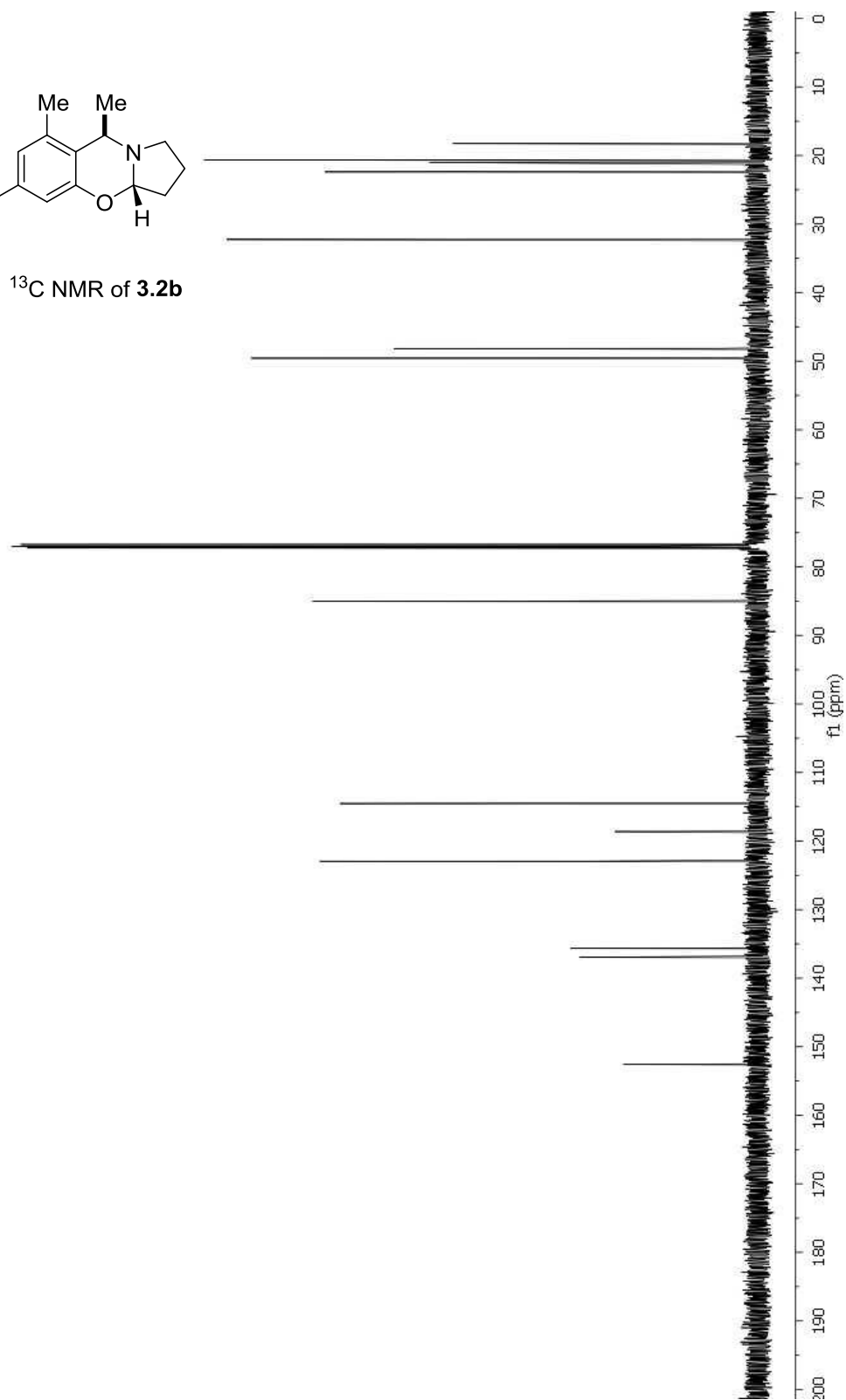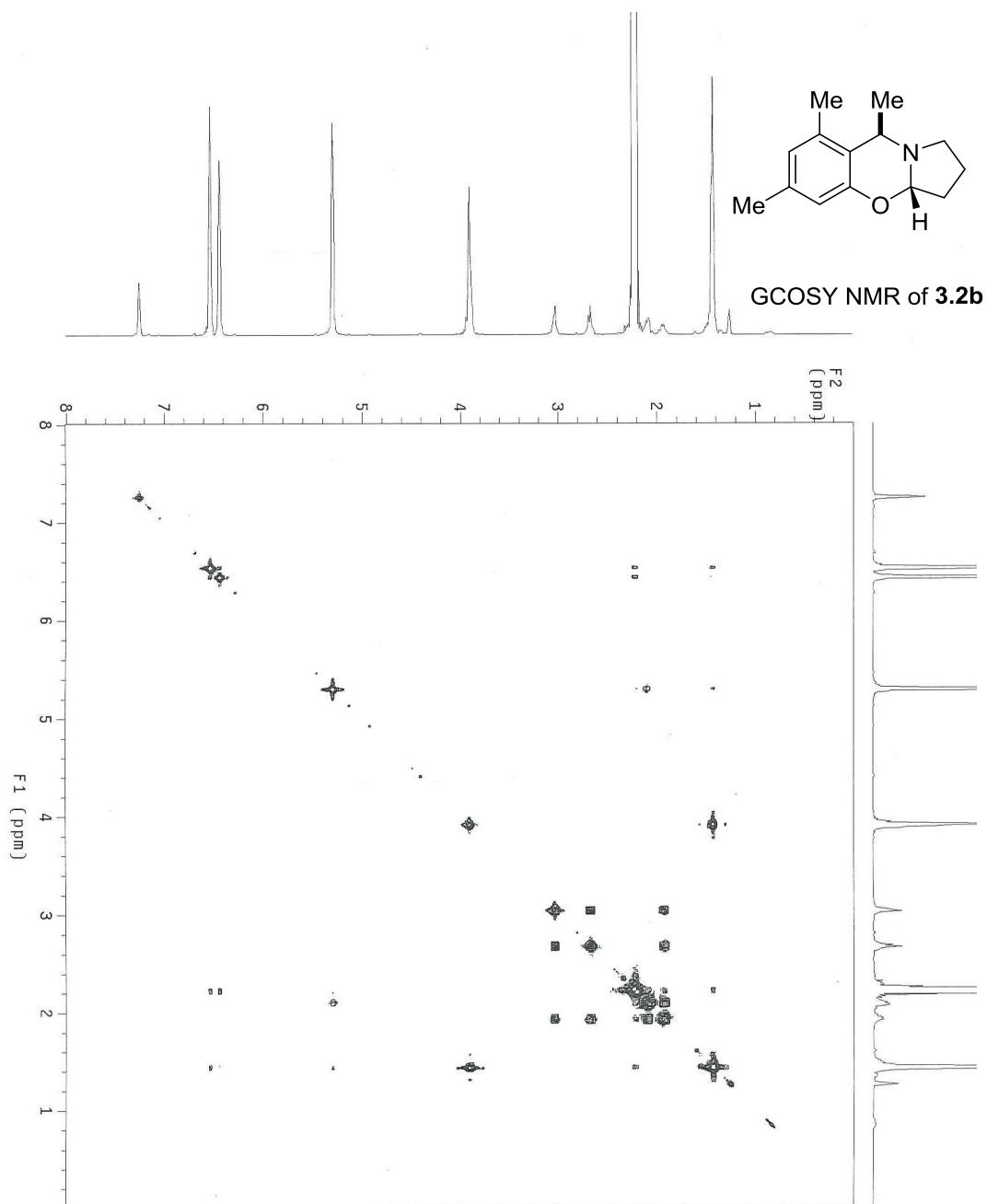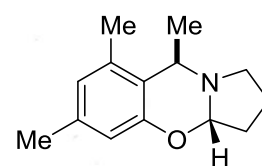
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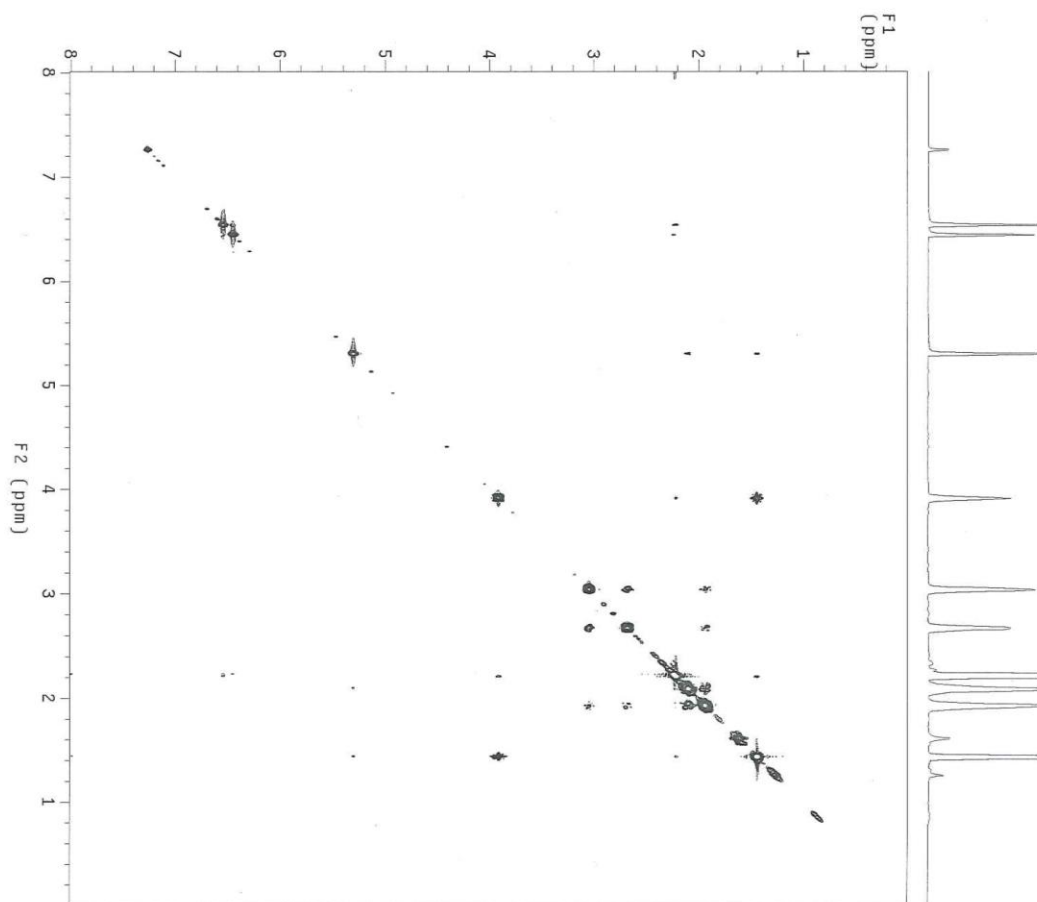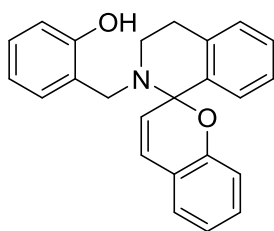
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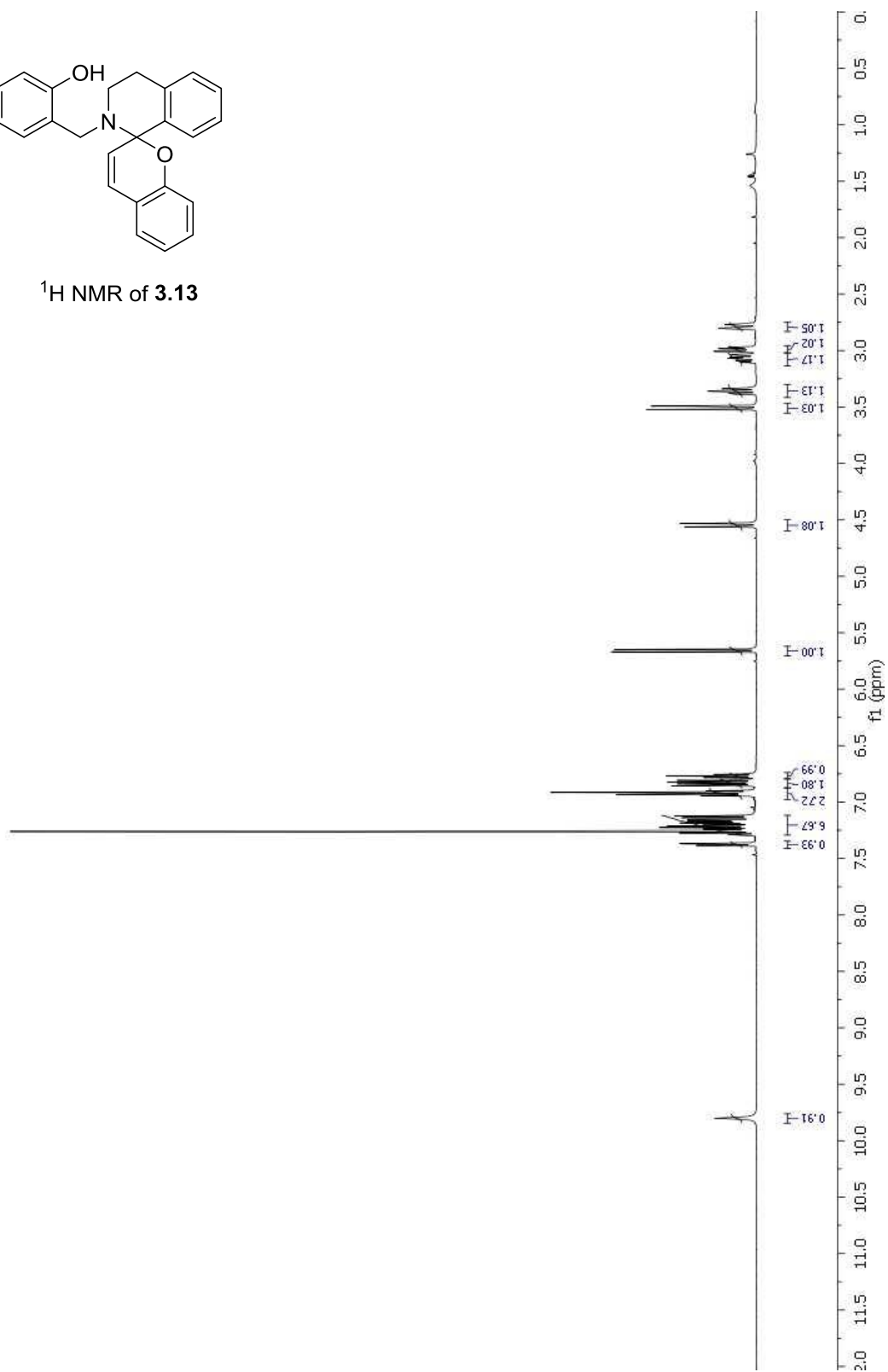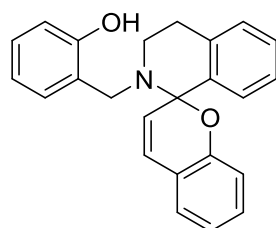
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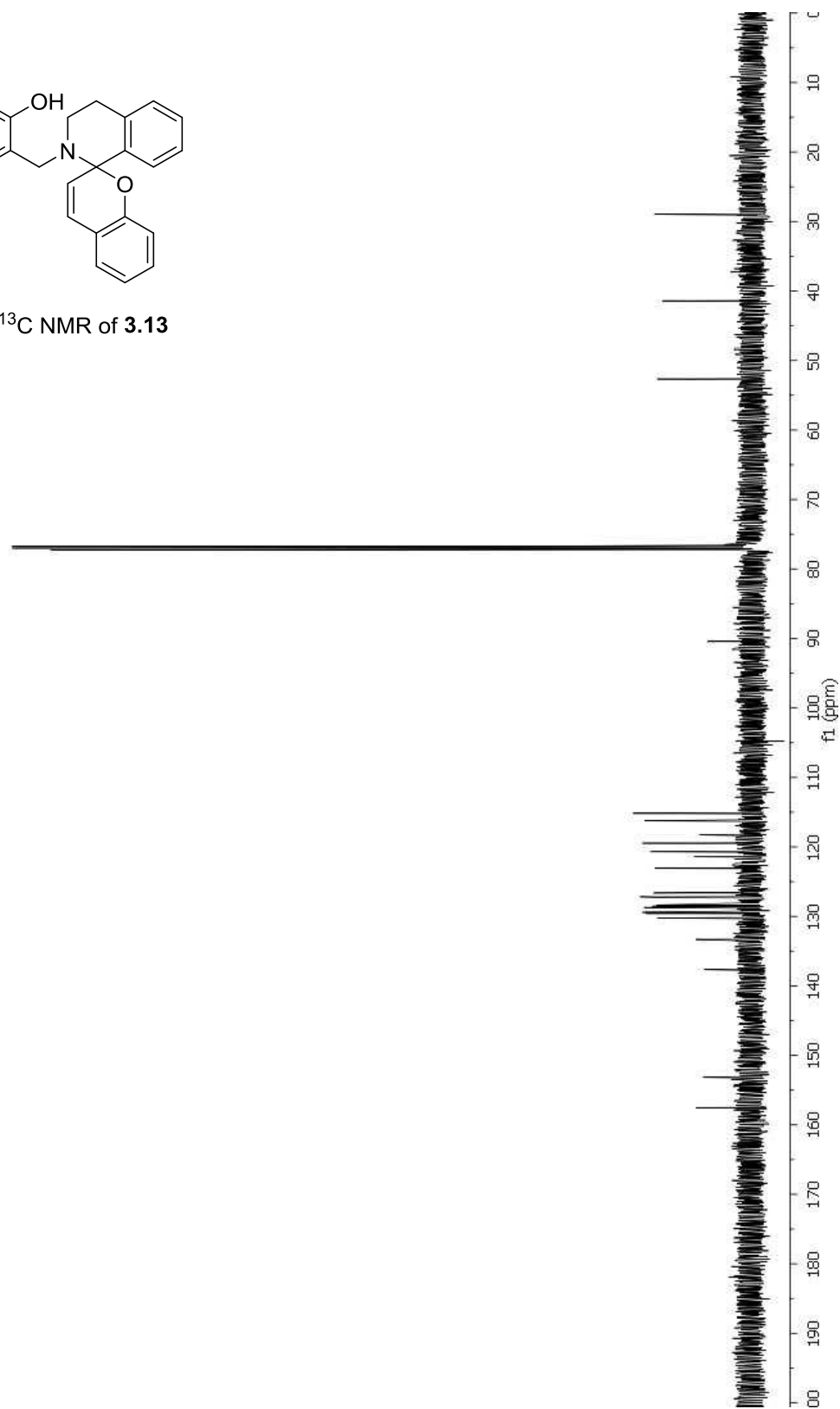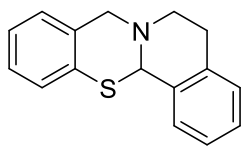
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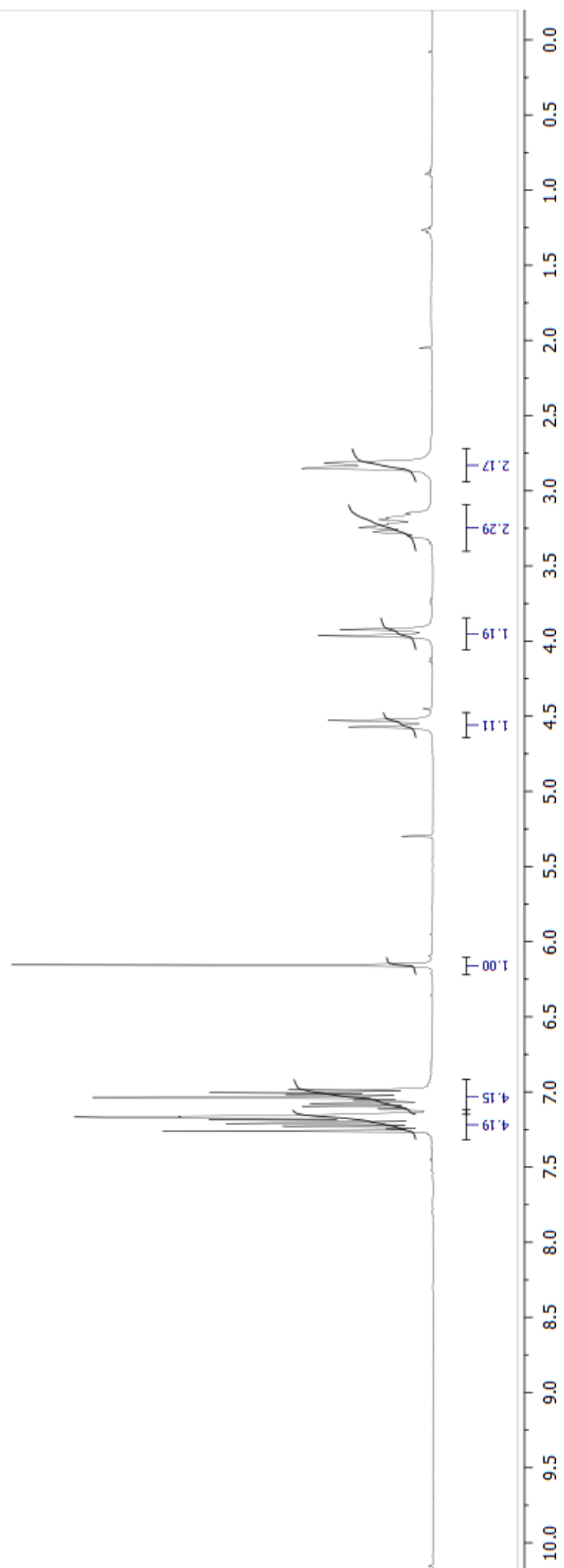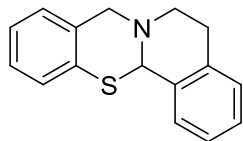
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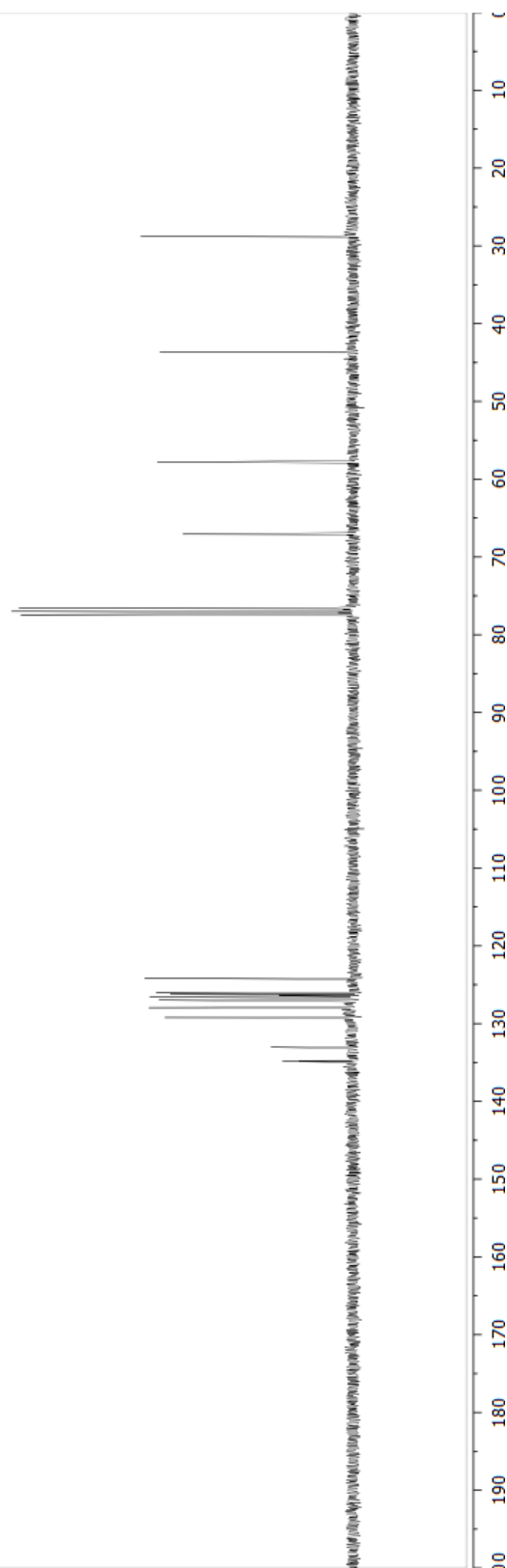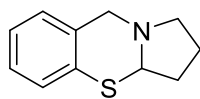
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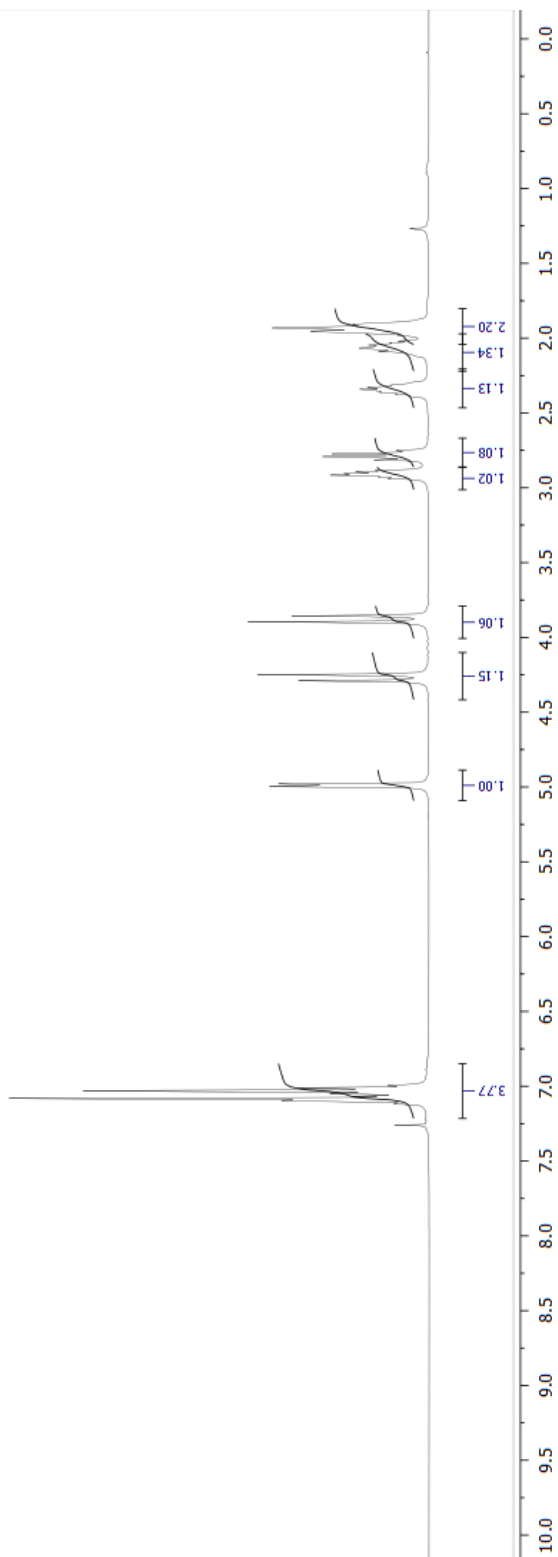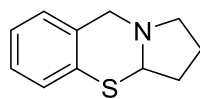
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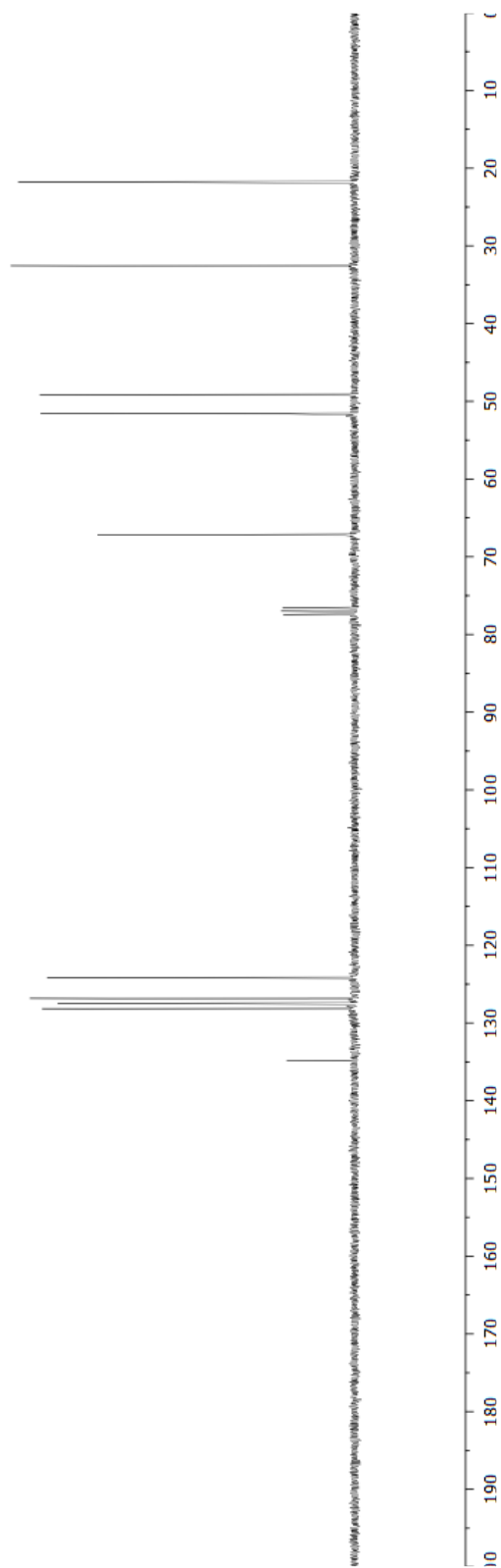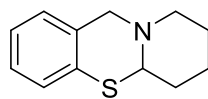
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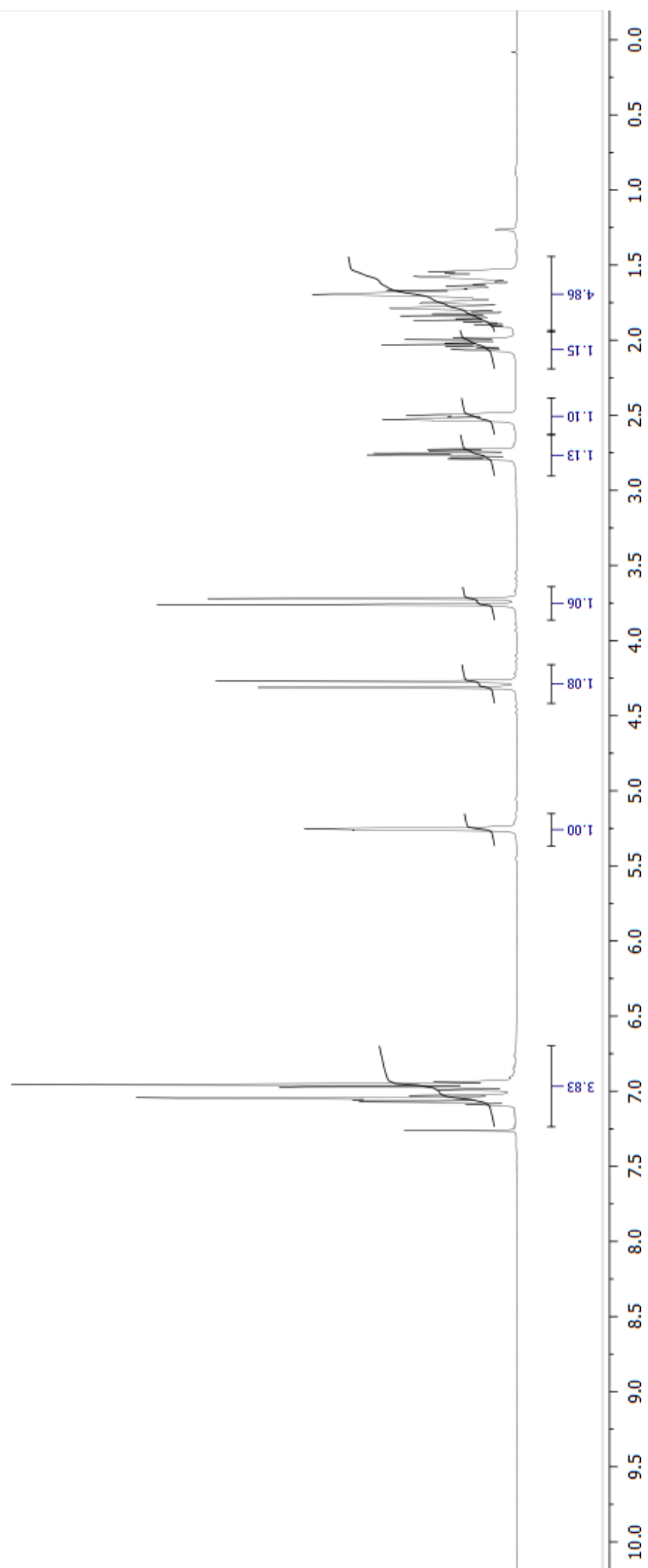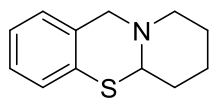
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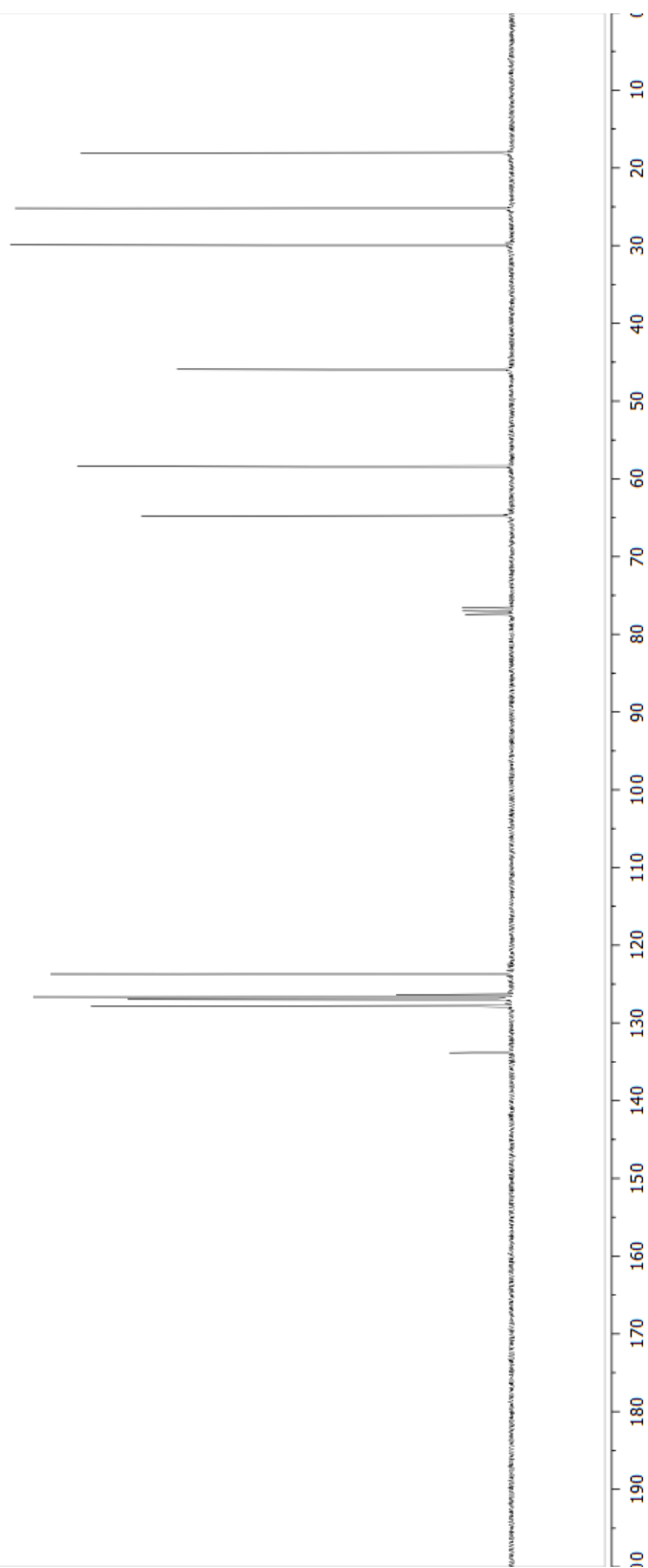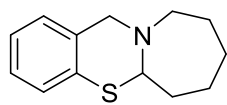
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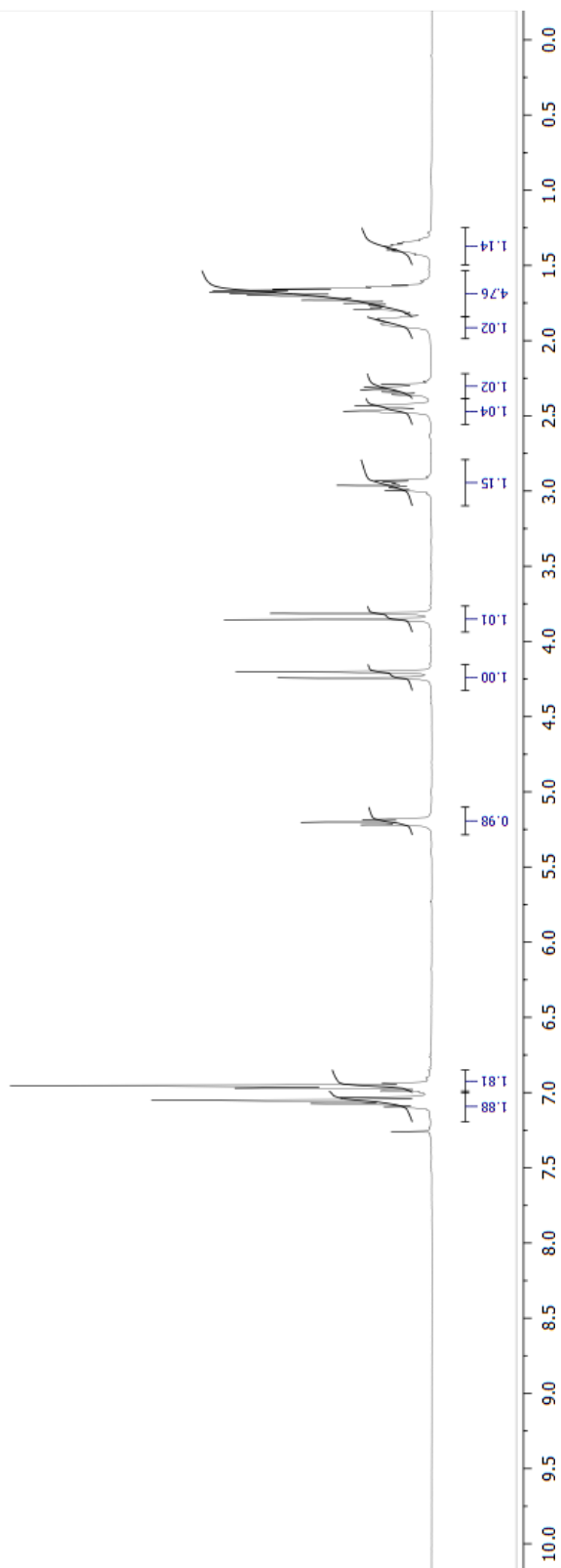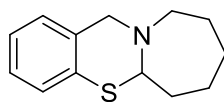
^{13}C NMR of **3.29d**
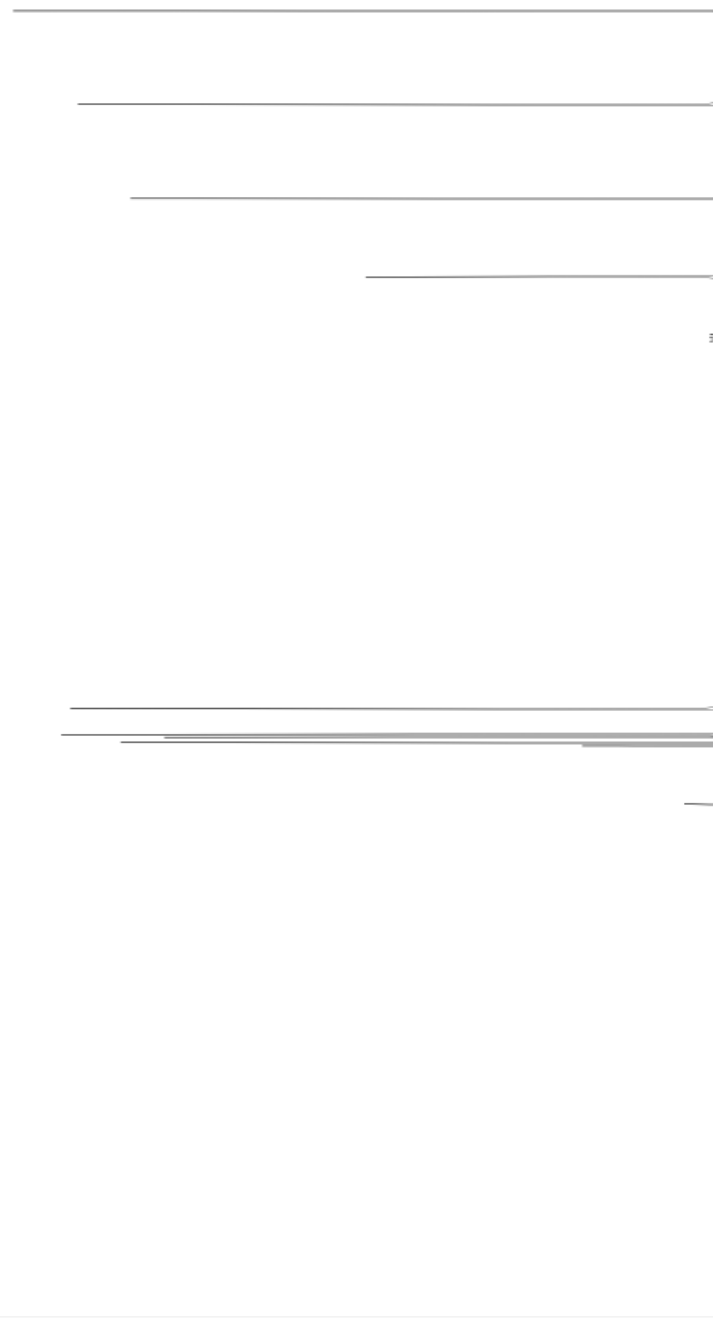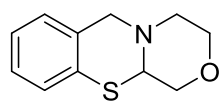
^{1}H NMR of **3.29e**
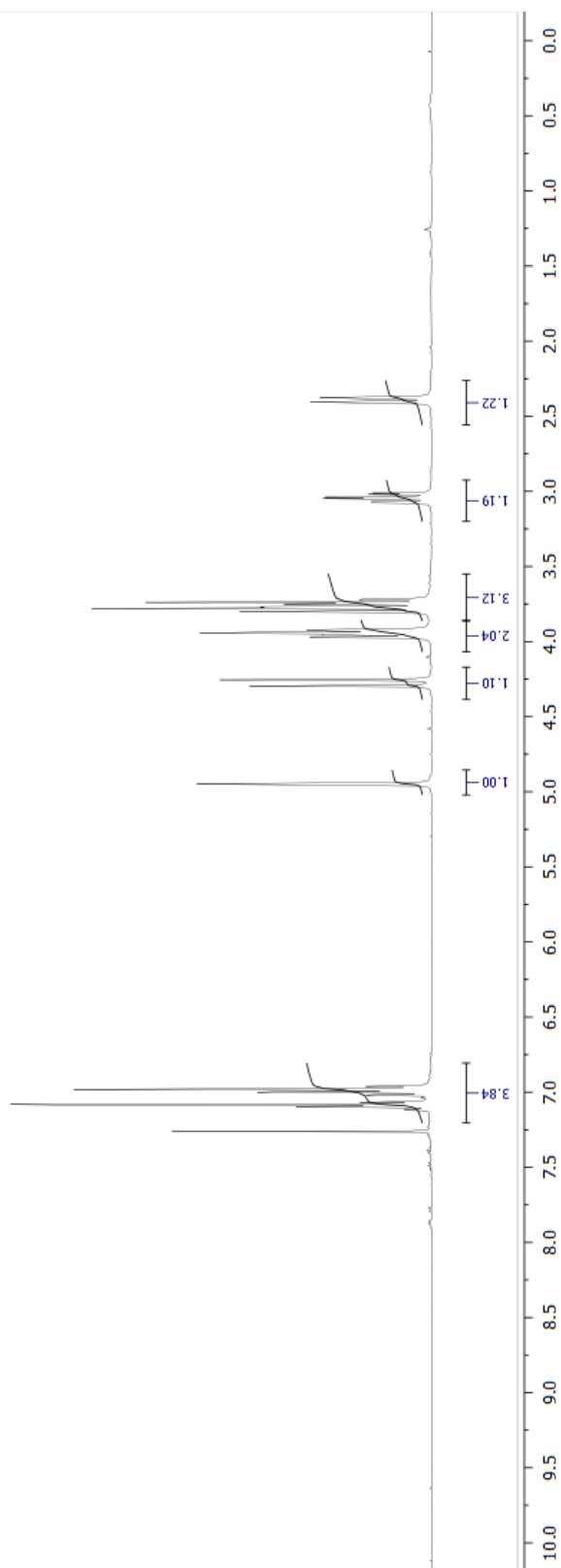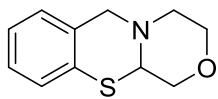
^{13}C NMR of **3.29e**
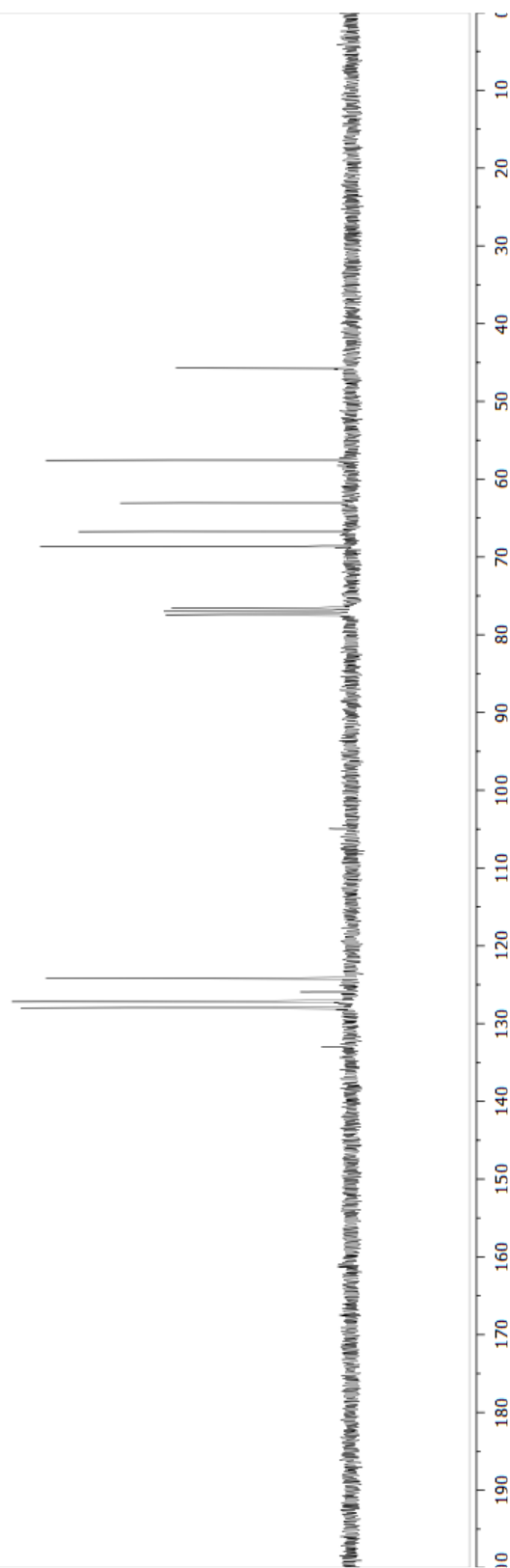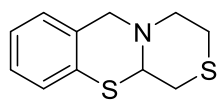
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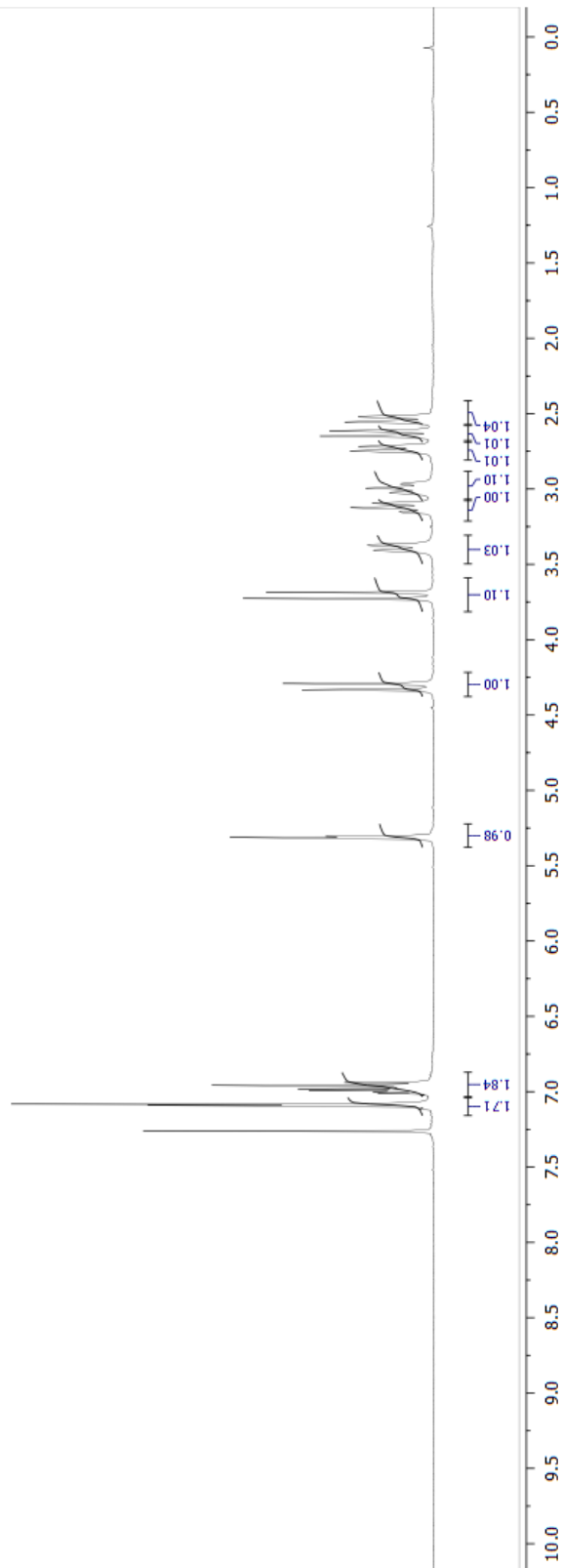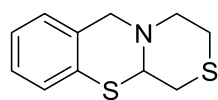
^{13}C NMR of **3.29f**
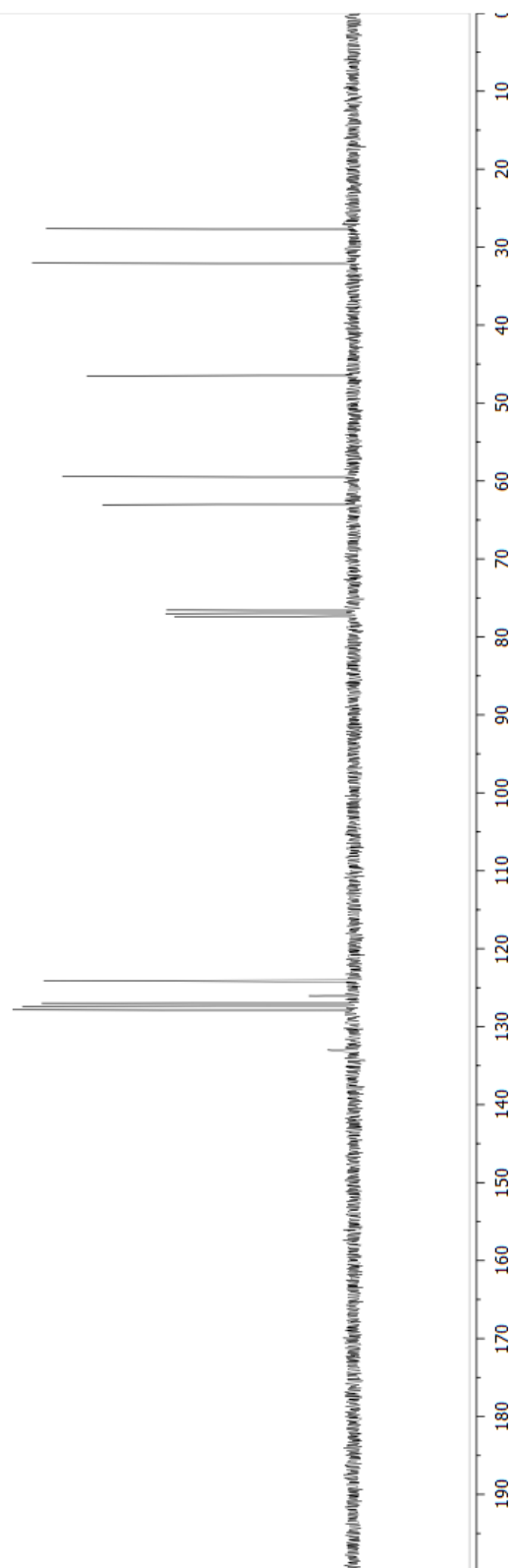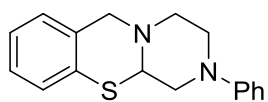
^{1}H NMR of **3.29g**
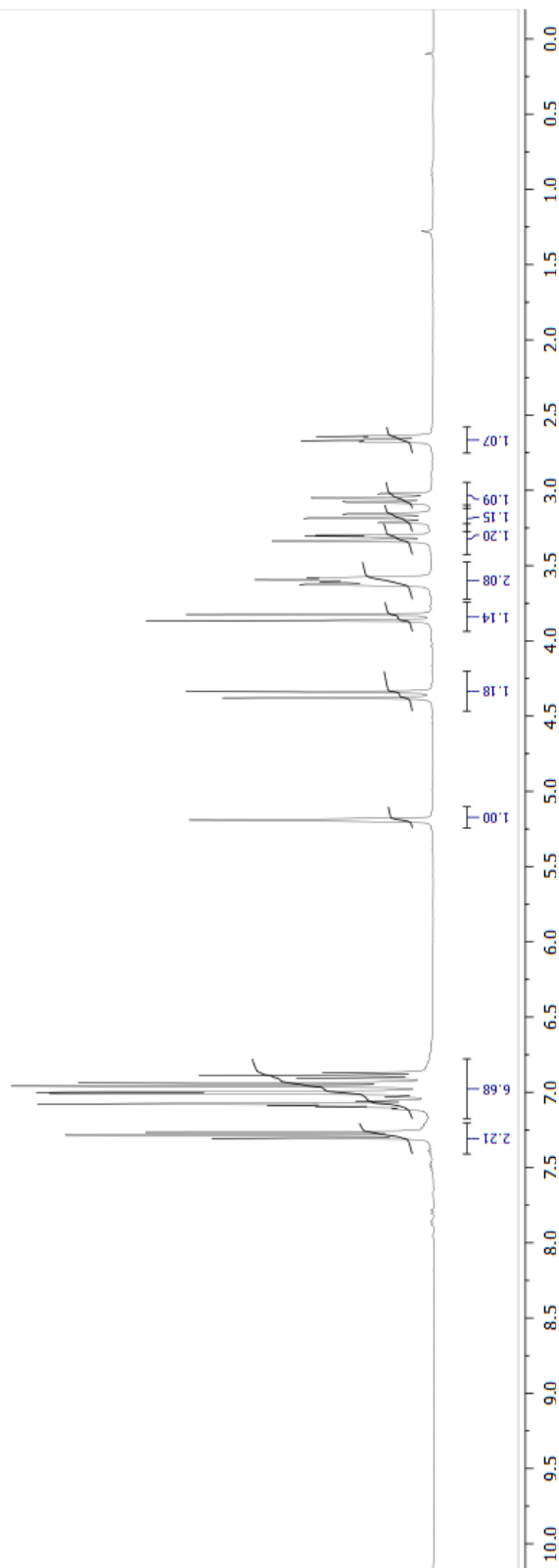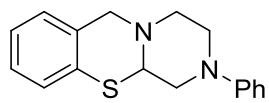
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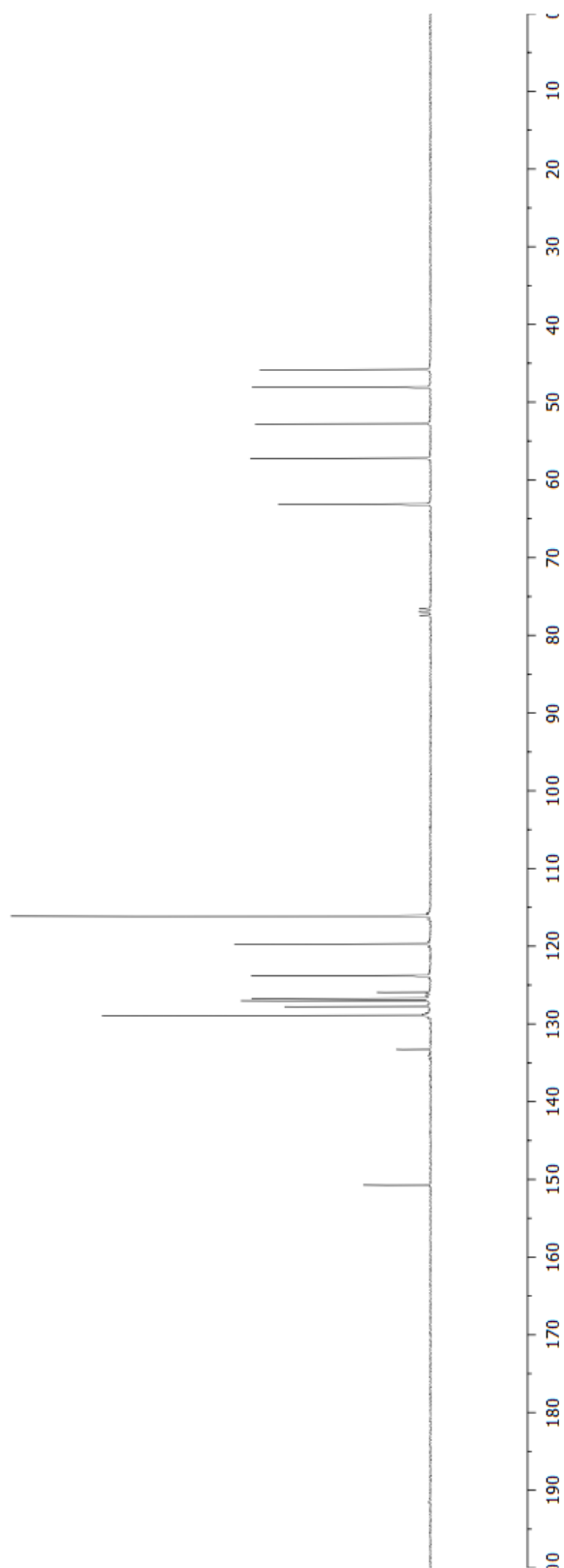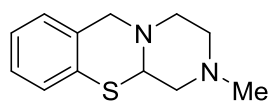
^{1}H NMR of **3.29h**
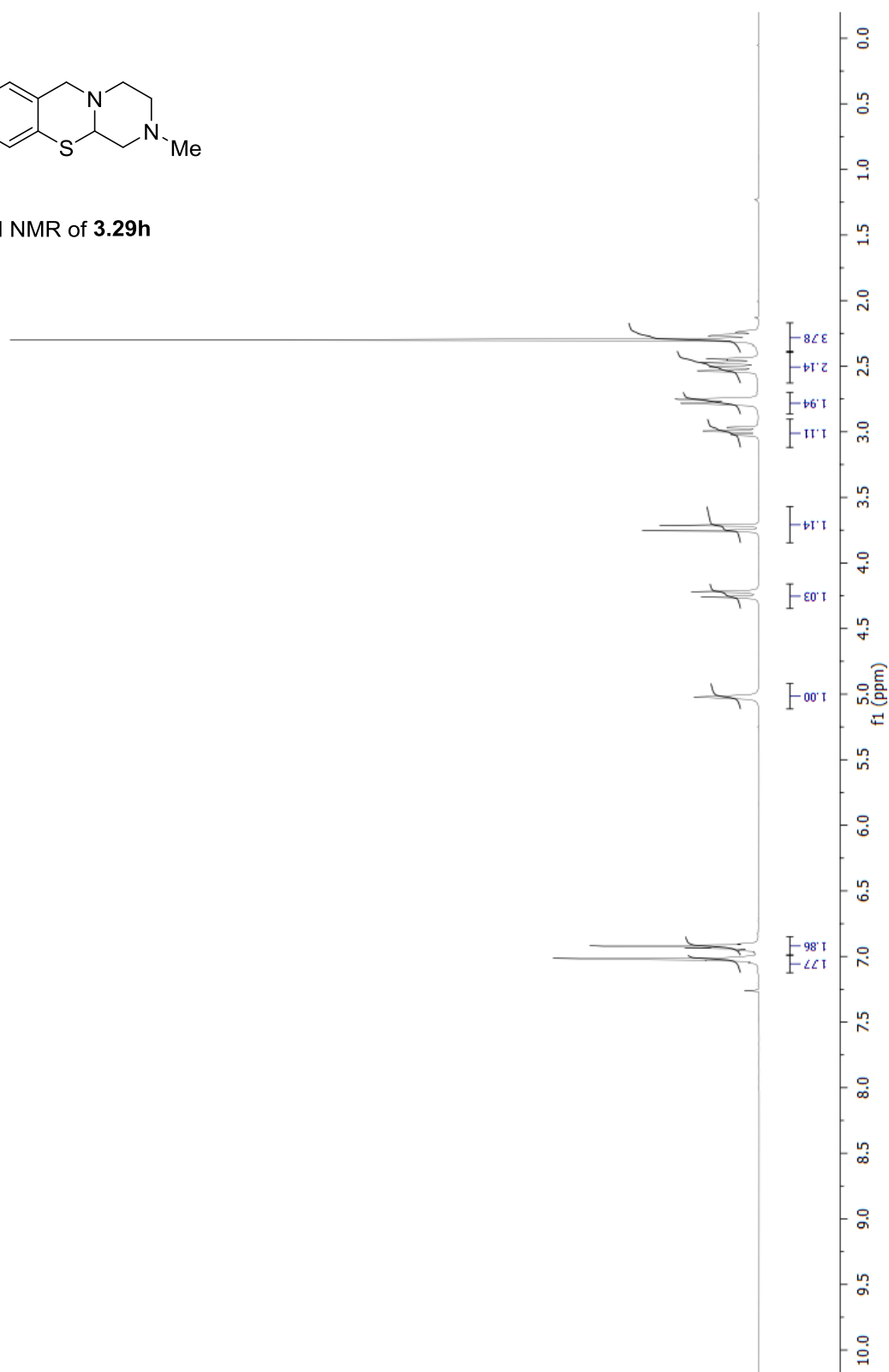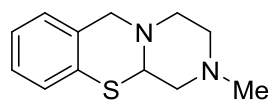
^{13}C NMR of **3.29h**
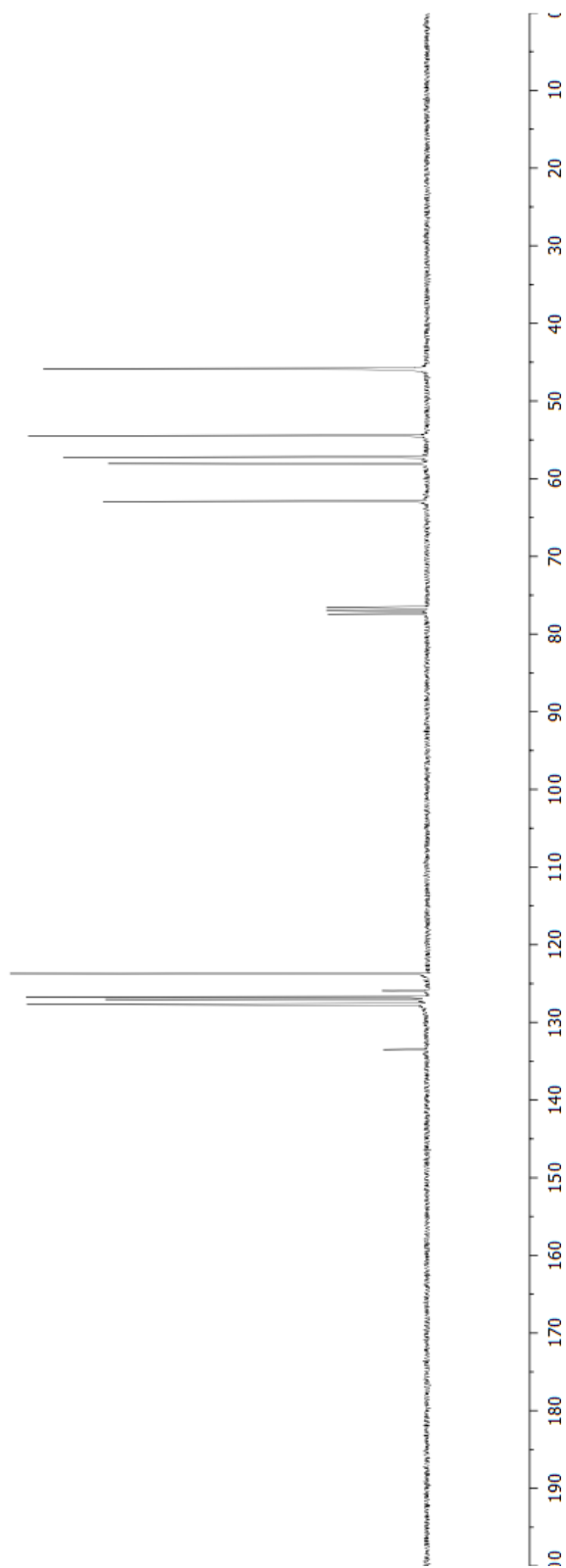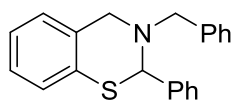
^{1}H NMR of **3.29i**
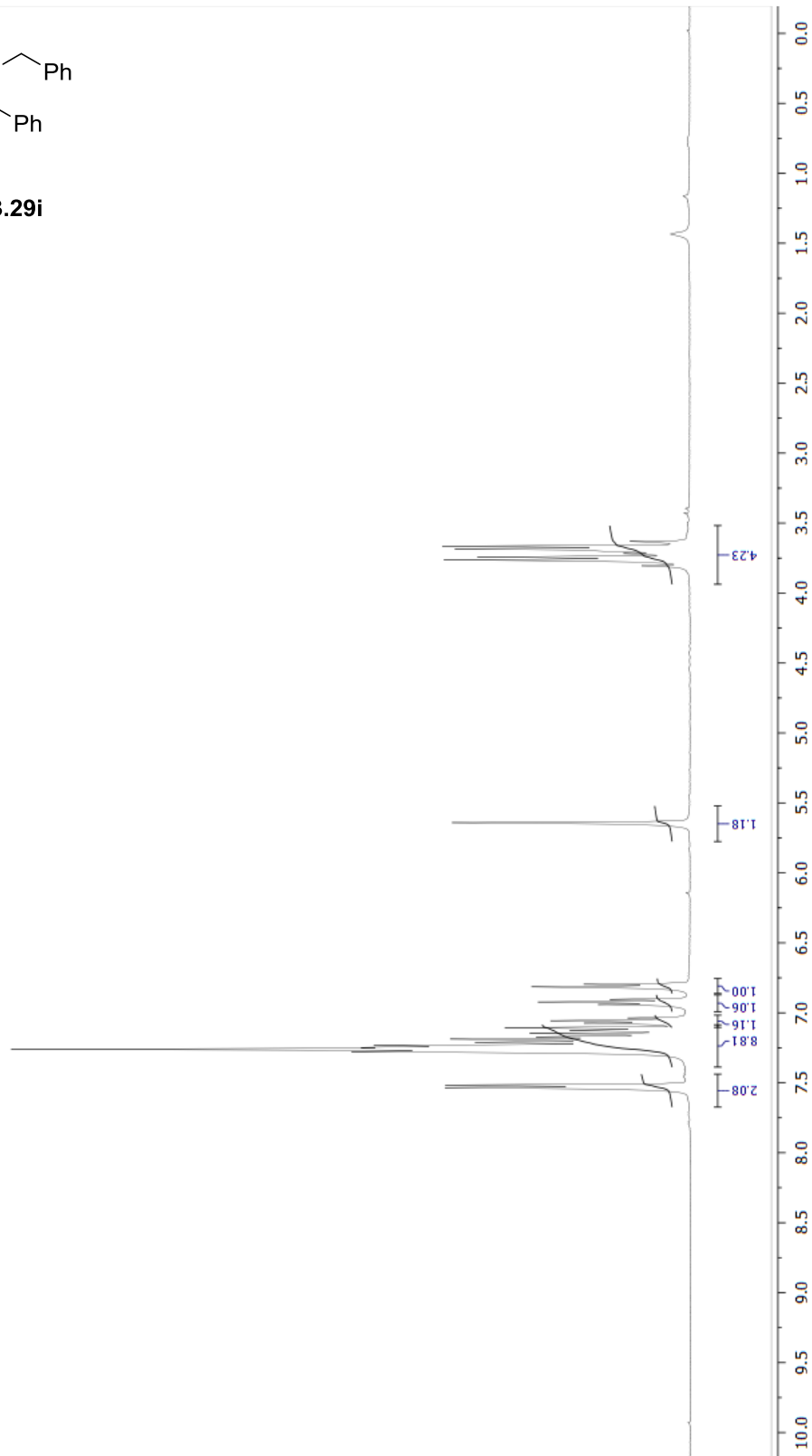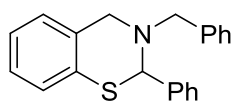
^{13}C NMR of **3.29i**
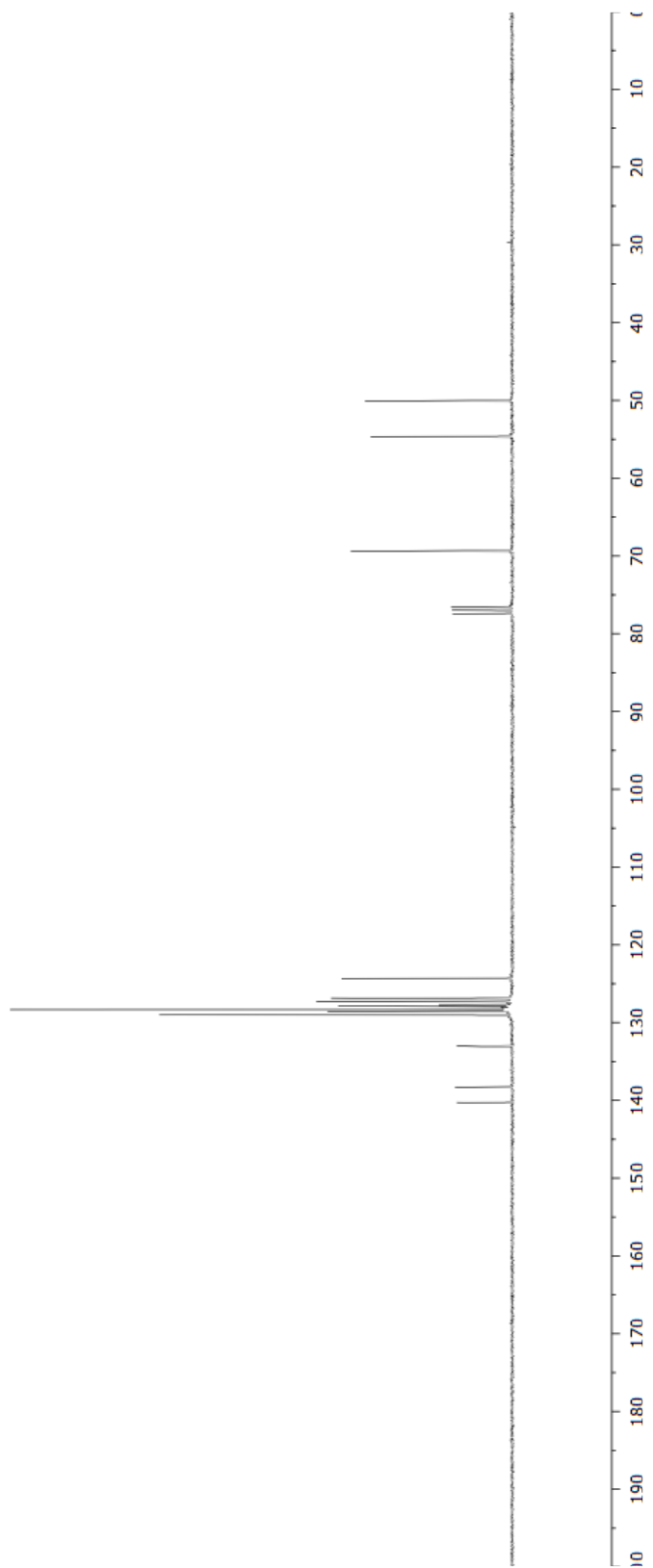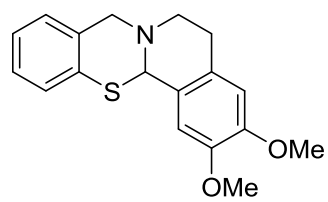
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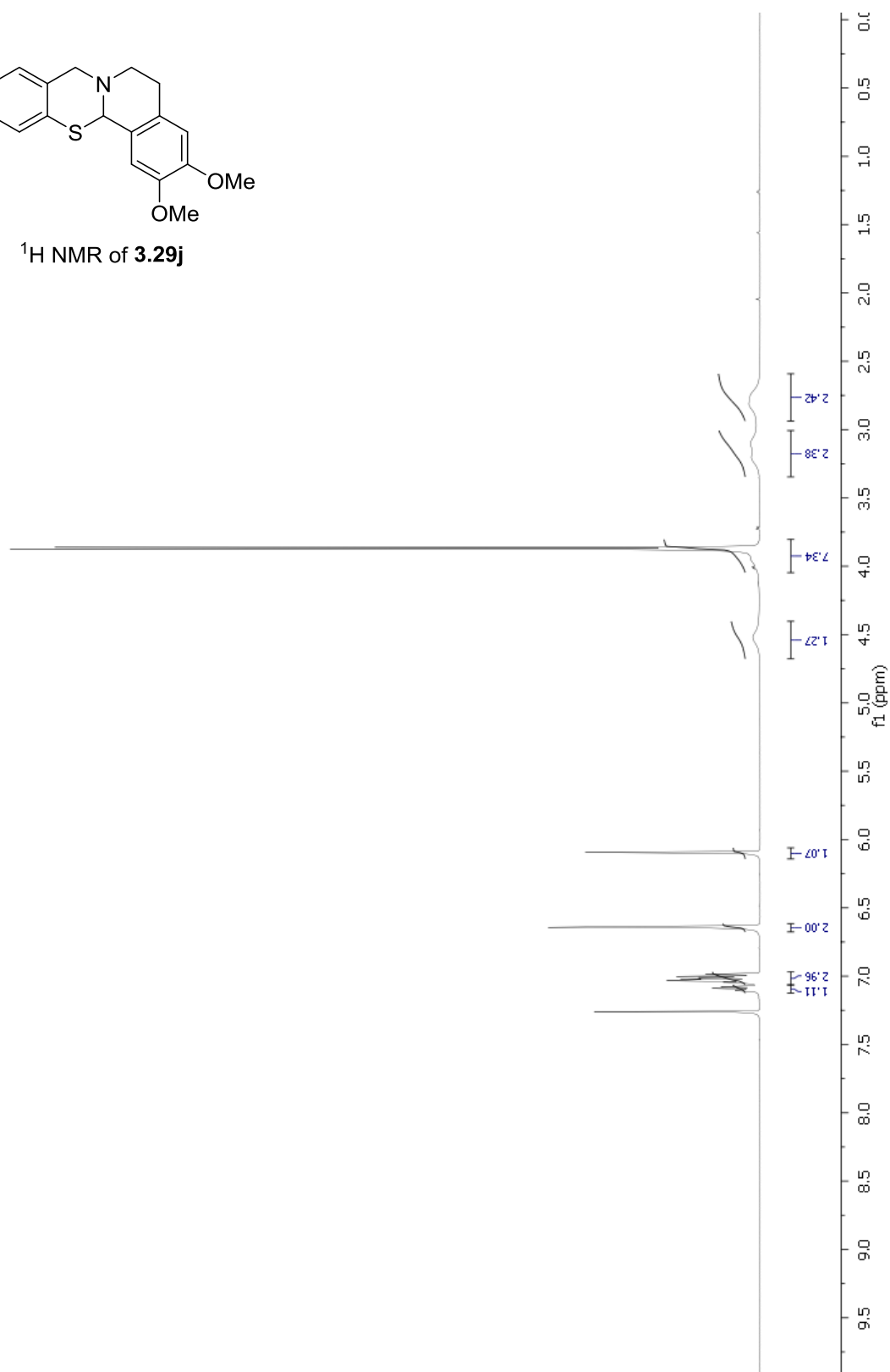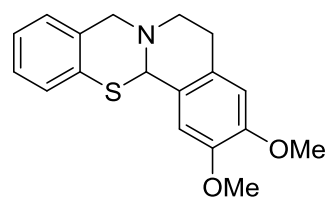
^{13}C NMR of **3.29j**
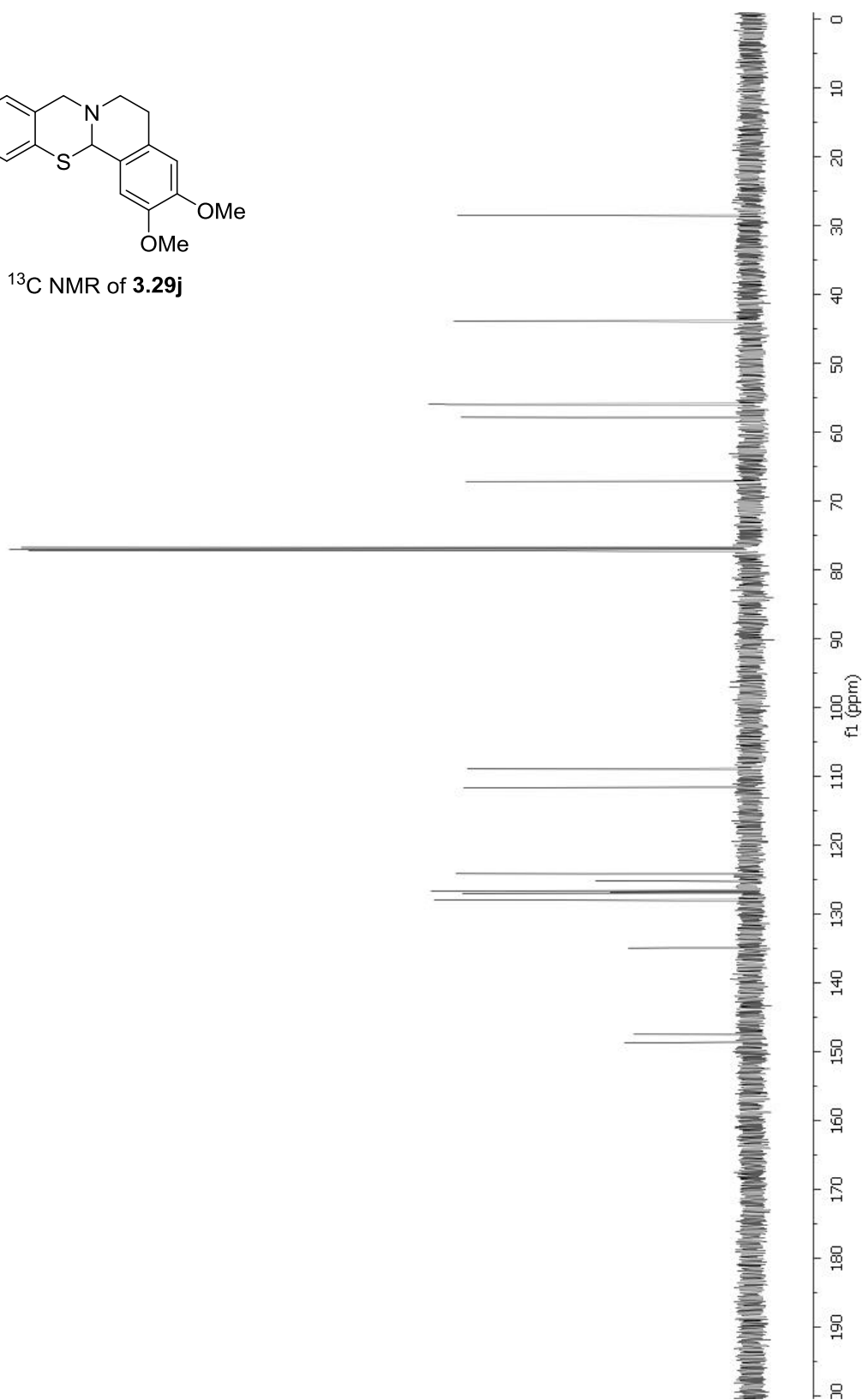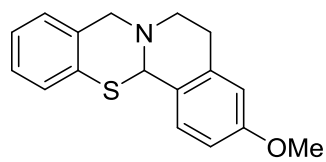
^{1}H NMR of **3.29k**
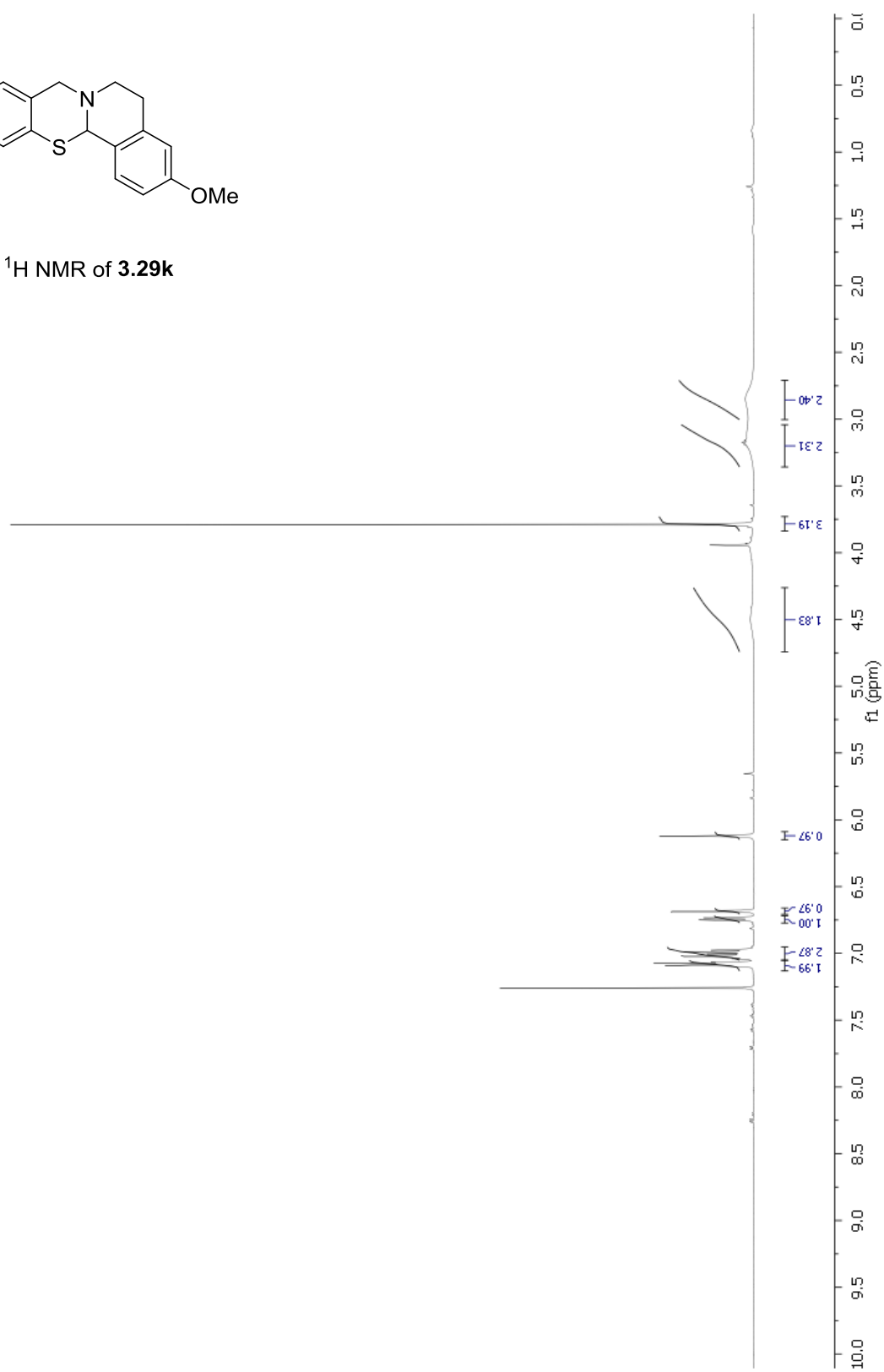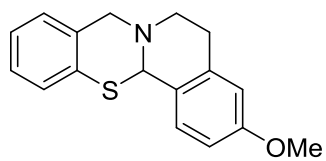
^{13}C NMR of **3.29k**

^{1}H NMR of **3.29l**
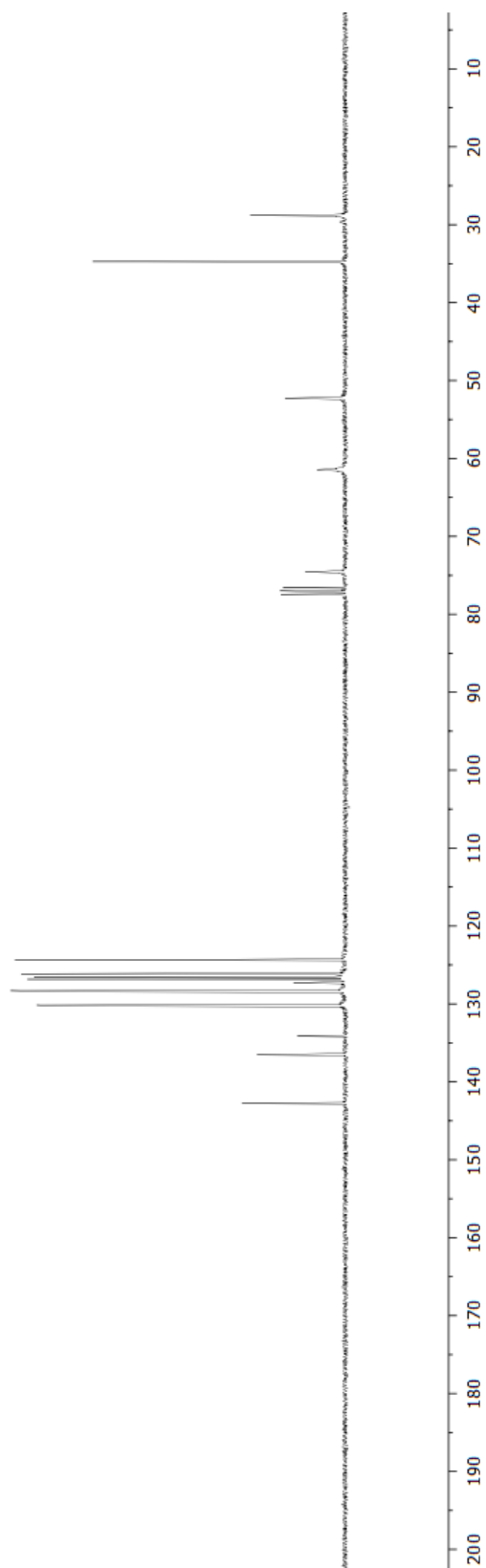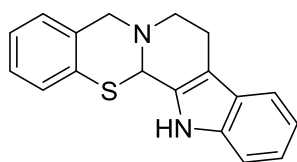
^{13}C NMR of **3.29l**
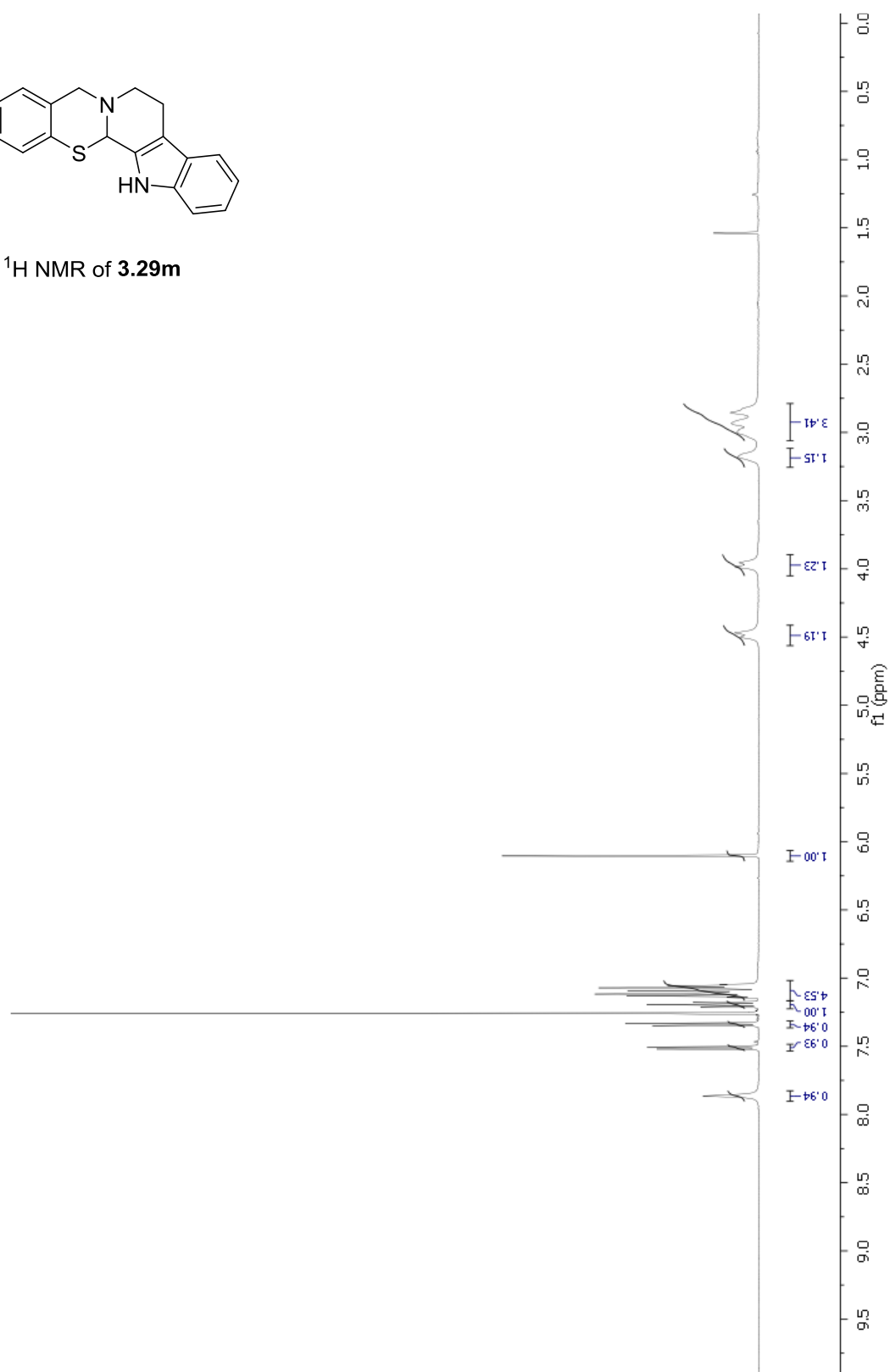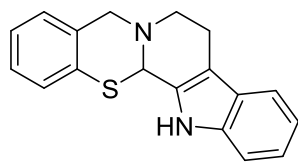
^{1}H NMR of **3.29m**

^{13}C NMR of **3.29m**
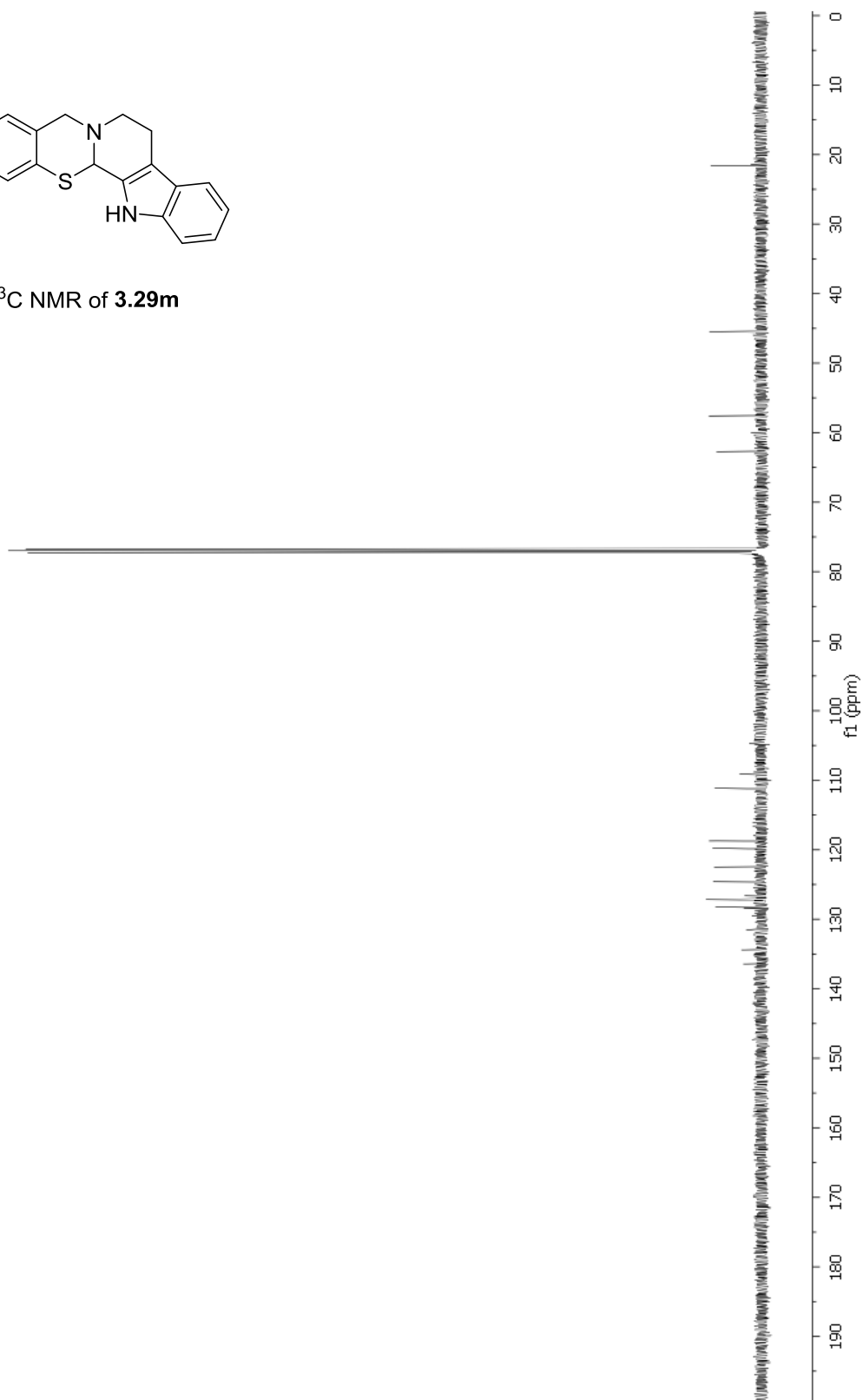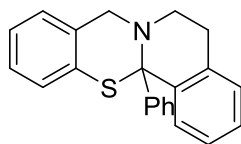
^{1}H NMR of **3.29n**

^{13}C NMR of **3.29n**

Me
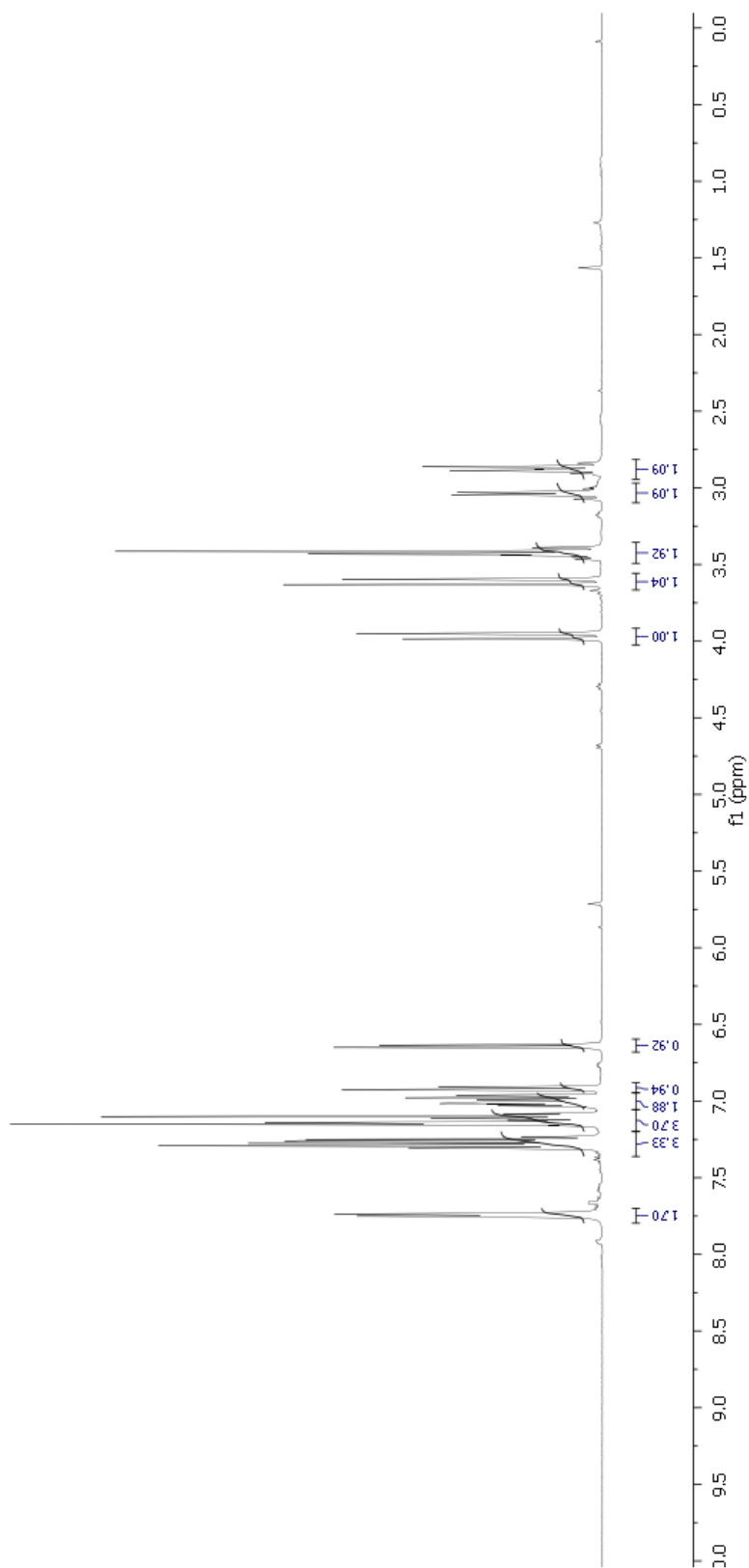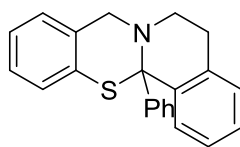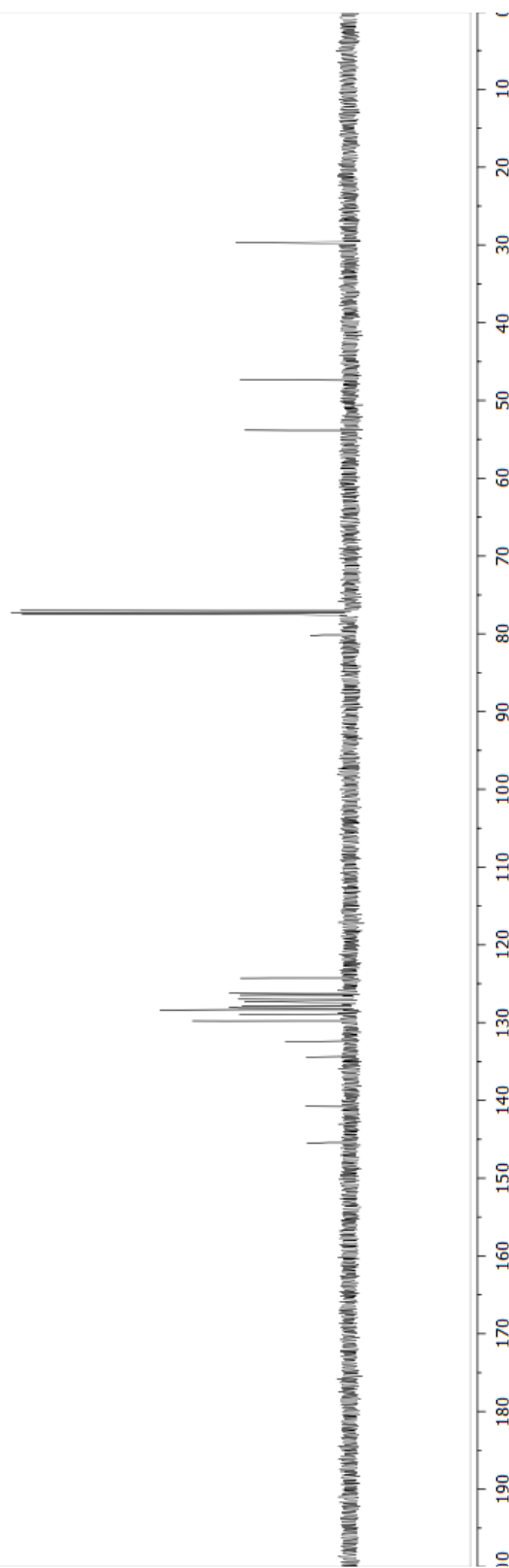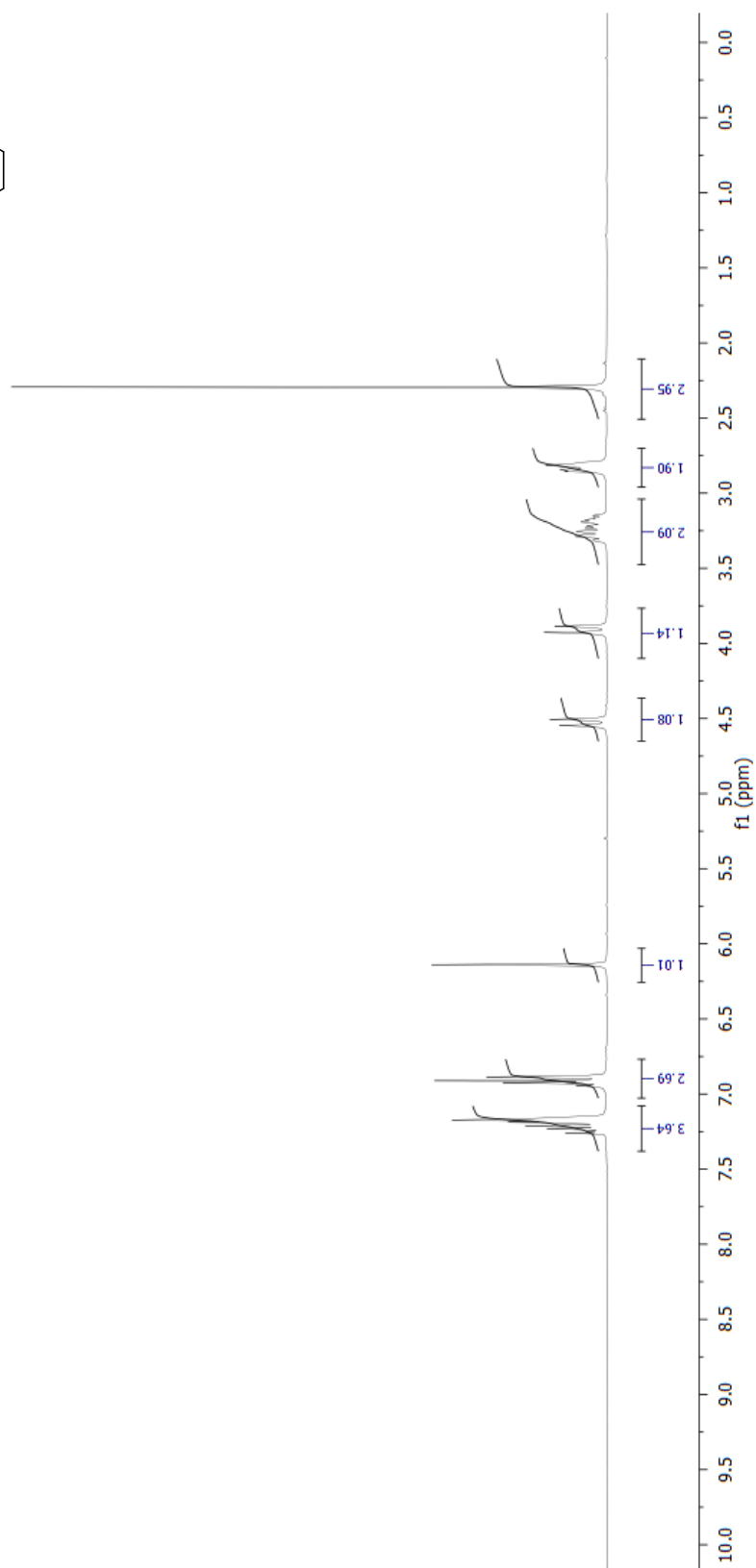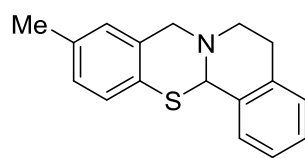
^{1}H NMR of **3.29o**

^{13}C NMR of **3.29o**
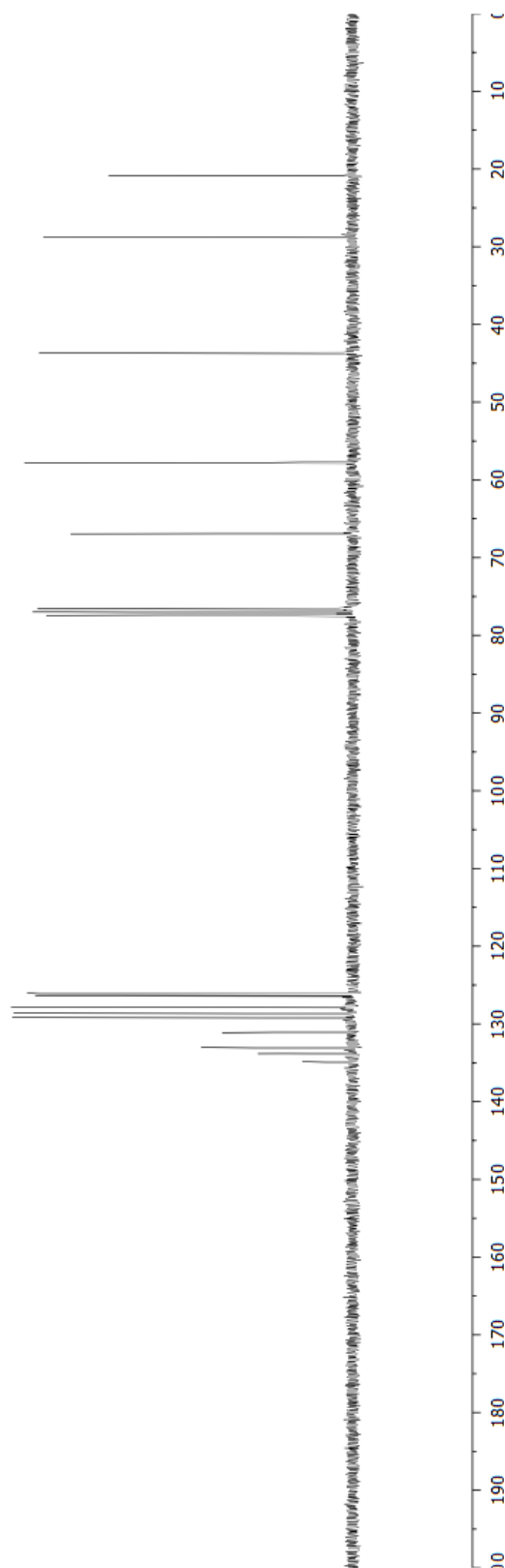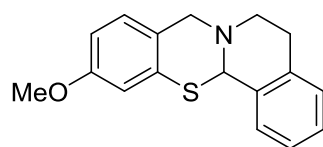
^{1}H NMR of **3.29p**
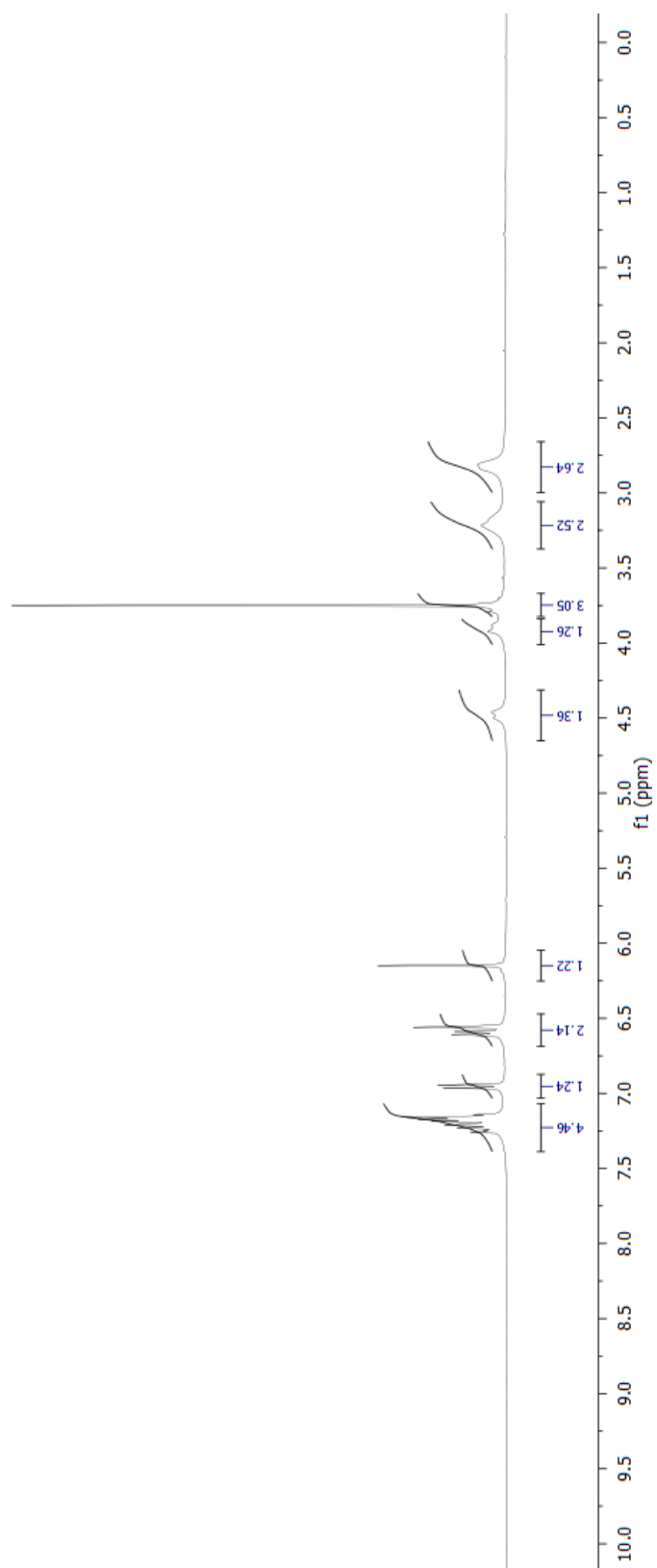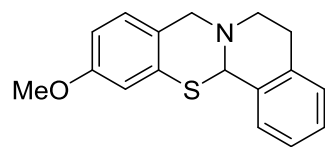
^{13}C NMR of **3.29p**
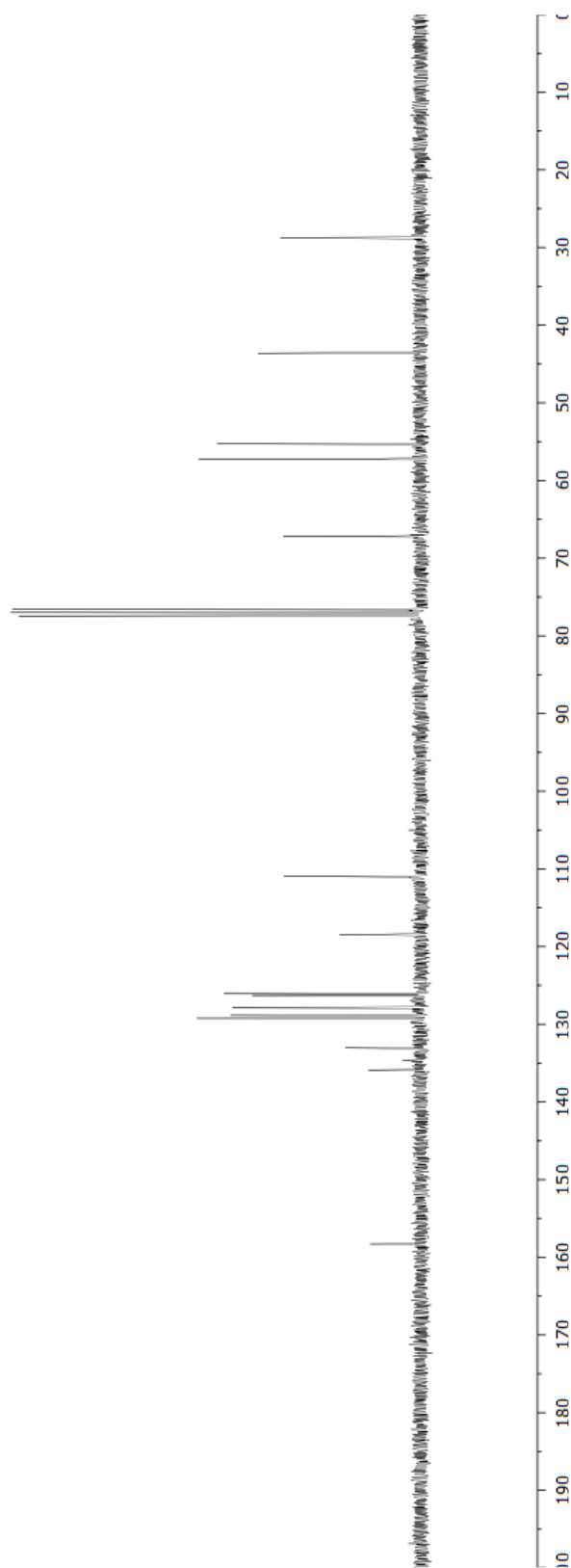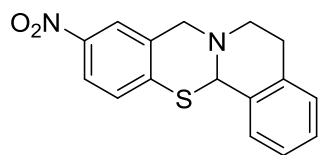
^{1}H NMR of **3.29q**
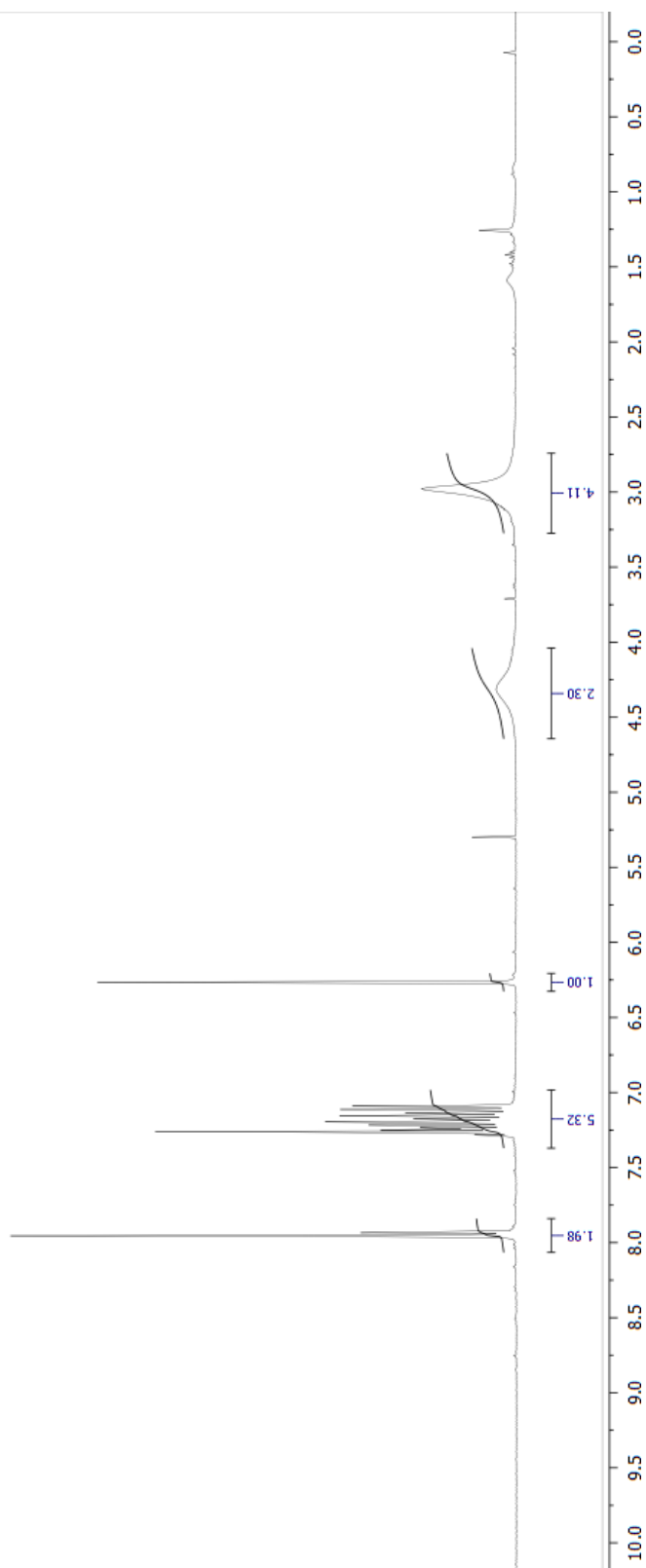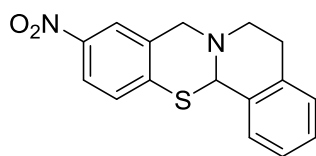
^{13}C NMR of **3.29q**
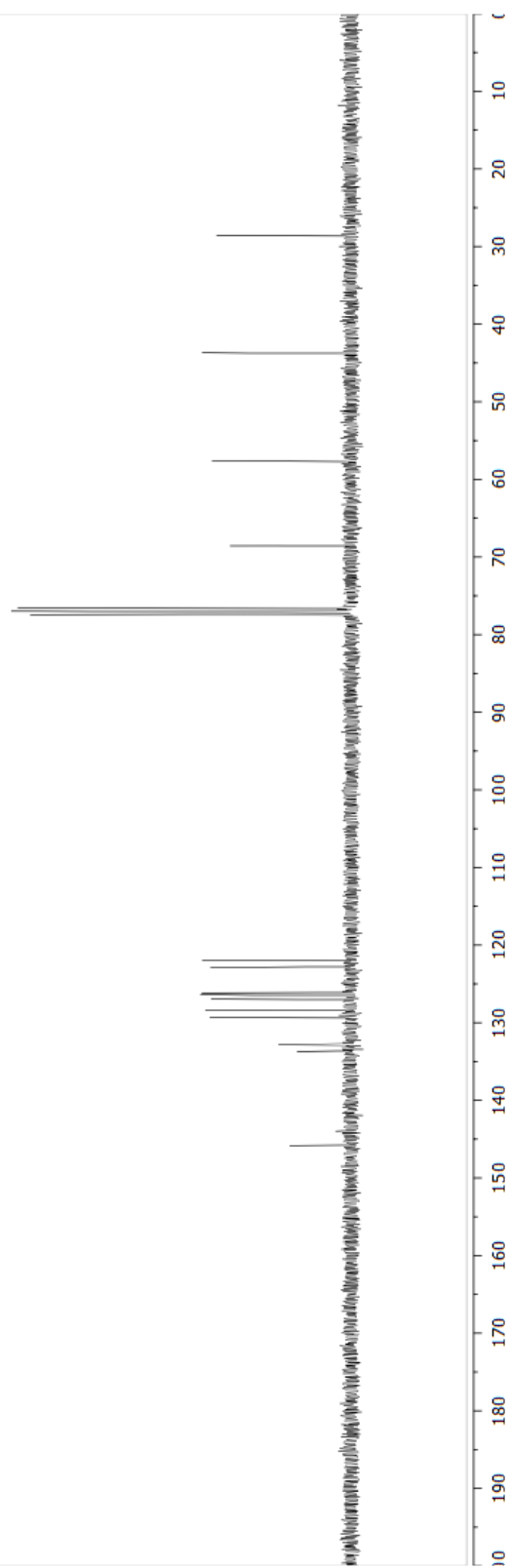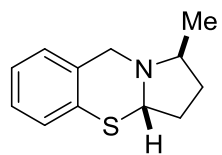
^{1}H NMR of **3.29r**

^{13}C NMR of **3.29r**
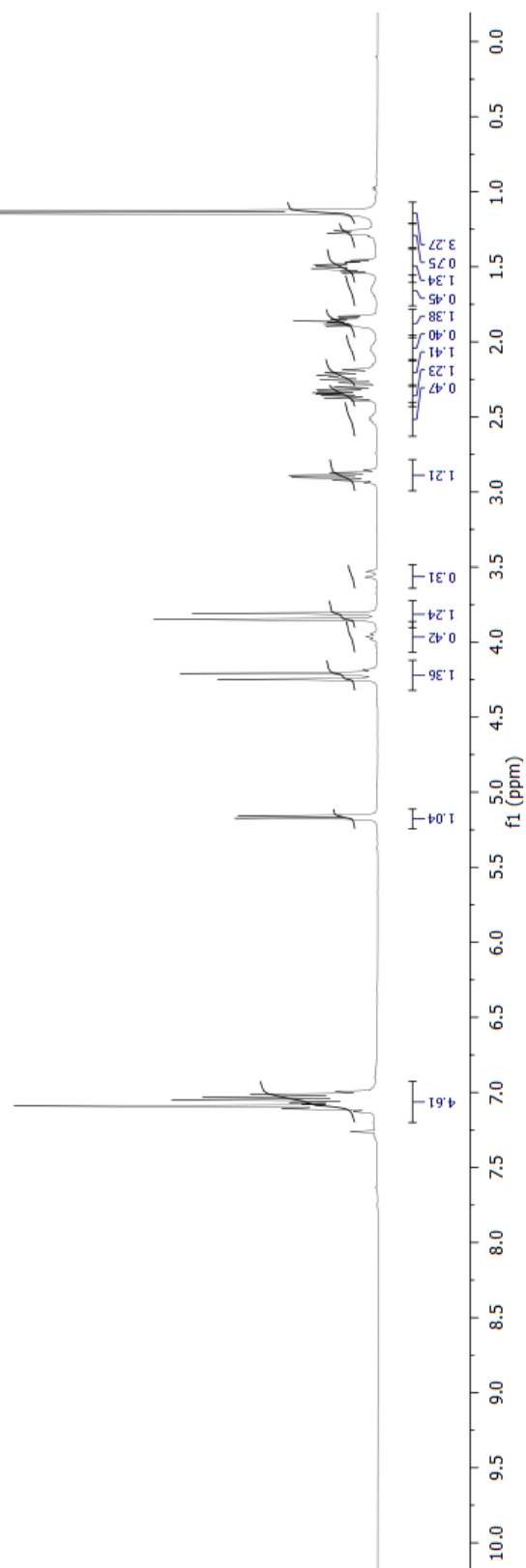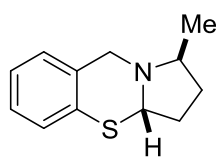
GCOSY NMR of **3.29r**
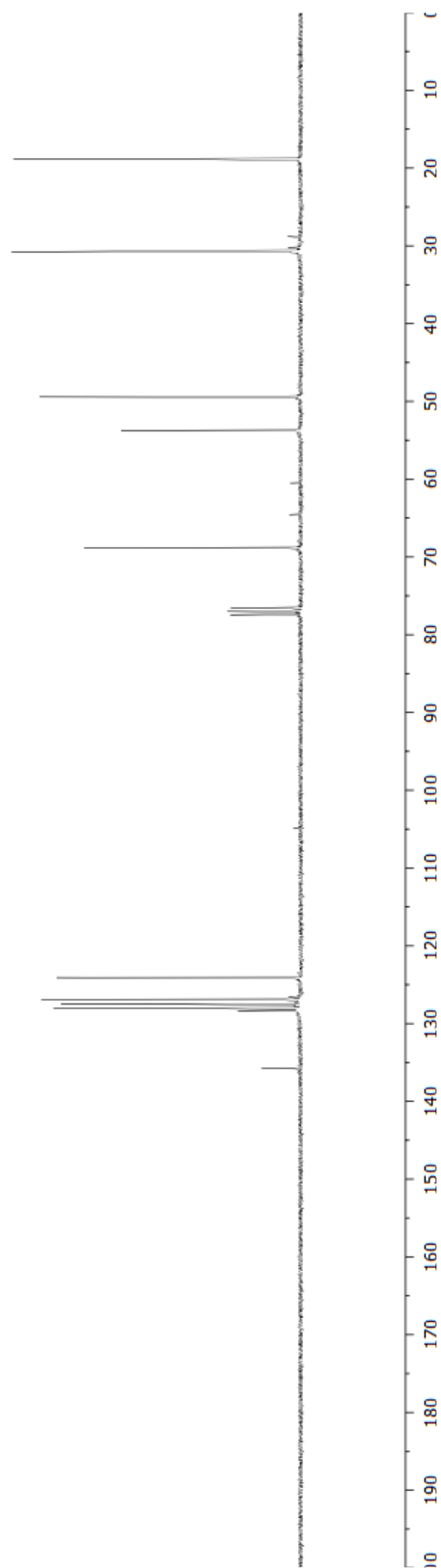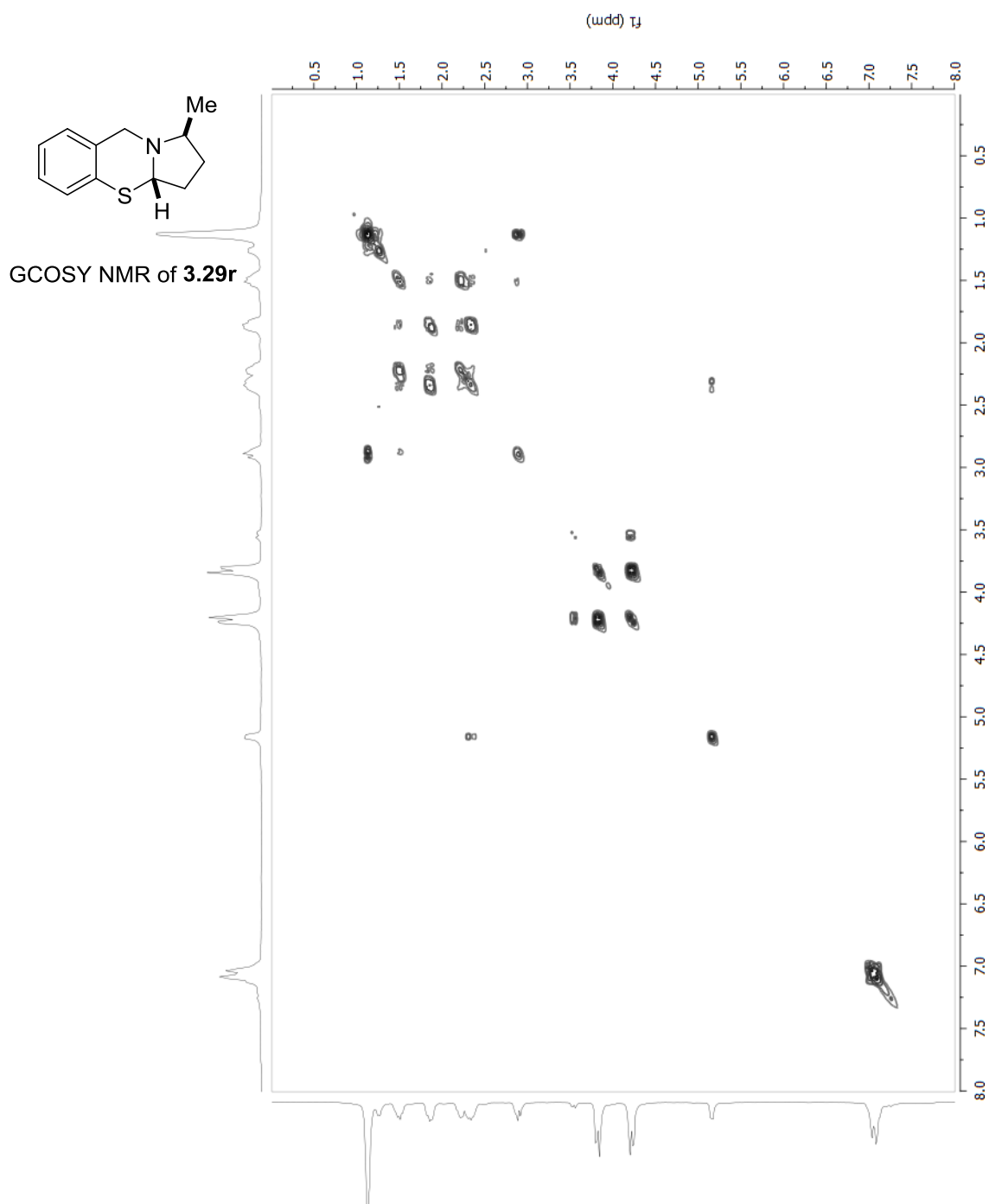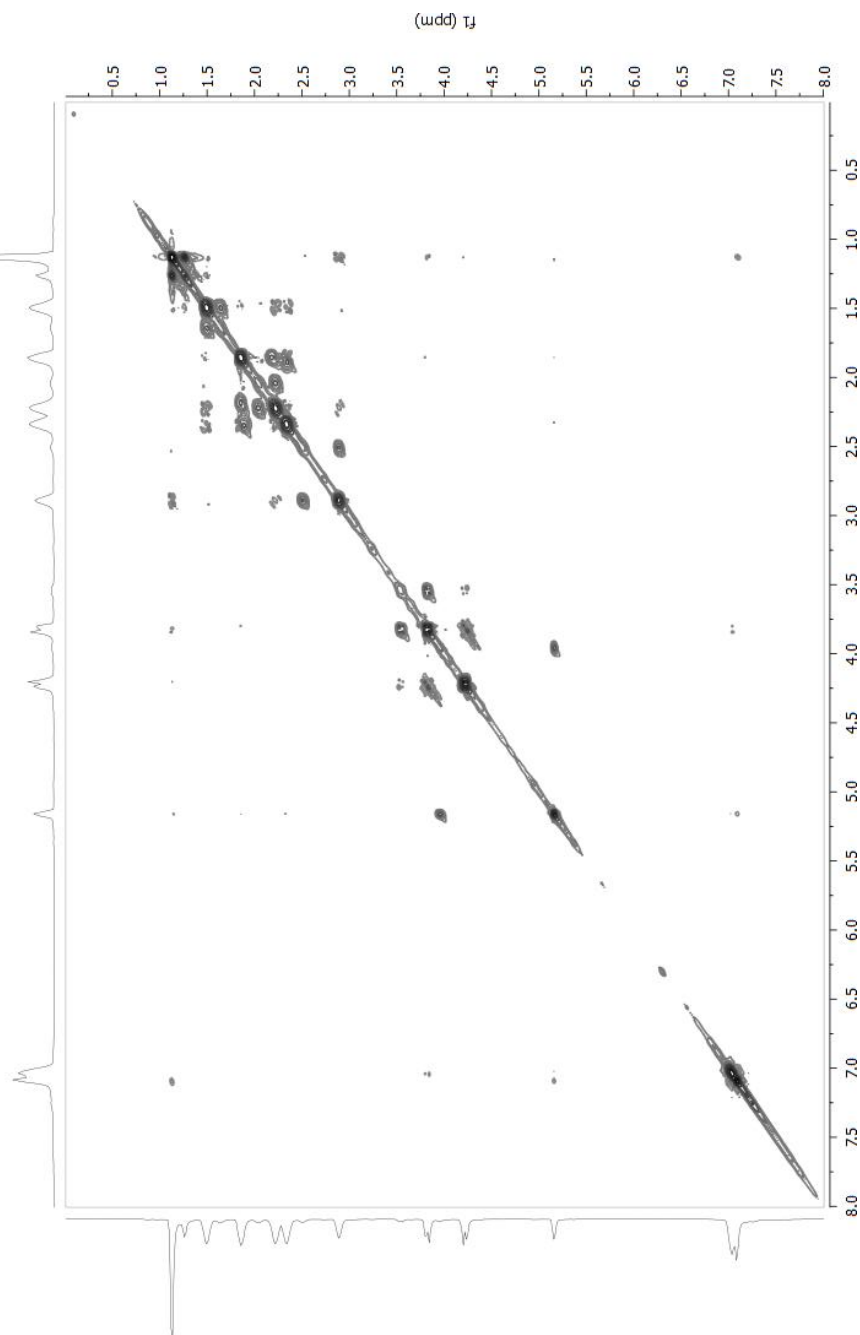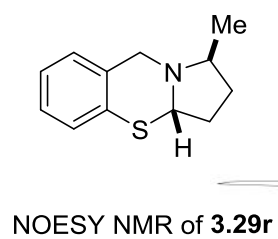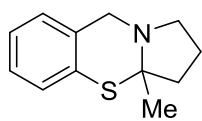
NOESY NMR of **3.29r**
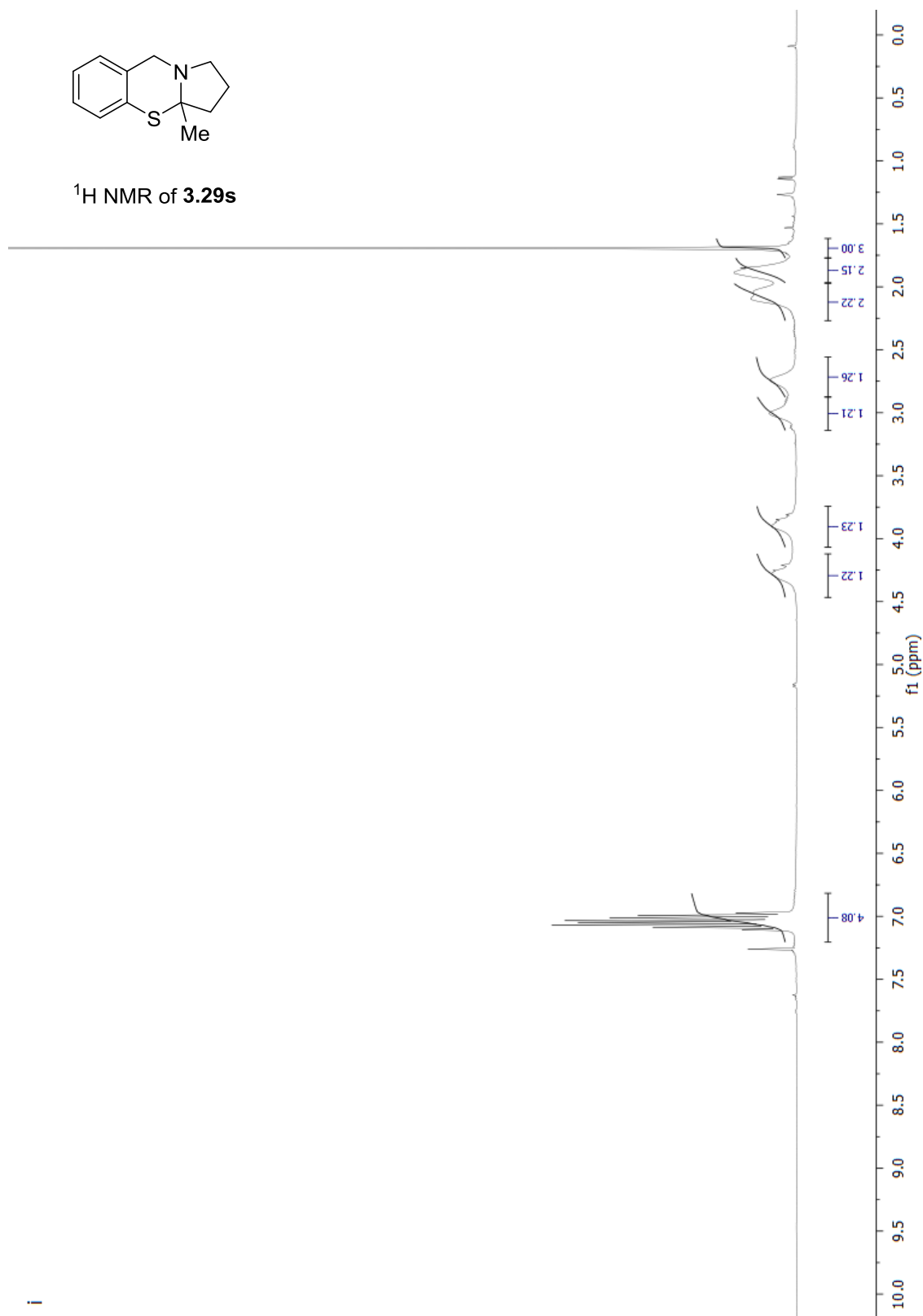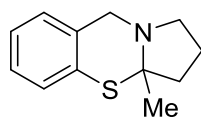
^{1}H NMR of **3.29s**

^{13}C NMR of **3.29s**
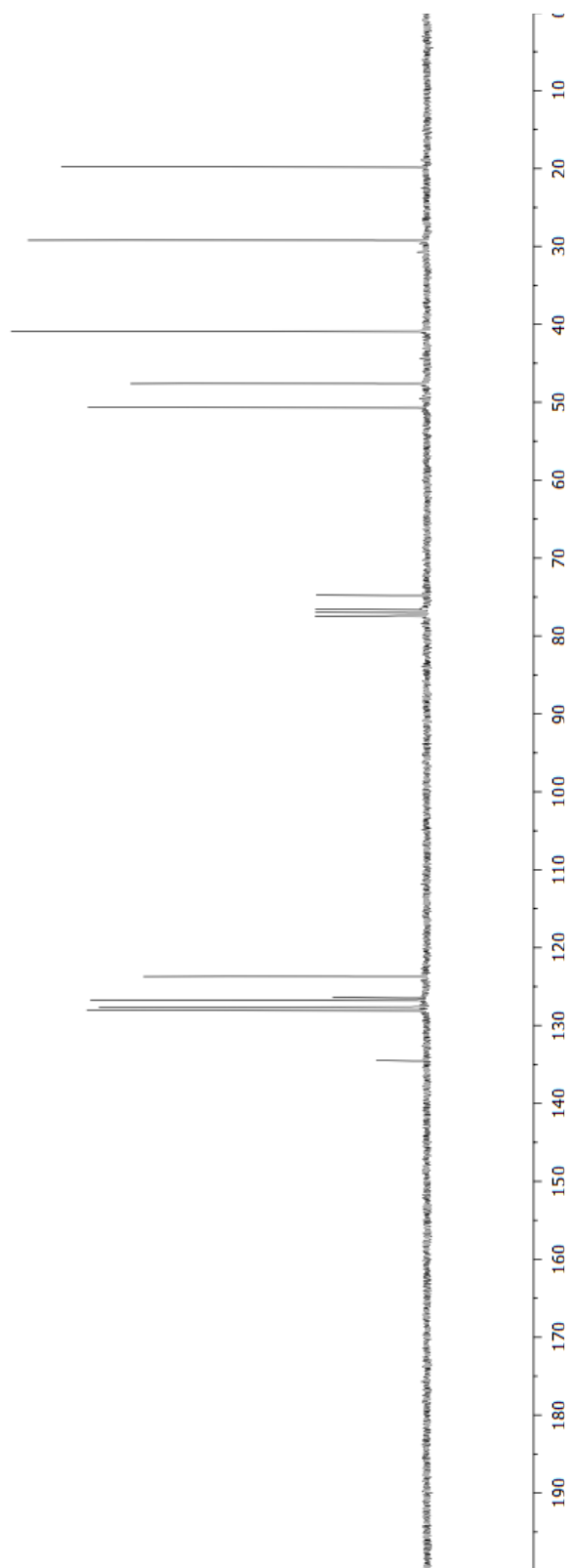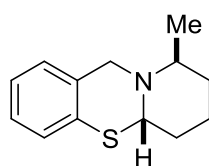
^{1}H NMR of **3.29t**
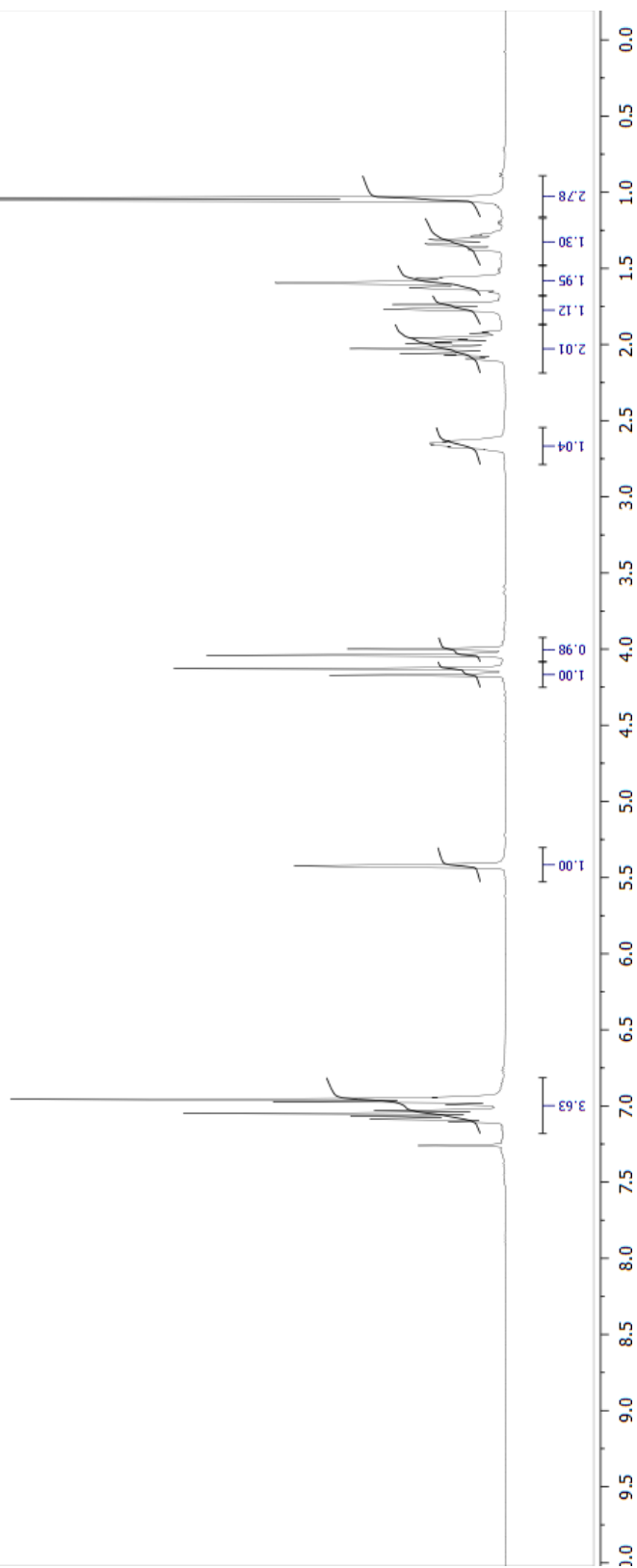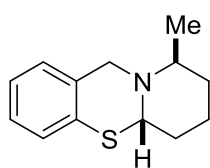
^{13}C NMR of **3.29t**
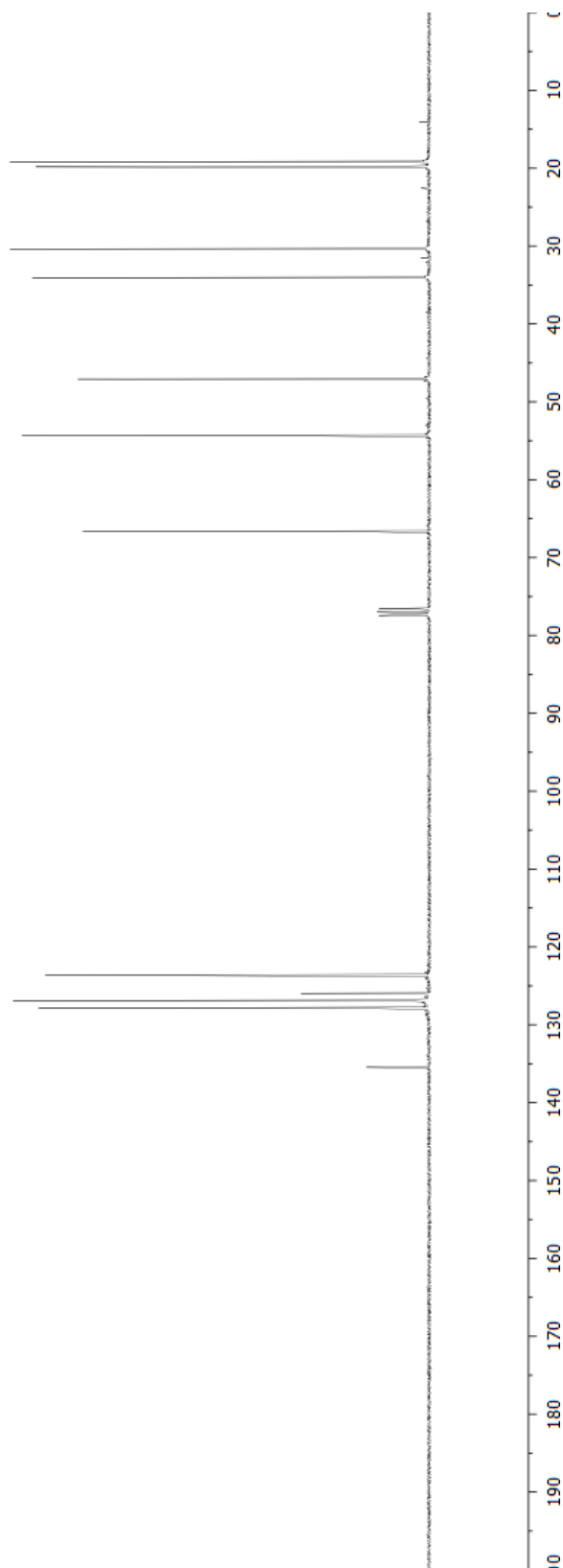
GCOSY NMR of **3.29t**

NOESY NMR of **3.29t**

^{1}H NMR of **4.20b**

^{13}C NMR of **4.20b**

22.0081

29.6744

51.1319
53.5452
53.5572

76.7462
77.0004
77.2550

118.2626

126.7373
128.6803
129.6701
130.5314
134.3198
135.2548

^{1}H NMR of **4.20c**

^{13}C NMR of **4.20c**

21.8078

29.4307

51.0865
53.1565
55.8367

76.7458
77.0014
77.2564

117.7136

126.7616
127.5914
128.6299
129.6684
134.2713

139.6742
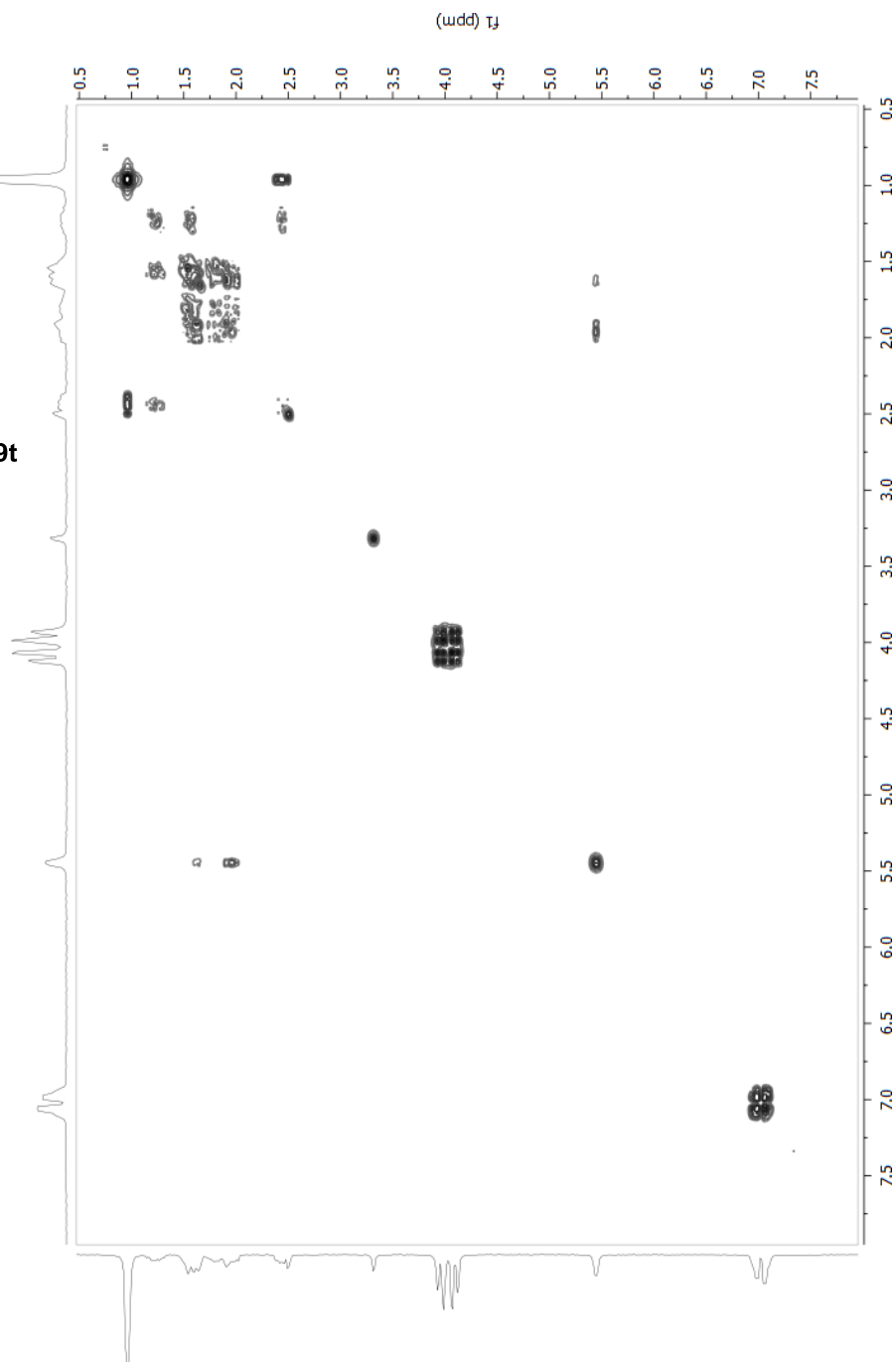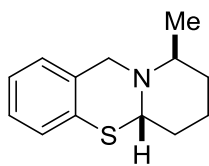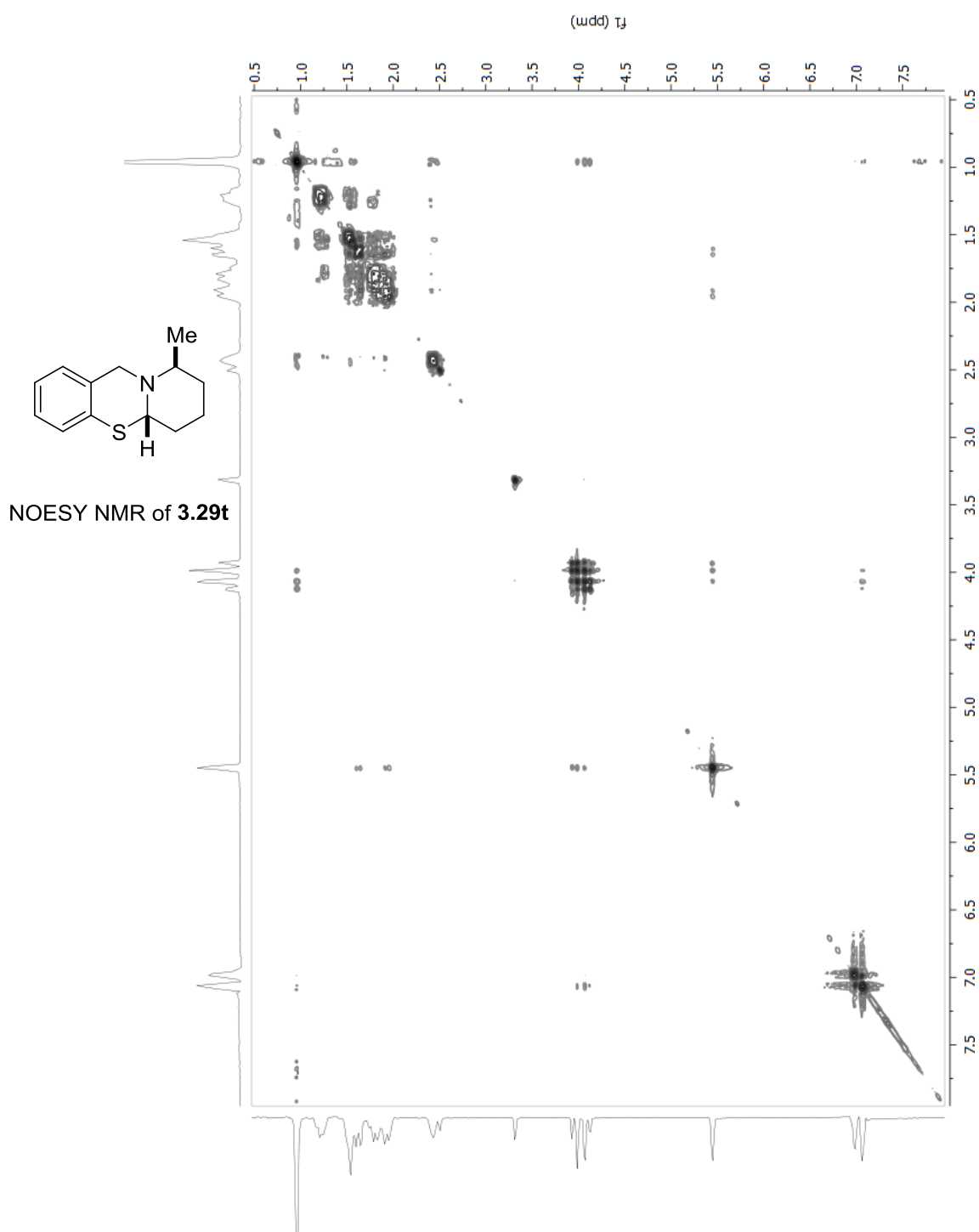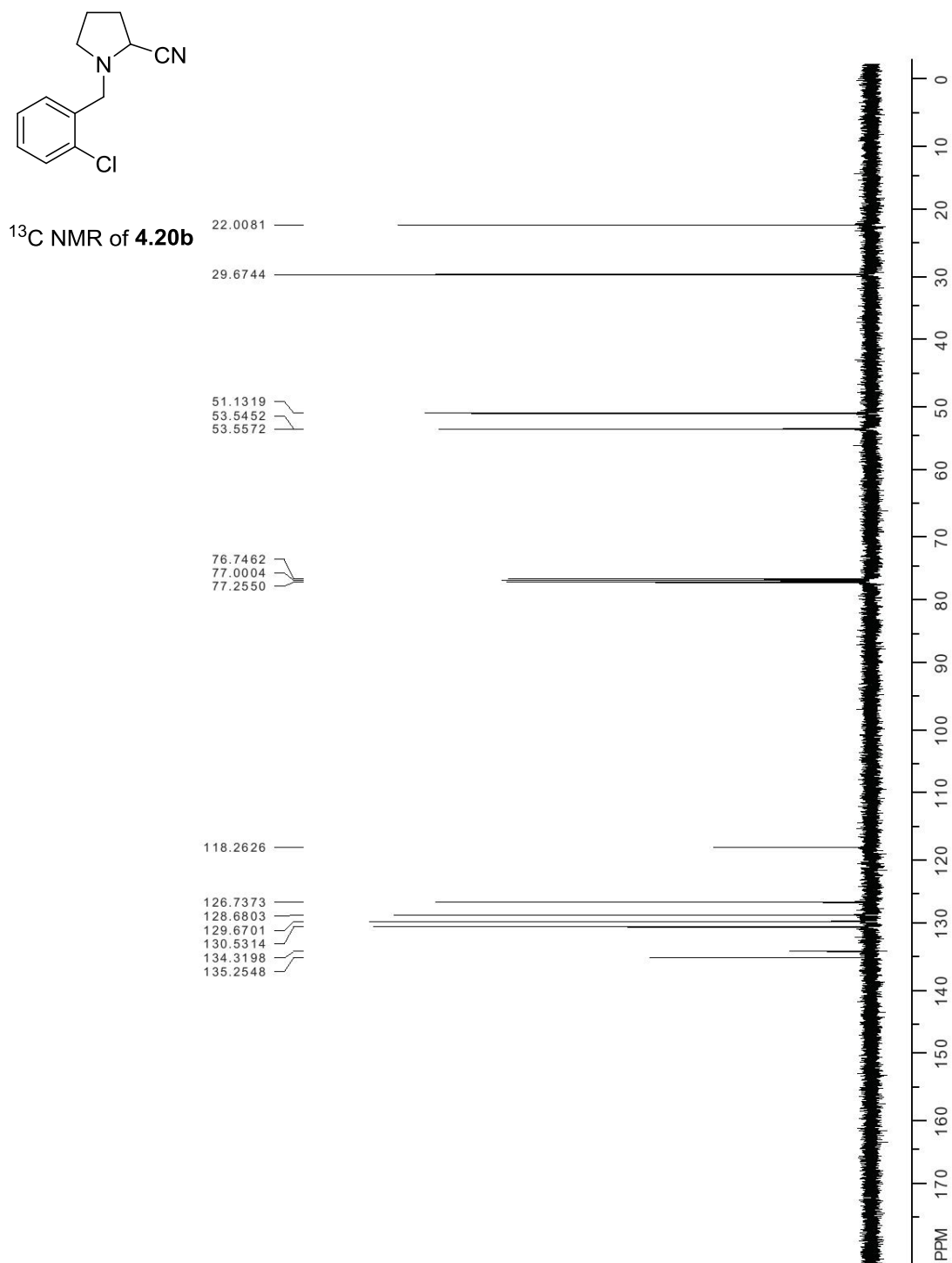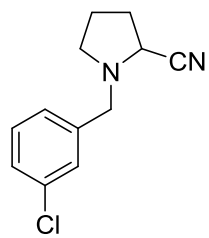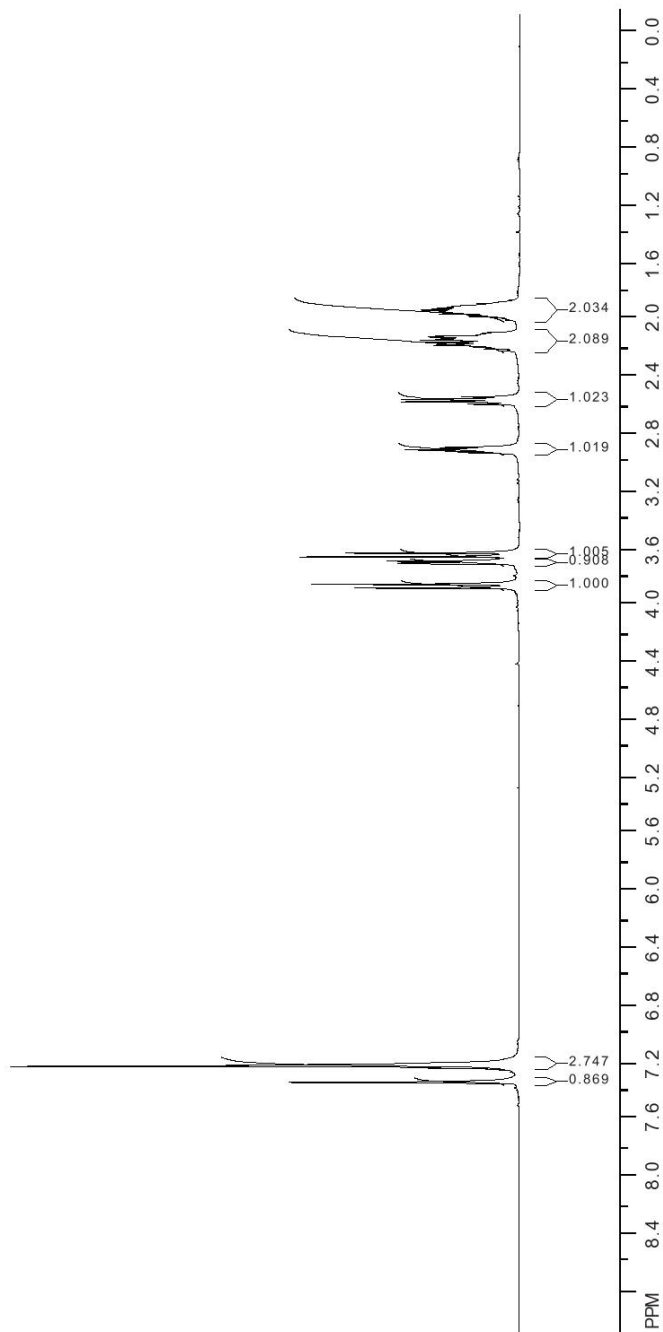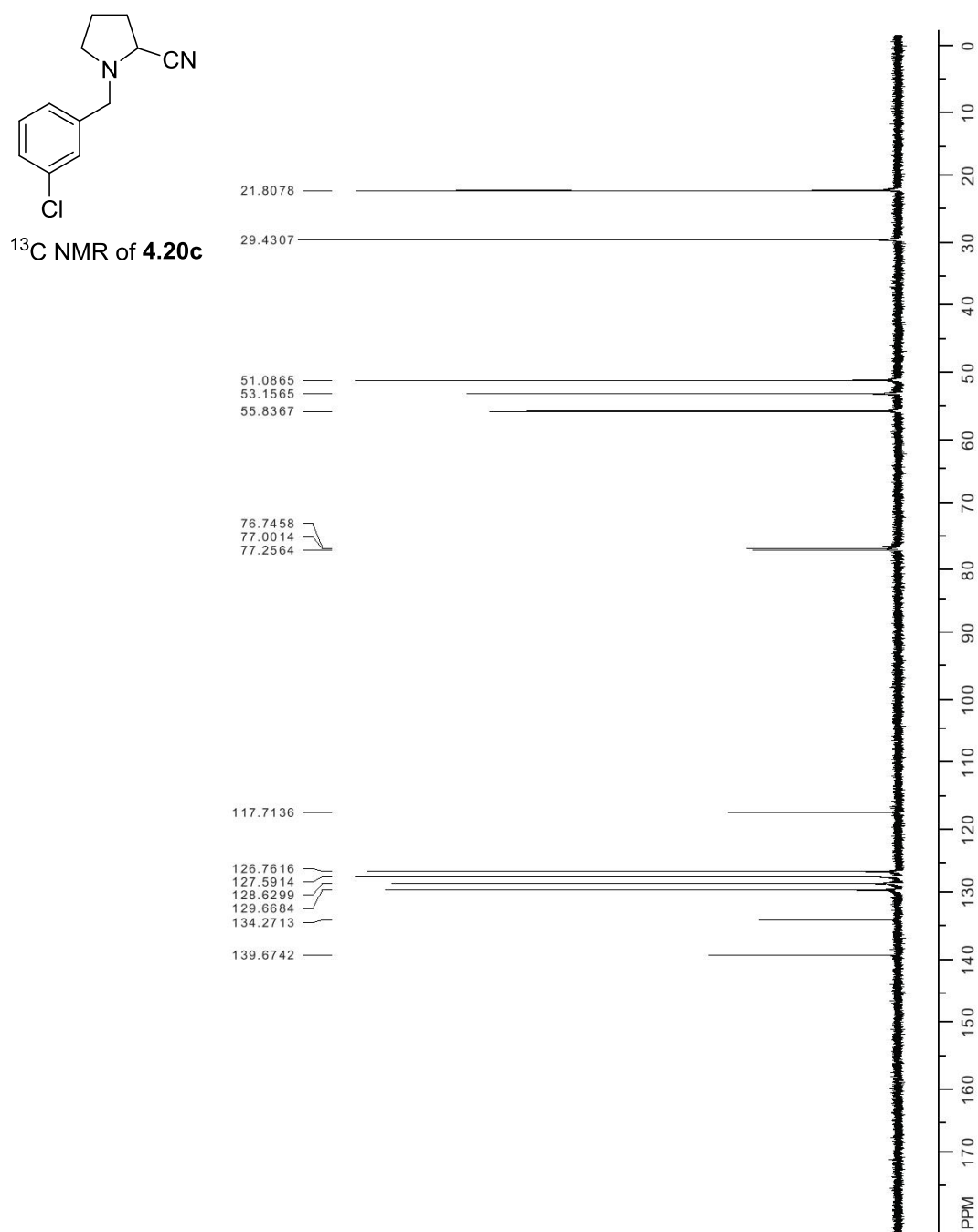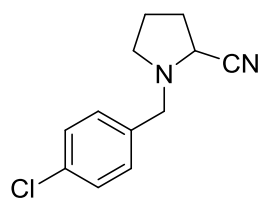
^{1}H NMR of **4.20d**

^{13}C NMR of **4.20d**

21.8109

29.4099

51.0878
53.0790
55.7032

76.7468
77.0007
77.2554

117.7441

128.5597
130.0400
133.1292
136.0572
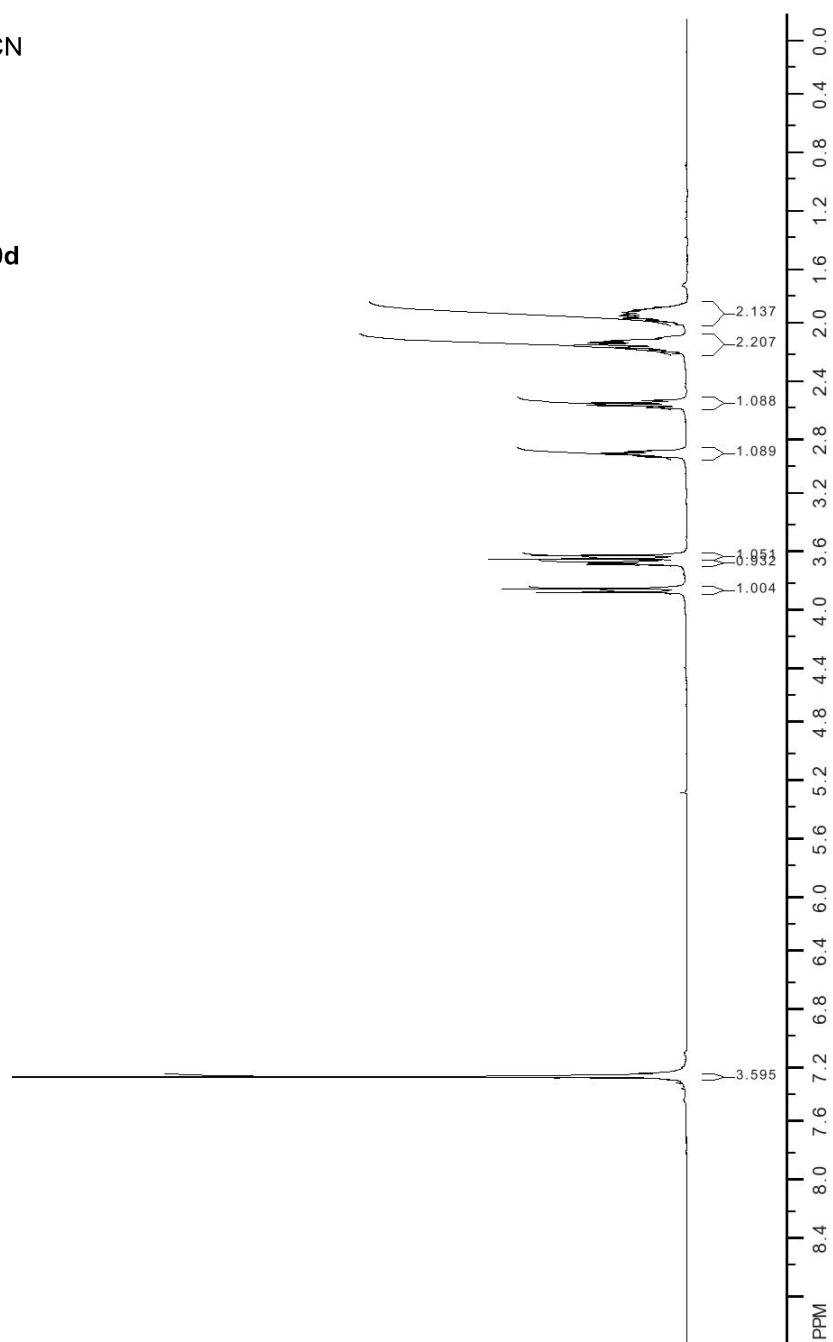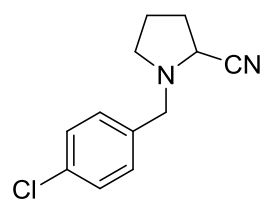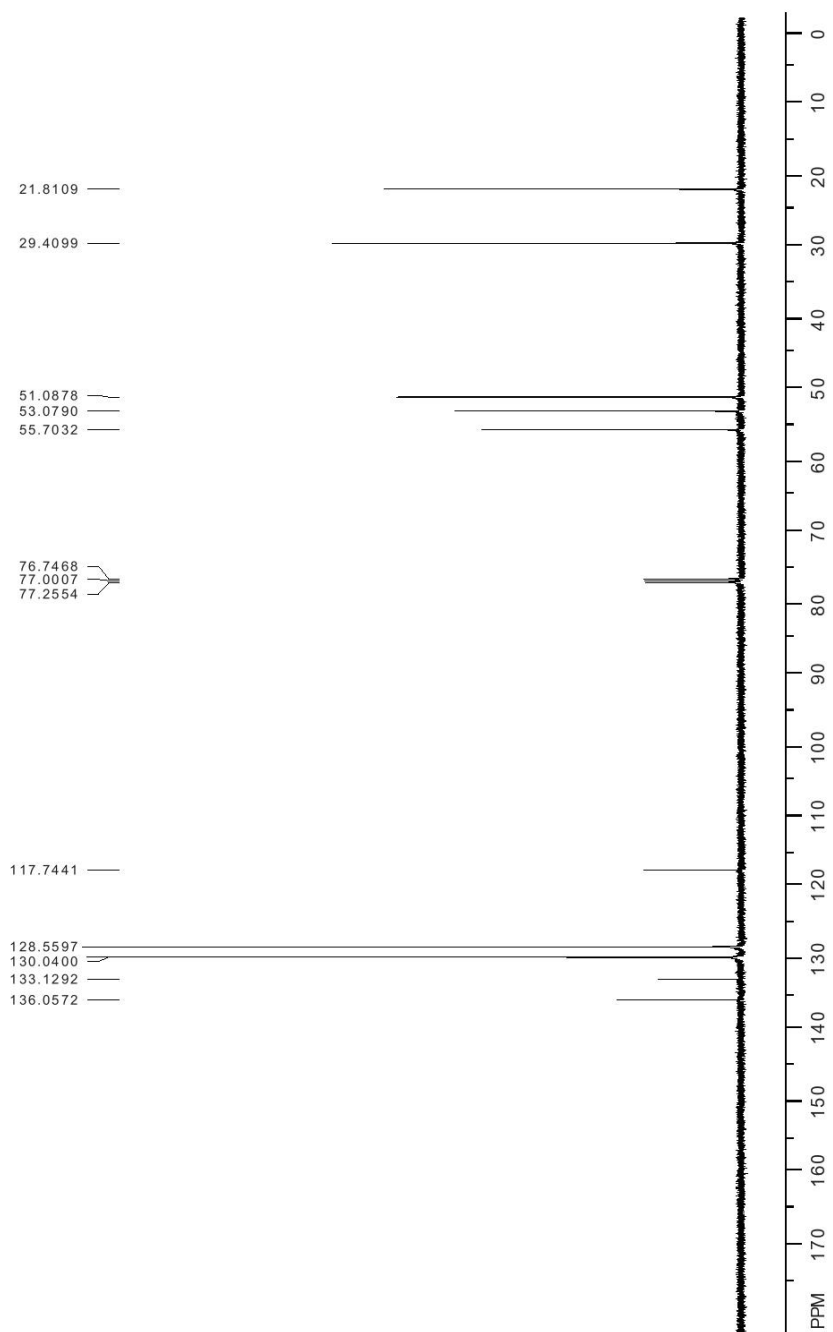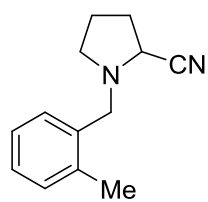
^{1}H NMR of **4.20e**

^{13}C NMR of **4.20e**

18.9066
21.8303

29.5081

51.0182
53.1700
54.3995

76.7444
76.9991
77.2538

118.0946

125.6904
127.4469
129.3307
130.2812

135.6235
137.2999
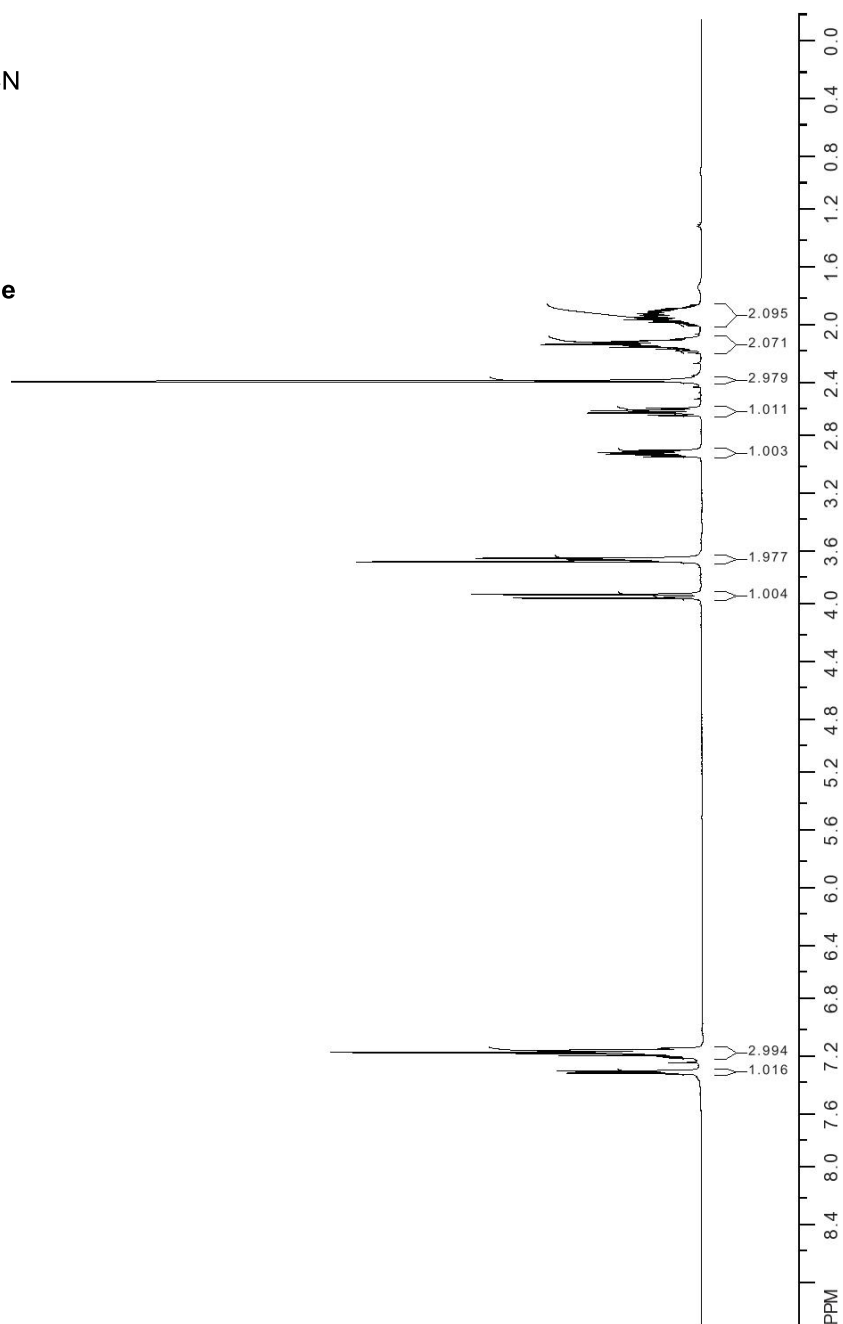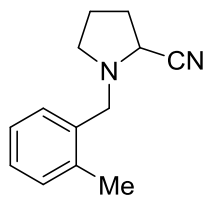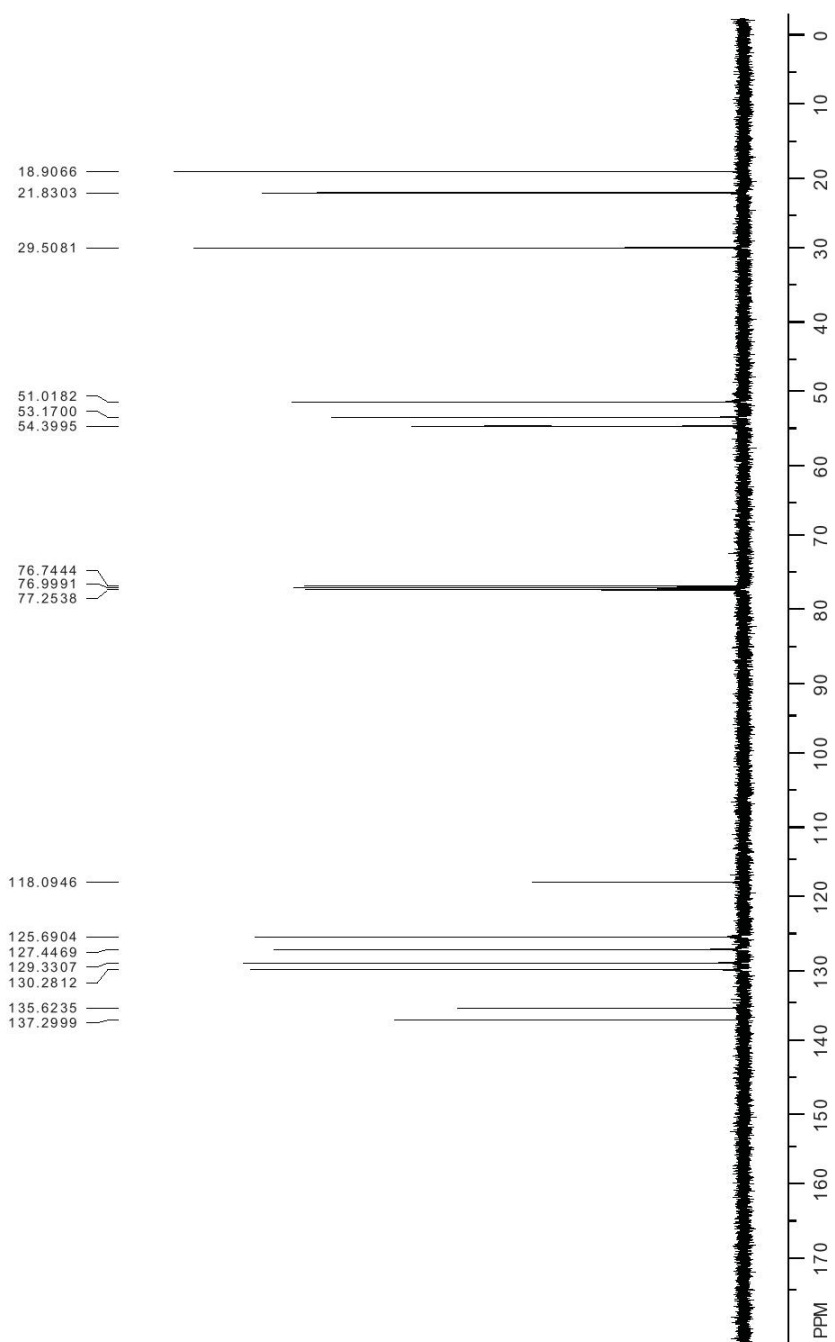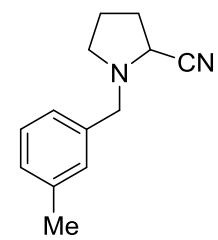
^{1}H NMR of **4.20f**

^{13}C NMR of **4.20f**

21.2353
21.7405

29.3919

51.0922
53.0739
56.3827

76.7460
77.0005
77.2553

117.8431

125.7665
128.0994
128.2407
129.4291

137.3637
137.9720

0
10
20
30
40
50
60
70
80
90
100
110
120
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140
150
160
170
PPM
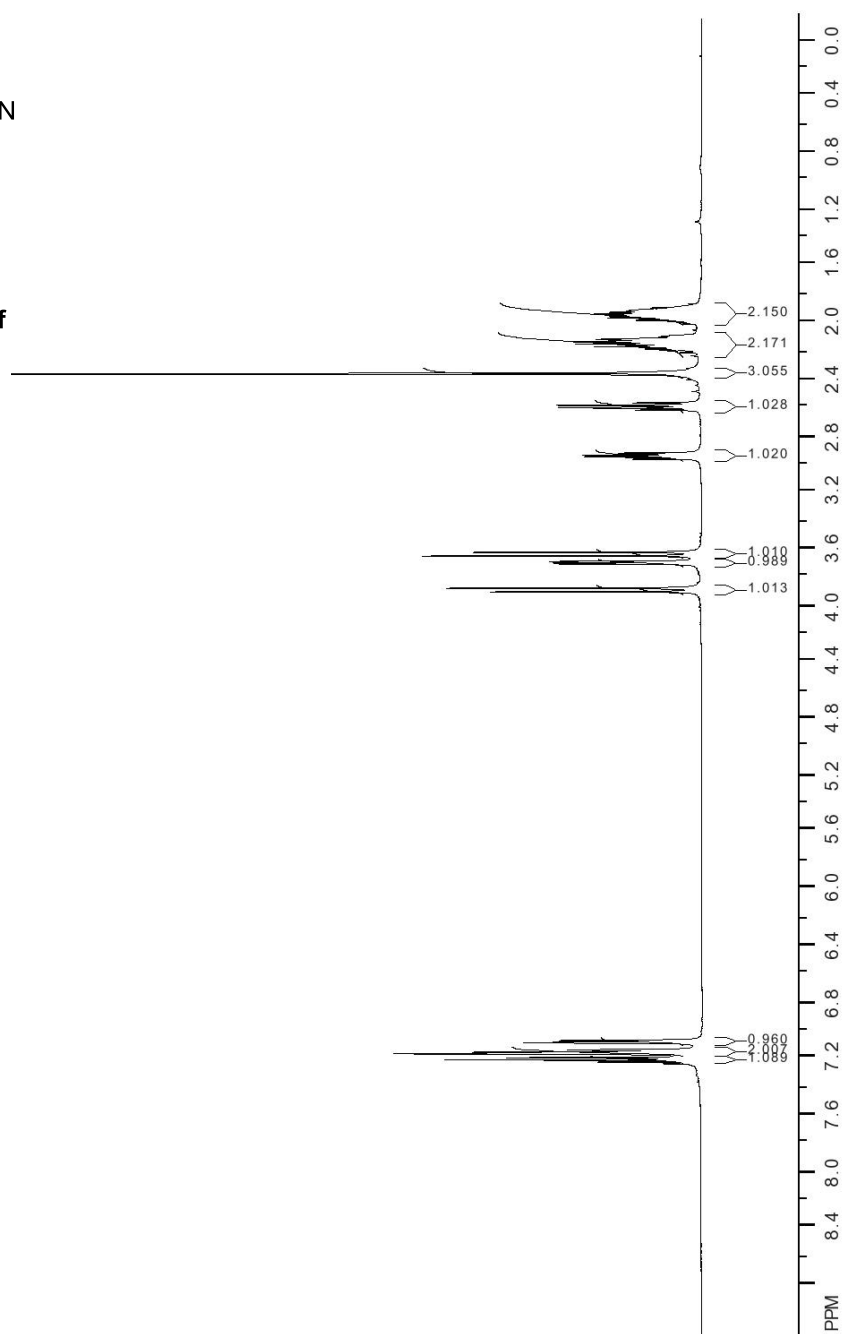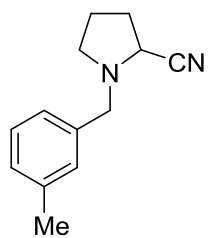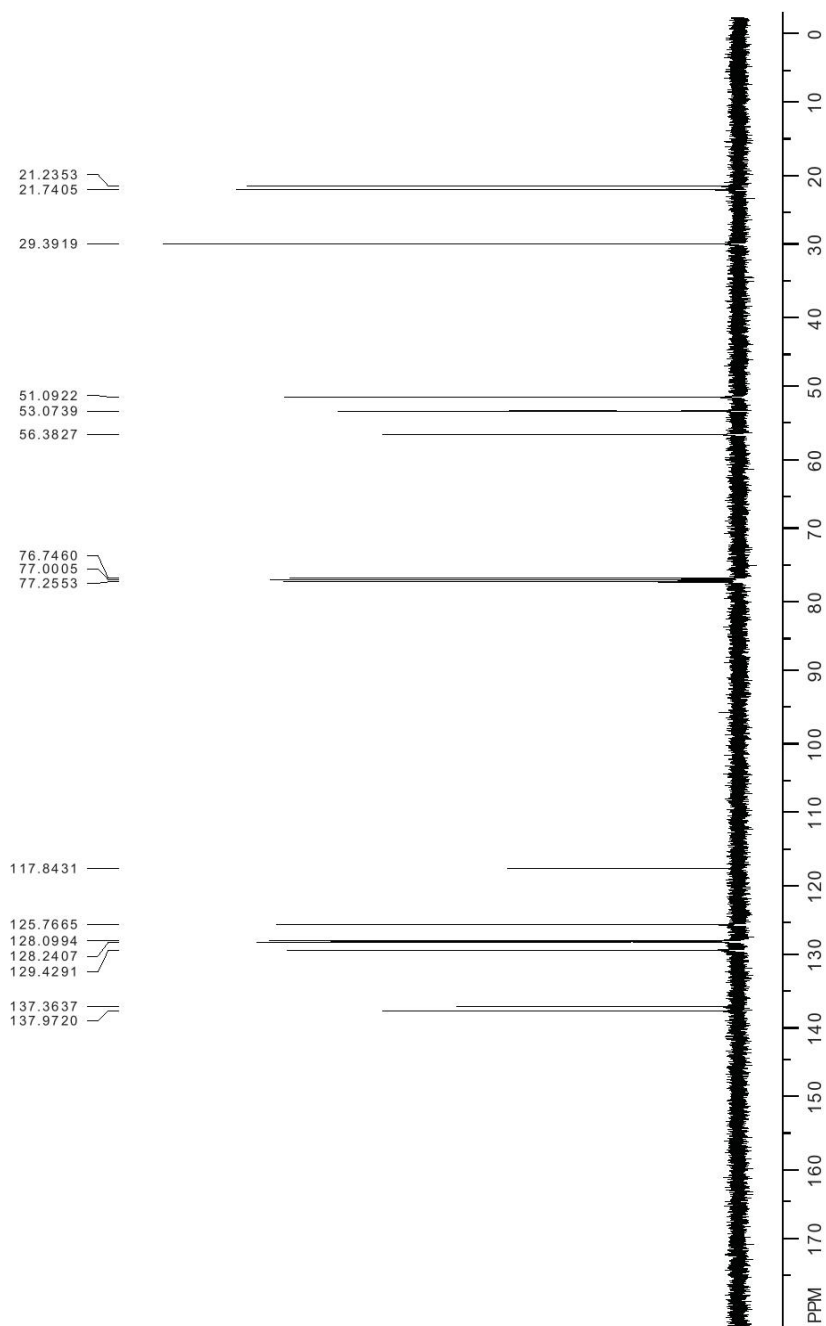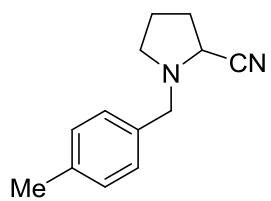
^{1}H NMR of **4.20g**

^{13}C NMR of **4.20g**

21.0126
21.7681

29.4014

51.0547
53.0170
56.1127

76.7458
77.0008
77.2549

117.8730

128.7180
129.0692
134.3854
137.0305

^{1}H NMR of **4.20h**

^{13}C NMR of **4.20h**

21.7377

29.3481

50.9793
52.8997
55.1180
55.7216

76.7459
77.0004
77.2552

113.7112

117.8779

129.5567
129.8980

158.8698

PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
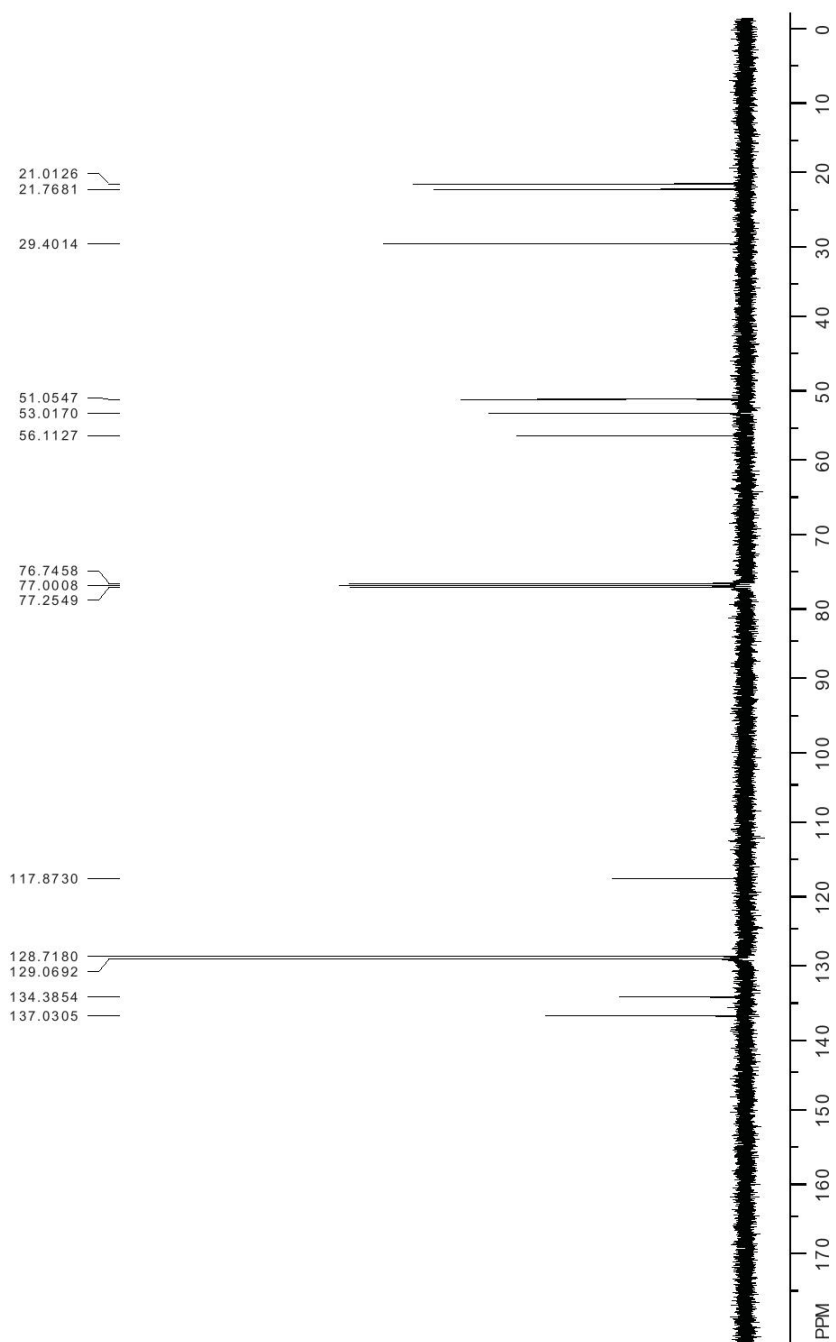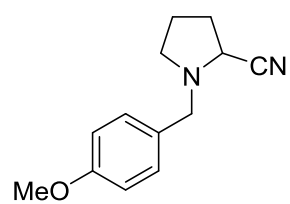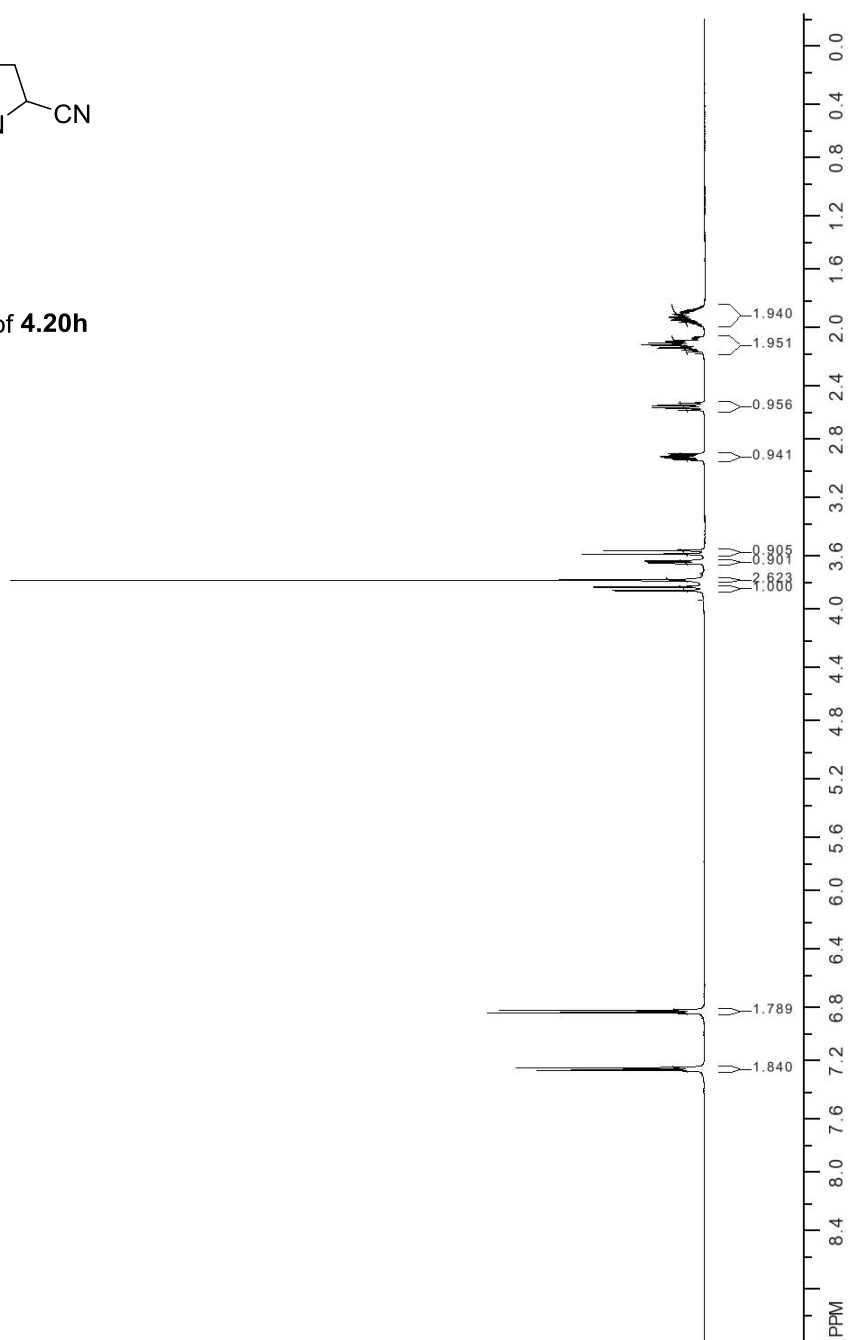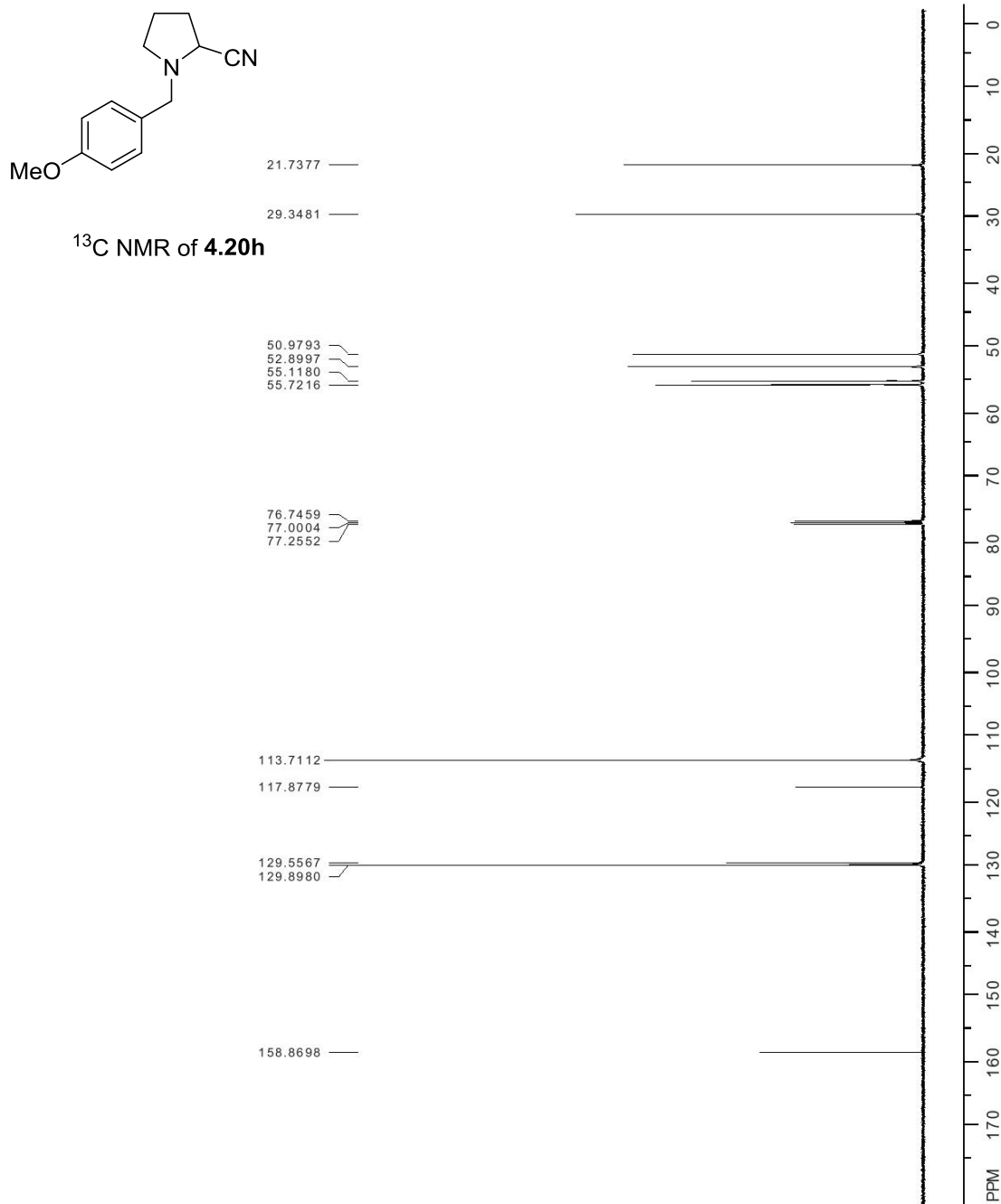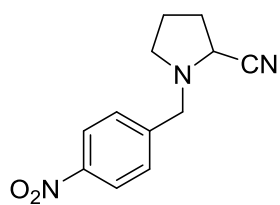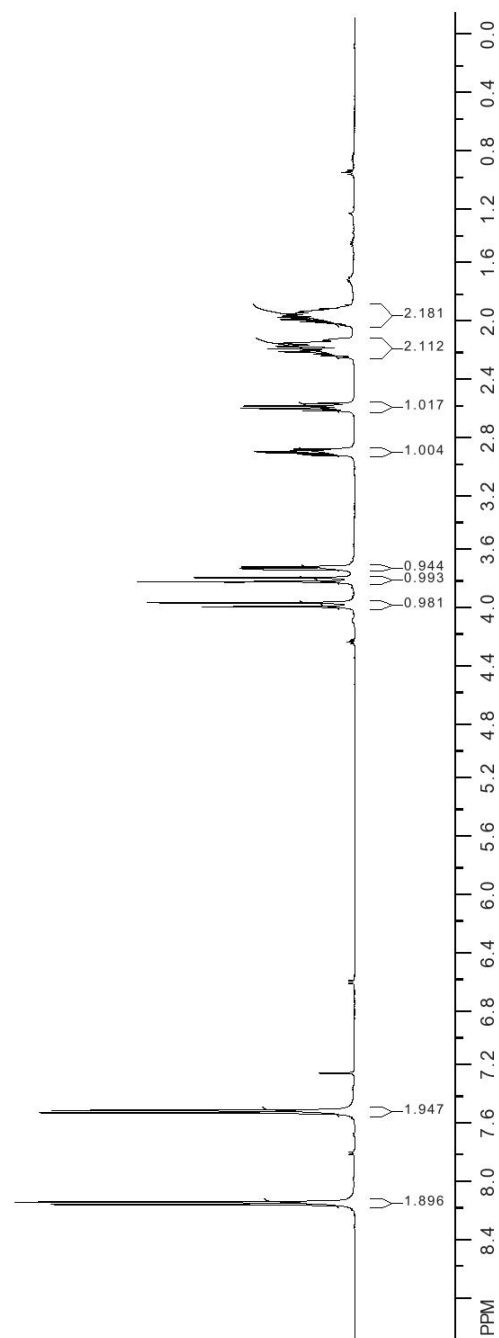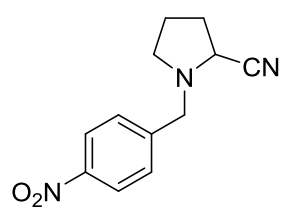
¹H NMR of **4.20i**

^{13}C NMR of **4.20i**

21.9448

29.5116

51.2629
53.3524
55.8045

76.7449
76.9996
77.2540

117.6286

123.6638

129.2669

145.2231
147.3229

0

10

20

30

40

50

60

70

80

90

100

110

120

130

140

150

160

170

PPM
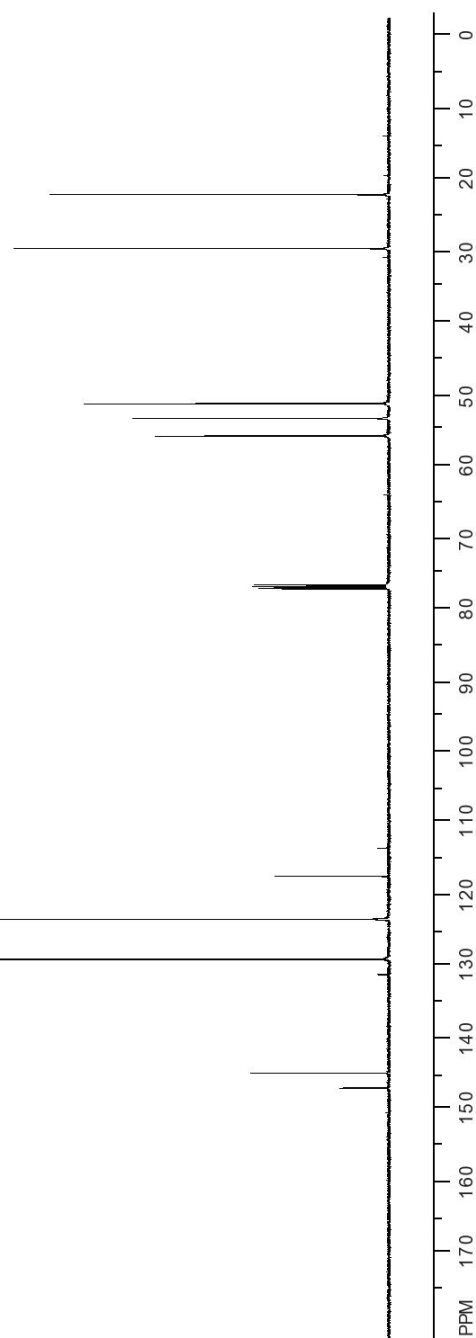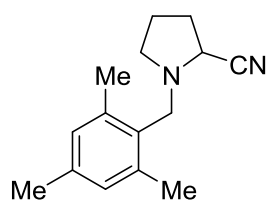
^{1}H NMR of **4.20j**

^{13}C NMR of **4.20j**

19.9677
20.8432
21.9663

29.7496

49.5262
50.2172
53.5079

76.7450
76.9990
77.2533

118.8196

129.0624
131.1710

136.7126
137.6686

PPM
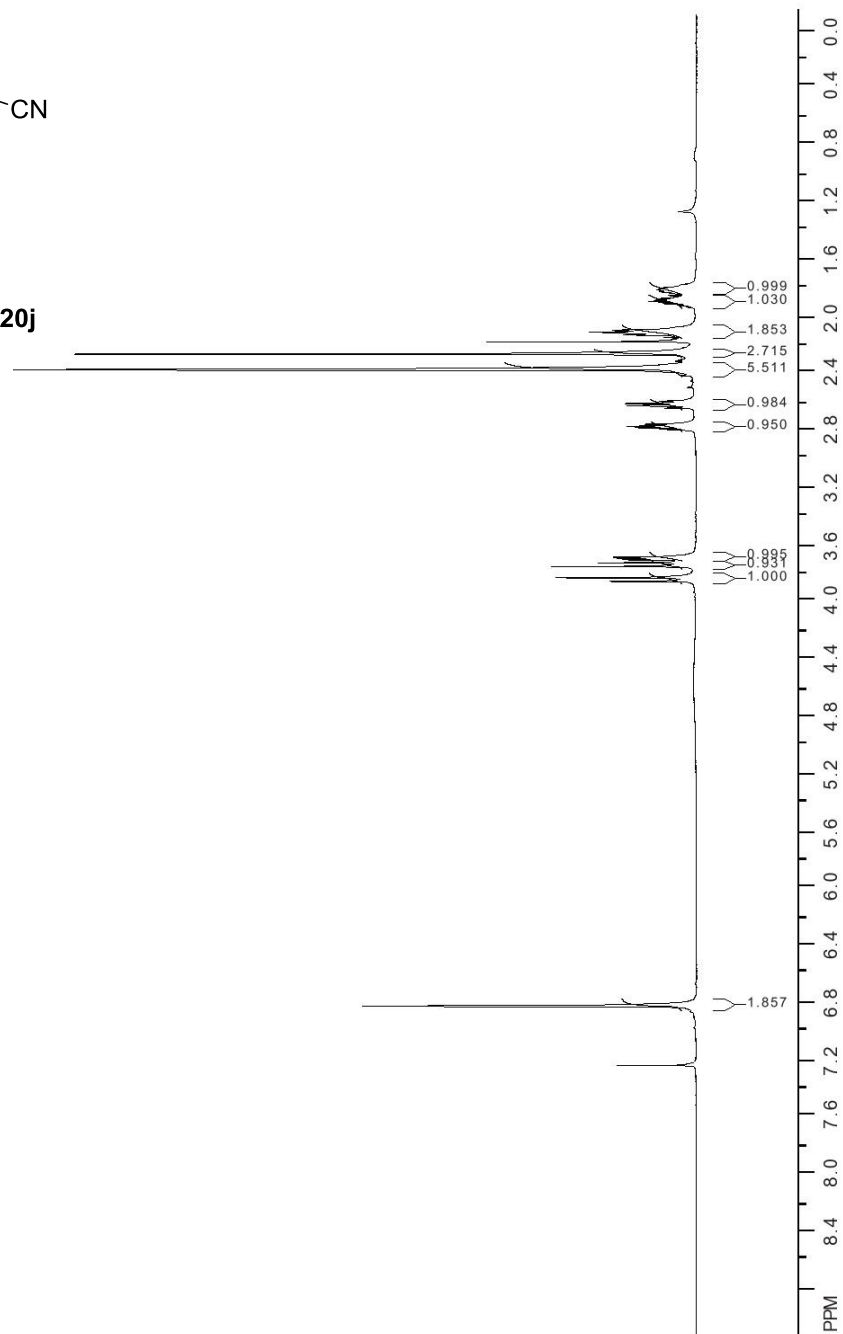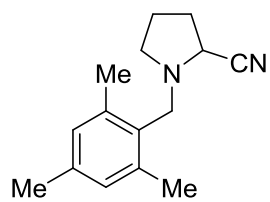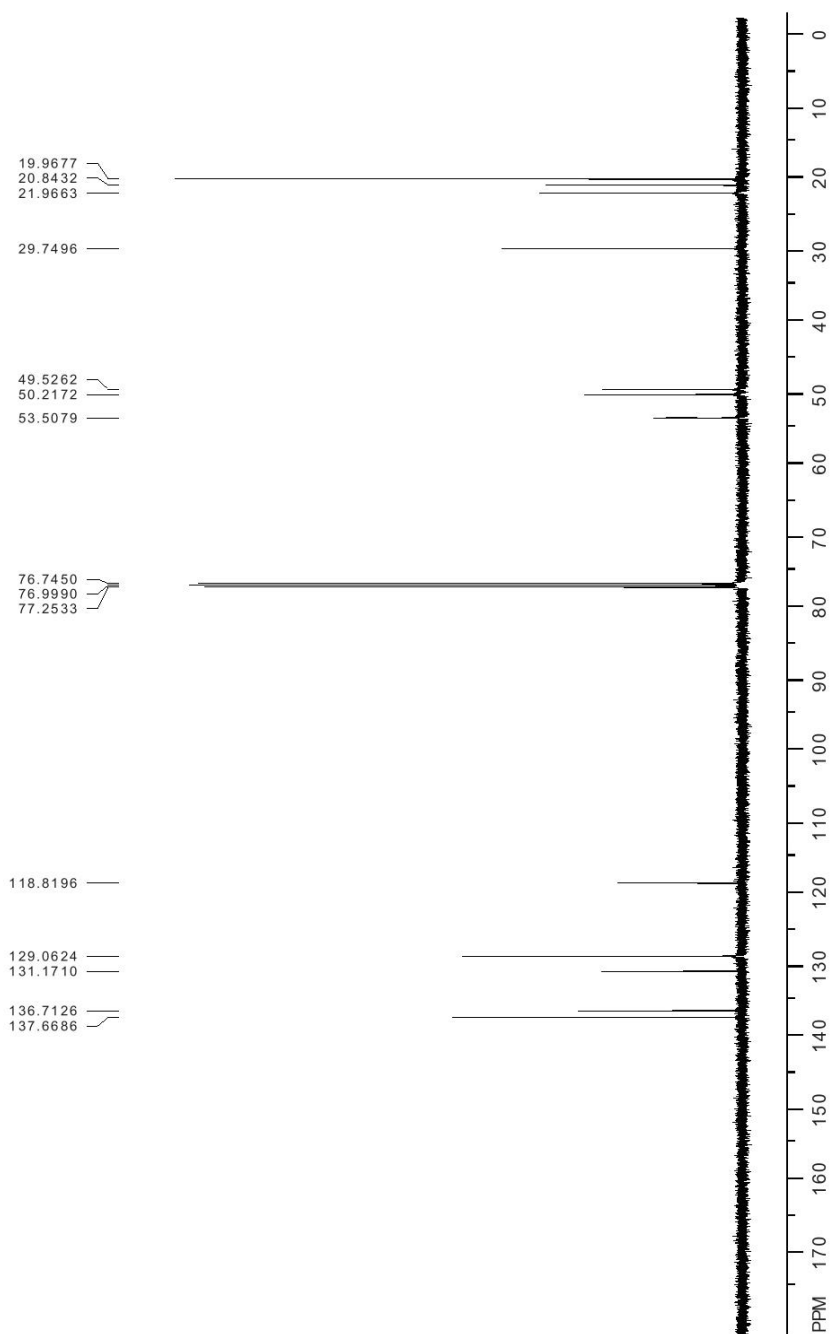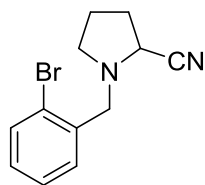
^{1}H NMR of **4.20k**

^{13}C NMR of **4.20k**

21.9505

29.5924

50.9578
53.4055
55.9238

76.7473
77.0017
77.2567

118.1652

124.4463
127.2724
128.8386
130.4643
132.8642

136.8097

^{1}H NMR of **4.20l**

^{13}C NMR of **4.20l**

21.8337

29.4853

51.1445
53.1705
54.7059

76.7442
76.9989
77.2533

118.0626
124.3245
125.1980
125.7062
125.9253
127.2342
128.3783
128.4171
132.1207
133.2562
133.7541
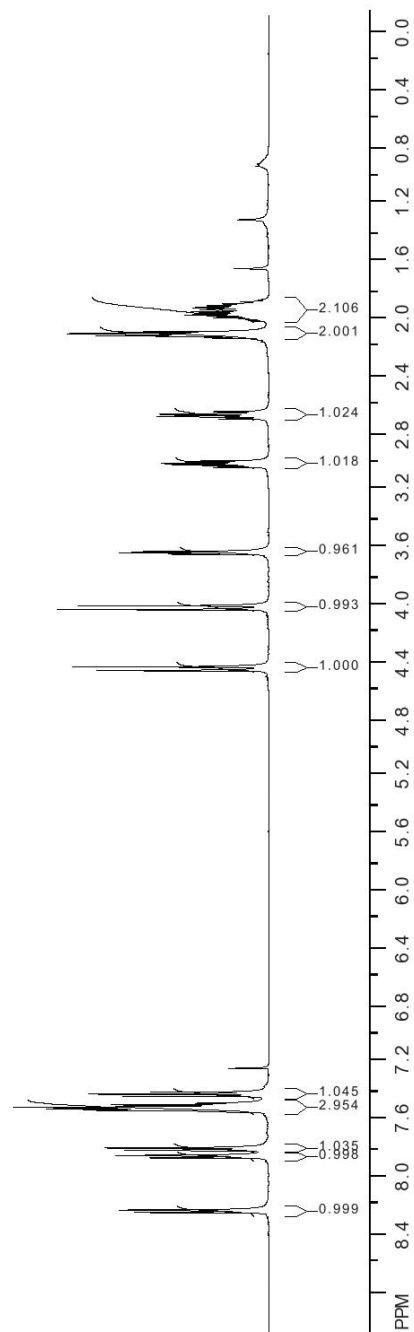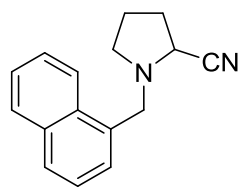
^{1}H NMR of **4.20m**

^{13}C NMR of **4.20m**

21.7585

29.3590

51.0227
53.1457
53.7352

76.7463
77.0005
77.2558

117.5550

123.3179

133.0107
136.3082

148.7403
149.8666
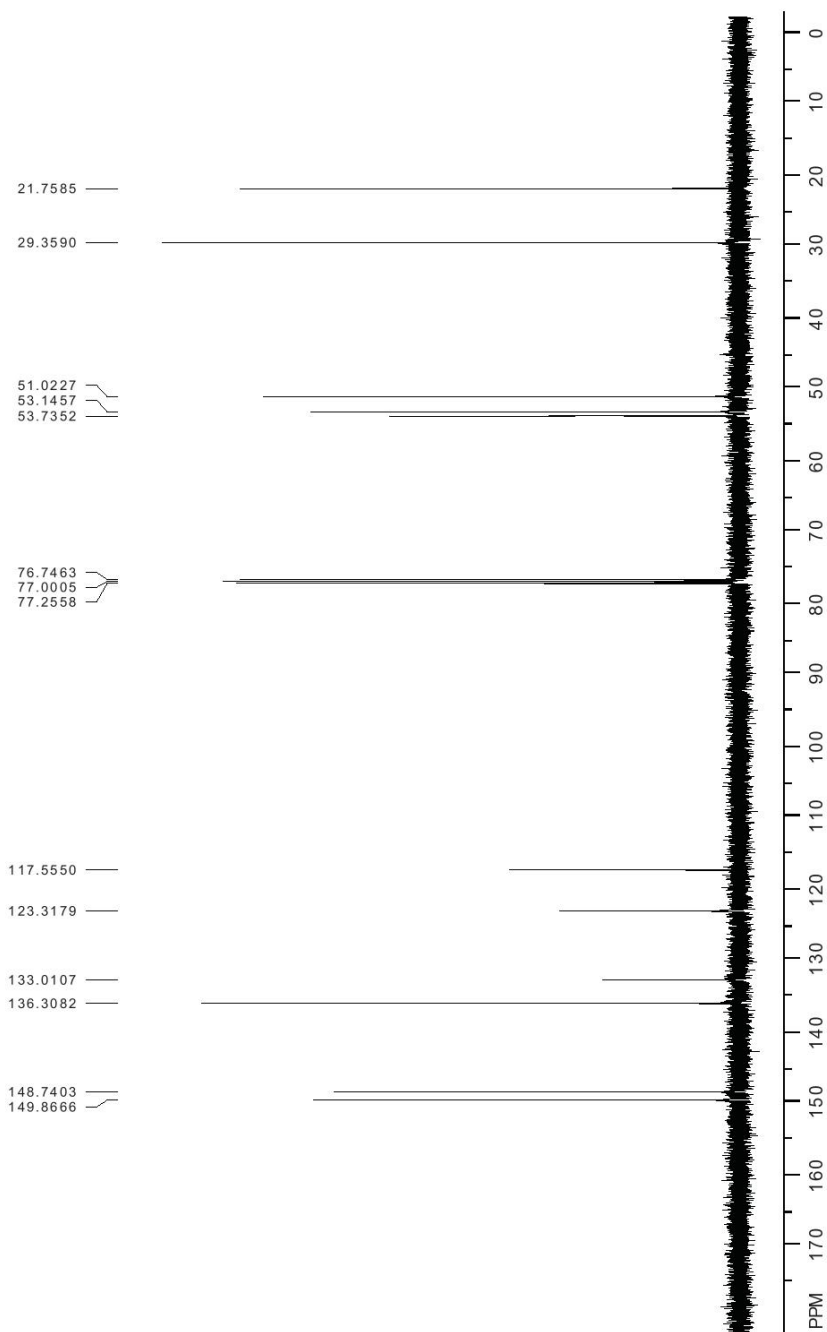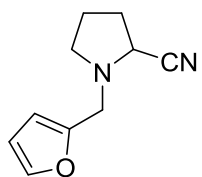
^{1}H NMR of **4.20n**

^{13}C NMR of **4.20n**

22.1552
29.7546
48.7253
51.4266
53.2192
77.0063
77.2606
77.5149
109.0739
110.4591
118.0220
142.7914
151.2331
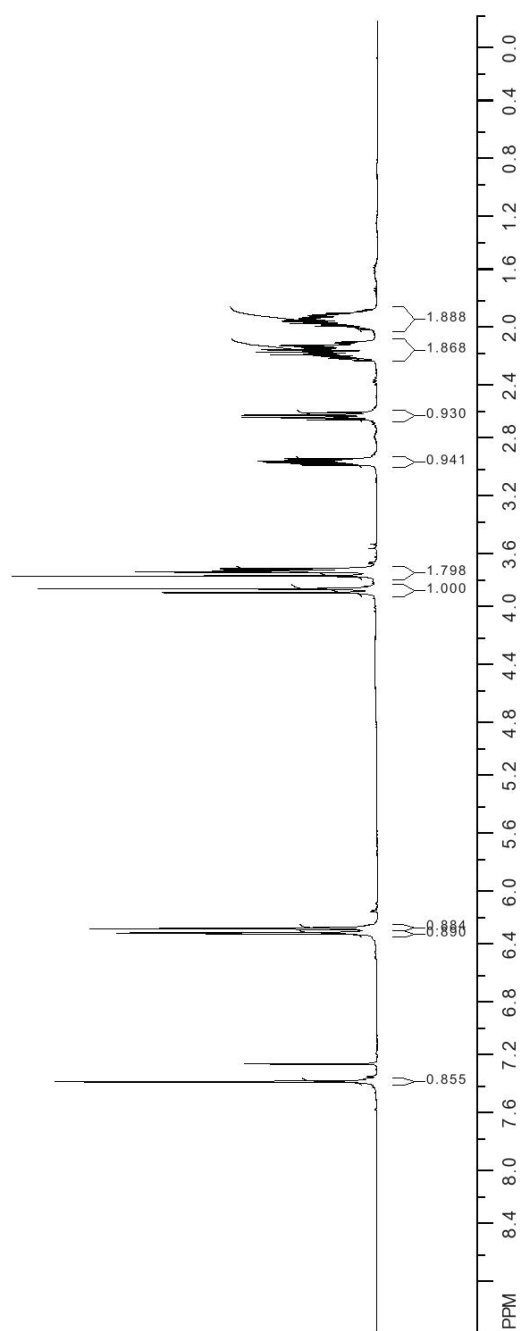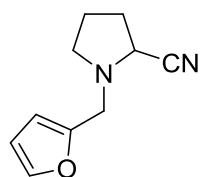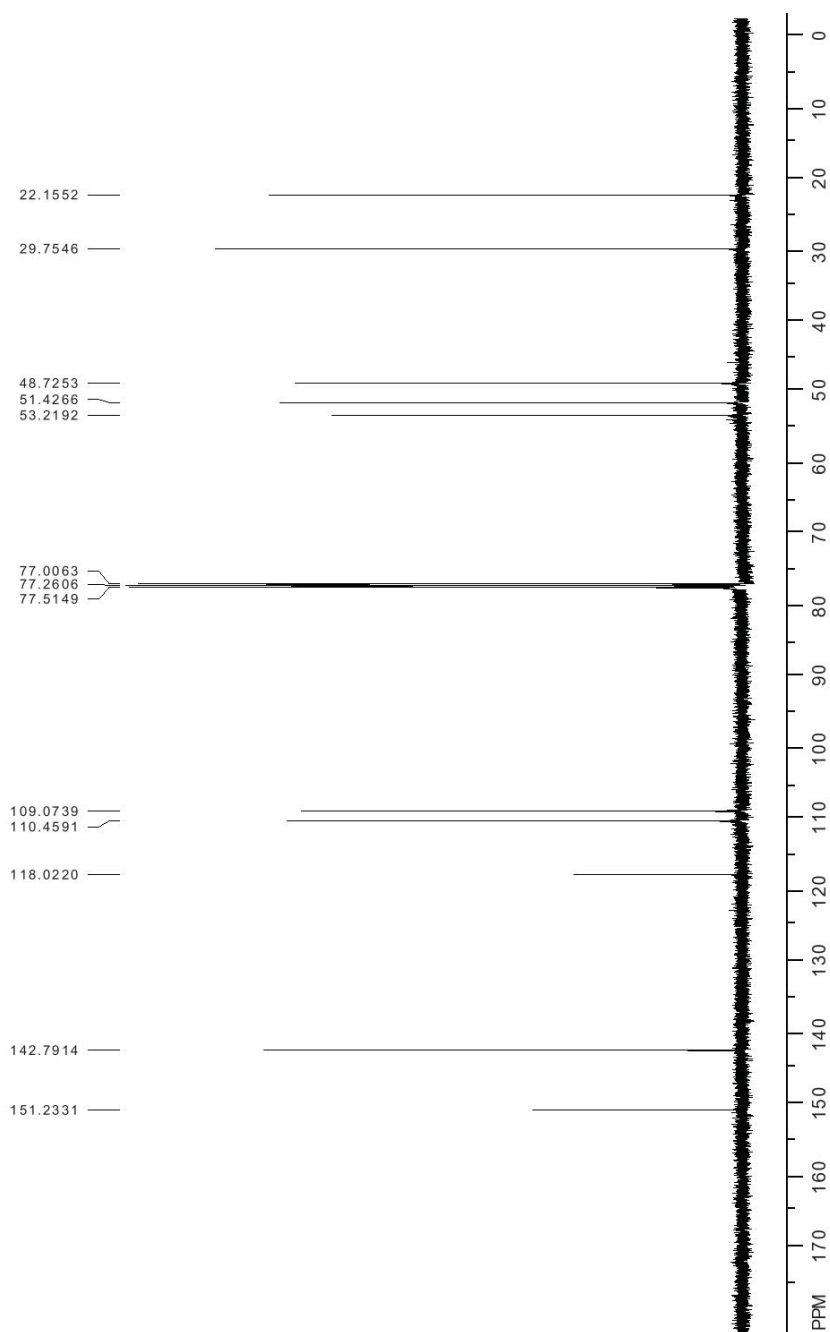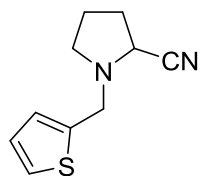
^{1}H NMR of **4.20o**

^{13}C NMR of **4.20o**

21.8301

29.3946

50.7091
50.9627
52.7523

76.7434
76.9979
77.2531

117.6779

125.4166
126.3123
126.5173

140.5869
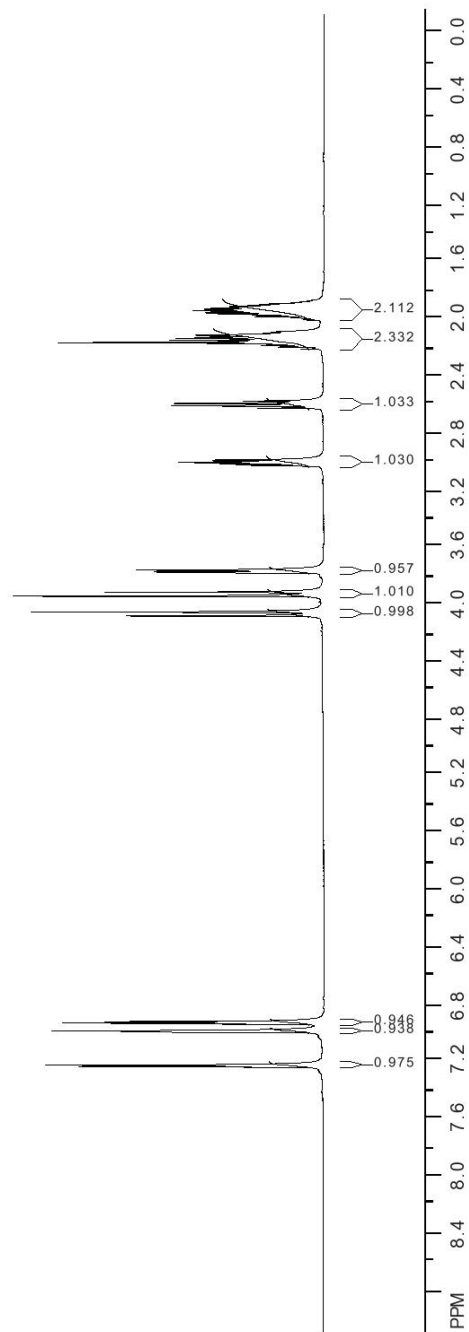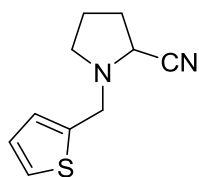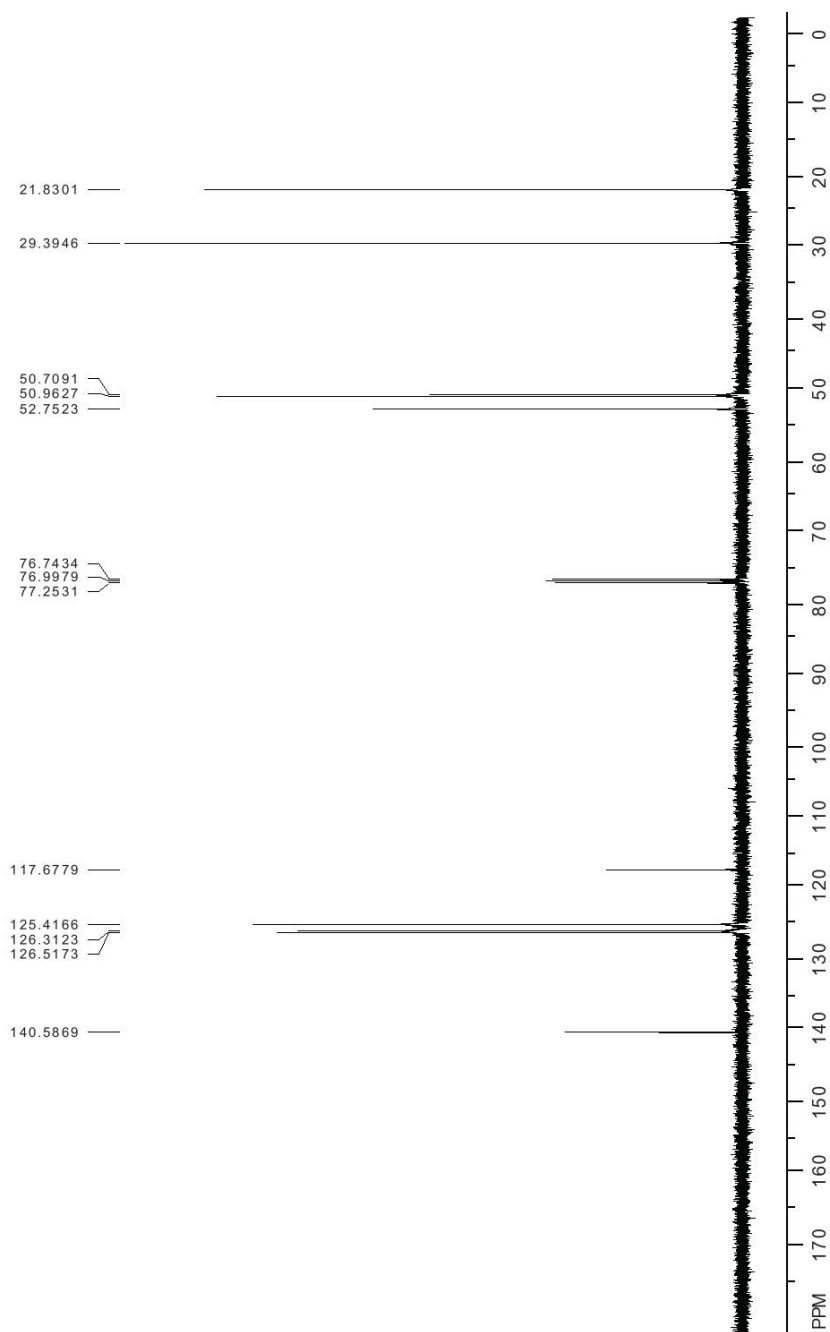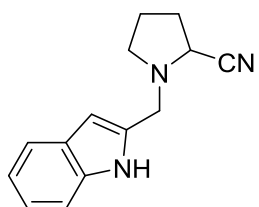
^{1}H NMR of **4.20p**

^{13}C NMR of **4.20p**

21.9439

29.4214

49.4674
51.2813
53.1807

76.7452
77.0000
77.2544

101.7712

110.6726

117.7762
119.7328
120.3659
121.8353

128.1410

134.6716
136.1391

PPM
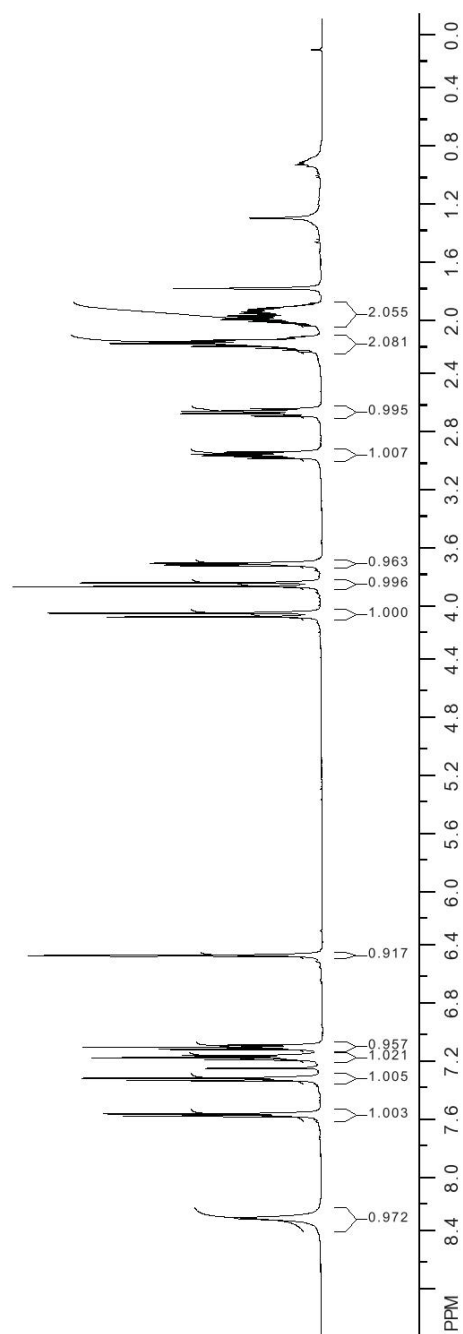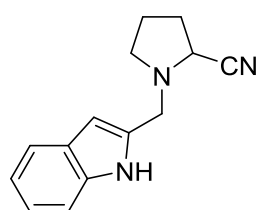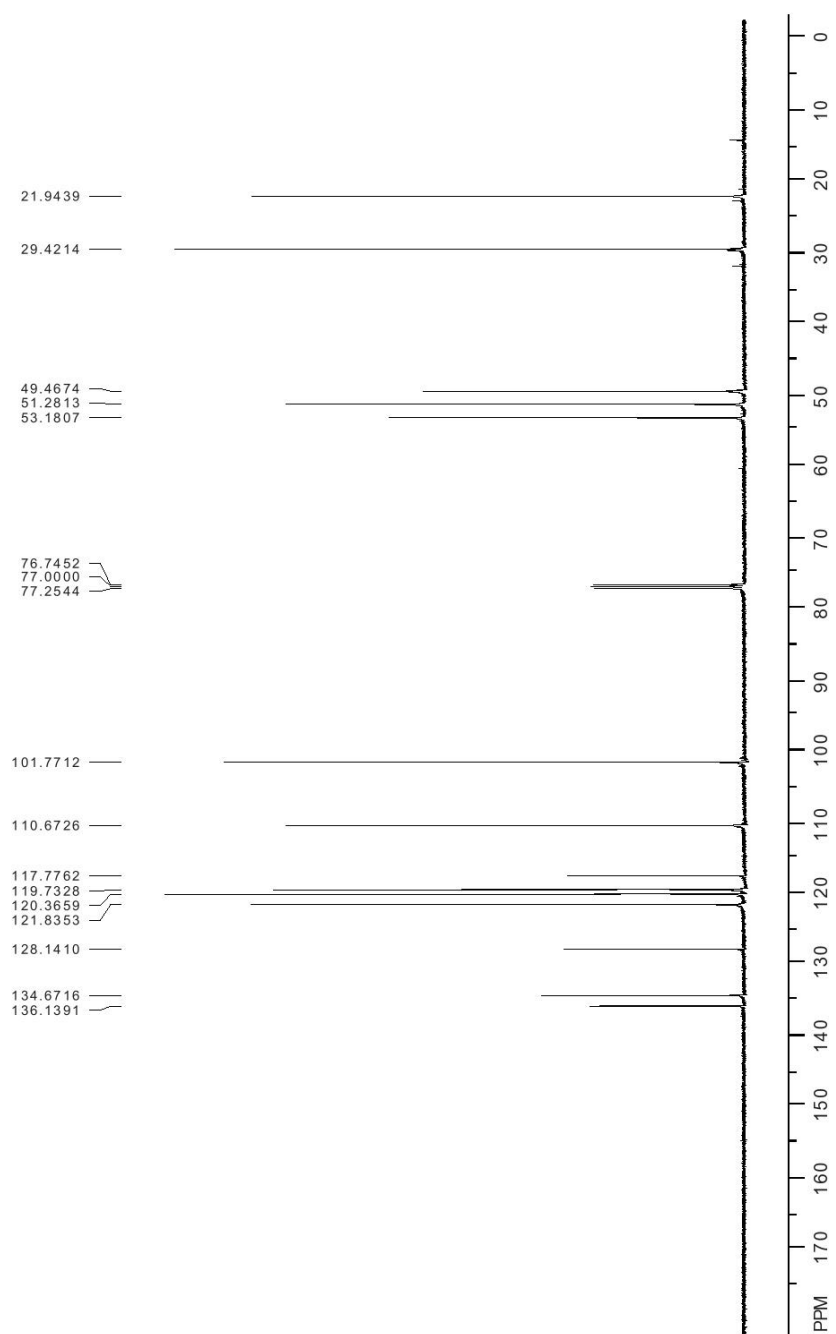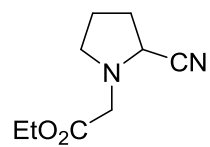
^{1}H NMR of **4.20q**

^{13}C NMR of **4.20q**

13.9387

22.0861

29.7791

51.2766
52.4298
52.7584

60.6902

76.7456
77.0005
77.2557

117.9523

169.6979

PPM
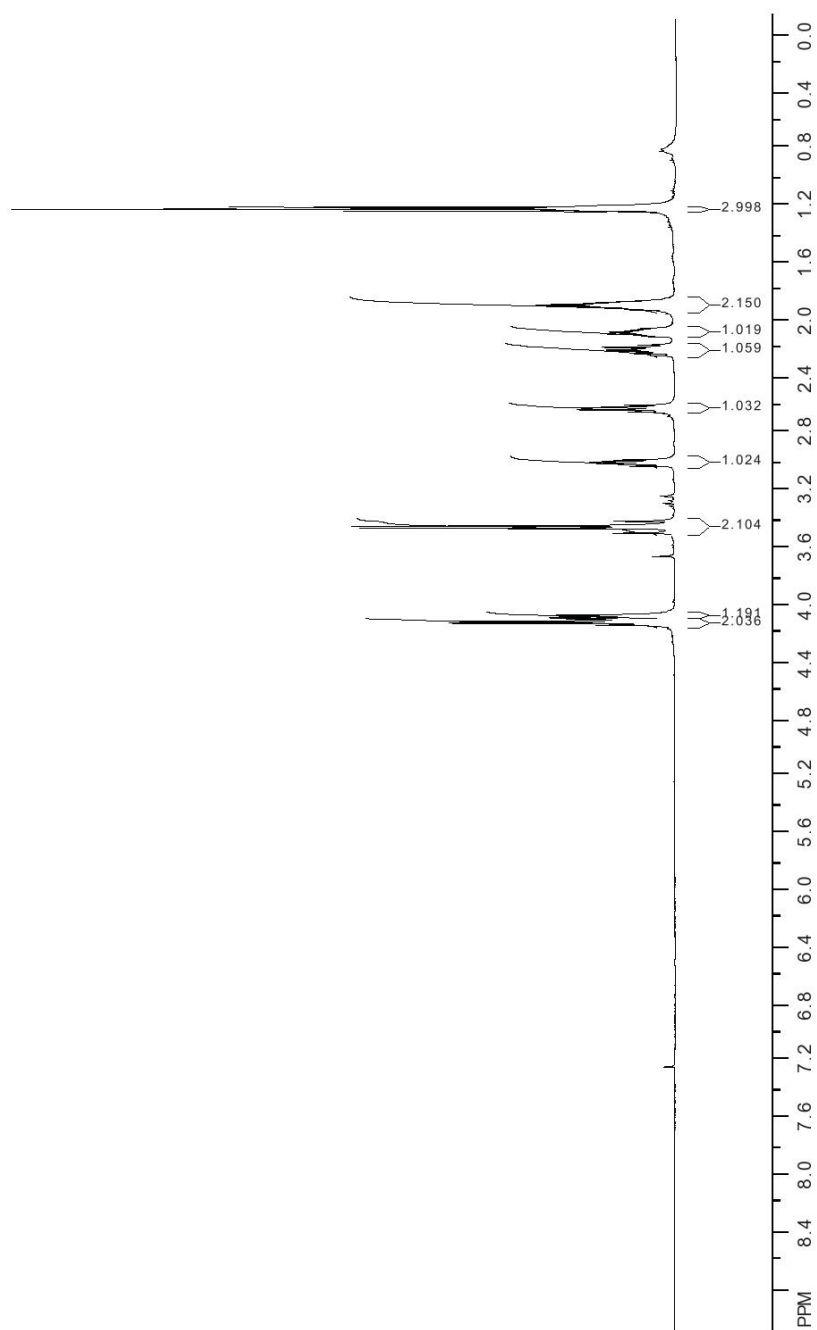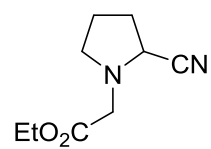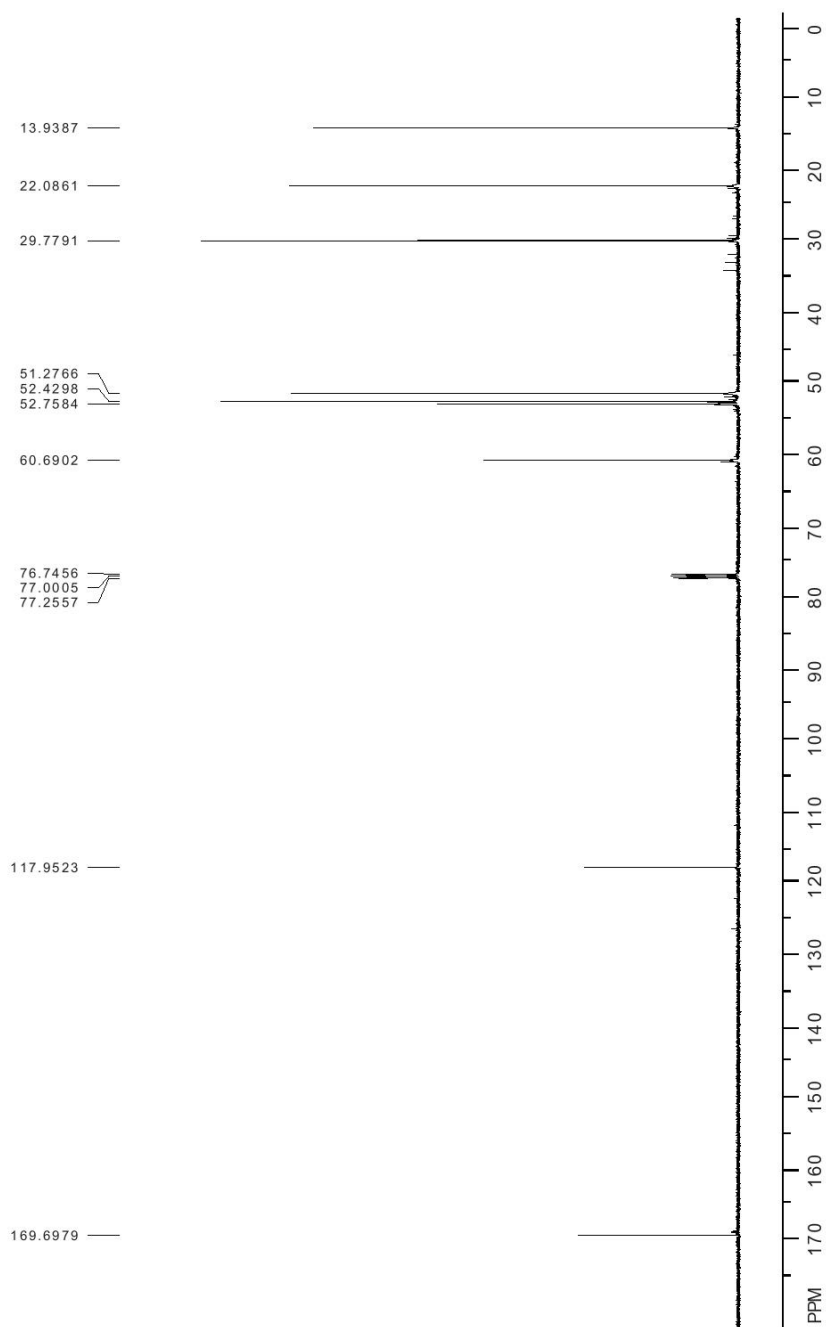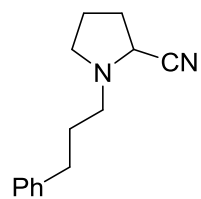
^{1}H NMR of **4.20r**

^{13}C NMR of **4.20r**

21.8377

29.5321
29.9605

33.2751

51.0401
51.8122
53.6166

76.7448
76.9996
77.2540

118.0815

125.7585
128.2510
128.3002

141.6595

PPM
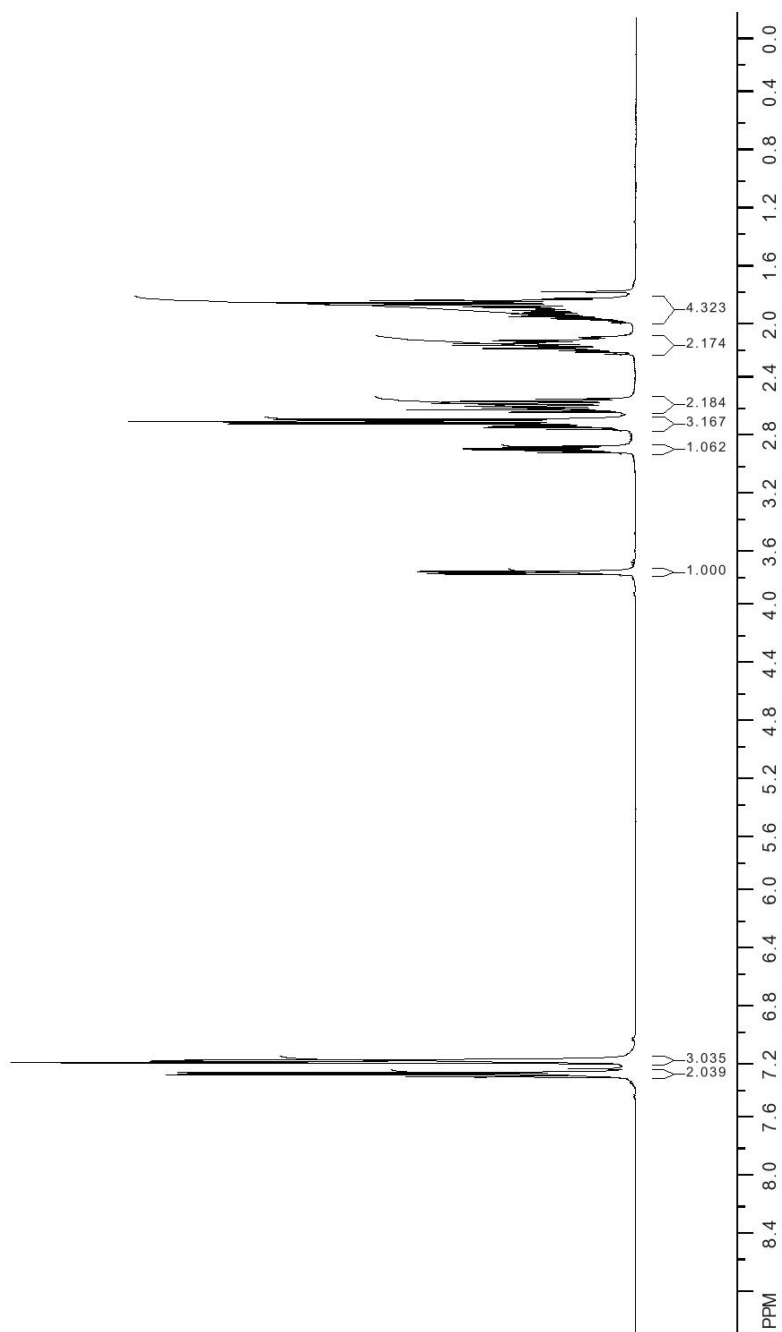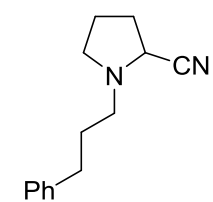
^{1}H NMR of **4.20s**

^{13}C NMR of **4.20s**

21.8582

29.5729

35.0779

51.2731
53.7003
54.1649

76.7458
77.0000
77.2544

118.0074

126.2445
128.4062
128.5748

139.4838

0
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170
PPM
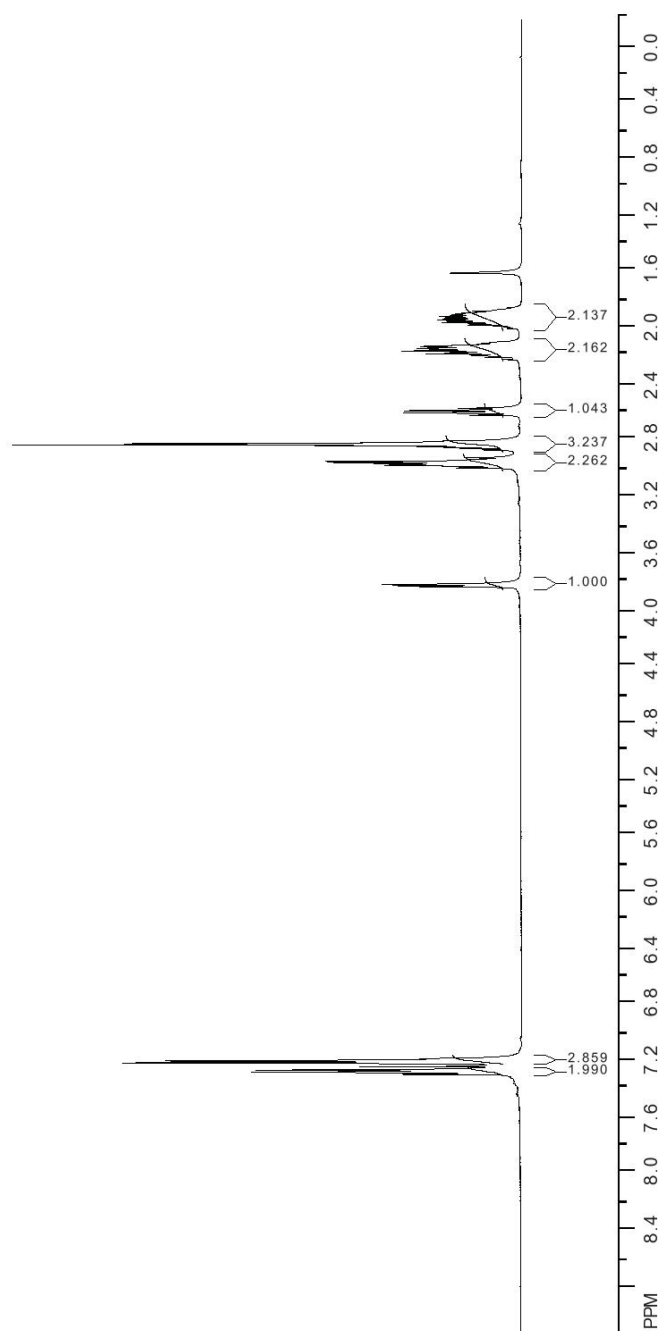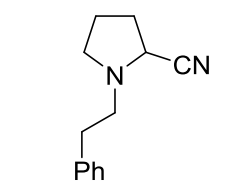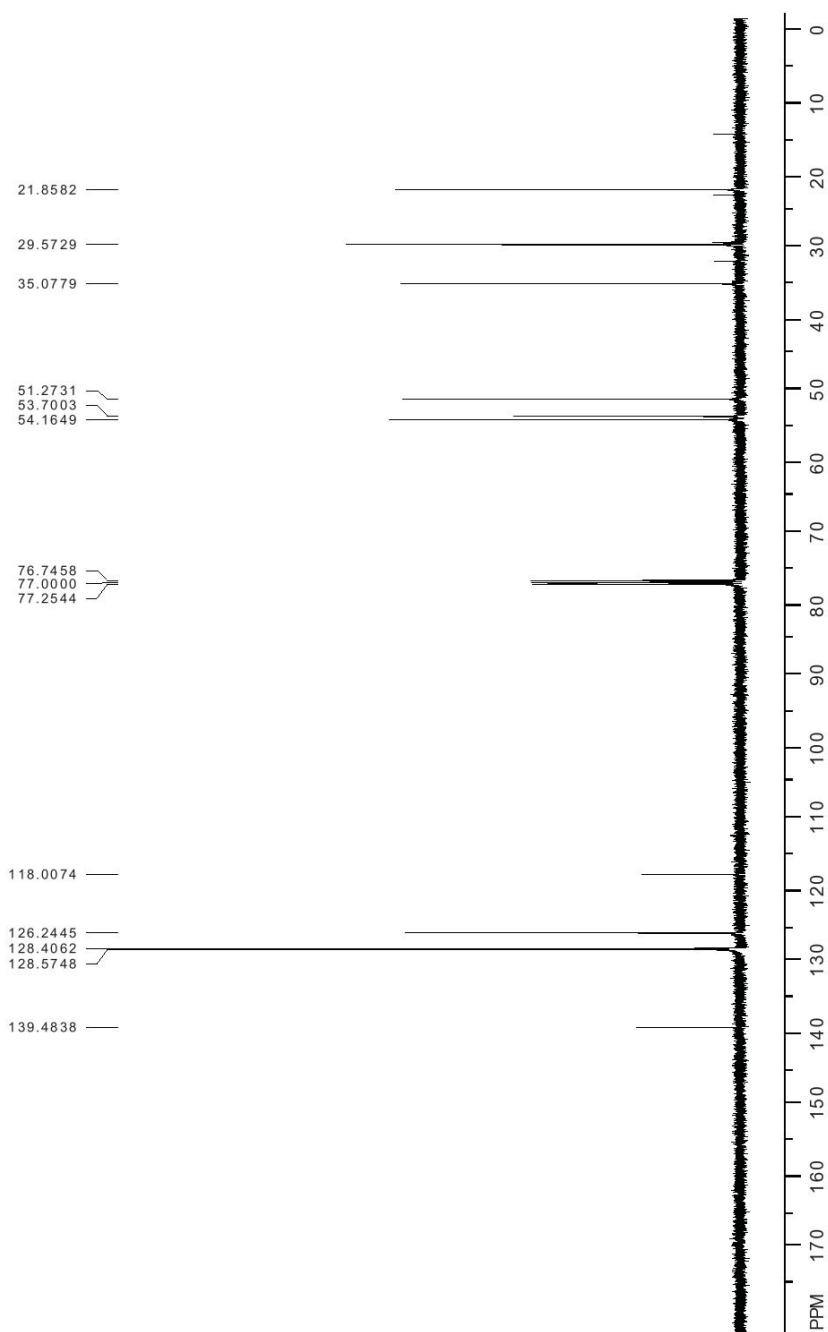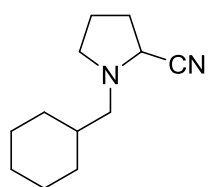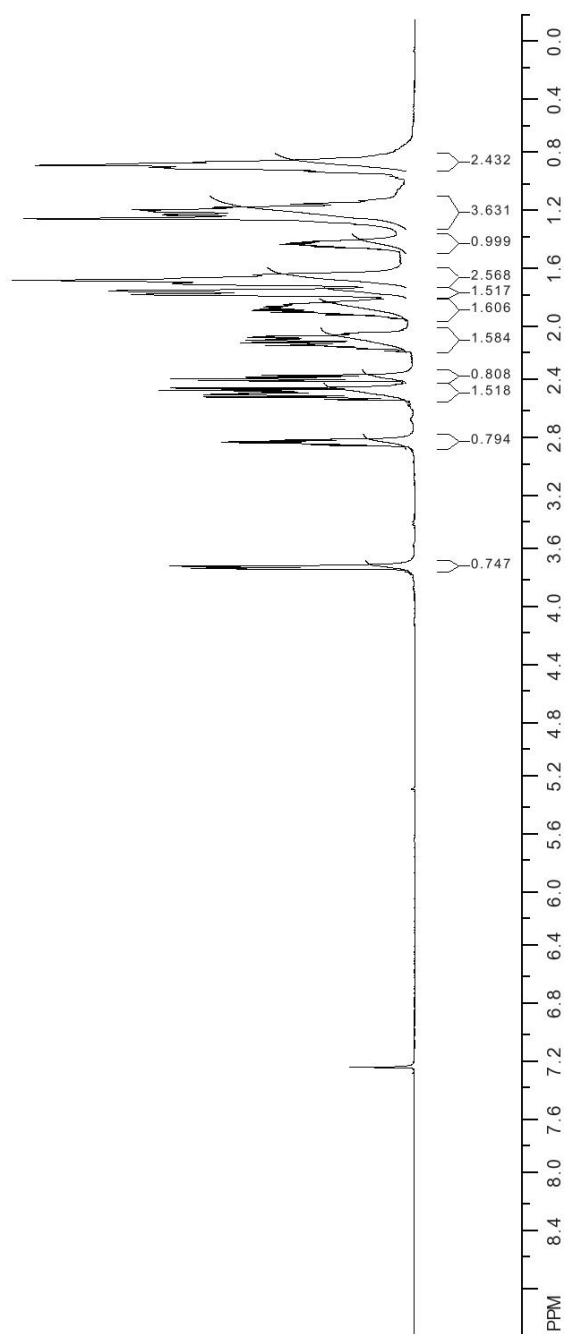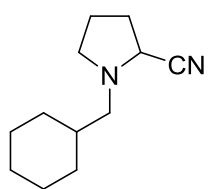
^{1}H NMR of **4.20t**

^{13}C NMR of **4.20t**

21.8907
25.9122
25.9251
26.6506
29.5789
31.5099
31.6049
36.5249

51.4234
54.0863

59.4428

76.7443
76.9986
77.2530

118.3371

¹H NMR of **4.20u**

^{13}C NMR of **4.20u**

21.7767
22.4729
22.6501
26.2087
29.4966

37.3054

50.7851
51.2248
53.6655

76.7447
76.9995
77.2538

118.0900
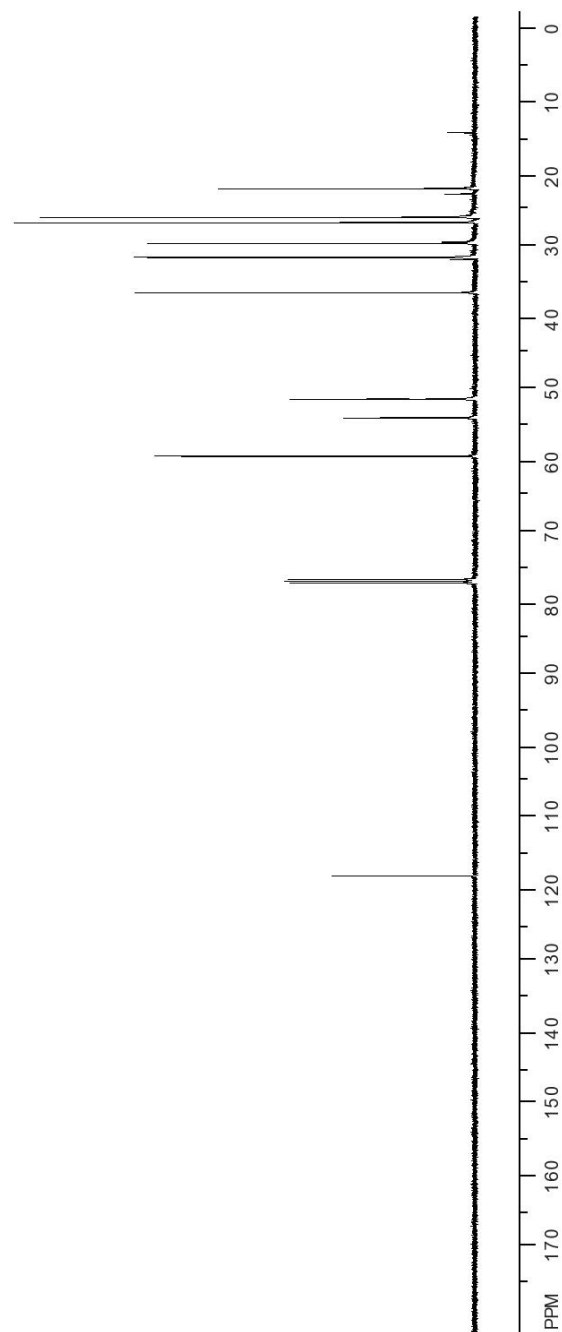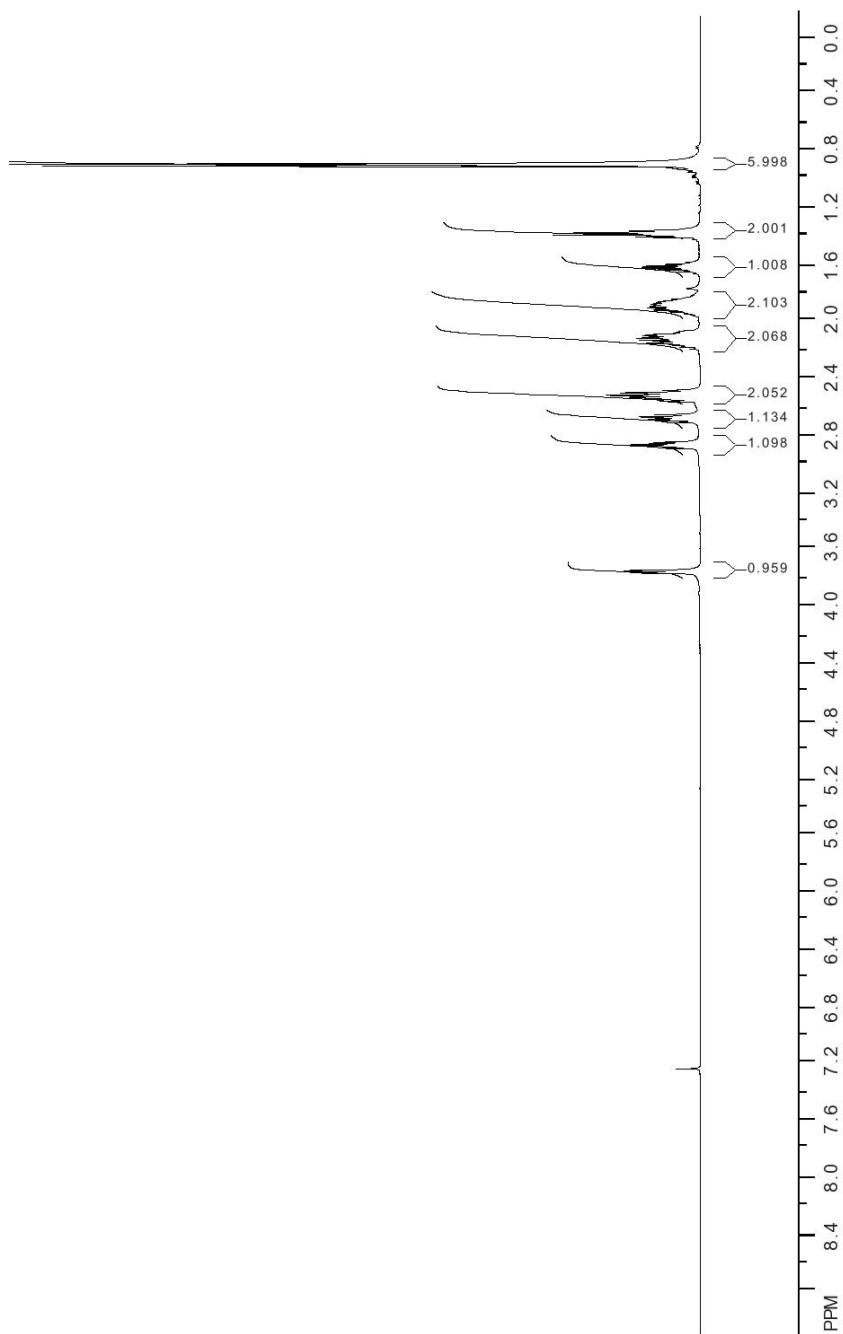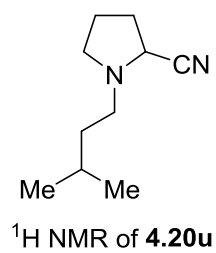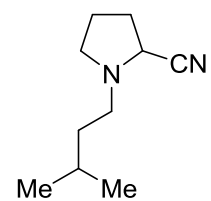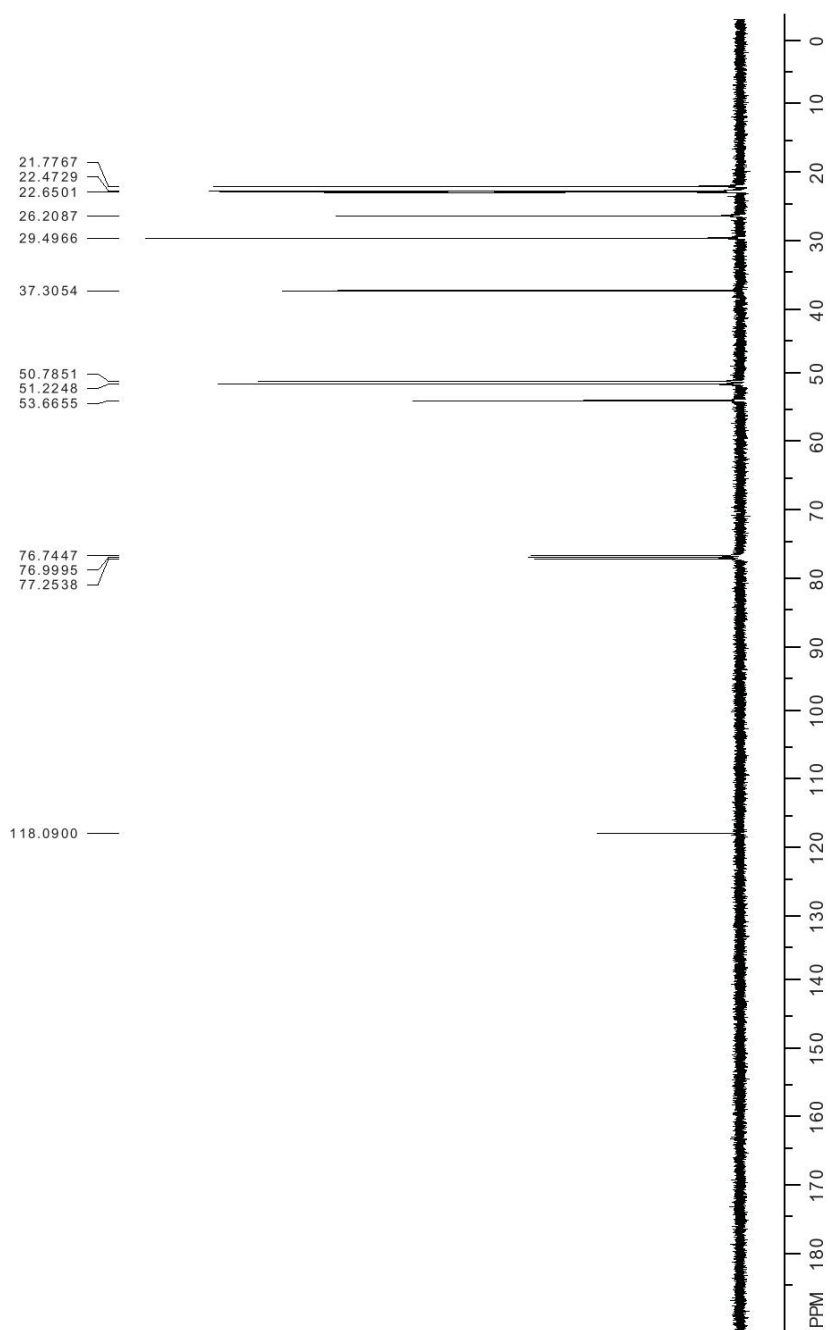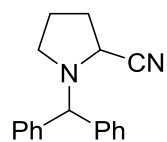
^{1}H NMR of **4.20v**

^{13}C NMR of **4.20v**

21.7558

29.3848

49.9003
53.0590

71.8362
76.7438
76.9983
77.2525

117.6899

127.3000
127.3117
127.5499
127.5700
128.5912
128.7752

142.0077
142.4599
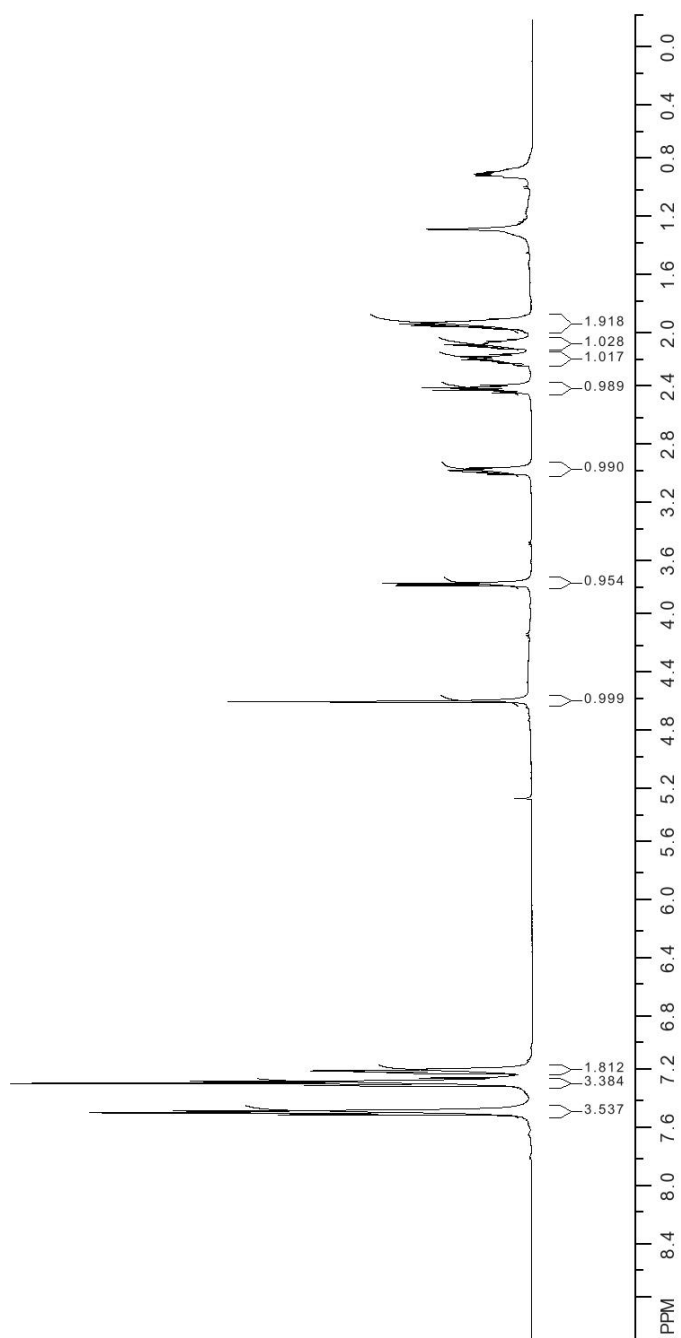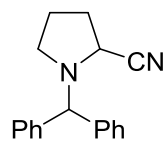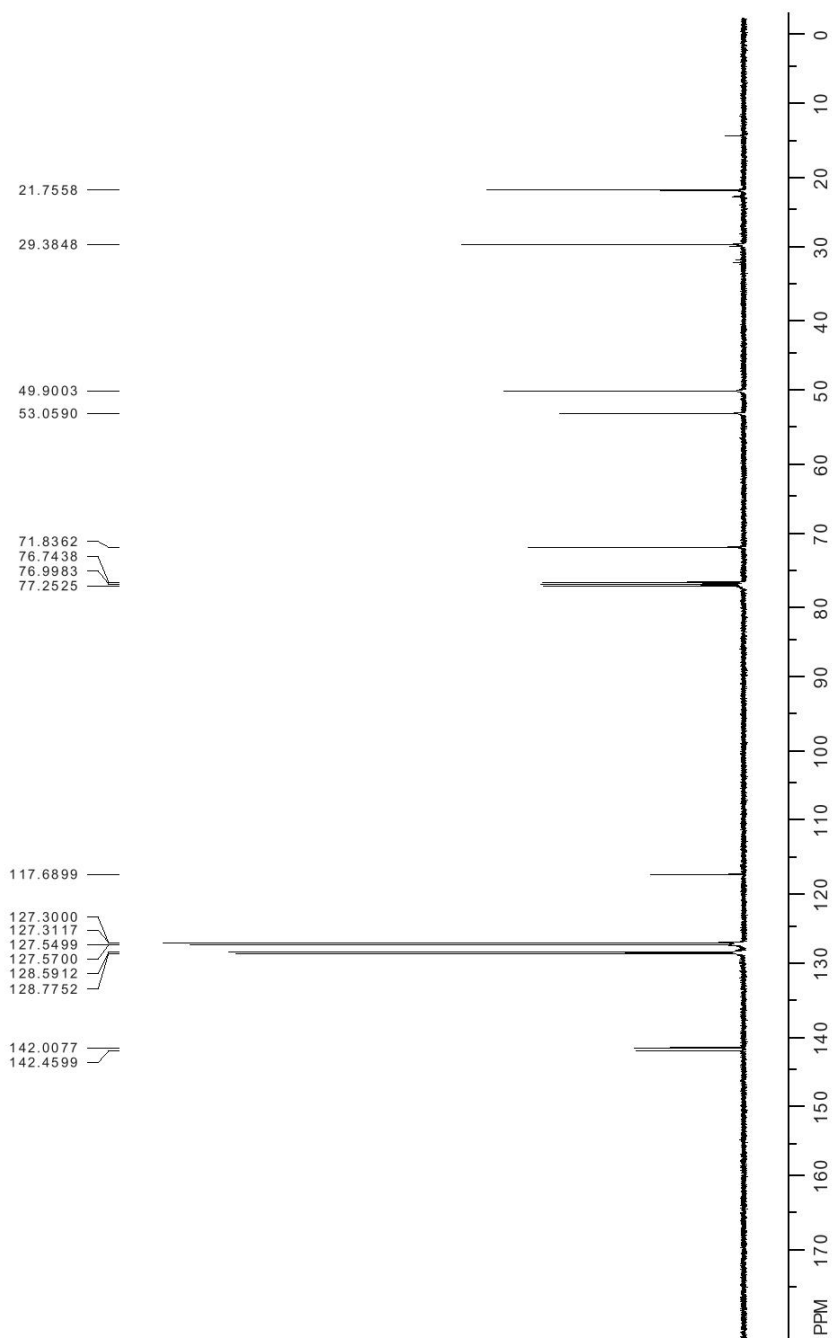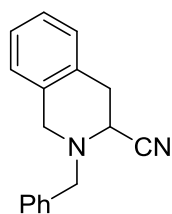
^{1}H NMR of **4.24**

^{13}C NMR of **4.24**

32.6050

49.2521
51.6416

60.1843

76.7454
76.9996
77.2536

16.2673
26.4937
26.6211
26.7120
27.8835
28.7016
28.7242
29.0005
29.7952
32.8490
36.4327
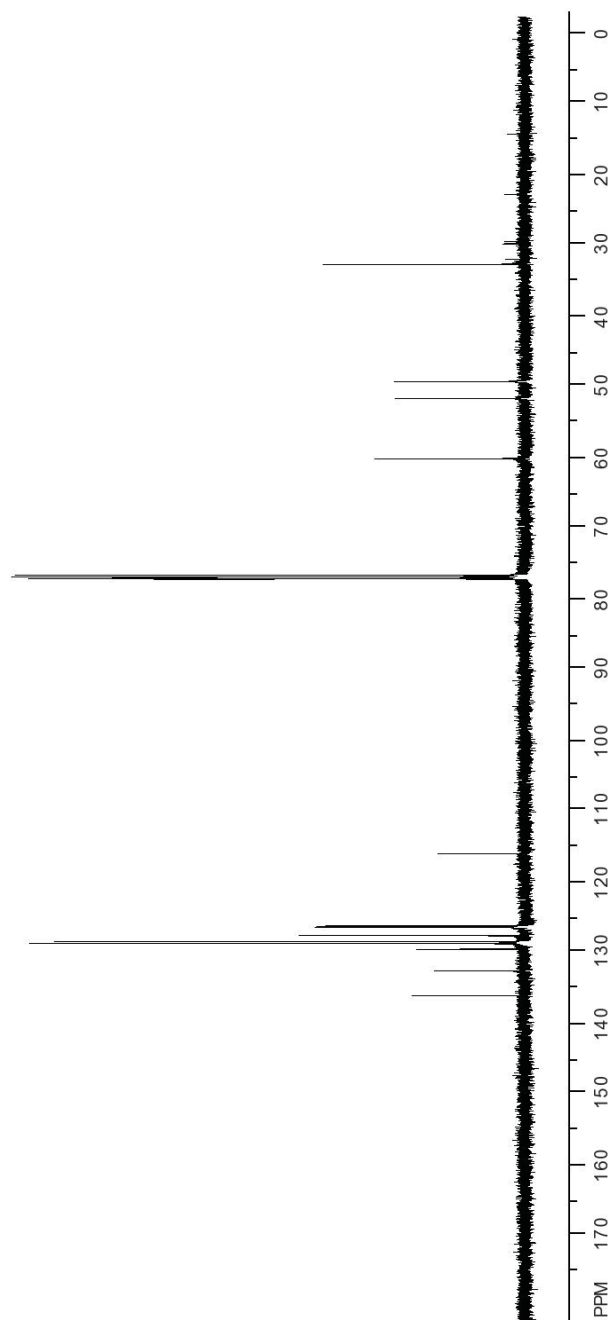
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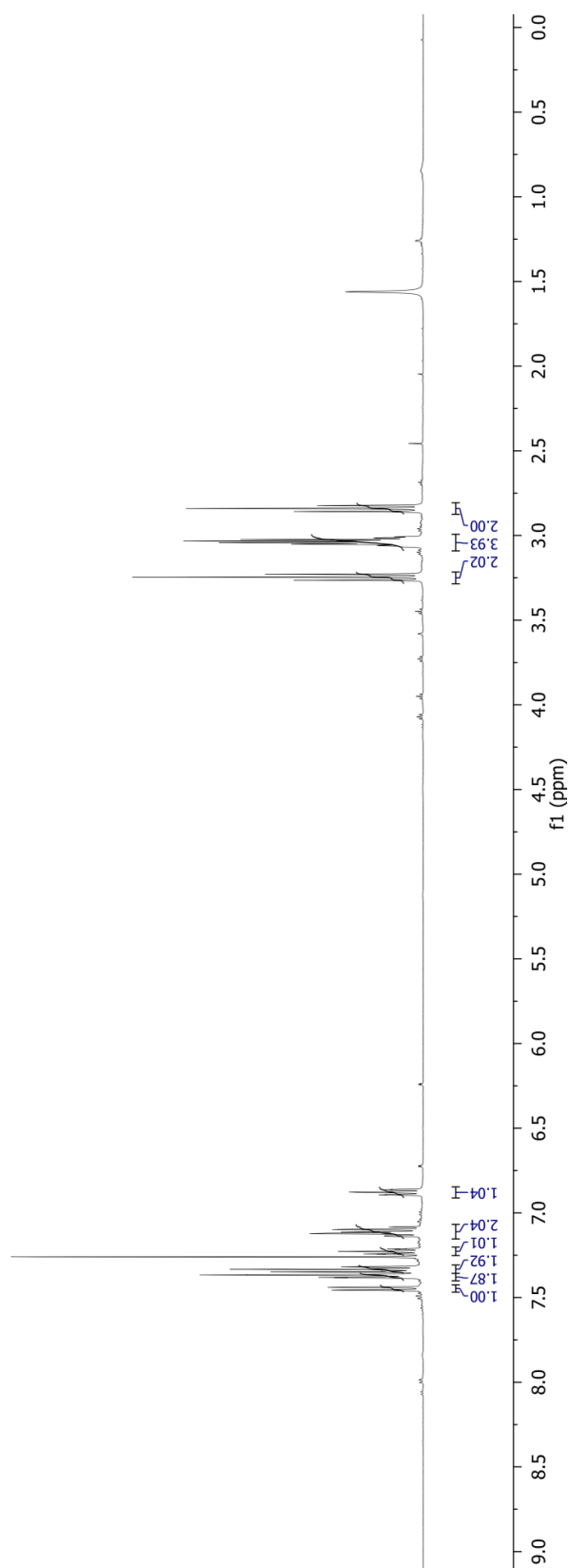20
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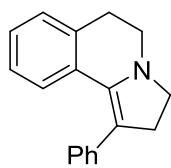90
100
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150
160
170
PPM
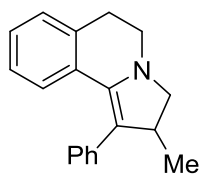
^{1}H NMR of **5.35a**
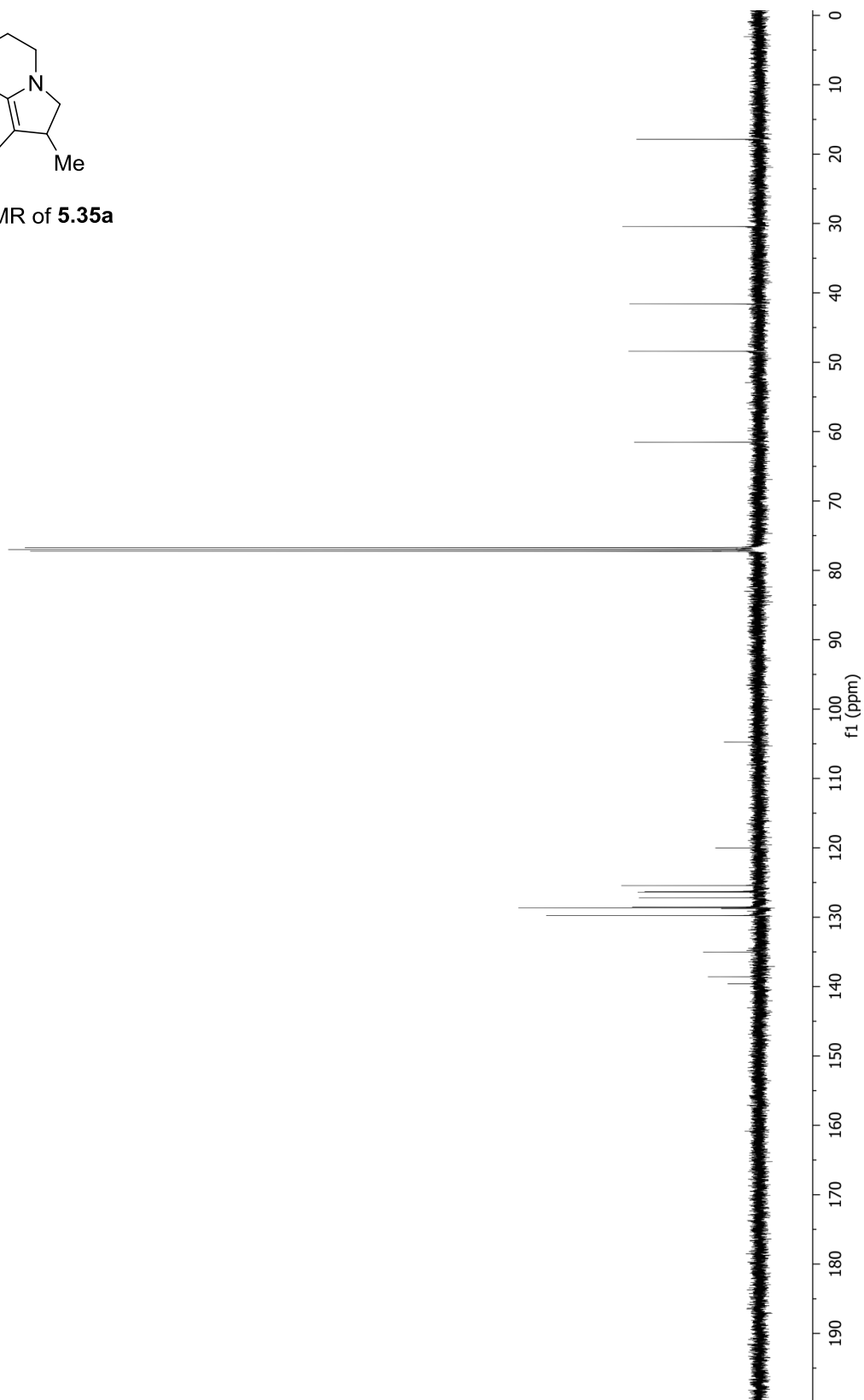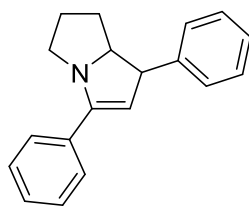
^{13}C NMR of **5.35a**

^{1}H NMR of **5.33a**
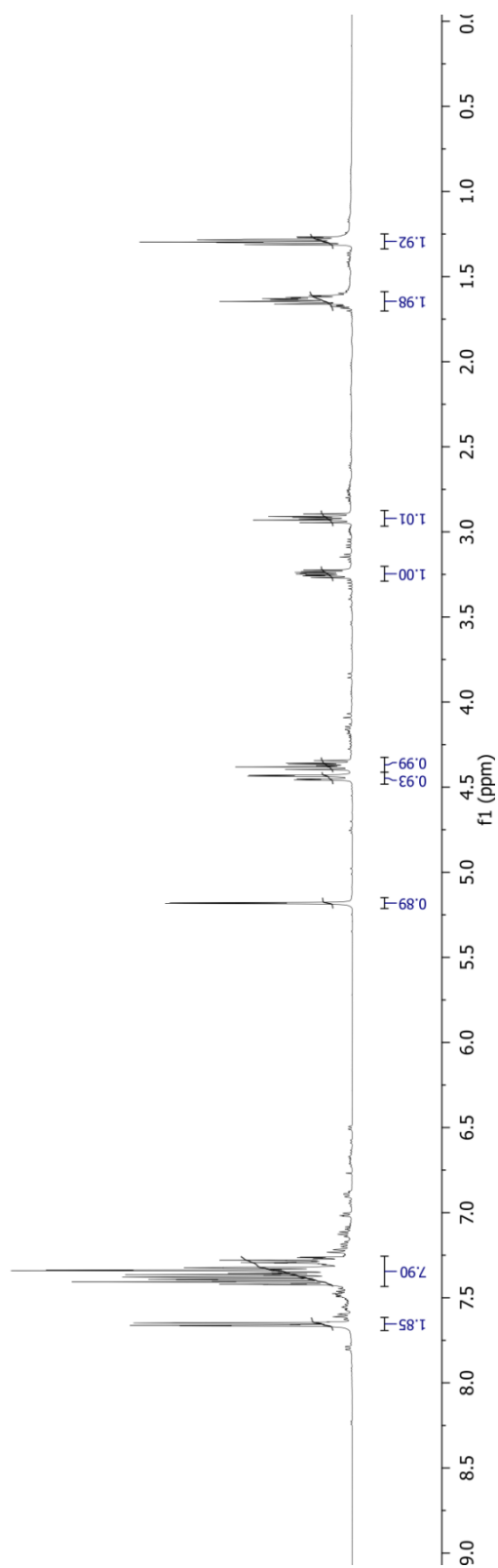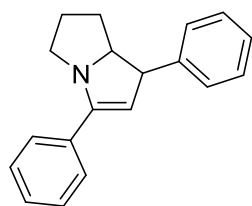
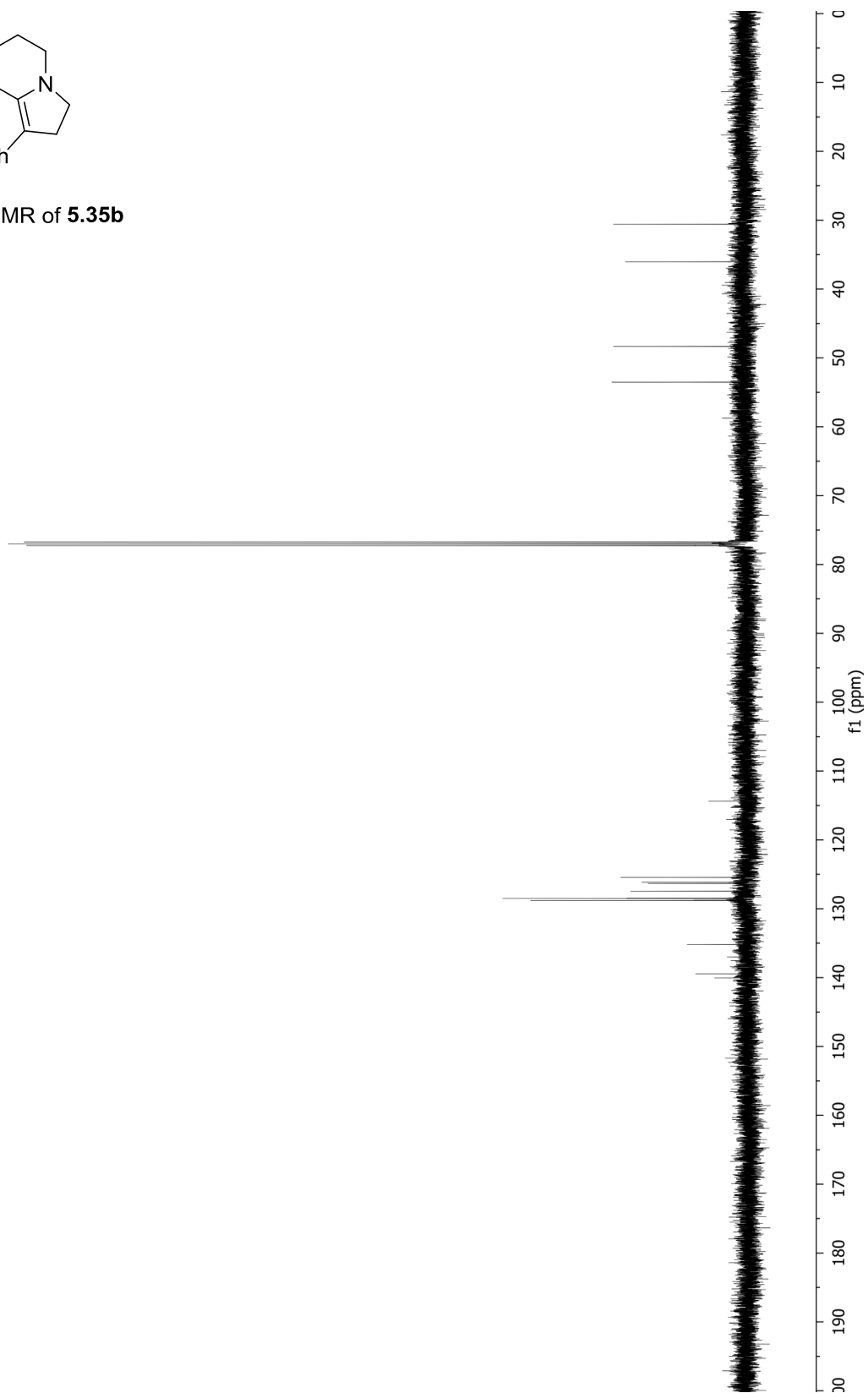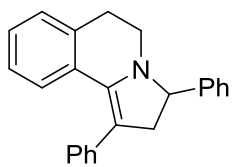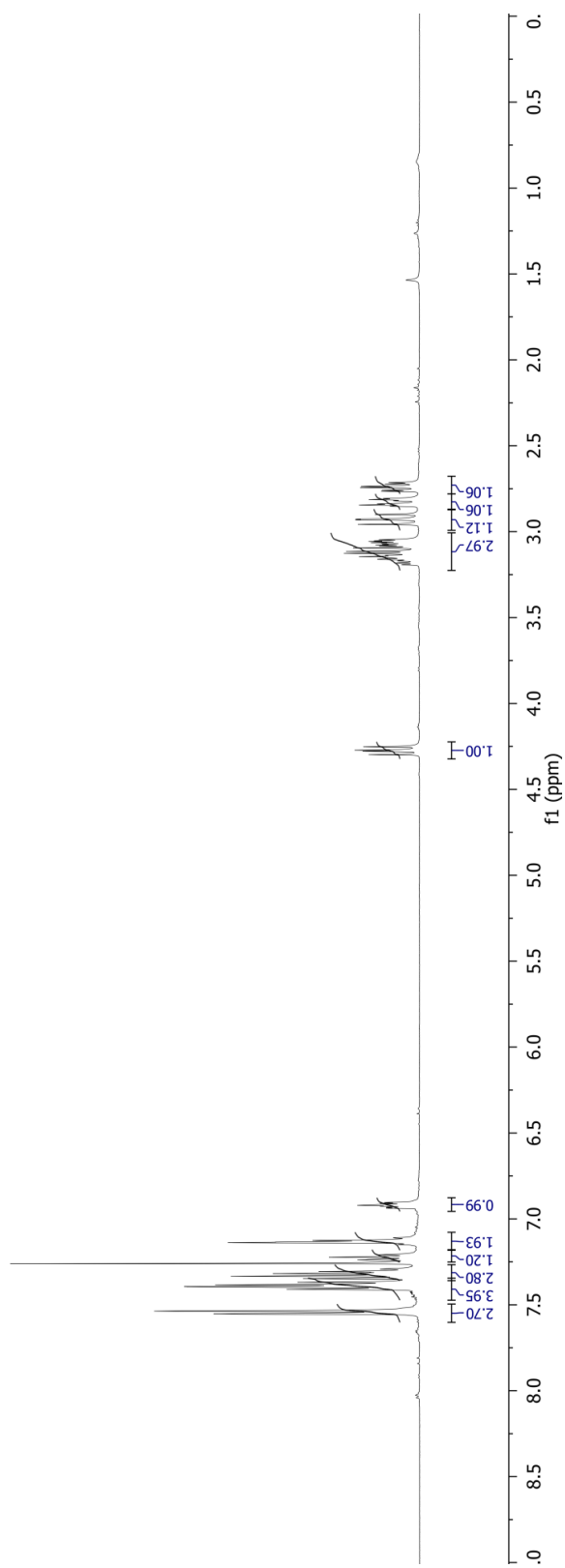^{13}C NMR of **5.33a**
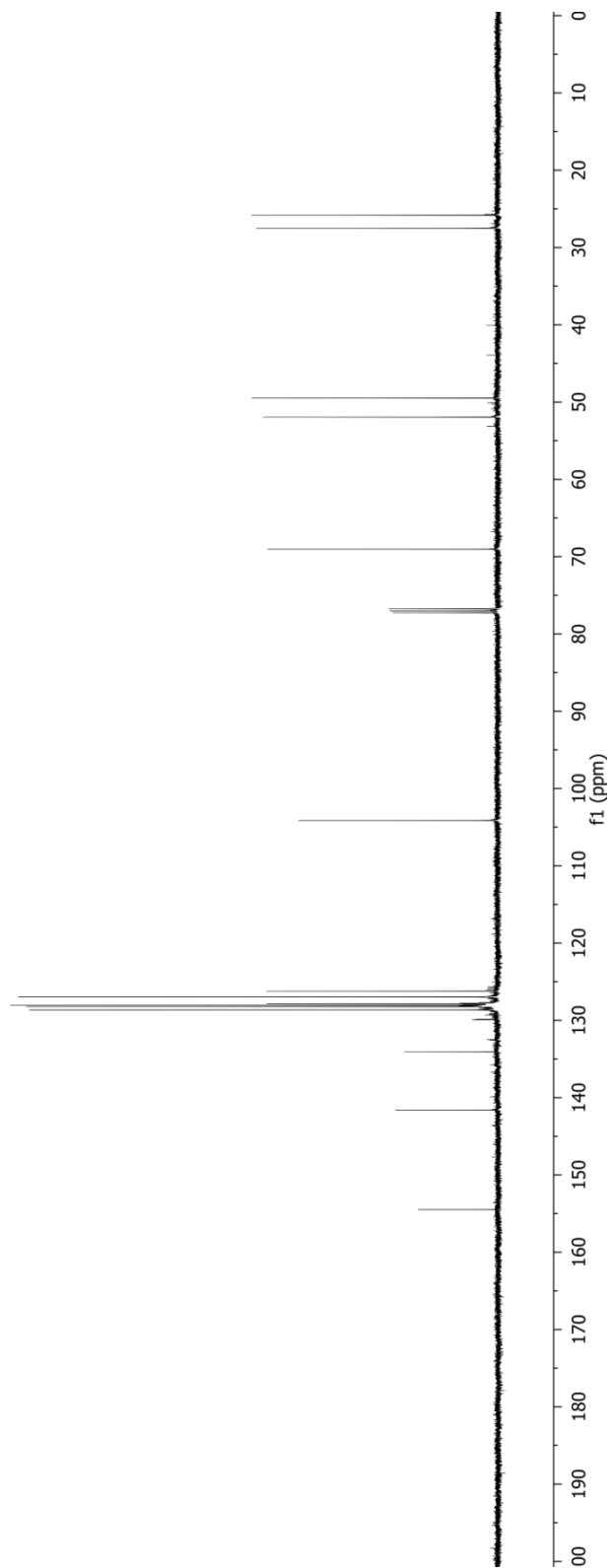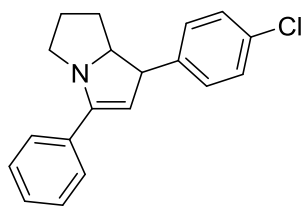
^{1}H NMR of **5.33b**
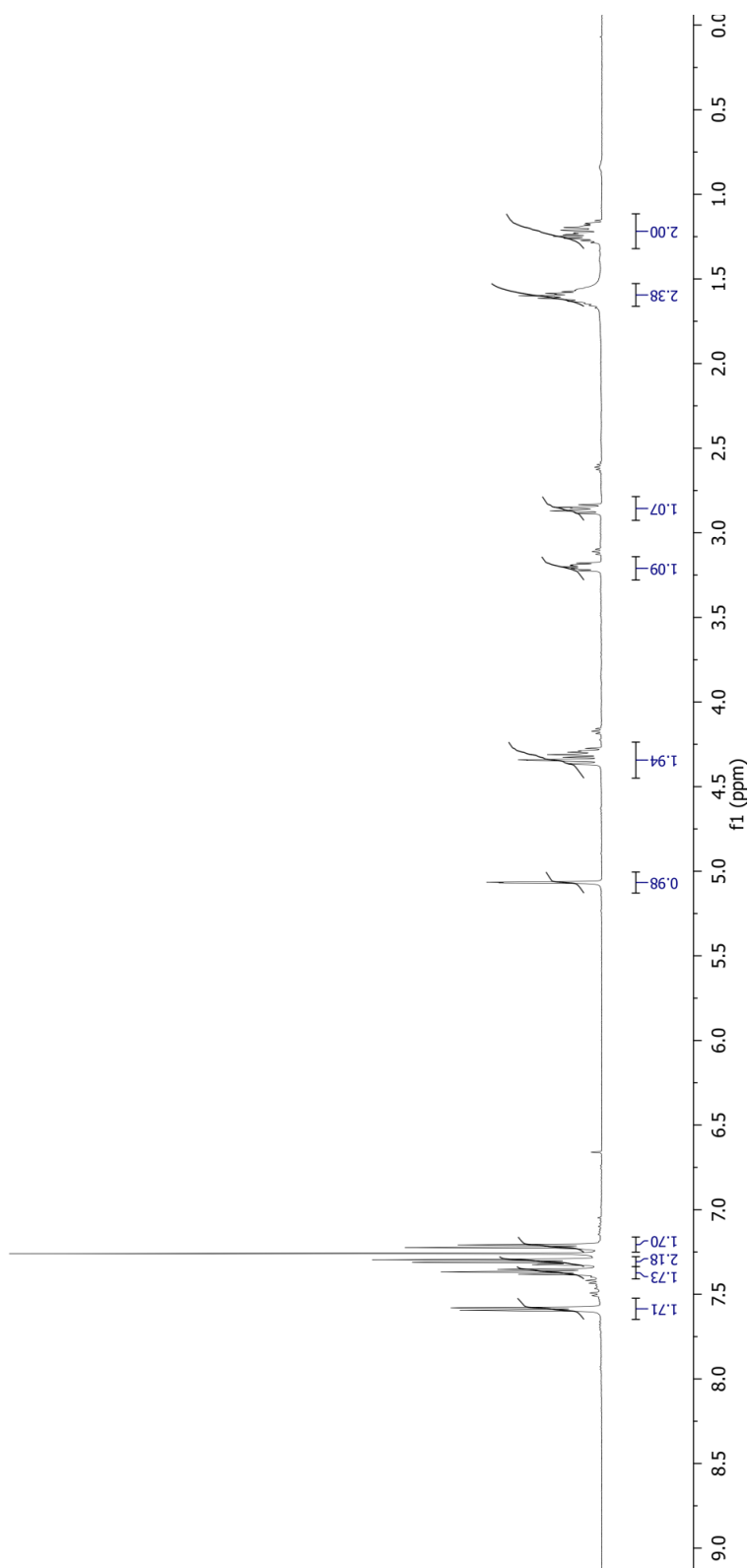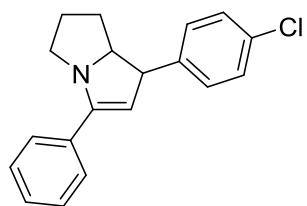
^{13}C NMR of **5.33b**
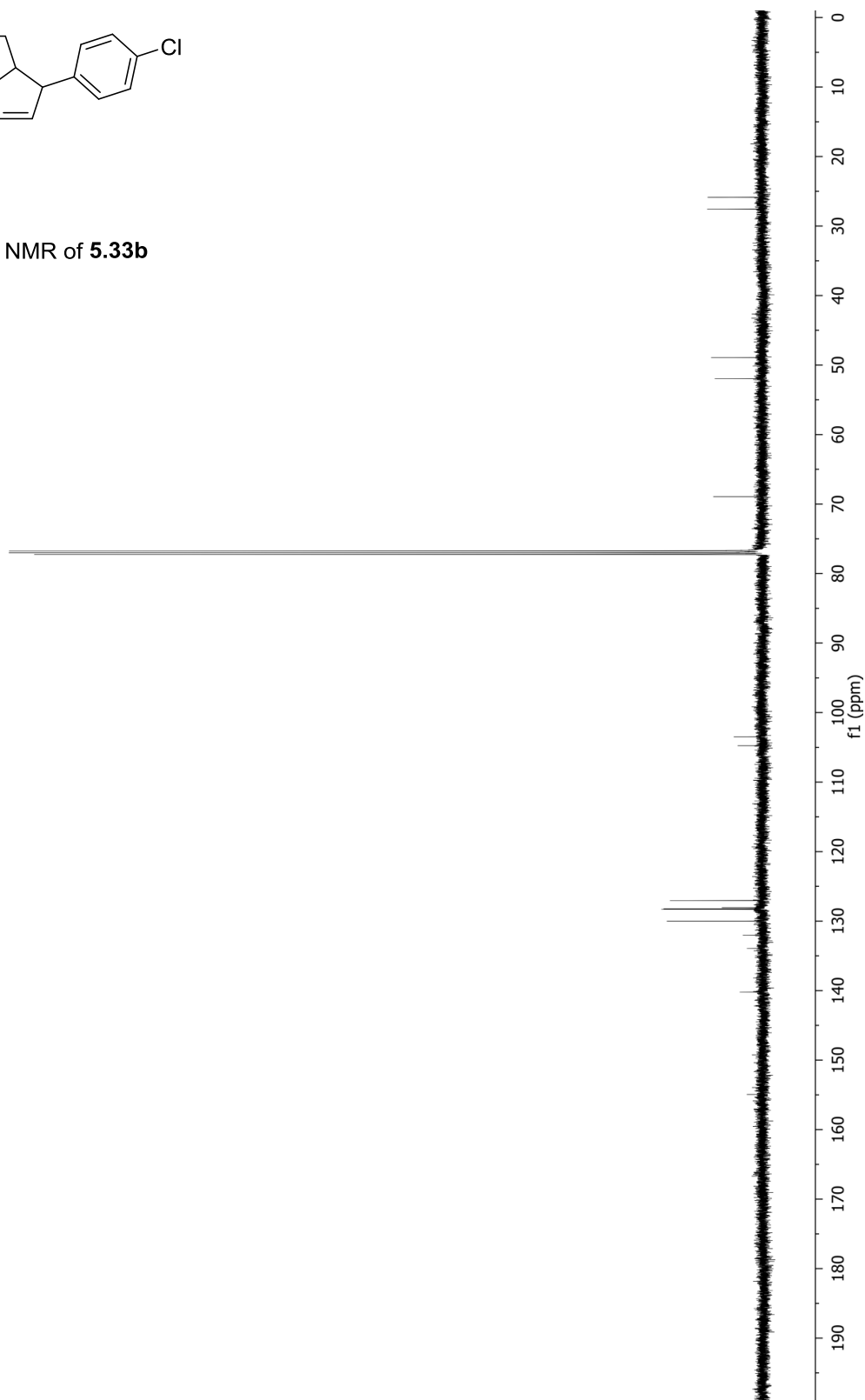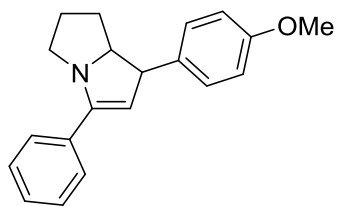
^{1}H NMR of **5.33c**
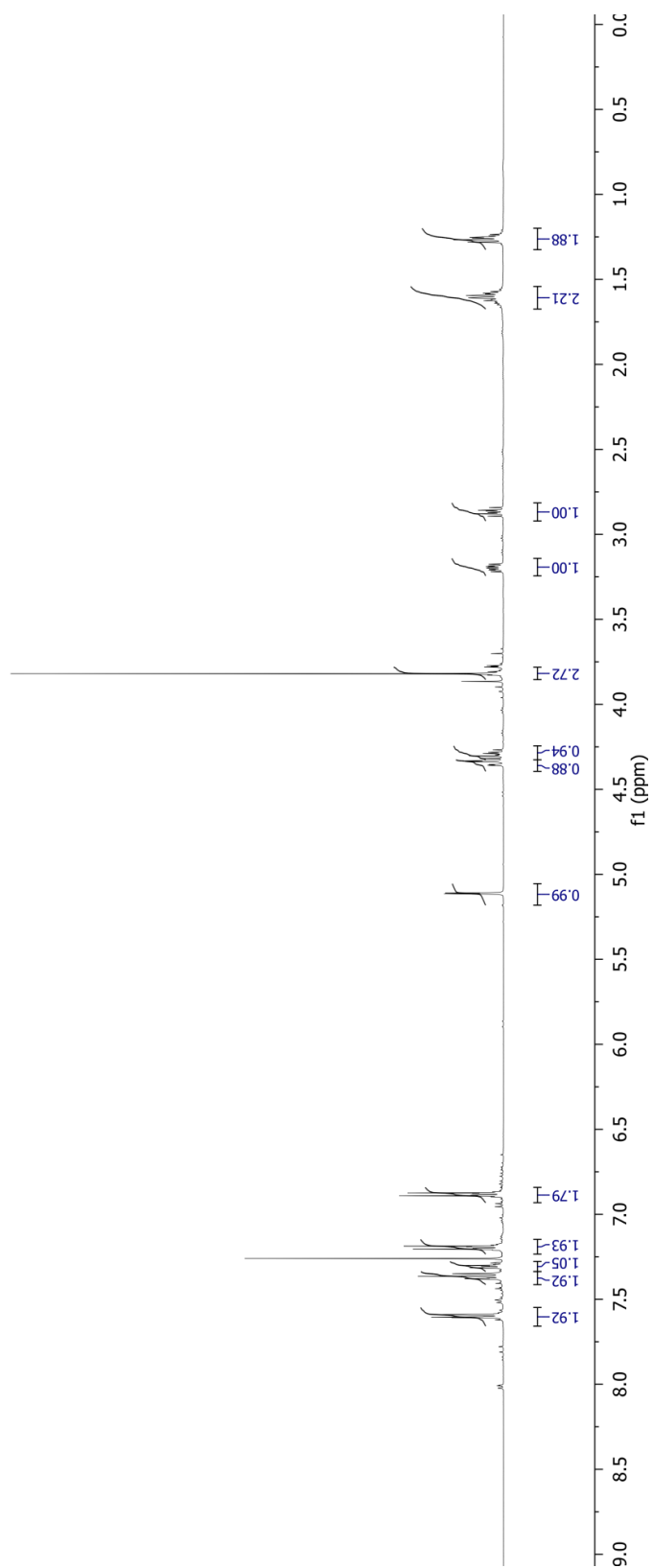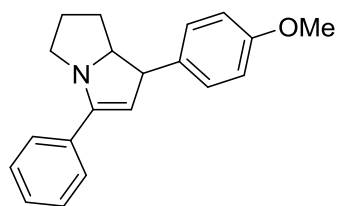
^{13}C NMR of **5.33c**
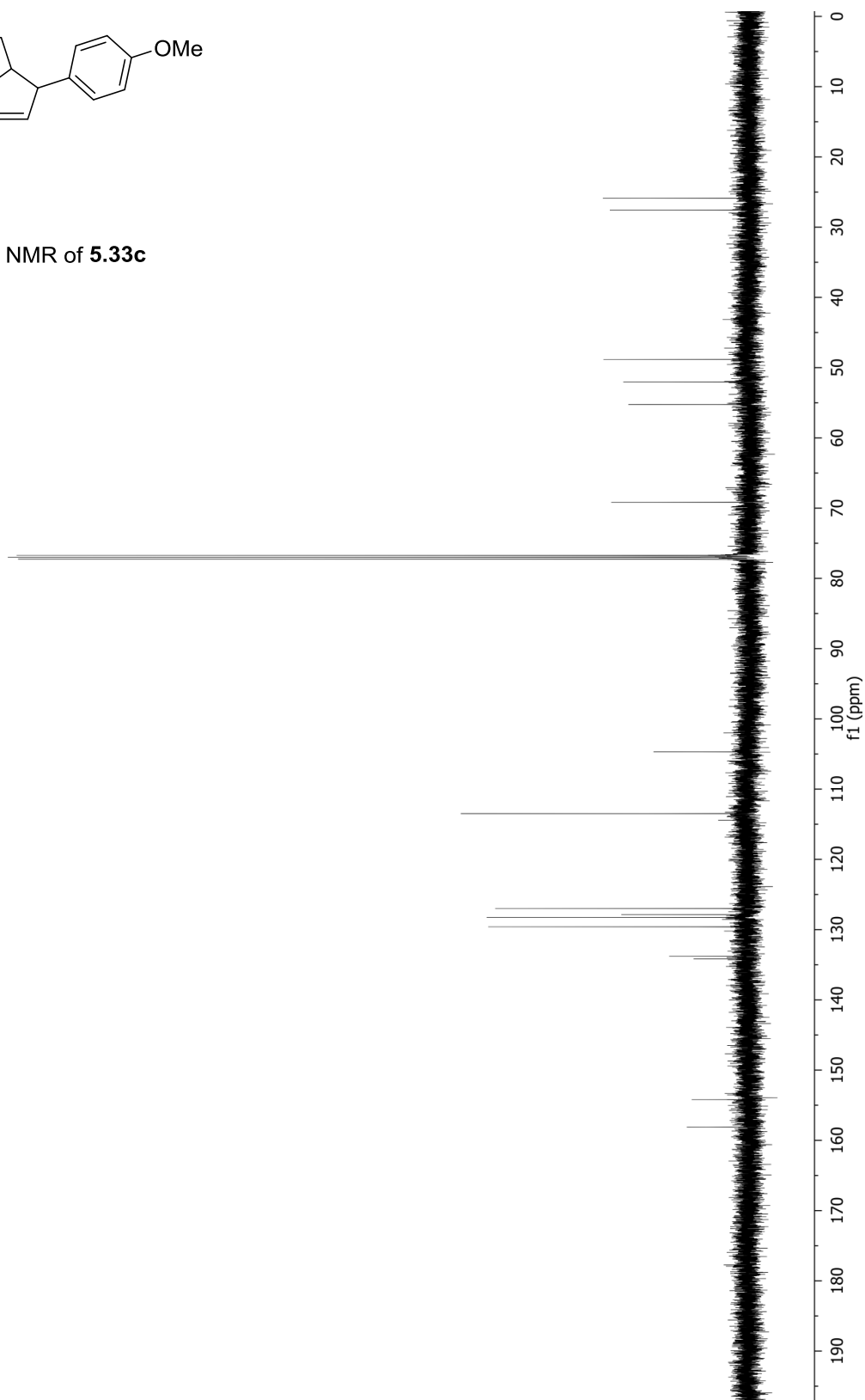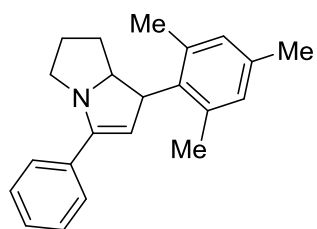
^{1}H NMR of **5.33d**
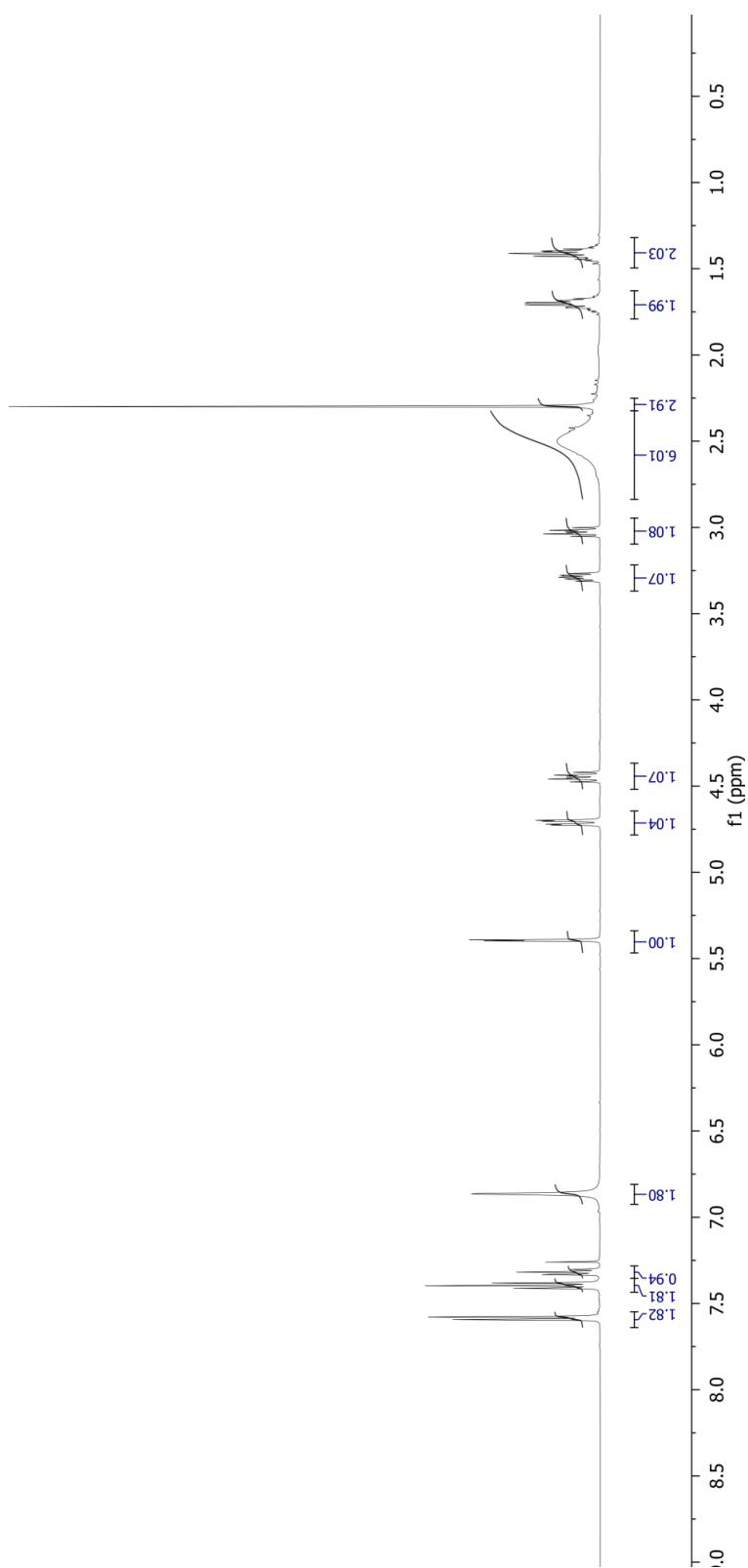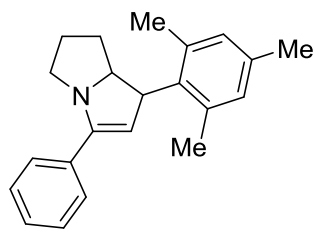
^{13}C NMR of **5.33d**
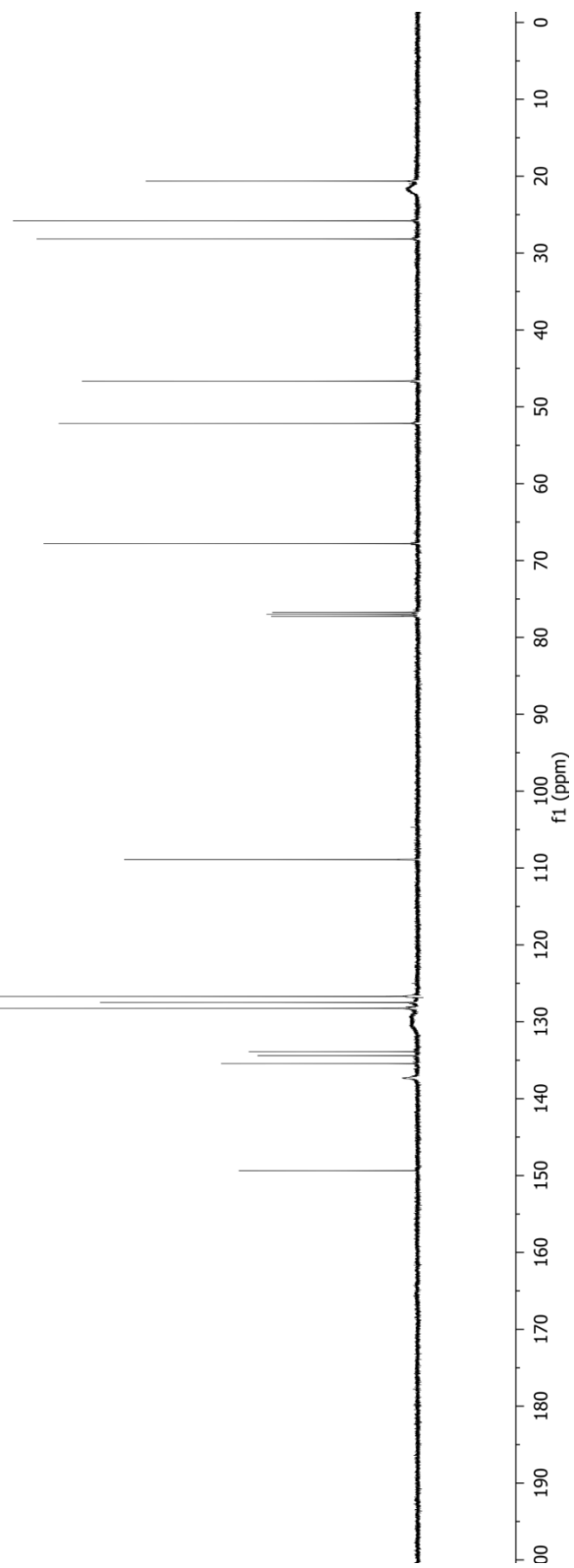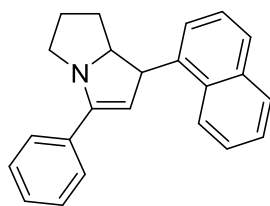
^{1}H NMR of **5.33e**

^{13}C NMR of **5.33e**

^{1}H NMR of **5.33f**
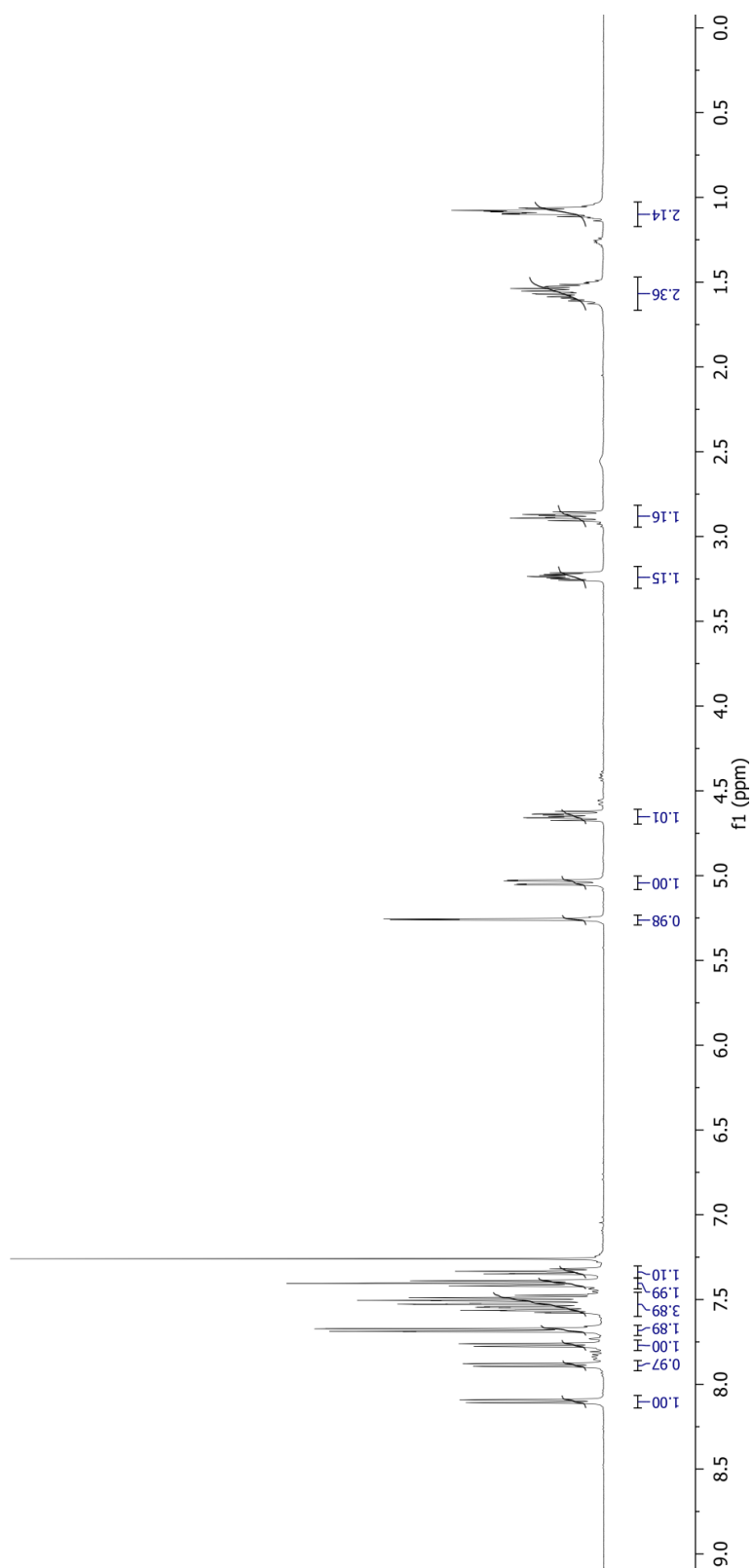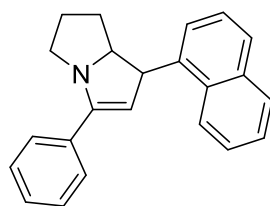
^{13}C NMR of **5.33f**
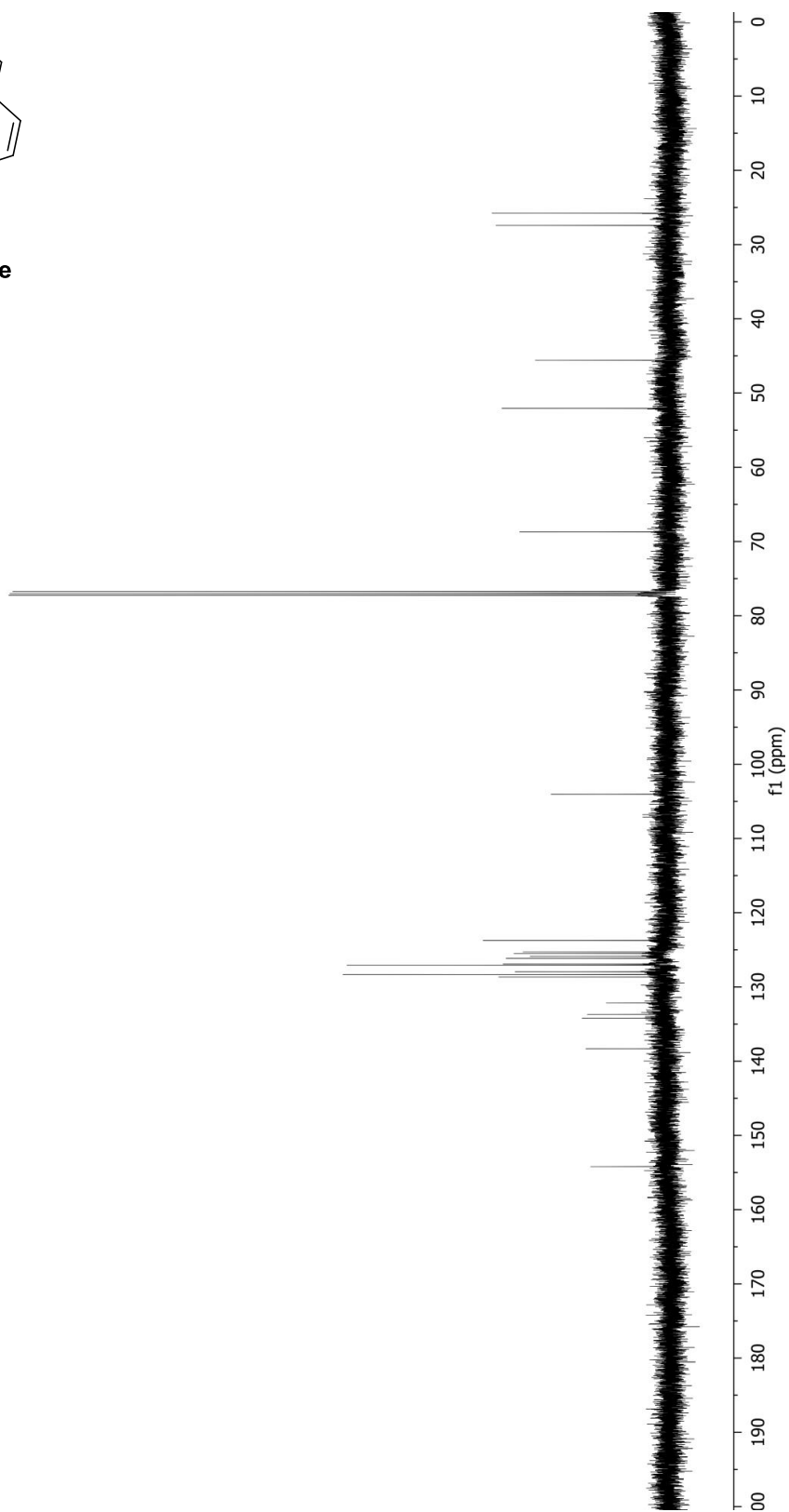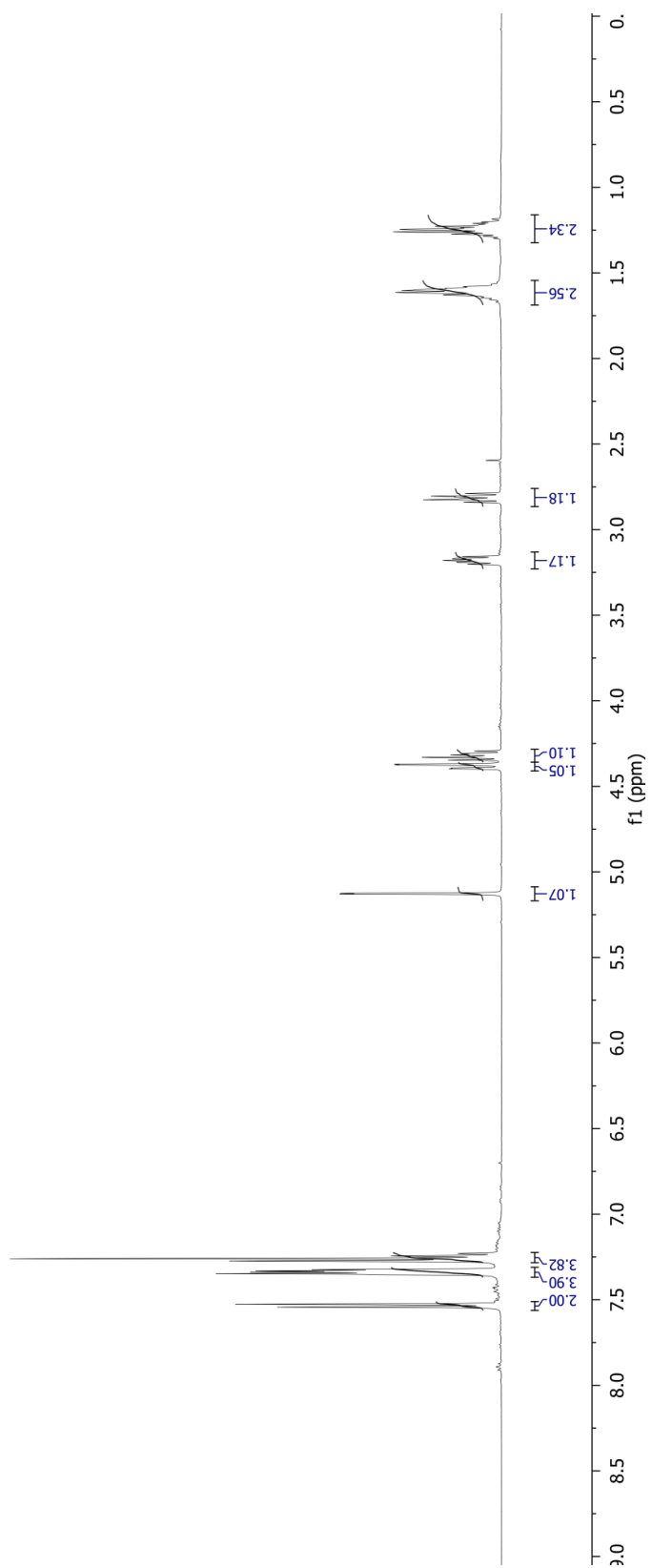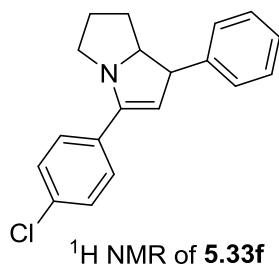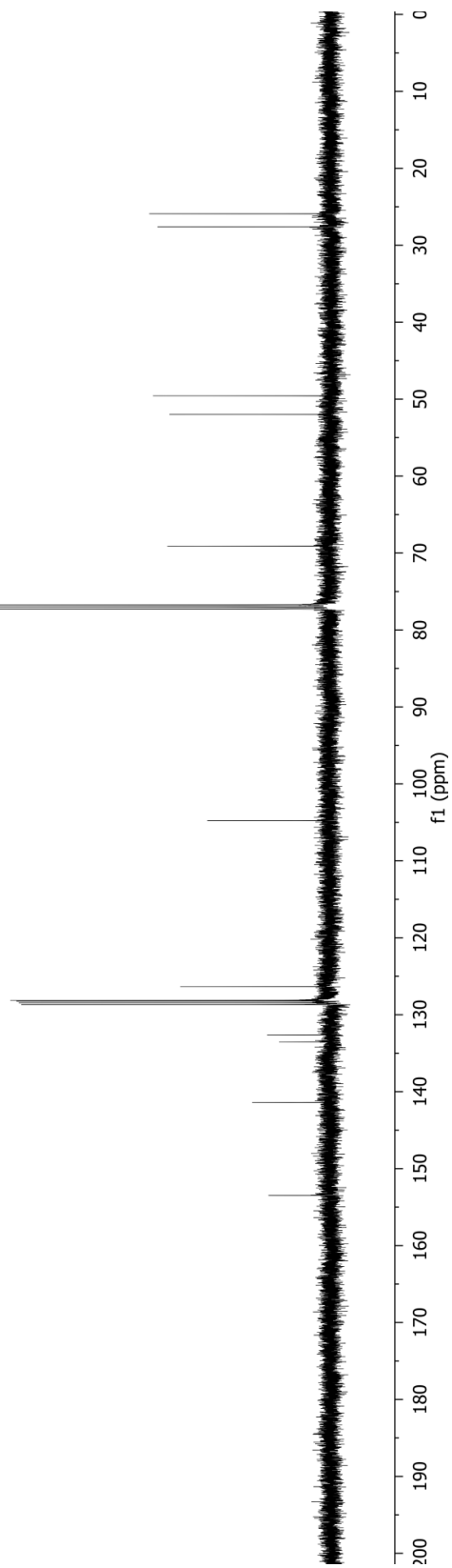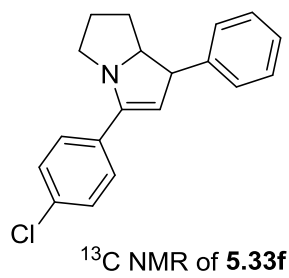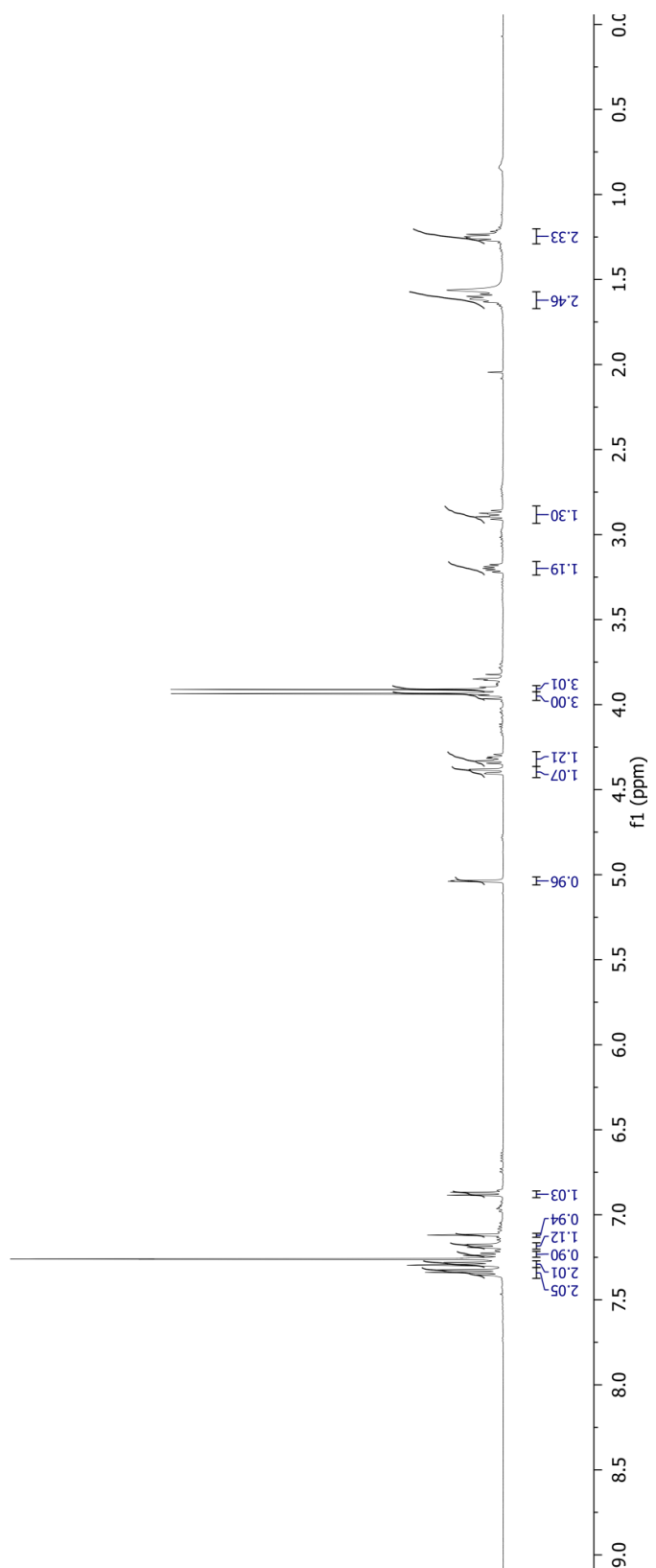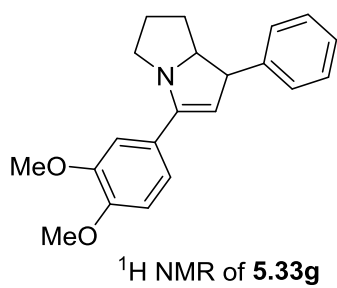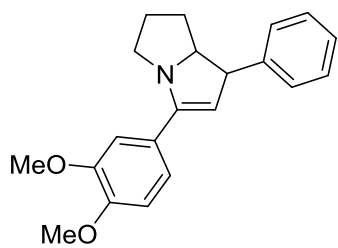
^{1}H NMR of **5.33g**
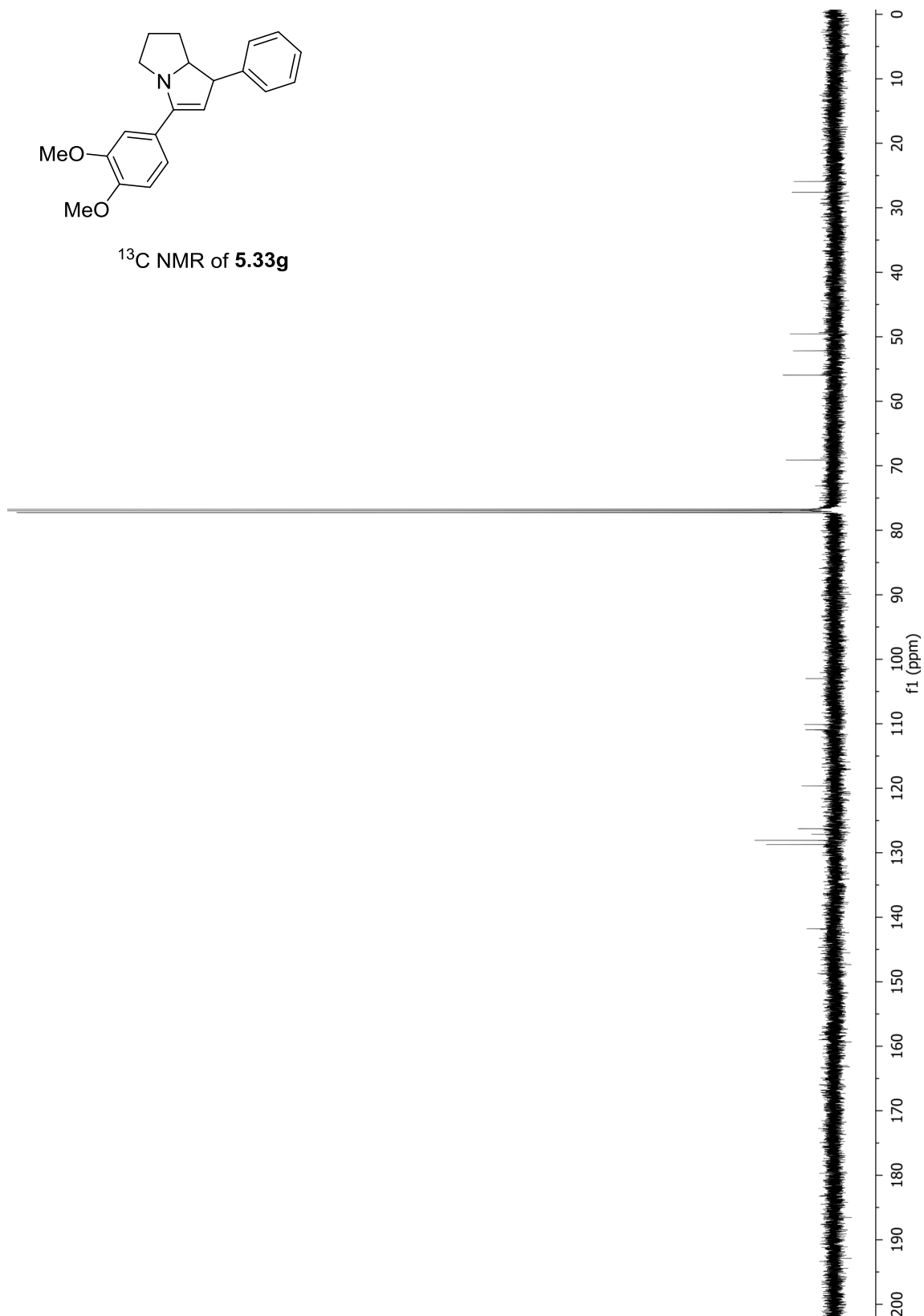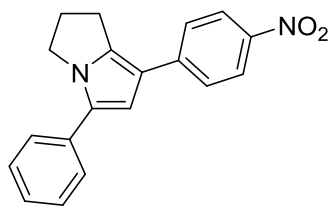
^{13}C NMR of **5.33g**

^{1}H NMR of **5.41**
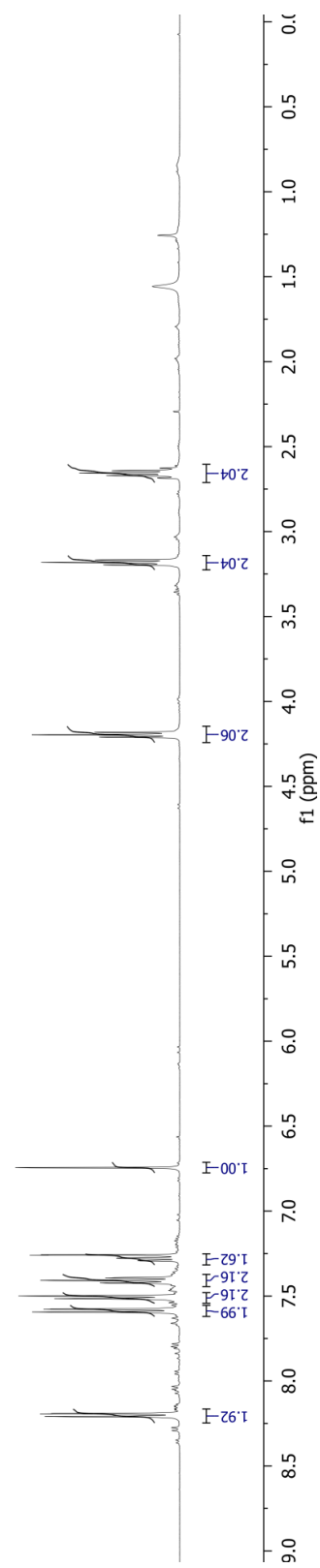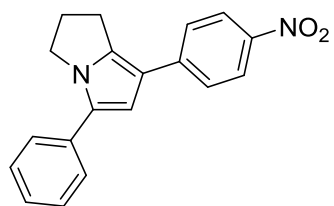
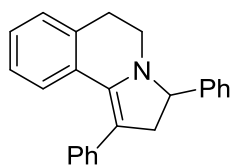^{13}C NMR of **5.41**
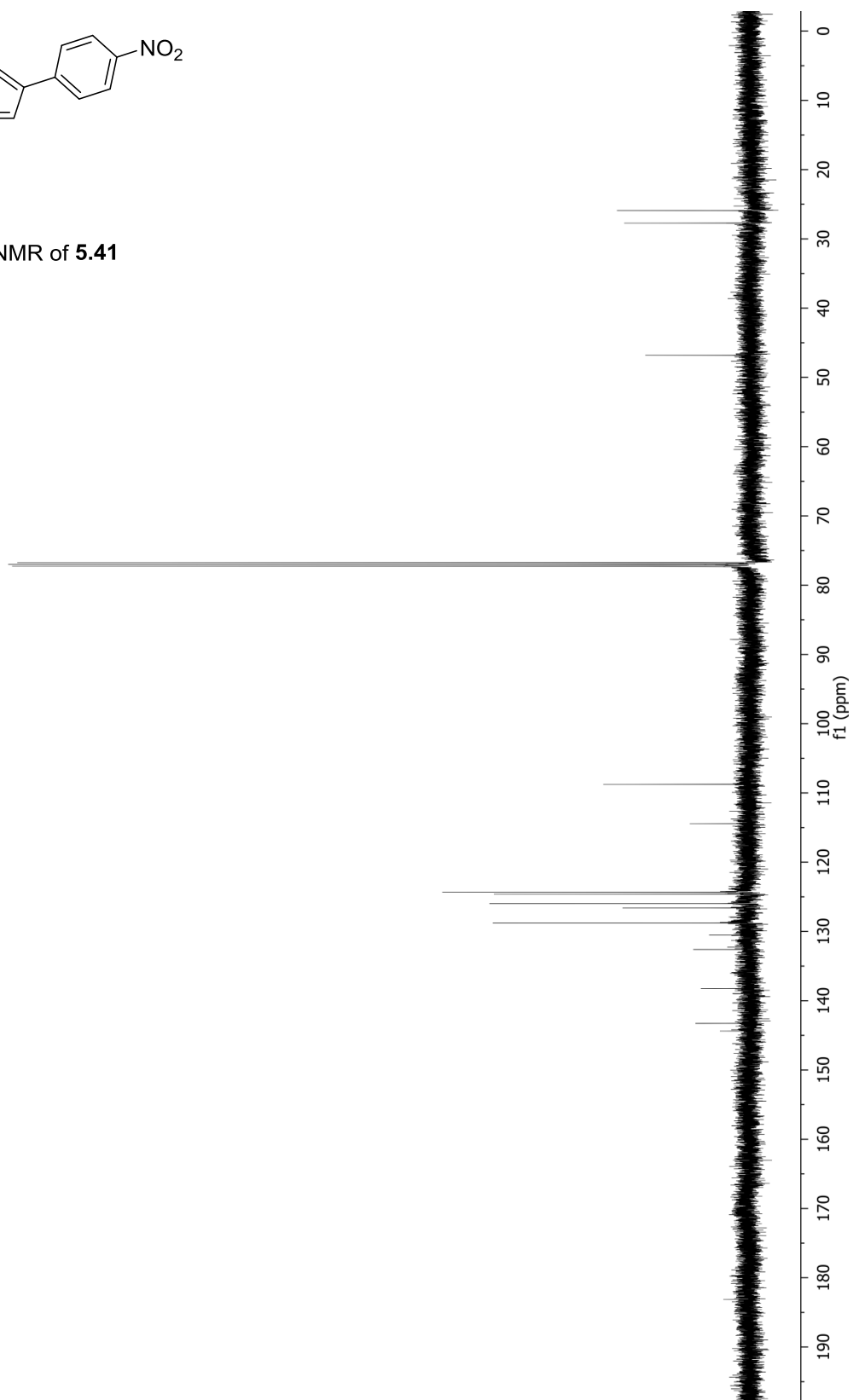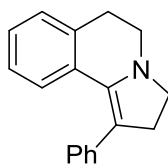
^{1}H NMR of **5.35b**

^{13}C NMR of **5.35b**

^{1}H NMR of **5.35c**

^{13}C NMR of **5.35c**