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Intramolecular cyclizations of alkyl pyridines & alkylidene dihydropyridines as synthetic intermediates toward synthesis of bis(piperidine) alkaloids

Ashabha Indrashika Lansakara
University of Iowa

INTRAMOLECULAR CYCLIZATIONS OF ALKYL PYRIDINES & ALKYLIDENE DIHYDROPYRIDINES AS SYNTHETIC INTERMEDIATES TOWARD SYNTHESIS OF BIS(PIPERIDINE) ALKALOIDS

by

Ashabha Indrashika Lansakara

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Thesis Supervisor: Associate Professor F. Christopher Pigge

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

Ashabha Indrashika Lansakara

has been approved by the Examining Committee for
the thesis requirement for the Doctor of Philosophy degree
in Chemistry at the August 2016 graduation.

Thesis Committee: _____
F. Christopher Pigge, Thesis Supervisor

_____
David F. Wiemer

_____
James B. Gloer

_____
Elizabeth A. Stone

_____
Robert J. Kerns

This thesis is dedicated,

to my parents

to my wife Chathurika

to my daughter Miheli

“Thousands of candles can be lighted from a single candle, and the life of the candle will not be shortened. Happiness never decreases by being shared”

Gautama Buddha

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Abstract

Nature provides fascinating and complicated molecular structures which offer synthetic organic chemists amazing opportunities for the design of new strategies for natural product synthesis. Among these, nitrogen containing aza-heterocycles are of unparalleled importance in natural product, bioorganic, and medicinal chemistry. Pyridine and its derivatives in particular are the most common aza-heterocycles encountered in natural products, medicinal and materials chemistry. Pyridine derivatives also serve as precursors to functionalized piperidines, which are likewise common structural motifs in bioactive and functionalized materials. Thus, developing synthetic methods suitable for the manipulation of pyridine ring systems remains an important objective in synthetic organic chemistry.

The functionalization of pyridine derivatives via manipulation at the benzylic position has been investigated. First, the nucleophilicity of the benzylic position of the 4-alkyl pyridine substrates was used to engage in Brønsted acid-catalyzed aldol-like cyclizations with attached carbonyl electrophiles. These conditions afforded substituted pyridines with functionalized lactams. These substrates underwent an unusual dehydration/oxidation reaction when treated with thionyl chloride.

In a similar study, 1,2-dialkylimidazoles afforded nucleophilic 2-alkylidene imidazolines upon treatment with an electrophilic activating group such as Boc_2O. Positioning a ketone electrophile with in an N1-alkyl side chain results in cyclization at the imidazole 2-position to afford fused ring imidazoles through an aldol-like cyclization reaction.

The stereoselective synthesis of a tricyclic analogue of the bis(piperidine) alkaloid xestoproxamine C was also investigated. Dearomatization of a tricyclic pyridine derivative afforded an alkylidene dihydropyridine (anhydrobase) intermediate which was subjected to catalytic heterogeneous hydrogenation to install the correct relative stereochemistry about the bis(piperidine) ring system. Other key features of these model studies included development of an efficient ring-closing metathesis procedure to prepare macrocyclic derivatives of 3,4-disusbstituted pyridines, intramolecular cyclizations of alkylidene dihydropyridines to establish pyridine-substituted pyrrolidines and piperidines, successful homologation of pyridine-4-carboxaldehydes using formaldehyde dimethyl thioacetal monoxide (FAMSO), and application of B-alkyl Suzuki coupling to assemble substituted pyridines.

Lastly, a study was done to assess the feasibility of synthesizing one of the two chiral precursors needed for the asymmetric synthesis of xestoproxamine C via enzyme catalyzed transesterification of symmetric 1,3-diols. This resulted in successful transesterification of a symmetric 1,3-diol substrate with high enantioselectivity.

Public Abstract

Nitrogen-containing heterocyclic ring systems are ubiquitous in many biologically active compounds. Bis(piperidine) alkaloids are one such group of compounds that have shown potent biological activity as anti-cancer, anti-viral, anti-bacterial agents. Despite their intriguing biological activity, the synthesis of bis(piperidine) alkaloids has not received much attention. We envision constructing bis(piperidine)s from substituted pyridines via novel alkylidene dihydropyridine (anhydrobase) intermediates. In the first part of this thesis, acid-catalyzed strategies to synthesize pyridine-pyrrolidine and pyridine-piperidine frameworks are discussed. Additionally, similar strategies for construction of substituted imidazoles are also described. In the second part of this thesis, model studies outlining a viable route to bis(piperidine) natural products, such as xestoproxamine C, are disclosed.

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Chapter One

Dearomatization Strategies in Organic Synthesis

1.1 Introduction

The assignment of the benzene structure by German chemist Friedrich A. Kekule, reported in 1865, suggested that it is a six-membered ring of carbon atoms with alternating single and double bonds.[1] Ever since this remarkable discovery, scientists have been enthusiastic about the concept of aromaticity owing to a new understanding of benzene stabilization through resonance energy. The resonance energy of a compound is a measure of the extra stability of the conjugated system compared to the corresponding number of isolated double bonds. Regardless of benzene's high resonance energy, examples of dearomatization by microorganisms either via oxidation (oxygenases) or reduction (reductases) are encountered in Nature.[2-4] Dearomatization of aromatic entities often leads to highly reactive intermediates that result in the formation of carbon-carbon and carbon-heteroatom bonds.

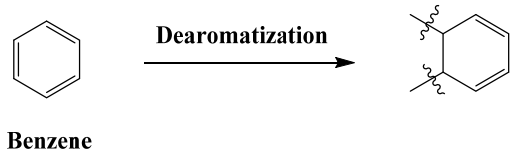


Figure 1.1 - Dearomatization of benzene

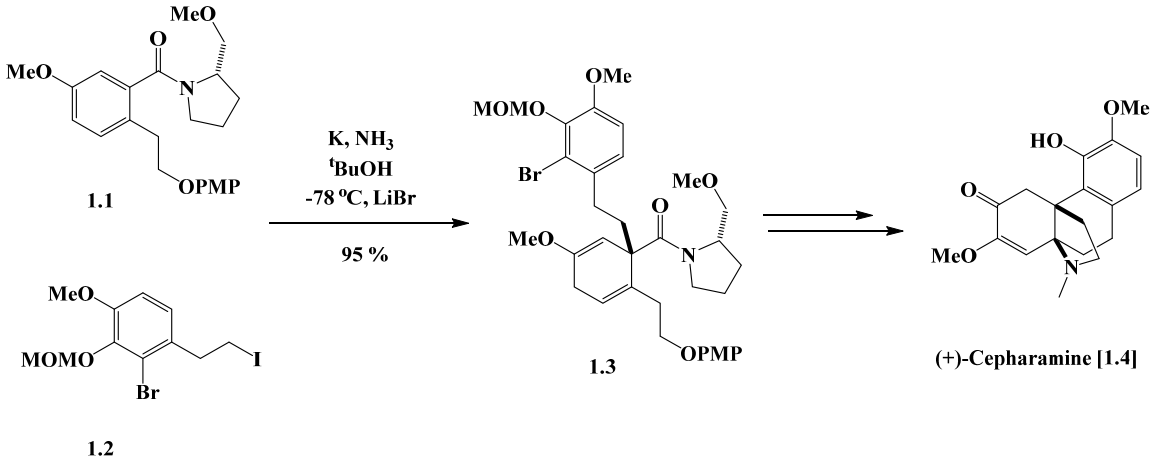
Aromatic moieties are abundantly available and represent versatile synthetic building blocks in organic chemistry. The ability to manipulate arenes through dearomatization reaction manifolds further enhances the utility of arenes as synthetic building blocks. Dearomatization reactions often result in formation of non-planar

alicyclic products from planar arenes. Consequently, stereoselective and chemoselective approaches to complex molecules via dearomatization of aromatic substrates have been developed, especially in the context of heterocyclic compound construction. Heterocyclic motifs are ubiquitous in natural products that show potent biological activity, and synthetic approaches based on dearomatization of carbocyclic and heterocyclic arenes may provide concise and practical routes for successful construction of these complex natural products.

Easily accessible aromatic substrates have been used to produce fused rings, spirocycles, azaspirocycles, and polycyclic systems through a number of dearomatization strategies. Transformations such as these include new carbon-carbon bond formation, carbon-heteroatom bond formation, and metal mediated transformations that deliver valuable intermediates for synthetic purposes. Enzyme catalysis has also been used to achieve oxidative and reductive dearomatizations.[3-5] With respect to heterocyclic natural product synthesis, photochemical and thermal cycloadditions,[6-8] nucleophilic additions,[9] radical cyclizations,[10,11] transition metal mediated strategies,[12,13] and oxidative dearomatization[14,15] have all been successfully applied in conversion of arenes or heteroarenes into various alicyclic aza- or oxa-cyclic intermediates. Regardless of these accomplishments, dearomatization remains an under-utilized tactic in synthetic organic chemistry and further investigations into new and broadly applicable dearomatization strategies are needed to expand the field of organic synthesis. Described herein are a few key examples of dearomatization strategies that have been employed in the construction of various molecular targets in synthetic organic chemistry.

1.2 Dearomatization via Birch Reduction

Birch reduction is a classic method for reductive dearomatization and this reaction is still being widely used. The reaction involves use of solvated electrons generated *in situ* to reduce aromatic species regioselectively to yield 1,4-dihydro cyclohexadienes. For example, in the synthesis of the alkaloid (+)-cepharamine (Scheme 1.1) Schultz and coworkers used a diastereoselective Birch reduction of aromatic substrate **1.1** in the presence of alkyl iodide **1.2** to yield 1,4-cyclohexadiene **1.3** as a single diastereomer, which was further manipulated into (+)-cepharamine (**1.4**).[16]

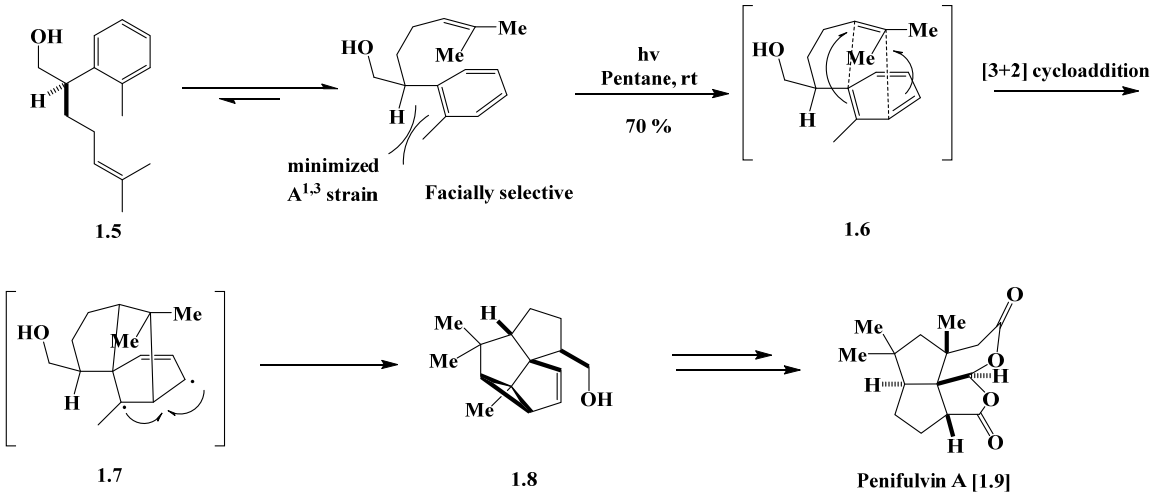


Scheme 1.1 - Diastereoselective Birch reduction in synthesis of (+)-cepharamine

1.3 Dearomatization via Cycloaddition Reactions

Cyclic systems are often synthesized via cycloaddition reactions with high stereo- and regioselectivity. Photocycloadditions are not limited to simple alkenes, and even the thermally very stable benzene core has been shown to become quite reactive upon excitation with photons. Such reactions of aromatic substrates result in complex structural motifs, both in intra- and inter-molecular fashion.[17,18] For example, Mulzer and

coworkers have employed Wender's photoinduced [3+2] cycloaddition of arenes and olefins as a key step in the synthesis of the sesquiterpenoid penifulvin A (**1.9**) (Scheme 1.2).[19]

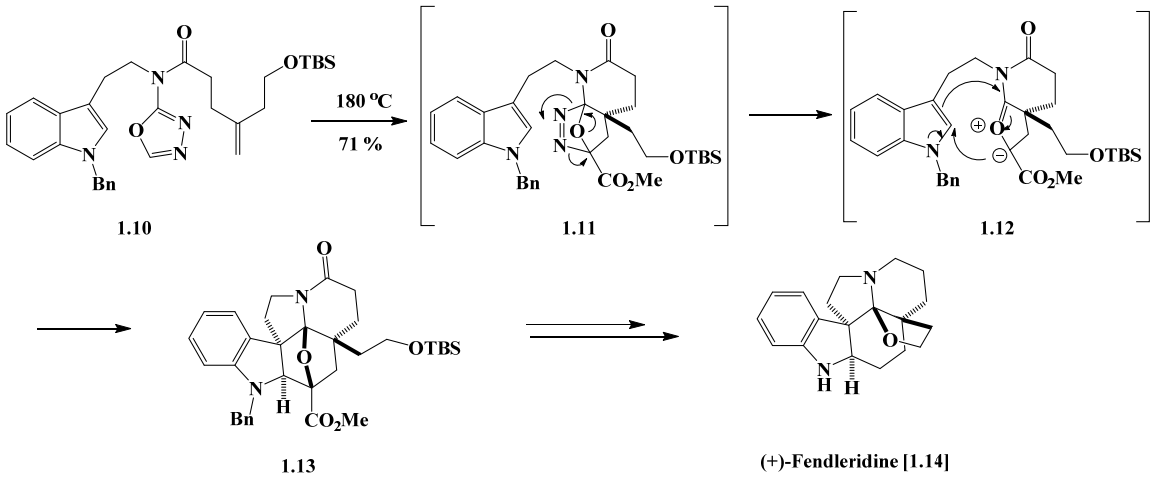


Scheme 1.2 - Synthesis of penifulvin A via photocyclization

Aromatic substrate **1.5** was irradiated to generate the excimer **1.6** which underwent formal cycloaddition to produce bi-radical **1.7**. The approach of the alkene arm was facially selective so that $A^{1,3}$ strain between the aryl methyl group and the benzylic position was minimized. Then radical recombination of **1.7** to form a cyclopropane ring yielded **1.8** as a mixture of diastereomers. The diastereomer **1.8** was further manipulated into penifulvin A (**1.9**).

Boger and coworkers have shown a powerful tandem [4+2] and [3+2] cycloaddition cascade reaction of 1,3,4-oxadiazoles in their efforts to synthesize *Aspidosperma* alkaloids such as (+)-fendleridine (**1.14**) (Scheme 1.3).[20] This strategy resulted in the successful construction of a pentacyclic ring system with three new rings, four new carbon-carbon bonds, and five stereocenters (See **1.13**) as a result of

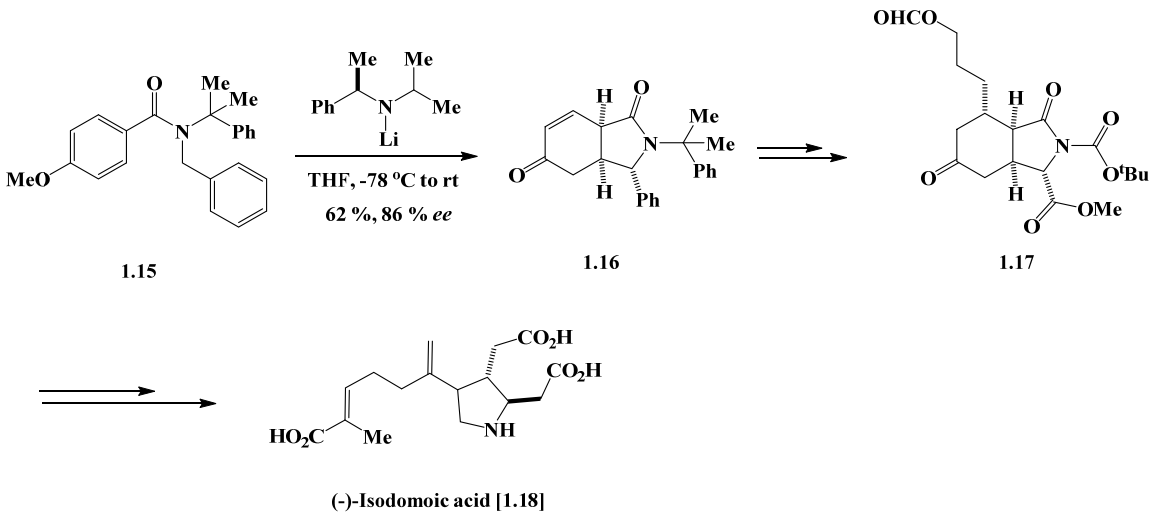
dearomatization of two heterocyclic rings. The cascade started with intramolecular [4+2] cycloaddition of 1,3,4-oxadiazole **1.10** substituted with a dienophile in the side chain to form cycloadduct **1.11**, which loses N_2 to give 1,3-dipole intermediate **1.12**. Rapid intramolecular [3+2] cycloaddition with dipolarophile tethered in the side chain afforded the regio-selective, endo cycloaddition intermediate **1.13** which was further manipulated into (+)-fendleridine (**1.14**).



Scheme 1.3 - Synthesis of (+)-fendleridine using cycloaddition cascade reaction

1.4 Dearomatization via Addition of Nucleophiles

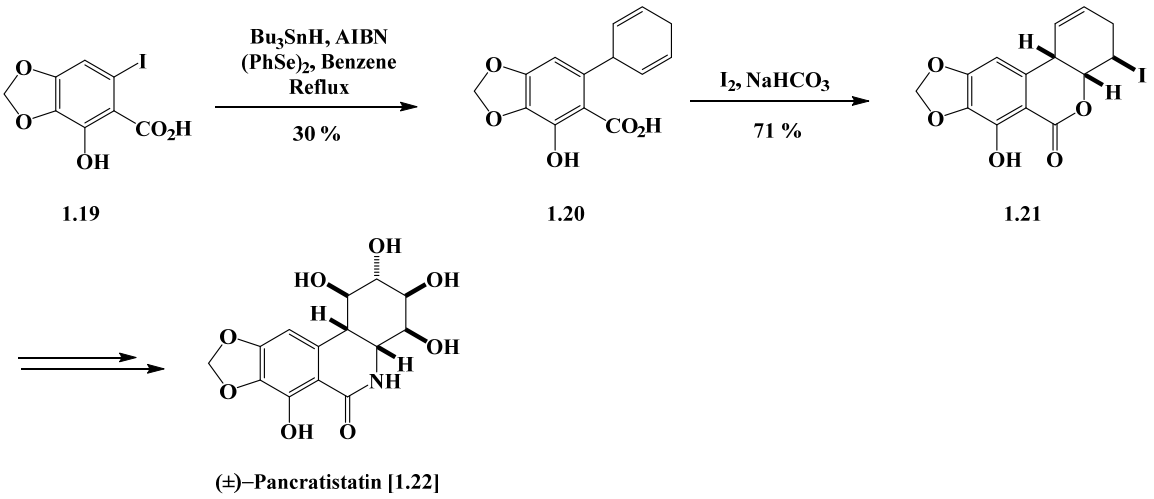
Carbanion addition to aromatic rings is another popular dearomatization technique.[21-23] Clayden and coworkers used this strategy in their enantioselective synthesis of an insecticidal cyclic kainoid amino acid, (-)-isodomoic acid C (**1.18**) (Scheme 1.4).[24] Dearomatization of the N-benzyl benzamide intermediate **1.15** to give bicyclic product **1.16** with desired stereochemistry was a significant step in their synthesis.



Scheme 1.4 - Dearomatization via anionic cyclization in the synthesis of (-)-isodomoic acid

1.5 Radical Mediated Dearomatization

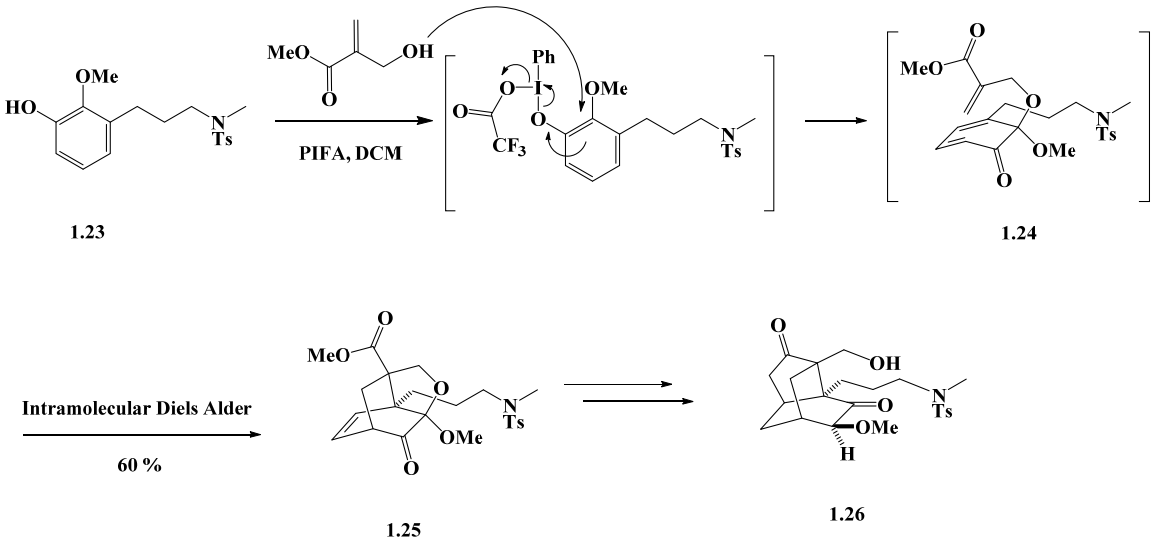
Radical-based chemistry has also been employed to effect dearomatization. *In situ* generated aryl radicals can react either inter- or intra-molecularly with substituted arenes to yield cyclohexadienyl radicals which generally are not reactive enough to propagate chain reactions. Crich and coworkers have shown that in the presence of a catalytic amount of diphenyl diselenide, stannane-mediated radical addition of aryl iodides such as **1.19** to arenes (e.g, benzene) results in cyclohexadienyl radicals, which would abstract a hydrogen radical and affords aryl substituted cyclohexadienes (e.g., **1.20**).[25,26] This chemistry is rendered practical by the rapid *in situ* reduction of diphenyl diselenide to benzeneselenol by the stannane. This radical-mediated dearomatization was used in their synthesis of bioactive phenanthridinone alkaloid (±)-pancratistatin (**1.22**) as shown in Scheme 1.5.[27]



Scheme 1.5 - Dearomatization using radical addition

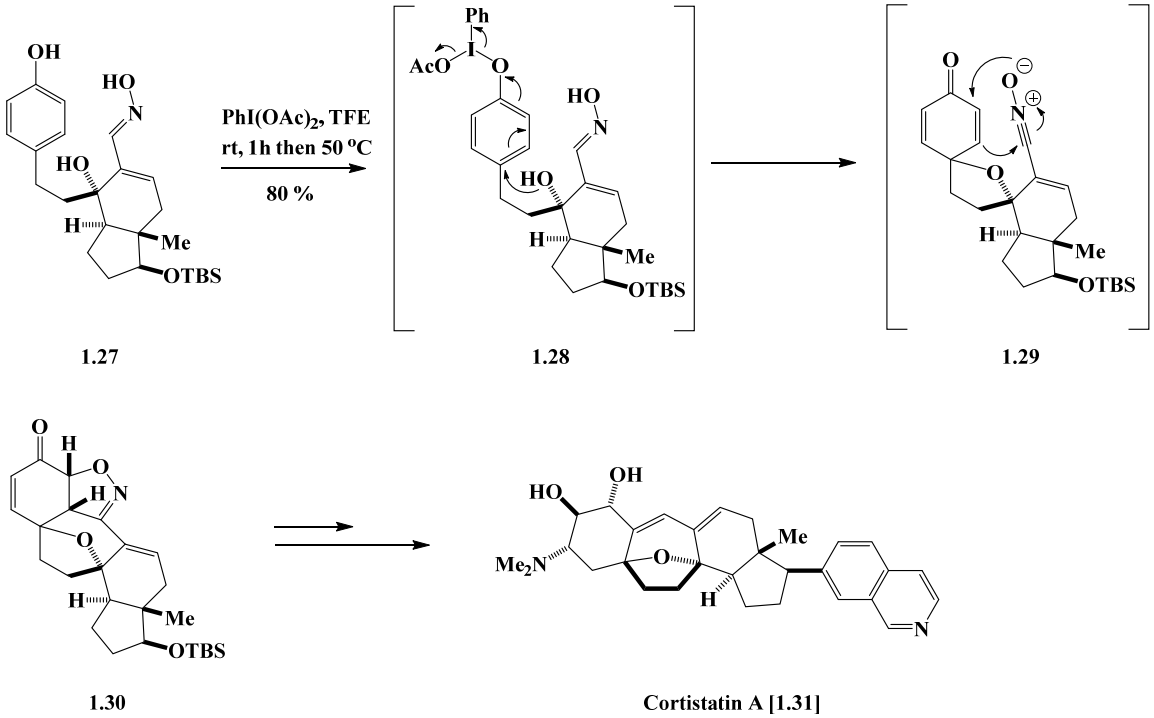
1.6 Oxidative Dearomatization

Oxidative dearomatization is very well known to be environmentally benign for accessing complex structural motifs.[28] Electrophilic hypervalent iodine reagents such as phenyliodine diacetate (PIDA) and phenyliodine trifluoroacetate (PIFA) are known to oxidize electron rich aryl substrates such as phenols and phenyl ethers.[29] This strategy is useful in obtaining both *ortho*- and *para*-cyclohexadienones through either inter- or intra-molecular oxidative dearomatization.[30,31] Zhao and coworkers have employed an intermolecular oxidative dearomatization reaction in tandem with an intramolecular Diels Alder reaction (IMDA) to synthesize the tricyclic core of palhinine A (Scheme 1.6).[32] Phenol substrate **1.23** and hydroxymethylacrylate were treated with PIFA to form the intermediate **1.24**, which in turn underwent intramolecular Diels Alder reaction to afford **1.25** in good overall yield. Substrate **1.25** was then further manipulated to **1.26**, which contains the tricyclic core of palhinine A.



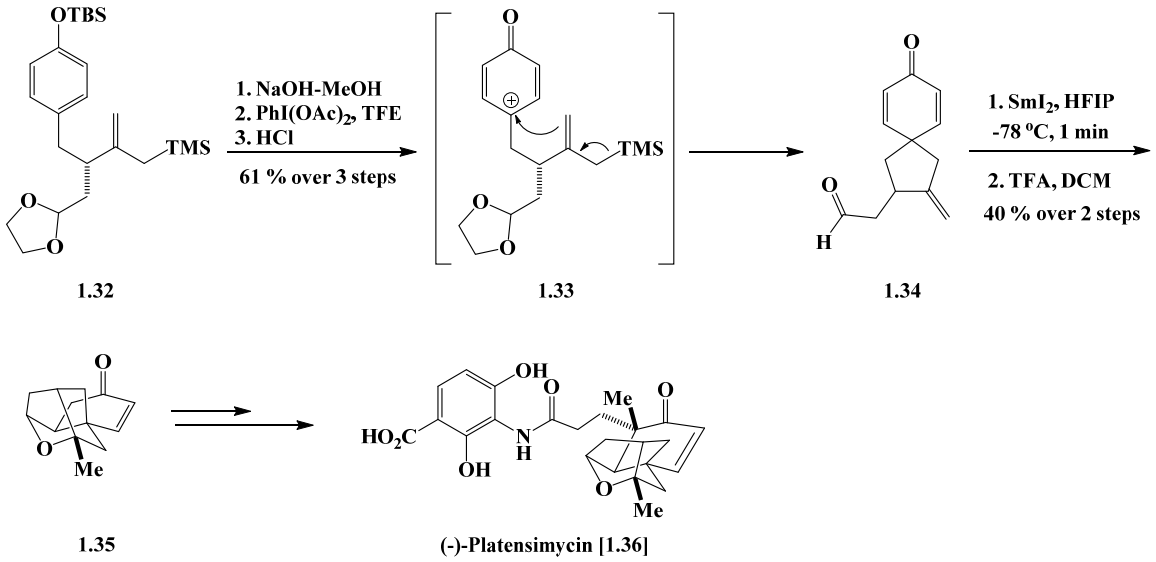
Scheme 1.6 - Synthesis of the tricyclic core of palhinine A

Sorensen and coworkers developed a cascade process initiated by hypervalent iodine-mediated oxidative dearomatization to synthesize the pentacyclic framework of cortistatin A (**1.31**).[33] Compound **1.27** underwent tandem cyclization at the *ipso* position by intramolecular nucleophilic attack of the hydroxyl group on the electrophilic aromatic ring generated upon treatment with PIDA to yield **1.28** as shown in Scheme 1.7. Nitrile oxide **1.29,** which was a result of further oxidation, underwent [3+2] dipolar cycloaddition and generated a single product **1.30**.



Scheme 1.7 - Synthesis of cortistatin A via PIDA mediated oxidative dearomatization

Nicolaou and coworkers have used a phenol substrate to form new carbon-carbon bonds via nucleophilic dearomatization in the presence of hypervalent iodine reagents (Scheme 1.8).[34] Deprotection of the TBS group in **1.32** resulted in the free phenol, which was then activated for nucleophilic attack using PIDA. Attack at the *ipso* position of **1.33** from the carbon nucleophile generated from an attached allyl silane group yielded the spiro product **1.34**, which was then further functionalized to afford the tetracyclic core structure (**1.35**) of (-)-platensimycin (**1.36**).

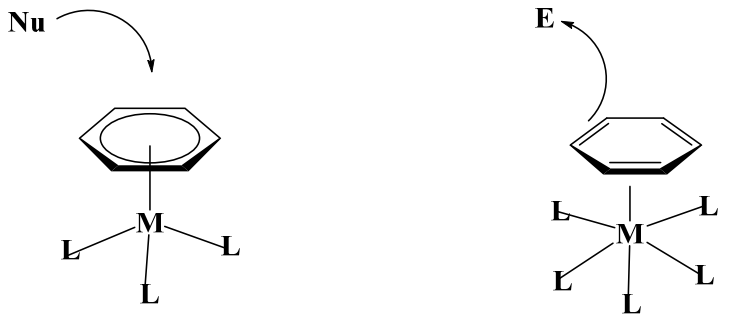


Scheme 1.8 - Synthesis of (-)-platensimycin using oxidative dearomatization

1.7 Transition Metal-Catalyzed Dearomatization

Transition metals in general play significant roles in synthetic organic chemistry. Transition metal mediated dearomatization of aromatic substrates is a powerful tool for conversion of substituted aromatics into functionalized alicyclic compounds in a controlled fashion.[9] There are two distinctive alternatives to the transition metal mediated dearomatization: electrophilic and nucleophilic dearomatization. The dearomatization mode is determined by the coordination of the metal to the aromatic ring (Figure 1.2). When metal coordinates to all the π-bonds in the aromatic ring (the η^6-coordination mode), the ring becomes electron-deficient and thus susceptible to nucleophilic addition. (e.g., (η^6-arene)Cr(0)$(CO)_3$, (η^6-arene)Mn(I)$(CO)_3$, (η^6-arene)Fe(II)Cp complexes).[13,35,36] Alternatively, in η^2-arene complexes, only one π-bond of the aromatic ring is coordinated to the metal. Activation of the ring by electron donation from the metal (metal dπ-arene π^* backbonding) renders the ring nucleophilic and facilitates electrophilic addition reactions (e.g., $Os(NH_3)_5^{2+}$).[37,38] Both types of organometallic reactions undergo

transformations with high regio- and stereoselectivity, and both have been applied in many complex molecule syntheses.

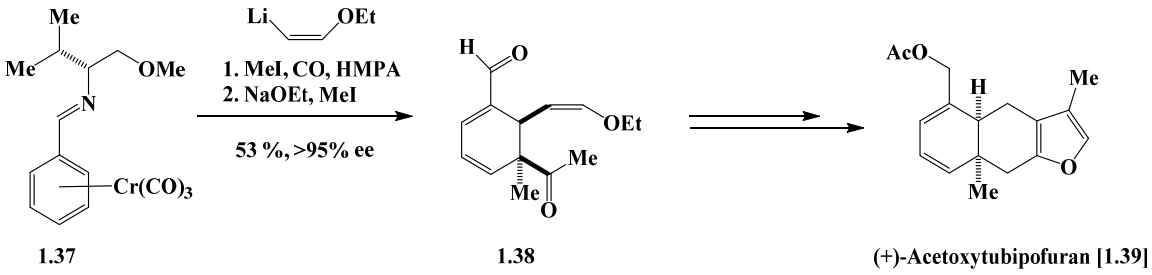


η^6 - arene complex
Nucleophilic dearomatization

η^2 - arene complex
Electrophilic dearomatization

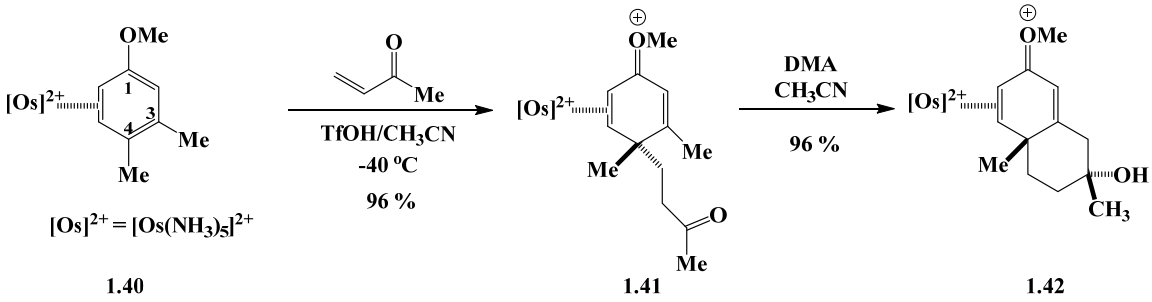
Figure 1.2 - Reactivity of transition metal arene complexes

Kündig and coworkers have developed a $Cr(CO)_3$ mediated asymmetric dearomatization method in the synthesis of both enatiomers of acetoxytubipofuran (**1.39**).[39] This syntheses has shown that the η^6-coordinated benzaldehyde derived imine-chromium complex **1.37** directed addition of ethoxyvinyl lithium to the *ortho* position, which was immediately followed by methylation at the chromium metal center. This followed insertion of carbon monoxide into the bond between the methyl carbon and the chromium metal. Then alkylation and imine hydrolysis was carried out to afford compound **1.38** with the desired relative configuration (Scheme 1.9). This product was then further manipulated into the ancitipated *cis*-decalin skeleton of the target natural product.



Scheme 1.9 - Nucleophilic dearomatization using η^6-coordinated chromium complex

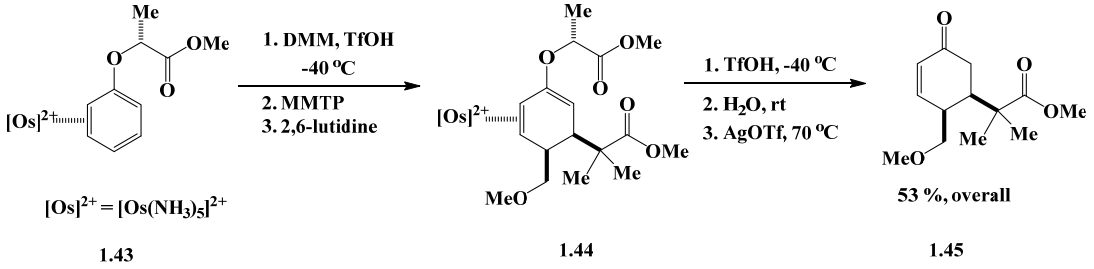
Pentaamineosmium(II)-arene complexes were employed by Harman and coworkers in η^2-coordinated fashion, to study the activation of *para* sp^2 carbon (*para* to the methoxy group) in **1.40** for the synthesis of a functionalized decaline scaffold. Successful dearomatization of 3-alkylated anisole complexes of $Os(NH_3)_5^{2+}$ (**1.40**) using Michael addition to methyl vinyl ketone in the presence of triflic acid yields 4H-anisolium Michael adducts such as **1.41** (Scheme 1.10).[40] This resulted in regioselective deprotonation in the presence of a weak base resulting in an intramolecular aldol reaction with a pendant ketone to form a bicyclic decalin system **1.42**.



Scheme 1.10 - η^2-Coordinated osmium-arene complex in electrophilic dearomatization

Addtionally, Harman has shown that η^2-coordinated pentaammineosmium(II)-arene complexes with a pre-existing chiral auxiliay attached to the arene, may be used to

induce high transfer of chirality to C4, C3, and C1 of the arene.[37,41] A phenyl ether-osmium complex with an enatiopure chiral auxiliary attached (**1.43**) underwent electrophilic addition with dimethoxymethane (DMM) followed by addition of 1-methoxy-2-methyl-1-trimethylsiloxypropene (MMTP) to afford functionalized cyclohexadiene **1.44** (Scheme 1.11). Decomplexation of the transition metal and removal of the chiral auxiliary from **1.44** resulted in the useful cyclohexenone **1.45**. More recently, the same group has developed methods to utilize less expensive and less toxic tungsten complexes [e.g, $TpW(NO)(PMe_3)$] to activate benzene and heteroaromatics for Michael type addition under neutral or basic conditions.[42,43]

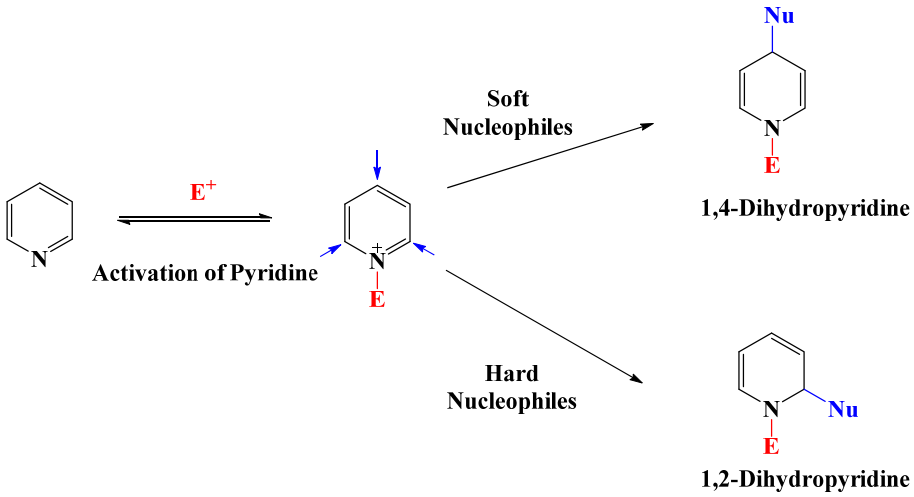


Scheme 1.11 - Electrophilic dearomatization using η^2-coordinated osmium complex

1.8 Dearomatization of Pyridine Substrates

Many bioactive natural products contain six-membered heterocycles with nitrogen atoms present. To access these biological active complex aza-heterocycles, synthetically pyridine derivatives provide a convenient pool of starting materials. It is well known that pyridine and pyridine substrates participate in regioselective dearomatization reactions with nucelophiles after conversion to pyridinium salts by treatment with either alkylating or acylating reagents.[44] Both inter- and intramolecular additions of different types of nucleophiles to activated pyridinium intermediates using various electrophiles as pyridine

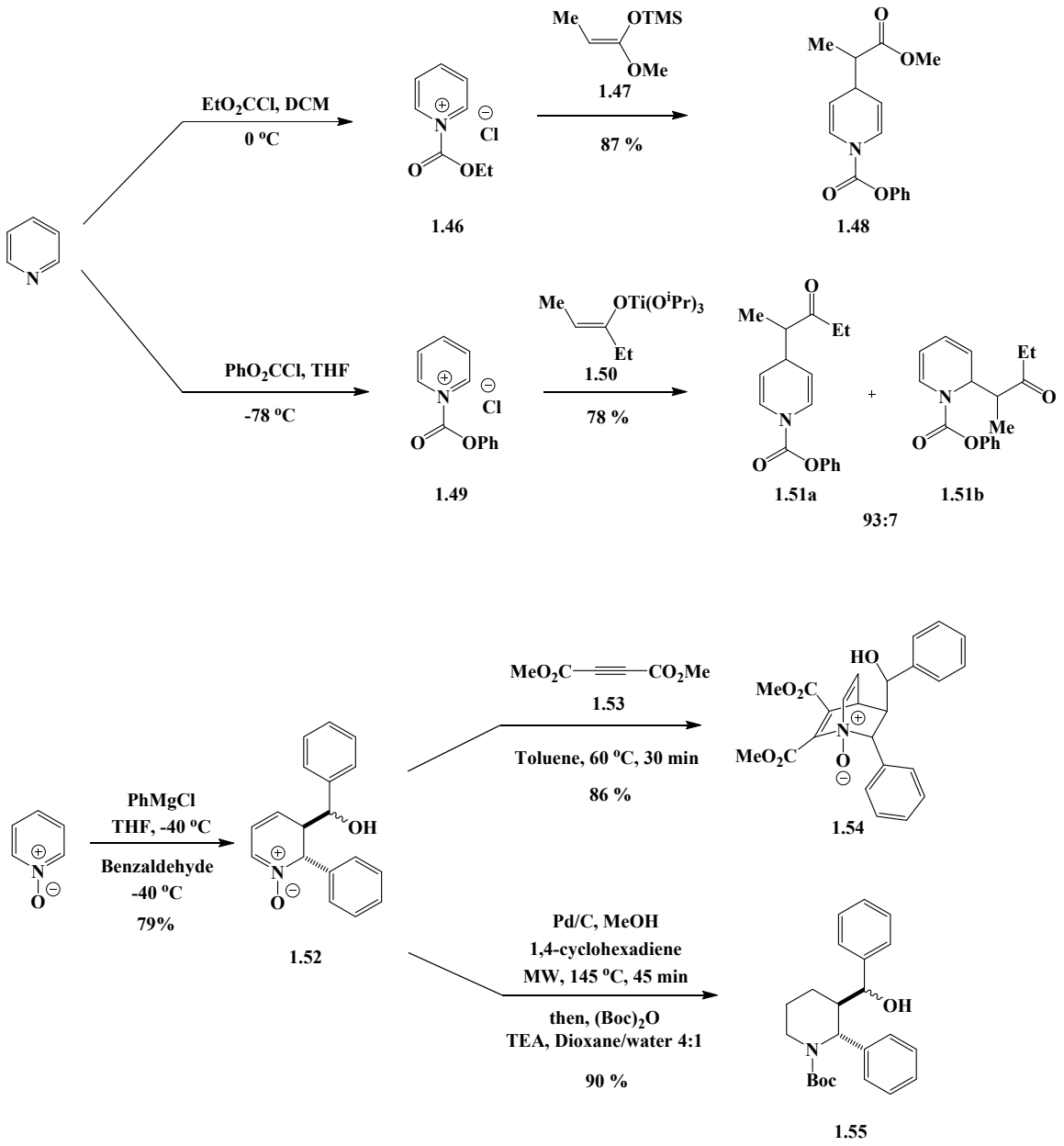
activating groups have been reported. In particular, intermolecular versions of this chemistry have been very well studied and utilized for the synthesis of functionalized heterocycles.[44] It has been shown that soft nucleophiles such as organocuprates, metal enolates (e.g., zinc enolates) and enol ethers (e.g., silyl enol ethers) will attack pyridinium salts preferentially at the C-4 position to afford 1,4-dihydropyridines (Scheme 1.12).[45-48] Alternatively, hard nucleophiles such as organolithium and organomagnesium reagents, add to the pyridinium intermediate preferentially at the C-2 position yielding 1,2-dihydropyridines (Scheme 1.12).[49-52]



Scheme 1.12 - Nucleophilic additions to activated pyridine ring

Many examples of intermolecular additions to activated pyridinium intermediates have been reported and several of them are illustrated in Scheme 1.13. Akiba and coworkers have shown that addition of silyl ketene acetal **1.47** to pyridinium salt **1.46** affords the corresponding 1,4-dihydropyridine regioisomer **1.48** in good yield.[53] Likewise, titanium enolates (**1.50**) reacted with the pyridinium salt **1.49** to afford the 1,4-dihydropyridine as the major product.[54] Pyridinium N-oxides are known to undergo ring

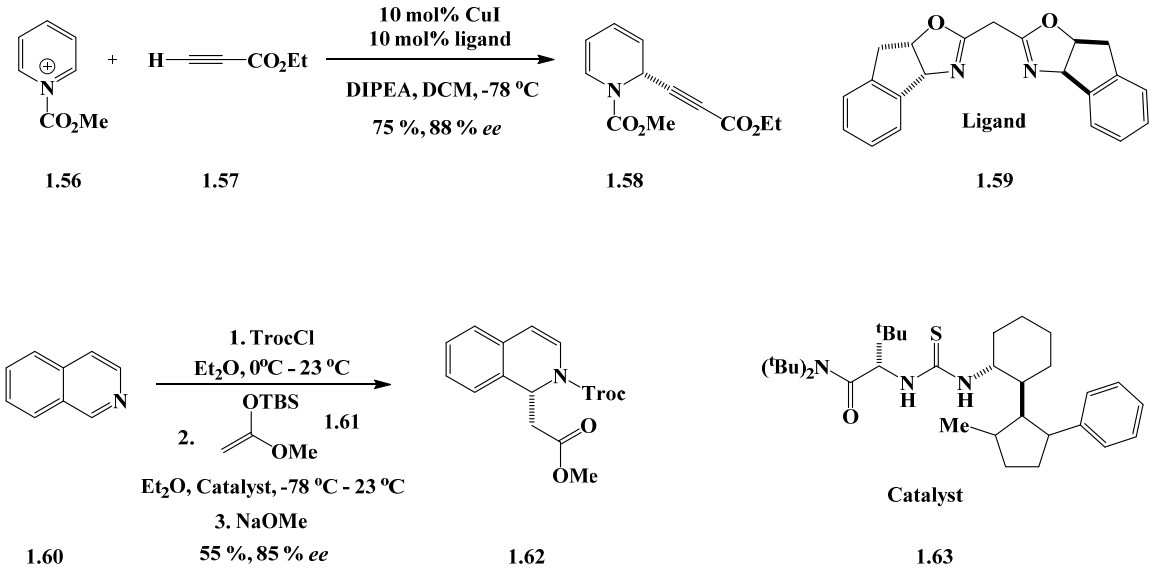
opening to yield dienyl oxime products upon addition of hard nucleophiles.[55] However, Almquist and coworkers have shown that organo-magnesium reagents can add to pyridinium N-oxides selectively at the C-2 position in the presence of suitable electrophiles (e.g., benzaldehyde) to obtain functionalized *trans*-2,3-dihydropyridines (**1.52**) in a completely regio- and stereoselective process (Scheme 1.13).[56] These stable intermediates can then be further manipulated via Diels-Alder cycloaddition reactions with dimethylactylene dicarboxylate (**1.53**) to afford **1.54** in excellent yield. They could also be converted into N-Boc protected piperidine derivatives such as **1.55**.



Scheme 1.13 - Nucleophilic additions to pyridinium salts and their regioselectivity

Another potentially powerful tool for heterocyclic synthesis is asymmetric addition of nucleophiles to activated pyridine substrates. Even though this has proven to be effective with the use of stoichimetric chiral auxiliaries, there are only a few reports describing catalytic asymmetric additions of nucleophiles to pyridinium salts.[57,58] Ma and

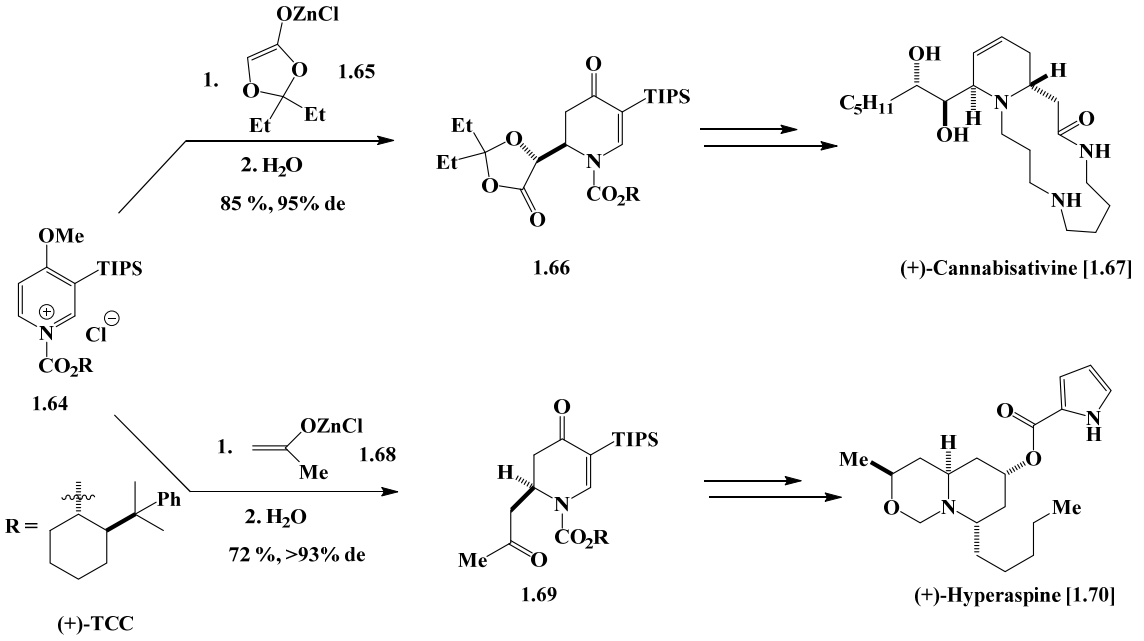
coworkers have developed the asymmetric addition of activated terminal alkynes (e.g., **1.57**) to acyl activated pyridines (**1.56**) using copper complexes with bis(oxazoline) ligands (**1.59**) (Scheme 1.14).[59] It has also been shown that varous terminal alkyne reagents can be used to add to the C-2 position of the pyridine ring upon activation using copper catalysts and R-QUINAP ligands.[60]



Scheme 1.14 - Asymmetric induction in nucleophilic addition to activated pyridines

Jacobsen and coworkers have incorporated an asymmetric acyl-Mannich type reaction involving thiourea catalysts (e.g., **1.63**) for enantioslective addition of silyl ketene actetal **1.61** to an acylated isoquinolinium intermediate to obtain dearomatized product **1.62** (Scheme 1.14).[61] It was also found that the enatioselectivity of such reactions depends upon the nature of the activating group (TrocCl gave better selectivity), and susbtitution on the hydrogen-bonding thiourea catalyst. These transformations show the great potential of catalytic asymmetric additions to pyridinum salts, proving that additional research needs to be performed to fully develop this chemistry.[57]

In contrast, chiral auxiliaries have been used to mediate diastereoseletive additions to pyridine in natural product synthesis. Comins and coworkers have extensively studied such chemistry involving activated pyridines and similar substrates,[62,63] and have used pyridine dearomatization strategies in the total synthesis of many biologically active natural products.

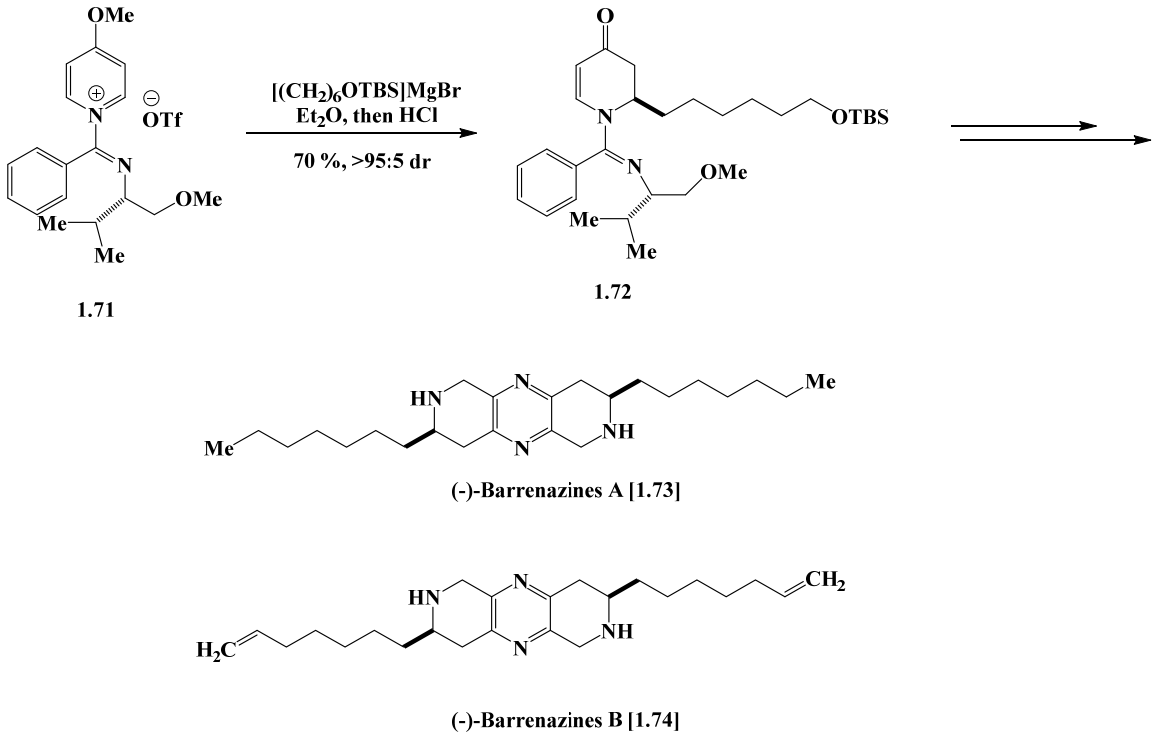


Scheme 1.15 - Intermolecular pyridine dearomatization in natural product synthesis

For example, addition of zinc enolate **1.65** to activated pyridine intermediate **1.64** via substrate-controlled asymmetric induction was used to obtain 1,2-dihydropyridine product **1.66**.[64] Further manipulation was done to synthesize the natural product (+)-cannabisativine (**1.67**) (Scheme 1.15). Moreover, the same starting material (**1.64**) was used in the synthesis of of several other alkaloid natural products, such as (+)-hyperaspine (**1.70**) by dearomatization strategy.[65] Addition of zinc enolate (**1.68**) resulted in the 1,6-dihydropyridine product (**1.69**) (steric repulsion of the TIPS group directed the

nucleophile to attack at the C-6 position) in a highly stereoselective manner, which was then further maipulated to obtain the target natural product (Scheme 1.15).

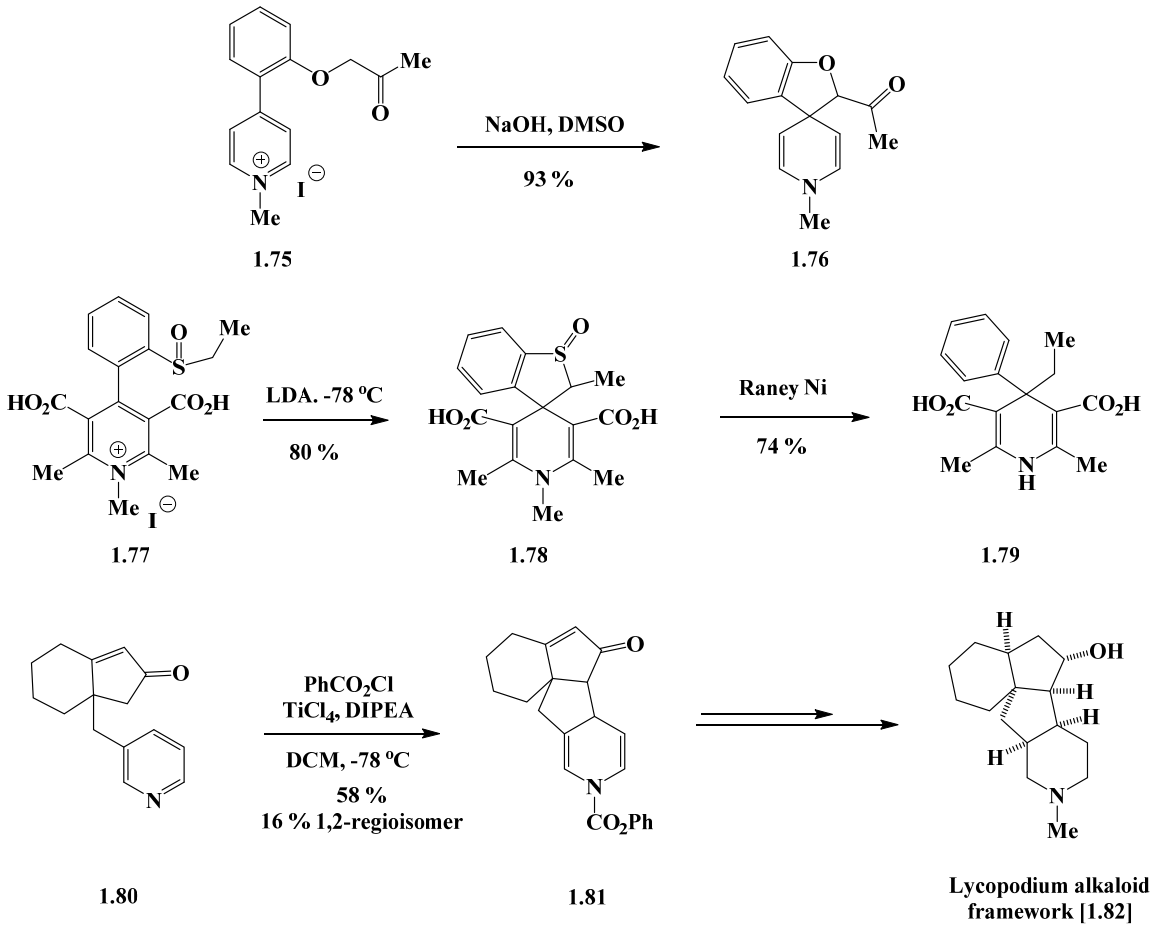
Charette and coworkers have also done comprehensive studies on pyridine dearomatization to synthesize enantiopure, polysubstituted piperidines from readily available starting materials. Chiral pyridinium salts such as **1.71** were synthesized using functionalized pyridines, secondary amides and triflic anhydride.[66,67] These pyridinium salts have proven to be very effective in participating in highly diastereoselective and regioselective addition of carbon nucleophiles to produce dihydropyridines.



Scheme 1.16 - Synthesis of (-)-barrenazines via intermolecular dearomatization of pyridines

Addition of Grignard reagents to chiral auxiliary-activated pyridinium salt **1.71**, produced 1,2-dihydropyridine **1.72** in good yield with excellent stereocontrol (Scheme 1.16). Barrenazines A (**1.73**) and B (**1.74**) were synthesized after a few additional chemical transformations in good overall yield.[68]

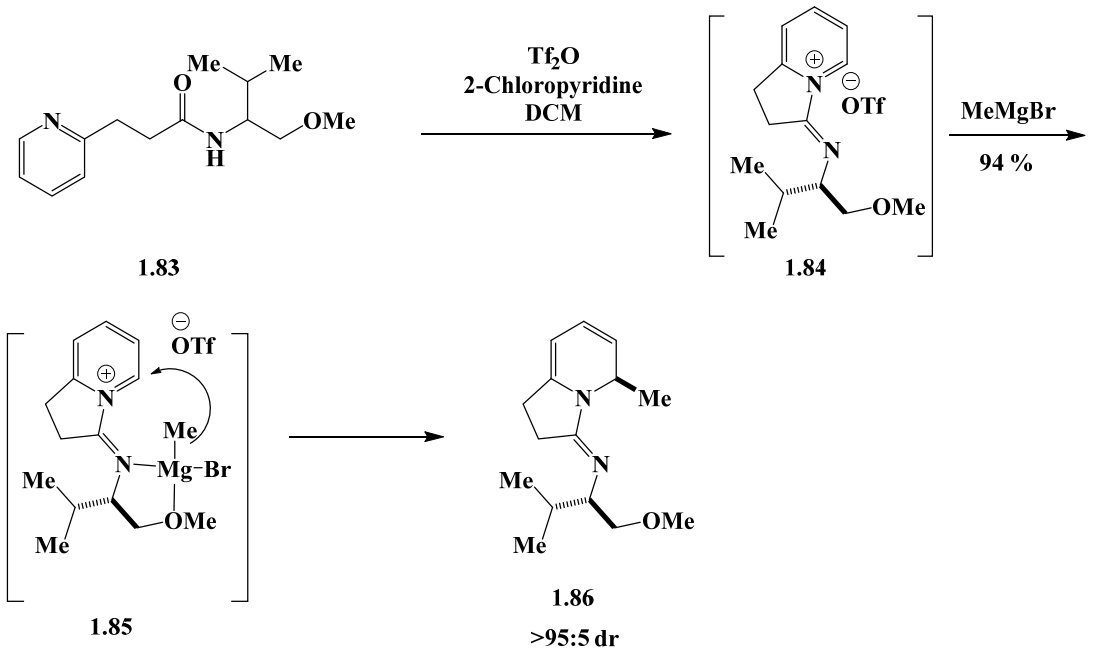
The intramolecular version of pyridine dearomatization offers potential synthetic access to azaspirocycles and piperidine based fused-ring systems. Surprisingly, studies on intramolecular dearomatization strategies of pyridine substrates are less common relative to intermolecular reactions. Weller and coworkers have shown that aza-spirocycles can be synthesized using substituted pyridines with carbon nucleophiles in the side chains (Scheme 1.17).[69] When alkyl pyridinium salts, such as **1.75**, are treated with NaOH, formation of spirocyclic products (**1.76**) has been observed in good yields. But the spirocycles were only stable at -20 ºC while showing decomposition at room temperature. Additionally, 4,4'-disubstituted-1,4-dihydropyridines were synthesized by Goldmann and coworkers via dearomatization (Scheme 1.17).[70] Treatment with LDA generates the sulfinyl carbanion resulting in a nucleophilic attack on to the C-4 position of the pyridine ring to afford 1,4-dihydropyridine product **1.78** which was further manipulated to synthesize **1.79** as a part of an effort to develop new antihypertension agents. Substrates such as **1.77** are synthesized from Hantzsch esters thus limiting the generality of this strategy. Meyers and coworkers employed a successful titanium enolate addition reaction to the C-4 position of a pyridine substrate (**1.81**) upon activation by phenyl chloroformate in the presence of DIPEA (Scheme 1.17).[71] This transformation resulted in a 5:1 mixture of regioisomers and provided a key intermediate for construction of the tetracyclic core of *Lycopodium* alkaloids (**1.82**).



Scheme 1.17 - Examples of intramolecular pyridine dearomatization

Charette and coworkers have shown an example of an intramolecular pyridine activation and asymmetric dearomatization by obtaining 5-substituted indolizidines and 6-quinolizidines with high regio- and diastereoselectivity (Scheme 1.18).[72] This was achieved by synthesizing an activated chiral pyridinium salt **1.84** by reacting **1.83** with triflic anhydride in the presence of 2-chloropyridine. Then addition of the Grignard reagent to **1.84** resulted in the formation of unsaturated indolizidine **1.86** as a single regio- and diastereomer. Even though an undesired deprotonation was expected due to the base sensitivity of the pyridine salt, it was not observed. Stereo- and regiocontrol can be attributed to precomplexation (**1.85**) of the Girgnard reagent with *E*-imidate lone pair

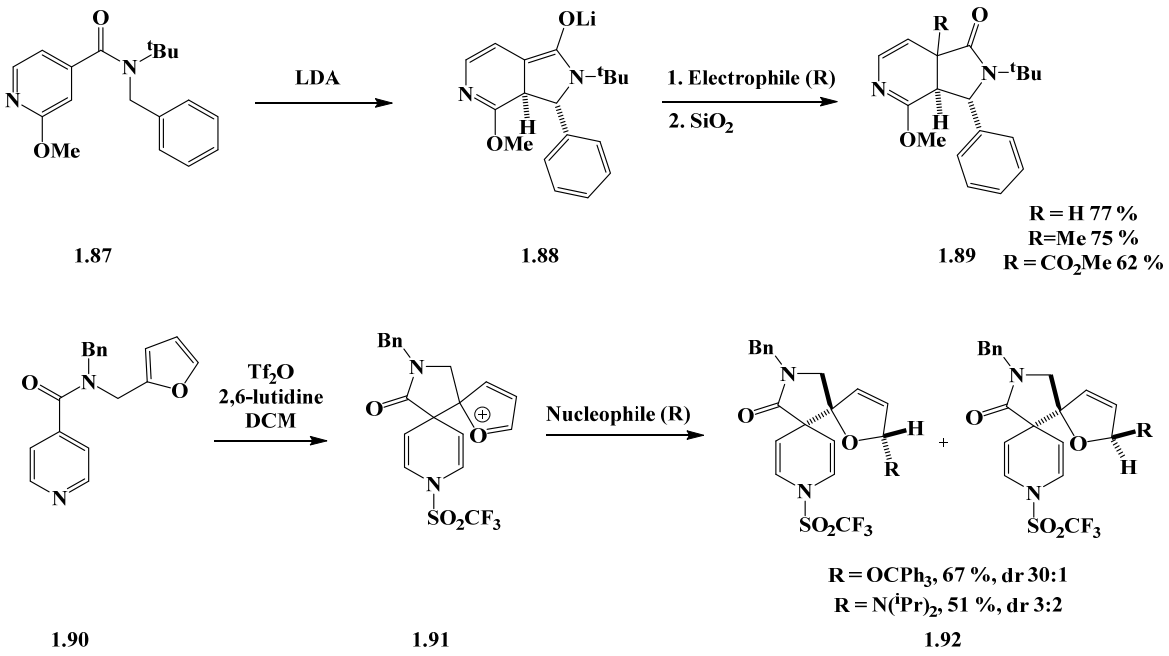
and also coordination with ether functionality, thus directing nucleophlic addition to the 6-position while minimizing 1,3-allylic strain with the auxiliary.



Scheme 1.18 - Asymmetric induction in intramolecular pyridine dearomatization

Clayden and coworkers have also utilized pyridine dearomatization to access functionalized piperidines. It was shown that anions generated by lithiation of N-benzyl pyridine derivatives can be directly added to the pyridine ring or to activated pyridine derivatives.[73] Isonicotinamide derivative **1.87** was lithiated and manipulated in an intramolecular manner to add to the pyridine ring and yielded corresponding dearomatized product **1.88** which on alkylation or acylation, resulted in **1.89** in good yield as a single diastereomer (Scheme 1.19). In another attempt, double dearomatization of electrophilic and nuclephilic arene pairs tethered together was exploited via tandem intramolecular cyclizations (Scheme 1.19).[74,75] The pyridine substrate **1.90** was activated by acylation and consequent nucleophilic attack by the electron rich furan ring afforded

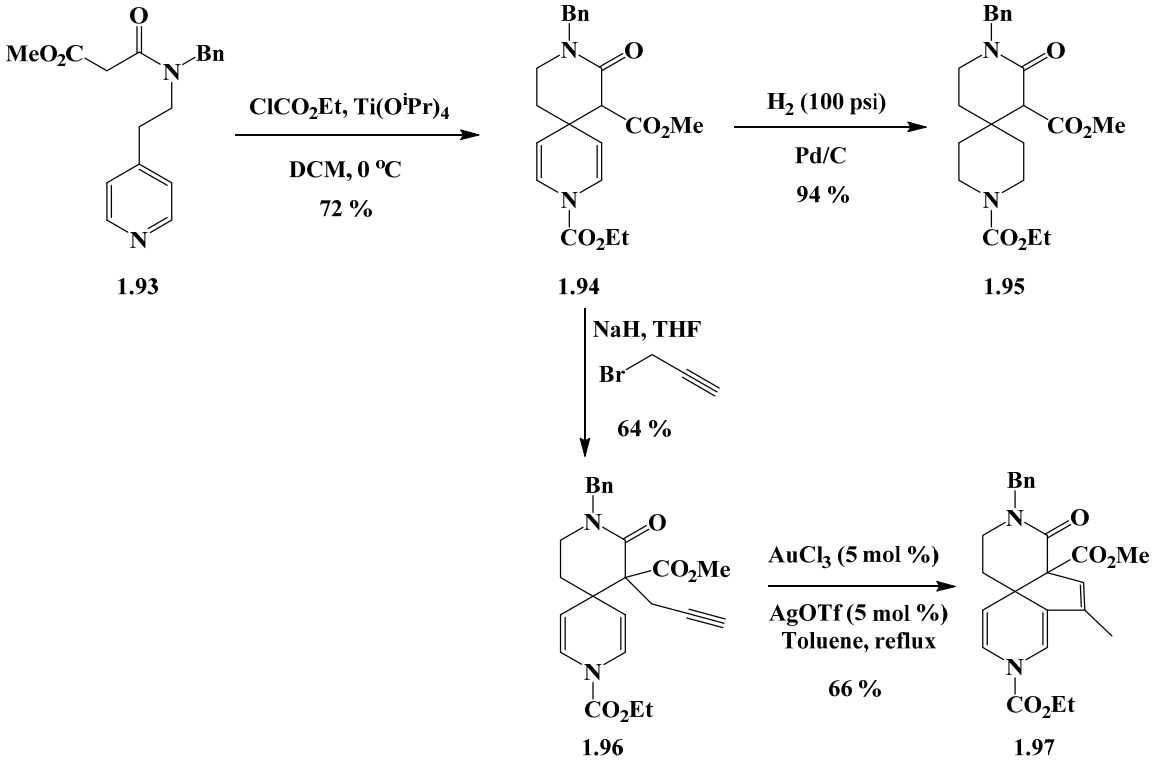
1.91. The oxonium intermediate was succeccfully trapped by added nucleophiles to yield **1.92** with high diastereoselectivity.



Scheme 1.19 - Examples of pyridine dearomatization from the Clayden group

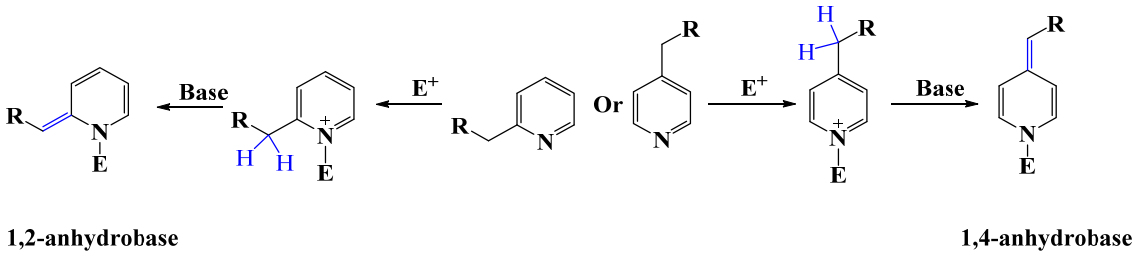
Pigge and coworkers have shown that construction of 3,9-diazaspiro[5,5]undecane derivatives (**1.94**) can be easily achived via intramolecular spiro-cyclization of 4-substituted pyridines (Scheme 1.20).[76] This reaction entails *in situ* activation of the pyridine substrate **1.93** with ethyl chloroformate followed by intramolecular addition of an attached β-dicarbonyl nucleophile in the presence of $Ti(O^iPr)_4$ to afford the dihydropyridine **1.94**. This intermediate was further manipulated via hydrogenation to afford the N-protected spiro-bis(piperidine) **1.95** in excellent yield. Furthermore, **1.94** was also amenable to alkylation with carbon electrophiles (e.g., propargyl bromide) to afford products similar to **1.96**. Subsequent gold catalayzed

cycloisomerization to afford **1.97** was found to proceed smoothly to provide the novel tricyclic compound **1.97**.



Scheme 1.20 - Examples of pyridine dearomatization from the Pigge group

In addition to activated pyridine and functionalized pyridine substrates being utilized as electrophiles to react with nucleophiles, there is another aspect to pyridine reactivity when a substituent on the C-2 or C4 positions is present along with benzylic protons. When such a substituent is present on the pyridine ring, activation and subsquent addition of a base, results in formation of an intermediate that is called an "anhydrobase" (Scheme 1.21).



Scheme 1.21 - Formation of anhydrobases from 2- and 4-alkylpyridines

Anhydrobases generally acts as nucleophiles and hence have been of interest to researchers for a long time. They have been used as intermediates in the construction of various heterocyclic ring systems, such as indolizines, pyridazines, and piperidines.[77-79] Anhydrobases are also of importance due to their presence in the skeletal frameworks of some alkaloids such as semepervarine (**1.98**), flavopereirine (**1.99**), flavocarpine (**1.100**), and alstonine (**1.101**) (Figure 1.3).[80-83]

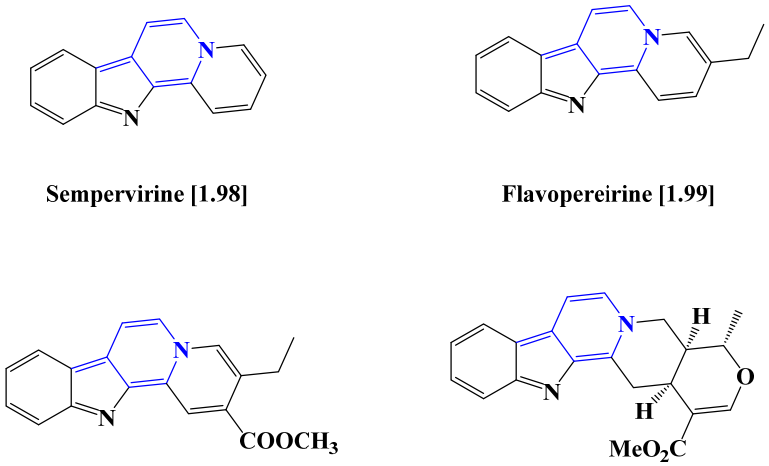
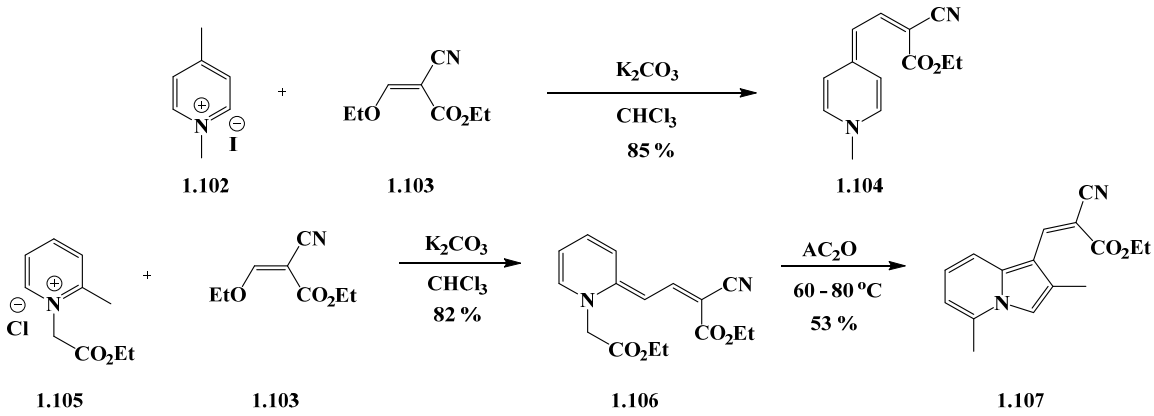


Figure 1.3 Anhydrobases in skeletal frameworks of alkaloids

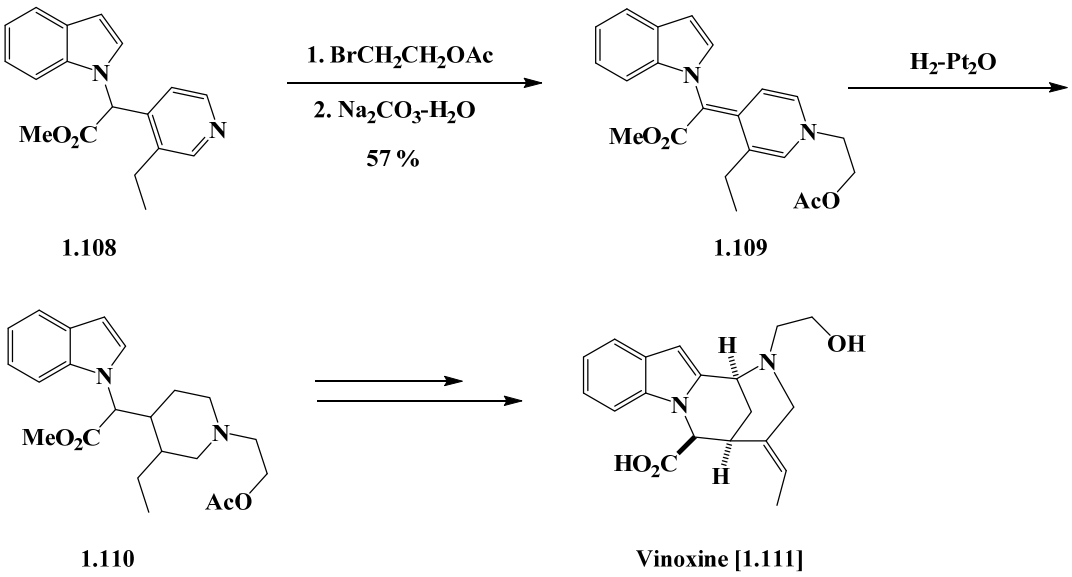
Kaheki and coworkers have examined anhydrobase chemistry by using simple 2- and 4-alkylpyridine substrates (Scheme 1.22).[84] In the presence of a base these activated

pyridines reacted with ethoxymethylene compounds. Pyridinium salt **1.102** was prepared by treating 4-picoline with iodomethane and was used without further purification. It was then allowed to react with ethoxymethylcyanoacetate (**1.103**) in the presence of potassium carbonate. This resulted in the formation of the initial anhydrobase which afforded the final anhydrobase product **1.104**. Similarly when activated pyridinium substrate **1.105** was subjected to similar reaction conditions, anhydrobase product **1.106** was isolated as a crystalline compound. Further manipulation of **1.106** provided the indolizine derivative **1.107** in good yield.[77]



Scheme 1.22 - Novel synthetic methods for indolizine derivatives

Bosch and coworkers utilized an anhydrobase intermediate in their synthesis of vinoxine (**1.111**), a tetracyclic indole alkaloid (Scheme 1.23).[85] Anhydrobase intermediate **1.109** was obtained by reaction of **1.108** with an alkyl activating group followed by addition of sodium carbonate. The anhydrobase **1.109** was then subjected to hydrogenation to reduce all the double bonds which resulted in the piperidine product **1.110**. Further manipulation afforded the final natural product vinoxine (**1.111**).



Scheme 1.23 - Total synthesis of vinoxine via an anhydrobase intermediate

In general, reports of anhydrobase intermediates in the synthesis of natural products are less common. Nonetheless, such intermediates are intriguing compounds, and their manipulation may offer new preparative routes for the synthesis of biologically active natural products.

It is notable that inter- and intramolecular dearomatization of pyridine plays a vital role in natural product synthesis. However, these reaction manifolds remain relatively under-explored and thereby offer researchers an opportunity to uncover new reaction methodologies that can aid in construction of complex molecular architectures.[86,87]

1.9 Conclusion

There are many methods available to achieve dearomatization in the context of natural product synthesis. Reaction strategies that convert readily available starting materials to complex materials with a minimum of synthetic operation are useful. Development of new dearomatization techniques may facilitate discovery of concise, efficient regioselective, and sterecontrolled routes to important synthetic building blocks in environmentally and economically friendly fashion. The remainder of this dissertation will detail efforts to harness the chemistry of dearomatized pyridine and related imidazole anhydrobases in new bond-forming reactions to synthesize new molecular frameworks that could be ultimately used for the synthesis of bioactive natural products. Moreover, successful efforts to access the bis(piperidine) molecular framework that is present in many biologically active marine alkaloids will be discussed.

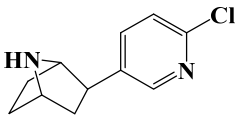
Chapter Two

Brønsted Acid-Catalyzed Cyclizations of Alkylpyridines[1]

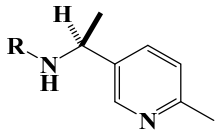
2.1 Introduction

Substituted pyridines and their reduced analogues (e.g., dihydropyridines and piperidines) are important structural scaffolds often seen in pharmacophores in medicinal chemistry, natural products, pharmaceuticals and other pharmacologically active compounds (Figure 2.1).[88-92] Highly conjugated heterocycles provide the molecular basis for many synthetic dyes, fluorescent (or colorimetric) indicators, and biological probes.[93,94] The structural complexity of aza-heterocycles is interesting from a synthetic standpoint, as they often serve as synthetic building blocks in the construction of more elaborate organic architectures. Therefore, it is very important to investigate methods for the synthesis of pyridine derivatives, along with strategies for elaboration of readily available pyridines.[95,96]

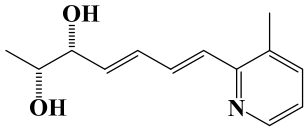
[1] This chapter is adapted from a published manuscript: Lansakara, A. I.; Farrell, D. P.; Pigge, F. C.: Brønsted acid catalyzed intramolecular benzylic cyclizations of alkylpyridines. *Org. Biomol. Chem.* **2014**, *12*, 1090.



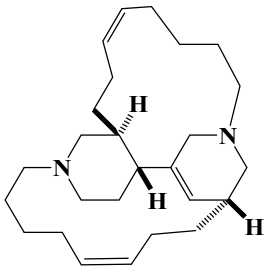
Epibatidine [2.1]



Bonagardine [2.2]



Fuzanin D [2.3]

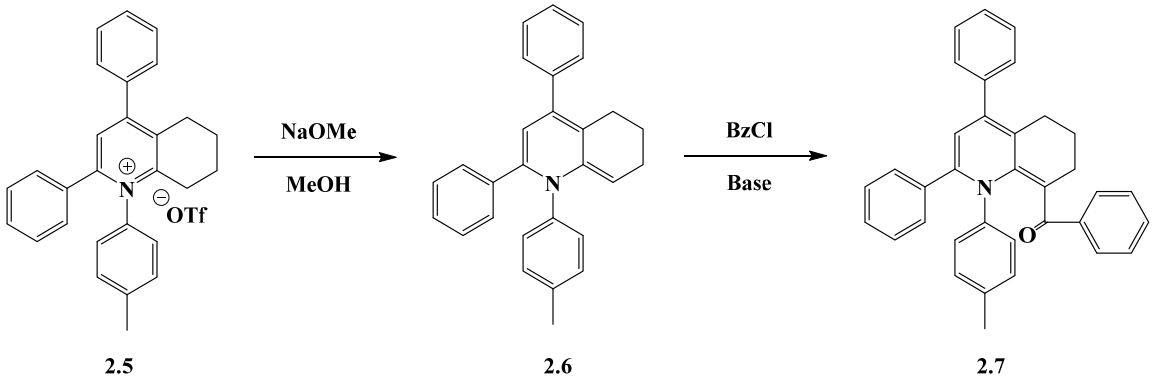


Halicyclamine B [2.4]

Figure 2.1 - Selected aza-heterocycles of biological importance

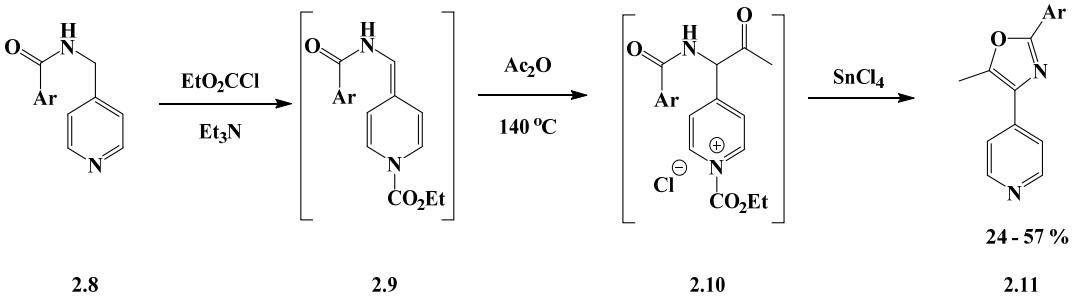
As discussed in Chapter 1 (Scheme 1.21), activated 2- or 4-alkylpyridines can be manipulated to form the corresponding nucleophilic anhydrobase intermediate under basic conditions by loss of one of the benzylic protons. Only a few examples have been reported illustrating the use of anhydrobases of activated pyridines for heterocyclic synthesis.

An orange colored anhydrobase (**2.6**) was reported by Katritzky and coworkers from a quinolinium salt (**2.5**) using sodium methoxide in methanol at room temperature as shown in Scheme 2.1.[97] This anhydrobase (**2.6**) was then treated with electrophiles such as benzoyl chloride under Schotten-Baumann conditions to generate the corresponding acylated anhydrobase (**2.7**). Additionally, it was found that these anhydrobase products were somewhat stable at room temperature, and on heating regeneration of starting materials was observed.



Scheme 2.1 - Synthesis of acylated anhydrobases by Katritzky

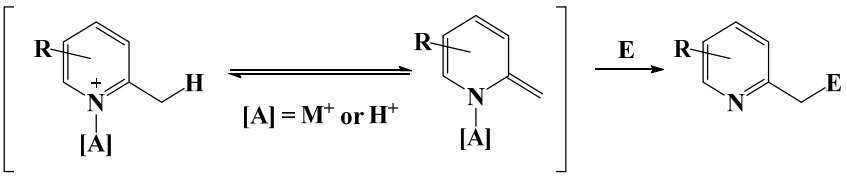
Brana and coworkers have reported that 4-(4-pyridyl)oxazoles can be synthesized when 4-acylaminomethyl-1-acyl pyridinium salts (**2.9**) are heated with acetic anhydride in the presence of trimethylamine and $SnCl_4$ (Scheme 2.2).[98] The unstable anhydrobase intermediate **2.9** reacted with the electrophile to give the acylated product **2.10** which, in turn, undergoes condensation reaction to yield the pyridine substituted oxazole (**2.11**) in low to moderate yield.



Scheme 2.2 - Synthesis of pyridine substituted oxazoles via anhydrobase intermediates

In addition to the use of stoichiometric amounts of electrophiles to activate pyridine, it has been shown that Lewis acids and Brønsted acids can also be used in catalytic amounts to effect aza-arene activation. Recently, several reports have described

condensation reactions of 2-methyl(aza-arenes) that proceed in the presence of Brønsted and Lewis acid catalysts (Scheme 2.3).

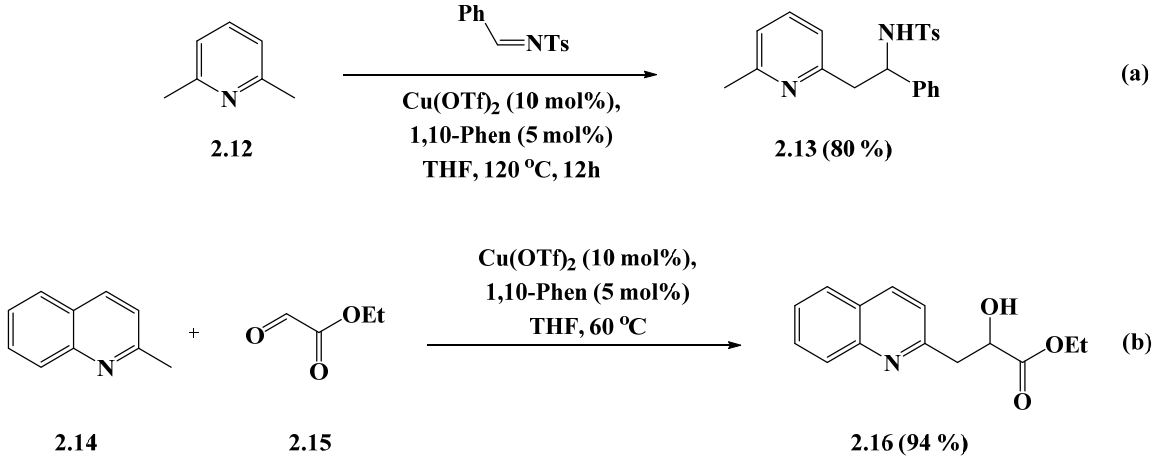


Scheme 2.3 - Lewis acid- or Brønsted acid-catalyzed activation of pyridine

In each of these transformations, the acid catalyst is assumed to facilitate interconversion between imine and enamine tautomers of the 2-methyl(aza-arene) substrate. Reaction of the enamine tautomer with added electrophile then leads to the observed products (Scheme 2.3). In some instances thermal activation alone has been shown to be effective in promoting similar reactions, presumably by also providing access to reactive enamine-like tautomers.[99-101] The activating effects observed under these reaction conditions, however, generally do not extend to 4-substituted aza-arenes, such as 4-picoline.[102-104] Thus, the proximity of the alkyl substituent to an aza-arene nitrogen atom appears to be an important structural feature.[105-108]

Rueping and coworkers have shown an efficient Lewis acid catalyzed condensation reaction of aza-arenes with N-sulfonyl aldimines as the electrophile (Scheme 2.4a).[102] They employed copper triflate and 1,10-phenanthroline as the catalytic system to activate pyridine substrate **2.12**. *In situ* generated anhydrobase reacts with the sulfonyl imine electrophile to afford **2.13** as the product. In another study, Jin and coworkers employed a similar catalytic system for direct C(sp^3)-H functionalization of 2-alkyl azaarenes (**2.14**) (Scheme 2.4b).[109] 2-Methylquinoline **2.14** reacted with ethyl

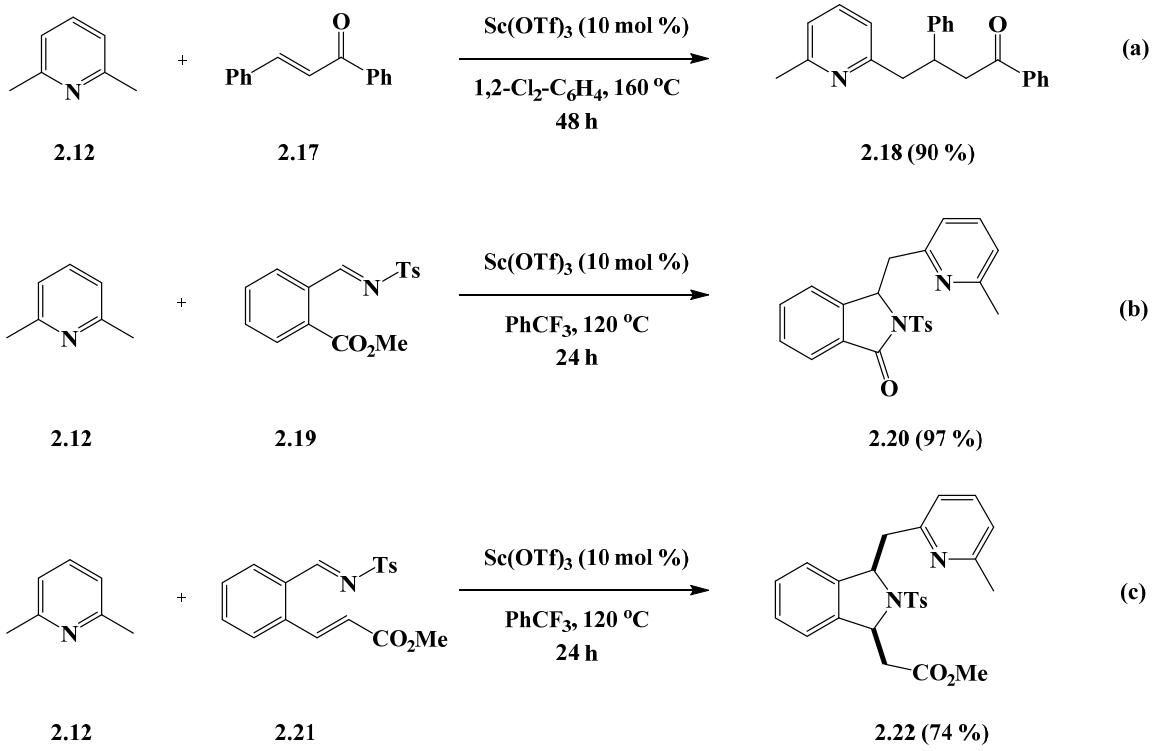
glyoxylate **2.15** (a carbonyl electrophile), in the presence of a copper catalyst to yield **2.16** as the final product.



Scheme 2.4 - Copper catalyzed activation 2-alkyl aza-arenes

Scandium is another Lewis acidic metal that has been widely used to activate aza-arenes for condensation reactions with various electrophiles. Komai and coworkers have used scandium triflate [$Sc(OTf)_3$] as a catalyst for C-H functionalization of alkyl substituted aza-arenes using enones as electrophiles (Scheme 2.5a).[103] At higher temperatures, 2,6-lutidine (**2.12**) was successfully activated with catalytic scandium triflate and reacted with the enone electrophile **2.17** to afford compound **2.18** as the Michael adduct. Similarly, Qian and coworkers have shown that $Sc(OTf)_3$ can also be used to activate aza-arenes to react with N-sulfonylaldimines, which provides a rapid approach for the synthesis of heterocycle-containing isoindolinones (**2.20**) and isoindolines (**2.22**) (Scheme 2.5b & 2.5c).[110] When 2,6-lutidine (**2.12**) was subjected to activation with Lewis acid catalyst in the presence of 2-[(tosyl-imine)methyl]benzoate (**2.19**), a tandem C-H addition followed by an amidination was observed to afford the desired isoindolinone (**2.20**) in good yield. Additionally, when the electrophile was

changed to the bifunctional substrate **2.21** containing an imine and a Michael acceptor, C-H functionalization was followed by an intramolecular aza-Michael addition to furnish the isoindoline **2.22** in high yield.

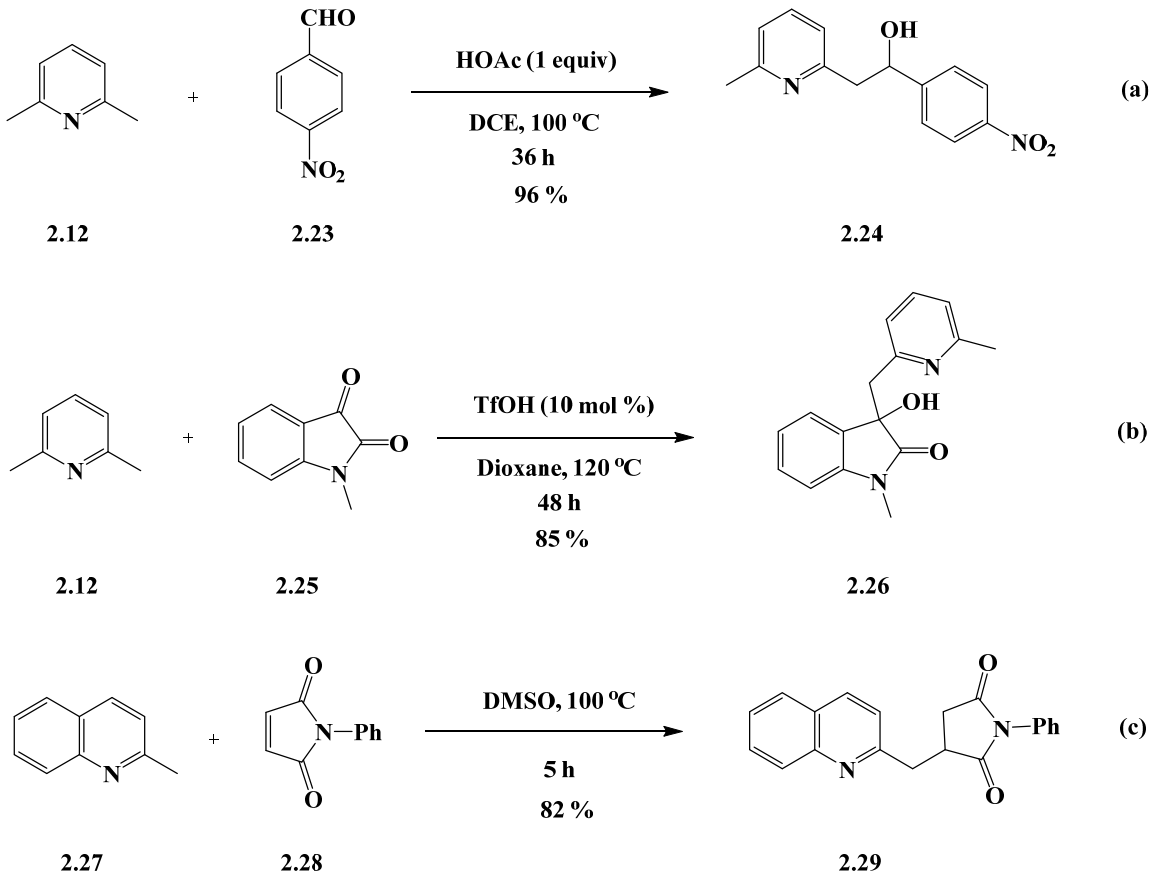


Scheme 2.5 - Scandium catalyzed activation 2-alkyl aza-arenes

In addition to copper (Cu) and scandium (Sc) there are reports of iron (Fe)[111] and ytterbium (Yb)[112] being used as Lewis acids to effect the activation of aza-arenes in condensation reactions. Similarly, Brønsted acids can also be used in the same manner to carry out such transformations.

For example, Wang and coworkers have shown that acetic acid (HOAc) can be used in stoichiometric amounts to activate 2-methyl pyridines for nucleophilic additions to aldehydes, affording aldol-like products (Scheme 2.6a).[104] Pyridine substrate **2.12** was

treated with a stoichiometric amount of HOAc, resulting in a reaction with p-nitrobenzaldehyde (**2.23**) to afford the aldol product **2.24**. Alternatively, Niu and coworkers have shown that trifluoromethanesulfonic acid (TfOH) is also a good Brønsted acid catalyst for similar transformations (Scheme 2.6b).[113] Under these conditions, an aldo- type reaction was observed between the α-methylazarene **2.12** and isatin **2.25** to afford the aza-arene substituted 3-hydroxy-2-oxindole **2.26** in good yield. In another study, Li and coworkers employed thermal activation without any added catalyst to perform Michael type reactions with 2-methyl aza-arenes (Scheme 2.6c).[114] Quinoline substrate **2.27** was combined with the Michael acceptor **2.28** under high temperature, resulting in activations of an sp^3 C-H bond of the quinoline substrate to afford Michael adduct **2.29**.

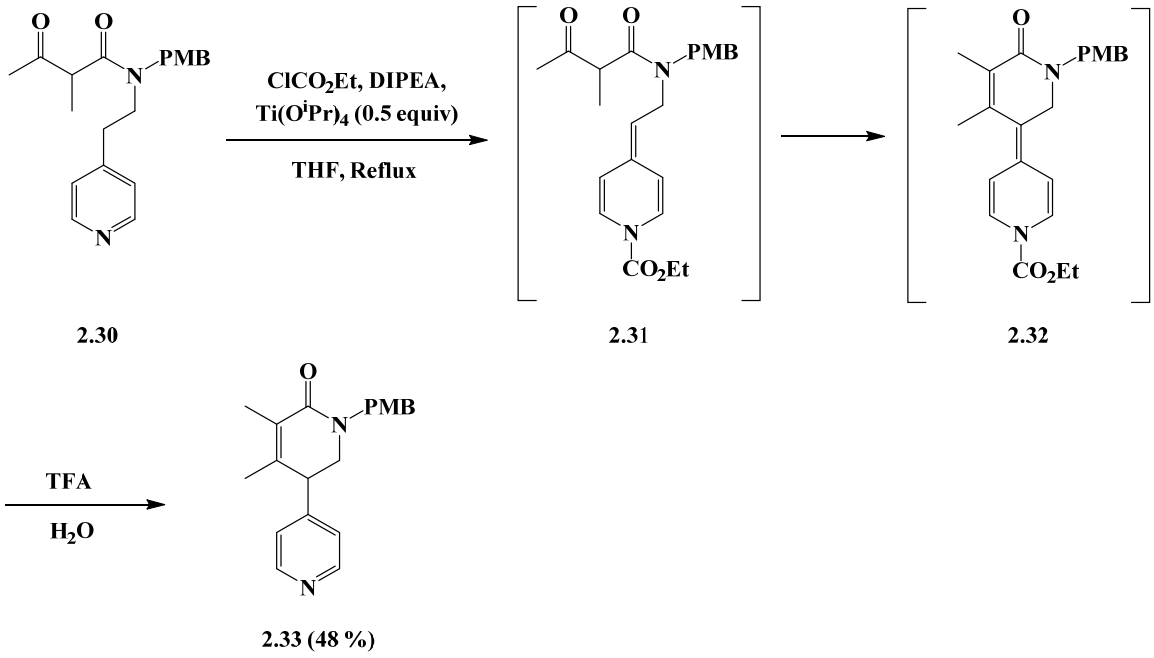


Scheme 2.6 - Brønsted acid catalyzed and thermally promoted activation of aza-arenes

2.2 Previous Work

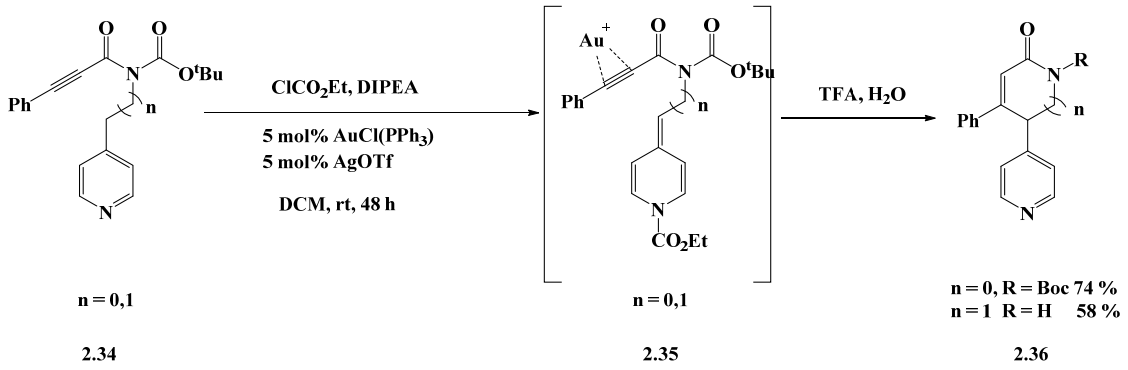
The Pigge group has been extensively working on aza-heterocycle anhydrobase chemistry (e.g., pyridines, imidazoles) for some time.[76,115-118] In a previous study it was observed that carbonyl electrophiles tethered to 4-alkylpyridine derivatives underwent aldol-like condensation reactions involving the C-4 alkyl carbon (Scheme 2.7).[117] Pyridine substrate **2.30** reacts initially with ethyl chloroformate and subsequently undergoes deprotonation at the benzylic carbon to yield the initial nucleophilic anhydrobase intermediate **2.31**. Aldol-like condensation reaction occurs at the benzylic carbon, followed by immediate elimination of water to afford the second anhydrobase

intermediate **2.32**, which was observed by NMR. Acidic water workup then yields the rearomatized pyridine product **2.33** in moderate to good yield.



Scheme 2.7 - 4-Pyridyl lactams via anhydrobase intermediates

Alternatively, in a related study it was observed that activated alkynes can also function as electrophiles toward nucleophilic anhydrobases (Scheme 2.8).[118] Alkylpyridine substrate **2.34** was activated using ethyl choloformate to form the initial anhydrobase intermediate **2.35**. Gold(I) catalyst was used for the purpose of activating the alkyne towards a nucleophilic attack. The nucleophilic anhydrobase was then expected to attack the activated alkyne to construct the carbon-carbon bond. Upon aqueous workup, pyridine substrate **2.36** was isolated in moderate to good yield.



Scheme 2.8 – Gold-catalyzed intramolecular cyclizations of alkyl pyridines

These chemical transformations can become very important in the context of heterocyclic natural product synthesis. For example, such routes can be synthetically manipulated to access the bis(piperidine) molecular framework seen in a number of bio-active marine alkaloids such as halicyclamine A (**2.37**), xestoproxamine C (**2.38**) arenosclerin A (**2.39**), neopetrosiamine A (**2.40**), saraines (**2.41**), and haliclonacyclamine C (**2.42**) (Figure 2.2).[119-124] Even though these diaza-macrocyclic products exhibit a range of biological properties, including anticancer, antibacterial, antiviral, and anti-malarial properties, reports related to their synthesis are rare. Previous syntheses of macrocyclic alkaloids such as haliclonacyclamine C (**2.42**) and related natural products proved to be complex and required lengthy preparative sequences.[125] The remainder of this chapter illustrates chemistry associated with intramolecular cyclizations of alkylpyridines under Brønsted acid-catalyzed conditions.

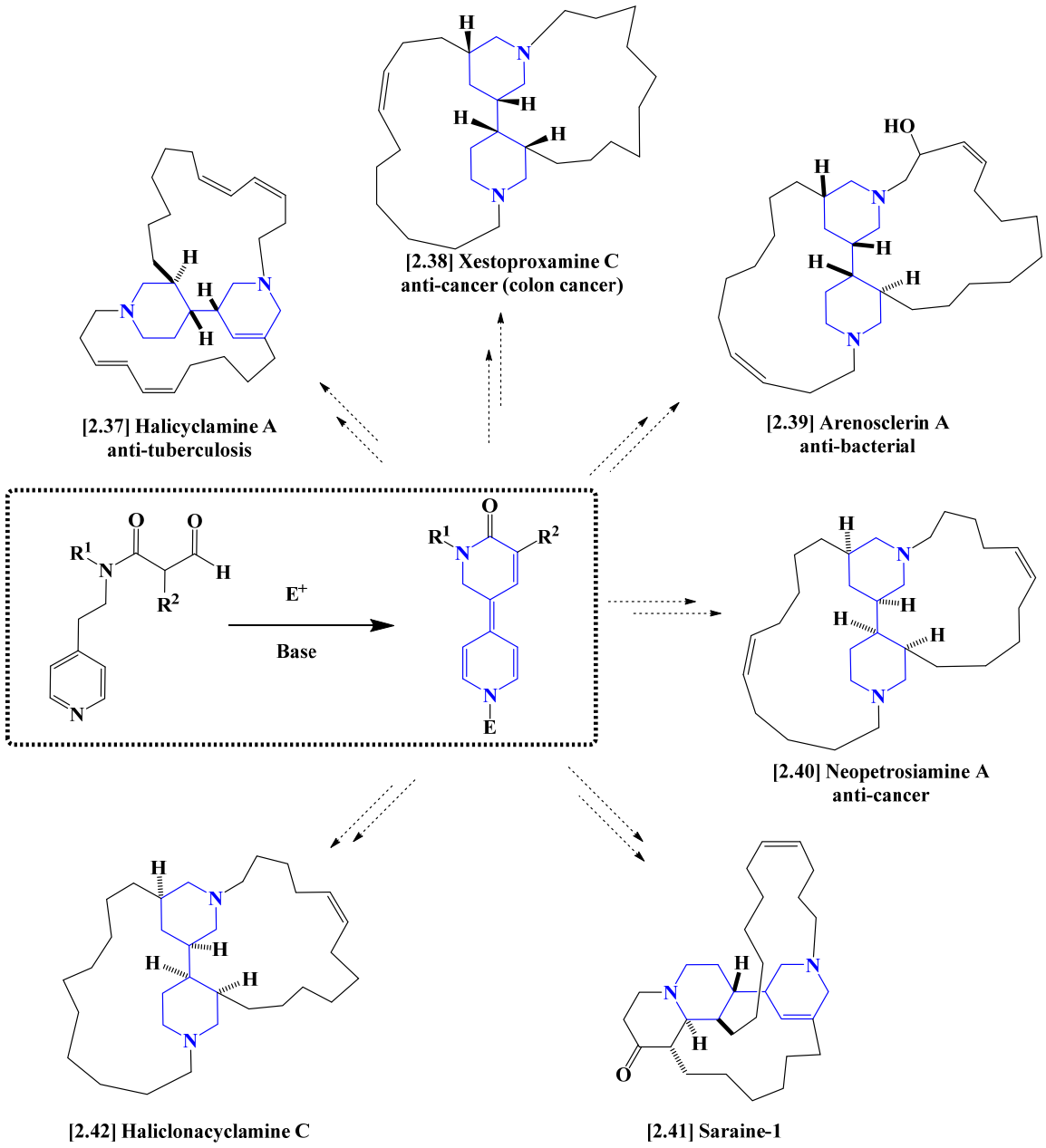
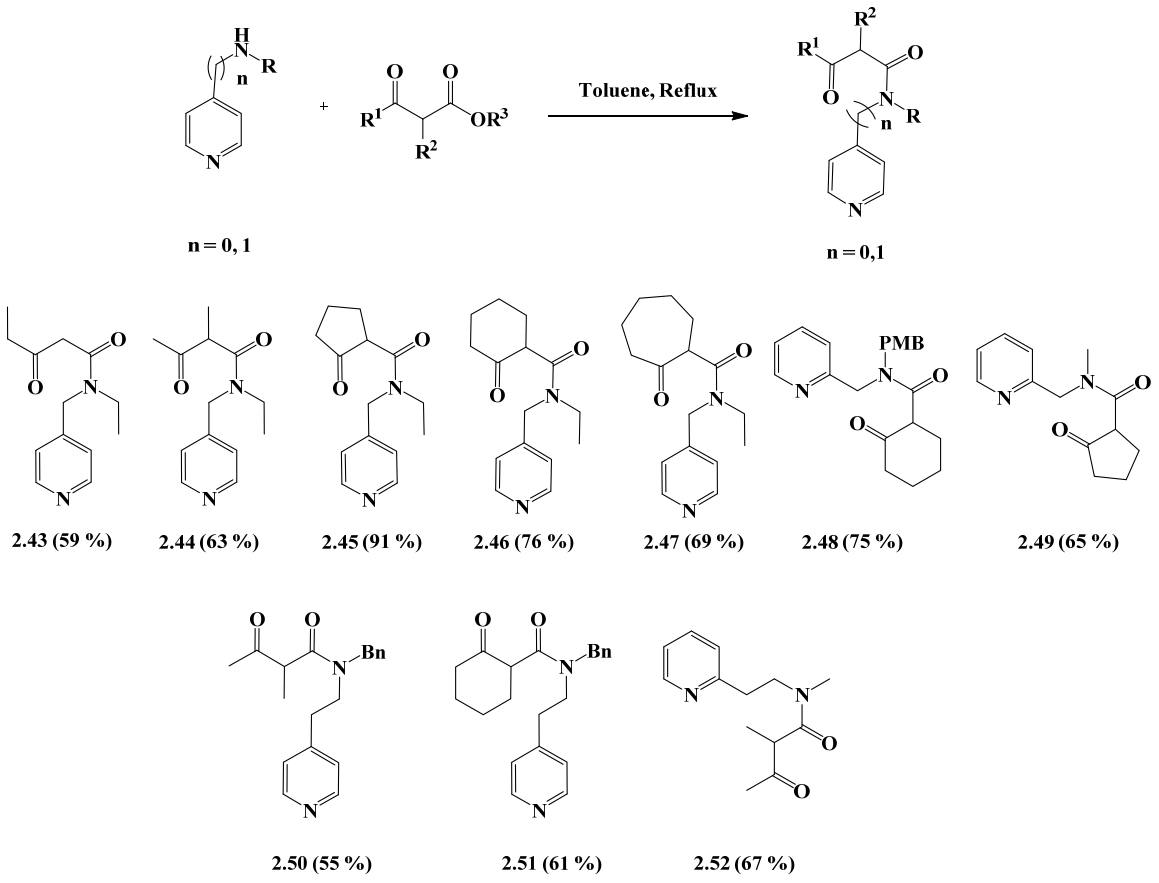


Figure 2.2 - Examples of marine alkaloids bearing a bis(piperidine) framework

2.3 Results and Discussion

Given the similarity of acyl anhydrobase intermediates **2.31**, **2.32**, and **2.35** to enamine tautomers of alkyl pyridines, we became interested by the possibility of using an acid catalyst to effect intramolecular alkylpyridine condensation reactions analogous to that depicted in Scheme 2.6. If successful, then the need for pyridine activation with stoichiometric quantities of an acylating agent would be avoided, resulting in greatly simplified cyclization procedures. With this goal in mind, we initiated a study examining the efficiency of Brønsted acid-catalyzed benzylic cyclization of 4- and 2-alkylpyridines.[126] The syntheses of 4-alkylpyridine substrates are shown in Scheme 2.9. These substrates were prepared from their corresponding aminomethyl or aminoethyl pyridines under reflux with the corresponding β-ketoesters (Scheme 2.9).

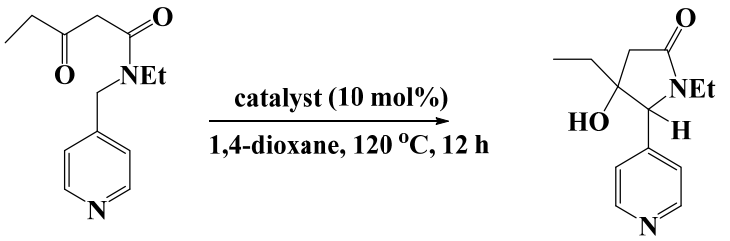


Scheme 2.9 - Synthesis of 2- & 4-aminomethyl substrates[117]

The 4-alkylpyridine derivative **2.43** was selected as a test substrate for initial experiments (Table 2.1) due to its straightforward preparation from commercially available N-ethyl-4-aminomethylpyridine and ethyl-3-oxo-valerate.[117] Dioxane was chosen as the reaction solvent as it features a reasonably high boiling point and has been used as a reaction medium in several related intermolecular alkyl(aza-arene) condensation reactions.[110,112,113,127] As a control experiment, **2.43** alone in dioxane was heated to 120 ºC to determine if thermal activation would result in cyclization.[101] No reaction was observed after 12 h (Table 2.1, entry 1). Next, **2.43** was heated (dioxane, 120 ºC) in the presence of various Brønsted acid catalysts (10 mol%). Gratifyingly, an aldol-like

condensation was observed in each case, and pyridine derivative **2.53** was isolated as a ~2:1 mixture of diastereomers inseparable by flash column chromatography (Table 2.1, entries 2-6). Reaction in the presence of TfOH afforded the highest isolated yield of **2.53**. Notably, however, all the Brønsted acids screened in this assay were effective to varying degrees in promoting benzylic cyclization.

Table 2.1 - Optimization conditions for acid-catalyzed cyclization



2.43 **2.53 (~ 2:1 dr)**

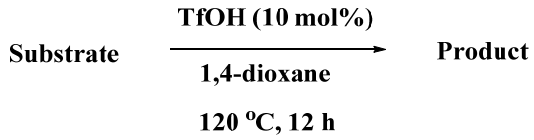
Entry	Catalyst[a]	% Yield of **2.53**[b]
1	None	0[c]
2	TfOH	97
3	TFA	90
4	AcOH	78
5	*p*-TSA	70
6	CSA[d]	72

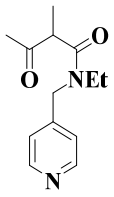
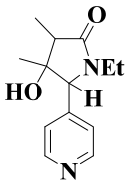
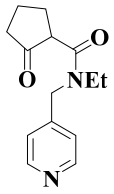
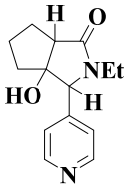
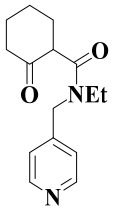
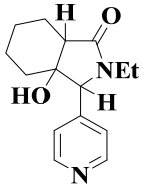
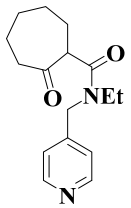
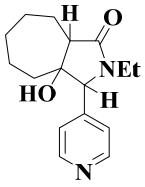
[a]Reactions performed on 100 mg scale, [**2.43**] ~ 0.3 M in dioxane. [b]Isolated yield after purification by chromatography. [c]Recovered starting material (93%). [d]Camphorsulfonic acid.

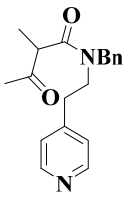
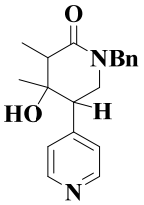
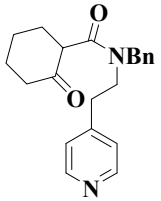
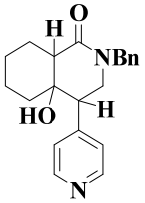
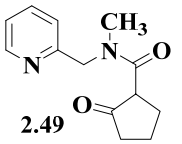
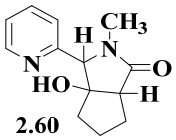
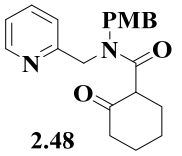
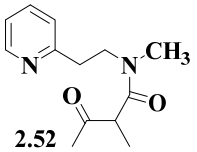
The reaction conditions outlined in Table 2.1, entry 2 represent a greatly simplified experimental protocol for achieving intramolecular alkylpyridine functionalization as compared to the published procedure (see Scheme 2.6).[117] To explore the generality of acid-catalyzed cyclization, several other 4- and 2-alkylpyridines

structurally related to **2.43** were also subjected to the reaction conditions illustrated in Table 2.1, and the results are shown in Table 2.2. The alkylpyridine substrates for this study were each prepared by condensation of the corresponding N-alkyl aminomethyl- or aminoethylpyridine with the appropriate β-ketoester to install the indicated β-amidocarbonyl side chains.[117] Cyclization reactions involved heating a solution of the substrate (~ 0.3 M) and 10 mol% TfOH in dioxane to 120 ºC for 12 h. Crude reaction mixtures were then directly purified by silica gel flash column chromatography to afford the isolated products as mixtures of diastereomers. Diastereomer ratios were estimated on the basis of ^{1}H NMR spectra.

Table 2.2 - TfOH-catalyzed benzylic cyclization of alkylpyridines



Entry	Substrate	Product	%Yield[a] (Diasteremoric ratio)
1	 **2.44**	 **2.54**	97% (3.4:2.6:2.3:1)
2	 **2.45**	 **2.55**	60% (3.9:1)
3	 **2.46**	 **2.56**	98% (9.0:1)
4	 **2.47**	 **2.57**	89% (3.0:1.6:1.3:1)

5	 **2.50**	 **2.58**	97%[b]
6	 **2.51**	 **2.59**	70% (7.5:1)
7	 **2.49**	 **2.60**	59% (1:1:1.2:1.5) (20%[d])
8	 **2.48**	n.p[c]	60 %[d]
9	 **2.52**	n.p[c]	68 %[d]

[a]Isolated yield. [b]Diastereomeric ratio could not be determined due to overlapping signals in the ^{1}H NMR spectrum. [c]No cyclized product was obtained. [d]Recovered starting material.

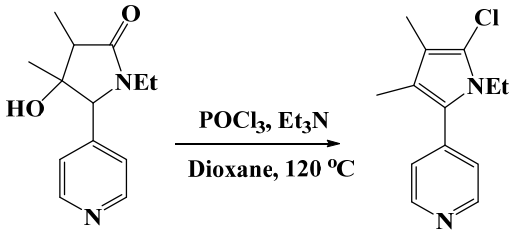
As shown in Table 2.2, entries 1-4, triflic acid catalysis was effective in converting **2.44-2.47** to the corresponding pyridine-substituted γ-lactams in good to excellent yield. Cyclized products **2.54-2.57** were isolated as mixtures of diastereomers (as indicated by ^{1}H NMR, particularly through examination of the signal corresponding to the benzylic hydrogen atom) which could not be separated readily by flash column chromatography. In the case of **2.55** and **2.56** (entries 2 and 3), two diastereomers were evident in the NMR spectra, which can be attributed to the formation of cis-ring fusions

in the 5,5- and 6,5-bicyclic moieties. Compounds **2.54** and **2.57** (Table 2.2, entries 1 and 4) however, were obtained as mixtures of all possible diastereomers. Due to overlapping signals for many of the hydrogens, the relative stereochemistry for individual diastereomers could not be assigned. In similar fashion, this procedure was effective for inducing cyclization of aminoethylpyridine derivatives as revealed in Table 2.2, entries 5 and 6. The pyridyl-substituted δ-lactams **2.58** and **2.59** also were isolated as mixtures of diastereomers in good yield. Table 2.2, entry 7, illustrates the successful conversion of 2-alkylpyridine substrate **2.49** to the corresponding cyclized product **2.60** in reasonable yield. This transformation represents an expansion of substrate scope compared to our original cyclization procedure (Scheme 2.6), under which 2-substituted pyridines are unreactive. Unfortunately, two other 2-alkylpyridine substrates (**2.47** & **2.51**) examined in this study failed to undergo benzylic cyclization, and only unreacted starting material was recovered (Table 2, entries 8 and 9). At present, factors responsible for the differing reactivity of 2-substituted pyridines remain obscure.

The results in Table 2.2 demonstrate the utility of Brønsted acid catalysis in promoting intramolecular aldol-type reactions of alkylpyridines. It is additionally noteworthy that 4-alkylpyridines are good substrates for this reaction, in contrast to related Lewis and Brønsted acid-catalyzed intermolecular condensation reactions of methyl-substituted aza-arenes.[110,112,113,127] We were somewhat surprised, however, to isolate tertiary alcohol products exclusively as it was anticipated that the initial aldol-like products would undergo facile elimination of H_2O under the acidic reaction conditions. Even in the presence of molecular sieves, the reaction did not show any indication of an elimination of the tertiary alcohol. Dehydration of initial cyclization products would

produce the added benefit of greatly simplified product mixtures by removing the possibility of diastereoisomers. Consequently, we briefly explored reaction conditions designed to effect dehydration of selected cyclized products.

Lactam **2.54** was selected as the initial substrate for these studies. Unexpectedly, however, we found **2.54** to be remarkably resistant to dehydration under a variety of reaction conditions. For example, in separate experiments **2.54** was exposed to $BF_3 \cdot OEt_2$, $MsCl/Et_3N$, Ac_2O/Et_3N, P_2O_5, H_2SO_4, H_3PO_4, HCl, KO^tBu, and NaH. In each case none of the anticipated unsaturated lactam was observed (in some cases unreacted **2.54** was recovered while in others substrate decomposition occurred). A reaction was observed upon treatment of **2.54** with $POCl_3/Et_3N$, but transformation of the amide group occurred concomitantly with elimination of the tertiary alcohol to afford chloropyrrole **2.61** (Scheme 2.10).

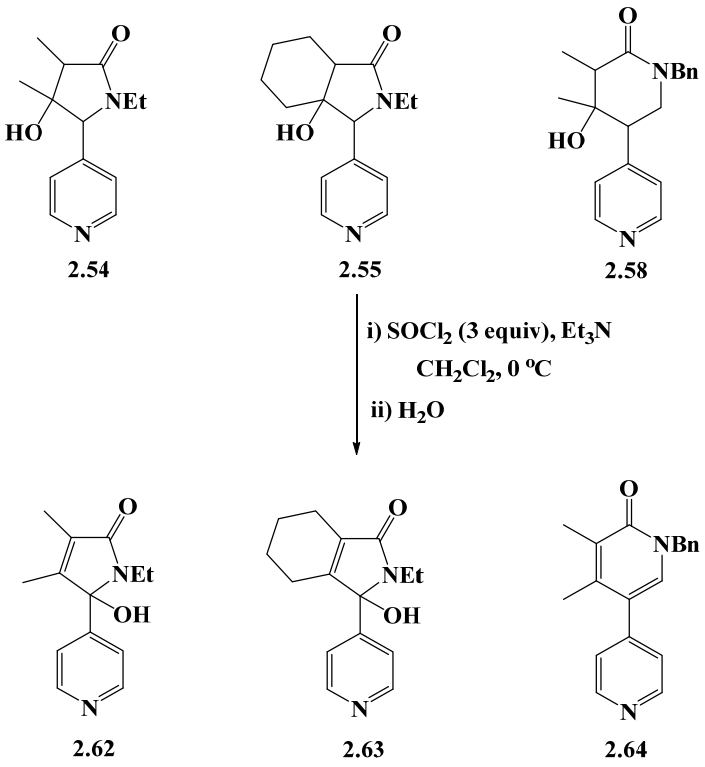


2.54 **2.61 (30%)**

Scheme 2.10 - Transformation of the amide functionality upon treatment of $POCl_3$

Several substrates (in addition to **2.54**) were examined for their reactivity toward thionyl chloride ($SOCl_2$) as a putative dehydration agent (Scheme 2.11). While loss of the 3º alcohol did occur in the presence of $SOCl_2$, oxidation of the lactam ring was also observed. Thus, **2.54** and **2.55** were converted to **2.62** and **2.63**, respectively, in moderate to good yield. The δ lactam **2.58** also suffered dehydrative oxidation in the

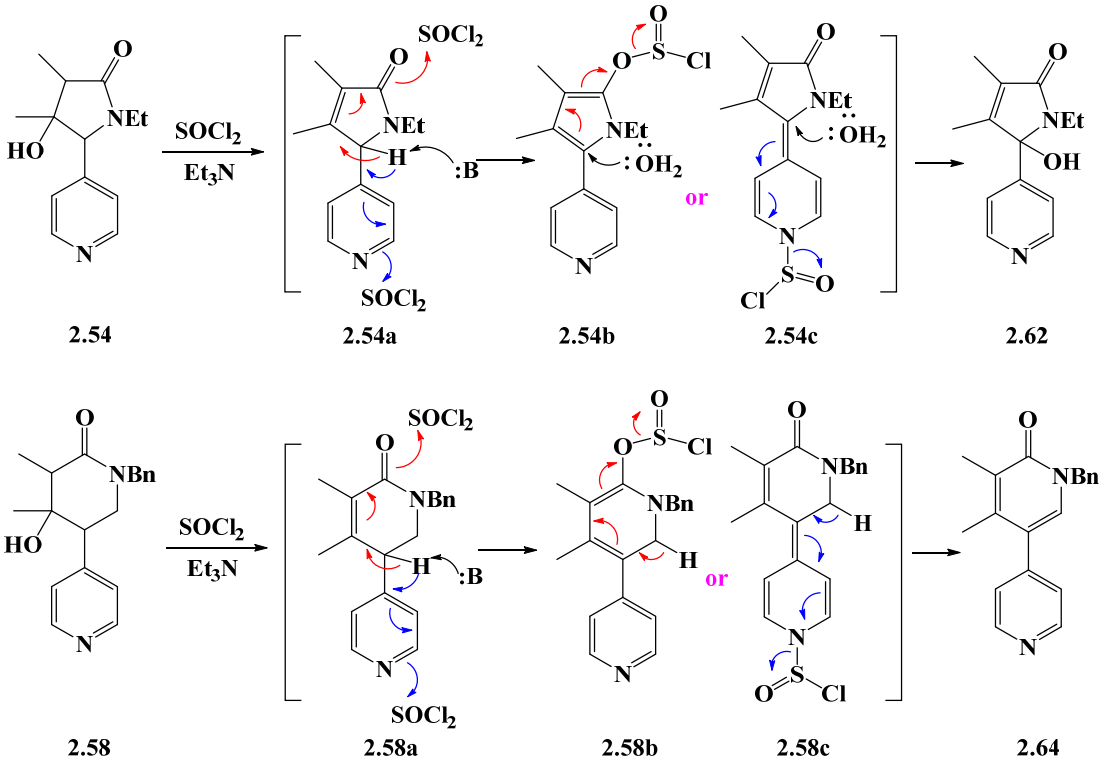
presence of $SOCl_2$ to afford **2.64**, albeit in modest yield. While oxidation was not the anticipated outcome, the use of $SOCl_2$ as an oxidizing agent is not unprecedented.[128-131] Moreover, a somewhat related $SOCl_2$-mediated oxidation has been studied in some detail by Cushman and co-workers.[132]



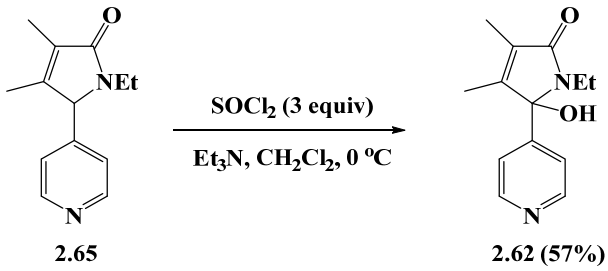
Scheme 2.11 - Lactam elimination oxidation with $SOCl_2$

Based on this previous work,[132] a plausible mechanistic rationale to account for these transformations is illustrated in Scheme 2.12. Initial loss of H_2O may give the unsaturated lactams **2.54a** and **2.58a**. Subsequently, the presence of excess $SOCl_2$ may result in further reaction at the lactam carbonyl and/or the pyridine ring to give species such as **2.54b, 2.54c** and **2.58b, 2.58c**. Addition of H_2O then leads to **2.62** while loss of H^+ leads to **2.64**. As a test of this mechanistic formulation, the known lactam **2.65**[117] was

treated with $SOCl_2/Et_3N$. Oxidized lactam **2.62** was obtained in 57% isolated yield (Scheme 2.13).



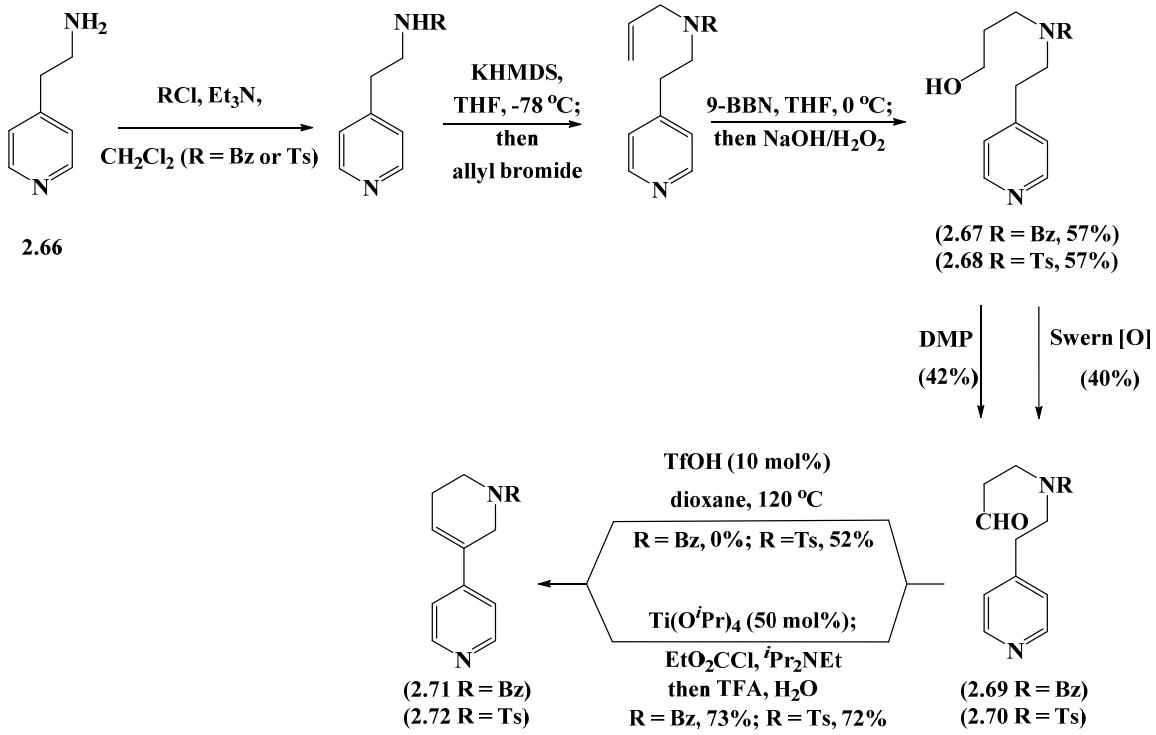
Scheme 2.12 - Mechanistic rationale to $SOCl_2$-mediated oxidation



Scheme 2.13 - Mechanistic study of $SOCl_2$ oxidation

Two additional types of cyclization substrates distinct from the β-amido carbonyl starting materials discussed thus far were also examined. An approach to pyridyl-substituted piperidines was explored through preparation of (aminoethyl)pyridine

derivatives featuring pendant aldehyde electrophiles as depicted in Scheme 2.14. 4-(Aminoethyl)pyridine was converted to the corresponding benzoyl or tosyl amide. Allylation of the amide nitrogen followed by hydroboration/oxidation provided primary alcohols **2.67** and **2.68** in good yield. Swern oxidation of the benzoyl amide derivative afforded aldehyde **2.69**. Exposure of **2.69** to acid catalyzed cyclization reaction conditions, however, failed to generate the expected cyclized product and only substrate decomposition was observed. Cyclization of **2.69** to **2.71** could be achieved in good yield via discrete anhydrobase intermediates using our previously reported procedure.[117] In contrast, the tosyl amide derivative **2.68** proved stable to acid catalysis and **2.72** was obtained in reasonable isolated yield (52%). Thus, in this reaction elimination of the secondary alcohol intermediate readily occurs to deliver the conjugated olefin. Tosyl amide **2.70** could also be cyclized in slightly higher yield upon activation with EtO_2CCl and $^{i}Pr_2NEt$ in the presence of $Ti(O^{i}Pr)_4$.[117]

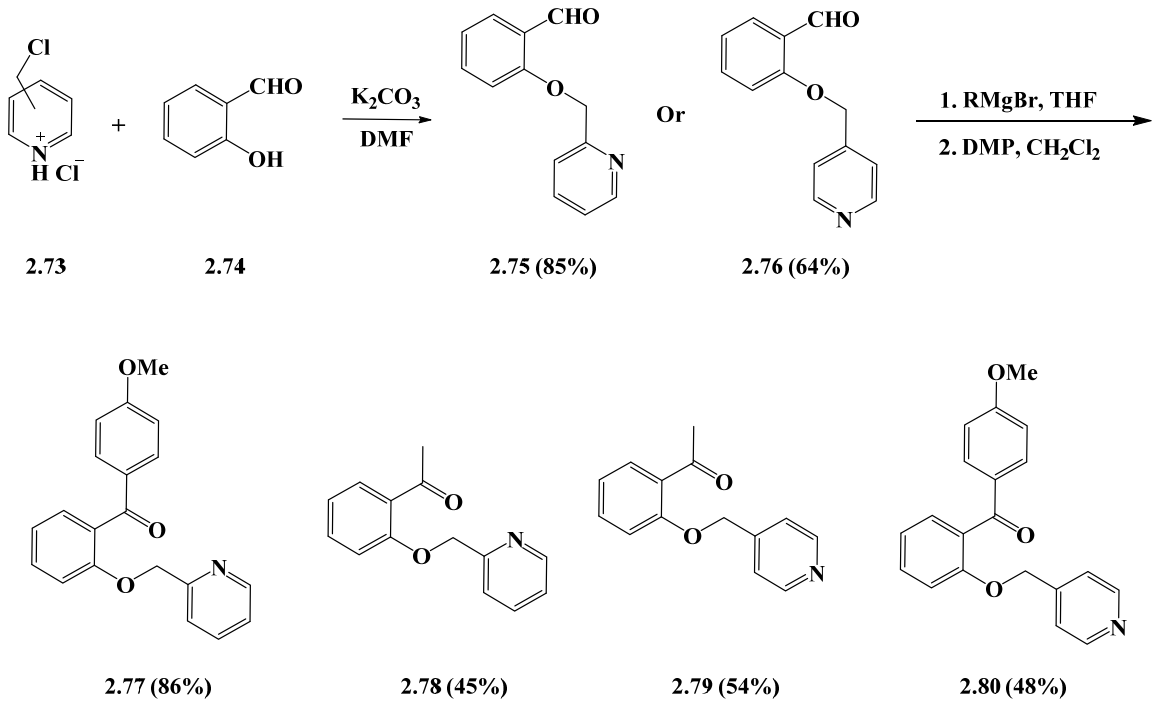


Scheme 2.14 – Brønsted acid-catalyzed pyridine benzylic cyclization with aldehyde electrophiles

Reactions of cyclization substrates based on derivatives of salicylaldehyde were also examined. We envisioned that alkylation of salicylaldehyde with appropriate aza-arenes would afford precursors to heterocycle-substituted benzofurans which could be assembled through subsequent intramolecular benzylic cyclization. Benzofurans in general possess a wealth of desirable activities in both biological and materials settings,[133-137] and incorporation of an aza-arene substituent (e.g., pyridine) provides a handle for further molecular and supramolecular (e.g., H-bonding, metal ion binding) elaboration.

To begin, 2- and 4-picolyl chloride hydrochloride (**2.73**) were treated with salicylaldehyde (**2.74**) in the presence of potassium carbonate to afford compounds **2.75**

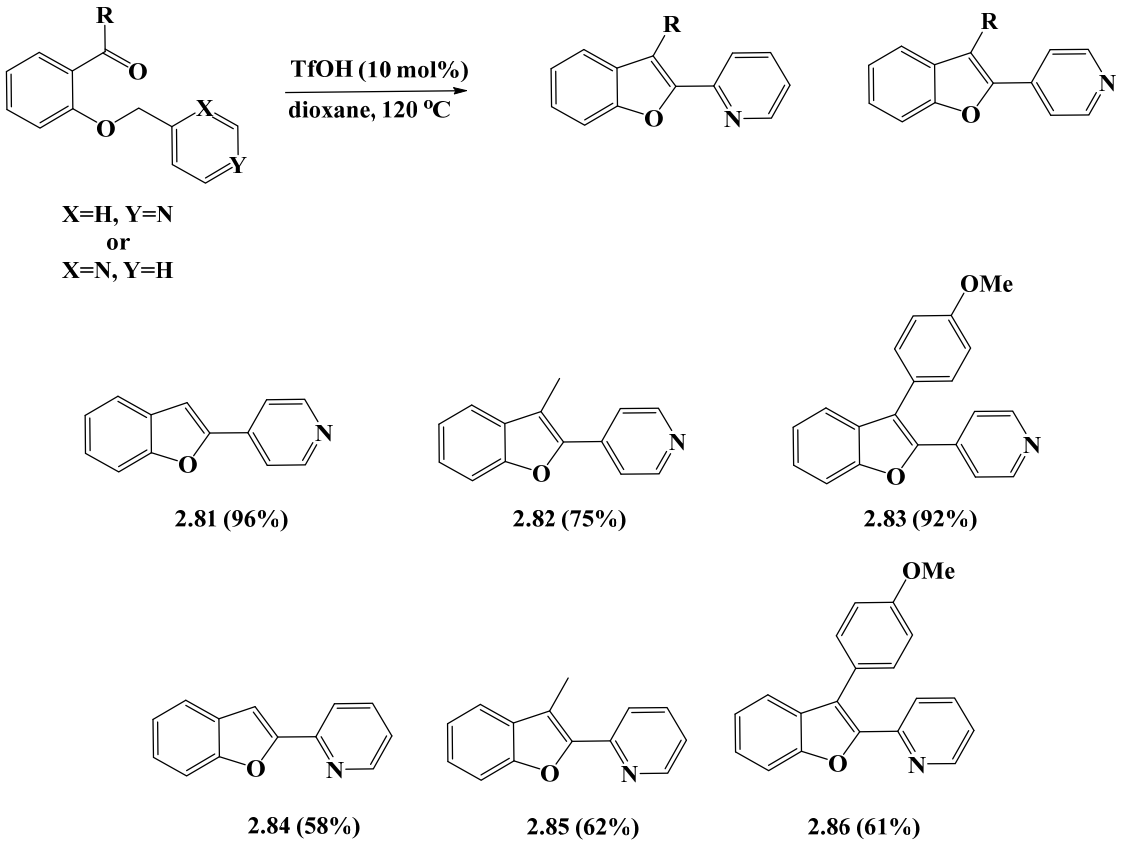
and **2.76** (Scheme 2.15), which were directly subjected to acid catalyzed conditions. These substrates also were further manipulated through a straightforward Grignard reaction followed by an oxidation to the corresponding ketones **2.77**-**2.80** in good overall yields.[138]



Scheme 2.15 - Synthesis of 2- and 4-pyridyl salicylaldehyde derivatives

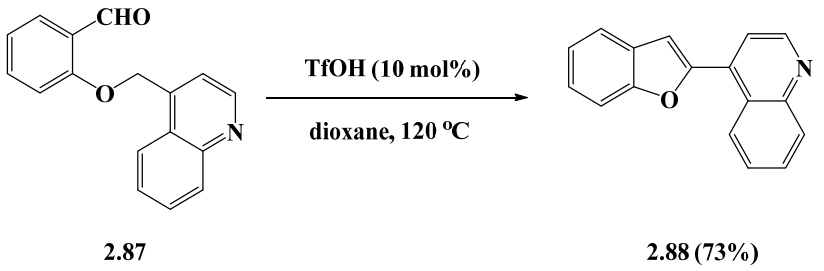
As anticipated, exposure of **2.75** and **2.76** to acid catalyzed benzylic cyclization reaction conditions returned the corresponding benzofuran products (**2.81**, **2.84**) in good to excellent yield (Scheme 2.16). Notably, the 2-substituted pyridine proved to be a suitable substrate for this transformation. In each case, elimination of H_2O was observed during the course of cyclization, undoubtedly facilitated by formation of the aromatic benzofuran ring system. This approach also proved amenable to construction of 2,3-disubstituted benzofurans. Acid catalyzed cyclizations of substrates **2.77**-**2.80** proceeded

smoothly, and benzofurans **2.82**, **2.83**, **2.85**, **2.86** were isolated in good to excellent yields (Scheme 2.16).



Scheme 2.16 - Pyridine-substituted benzofurans via acid catalyzed cyclization

This transformation also has been extended to include incorporation of a quinoline moiety as a benzofuran substituent, as shown in Scheme 2.17. Similar to pyridine analogues, exposure of **2.87** to TfOH (10 mol%) in dioxane at 120 ºC produced benzofuran **2.88** in 73% isolated yield. The successful cyclization of **2.87** indicates that this acid catalyzed procedure may be applicable to transformations of aza-arenes other than pyridine.



2.87 **2.88 (73%)**

Scheme 2.17 - Acid-catalyzed cyclization of a quinoline substrate

2.4 Conclusion

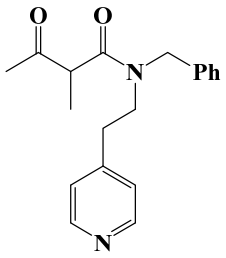
An experimentally simple Brønsted acid-catalyzed procedure effective for inducing intramolecular aldol-like condensations of alkylpyridine derivatives has been developed. Positioning of carbonyl electrophiles in the side chain of 4-alkylpyridines in particular affords viable cyclization precursors across a range of substrate types. Appropriately functionalized 2-alkylpyridines also gave the reaction, especially those featuring a salicylaldehyde-derived side chain. Other 2-alkylpyridines, however, were resistant to acid catalyzed benzylic cyclization for reasons that remain under investigation. An unusual $SOCl_2$-mediated oxidation of pyridyl-substituted lactams has also been uncovered. The construction of intriguing heterocyclic ring systems of relevance to medicinal, natural product, and materials chemistry has been demonstrated. Continuing research seeks to expand upon these results by harnessing the reactivity of putative enamine-like anhydrobase intermediates available to pyridine and related aza-arenes in additional and novel bond-forming processes.

2.5 Experimental Section

All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.

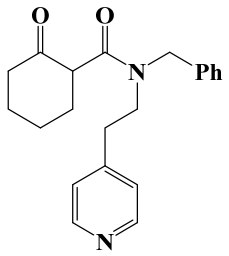
Experimental Procedures and Characterization Data for 2 and 4-Alkyl Pyridine Substrates:

Substrates **2.43** – **2.47** were prepared according to a known procedure.[117]



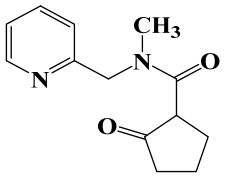
N-Benzyl-2-methyl-3-oxo-N-(2-(pyridin-4-yl)ethyl)butanamide (2.50): N-benzyl-2-(pyridin-4-yl)ethanamine (0.5 g, 2.4 mmol, 1.0 equiv) was placed in a 50 mL round bottom flask and dissolved in toluene (10 mL). Then ethyl 2-methylacetoacetate (0.37

mL, 2.6 mmol, 1.1 equiv) was added to the reaction mixture. The reaction mixture was refluxed for 36 h. After cooling down to room temperature solvent was evaporated under vacuum. The crude product was taken and purified by flash column chromatography using 70-100% EtOAc in hexanes. **2.49** (mixture of rotamers, 0.40 g, 55%) was isolated as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.0 Hz, 0.7H), 8.50 (dd, *J* = 4.4, 1.6 Hz, 1.3H), 7.41 – 7.21 (m, 4H), 7.12 (dd, *J* = 8.6, 4.2 Hz, 2.3H), 7.06 (dd, *J* = 4.5, 1.4 Hz, 0.7H), 4.78 (d, *J* = 14.9 Hz, 0.3H), 4.61 – 4.50 (m, 1H), 4.34 (d, *J* = 17.1 Hz, 0.7H), 3.88 – 3.73 (m, 0.7H), 3.65 – 3.54 (m, 1H), 3.54 – 3.41 (m, 1.3H), 2.94 – 2.70 (m, 2H), 2.12 (s, 3H), 1.35 (dd, *J* = 13.9, 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.5, 205.1, 171.1, 170.4, 150.4, 150.1, 147.9, 146.8, 137.1, 136.3, 129.3, 129.0, 128.19, 128.17, 127.9, 126.4, 124.4, 124.2, 52.1, 52.0, 51.8, 48.7, 47.7, 34.4, 33.3, 27.3, 26.9, 14.2, 14.1. IR (film) 3026, 2986, 2932, 1719, 1632 cm^{-1}. HRMS (ESI) $C_{19}H_{23}N_2O_2$ $[M+H]^+$, Calculated 311.1760; Found 311.1755.

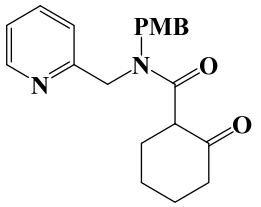


N-Benzyl-2-oxo-N-(2-(pyridin-4-yl)ethyl)cyclohexanecarboxamide (2.51): Using the procedure described for the preparation of **2.50**, N-benzyl-2-(pyridin-4-yl)ethanamine (1.0 g, 4.7 mmol, 1.0 equiv) and ethyl 2-oxocyclohexanecarboxylate (0.83 mL, 5.2 mmol, 1.1 equiv) were reacted to give **2.51** (mixture of rotamers, 0.97 g, 61%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 8.52 (m, 0.7H), 8.52 – 8.46 (m, 1.3H), 7.39 –

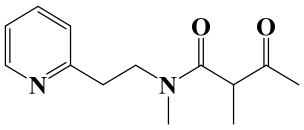
7.23 (m, 3.5H), 7.22 – 7.15 (m, 1.5H), 7.09 (d, J = 7.2 Hz, 1.3H), 7.03 (d, J = 5.9 Hz, 0.7H), 5.01 (d, J = 15.2 Hz, 0.3H), 4.45 – 4.34 (m, 1H), 4.17 – 4.07 (m, 0.7H), 4.01 – 3.90 (m, 0.7H), 3.55 – 3.45 (m, 0.7H), 3.41 – 3.32 (m, 0.6H), 3.26 – 3.15 (m, 1H), 2.97 – 2.85 (m, 1H), 2.85 – 2.69 (m, 1H), 2.54 (m, 1H), 2.34 – 2.10 (m, 2H), 2.02 (m, 2H), 1.90 – 1.73 (m, 2H), 1.65 – 1.43 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 170.4, 150.3, 150.0, 148.5, 137.1, 136.6, 129.2, 128.9, 128.0, 127.9, 127.6, 126.4, 124.5, 124.2, 54.6, 54.5, 52.1, 47.9, 47.6, 42.1, 42.0, 34.4, 33.4, 30.5, 27.1, 27.0, 23.8. IR (film) 3018, 2981, 2951, 1716, 1641 cm^{-1}. HRMS (ESI) $C_{21}H_{25}N_2O_2$ $[M+H]^+$, Calculated 337.1916; Found 337.1918.



N-Methyl-2-oxo-N-(pyridin-2-ylmethyl)cyclopentanecarboxamide (2.49): Using the procedure described for the preparation of **2.50**, N-methyl-1-(pyridin-2-yl)methanamine (1.4 g, 11.5 mmol, 1.0 equiv) and ethyl 2-oxocyclopentanecarboxylate (2.8 mL, 17 mmol, 1.5 equiv) were reacted to give **2.49** (mixture of rotamers, 1.74 g, 65%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.56 (m, 0.4H), 8.56 – 8.50 (m, 0.6H), 7.74 – 7.64 (m, 1H), 7.31 (d, J = 7.9 Hz, 0.6H), 7.26 – 7.14 (m, 1.4H), 5.06 (d, J = 17.4 Hz, 0.4H), 4.98 (d, J = 15.5 Hz, 0.6H), 4.59 – 4.49 (m, 1H), 3.64 – 3.55 (m, 1H), 3.19 (s, 1.9H), 3.02 (s, 1.1H), 2.61 – 2.46 (m, 1H), 2.39 – 2.11 (m, 4H), 1.98 – 1.72 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 169.2, 157.2, 150.0, 149.3, 137.2, 122.8, 122.4, 121.8, 121.1, 55.6, 53.6, 52.3, 38.7, 36.2, 34.8, 27.9, 27.3, 21.1. IR (film) 2965, 2917, 2881, 1734, 1640, 1617 cm^{-1}. HRMS (ESI) $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$, Calculated 255.1109; Found 255.1110.

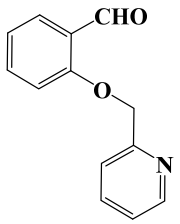


N-(4-Methoxybenzyl)-2-oxo-N-(pyridin-2-ylmethyl)cyclohexanecarboxamide (2.48): Using the procedure described for the preparation of **2.50**, N-(4-methoxybenzyl)-1-(pyridin-2-yl)methanamine (1.5 g, 6.6 mmol, 1.0 equiv) and ethyl 2-oxocyclohexanecarboxylate (1.2 mL, 7.3 mmol, 1.1 equiv) were reacted to give **2.48** (mixture of rotamers, 1.73 g, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 – 8.52 (m, 0.5H), 8.52 – 8.42 (m, 0.5H), 7.78 – 7.56 (m, 1.5H), 7.31 – 7.02 (m, 3.5H), 6.92 – 6.80 (m, 2H), 5.27 (d, *J* = 15.9 Hz, 0.5H), 5.11 (d, *J* = 14.9 Hz, 0.5H), 4.50 (d, *J* = 17.2 Hz, 1H), 4.24 (m, 2H), 3.85 – 3.74 (m, 3.5H), 3.66 (dd, *J* = 11.0, 5.8 Hz, 0.5H), 2.67 – 2.44 (m, 1H), 2.44 – 2.20 (m, 2H), 2.20 – 1.92 (m, 3H), 1.92 – 1.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 207.7, 170.7, 170.4, 159.1, 158.8, 157.2, 156.6, 149.8, 149.0, 137.0, 136.9, 129.3, 128.9, 128.0, 127.6, 122.6, 122.1, 121.7, 121.1, 114.3, 113.9, 55.3, 55.2, 54.6, 54.5, 51.8, 50.8, 50.4, 48.3, 42.0, 41.9, 30.4, 30.3, 26.9, 23.7. IR (film) 3066, 3008, 2936, 2870, 1712, 1639 cm^{-1}. HRMS (ESI) $C_{21}H_{25}N_2O_3$ $[M+H]^+$, Calculated 353.1865; Found 353.1866.



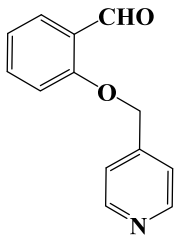
N,2-Dimethyl-3-oxo-N-(2-(pyridin-2-yl)ethyl)butanamide (2.52): Using the procedure described for the preparation of **2.50**, N-methyl-2-(pyridin-2-yl)ethanamine (2.0 g, 15

mmol, 1.0 equiv) and ethyl 2-methylacetoacetate (2.3 mL, 16 mmol, 1.1 equiv) were reacted to give **2.52** (mixture of rotamers, 2.4 g, 67%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 14.8, 4.6 Hz, 1H), 7.70 – 7.56 (m, 1H), 7.32 – 7.04 (m, 2H), 3.94 – 3.79 (m, 1.5H), 3.79 – 3.63 (m, 1.5H), 3.16 – 3.00 (m, 2H), 2.97 (s, 3H), 2.10 (s, 1.5H), 1.99 (s, 1.5H), 1.28 (d, *J* = 6.9 Hz, 1.5H), 1.20 (d, *J* = 6.9 Hz, 1.5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 203.7, 170.0, 169.6, 158.2, 157.1, 148.8, 148.4, 136.0, 135.7, 123.1, 122.7, 121.1, 120.7, 50.5, 49.6, 48.7, 47.4, 36.0, 35.4, 35.0, 32.5, 26.8, 26.7, 12.6, 12.4. IR (film) 3517, 3055, 2976, 2936, 1734 cm^{-1}. HRMS (ESI) $C_{13}H_{19}N_2O_2$ $[M+H]^+$, Calculated 235.1447; Found 235.1429.



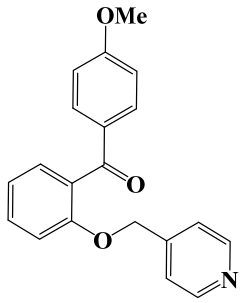
2-(Pyridin-2-ylmethoxy)benzaldehyde (2.75): 2-(chloromethyl)pyridine hydrochloride (10 g, 61 mmol, 1.0 equiv) and anhydrous potassium carbonate (25 g, 180 mmol, 3.0 equiv) were suspended in DMF (100 mL). Then 2-hydroxybenzaldehyde (7.1 mL, 67 mmol, 1.1 equiv), was added, and then the reaction was stirred overnight (12 h) at 80 °C. Finally brine (50 mL) and ethyl acetate (50 mL) were added to the reaction mixture. The mixture was then filtered via suction through Celite and washed with more EtOAc (100 mL). Water (100 mL) was added to the filtrate, and extracted with EtOAc (100 mL x 4). Combined organic layers were dried (Na_2SO_4) and concentrated. Then the crude was purified through flash column chromatography using 30-50% EtOAc in hexanes. 2-(Pyridin-2-ylmethoxy)benzaldehyde (**2.75)** (11 g, 85%) was isolated as a white solid.

MP:60-65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 7.87 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.75 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 – 7.47 (m, 2H), 7.27 (dd, *J* = 9.7, 2.7 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 2H), 5.33 (s, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 189.7, 160.8, 156.5, 149.5, 137.2, 136.2, 129.0, 125.3, 123.2, 121.44, 121.43 113.2, 71.2. IR (film) 3070, 3023, 2925, 2849, 2765, 1690 cm^{-1}. HRMS (ESI) $C_{13}H_{12}NO_2$ $[M+H]^+$, Calculated 214.0868; Found 214.0860.



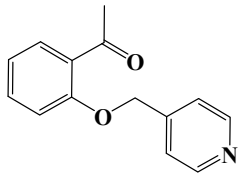
2-(Pyridin-4-ylmethoxy)benzaldehyde (2.76): 4-(Chloromethyl)pyridine hydrochloride (1.0 g, 6.1 mmol, 1.0 equiv) and anhydrous Potassium carbonate (2.5 g, 18 mmol, 3.0 equiv) were suspended in DMF (13 mL). Then 2-hydroxybenzaldehyde (0.71 mL, 6.7 mmol, 1.1 equiv), was added, and then the reaction was stirred for 12 hrs at room temperature. Finally, brine (10 mL) and EtOAc (10 mL) were added to the mixture. The mixture was then filtered via suction through celite and washed with more EtOAc (10 mL). water (100 mL) was added to the filtrate, and extracted with EtOAc (15 mL x 4). Combined organic layers were dried (Na_2SO_4) and concentrated. Then the crude was purified through flash column chromatography using 30-50% EtOAc in hexanes. 2-(pyridin-4-ylmethoxy)benzaldehyde (**2.76)** (0.90 g, 70%) was isolated as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.65 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.88 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.23 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4,

160.3, 150.4, 145.3, 136.1, 129.2, 125.3, 121.7, 121.4, 112.8, 68.6. IR (film) 3077, 3044, 2934, 2868, 2766, 1687, 1597 cm^{-1}. HRMS (ESI) $C_{13}H_{12}NO_2$ $[M+H]^+$, Calculated 214.0868; Found 214.0858.



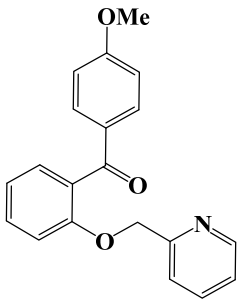
(4-Methoxyphenyl)(2-(pyridin-4-ylmethoxy)phenyl)methanone (**2.80**): Pyridine **2.76** (0.250 g, 1.172 mmol) was added to a flame-dried 100 mL round-bottom flask, and then the flask was purged with Ar. Tetrahydrofuran (12.5 ml) was added, and the mixture was cooled to 0 °C. (4- Methoxyphenyl)magnesium bromide (1.0 M, 2.93 mL, 2.93 mmol) was added dropwise to the mixture, and then the reaction mixture was allowed to warm to room temperature and maintained for 12 h. The reaction was quenched with saturated aq. NH_4Cl (15 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified via flash column chromatography (SiO_2, 30-50% EtOAc/hexanes) to yield (4-methoxyphenyl)(2-(pyridin-4- ylmethoxy)phenyl)methanol (0.196 g, 0.610 mmol, 52 % yield) as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 5.6 Hz, 2H), 7.55 – 7.46 (m, 1H), 7.32 – 7.18 (m, 3H), 7.07 – 7.01 (m, 3H), 6.86 – 6.82 (m, 3H), 6.09 (s, 1H), 5.01 (s, 2H), 3.78 (s, 3H), 3.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.1, 150.1, 146.1, 135.9, 132.7, 128.8, 128.2, 128.0, 121.7, 121.6, 113.9, 111.9, 71.8, 68.4, 55.5. Without further characterization, the alcohol was subjected

to Dess-Martin oxidation. Dess-Martin periodinane (0.24 g, 0.56 mmol, 1.2 equiv) was added to a 50 mL round bottom flask along with 5 mL of DCM. The alcohol (0.15 g, 0.47 mmol, 1.0 equiv) dissolved in DCM (5 mL) and then slowly added to the reaction mixture. The resulting mixture was then stirred at room temperature for 12 h. The reaction was quenched with 1 M aq. sodium hydroxide solution (10 mL). The layers were separated and the aqueous phase was extracted with additional DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by SiO_2 flash column chromatography (30-50% EtOAc/hexanes) yielded **2.80** (0.092 g, 0.29 mmol, 62 %) as a light brown liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, J = 4.5, 1.5 Hz, 2H), 7.87 – 7.79 (m, 2H), 7.50 – 7.40 (m, 2H), 7.10 (td, J = 7.5, 0.8 Hz, 1H), 7.01 – 6.88 (m, 5H), 5.04 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 163.9, 155.8, 150.0, 145.9, 132.4, 131.9, 131.2, 130.1, 130.0, 121.8, 121.2, 113.8, 112.9, 68.6, 55.8. IR (film) 3060, 2929, 2839, 1654, 1597, 1507 cm-1. HRMS (ESI) $C_{20}H_{18}NO_3$ $[M+H]^+$, Calculated 320.1287; Found 320.1295.



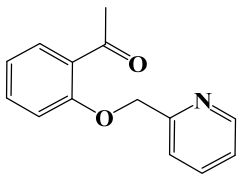
1-(2-(Pyridin-4-ylmethoxy)phenyl)ethan-1-one (2.79): Using the procedure described for the preparation of **2.80**, **2.76** (0.94 ml, 2.3 mmol, 1.0 equiv) and MeMgBr (3.0 M, 0.86 mL, 2.6 mmol, 1.1 equiv) were reacted to yield 1-(2-(pyridin-4-ylmethoxy)phenyl)ethan-1-ol (0.37 g, 1.6 mmol, 69%) as a yellow liquid. ^{1}H NMR (300 MHz, CDCl3) δ 8.61 (d, *J* = 6.0 Hz, 2H), 7.47 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.34 (d, *J* = 6.0

Hz, 2H), 7.26 – 7.17 (m, 1H), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.35 – 5.21 (m, 1H), 5.14 (s, 2H), 2.71 (s, 1H), 1.55 (d, *J* = 6.5 Hz, 3H), ^{13}C NMR (75 MHz, CDCl3) δ 155.0, 150.3, 146.2, 134.3, 128.5, 126.5, 121.8, 121.5, 111.6, 68.3, 65.9, 23.5. Without further characterization, the alcohol (0.37 g, 1.6 mmol, 1.0 equiv) was treated with Dess-Martin periodinane (0.82 g, 1.9 mmol, 1.2 equiv) to yield **2.79** (0.28 g, 1.3 mmol, 78%) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 6.0 Hz, 2H), 7.75 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.50 – 7.35 (m, 3H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.4, 150.4, 145.6, 133.8, 130.9, 129.1, 121.8, 121.7, 112.9, 69.1, 32.1. IR (film) 3064, 3032, 2929, 2868, 1683, 1597 cm^{-1}. HRMS (ESI) $C_{14}H_{14}NO_2$ $[M+H]^+$, Calculated 228.1025; Found 228.1017.



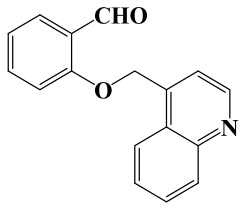
(4-Methoxyphenyl)(2-(pyridin-2-ylmethoxy)phenyl)methanone (2.77): Using the procedure described for the preparation of **2.80**, **2.75** (0.30 g, 1.4 mmol, 1.0 equiv) was treated with (4-methoxyphenyl)magnesium bromide (1.0 M, 3.5 mL, 3.5 mmol, 2.5 equiv) to yield (4-methoxyphenyl)(2-(pyridin-2-ylmethoxy)phenyl)methanol (0.35 g, 1.1 mmol, 77 %) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 – 8.54 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.30 – 7.24 (m, 1H), 7.24 – 7.16 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.88 –

6.81 (m, 2H), 6.12 (s, 1H), 5.20 (s, 2H), 4.17 – 3.88 (m, 1H), 3.79 (d, J = 2.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 156.9, 155.9, 149.4, 137.1, 135.8, 133.2, 128.9, 128.2, 128.1, 123.0, 121.5, 121.4,113.8, 112.6, 72.0, 70.8, 55.5. Oxidation of the intermediate alcohol (0.3 g, 0.93 mmol, 1.0 equiv) with the Dess-Martin reagent (0.48 g, 1.1 mmol, 1.2 equiv) afforded **2.77** (0.18 g, 0.55 mmol, 59 %) as a light brown solid. M.p.: 70-72 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.55 – 7.38 (m, 3H), 7.16 – 7.01 (m, 3H), 6.98 – 6.88 (m, 3H), 5.15 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 163.8, 157.0, 155.9, 148.9, 136.9, 132.4, 131.9, 131.2, 129.8, 129.7, 122.6, 121.3, 120.9, 113.7, 112.8, 70.8, 55.7. IR (film) 3064, 3027, 2925, 2844, 1667, 1601, 1507 cm^{-1}. HRMS (ESI) $C_{20}H_{18}NO_3$ $[M+H]^+$, Calculated 320.1287; Found 320.1272.



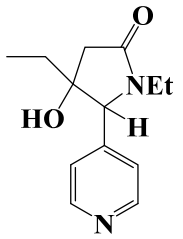
1-(2-(2-(Pyridin-2-yl)ethyl)phenyl)ethan-1-one (2.78): Using the procedure described for the preparation of **2.80**, **2.75** (0.55 g, 2.6 mmol, 1.0 equiv) was trerated with methylmagnesium bromide (3.0 M, 1.3 mL, 3.87 mmol, 1.5 equiv) to yield 1-(2-(2-pyridin-2-yl)ethyl)phenyl)ethan-1-ol (0.56 g, 2.5 mmol, 96 %) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.71 (td, J = 7.7, 1.8 Hz, 1H), 7.48 – 7.36 (m, 2H), 7.26 – 7.16 (m, 2H), 6.98 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (dd, J = 8.2, 0.8 Hz, 1H), 5.32 – 5.17 (m, 3H), 3.74 (s, 1H), 1.57 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 157.0, 155.7, 149.5, 137.2, 134.4, 128.5, 126.5, 123.0, 121.6, 121.3, 112.4, 70.8, 66.1, 22.9. Dess-Martin oxidation of this alcohol (0.55 g of the alcohol, 1.2

equiv DMP) gave **2.78** (0.49 g, 2.2 mmol, 90%) as a white solid. M.p.: 34-35 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.29 – 7.19 (m, 1H), 7.02 – 6.98 (m, 2H), 5.30 (s, 2H), 2.67 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 199.6, 157.5, 156.4, 149.3, 137.0, 133.6, 130.4, 128.6, 122.9, 121.4, 121.0, 112.9, 71.2, 31.9. IR (film) 3068, 3015, 2925, 2868, 1679, 1593 cm^{-1}. HRMS (ESI) $C_{14}H_{14}NO_2$ $[M+H]^+$, Calculated 228.1025; Found 228.1021.



2-(Quinolin-4-ylmethoxy)benzaldehyde (2.87): 4-(Chloromethyl)quinoline (0.50 g, 2.8 mmol, 1.0 equiv) and anhydrous potassium carbonate (0.78 g, 5.6 mmol, 2.0 equiv) were added to a 50 mL round-bottom flask which was then purged with Ar. DMF (10 mL) was added and the resulting mixture was cooled to 0 °C. Salicylaldehyde (0.33 mL, 3.1 mmol, 1.1 equiv) was added and the reaction was stirred at 0 ºC for 30 min, then allowed to warm to room temperature and maintained overnight. Brine (10 mL) and EtOAc (10 mL) were then added and the mixture was filtered through Celite. Water (100 mL) was added to the filtrate and this solution was extracted with EtOAc (4 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 30-50% EtOAc/hexanes) to afford **2.87** (0.31 g, 1.2 mmol, 41 %) as a white solid. M.p.: 118-120 °C. ^{1}H NMR (300 MHz, CDCl3) δ 10.56 (s, 1H), 8.94 (d, *J* = 4.4 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* =

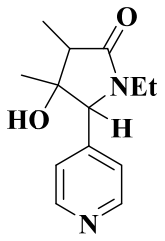
8.4 Hz, 1H), 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.86 – 7.71 (m, 1H), 7.71 – 7.48 (m, 3H), 7.11 (dd, J = 7.9, 5.1 Hz, 2H), 5.68 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 160.5, 150.6, 148.3, 141.2, 136.2, 130.7, 129.8, 129.3, 127.4, 125.8, 125.5, 122.8, 121.8, 119.5, 113.0, 67.4. IR (film) 3052, 2925, 2856, 2762, 1683, 1593 cm^{-1}. HRMS (ESI) $C_{17}H_{14}NO_2$ [M+H]+, Calculated 264.1025; Found 264.1017.



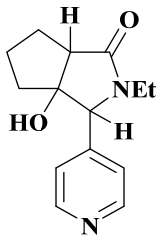
General procedure for intramolecular acid catalyzed benzylic cyclization The preparation of **1,4-diethyl-4-hydroxy-5-(pyridin-4-yl)pyrrolidin-2-one (2.53)** is representative. Pyridine **2.52** (100 mg, 0.40 mmol, 1 equiv) was placed in a scintillation vial equipped with a Teflon-lined screw cap and dissolved in 1,4-dioxane (1 mL). Trifluoromethanesulfonic acid (TfOH) (4 μL, 0.04 mmol, 0.1 equiv) was added and the reaction was heated to 120 ºC. The reaction was maintained at this temperature for 12 h, then allowed to cool to room temperature. The solvent was removed under vacuum and the crude product was purified by silica gel flash column chromatography using 70-100 % EtOAc in hexanes as eluent. *N*,4-Diethyl-4-hydroxy-5-(pyridin-4-yl)pyrrolidin-2-one **2.53** (~2:1 mixture of diastereomers, 96 mg, 96%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 5.4 Hz, 0.7H), 8.46 (d, J = 5.7 Hz, 1.3H), 7.18 (d, J = 5.9 Hz, 1.3H), 7.09 (d, J = 4.9 Hz, 0.7H), 4.55 (s, 0.35H), 4.47 (s, 0.65H), 3.93 – 3.67 (m, 1H), 3.48 (s, 1H), 2.81 – 2.60 (m, 1H), 2.60 – 2.39 (m, 2H), 1.77 (q, J = 7.4 Hz, 1H), 1.39 – 1.29 (m, 1H), 1.09 – 1.02 (m, 3H), 0.99 (t, J = 7.2 Hz, 2H), 0.93 – 0.88 (m, 1H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ 173.7, 173.4, 150.2, 149.4, 146.7, 145.0, 124.0, 77.3, 75.5, 73.8, 70.0, 43.3, 36.3, 35.8, 33.1, 30.6, 12.4, 12.1, 8.2, 8.1. IR (film) 3350, 2972, 2936, 2874, 1672 cm^{-1}. HRMS (ESI) $C_{13}H_{19}N_2O_2$ $[M+H]^+$, calculated 235.1447; found 235.1434.

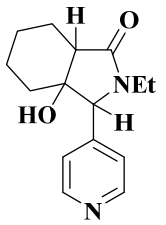
Cyclized products **2.54-2.60** (Table 2.2) were prepared from 100 mg of the corresponding pyridine substrates using the procedure given above.



***N*-Ethyl-4-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)pyrrolidin-2-one (2.54)** Mixture of diastereomers, 97 mg, 97%, yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 4.9 Hz, 0.7H), 8.50 – 8.41 (m, 1.3H), 7.22 (d, J = 5.3 Hz, 0.5H), 7.16 (d, J = 5.1 Hz, 0.9H), 7.11 (d, J = 3.8 Hz, 0.5H), 7.06 (d, J = 4.2 Hz, 0.1H), 4.61 (s, 0.1H), 4.50 (s, 0.3H), 4.43 (s, 0.2H), 4.34 (m, 0.4H), 3.96 – 3.68 (m, 1H), 3.41 (s, 1H), 2.86 – 2.59 (m, 1H), 2.59 – 2.49 (m, 0.4H), 2.49 – 2.33 (m, 0.6H), 1.38 (d, J = 7.2 Hz, 2H), 1.29 – 1.21 (m, 1H), 1.21 – 1.12 (m, 2.5H), 1.07 – 0.96 (m, 3H), 0.93 (t, J = 7.1 Hz, 0.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 176.7, 175.8, 175.5, 150.2, 149.8, 149.4, 149.3, 146.8, 145.8, 145.4, 143.9, 124.5, 123.6, 123.1, 77.1, 76.9, 76.1, 74.9, 72.1, 71.4, 69.8, 69.6, 60.5, 49.9, 48.1, 46.6, 45.3, 36.4, 36.0, 35.6, 24.2, 23.4, 23.3, 20.7, 14.3, 12.5, 12.3, 11.9, 11.3, 9.6, 7.8, 7.2. IR (film) 3368, 2976, 2939, 2870, 1683, 1657 cm^{-1}. HRMS (ESI) $C_{13}H_{19}N_2O_2$ $[M+H]^+$, calculated 235.1447; found 235.1466.

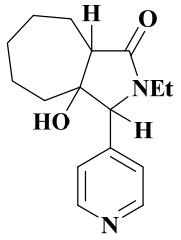


***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)hexahydrocyclopenta[*c*]pyrrol-1(2*H*)-one (2.55)** Mixture of diastereomers, 60 mg, 60%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 – 8.43 (m, 0.4H), 8.38 (d, *J* = 5.9 Hz, 1.6H), 7.12 (d, *J* = 6.0 Hz, 2H), 4.52 (s, 0.3H), 4.49 (s, 0.7H), 3.81 (dq, *J* = 14.6, 7.4 Hz, 1H), 3.27 (dd, *J* = 14.0, 6.8 Hz, 0.4H), 2.85 (dd, *J* = 9.6, 4.3 Hz, 0.2H), 2.76 (dd, *J* = 9.0, 2.8 Hz, 0.8H), 2.65 (dq, *J* = 14.1, 7.1 Hz, 0.6H), 2.21 – 1.80 (m, 5H), 1.80 – 1.58 (m, 1H), 1.11 – 0.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 149.8, 149.5, 146.8, 123.3, 83.8, 69.1, 52.9, 42.3, 36.3, 27.6, 24.8, 12.2. IR (film) 3367, 2958, 2872, 1667, 1601 cm^{-1}. HRMS (ESI) $C_{14}H_{19}N_2O_2$ $[M+H]^+$, Calculated 247.1447; Found 247.1436.



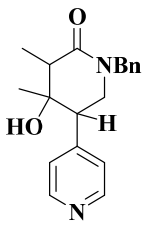
***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)octahydro-1*H*-isoindol-1-one (2.56)** Mixture of diastereomers, 98 mg, 98%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.9 Hz, 0.2H), 8.28 (d, *J* = 6.0 Hz, 1.8H), 7.19 (d, *J* = 6.0 Hz, 0.2H), 7.08 (d, *J* = 6.0 Hz, 1.8H), 4.52 (s, 0.1H), 4.20 (s, 0.9H), 3.98 – 3.79 (m, *J* = 14.6, 7.3 Hz, 1H), 3.70 (s, 1H), 2.77 (dq, *J* = 14.1, 7.0 Hz, 1H), 2.56 (d, *J* = 5.8 Hz, 0.1H), 2.49 – 2.36 (m, 0.9H), 2.01 – 1.83 (m, *J* = 15.9, 5.3 Hz, 2H), 1.80 – 1.48 (m, 4H), 1.43 – 1.29 (m, 2H), 1.06 (t, *J* = 7.2

Hz, 2.7H), 0.96 (t, J = 7.1 Hz, 0.3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.2, 145.6, 123.3, 74.7, 68.8, 46.1, 36.11, 36.08, 22.7, 21.46, 21.42, 12.3. IR (film) 3404, 2939, 2859, 1676, 1665, 1603 cm^{-1}. HRMS (ESI) $C_{15}H_{21}N_2O_2$ $[M+H]^+$, Calculated 261.1603; Found 261.1594.

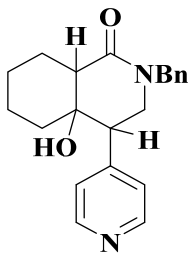


***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)octahydrocyclohepta[*c*]pyrrol-1(2*H*)-one (2.57)**

Mixture of diastereomers, 89 mg, 89%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.9 Hz, 0.8H), 8.54 – 8.41 (m, J = 5.9 Hz, 1.2H), 7.26 – 7.13 (m, J = 5.5 Hz, 1.5H), 7.14 – 6.94 (m, 0.5H), 4.61 (s, 0.1H), 4.46 (s, 0.2H), 4.44 (s, 0.5H), 4.40 (s, 0.2H), 4.02 – 3.59 (m, 1H), 3.39 – 2.85 (m, 1H), 2.85 – 2.38 (m, 2H), 2.26 – 1.93 (m, 2H), 1.93 – 1.12 (m, 8H), 1.12 – 1.00 (m, 1H), 1.00 – 0.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 176.9, 176.3, 175.4, 174.4, 150.2, 150.2, 149.5, 149.3, 147.5, 146.8, 144.4, 143.8, 143.5, 124.5, 124.3, 124.2, 79.6, 79.4, 78.5, 77.9, 73.9, 73.0, 70.3, 70.0, 58.3, 56.4, 50.5, 47.7, 42.7, 39.5, 38.4, 37.9, 37.8, 36.4, 36.2, 35.7, 31.2, 31.1, 30.9, 30.0, 29.9, 28.0, 26.2, 26.1, 25.5, 25.4, 24.7, 22.7, 20.8, 12.6, 12.2, 12.0. IR (film) 3364, 2932, 2849, 1683, 1661 cm^{-1}. HRMS (ESI) $C_{16}H_{23}N_2O_2$ $[M+H]^+$, calculated 275.1760; found 275.1755.

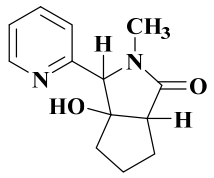


***N*-Benzyl-4-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)piperidin-2-one (2.58)** Mixture of diastereomers, 97 mg, 97%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 – 8.31 (m, 2H), 7.48 – 7.19 (m, 6H), 7.19 – 6.92 (m, 1H), 4.95 – 4.26 (m, 2H), 3.99 – 2.77 (m, 4H), 2.76 – 2.67 (m, 0.1H), 2.67 – 2.54 (m, 0.2H), 2.54 – 2.38 (m, 0.7H), 1.50 – 1.29 (m, 3H), 1.26 (s, 0.3H), 1.18 (s, 0.2H), 1.10 – 0.81 (m, 2.5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 171.2, 149.6, 149.5, 149.4, 149.2, 148.2, 147.9, 137.0, 136.9, 136.8, 129.2, 128.8, 128.77, 128.74, 128.4, 128.2, 127.9, 127.8, 127.4, 126.3, 125.0, 124.9, 124.5, 124.4, 72.3, 71.7, 51.7, 50.4, 50.2, 50.08, 50.02, 49.2, 48.4, 47.6, 47.2, 47.1, 44.6, 25.7, 25.2, 16.3, 10.1. . IR (film) 3419, 2983, 2928, 1697, 1625, 1617 cm^{-1}. HRMS (ESI) $C_{19}H_{23}N_2O_2$ $[M+H]^+$, calculated 311.1760; found 311.1764.

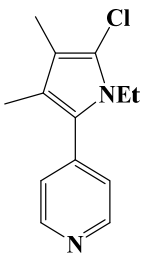


***N*-Benzyl-4a-hydroxy-4-(pyridin-4-yl)octahydroisoquinolin-1(2*H*)-one (2.59)** Mixture of diastereomers, 70 mg, 70%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 5.9 Hz, 1.8H), 8.39 (dd, J = 4.6, 1.4 Hz, 0.2H), 7.41 – 7.19 (m, 6.8H), 7.00 (d, J = 6.1 Hz, 0.2H), 4.86 (d, J = 14.9 Hz, 1H), 4.49 (d, J = 14.4 Hz, 0.1H), 4.37 (d, J = 14.9 Hz, 0.9H), 3.83 – 3.68 (m, 1H), 3.23 (dd, J = 11.8, 6.0 Hz, 1H), 2.98 (dd, J = 12.2, 6.0 Hz, 1H), 2.71 (s, 1H), 2.37 (dd, J = 13.9, 2.3 Hz, 1H), 2.29 (dd, J = 12.5, 3.8 Hz, 1H), 1.93 – 1.78 (m, 1H), 1.66 – 1.47 (m, 2H), 1.47 – 1.34 (m, 1H), 1.34 – 1.06 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.8, 147.2, 137.2, 128.79, 128.72, 128.0, 127.5, 124.7, 124.0, 71.0,

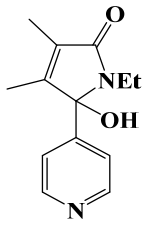
50.2, 50.2, 50.0, 48.9, 35.9, 25.3, 22.4, 20.6. IR (film) 3386, 2928, 2852, 1630, 1625 cm^{-1}. HRMS (ESI) $C_{21}H_{25}N_2O_2$ $[M+H]^+$, Calculated 337.1916; Found 337.1907.



3a-Hydroxy-2-methyl-3-(pyridin-2-yl)hexahydrocyclopenta[c]pyrrol-1(2H)-one (2.60) Mixture of diastereomers, 47 mg, 59%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.57 (m, 0.8H), 8.57 – 8.50 (m, 0.2H), 8.30 (s, 0.2H), 8.19 (s, 0.2H), 7.80 – 7.63 (m, 1H), 7.31 – 7.14 (m, 2H), 4.85 (s, 0.3H), 4.66 (s, 0.4H), 4.53 (s, 0.5H), 4.50 (s, 0.3H), 3.43 – 3.06 (m, 0.4H), 2.99 (s, 0.6H), 2.97 – 2.90 (m, 0.6H), 2.85 (s, 0.7H), 2.83 (s, 0.8H), 2.72 (s, 0.9H), 2.60 – 2.25 (m, 0.5H), 2.24 – 2.07 (m, 1H), 2.07 – 1.80 (m, 1.5H), 1.80 – 1.60 (m, 0.7H), 1.60 – 1.44 (m, 0.3H), 1.44 – 1.29 (m, 0.5H), 1.29 – 1.08 (m, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 176.4, 163.3, 162.8, 157.2, 157.0, 156.3, 156.1, 150.1, 150.0, 149.7, 149.4, 137.4, 137.2, 137.1, 136.9, 123.4, 123.2, 123.0, 123.0, 122.7, 122.4, 121.5, 86.0, 84.1, 74.8, 73.3, 55.3, 55.0, 53.8, 49.9, 42.4, 38.2, 34.9, 30.1, 29.5, 29.0, 28.2, 28.1, 25.3, 25.0. IR (film) 3404, 2965, 2885, 1665, 1643 cm^{-1}. HRMS (ESI) $C_{13}H_{17}N_2O_2$ $[M+H]^+$, calculated 233.1290; found 233.1286.

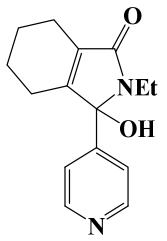


4-(5-Chloro-*N*-ethyl-3,4-dimethyl-1*H*-pyrrol-2-yl)pyridine (2.61) Pyridine substrate **2.54** (100 mg, 0.4 mmol, 1 equiv) was dissolved in 1,4-dioxane (1 mL). $POCl_3$ (0.12 mL, 1.3 mmol, 3.0 equiv) was added dropwise. The reaction was maintained for 10 min, then Et_3N (0.24 mL, 1.7 mmol, 4.0 equiv) was added and the reaction was heated to 120 ºC for 12 h. After cooling to room temperature the solvent was removed under vacuum. The residue was combined with saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 10 mL). The combined organic layer was concentrated under vacuum and purified via flash column chromatography (SiO_2, 70-100 % EtOAc/hexanes) to afford **2.61** (30 mg, 30%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.5 Hz, 2H), 7.19 (dd, *J* = 4.5, 1.6 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 2.01 (s, 3H), 1.99 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 140.6, 126.9, 124.6, 118.3, 116.2, 115.4, 39.9, 16.2, 10.4, 9.35. IR (film) 1654, 1636, 1632 cm^{-1}. HRMS (ESI) $C_{13}H_{16}N_2Cl$ $[M+H]^+$, calculated 235.1002; found 235.1017.



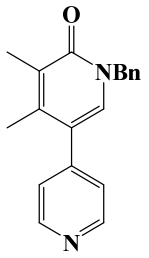
General procedure for $SOCl_2$-mediated oxidation of hydroxyl lactams: The preparation of **2.62** is representative. Compound **2.54** (100 mg, 0.4 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) and the resulting solution cooled to 0 ºC. Thionyl chloride (100 µL, 1.3 mmol, 3.0 equiv) was added dropwise. After stirring at 0 ºC for 10 min, Et_3N (0.30 mL, 2.2 mmol, 5.0 equiv) was added dropwise over 5 min. The reaction was maintained at 0 ºC for 12 h, and then quenched by addition of saturated aqueous Na_2CO_3

solution. After warming to room temperature the layers were separated and the aqueous was re-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified via flash column chromatography (SiO_2, 70-100% EtOAc/hexanes as eluent) to give N-ethyl-5-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)-1*H*-pyrrol-2(5*H*)-one **2.62** (45 mg, 45%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.2 Hz, 2H), 7.35 (d, *J* = 3.4 Hz, 2H), 5.52 – 4.86 (m, 1H), 3.42 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.02 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.82 (s, 3H), 1.66 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 151.9, 149.6, 148.5, 128.9, 121.6, 91.6, 34.5, 14.7, 9.9, 8.6. IR (film) 3436, 1659, 1638, 1630 cm^{-1}. HRMS (ESI) $C_{13}H_{17}N_2O_2$ $[M+H]^+$, calculated 233.1290; found 233.1313.

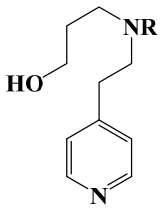


N-Ethyl-3-hydroxy-3-(pyridin-4-yl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (2.63)

Using the procedure given for the preparation of **2.62**, **2.55** (100 mg, 0.4 mmol) was converted to **2.63** (65 mg, 70%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.36 (d, *J* = 6.0 Hz, 2H), 5.97 (s, 1H), 3.44 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.02 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.37 – 2.06 (m, 4H), 1.72 – 1.43 (m, 4H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 156.0, 149.6, 148.6, 132.0, 121.5, 91.2, 34.2, 22.0, 21.8, 20.62, 20.1, 14.8. IR (film) 3383, 2983, 2925, 2848, 1667 cm^{-1}. HRMS (ESI) $C_{15}H_{19}N_2O_2$ $[M+H]^+$, calculated 259.1447; found 259.1455.



N-Benzyl-[3,4'-bipyridin]-6(1*H*)-one (2.64) Using the procedure for the preparation of **2.62**, compound **2.58** (27 mg, 30%) was isolated as a yellow oil from 100 mg of **2.58**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.38 – 7.28 (m, 5H), 7.14 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.08 (s, 1H), 5.18 (s, 2H), 2.22 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 150.0, 145.8, 143.7, 136.5, 132.9, 129.0, 128.3, 128.2, 127.7, 124.6, 120.5, 52.6, 17.9, 13.6. IR (film) 1654, 1639, 1625 cm^{-1}. HRMS (ESI) $C_{19}H_{19}N_2O$ $[M+H]^+$, calculated 291.1497; found 291.1512.



2.67 R = Bz
2.68 R = Ts

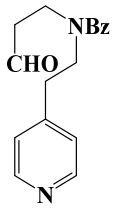
N-(3-Hydroxypropyl)-N-(2-(pyridine-4-yl)ethyl)benzamide (2.67) and N-(3-hydroxypropyl)-N-(2-(pyridine-4-yl)ethyl)toluenesulfonamide (2.68) 4-(2-aminoethyl)pyridine (2.9 mL, 24 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (100 mL) and Et_3N (5.1 mL, 36 mmol, 1.5 equiv) was added. The reaction was cooled to 0 ºC and benzoyl chloride (3.1 mL, 27 mmol, 1.1 equiv) dissolved in CH_2Cl_2 (50 mL) was added dropwise via addition funnel. Once the addition was complete, the reaction was maintained at 0 ºC for an additional 20 min, then quenched with H_2O (100 mL). The

layers were separated and the aqueous was re-extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the crude benzamide derivative (4.40 g, 80%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.76 (dd, *J* = 7.1, 1.5 Hz, 2H), 7.54 – 7.27 (m, 3H), 7.08 (dd, *J* = 4.5, 1.5 Hz, 2H), 3.67 (dd, *J* = 13.0, 6.9 Hz, 2H), 2.90 (t, *J* = 7.0 Hz, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 149.6, 148.5, 134.4, 131.5, 128.5, 127.0, 124.3, 40.4, 35.0). Without further purification/characterization, the benzamide (4.40 g, 19.5 mmol, 1.00 equiv) was dissolved in THF (100 mL) and cooled to -78 ºC. A solution of KHMDS (0.5 M in THF, 98 mL, 49 mmol, 2.5 equiv) was added dropwise. After stirring at -78 ºC for 1 h, allyl bromide (5.1 mL, 59 mmol, 3.0 equiv) was added and the reaction was maintained an additional 1 h at -78 ^{0}C, and then allowed to warm to room temperature and stirred overnight. The reaction was quenched with H_2O and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified via flash column chromatography (SiO_2, 50-100% EtOAC/hexanes as eluent) to afford the desired N-allyl amide as a brown oil (4.0 g, 77%, mixture of rotamers, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 – 8.32 (m, 2H), 7.56 – 7.03 (m, 6.5H), 7.00 – 6.54 (m, 0.5H), 6.06 – 5.51 (m, 1H), 5.40 – 5.01 (m, 2H), 4.37 – 3.96 (m, 0.5H), 3.94 – 3.31 (m, 3.5H), 3.16 – 2.61 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 149.9, 148.2, 136.2, 133.2, 129.7, 128.5, 126.4, 124.3, 117.8, 52.5, 45.9, 32.9). Without further characterization, the allyl amide (4.0 g, 15 mmol, 1 equiv) was dissolved in THF (100 mL) and cooled to 0 ºC. 9-BBN (30 mL, 45 mmol, 3.0 equiv) was added via syringe and reaction was stirred at 0 ^{0}C overnight. A solution (20 mL) was prepared using 10 mL of 1M NaOH and 10 mL of 30% H_2O_2 which was added to the reaction mixture. After

warming up to the room temperature, reaction mixture was quenched with water and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. purification via flash column chromatography (SiO_2, 50-100% EtOAc/hexanes as eluent) gave **2.67** as a yellow oil (3.9 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.56 – 8.36 (m, 2H), 7.47 – 7.07 (m, 6H), 6.91 – 6.72 (m, 1H), 3.84 – 3.57 (m, 3H), 3.56 – 3.34 (m, 2H), 3.25 (m, 1H), 3.13 – 2.89 (m, 1H), 2.89 – 2.66 (m, 2H), 1.97 – 1.79 (m, 1H), 1.79 – 1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 149.9, 146.7, 136.0, 129.7, 128.7, 126.2, 124.1, 58.6, 49.8, 41.4, 34.6, 30.5. IR (film) 3266, 3063, 2928, 2867, 1607 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O_2$ $[M+H]^+$, calculated 285.1603; found 285.1598.

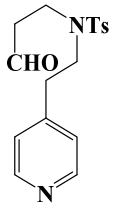
Tosylamide **2.68** was prepared in similar fashion starting from 4-(2-aminoethyl)pyridine and tosyl chloride (90%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.21 (m, 2H), 7.03 (dd, *J* = 4.5, 1.5 Hz, 2H), 5.32 (t, *J* = 6.2 Hz, 1H), 3.23 (q, *J* = 6.8 Hz, 2H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.43 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.3, 143.7, 137.0, 129.9, 127.2, 124.3, 43.4, 35.6, 21.7). Allylation was performed as described above (70%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.8 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 5.6 Hz, 2H), 5.60 (ddt, *J* = 16.4, 9.8, 6.5 Hz, 1H), 5.26 – 5.11 (m, 2H), 3.78 (d, *J* = 6.4 Hz, 2H), 3.46 – 3.20 (m, 2H), 2.98 – 2.75 (m, 2H), 2.43 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 147.6, 143.7, 136.7, 133.1, 129.9, 127.3, 124.3, 119.4, 51.4, 47.9, 35.0, 21.7). Hydroboration/oxidation of the allyl tosylamide afforded **2.68** (90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.7 Hz, 2H), 7.70 – 7.63 (m, 2H), 7.31 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 3.39 – 3.31 (m, 2H),

3.27 (t, J = 6.7 Hz, 2H), 2.89 (dd, J = 8.8, 6.9 Hz, 2H), 2.43 (s, 4H), 1.77 – 1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 147.6, 143.8, 136.2, 130.0, 127.2, 124.3, 58.9, 49.7, 45.8, 35.3, 31.4, 21.7. IR (film) 3291, 2925, 2870 cm^{-1}. HRMS (ESI) $C_{17}H_{23}N_2O_3S$ $[M+H]^+$, Calculated 335.1429; Found 335.1422.

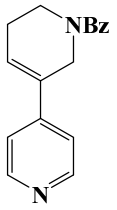


2.69

N-(3-Oxopropyl)-N-(2-(pyridine-4-yl)ethyl)benzamide (2.69) Dichloromethane (40 mL) was cooled to -78 ºC. Oxalyl chloride (0.6 mL, 7 mmol, 2 equiv) and DMSO (1 mL, 14 mmol, 4 equiv) were added dropwise while maintaining the temperature below -70 ºC. After 10 min, a solution of **2.67** (1.0 g, 3.5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added dropwise. Once the addition was complete the reaction was stirred an additional 15 min followed by addition of Et_3N (2 mL, 14 mmol, 4 equiv). The reaction was allowed to warm to 0 ºC and stirred for 10 min. The solvent was then evaporated and the residue was purified by flash column chromatography (SiO_2, 50-100% EtOAc/hexanes as eluent) to give **2.69** (0.4 g, 40%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$ mixture of rotamers) δ 9.93 – 9.47 (m, 1H), 8.65 – 8.19 (m, 2H), 7.48 – 6.96 (m, 6H), 6.96 – 6.53 (m, 1H), 4.02 – 3.22 (m, 4H), 3.15 – 2.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 172.0, 170.5, 149.8, 149.4, 146.7, 135.9, 129.6, 128.5, 126.8, 126.2, 124.1, 123.5, 50.6, 42.6, 39.4, 34.6. IR (film) 2921, 2856, 1726, 1636 cm^{-1}. HRMS (ESI) $C_{17}H_{19}N_2O_2$ $[M+H]^+$, calculated 283.1447; found 283.1452.

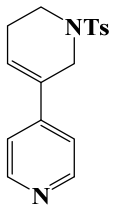


N-(3-Oxopropyl)-N-(2-(pyridine-4-yl)ethyl)toluenesulfonamide (2.70) To a solution of **2.68** (1.0 g, 3.0 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added the Dess-Martin periodinane (1.9 g, 4.5 mmol, 1.5 equiv) at room temperature. After 30 min the reaction was quenched with 1M aqueous NaOH solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 50-100% EtOAc/hexanes as eluent) gave **2.70** (0.42 g, 42%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.49 (d, J = 5.8 Hz, 2H), 7.68 – 7.63 (m, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 4.5, 1.5 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 3.39 – 3.31 (m, 2H), 2.89 – 2.83 (m, 2H), 2.75 (td, J = 6.8, 0.6 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 149.8, 147.2, 143.8, 135.7, 129.9, 127.1, 124.2, 49.7, 43.7, 42.0, 34.7, 21.5. IR (film) 3291, 2925, 2870 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O_3S$ $[M+H]^+$, calculated 333.1265; found 333.1284.



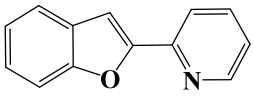
N-Benzoyl-1,2,5,6-tetrahydro-3,4'-bipyridine (2.71) Cyclization of **2.69** (100 mg) was achieved according to a previously reported procedure[117] to yield **2.71** (68 mg, 73%) as a

yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.71 – 8.41 (m, 2H), 7.54 – 6.90 (m, 7H), 6.55 – 6.43 (m, 1H), 4.72 – 4.44 (m, 1.4H), 4.44 – 4.18 (m, 0.6H), 4.02 – 3.73 (m, 0.6H), 3.73 – 3.27 (m, 1.4H), 2.62 – 2.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 150.3, 145.8, 136.0, 132.8, 130.1, 128.8, 127.0, 125.7, 119.6, 44.1, 43.2, 26.5. IR (film) 3060, 3027, 2921, 2893, 2852, 1626 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ $[M+H]^+$, Calculated 265.1341; Found 265.1334.

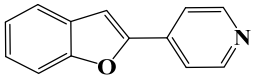


N-Tosyl-1,2,5,6-tetrahydro-3,4'-bipyridine (2.72) This material was obtained as a yellow oil in 72% isolated yield using a previously reported procedure,[117] and in 52% isolated yield using the TfOH-catalyzed procedure given above for the preparation of **2.53**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J = 4.6, 1.6 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 4.6, 1.7 Hz, 2H), 6.35 (tt, J = 4.0, 1.9 Hz, 1H), 3.93 (dd, J = 4.6, 2.5 Hz, 2H), 3.24 (dt, J = 6.9, 4.0 Hz, 2H), 2.48 – 2.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 145.7, 144.0, 133.4, 131.4, 130.0, 127.8, 126.0, 119.5, 45.6, 42.3, 25.9, 21.7. IR (film) 3026, 2917, 2852 cm^{-1}. HRMS (ESI) $C_{17}H_{19}N_2O_2S$ $[M+H]^+$, Calculated 315.1167; Found 315.1170.

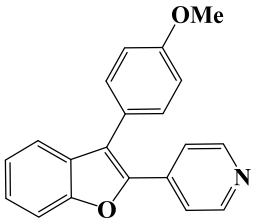
General procedure for the preparation of pyridylbenzofurans Benzofuran derivatives shown in Scheme 6 were prepared using the TfOH-catalyzed procedure given for the preparation of **2.53**. Reactions were performed using 100 mg of alkylated salicylaldehyde substrates.



2-(Benzofuran-2-yl)pyridine (2.84) Colorless solid, 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.87 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.64 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.42 (d, *J* = 0.9 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.28 – 7.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.2, 150.1, 149.4, 136.9, 129.0, 125.4, 123.4, 123.1, 121.9, 120.0, 111.7, 105.0. IR (film) 3056, 3007, 2921, 2844, 1610, 1556 cm^{-1}. HRMS (ESI) $C_{13}H_{10}NO$ $[M+H]^+$, calculated 196.0762; found 196.0754.

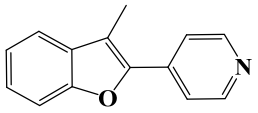


4-(Benzofuran-2-yl)pyridine (2.81) Colorless solid, 96%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.3 Hz, 2H), 7.67 (d, *J* = 5.6 Hz, 2H), 7.64 – 7.48 (m, 2H), 7.35 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.30 – 7.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 152.9, 150.3, 137.4, 128.5, 125.7, 123.4, 121.6, 118.7, 111.5, 105.0. IR (film) 3081, 3034, 2928, 2852, 1610, 1541. HRMS (ESI) $C_{13}H_{10}NO$ $[M+H]^+$, calculated 196.0762; found 196.0747.

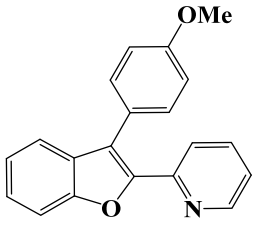


4-(3-(4-Methoxyphenyl)benzofuran-2-yl)pyridine (2.83) Yellow solid, 92%, Mp. 105-108 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 6.0 Hz, 2H), 7.60 – 7.51 (m, 3H),

7.48 (dd, J = 7.8, 0.6 Hz, 1H), 7.44 – 7.34 (m, 3H), 7.25 (t, J = 7.5 Hz, 1H), 7.09 – 7.00 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 154.4, 149.9, 147.2, 138.4, 130.9, 130.3, 126.2, 123.9, 123.5, 121.6, 120.9, 120.4, 114.9, 111.6, 55.5. IR (film) 3065, 3040, 2960, 2915, 2841, 1603, 1516. HRMS (ESI) $C_{20}H_{16}NO_2$ $[M+H]^+$, calculated 302.1181; found 302.1169.

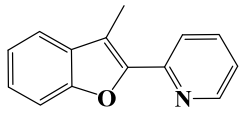


4-(3-Methylbenzofuran-2-yl)pyridine (2.82) Yellow solid, 75%, Mp. 40-45 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.4 Hz, 2H), 7.66 – 7.57 (m, 2H), 7.55 – 7.46 (m, 1H), 7.46 – 7.37 (m, 1H), 7.33 – 7.24 (m, 1H), 7.24 – 7.13 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 150.2, 147.7, 138.8, 130.8, 126.0, 123.0, 120.3, 120.1, 115.9, 111.5, 9.9. IR (film) 3036, 2929, 2852, 1609, 1540. HRMS (ESI) $C_{14}H_{12}NO$ $[M+H]^+$, calculated 210.0919; found 210.0913.

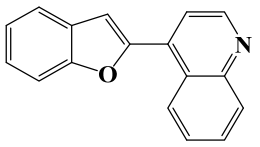


2-(3-(4-Methoxyphenyl)benzofuran-2-yl)pyridine (2.86) Colorless solid, 61%, Mp. 50-53 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.60 – 7.42 (m, 5H), 7.37 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.16 (ddd, J = 7.2, 4.8, 1.4 Hz, 1H), 7.06 – 6.98 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 154.4, 150.1, 149.9, 149.1, 136.2, 131.2, 130.2, 125.8, 124.6,

123.3, 122.8, 122.5, 120.8, 120.6, 114.6, 111.9, 55.5. IR (film) 3052, 2997, 2925, 2828, 1598, 1581, 1556, 1507. HRMS (ESI) $C_{20}H_{16}NO_2$ $[M+H]^+$, calculated 302.1181; found 302.1163.



2-(3-Methylbenzofuran-2-yl)pyridine (2.85) Colorless solid, 62%, Mp. 34-35 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.85 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.70 (td, *J* = 7.8, 1.8 Hz, 1H), 7.56 (ddd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.35 – 7.27 (m, 1H), 7.27 – 7.20 (m, 1H), 7.13 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.5, 149.7, 149.2, 136.6, 131.3, 125.4, 122.8, 122.1, 121.1, 120.2, 116.0, 111.4, 9.8. IR (film) 3048, 2928, 2863,1603, 1585 cm^{-1}. HRMS (ESI) $C_{14}H_{12}NO$ $[M+H]^+$, calculated 210.0919; found 210.0906.



4-(3-(4-Methoxyphenyl)benzofuran-2-yl)quinoline (2.88) Brown oil, 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, *J* = 4.6 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.84 – 7.73 (m, 2H), 7.73 – 7.57 (m, 3H), 7.47 – 7.36 (m, 1H), 7.36 – 7.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.9, 150.1, 149.2, 135.9, 130.5, 129.8, 128.7, 127.6, 125.8, 125.5, 125.00, 123.6, 121.8, 120.0, 111.7, 108.8. IR (film) 3060, 3027, 2962, 2917, 2856, 1593, 1561. HRMS (ESI) $C_{17}H_{12}NO$ $[M+H]^+$, calculated 246.0919; found 246.0914.

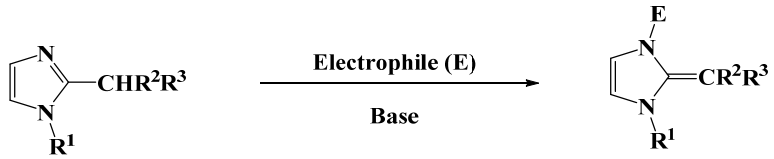
Chapter Three

Intramolecular Cyclization of Alkylimidazoles[2]

3.1 Introduction

Nitrogen containing heterocyclic compounds play an important role in natural product and medicinal chemistry.[89,139,140] Due to the wide range of biological activities exhibited by azaheterocyclic natural products and unnatural pharmacologic agents, developing new synthetic strategies to both synthesize azaheterocycles and manipulate existing azaheterocyclic ring systems remain important objectives.

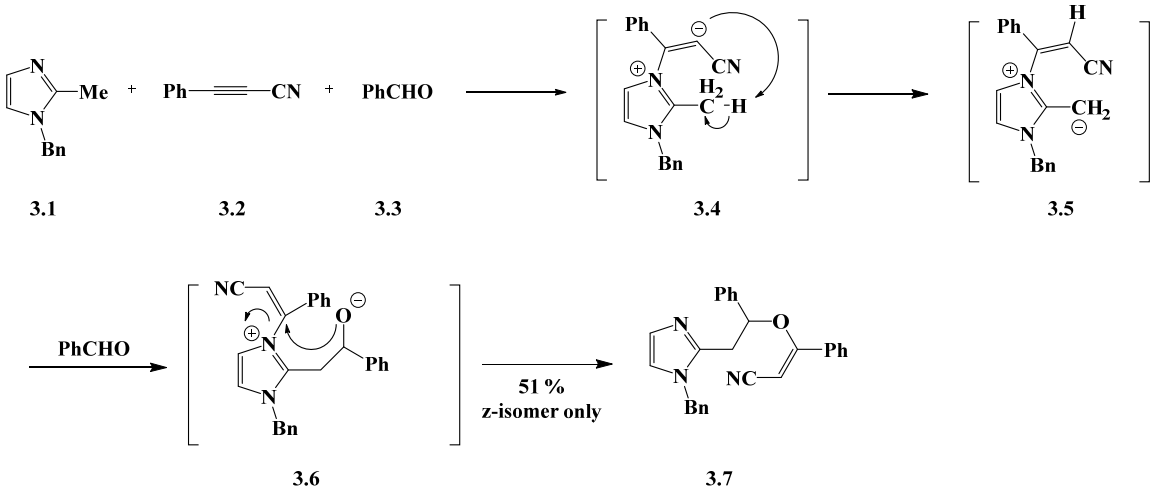
As discussed in Chapter 2, we have been investigating intramolecular cyclization reactions of substituted pyridines via anhydrobase intermediates (Schemes 2.6 & 2.7).[116-118,126] Besides pyridines, imidazoles also offer opportunities for the generation of nucleophilic alkylidene imidazolines via electrophilic activation (Scheme 3.1).[141] Consequently, appropriately substituted 2-alkylimidazoles and/or 1,2-dialkylimidazoles should also be capable of participating in intramolecular cyclizations analogous to those depicted in Scheme 2.6 and 2.7.



Scheme 3.1 - Generation of the nucleophilic alkylidene intermediate

[2] This chapter is adapted from a published manuscript: Joshi, M. S.; Lansakara, A. I.; Pigge, F. C.: Intramolecular cyclization of alkylimidazoles. *Tetrahedron Lett.* **2015**, *56*, 3204.

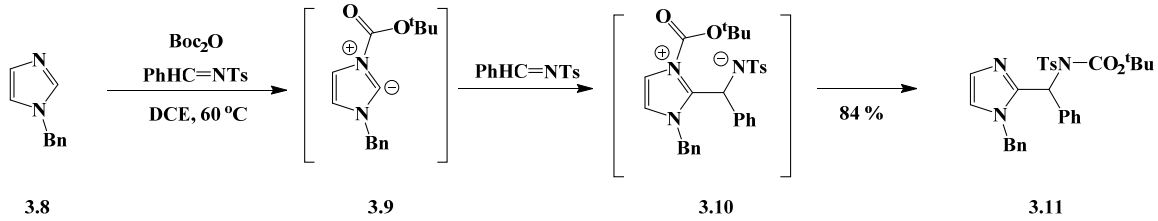
There are only a few examples of intermolecular aldol- and Mannich-type condensations involving electrophilic activation of 1,2-dialkyl imidazoles in the literature. Trofimov and coworkers reported a three component reaction between 1-alkyl-2-methylimidazoles, cyanophenylacetylene, and aliphatic/aromatic aldehydes, which occurs without a catalyst or a solvent at room temperature (Scheme 3.2).[142] The reaction is triggered by the formation of zwitterion **3.4**, which is the adduct of imidazole **3.1** and cyanophenylacetylene (**3.2**). The next step is proton abstraction from the 2-methyl group by the anionic center of **3.4**, to generate a zwitterion (**3.5**). The intermediate **3.5** is then intercepted by the aldehyde **3.3** to yield the oxygen centered zwitterion **3.6**, which undergoes rearrangement with migration of the positively charged vinyl moiety onto the oxygen anionic center to give vinyl ether **3.7**.



Scheme 3.2 - Three component reaction via activation of 1,2-dialkylimidazole

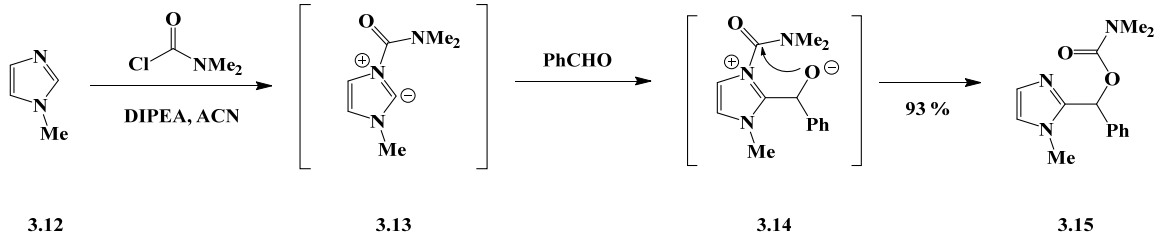
In another study Zificsak and coworkers have shown that imidazolium ylides can be added to electron deficient imines to afford orthogonally protected 2-(α-substituted amidoalkyl)-imidazoles (Scheme 3.3).[143] N-Benzylimidazole (**3.8**) first reacts with di-

tert-butyldicarbonate (Boc_2O) followed by deprotonation of C2 by *in situ* generated *tert*-butylate anion to generate **3.9**. This ylide intermediate **3.9** readily adds to electron deficient N-sulfonyl imine to yield the intermediate **3.10**. Intra- or intermolecular transfer of the activating group affords the final product **3.11**.



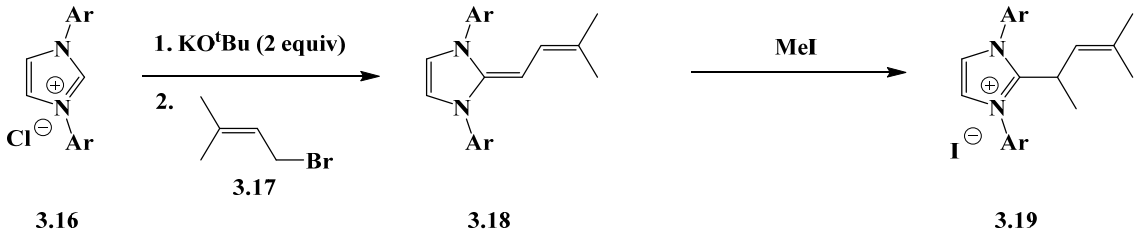
Scheme 3.3 - Addition reaction of imidazolium ylides to electron deficient imines

Deng and coworkers have shown that 2-substituted imidazoles can be synthesized by reacting an azolium ylide with aldehydes (Scheme 3.4).[144] First, the imidazole substrate **3.12** reacts with dimethylcarbamoyl chloride followed by deprotonation to form the azolium ylide **3.13**, which then reacts with the electrophilic benzaldehyde to afford the zwitterionic intermediate **3.14**. Once again intra- and/or intermolecular acyl transfer occurs to afford the final product **3.15**.



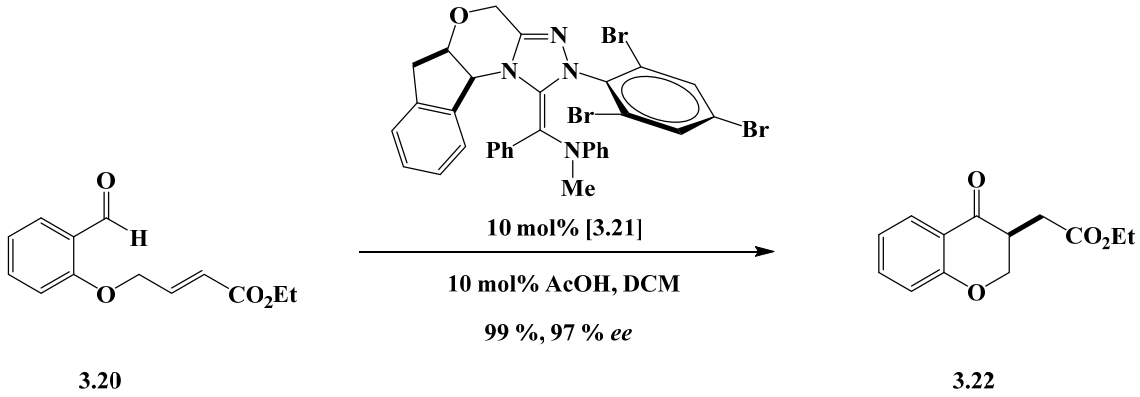
Scheme 3.4 - 2-Substituted imidazoles through nucleophilic azolium intermediates

More recently Knappke and coworkers have shown that 2-alkylidene imidazolines can be synthesized from imidazolium halides and substituted alkyl halides in the presence of base (Scheme 3.5).[145] Imidazolium substrate **3.16** first undergoes deprotonation by potassium tert-butoxide and then the resulting anion reacts with the added bromo electrophile (**3.17**) to afford the exocyclic enediamine product **3.18**, which was further reacts with methyl iodide (another halo electrophile) to afford the imidazolium product **3.19**.



Scheme 3.5 - Reaction between imidazolium ylides and alkyl halides

Notably, imidazolines such as in Scheme 3.1 represent deoxy analogues of intermediates potentially encountered in imidazolium based N-hetereocyclic carbene catalyzed transformations of aldehydes (i.e., Breslow intermediates), thus further stimulating interest in reactive species of this type. In related work, DiRocco and coworkers have synthesized isolable analogues of the Breslow intermediate derived from chiral triazolylidene carbenes (Scheme 3.6).[146] These analogues (such as **3.21**) were successful in catalyzing the Stetter reaction to convert the aldehyde substrate **3.20** to keto ester product **3.22** in high yield and high enantiomeric excess.

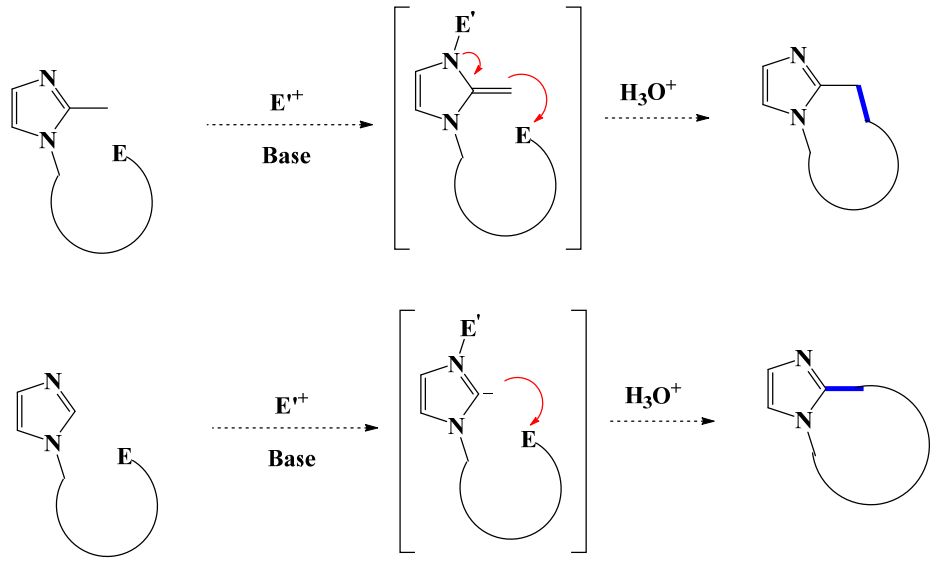


Scheme 3.6 - Catalytic activity of aza-Breslow intermediate

Given the general importance of imidazole-based heterocycles in natural product/medicinal chemistry[147] along with increasing interest in chemistry of alkylidene imidazolines and our previous experience with anhydrobases generated from pyridine substrates, a study was initiated to explore intramolecular reaction manifolds available to relatively simple 1,2-disubstituted imidazoles in the presence of electrophilic activating agents.[115]

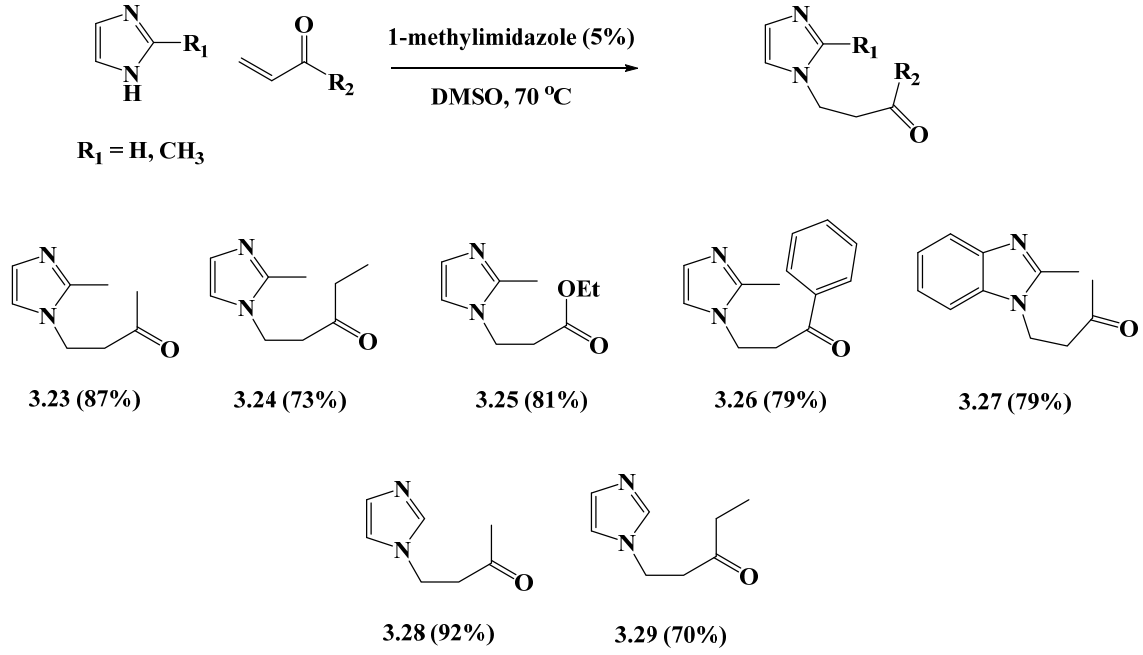
3.2 Results and Discussion

The objective of this study was to synthesize fused-ring imidazo-derivatives via intramolecular cyclization of N-alkylimidazoles under reaction conditions expected to generate nucleophilic imidazoline intermediates (Scheme 3.7).



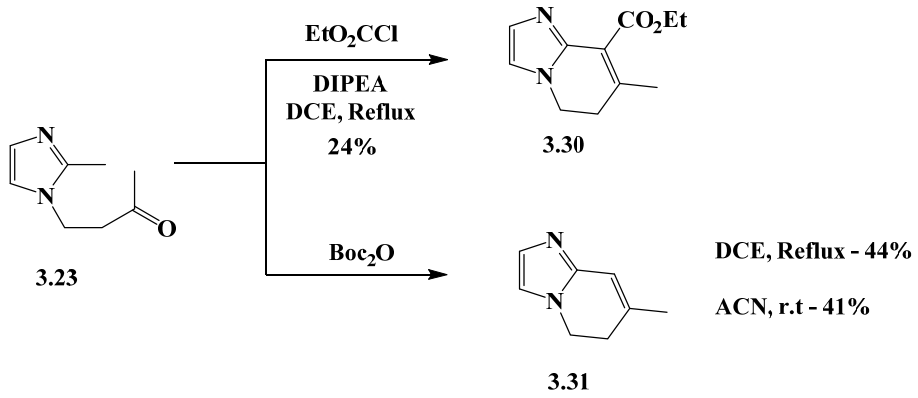
Scheme 3.7 - Anticipated intramolecular cyclization manifolds of N-alkylimidazoles

N-Alkyl-2-methylimidazole and N-alkylimidazole substrates were prepared according to published procedure (Scheme 3.8).[148]



Scheme 3.8 - Synthesis of N-alkylimidazole substrates

Compound **3.23** was tested for its reactivity with several electrophiles including ethyl chloroformate, di-*tert*-butyldicarbonate, and diisopropylcarbamoyl chloride (Scheme 3.9).

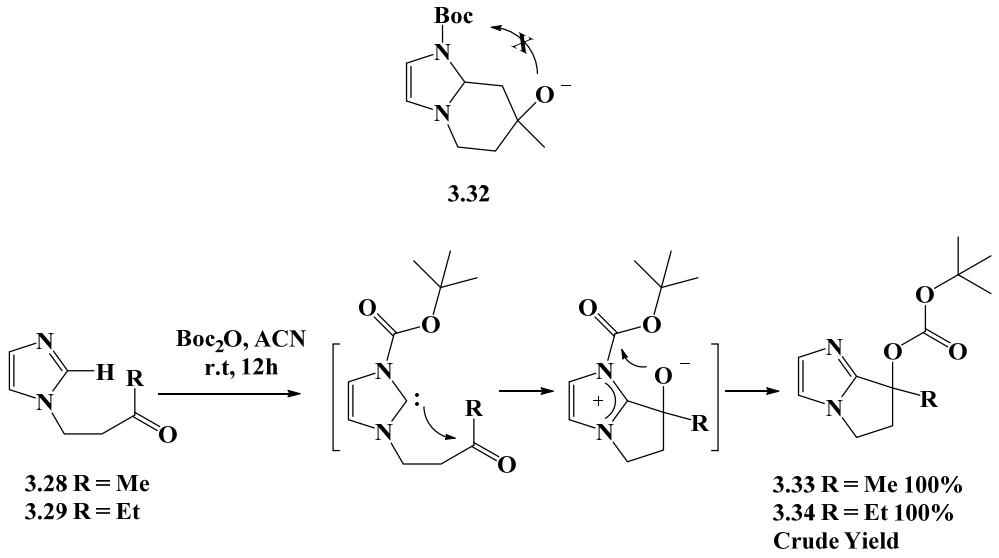


Scheme 3.9 - Optimization with various electrophiles

First, a reaction was observed when ethyl chloroformate was used as the electrophile. An intramolecular cyclization reaction was observed and imidazo[1,2-a]dihydropyridine **3.30** was isolated in low yield of 24% as a stable product. Somewhat unexpectedly, the ethoxycarbonyl group was also observed to be present in the final product. All our attempts to improve the yield of this reaction by changing reaction conditions such as solvent, temperature, and equivalents of the electrophile were not successful. When the electrophile was changed to di-*tert*-butyldicarbonate, similar reaction was observed and imidazo[1,2-a]dihydropyridine **3.31** was isolated in moderate yield as a stable compound. No added base was used in this process as tert-butoxide anion should be generated upon reaction of imidazole with Boc_2O.[143,144] Efforts to improve this transformation revealed that performing the reaction at room temperature in acetonitrile gave comparable results, but the yield of **3.31** never rose above ~40%. Moreover,

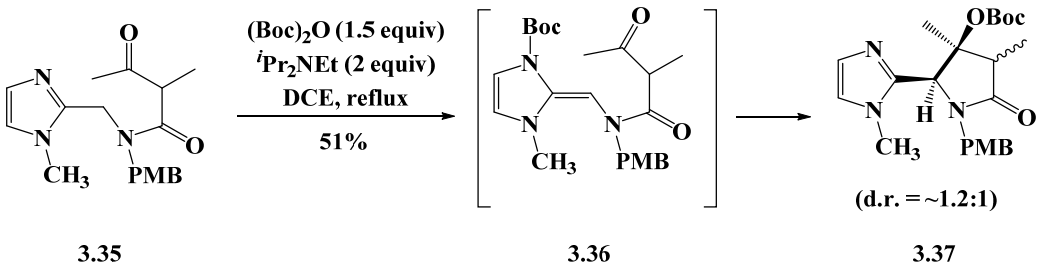
structurally related substrates such as **3.24**, **3.25**, **3.26** and **3.27** afforded intractable reaction mixtures under both sets of conditions.

A common feature in successful intramolecular cyclization reactions involving imidazoline intermediates described above (Schemes 3.2, 3.3 and 3.4) and mechanistically analogous intermolecular transformations of 2-alkylimidazoles reported previously[142-144] is the transfer of an electrophilic activating group (e.g., tert-butoxy carbonyl) from an imidazolium ring to a nucleophilic oxygen generated in the course of aldol-like condensation. Conversion of **3.23** to **3.31**, however, necessitates formation of an intermediate oxyanion that is structurally impeded from participating in an intramolecular acyl transfer involving a Boc-substituted imidazolium species (Scheme 3.10, **3.32**). To probe the importance of this feature in reactions leading to fused-ring imidazo products, 2-unsubstituted imidazoles were treated with $(Boc)_2O$ with the aim of generating nucleophilic acyl imidazolium carbenes capable of participating in intramolecular cyclizations to give oxyanion intermediates.[149-152] Indeed, both **3.28** and **3.29** were transformed to the pyrrolo[1,2-a]imidazoles **3.33**, **3.34** in virtually quantitative yield according to NMR analysis of crude products (Scheme 3.10).



Scheme 3.10 - Intramolecular reactions of N-alkyl-2-H-imidazole substrates

Unfortunately, both compounds (**3.33** and **3.34**) proved to be unstable, readily decomposing upon attempted purification, thus characterization was performed on impure material obtained directly from reaction mixtures. In another set of experiments that were done parallel to this study, transfer of the acyl activating group to an *in situ* generated oxy anion was again observed.[115] When imidazole substrate **3.35** was treated with di-*tert*-butyldicarbonate, nucleophilic alkylidene **3.36** was generated, and product **3.37** was ultimately isolated in moderate yield (Scheme 3.11).



Scheme 3.11 - Intramolecular cyclizations of N-methyl-2-alkyl-imidazole substrates

Therefore, the difference in reactivity between **3.23** and **3.28/3.35** seemingly supports the notion that a pathway for facile conversion of acyl imidazolium intermediates to stable imidazoles is an important parameter for successful intramolecular cyclizations of *in situ* generated 2-alkylidene imidazolines and imidazolium carbenes.

3.3 Conclusion

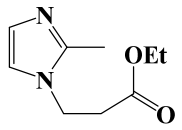
In conclusion, attempts to prepare fused ring imidazo[1,2-a]-dihydropyridines and pyrrolo[1,2-a]imidazoles via intramolecular cyclization of 2-methylimidazoles and 2-unsubstituted imidazoles, respectively, indicate that the ability to regenerate a stable imidazole at the conclusion of the cyclization event by transfer of an acyl activating group to a nucleophilic center in the newly-formed ring may be an important feature of successful transformations. These results show the potential to generate functionalized imidazole derivatives by manipulation of peripheral substituents. Current studies seek to further define the synthetic utility of alkylidene imidazolines in organic and organometallic reaction manifolds.

3.4 Experimental Section

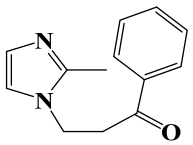
All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds

reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.

Experimental Procedures and Characterization Data for the synthesis of N-Alkylimidazole and N-alkyl-2-methylimidazole substrates:

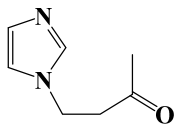


Ethyl 3-(2-methyl-1H-imidazol-1-yl)propanoate (3.25): 2-Methylimidazole (1 g, 12.2 mmol, 1 equiv) and ethyl acrylate (6.5 mL, 61 mmol, 5 equiv) were added to a solution of 1-methylimidazole (50 µL, 0.61 mmol, 0.05 equiv) in DMSO (12 mL) and the mixture was heated at 70 ºC for 1h. Upon the completion of the reaction DMSO was evaporated and the crude mixture was purified by flash column chromatography using 75-100% EtOAc in hexanes as the solvent. **3.25** (1.79 g, 81%) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 – 6.88 (m, 1H), 6.87 – 6.82 (m, 1H), 4.24 – 4.08 (m, 4H), 2.72 (t, J = 6.9 Hz, 2H), 2.40 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 144.6, 127.7, 119.1, 61.3, 41.5, 35.6, 14.3, 13.2. LRMS (ESI) $C_9H_{15}N_2O_2$ $[M+H]^+$, Calculated 183.2; Found 183.1.



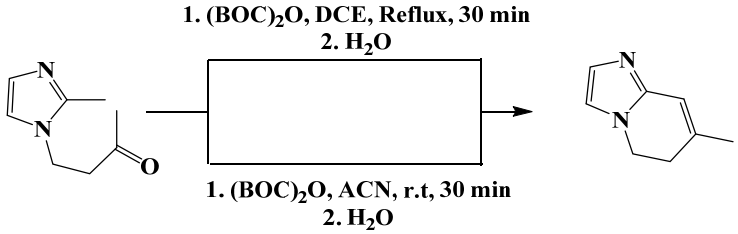
3-(2-Methyl-1H-imidazol-1-yl)-1-phenylpropan-1-one (3.26): Using the procedure described for the preparation of **3.25**, 2-methylimidazole (0.3 g, 3.6 mmol, 1.0 equiv) and 1-phenylprop-2-en-1-one (0.96 g, 7.3 mmol, 2 equiv) were reacted to give **3.26** (0.62 g, 80%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.63 – 7.56 (m,

1H), 7.51 – 7.44 (m, 2H), 6.91 – 6.88 (m, 2H), 4.32 (t, J = 6.9 Hz, 2H), 3.40 (t, J = 6.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 144.7, 136.3, 133.9, 128.9, 128.1, 127.6, 119.3, 40.8, 39.4, 13.2. LRMS (ESI) $C_{13}H_{15}N_2O$ $[M+H]^+$, Calculated 215.3; Found 215.1.



1-(1H-Imidazol-1-yl)pentan-3-one (3.28): Using the procedure described for the preparation of **3.25**, Imidazole (0.2 g, 2.9 mmol, 1.0 equiv) and ethyl vinyl ketone (0.87 mL, 8.8 mmol, 3 equiv) were allowed to react to give **3.28** (0.31 g, 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.02 (s, 1H), 6.92 – 6.89 (m, 1H), 4.24 (t, J = 6.4 Hz, 2H), 2.88 (t, J = 6.4 Hz, 2H), 2.41 (q, J = 7.3 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 137.4, 129.6, 119.1, 43.3, 41.2, 36.5, 7.6. HRMS (ESI) $C_8H_{13}N_2O$ $[M+H]^+$, Calculated 153.1028; Found 153.1019.

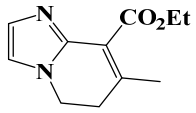
Experimental Procedures and Characterization Data for Intramolecular Cyclizations of N-Alkyl-2-methylimidazole and N-alkylimidazole substrates:



7-Methyl-5,6-dihydroimidazo[1,2-a]pyridine (3.31): 4-(2-Methyl-1H-imidazol-1-yl)butan-2-one (0.05 g, 0.33 mmol, 1.0 equiv) was taken in a 10 mL round bottom flask and dissolved in 1,2-DCE (1 mL). Then $(BOC)_2O$ (83 µL, 0.36 mmol, 1.1 equiv) was added to the reaction mixture. Reaction mixture was heated at reflux for 30 min. After

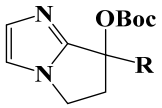
cooling down to room temperature water (2 mL) was added and reaction mixture was extracted with DCM (5 mL x 3). Combined organic layers were dried and concentrated. Crude was then purified via flash column chromatography using 50-100% EtOAc in hexanes as the solvent. **3.31** (0.019 g, 44%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, J = 1.2 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.30 (d, J = 1.25 Hz, 1H), 4.02 (t, J = 7.7 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 1.95 (d, J = 1.25 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 128.2, 117.9, 114.8, 107.4, 42.6, 29.2, 23.0. HRMS (ESI) $C_8H_{11}N_2$ $[M+H]^+$, Calculated 135.0922; Found 135.0902.

Alternatively 4-(2-methyl-1H-imidazol-1-yl)butan-2-one (0.05 g, 0.33 mmol, 1.0 equiv) was taken in a 10 mL round bottom flask and dissolved in ACN (1 mL). Then $(BOC)_2O$ (83 µL, 0.36 mmol, 1.1 equiv) was added to the reaction mixture. Reaction mixture was then stirred at room temperature for 30 min. Then H_2O was added and mixture was extracted with EtOAc (5 mL x 3). Combined organic layers were dried, concentrated and purified via flash column chromatography using 50-100% EtOAc in hexanes as the solvent. **3.31** (0.018 g, 41%) was isolated as a yellow oil.



Ethyl 7-methyl-5,6-dihydroimidazo[1,2-a]pyridine-8-carboxylate (3.30): 4-(2-Methyl-1H-imidazol-1-yl)butan-2-one (0.05 g, 0.33 mmol, 1.0 equiv) was taken in a 10 mL round bottom flask and dissolved in 1,2-DCE (1 mL). Then EtO_2CCl (35 µL, 0.36 mmol, 1.1 equiv) and DIPEA (87 µL, 0.5 mmol, 1.5 equiv) were added to the reaction mixture. Reaction mixture was heated at reflux for 30 min. After cooling down to room temperature water (2 mL) was added and reaction mixture was extracted with DCM (5

mL x 3). Combined organic layers were dried and concentrated. The crude product was then purified via flash column chromatography using 50-100% EtOAc in hexanes as the solvent. **3.30** (0.016 g, 24 %) was isolated as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 1.05 Hz, 1H), 6.79 (d, J = 1.05 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.04 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.06 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 141.9, 137.9, 129.2, 122.1, 118.4, 61.3, 41.9, 30.5, 20.7, 14.3. HRMS (ESI) $C_{11}H_{15}N_2O_2$ $[M+H]^+$, Calculated 207.1134; Found 207.1115.



3.33 R = Me
3.34 R = Et

tert-Butyl (7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-7-yl) carbonate (3.33): 4-(1H-Imidazol-1-yl)butan-2-one (0.1 g, 0.72 mmol, 1 equiv) was dissolved in ACN (2 mL) and $(BOC)_2O$ (0.18 mL, 0.79 mmol, 1.1 equiv) was added to it. Reaction mixture was then stirred at room temperature for 12h. Once the reaction is completed ACN was evaporated to dryness and **3.33** (0.171 g, 100%) was isolated as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.13 (m, 1H), 6.88 – 6.87 (m, 1H), 4.25 – 4.18 (m, 1H), 3.97 – 3.91 (m, 1H), 3.12 – 3.05 (m, 1H), 2.77 – 2.70 (m, 1H), 1.85 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 152.1, 134.5, 114.9, 82.3, 79.2, 42.9, 41.0, 27.9, 25.3. HRMS (ESI) $C_{12}H_{19}N_2O_3$ $[M+H]^+$, Calculated 239.1396; Found 239.1392.

tert-Butyl (7-ethyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-7-yl) carbonate (3.34): Using the procedure described for the preparation of **3.33**, 1-(1H-imidazol-1-yl)pentan-3-one (0.05 g, 0.33 mmol, 1 equiv) and $(BOC)_2O$ were reacted to give **3.34** (0.082 g,

100%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 1.1 Hz, 1H), 6.88 (d, J = 1.1 Hz, 1H), 4.22 (ddd, J = 10.4, 8.6, 6.1 Hz, 1H), 3.93 (ddd, J = 10.4, 8.9, 3.6 Hz, 1H), 2.97 (ddd, J = 14.4, 8.6, 3.6 Hz, 1H), 2.79 (ddd, J = 14.6, 8.9, 6.1 Hz, 1H), 2.17 (qd, J = 7.4, 2.8 Hz, 2H), 1.40 (s, 9H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 152.1, 134.3, 114.7, 82.10, 82.14, 43.0, 38.6, 31.6, 27.8, 8.1. HRMS (ESI) $C_{13}H_{21}N_2O_3$ $[M+H]^+$, Calculated 253.1552; Found 253.1545.

Chapter Four

Model Studies Toward the Synthesis of the Bis(piperidine) Alkaloid Xestoproxamine C[3]

4.1 Introduction

The bis(piperidine) alkaloids are a collection of marine sponge metabolites isolated from different species of the order Haplosclerida, and include haliclonacyclamines A-F,[153-155] halicyclamines A and B,[121,156,157] arenosclerines A-E,[122,158] halichondramine,[159] neopetrosiamine A,[123] acanthocyclamine A,[160] and xestoproxamines A-C.[161] Some of these natural alkaloids (mainly the halicyclamines and the haliclonacyclamines) have been found to display promising cytotoxicity toward various cancer cell lines, along with antibacterial (anti-tubercular) activity.[119] However, biological activity of many of these natural products has not yet been fully evaluated. Representative examples of these natural products are illustrated in Figure 4.1 and highlight several distinguishing structural features. All the bis(piperidine) alkaloids possess tetracyclic ring systems with covalently linked 3,4'-bis(piperidine) rings at the core. The piperidine rings are additionally linked through two macrocycles that change in terms of size, unsaturation, and substitution, according to the identity of the metabolite. Furthermore, the relative (and absolute) stereochemistry of the methine carbons distributed with in the piperidine rings differentiates individual members. For example, both haliclonacyclamine A (**4.1**) and xestoproxamine C (**2.38**) exhibit an all-*cis* relative configuration of four piperidine methine hydrogens (although these two compounds

[3] This chapter is adapted from a published manuscript: Lansakara, A. I.: Mariappan, S. V. S.; Pigge, F. C. *J. Org. Chem.* **2016** doi: 10.1021/acs.joc.6b01269.

possess opposite absolute stereochemistry – all (R) in **4.1** and all (S) in **2.38**). In contrast, arenosclerin B (**4.2**) exhibits a "*cis*-anti-*cis*" array of stereogenic centers, while some other bis(piperidine) alkaloids feature *trans*-substituted piperidine rings (e.g., halicyclamine A).

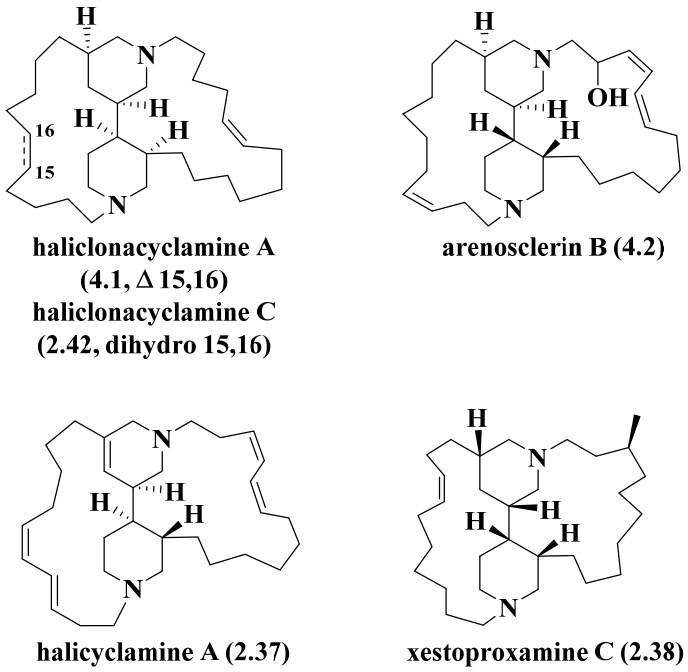
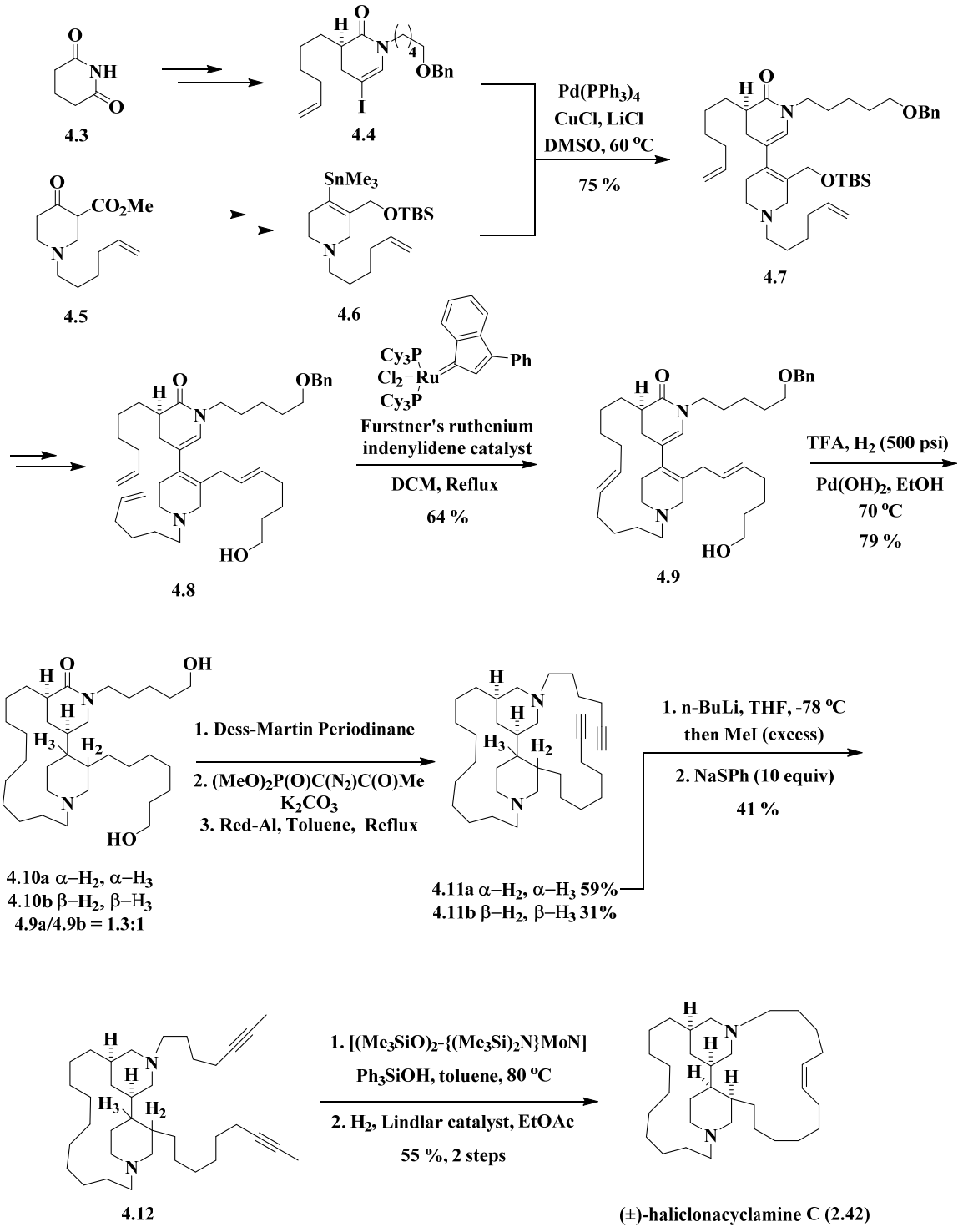


Figure 4.1 - Representative examples of bis(piperidine) alkaloids

These bis(piperidine) alkaloids are postulated to be biogenetically related to other important 3-alkyl pyridine/piperidine alkaloids also isolated from Haplosclerids, such as manzamines, sarines, and madangamines.[162] All of these compounds are envisioned to arise from biosynthetic pathways involving intramolecular cycloaddition of macrocyclic bis(dihydropyridines), and several biogenetically-inspired approaches to truncated models of the halicyclamine ring systems have been reported.[163] The total synthesis of these bis(piperidine) alkaloids, however, has not received a great deal of attention, despite their interesting structures and bioactivity profiles. To date, the racemic synthesis of only one

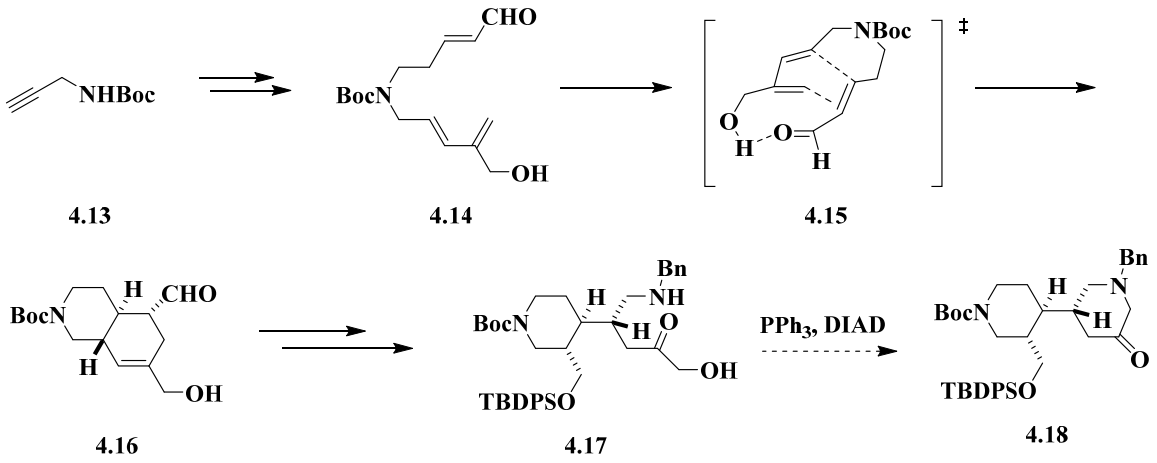
member of the family, haliclonacyclamine C (**2.42**) has been successfully completed as reported by Sulikowski in 2010.[125] The key features of this synthesis are outlined in Scheme 4.1. Synthesis was started with a six-step preparation of 3-iodoenamide **4.4** from glutarimide (**4.3**), which was used as one of two piperidine units for a cross-coupling reaction leading to formation of **4.7**. Stannane **4.6** was derived from β-keto ester **4.5**. A Pd catalyzed cross-coupling reaction was performed using copper(I) chloride as an accelerant and furnished bis(piperidine) **4.7** in good yield. This Stille coupling reaction was a key step in their synthesis of (±)-haliclonacyclamine C to construct the bis(piperidine) framework in good yield. Intermediate **4.7** was converted to **4.8** through use of another Stille coupling reaction. A ring closing metathesis (RCM) reaction was carried out using Furstner's ruthenium indenylidene catalyst to afford **4.9** in good yield. Exhaustive hydrogenation **4.9**.TFA at 500 psi in EtOH over Pearlman's catalyst at 70 ºC for 8 days led to an inseparable 1.3:1 mixture of two isomers that were tentatively assigned **4.10a** and **4.10b**, respectively. The mixture of diols (**4.10**) was then converted to the bis(aldehyde), which was then treated with excess of the Bestmann-Ohira reagent to afford a mixture of diynes. Reduction of the lactam carbonyl with Red-Al gave a now separable mixture of amines **4.11a** and **4.11b**. Bis(methylation) of terminal alkyne **4.11a** was invariably accompanied by N-methylation to give quaternary salt, which was then reacted with sodium thiophenoxide to afford the diamine **4.12**. Then compound **4.12** was subjected to ring closing alkyne metathesis (RCAM) followed by semihydrogenation of the cycloalkyne with Lindlar catalyst to afford haliclonacyclamine C (**2.42**). Furthermore, the synthetic route developed in this effort was also subsequently applied to the construction of fully saturated racemic tetrahydrohaliclonacyclamine A.[164]

A key transformation in Sulikovski's synthesis was the hydrogenation leading to a mixture of **4.10a** and **4.10b**. The diastereoselectivity of this reduction was disappointing, resulting in almost half of the material featuring the wrong relative stereochemistry about the bis(piperidine) core. From a total synthetic standpoint this is not a desirable outcome and detracts from the efficiency of the preparative route. We hope to address this shortcoming through design of an alternative approach to these alkaloids as described below.



Scheme 4.1 - Total synthesis of (±)-haliclonacyclamine C

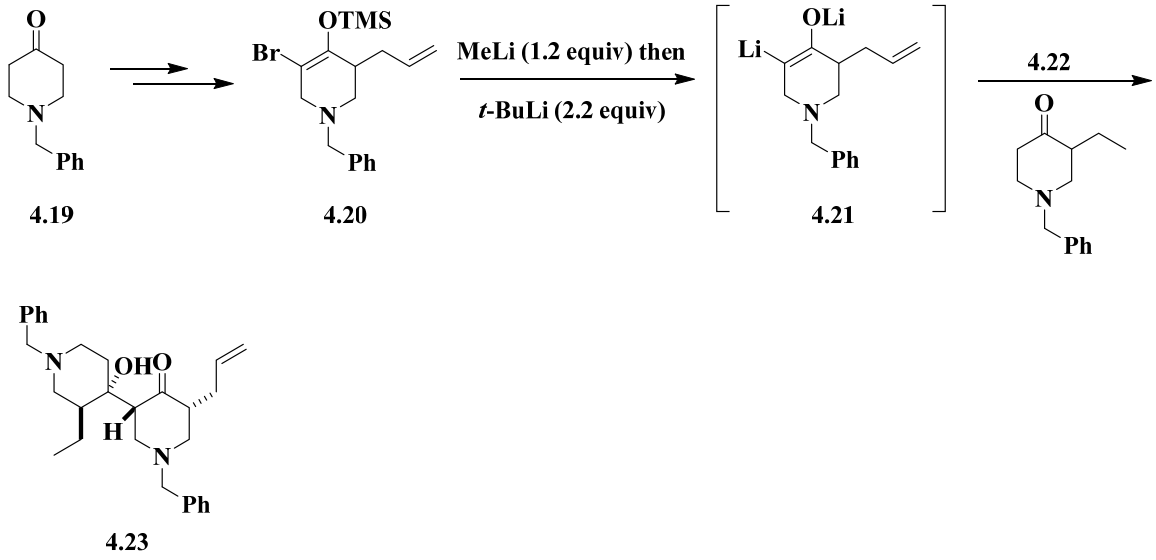
Apart from these studies, only two additional reports describing approaches to functionalized bis(piperidine) ring systems have appeared. Molander and coworkers described a diastereoselective approach to bis(piperidine) core of halicyclamine A which envisioned using a Diels-Alder cycloaddition to establish the correct relative stereochemistry within the piperidine rings (Scheme 4.2).[165] Boc-protected propargyl amine (**4.13**) was converted to intermediate product **4.14** which was the substrate needed for the Diels Alder reaction. The attempted reaction worked well resulting in only one diastereomer (via **4.15**) of the bicyclic alcohol **4.16**. Further manipulation of **4.16** gave **4.17** which contains the stereogenic triad of halicyclamine A. Attempted transformation of **4.17** into **4.18** via a Mitsunobu reaction to synthesize the second piperidine ring was not successful.



Scheme 4.2 - Synthesis of the stereogenic triad of the halicyclamine A core

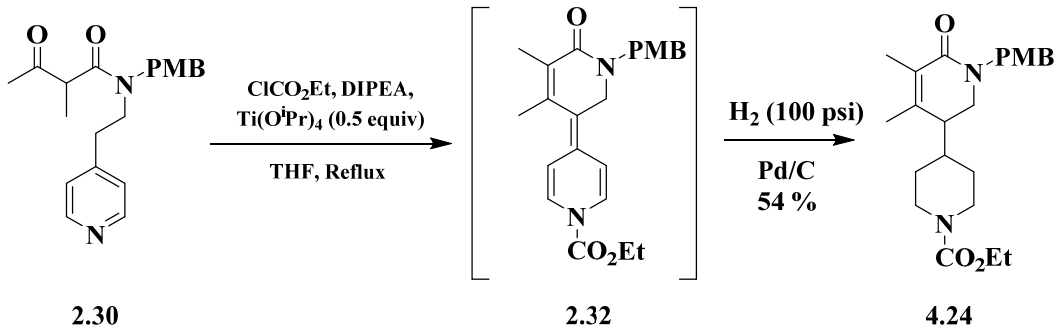
Banwell, *et al*. examined the feasibility of crossed aldol condensation between substituted 4-pyridinones as a means to 3,4' bis(piperidine) derivatives (Scheme 4.3).[166] Piperidinone **4.19** was converted into **4.20** via multiple chemical transformations. Then

4.20 was treated sequentially with methyl lithium followed by *t*-butyllithium, and the resulting α-keto dianion **4.21** was trapped with 1-benzyl-3-ethyl-4-piperidinone (**4.22**) which resulted in formation of β-hydroxyketone **4.23** along with other separable diastereomers.



Scheme 4.3 - Synthesis of 3,4'-linked bis(piperidines) by Banwell

Notably, in the Pigge group, anhydrobase-mediated pyridine benzylic cyclization in tandem with catalytic hydrogenation for direct conversion of pyridine substrates to functionalized piperidines (e.g., **2.30** to **4.24** via aldol-like condensation intermediate **2.32**, Scheme 4.4) has been performed.[117] Thus, when applied to an aminoethyl pyridine such as **2.30**, this sequence delivers products (**4.24**) that may serve as precursors to 3,4'-linked bis(piperidine) derivatives.



2.30 **2.32** **4.24**

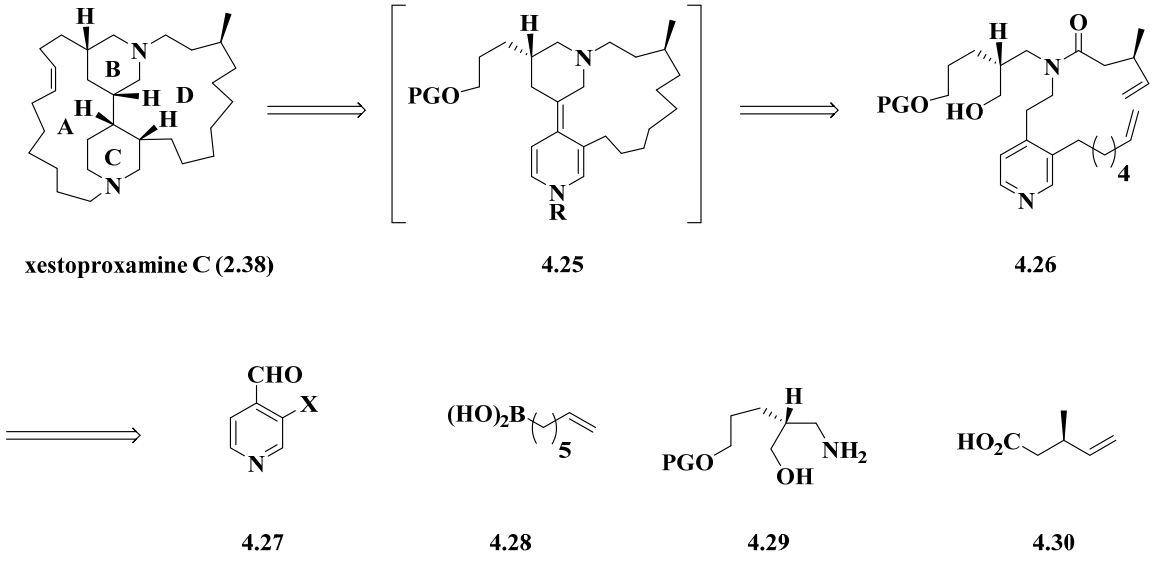
Scheme 4.4 - Generation and manipulation of alkylidene dihydropyridines

Moreover, stereoselectivity inherent in heterogeneous catalytic hydrogenation may provide a convenient means to control relative stereochemistry in substituted bis(piperidines) prepared through this sequence, avoiding a major shortcoming of the Sulikowski approach. Consequently, a study was initiated to apply this chemistry in the stereoselective asymmetric total synthesis of bis(piperidine) alkaloids, and xestoproxamine C was selected as the initial target. Described herein are the results of model studies that demonstrate the feasibility of this approach.[167]

4.2 Results and Discussion

A retrosynthetic analysis of xestoproxamine C is shown in Scheme 4.5. The diastereoselective hydrogenation of alkylidene dihydropyridine **4.25** (equipped with two of the five stereogenic centers present in the target) is envisioned to be the key transformation leading to the desired relative and absolute stereochemistry found in **2.38**. The final macrocyclic ring (A ring) can then be constructed using ring-closing metathesis (RCM). Macrocycle ring D should also be accessible via RCM on pyridine derivative **4.26**, either before or after pyridine benzylic cyclization to assemble ring B of the bis(piperidine) ring system. In turn, construction of **4.26** is expected to be achieved from

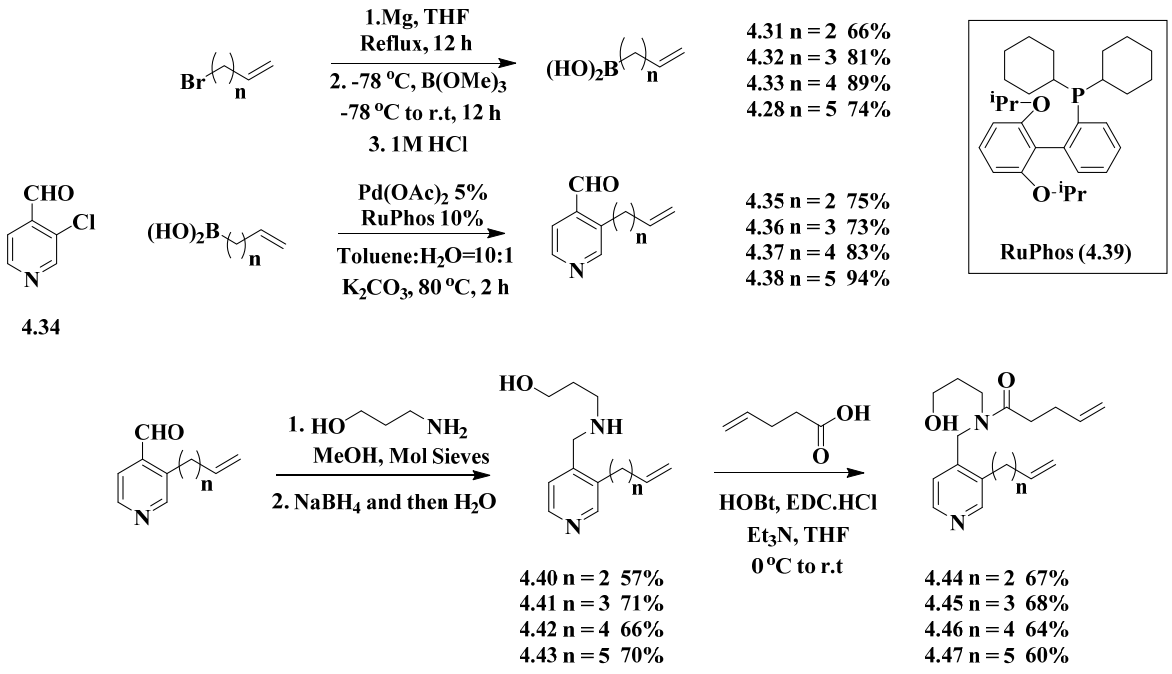
readily available starting fragments **4.27-4.30**. Significantly, the modular synthetic design implemented in this study should facilitate construction of other bis(piperidine) alkaloids, as well as numerous unnatural analogues in which the size, unsaturation, and substitution of the macrocyclic rings can be varied, along with the identity of the central B-C ring system (e.g., pyrrolidine-piperidine analogues).



Scheme 4.5 - Retrosynthetic analysis of xestoproxamine C

The objectives of these model studies were to demonstrate the general advantages of our modular design and, more specifically, the feasibility of preparing a tricyclic alkylidene dihydropyridine resembling **4.25** and its successful conversion to a saturated bis(piperidine) derivative. To address the first objective, pyridine macrocycles were prepared via ring closing metathesis (RCM) of 3,4-disubstituted pyridines. Initial attempts to construct metathesis substrates from 3-bromo-4-pyridine carboxaldehyde proved problematic as attempted B-alkyl Suzuki coupling with alkyl pinacol boronic esters and various combinations of Pd complex ($Pd(PPh_3)_4$, $Pd(OAc)_2$), ligand (PPh_3,

PCy_3, JohnPhos, DavePhos, MePhos, dppf), solvent (THF/H_2O, dioxane/H_2O, PhMe/H_2O), and K_2CO_3 failed to give the desired coupling product. Use of reaction conditions reported by Molander to be effective for B-alkyl Suzuki couplings of aryl chlorides, however, worked well when applied to less expensive 3-chloropyridine-4-carboxaldehyde in combination with alkyl boronic acids **4.28, 4.31, 4.32,** and **4.33**.[168] The 3-alkylpyridines **4.35 – 4.38** were isolated in good to excellent yield (Scheme 4.6). Direct reductive amination of the aldehyde group in **4.35 – 4.38** with 3-aminopropanol followed by acylation with 4-pentenoic acid gave a homologous series of RCM substrates from which various unnatural analogues of bis(piperidine) alkaloids might be constructed (Scheme 4.6).

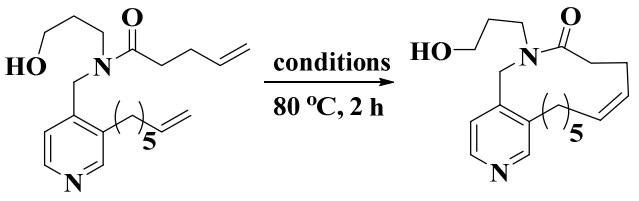


Scheme 4.6 - Synthesis of 3-alkenylpyridines via Suzuki coupling

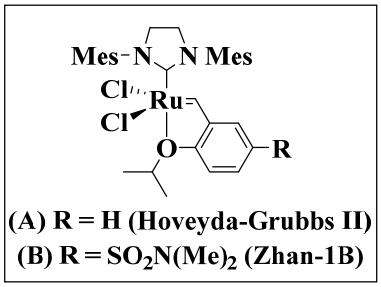
3-Alkylpyridine **4.47** was selected for initial screening of RCM reaction conditions (Table 4.1). Preliminary experiments were performed using both Grubbs-II

and Hoveyda-Grubbs-II catalysts, but the Zhan-1B catalyst was ultimately selected for optimization owing to its greater air-stability and lower cost. Not surprisingly, high dilution reaction conditions proved to be critical for successful macrocyclization (entries 3-6). Catalyst quenching with a vinyl ether additive prior to concentration of reaction mixtures was also important to obtain the desired macrocycle in high isolated yield (entries 3 vs 4).[169] This was further confirmed by development of baseline material (presumably formation of oligomers via further reactions due to the active catalyst) on TLC upon concentration of the reaction mixture without any catalyst quenching. The best reaction conditions uncovered in this screen are indicated in entry 6 and feature continuous slow syringe-pump addition of catalyst to a 0.0005 M solution of **4.47** in toluene at 80 °C. Macrocyclization was complete in 2 h under these conditions and, after catalyst quenching, **4.48** was isolated in excellent 92% yield as a mixture of *E* and *Z* isomers (Assignment of E/Z ratio was confounded by overlapping signals and the presence of amide rotamers in the ^{1}H-NMR spectrum.). In addition to *E* and *Z* isomers, amide rotamers were also observed in the ^{1}H and ^{13}C spectra. It was concluded that the presence of the macrocycle in the system was causing hindered rotation around the amide resulting rotamer behavior on the NMR time scale. Notably, neither the pyridine nitrogen nor the Lewis basic amide functional group appear to interfere with metathesis.

Table 4.1 - Screening of RCM macrocyclization



4.47 4.48



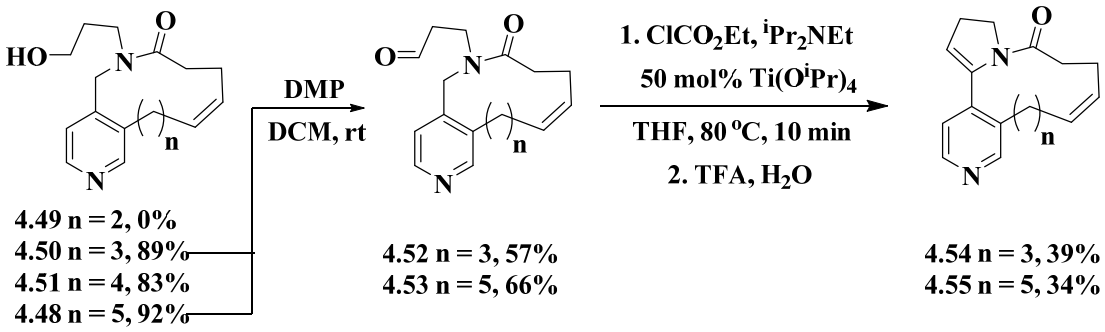
(A) R = H (Hoveyda-Grubbs II)
(B) R = $SO_2N(Me)_2$ (Zhan-1B)

Entry	Catalyst[a]	Solvent	[**4.36**] (mM)	% Yield
1	**A**	DCE[b]	1.5	42
2	**B**	DCE	1.5	51[c]
3	**B**	DCE	0.5	59
4	**B**	DCE	0.5	72[d,e]
5	**B**	Toluene	0.5	66[d,f]
6	**B**[g]	Toluene	0.5	92[d]

[a]Catalyst loading: 3 mol%. [b]1,2-Dichloroethane. [c]Based on 22% recovered **4.47**. [d]Catalyst quenched by addition of diethylene glycol vinyl ether prior to concentration. [e]Based on 26% recovered **4.47**. [f]Based on 20% recovered **4.47**. [g]Continuous slow addition of catalyst (syringe pump).

The remaining macrocyclization substrates **4.44 – 4.46** were also subjected to the RCM reaction conditions highlighted in Table 4.1, entry 6. As indicted in Scheme 4.7, 3-butenylpyridine derivative **4.44** was not converted to the corresponding 11-membered macrocycle, and only formation of intractable materials (presumably oligomers) was observed. The pentenyl- and hexenyl-substituted pyridines, however, underwent smooth

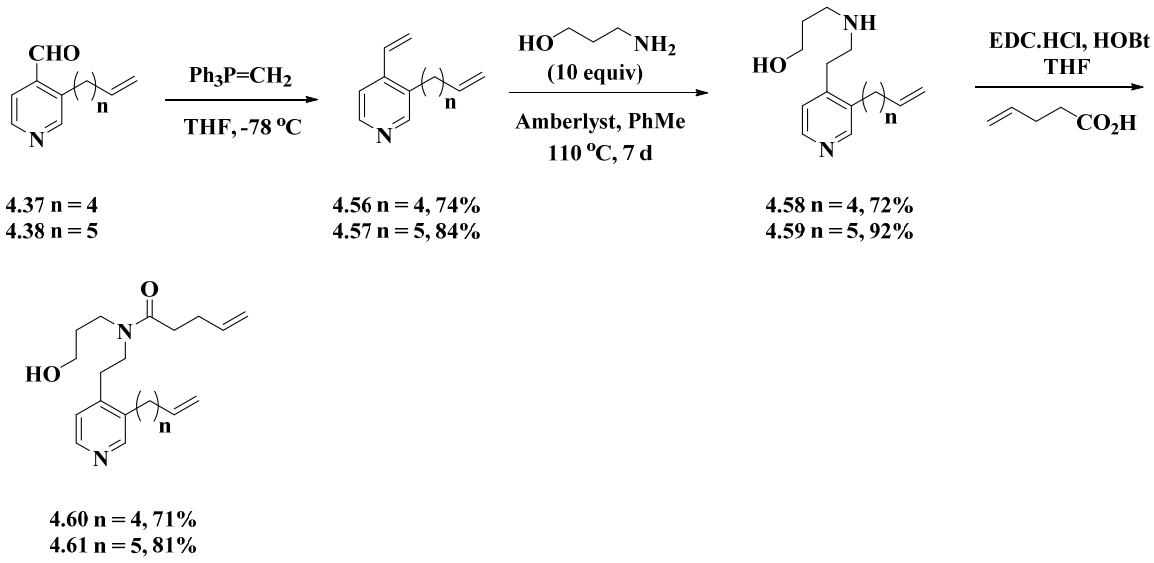
cyclization to afford **4.50 – 4.51** in high yield. Pyridine macrocycles **4.48** and **4.50** were further transformed via alcohol oxidation in the presence of the Dess-Martin periodinane (DMP) to somewhat unstable aldehydes **4.52 – 4.53**. Exposure of these aldehydes to reaction conditions previously developed in our laboratory for intramolecular benzylic cyclization of 4-alkylpyridines via generation of alkylidene dihydropyridine intermediates (see Scheme 4.2)[117] followed by acidic workup conditions to rearomatize the pyridine ring afforded **4.54** and **4.55** in comparable, albeit modest, isolated yields (Scheme 4.7). Nonetheless, the concise (six step) synthesis of tricyclic pyridines **4.54 – 4.55** offers rapid access to structural mimics of the BCD ring systems found in bis(piperidine) alkaloids, and should facilitate future construction of additional and more advanced analogues.



Scheme 4.7 - Synthesis of pyridine-dehydropyrrolidine derivatives

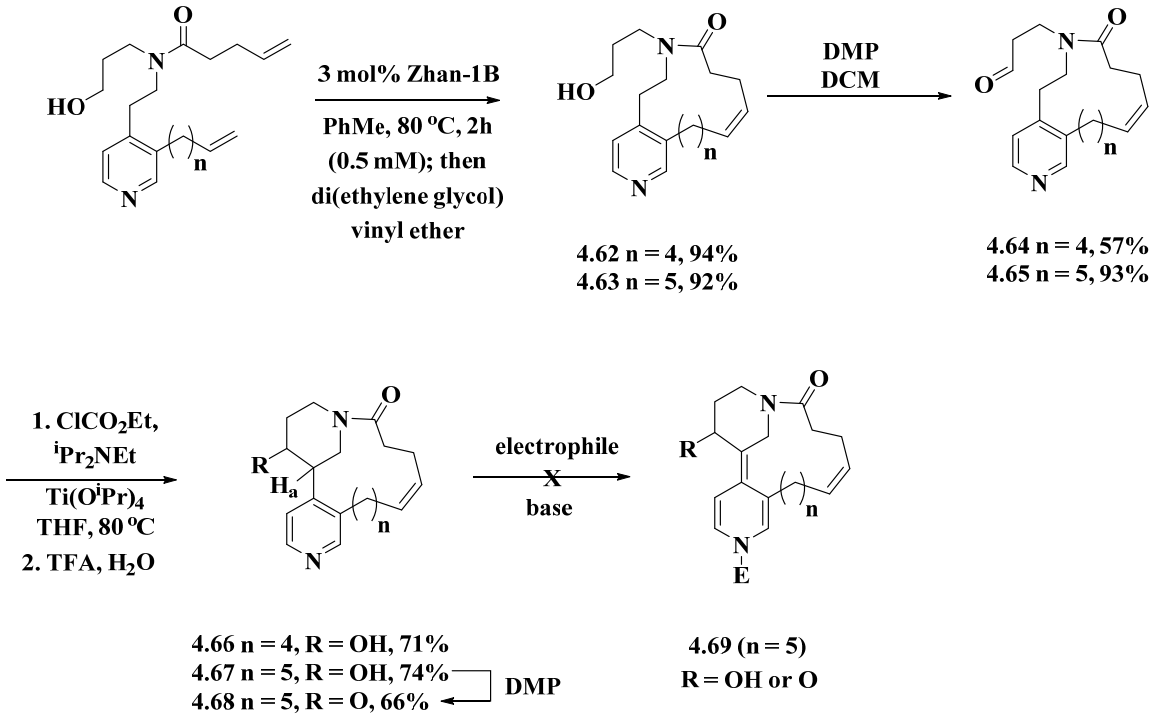
Next, substrates for RCM macrocyclization that would ultimately afford polycyclic products more closely resembling the ring systems encountered in **2.38** were prepared (Scheme 4.6). This required access to 4-(aminoethyl)pyridines, which were envisioned to be obtained by homologation and amination of 3-alkylpyridine-4-carboxaldehydes. Indeed, a straightforward method to achieve this goal starting from **4.37** or **4.38** entailed a Wittig reaction to give the corresponding 4-vinylpyridines (**4.56** and

4.57) in good yields. These vinyl pyridines were subjected to hydroamination with aminopropanol under acidic conditions (Scheme 4.8) to afford **4.58** and **4.59**. Various Brønsted acids (such as AcOH, TFA, CF_3SO_3H) in both catalytic and stoichiometric amounts were tested for this reaction. Surprisingly no product formed and starting materials were recovered without any significant loss. When Amberlyst was employed as a catalyst (0.1 % w.r.t mass of the starting material) the desired product was obtained in a very low yield over a period of 7 days. When the catalyst quantity was increased (100 % w.r.t mass of the starting material) a much faster reaction was observed with improved yield in addition to a small amount of starting material remaining. With the use of a large excess of aminopropanol (10 equiv), the reaction went to completion and amines **4.58** and **4.59** were each obtained in good isolated yield over the two steps. Then acylation with 4-pentenoic acid afforded **4.60** and **4.61** in good isolated yields.



Scheme 4.8 - Synthesis of aminoethylpyridine substrates for RCM

RCM of the substrates **4.60** and **4.61** using the reaction conditions developed in the (aminomethyl)pyridine series (Table 4.1, entry 6) proceeded smoothly (yields for the RCM step > 90% in each case), affording macrocycles **4.62** and **4.63**. It is noteworthy that the 15-membered macrocycle in **4.63** matches the size of the D ring macrocycle in xestoproxamine C (**2.38**) and related bis(piperidine) alkaloids. Dess-Martin oxidation of **4.62**/**4.63** afforded the corresponding aldehydes (of limited stability), which were then directly exposed to electrophile activation/anhydrobase formation/intramolecular cyclization to give the linked piperidine – pyridine derivatives **4.66** and **4.67** in good yields. Unlike similar cyclizations that generate 5-membered unsaturated aza-heterocycles, elimination of water did not occur in these reactions, and **4.66**/**4.67** were obtained as diastereomeric mixtures of secondary alcohols (Scheme 4.9).

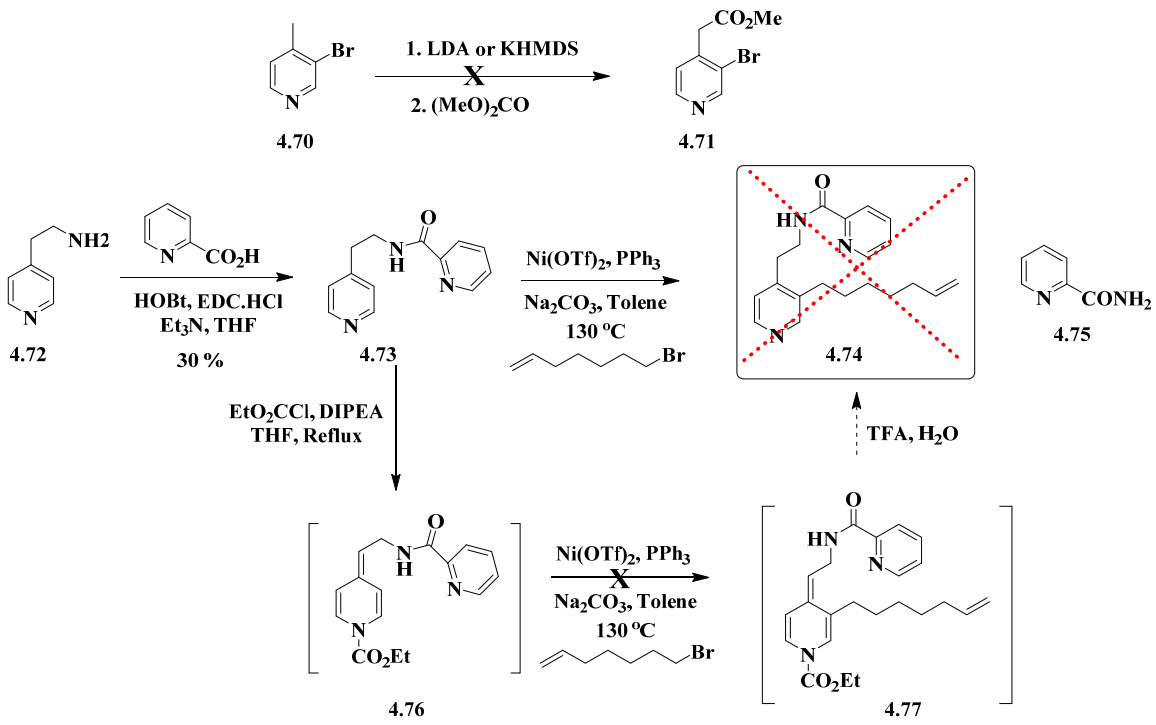


Scheme 4.9 - Initial approach to bis(piperidine) alkaloid ring systems

Unfortunately, attempted conversion of **4.67** to an observable alkylidene dihydropyridine (i.e., **4.69**) that might then be subjected to hydrogenation was unsuccessful. These efforts involved treating **4.67** first with an acyl ($ClCO_2Et$) or alkyl (MeI, BnBr) electrophile to form putative pyridinium salts (formation of the pyridinium salt was evident by NMR), followed by treatment with various bases (Et_3N, $^iPr_2NEt$, NaH). Monitoring reactions by TLC and NMR, however, presented no evidence for the formation of **4.69**. Likewise, conversion of **4.67** to ketone **4.68**, followed by attempted generation of anhydrobase **4.69** also failed, despite the presumably more activated benzylic hydrogen in **4.68**. It was speculated that the inability to obtain **4.69** from either **4.67** or **4.68** stems from conformational constraints in the tricyclic ring system that impede alignment of the benzylic hydrogen (H_a) with the pyridine π-system in an orientation conducive to deprotonation. Molecular modeling studies (Spartan) performed on a simpler analogue of **4.67** were consistent with this notion as the ground state conformation of the molecule featured an approximately 90° angle between the piperidine and pyridine rings. This conformation places H_a roughly in the plane of the pyridine and thus mandates that the molecule undergo significant conformational changes to achieve the pyridine/piperidine coplanar alignment leading to anhydrobase **4.69**. Further evidence in support of this notion is found in the crystal structure of a closely related compound (**4.89**), as discussed below. Notably, a similar ~90° angle between piperidine rings has been observed in the actual bis(piperidine) alkaloid natural products.[121-123,153-161]

Failure to generate alkylidene dihydropyridine **4.69** coupled with the unattractive hydroamination transformation utilized in the preparation of **4.66**/**4.67** prompted re-examination of the initial synthetic route to macrocyclic bis(piperidine) scaffolds.

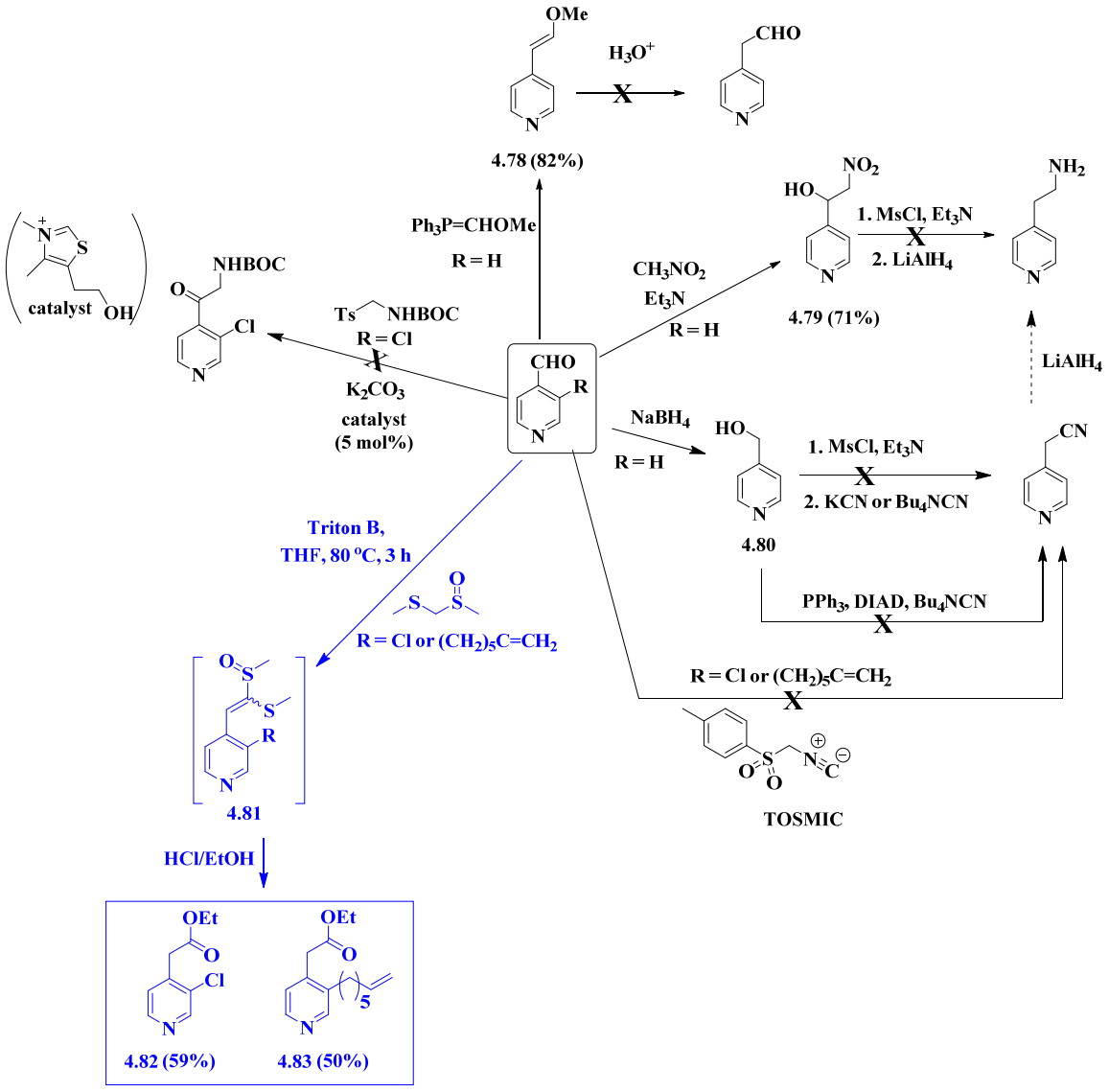
Additionally alternative methods for homologation of pyridine-4-carboxaldehyde and other related derivatives that would deliver products amenable to eventual elaboration into 4-(aminoethyl)pyridines was attempted, as summarized in Schemes 4.10 and 4.11. First, simple deprotonation of 3-bromo-4-methylpyridine (**4.70**) to generate a nucleophile followed by reaction with dimethylcarbonate gave no desired product. Only the starting pyridine substrate was recovered. Then, possible routes via C-H activation of pyridine substrate **4.73** were attempted. Compound **4.73** was synthesized via acid coupling from commercially available aminoethylpyridine and 2-picoloinic acid. When conditions reported by Chatani[170] were applied to effect C-H activation of **4.73**, no desired product (**4.74**) was observed. But formation of 2-picolinamide (**4.75**) was observed under these conditions. It was concluded that coordination of the aminoethylpyridine 'N' atom of **4.73** is interfering with the desired reaction and hence resulting in 2-picolonimaide as the only observed product. Therefore, this reaction was attempted on substrate **4.76** which is the corresponding anhydrobase of **4.73** formed from our previously reported conditions.[117] No reaction was observed and decomposition of the anhydrobase over time was seen by TLC.



Scheme 4.10 - Attempts to synthesize aminoethylpyridine derivatives

We then turned to manipulation of pyridine-4-carboxaldehydes as a means to prepare 4-aminoethylpyridines (Scheme 4.11). A Wittig reaction between pyridine-4-carboxaldehyde and (methoxymethylene)phosphorane gave vinyl ether **4.78** in good yield, but all attempts to hydrolyze this material to the corresponding aldehyde returned intractable reaction mixtures. Similarly, pyridine carboxaldehyde underwent smooth nitro-aldol reaction to give the known nitro alcohol **4.79**,[171,172] but we were unsuccessful in converting this compound to 4-(aminoethyl)pyridine via reduction of an intermediate nitroethylene. Moreover, simple S_N2 displacement of hydroxyl group of 4-hydroxymethylpyridine (**4.80**) by a nucleophile such as cyanide to construct the corresponding 2-(pyridin-4-yl)acetonitrile also failed. Efforts to react 3-chloro-4-pyridinecarboxaldehyde (**4.34**) with toluenesulfonylmethyl isocyanide (TOSMIC) gave

intractable product mixtures. Attempted thiazolium catalyzed aza-benzoin condensation between 3-chloropyridine-4-carboxaldehyde (**4.34**) and a BOC-protected imine (generated *in situ*) also failed.[173] Encouragingly, however, homologation of both 3-chloropyridine-4-carboxaldehdye (**4.34**) and 3-heptenylpyridine-4-carboxaldehyde (**4.38**) with formaldehyde dimethyl thioacetal monoxide (FAMSO) followed by immediate hydrolysis of the resulting dithio ketene acetal with anhydrous HCl in ethanol gave the pyridine acetic acid esters **4.82** and **4.83** in serviceable yield.[174]

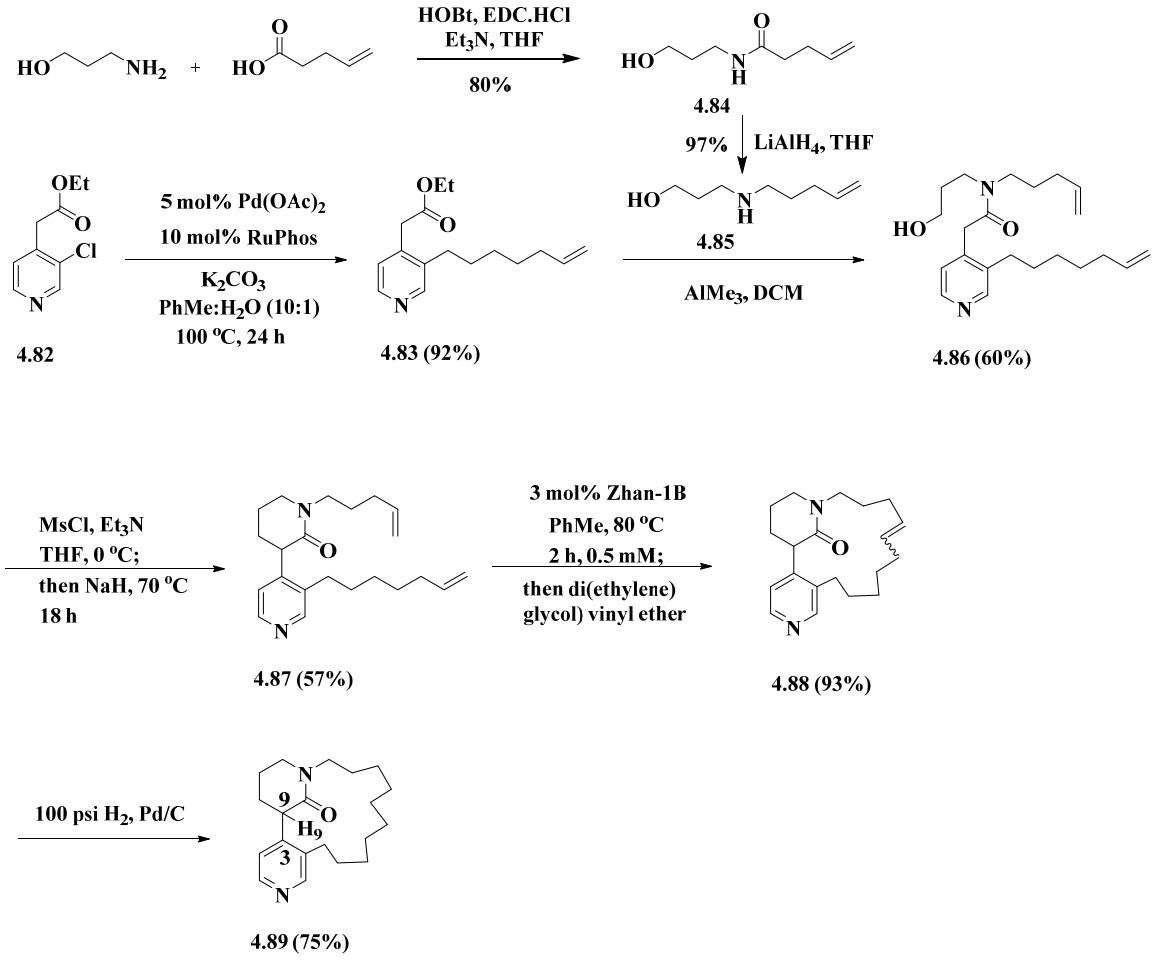


Scheme 4.11 - Homologation of pyridine-4-carboxaldehyde derivatives

It was envisioned that the ester moiety in **4.82** or **4.83** would serve as a convenient handle for introduction of a substituted nitrogen appropriately positioned for eventual construction of 3,4'-bis(aza-heterocycles) as required in xestoproxamine C. Thus, model studies were continued with 3-chloropyridine **4.82**. B-Alkyl Suzuki coupling under the conditions outlined above (see Scheme 4.4) gave **4.83** in excellent yield, although a

longer reaction time was required for completion compared to Suzuki coupling of **4.35** (Scheme 4.12). Ester **4.83** was then treated with secondary amine **4.85** in the presence of $AlMe_3$ to give bifunctional amide **4.86** equipped with functional groups to enable both piperidine ring construction and macrocyclization. Since the pyridine benzylic position is additionally activated by the amide carbonyl, it was envisioned to attempt 6-membered ring closure first via simple intramolecular alkylation of an alkyl electrophile generated *in situ*. In the event, **4.86** was treated with $MsCl/Et_3N$ to convert the alcohol to the corresponding mesylate. Monitoring the reaction by TLC and NMR, however, indicated the initially-formed mesylate was slowly converted to the alkyl chloride under the reaction conditions. Addition of NaH with heating facilitated intramolecular alkylation to give **4.87**. Ring-closing metathesis proceeded as expected to afford a macrocyclic alkene (**4.88**, presumably as a mixture of *E*/*Z* diastereomers), and was followed by reduction of the olefin to provide **4.89** in good yield for the two steps. Notably, the ^{1}H-NMR of **4.89** exhibited somewhat broadened signals (especially in the aliphatic region) that we attribute to hindered rotation about the C3-C9 bond (i.e., atropisomerism). The structure of **4.89** was definitively established through X-ray diffractometry performed on a crystal of **4.89**·HCl, obtained from slow evaporation of a solvent mixture of $CHCl_3$ and EtOAc (Figure 4.2, This structure has been deposited with the Cambridge Crystallographic Data Center, CCDC 1481779). The molecular structure of the cation clearly reveals the ~90° angle between the pyridine and piperidinone rings that places the H9 hydrogen parallel to the plane of the pyridine ring. Consideration of the structure also highlights the likelihood of atropisomerism in the molecule as free rotation about the pyridine-piperidinone bond

would clearly engender severe strain, thus only limited rotation that involves passing the lactam carbonyl through the mean plane of the macrocyclic ring is possible.



Scheme 4.12 - Second-generation approach to bis(piperidine) BCD ring system

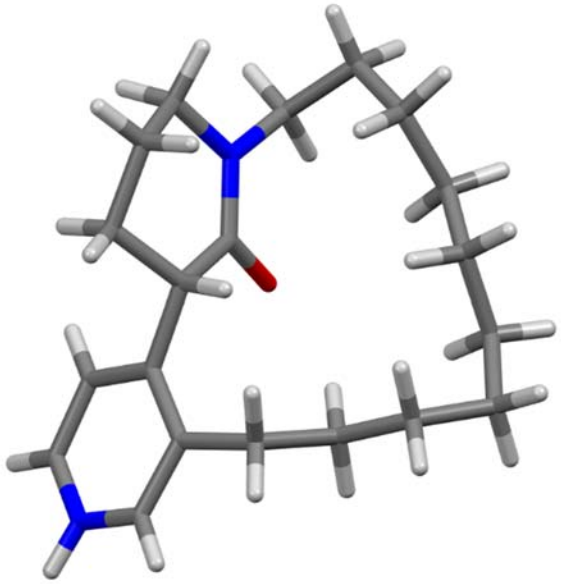
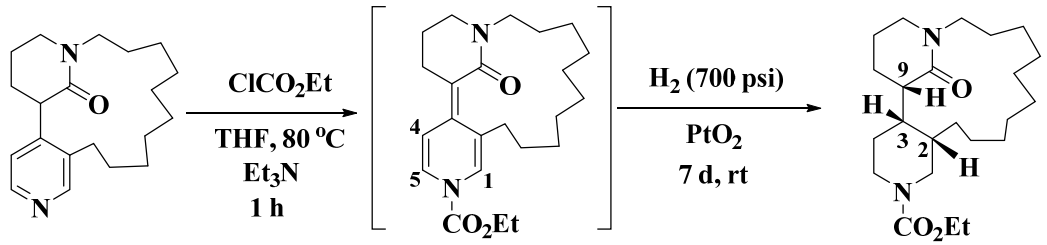


Figure 4.2 - Molecular structure of **4.89**.HCl determined from X-ray crystallography. Chloride anion omitted

Amide **4.89** presents an alternative substrate on which to attempt conversion to a bis(piperidine) system via reduction of the corresponding alkylidene dihydropyridine. Unlike substrates **4.66**/**4.67** (Scheme 4.9), **4.89** features a completely saturated 10-carbon macrocyclic linker between the pyridine and piperidinone rings that is expected to impart greater conformational flexibility to the tricyclic ring system. Additionally, an amide carbonyl is positioned to assist in benzylic deprotonation and provide extended conjugation in any putative anhydrobase intermediate. Gratifyingly, exposure of **4.89** to $ClCO_2Et$ and Et_3N in refluxing THF gave rise to a new nonpolar species (**4.90**) with a TLC profile in line with other pyridine anhydrobases generated in our laboratory (Scheme 4.13). Moreover, the ^{1}H-NMR spectrum of the crude reaction mixture revealed the clear presence of dihydropyridine resonances at 7.22 and 7.09 ppm, corresponding to the hydrogens at C1 and C5, along with a signal at 6.06 ppm corresponding to the hydrogen

at C4. Each of these signals was observed as a broad singlet due to the presence of amide rotamers arising from the NCO_2Et moiety. Without further characterization, **4.90** was subjected to heterogeneous hydrogenation over PtO_2. The course of reduction over time was monitored by NMR, LRMS and it was observed that hydrogenation of the dihydropyridine olefins occurred first, followed by much slower reduction of the tetrasubstituted alkene. After 7 days the reaction appeared to be complete, and bis(piperidine) analogue **4.91** was isolated after filtration to remove the catalyst and purification by flash column chromatography.



Scheme 4.13 - Formation and hydrogenation of alkylidene dihydropyridine **4.91**

Assignment of the relative stereochemistry in **4.91**, however, is non-trivial due to overlapping signals in the ^{1}H-NMR spectrum, the presence of amide rotamers about the N-CO_2Et linkage, and the hindered rotation about the piperidine-piperidinone C–C bond (C3-C9) leading to the possibility of atropisomerism on the NMR time scale. Indeed, difficulties in spectroscopic analysis of **4.91** somewhat mirror those encountered in characterization of the target bis(piperidine) alkaloids[161] and in the characterization of intermediates in Smith and Sulikowski's synthesis of haliclonacyclamine C.[125] In considering conversion of **4.90** to **4.91**, it seems reasonable to postulate *syn* addition of

H_2 across the C3-C9 alkene, giving rise to the relative stereochemistry at these positions shown in **4.91**. Monitoring of the hydrogenation reaction indicated that the C1-C2 and C4-C5 alkenes undergo reaction faster than the C3-C9 olefin, thus a product possessing the epimeric relative configuration at C2 is possible if reduction of C3-C9 is not diastereoselective. Nonetheless, results of extensive variable temperature 1D- and 2D-NMR experiments are consistent with isolation of **4.91** as a single diastereomer possessing the *syn-cis* stereochemistry as depicted in Scheme 4.13.

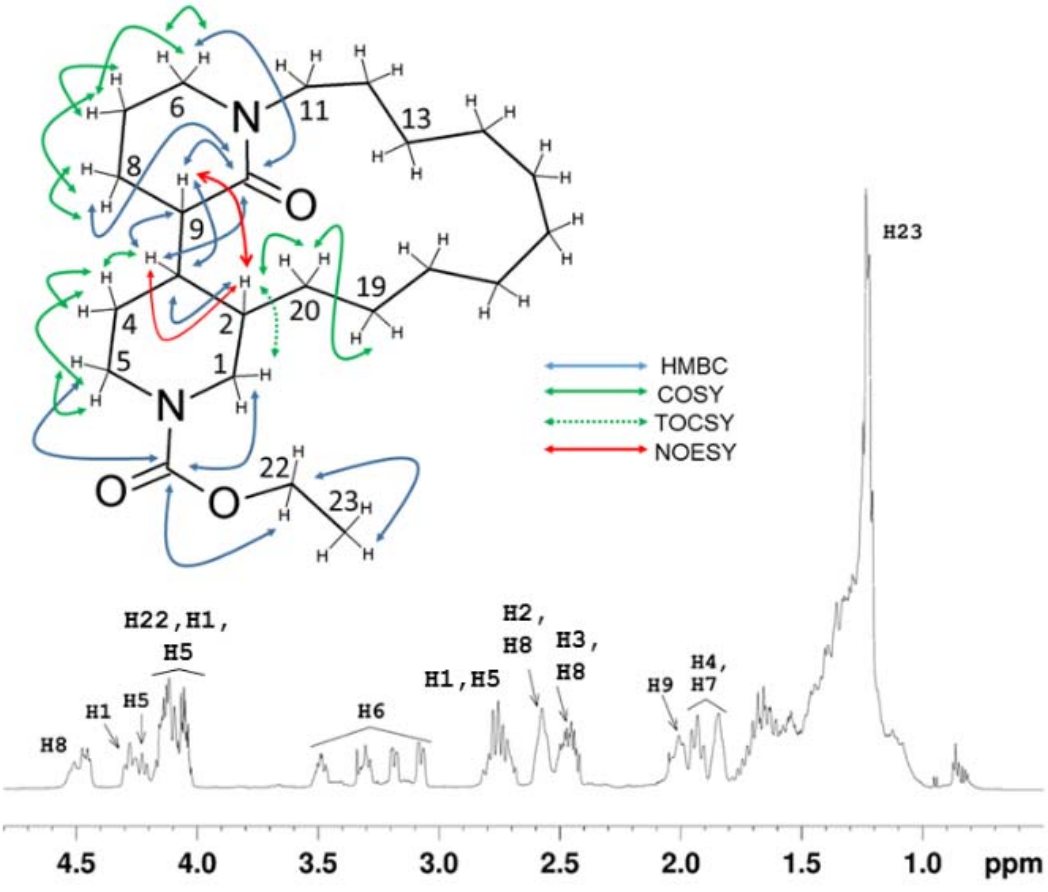


Figure 4.3 - ^{1}H-NMR spectrum of **4.91** ($CDCl_3$, 278 K) with selected 2-D NMR correlations

Figure 4.3 shows the ^{1}H NMR spectrum of **4.91** and selected representative homonuclear and heteronuclear correlations. The location of the carbonyl groups and the presence of extensive scalar coupling network (Figure 4.4) among protons allowed the assignment of ^{1}H and ^{13}C resonances of piperidine and piperidinone rings (Table 4.2). The bridging carbon atoms are also unique so that the HSQC-editing experiments differentiated them from other protons; note that H2, H3 and H9 are the only methine CH hydrogens in the molecule (Figure 4.5, the CH (black) and CH_2 cross peaks (red) have opposite signs in the HSQC data).

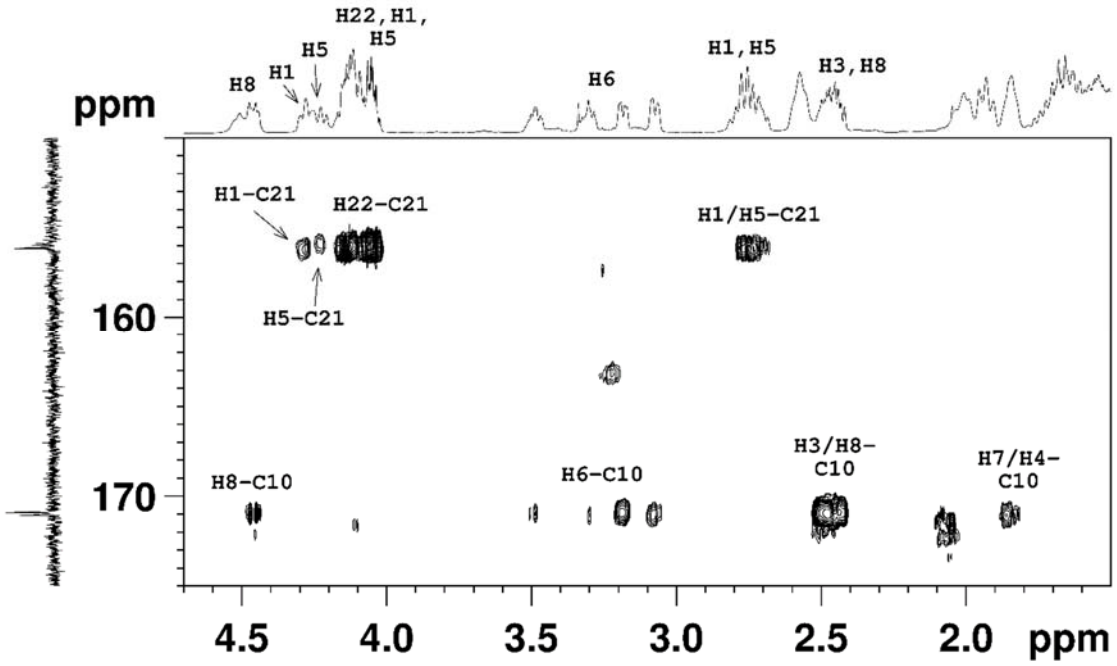


Figure 4.4 - ^{1}H-^{13}C HMBC cross-section of **4.91**

Table 4.2 - ^{1}H and ^{13}C Chemical shift table for **4.91**

Atom Number	^{1}H	^{13}C
1	2.77, 4.16, 4.29	45.2
2	2.58	39.4, 39.9
3	2.48	46.4, 46.7
4	1.63, 1.72, 1.84, 1.94	23.9, 24.7
5	2.74, 4.11, 4.24	47.6
6	3.09, 3.19, 3.32, 3.5	47.4, 50.6
7	1.62, 1.92, 1.95	23.9
8	2.43, 2.56, 4.46, 4.52	46.5, 49.2
9	2.01	35.1, 35.6
10	-	155.7, 155.8, 155.9, 156.0
21	-	170.8, 170.9
22	4.07, 4.14	61.2
23	1.24	14.4, 14.9

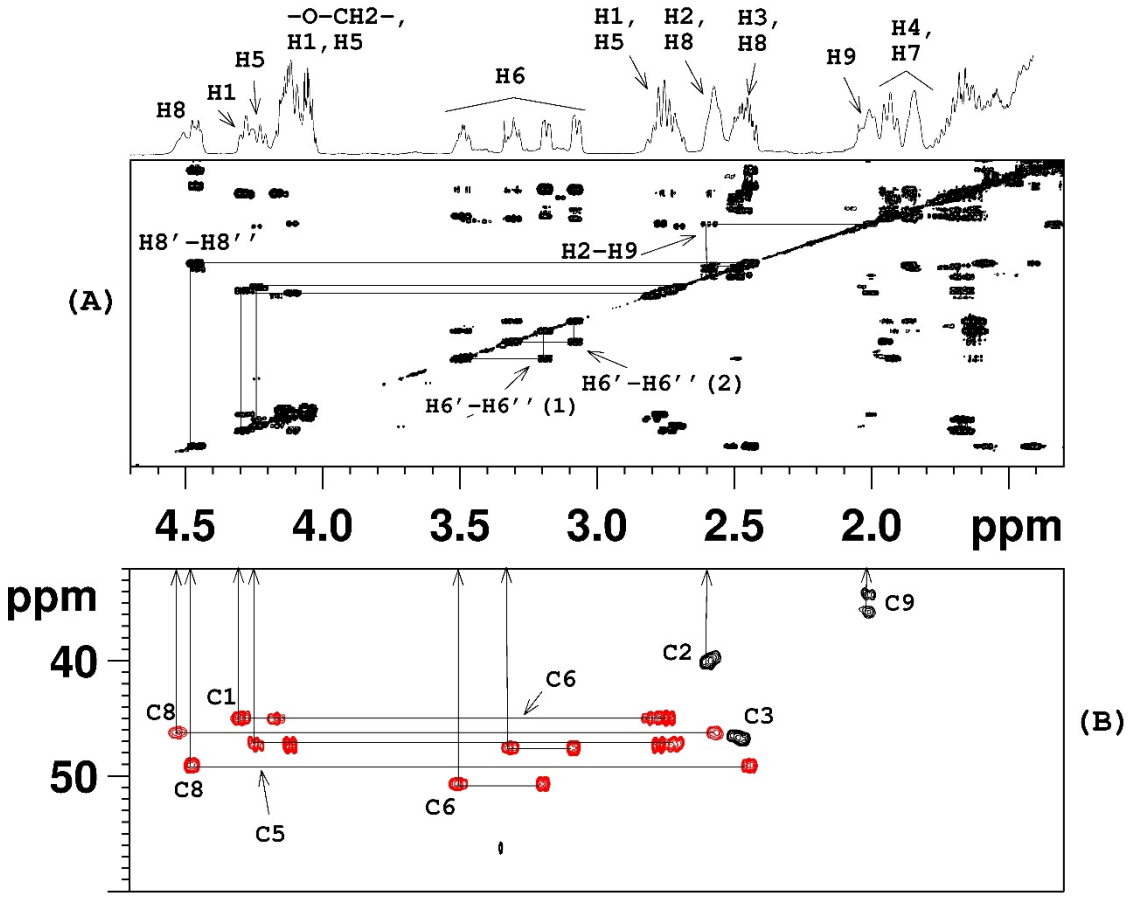


Figure 4.5 - ^{1}H-^{1}H COSY (A) and ^{1}H-^{13}C HSQC (B) cross-sections of **4.91**

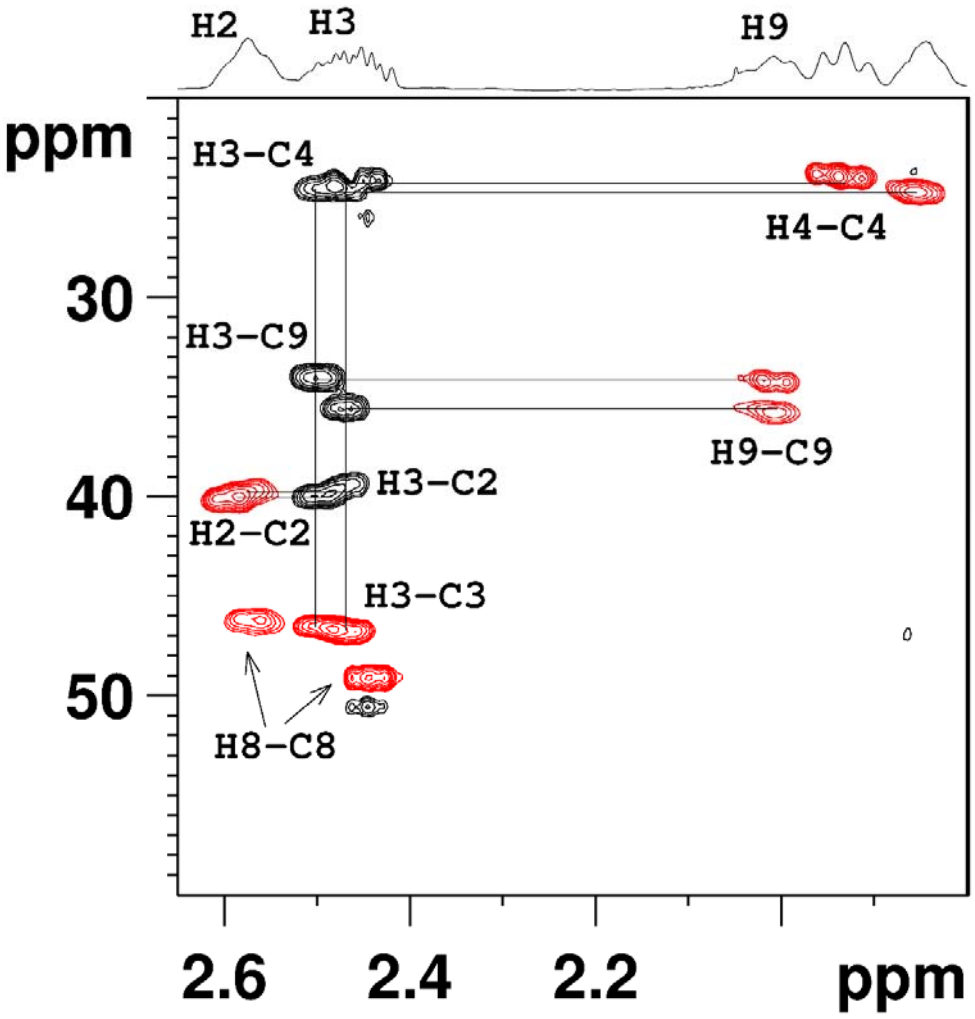


Figure 4.6 - ^{1}H-^{13}C HSQC/HMBC overlaid cross-section of **4.91**

In addition, the NMR data (1D and 2D) revealed more than one rotamer/atropisomer, as indicated by the resonance doubling in the ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H resonances centered at 3.49 and 3.18 ppm correspond to the H6' and H6'' hydrogens of one rotamer/atropisomer, while resonances at 3.30 and 3.07 ppm correspond to H6' and H6'' of a different rotamer/atropisomer (Figure 4.5). The absence of exchange correlated cross peaks in NOESY between the resonances at 3.49

and 3.30 ppm, as well as the 3.18 and 3.07 ppm resonances, indicate that the structures are not interconverting under current experimental conditions ($CDCl_3$, 278 K). However, the stereochemistry of C9H-C3H-C2H is the same in both atropisomers as established by the J-coupling correlated peaks and NOE's observed in COSY and NOESY experiments (Figure 4.7), respectively. COSY cross peaks were observed between H3-H2 and H9-H2, but not between H9-H3, consistent with a dihedral angle close to 90° for the latter pair of hydrogens. The TOCSY experimental data also did not show any cross peaks between H3 and H9, confirming $^3J_{H9\text{-}H3} \approx 0$. Absence of H3-H9 coupling is also observed in the NMR spectra of bis(piperidine) natural products.[121-123,153-161]

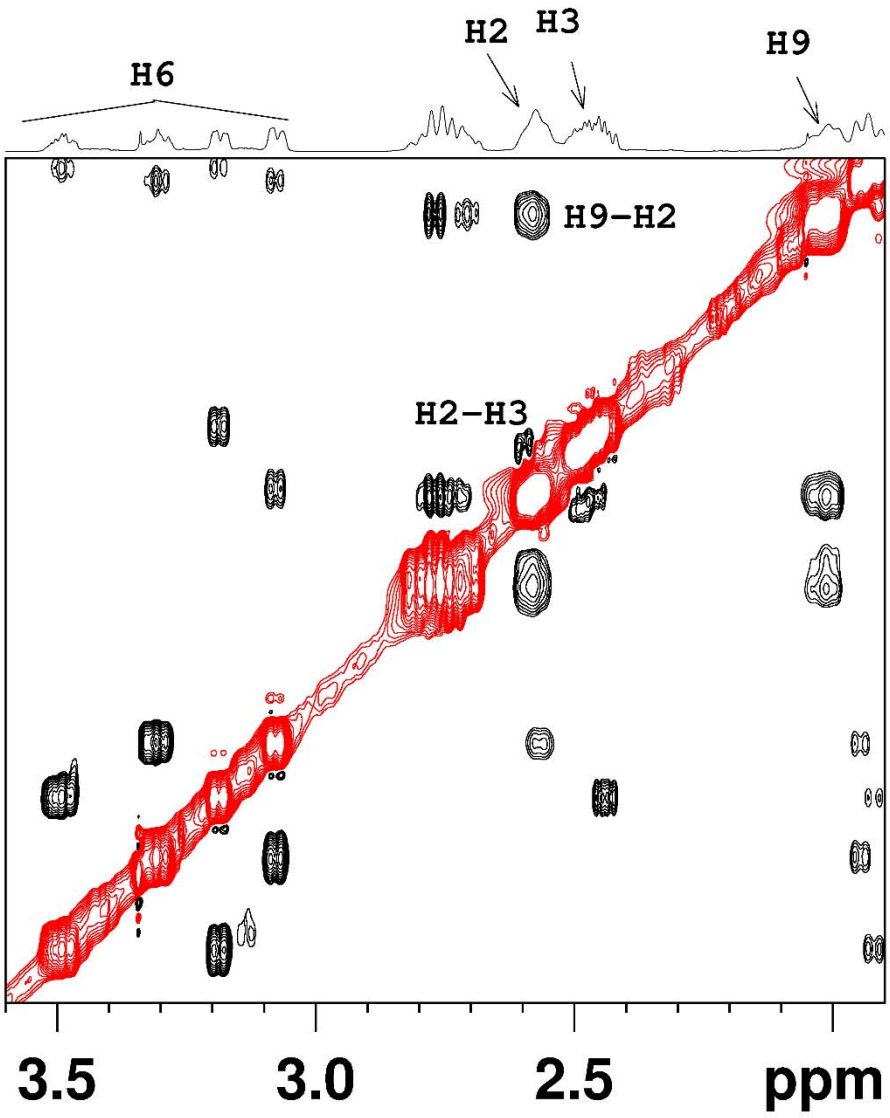


Figure 4.7 - NOESY (mixing time = 0.7 s) cross-section of **4.91**

Attempts to measure individual coupling constants were marred due to extensive resonance overlap and presence of rotamers/atropisomers. However, a medium-intensity NOE was observed between H2-H3. The semiquantitative analysis of the mixing time dependent NOEs of H2-H3 using the correlation between H6'-H6'' as a reference gives a distance of 2.52 Å between H2 and H3. Significantly, this distance is indicative of a *cis*

relationship between these two hydrogens (one equatorial and the other axial). The alternative diastereomer would feature a *trans*-diaxial arrangement of the H2-H3 hydrogens that would place them > 2.8 Å apart, well beyond the distance calculated from NOE analysis. The lowest energy conformation of **4.91** was calculated using DFT (B3LYP/6-31G(d), Gaussian 09) and the result is shown in Figure 4.8. The model nicely correlates with information obtained from NMR analysis. Specifically, the H2-H3 distance in the calculated structure is 2.50 Å, consistent with the results of semiquantitative NOE analysis described above. The calculated structure also accounts for an NOE correlation empirically observed between H2 and H9 in the NOESY spectrum.

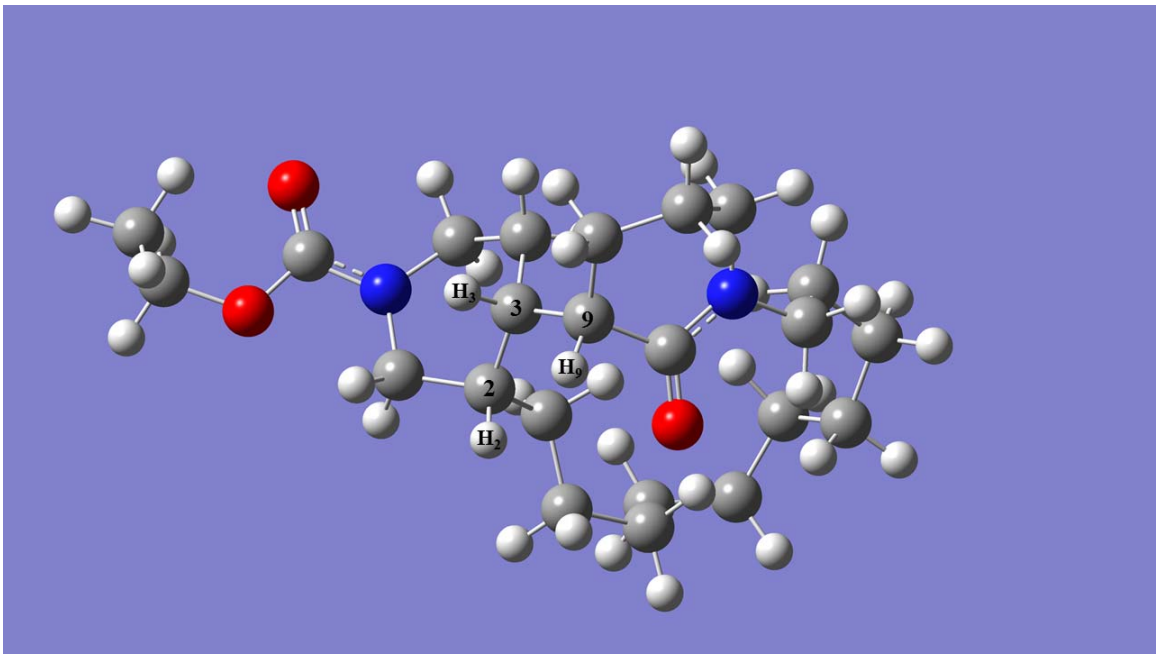


Figure 4.8 - DFT calculated lowest energy conformation of **4.91**

4.3 Conclusion

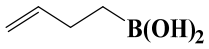
A model of the bis(piperidine) macrocyclic BCD tricyclic ring system found in xestoproxamine C and structurally related marine alkaloids was successfully prepared. Heterogeneous catalytic hydrogenation of a macrocyclic alkylidene dihydropyridine intermediate was used to convert a pyridine precursor to the desired linked piperidine-piperidinone product with apparent control of relative stereochemistry at three contiguous stereocenters. We are now seeking to adopt the key features of the synthetic route used to assemble this model structure in the total synthesis of the target natural product through incorporation of chiral non-racemic building blocks **4.29** and **4.30**. In a more general sense, this work also demonstrates the utility of alkylidene dihydropyridine intermediates in constructing more elaborate polycyclic heterocyclic ring systems. Future efforts will continue to explore the reactivity of pyridine and related azine/azole anhydrobases in a variety of bond forming transformations.

4.4 Experimental Section

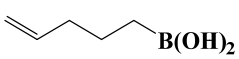
All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for 1H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI) and electron

ionization (EI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.

Experimental Procedures and Characterization Data for preparation of B-alkylboronic acids:



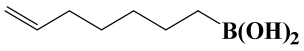
But-3-en-1-ylboronic acid (4.31) – 4-bromobut-1-ene (2.0 mL, 19.7 mmol, 1.00 equiv) was dissolved in THF (~200 mL) and Mg turnings (0.575 g, 23.6 mmol, 1.20 equiv) were added to the reaction mixture. Then the mixture was refluxed for 12 h, which was then cooled to -78 ºC. Trimethylborate (6.7 mL, 59.1 mmol, 3.00 equiv) was drop wisely added followed by maintaining the temperature at -78 ºC for additional 2 h. Thereafter, reaction mixture was warmed to room temperature overnight. It was then quenched with 1 M HCl (100 mL) and concentrated to remove all the THF. Crude mixture was extracted with ethyl acetate (100 mL x 5). All the organic extracts were dried, combined and concentrated. Crude product was dissolved in hot hexane (100 mL) and filtered to remove insoluble inorganics. Finally, hexane was removed in vacuum to isolate **4.31** (1.30 g, 66 %) as a yellow liquid. This was taken in to the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.05 – 4.86 (m, 2H), 2.22 (m, 2H), 1.05 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 113.5, 27.5, 14.2. IR (film) 3230, 1650 cm^{-1}.



Pent-4-en-1-ylboronic acid (4.32) - Using the procedure described for the preparation of **4.31**, 5-bromopent-1-ene (3.0 mL, 25.5 mmol, 1.00 equiv), Mg (0.735 g, 30.3 mmol, 1.20

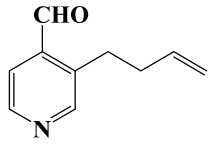
equiv) and trimethylborate (8.7 mL, 76.5 mmol, 3.00 equiv) were reacted to give **4.32** (2.35 g, 81%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.17 – 4.70 (m, 2H), 2.07 (m, 2H), 1.56 (m, 2H), 0.93 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 114.9, 36.4, 22.9, 15.1. IR (film) 3245, 1637 cm^{-1}.

Hex-5-en-1-ylboronic acid (4.33) - Using the procedure described for the preparation of **4.31**, 6-bromohex-1-ene (5.00 g, 30.6 mmol, 1.00 equiv), Mg (0.894 g, 36.7 mmol, 1.20 equiv) and trimethylborate (10.4 mL, 91.8 mmol, 3.00 equiv) were reacted to give **4.33** (3.48 g, 89%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 – 5.57 (m, 1H), 5.20 – 4.75 (m, 2H), 2.20 – 1.93 (m, 2H), 1.57 – 1.32 (m, 4H), 0.93 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 114.4, 33.9, 31.7, 25.3, 23.1. IR (film) 3255, 1639 cm^{-1}.

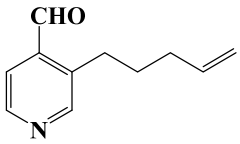


Hept-6-en-1-ylboronic acid (4.28) - Using the procedure described for the preparation of **4.31**, 6-bromohex-1-ene (5.00 g, 28.2 mmol, 1.00 equiv), Mg (0.823 g, 33.8 mmol, 1.20 equiv) and trimethylborate (9.6 mL, 84.6 mmol, 3.00 equiv) were reacted to give **4.28** (3.65 g, 90%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.61 (m, 1H), 5.11 – 4.81 (m, 2H), 2.17 – 1.90 (m, 2H), 1.57 – 1.14 (m, 6H), 0.92 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 114.3, 33.9, 31.9, 28.9, 23.4, 15.8. IR (film) 3280, 1637 cm^{-1}.

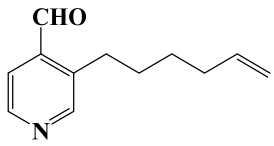
Experimental Procedures and Characterization Data for preparation of 3-alkylpyridine carboxaldehydes:



3-(But-3-en-1-yl)isonicotinaldehyde (4.35) – 3-chloroisonicotanaldehyde (0.200 g, 1.41 mmol, 1.00 equiv), but-3-en-1-ylboronic acid (0.176 g, 1.76 mmol, 1.25 equiv), and K_2CO_3 (0.580 g, 4.23 mmol, 3.00 equiv) were dissolved in toluene:water (6 mL, 10:1, 0.25 M) and deoxygenated via bubbling Ar through the mixture for 30 min. Then $Pd(OAc)_2$ (0.016 g, 0.710 mmol, 0.05 equiv) and RuPhos (0.066 g, 1.41 mmol, 0.100 equiv) were added and mixture was heated at 80 ºC for 3 hours. After 3 hours TLC showed completion of the reaction and then it was quenched with 1 M NaOH. Mixture was cooled to room temperature and extracted with EtOAc (20 mL x 3). Organic extracts were combined, dried and concentrated. Crude product was purified via flash column chromatography using 0 – 20 % EtOAc in hexanes. Compound **4.35** was isolated as a yellow liquid (0.227 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.72 (d, J = 4.9 Hz, 1H), 8.64 (s, 1H), 7.72 – 7.54 (d, J = 4.9 Hz, 1H), 6.06 – 5.55 (m, 1H), 5.25 – 4.82 (m, 2H), 3.35 – 2.79 (m, 2H), 2.51 – 2.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 153.2, 149.0, 138.9, 136.9, 136.6, 123.1, 116.5, 35.9, 29.2. IR (film) 2986, 1708, 1657 cm^{-1}. HRMS (ESI) $C_{10}H_{12}NO$ $[M+H]^+$, Calculated 162.0919; Found 162.0933.

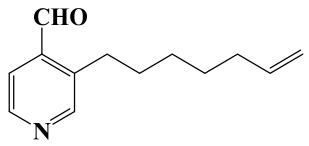


3-(Pent-4-en-1-yl)isonicotinaldehyde (4.36) - Using the procedure described for the preparation of **4.35**, 3-chloroisonicotanaldehyde (0.200 g, 1.41 mmol, 1.00 equiv), pent-4-en-1-ylboronic acid (0.200 g, 1.76 mmol, 1.25 equiv), and K_2CO_3 (0.580 g, 4.23 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.016 g, 0.710 mmol, 0.05 equiv) and RuPhos (0.066 g, 1.41 mmol, 0.100 equiv) were reacted to give **4.36** as a yellow liquid (0.165 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.71 (d, *J* = 4.9 Hz, 1H), 8.65 (s, 1H), 7.78 – 7.51 (d, *J* = 4.9 Hz, 1H), 6.15 – 5.60 (m, 1H), 5.23 – 4.75 (m, 2H), 3.33 – 2.84 (m, 2H), 2.39 – 1.96 (m, 2H), 1.85 – 1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 152.9, 148.8, 138.8, 137.7, 137.6, 122.9, 115.6, 33.4, 31.3, 28.9. IR (film) 3078, 1711, 1637 cm^{-1}. HRMS (ESI) $C_{11}H_{14}NO$ $[M+H]^+$, Calculated 176.1075; Found 176.1087.



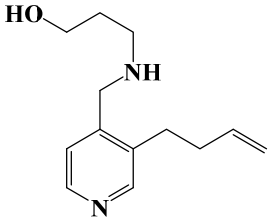
3-(Hex-5-en-1-yl)isonicotinaldehyde (4.37) - Using the procedure described for the preparation of **4.35**, 3-chloroisonicotanaldehyde (0.100 g, 0.71 mmol, 1.00 equiv), hex-5-en-1-ylboronic acid (0.113 g, 0.89 mmol, 1.25 equiv), and K_2CO_3 (0.290 g, 2.13 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.008 g, 0.03 mmol, 0.05 equiv) and RuPhos (0.033 g, 0.071 mmol, 0.100 equiv) were reacted to give **4.37** as a yellow liquid (0.111 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.70 (d, *J* = 4.9 Hz, 1H), 8.64 (s, 1H), 7.71 – 7.50 (d, *J* = 4.9 Hz, 1H), 5.95 – 5.66 (m, 1H), 5.14 – 4.87 (m, 2H), 3.09 – 2.89 (m, 2H), 2.26 – 2.00 (m, 2H), 1.80 – 1.57 (m, 2H), 1.57 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 153.1, 148.9, 138.9, 138.4, 137.9, 122.9, 115.00, 33.5, 31.8, 29.6, 28.7. IR (film)

3073, 1708, 1650 cm^{-1}. HRMS (ESI) $C_{12}H_{16}NO$ $[M+H]^+$, Calculated 190.1232; Found 190.1244.

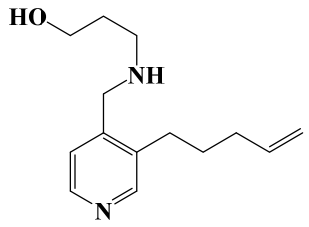


3-(Hept-6-en-1-yl)isonicotinaldehyde (4.38) - Using the procedure described for the preparation of **4.35**, 3-chloroisonicotanaldehyde (2.19 g, 15.5 mmol, 1.00 equiv), hept-6-en-1-ylboronic acid (2.75 g, 19.3 mmol, 1.25 equiv), and K_2CO_3 (6.43 g, 46.5 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.174 g, 0.78 mmol, 0.05 equiv) and RuPhos (0.720 g, 1.55 mmol, 0.100 equiv) were reacted to give **4.38** as a yellow liquid (2.96 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.71 (d, J = 4.9 Hz, 1H), 8.64 (s, 1H), 7.63 (d, J = 4.9 Hz, 1H), 5.89 – 5.63 (m, 1H), 5.12 – 4.80 (m, 2H), 3.09 – 2.91 (m, 2H), 2.23 – 1.90 (m, 2H), 1.76 – 1.51 (m, 2H), 1.55 – 1.28 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 152.9, 148.7, 138.7, 138.7, 137.9, 122.7, 114.5, 33.6, 32.1, 29.6, 28.9, 28.6. IR (film) 2924, 1708, 1640 cm^{-1}. HRMS (ESI) $C_{13}H_{18}NO$ $[M+H]^+$, Calculated 204.1388; Found 204.1394.

Experimental Procedures and Characterization Data for preparation of aminomethyl pyridine analogues

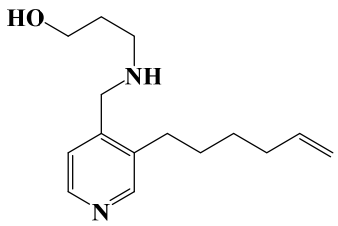


3-(((3-(But-3-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (4.40) – 3-(But-3-en-1-yl)isonicotinaldehyde (0.62 g, 3.85 mmol, 1.00 equiv), 3-aminopropanol (0.350 mL, 4.6 mmol, 1.20 equiv), and molecular sieves were dissolved in anhydrous MeOH (40 mL) and was stirred at room temperature for 30 min until complete formation of the imine was observed by NMR. Then it was cooled to 0 ºC and $NaBH_4$ (0.439 g, 11.6 mmol, 3.00 equiv) was added in dropwise portions. After 15 min ice bath was removed and reaction was stirred at room temperature for additional 4 h. Then it was quenched with water (30 mL) and mixture was filtered through celite to remove molecular sieves. Filtrate was concentrated in vacuum to remove all the methanol. Thereafter mixture was extracted with EtOAc (30 mL x 3). Organic layers were combined, dried and concentrated. Crude mixture was purified via flash column chromatography using 0 - 30% MeOH in EtOAc to afford **4.40**. (0.488 g, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.0 Hz, 1H), 8.38 (s, 1H), 7.26 (d, *J* = 5.0 Hz, 1H), 5.90 – 5.75 (m, 1H), 5.16 – 4.83 (m, 2H), 3.88 – 3.65 (m, 4H), 3.12 (s, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.78 – 2.68 (m, 2H), 2.45 – 2.26 (m, 2H), 1.84 – 1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.9, 146.3, 137.2, 135.1, 122.7, 115.9, 63.6, 49.9, 49.5, 34.8, 31.5, 29.3. IR (film) 3287, 2920, 1635 cm^{-1}. HRMS (ESI) $C_{13}H_{21}N_2O$ $[M+H]^+$, Calculated 221.1654; Found 221.1660.

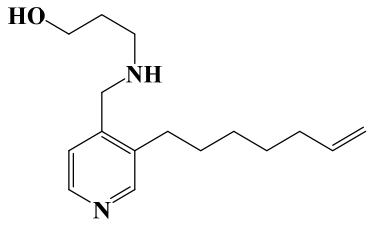


3-(((3-(Pent-4-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (4.41) - Using the procedure described for the preparation of **4.40**, 3-(pent-4-en-1-yl)isonicotinaldehyde

(0.500 g, 2.85 mmol, 1 equiv), 3-aminopropanol (0.22 mL, 2.85 mmol, 1.00 equiv), and $NaBH_4$ (0.323 g, 8.55 mmol, 3.00 equiv) were reacted to give **4.41** as a colorless oil (0.474 g, 71%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.1 Hz, 1H), 8.38 (s, 1H), 7.25 (d, *J* = 5.1, Hz, 1H), 5.93 – 5.60 (m, 1H), 5.23 – 4.89 (m, 2H), 3.88 – 3.74 (m, 4H), 2.92 (t, *J* = 6 Hz 2H), 2.79 – 2.51 (m, 2H), 2.25 – 1.97 (m, 2H), 1.87 – 1.47 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.9, 146.2, 138.1, 135.7, 122.7, 115.53, 63.9, 49.9, 49.7, 33.6, 31.4, 30.1, 29.3. IR (film) 3272, 3076, 1638 cm^{-1}. HRMS (ESI) $C_{14}H_{23}N_2O$ $[M+H]^+$, Calculated 235.1810; Found 235.1827.

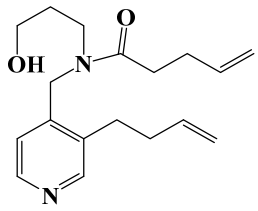


3-(((3-(Hex-5-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (4.42) - Using the procedure described for the preparation of **4.40**, 3-(hex-5-en-1-yl)isonicotinaldehyde (0.900 g, 4.76 mmol, 1.00 equiv), 3-aminopropanol (0.36 mL, 4.75 mmol, 1.00 equiv), and $NaBH_4$ (0.900 g, 14.3 mmol, 3.00 equiv) were reacted to give **4.42** as a colorless oil (1.18 g, 66%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.0 Hz, 1H), 8.37 (s, 1H), 7.25 (d, *J* = 5.0 Hz, 1H), 5.96 – 5.73 (m, 1H), 5.06 – 4.91 (m, 2H), 3.84 – 3.79 (m, 4H), 2.92 (t, *J* = 5.9 Hz, 2H), 2.84 – 2.69 (m, 2H), 2.69 – 2.59 (m, 2H), 2.18 – 2.05 (m, 2H), 1.83 – 1.73 (m, 2H), 1.65 – 1.54 (m, 2H), 1.54 – 1.38 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.9, 146.1, 138.6, 135.9, 122.6, 114.9, 63.9, 49.9, 49.6, 33.6, 31.4, 30.4, 29.9, 28.9. IR (film) 3288, 1639 cm^{-1}. HRMS (ESI) $C_{14}H_{23}N_2O$ $[M+H]^+$, Calculated 249.1967; Found 249.1962.



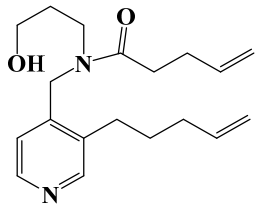
3-(((3-(Hept-6-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (4.43) - Using the procedure described for the preparation of **4.40**, 3-(hept-6-en-1-yl)isonicotinaldehyde (0.740 g, 3.60 mmol, 1.00 equiv), 3-aminopropanol (0.28 mL, 3.60 mmol, 1.00 equiv), and $NaBH_4$ (0.410 g, 10.8 mmol, 3.00 equiv) were reacted to give **4.43** as a colorless oil (0.658 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.1 Hz, 1H), 8.36 (s, 1H), 7.26 (d, *J* = 5.1 Hz, 1H), 5.89 – 5.66 (m, 1H), 5.07 – 4.76 (m, 2H), 3.89 – 3.73 (m, 4H), 3.20 (s, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.73 – 2.50 (m, 2H), 2.13 – 1.96 (m, 2H), 1.84 – 1.69 (m, 2H), 1.62 – 1.53 (m, 2H), 1.49 – 1.31 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 147.6, 145.6, 138.8, 135.8, 122.5, 114.5, 63.3, 49.5, 49.2, 33.6, 31.2, 30.6, 29.8, 28.9, 28.7. IR (film) 3309, 1657 cm^{-1}. HRMS (ESI) $C_{16}H_{26}N_2O$ $[M+H]^+$, Calculated 263.2123; Found 263.2109.

Experimental Procedures and Characterization Data for preparation of aminomethylpyridine precursors for RCM



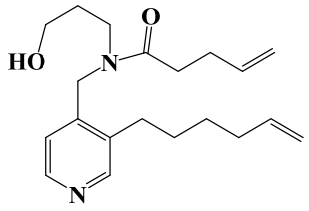
***N*-((3-(But-3-en-1-yl)pyridin-4-yl)methyl)-*N*-(3-hydroxypropyl)pent-4-enamide (4.44)** – Pyridine substrate **4.40** (0.480 g, 2.18 mmol, 1.00 equiv), 4-penten-1-oic acid

(0.25 mL, 2.40 mmol, 1.10 equiv), triethylamine (0.91 mL, 6.54 mmol, 3.00 equiv), and HOBt (0.324 g, 2.40 mmol, 1.10 equiv) were dissolved in THF (20 mL) and cooled to 0 ^{o}C using an ice bath. After 10 min EDC.HCl (0.460 g, 2.40 mmol, 1.10 equiv) was added and mixture was allowed to warm up to room temperature while continuous stirring. After 18 h TLC showed completion of the reaction which was then quenched with saturated sodium bicarbonate (20 mL). Reaction mixture was concentrated to remove THF and then was extracted with EtOAc (20 mL x 3). Combined organic layers were dried and concentrated. Crude mixture was purified via flash column chromatography using 0 - 10 % MeOH in EtOAc to afford **4.44** as a yellow oil (mixture of rotamers, 0.441 g, 67 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.1 Hz, 0.65H), 8.43 (s, 0.65H), 8.36 – 8.32 (m, 0.7H), 6.98 (d, *J* = 5.1 Hz, 0.63H), 6.96 (d, *J* = 5.1 Hz, 0.37H), 6.00 – 5.66 (m, 2H), 5.16 – 4.94 (m, 4H), 4.65 (s, 0.7H), 4.53 (s, 1.3H), 3.67 (t, *J* = 5.8 Hz, 0.7H), 3.60 – 3.52 (m, 2.6H), 3.46 – 3.41 (m, 0.7H), 2.77 – 2.68 (m, 2H), 2.66 – 2.57 (m, 0.7H), 2.55 – 2.27 (m, 5.3H), 1.87 – 1.77 (m, 0.7H), 1.76 – 1.69 (m, 1.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 172.9, 150.7, 150.4, 148.5, 147.7, 144.7, 143.5, 137.5, 137.1, 136.9, 136.6, 135.0, 134.3, 121.4, 119.6, 116.5, 115.97, 115.92, 115.6, 59.1, 58.5, 47.9, 45.3, 44.9, 42.9, 34.4, 34.2, 32.5, 32.3, 31.6, 30.2, 29.5, 29.4, 29.3, 29.1. IR (film) 3400, 1632 cm^{-1}. HRMS (ESI) $C_{18}H_{27}N_2O_2$ $[M+H]^+$, Calculated 303.2073; Found 303.2074.



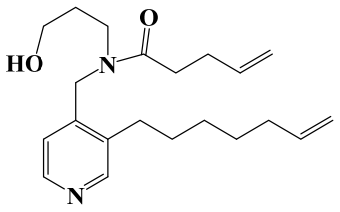
N-(3-Hydroxypropyl)-N-((3-(pent-4-en-1-yl)pyridin-4-yl)methyl)pent-4-enamide (4.45) – Using the procedure described for the preparation of **4.44**, pyridine substrate

4.41 (0.98 g, 4.18 mmol, 1.00 equiv), 4-penten-1-oic acid (0.47 mL, 4.60 mmol, 1.10 equiv), triethylamine (1.80 mL, 12.5 mmol, 3.00 equiv), HOBt (0.62 g, 4.60 mmol, 1.10 equiv), and EDC.HCl (0.882 g, 4.60 mmol, 1.10 equiv) were reacted to give **4.45** as a yellow oil (mixture of rotamers, 0.899 g, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.32 (m, 2H), 7.01 – 6.93 (m, 1H), 5.98 – 5.69 (m, 2H), 5.19 – 4.88 (m, 4H), 4.65 (s, 0.8H), 4.51 (s, 1.2H), 3.67 (t, *J* = 5.8 Hz, 0.8H), 3.61 – 3.52 (m, 2.4H), 3.47 – 3.37 (m, 0.8H), 2.69 – 2.56 (m, 2H), 2.54 – 2.25 (m, 4.5H), 2.22 – 2.09 (m, 1.5H), 1.89 – 1.50 (m, 2H), 1.42 – 1.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 148.5, 148.4, 143.28, 143.20, 137.7, 136.9, 135.3, 134.9, 121.46, 121.40, 119.74, 119.70, 115.98, 115.92, 115.69, 115.66, 59.4, 58.5, 47.7, 45.2, 44.8, 42.9, 32.5, 32.4, 31.9, 31.6, 30.2, 29.99, 29.93, 29.36, 29.30, 29.2, 22.7, 14.18, 14.15. IR (film) 3402, 1641, 1631 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ $[M+H]^+$, Calculated 317.2229; Found 317.2232.



N-((3-(Hex-5-en-1-yl)pyridin-4-yl)methyl)-N-(3-hydroxypropyl)pent-4-enamide (4.46) – Using the procedure described for the preparation of **4.44**, pyridine substrate **4.42** (0.580 g, 2.33 mmol, 1.00 equiv), 4-penten-1-oic acid (0.260 mL, 2.56 mmol, 1.10 equiv), triethylamine (0.980 mL, 7.00 mmol, 3.00 equiv), HOBt (0.350 g, 2.56 mmol, 1.10 equiv), and EDC.HCl (0.490 g, 2.56 mmol, 1.10 equiv) were reacted to give **4.46** as a yellow oil (mixture of rotamers, 0.489 g, 64 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.1 Hz, 0.7H), 8.42 (s, 0.7H), 8.36 – 8.33 (m, 0.6H), 6.98 (d, *J* = 5.1 Hz, 0.7H), 6.95 (d, *J* = 5.1 Hz, 0.3H), 5.96 – 5.85 (m, 0.3H), 5.84 – 5.73 (m, 1.7H), 5.15 – 4.92 (m, 4H),

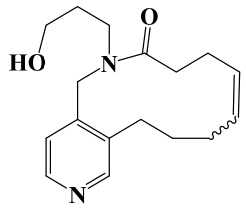
4.65 (s, 0.6H), 4.51 (s, 1.4H), 3.67 (t, J = 5.8 Hz, 0.7H), 3.60 – 3.54 (m, 2.6H), 3.46 – 3.36 (m, 0.7H), 2.66 – 2.59 (m, 2.3H), 2.52 – 2.45 (m, 0.7H), 2.43 – 2.37 (m, 1.4H), 2.37 – 2.28 (m, 1.4H), 2.17 – 2.04 (m, 2.2H), 1.85 – 1.78 (m, 0.6H), 1.77 – 1.69 (m, 1.4H), 1.65 – 1.55 (m, 2H), 1.55 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 150.5, 148.5, 147.8, 144.4, 143.2, 138.6, 138.3, 137.6, 136.9, 135.8, 135.0, 121.4, 119.7, 115.9, 115.6, 115.2, 114.9, 59.3, 58.5, 47.7, 45.1, 44.8, 42.9, 33.6, 33.5, 32.5, 32.3, 31.6, 30.2, 30.0, 29.9, 29.8, 29.6, 29.3, 28.9, 28.8. IR (film) 3404, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{31}N_2O_2$ $[M+H]^+$, Calculated 331.2386; Found 331.2392.



N-((3-(Hept-6-en-1-yl)pyridin-4-yl)methyl)-N-(3-hydroxypropyl)pent-4-enamide (4.47) – Using the procedure described for the preparation of **4.44**, pyridine substrate **4.43** (0.658 g, 2.50 mmol, 1.00 equiv), 4-penten-1-oic acid (0.280 mL, 2.75 mmol, 1.10 equiv), triethylamine (1.0 mL, 7.50 mmol, 3.00 equiv), HOBt (0.372 g, 2.75 mmol, 1.10 equiv), and EDC.HCl (0.527 g, 2.75 mmol, 1.10 equiv) were reacted to give **4.47** as a yellow oil (mixture of rotamers, 0.517 g, 60 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 5.1 Hz, 0.7H), 8.42 (s, 0.7H), 8.37 – 8.32 (m, 0.6H), 6.98 (d, J = 5.1 Hz, 0.7H), 6.95 (d, J = 5.1 Hz, 0.3H), 5.96 – 5.85 (m, 0.5H), 5.85 – 5.73 (m, 1.5H), 5.15 – 4.90 (m, 4H), 4.65 (s, 0.6H), 4.51 (s, 1.4H), 3.67 (t, J = 5.8 Hz, 0.6H), 3.62 – 3.50 (m, 2.8H), 3.50 – 3.37 (m, 0.6H), 2.66 – 2.55 (m, 2.6H), 2.52 – 2.44 (m, 0.6H), 2.44 – 2.35 (m, 1.4H), 2.36 – 2.27 (m, 1.4H), 2.11 – 2.01 (m, 2H), 1.85 – 1.77 (m, 0.6H), 1.77 – 1.68 (m, 1.4H), 1.68 – 1.51 (m, 3H), 1.51 – 1.34 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 150.5,

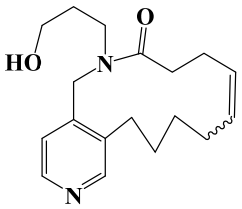
148.4, 147.7, 144.4, 143.2, 138.9, 138.7, 137.6, 136.9, 135.9, 135.1, 121.4, 119.7, 115.9, 115.6, 114.8, 114.6, 59.3, 58.5, 47.7, 45.2, 44.8, 42.9, 33.81, 33.75, 32.5, 32.3, 30.4, 30.2, 30.13, 30.10, 29.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 28.84, 28.80. IR (film) 3400, 3073, 1635 cm^{-1}. HRMS (ESI) $C_{21}H_{33}N_2O_2$ $[M+H]^+$, Calculated 345.2542; Found 345.2544.

Experimental Procedures and Characterization Data for ring closing metathesis of aminomethylpyridine substrates



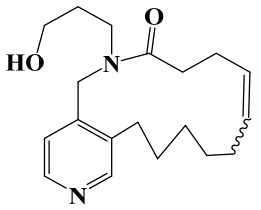
6-(3-Hydroxypropyl)-5,8,9,12,13,14-hexahydropyrido[4,3-c][1]azacyclododecin-7(6H)-one (4.50) – Pyridine substrate **4.45** (0.240 g, 0.760 mmol, 1.00 equiv) was dissolved in Toluene (1.50 L, 0.500 mM) and Ar was bubbled through the reaction mixture while allowing it to heat to 80 ºC in an oil bath for 1 hour. Simultaneously toluene (20 mL) was added to a 50 mL round bottom flask and Ar was bubbled through it for 30 min. Then Zhan 1B catalyst (0.0167 g, 0.023 mmol, 0.030 equiv) was added to the small toluene solution and stirred for additional 30 min until it was completely dissolved. Catalyst solution was taken in to a 20 mL syringe, and was drop wisely added to the reaction mixture via a syringe pump over the period of 2 h. After 2 h completion of the reaction by TLC was observed and di(ethyleneglycol)vinyl ether (0.400 mL, 3.04 mmol, 4.00 equiv) was added to the reaction mixture to kill the catalyst. Reaction mixture was then cooled down to room temperature while stirring. Then it was concentrated portion by portion to remove all the toluene. Crude product was purified via flash column

chromatography using 0 - 10% MeOH in EtOAc to afford **4.50** as a yellow brown oil (a mixture of diastereomers and rotamers, 0.195 g, 89 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.07 (m, 2H), 7.17 – 6.77 (m, 1H), 6.00 – 5.09 (m, 3H), 5.13 – 4.76 (m, 0.3H), 4.76 – 4.30 (m, 0.7H), 3.94 – 3.06 (m, 4H), 2.96 – 1.09 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 172.6, 151.4, 151.2, 151.0, 150.7, 147.8, 147.2, 146.9, 146.8, 143.7, 143.1, 141.0, 138.3, 133.6, 132.3, 131.3, 130.9, 130.4, 129.54 128.7, 126.7, 126.4, 126.2, 59.0, 58.8, 58.6, 58.4, 58.3, 50.9, 45.9, 44.8, 42.7, 42.4, 39.8, 34.1, 33.7, 33.3, 32.3, 31.7, 31.2, 30.8, 30.7, 30.4, 30.1, 29.9, 29.7, 29.5, 29.3, 29.2, 28.3, 27.3, 25.9, 25.8, 24.4, 22.5. IR (film) 3381, 1634 cm^{-1}. HRMS (ESI) $C_{17}H_{25}N_2O_2$ $[M+H]^+$, Calculated 289.1916; Found 289.1929.



6-(3-Hydroxypropyl)-5,6,8,9,12,13,14,15-octahydro-7H-pyrido[4,3-c][1]azacyclotridecin-7-one (4.51) – Using the procedure described for the preparation of **4.50**, pyridine substrate **4.46** (0.100 g, 0.300 mmol, 1.00 equiv), Zhan 1B catalyst (0.007 g, 0.009 mmol, 0.030 equiv), and di(ethyleneglycol) vinyl ether (0.160 mL, 1.20 mmol, 4.00 equiv) were reacted to give **4.51** as a yellow brown oil (mixture of diastereomers and rotamers, 0.075 g, 83 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 – 8.24 (m, 2H), 7.21 – 6.98 (m, 1H), 5.95 – 5.77 (m, 0.7H), 5.70 – 5.10 (m, 2H), 4.74 – 4.54 (m, 1.3H), 3.78 – 3.35 (m, 4H), 3.07 – 2.86 (m, 0.7H), 2.82 – 1.89 (m, 7.3H), 1.89 – 1.17 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 174.9, 173.4, 172.7, 151.34, 151.25, 150.9, 150.1, 148.0, 147.9, 147.2, 147.0, 143.8, 143.4, 142.9, 141.2, 137.9, 134.8, 134.2,

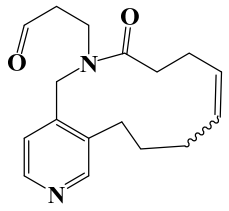
132.5, 132.1, 131.8, 130.4, 128.7, 128.6, 128.2, 127.6, 126.4, 126.3, 124.9, 119.7, 59.3, 58.22, 58.16, 49.9, 48.4, 46.44, 46.37, 43.2, 42.89, 42.84, 40.0, 36.4, 33.8, 32.2, 32.1, 31.9, 31.5, 31.2, 31.0, 30.5, 30.3, 30.2, 30.0, 29.6, 29.5, 29.4, 29.3, 28.5, 28.2, 27.8, 27.7, 27.5, 27.2, 26.9, 26.5, 26.3, 26.2, 24.6, 24.3. IR (film) 3377, 1631 cm^{-1}. HRMS (ESI) $C_{18}H_{27}N_2O_2$ $[M+H]^+$, Calculated 303.2072; Found 303.2069.



6-(3-Hydroxypropyl)-5,8,9,12,13,14,15,16-octahydropyrido[4,3-c][1]azacyclotetradecin-7(6H)-one (4.48) – Using the procedure described for the preparation of **4.50**, pyridine substrate **4.47** (0.050 g, 0.150 mmol, 1.00 equiv), Zhan 1B catalyst (0.0033 g, 0.0050 mmol, 0.030 equiv), and di(ethyleneglycol) vinyl ether (0.0820 mL, 0.600 mmol, 4.00 equiv) were reacted to give **4.48** as a yellow brown oil (mixture of diastereomers and rotamers, 0.0440 g, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.31 (m, 2H), 7.20 – 6.98 (m, 1H), 5.84 (d, *J* = 14.3 Hz, 0.3H), 5.71 – 5.12 (m, 2H), 4.79 – 4.46 (m, 1.7H), 3.88 – 3.40 (m, 4.4H), 3.39 – 3.19 (m, 0.6H), 2.82 – 1.93 (m, 8H), 1.91 – 1.11 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 175.8, 174.9, 172.7, 171.9, 151.4, 151.3, 150.9, 150.8, 150.6, 150.0, 148.4, 148.3, 147.9, 147.2, 146.6, 144.4, 143.8, 143.7, 143.5, 143.4, 135.2, 134.9, 134.6, 134.2, 132.5, 132.1, 131.7, 131.5, 131.3, 130.4, 129.7, 128.7, 128.2, 127.7, 127.55, 126.60, 126.5, 124.9, 119.8, 119.3, 119.2, 59.4, 59.3, 58.3, 58.2, 49.9, 48.4, 48.1, 46.4, 45.5, 44.1, 43.2, 43.0, 42.84, 42.78, 40.0, 36.4, 35.6, 34.8, 33.8, 32.5, 32.3, 32.1, 31.9, 31.5, 31.1, 31.0, 30.5, 30.33, 30.28, 30.2, 30.14, 30.08, 29.99, 29.97, 29.7, 29.52, 29.45, 29.3, 28.9, 28.6, 28.5, 28.2, 27.5, 27.2, 27.1, 27.0, 26.9, 26.5,

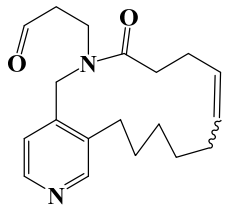
26.3, 26.2, 26.1, 25.4, 24.4, 24.3. IR (film) 3377, 1631 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ $[M+H]^+$, Calculated 317.2229; Found 317.2234.

Experimental Procedures and Characterization Data for DMP oxidation of aminomethylpyridine substrates



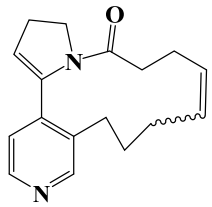
3-(7-Oxo-7,8,9,12,13,14-hexahydropyrido[4,3-c][1]azacyclododecin-6(5H)-yl)propanal (4.52) – Pyridine substrate **4.50** (0.220 g, 0.760 mmol, 1.00 equiv) was dissolved in DCM (8 mL) and K_2CO_3 (0.315 g, 2.28 mmol, 3.00 equiv) was added to it. Then Dess-Martin Periodinane (0.490 g, 1.14 mmol, 1.50 equiv) was added and stirred at room temperature for 2 h at which time reaction was completed. Then it was quenched with 1 M NaOH stirred for 15 min. Crude mixture was extracted with DCM (10 mL x 3) and all the organic layers were combined, dried and concentrated. Crude product was purified via flash column chromatography using 0 - 10 % MeOH in EtOAc to afford **4.52** as a yellow oil (mixture of diastereomers and rotamers, 0.124 g, 57 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 – 9.51 (m, 1H), 8.53 – 8.09 (m, 2H), 7.21 – 6.81 (m, 1H), 5.88 – 5.11 (m, 3H), 5.09 – 4.77 (m, 0.1H), 4.67 – 4.25 (m, 0.4H), 3.86 – 2.93 (m, 2.5H), 2.93 – 0.99 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 200.5, 199.1, 199.0, 174.0, 172.9, 172.2, 151.6, 151.3, 151.2, 151.1, 147.9, 147.7, 147.2, 147.0, 143.2, 142.6, 141.5, 138.2, 133.9, 132.1, 131.5, 131.2, 130.8, 129.3, 128.5, 126.7, 126.5, 126.3, 51.1, 46.2, 46.0, 45.2, 43.2, 43.0, 42.8, 42.3, 42.2, 42.0, 38.9, 38.7, 37.8, 37.0, 34.2, 33.6, 33.4, 31.9, 31.7, 31.3, 31.0, 30.8, 30.7, 30.4, 29.9, 29.7, 29.6, 29.5, 29.4, 28.2, 27.4, 26.0, 25.8, 24.4, 22.5.

IR (film) 1723, 1632 cm^{-1}. HRMS (ESI) $C_{17}H_{23}N_2O_2$ $[M+H]^+$, Calculated 287.1760; Found 287.1760.

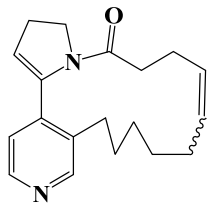


3-(7-Oxo-7,8,9,12,13,14,15,16-octahydropyrido[4,3-c][1]azacyclotetradecin-6(5H)-yl)propanal (4.53) – Using the procedure described for the preparation of **4.52**, pyridine substrate **4.48** (0.200 g, 0.630 mmol, 1.00 equiv), Dess-Martin Periodinane (0.400 g, 0.950 mmol, 1.50 equiv), and K_2CO_3 (0.261 g, 1.89 mmol, 3.00 equiv) were reacted to give **4.53** as a yellow oil (mixture of diastereomers and rotamers, 0.130 g, 66 %). ^1H NMR (500 MHz, $CDCl_3$) δ 9.86 – 9.58 (m, 1H), 8.54 – 8.21 (m, 2H), 7.20 – 6.88 (m, 1H), 5.87 – 5.77 (m, 0.2H), 5.63 – 5.14 (m, 2H), 4.82 – 4.45 (m, 1.8H), 3.89 – 3.20 (m, 2H), 2.96 – 2.77 (m, 1H), 2.77 – 1.87 (m, 8H), 1.87 – 1.07 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 200.6, 199.1, 198.9, 175.8, 174.5, 172.4, 171.5, 151.6, 150.8, 150.6, 150.1, 148.2, 148.1, 147.4, 146.9, 145.2, 144.56, 143.2, 137.9, 135.0, 134.8, 134.7, 134.6, 131.60, 131.56, 131.3, 129.6, 129.1, 128.0, 127.8, 126.4, 119.5, 50.4, 50.1, 50.0, 49.9, 46.7, 45.9, 43.3, 43.2, 42.9, 42.7, 41.8, 39.0, 35.6, 34.9, 33.9, 32.2, 32.22, 32.16, 31.2, 30.4, 30.2, 30.1, 30.0, 29.74, 29.66, 29.5, 29.3, 29.2, 28.8, 28.5, 28.1, 27.6, 27.6, 27.3, 27.2, 26.9, 26.1, 25.5, 24.3. IR (film) 1720, 1642 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ $[M+H]^+$, Calculated 315.2073; Found 315.2071.

Experimental Procedures and Characterization Data for anhydrobase mediated cyclization of aldehyde substrates

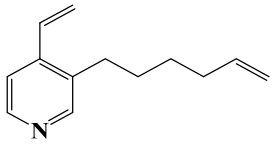


6,7,10,11,14,15-Hexahydropyrido[4,3-c]pyrrolo[1,2-a][1]azacyclododecin-12(5H)-one (4.54) – Pyridine substrate **4.52** (0.128 g, 0.45 mmol, 1.00 equiv) was dissolved in THF (5 mL). Then $Ti(O^iPr)_4$ (0.067 mL, 0.220 mmol, 0.500 equiv) and DIPEA (0.110 mL, 0.68 mmol, 1.50 equiv) were added to it. Reaction mixture was then refluxed at 80 ^oC for 2 min and $EtCO_2Cl$ (0.0470 mL, 0.500 mmol, 1.10 equiv) was added. After 10 min a drop of TFA and H_2O (5 mL) were added and refluxing was continued for additional 10 min. Thereafter reaction mixture was basified with sat. Na_2CO_3 and extracted with EtOAc (10 mL x 3). Combined organic layers were dried and concentrated. Crude product was purified via flash column chromatography using 0 - 10 % MeOH in EtOAc to afford **4.54** as a yellow oil (mixture of diastereomers and rotamers, 0.0466 g, 39 %). ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 – 8.22 (m, 2H), 7.40 – 7.29 (m, 0.1H), 7.22 – 6.89 (m, 0.9H), 5.97 – 4.74 (m, 3H), 4.44 – 3.72 (m, 2H), 2.99 – 0.68 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 169.5, 154.6, 152.2, 151.5, 151.2, 148.7, 147.5, 146.3, 146.2, 142.8, 136.4, 133.9, 133.8, 132.8, 131.4, 131.1, 129.4 129.2, 123.9, 123.3, 118.9, 116.4, 83.8, 82.5 64.8, 64.4, 49.7, 49.6, 49.1, 46.1, 35.7, 35.1, 34.8, 33.7, 31.8, 31.1, 29.9, 29.7, 29.5, 29.4, 29.0, 28.9, 28.1, 27.1, 26.0, 25.4, 22.9, 22.8, 14.4, 14.3, 11.6. IR (film) 1737, 1658 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O$ $[M+H]^+$, Calculated 269.1654; Found 269.1653.



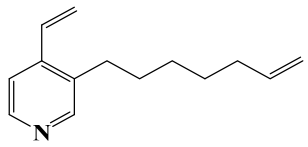
6,7,8,9,12,13,16,17-Octahydropyrido[4,3-c]pyrrolo[1,2-a][1]azacyclotetradecin-14(5H)-one (4.55) – Using the procedure described for the preparation of **4.54**, pyridine substrate **4.53** (0. 0637 g, 0.200 mmol, 1.00 equiv), $Ti(O^iPr)_4$ (0.030 mL, 0.100 mmol, 0.500 equiv), DIPEA (0.050 mL, 0.300 mmol, 1.50 equiv), and $EtCO_2Cl$ (0.0210 mL, 0.220 mmol, 1.10 equiv) were reacted to give **4.55** as a yellow oil (mixture of diastereomers and rotamers, 0.0201 g, 34 %). ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 – 8.24 (m, 2H), 7.26 – 7.13 (m, 0.3H), 7.06 – 6.91 (m, 0.7H), 5.66 – 4.86 (m, 3H), 4.41 – 3.65 (m, 4H), 3.16 – 0.95 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 172.8, 154.6, 154.5, 151.7, 151.4, 148.6, 135.6, 135.5, 131.4, 128.1, 128.0, 120.5, 120.4, 82.6, 82.6, 64.9, 64.8, 64.7, 64.6, 60.6, 45.3, 36.0, 35.9, 33.7, 30.9, 30.5, 30.1, 30.0, 29.2, 28.2, 27.7, 27.6, 27.2, 26.9, 26.5, 26.3, 25.2, 24.2, 21.2, 14.50, 14.46, 14.4. IR (film) 1728, 1643 cm^{-1}. HRMS (ESI) $C_{19}H_{25}N_2O$ $[M+H]^+$, Calculated 297.1966; Found 297.1971.

Experimental Procedures and Characterization Data for preparation of aminoethyl pyridine analogues



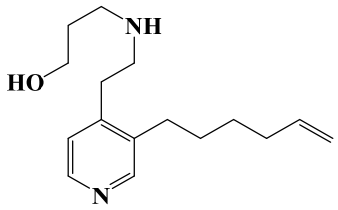
3-(Hex-5-en-1-yl)-4-vinylpyridine (4.56) - Methyltriphenylphosphonium bromide (3.98 g, 11.1 mmol, 1.05 equiv) was dissolved in THF (80 mL) and cooled to 0 ºC using an ice bath. Then n-BuLi (2.5 M, 4.4 mL, 11.1 mmol, 1.05 equiv) was added and the reaction

maintained at 0 ºC for 1 h, followed by cooling to -78 ºC. Thereafter 3-(hex-5-en-1-yl)isonicotinaldehyde (**4.37**) (2.00 g, 10.6 mmol, 1.00 equiv) dissolved in THF (10 mL) was added and the reaction mixture was stirred at -78 ºC for 2 h. Reaction mixture was then allowed to warm to room temperature overnight, and quenched with saturated aqueous NH_4Cl (40 mL). Reaction mixture was concentrated to remove THF and extracted with EtOAc (40 mL x 3). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude mixture was purified with flash column chromatography using 0-30% EtOAc in hexanes to afford **4.56** as a colorless liquid (1.47 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.1 Hz, 1H), 8.35 (s, 1H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.88 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.82 (dd, *J* = 17.4, 1.0 Hz, 1H), 5.79 – 5.71 (m, 1H), 5.46 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.03 – 4.86 (m, 2H), 2.72 – 2.55 (m, 2H), 2.05 (dt, *J* = 8.5, 7.0 Hz, 2H), 1.55 (dtd, *J* = 9.2, 7.5, 5.9 Hz, 2H), 1.48 – 1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 147.8, 143.5, 138.7, 134.9, 132.6, 119.6, 119.3, 114.8, 33.7, 30.5, 30.4, 28.8. IR (film) 3077, 1639 cm^{-1}. HRMS (ESI) $C_{13}H_{18}N$ $[M+H]^+$, Calculated 188.1439; Found 188.1450.

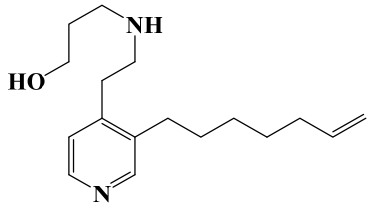


3-(Hept-6-en-1-yl)-4-vinylpyridine (4.57) - Using the procedure described for the preparation of **4.56**, 3-(hept-6-en-1-yl)isonicotinaldehyde (**4.38**) (0.950 g, 4.67 mmol, 1 equiv), Methyltriphenylphosphonium bromide (1.75 g, 4.90 mmol, 1.05 equiv), and n-BuLi (2.5 M) (1.90 mL, 4.90 mmol, 1.05 equiv) were reacted to give **4.57** as a colorless liquid (0.790 g, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 5.2 Hz, 1H), 8.34 (s,

1H), 7.29 (d, *J* = 5.2 Hz, 1H), 6.87 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.85 – 5.71 (m, 2H), 5.45 (dd, *J* = 11.0, 1.1 Hz, 1H), 4.99 – 4.87 (m, 2H), 2.69 – 2.52 (m, 2H), 2.08 – 1.94 (m, 2H), 1.57 – 1.46 (m, 2H), 1.43 – 1.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 147.8, 143.6, 139.0, 134.9, 132.6, 119.6, 119.3, 114.6, 33.8, 30.9, 30.6, 29.0, 28.8. IR (film) 2932, 1636 cm^{-1}. HRMS (ESI) $C_{14}H_{20}N$ $[M+H]^+$, Calculated 202.1596; Found 202.1611.

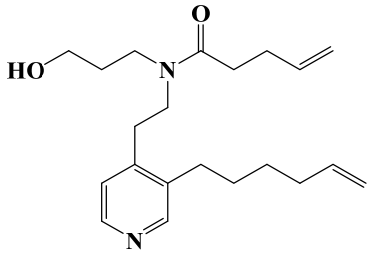


3-((2-(3-(Hex-5-en-1-yl)pyridin-4-yl)ethyl)amino)propan-1-ol (4.58) – Pyridine **4.56** (1.47 g, 7.85 mmol, 1.00 equiv) and 3-aminopropanol (6.0 mL, 78.5 mmol, 10.0 equiv) were dissolved in toluene (40 mL) and Amberlyst-15 (1.47 g, 100% w.r.t pyridine substrate) was added. Reaction mixture was then heated in a 120 ºC oil bath until complete consumption of starting material was observed by TLC (~7 days). After cooling to room temperature, the mixture was filtered through Celite® and the celite was further rinsed with MeOH to maximize product yield. The filtrate was concentrated to remove solvent. Crude product was purified via flash column chromatography using 0-30% MeOH in EtOAc to afford **4.58** as a yellow oil (1.47 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.28 (d, *J* = 5.0 Hz, 1H), 7.01 (d, *J* = 5.0 Hz, 1H), 5.83 – 5.61 (m, 1H), 5.05 – 4.84 (m, 2H), 3.78 – 3.72 (m, 2H), 2.87 – 2.79 (m, 4H), 2.78 – 2.73 (m, 2H), 2.61 – 2.55 (m, 2H), 2.10 – 2.00 (m, 2H), 1.71 – 1.62 (m, 2H), 1.59 – 1.50 (m, 2H), 1.48 – 1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 147.5, 146.4, 138.6, 136.4, 124.1, 114.9, 64.0, 49.9, 49.8, 33.6, 32.4, 31.1, 30.6, 30.0, 28.8. IR (film) 3270, 1632 cm^{-1}. HRMS (ESI) $C_{16}H_{27}N_2O$ $[M+H]^+$, Calculated 263.2123; Found 263.2130.



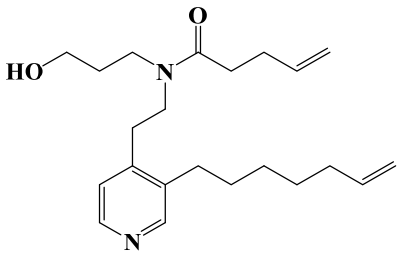
3-((2-(3-(Hept-6-en-1-yl)pyridin-4-yl)ethyl)amino)propan-1-ol (4.59) – Using the procedure described for the preparation of **4.58**, 3-(hept-6-en-1-yl)-4-vinylpyridine (**4.57**) (0.080 g, 0.40 mmol, 1 equiv), 3-aminopropanol (0.30 mL, 78.5 mmol, 10 equiv), and amberlyst 15 (0.080 g, 100 % w.r.t pyridine substrate) were reacted to give **4.59** as a yellow oil (0.102 g, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.26 (d, *J* = 5.0 Hz, 1H), 6.99 (d, *J* = 5.0 Hz, 1H), 5.83 – 5.65 (m, 1H), 4.98 – 4.81 (m, 2H), 3.79 – 3.67 (m, 2H), 2.99 (s, 2H), 2.84 – 2.77 (m, 4H), 2.77 – 2.67 (m, 2H), 2.59 – 2.50 (m, 2H), 2.04 – 1.88 (m, 2H), 1.70 – 1.60 (m, 2H), 1.55 – 1.45 (m, 2H), 1.40 – 1.27 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.4, 146.4, 138.9, 136.4, 124.0, 114.5, 63.6, 49.8, 49.6, 33.7, 32.3, 31.2, 30.9, 30.1, 29.1, 28.8. IR (film) 3284, 1636 cm^{-1}. HRMS (ESI) $C_{17}H_{29}N_2O$ $[M+H]^+$, Calculated 277.2280; Found 277.2282.

Experimental Procedures and Characterization Data for preparation of aminoethylpyridine precursors for RCM



N-(2-(3-(Hex-5-en-1-yl)pyridin-4-yl)ethyl)-N-(3-hydroxypropyl)pent-4-enamide (4.60) – Using the procedure described for the preparation of **4.44**, Pyridine **4.58** (1.40 g,

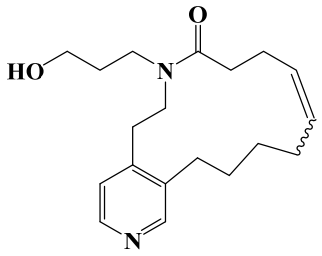
5.34 mmol, 1.0 equiv), 4-penten-1-oic acid (0.60 mL, 5.87 mmol, 1.1 equiv), triethylamine (2.30 mL, 16.0 mmol, 3.0 equiv), HOBt (0.794 g, 5.87 mmol, 1.1 equiv), and EDC.HCl (1.13 g, 5.87 mmol, 1.1 equiv) were reacted to give **4.60** as a yellow oil (mixture of rotamers, 1.30 g, 71 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 0.6H), 8.30 (d, *J* = 5.0 Hz, 0.6H), 8.27 (s, 0.4H), 8.23 (d, *J* = 5.0 Hz, 0.4H), 7.02 (d, *J* = 5.0 Hz, 0.4H), 6.95 (d, *J* = 5.0 Hz, 0.6H), 5.89 – 5.61 (m, 2H), 5.07 – 4.79 (m, 4H), 3.63 – 3.57 (m, 0.4H), 3.52 – 3.37 (m, 5.2H), 3.36 – 3.28 (m, 0.4H), 2.88 – 2.76 (m, 2H), 2.68 – 2.51 (m, 2H), 2.46 – 2.21 (m, 4H), 2.07 – 1.99 (m, 2H), 1.76 – 1.50 (m, 4H), 1.47 – 1.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 172.5, 150.9, 150.5, 147.7, 147.2, 146.2, 144.5, 138.6, 138.3, 137.6, 137.0, 136.6, 136.1, 124.5, 124.26, 115.8, 115.3, 115.0, 114.8, 58.9, 58.3, 48.1, 47.0, 45.3, 41.9, 33.6, 33.5, 32.4, 32.3, 31.9, 31.3, 30.7, 30.6, 30.3, 30.2, 30.0, 29.8, 29.45, 29.43, 28.8, 28.4. IR (film) 3397, 3069 1643 cm^{-1}. HRMS (ESI) $C_{21}H_{33}N_2O_2$ $[M+H]^+$, Calculated 345.2542; Found 345.2543.



N-(2-(3-(Hept-6-en-1-yl)pyridin-4-yl)ethyl)-N-(3-hydroxypropyl)pent-4-enamide (4.61) – Using the procedure described for the preparation of **4.44**, pyridine **4.59** (0.060 g, 0.220 mmol, 1.0 equiv), 4-penten-1-oic acid (25.0 μL, 0.240 mmol, 1.1 equiv), triethylamine (0.10 mL, 0.660 mmol, 3.0 equiv), HOBt (0.032 g, 0.240 mmol, 1.1 equiv), and EDC.HCl (0.046 g, 0.240 mmol, 1.1 equiv) were reacted to give **4.61** as a yellow oil (mixture of rotamers, 0.064 g, 81 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 0.6H), 8.29

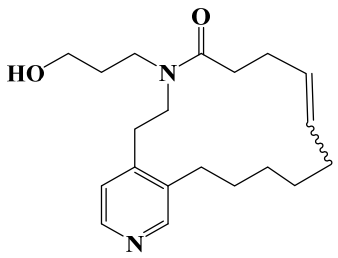
(d, J = 5.0 Hz, 0.6H), 8.26 (s, 0.4H), 8.23 (d, J = 5.0 Hz, 0.4H), 7.02 (d, J = 5.0 Hz, 0.4H), 6.95 (d, J = 5.1 Hz, 0.6H), 5.87 – 5.64 (m, 2H), 5.04 – 4.81 (m, 4H), 3.64 – 3.53 (m, 1H), 3.52 – 3.35 (m, 4.4H), 3.35 – 3.24 (m, 0.6H), 2.88 – 2.74 (m, 2H), 2.66 – 2.51 (m, 2H), 2.46 – 2.16 (m, 4H), 2.05 – 1.89 (m, 2H), 1.77 – 1.60 (m, 2H), 1.60 – 1.44 (m, 2H), 1.43 – 1.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.47, 172.48, 150.9, 150.4, 147.7, 147.2, 146.2, 144.5, 138.9, 138.7, 137.6, 137.0, 136.7, 136.2, 124.5, 124.3, 115.8, 115.3, 114.7, 114.5, 58.9, 58.3, 48.1, 47.0, 45.3, 41.9, 33.8, 33.7, 32.4, 32.3, 31.9, 31.3, 31.2, 31.1, 30.4, 30.2, 29.9, 29.46, 29.45, 29.2, 29.1, 28.82, 28.77. IR (film) 3399, 3077, 1642 cm^{-1}. HRMS (ESI) $C_{22}H_{34}N_2O_2$ $M^{\cdot+}$, Calculated 358.2620; Found 358.2613.

Experimental Procedures and Characterization Data for ring closing metathesis of aminoethylpyridine substrates



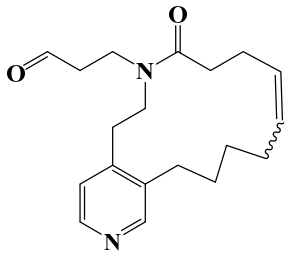
7-(3-Hydroxypropyl)-6,7,9,10,13,14,15,16-octahydropyrido[4,3-d][1]azacyclotetradecin-8(5H)-one (4.62) – Using the procedure described for the preparation of **4.50**, pyridine **4.60** (0.650 g, 1.89 mmol, 1.0 equiv), Zhan 1B catalyst (0.041 g, 0.057 mmol, 0.03 equiv), and di(ethyleneglycol) vinyl ether (1.0 mL, 7.60 mmol, 4.0 equiv) were reacted to give **4.62** as a yellow brown oil (mixture of diastereomers and rotamers, 0.558 g, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.28 (m, 2H), 7.23 (d, J = 5.2 Hz, 0.1H), 7.11 – 6.95 (m, 0.9H), 5.68 – 5.34 (m, 2H), 3.87 (s, 1H), 3.71 – 3.20 (m, 6H), 3.02 – 2.82 (m, 2H), 2.68 – 2.36 (m, 6H), 2.37 – 2.09 (m, 2H),

1.89 – 1.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 151.5, 147.9, 147.8, 147.4, 145.1, 143.9, 137.4, 136.6, 133.2, 132.6, 132.1, 129.6, 128.6, 124.2, 122.5, 58.3, 58.3, 49.7, 48.2, 46.8, 43.1, 42.8, 32.7, 32.5, 32.2, 31.2, 30.9, 30.5, 30.5, 30.0, 29.9, 29.5, 29.1, 28.5, 28.4, 27.5, 27.3, 24.3, 24.1. IR (film) 3379, 1628 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ $[M+H]^+$, Calculated 317.2229; Found 317.2239.

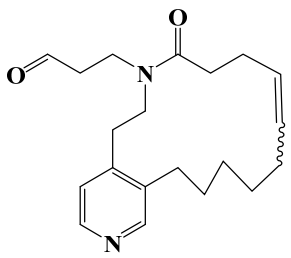


7-(3-Hydroxypropyl)-5,6,7,9,10,13,14,15,16,17-decahydro-8H-pyrido[4,3-d][1]azacyclopentadecin-8-one (4.63) – Using the procedure described for the preparation of **4.50**, pyridine **4.61** (0.064 g, 0.18 mmol, 1.0 equiv), Zhan 1B catalyst (0.004 g, 0.005 mmol, 0.03 equiv), and di(ethyleneglycol) vinyl ether (0.097 mL, 0.72 mmol, 4.0 equiv) were reacted to give **4.63** as a yellow brown oil (mixture of diastereomers and rotamers, 0.547 g, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.27 (m, 2H), 7.27 – 7.20 (m, 0.1H), 7.20 – 7.10 (m, 0.2H), 7.10 – 6.97 (m, 0.7H), 5.64 – 5.30 (m, 2H), 3.82 – 3.23 (m, 7H), 3.04 – 2.86 (m, 2H), 2.68 – 2.24 (m, 6H), 2.24 – 2.17 (m, 0.3H), 2.15 – 2.05 (m, 1.7H), 1.84 – 1.35 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 174.2, 151.7, 151.4, 151.3, 147.8, 144.7, 144.2, 136.7, 136.6, 133.1, 132.4, 131.4, 129.8, 129.6, 129.2, 128.5, 128.4, 124.5, 123.1, 58.3, 58.3, 58.2, 49.3, 48.1, 43.1, 42.6, 42.1, 34.7, 34.1, 32.5, 32.4, 32.3, 32.2, 32.1, 31.8, 31.5, 31.24, 31.19, 30.9, 30.7, 30.5, 29.9, 29.5, 29.3, 28.3, 27.5, 27.4, 27.3, 26.7, 25.1, 24.8. IR (film) 3390, 1636 cm^{-1}. HRMS (ESI) $C_{20}H_{31}N_2O_2$ $[M+H]^+$, Calculated 331.2386; Found 331.2386.

Experimental Procedures and Characterization Data for DMP oxidation of aminoethylpyridine substrates

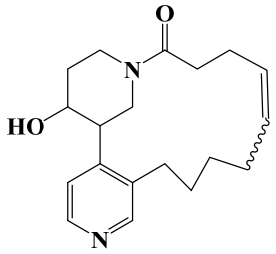


3-(8-Oxo-5,8,9,10,13,14,15,16-octahydropyrido[4,3-d][1]azacyclotetradecin-7(6H)-yl)propanal (4.64) – Using the procedure described for the preparation of **4.52**, Pyridine **4.62** (0.200 g, 0.63 mmol, 1.0 equiv), Dess-Martin Periodinane (0.400 g, 0.950 mmol, 1.50 equiv), and K_2CO_3 (0.261 g, 1.89 mmol, 3.0 equiv) were reacted to give **4.64** as a yellow oil (mixture of diastereomers and rotamers, 0.113 g, 57 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 0.3H), 9.73 (s, 0.4H), 9.59 (s, 0.3H), 8.47 – 8.31 (m, 2H), 7.18 – 7.00 (m, 1H), 5.63 – 5.33 (m, 2H), 3.85 – 3.67 (m, 2H), 3.54 – 3.43 (m, 1H), 3.37 (t, J = 6.1 Hz, 1H), 2.97 – 2.76 (m, 2H), 2.76 – 2.11 (m, 10H), 1.77 – 1.36 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 173.2, 173.1, 151.6, 151.5, 147.9, 147.7, 145.1, 136.6, 133.1, 131.9, 129.7, 128.8, 124.3, 122.9, 50.7, 49.5, 43.5, 43.3, 41.8, 41.1, 32.8, 32.7, 32.6, 32.5, 31.4, 30.6, 29.9, 29.6, 29.3, 29.2, 27.6, 27.4, 24.4, 23.9. IR (film) 1690, 1672 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ $[M+H]^+$, Calculated 315.2073; Found 315.2063.



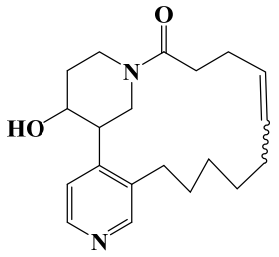
3-(8-Oxo-5,6,8,9,10,13,14,15,16,17-decahydro-7H-pyrido[4,3-d][1]azacyclopentadecin-7-yl)propanal (4.65) – Using the procedure described for the preparation of **4.52**, pyridine **4.63** (0.491 g, 1.49 mmol, 1.0 equiv), Dess-Martin Periodinane (0.950 g, 2.23 mmol, 1.50 equiv), and K_2CO_3 (0.618 g, 4.47 mmol, 3.0 equiv) were reacted to give **4.65** as a yellow oil (mixture of diastereomers and rotamers, 0.455 g, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 – 9.69 (m, 1H), 8.50 – 8.29 (m, 2H), 7.20 – 6.96 (m, 1H), 5.66 – 5.25 (m, 2H), 3.83 – 3.29 (m, 4H), 2.99 – 2.76 (m, 4H), 2.75 – 2.01 (m, 8H), 1.76 – 1.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 174.8, 174.5, 173.1, 151.7, 151.3, 147.9, 144.8, 144.3, 136.6, 132.2, 131.4, 129.9, 128.7, 124.6, 123.3, 50.7, 50.5, 49.5, 49.2, 43.4, 43.3, 43.2, 41.2, 40.8, 34.8, 34.2, 32.7, 32.4, 32.1, 31.7, 31.4, 30.9, 29.0, 28.3, 27.5, 26.7, 25.2, 24.5. IR (film) 1719, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{29}N_2O_2$ $[M+H]^+$, Calculated 329.2229; Found 329.2225.

Experimental Procedures and Characterization Data for anhydrobase mediated cyclization of aldehyde substrates



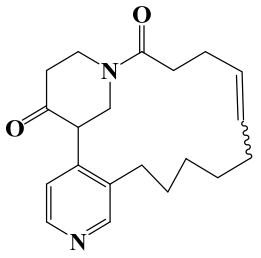
24-Hydroxy-1(4,3)-pyridina-2(3,1)-piperidinacycloundecaphan-6-en-3-one (4.66) – Using the procedure described for the preparation of **4.54**, pyridine **4.64** (0.100 g, 0.32 mmol, 1.0 equiv), $Ti(O^iPr)_4$ (0.048 mL, 0.16 mmol, 0.50 equiv), DIPEA (0.079 mL, 0.48 mmol, 1.5 equiv), and $EtCO_2Cl$ (0.033 mL, 0.35 mmol, 1.1 equiv) were reacted to give **4.66** as a yellow oil (crude yield, mixture of diastereomers and rotamers, 0.0714 g, 71 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 – 8.25 (m, 2H), 7.25 – 6.92 (m, 1H), 5.73 – 5.33 (m, 2H), 4.76 – 4.46 (m, 2H), 3.79 – 3.26 (m, 4H), 2.83 – 1.92 (m, 7H), 1.94 – 1.19 (m, 8H). IR (film) 3342, 1621 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ $[M+H]^+$, Calculated 315.2073; Found 315.2070.



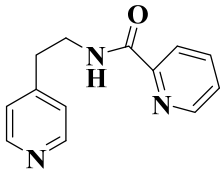
24-Hydroxy-1(4,3)-pyridina-2(3,1)-piperidinacyclododecaphan-6-en-3-one (4.67) – Using the procedure described for the preparation of **4.54**, pyridine **4.65** (0.050 g, 0.15 mmol, 1.0 equiv), $Ti(O^iPr)_4$ (0.023 mL, 0.075 mmol, 0.50 equiv), DIPEA (0.038 mL, 0.23 mmol, 1.5 equiv), and $EtCO_2Cl$ (0.017 mL, 0.17 mmol, 1.1 equiv) were reacted to give **4.67** as a yellow oil (mixture of diastereomers and rotamers, 0.0344 g, 74 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 – 8.03 (m, 2H), 7.41 (d, J = 5.2 Hz, 0.1H), 7.22 – 6.95 (m, 0.9H), 5.80 – 5.17 (m, 2H), 4.81 – 4.39 (m, 1H), 4.29 – 1.09 (m, 22H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.4, 170.5, 151.2, 150.9, 147.5, 147.3, 147.1, 136.6, 136.4, 134.48, 132.2, 131.5, 130.0, 129.9, 128.8, 122.6, 122.2, 66.6, 66.5, 44.5, 44.5, 44.4, 44.1, 37.0, 33.8, 33.4, 33.3, 33.2, 32.4, 32.2, 31.6, 30.6, 30.2, 30.0, 29.6, 28.3, 28.0, 27.8, 25.9, 22.4. IR (film) 3371, 1631 cm^{-1}. HRMS (ESI) $C_{20}H_{29}N_2O_2$ $[M+H]^+$, Calculated 329.2229; Found 329.2236.

Experimental Procedures and Characterization Data for DMP oxidation of compound **4.67**



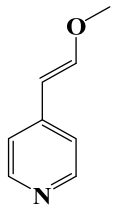
1(4,3)-Pyridina-2(3,1)-piperidinacyclododecaphan-6-ene-24,3-dione (4.68) - Using the procedure described for the preparation of **4.52**, pyridine **4.56** (0.058 g, 0.18 mmol, 1.0 equiv), Dess-Martin Periodinane (0.112 g, 0.26 mmol, 1.50 equiv), and K_2CO_3 (0.075 g, 0.54 mmol, 3.0 equiv) were reacted to give **4.68** as a yellow oil (mixture of diastereomers and rotamers, 0.0388 g, 66 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.32 (m, 2H), 7.22 – 6.77 (m, 1H), 5.88 – 5.26 (m, 2H), 5.20 – 4.74 (m, 1H), 4.48 – 3.22 (m, 4H), 3.22 – 1.85 (m, 10H), 1.84 – 1.05 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 204.4, 172.5, 170.8, 151.5, 147.5, 147.4, 147.3, 141.7, 141.3, 136.7, 132.9, 132.6, 131.7, 129.1, 128.4, 123.8, 123.1, 122.5, 53.0, 52.6, 51.5, 50.5, 42.0, 41.9, 41.6, 41.2, 41.1, 40.9, 33.7, 32.7, 32.2, 31.4, 30.5, 30.3, 29.7, 29.0, 28.0, 27.8, 27.7, 27.3, 26.8, 25.4, 22.5. IR (film) 1720, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{29}N_2O_2$ $[M+H]^+$, Calculated 327.2073; Found 327.2079.

Experimental Procedures and Characterization Data for the synthesis of enol ether **4.73**



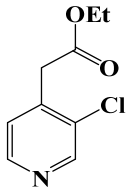
N-(2-(Pyridin-4-yl)ethyl)picolinamide (4.73) - Using the procedure described for the preparation of **4.44**, pyridine **4.72** (1.0 mL g, 8.35 mmol, 1.0 equiv), 2-picolinic acid (1.13 g, 9.20 mmol, 1.1 equiv), triethylamine (3.5 mL, 25.1 mmol, 3.0 equiv), HOBt (1.24 g, 9.20 mmol, 1.1 equiv), and EDC.HCl (1.76 g, 9.20 mmol, 1.1 equiv) were reacted to give **4.73** as a colorless oil (0.520 g, 30 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 – 8.47 (m, 3H), 8.23 – 8.05 (m, 2H), 7.93 – 7.78 (m, 1H), 7.47 – 7.37 (m, 1H), 7.24 – 7.14 (m, 2H), 3.85 – 3.67 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 150.2, 149.8, 148.3, 148.1, 137.6, 126.5, 124.4, 122.4, 39.8, 35.5. HRMS (ESI) $C_{13}H_{14}N_3O$ $(M^{\cdot}+H)^+$, Calculated 228.1137; Found 228.1129.

Experimental Procedures and Characterization Data for the synthesis of enol ether **4.78**

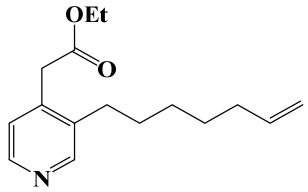


(*E*)-4-(2-Methoxyvinyl)pyridine (4.78) – Using the procedure described for the preparation of **4.56**, 4-pyridinecarboxaldehyde (1.0 mL, 10.6 mmol, 1 equiv), Methoxymethyltriphenylphosphonium chloride (3.82g, 11.1 mmol, 1.05 equiv), and n-BuLi (2.5 M) (4.4 mL, 11.1 mmol, 1.05 equiv) were reacted to give **4.78** as a colorless liquid (1.17 g, 82 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.38 (m, 2H), 7.34 – 7.21 (m, 2H), 7.11 (d, *J* = 5.0 Hz, 2H), 5.71 (d, *J* = 13.0 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2, 149.9, 144.4, 119.7, 102.9, 56.8. HRMS (ESI) C_8H_9NO $[M+H]^+$, Calculated 136.0762; Found 136.0751.

Experimental Procedures and Characterization Data for the synthesis of bis(piperidine) substrate **4.69**

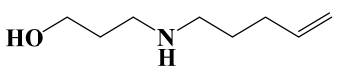


Ethyl 2-(3-chloropyridin-4-yl)acetate (4.82) – 3-chloro-4-pyridinecarboxaldehyde (1.00 g, 7.10 mmol, 1.00 equiv) was dissolved in THF (70 mL). Then Triton B (40 % weight in MeOH) (3.3 mL, 7.10 mmol, 1.00 equiv) and formaldehyde dimethyl thioacetal monoxide (FAMSO) (0.72 mL, 7.10 mmol, 1.00 equiv) were also added to the same reaction mixture followed by refluxing for 3h. Complete consumption of the aldehyde was observed by proton NMR. Then water (70 mL) was added and mixture was concentrated to remove all the THF. Resulting solution was extracted with EtOAc (70 mL x 2). Combined organic layers were dried and concentrated. Crude intermediate was dissolved in EtOH (70 mL) and sat. HCl in EtOH (10 mL) was added. Solution was refluxed for 48h. Then reaction mixture was evaporated to remove EtOH and basified with sat. $NaHCO_3$. Crude mixture was then extracted with EtOAc (70 mL x 3). Combined organic layers were dried and concentrated. Crude product was purified via flash column chromatography using 0 – 50 % EtOAc in hexanes to afford **4.82** as a yellow liquid (0.836 g, 59 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.45 (d, J = 4.9 Hz, 1H), 7.26 (d, J = 4.9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.77 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 149.7, 148.0, 141.2, 132.7, 125.9, 61.7, 38.6, 14.3. HRMS (ESI) $C_9H_{11}NO_2Cl$ $[M+H]^+$, Calculated 200.0478; Found 200.0466.



Ethyl 2-(3-(hept-6-en-1-yl)pyridin-4-yl)acetate (4.83) - Using the procedure described for the preparation of **4.82**, 3-(hept-6-en-1-yl)isonicotinaldehyde (1.80 g, 8.87 mmol, 1.00 equiv), Triton B (40 % weight in MeOH) (4.0 mL, 8.87 mmol, 1.00 equiv), formaldehyde dimethyl thioacetal monoxide (FAMSO) (0.90 mL, 8.87 mmol, 1.00 equiv), and sat. HCl in EtOH (13 mL) were reacted to give **4.83** as a yellow oil (1.16 g, 50 %).

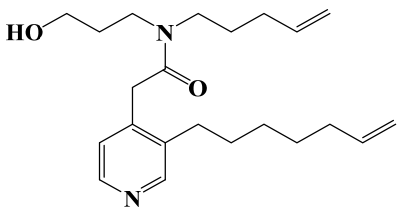
Similarly, using the procedure described for the preparation of **4.35**, ethyl 2-(3-chloropyridin-4-yl)acetate (**4.82**) (1.16 g, 5.80 mmol, 1 equiv), hept-6-en-1-ylboronic acid (0.991 g, 6.97 mmol, 1.20 equiv), and K_2CO_3 (2.40 g, 17.4 mmol, 3 equiv), $Pd(OAc)_2$ (0.065 g, 0.29 mmol, 0.05 equiv) and RuPhos (0.270 g, 0.580 mmol, 0.1 equiv) were reacted at 100 °C for 24 h to give **4.83** as a yellow liquid (1.39 g, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 5.89 – 5.72 (m, 1H), 5.12 – 4.74 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.64 (s, 2H), 2.74 – 2.56 (m, 2H), 2.16 – 1.96 (m, 2H), 1.70 – 1.51 (m, 2H), 1.51 – 1.33 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 150.7, 147.5, 140.9, 138.8, 136.5, 124.9, 114.4, 61.2, 37.9, 33.6, 30.4, 30.2, 28.9, 28.7, 14.1. HRMS (ESI) $C_{16}H_{24}NO_2$ $[M+H]^+$, Calculated 262.1807; Found 262.1808.



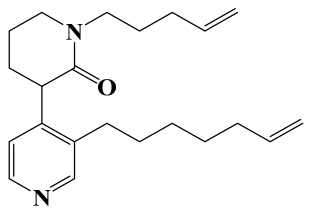
3-(Pent-4-en-1-ylamino)propan-1-ol (4.85) – Using the procedure described for the preparation of **4.44**, 3-aminopropanol (3.0 mL, 39.2 mmol, 1 equiv), 4-penten-1-oic acid

(4.4 mL, 43.1 mmol, 1.1 equiv), triethylamine (17.0 mL, 117 mmol, 3.0 equiv), HOBt (5.82 g, 43.1 mmol, 1.1 equiv), and EDC.HCl (8.26 g, 43.1 mmol, 1.1 equiv) were reacted to give N-(3-hydroxypropyl)pent-4-enamide (**4.84**) as a colorless liquid (4.93 g, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.93 – 5.70 (m, 1H), 5.16 – 4.92 (m, 2H), 3.76 – 3.51 (m, 3H), 3.48 – 3.31 (m, 2H), 2.47 – 2.33 (m, 2H), 2.35 – 2.23 (m, 2H), 1.80 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 137.0, 115.9, 59.4, 36.4, 35.9, 32.4, 29.8. IR (film) 3302, 3085, 1657 cm^{-1}. HRMS (ESI) $C_8H_{16}NO_2$ $[M+H]^+$, Calculated 158.1181; Found 158.1169. This was taken in to the next step.

Lithium Aluminumhydride (1.70 g, 44.5 mmol, 3 equiv) was dissolved in THF (225 mL) and cooled down to 0 ºC using an ice bath. Then N-(3-hydroxypropyl)pent-4-enamide (**4.84**) (3.50 g, 22.2 mmol, 1.00 equiv) dissolved in THF (10 mL) was dropwisely added to the above reaction mixture. Reaction mixture was warmed up to room temperature overnight. Then it was quenched with a solution of sat. Rochell's salt (100 mL) at 0 ºC. THF was removed under vaccuo. Mixture was then extracted with EtOAc (100 mL x 3). Combined organic layers were dried and concentrated to yield **4.85** as a colorless oil (3.08 g, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 – 5.64 (m, 1H), 5.13 – 4.85 (m, 2H), 3.84 – 3.76 (m, 2H), 2.90 – 2.83 (m, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.17 – 2.01 (m, 2H), 1.76 – 1.62 (m, 2H), 1.63 – 1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 114.8, 64.4, 50.0, 49.2, 31.4, 30.7, 29.0. HRMS (ESI) $C_8H_{18}NO$ $[M+H]^+$, Calculated 144.1388; Found 144.1384.

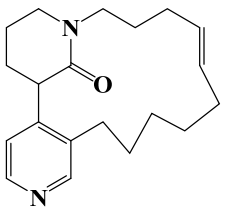


2-(3-(Hept-6-en-1-yl)pyridin-4-yl)-N-(3-hydroxypropyl)-N-(pent-4-en-1-yl)acetamide (4.86) – 3-(Pent-4-en-1-ylamino)propan-1-ol (0.815 g, 5.7 mmol, 1.1 equiv) was dissolved in DCM (50 mL) and trimethylaluminum (2.0 M) (6.8 mL, 13.4 mmol, 2.6 equiv) was drop wisely added to it. After 30 min Pyridine **4.83** (1.35 g, 5.17 mmol, 1.00 equiv) dissolved in DCM (5 mL) was added and reaction mixture was refluxed for 48 h. Thereafter reaction was quenched with 1 M HCl (30 mL) and stirred for 30 min. After basification with sat. Na_2CO_3 mixture was extracted with DCM (50 mL x 3). Combined organic layers were dried and concentrated. Crude product was purified via flash column chromatography using 10 % MeOH in EtOAc to afford compound **4.86** as yellow oil (mixture of rotamers, 1.11 g, 60 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 – 8.31 (m, 2H), 7.13 – 7.01 (m, 1H), 5.92 – 5.66 (m, 2H), 5.15 – 4.87 (m, 4H), 3.76 (s, 0.4H), 3.72 (s, 1.6H), 3.63 – 3.47 (m, 4H), 3.46 – 3.32 (m, 1H), 3.31 – 3.18 (m, 1H), 2.72 – 2.52 (m, 2H), 2.17 – 1.95 (m, 4H), 1.88 – 1.48 (m, 6H), 1.50 – 1.31 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 169.5, 150.6, 150.4, 147.6, 147.5, 141.9, 138.7, 137.7, 136.6, 136.2, 124.2, 124.1, 116.2, 115.1, 114.5, 114.4, 59.1, 58.4, 47.8, 45.6, 44.9, 42.2, 36.9, 36.7, 33.6, 31.5, 31.2, 30.8, 30.5, 30.4, 30.4, 30.2, 30.1, 29.4, 29.0, 28.7, 27.9, 26.7. HRMS (ESI) $C_{22}H_{35}N_2O_2$ $[M+H]^+$, Calculated 359.2699; Found 359.2698.



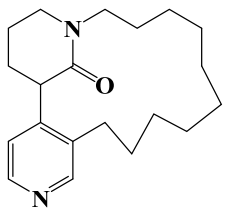
3-(3-(Hept-6-en-1-yl)pyridin-4-yl)-1-(pent-4-en-1-yl)piperidin-2-one (4.87) – Pyridine substrate **4.86** (0.744 g, 2.1 mmol, 1.00 equiv) was dissolved in THF (20 mL) and triethylamine (0.74 mL, 5.25 mmol, 2.5 equiv) was added to it. Reaction mixture was

cooled down to 0 ºC using an ice bath and then MsCl (0.177 mL, 2.30 mmol, 1.10 equiv) was added and stirred for 20 min at the same temperature. TLC (10 % MeOH in EtOAc) showed complete consumption of the starting material. Then NaH (0.30 g, 6.3 mmol, 3.00 equiv) and NaI (0.032 g, 0.21 mmol, 0.10 equiv) were added to the reaction mixture. It was allowed to warm up to room temperature over 1 hour and then stirred at room temperature for additional 3 hours. Thereafter reaction mixture was refluxed for additional 18 h, after which TLC and crude proton NMR confirmed complete formation of the product. It was quenched with water (20 mL) and then extracted with EtOAc (20 mL x 3). Combined organic layers were dried and concentrated. Crude was purified via flash column chromatography using 10 % MeOH in EtOAc to afford compound **4.87** as a yellow oil (0.406 g, 57 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.36 (d, *J* = 5.1 Hz, 1H), 6.94 (d, *J* = 5.1 Hz, 1H), 5.92 – 5.73 (m, 2H), 5.16 – 4.88 (m, 4H), 3.82 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.61 – 3.46 (m, 2H), 3.46 – 3.28 (m, 2H), 2.72 – 2.56 (m, 2H), 2.22 – 1.56 (m, 12H), 1.54 – 1.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 151.0, 149.0, 147.7, 139.1, 137.9, 136.1, 122.9, 115.3, 114.6, 48.5, 47.6, 44.9, 33.9, 31.3, 31.2, 30.4, 30.2, 29.4, 28.9, 26.5, 22.0. HRMS (ESI) $C_{22}H_{33}N_2O$ $[M+H]^+$, Calculated 341.2593; Found 341.2611.

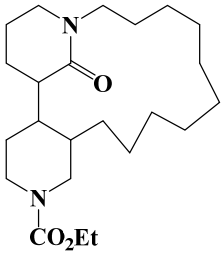


(E)-1(4,3)-Pyridina-2(3,1)-piperidinacyclododecaphan-6-en-22-one (4.88) - Using the procedure described for the preparation of **4.50**, pyridine **4.87** (0.739 g, 2.17 mmol, 1.0 equiv), Zhan 1B catalyst (0.048 g, 0.065 mmol, 0.03 equiv), and di(ethyleneglycol) vinyl

ether (1.20 mL, 8.68 mmol, 4.0 equiv) were reacted to afford **4.88** as a yellow brown oil (0.630 g, 93 % mixture of atropisomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 – 8.17 (m, 2H), 7.18 – 6.89 (m, 1H), 5.77 – 5.18 (m, 2H), 4.24 – 3.00 (m, 5H), 2.90 – 1.10 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.7, 151.7, 147.9, 147.7, 147.6, 147.6, 147.5, 147.4, 147.3, 137.1, 136.6, 136.3, 131.0, 131.0, 130.7, 130.5, 130.2, 129.7, 125.2, 47.9, 47.2, 46.9, 45.3, 31.5, 31.3, 30.7, 30.2, 29.9, 29.8, 29.6, 28.7, 28.3, 27.8, 27.5, 27.5, 27.4, 26.8, 26.4, 26.2, 25.4, 25.2, 23.7, 23.5, 23.4. HRMS (ESI) $C_{20}H_{29}N_2O$ $[M+H]^+$, Calculated 313.2280; Found 313.2276.



1(4,3)-Pyridina-2(3,1)-piperidinacyclododecaphan-2^2-one (4.89) – Pyridine **4.88** (0.630 g, 2.02 mmol, 1 equiv) was dissolved in EtOH (20 mL) and Pd/C (0.060 g, 10 % by wt) was added to the reaction mixture. This solution was kept in a hydrogenation bomb under 100 psi for 12h. Thereafter solution was filtered through Celite and filtrate was concentrated and purified via flash column chromatography using 20 % MeOH in EtOAc to afford compound **4.89** as a yellow oil (0.472 g, 69 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.41 (m, 1H), 8.37 (d, J = 5.1 Hz, 1H), 7.05 (d, J = 5.1 Hz, 1H), 3.90 – 3.13 (m, 5H), 2.73 – 2.33 (m, 2H), 2.17 – 1.88 (m, 4H), 1.84 – 1.10 (m, 16H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 150.7, 150.6, 147.3, 147.3, 136.4 124.1, 47.5, 46.3, 30.1, 30.1, 28.7, 28.5, 27.6, 27.4, 26.9, 26.5, 26.4, 26.3, 25.7, 25.0, 23.4. HRMS (ESI) $C_{20}H_{31}N_2O$ $[M+H]^+$, Calculated 315.2436; Found 315.2433.



Bis(piperidine) model substrate (4.91) – Pyridine substrate **4.89** (0.200 g, 0.640 mmol, 1.00 equiv) was dissolved in THF (7 mL) and triethylamine (0.450 mL, 3.20 mmol, 5.00 equiv) was added to it. Then ethyl chloroformate (0.092 mL, 0.96 mmol, 1.50 equiv) was added and refluxed for 30 min. Thereafter reaction mixture was immediately filtered to remove triehtylammonium chloride salt. This filtration was crucial to prevent re-aromatization of the anhydrobase back to pyridine. Then the filtrate was concentrated to remove all the solvent and excess triethylamine. The ^{1}H-NMR of the remaining residue confirmed the presence of **4.90** (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.22 (br. s, 1H), 7.09 (br. s, 1H), 6.06 (br. s, 1H), 4.44 – 4.25 (m, 2H), 3.66 – 2.84 (m, 4H), 2.71 – 2.30 (m, 4H), 1.76 – 0.97 (m, 21H). LRMS (ESI) $C_{23}H_{35}N_2O_3$ $[M+H]^+$, Calculated 387.3; Found 387.3. Crude anhydrobase was re-dissolved in anhydrous THF (7 mL) and PtO_2 (0.010 g, 5 % by wt) was added. Reaction mixture was then placed in a tightly closed hydrogenation bomb and pressurized to 700 psi. Pressure was maintained for 7 days. Then reaction was filtered to remove the catalyst and the concentrated filtrate was purified via flash column chromatography using 0 – 75 % EtOAc in hexanes to afford **4.91** as a colorless oil. (mixture of rotamers, 0.105 g, 50 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.58 – 4.43 (m, 1H), 4.38 – 4.02 (m, 3H), 3.58 – 3.45 (m, 0.5H), 3.39 – 3.31 (m, 0.5H), 3.25 – 3.16 (m, 0.5H), 3.13 – 3.07 (m, 0.5H), 2.89 – 2.67 (m, 2H), 2.67 – 2.54 (m, 1.5H), 2.54 – 2.41 (m, 1.5H), 2.12 – 2.01 (m, 1H), 2.01 – 1.91 (m, 1H), 1.91 – 1.82 (m, 1H),

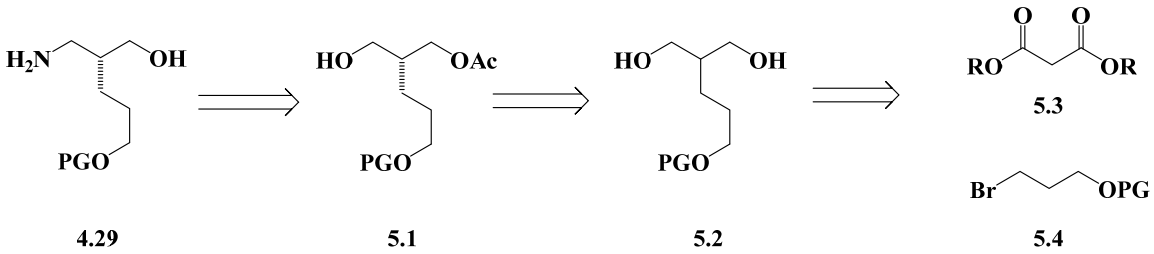
1.82 – 1.01 (m, 26H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 156.1, 61.3, 61.2, 53.6, 50.5, 49.3, 48.9, 47.7, 47.6, 47.2, 47.0, 46.7, 46.4, 45.1, 44.9, 40.9, 40.2, 39.7, 35.7, 34.4, 29.9, 29.3, 27.6, 27.5, 27.0, 26.8, 26.7, 26.5, 26.4, 25.9, 25.7, 25.5, 25.3, 24.8, 24.7, 24.6, 24.4, 24.2, 24.2, 24.1, 23.9, 23.9, 23.6, 23.5, 22.9, 22.8, 22.0, 14.9, 14.9, 14.3. HRMS (ESI) $C_{23}H_{41}N_2O_3$ $[M+H]^+$, Calculated 393.3117; Found 393.3116.

Chapter Five

Enzyme Catalyzed *trans*-Esterification of 1,3-Diols

5.1 Introduction

As discussed in chapter 4, synthesis of xestoproxamine C (**2.38**) requires a parallel synthesis of an enantiopure 2-substituted-3-aminopropanol (**4.29**, Scheme 4.3) that would be employed as a chiral building block later in the synthesis. It was envisioned that this chiral amino alcohol could be synthesized from a 2-substituted-1,3-diol substrate (**5.2**) (Scheme 5.1).



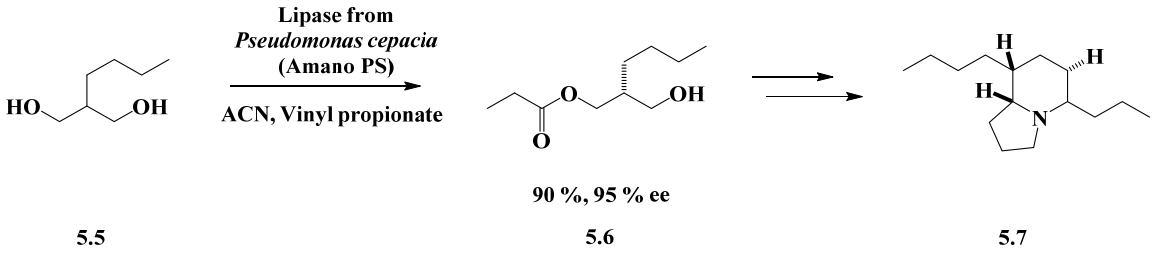
Scheme 5.1 - Retrosynthetic analysis of the aminopropanol precursor **4.29**

Aminopropanol **4.29** can be synthesized via a substitution reaction of the alcohol group in **5.1** with an azide, followed by reduction of both azide and ester functionalities. Substrate **5.1** will then be synthesized via an enzyme catalyzed transesterification of the 1,3-diol substrate **5.2**. It is important that this reaction proceed with high enantioselection (*ee*) to establish the correct absolute stereochemistry in **4.29** and, ultimately, in xestoproxamine C. In turn, construction of **5.2** is expected to be achieved from starting fragments **5.3** and **5.4** that are easily accessible from commercial sources.

Lipases have moved on from their original applications to the biotechnological processing of fats and other lipids.[175] However, in addition to those applications, these

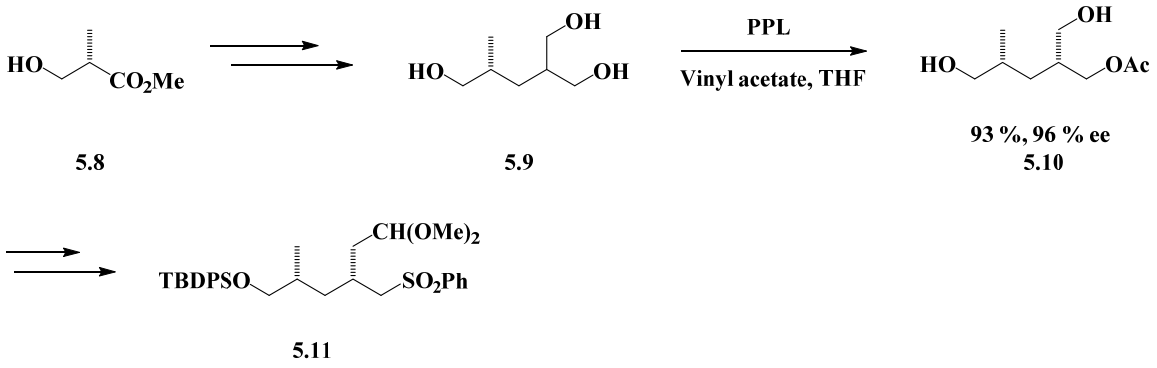
hydrolytic enzymes have recently been used to catalyze the same reactions of hydrolysis and esterification on a wide variety of substrates.[176] Lipases are probably the most frequently used enzymes in organic synthesis as several preparations from different sources are commercially available at low cost with a satisfactory degree of purity, and they do not need cofactors for their catalytic activity.[177] Moreover, these enzymes seem especially well suited to applications in organic chemistry, since their inherent activity involves reaction at the lipid-water interface. This provides lipases with higher affinity for hydrophobic media, thus distinguishing them from other hydrolytic systems.[178] The general aspects of the synthesis of enantiomerically pure optically active compounds making use of various biocatalysts have been reviewed.[177,179]

Enzyme catalyzed acylation by desymmetrization of 1,3-diols is a useful method for the preparation of chiral building blocks.[176,180-184] Many examples are available in the literature describing preparation of enantiopure materials from symmetrical 2-alkyl-1,3-diols with lipases from *Pseudomonas fluorescenes* (PFL), porcine pancreas (PPL), and *Pseudomonas cepacia* (Amano PS lipase).[185-187] Daly and coworkers have used a lipase from *Pseudomonas cepacia* (Amano PS lipase) for the transesterification of the symmetrical diol **5.5** to afford the mono-propionate **5.6** in a good yield and enantiopurity. This was used in their synthesis of the indolizidine alkaloid **5.7** (Scheme 5.2).[188]



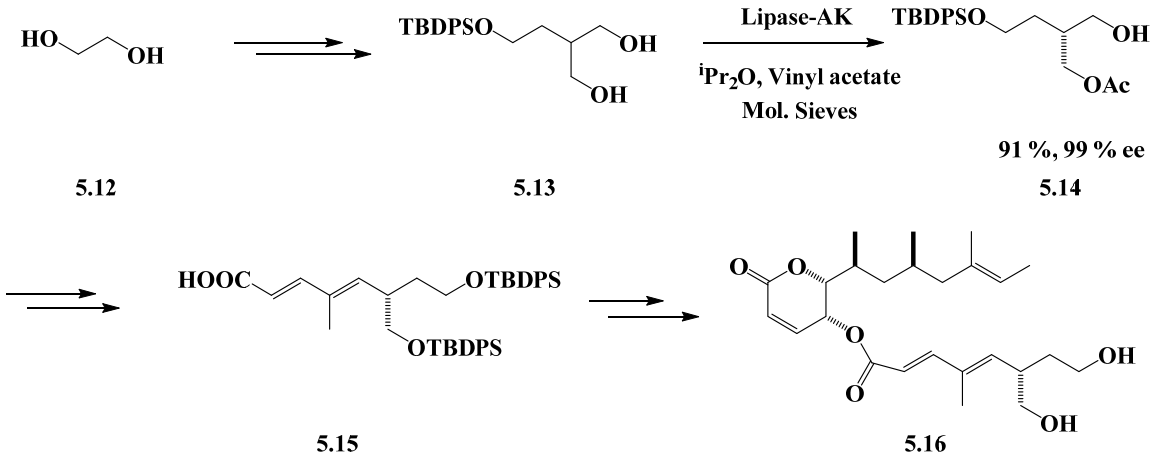
Scheme 5.2 - Amano PS lipase-mediated transesterification of **5.5**

Uguen and Oddon have used lipase from pig pancreas (PPL) to carry out a another enzymatic acetyl transfer to synthesize a chiral precursor in their synthesis of a fragment toward a total synthesis of the aglycone of spiramycine (Scheme 5.3).[189] Substrate **5.8** was converted to 1,3-diol **5.9** via several chemical transformations. Then PPL enzyme was used to afford the mono acetate in good yield with a high enantiomeric purity. Substrate **5.10** was then further transformed into **5.11**.



Scheme 5.3 - PPL catalyzed transesterification of **5.9**

Nanda and Bhuniya have used lipase-AK (*Pseudomonas fluorescens*) enzyme to carry out another similar reaction in the synthesis of (-)-rasfonin (**5.16**).[190] 1,2-Diol **5.12** was transformed into the symmetrical 1,3-diol **5.13**, which was then reacted with vinyl acetate and lipase-AK to afford **5.14** in excellent enantiomeric excess (Scheme 5.4). Substrate **5.14** was then further manipulated to **5.15** which was one of the synthetic precursors in the total synthesis of (-)-rasfonin (**5.16**).

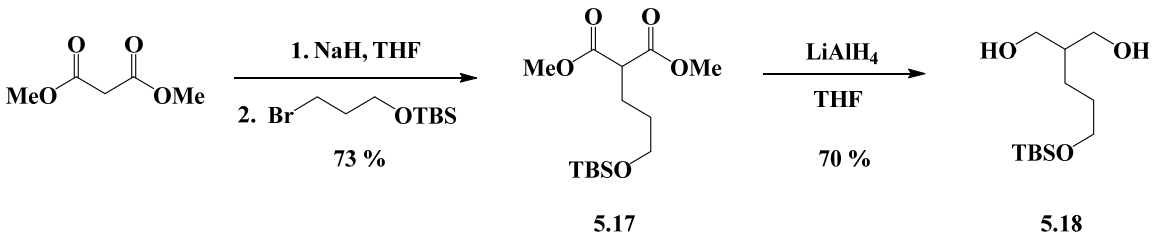


Scheme 5.4 - Use of lipase-AK enzyme in the synthesis of (-)-rasfonin

These examples illustrate the significance of biocatalysis using lipase enzymes to synthesize chiral building blocks from achiral precursors. Hence, a study was initiated to assess the feasibility of employing this chemistry for enantioselective synthesis of **4.29**. Described herein are the results that demonstrate the feasibility of this approach.

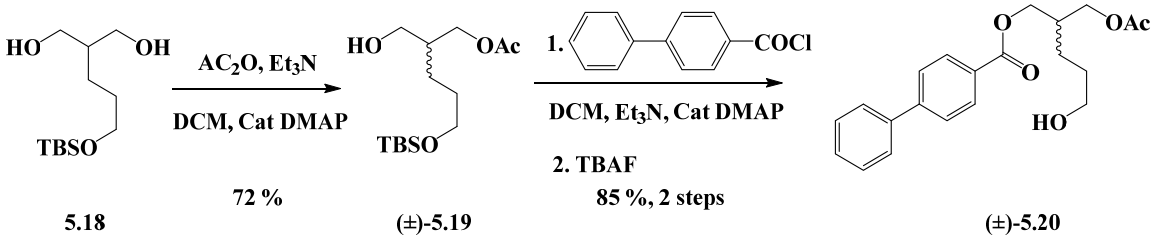
5.2 Results and Discussion

The objective of this study was to prepare the intermediate **5.1** in highly enantioenriched form for subsequent conversion to **4.29**, which would then be used in the synthesis of xestoproxamine C (**2.38**). A suitable substrate **5.18** was synthesized from commercially available dimethyl malonate via two chemical transformations (Scheme 5.4). First, dimethyl malonate was converted to **5.17** through a simple S_N2 reaction, and without further purification **5.17** was reduced to the corresponding 1,3-diol **5.18** with excess lithium aluminum hydride ($LiAlH_4$). Substrate **5.18** was identified as a suitable candidate to attempt enzyme-catalyzed transesterification for the synthesis of **5.1** (Scheme 5.5).



Scheme 5.5 - Synthesis of the symmetrical 1,3-diol substrate for enzyme catalysis

Concomitantly, it was necessary to synthesize a racemic monoacetate of **5.18** and develop a technique to assay the enantiopurity of the enzyme catalyzed transesterification reactions. Therefore, substrate **5.18** was converted to the monoacetate **(±)-5.19**, which was then transformed into **(±)-5.20** with a chromophoric biphenyl group to facilitate HPLC detection (Scheme 5.6). Racemic compound **5.20** was successfully separated on a chiral HPLC such that both enantiomers were clearly observable (see experimental). The same transformative sequence was used to determine the enantiomeric excess (*ee*) in each of the desymmetrization reactions performed with different enzymes (see table 5.1).

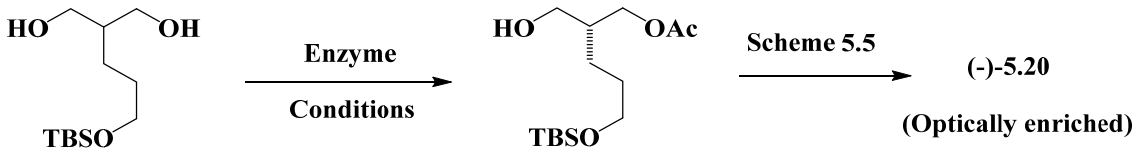


Scheme 5.6 - Derivatization of the racemic monoacetate **5.19**

Based on similar substrates that have been previously subjected to enzymatic resolution, it was determined that the best enzymes to screen for this particular reaction would be porcine pancreatic lipase (PPL) and lipase from *Pseudomonas cepacia* (Amano

lipase PS).[188,189,191] When PPL was used at room temperature (Table 5.1 entry 1) optically enriched **5.19** was obtained in 76 % chemical yield, but the enantiomeric excess of **5.20** was only 79 %. No significant change in *ee* was observed by increasing or decreasing temperature (entries 2 and 3). Even when the enzyme was changed to lipase PS, the *ee* remains ~80 % (entry 4). When the acetate transfer reagent (vinyl acetate) was employed as the solvent at low temperature, however, a significant increase in *ee* was observed accompanied by an excellent yield (Table 5.1 entry 5). Further experiments are underway to confirm the absolute stereochemistry of **(+)-5.19**.

Table 5.1 - Enzymatic desymmetrization of **5.19**



5.18 **(+)-5.19 (Optically enriched)**

Entry	Enzyme and Reagent	Temperature	Solvent	Time	Yield[a]	ee[b]
1	PPL, Vinyl acetate	r.t	THF	72 h	76 %	79 %
2	PPL, Vinyl acetate	35 ºC	THF	24 h	72 %	81 %
3	PPL, Vinyl acetate	15 ºC	THF	7 d	83 %	79 %
4	Lipase PS, Vinyl propionate	r.t	ACN	72 h	75 %	78 %
5	Lipase PS, Vinyl acetate	-10 ºC	-	18 h	99 %	88 %

[a]Yield of **(+)-5.19**. [b]Based on HPLC assay of **(-)-5.20**

According to the results discussed above it is certain that enzyme catalysis can be successfully employed to synthesize the building block **4.29** to be used in the synthesis of

xestoproxamine C. Conditions outlined in Table 5.1 entry 5 would be suitable for the synthesis of monoacetate **5.19** which can then be chemically transformed in to **4.29**.

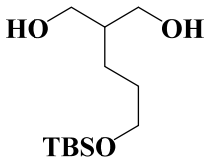
5.3 Conclusion

Synthesis of a chiral synthetic intermediate from a symmetrical 1,3-diol substrate has been achieved in high enantiomeric excess. This was accomplished via use of a lipase enzyme catalyzed reaction. Further experiments are underway to confirm the absolute stereochemistry of the intermediate **(+)-5.19** and transform it into the compound **4.29** that will be used in the total synthesis of xestoproxamine C. Based on literature precedence the absolute stereochemistry of **(+)-5.19** is expected to be R, which is what would be needed for the synthesis of xestoproxamine C.[188,189,191] If the absolute stereochemistry turns out to be opposite in configuration, the reaction pathway could be modified accordingly.

5.4 Experimental Section

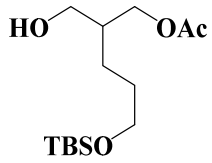
All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI) and electron

ionization (EI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.

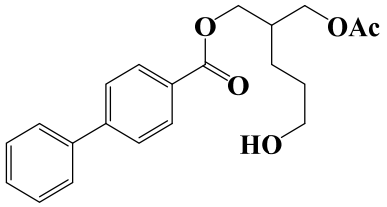


2-(3-((tert-Butyldimethylsilyl)oxy)propyl)propane-1,3-diol (5.18) – Dimethyl malonate (4.8 mL, 41.9 mmol, 1.00 equiv) was dissolved in THF (400 mL) and cooled down to 0 ºC using an ice bath. Then NaH (50% dispersion) (1.00 g, 41.9 mmol, 1.00 equiv) was added and stirred at 0 ºC for 1 hour followed by addition of (3-bromopropoxy)(tert-butyl)dimethylsilane (10.6 g, 41.9 mmol, 1.00 equiv) dissolved in THF (50 mL). The reaction mixture was then refluxed for 12 hours. It was then quenched with water (100 mL) and THF was removed in vacuum. The crude mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated to afford crude **5.17**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 6H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.47 – 3.34 (m, 1H), 2.03 – 1.88 (m, 2H), 1.64 – 1.44 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). Without further purification this was taken to the next step. $LiAlH_4$ (4.80 g, 126 mmol, 3.00 equiv) was dissolved in THF (350 mL) and cooled to 0 ºC. Then crude **5.17** dissolved in THF (50 mL) was added dropwise and the reaction was stirred overnight. Thereafter, it was quenched with a solution of saturated sodium potassium tartrate. THF was removed under vacuum. Reaction mixture was extracted with EtOAc (100 mL x 3) and organic layers were combined and dried (Na_2SO_4). Concentrated crude product was purified via flash column chromatography using 50 % EtOAc in hexanes to afford **5.18** as a colorless oil. (5.31 g, 51 %, 2 steps). ^{1}H NMR (300 MHz, Chloroform-*d*)

δ 3.79 (dd, *J* = 10.7, 3.9 Hz, 2H), 3.72 – 3.58 (m, 4H), 2.97 (s, 2H), 1.84 – 1.68 (m, 1H), 1.65 – 1.44 (m, 2H), 1.38 – 1.18 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.3, 63.5, 41.9, 30.4, 26.1, 24.1, 18.6, 0.2, -5.1. HRMS (ESI) $C_{12}H_{29}O_3Si$ $[M+H]^+$, Calculated 249.1886; Found 249.1879.



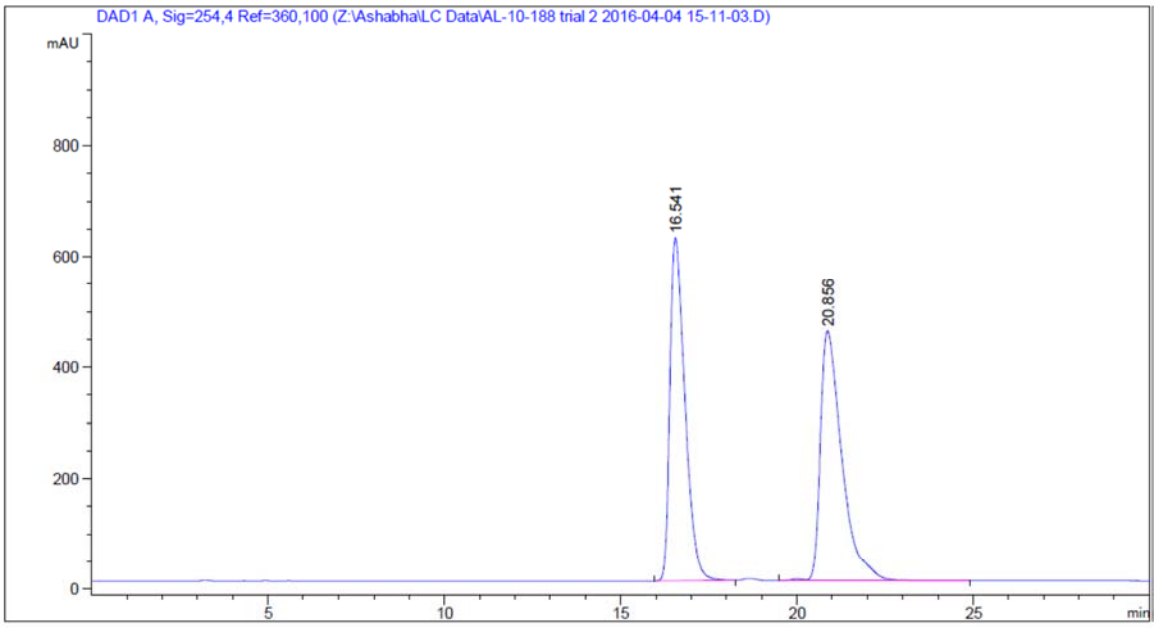
(±)-5-((tert-Butyldimethylsilyl)oxy)-2-(hydroxymethyl)pentyl acetate (5.19) – Compound **5.18** (0.250 g, 1.01 mmol, 1.00 equiv) was dissolved in DCM (25 mL) and cooled to 0 ºC. Then triethylamine (0.21 mL, 1.51 mmol, 1.50 equiv) and Ac_2O (0.095 mL, 1.01 mmol, 1.00 equiv) were added and reaction was stirred overnight. The reaction was quenched with saturated sodium bicarbonate (20 mL) and extracted with DCM (20 mL x 2). Combined organic layers were dried (Na_2SO_4) and concentrated. Crude product was purified via flash column chromatography using 25 % EtOAc in hexanes to afford **5.19** as a colorless oil (0.211 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (dd, *J* = 11.2, 4.6 Hz, 1H), 4.10 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.70 – 3.59 (m, 3H), 3.54 (dd, *J* = 11.3, 6.5 Hz, 1H), 2.08 (s, 3H), 1.90 – 1.78 (m, 1H), 1.66 – 1.53 (m, 2H), 1.46 – 1.34 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 64.9, 63.3, 62.9, 40.5, 30.2, 26.1, 24.3, 21.1, 18.5, -5.1. HRMS (ESI) $C_{14}H_{31}O_4Si$ $[M+H]^+$, Calculated 291.1992; Found 291.1995.



(±)-2-(Acetoxymethyl)-5-hydroxypentyl [1,1'-biphenyl]-4-carboxylate (5.20) – Compound **5.19** (0.250 g, 0.86 mmol, 1.00 equiv) was dissolved in DCM (10 mL). Biphenyl-4-carbonyl chloride (0.210 g, 0.950 mmol, 1.10 equiv) and triethylamine (0.300 mL, 2.15 mmol, 2.50 equiv) were added. After 30 min completion of the reaction was observed by TLC (50 % EtOAc in Hexane). The reaction mixture was directly loaded onto a silica column and purified using 10 % EtOAc in hexanes to afford the TBS-protected intermediate which was directly taken to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.04 (m, 2H), 7.79 – 7.62 (m, 4H), 7.57 – 7.35 (m, 3H), 4.47 – 4.29 (m, 2H), 4.28 – 4.03 (m, 2H), 3.66 (t, *J* = 5.9 Hz, 2H), 2.27 – 2.17 (m, 1H), 2.08 (s, 3H), 1.75 – 1.48 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 166.6, 145.9, 140.2, 130.3, 129.1, 129.0, 128.4, 127.5, 127.3, 64.9, 64.7, 63.1, 37.5, 30.2, 26.1, 24.9, 21.1, 18.5, -5.1. This intermediate product was dissolved in THF (10 mL) and TBAF (1.3 mL, 1.30 mmol, 1.50 equiv) was added. After 15 min reaction was complete. It was then quenched with water and extracted with EtOAc (10 mL x 3). The combined organic layers were dried and concentrated. The crude product was purified via flash column chromatography using 80 % EtOAc in hexanes to afford **5.20** as a colorless oil (0.339 g, 85 %, 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.44 – 7.38 (m, 1H), 4.49 – 4.31 (m, 2H), 4.29 – 4.15 (m, 2H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.29 – 2.17 (m, 1H), 2.08 (s, 3H), 1.79 – 1.67 (m, 2H), 1.63 – 1.52 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1,

166.4, 145.8, 139.9, 130.1, 128.9, 128.8, 128.2, 127.3, 127.1, 64.7, 64.4, 62.7, 37.4, 29.9, 24.7, 20.9. HRMS (ESI) $C_{21}H_{25}O_5$ $[M+H]^+$, Calculated 357.1702; Found 357.1712.

HPLC: 4.6 x 250 mm chiracel OJ-3 column, 3 μm particle size, 0.6 mL/min, elution with 30 % IPA in hexanes. Retention times: 16.54 min, 20.86 min.

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                      Area Percent Report
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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


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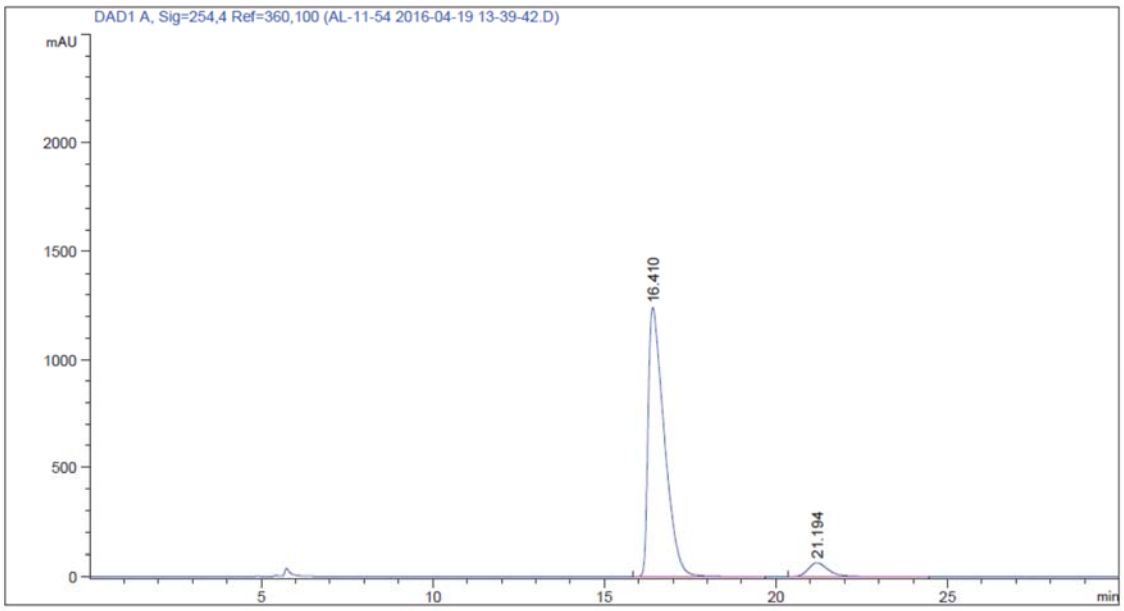
   2  20.856 VB R  0.6338 1.91403e4   450.38925  51.1152
```

(+)-5-((tert-Butyldimethylsilyl)oxy)-2-(hydroxymethyl)pentyl acetate [(+)-5.19] – Compound **5.18** (1.50 g, 6.00 mmol, 1.00 equiv) was dissolved in vinyl acetate (30 mL) and cooled to -10 ºC. Then lipase PS Amano enzyme (1.5 g) was added and the reaction

stirred overnight for 12 hours. Thereafter reaction mixture was filtered through Celite to remove the enzyme, and vinyl acetate was removed under vacuum without. Crude mixture was purified via flash column chromatography using 50 % EtOAc in hexanes to afford **(-)-5.19** (1.73 g, 99 %). $[\alpha]_D^{22.8}$ = +5.87 (3.66, $CHCl_3$).

(+)-5.19 was derivatized using same procedure above [used for **(±)-5.20**] to afford **(-)-5.20** which was used to determine the *ee* via HPLC. 88 % *ee*. $[\alpha]_D^{23.2}$ = -0.489 (1.84, $CHCl_3$).

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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   2  21.194 BB    0.6136 2525.67773   63.01820   5.9098
```

Chapter Six

Summary and Future Directions

6.1 Summary

The objective of the research described in this thesis was to explore novel intra- or intermolecular dearomatization strategies of aromatic scaffolds that would ultimately be used in the synthesis of bioactive natural products. Specifically, our efforts were directed toward intramolecular dearomatization of substituted pyridines and imidazoles to obtain an array of structurally unique synthetic building blocks. 4-Alkylpyridine derivatives were successfully subjected to an experimentally simple Brønsted acid-catalyzed procedure to uncover a novel aldol-like reaction to afford 4-substituted pyridyl lactams. Positioning of carbonyl electrophiles in the side chain of 4-alkylpyridines in particular afforded viable cyclization precursors across a range of substrate types. Appropriately positioned 2-alkylpyridines also underwent successful conversion under the same conditions. An unusual $SOCl_2$ mediated oxidation of pyridyl-substituted lactams was also uncovered. With regard to imidazoles, nucleophilic 2-alkylidene imidazolines were generated from 1,2-dialkylimidazoles under mild conditions, and these substrates participated in intramolecular cyclization reactions with appropriately positioned electrophiles. Results from attempts to prepare fused ring imidazo[1,2-a] dihydropyridines and pyrrolo[1,2-a]imidazoles via intramolecular cyclization of 2-methylimidazoles and 2-unsubstituted imidazoles, respectively, indicated that the ability to regenerate a stable imidazole at the conclusion of the cyclization event by transfer of an acyl activating group to a nucleophilic center in the newly-formed ring may be an important feature of successful transformations.

It was also our intention to develop a general synthetic route to access the bis(piperidine) molecular framework found in various marine alkaloids. Our synthetic route successfully generated a model of the bis(piperidine) macrocyclic BCD tricyclic ring system found in xestoproxamine C and structurally related alkaloids. Heterogeneous catalytic hydrogenation of a macrocyclic alkylidene dihydropyridine intermediate was used to convert a pyridine precursor to the desired linked piperidine-piperidinone product with apparent control of relative stereochemistry at three contiguous stereocenters. This strategy could ultimately be used in the synthesis of many biologically active bis(piperidine) alkaloids with the appropriate modifications to the generated synthetic route. In a more general sense, this work demonstrates the utility of alkylidene dihydropyridine intermediates in constructing more elaborate polycyclic heterocyclic ring systems.

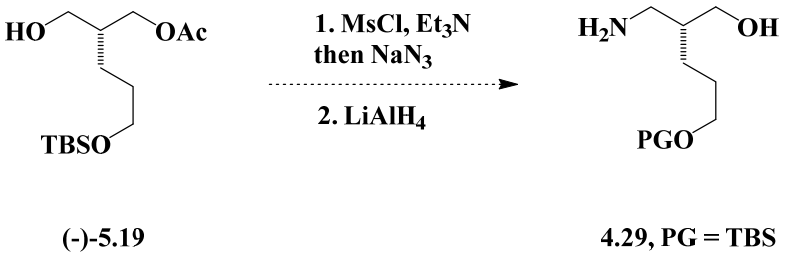
Finally, we have successfully investigated the feasibility of employing enzyme catalysis to synthesize one of the two chiral precursors needed for the total synthesis of xestoproxamine C. From the optimization studies it was found that Amano lipase enzyme would be the most suitable enzyme to catalyze the transesterification reaction to introduce the chirality needed for the precursor.

6.2 Future Directions

6.2.1 Total Synthesis of Xestoproxamine C

After successful completion of model studies discussed in Chapter 4, this synthetic route can be modified for completion of the total synthesis of xestoproxamine C. First, it is necessary to access the two chiral building blocks **4.29** and **4.30** that would

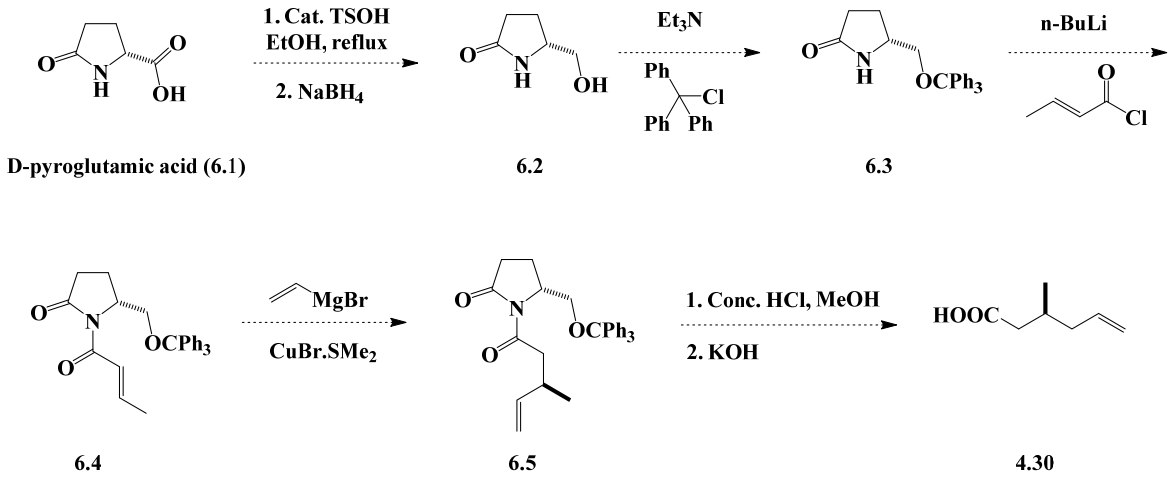
be incorporated in the synthesis. As discussed in Chapter 5, **4.29** can be synthesized from enantio enriched **5.19** as shown in Scheme 6.1.



(-)-5.19 **4.29, PG = TBS**

Scheme 6.1 - Synthesis of the chiral aminopropanol precursor **4.29**

Next, **4.30** will be prepared using a previously published synthetic route for its enantiomer as shown in Scheme 6.2.[192] D-Pyroglutamic acid (**6.1**) will be used as the chiral auxiliary to induce the chirality observed in **4.30**. Simple esterification followed by reduction will afford **6.2**, which will then be subjected to tritylation with triethylamine to synthesize **6.3**. Deprotonation and subsequent reaction of **6.3** with *trans*-crotonyl chloride will afford **6.4**. Then, a conjugate addition reaction will be carried out using an *in situ* generated cuprate to afford **6.5**, which would deliver the desired **4.30** upon acidic hydrolysis.

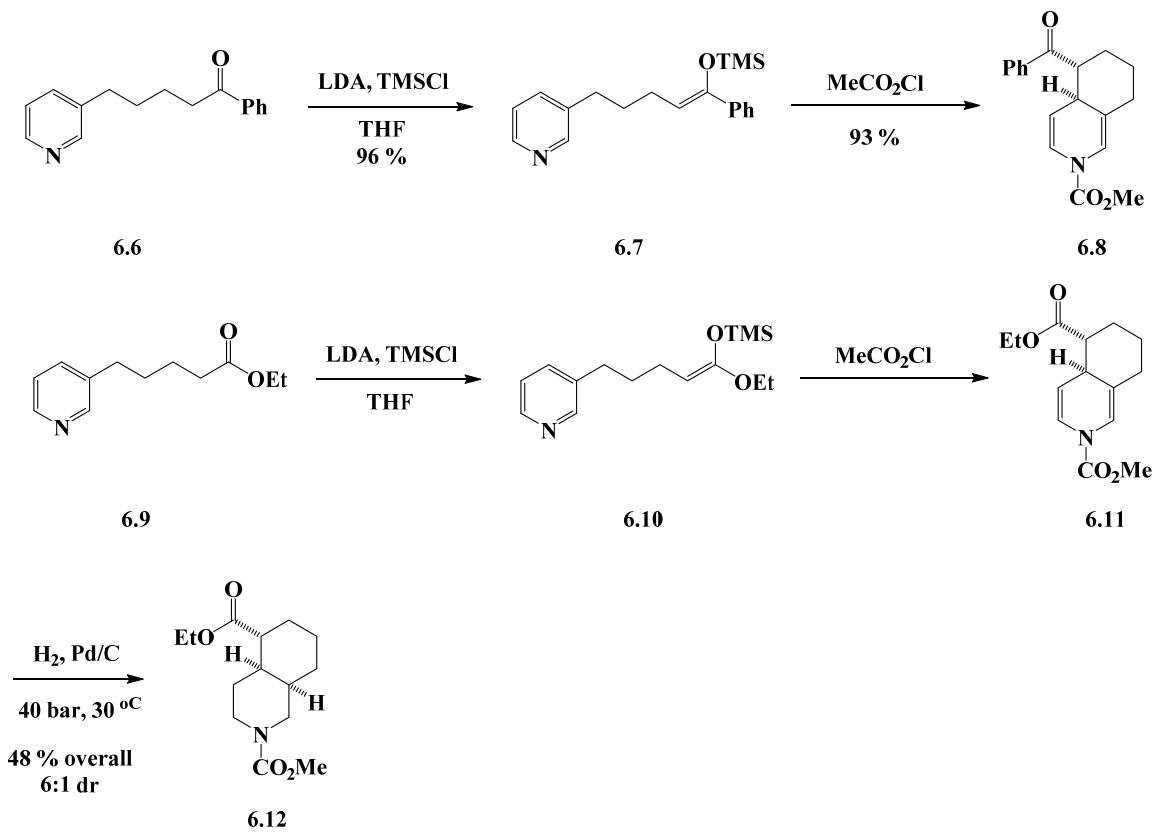


Scheme 6.2 - Proposed synthesis of **4.30**

With access to both of these chiral precursors, the asymmetric total synthesis of xestoproxamine C can be pursued.

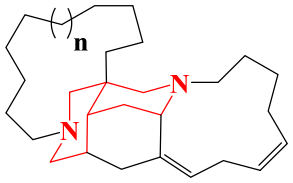
6.2.2 3-Alkylpyridyl Substrates in Natural Product Synthesis

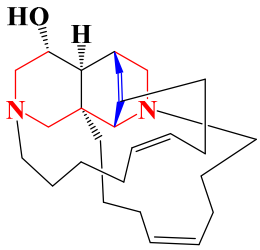
Fused ring systems are abundant in natural products and particularly alkaloids containing 3,4-fused ring piperidines are very common. There are only a few reports related to synthesis of these frameworks from pyridine precursors. Earlier, Clayden and coworkers reported that addition of silyl ether **6.7** and silyl ketene acetal **6.10** to the corresponding 3-pyridinium salt gave fused ring systems **6.8** and **6.11** respectively (Scheme 6.3).[193] The intermediate **6.11** was found to be unstable and hydrogenation yielded completely reduced bicyclic ring system **6.12**.



Scheme 6.3 - Bicyclic ring systems from 3-alkylpyridines

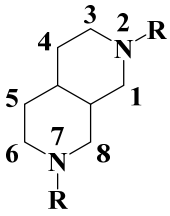
Many alkaloids such as the madangamines (**6.13** and **6.14**) and xestocyclamine A (**6.15**) contain polycyclic rings along with azacycles in their core structures.[194-197] A possible synthetic route to these diazadecaline scaffolds entails cyclization of 3-substituted pyridines to afford fused ring dihydropyridines. Moreover, stereoselective cyclizations might be realized if side chain substituents could exert diastereocontrol over the cyclization event. For initial studies along these lines, we focused on investigating the effect of a methyl group on an intramolecular cyclization.





[6.13] Madangamine D, n = 2
[6.14] Madangamine E, n = 1

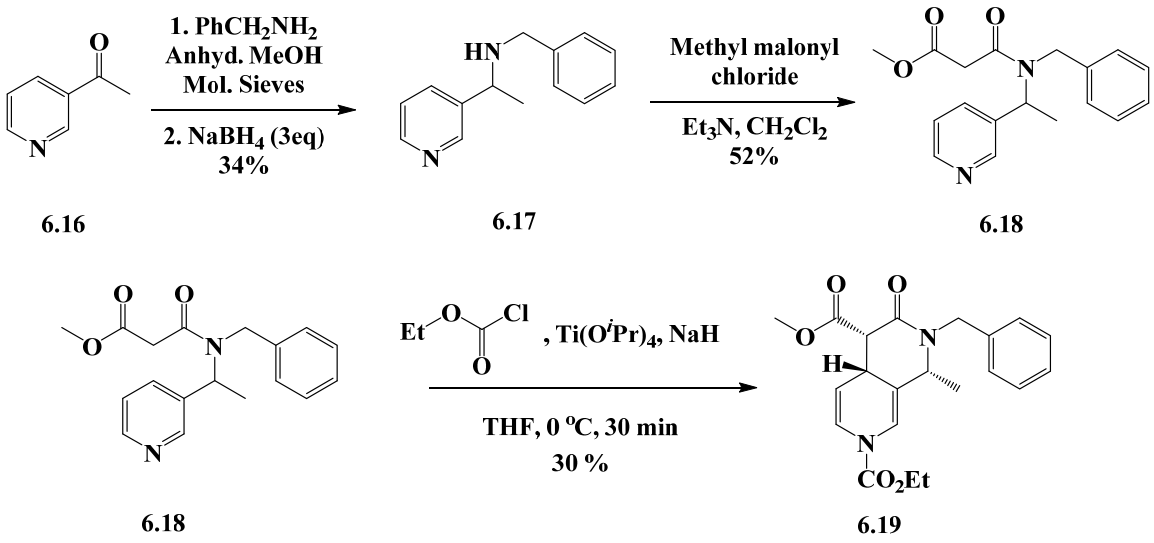
[6.15] Xestocyclamine A



2,7-diazadecaline skeleton

Figure 6.1 - Natural products with the diazadecaline framework

Our synthesis started with a reductive amination of commercially available 3-acetylpyridine (**6.16**) with benzyl amine. Amine substrate **6.17** was then reacted with methyl malonyl chloride to afford **6.18**, which would be a suitable substrate to attempt the intramolecular cyclization via pyridine activation. When substrate **6.18** was subjected to pyridine activation in the presence of NaH and $Ti(O^iPr)_4$ a cyclization reaction leading to one diastereomer was observed, and bicyclic compound **6.19** was isolated in low yield (Scheme 6.4).



Scheme 6.4 - Intramolecular dearomatization of the 3-alkylpyridine substrate **6.19**

Both 1D and 2D NMR studies confirmed that **6.19** was present as a single diastereomer. The relative stereochemistry was assigned based on the NOESY correlations (Figure 6.2).

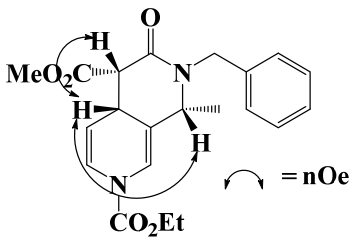


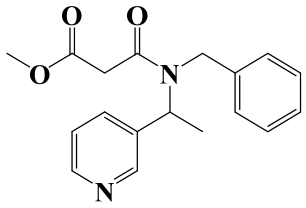
Figure 6.2 - Selected NOESY correlations of **6.19**

This preliminary study has established that fused ring systems can be synthesized by the intramolecular addition of an enolate nucleophile to the C4 position of a pyridinium salt formed *in situ* from 3-alkylpyridine substrates. This reaction is diastereoselective and the relative stereochemistry of the methine hydrogens is parallel to the stereochemistry seen in xestocyclamine A. Additional work is needed to improve

reaction efficiency, perhaps by modifying parameters such as temperature, solvent, Lewis acid, and base. If successful, this strategy could be employed in the synthesis of diazadecaline natural products such as xestocyclamine A.

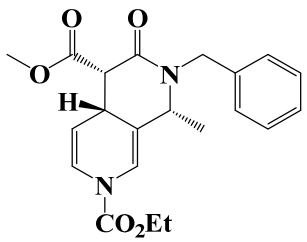
6.3 Experimental Section

All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI) and electron ionization (EI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.



Methyl 3-(benzyl(1-(pyridin-3-yl)ethyl)amino)-3-oxopropanoate (6.18) – 3-Acetylpyridine (1.0 mL, 9.10 mmol, 1.00 equiv) was dissolved in anhydrous MeOH (100 mL). Molecular sieves and benzyl amine (1.10 mL, 10.0 mmol, 1.10 equiv) were added. The reaction mixture was stirred overnight to allow complete formation of imine. Sodium

borohydride (0.863 g, 22.8 mmol, 2.50 equiv) was then added at 0 ºC and the reaction was allowed to warm up to room temperature over 4h. Thereafter, the reaction mixture was quenched with water (50 mL) and filtered through Celite to remove the molecular sieves. The concentrated mixture was extracted with EtOAc (50 mL x 3) and the combined organic layers were dried (Na_2SO_4) and concentrated to give the crude amine (0.722 g, 37 %). Without further purification this was taken on to the next step. Crude amine (0.72 g, 3.40 mmol, 1.00 equiv) was dissolved in DCM (35 mL) and methyl malonyl chloride (0.400 mL, 3.74 mmol, 1.10 equiv) and triethylamine (0.71 mL, 5.10 mmol, 1.50 equiv) were added to it. After stirring overnight, the reaction was complete and quenched with water (30 mL). The reaction mixture was extracted with DCM (30 mL x 3) and the combined organic layers were dried (Na_2SO_4) and concentrated to afford crude **6.18** (0.722 g, 68 %).

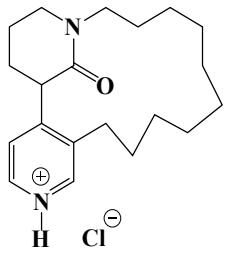


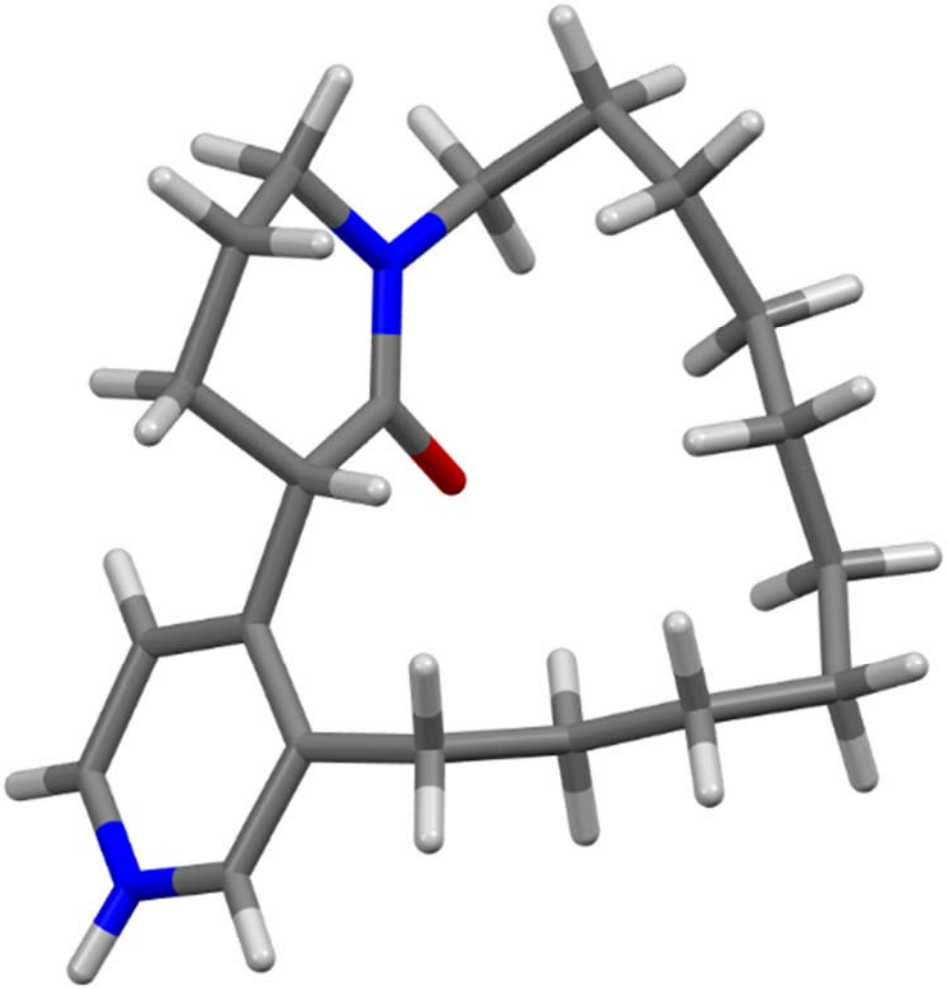
2-Ethyl 5-methyl (4aR,5S,8R)-7-benzyl-8-methyl-6-oxo-5,6,7,8-tetrahydro-2,7-naphthyridine-2,5(4aH)-dicarboxylate (6.19) – Pyridine **6.18** (0.200 g, 0.640 mmol, 1.00 equiv) was dissolved in THF (7 mL) and cooled to 0 ºC. Then $Ti(O^iPr)_4$ (0.096 mL, 0.32 mmol, 0.500 equiv), ethyl chloroformate (0.061 mL, 0.64 mmol, 1.00 equiv), and NaH (0.022 g, 0.9 mmol, 1.3 equiv) were added. After 30 min, the reaction was complete by TLC. Then water (5 mL) was added and the crude mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated. The

crude product was purified via flash column chromatography using 25 % EtOAc in hexanes to afford **6.19** (0.074 g, mixture of rotamers, 30 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 6.95 – 6.83 (m, 1H), 6.83 – 6.69 (m, 1H), 5.37 (d, *J* = 15.0 Hz, 0.2H), 5.28 (d, *J* = 15.0 Hz, 0.8H), 4.86 – 4.72 (m, 1H), 4.35 – 4.22 (m, 2H), 4.19 (d, *J* = 15.0 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.87 (s, 2.2H), 3.85 (s, 0.8H), 3.77 – 3.66 (m, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 1.49 – 1.22 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 169.8, 169.2, 167.5, 151.4, 136.9, 128.9, 128.7, 127.9, 127.6, 123.9, 119.5, 116.6, 105.0, 104.8, 63.1, 62.8, 60.5, 58.5, 57.4, 53.3, 52.7, 52.6, 47.7, 47.3, 33.9, 30.9, 21.9, 21.2, 20.1, 19.9, 14.5, 14.3. HRMS (ESI) $C_{21}H_{25}N_2O_5$ $[M+H]^+$, Calculated 385.1763; Found 385.1769.

Appendix A

X-Ray Crystallographic Data for Pyridine-Piperidine Analogue 4.89.HCl





Single crystals of **59**·HCl were grown from slow evaporation of a 1:1 mixture of $CHCl_3$ and EtOAc. A suitable crystal was selected and mounted on a Bruker Nonius

APEX II Kappa diffractometer. The crystal was kept at 190.15 K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimisation.[1-3]

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

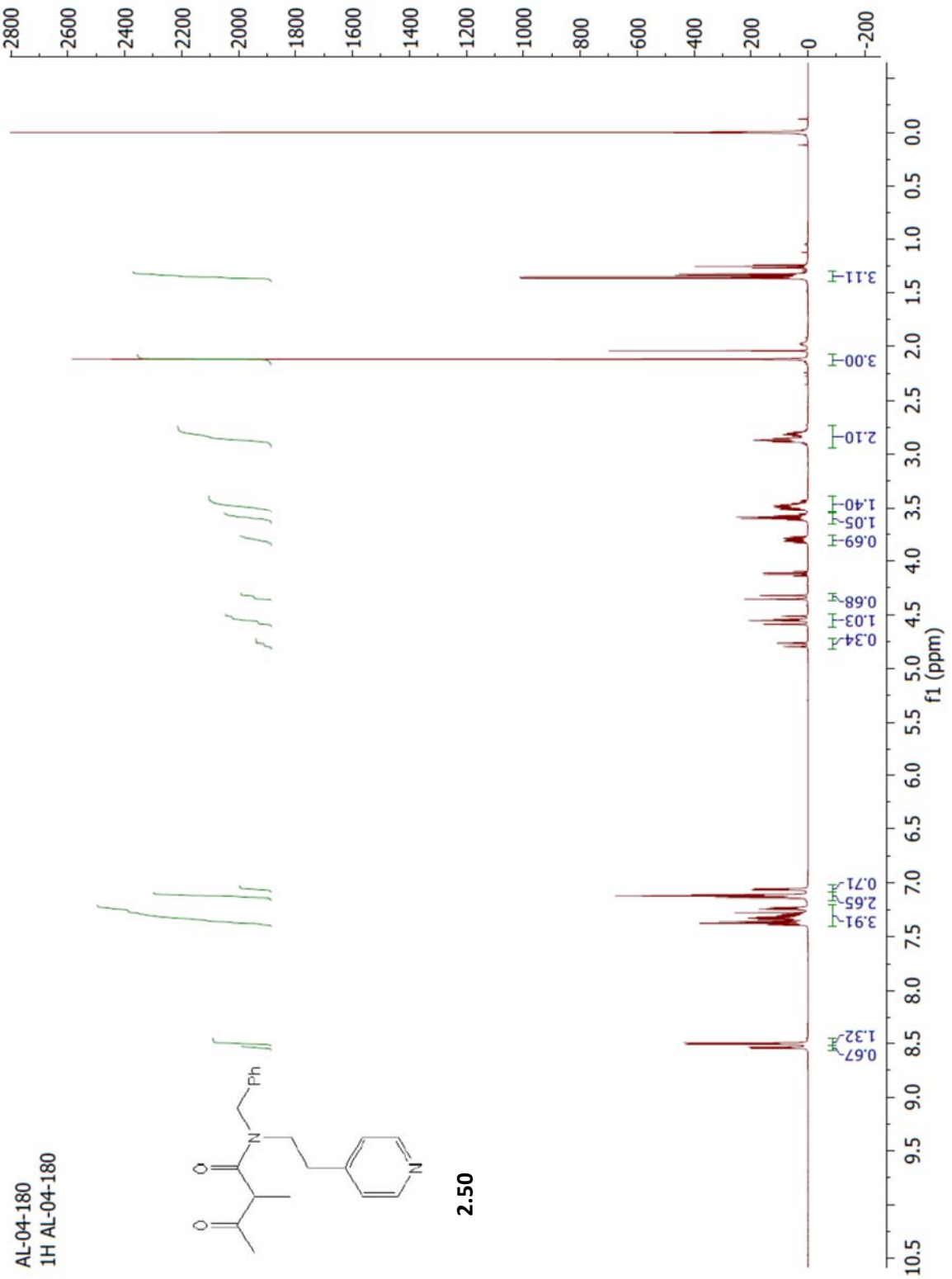
Table S1. Crystallographic data for **59**·HCl

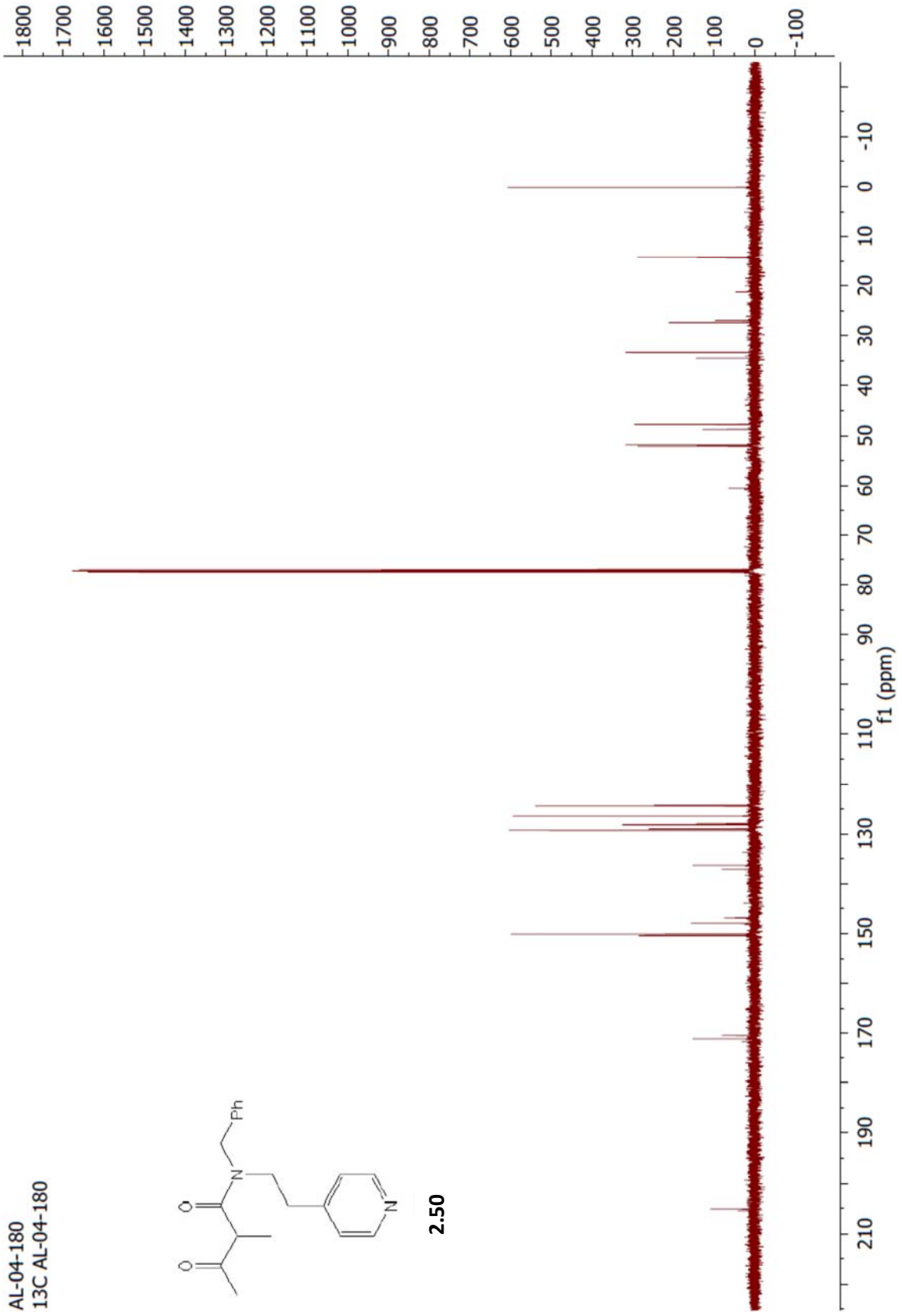
CCDC	1481779
Empirical formula	$C_{20}H_{31}ClN_2O$
Formula weight	350.92
Temperature/K	190.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	19.0891(19)
b/Å	10.1206(10)
c/Å	9.7640(10)
α/°	90
β/°	95.083(5)
γ/°	90

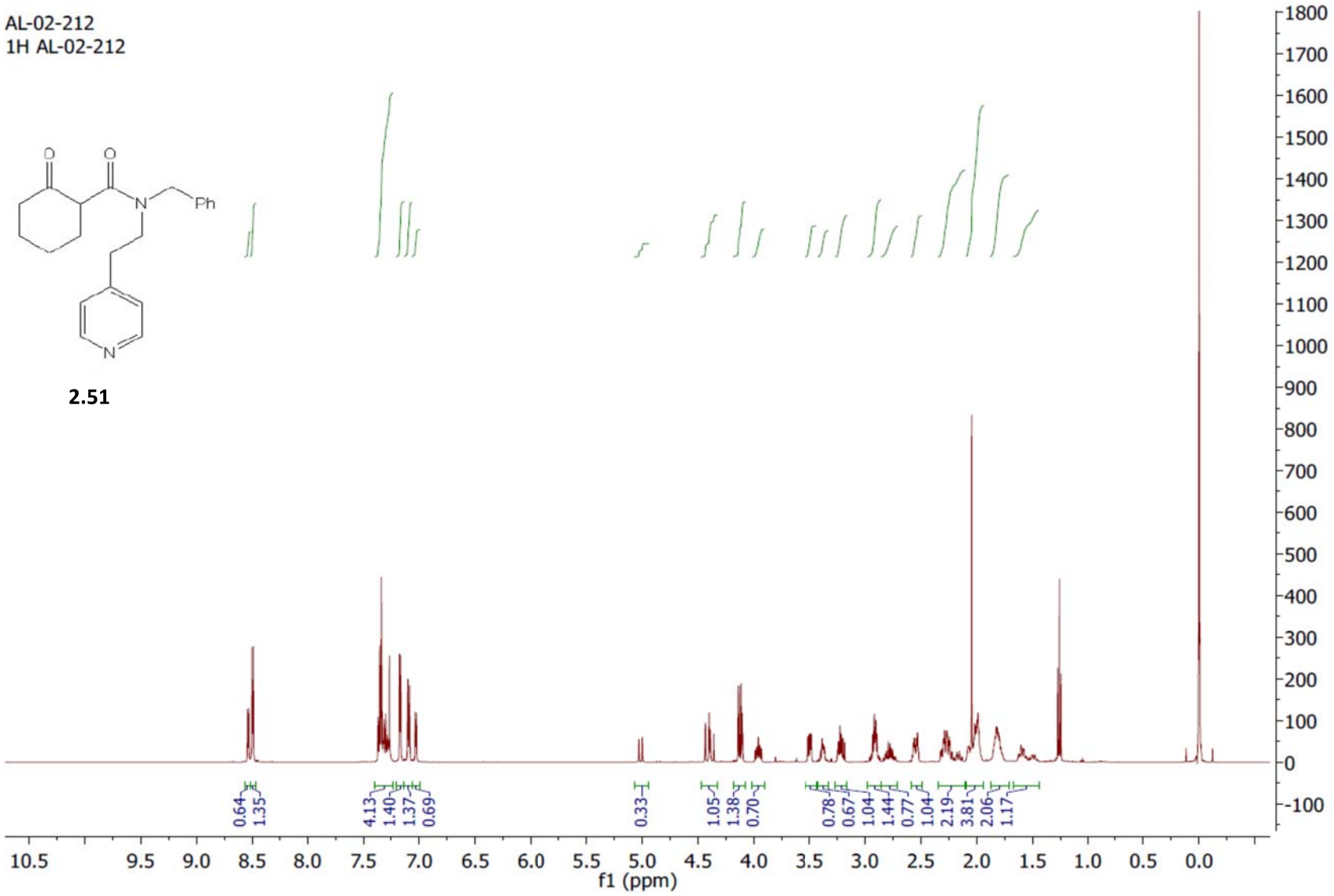
Volume/$Å^3$	1878.9(3)
Z	4
$\rho_{calc}g/cm^3$	1.241
μ/mm^{-1}	0.213
F(000)	760.0
Crystal size/mm^3	0.41 × 0.35 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.56 to 49.994
Index ranges	-22 ≤ h ≤ 22, -12 ≤ k ≤ 12, -11 ≤ l ≤ 11
Reflections collected	25776
Independent reflections	3303 [R_{int} = 0.0280, R_{sigma} = 0.0191]
Data/restraints/parameters	3303/51/221
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0541, wR_2 = 0.1524
Final R indexes [all data]	R_1 = 0.0625, wR_2 = 0.1602
Largest diff. peak/hole / e $Å^{-3}$	0.55/-0.33

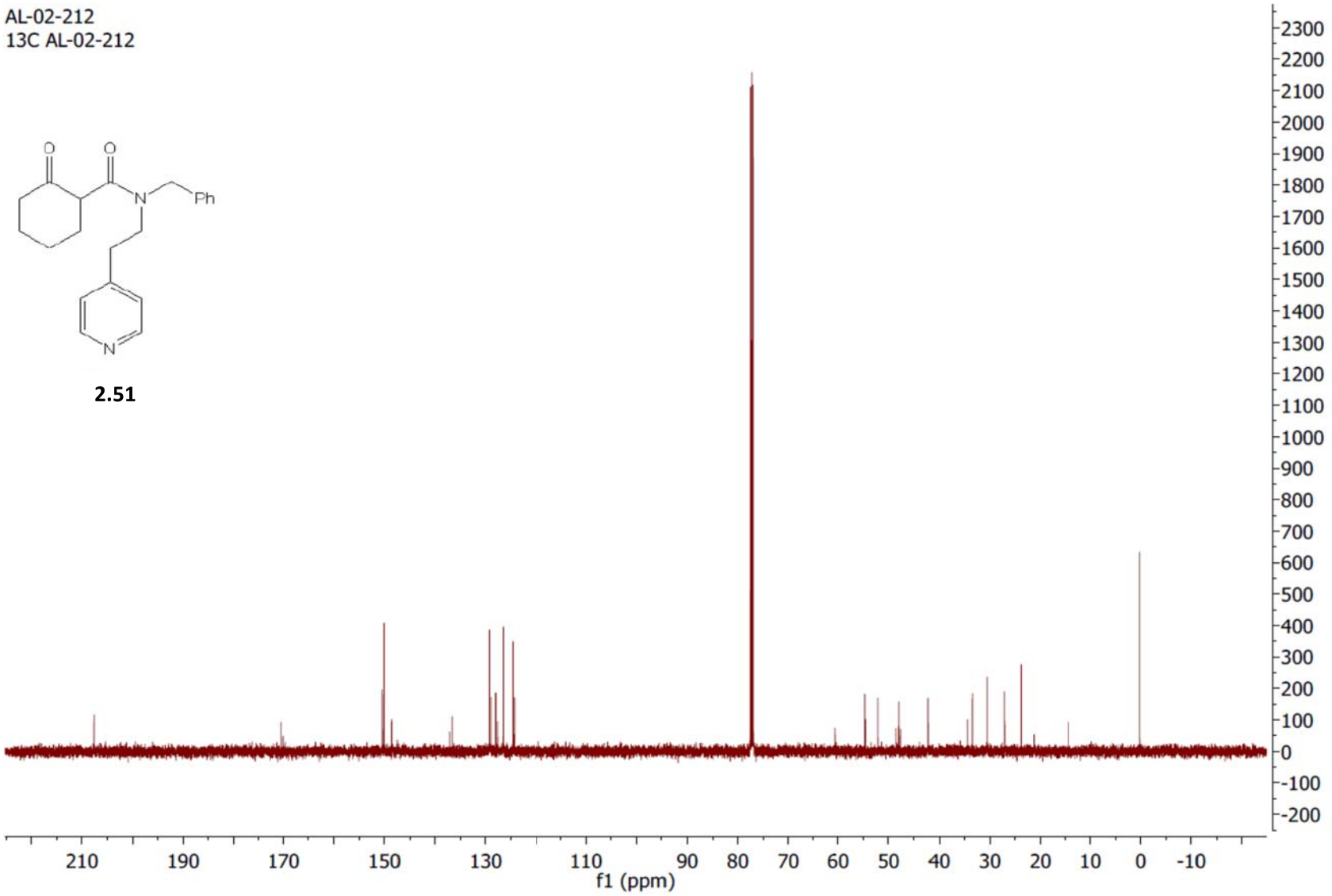
Appendix B

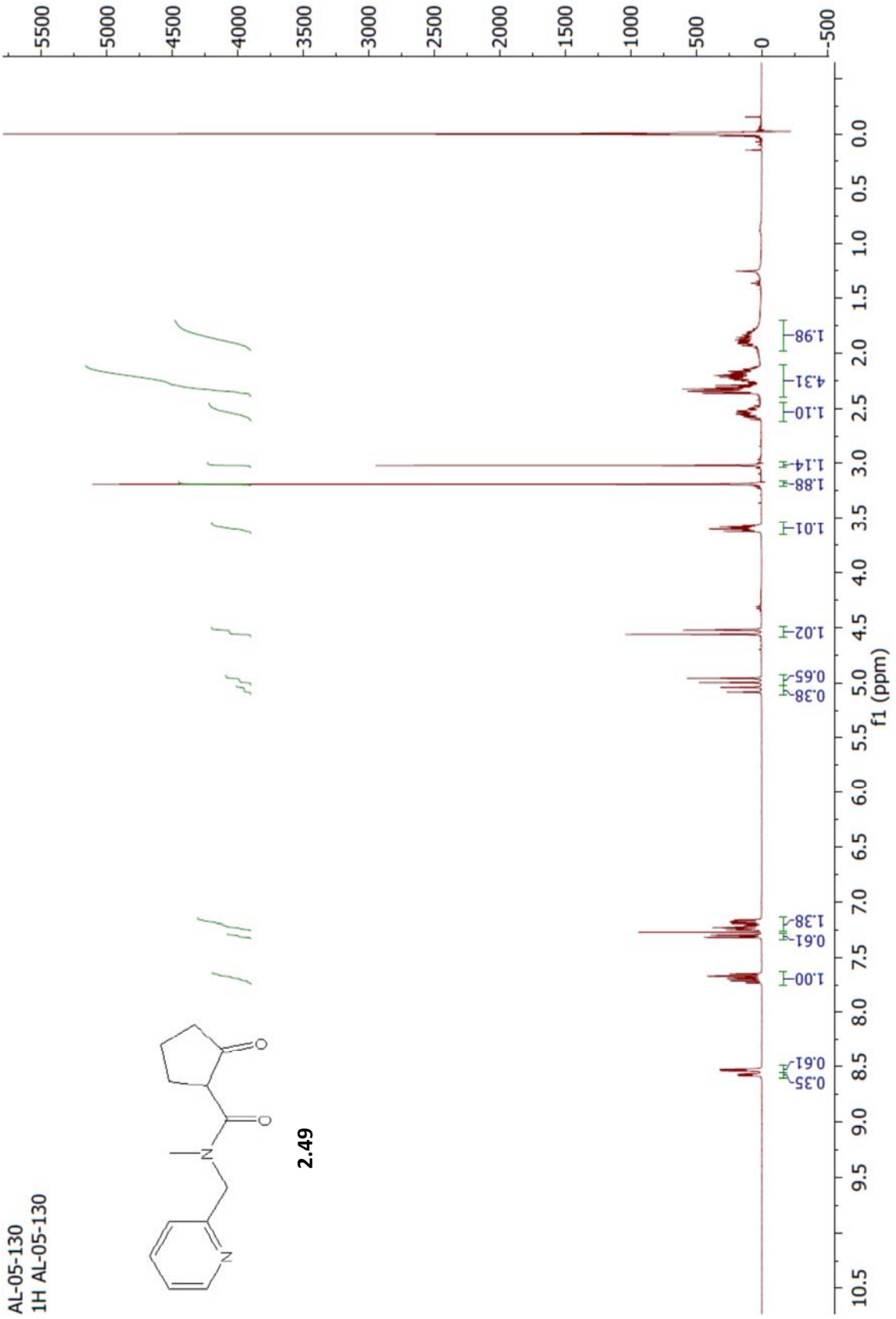
NMR Spectra for Compounds

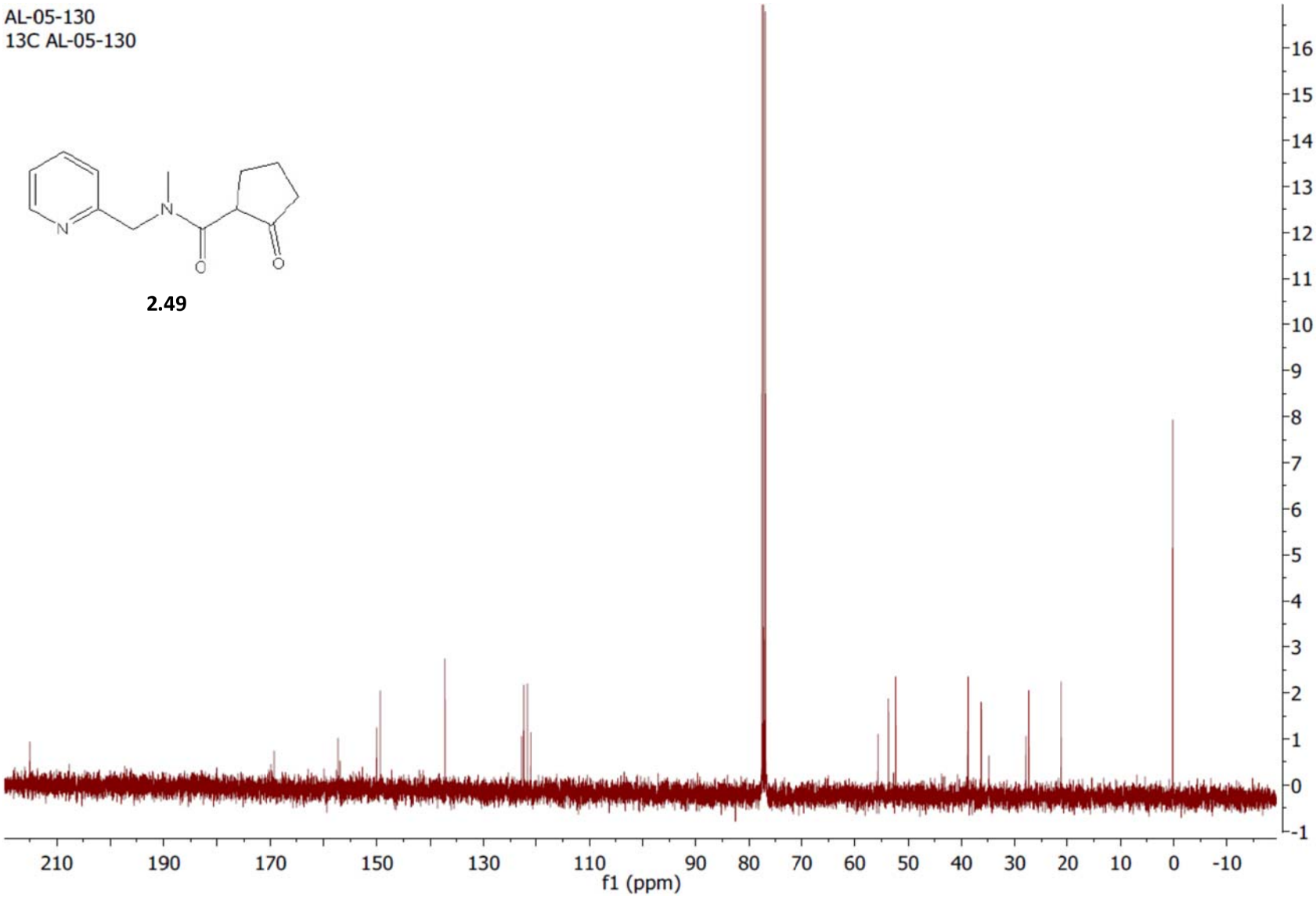


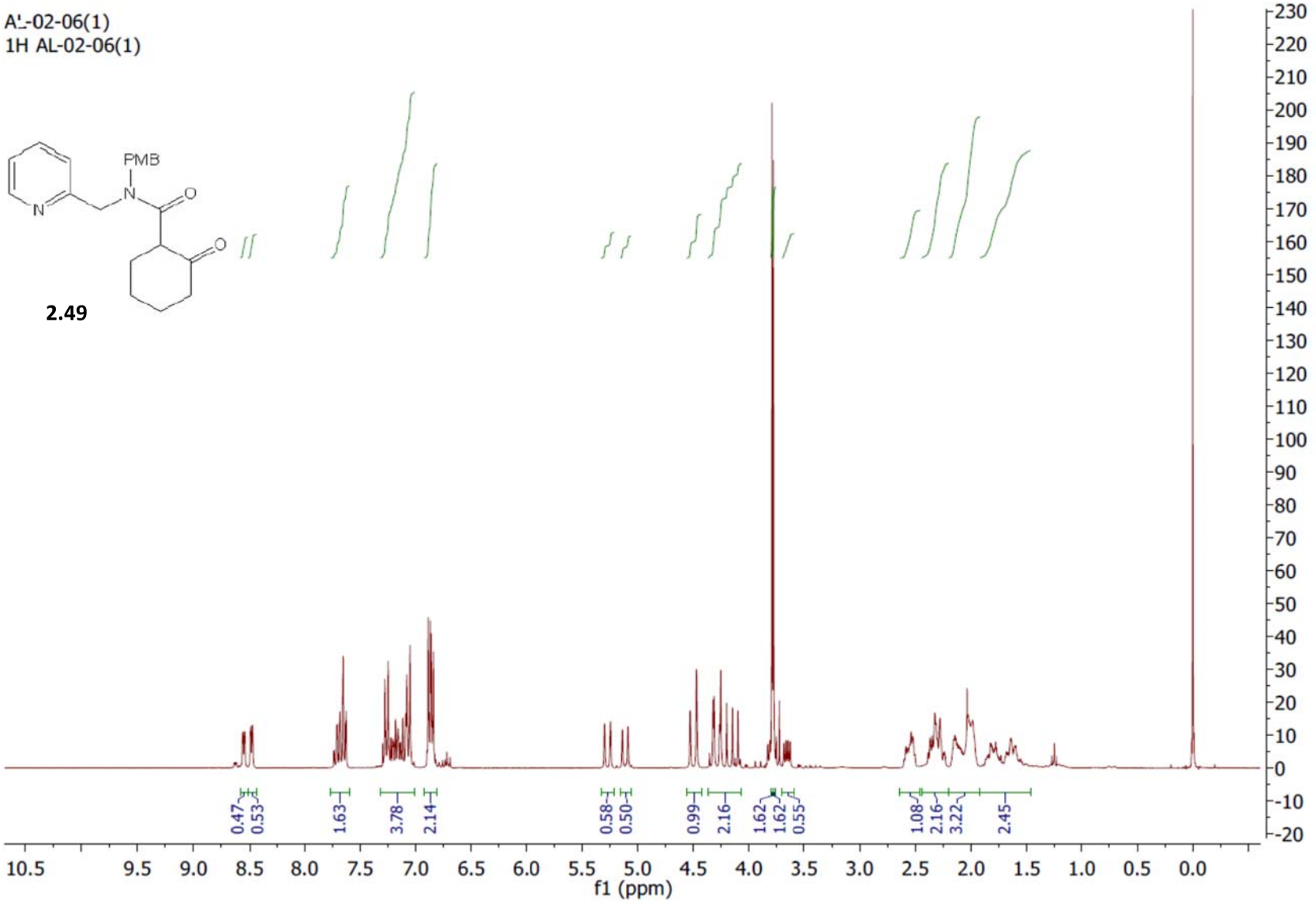

AL-04-180
13C AL-04-180
Ph
N
O
O
N
2.50
f1 (ppm)


AL-02-212
1H AL-02-212
O
O
N
Ph
N
2.51
0.64
1.35
4.13
1.40
1.37
0.69
0.33
1.05
1.38
0.70
0.78
0.67
1.04
1.44
0.77
1.04
2.19
3.81
2.06
1.17
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

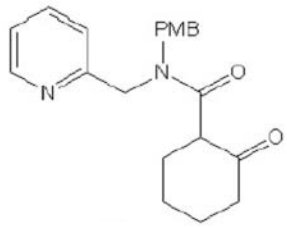

AL-02-212
13C AL-02-212
O
O
N
Ph
N
2.51
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


AL-05-130
1H AL-05-130
2.49
f1 (ppm)

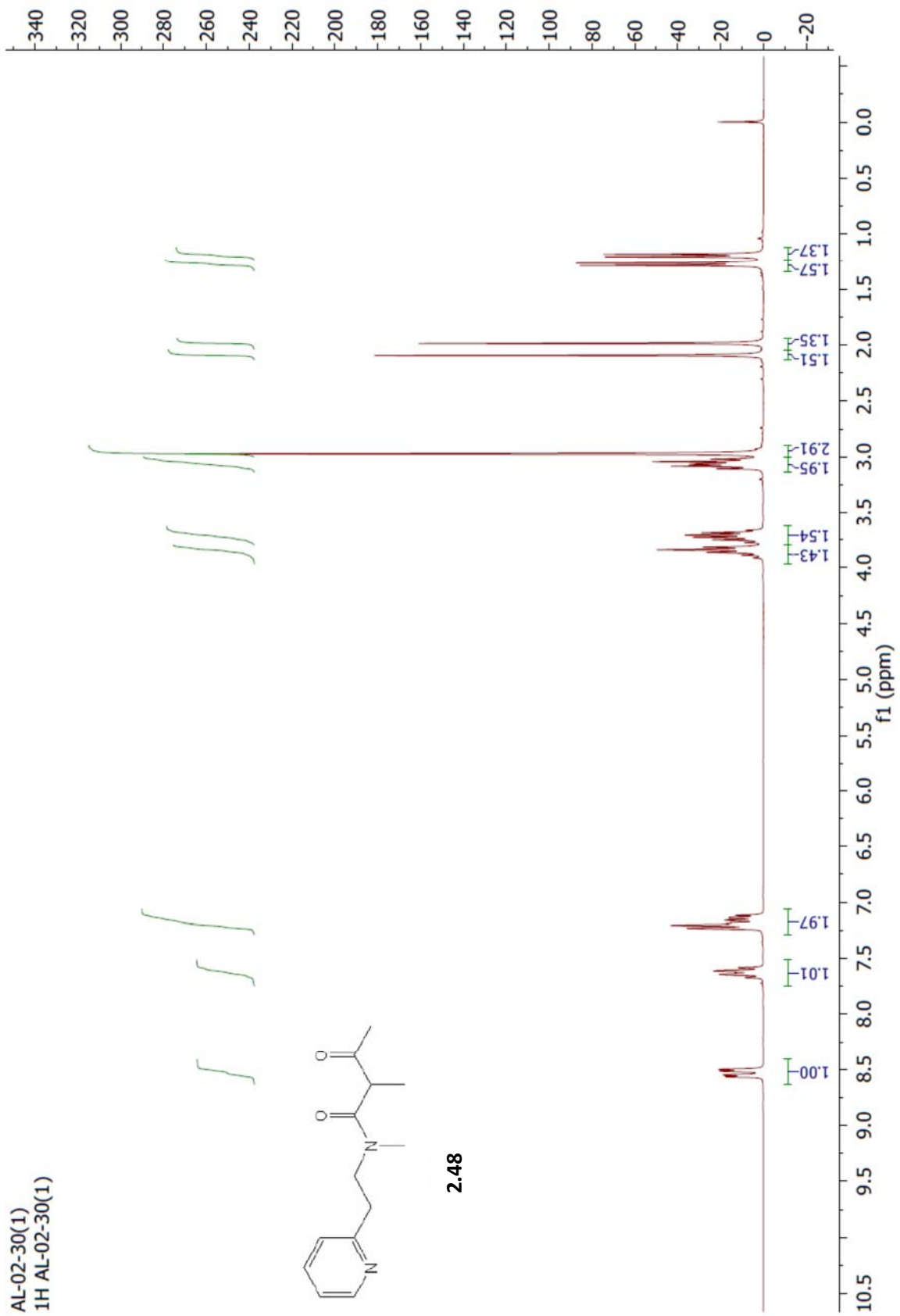

AL-05-130
13C AL-05-130
N
N
O
O
2.49
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


AL-02-06(1)
1H AL-02-06(1)
PMB
N
N
O
O
2.49
0.47
0.53
1.63
3.78
2.14
0.58
0.50
0.99
2.16
1.62
1.62
0.55
1.08
2.16
3.22
2.45
f1 (ppm)

AL-02-06(1)
13C AL-02-06(1)

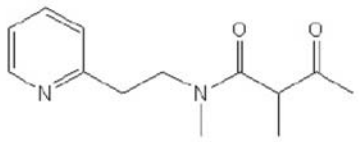


2.49

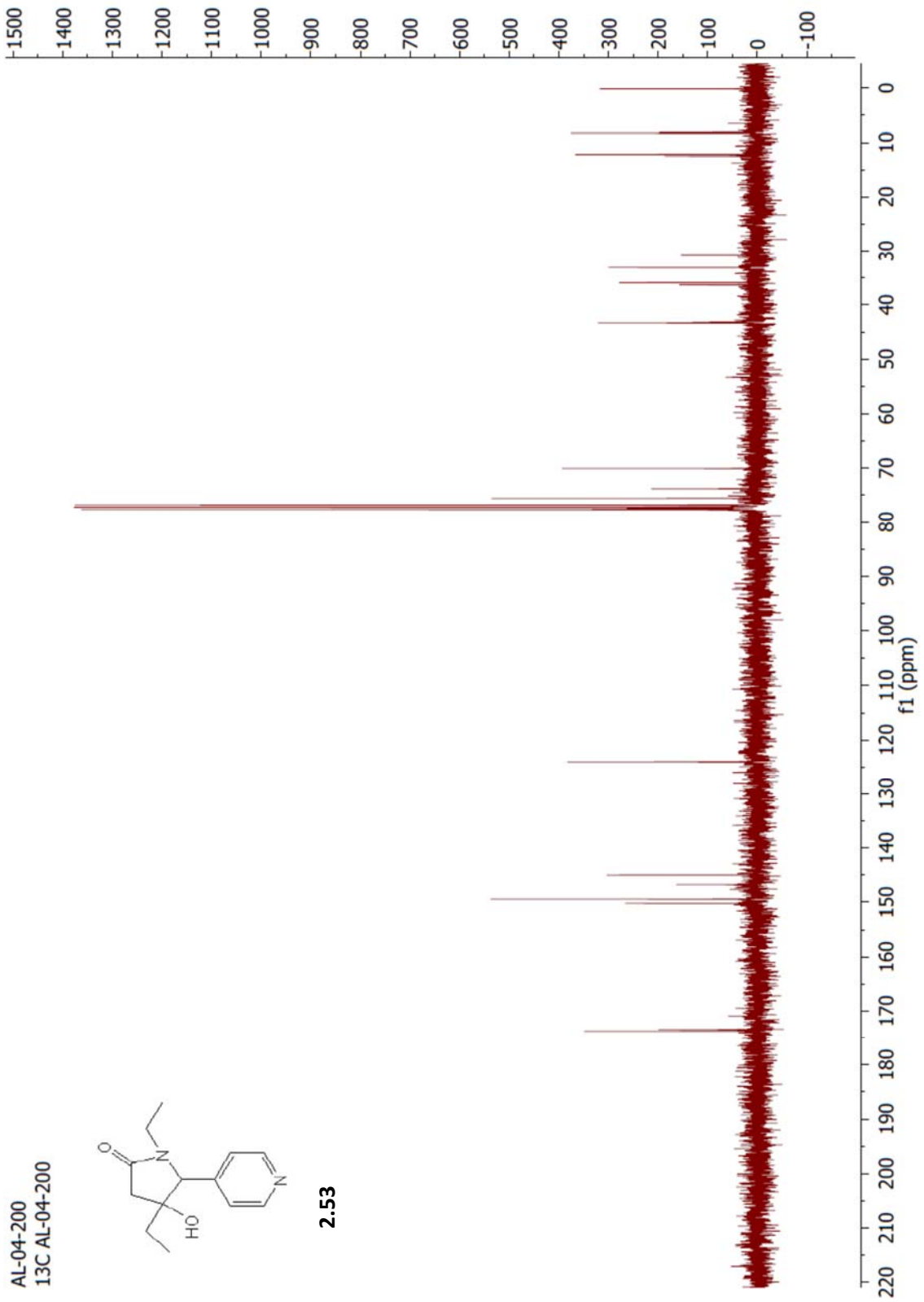

AL-02-30(1)
1H AL-02-30(1)
1.00
1.01
1.97
1.43
1.54
1.95
2.91
1.51
1.35
1.57
1.37
f1 (ppm)

2.48

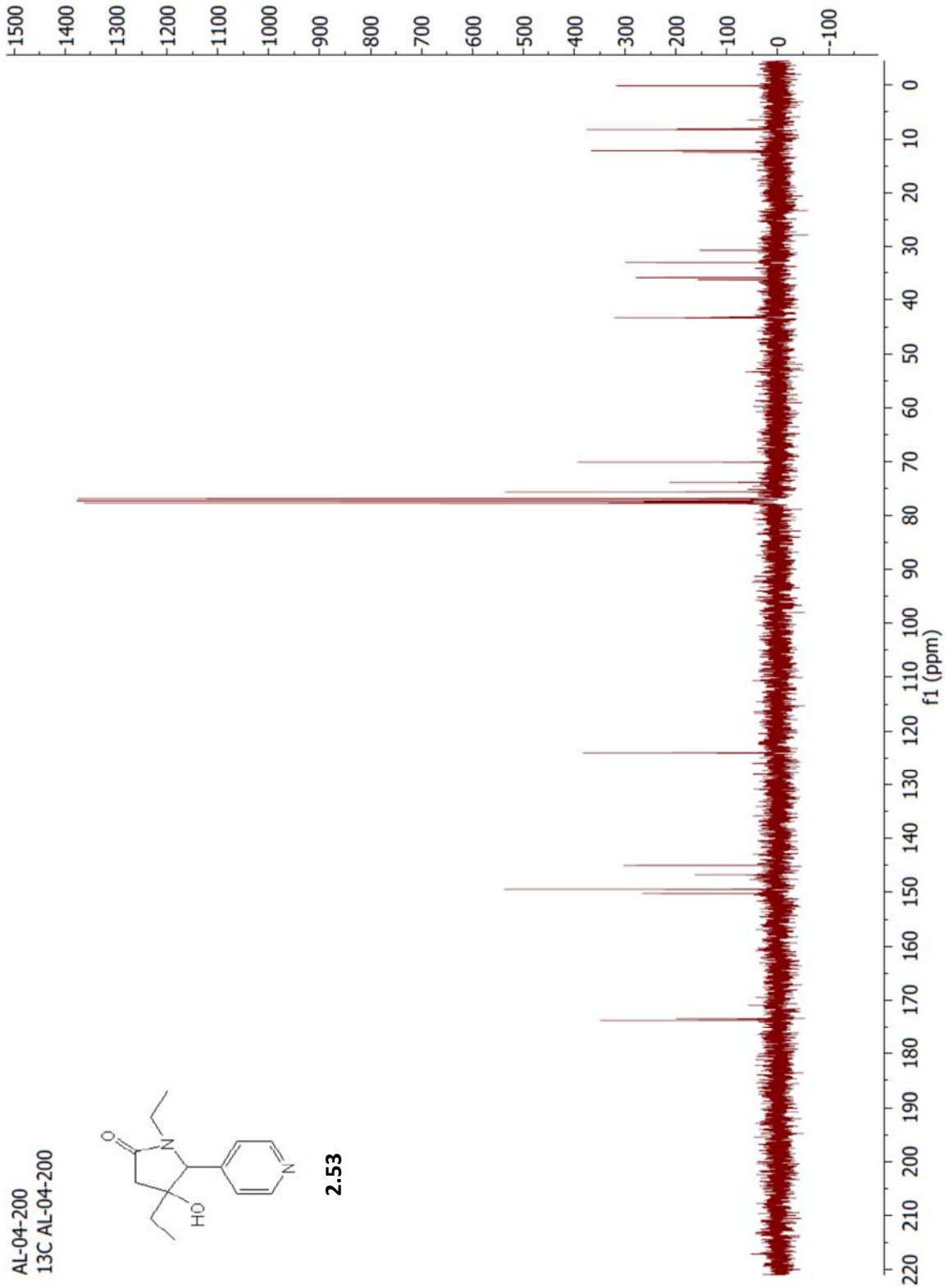
AL-02-30(1)
13C AL-02-30(1)



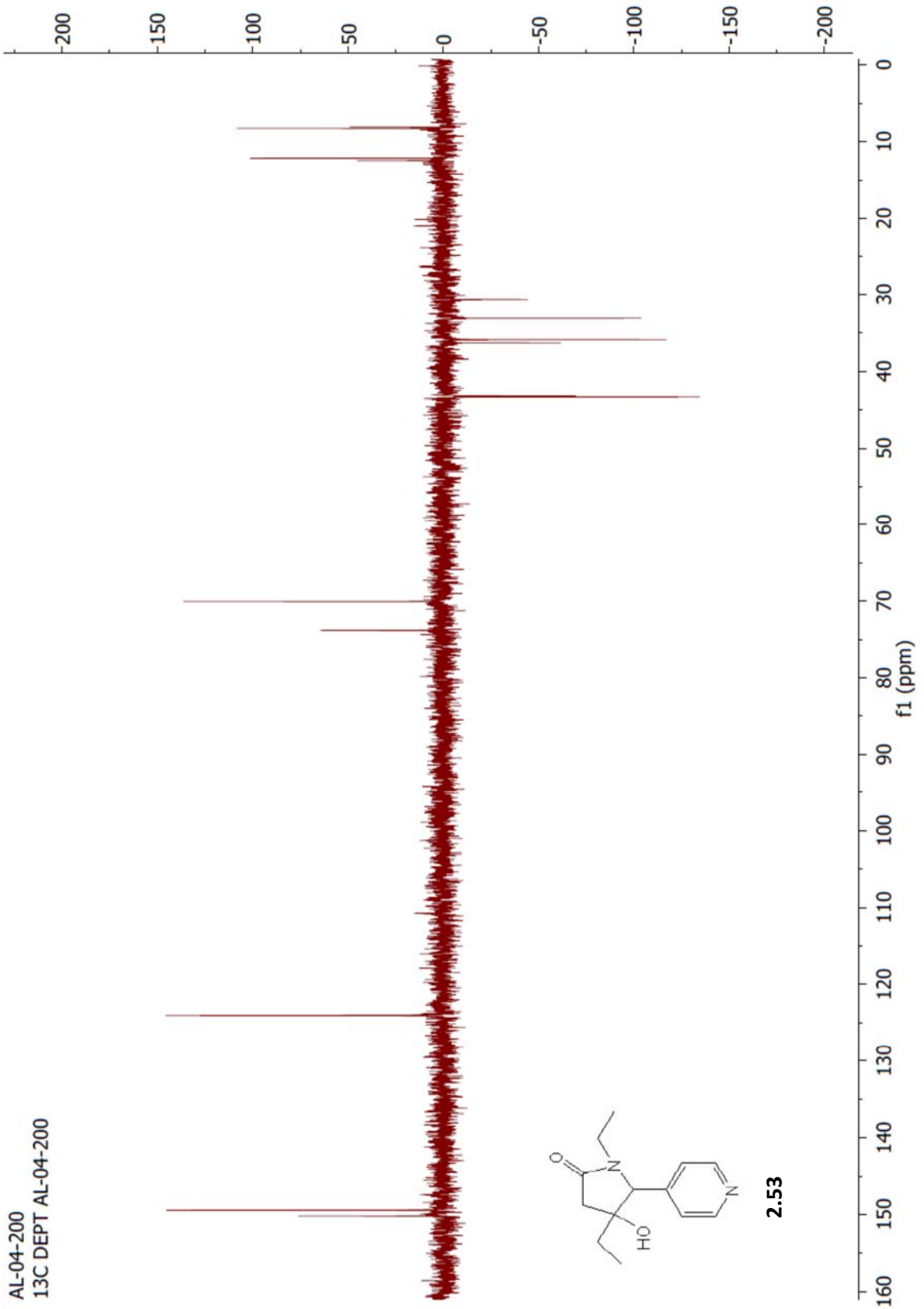
2.48



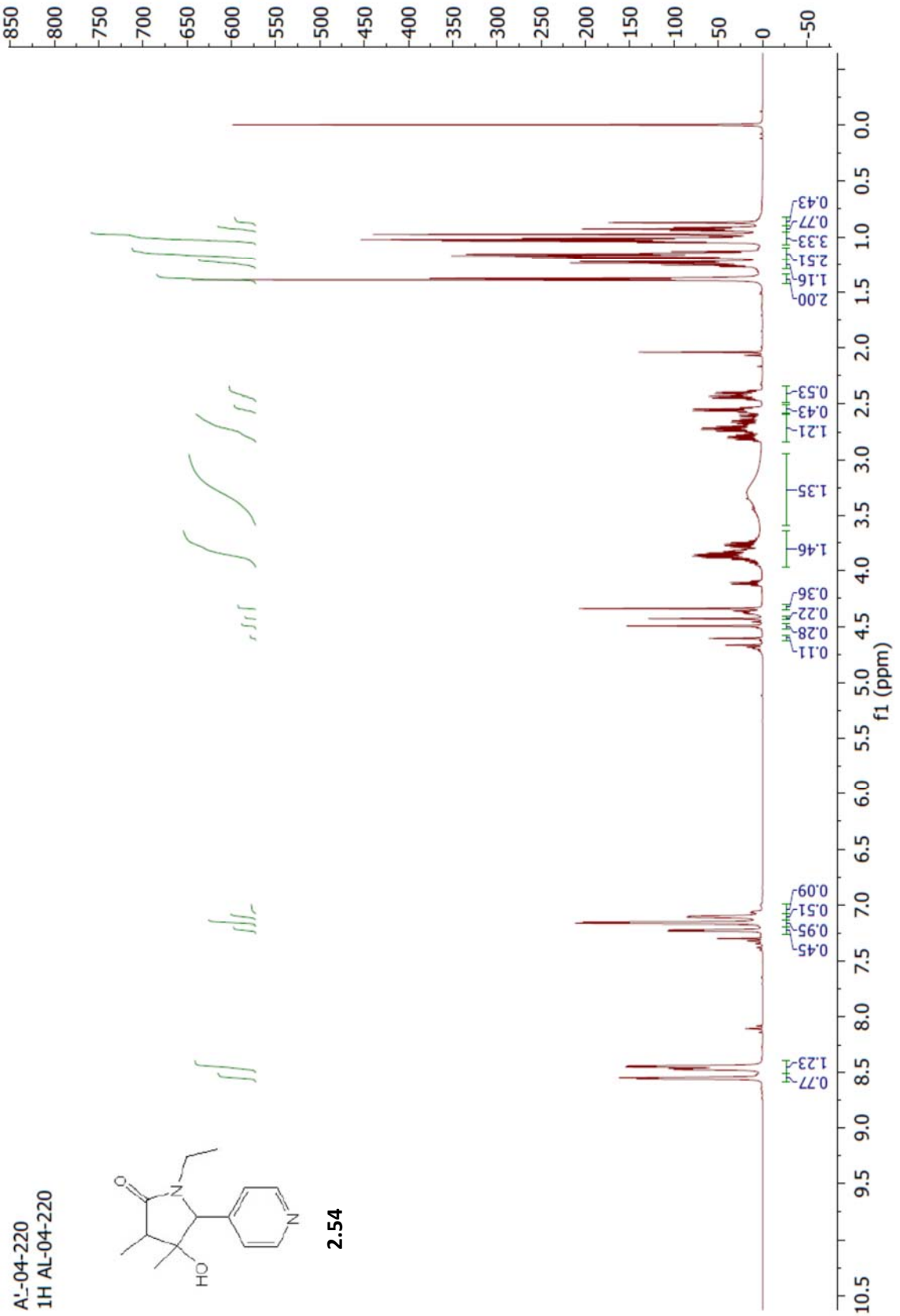
2.53

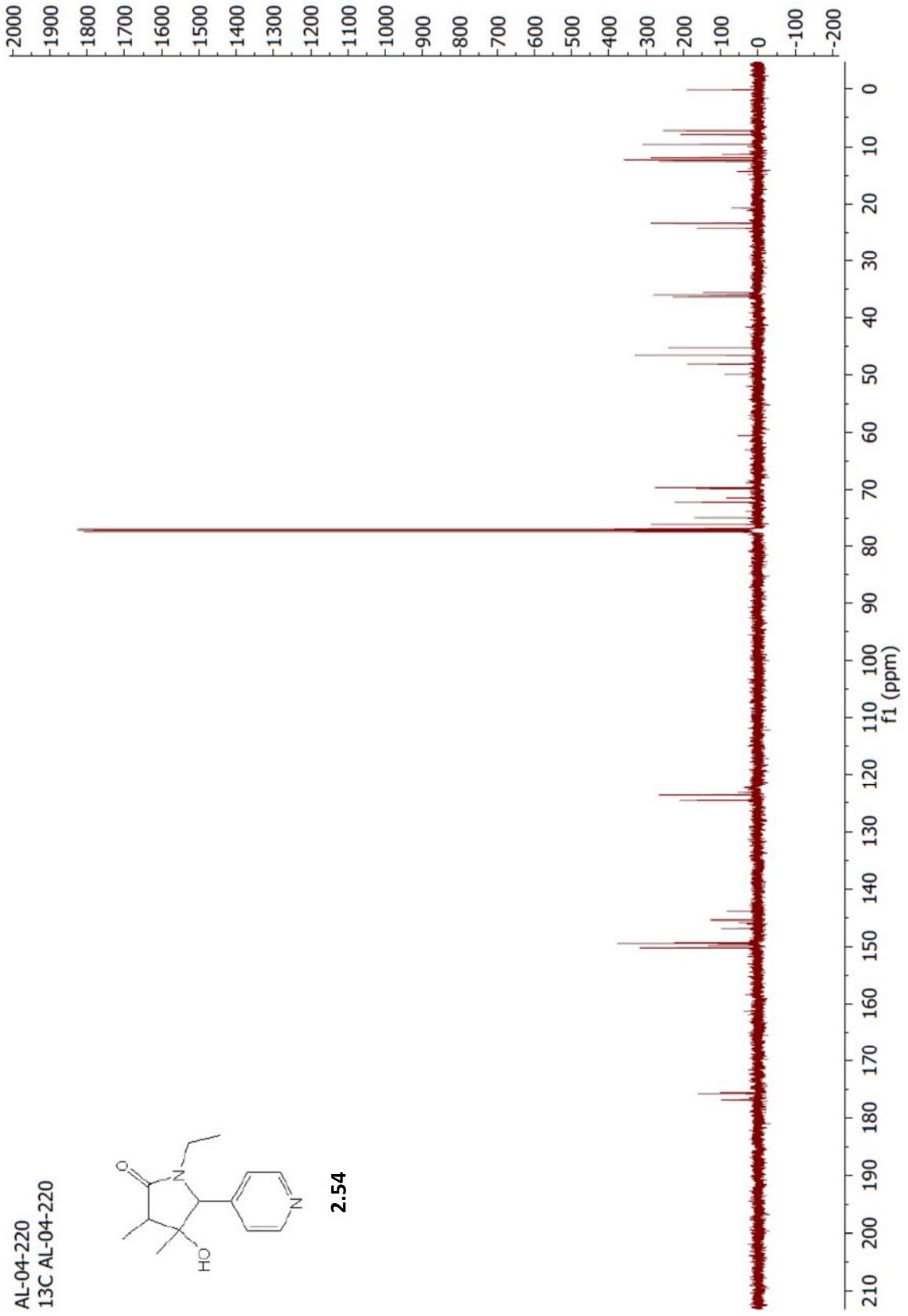


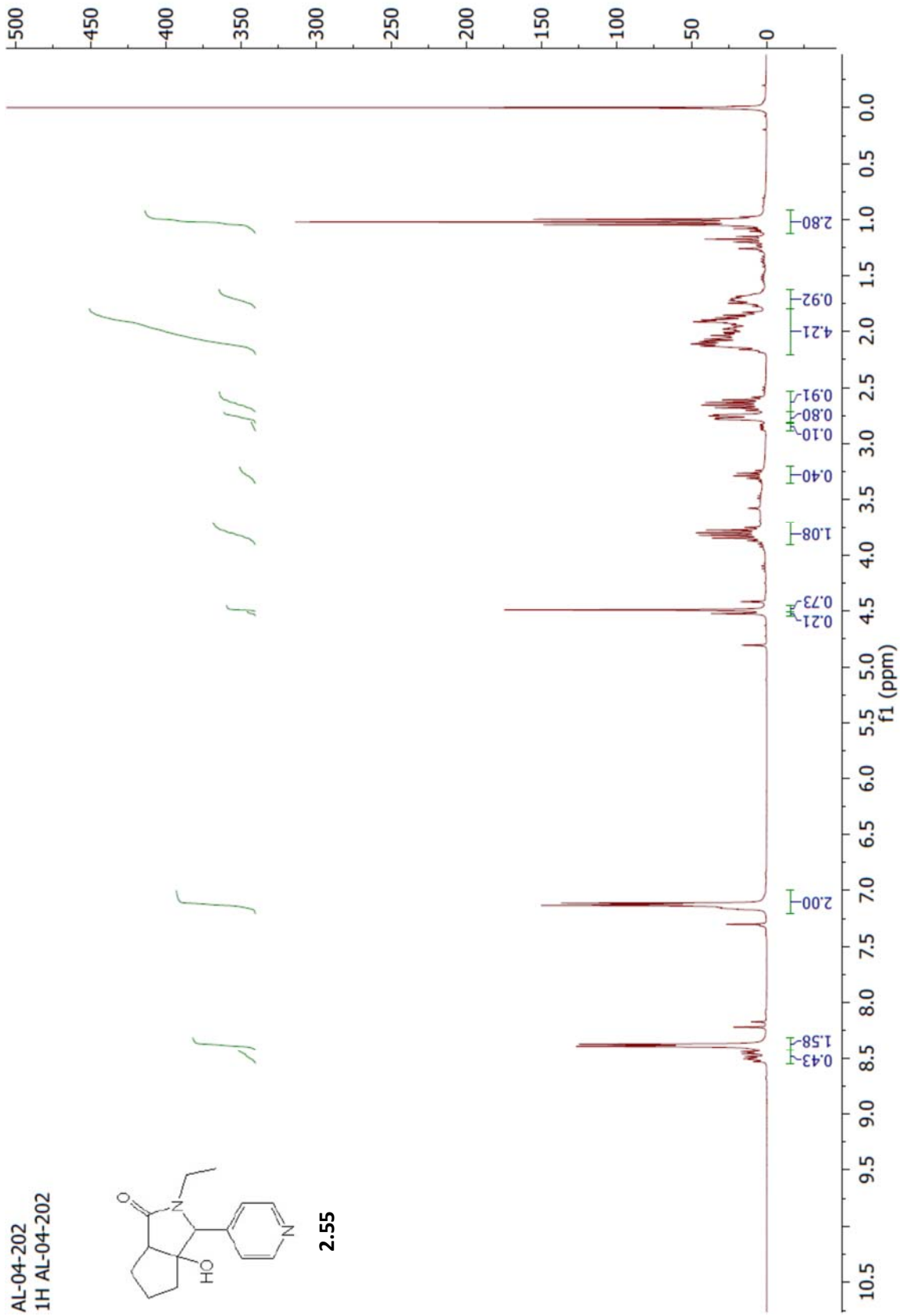
2.53

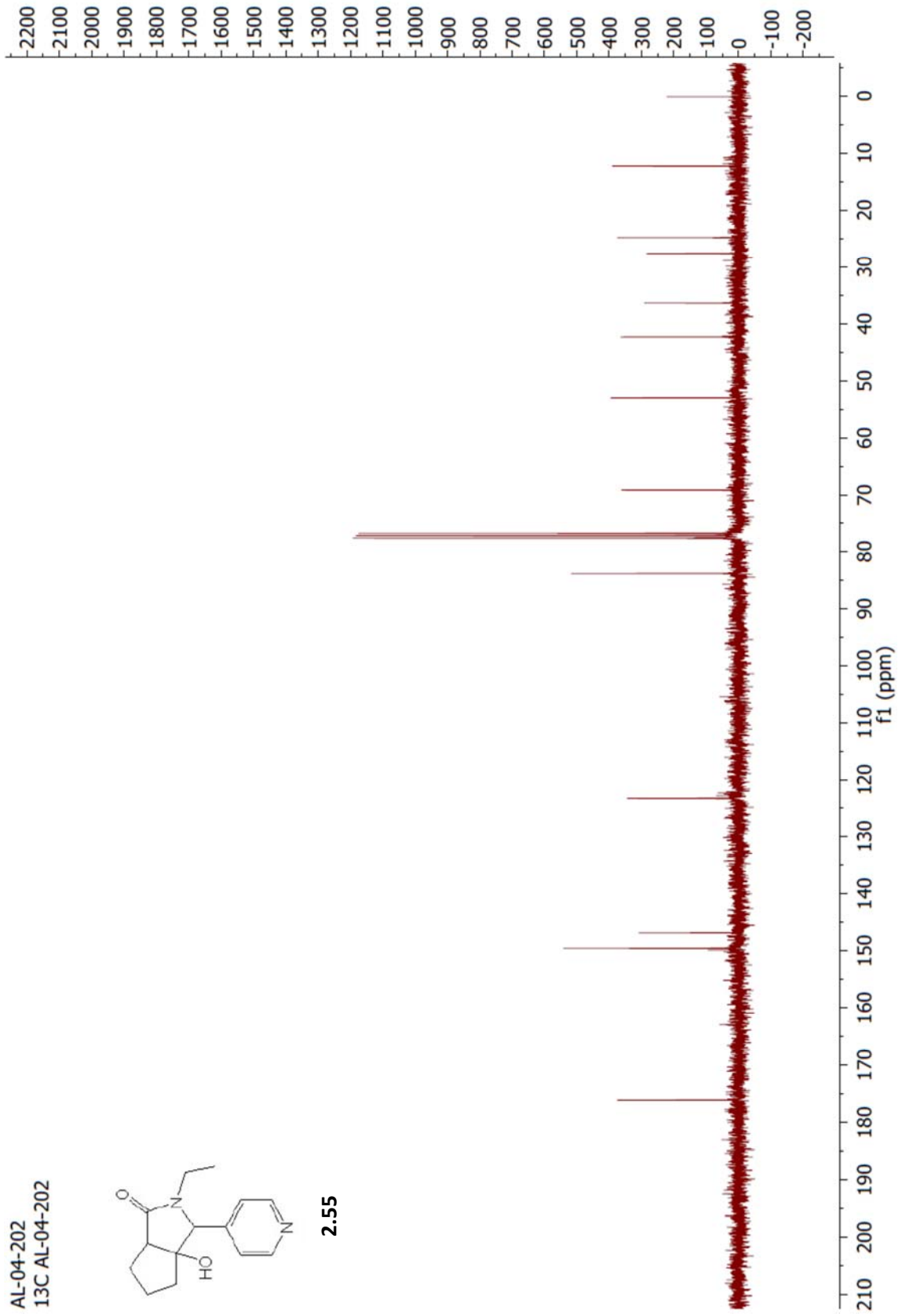

AL-04-200
13C DEPT AL-04-200
200
150
100
50
0
-50
-100
-150
-200
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)
O
N
HO
N

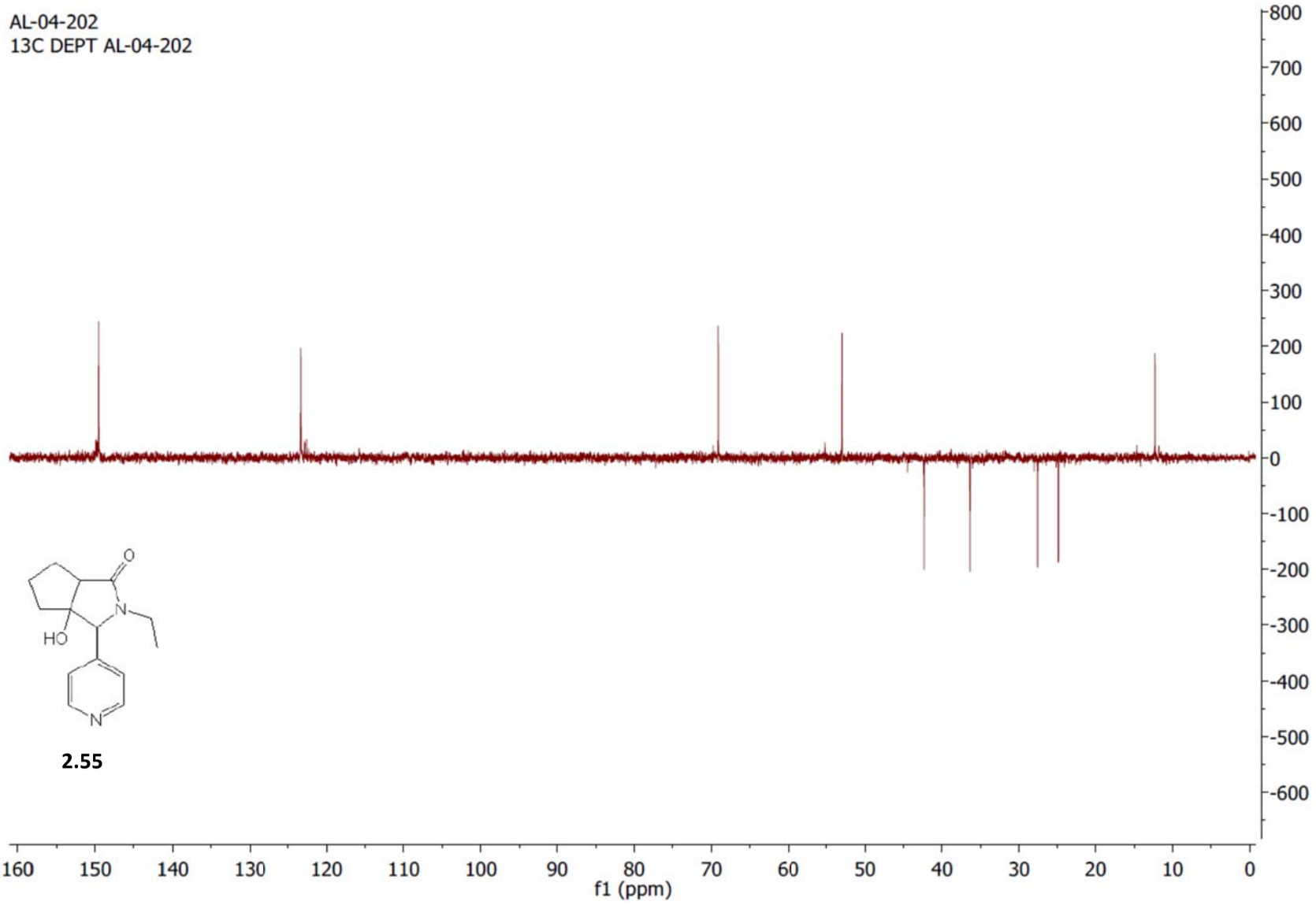
2.53


A'_-04-220
1H AL-04-220
2.54
f1 (ppm)

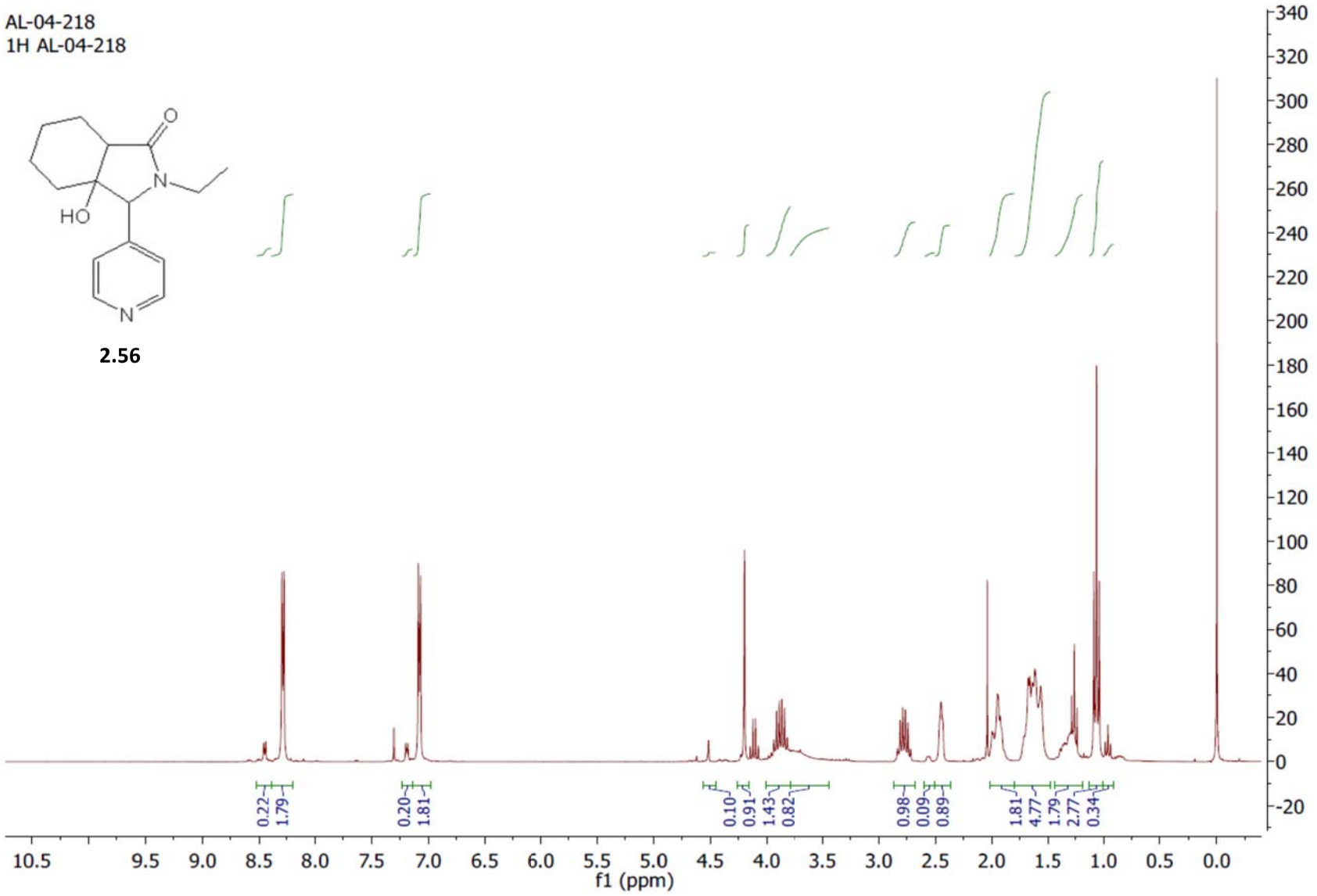

AL-04-220
13C AL-04-220
2.54
f1 (ppm)


AL-04-202
1H AL-04-202
2.55
f1 (ppm)

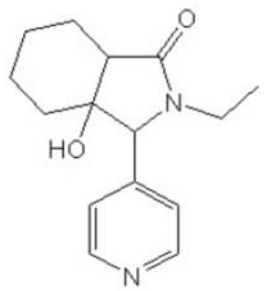

AL-04-202
13C AL-04-202
2.55
f1 (ppm)


AL-04-202
13C DEPT AL-04-202
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
-600
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
O
N
HO
N

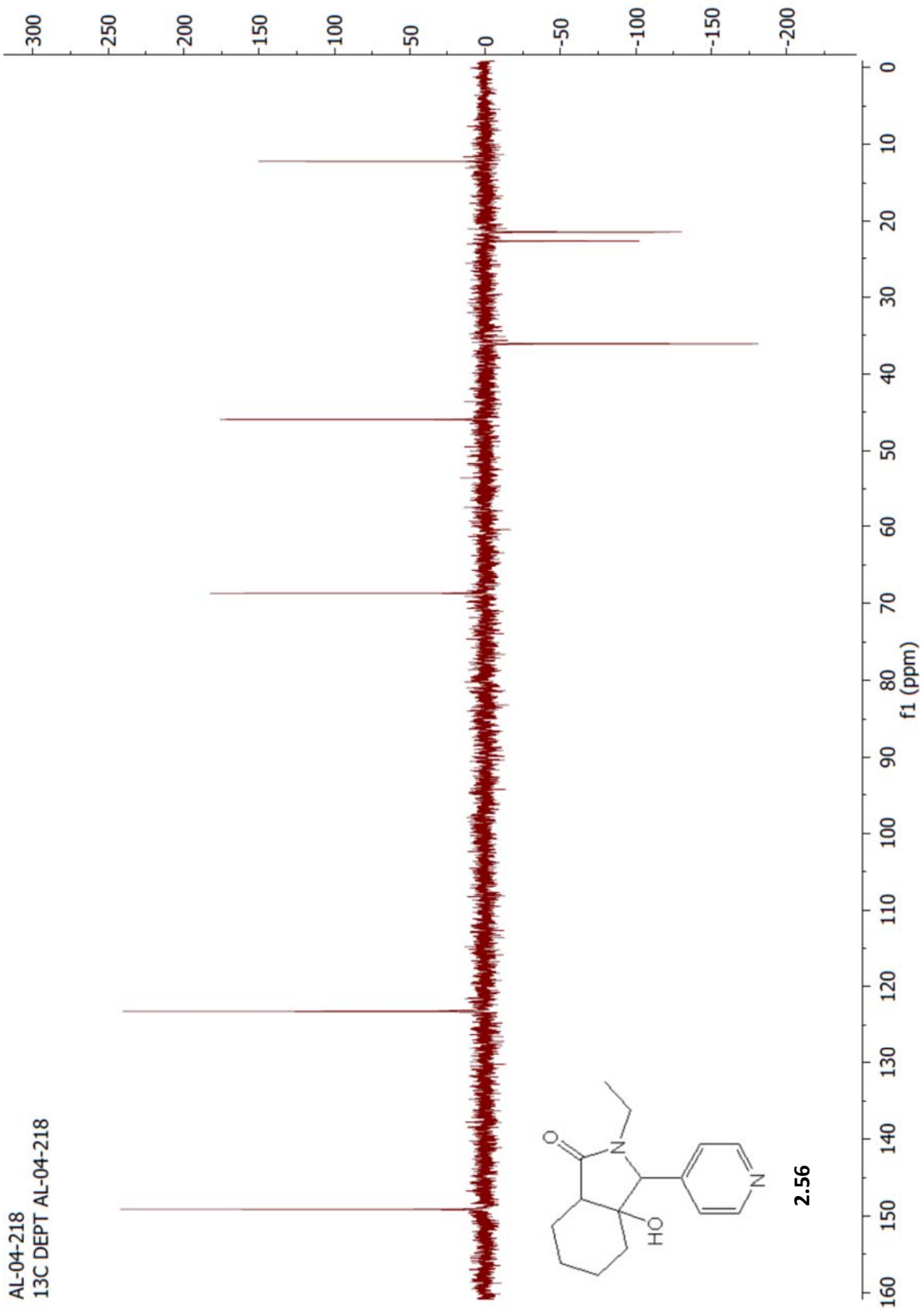
2.55


AL-04-218
1H AL-04-218
O
N
HO
N
2.56
0.22
1.79
0.20
1.81
0.10
0.91
1.43
0.82
0.98
0.09
0.89
1.81
4.77
1.79
2.77
0.34
f1 (ppm)

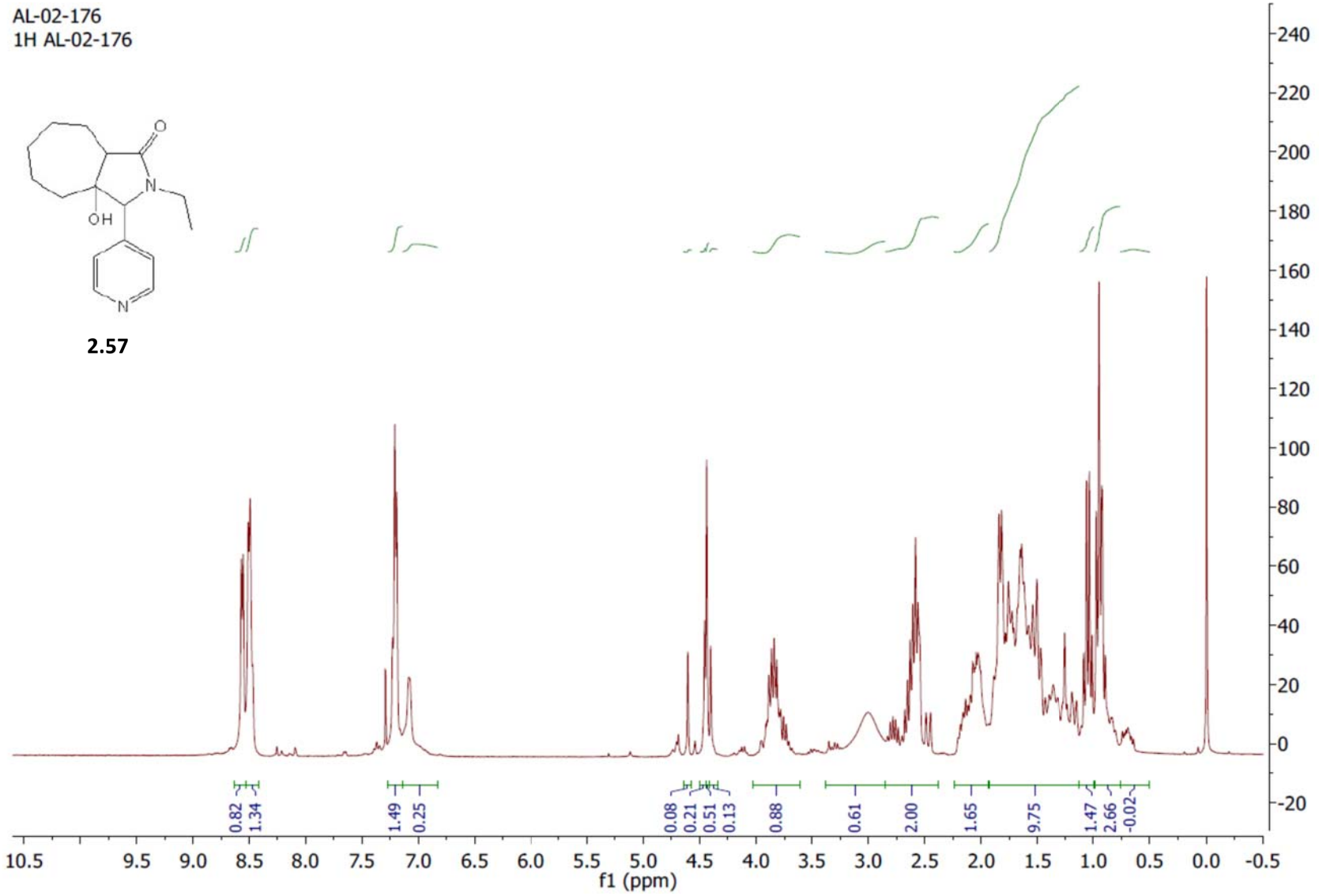
AL-04-218
13C AL-04-218

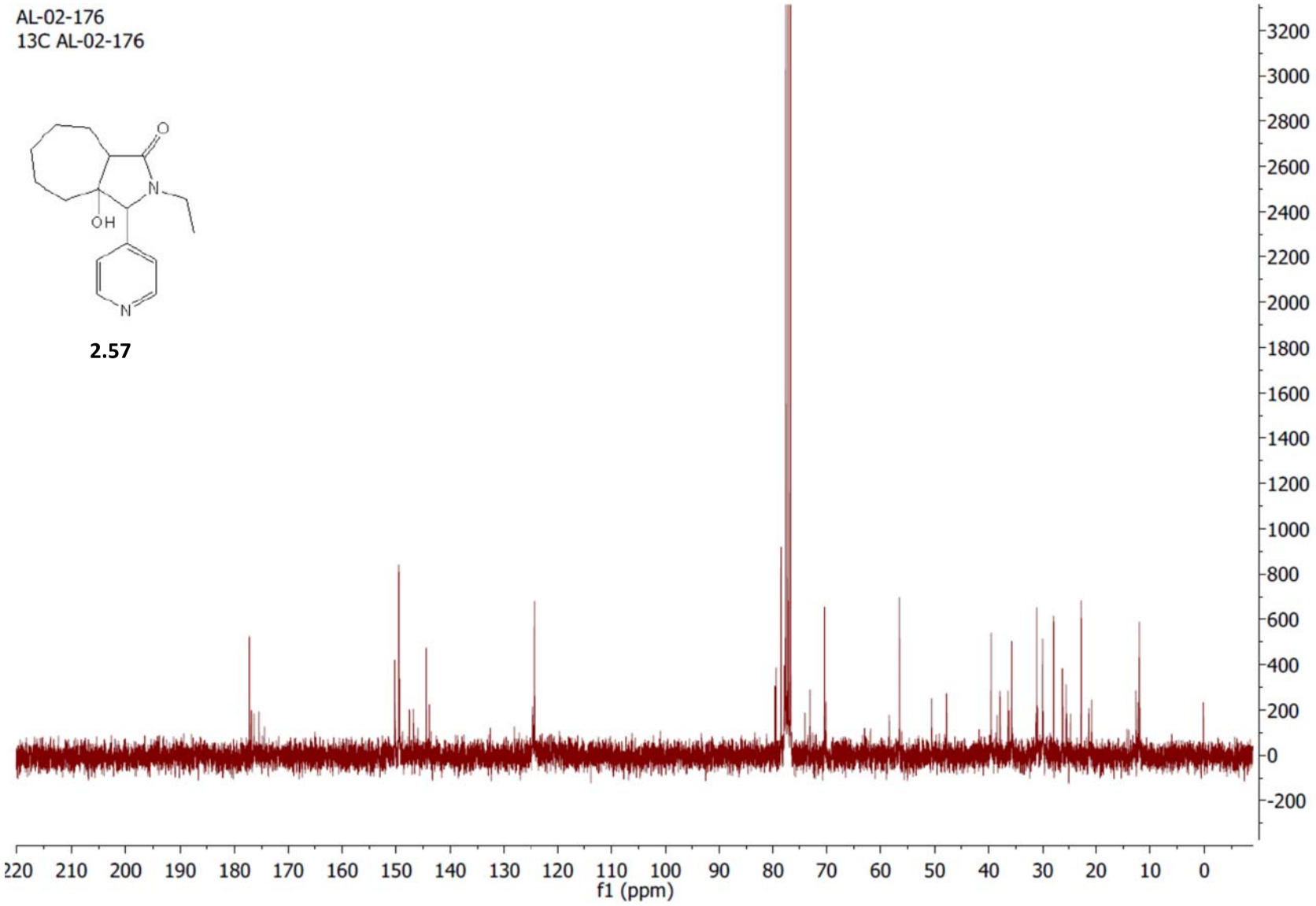


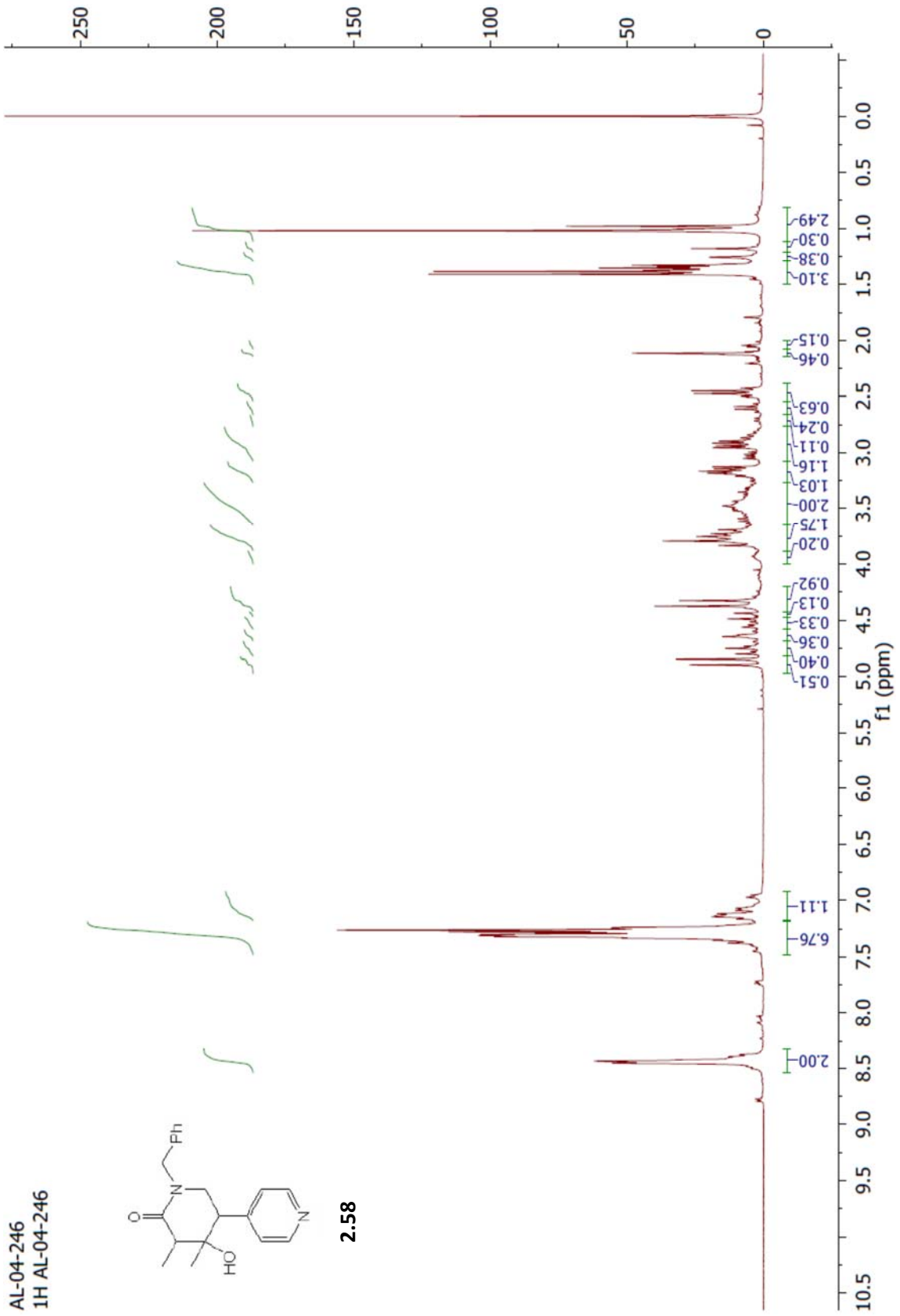
2.56

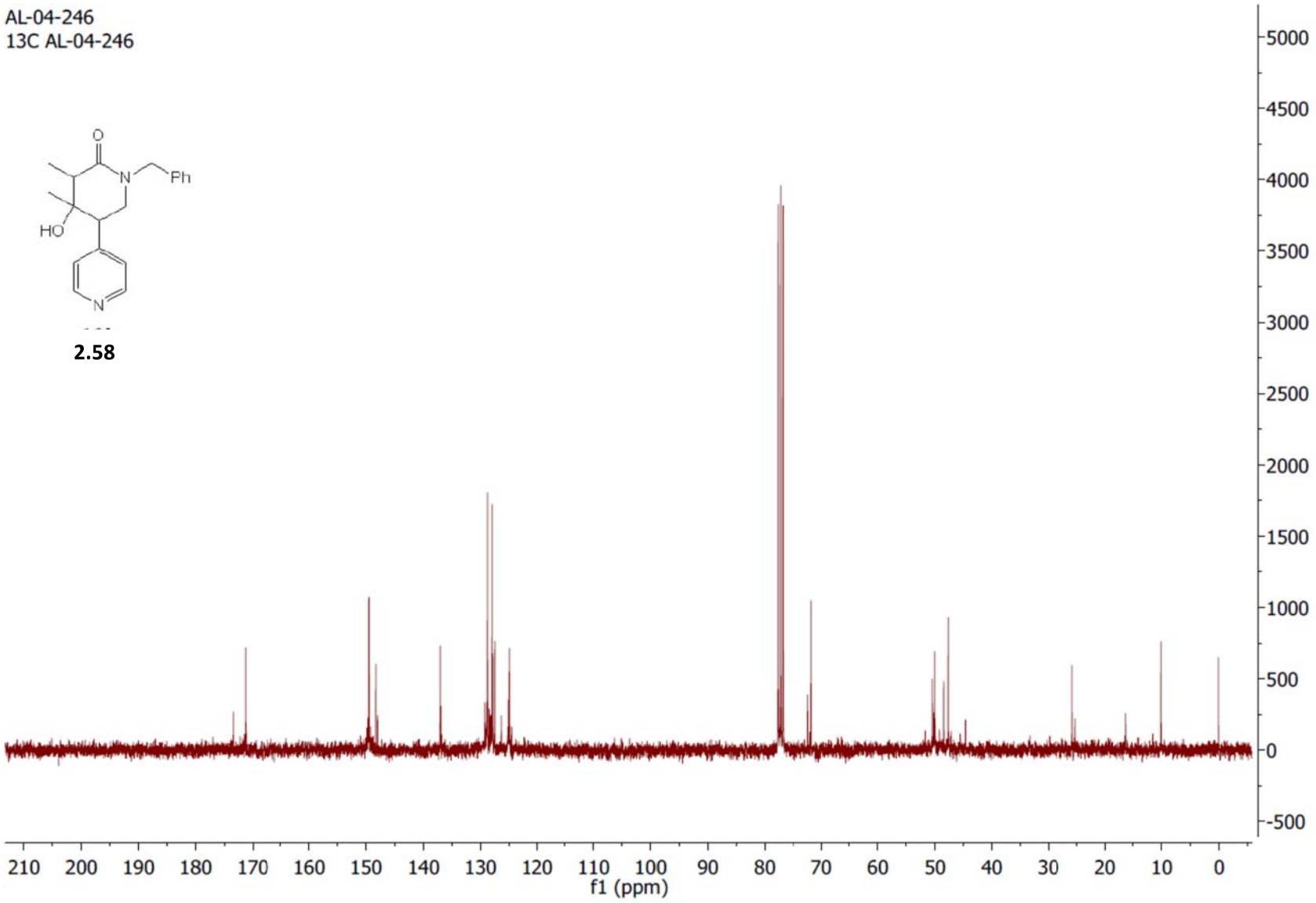


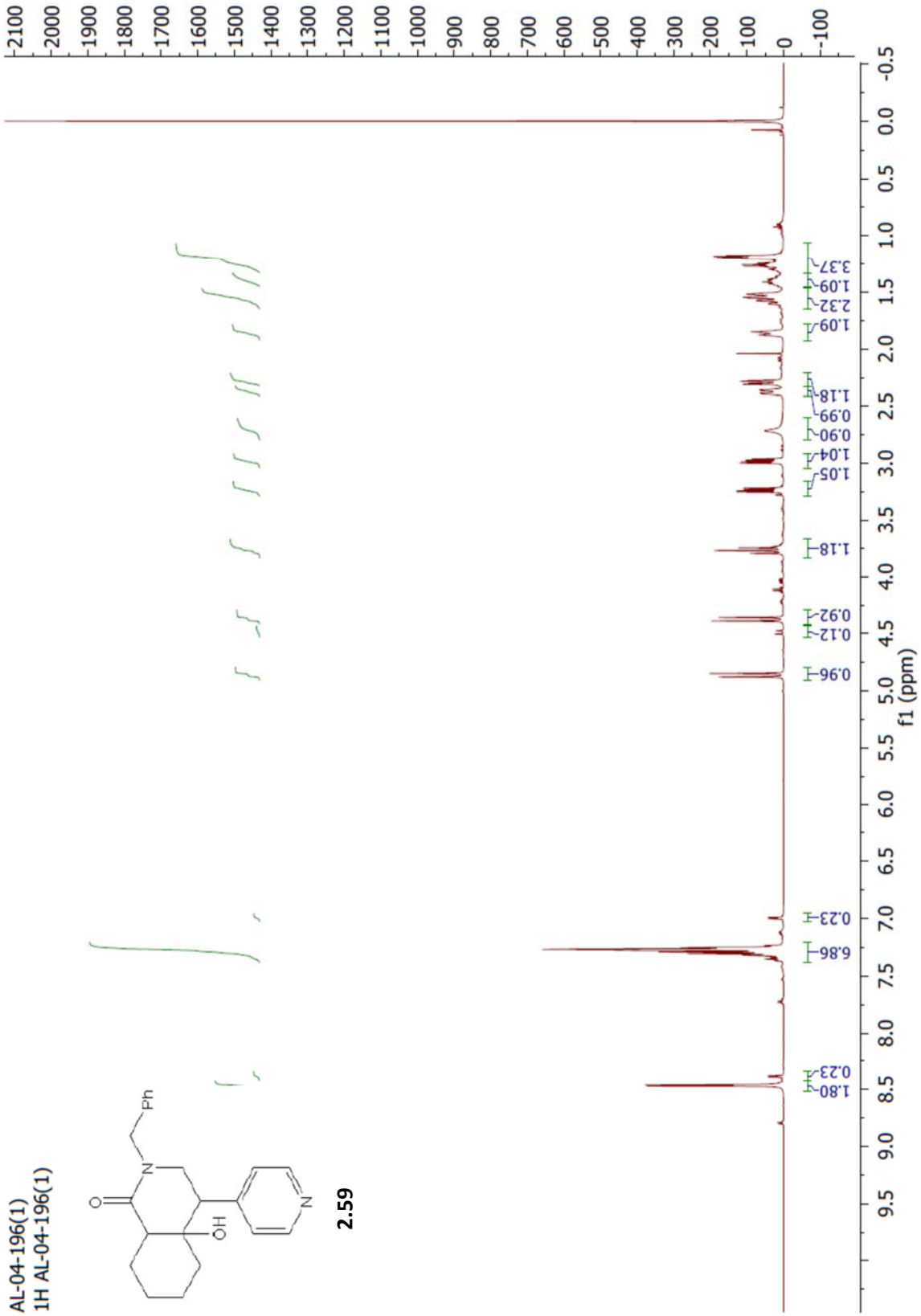
2.56

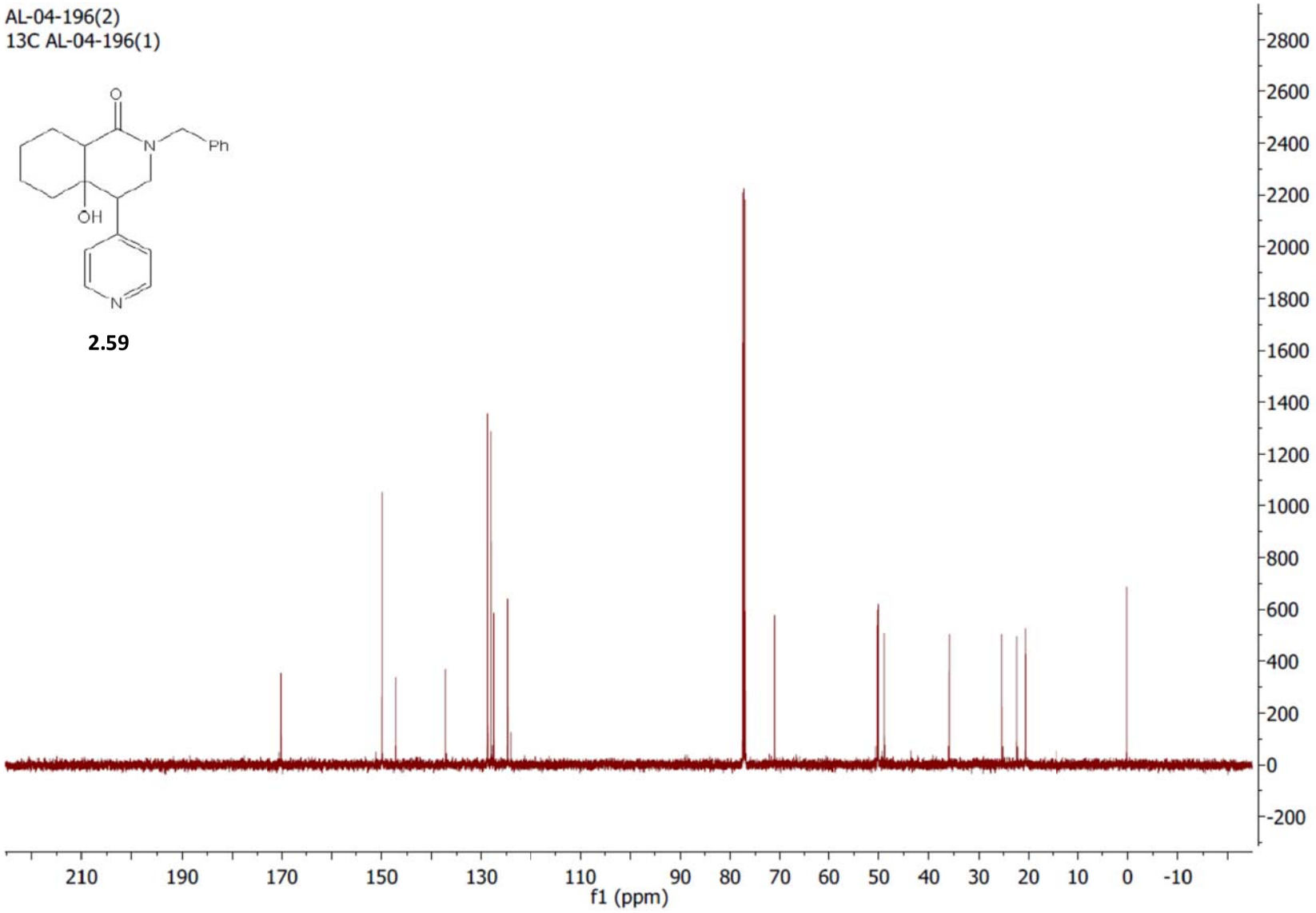

AL-02-176
1H AL-02-176
O
N
OH
N
2.57
0.82
1.34
1.49
0.25
0.08
0.21
0.51
0.13
0.88
0.61
2.00
1.65
9.75
1.47
2.66
-0.02
f1 (ppm)

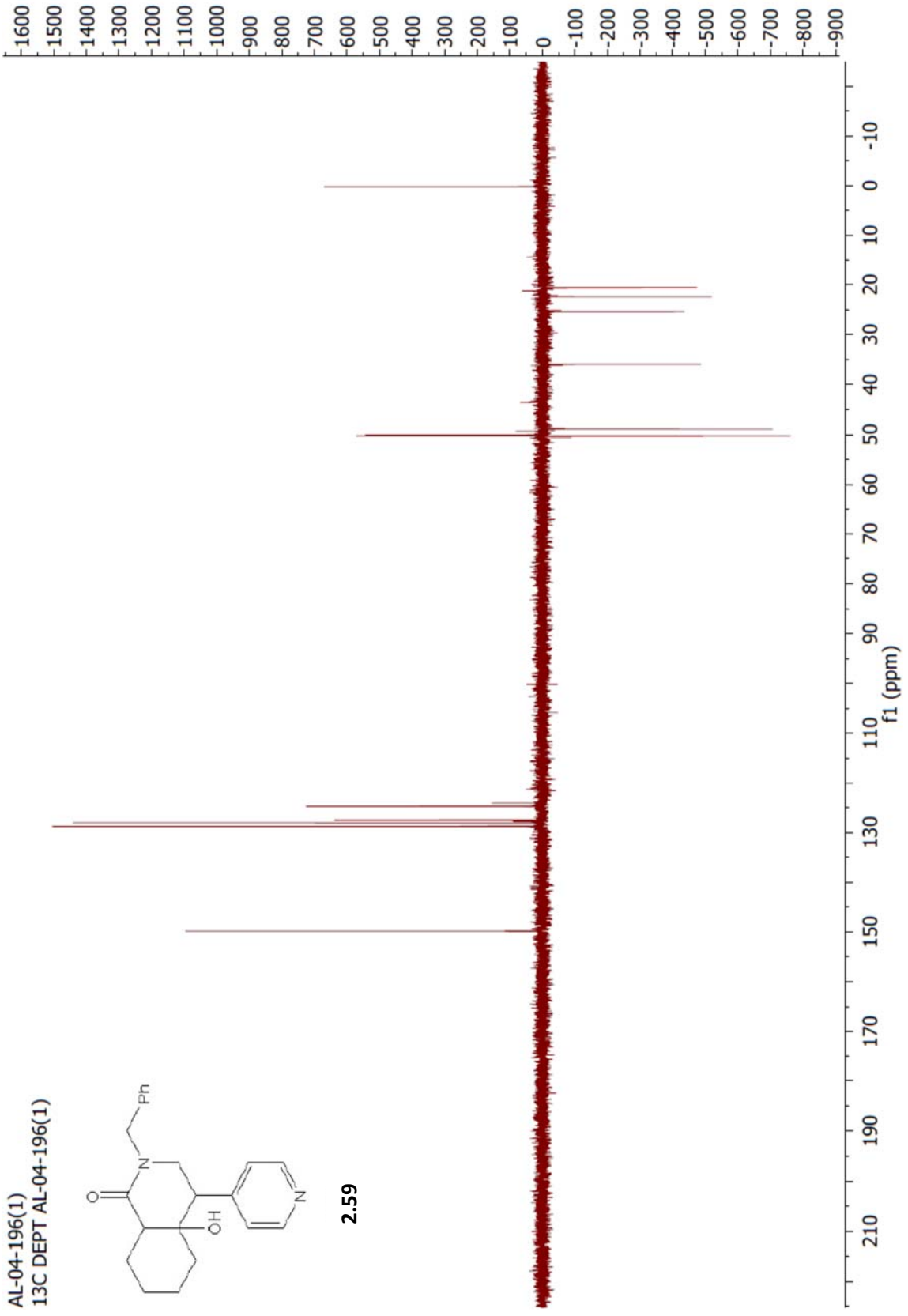

AL-02-176
13C AL-02-176
O
N
OH
N
2.57
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

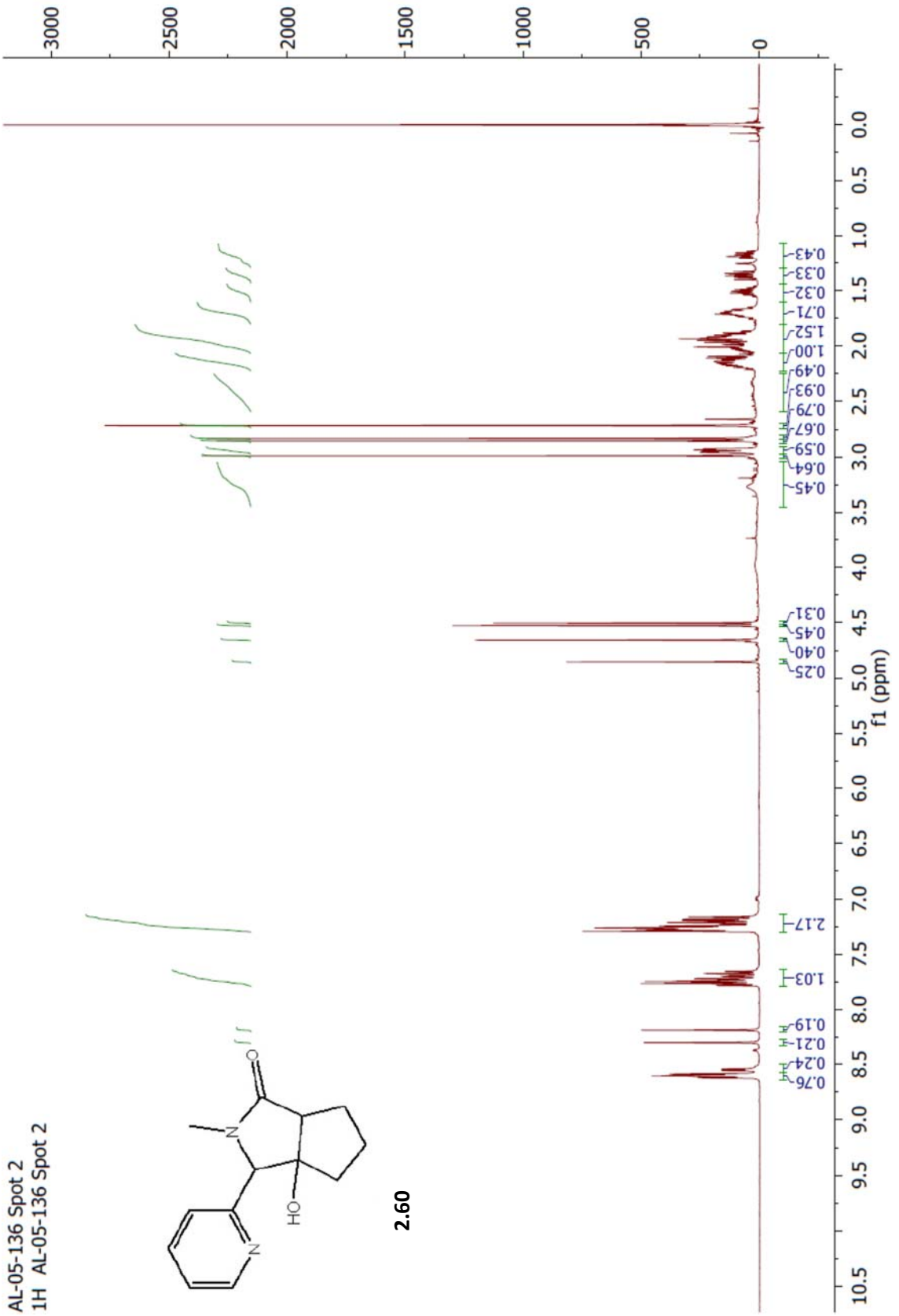

AL-04-246
1H AL-04-246
2.58
f1 (ppm)


AL-04-246
13C AL-04-246
O
N
Ph
HO
N
2.58
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

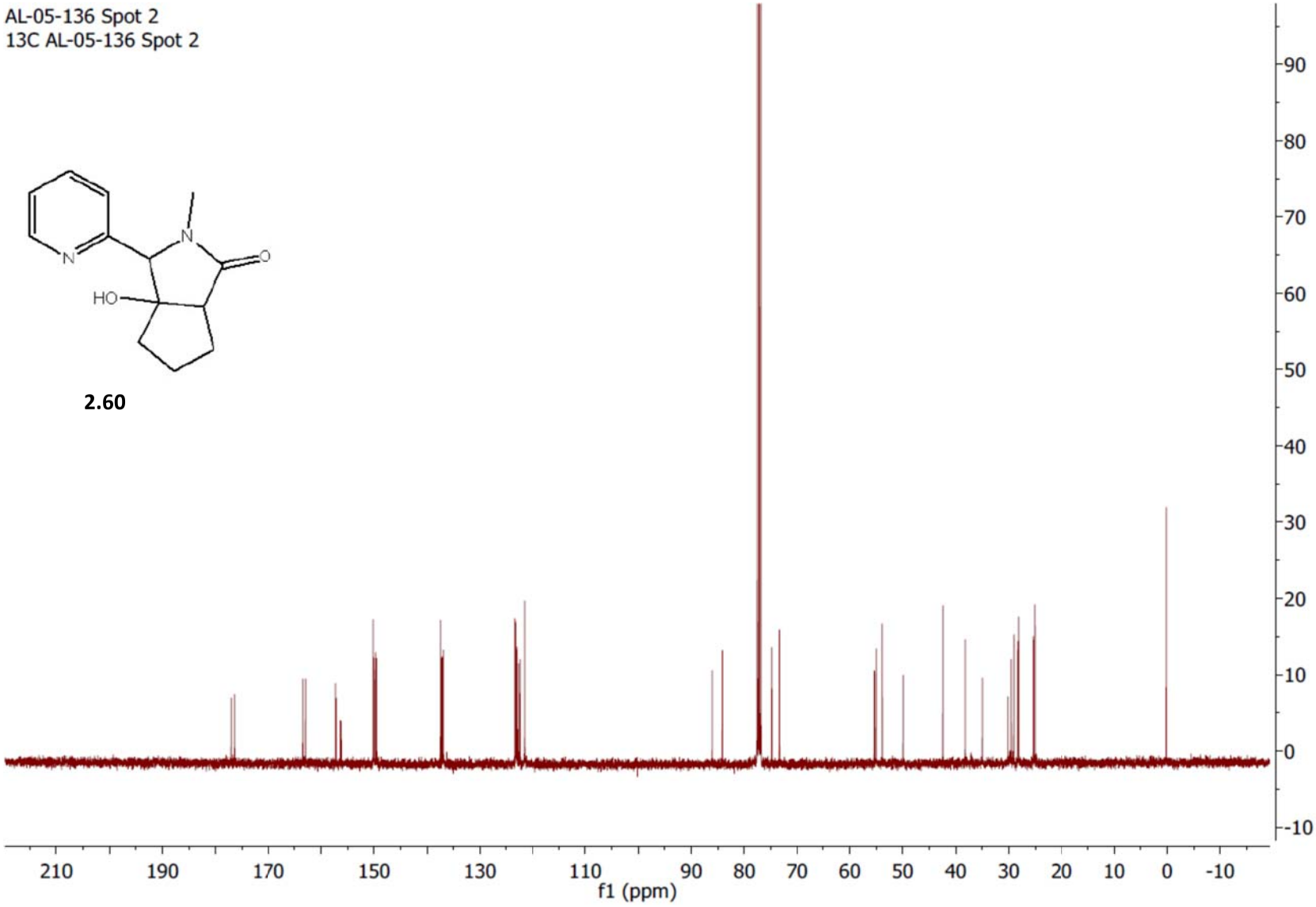

AL-04-196(1)
1H AL-04-196(1)
Ph
N
O
OH
N
2.59
f1 (ppm)

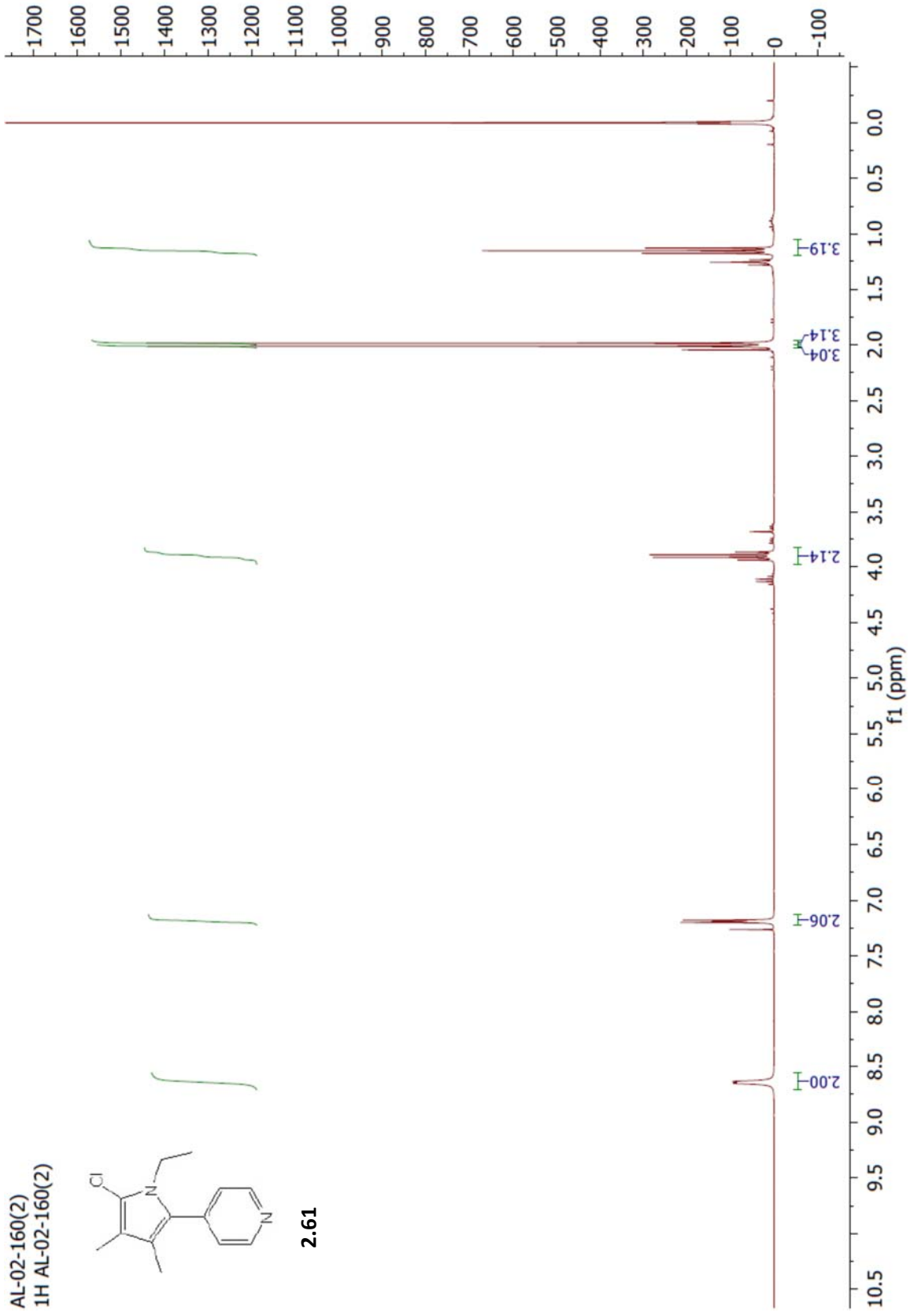

AL-04-196(2)
13C AL-04-196(1)
O
N
Ph
OH
N
2.59
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

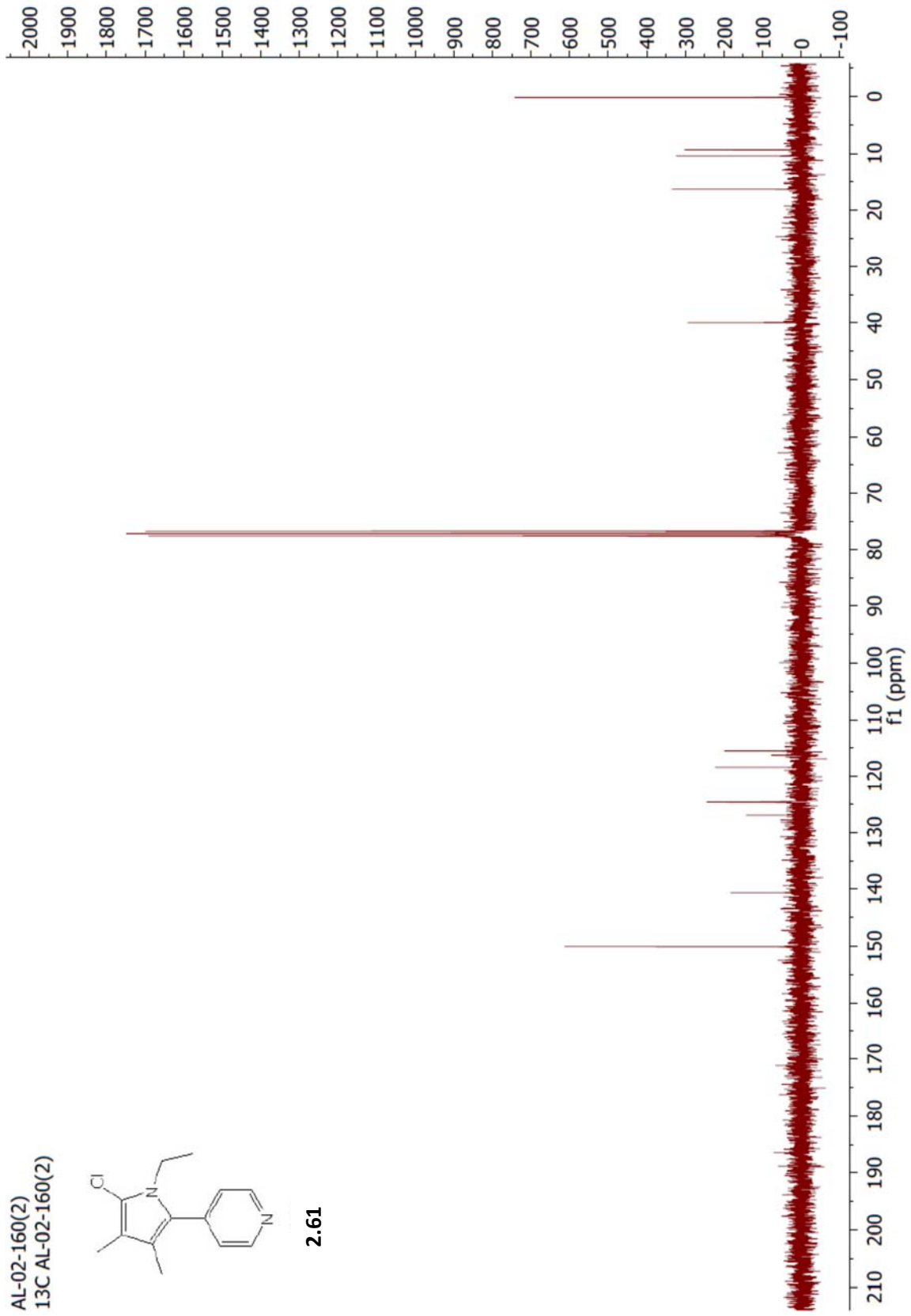

AL-04-196(1)
13C DEPT AL-04-196(1)
Ph
N
O
OH
N
2.59
f1 (ppm)

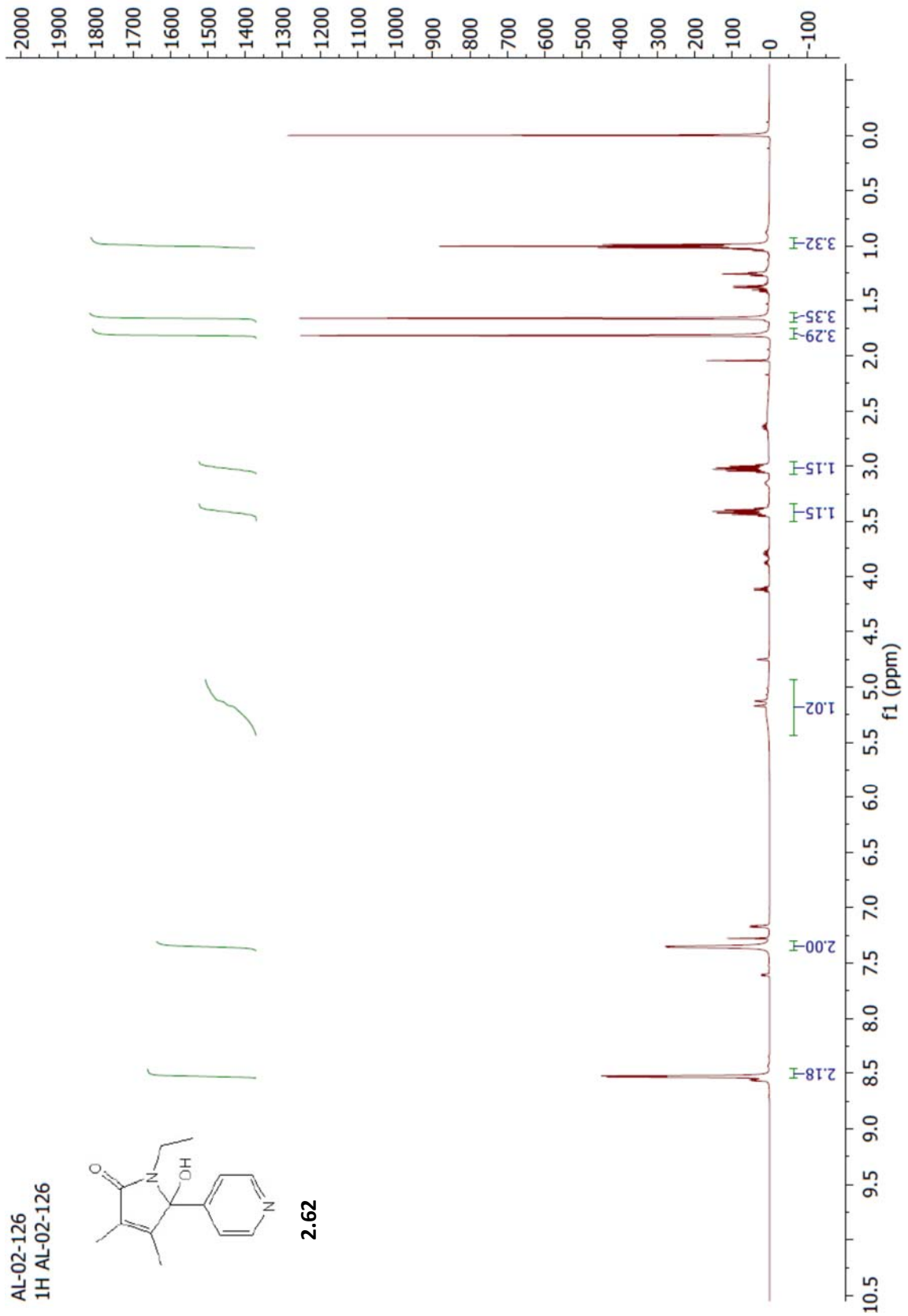


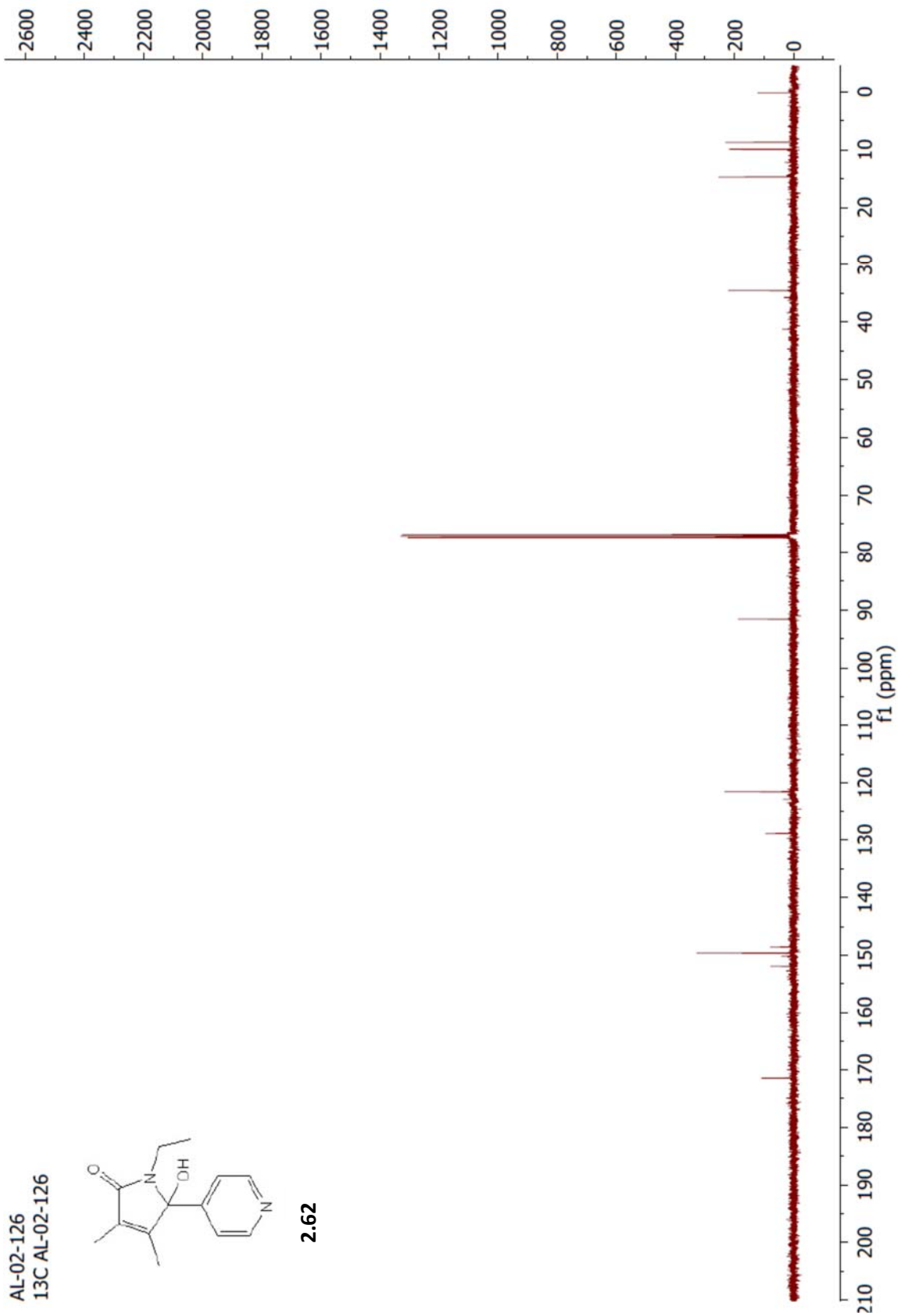
2.60


AL-05-136 Spot 2
13C AL-05-136 Spot 2
N
N
O
HO
2.60
90
80
70
60
50
40
30
20
10
0
-10
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

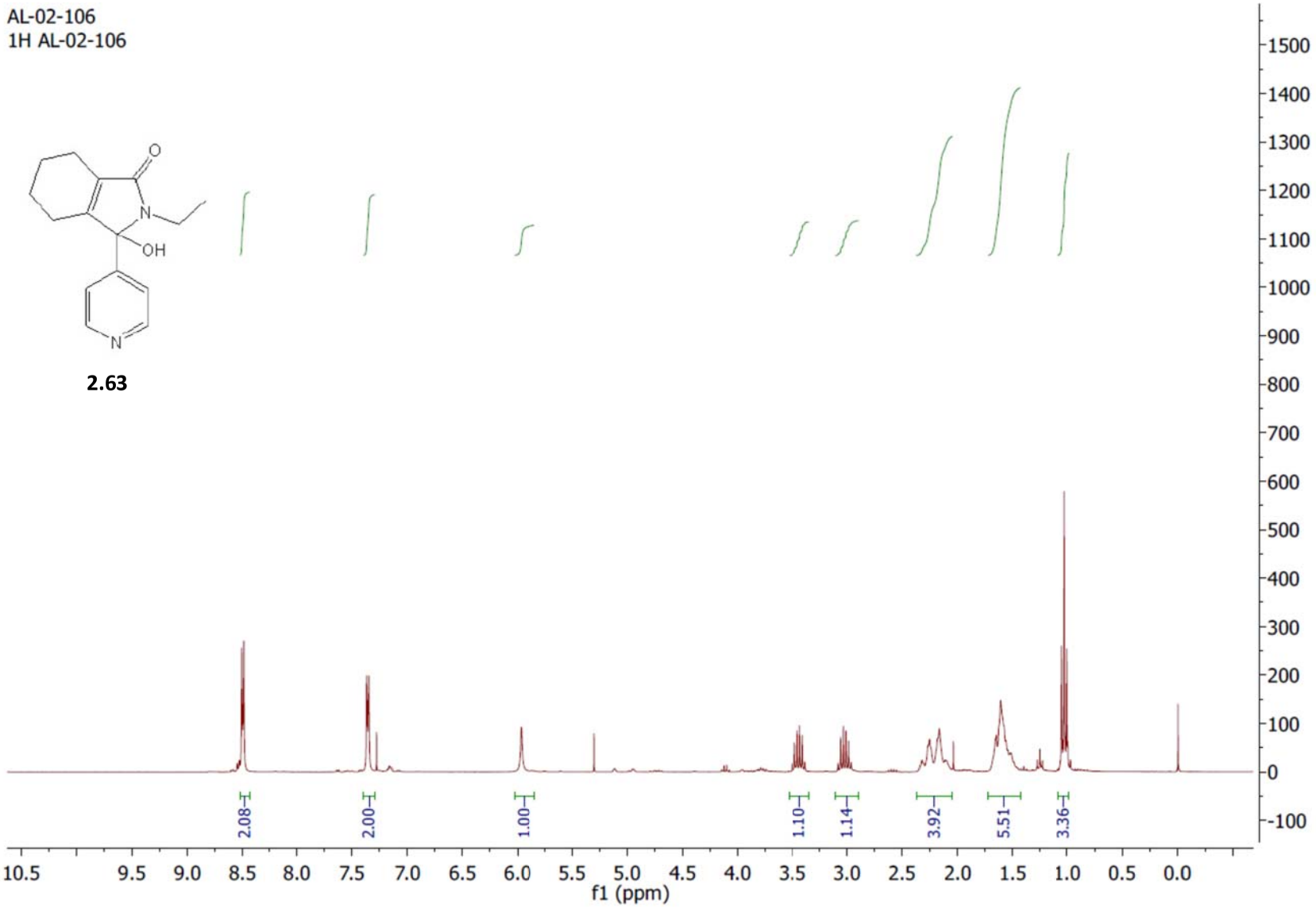

AL-02-160(2)
1H AL-02-160(2)
Cl
N
N
2.61
3.19
3.04
3.14
2.14
2.06
2.00
f1 (ppm)

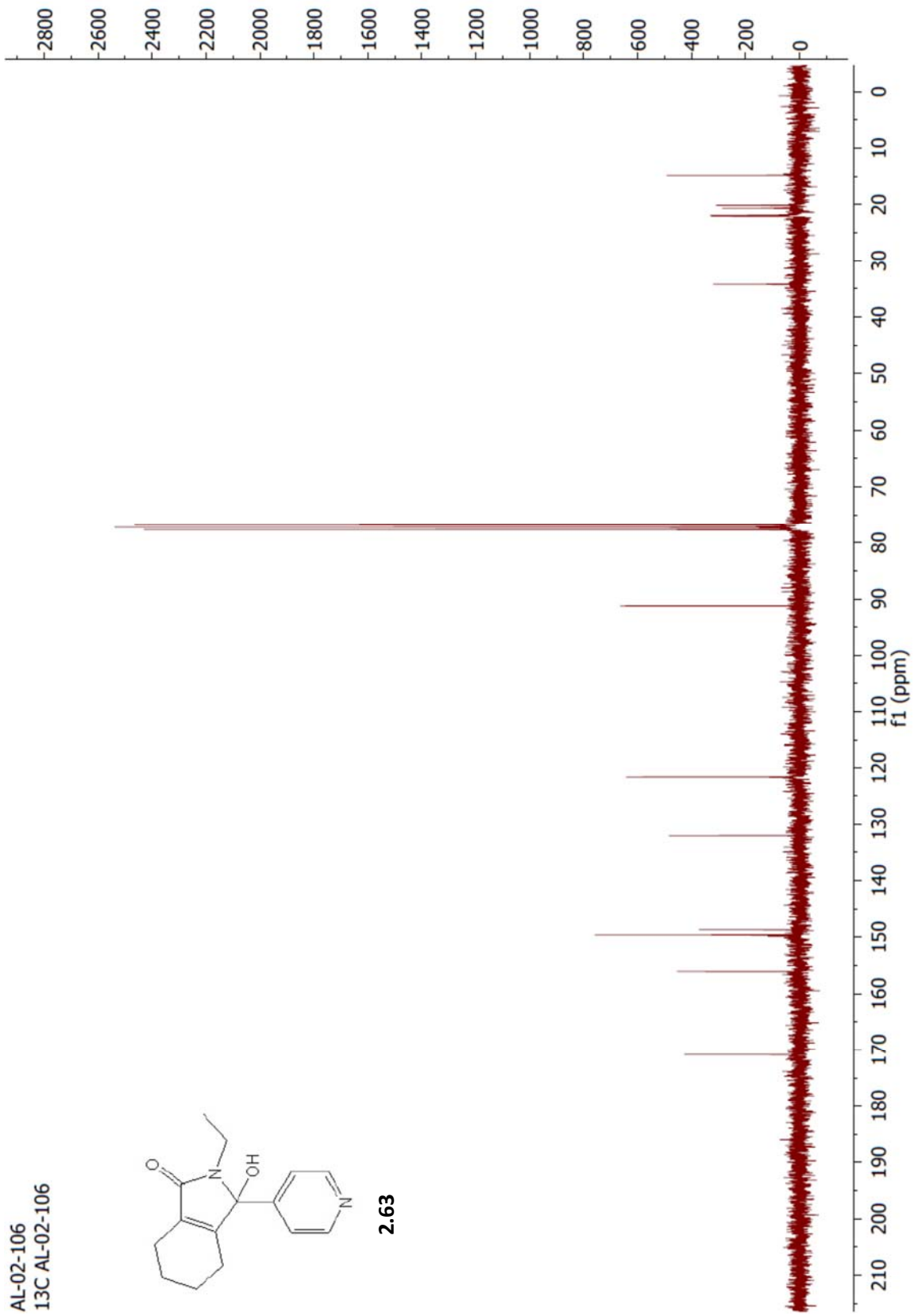

AL-02-160(2)
13C AL-02-160(2)
Cl
N
N
2.61
f1 (ppm)

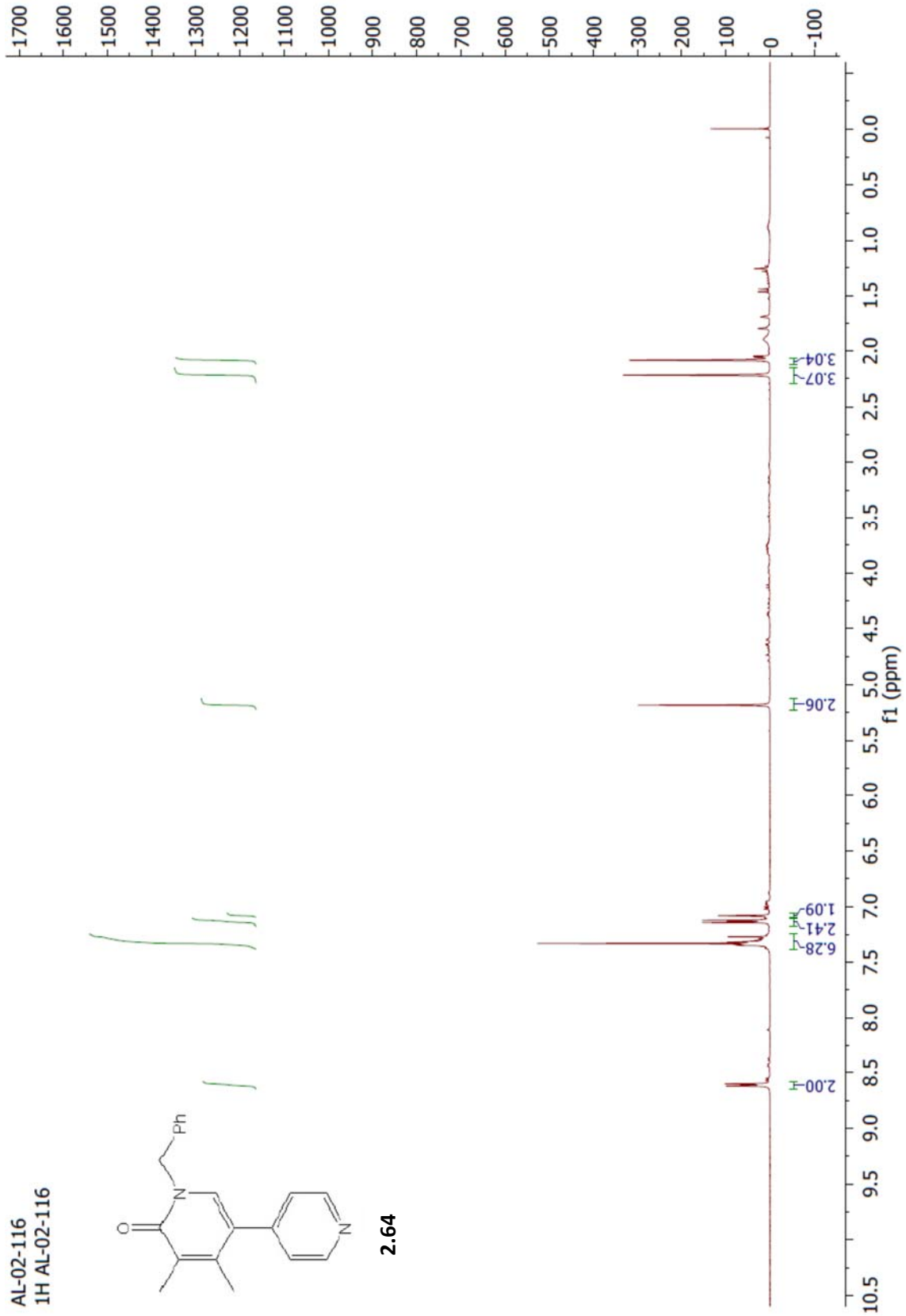

AL-02-126
1H AL-02-126
2.62
f1 (ppm)
2.18
2.00
1.02
1.15
1.15
3.29
3.35
3.32

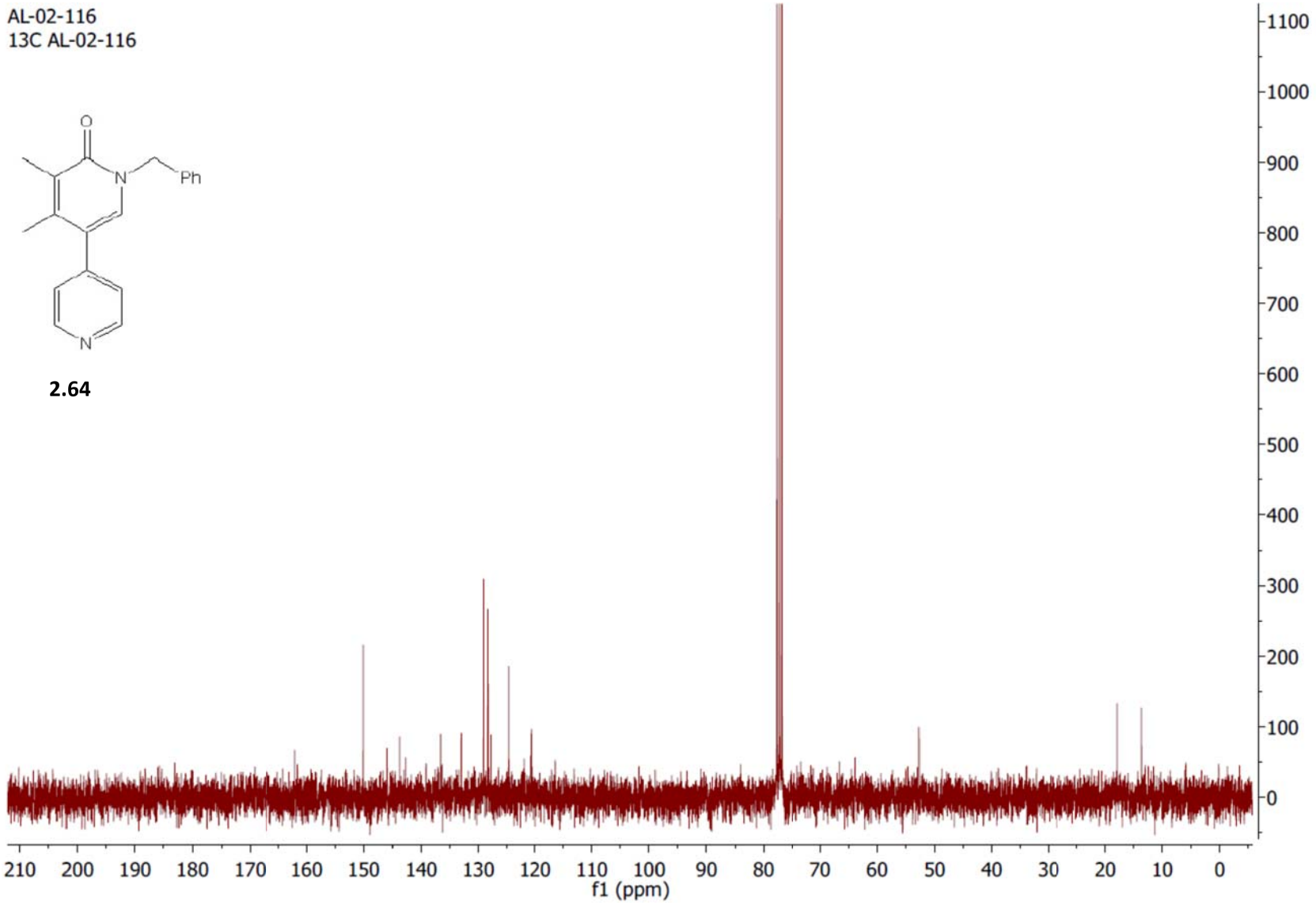


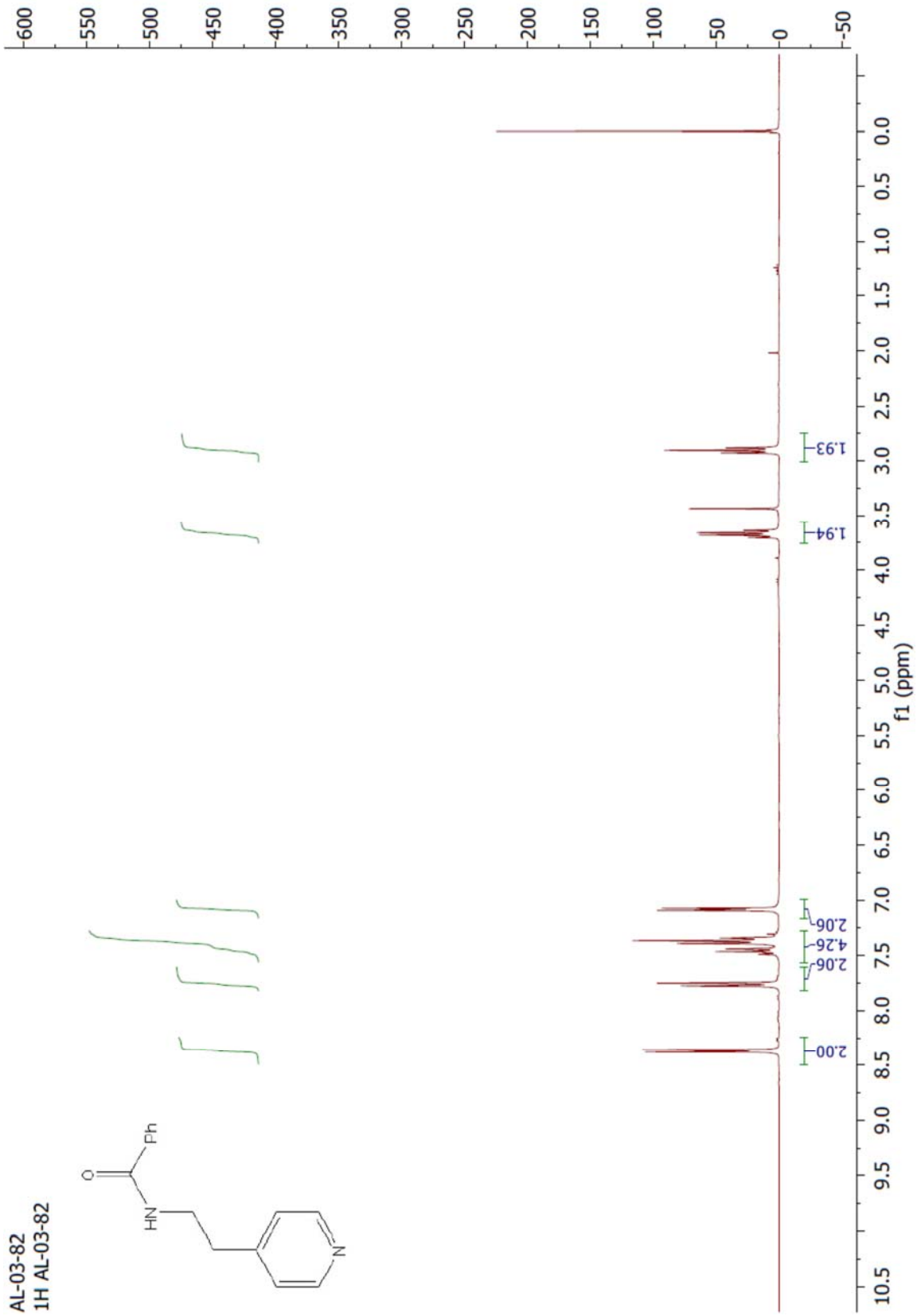
2.62

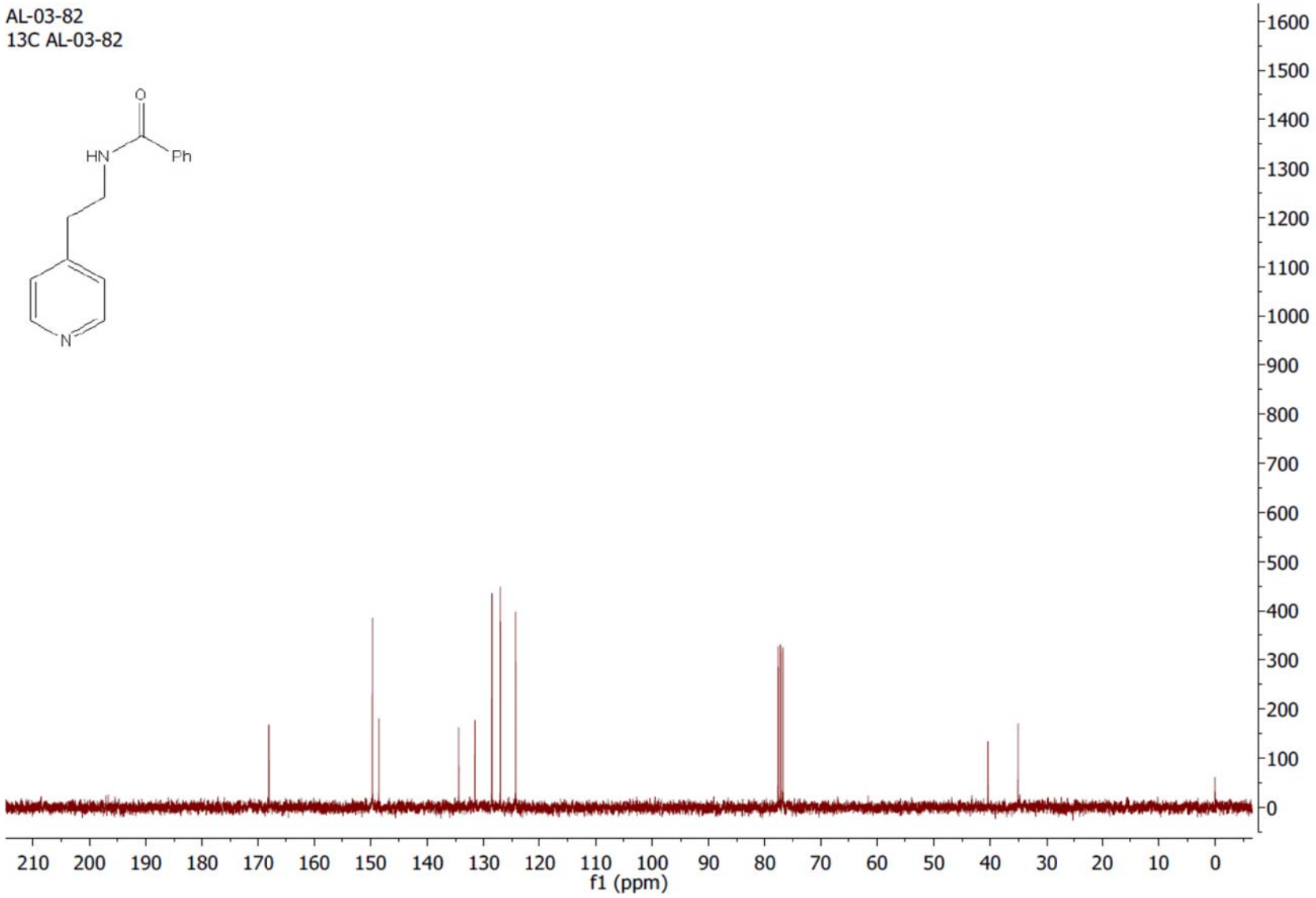

AL-02-106
1H AL-02-106
O
N
OH
N
2.63
2.08
2.00
1.00
1.10
1.14
3.92
5.51
3.36
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

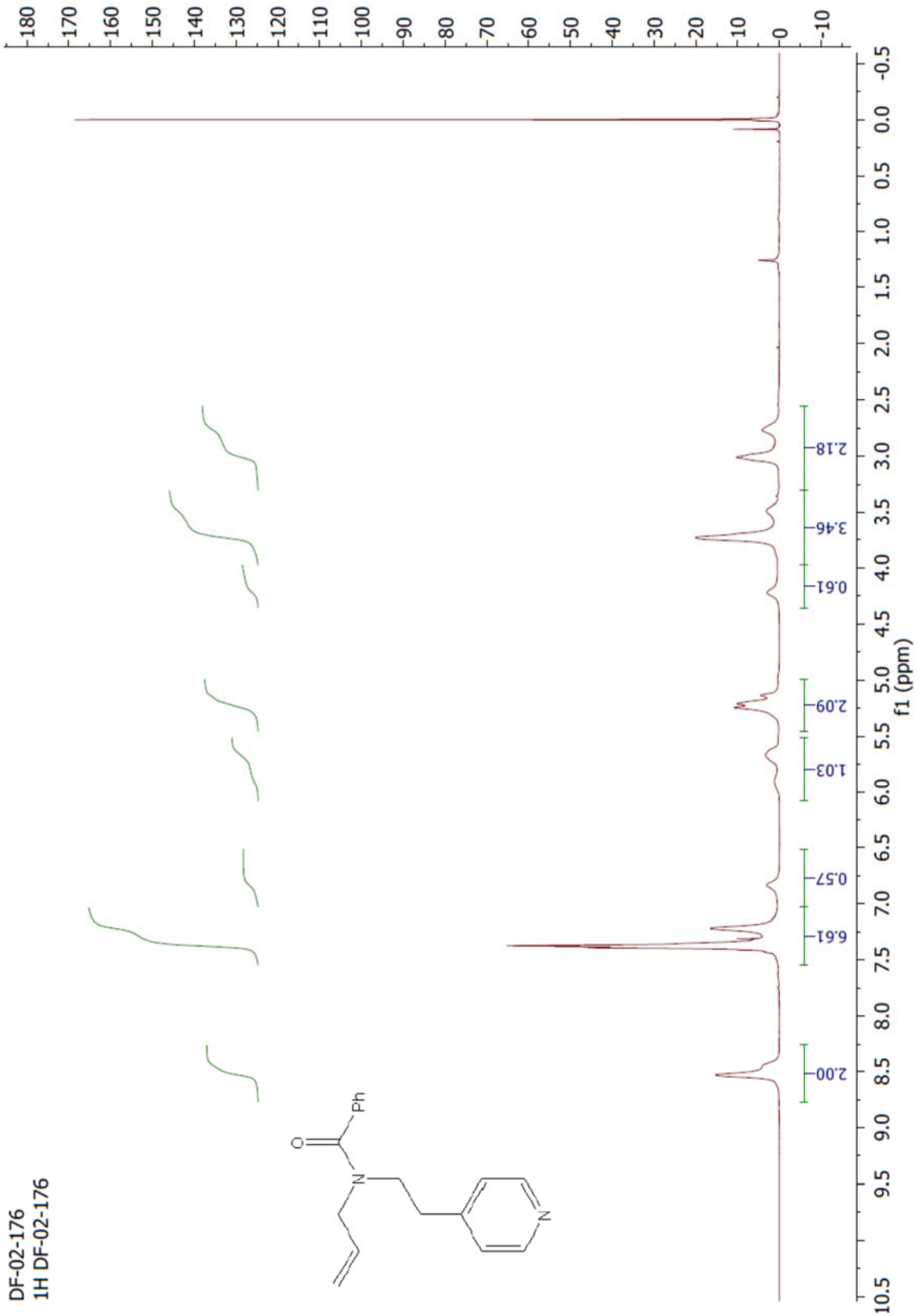

AL-02-106
13C AL-02-106
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
O
N
OH
N
2.63
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

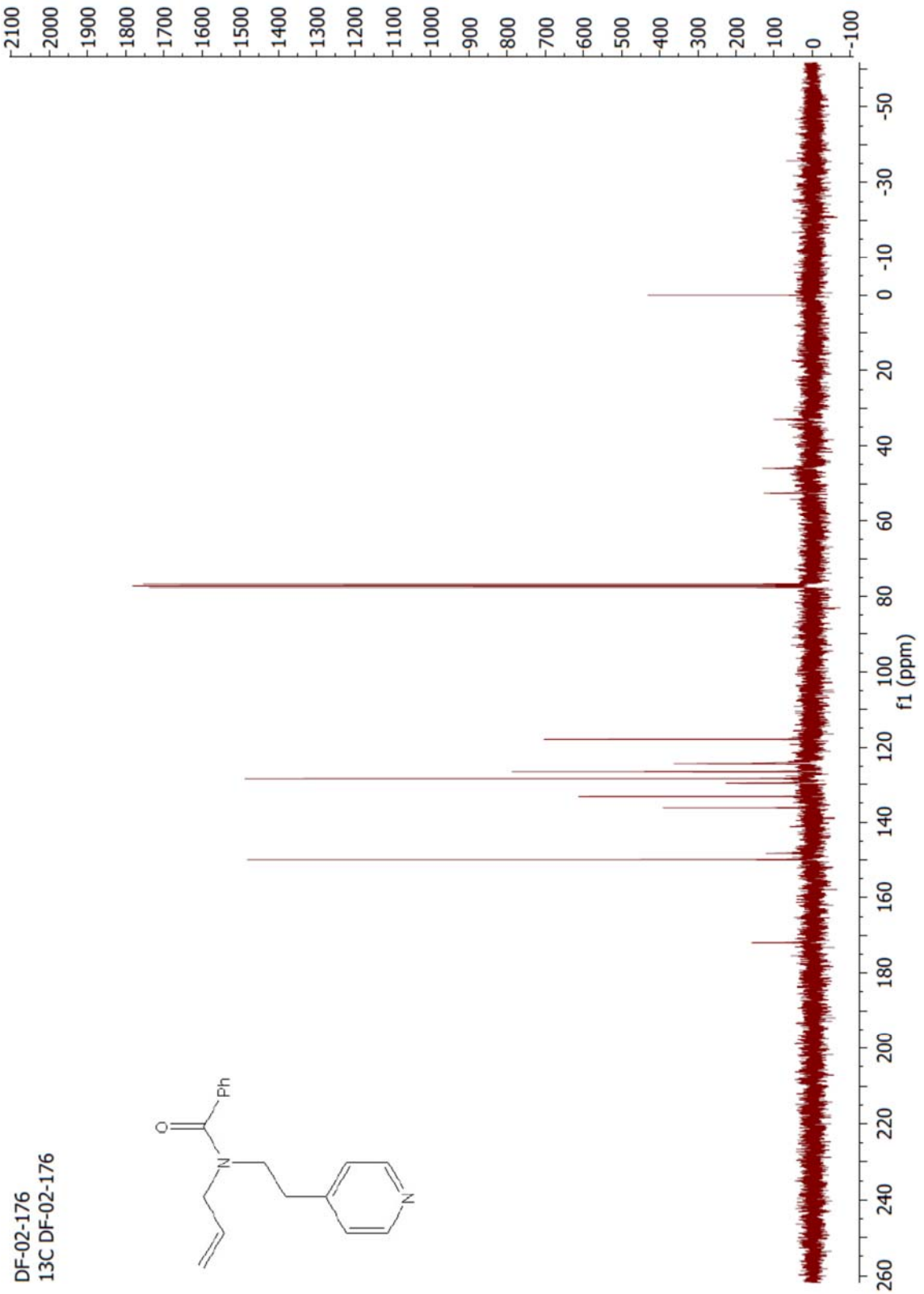

AL-02-116
1H AL-02-116
Ph
N
O
N
2.64
2.00
6.28
2.41
1.09
2.06
3.07
3.04
f1 (ppm)

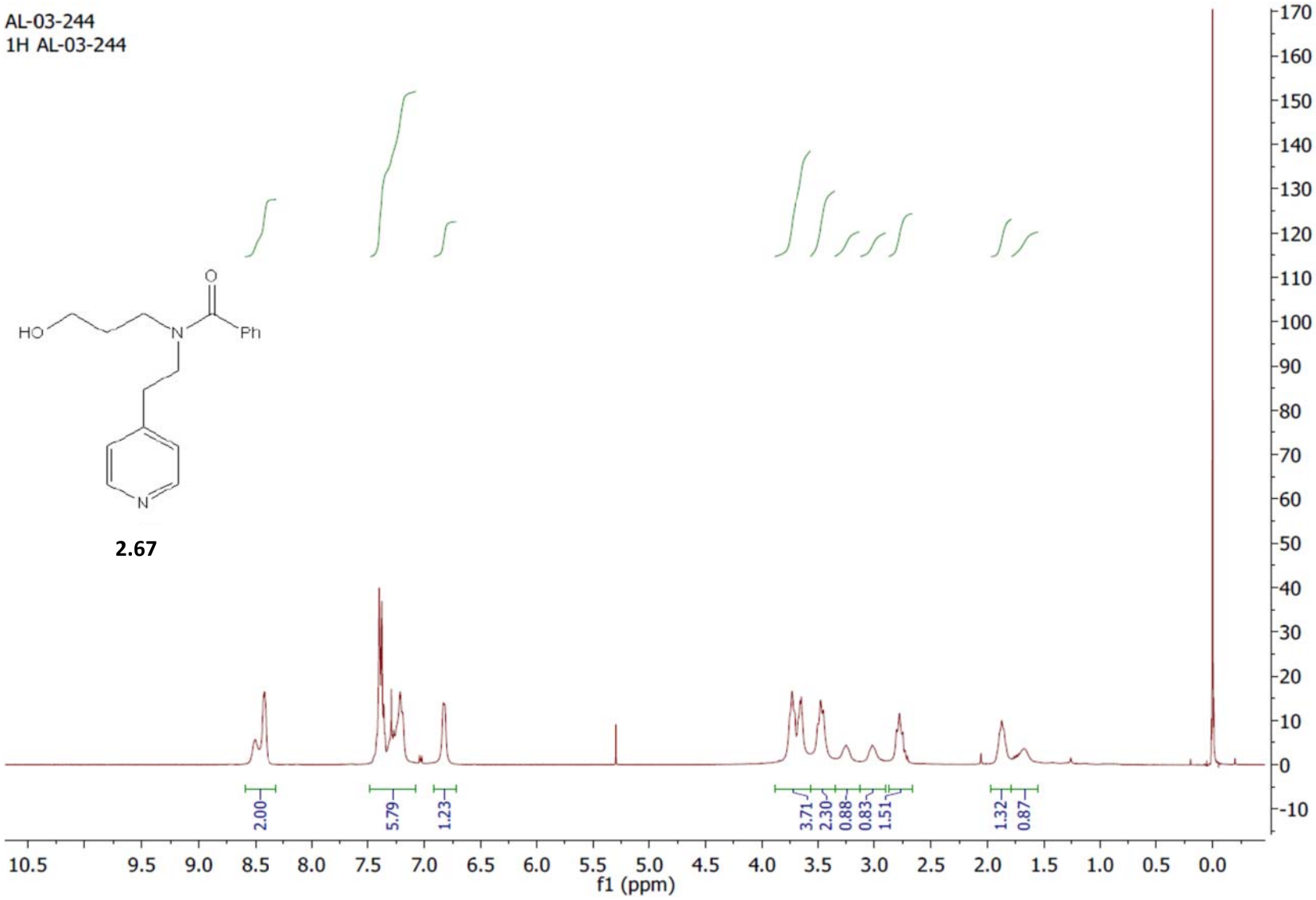

AL-02-116
13C AL-02-116
O
N
Ph
N
2.64
1100
1000
900
800
700
600
500
400
300
200
100
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

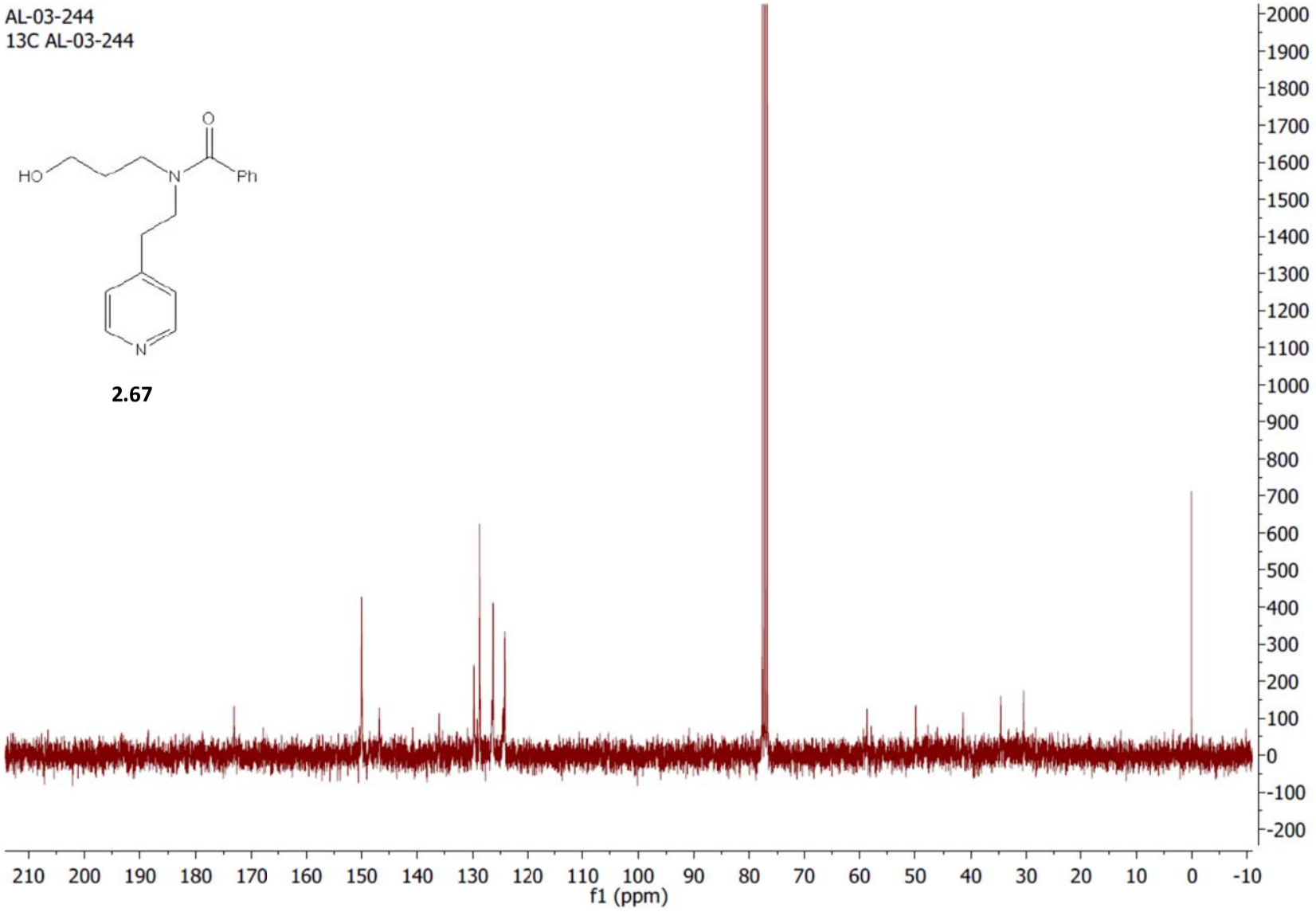

AL-03-82
1H AL-03-82
Ph
O
HN
N
1.93
1.94
2.06
4.26
2.06
2.00
f1 (ppm)

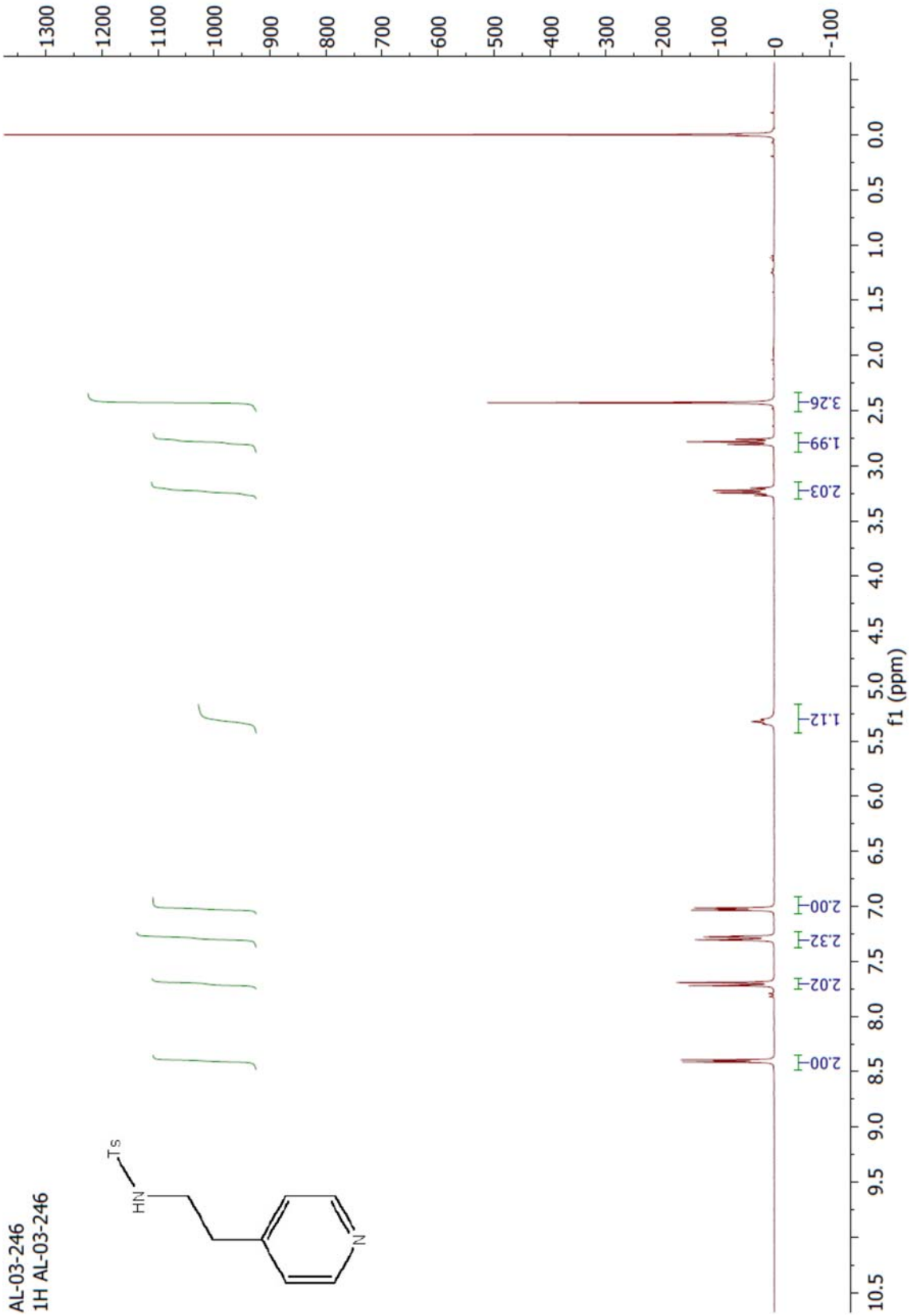

AL-03-82
13C AL-03-82
O
HN
Ph
N
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

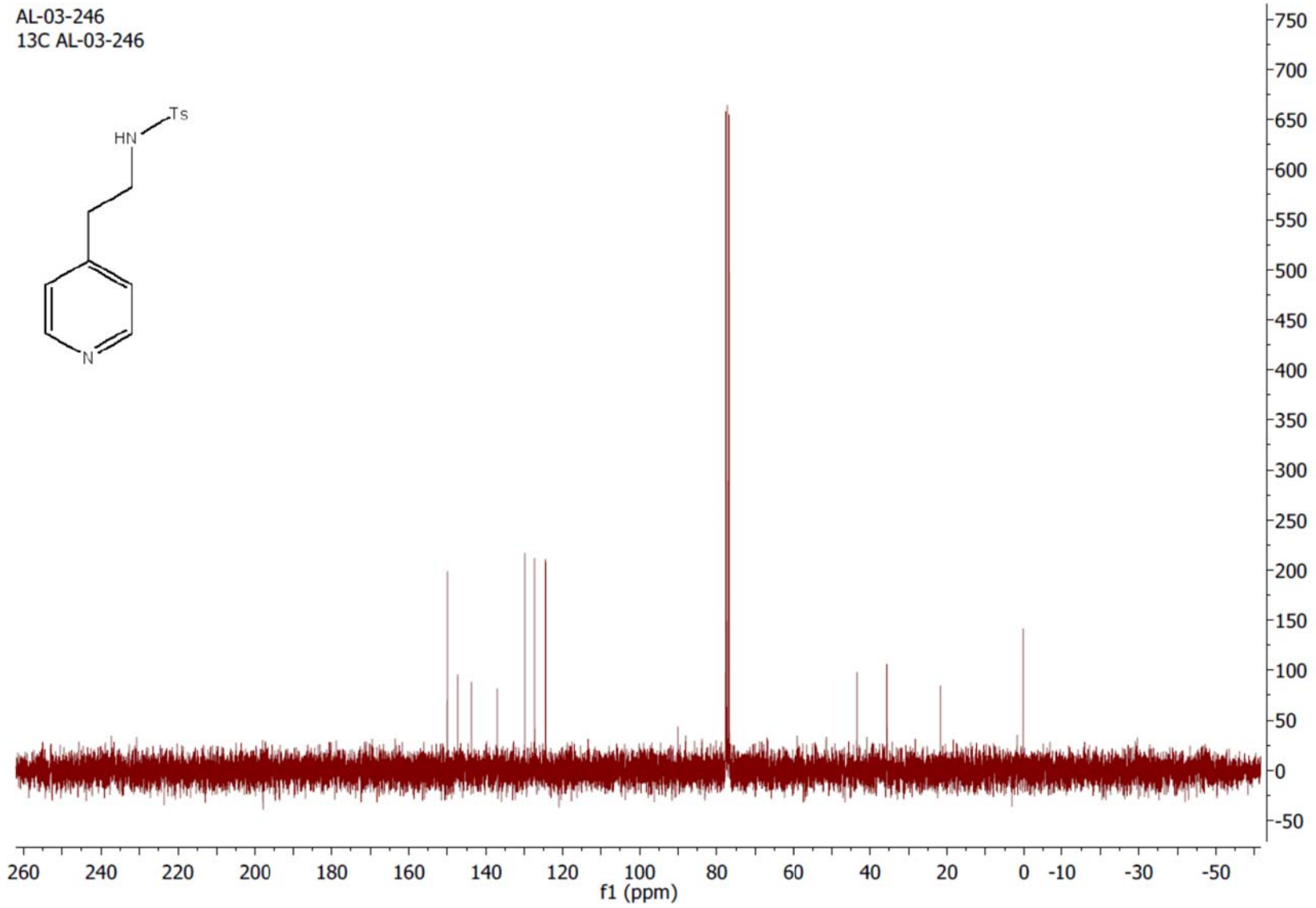

DF-02-176
1H DF-02-176
f1 (ppm)
2.00
6.61
0.57
1.03
2.09
0.61
3.46
2.18
Ph
O
N
N

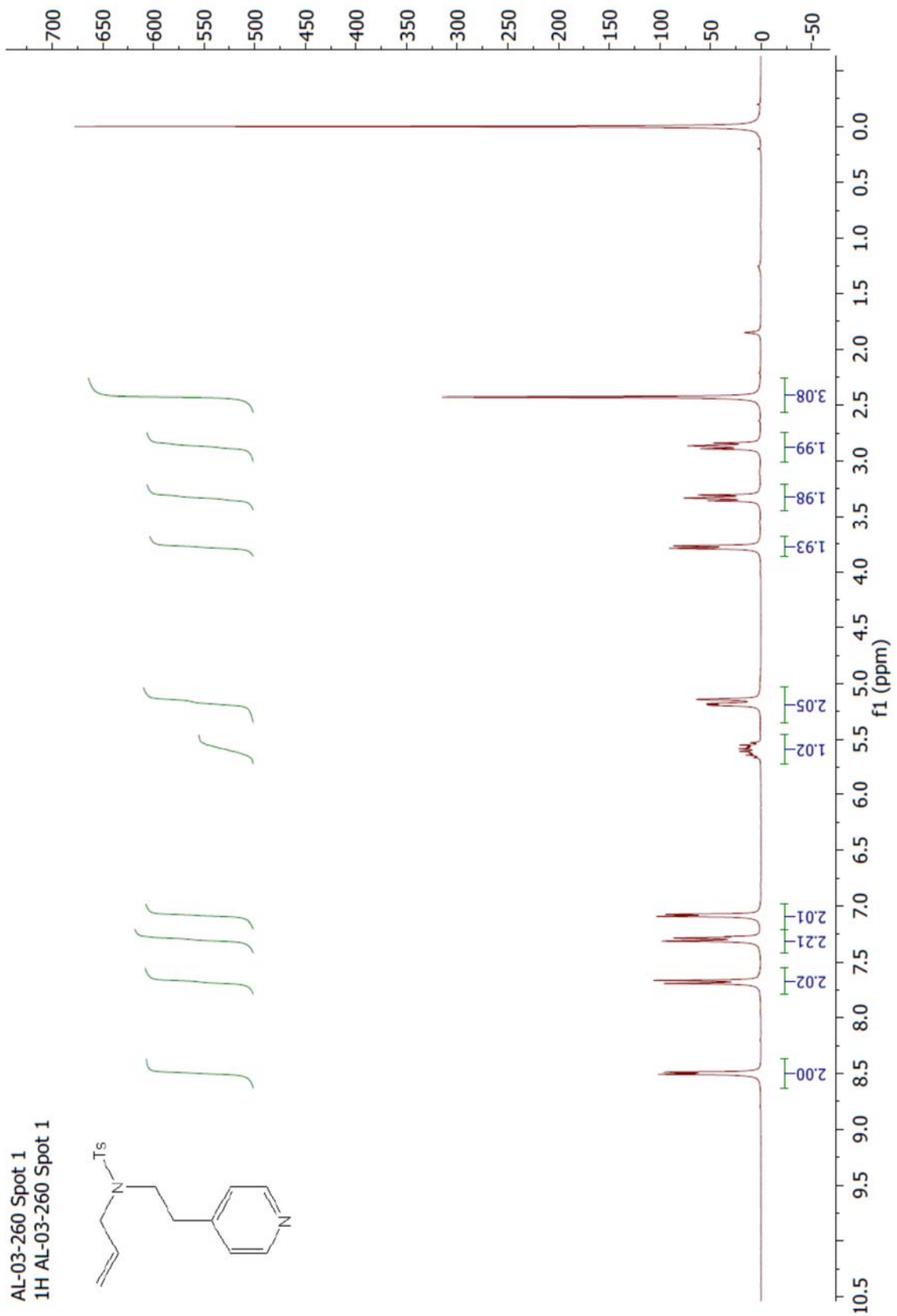

DF-02-176
13C DF-02-176
Ph
O
N
N
f1 (ppm)

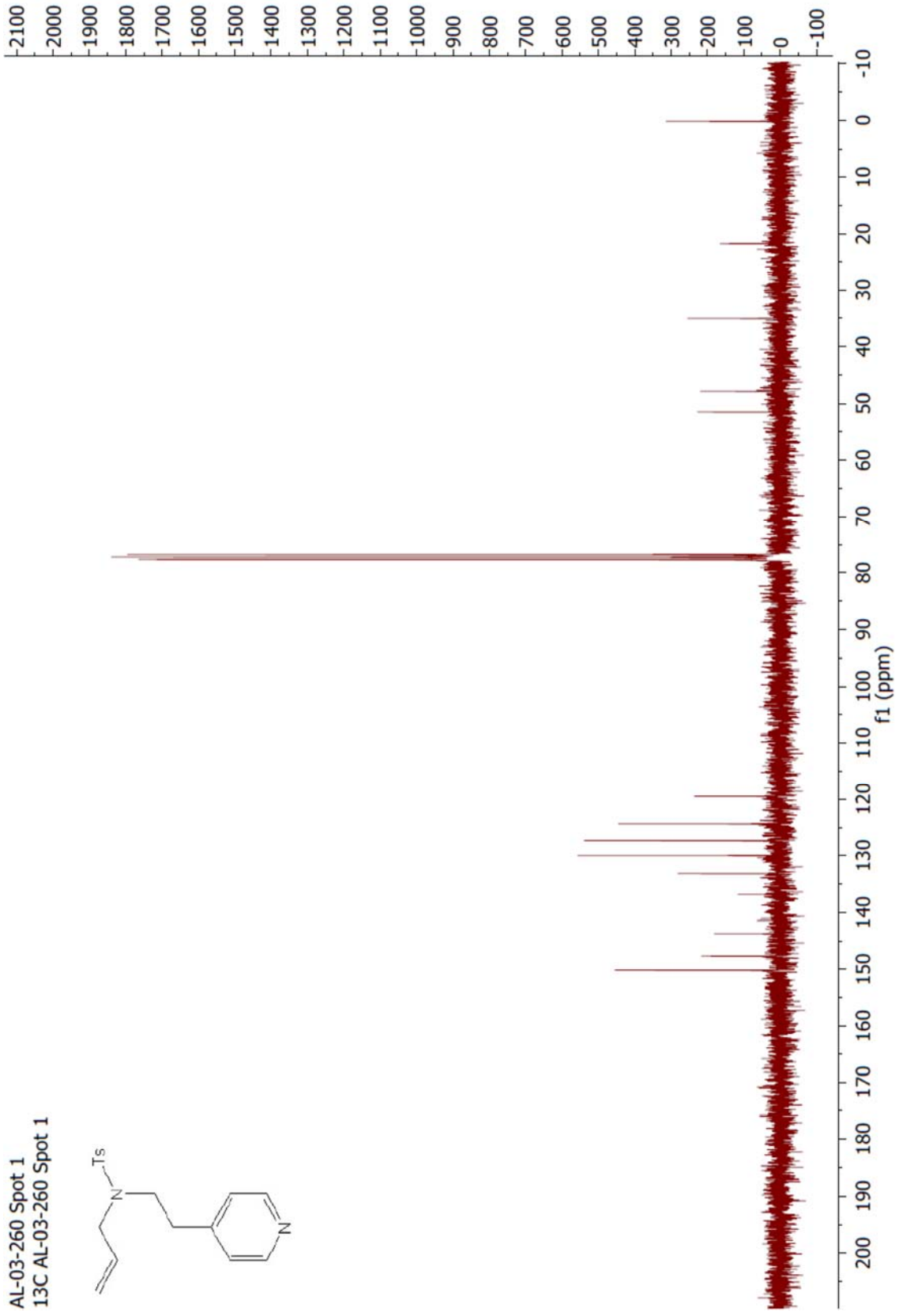

AL-03-244
1H AL-03-244
HO
N
O
Ph
N
2.67
2.00
5.79
1.23
3.71
2.30
0.88
0.83
1.51
1.32
0.87
f1 (ppm)

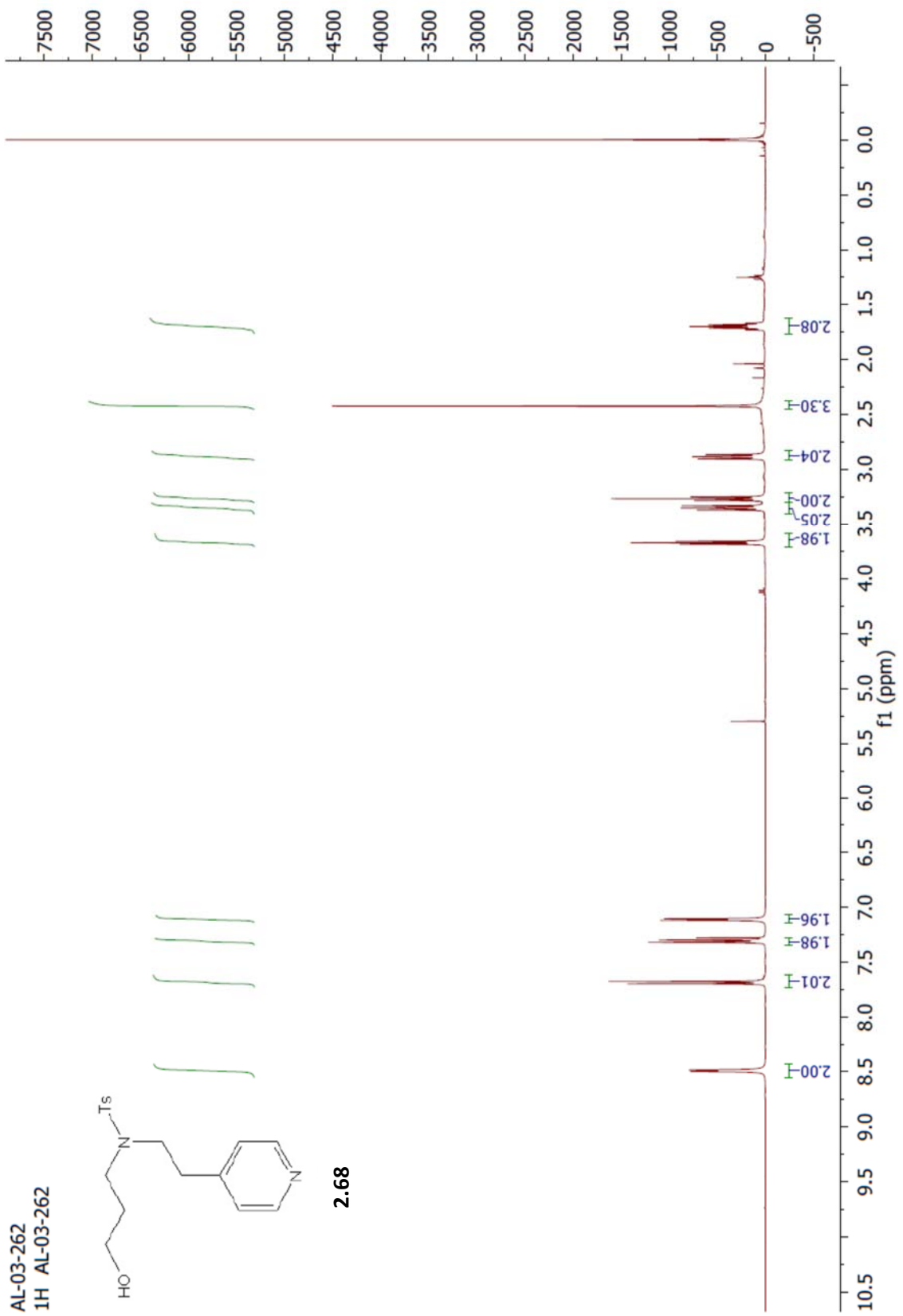

AL-03-244
13C AL-03-244
HO
N
O
Ph
N
2.67
f1 (ppm)


AL-03-246
1H AL-03-246
Ts
HN
N
3.26
1.99
2.03
1.12
2.00
2.32
2.02
2.00
f1 (ppm)

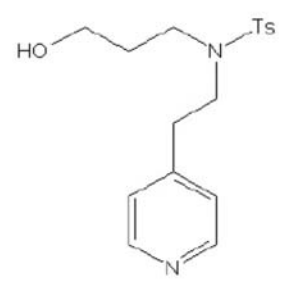

AL-03-246
13C AL-03-246
HN
Ts
N
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
f1 (ppm)


AL-03-260 Spot 1
1H AL-03-260 Spot 1
Ts
N
N
3.08
1.99
1.98
1.93
2.05
1.02
2.01
2.21
2.02
2.00
f1 (ppm)

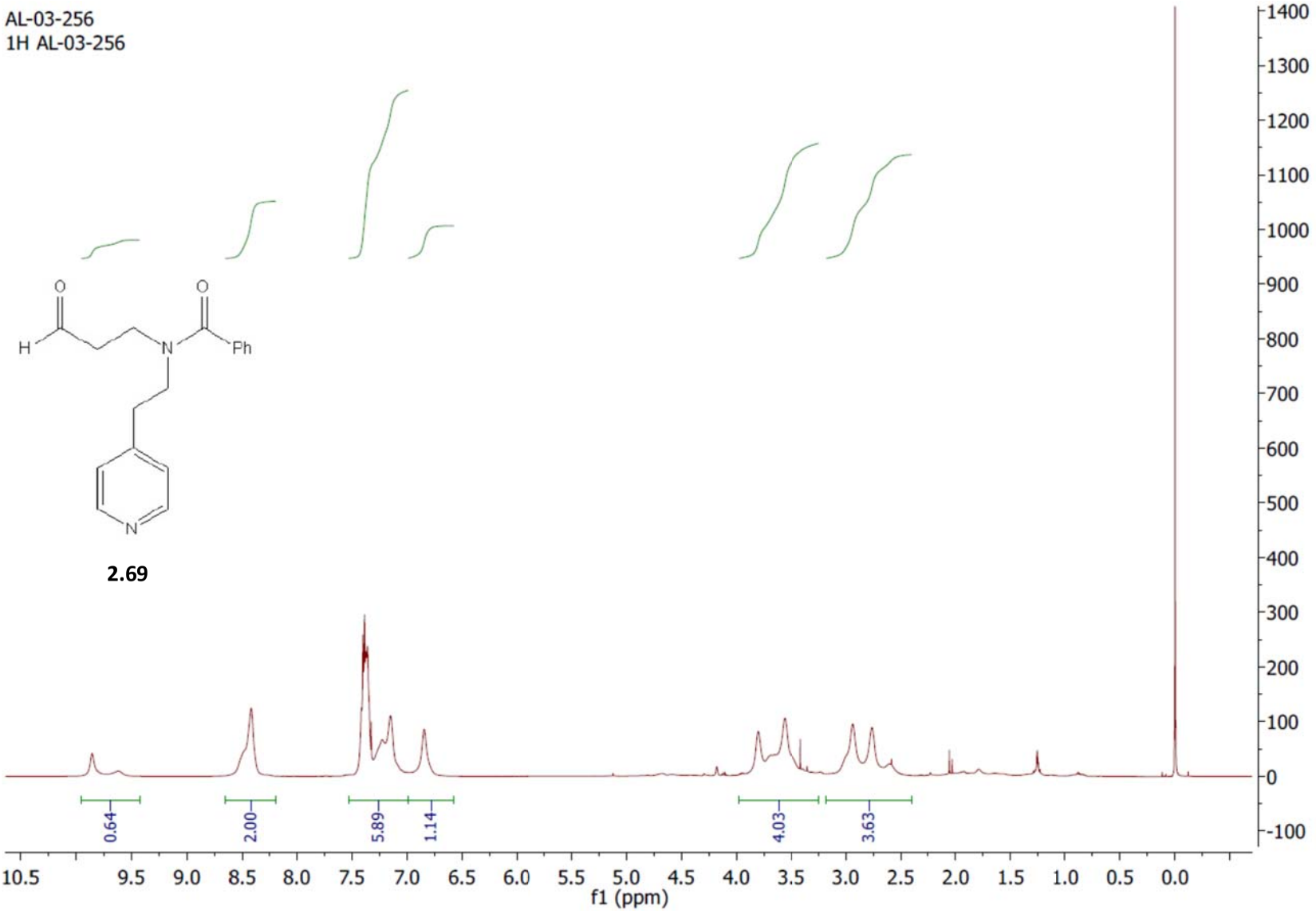

AL-03-260 Spot 1
13C AL-03-260 Spot 1
Ts
N
N
f1 (ppm)

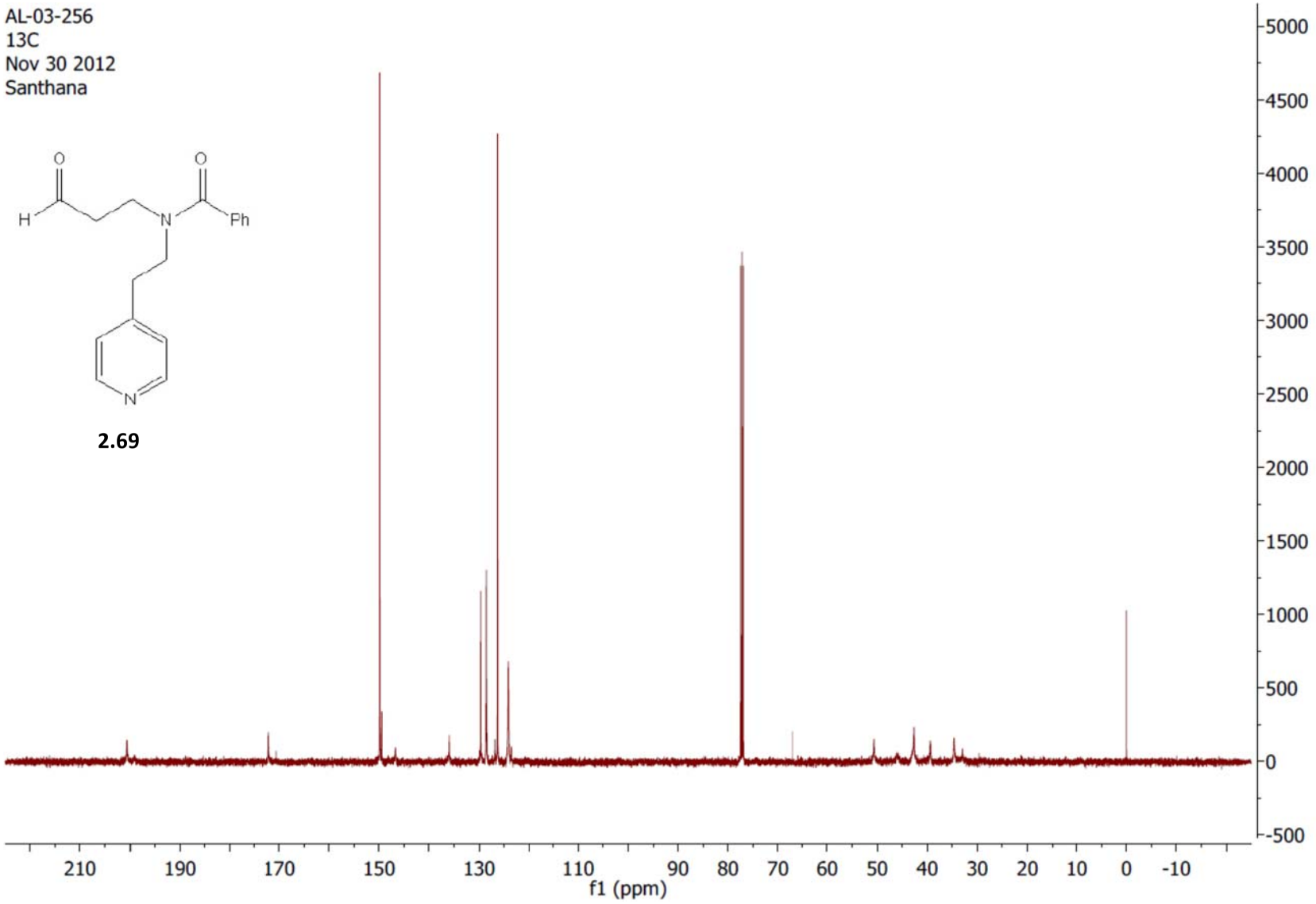

AL-03-262
1H AL-03-262
Ts
N
HO
N
2.68
2.08
3.30
2.04
2.00
2.05
1.98
1.96
1.98
2.01
2.00
f1 (ppm)

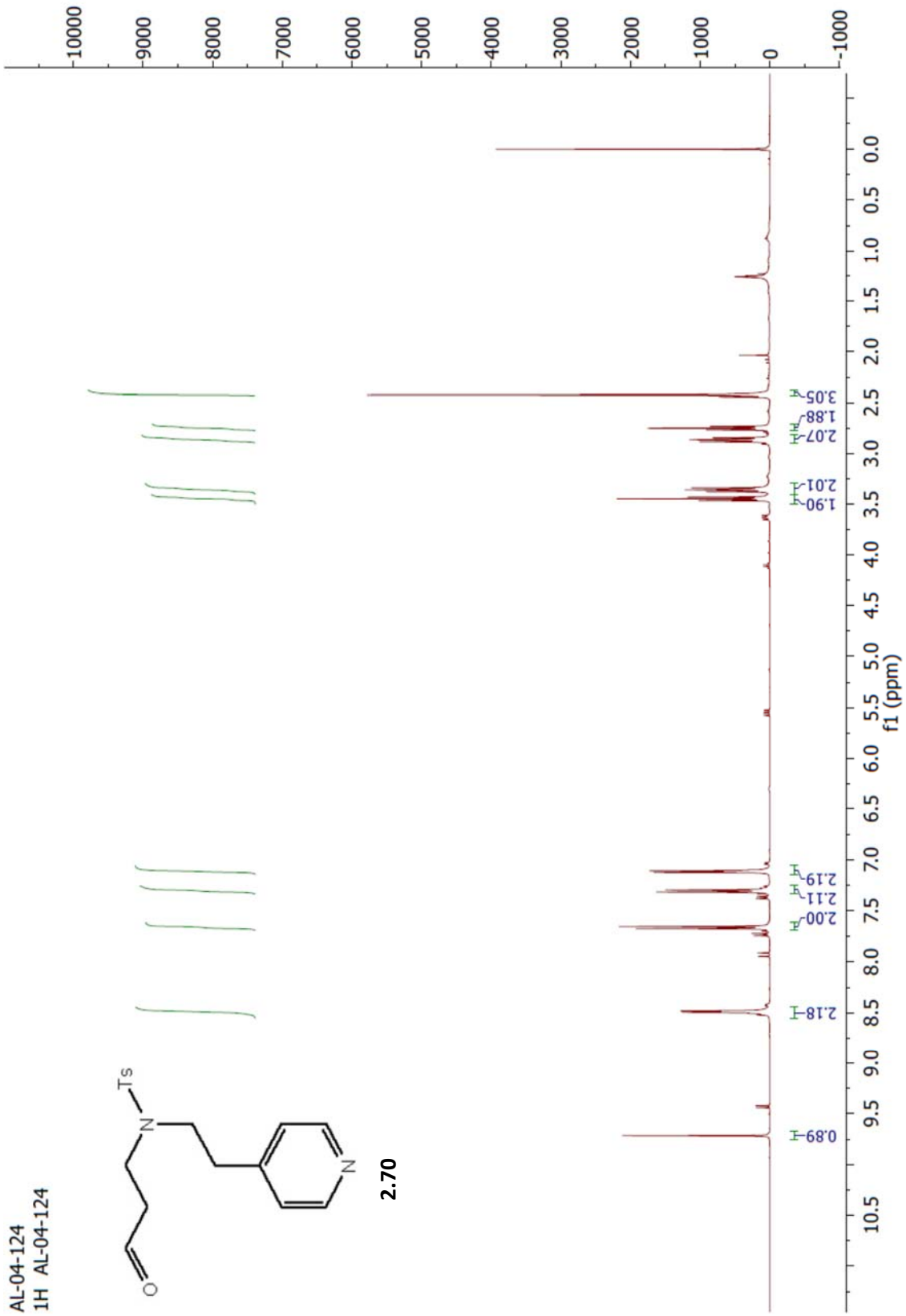
AL-03-262
13C AL-03-262



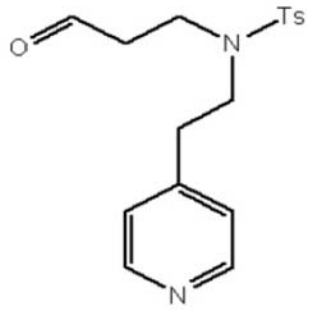
2.68


AL-03-256
1H AL-03-256
O
H
N
O
Ph
N
2.69
0.64
2.00
5.89
1.14
4.03
3.63
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

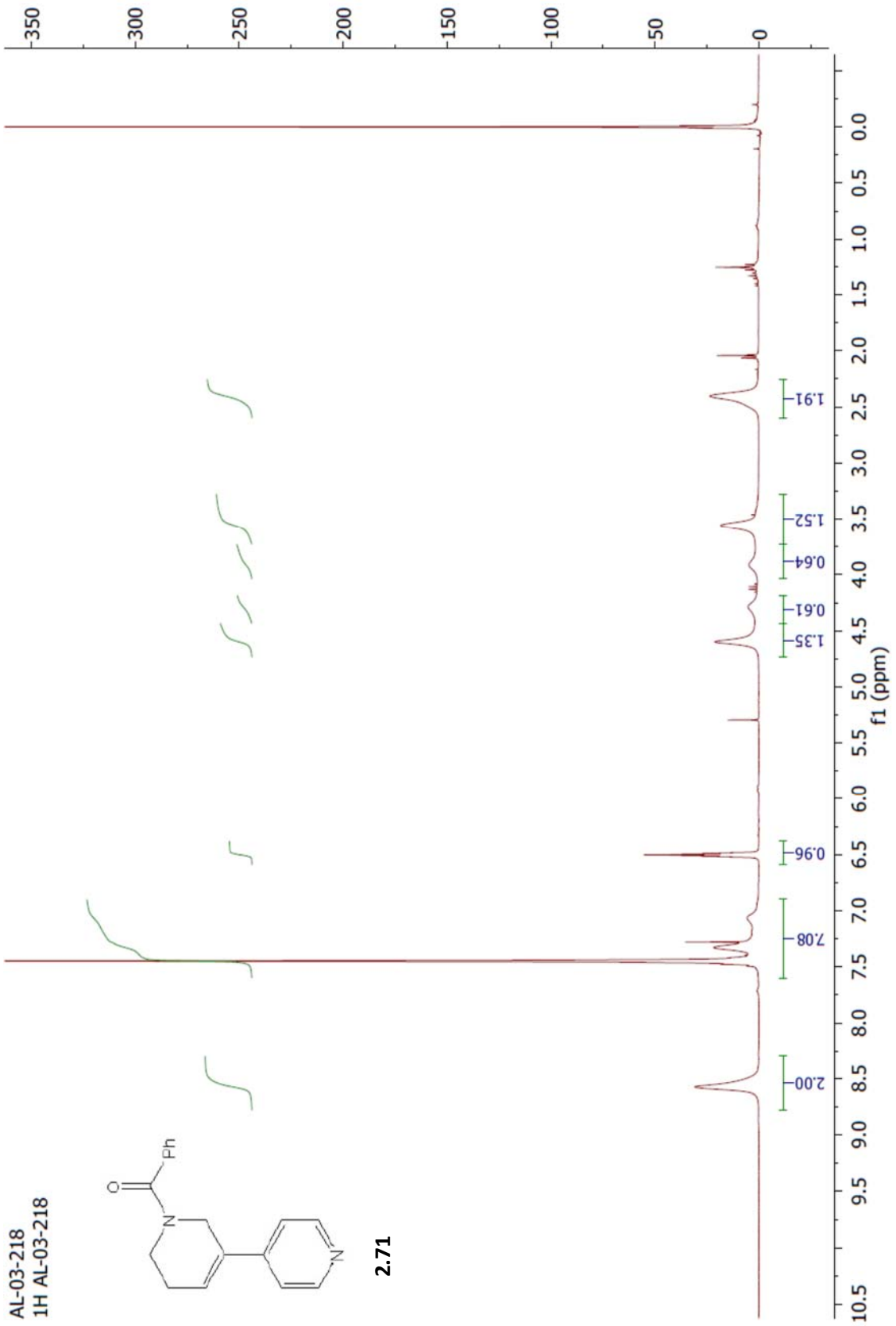

AL-03-256
13C
Nov 30 2012
Santhana
O
O
H
N
Ph
N
2.69
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

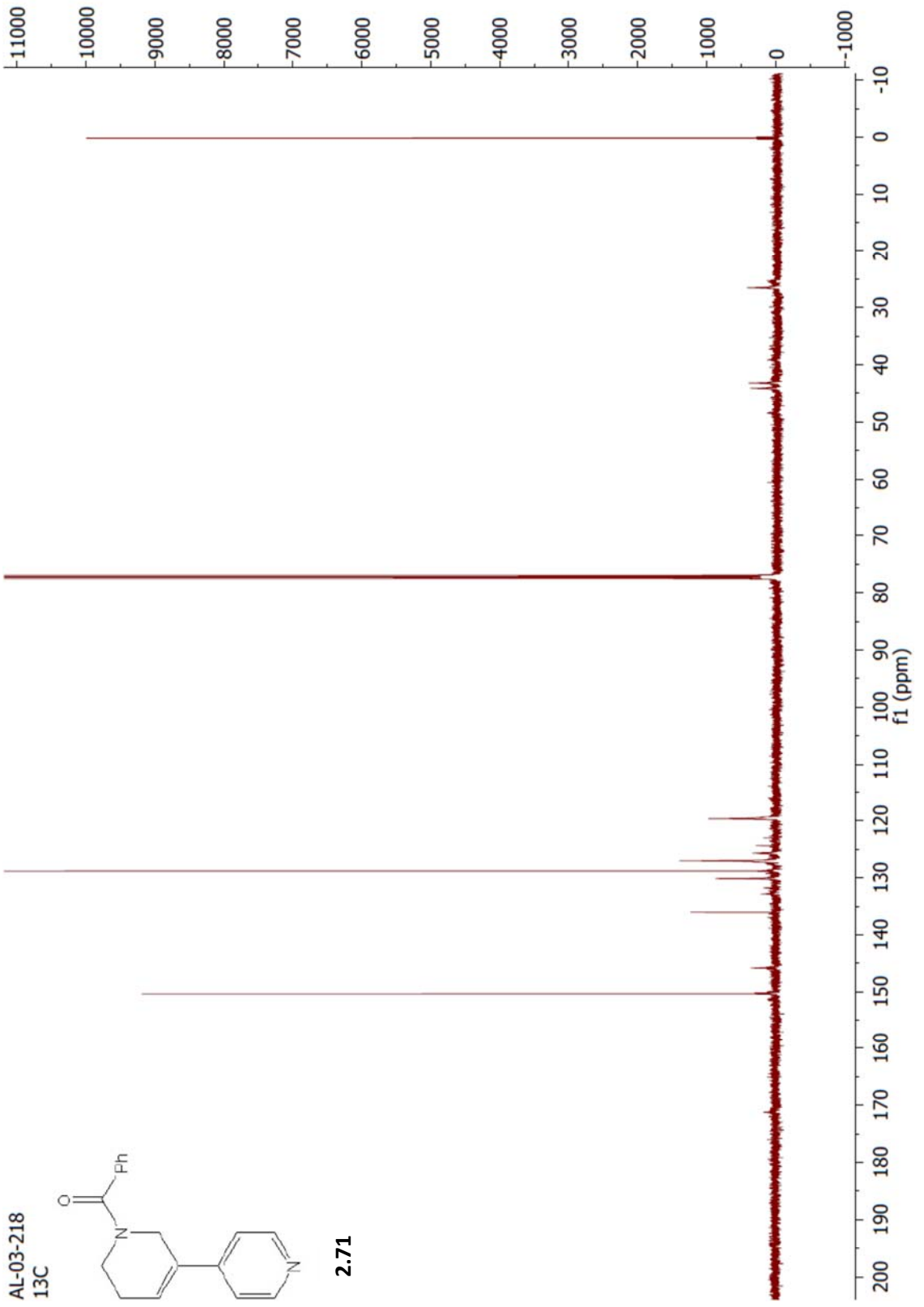

AL-04-124
1H AL-04-124
Ts
N
N
O
2.70
f1 (ppm)
0.89
2.18
2.00
2.11
2.19
1.90
2.01
2.07
1.88
3.05

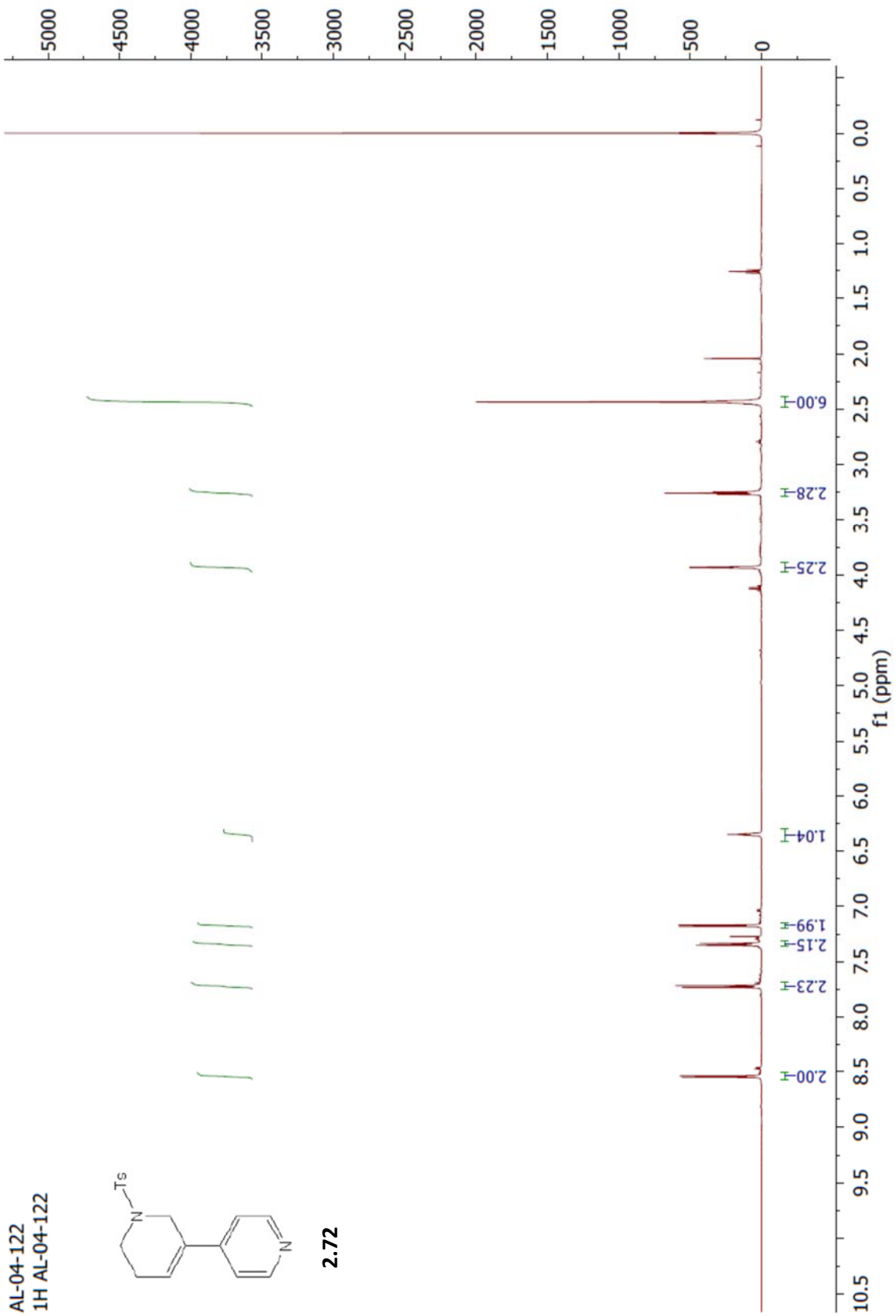
AL-04-124
13C AL-04-124

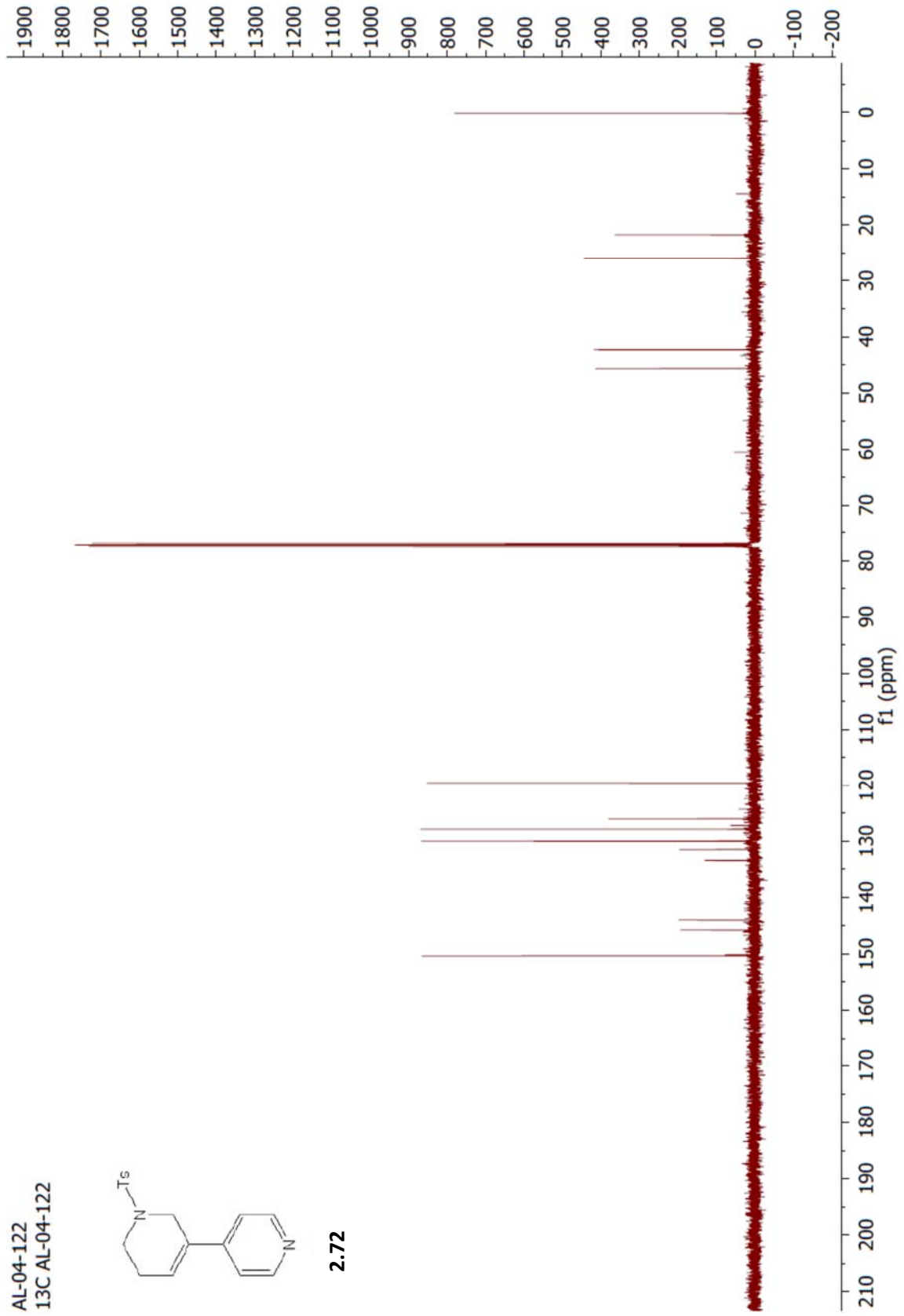


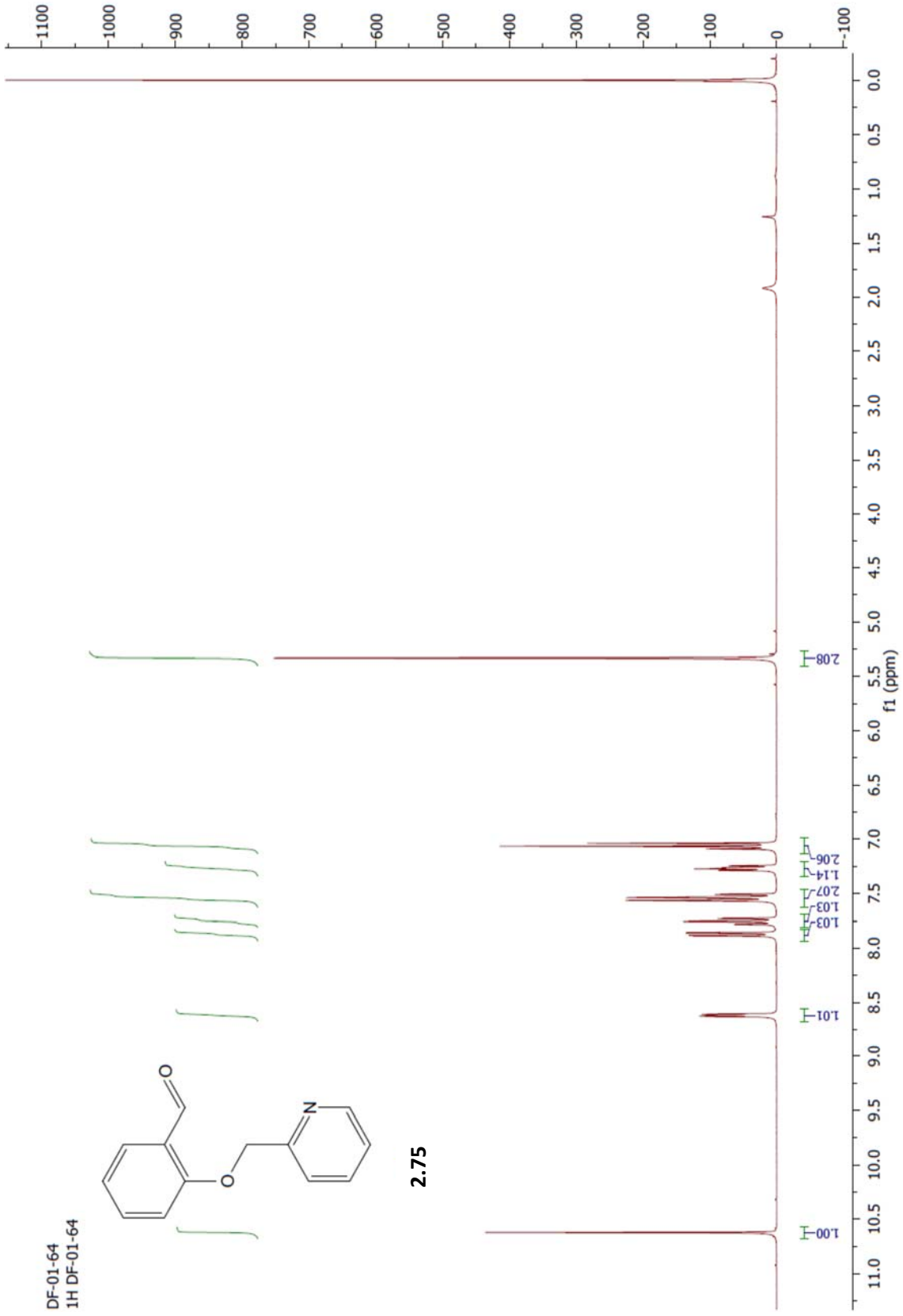
2.70

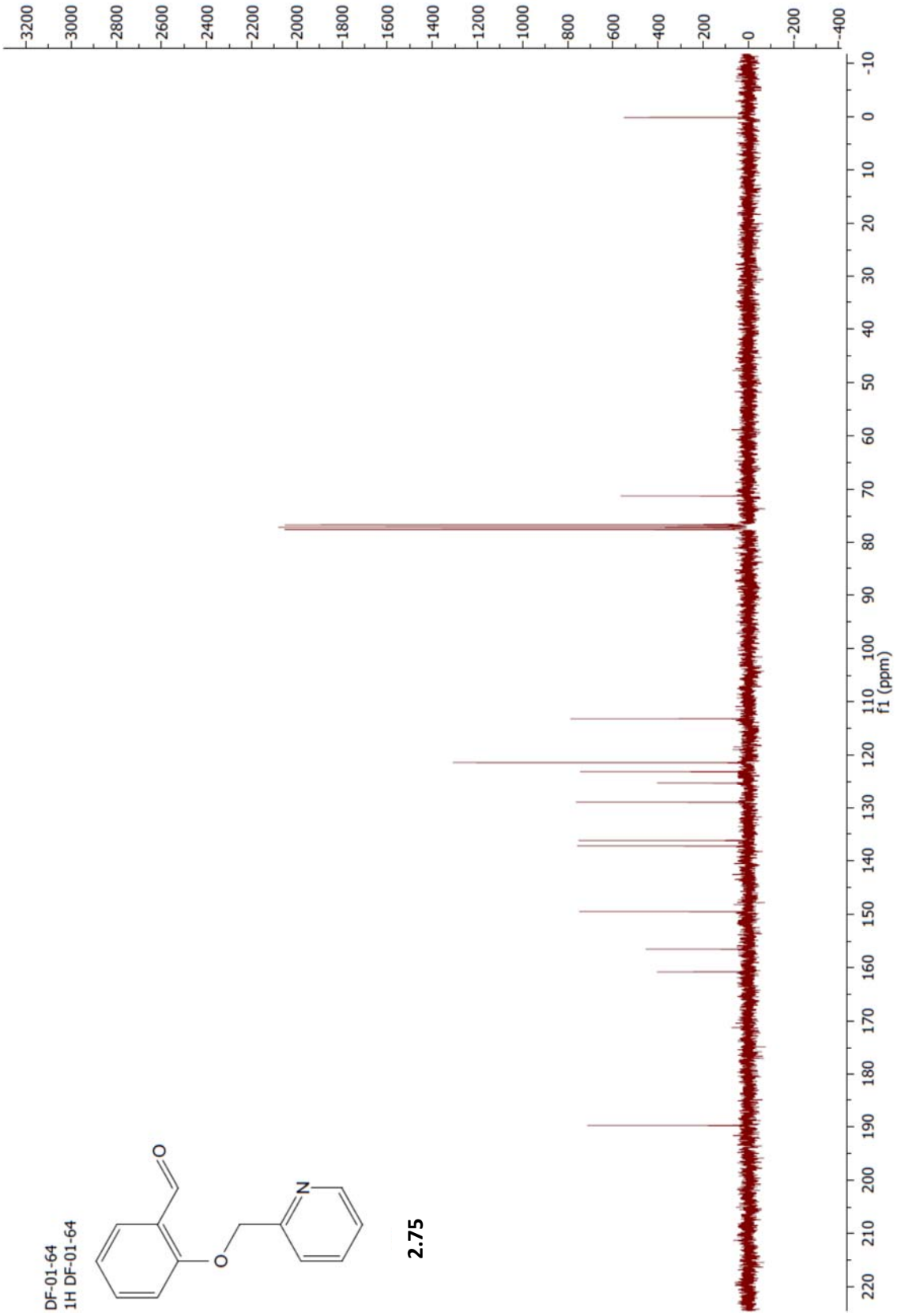

AL-03-218
1H AL-03-218
Ph
O
N
N
2.71
2.00
7.08
0.96
1.35
0.61
0.64
1.52
1.91
f1 (ppm)

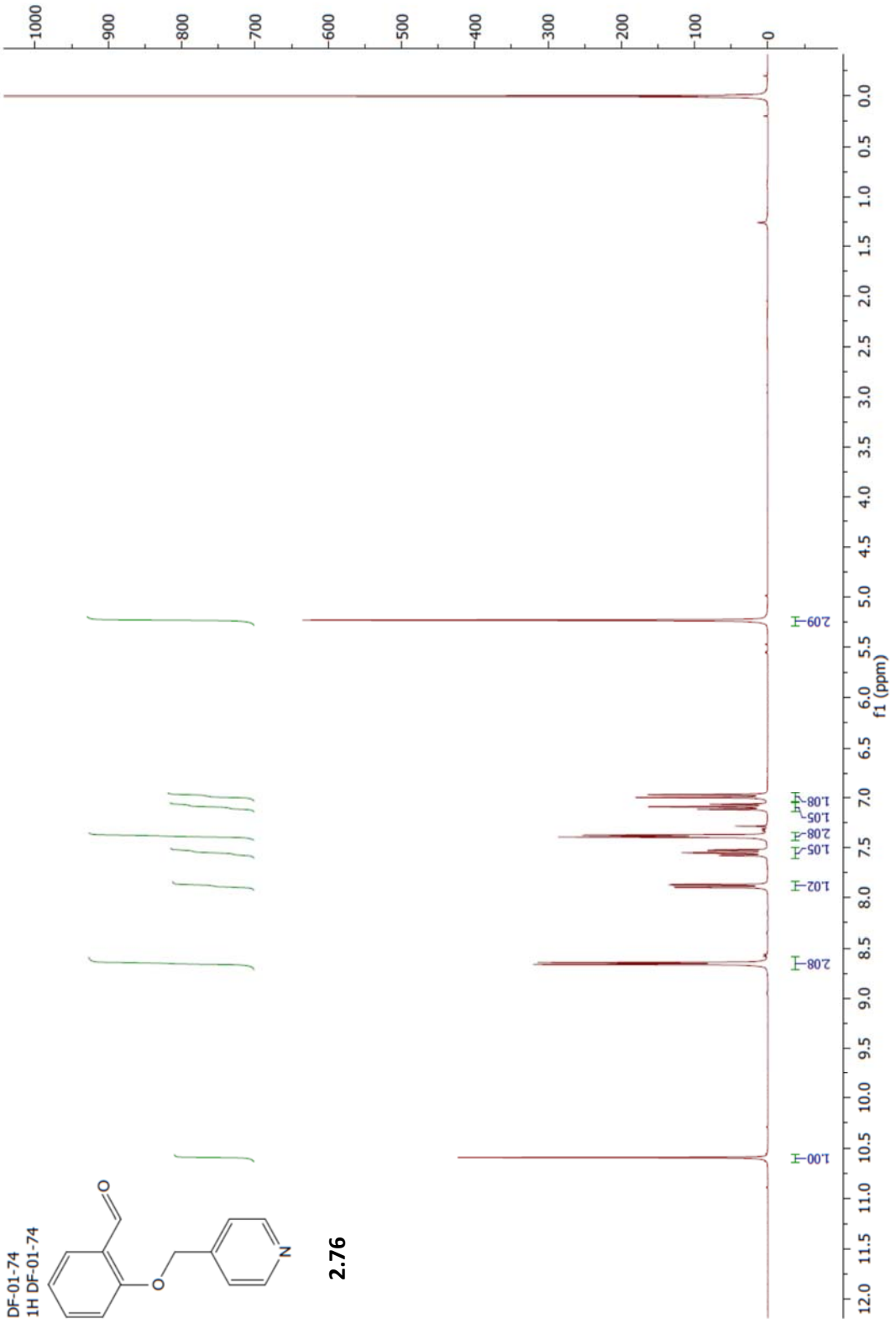

AL-03-218
13C
Ph
O
N
N
2.71
f1 (ppm)

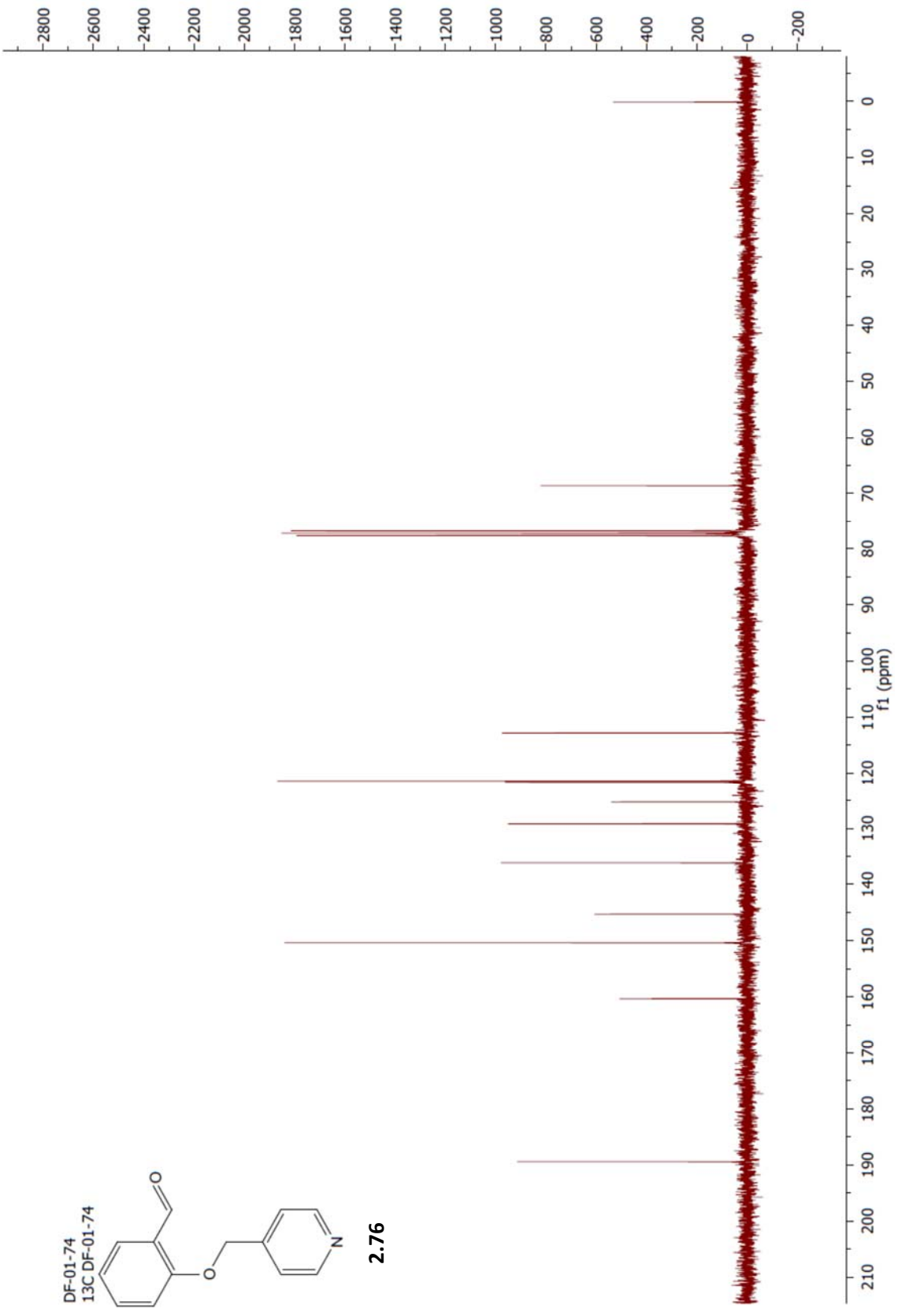

AL-04-122
1H AL-04-122
Ts
N
N
2.72
6.00
2.28
2.25
1.04
1.99
2.15
2.23
2.00
f1 (ppm)

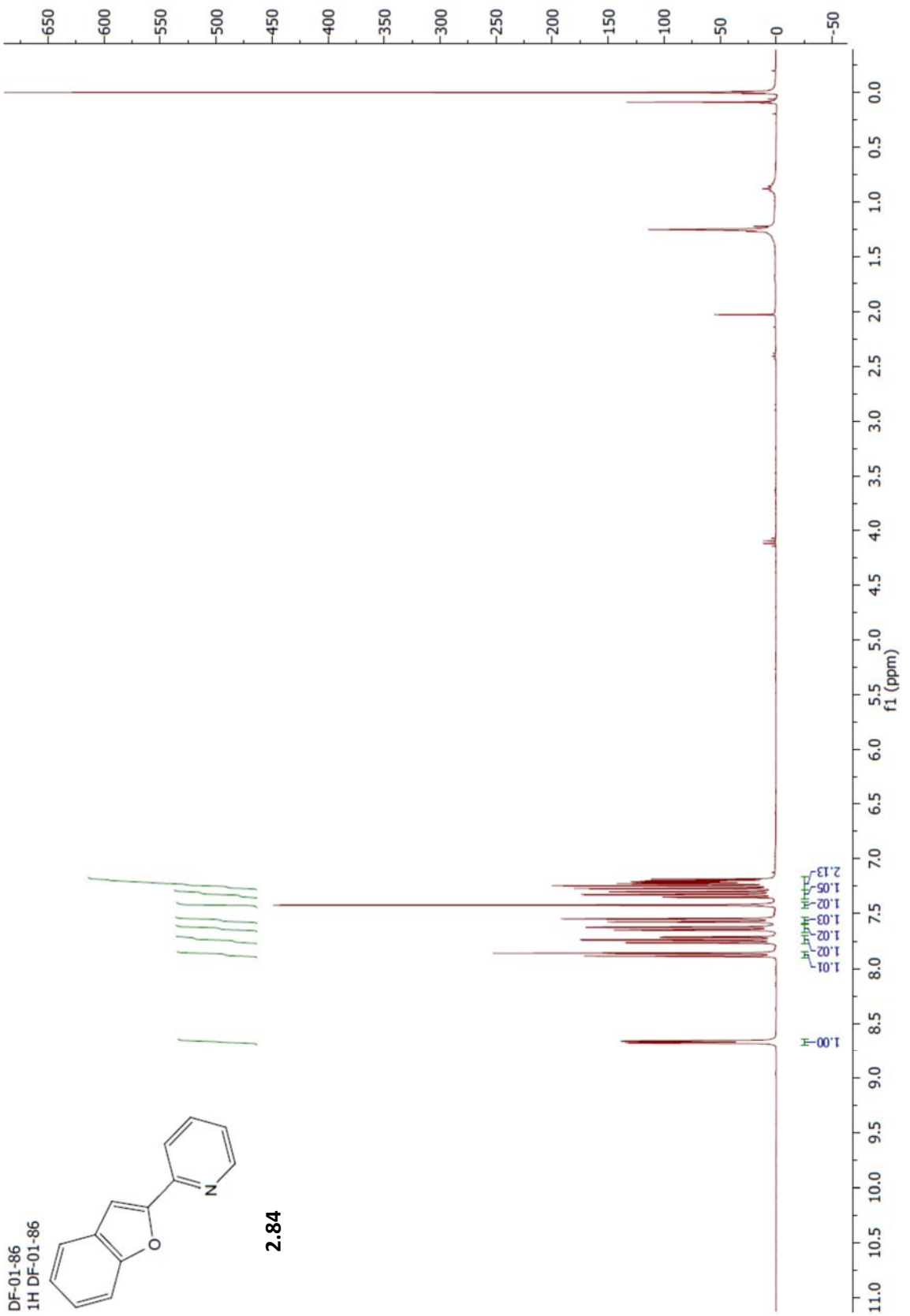

AL-04-122
13C AL-04-122
Ts
N
N
2.72
f1 (ppm)

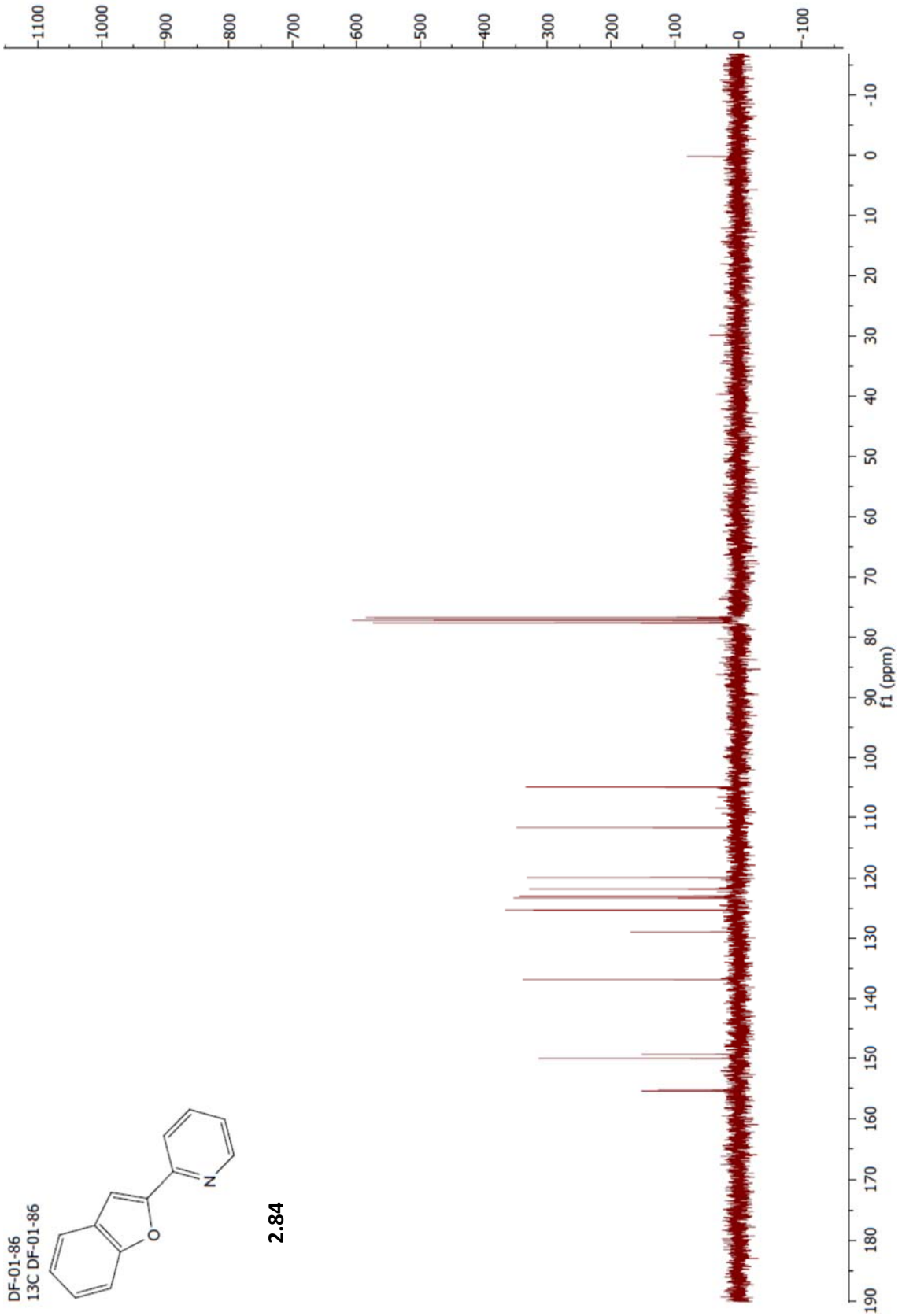

DF-01-64
1H DF-01-64
2.75
f1 (ppm)

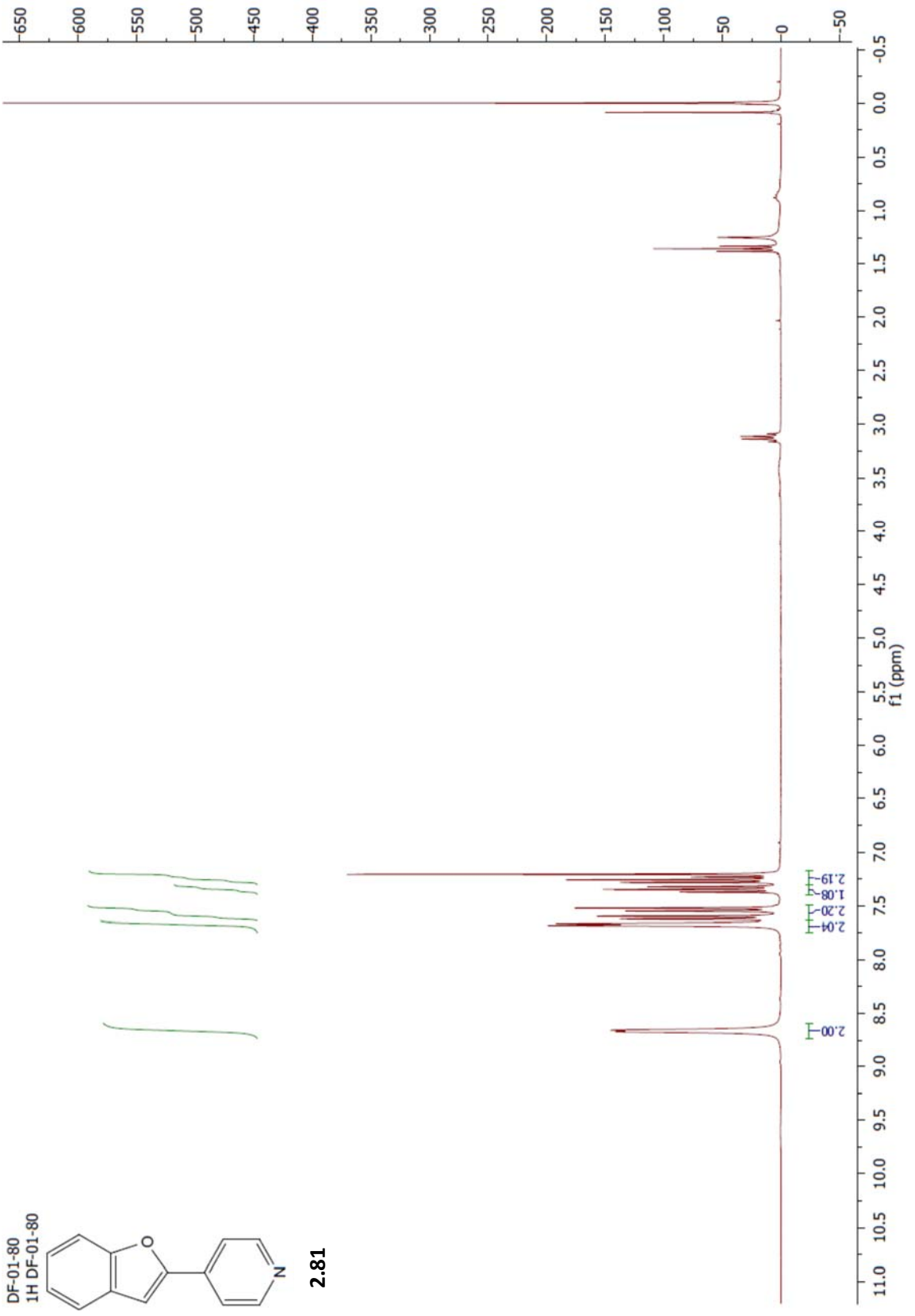

DF-01-64
1H DF-01-64
2.75
f1 (ppm)

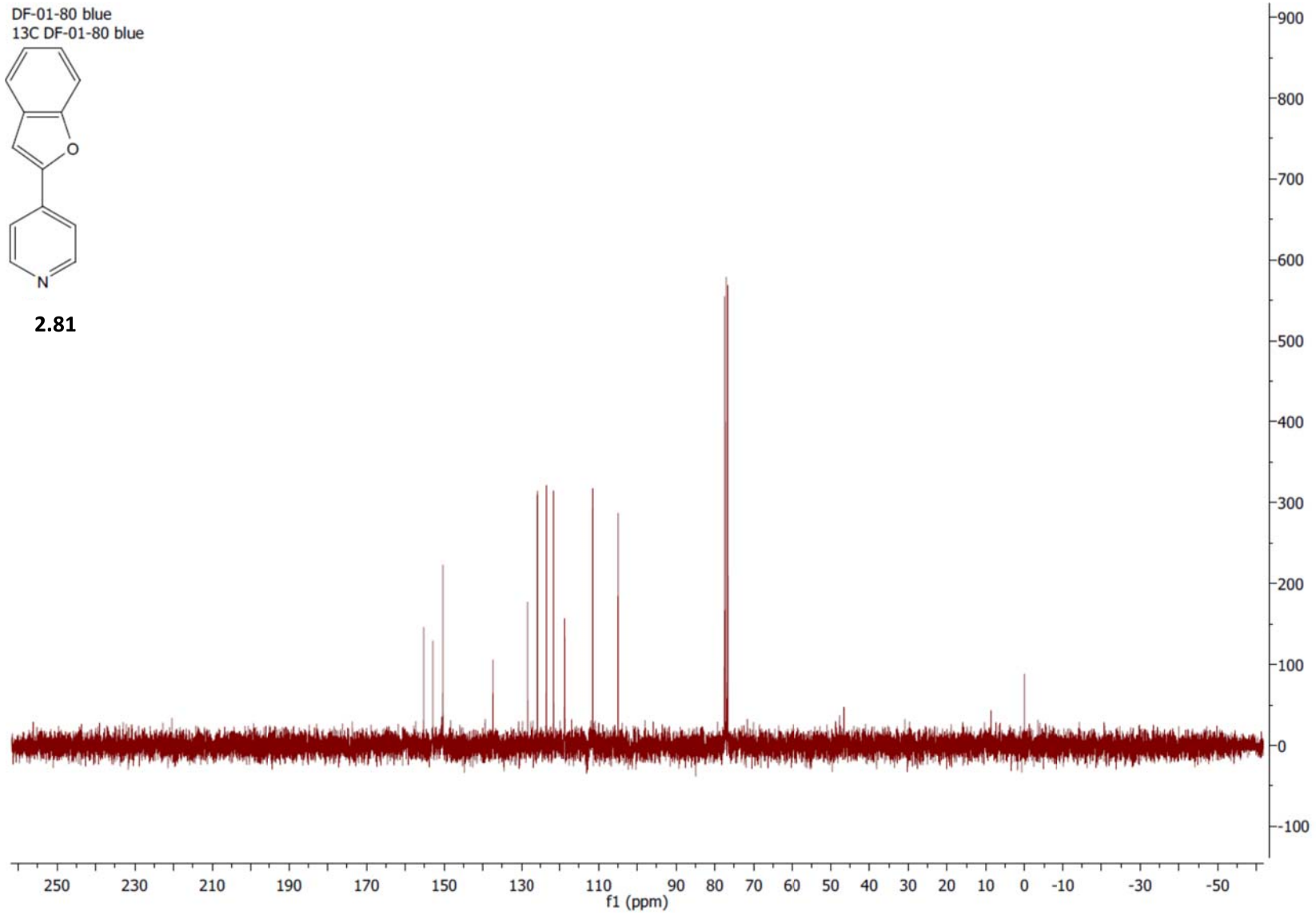

DF-01-74
1H DF-01-74
2.76
f1 (ppm)

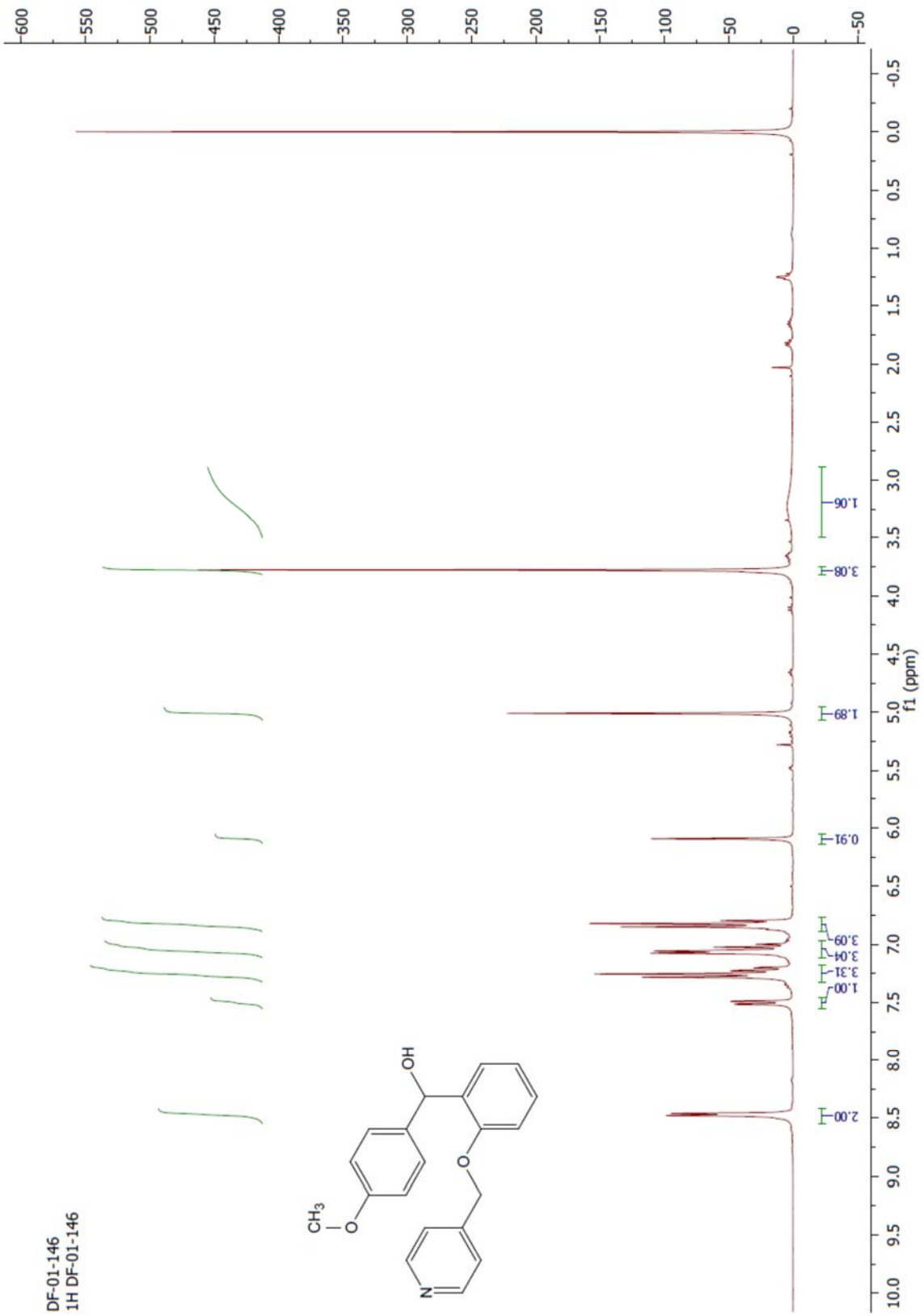

DF-01-74
13C DF-01-74
O
O
N
2.76
f1 (ppm)

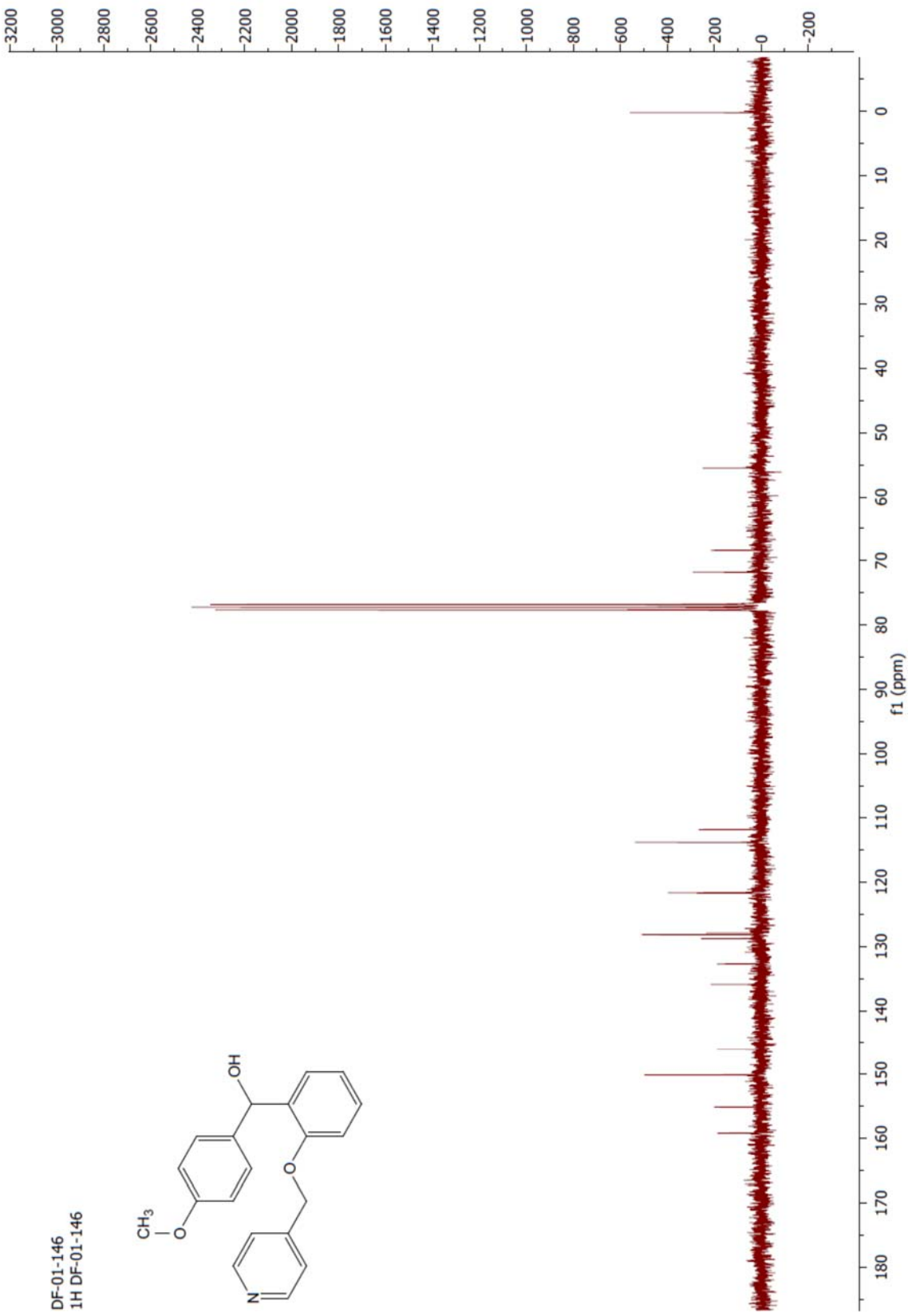

DF-01-86
1H DF-01-86
2.84
f1 (ppm)

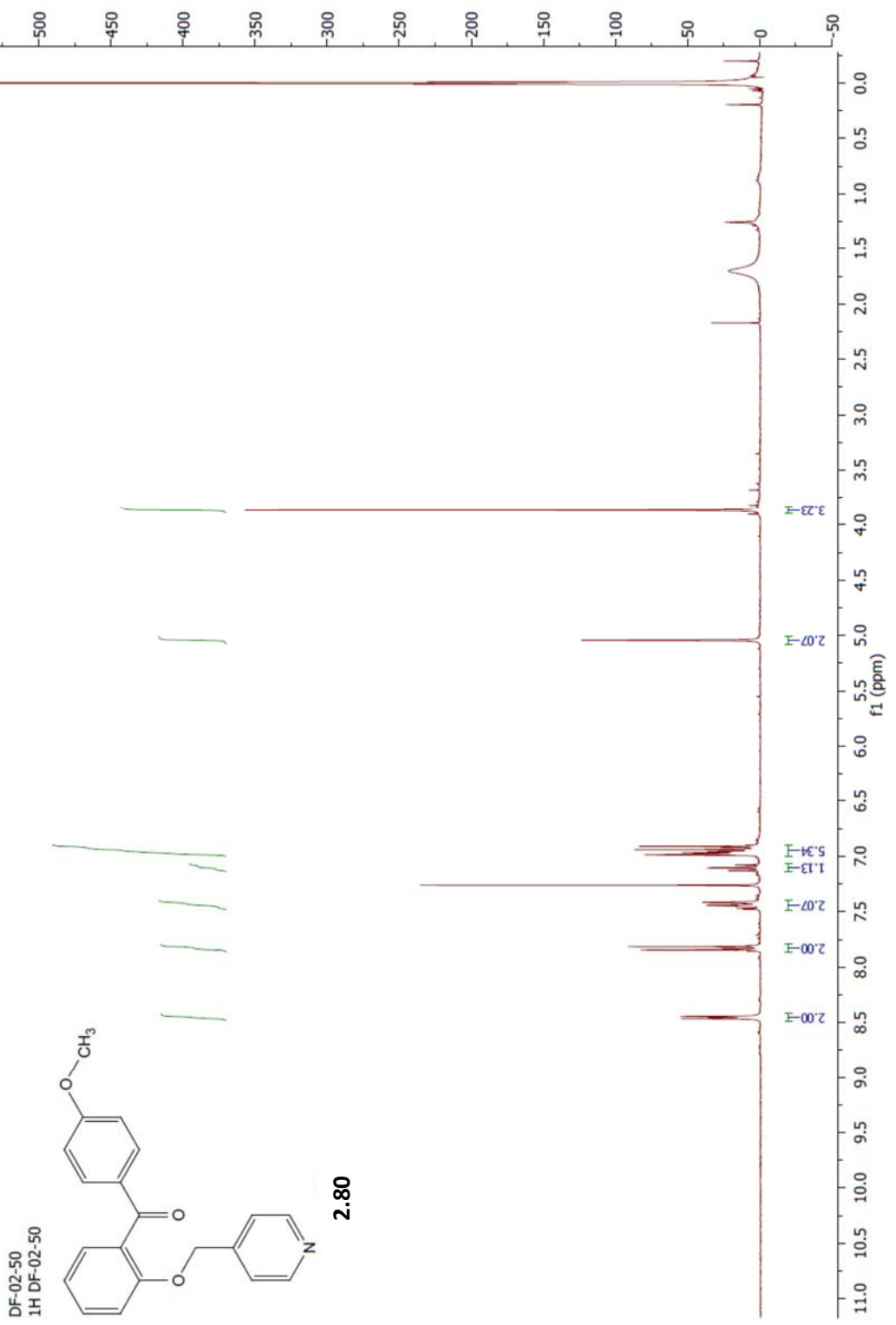

DF-01-86
13C DF-01-86
N
O
2.84
f1 (ppm)

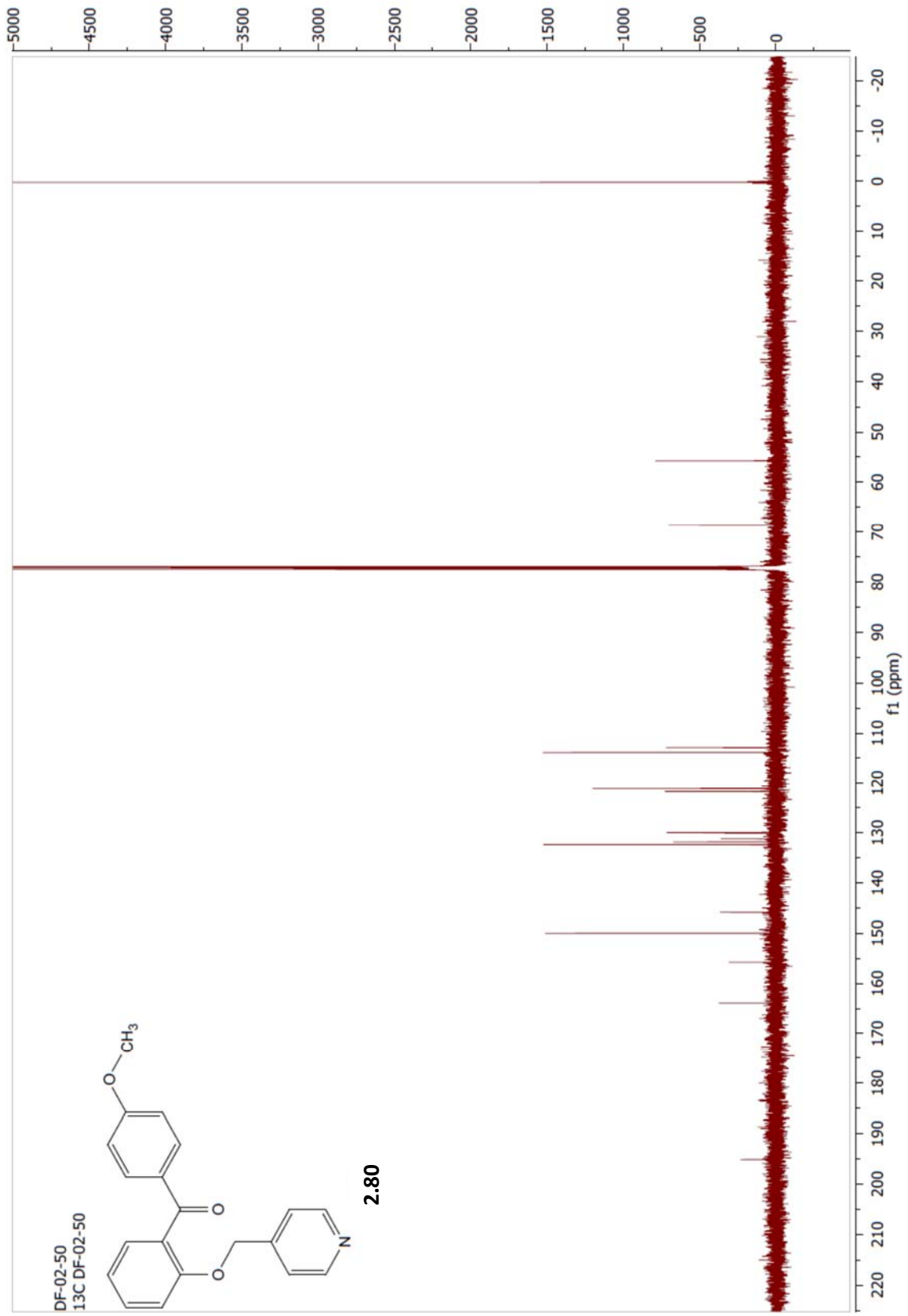

DF-01-80
1H DF-01-80
2.81
f1 (ppm)
2.00
2.04
2.20
1.08
2.19

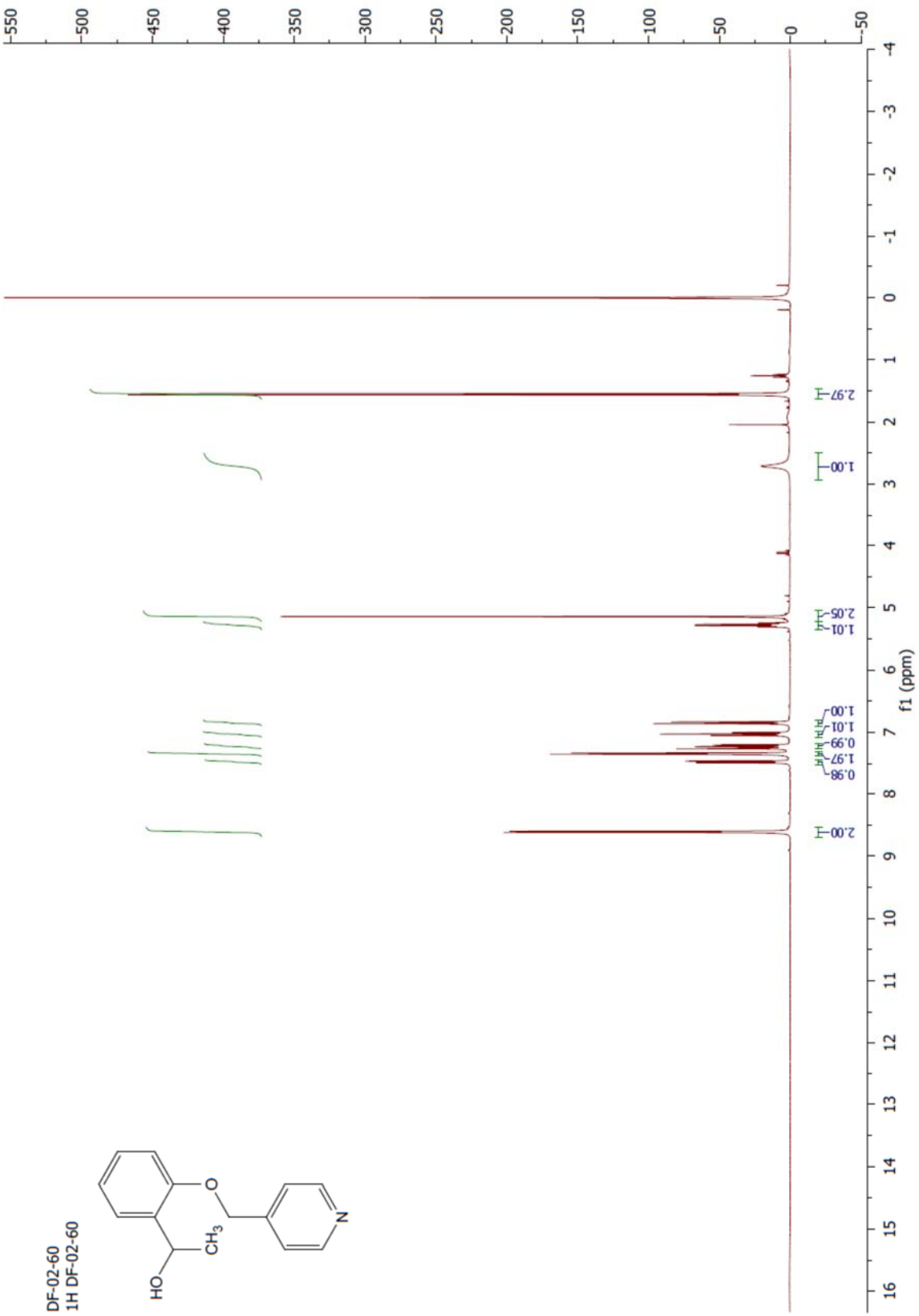

DF-01-80 blue
13C DF-01-80 blue
O
N
2.81
900
800
700
600
500
400
300
200
100
0
-100
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-30
-50
f1 (ppm)

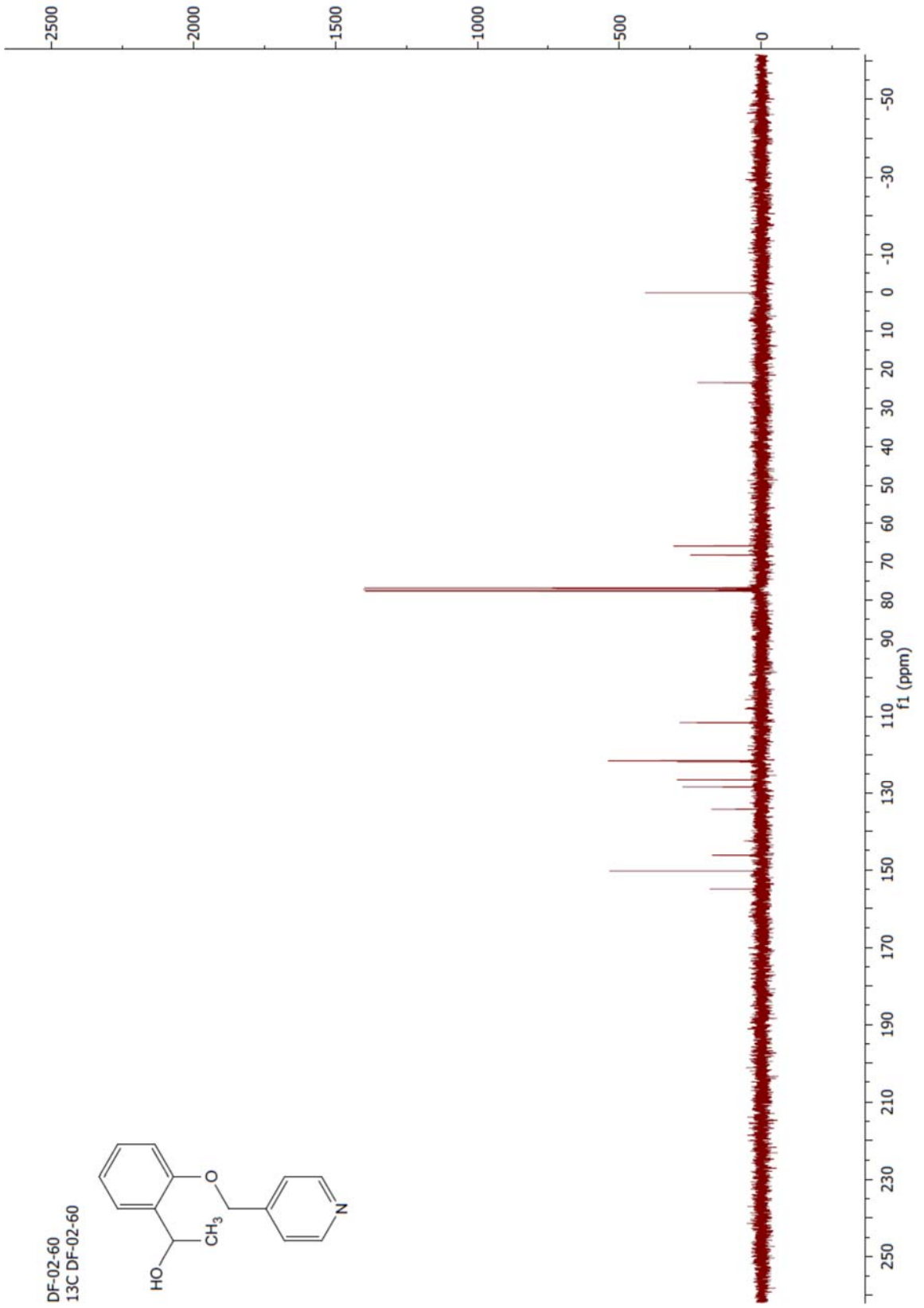

DF-01-146
1H DF-01-146
f1 (ppm)
1.06
3.08
1.89
0.91
3.09
3.04
3.31
1.00
2.00
OH
O
N
CH3
O

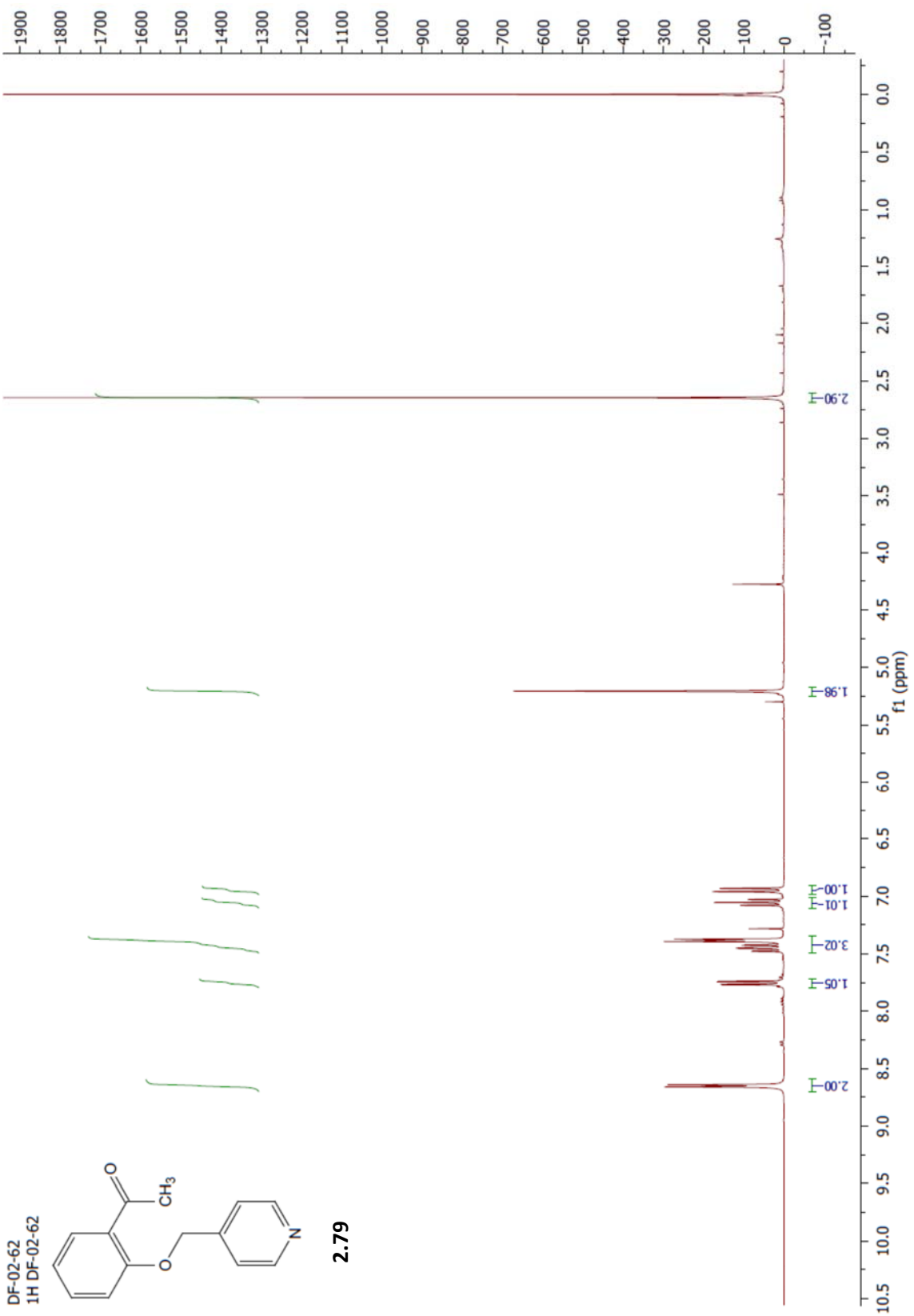

DF-01-146
1H DF-01-146
OH
O
CH3
O
N
f1 (ppm)

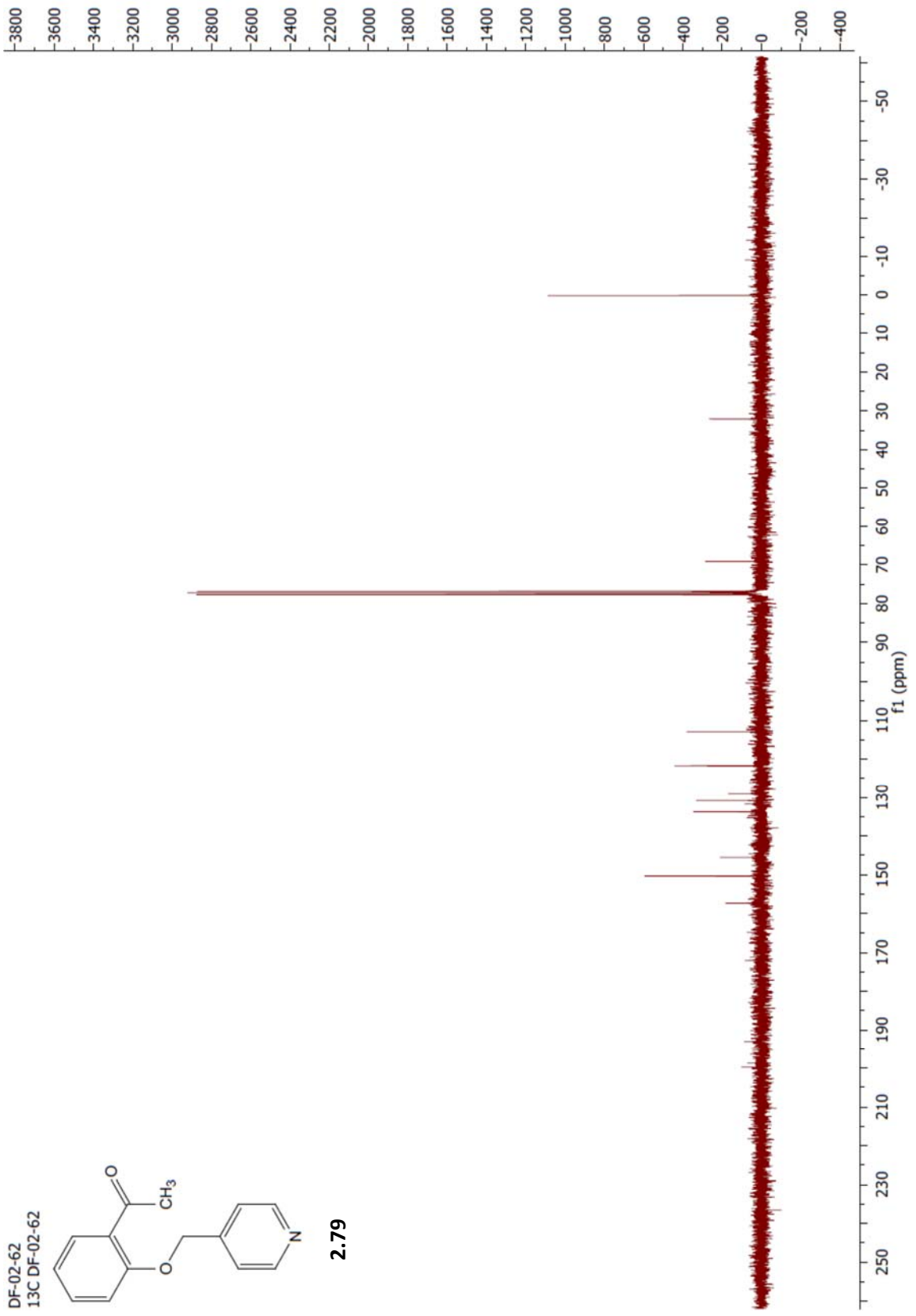

DF-02-50
1H DF-02-50
2.80
f1 (ppm)

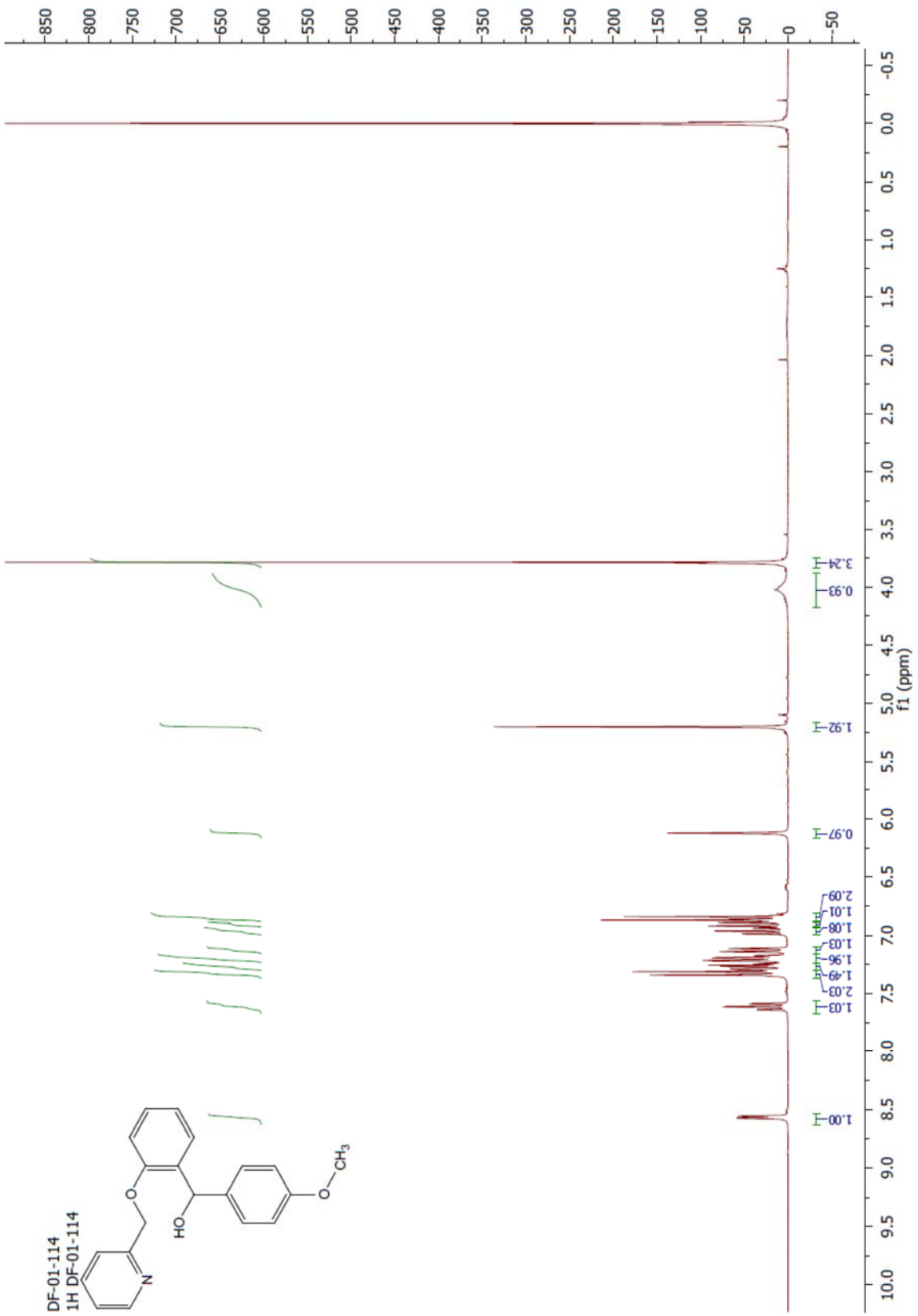

DF-02-50
13C DF-02-50
2.80
f1 (ppm)

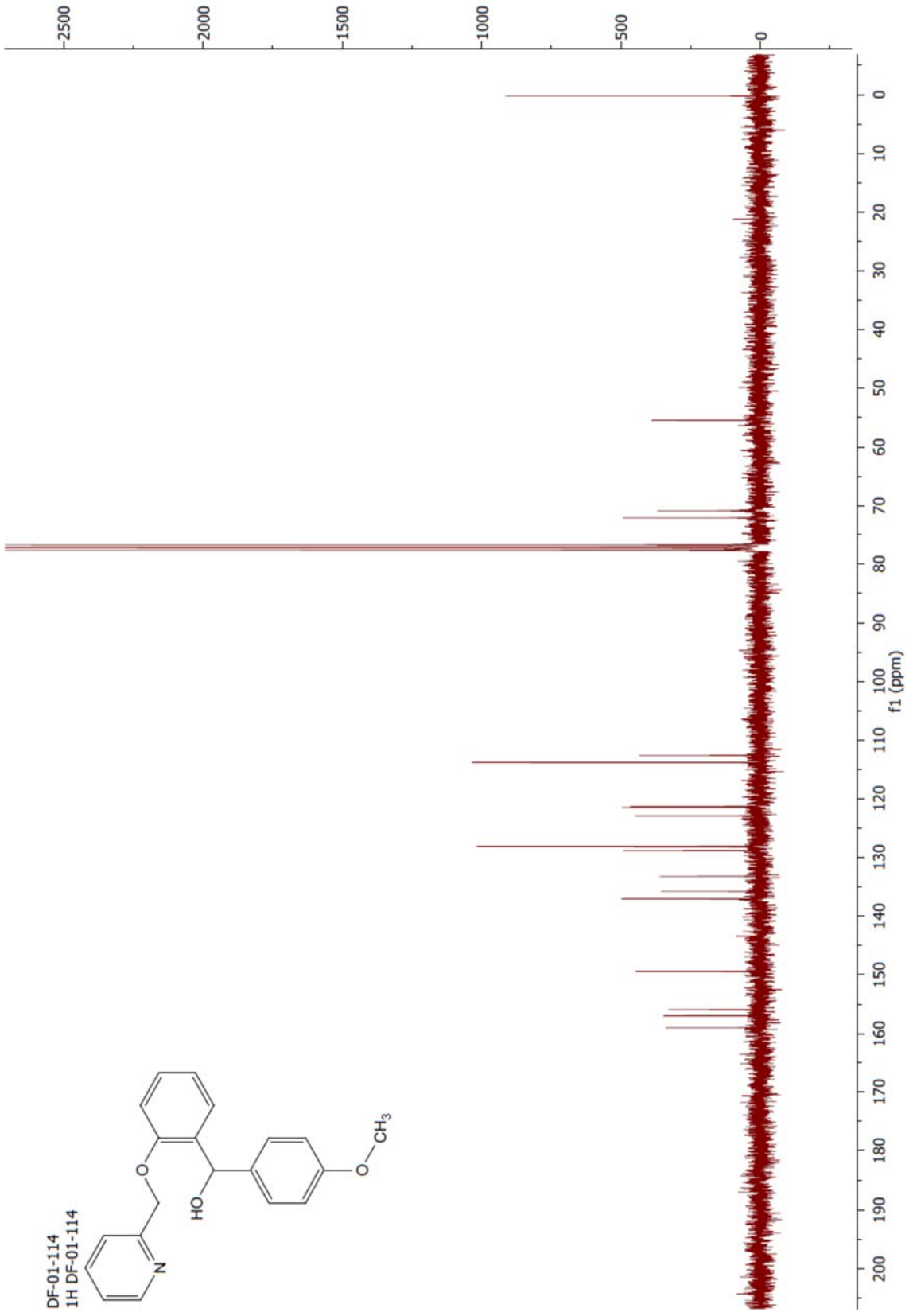

DF-02-60
1H DF-02-60
HO
CH3
O
N
2.00
0.98
1.97
0.99
1.01
1.00
1.01
2.05
1.00
2.97
f1 (ppm)

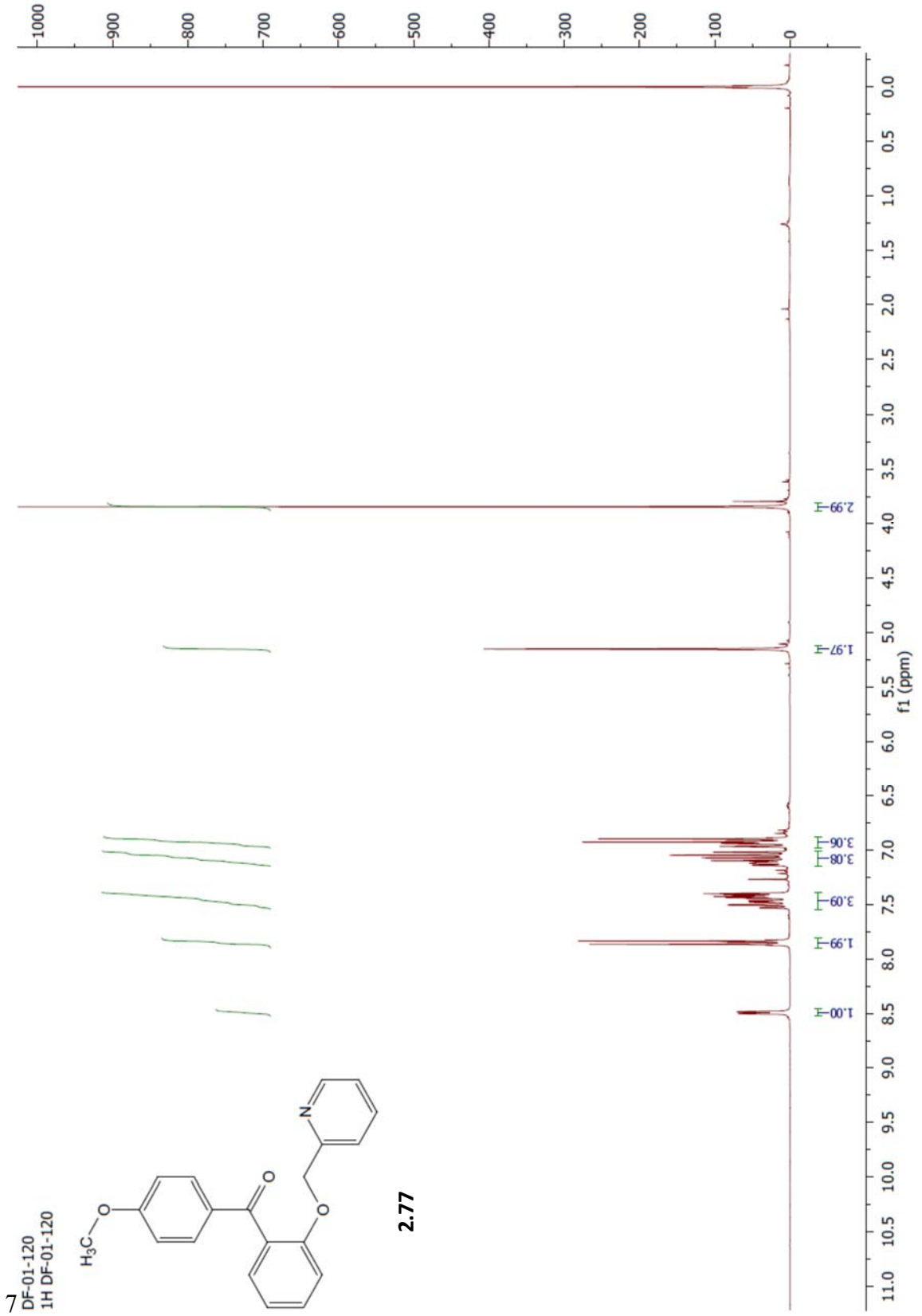

DF-02-60
13C DF-02-60
HO
CH3
O
N
f1 (ppm)

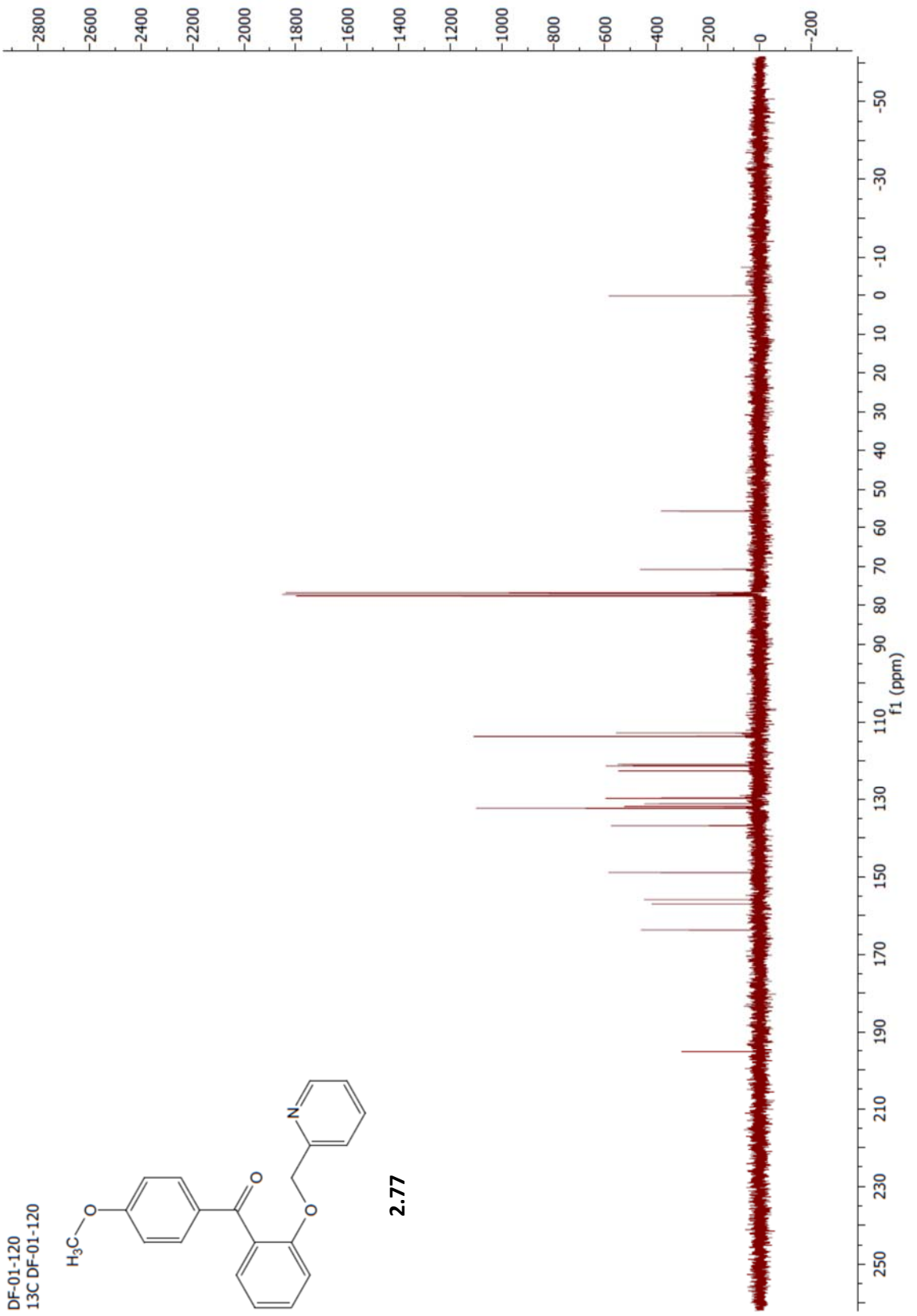

DF-02-62
1H DF-02-62
O
CH3
O
N
2.79
2.90
1.98
1.00
1.01
3.02
1.05
2.00
f1 (ppm)

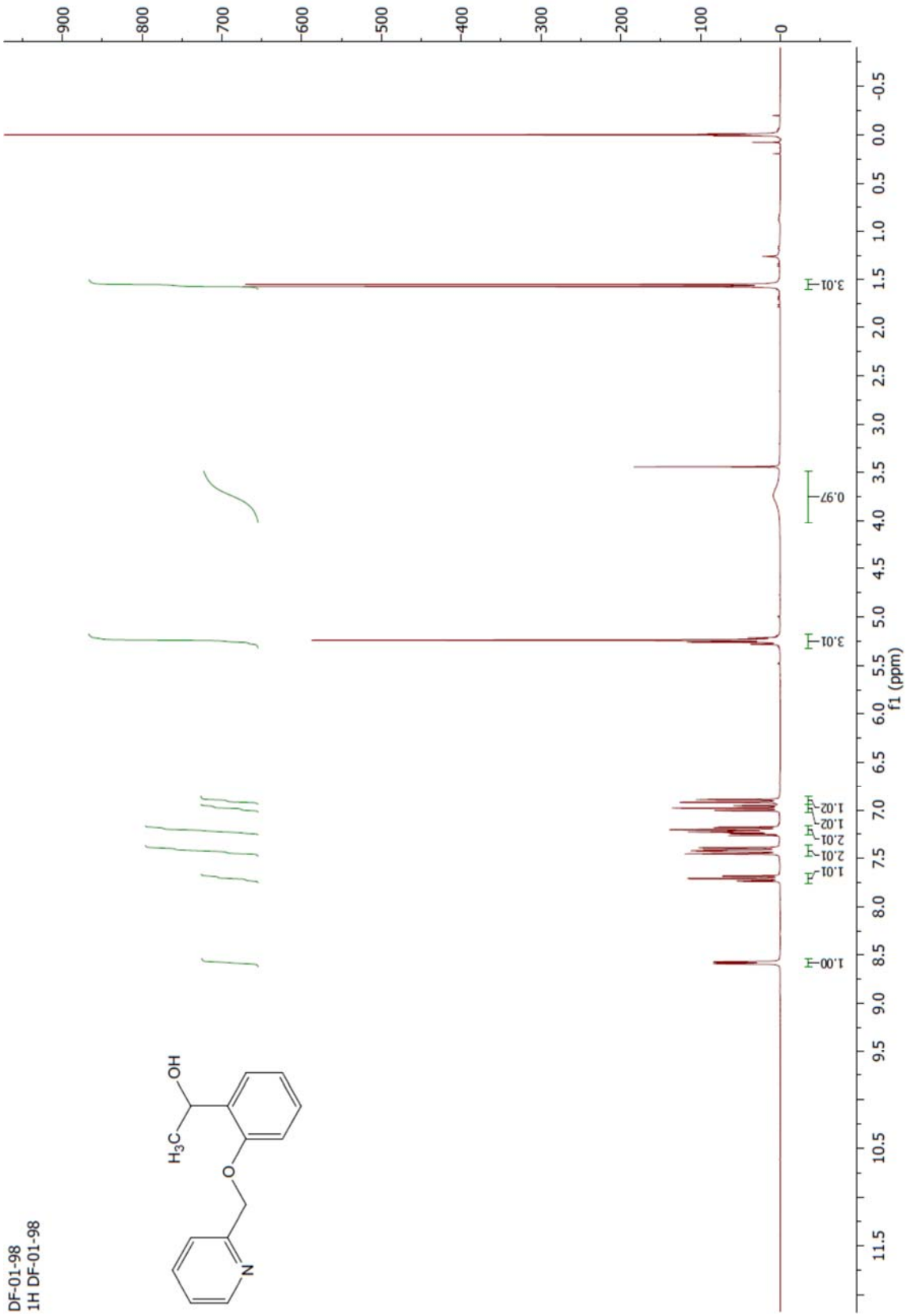

DF-02-62
13C DF-02-62
O
CH3
O
N
2.79
f1 (ppm)

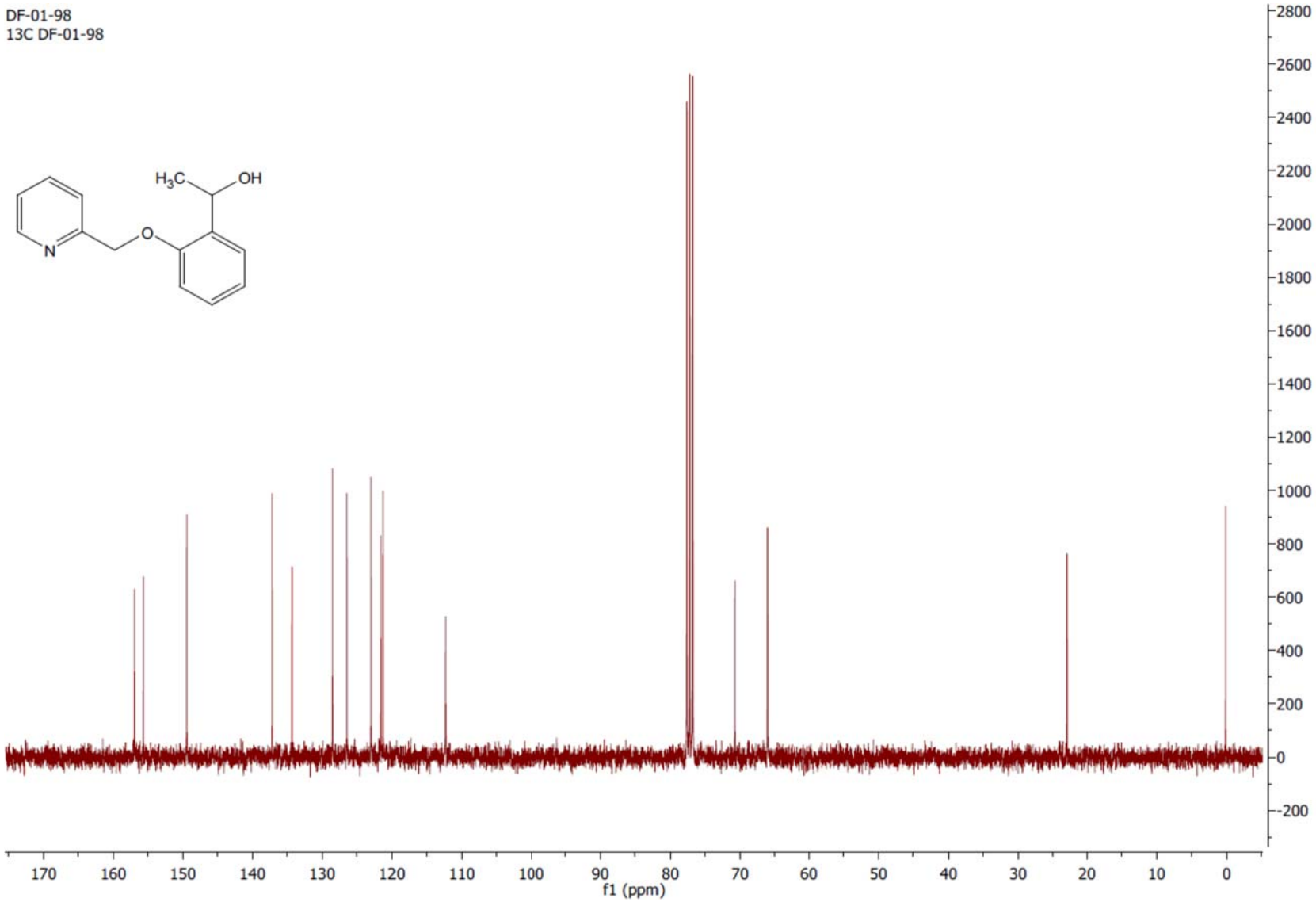

DF-01-114
1H DF-01-114
f1 (ppm)
3.24
0.93
1.92
0.97
2.09
1.01
1.08
1.03
1.96
1.49
2.03
1.03
1.00

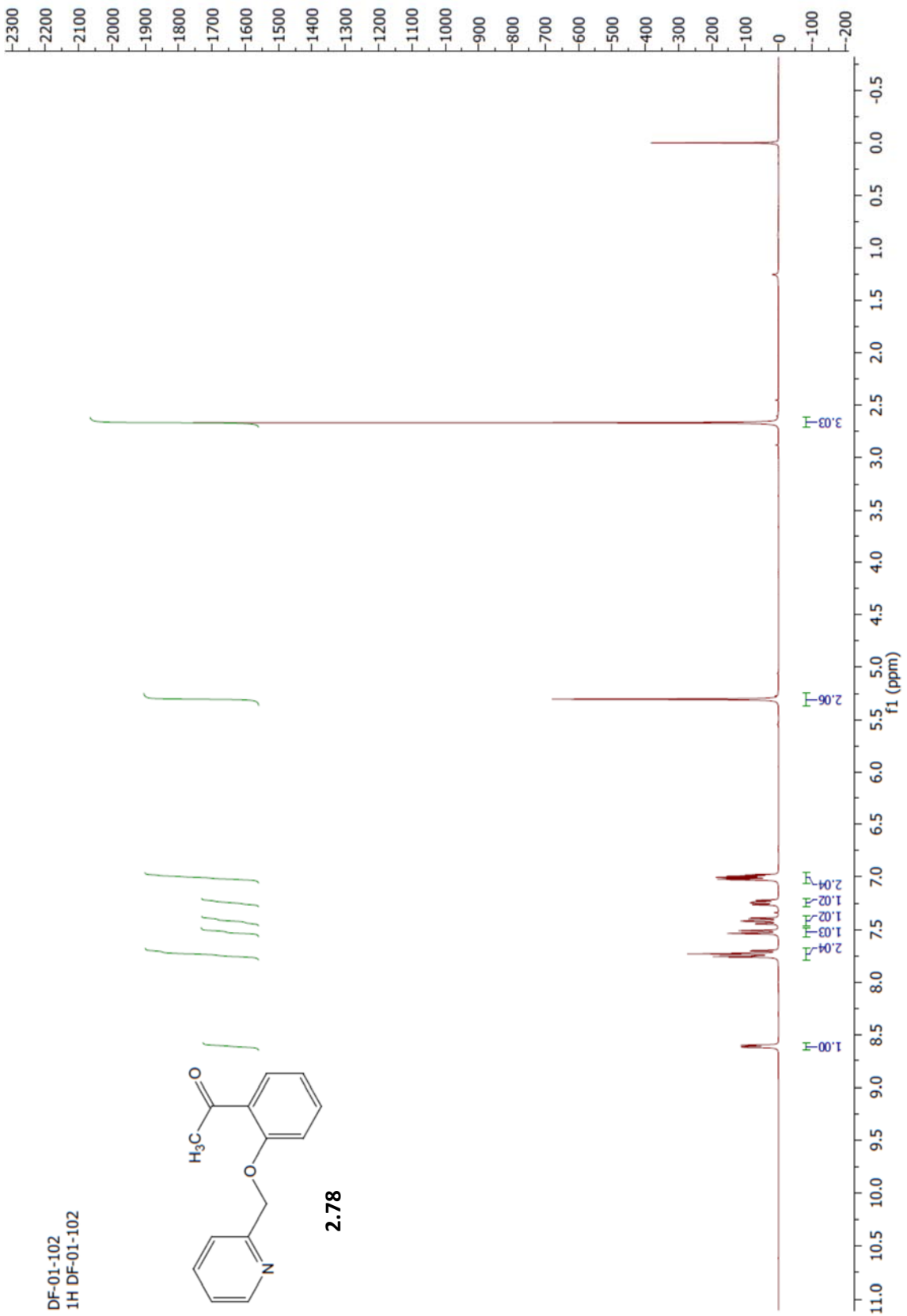

DF-01-114
1H DF-01-114
HO
O
N
O
CH3
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

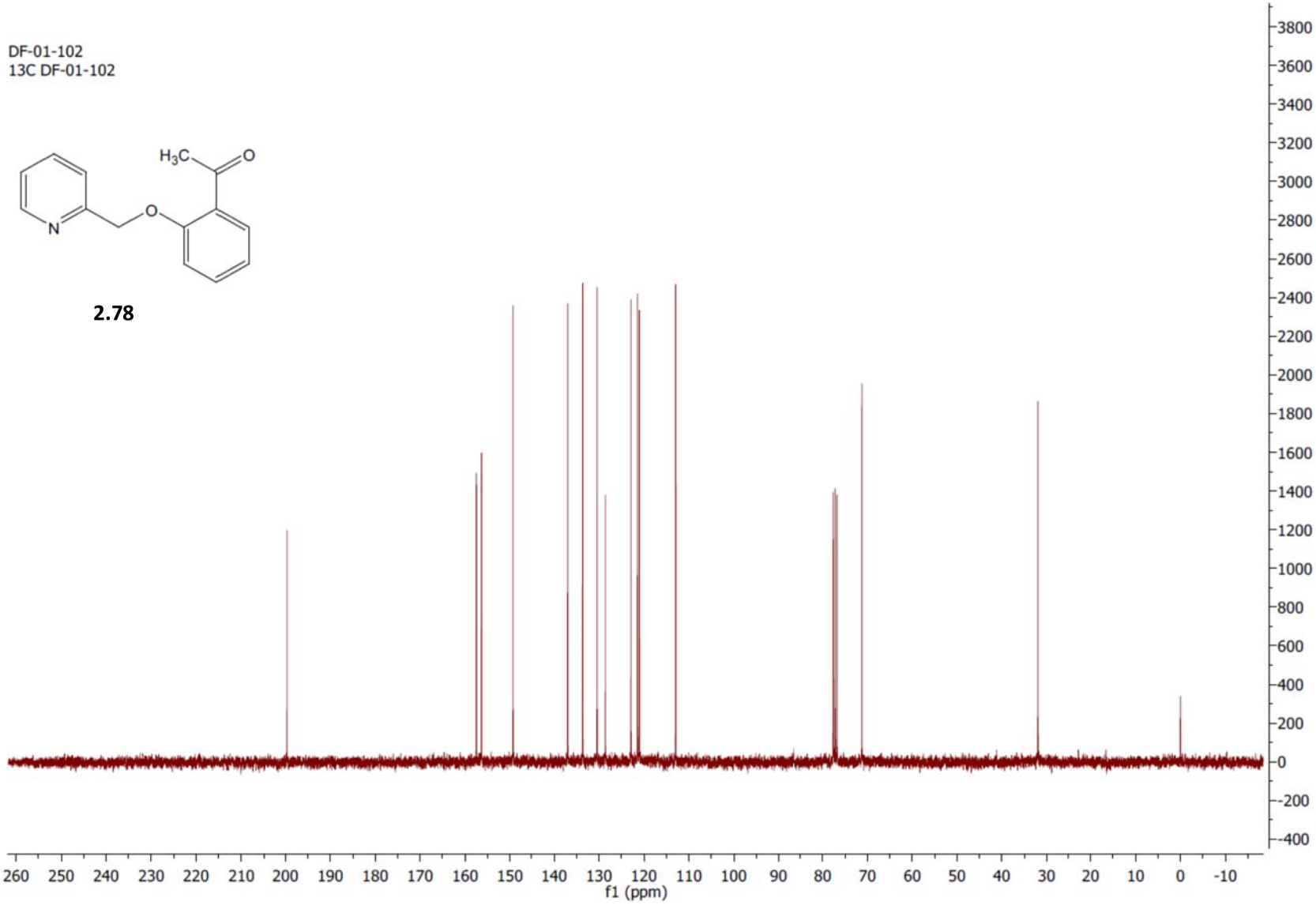

DF-01-120
1H DF-01-120
H3C
O
O
O
N
2.77
2.99
1.97
3.06
3.08
3.09
1.99
1.00
f1 (ppm)

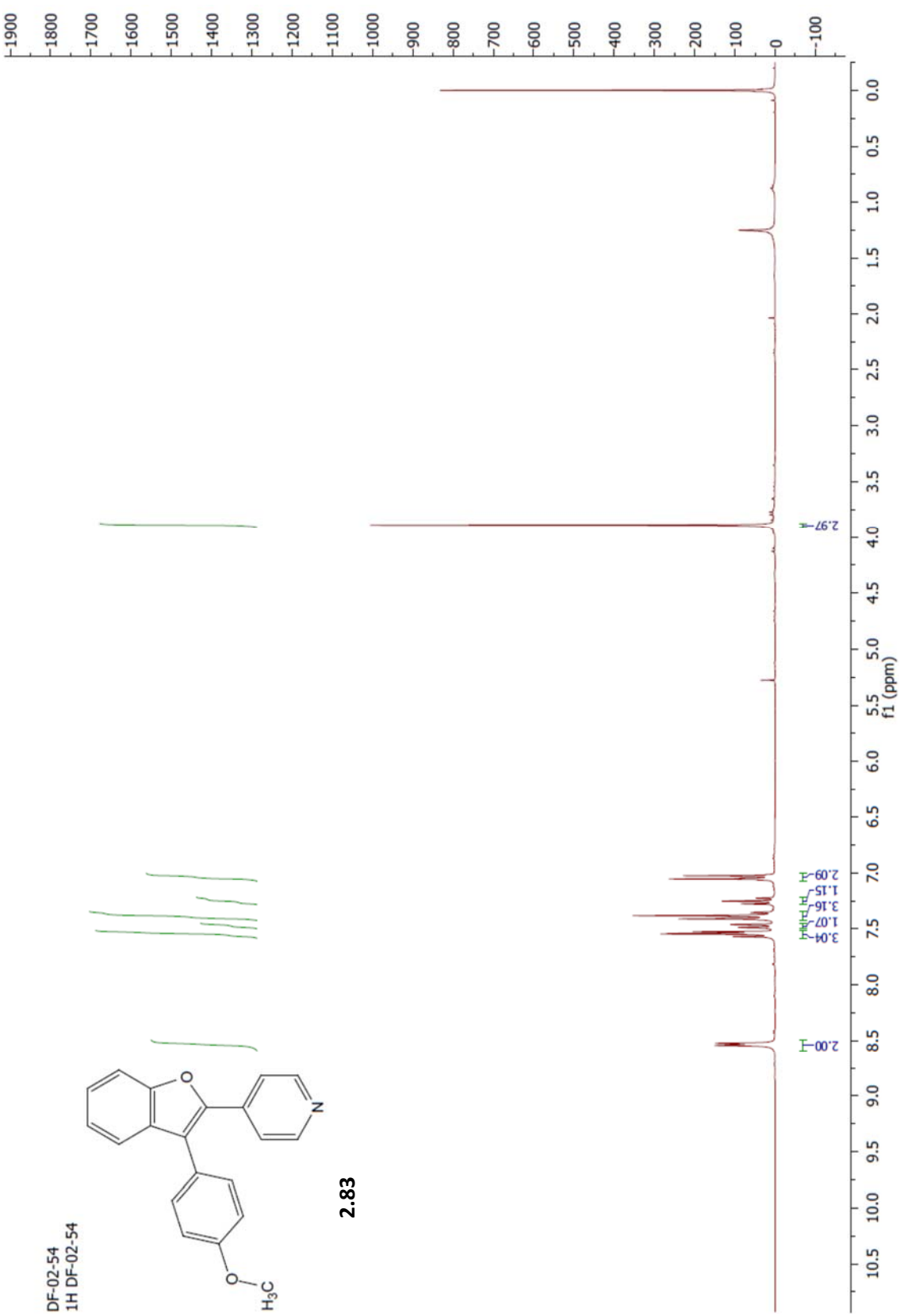

DF-01-120
13C DF-01-120
H3C
O
O
O
N
2.77
f1 (ppm)

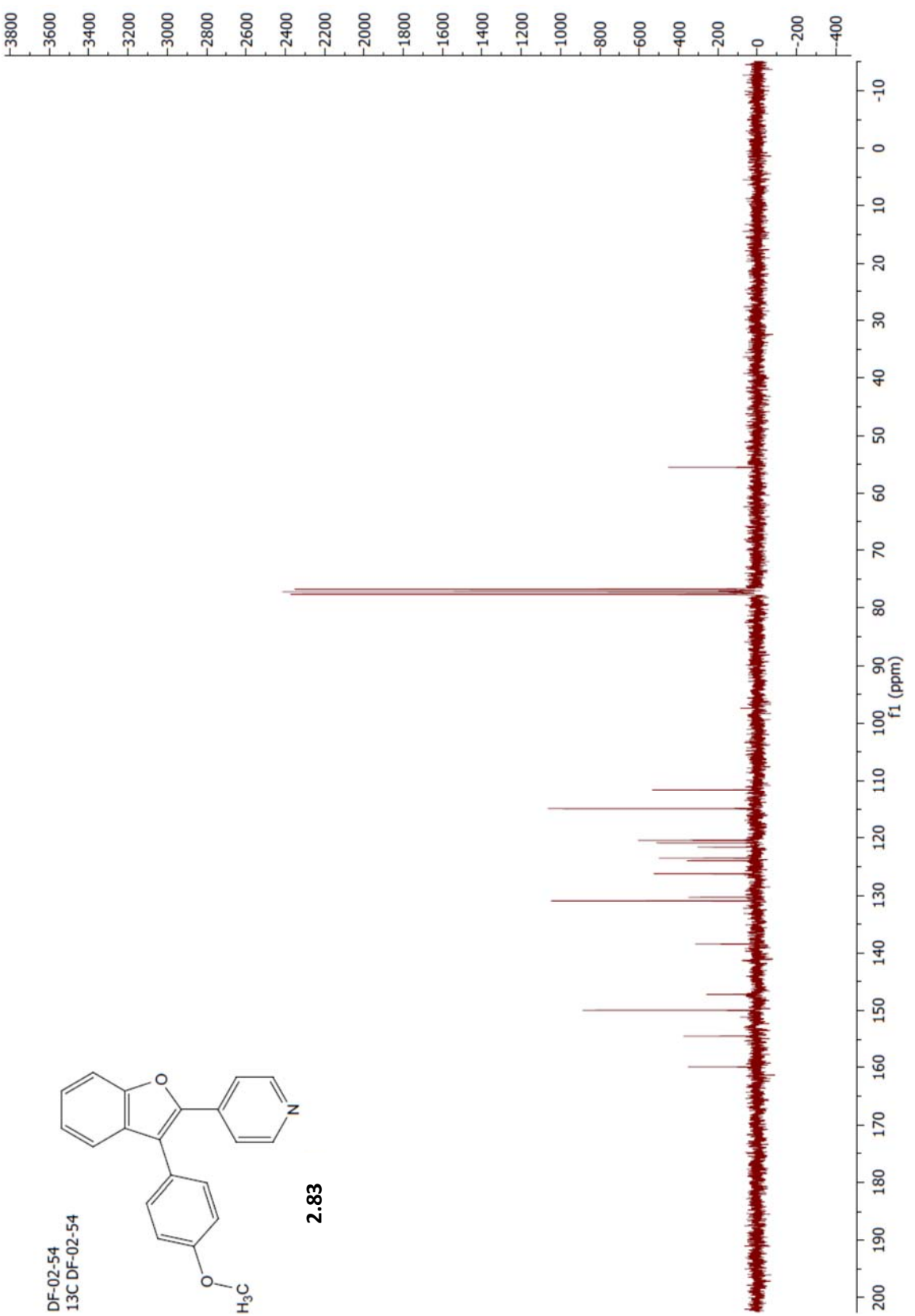

DF-01-98
1H DF-01-98
OH
H3C
O
N
3.01
0.97
3.01
1.02
1.02
2.01
2.01
1.01
1.00
f1 (ppm)


DF-01-98
13C DF-01-98
H3C
OH
N
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

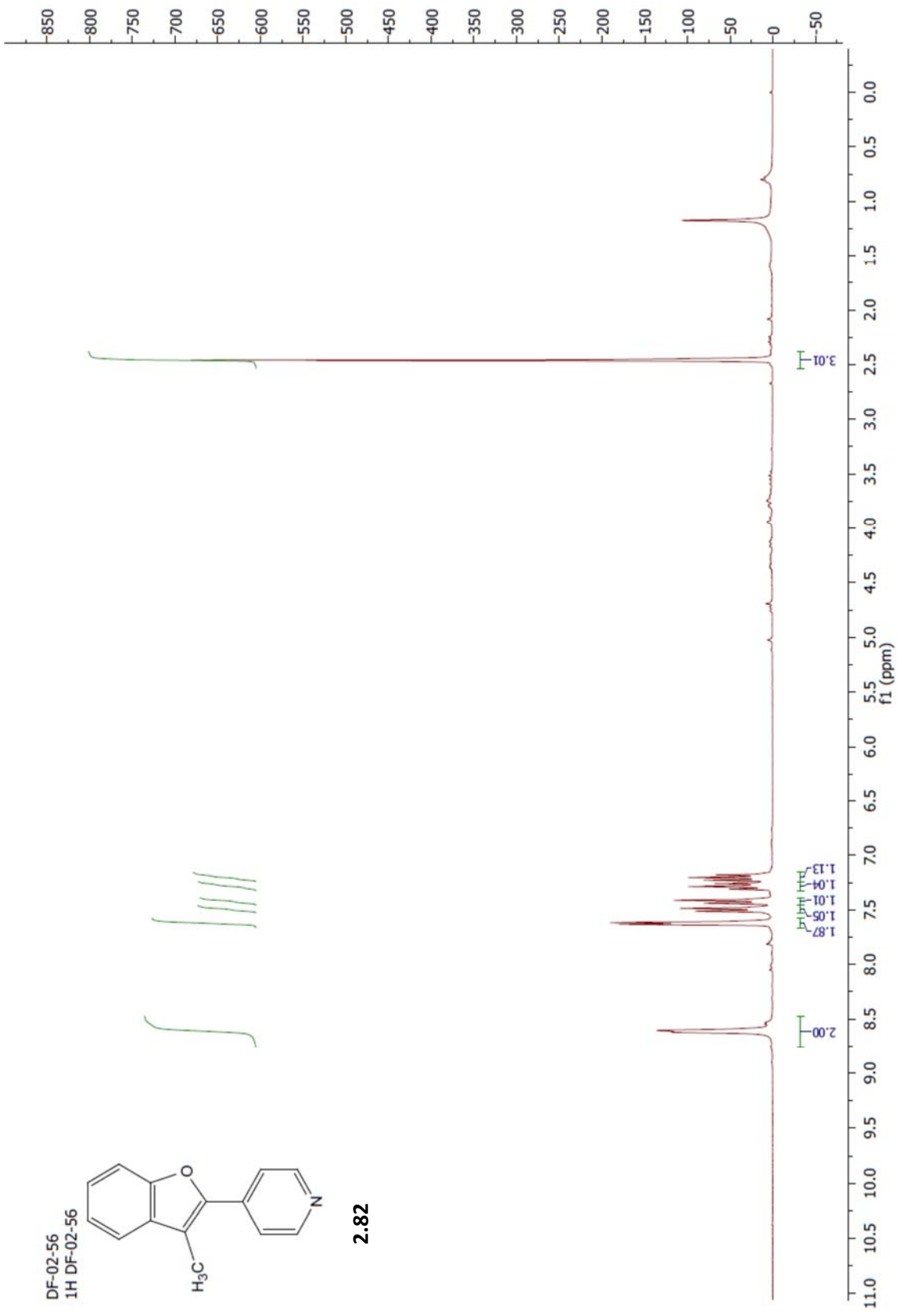

DF-01-102
1H DF-01-102
H3C
O
O
N
2.78
f1 (ppm)

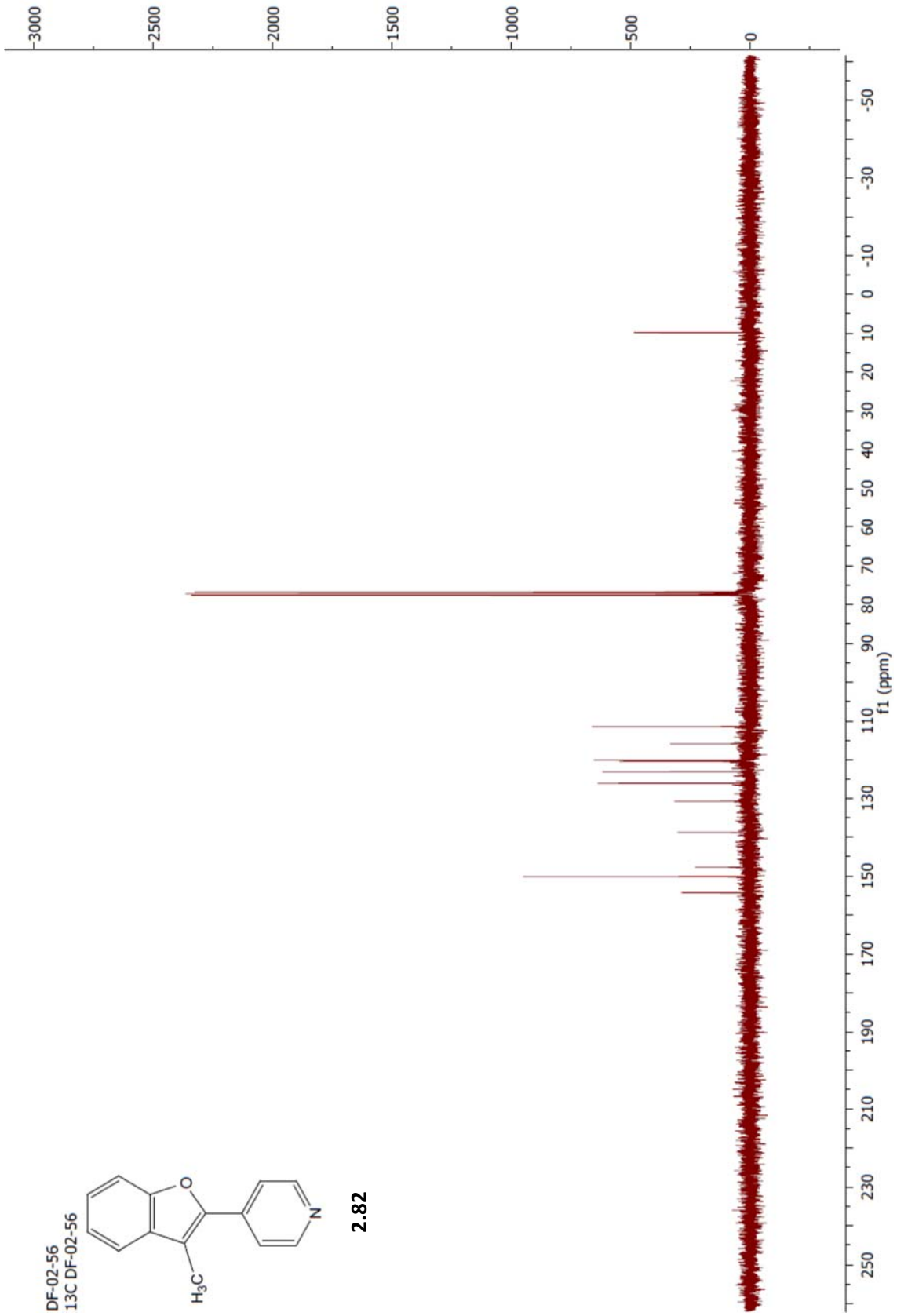

DF-01-102
13C DF-01-102
H3C
O
N
O
2.78
f1 (ppm)

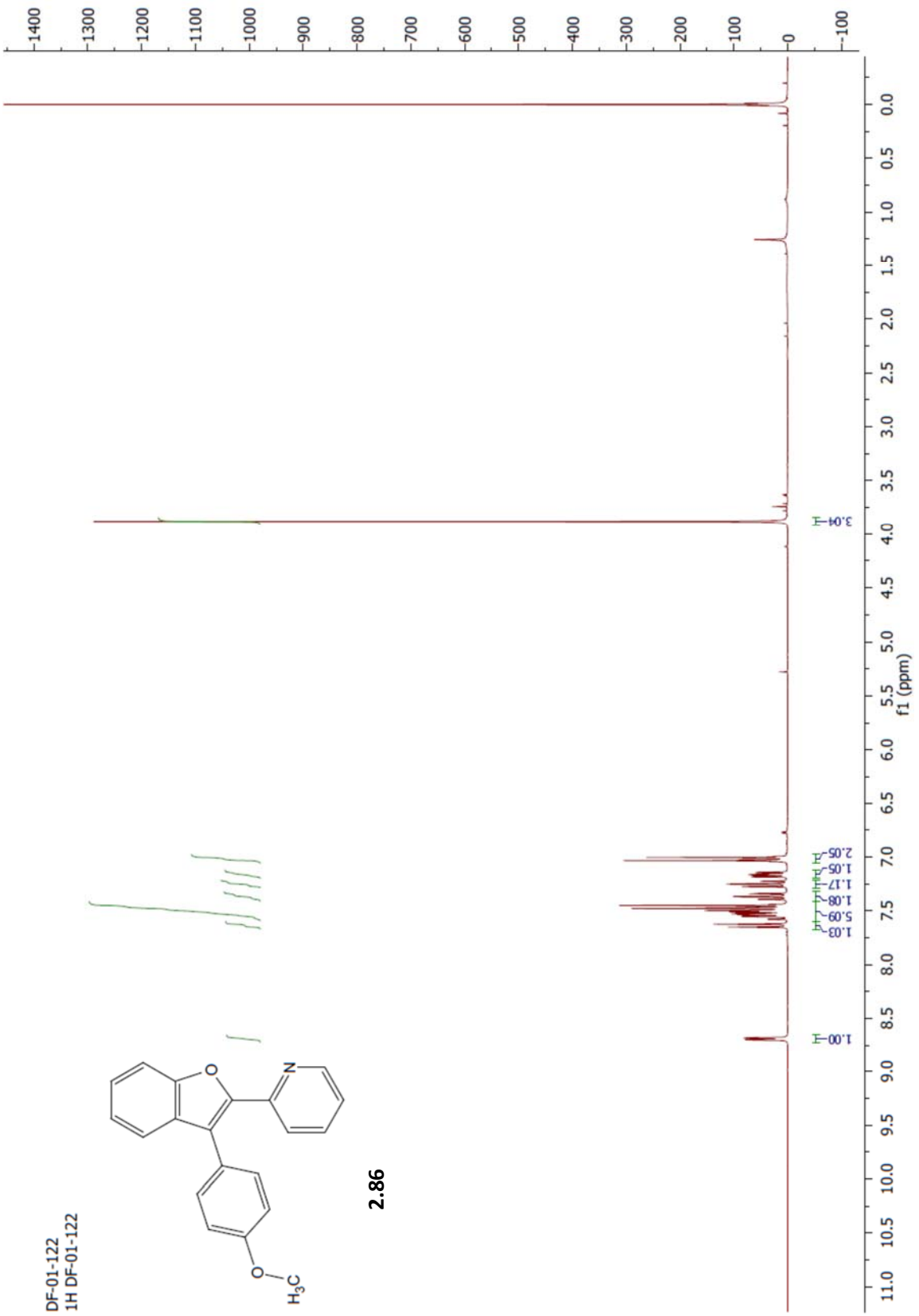

DF-02-54
1H DF-02-54
2.83
f1 (ppm)

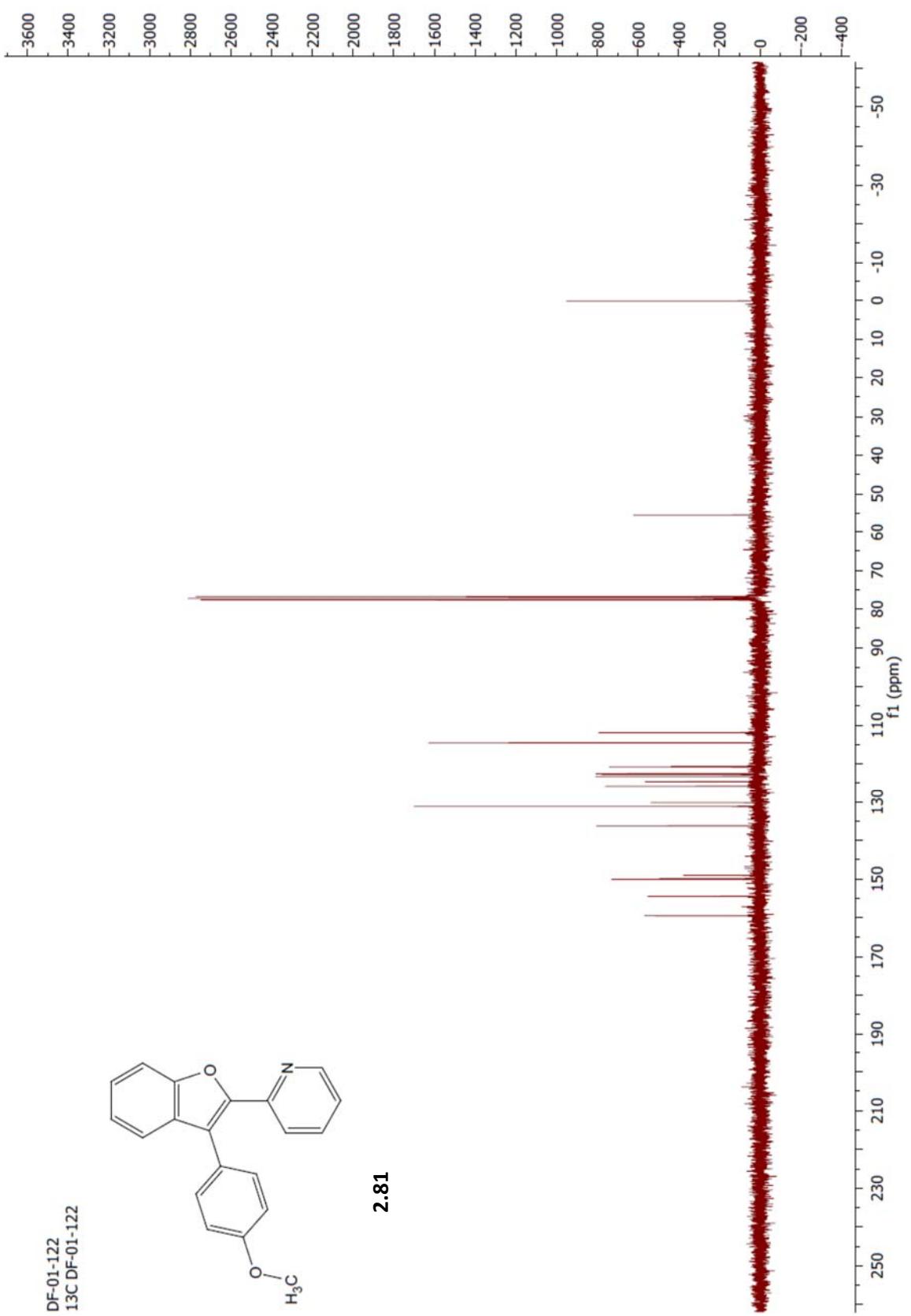


2.83

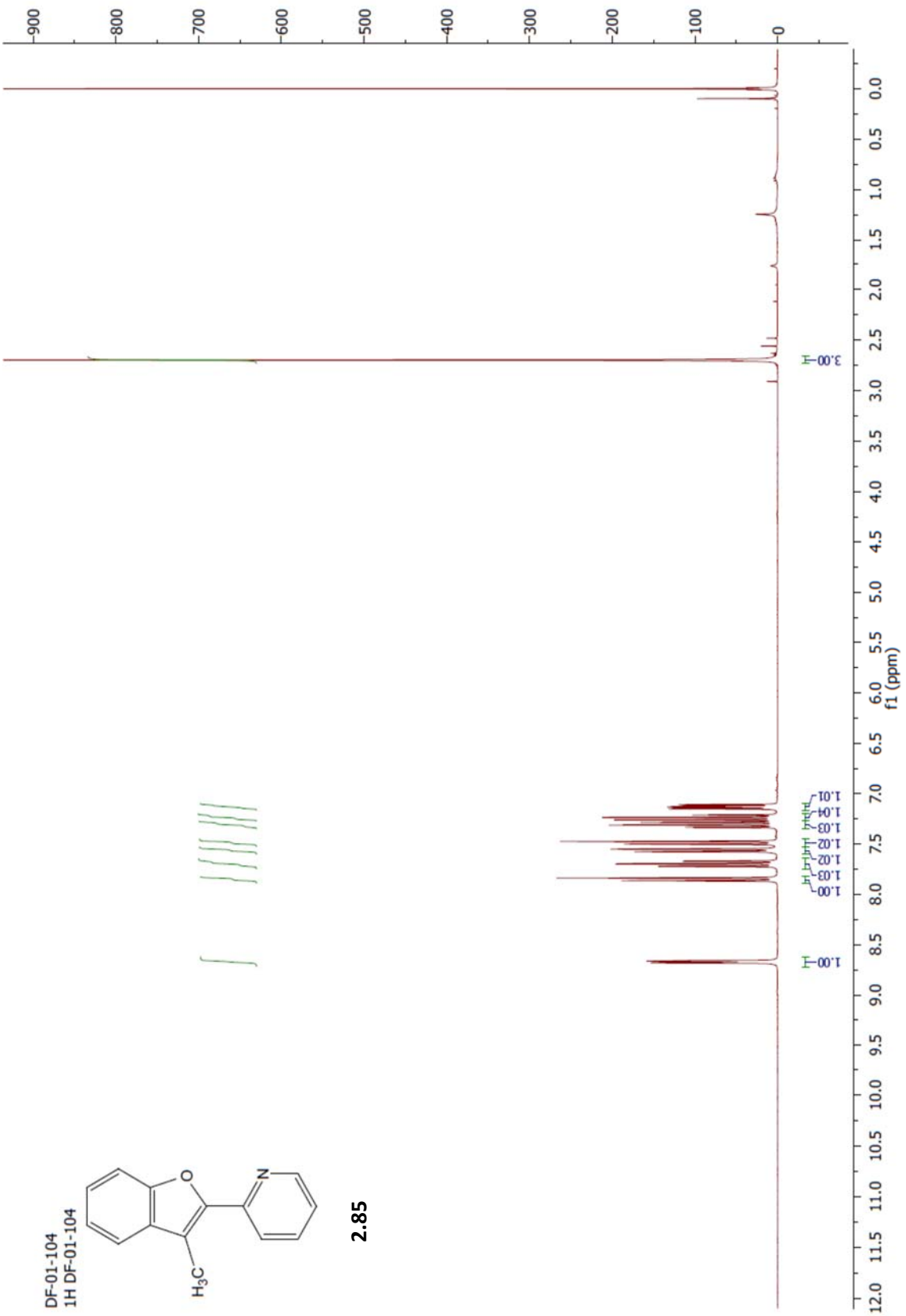

DF-02-56
1H DF-02-56
O
N
H_3C
2.82
3.01
2.00
1.87
1.05
1.01
1.04
1.13
f1 (ppm)

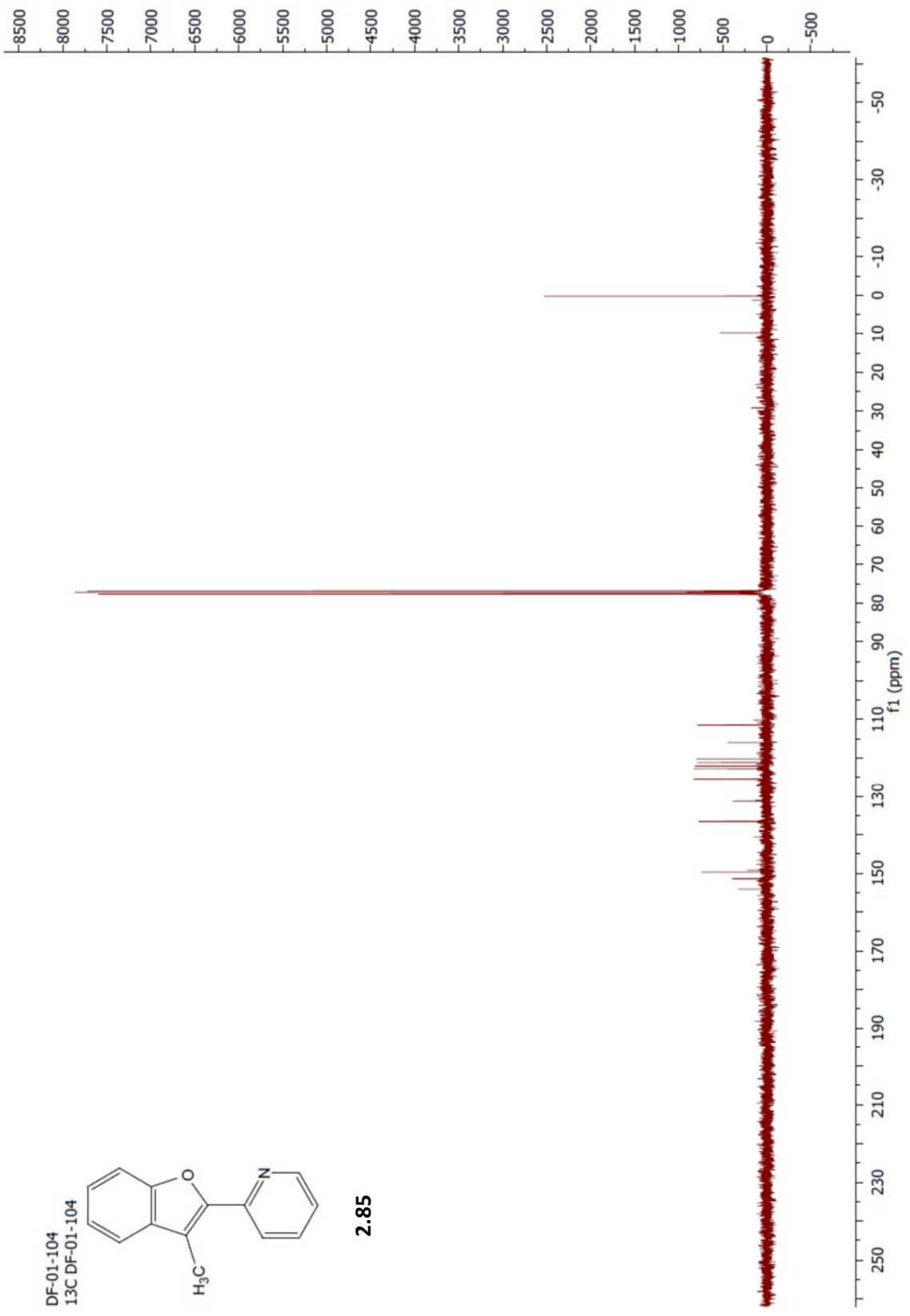

DF-02-56
13C DF-02-56
O
N
H3C
2.82
f1 (ppm)

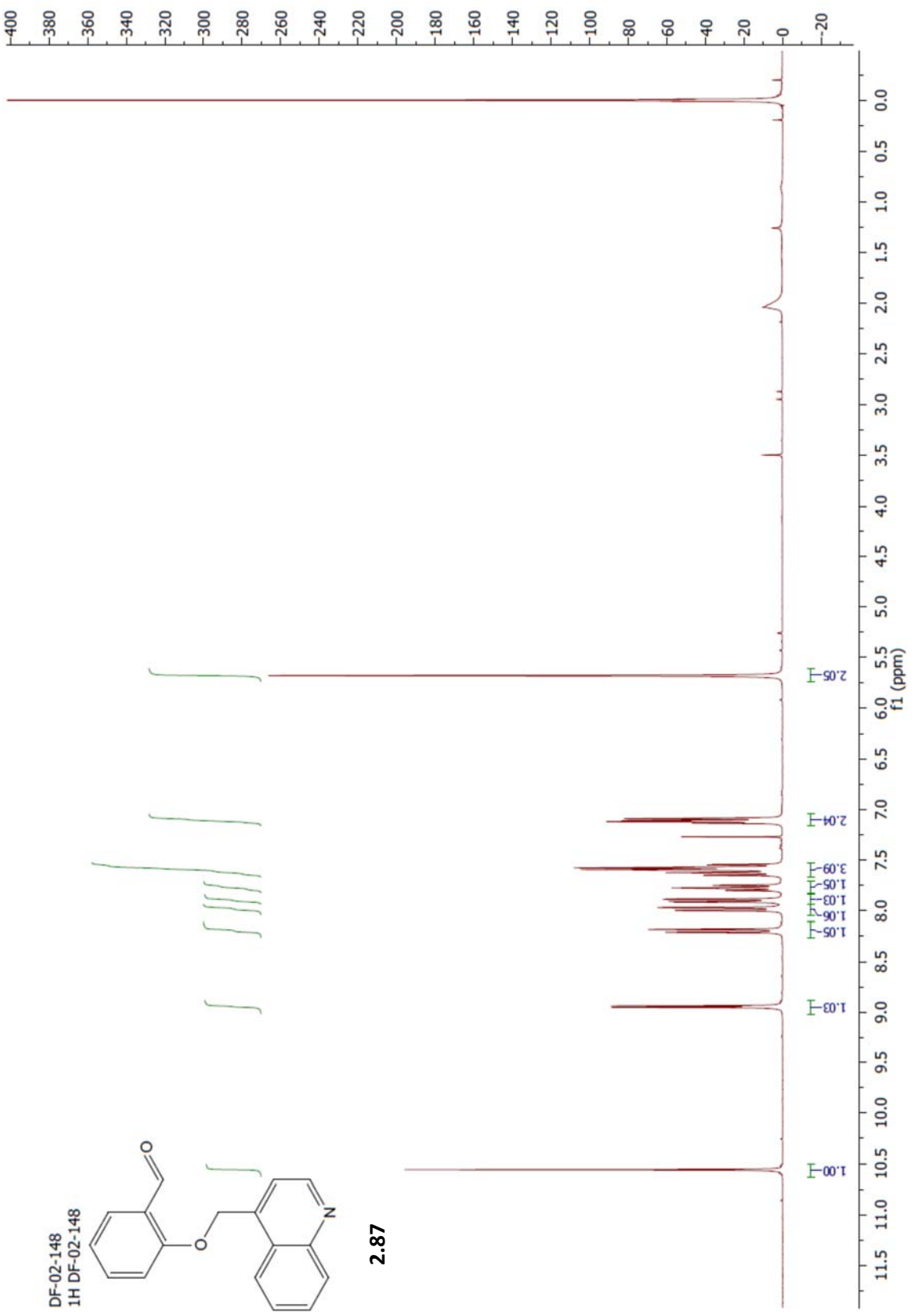

DF-01-122
1H DF-01-122
2.86
O
N
O
H3C
3.04
1.00
1.03
5.09
1.08
1.17
1.05
2.05
f1 (ppm)

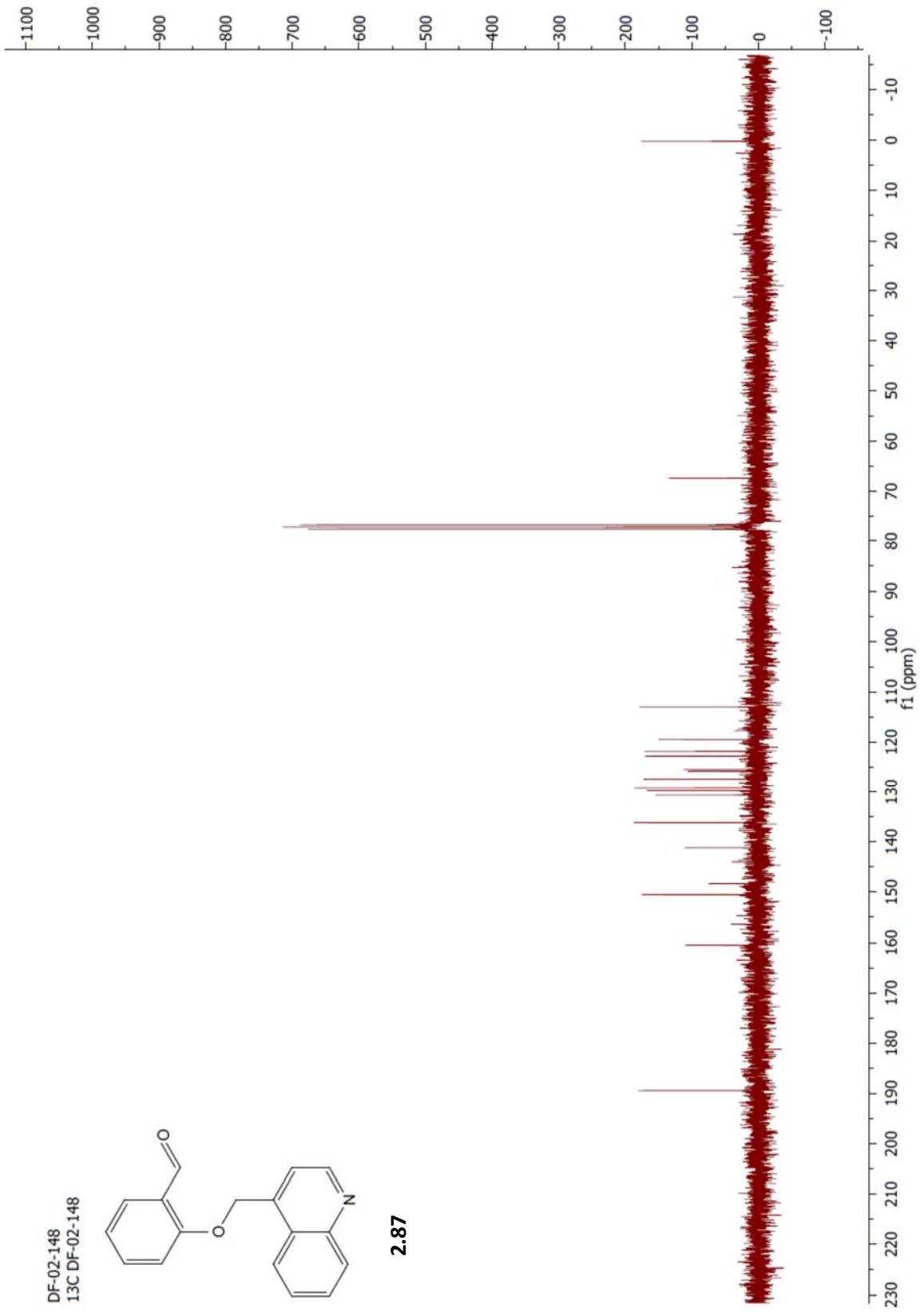


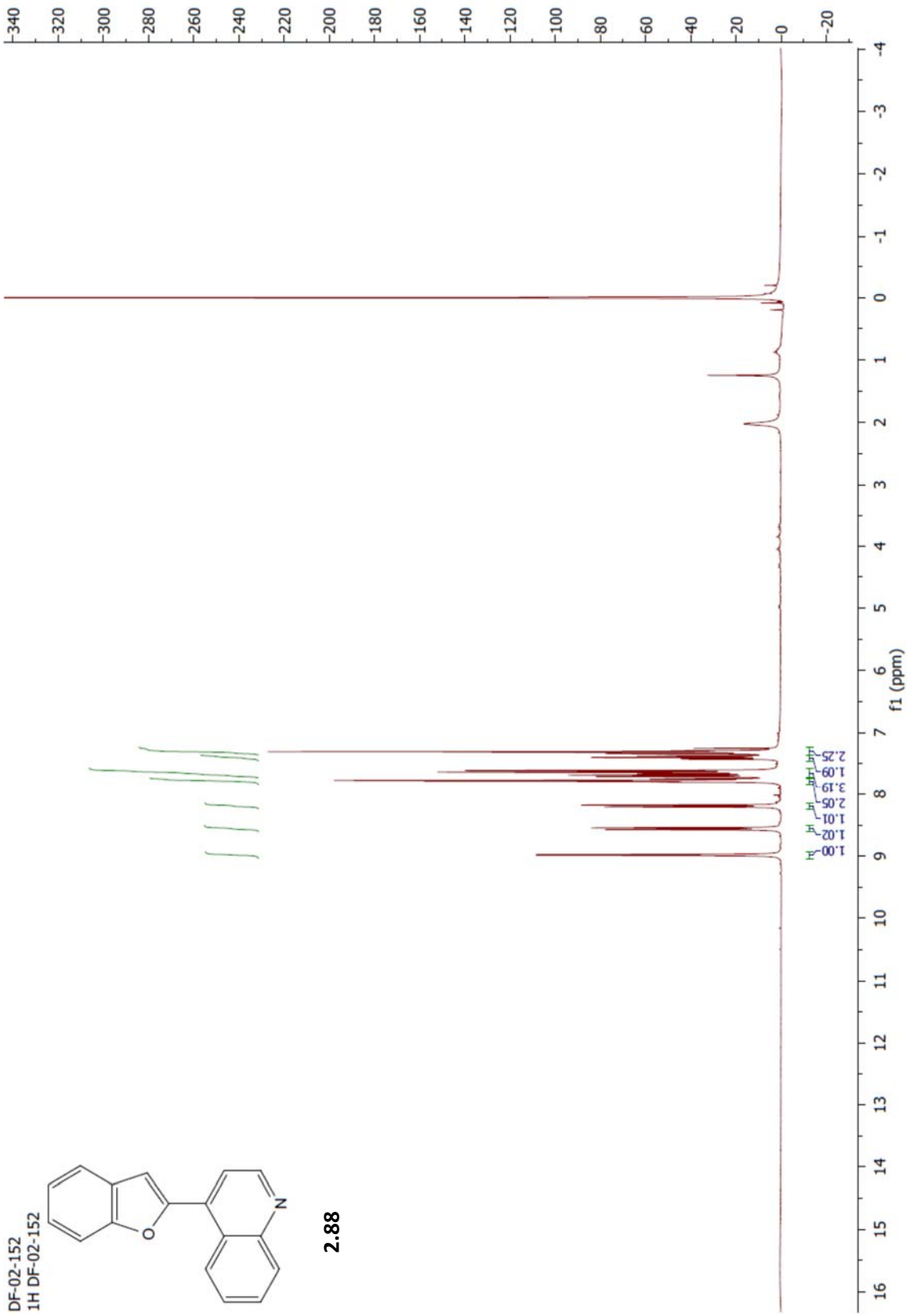
2.81

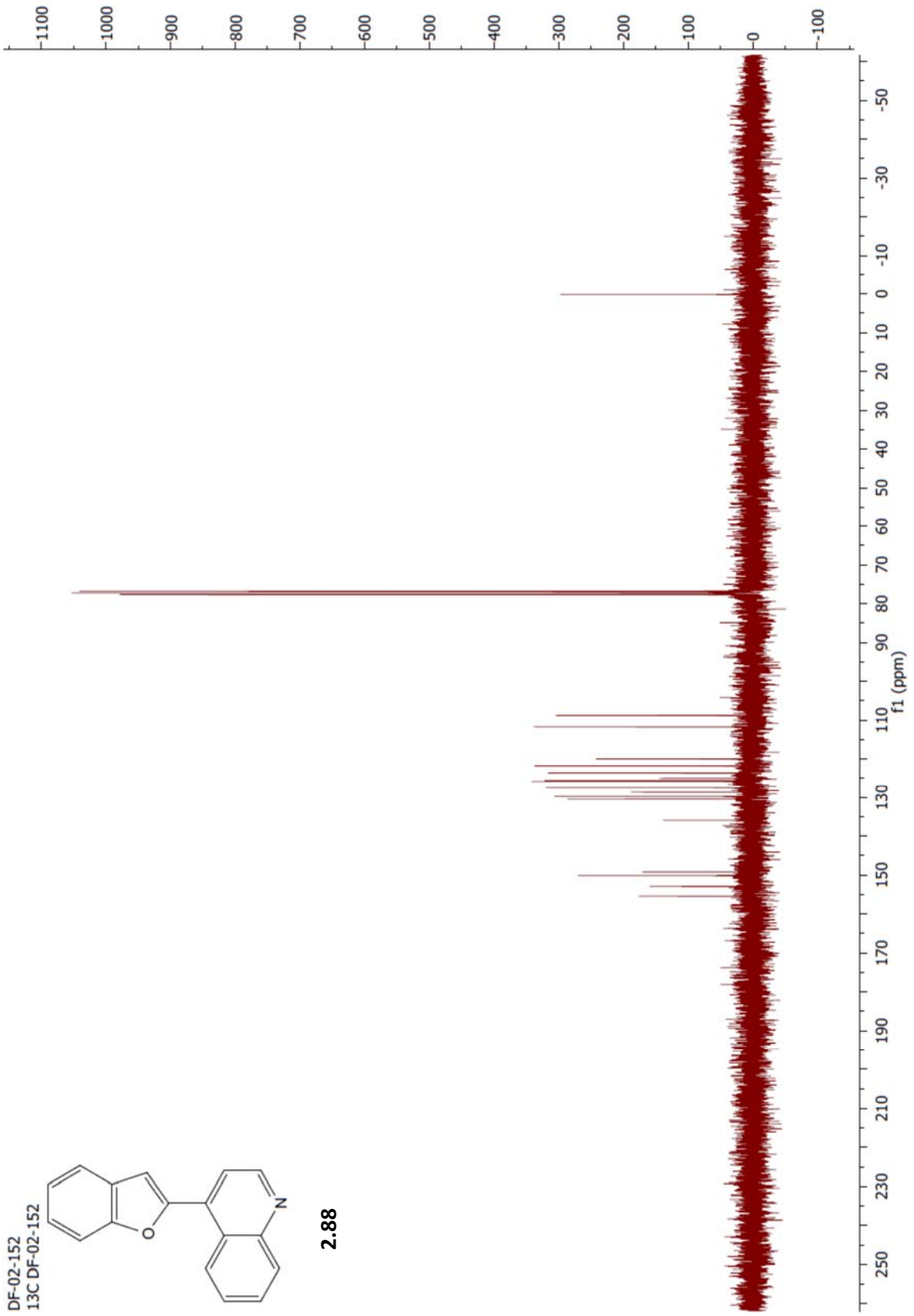

DF-01-104
1H DF-01-104
O
N
H3C
2.85
f1 (ppm)

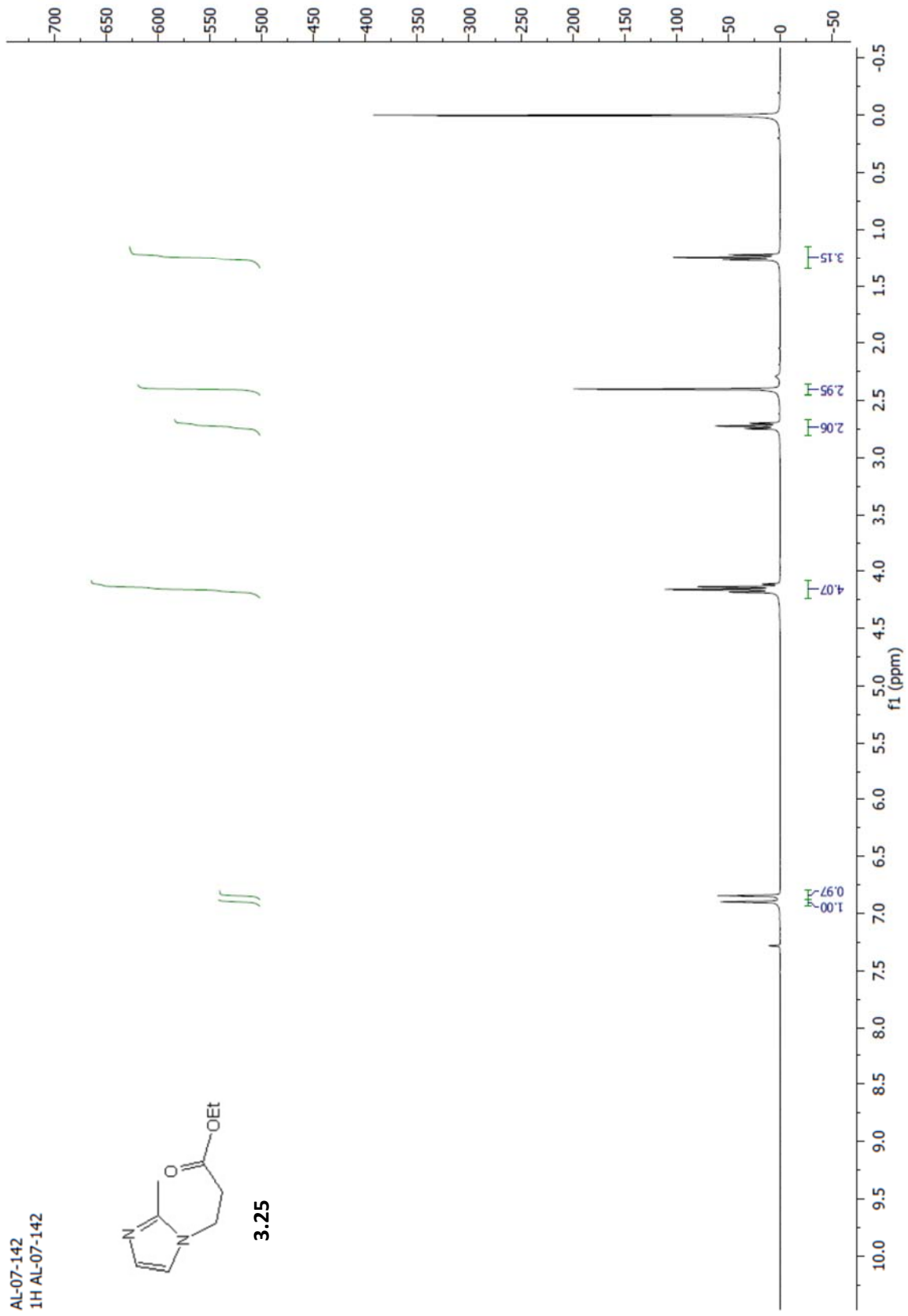

DF-01-104
13C DF-01-104
O
N
H3C
2.85
f1 (ppm)

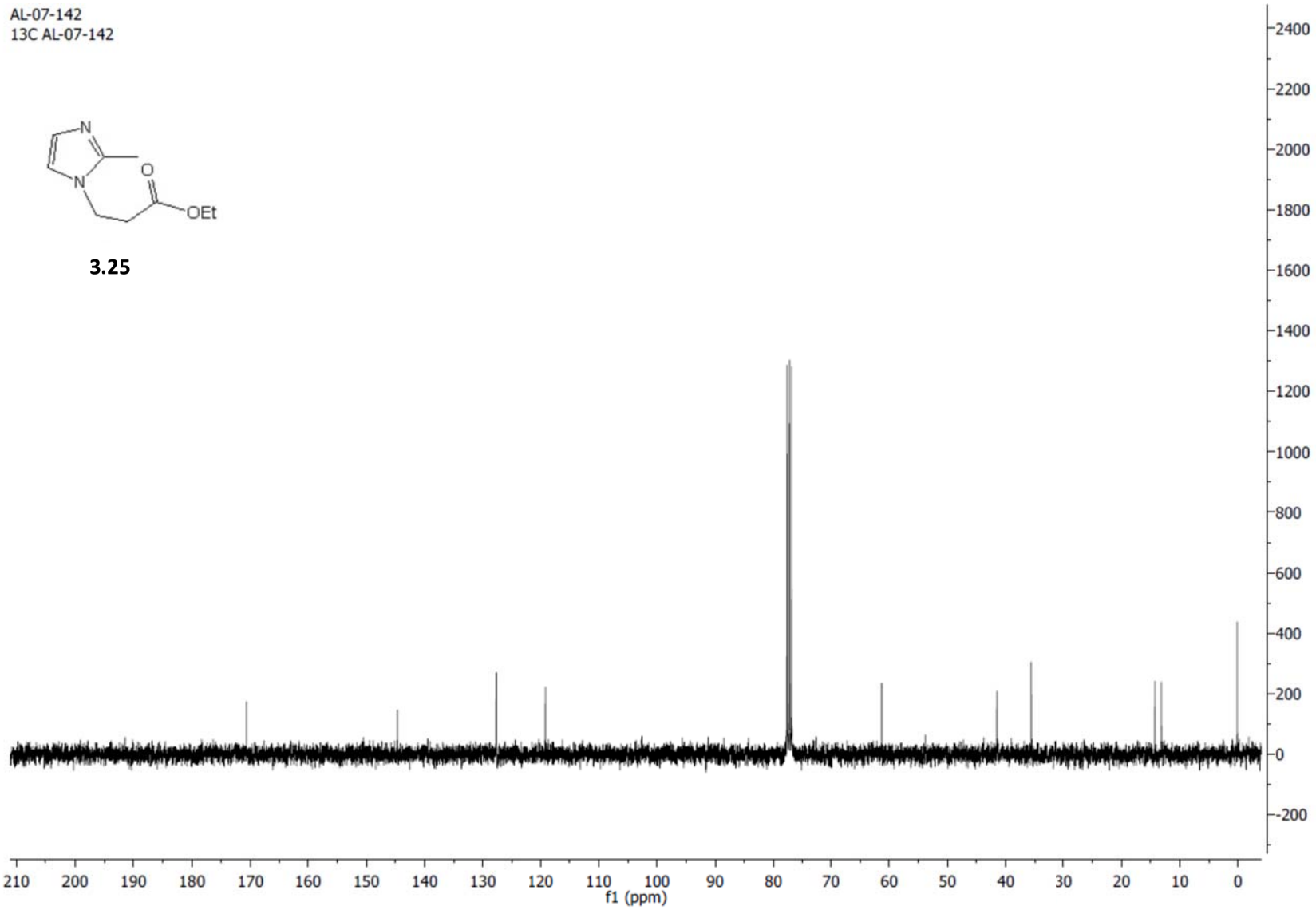

DF-02-148
1H DF-02-148
O
O
N
2.87
f1 (ppm)

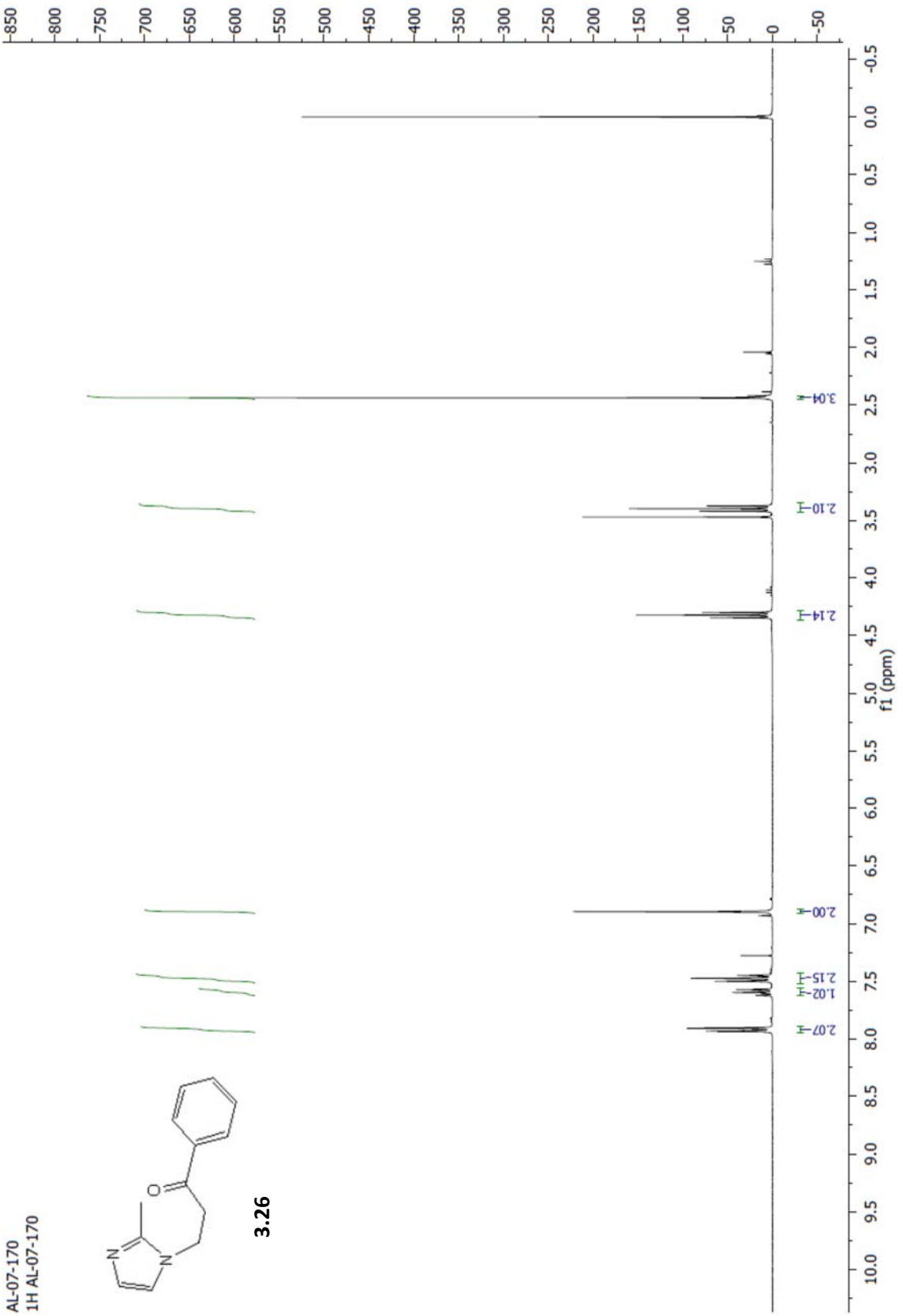

DF-02-148
13C DF-02-148
O
O
N
2.87
f1 (ppm)

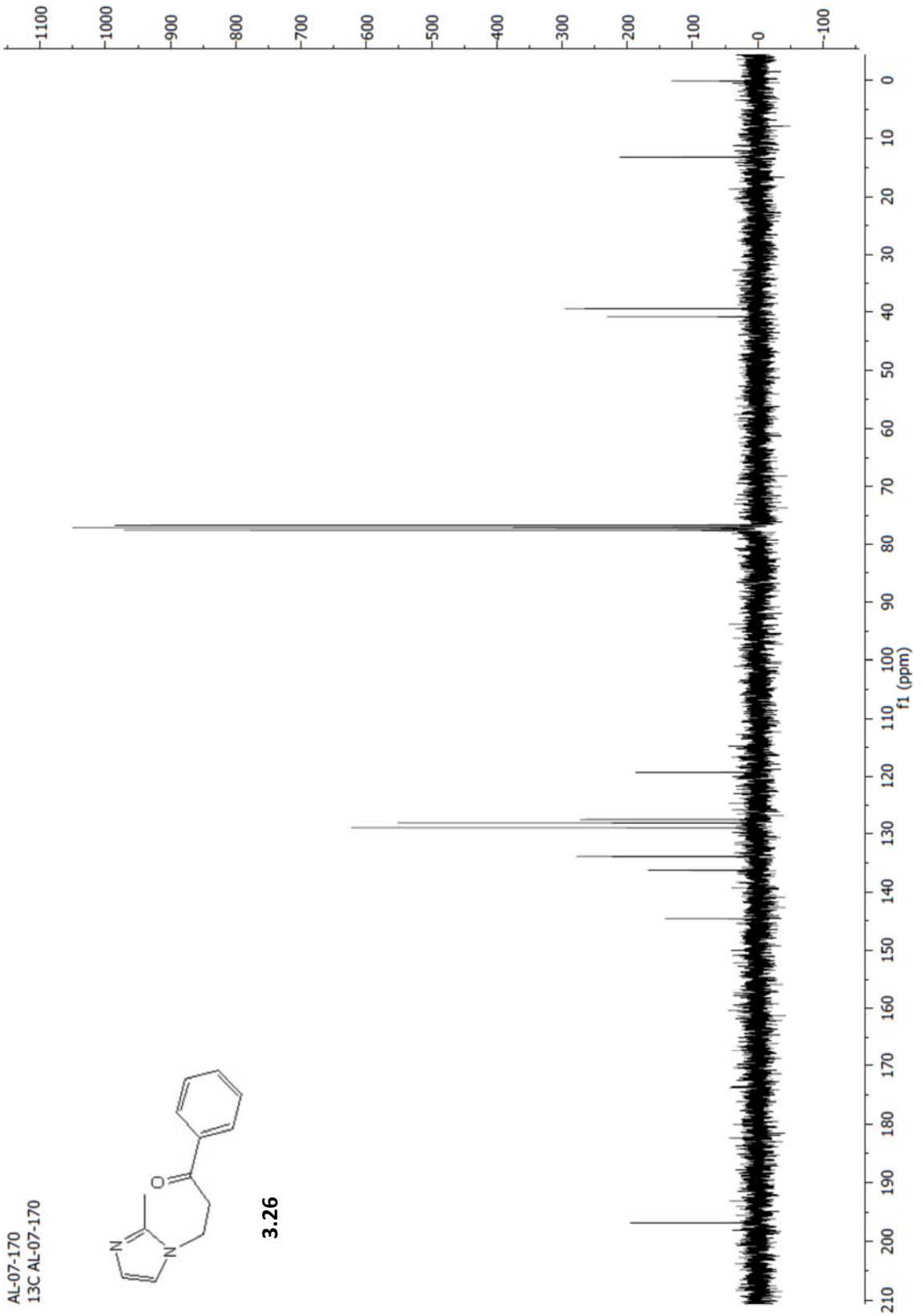

DF-02-152
1H DF-02-152
O
N
2.88
1.00
1.02
1.01
2.05
3.19
1.09
2.25
f1 (ppm)

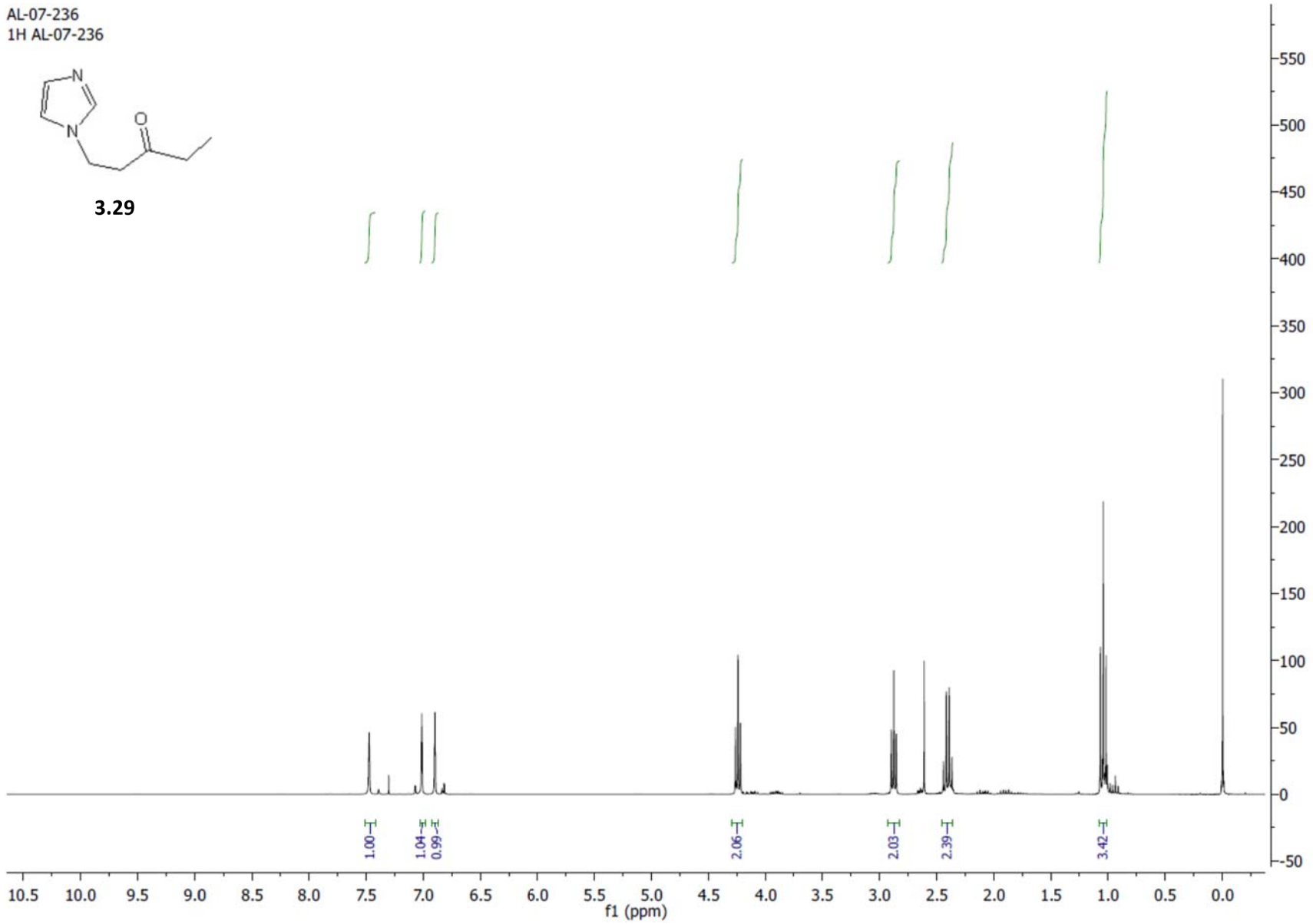

DF-02-152
13C DF-02-152
O
N
2.88
f1 (ppm)

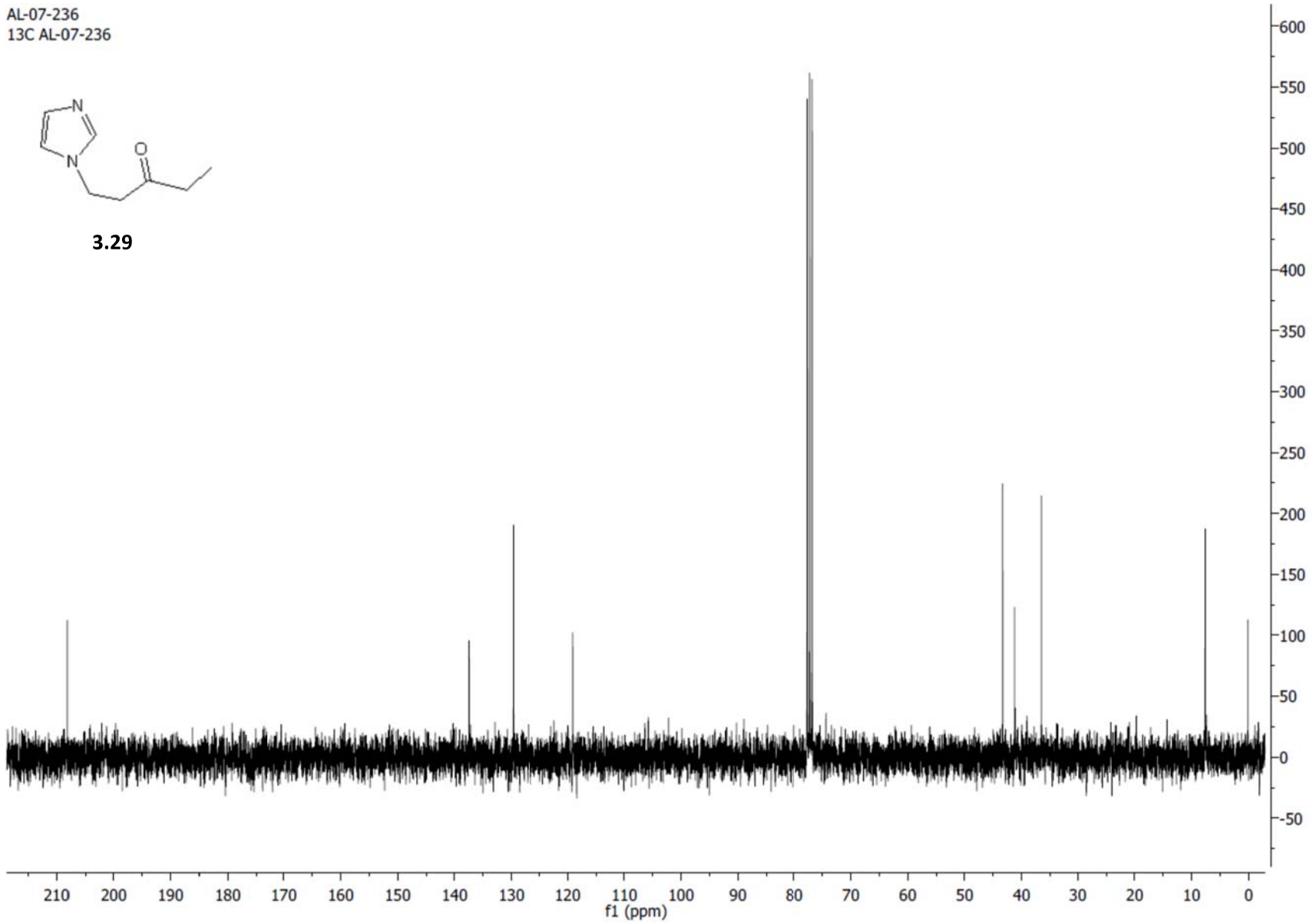

AL-07-142
1H AL-07-142
3.25
OEt
O
N
N
3.15
2.95
2.06
4.07
1.00
0.97
f1 (ppm)

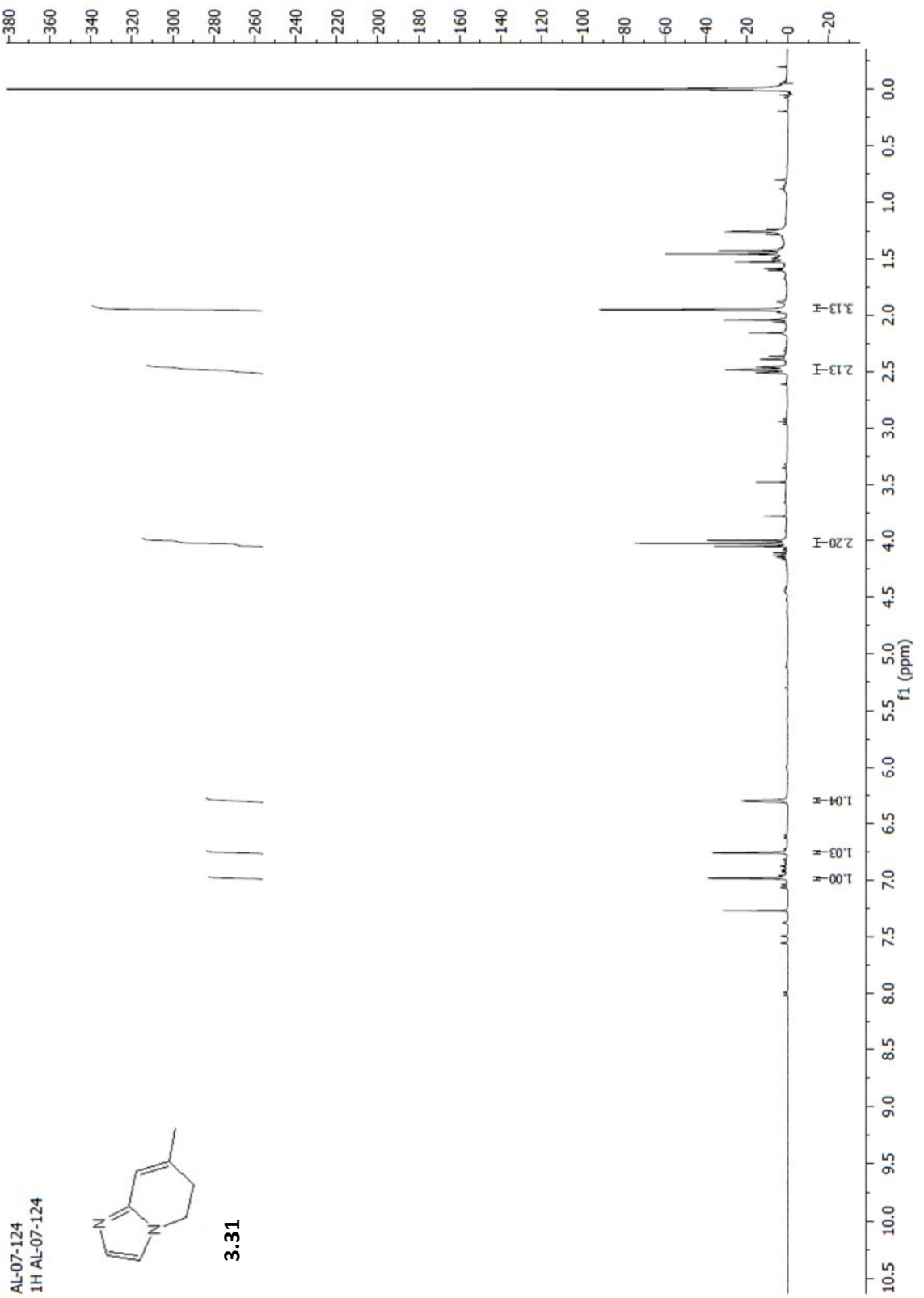

AL-07-142
13C AL-07-142
N
N
O
OEt
3.25
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

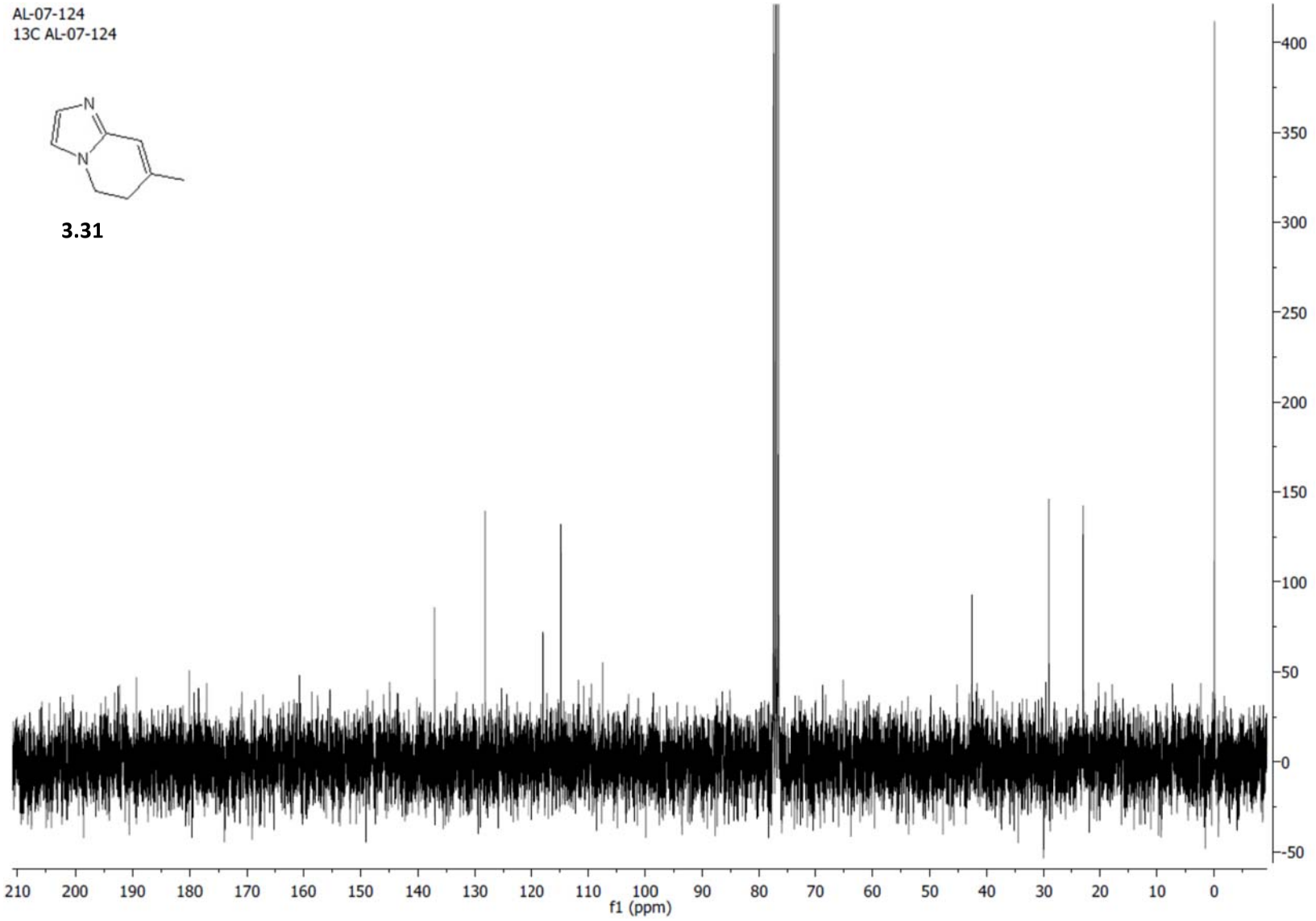

AL-07-170
1H AL-07-170
3.26
f1 (ppm)
3.04
2.10
2.14
2.00
2.15
1.02
2.07

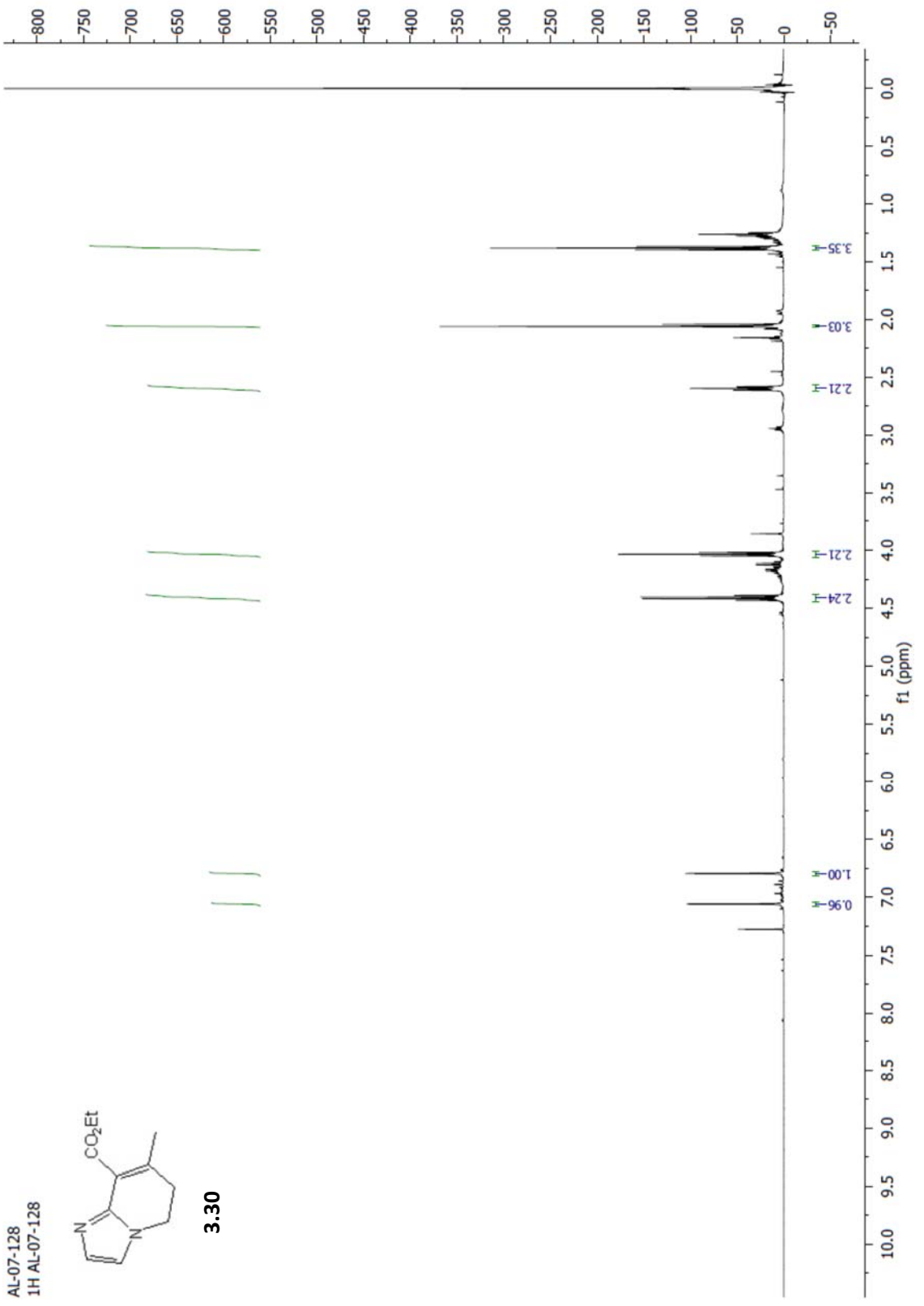

AL-07-170
13C AL-07-170
3.26
f1 (ppm)

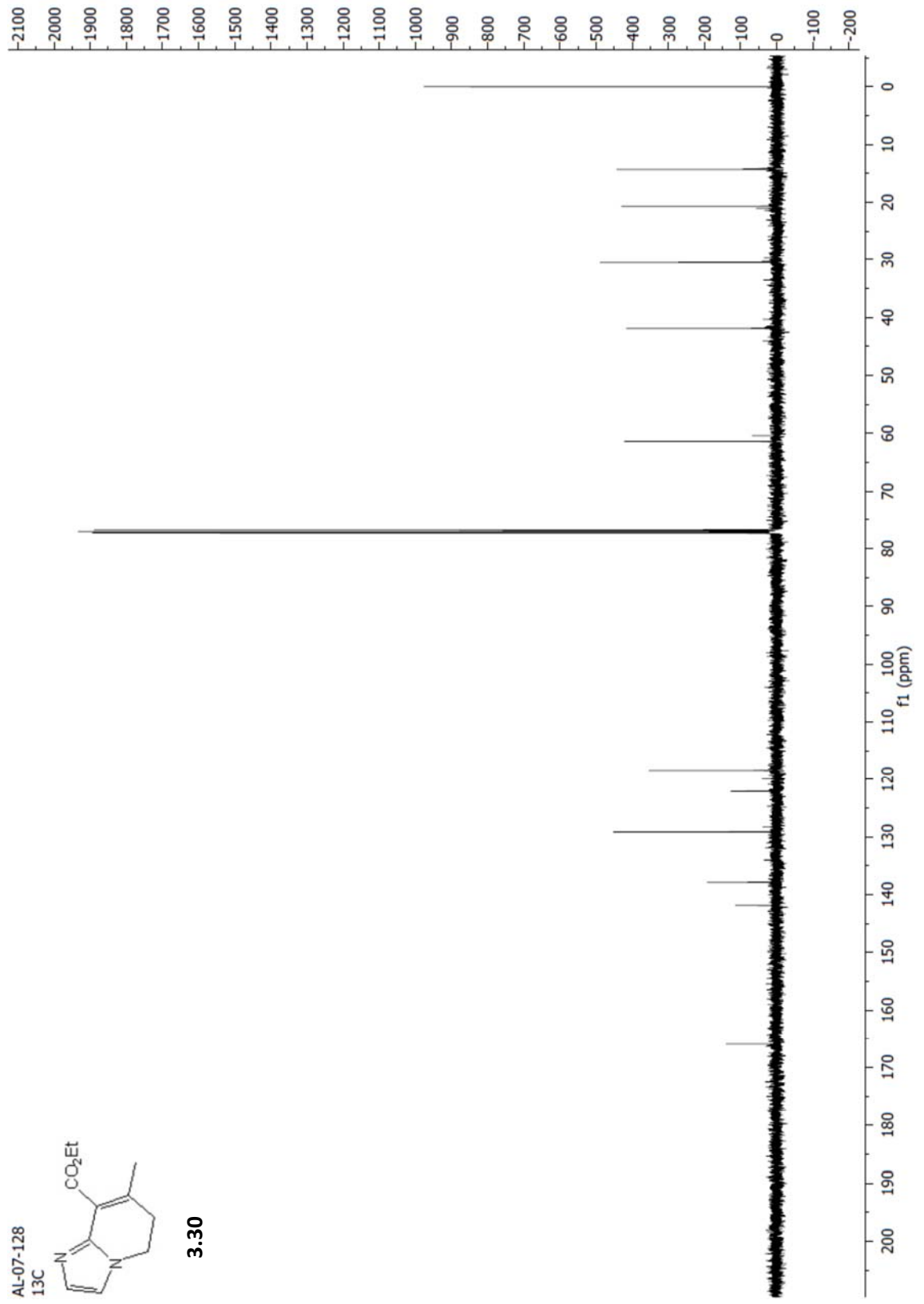

AL-07-236
1H AL-07-236
N
N
O
3.29
1.00
1.04
0.99
2.06
2.03
2.39
3.42
f1 (ppm)

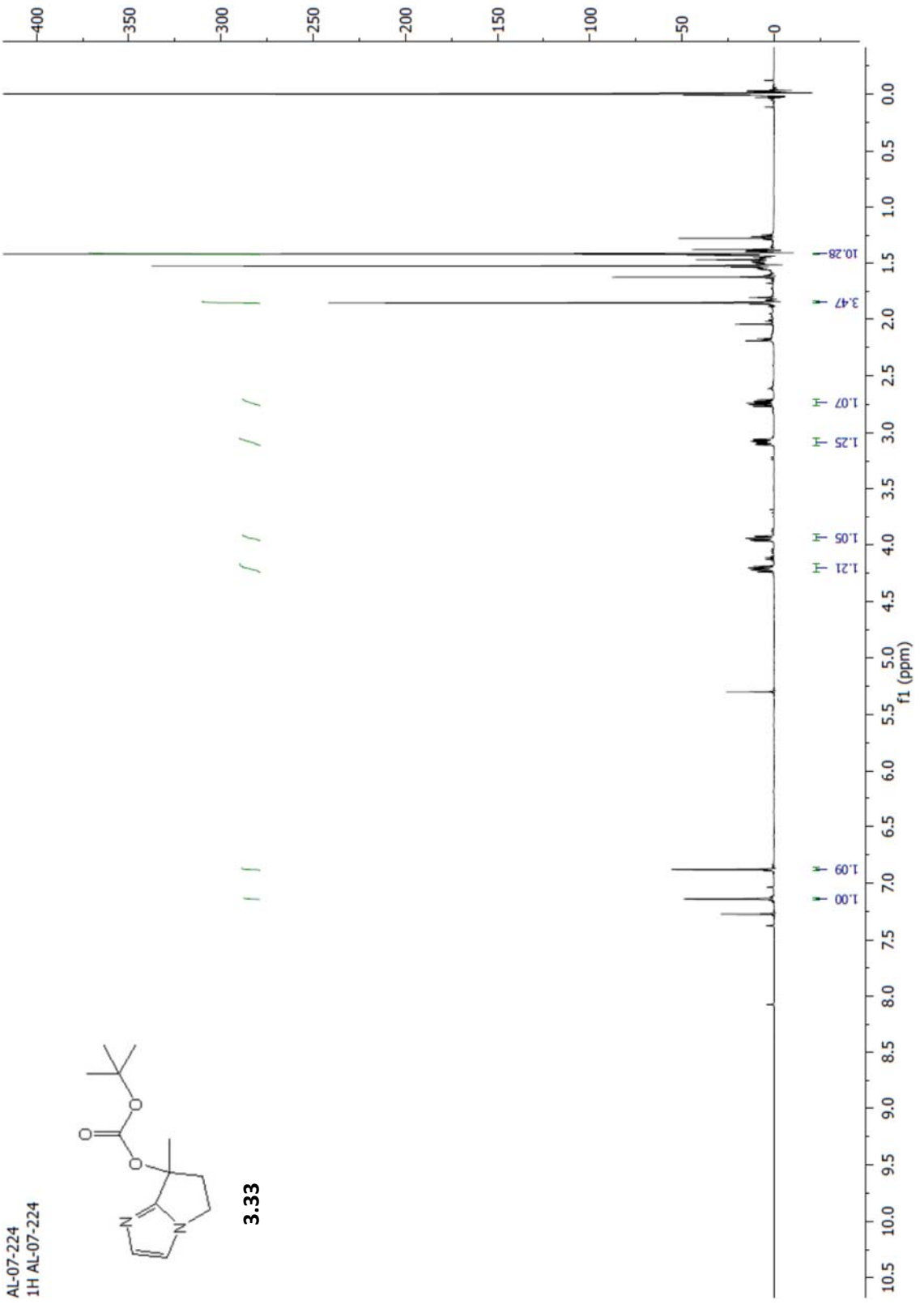

AL-07-236
13C AL-07-236
N
N
O
3.29
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

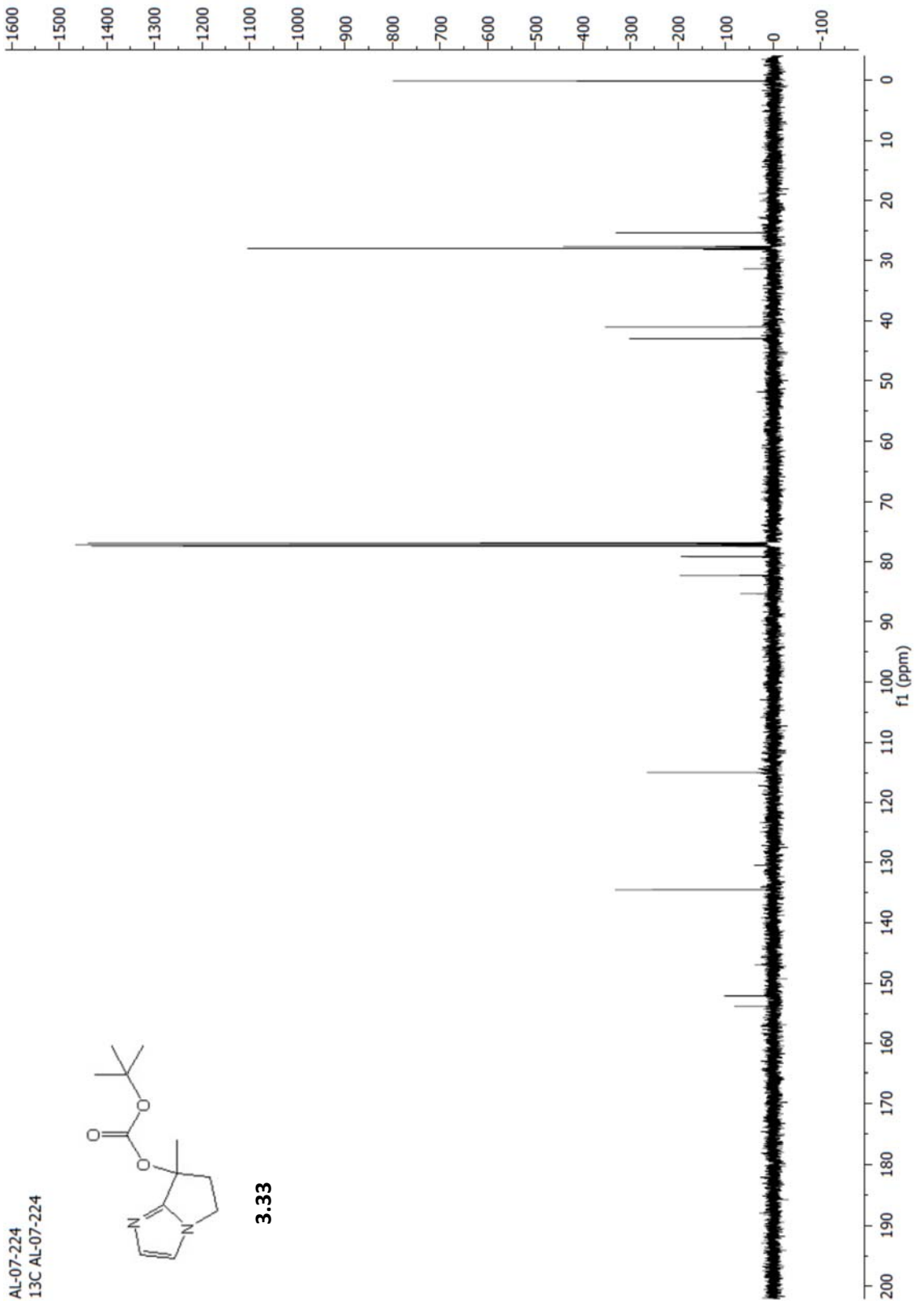

AL-07-124
1H AL-07-124
3.31
3.13-H
2.13-H
2.20-H
1.04-H
1.03-H
1.00-H
f1 (ppm)

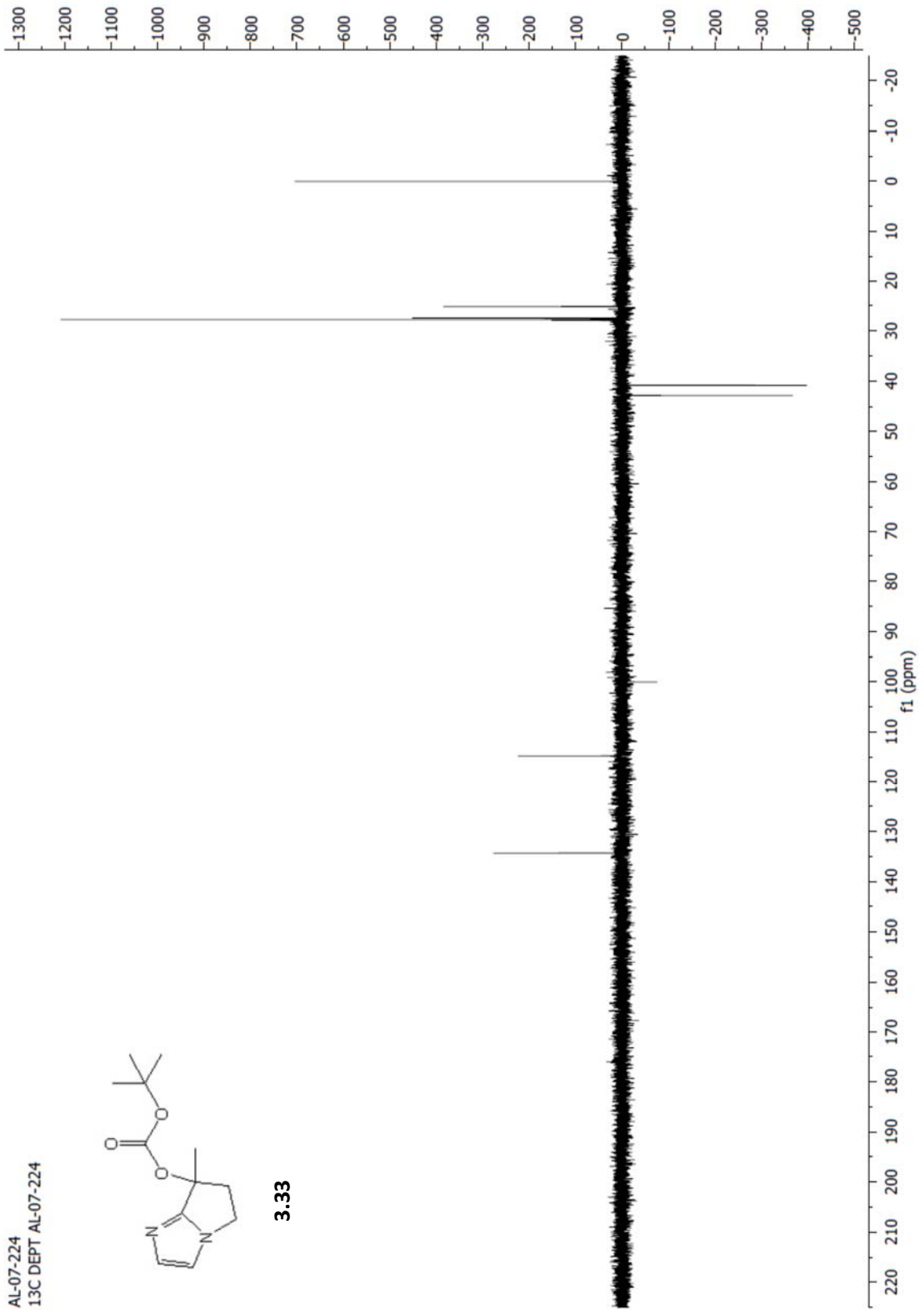

AL-07-124
13C AL-07-124
N
N
3.31
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

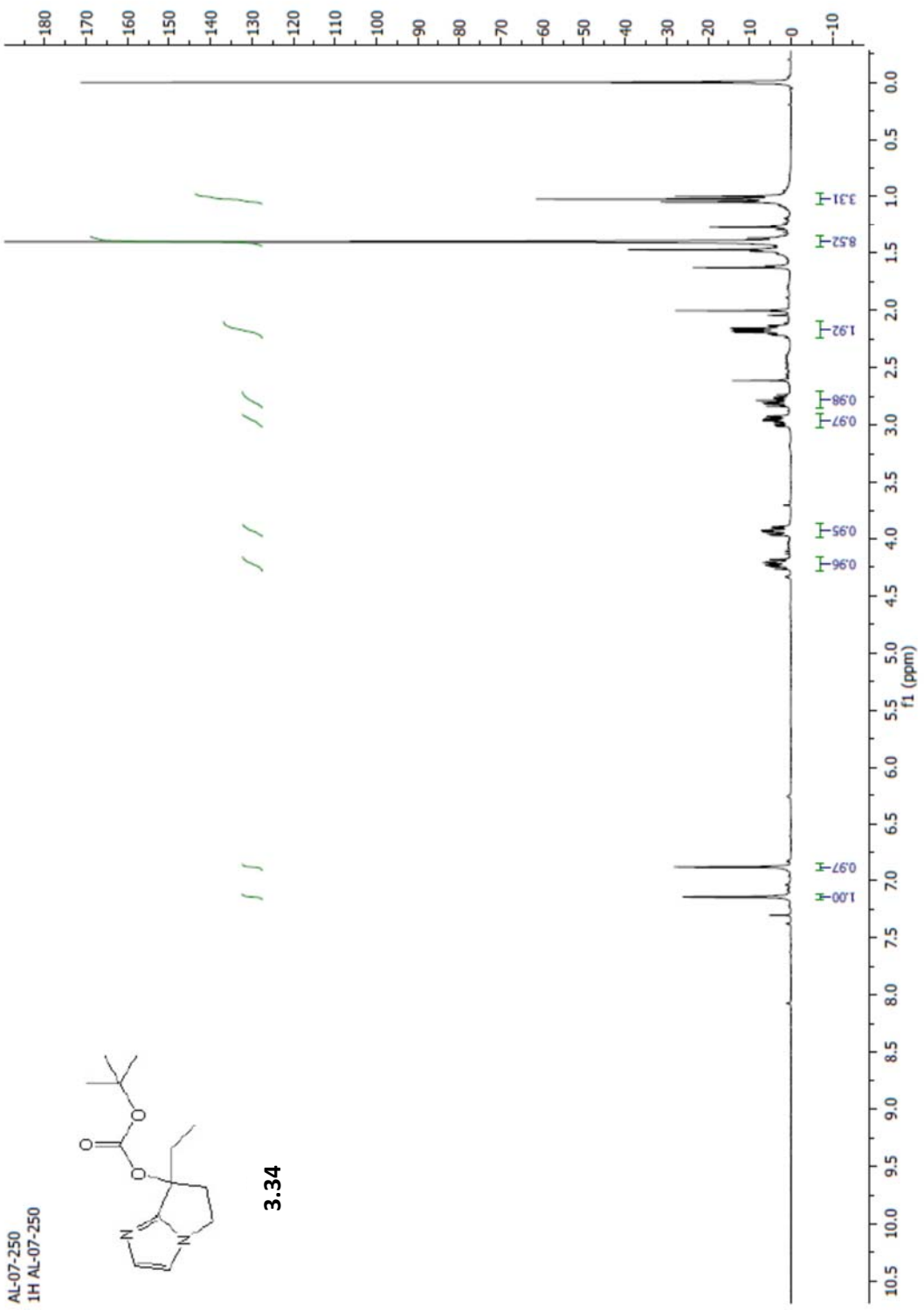

AL-07-128
1H AL-07-128
CO2Et
3.30
3.35
3.03
2.21
2.21
2.24
1.00
0.96
f1 (ppm)

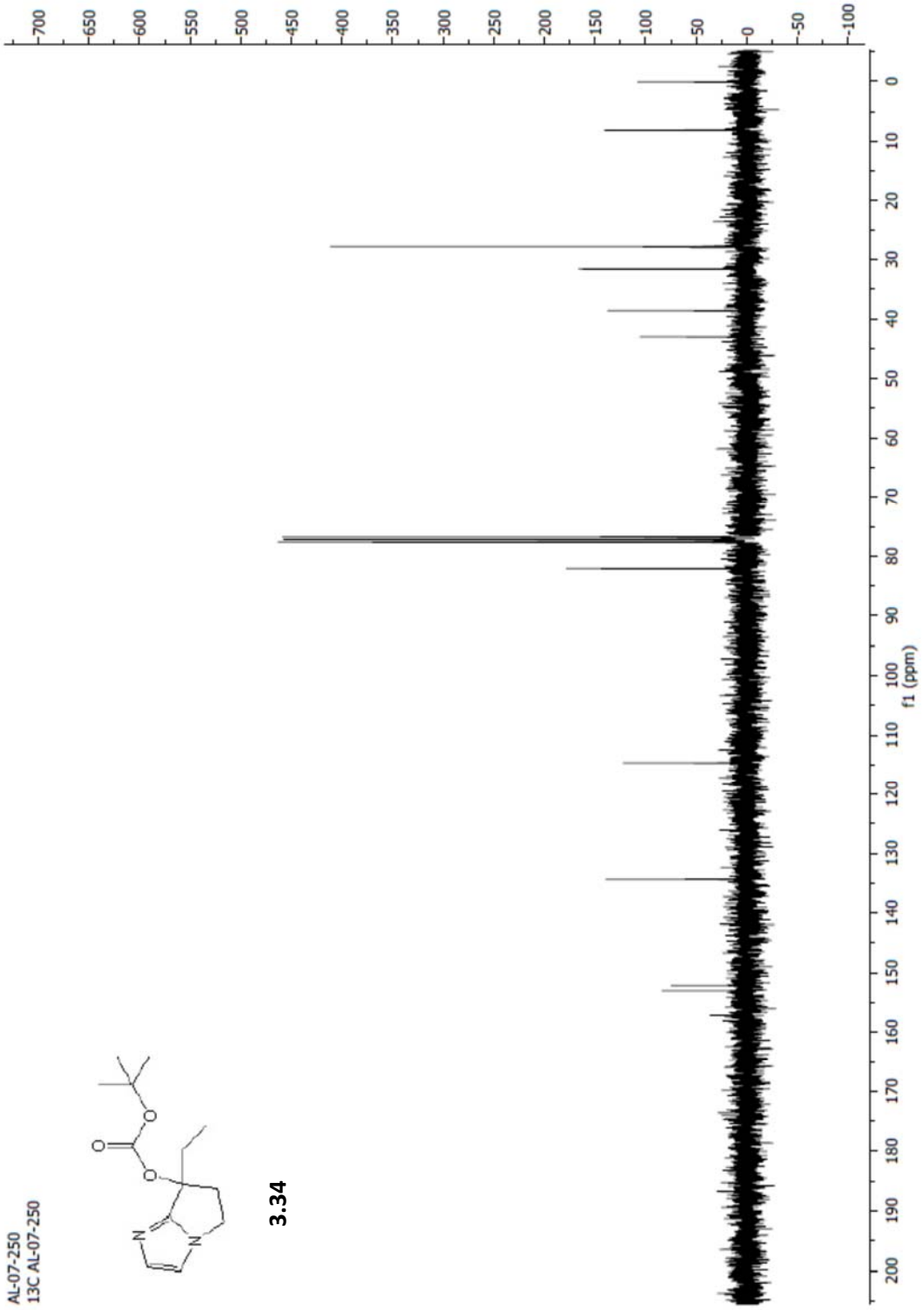

AL-07-128
13C
CO2Et
N
N
3.30
f1 (ppm)

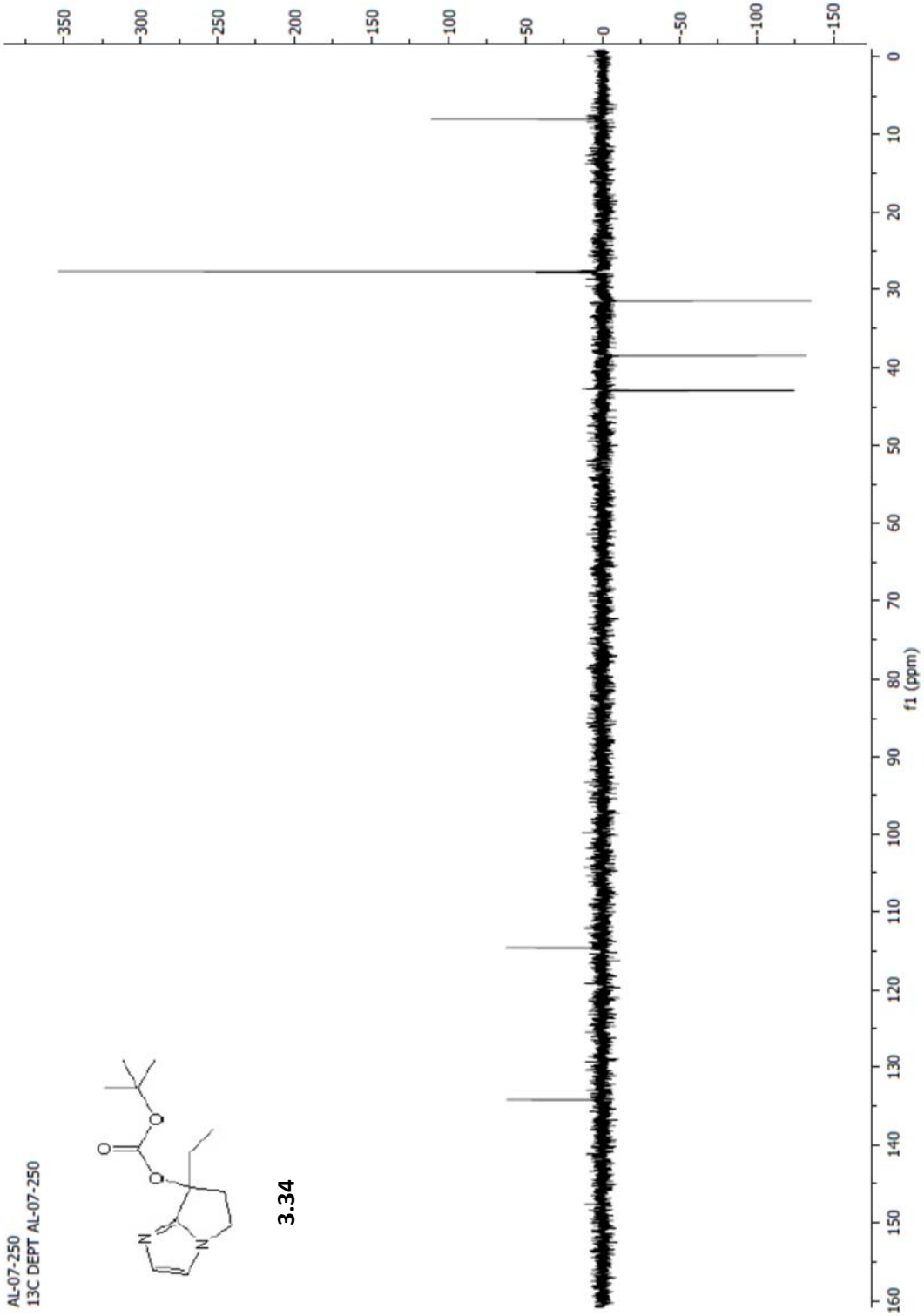

AL-07-224
1H AL-07-224
3.33
10.28
3.47
1.07
1.25
1.05
1.21
1.09
1.00
f1 (ppm)


AL-07-224
13C AL-07-224
3.33
f1 (ppm)

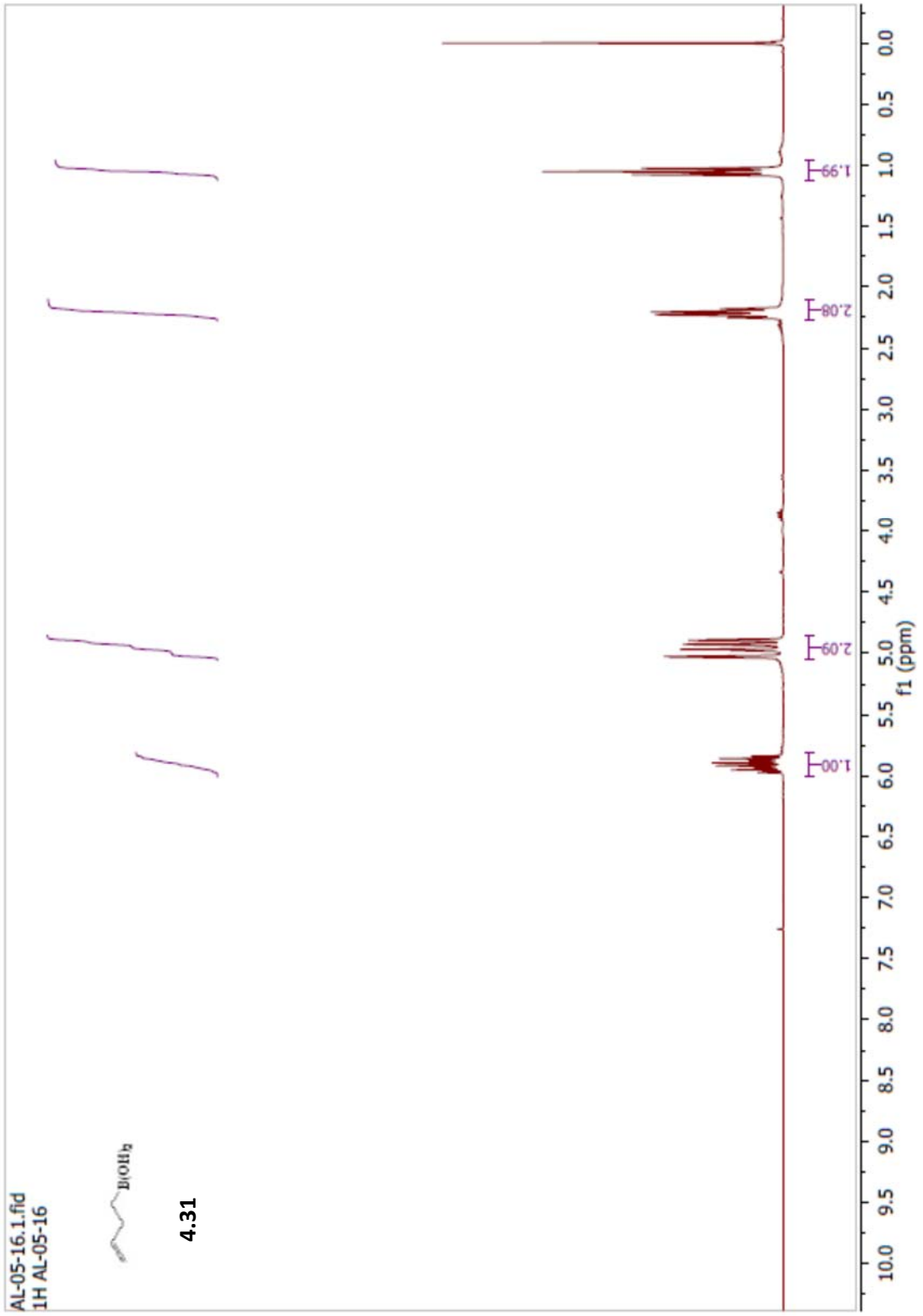

AL-07-224
13C DEPT AL-07-224
3.33
f1 (ppm)

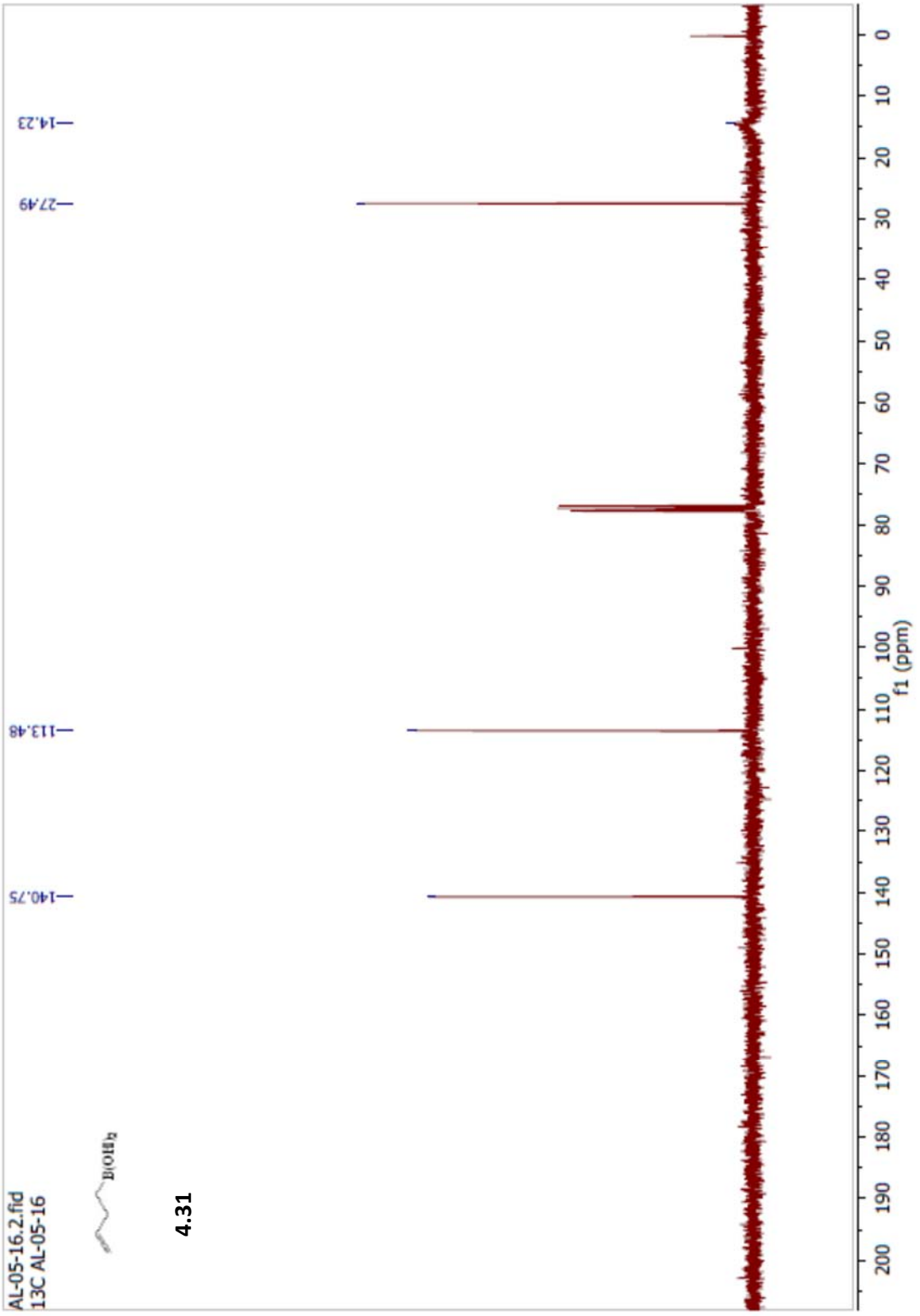

AL-07-250
1H AL-07-250
3.34
f1 (ppm)
3.31
8.52
1.92
0.98
0.97
0.95
0.96
0.97
1.00

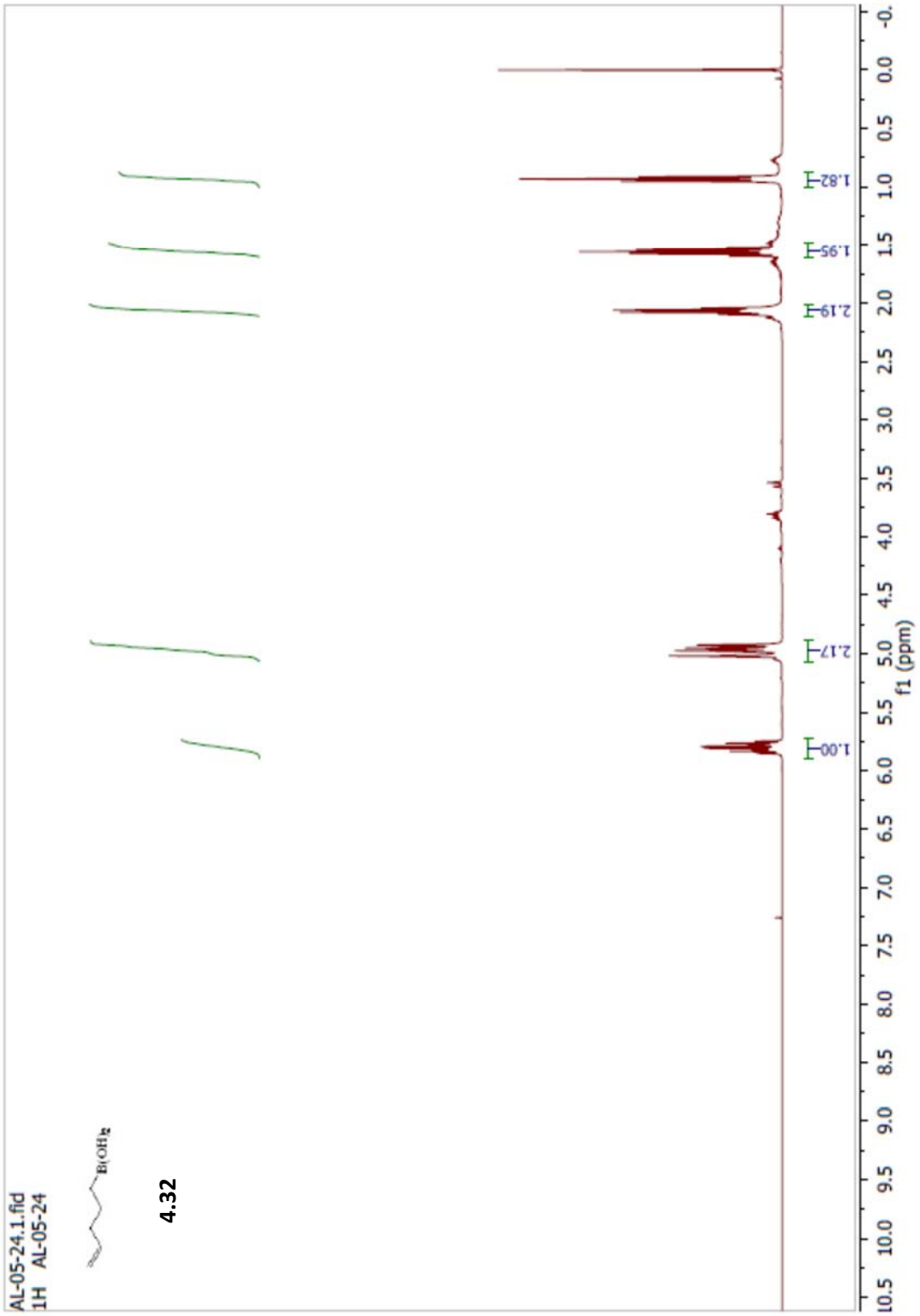

AL-07-250
13C AL-07-250
3.34
f1 (ppm)

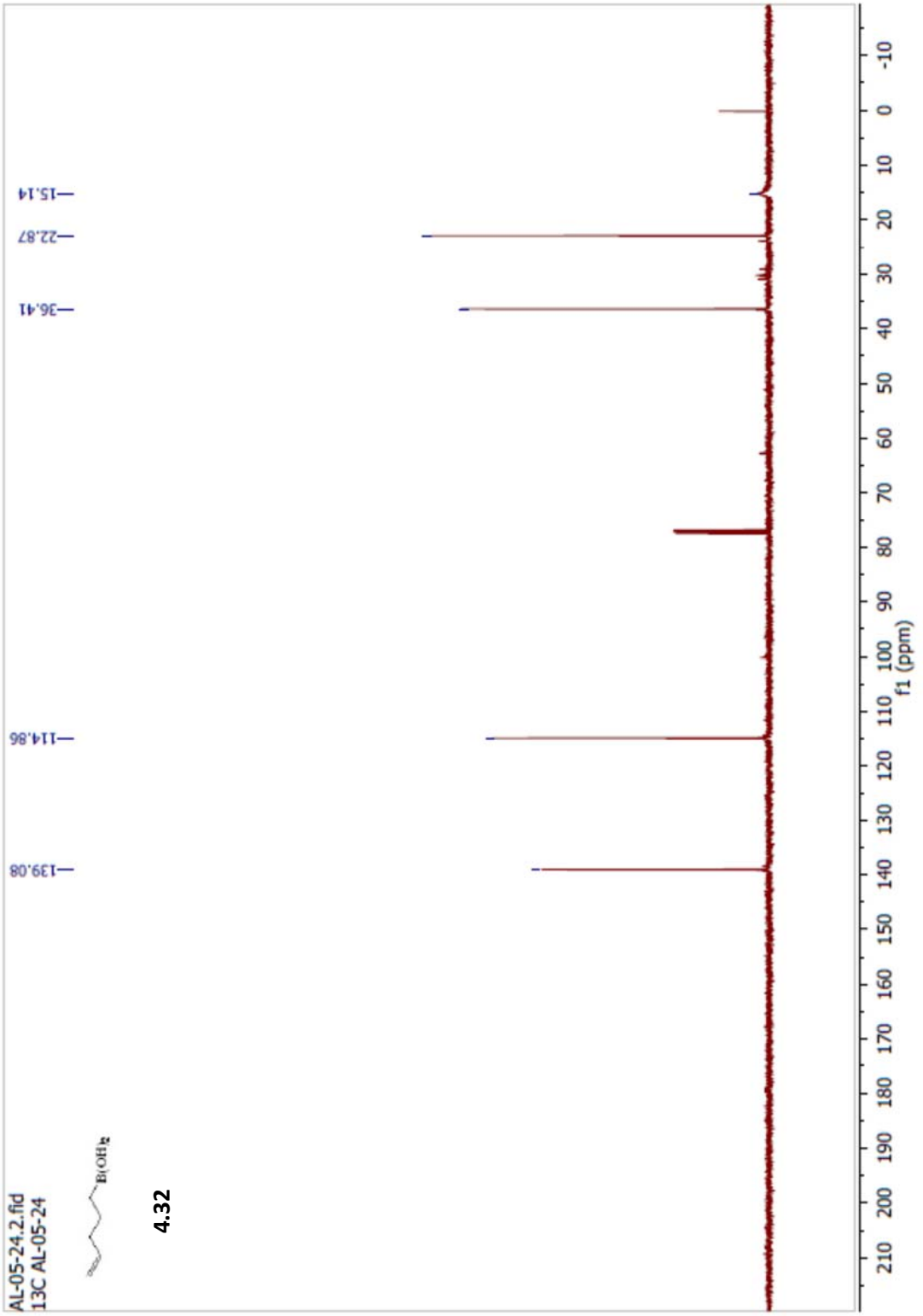


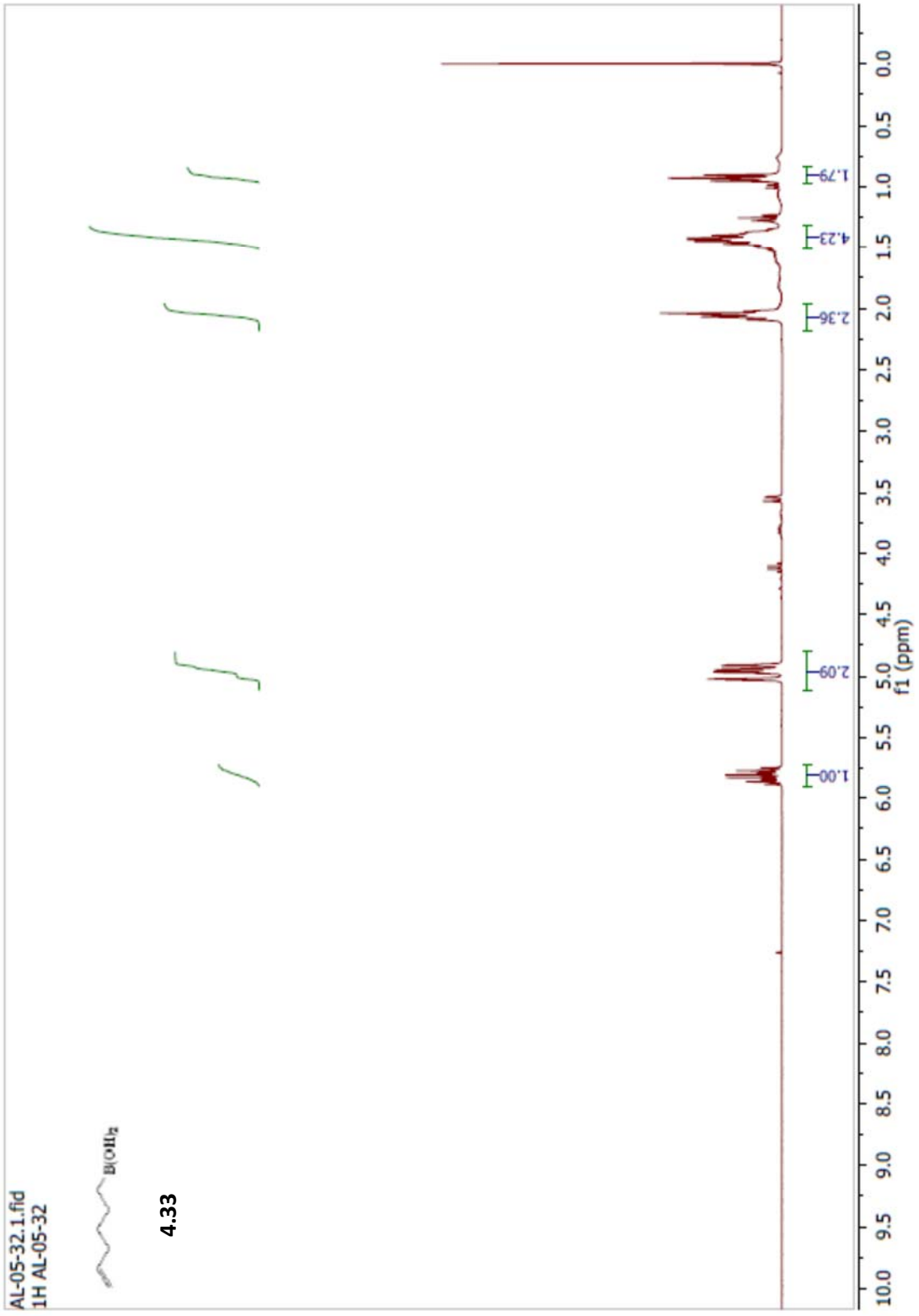
3.34

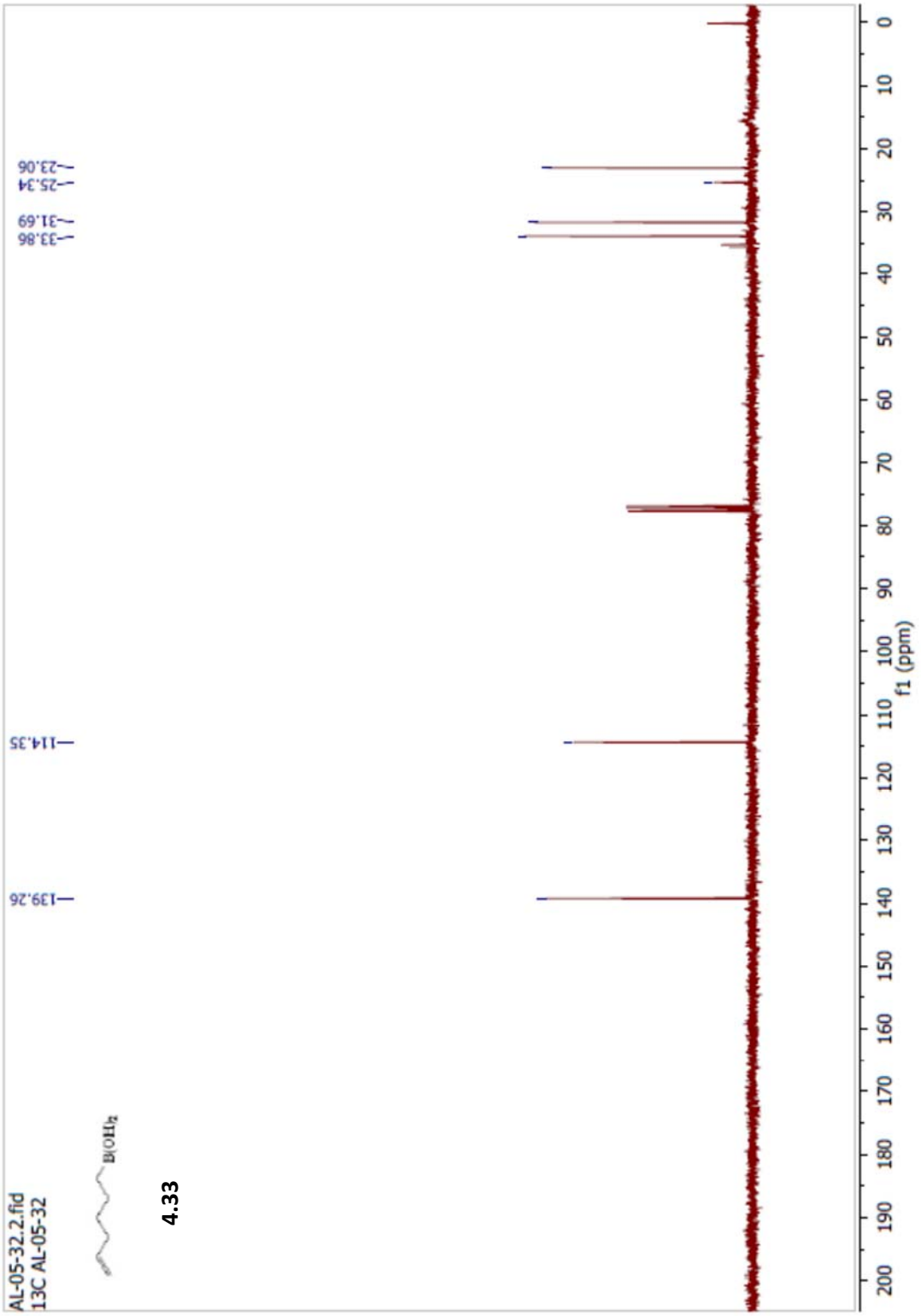

AL-05-16.1.fid
1H AL-05-16
B(OH)2
4.31
1.99
2.08
2.09
1.00
f1 (ppm)

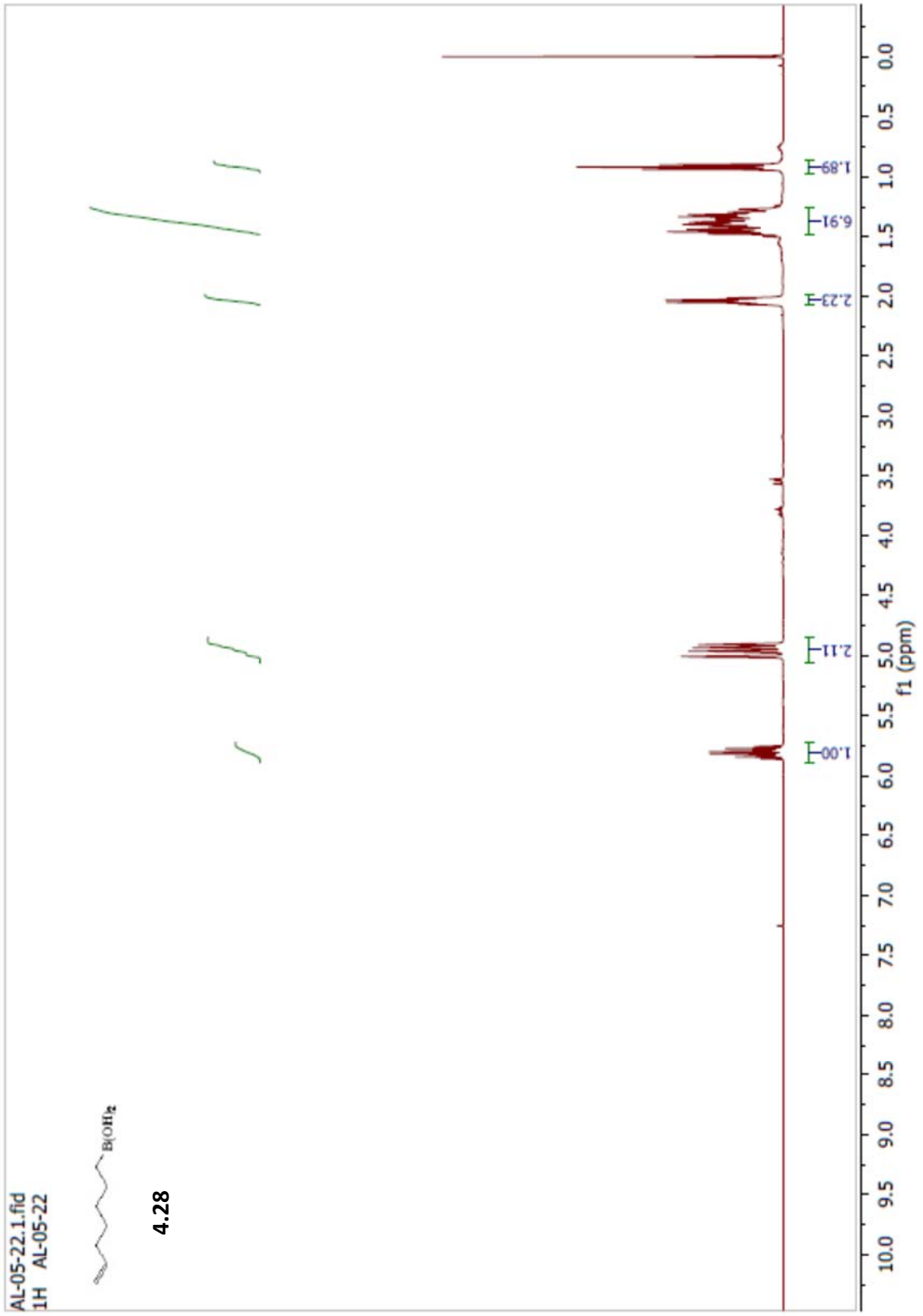

AL-05-16.2.fid
13C AL-05-16
4.31
140.75
113.48
27.49
14.23
f1 (ppm)

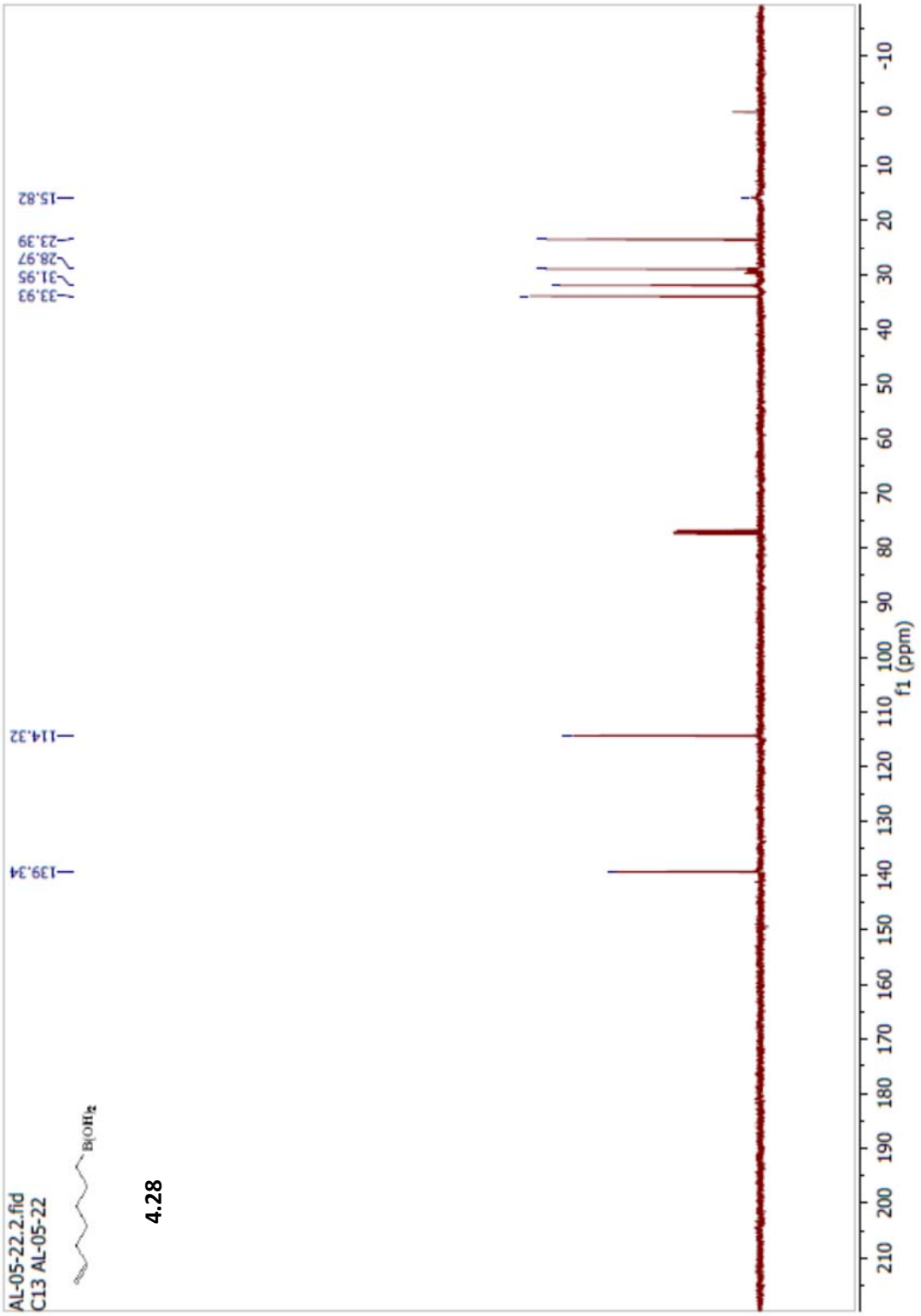

AL-05-24.1.fid
1H AL-05-24
4.32
1.00
2.17
2.19
1.95
1.82
f1 (ppm)

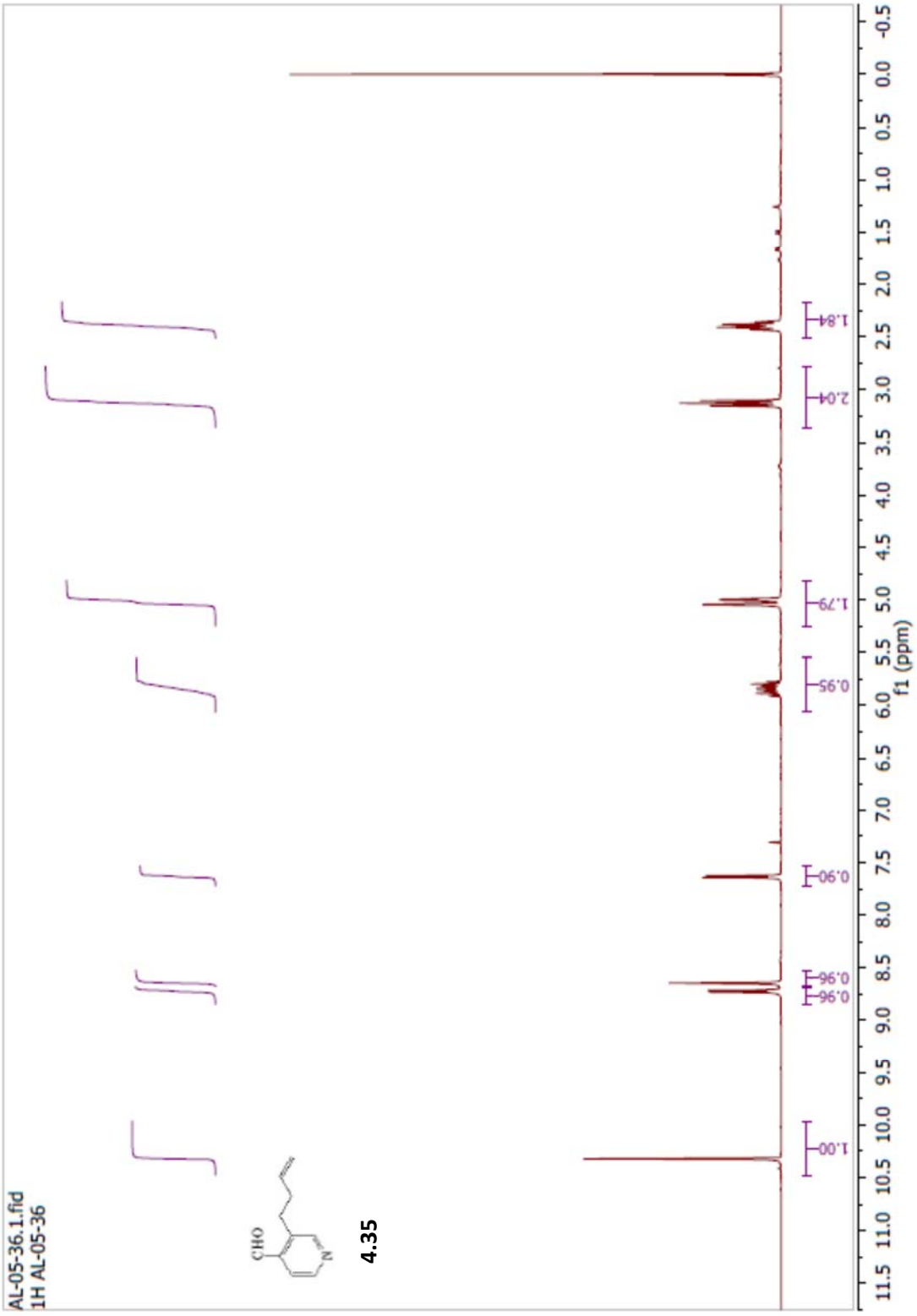

AL-05-24.2.fid
13C AL-05-24
4.32
139.08
114.86
36.41
22.87
15.14
f1 (ppm)

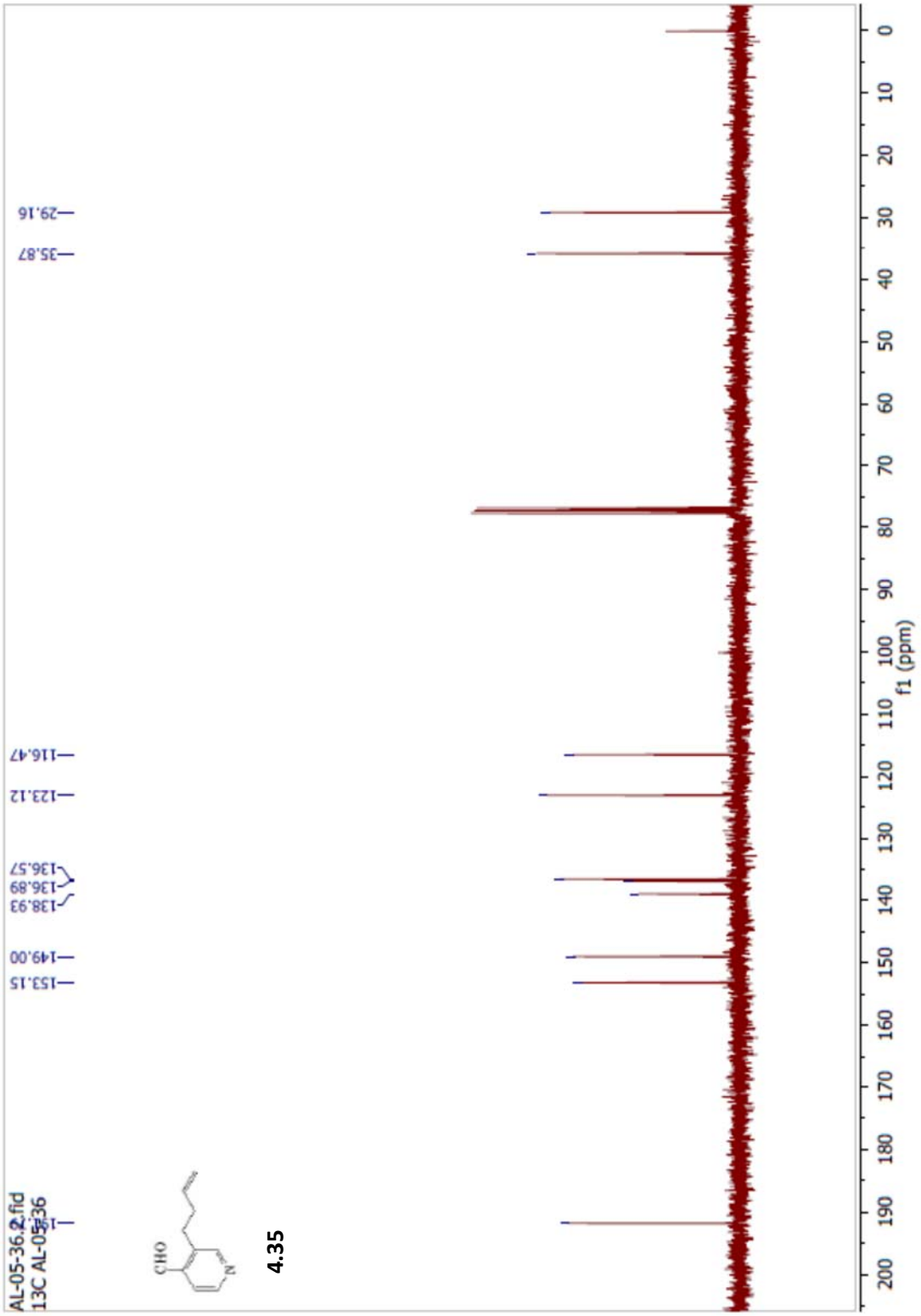

AL-05-32.1.fid
1H AL-05-32
B(OH)2
4.33
1.00
2.09
2.36
4.23
1.79
f1 (ppm)

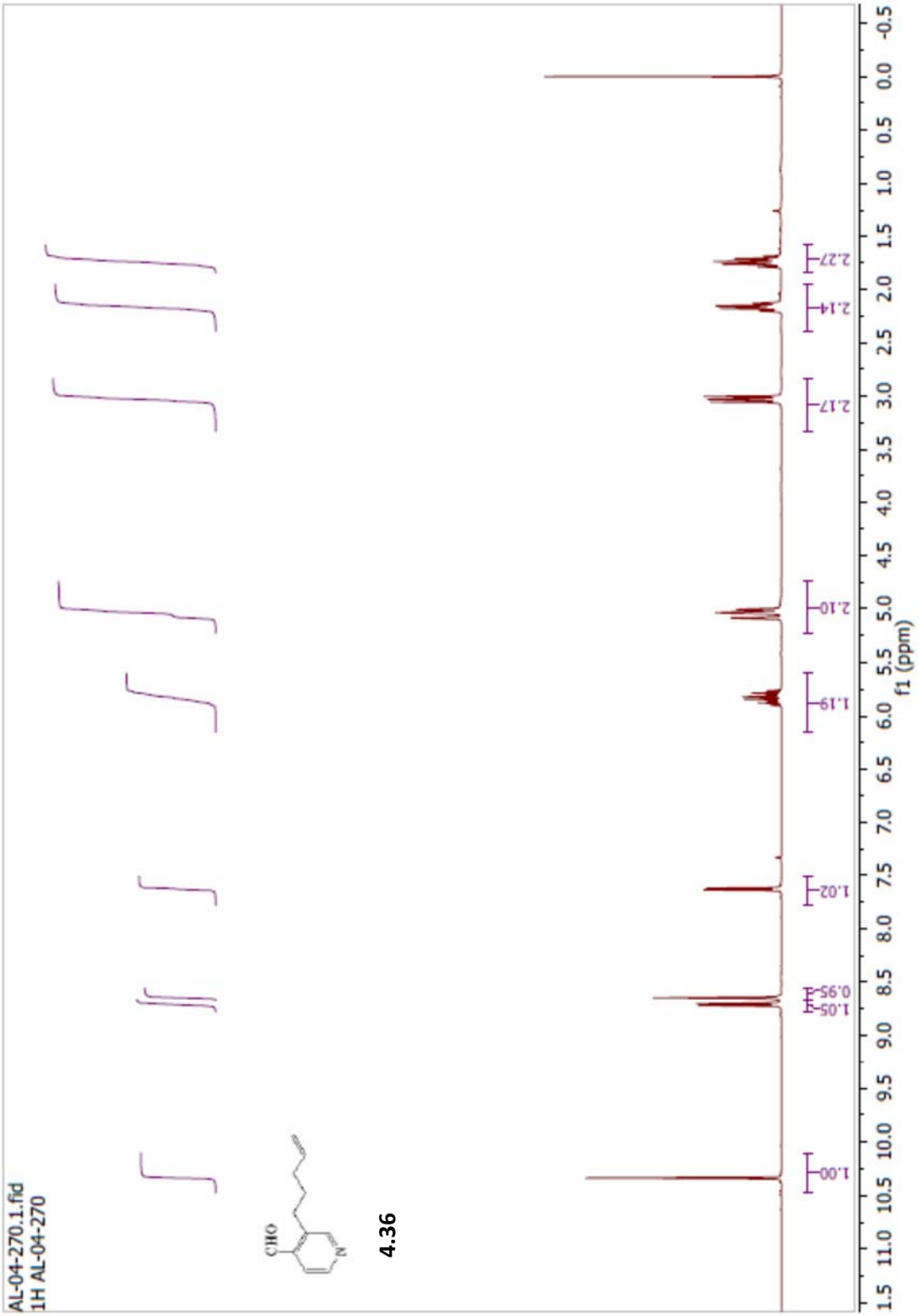

AL-05-32.2.fid
13C AL-05-32
4.33
139.26
114.35
33.86
31.69
25.34
23.06
f1 (ppm)

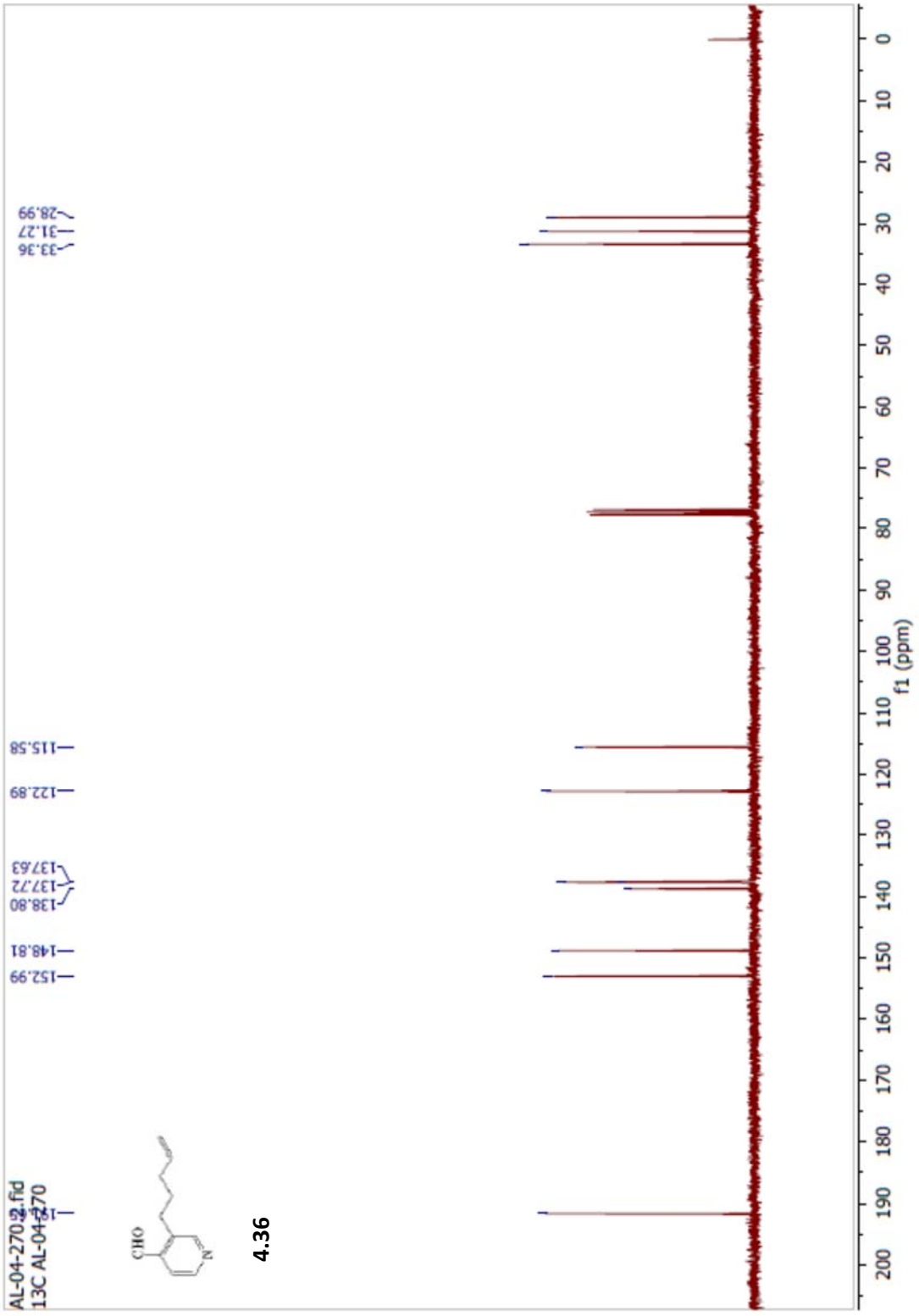

AL-05-22.1.fid
1H AL-05-22
B(OH)2
4.28
1.89
6.91
2.23
2.11
1.00
f1 (ppm)

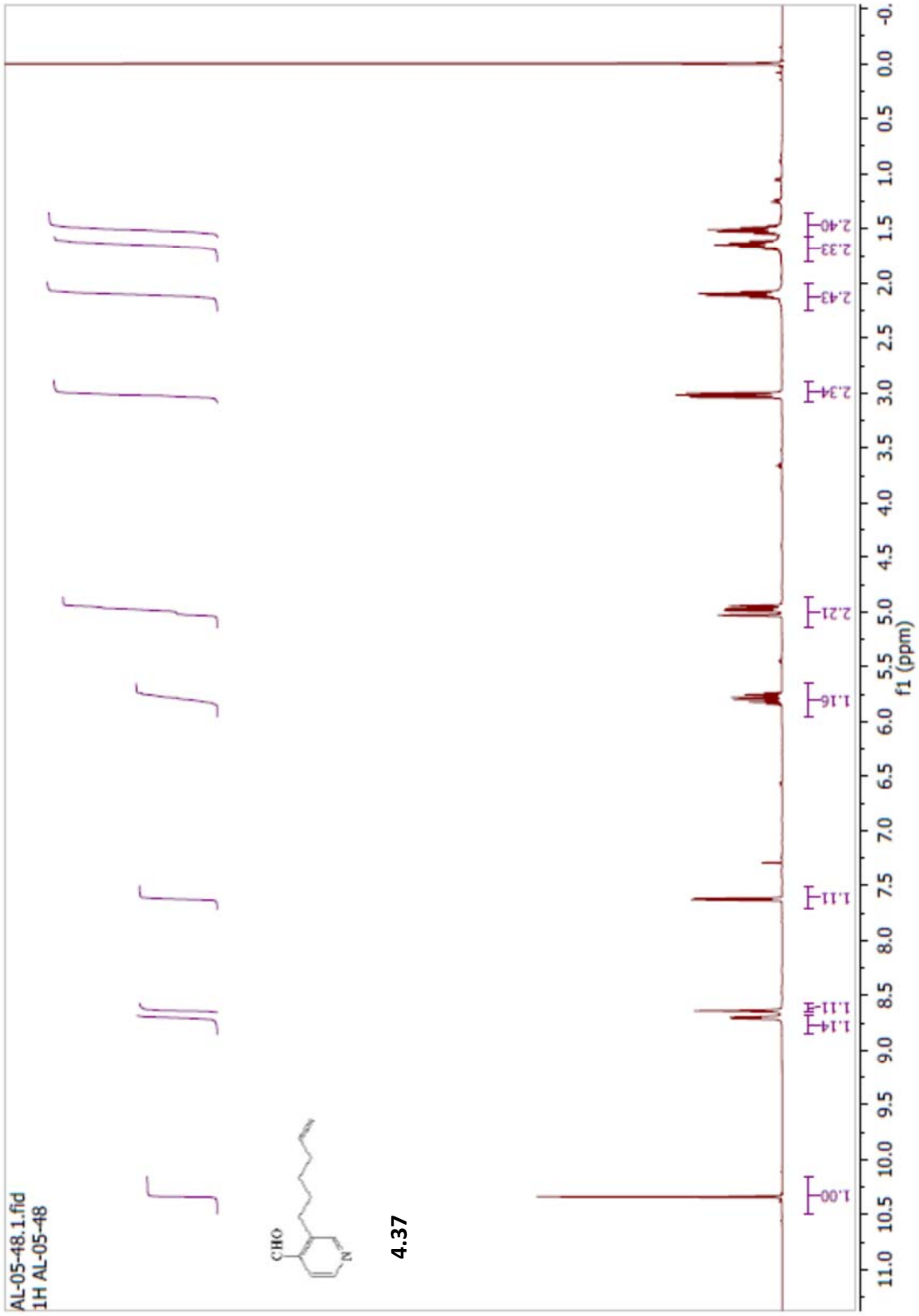

AL-05-22.2.fid
C13 AL-05-22
B(OH)2
4.28
139.34
114.32
33.93
31.95
28.97
23.39
15.82
f1 (ppm)

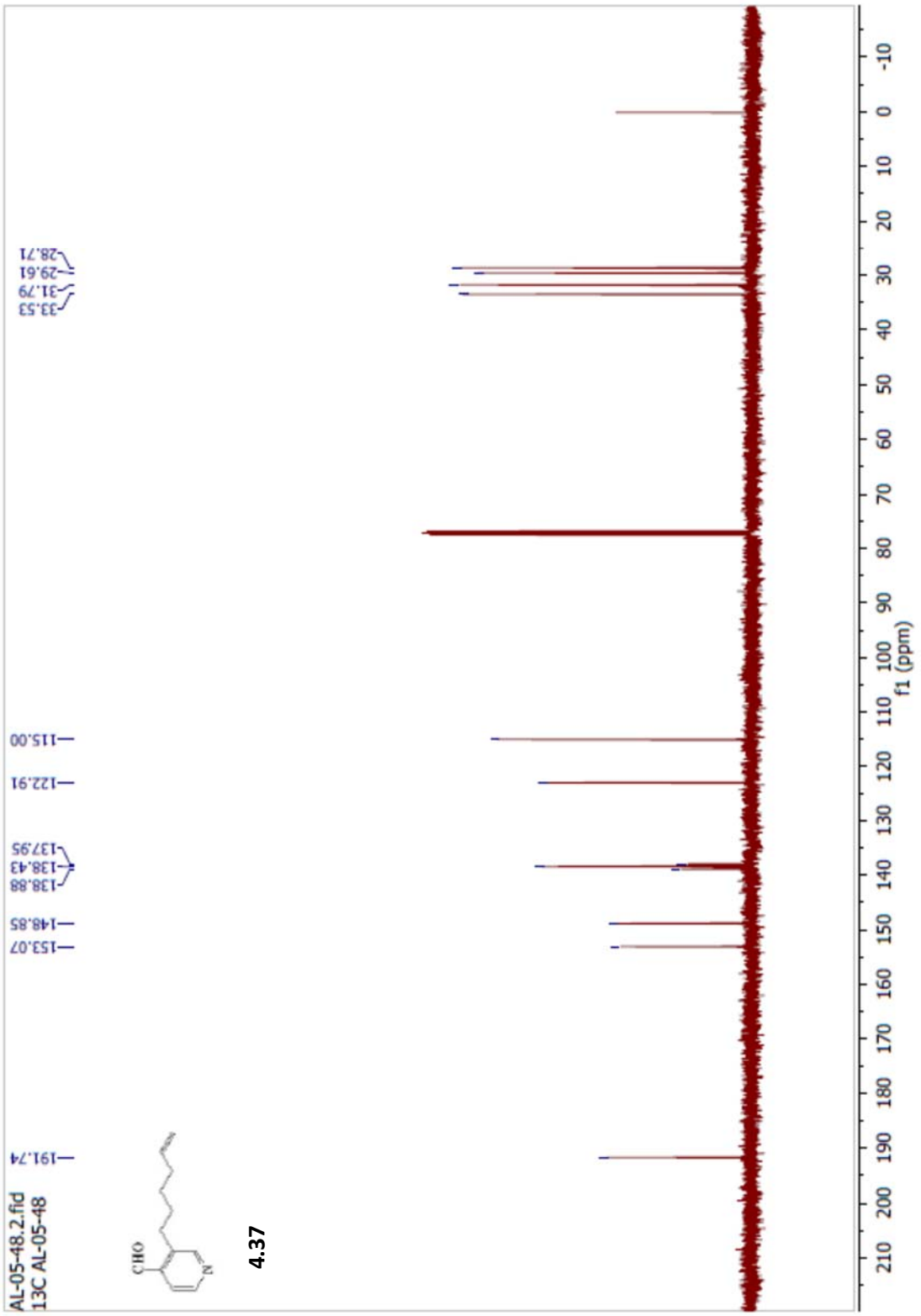

AL-05-36.1.fid
1H AL-05-36
CHO
N
4.35
1.00
0.96
0.96
0.90
0.95
1.79
2.04
1.84
f1 (ppm)

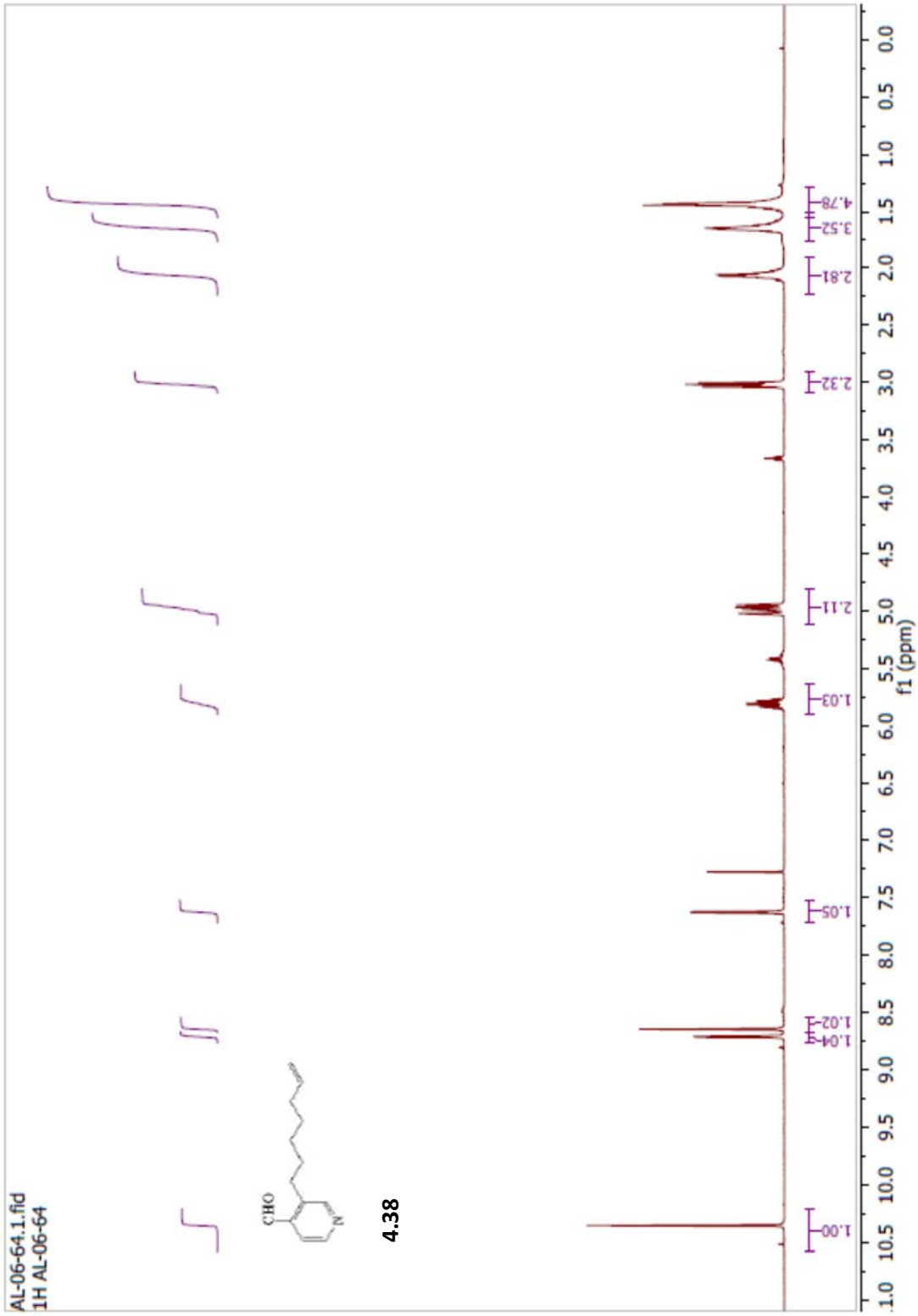

AL-05-36-2.fid
13C AL-05-36
193.36
153.15
149.00
138.93
136.89
136.57
123.12
116.47
35.87
29.16
CHO
N
4.35
f1 (ppm)

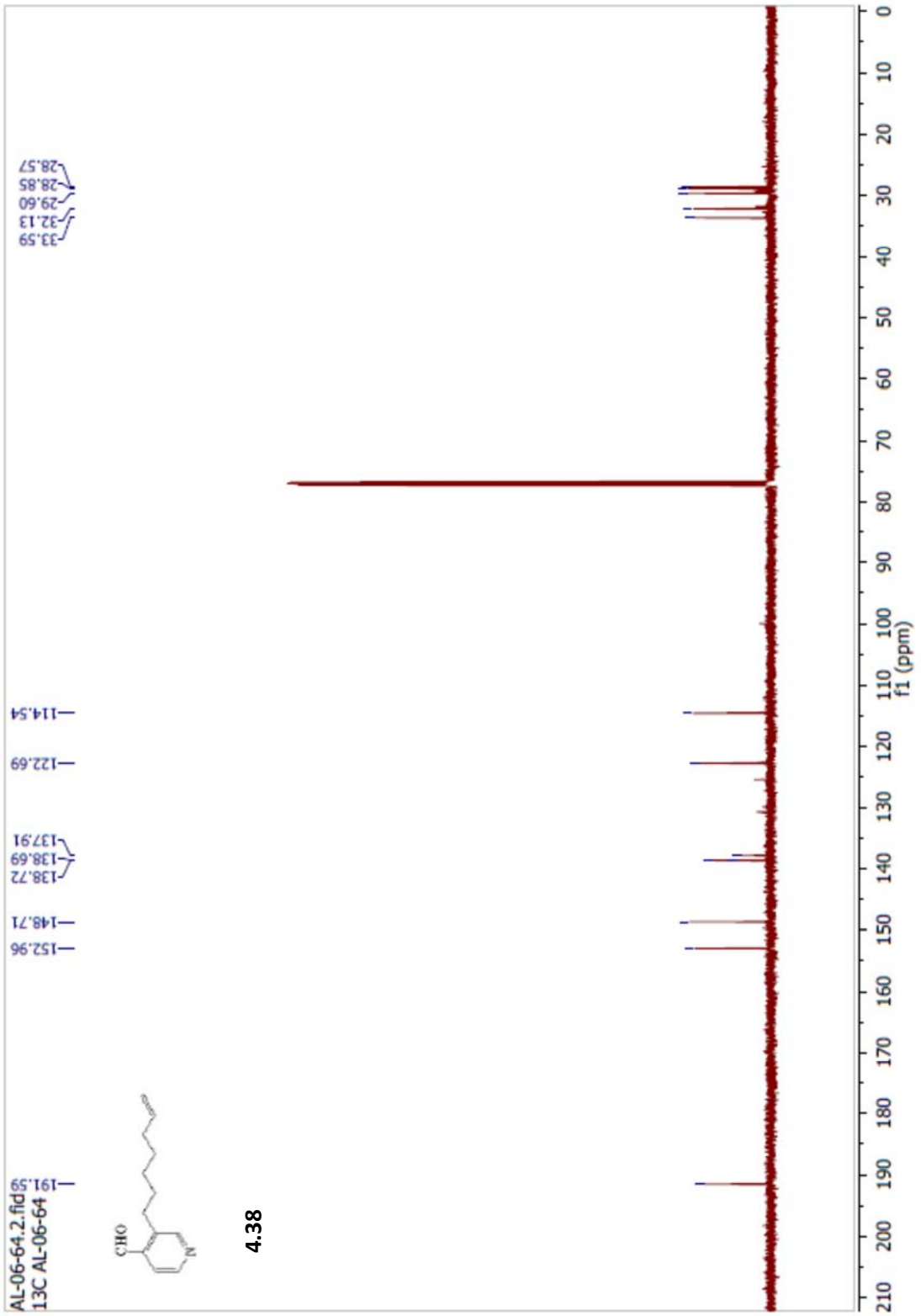

AL-04-270.1.fid
1H AL-04-270
CHO
N
4.36
1.00
0.95
1.05
1.02
1.19
2.10
2.17
2.14
2.27
f1 (ppm)


AL-04-270-2.fid
13C AL-04-270
193.97
152.99
148.81
138.80
137.72
137.63
122.89
115.58
33.36
31.27
28.99
CHO
N
4.36
f1 (ppm)

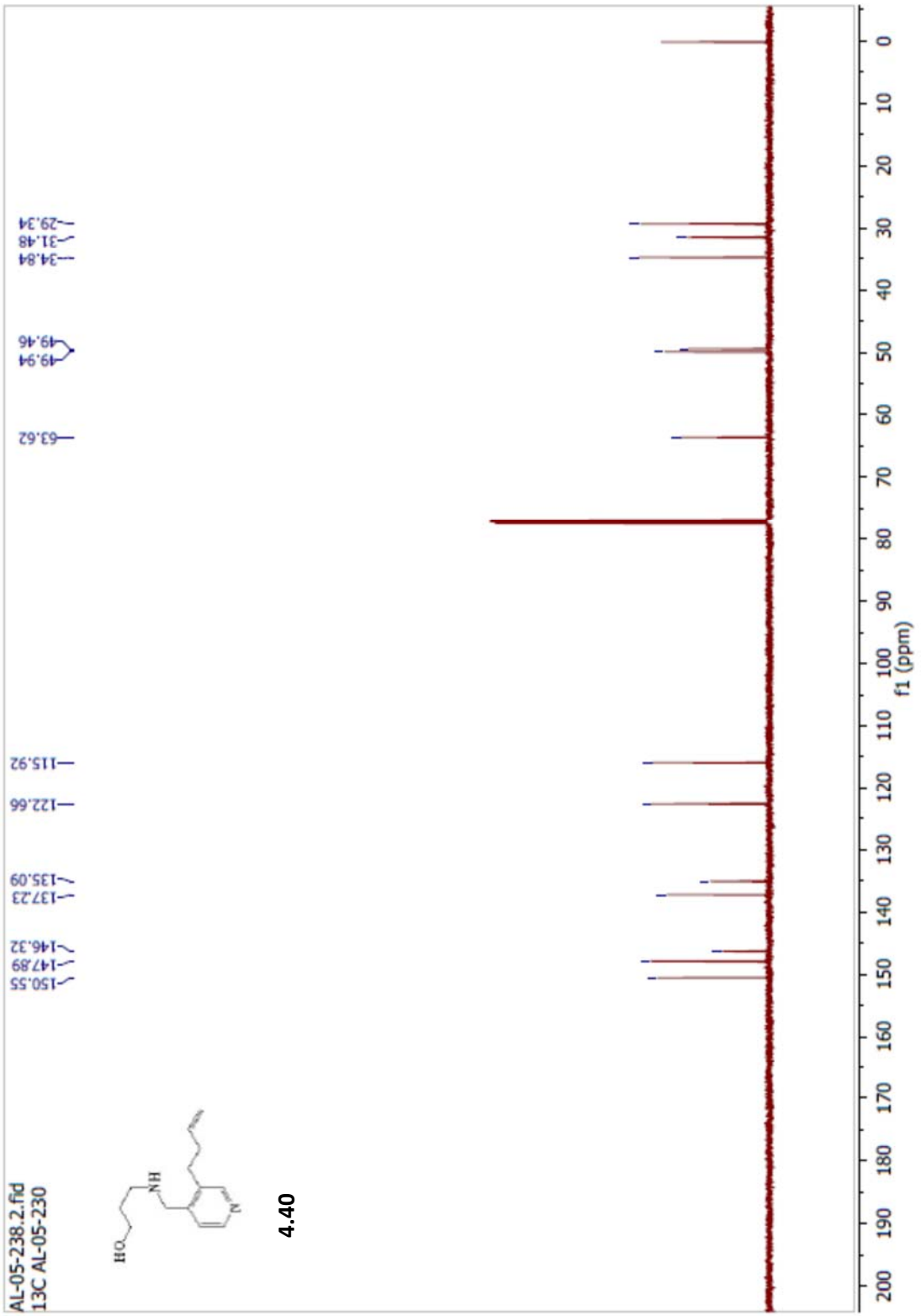

AL-05-48.1.fid
1H AL-05-48
CHO
N
4.37
1.00
1.11
1.14
1.11
1.11
1.16
2.21
2.34
2.43
2.33
2.40
f1 (ppm)

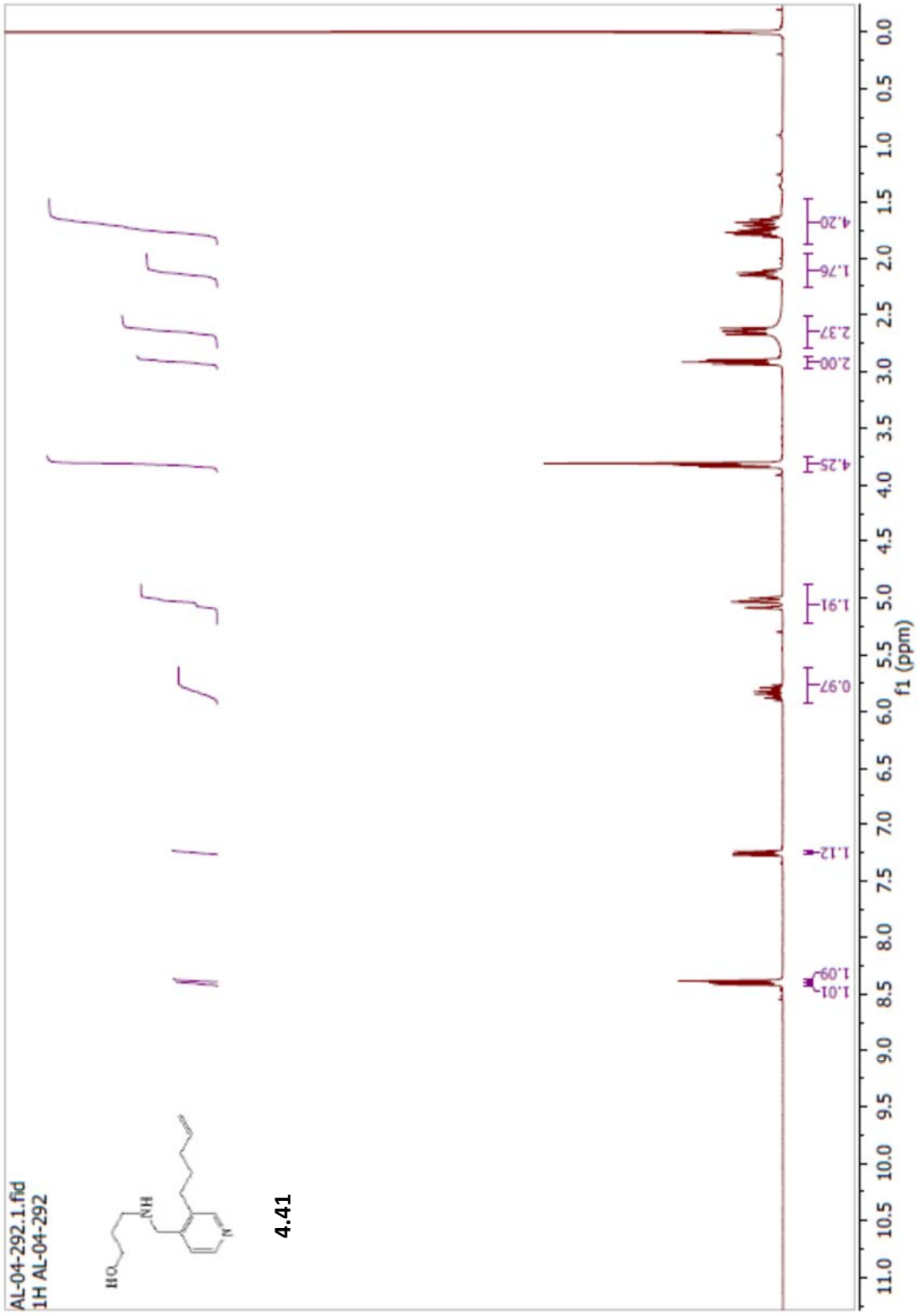

AL-05-48.2.fid
13C AL-05-48
191.74
153.07
148.85
138.88
138.43
137.95
122.91
115.00
33.53
31.79
29.61
28.71
CHO
N
4.37
f1 (ppm)

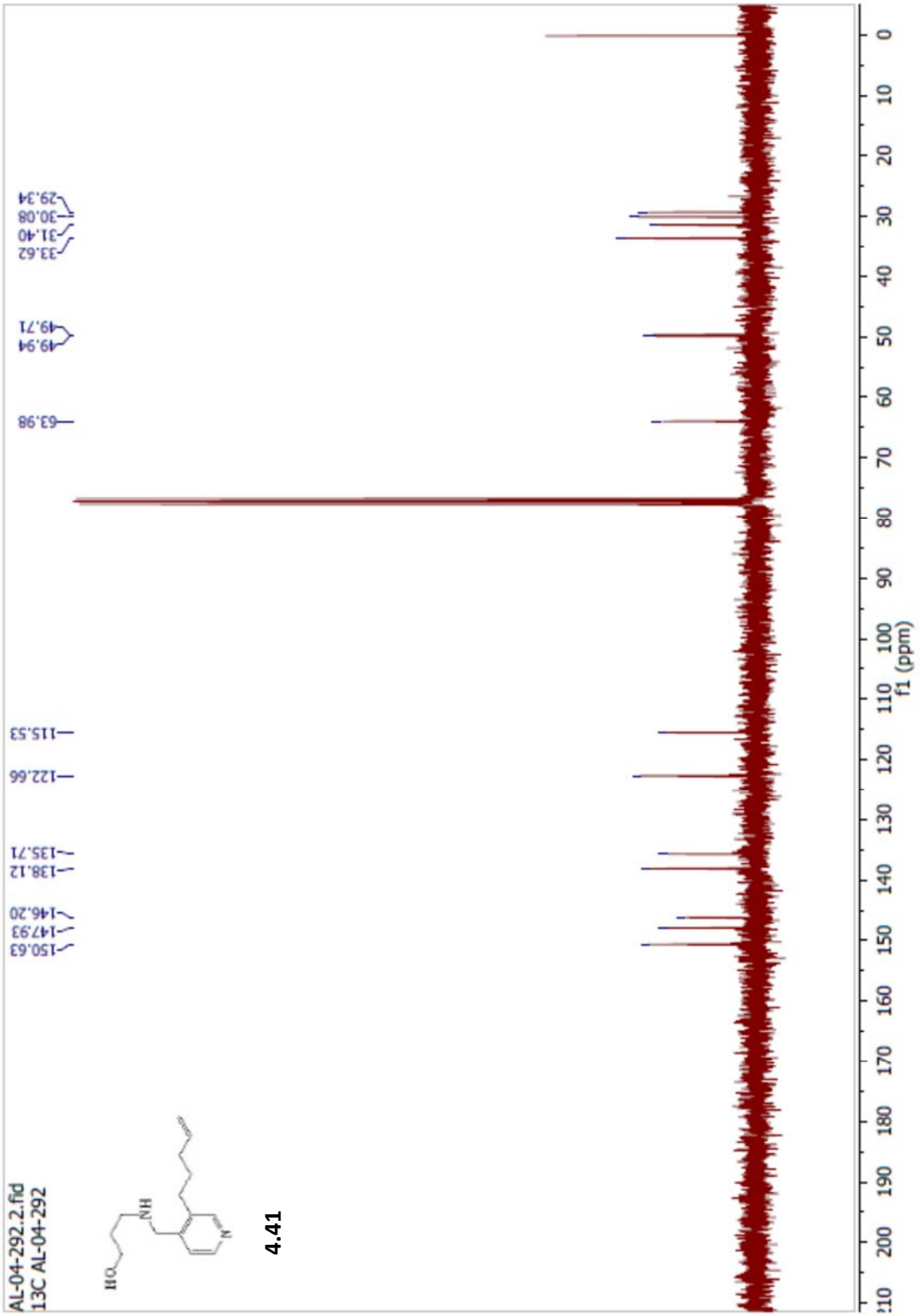

AL-06-64.1.fid
1H AL-06-64
CHO
N
4.38
1.00
1.04
1.02
1.05
1.03
2.11
2.32
2.81
3.52
4.78
f1 (ppm)

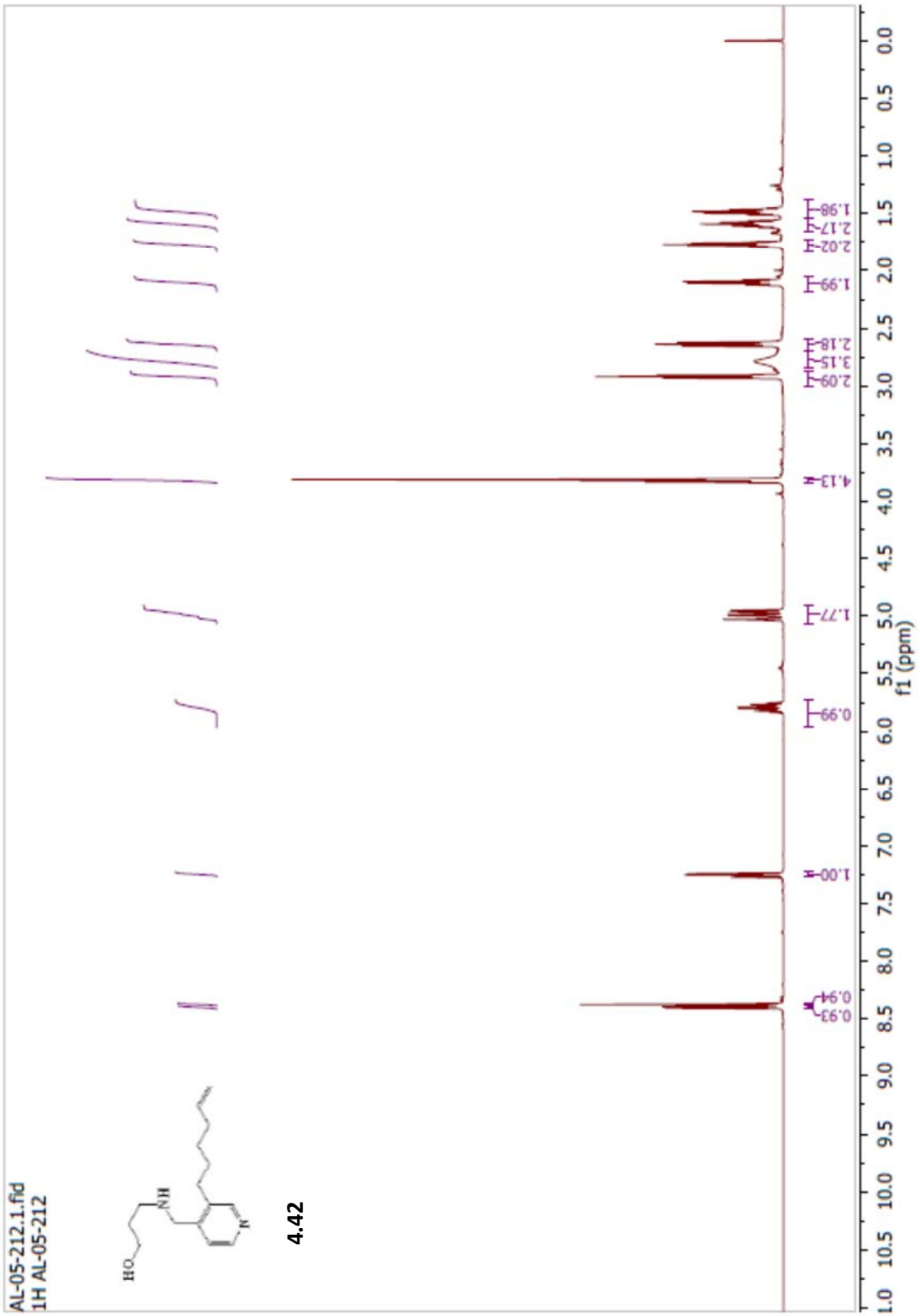

AL-06-64.2.fid
13C AL-06-64
191.59
152.96
148.71
138.72
138.69
137.91
122.69
114.54
33.59
32.13
29.60
28.85
28.57
CHO
N
4.38
f1 (ppm)

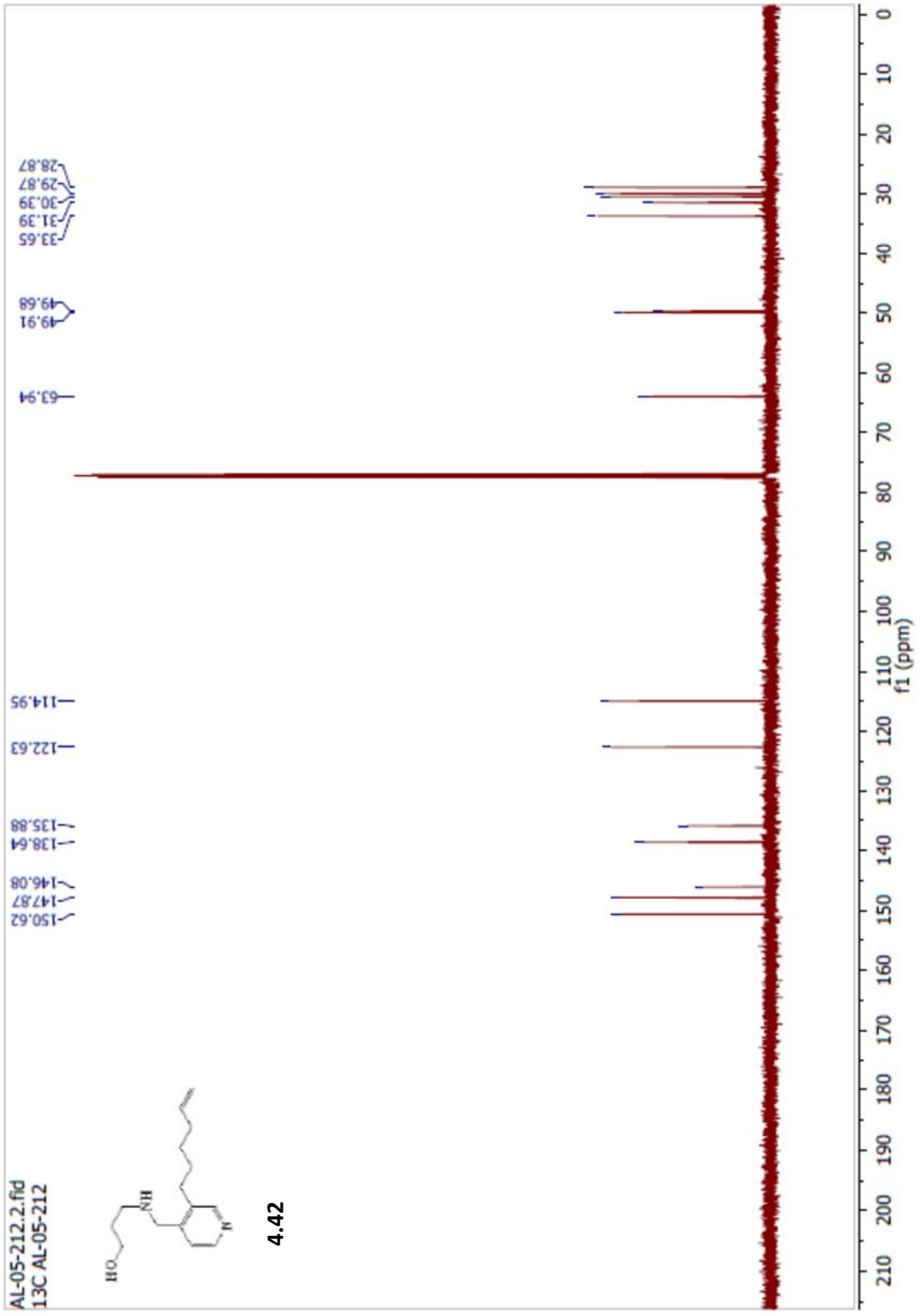
4.40

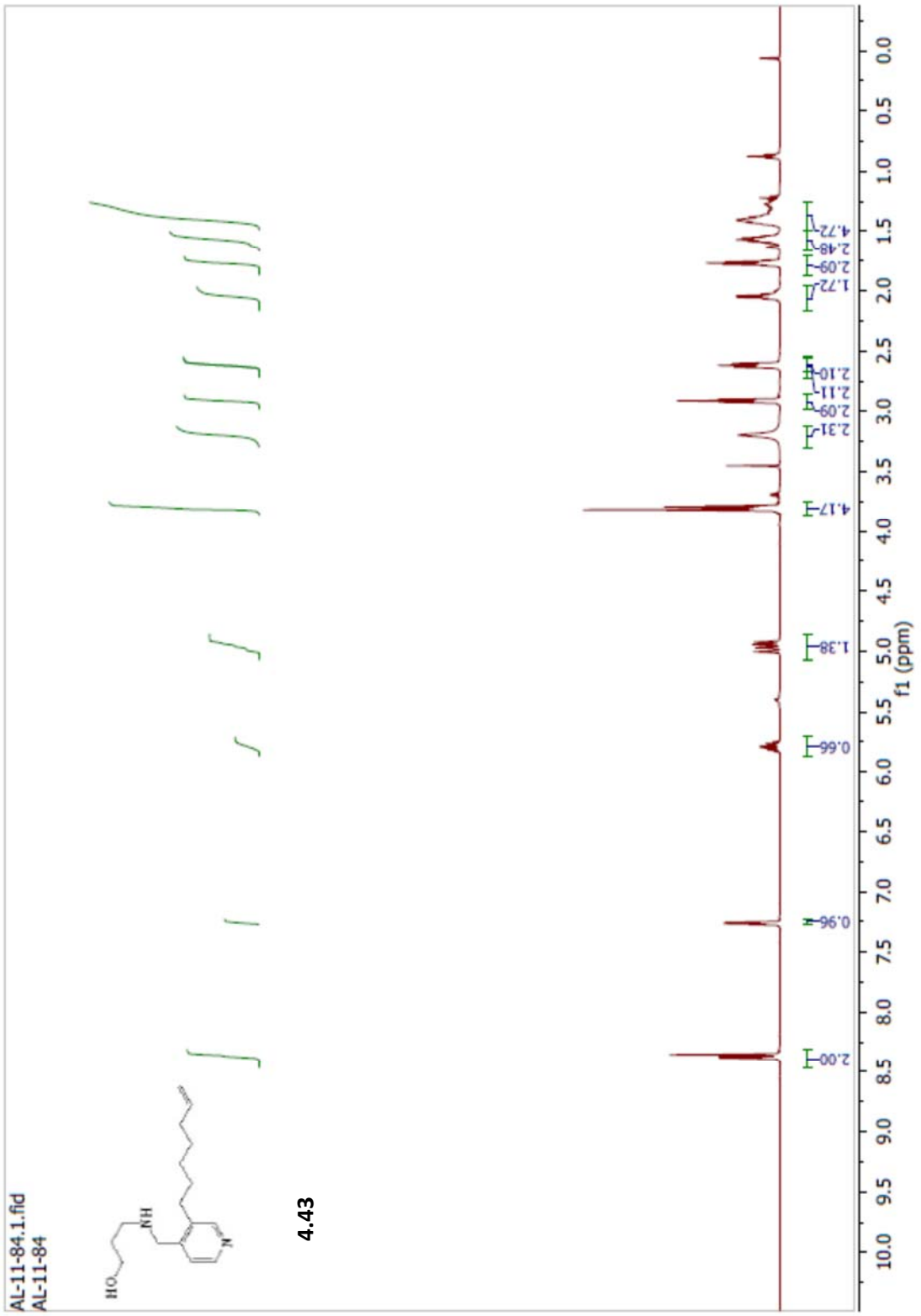

AL-05-238.2.fid
13C AL-05-230
150.55
147.89
146.32
137.23
135.09
122.66
115.92
63.62
49.94
49.46
34.84
31.48
29.34
HO
HN
N
4.40
f1 (ppm)

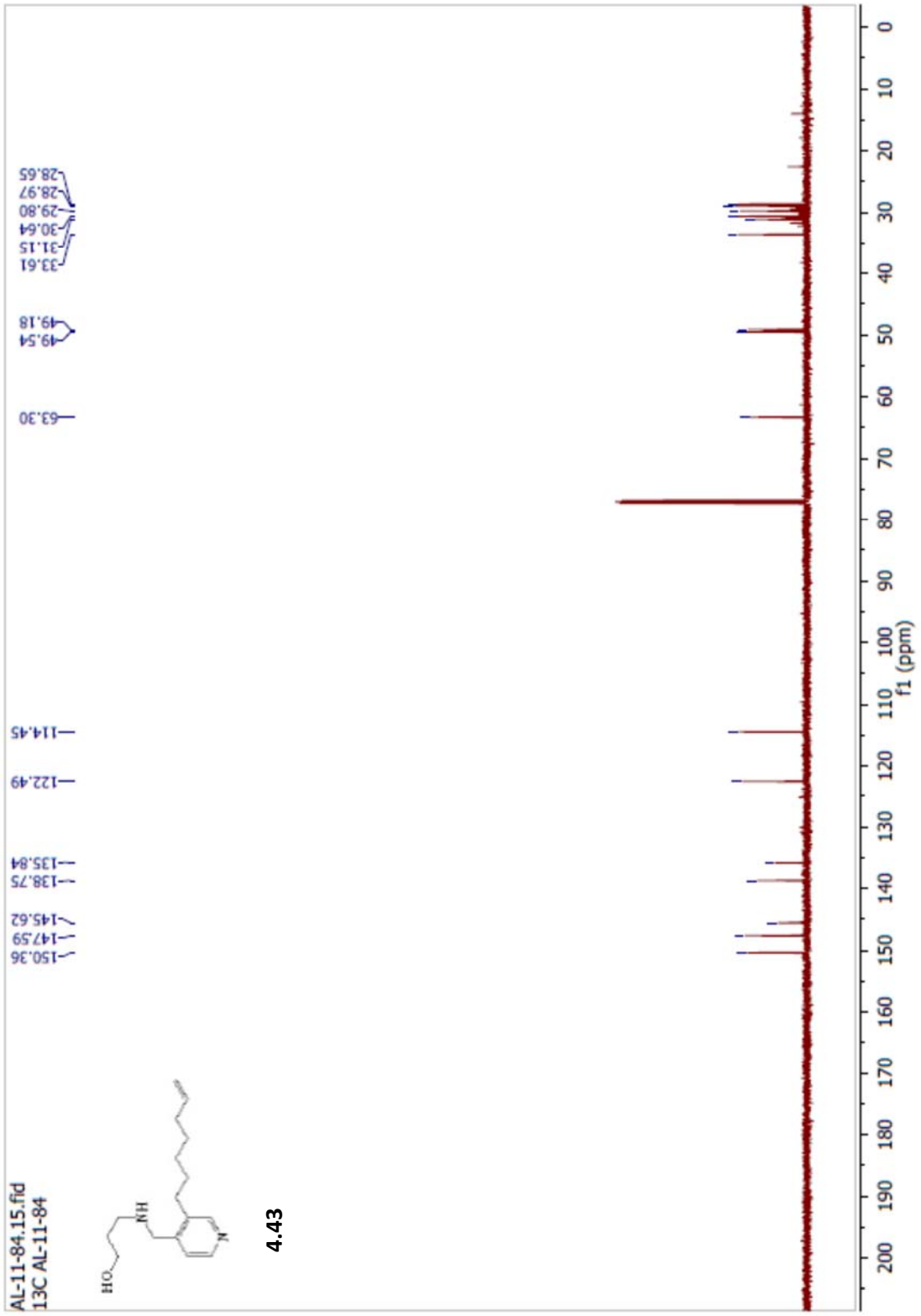

AL-04-292.1.fid
1H AL-04-292
4.41
1.01
1.09
1.12
0.97
1.91
4.25
2.00
2.37
1.76
4.20
f1 (ppm)


AL-04-292.2.fid
13C AL-04-292
4.41
150.63
147.93
146.20
138.12
135.71
122.66
115.53
63.98
49.94
49.71
33.62
31.40
30.08
29.34
f1 (ppm)

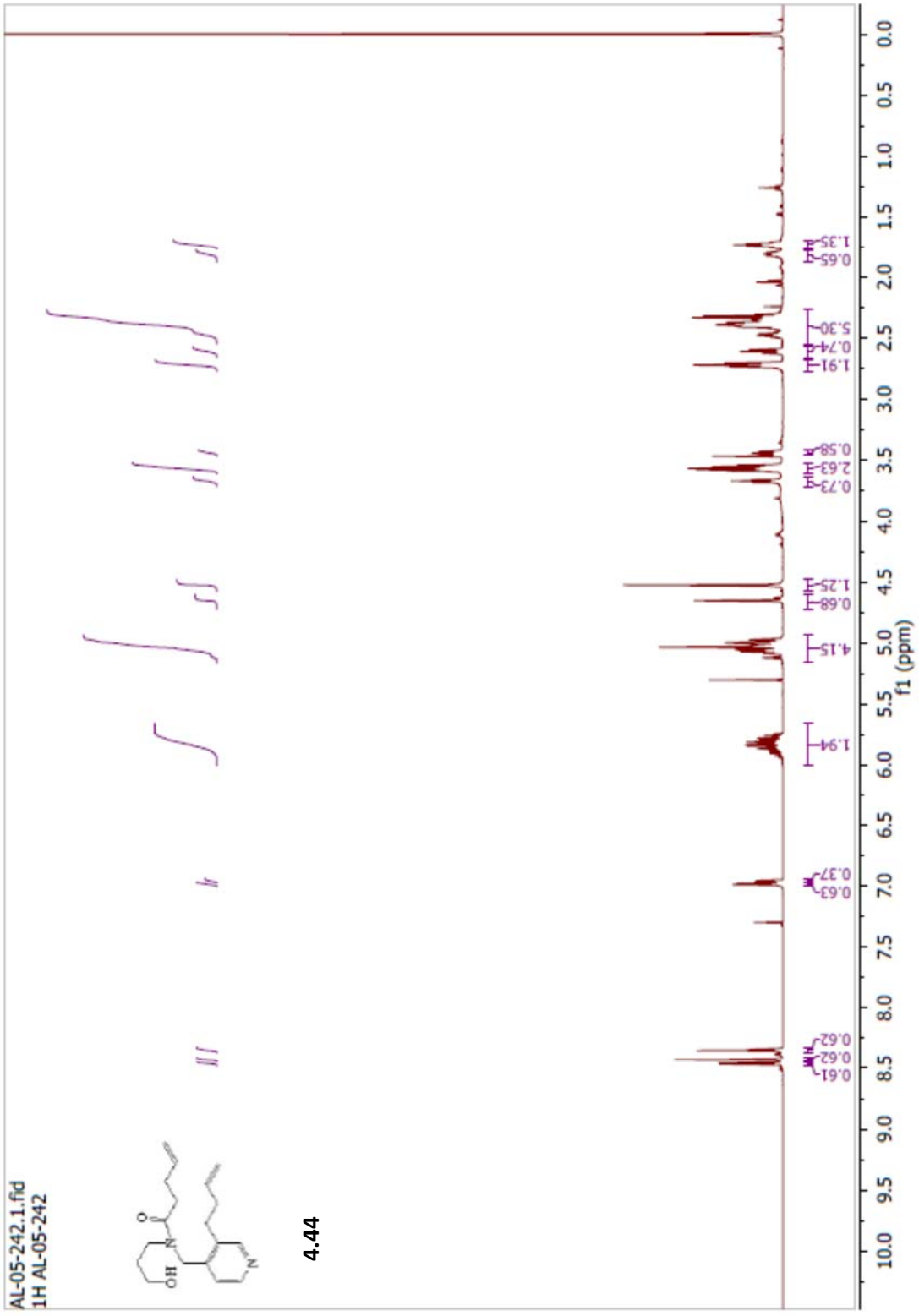

AL-05-212.1.fid
1H AL-05-212
HO
NH
N
4.42
0.93
0.94
1.00
0.99
1.77
4.13
2.09
3.15
2.18
1.99
2.02
2.17
1.98
f1 (ppm)


AL-05-212.2.fid
13C AL-05-212
4.42
150.62
147.87
146.08
138.64
135.88
122.63
114.95
63.94
49.91
49.68
33.65
31.39
30.39
29.87
28.87
f1 (ppm)

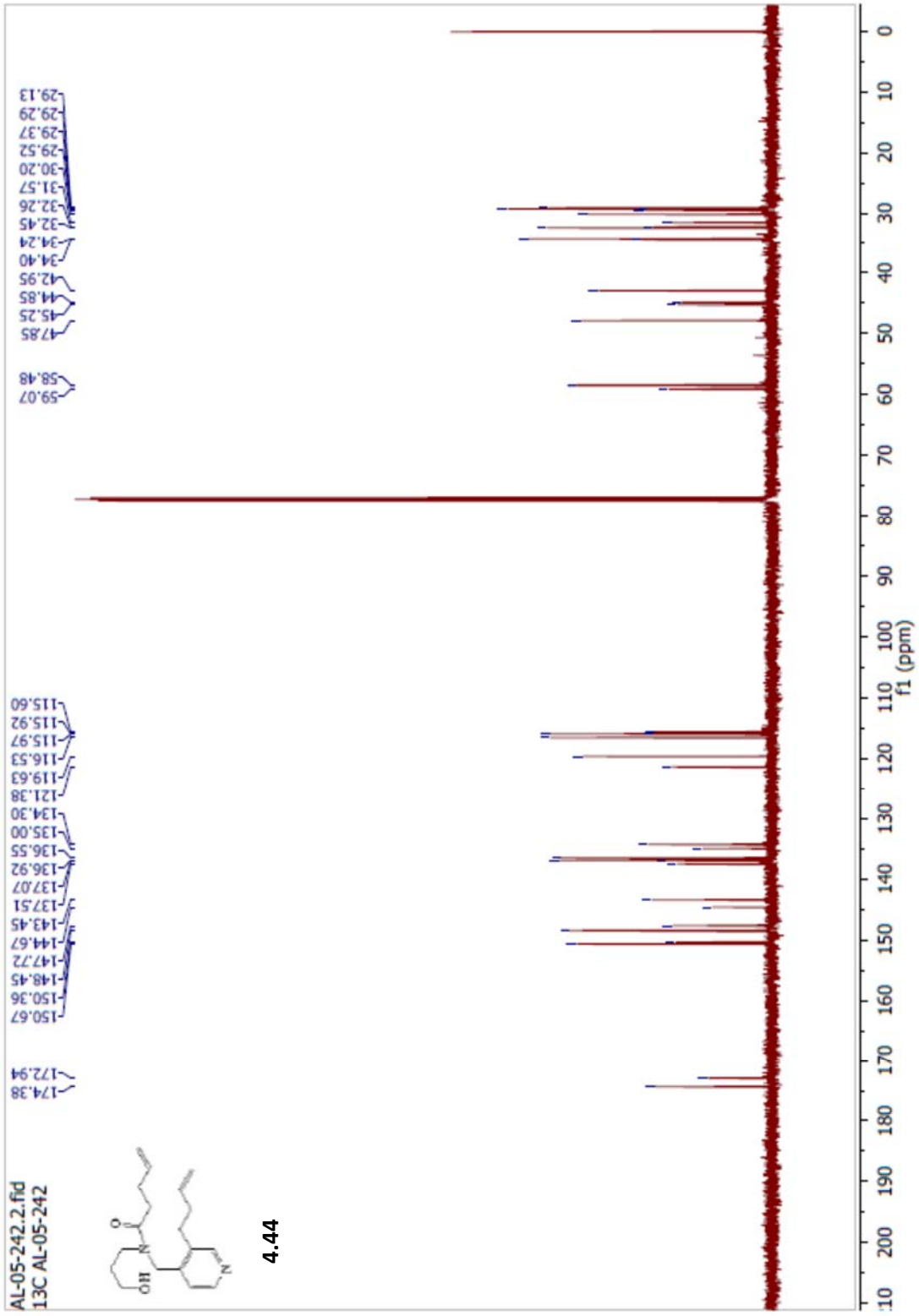

AL-11-84.1.fid
AL-11-84
4.43
f1 (ppm)

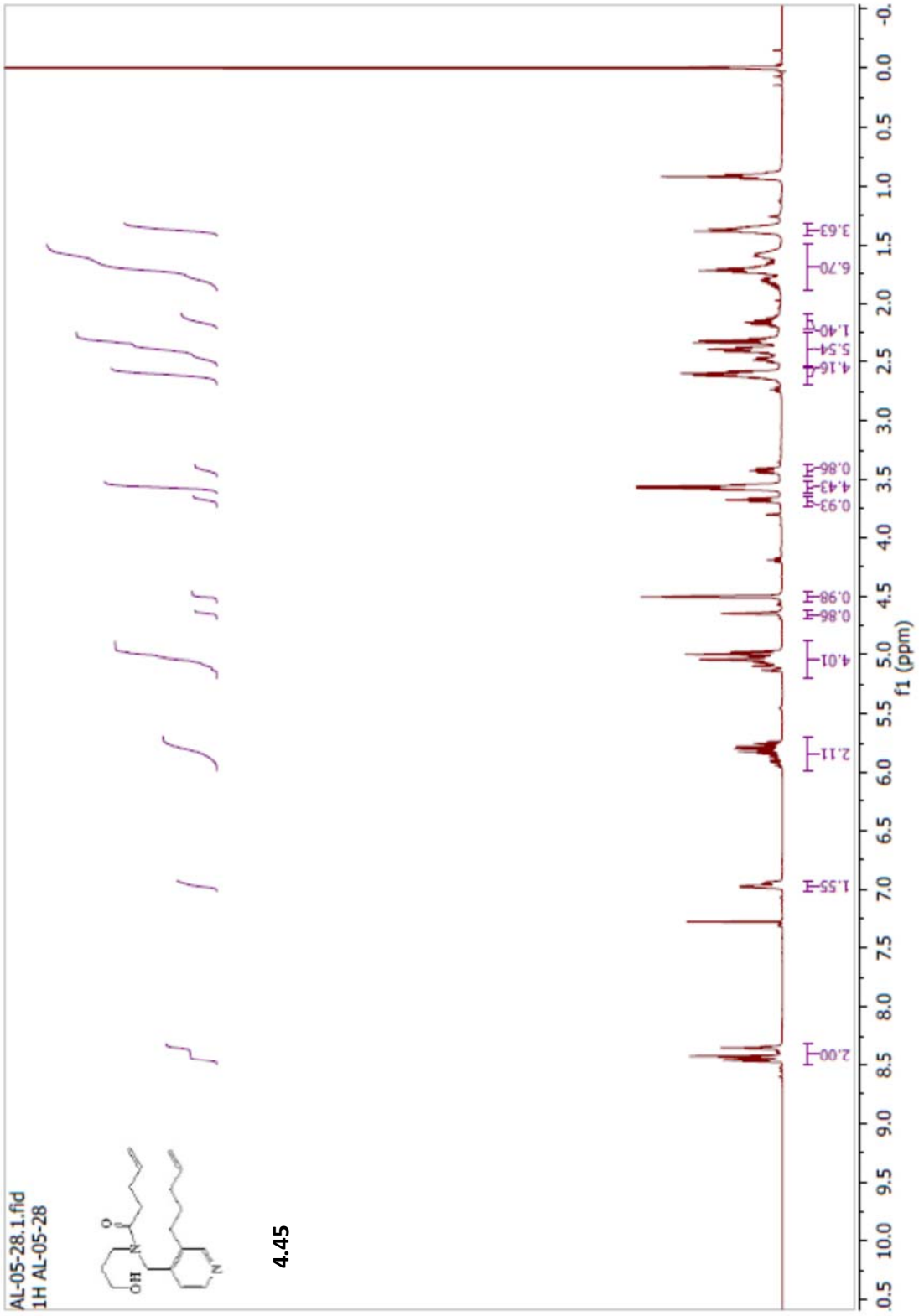

AL-11-84.15.fid
13C AL-11-84
150.36
147.59
145.62
138.75
135.84
122.49
114.45
63.30
49.54
49.18
33.61
31.15
30.64
29.80
28.97
28.65
f1 (ppm)

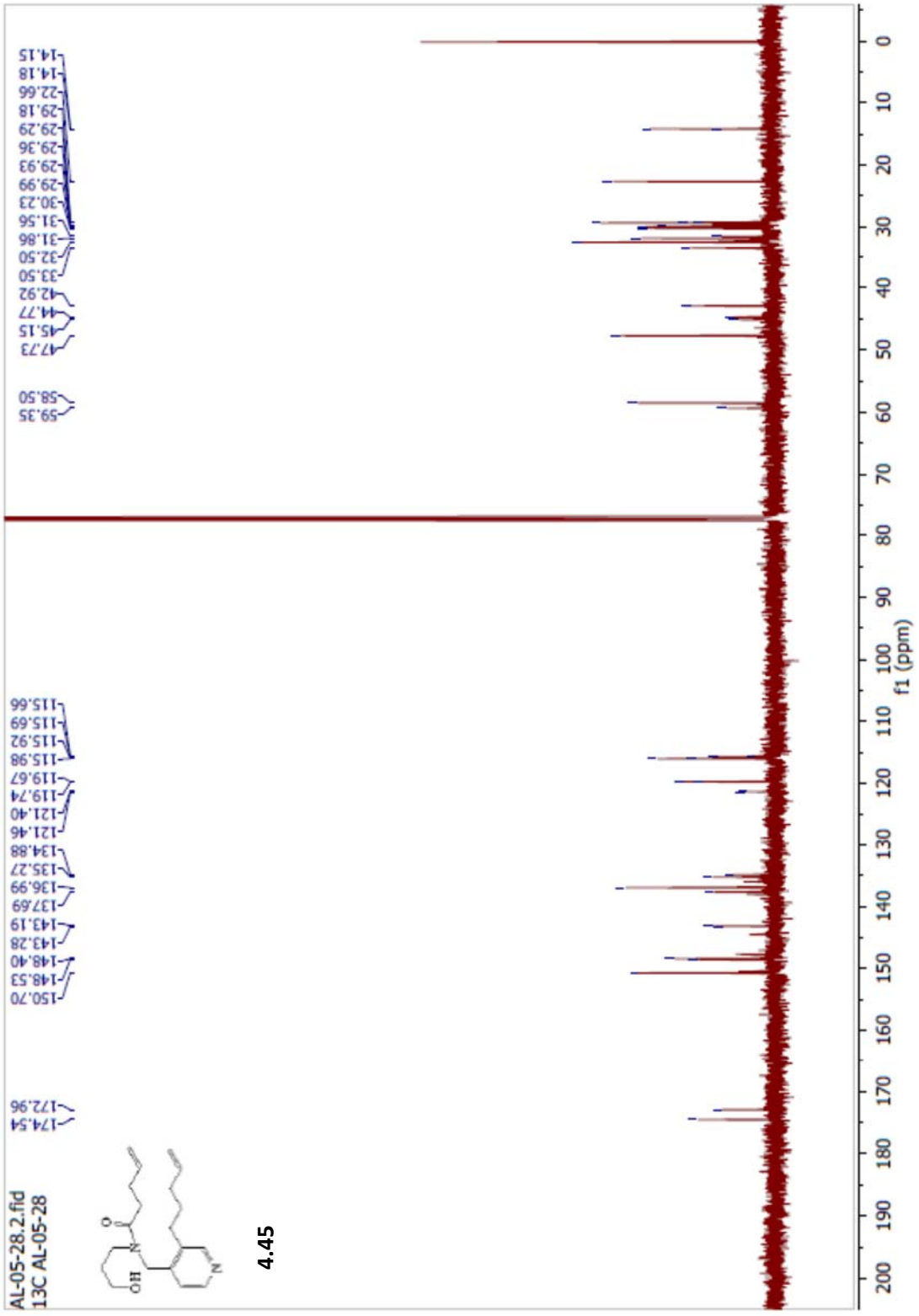
4.43



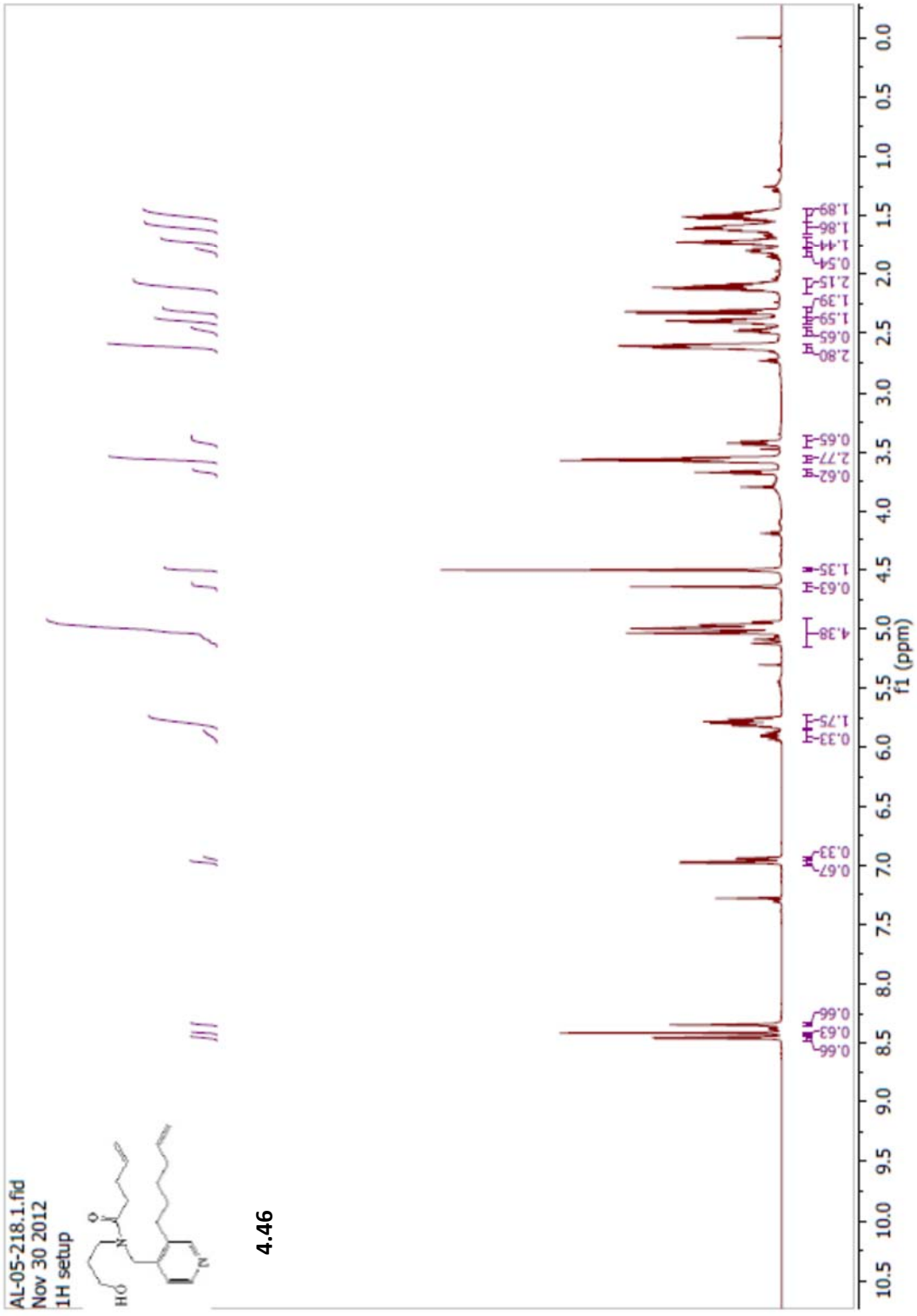
4.44

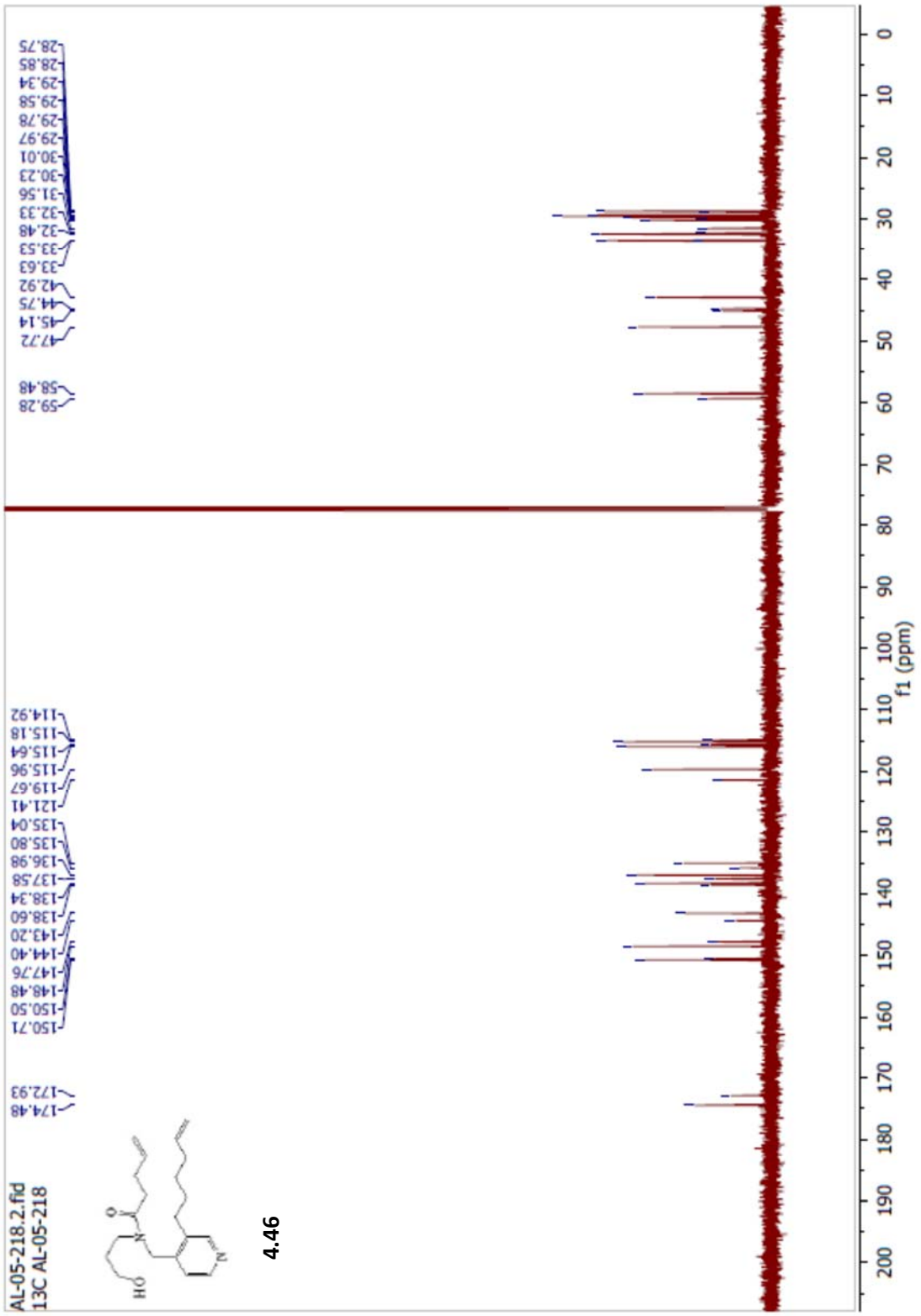

AL-05-242.2.fid
13C AL-05-242
4.44
f1 (ppm)

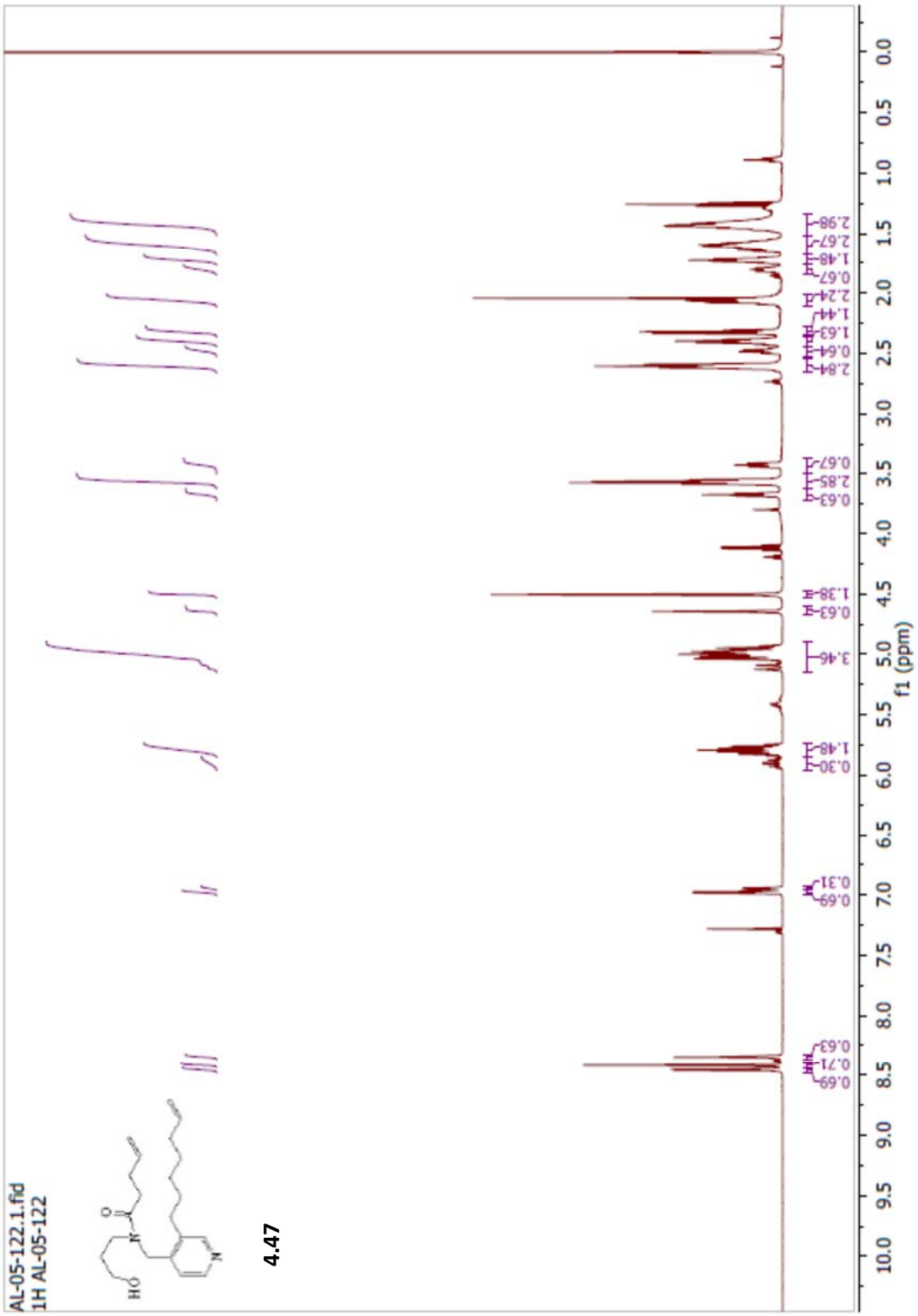

AL-05-28.1.fid
1H AL-05-28
4.45
f1 (ppm)

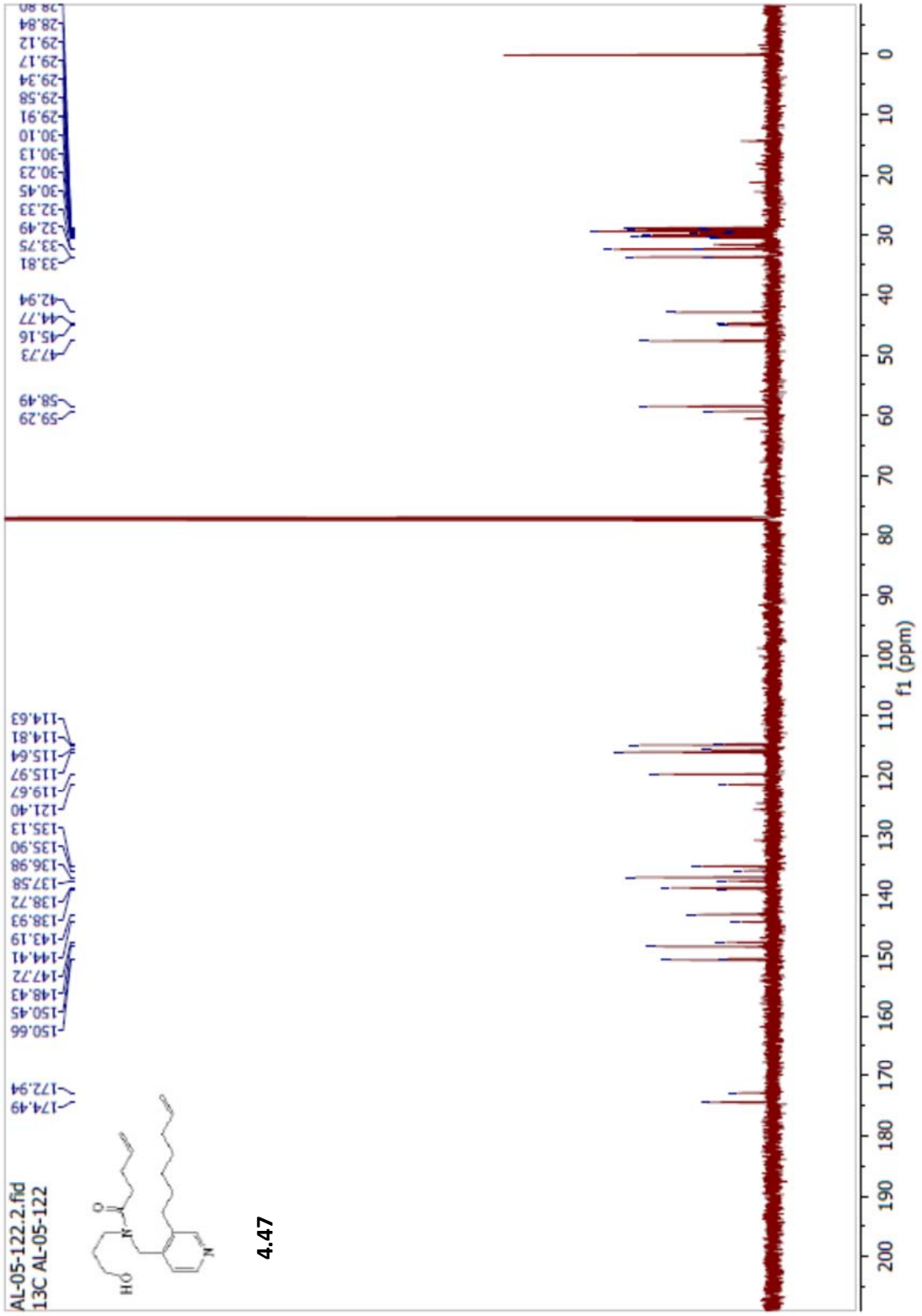

AL-05-28.2.fid
13C AL-05-28
174.54
172.96
150.70
148.53
148.40
143.28
143.19
137.69
136.99
135.27
134.88
121.46
121.40
119.74
119.67
115.98
115.92
115.69
115.66
59.35
58.50
47.73
45.15
44.77
42.92
33.50
32.50
31.86
31.56
30.23
29.99
29.93
29.36
29.29
29.18
22.66
14.18
14.15
f1 (ppm)

4.45

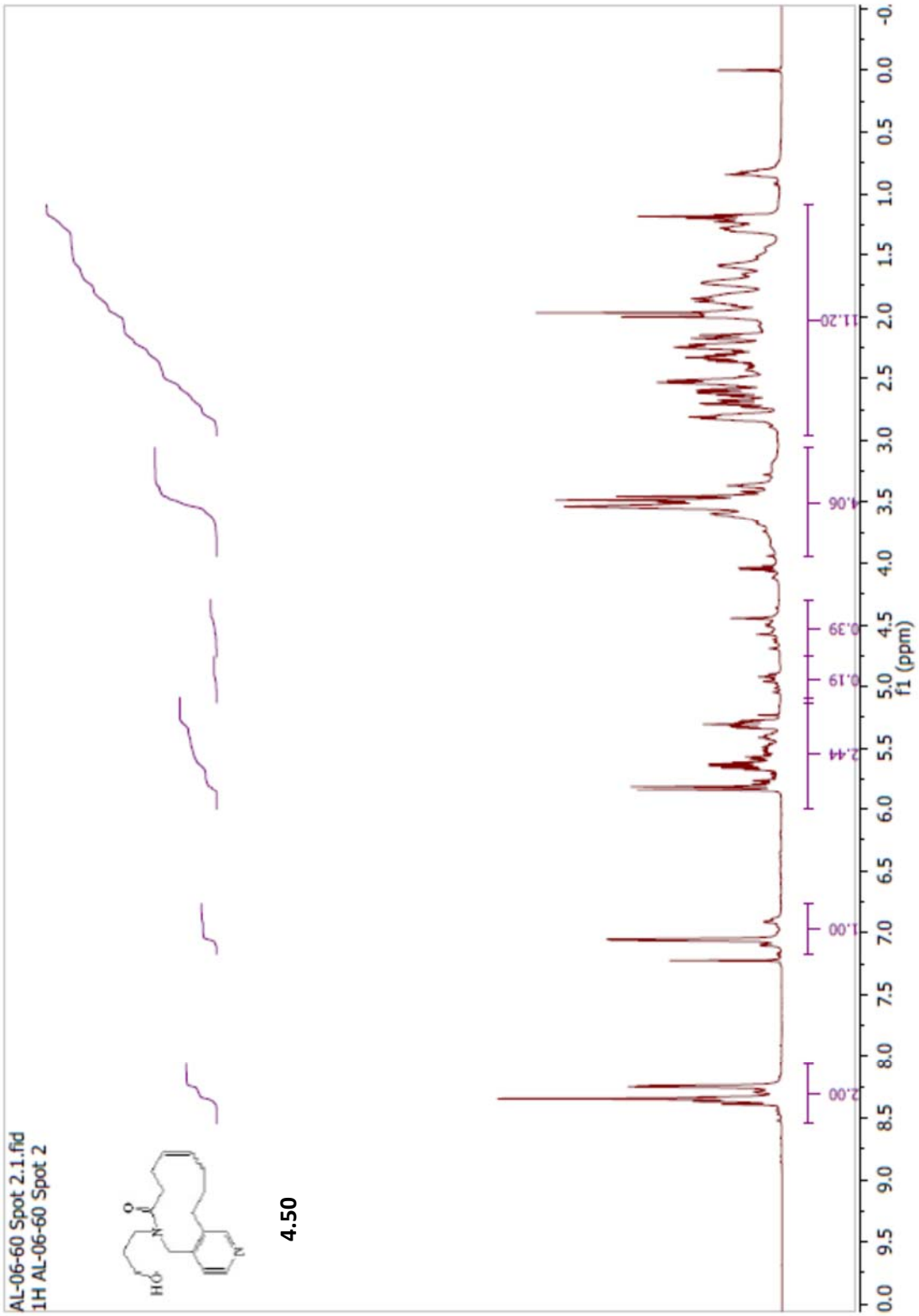

AL-05-218.1.fid
Nov 30 2012
1H setup
4.46
f1 (ppm)

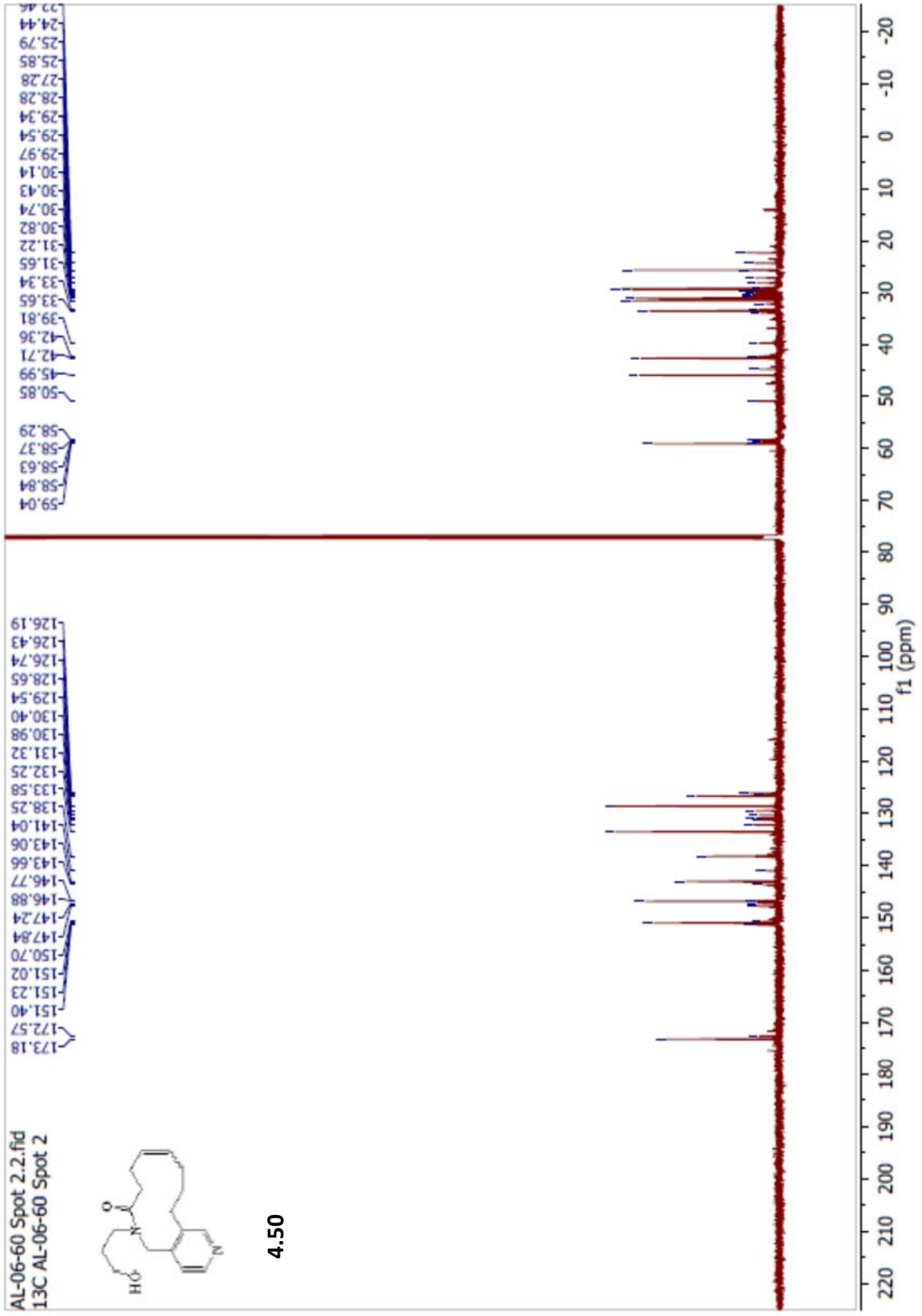

AL-05-218.2.fid
13C AL-05-218
4.46
f1 (ppm)

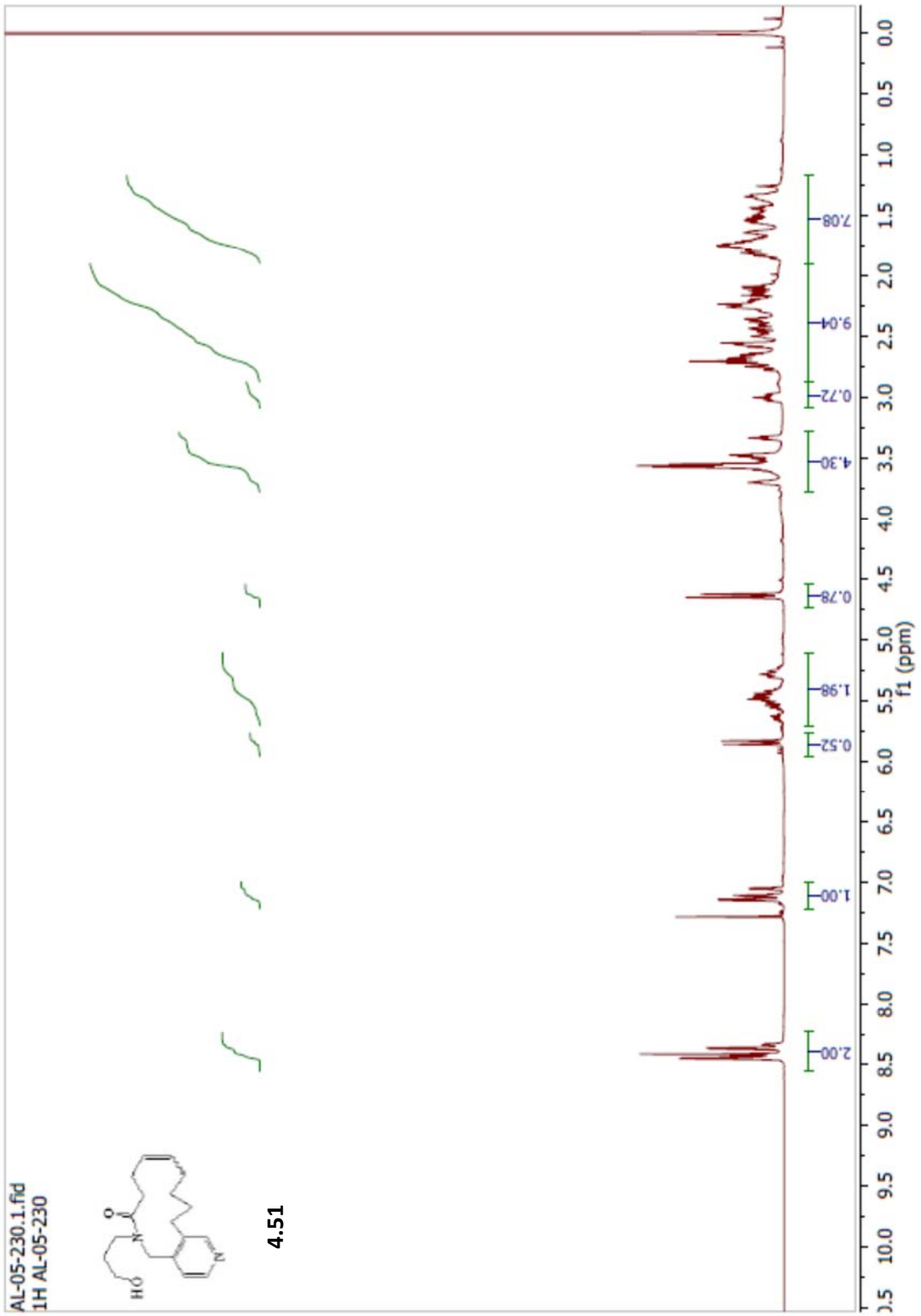

AL-05-122.1.fid
1H AL-05-122
HO
O
N
N
4.47
0.69
0.71
0.63
0.69
0.31
1.48
0.30
3.46
1.38
0.63
0.67
2.85
0.63
2.84
0.64
1.63
1.44
2.24
0.67
1.48
2.67
2.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

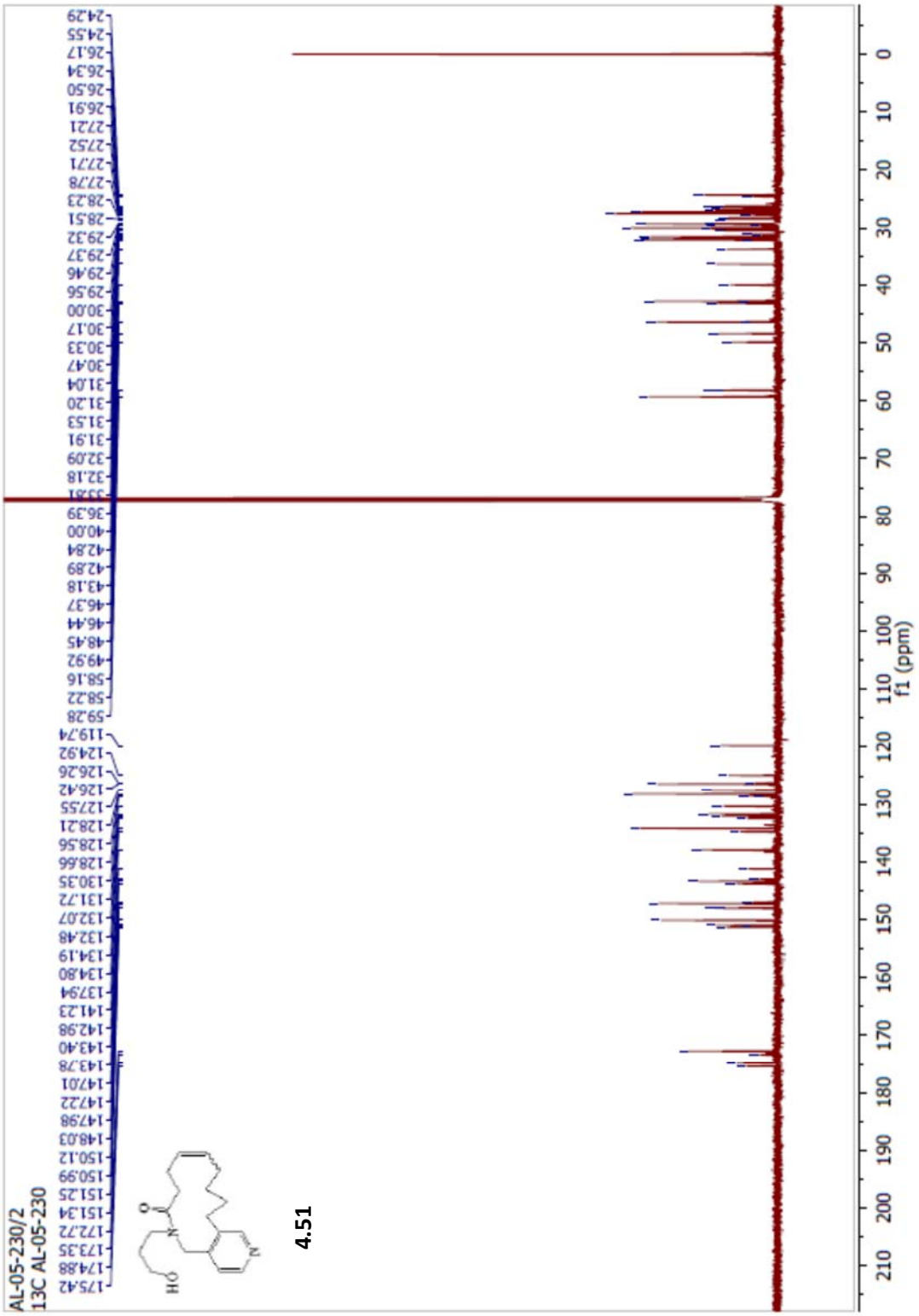

AL-05-122.2.fid
13C AL-05-122
174.49
172.94
150.66
150.45
148.43
147.72
144.41
143.19
138.93
138.72
137.58
136.98
135.90
135.13
121.40
119.67
115.97
115.64
114.81
114.63
59.29
58.49
47.73
45.16
44.77
42.94
33.81
33.75
32.49
32.33
30.45
30.23
30.13
30.10
29.91
29.58
29.34
29.17
29.12
28.84
28.80
f1 (ppm)

4.47

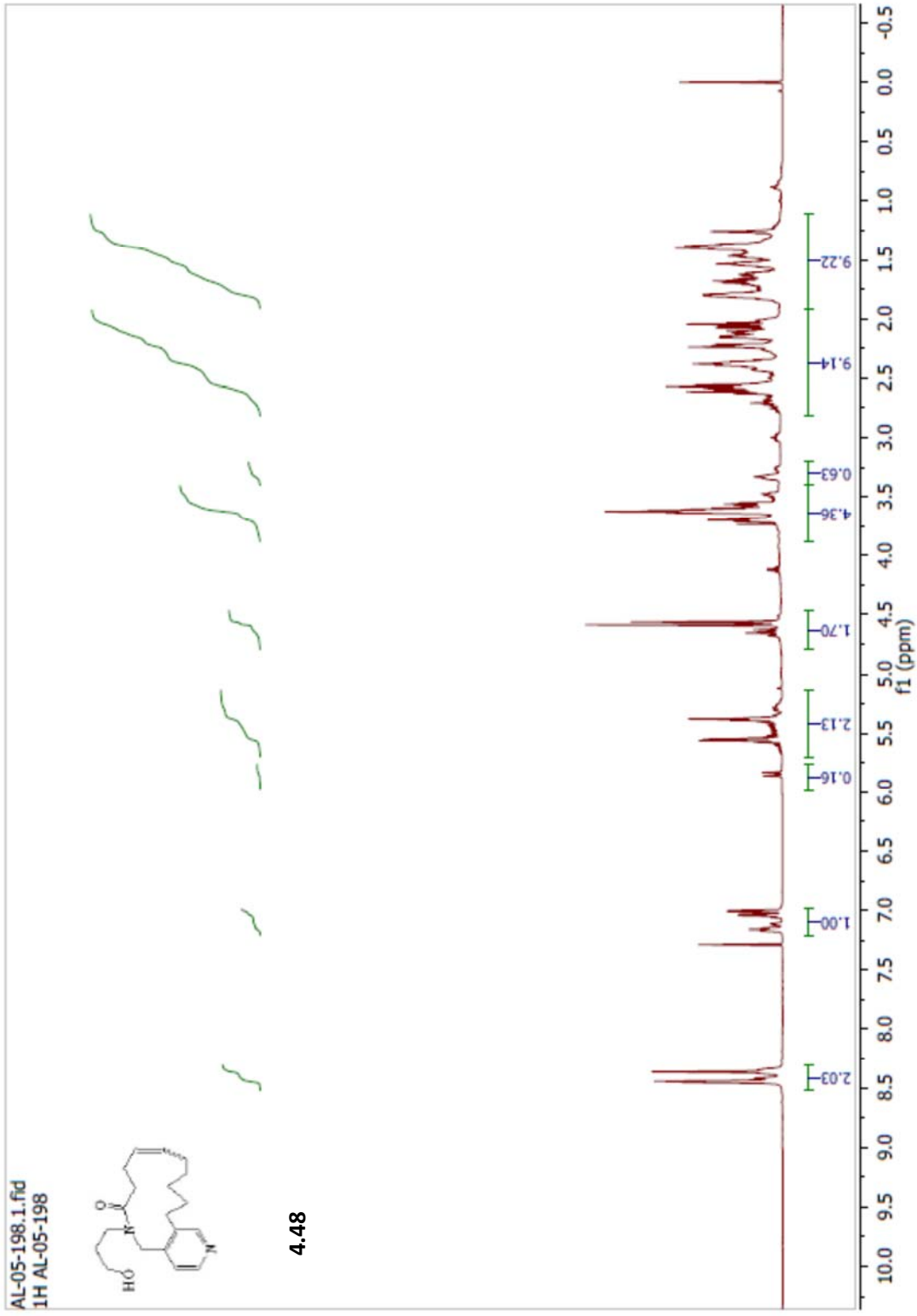

AL-06-60 Spot 2.1.fid
1H AL-06-60 Spot 2
4.50
f1 (ppm)

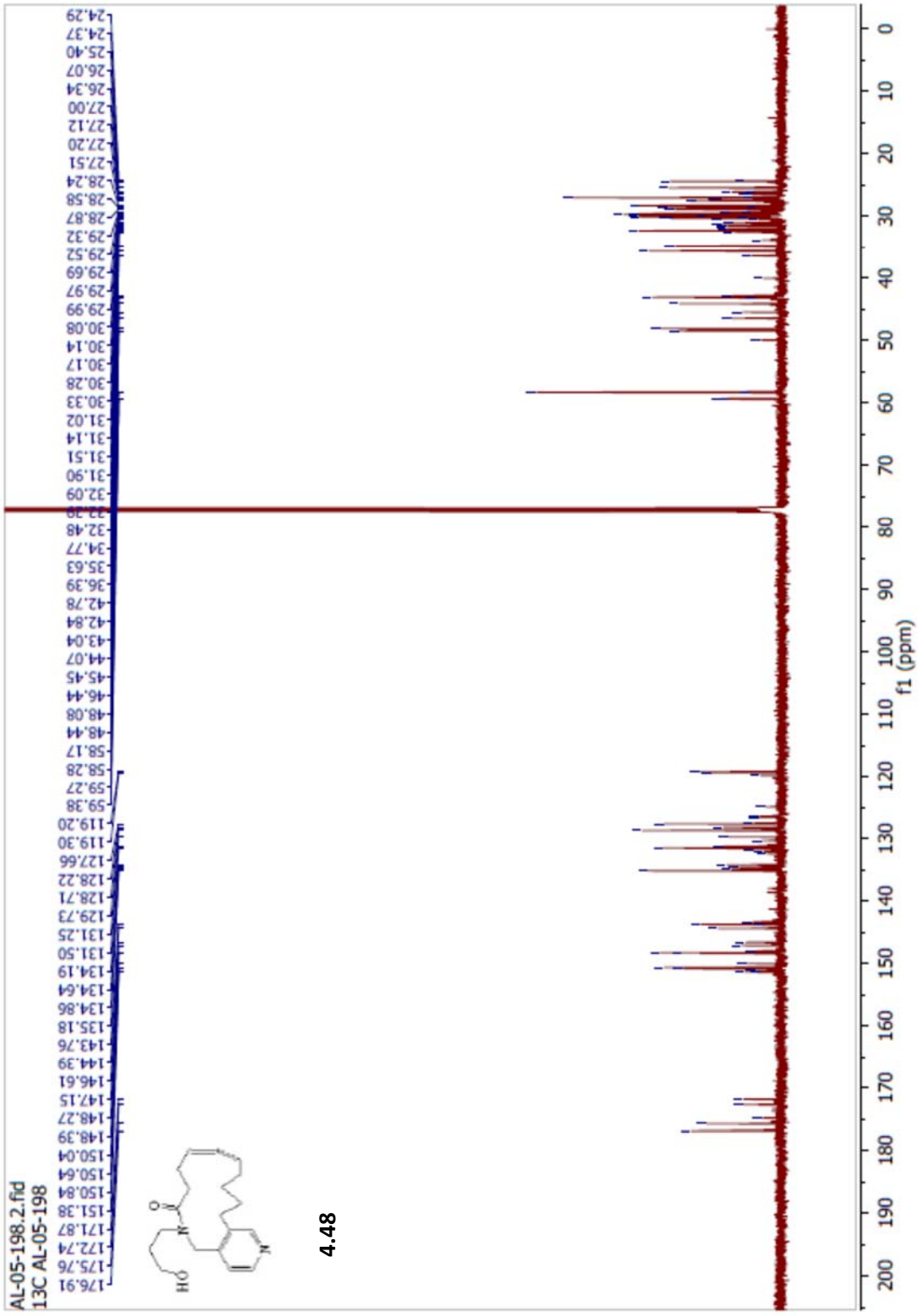

AL-06-60 Spot 2.2.fid
13C AL-06-60 Spot 2
4.50
f1 (ppm)

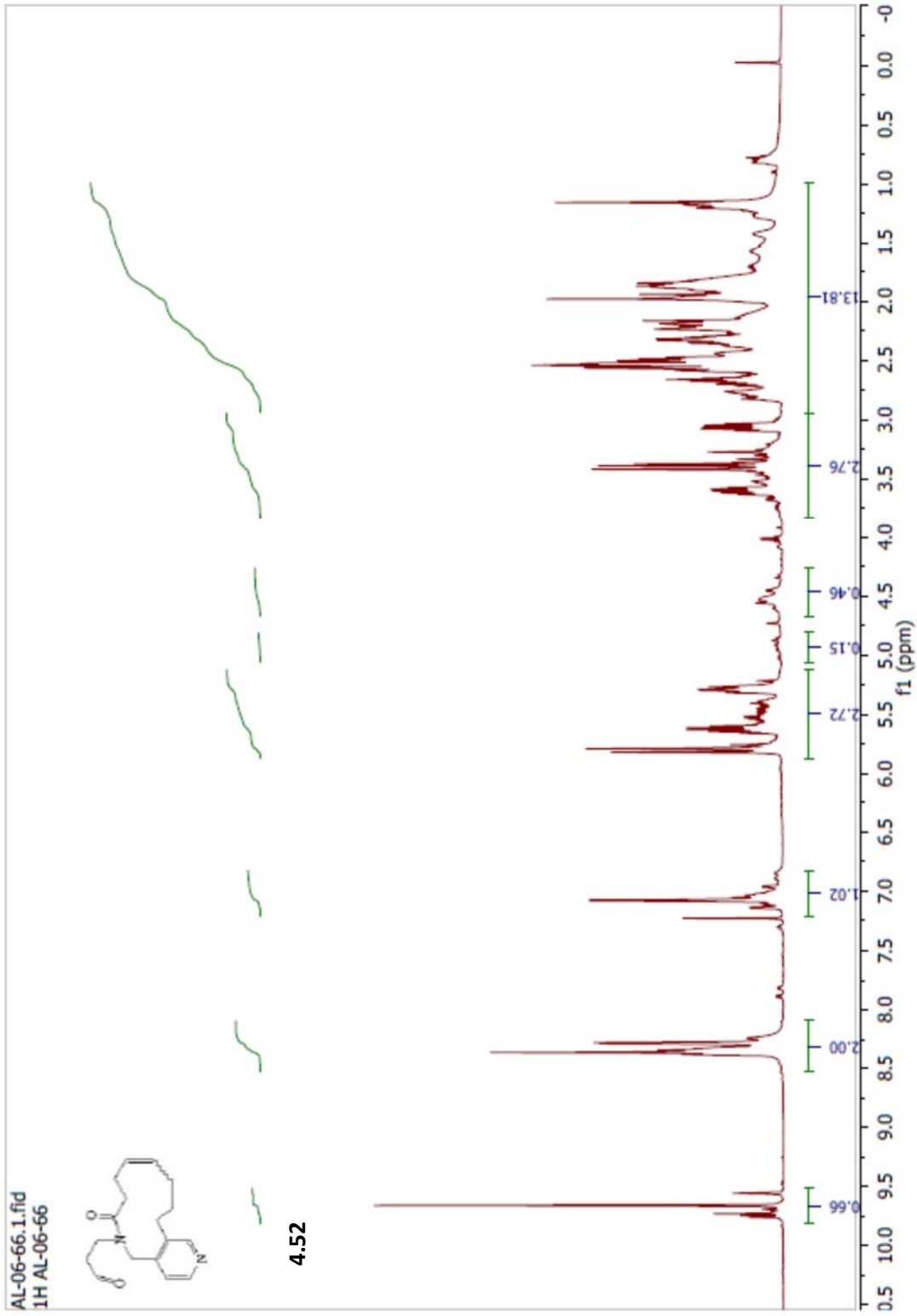

AL-05-230.1.fid
1H AL-05-230
4.51
2.00
1.00
0.52
1.98
0.78
4.30
0.72
9.04
7.08
f1 (ppm)

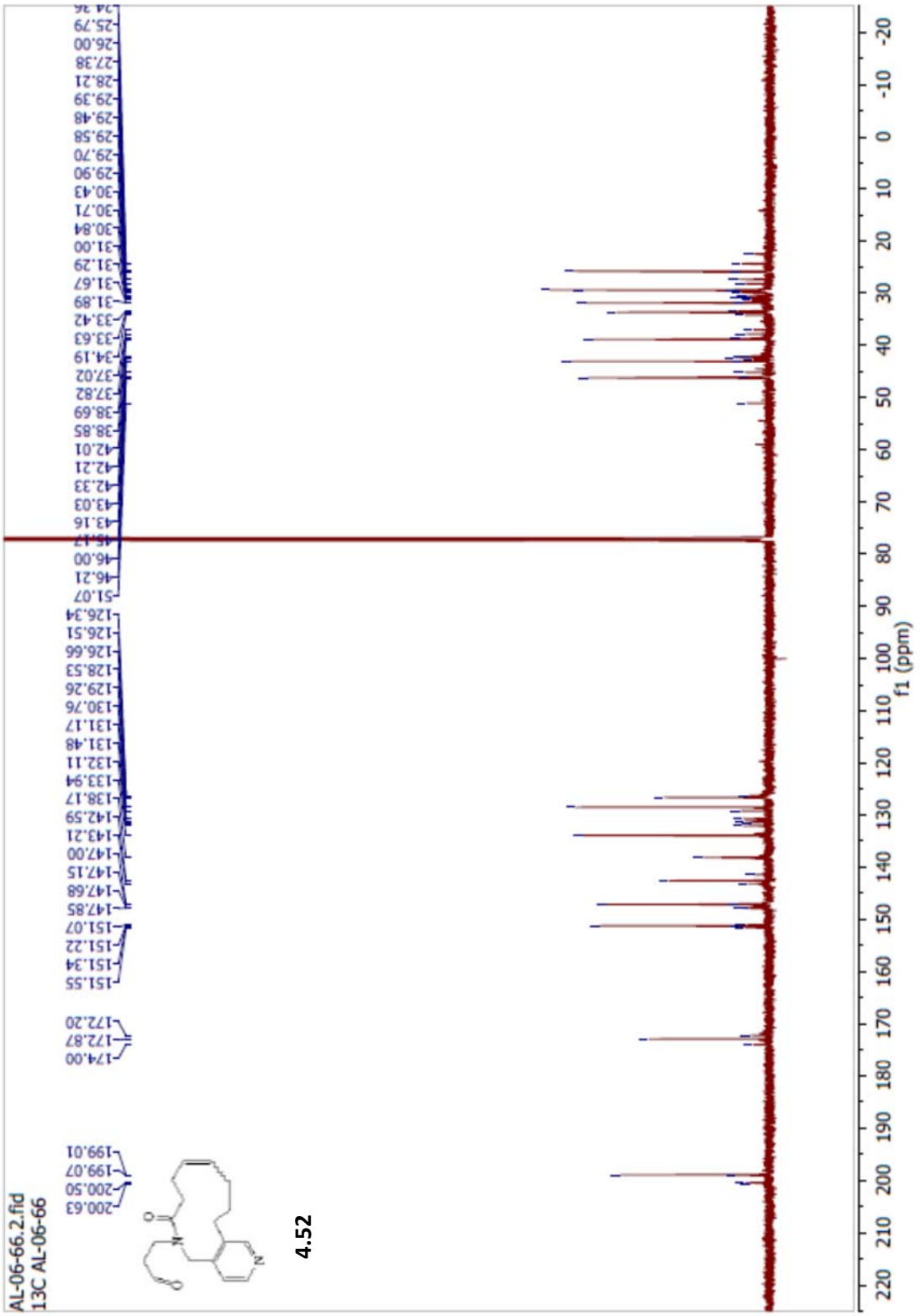


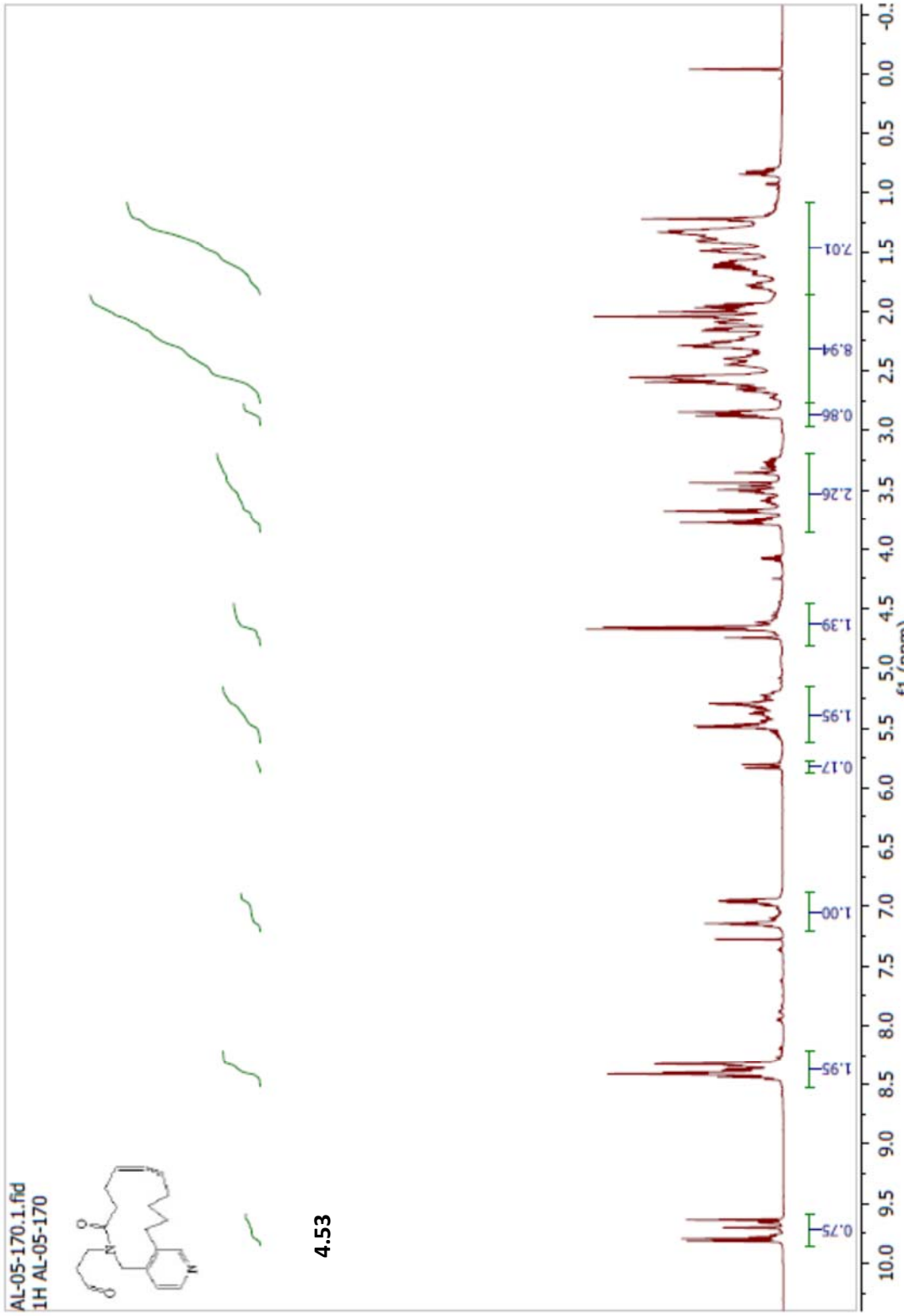
4.51

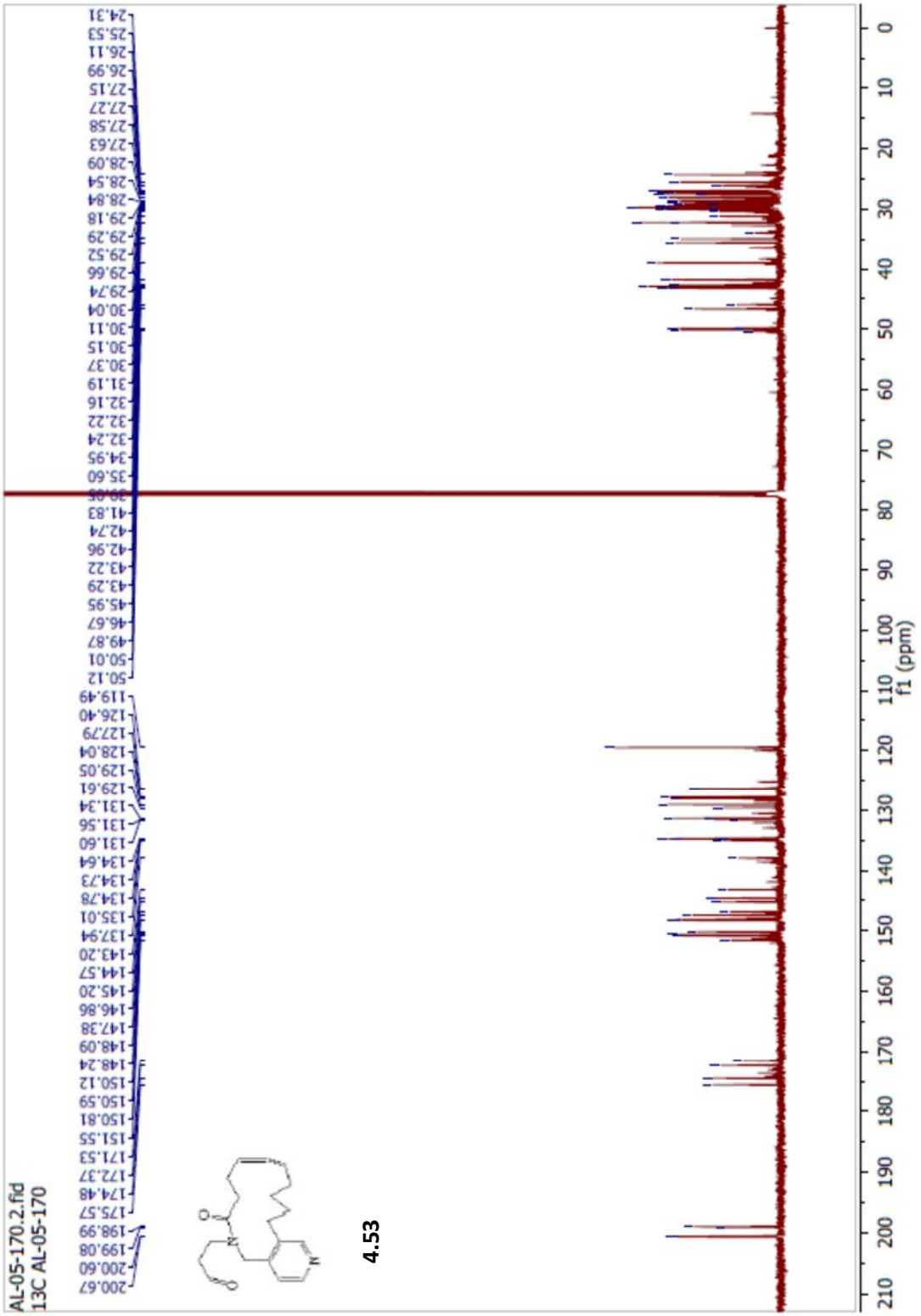

AL-05-198.1.fid
1H AL-05-198
4.48
2.03
1.00
0.16
2.13
1.70
4.36
0.63
9.14
9.22
f1 (ppm)


AL-05-198.2.fid
13C AL-05-198
4.48
f1 (ppm)

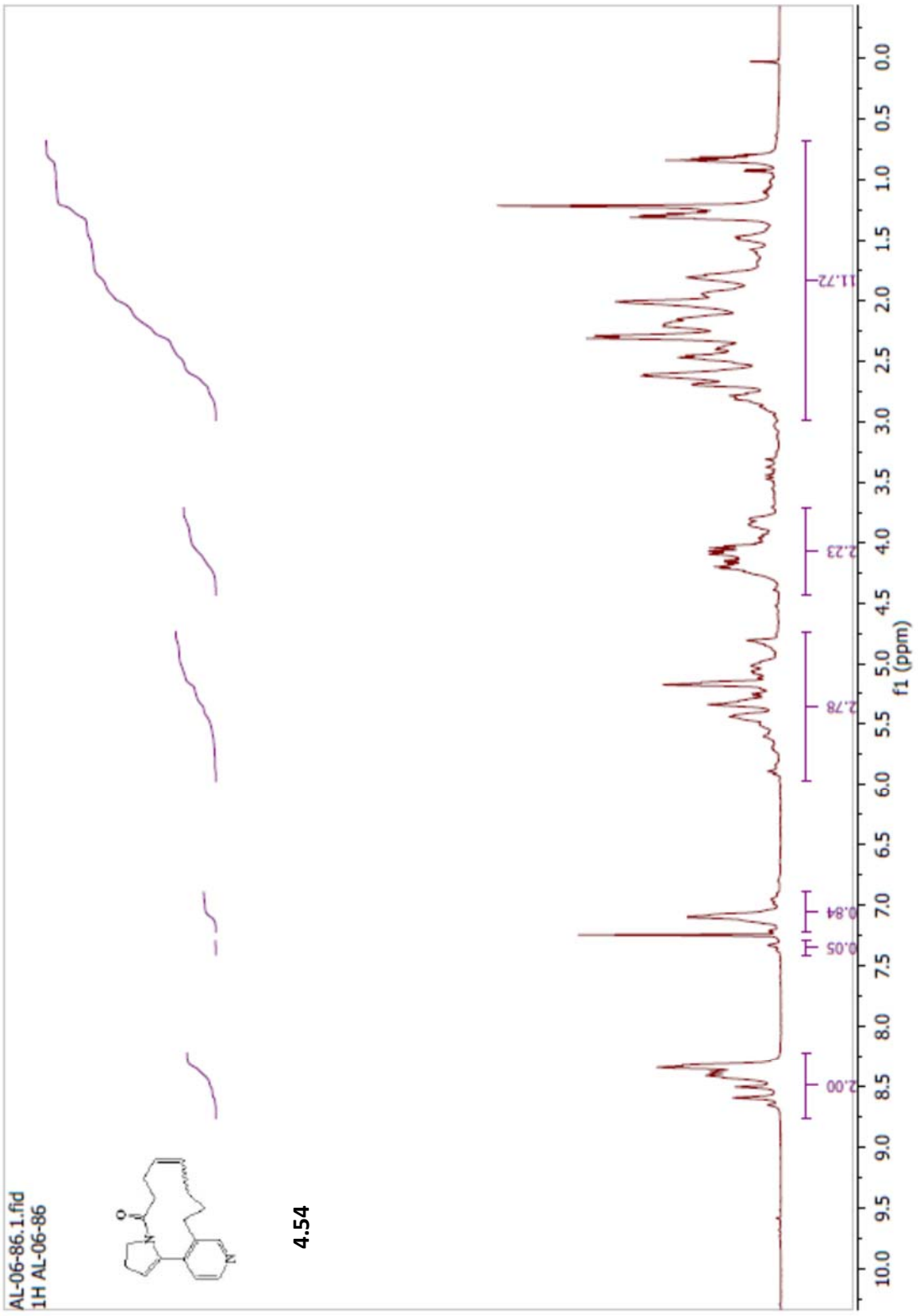

AL-06-66.1.fid
1H AL-06-66
4.52
f1 (ppm)

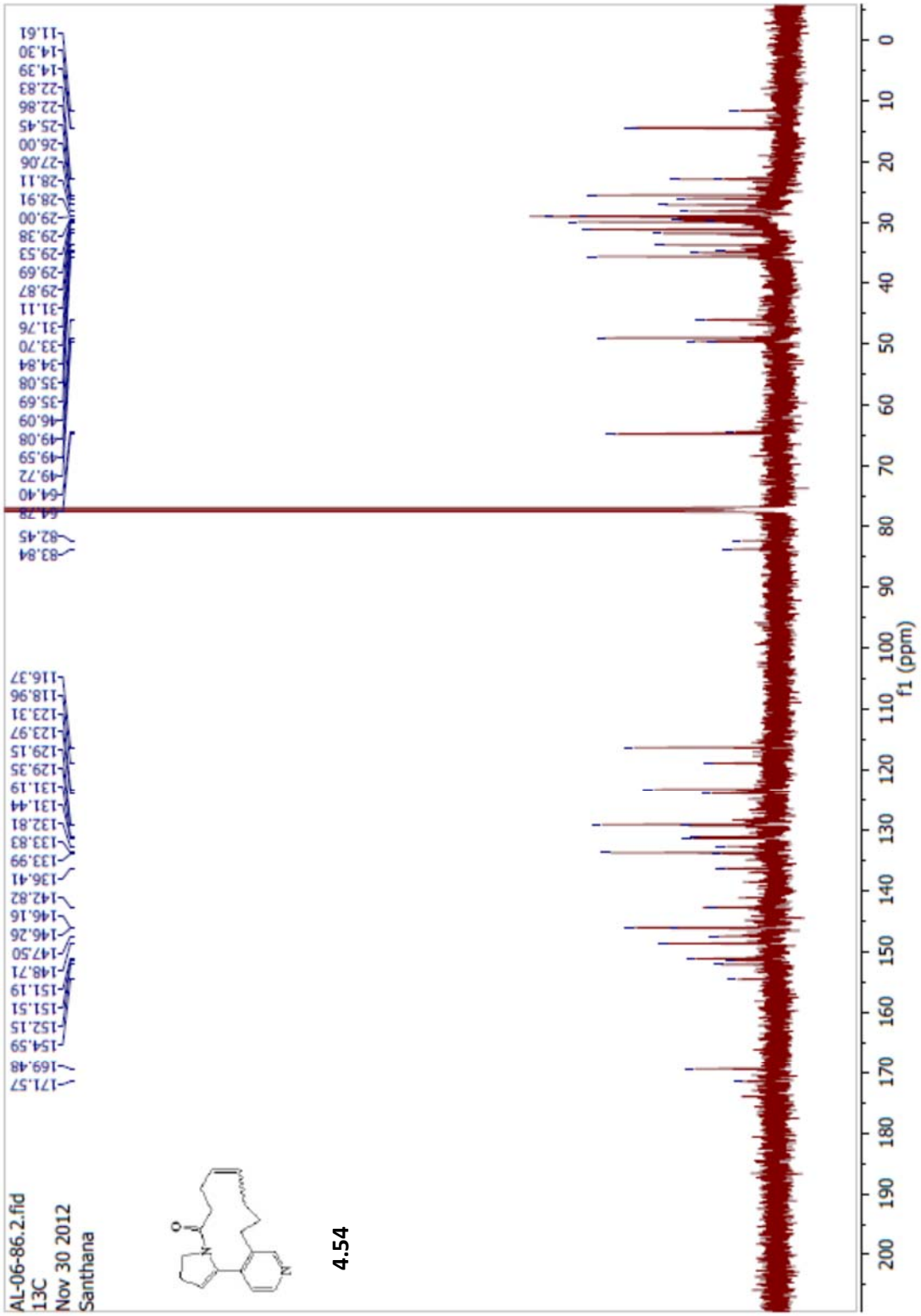

AL-06-66.2.fid
13C AL-06-66
4.52
f1 (ppm)

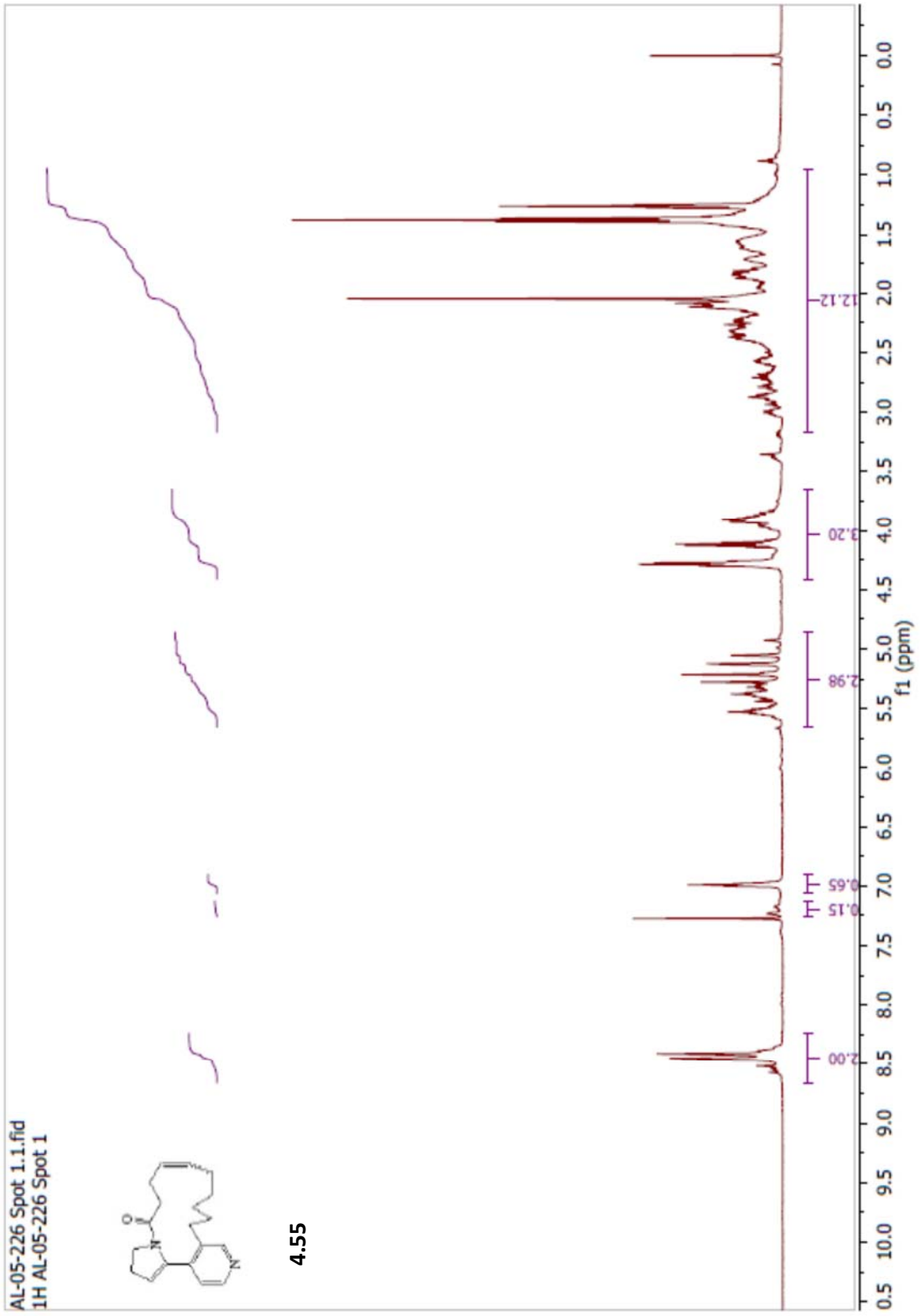

AL-05-170.1.fid
1H AL-05-170
4.53
f1 (ppm)

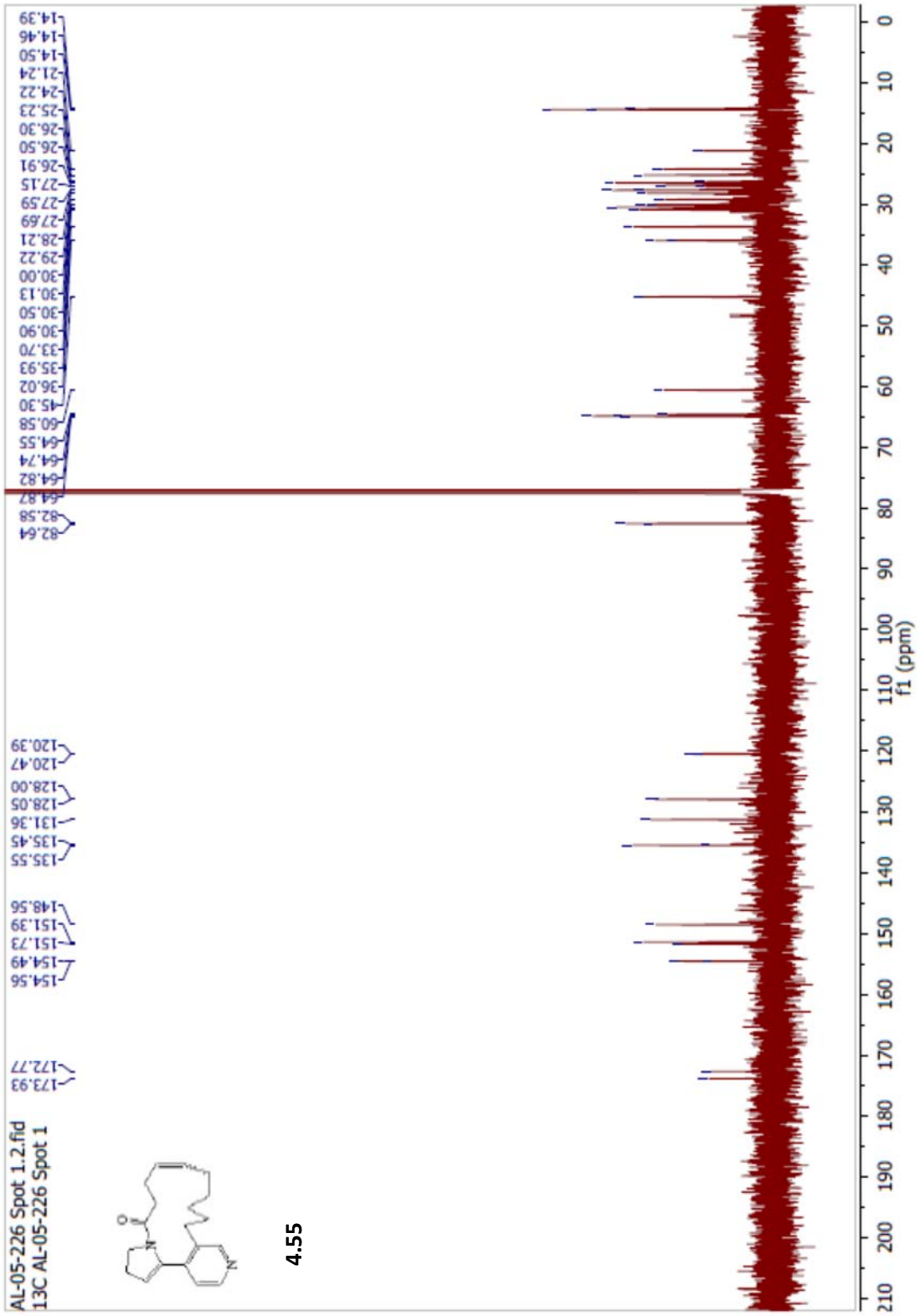


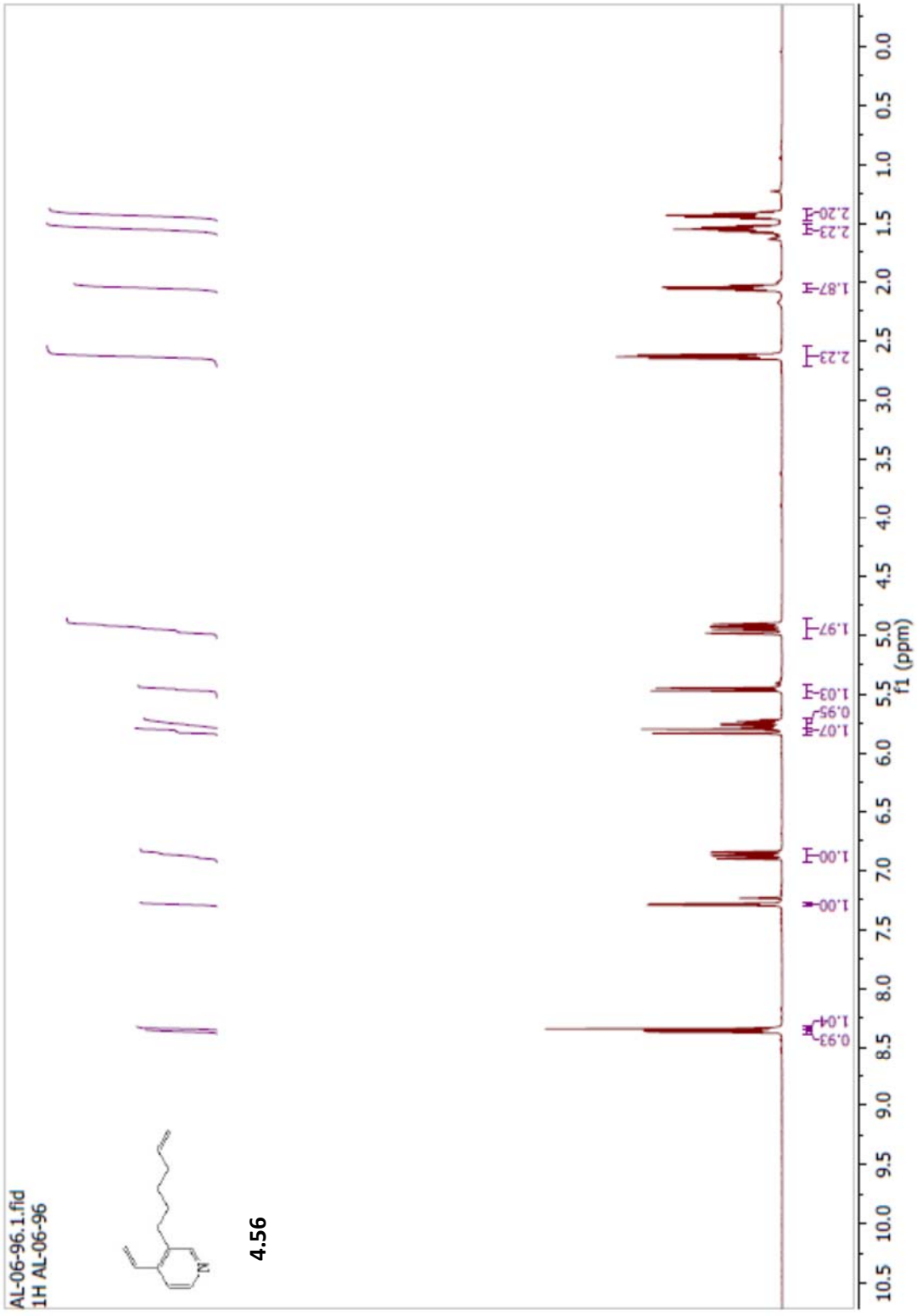
4.53

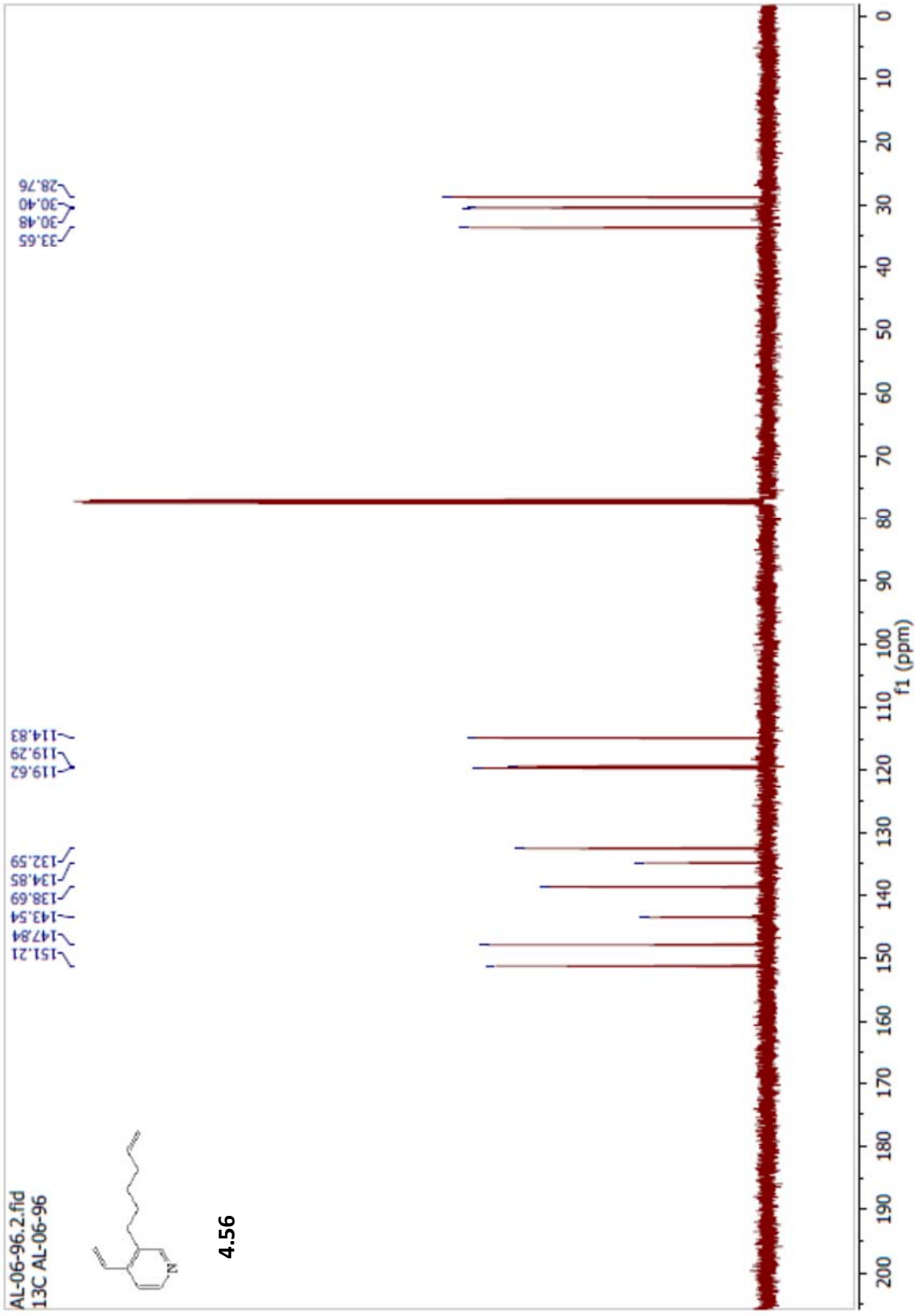

AL-06-86.1.fid
1H AL-06-86
O
N
N
4.54
2.00
0.05
0.84
2.78
2.23
11.72
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

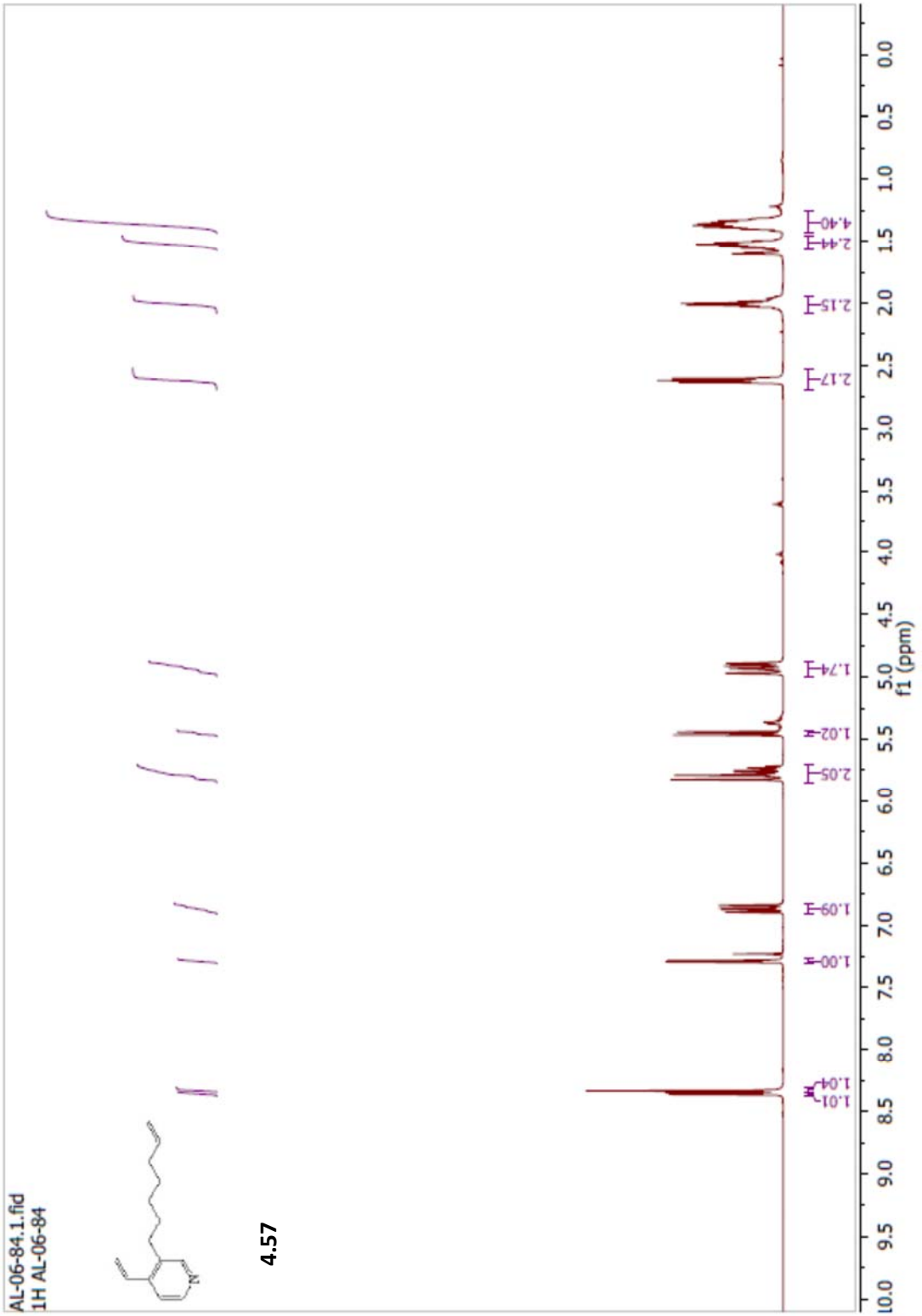

AL-06-86.2.fid
13C
Nov 30 2012
Santhana
4.54
f1 (ppm)

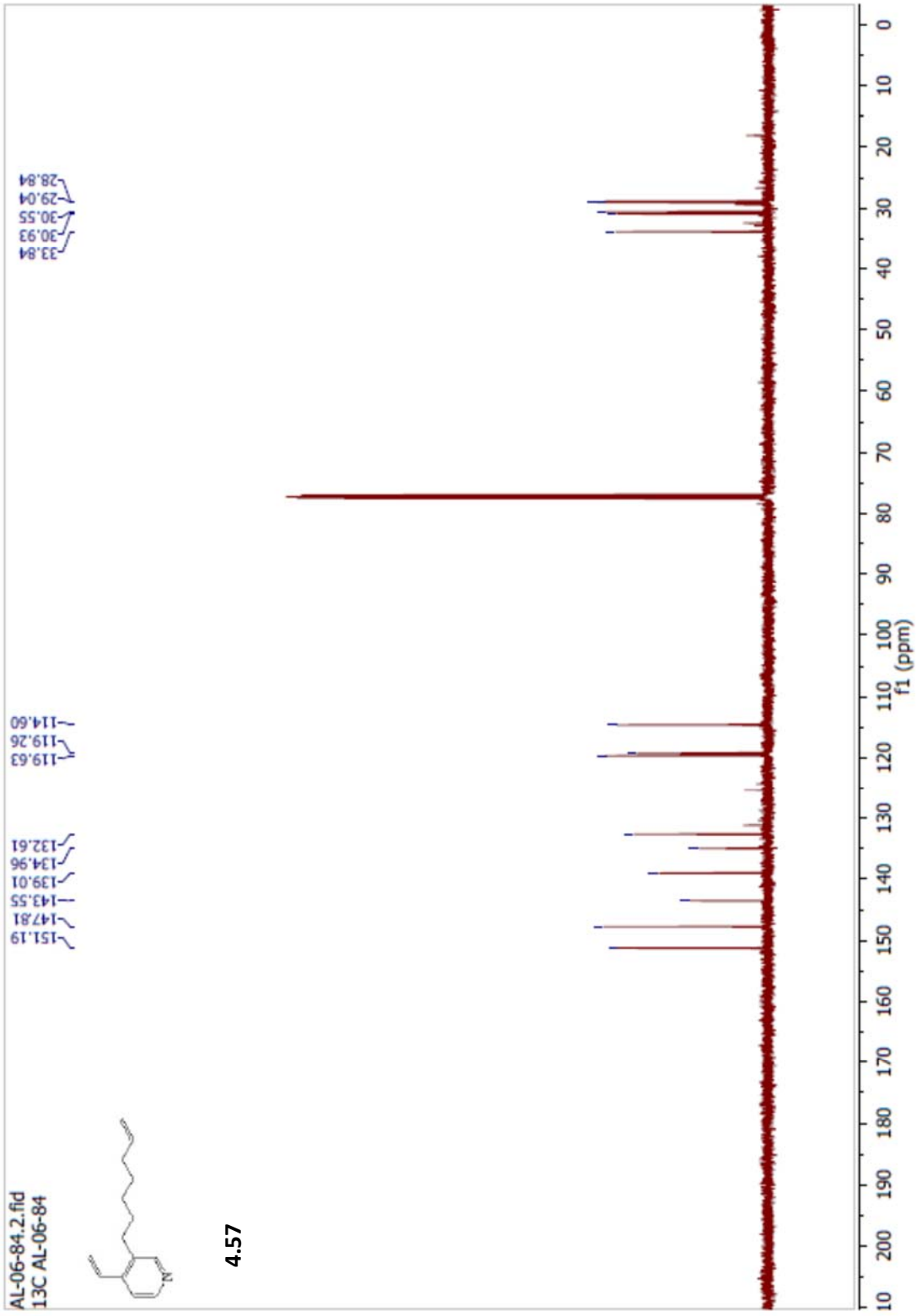

AL-05-226 Spot 1.1.fid
1H AL-05-226 Spot 1
4.55
2.00
0.15
0.65
2.98
3.20
12.12
f1 (ppm)

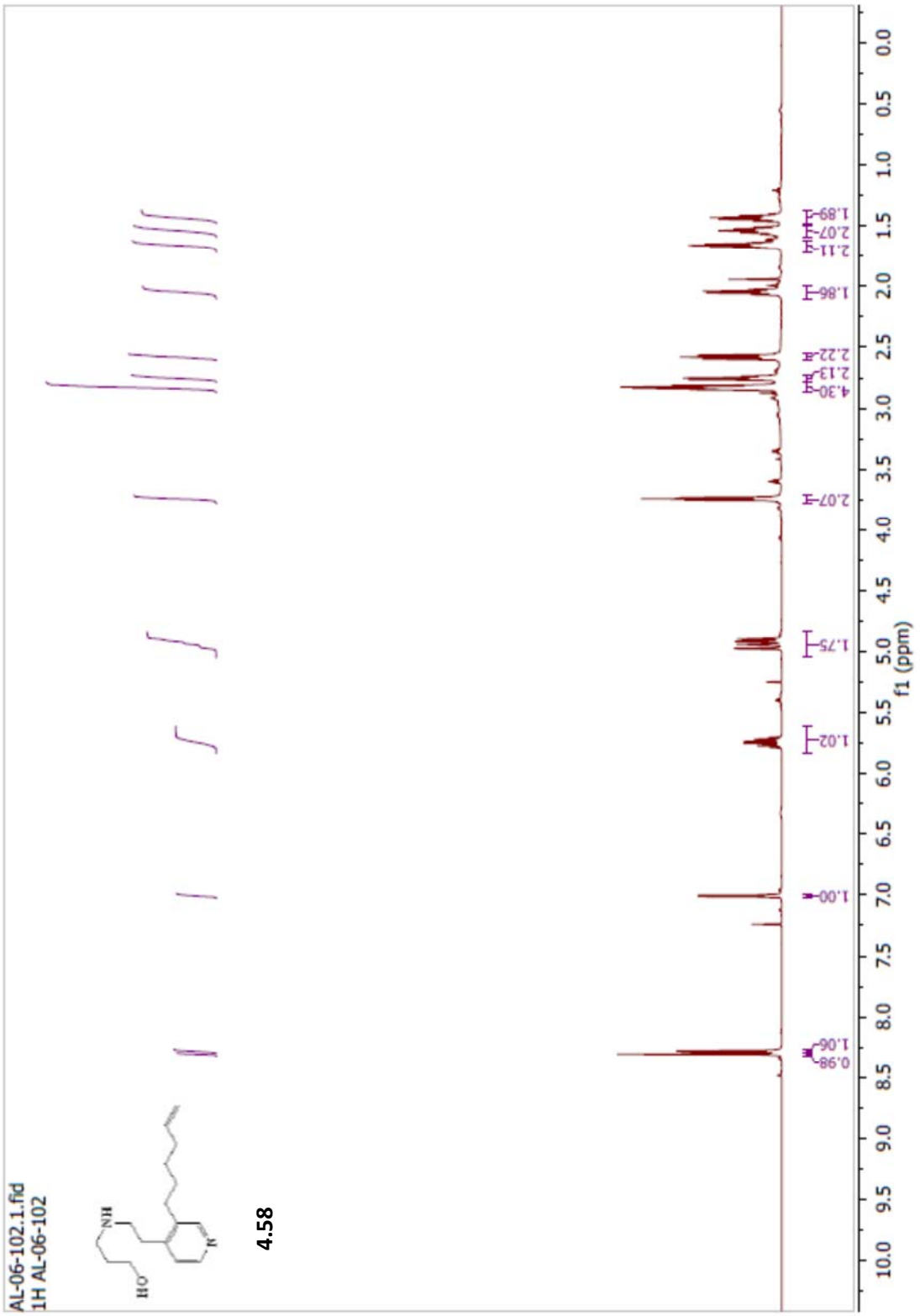

AL-05-226 Spot 1.2.fid
13C AL-05-226 Spot 1
14.39
14.46
14.50
21.24
24.22
25.23
26.30
26.50
26.91
27.15
27.59
27.69
28.21
29.22
30.00
30.13
30.50
30.90
33.70
35.93
36.02
45.30
60.58
64.55
64.74
64.82
64.87
82.58
82.64
120.39
120.47
128.00
128.05
131.36
135.45
135.55
148.56
151.39
151.73
154.49
154.56
172.77
173.93
4.55
f1 (ppm)

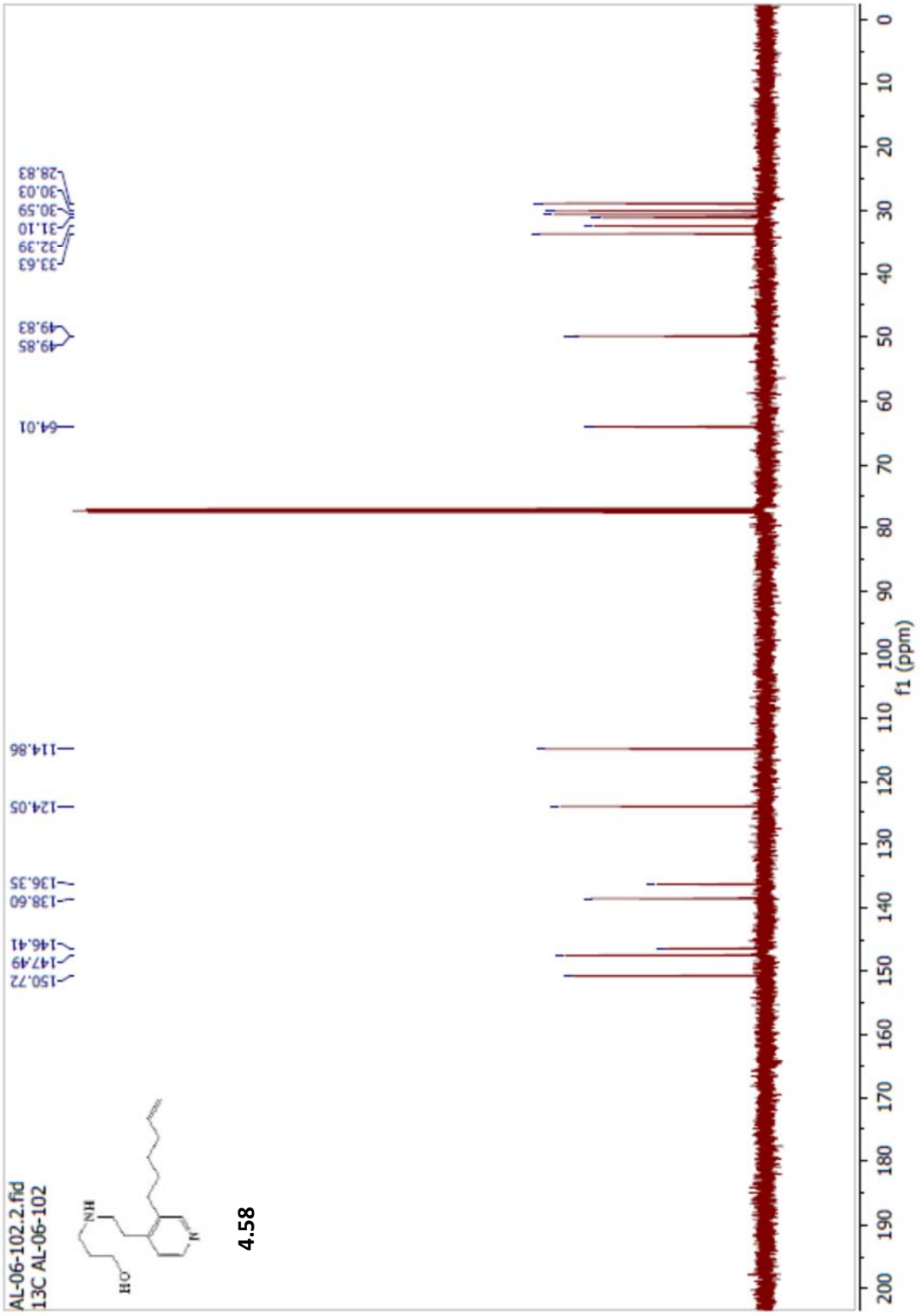

AL-06-96.1.fid
1H AL-06-96
4.56
f1 (ppm)


AL-06-96.2.fid
13C AL-06-96
4.56
151.21
147.84
143.54
138.69
134.85
132.59
119.62
119.29
114.83
33.65
30.48
30.40
28.76
f1 (ppm)


AL-06-84.1.fid
1H AL-06-84
4.57
1.01
1.04
1.00
1.09
2.05
1.02
1.74
2.17
2.15
2.44
4.40
f1 (ppm)


AL-06-84.2.fid
13C AL-06-84
4.57
151.19
147.81
143.55
139.01
134.96
132.61
119.63
119.26
114.60
33.84
30.93
30.55
29.04
28.84
f1 (ppm)


AL-06-102.1.fid
1H AL-06-102
4.58
f1 (ppm)


AL-06-102.2.fid
13C AL-06-102
4.58
150.72
147.49
146.41
138.60
136.35
124.05
114.86
64.01
49.85
49.83
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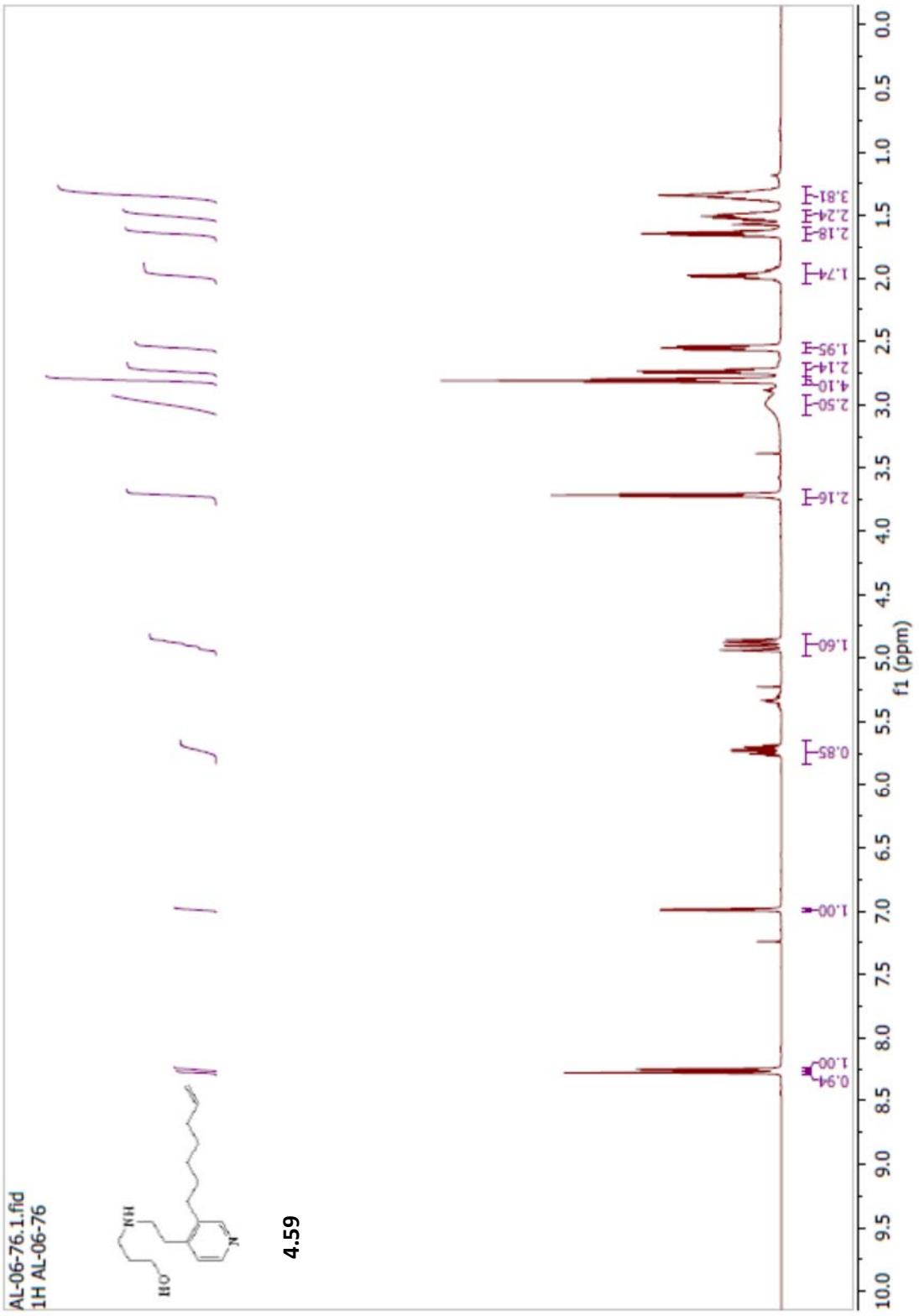
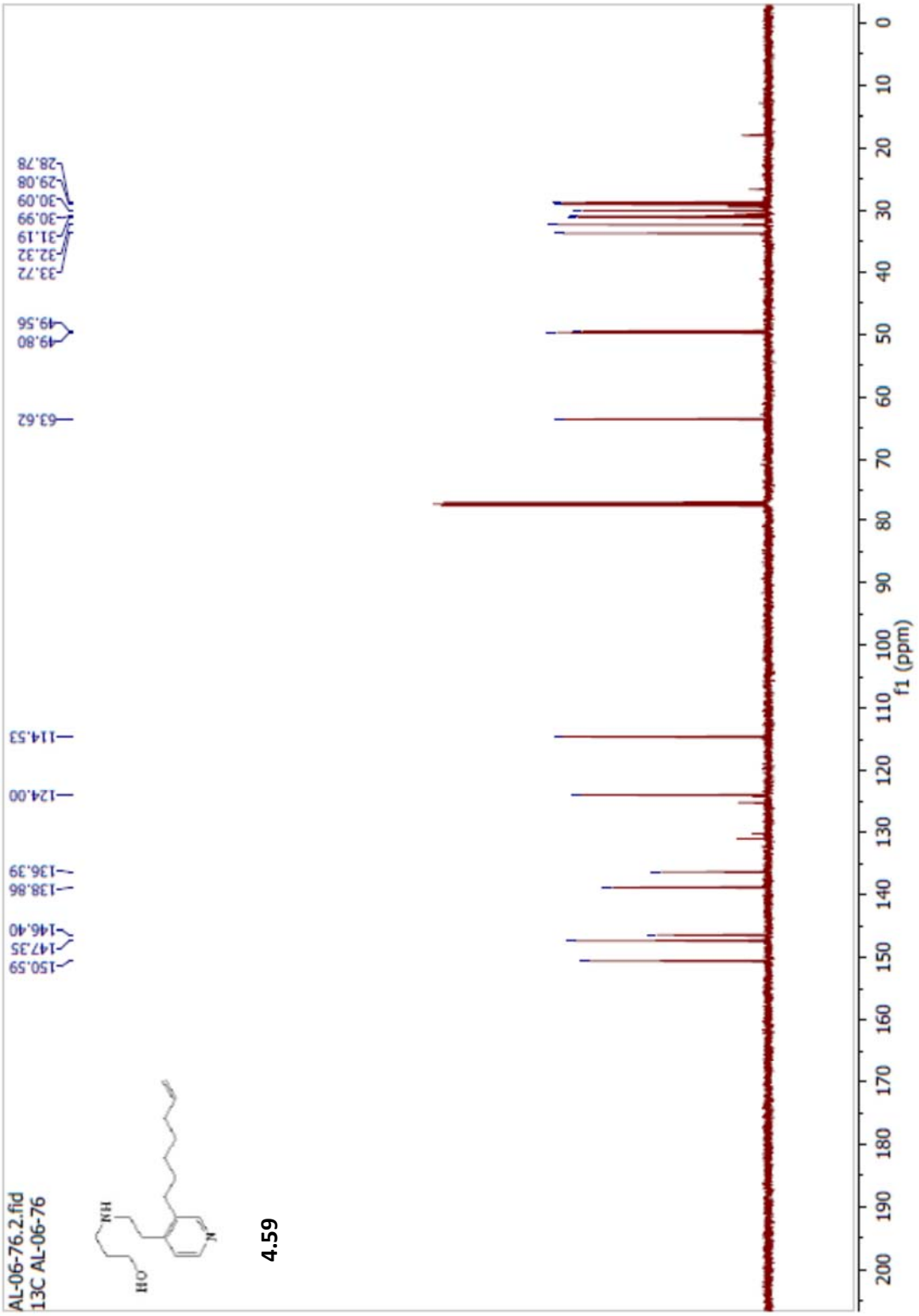
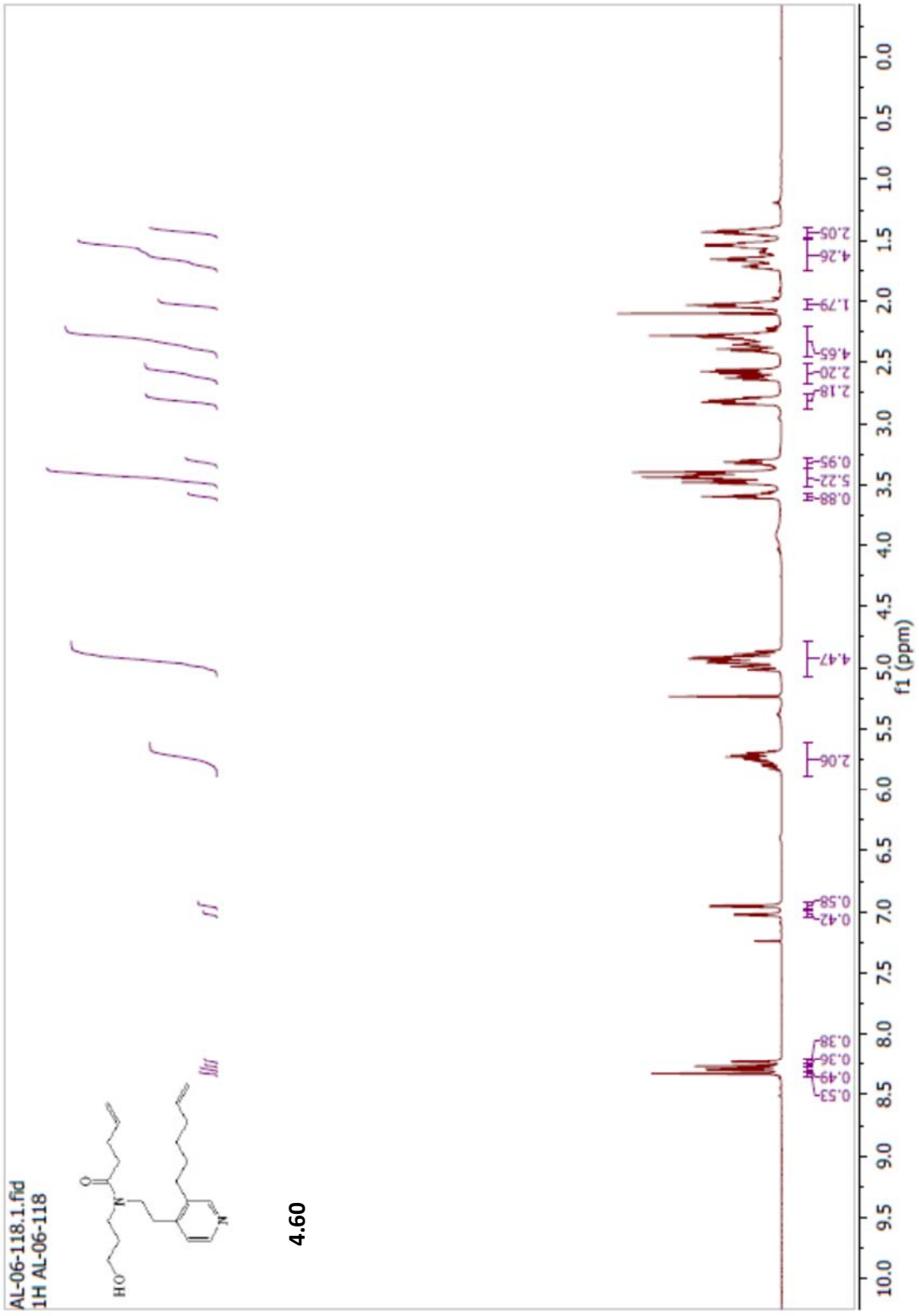
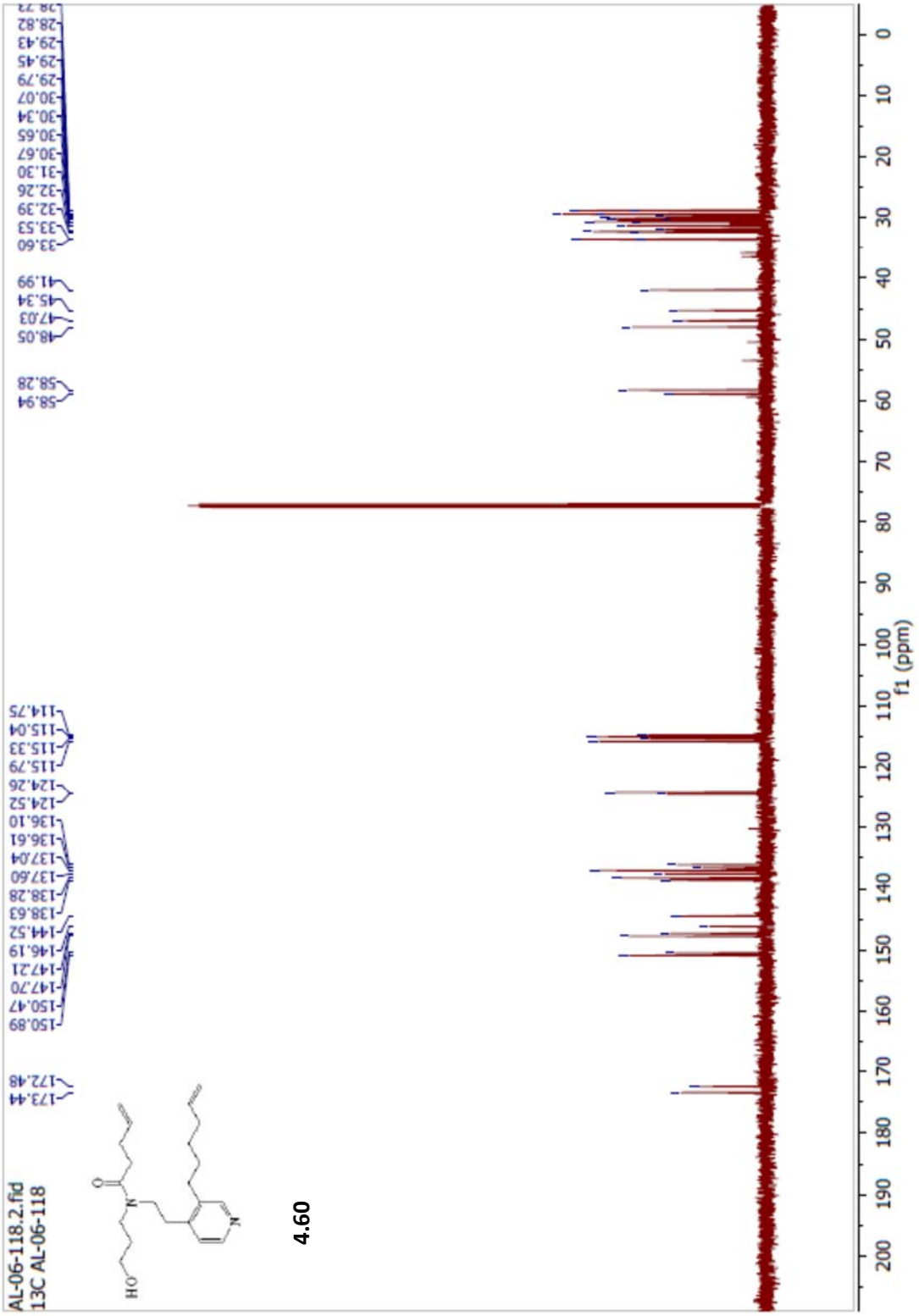
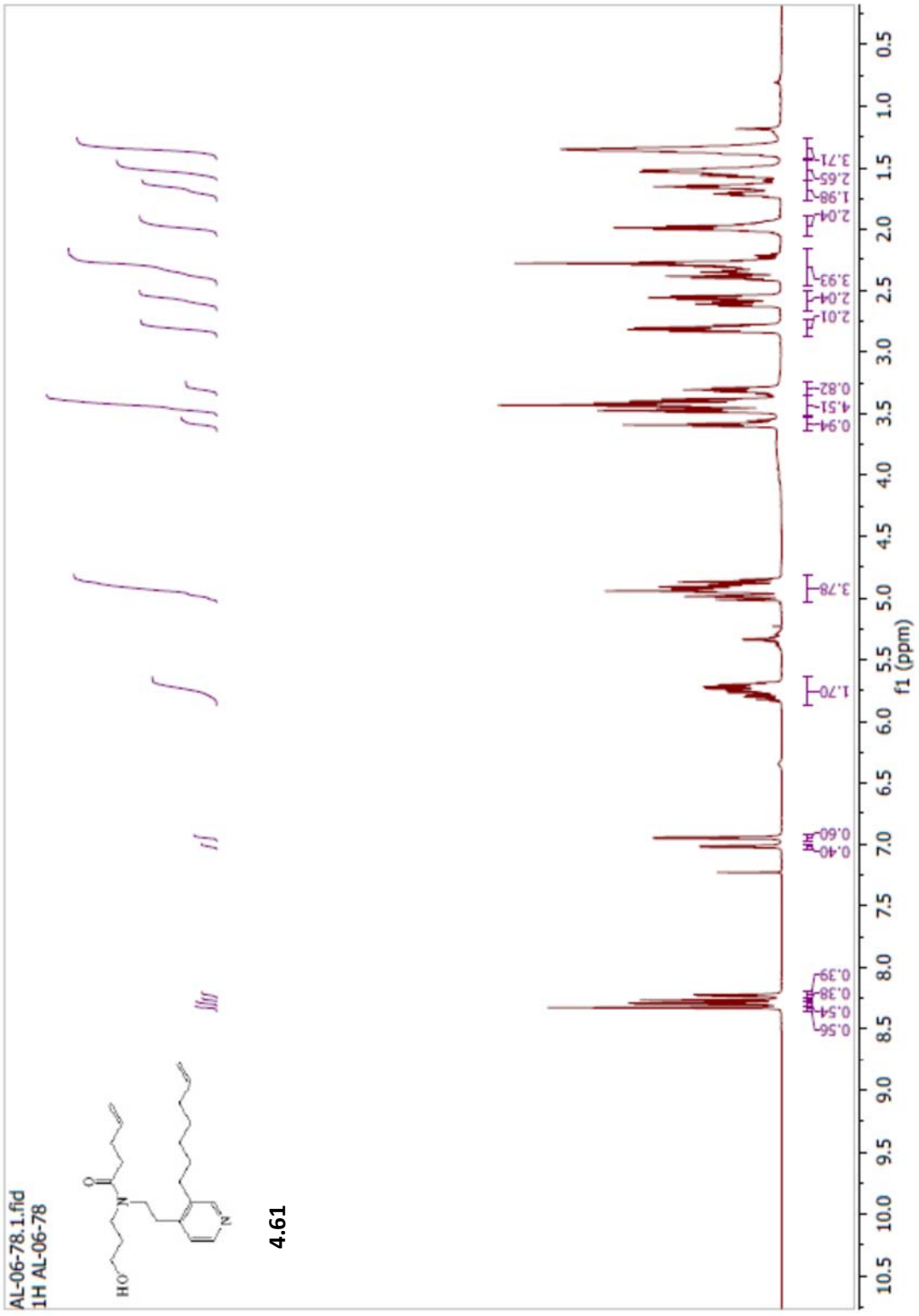
32.39
31.10
30.59
30.03
28.83
f1 (ppm)


AL-06-76.1.fid
1H AL-06-76
HN
HO
N
4.59
0.94
1.00
1.00
0.85
1.60
2.16
2.50
4.10
2.14
1.95
1.74
2.18
2.24
3.81
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

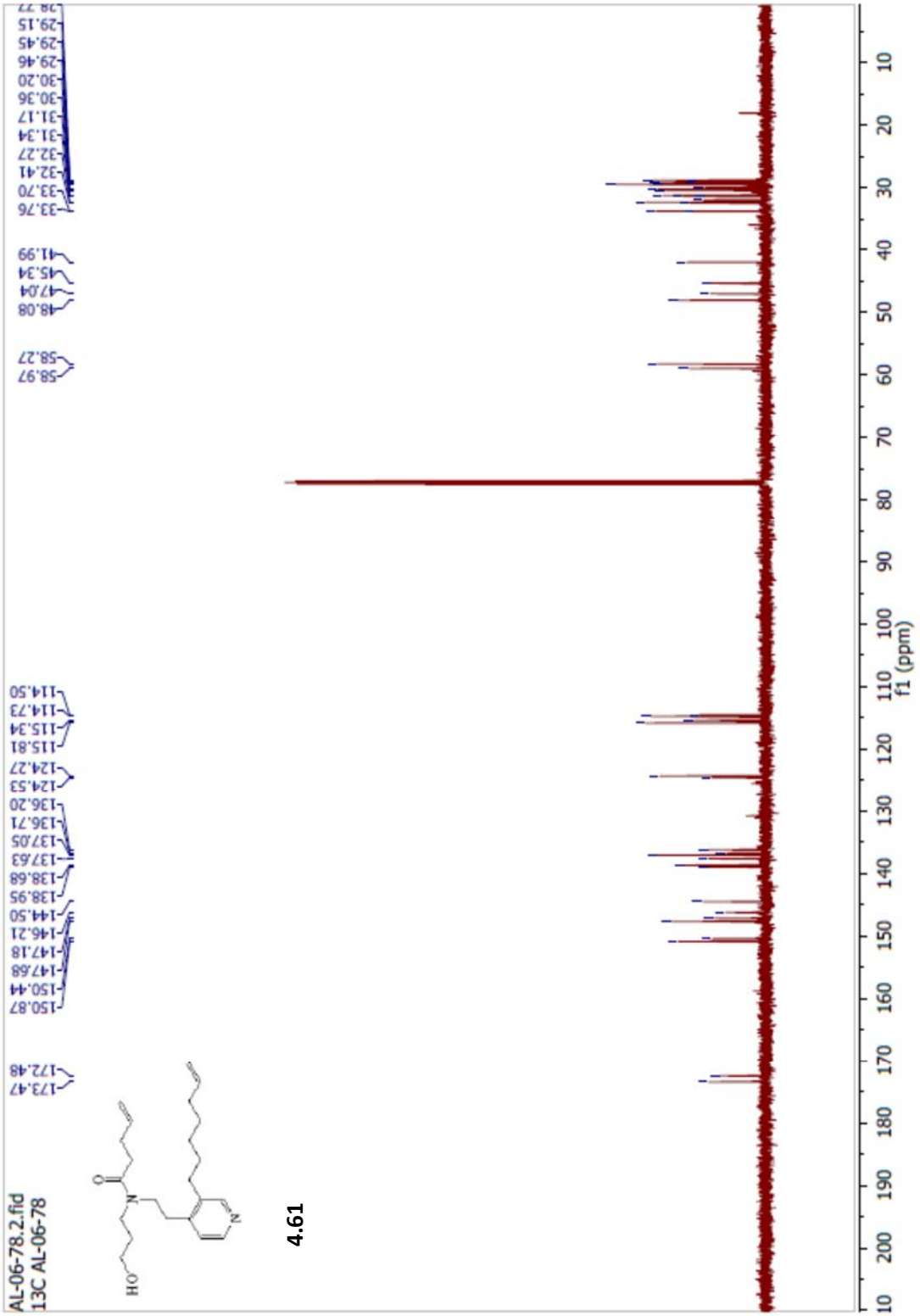

AL-06-76.2.fid
13C AL-06-76
4.59
150.59
147.35
146.40
138.86
136.39
124.00
114.53
63.62
49.80
49.56
33.72
32.32
31.19
30.99
30.09
29.08
28.78
f1 (ppm)

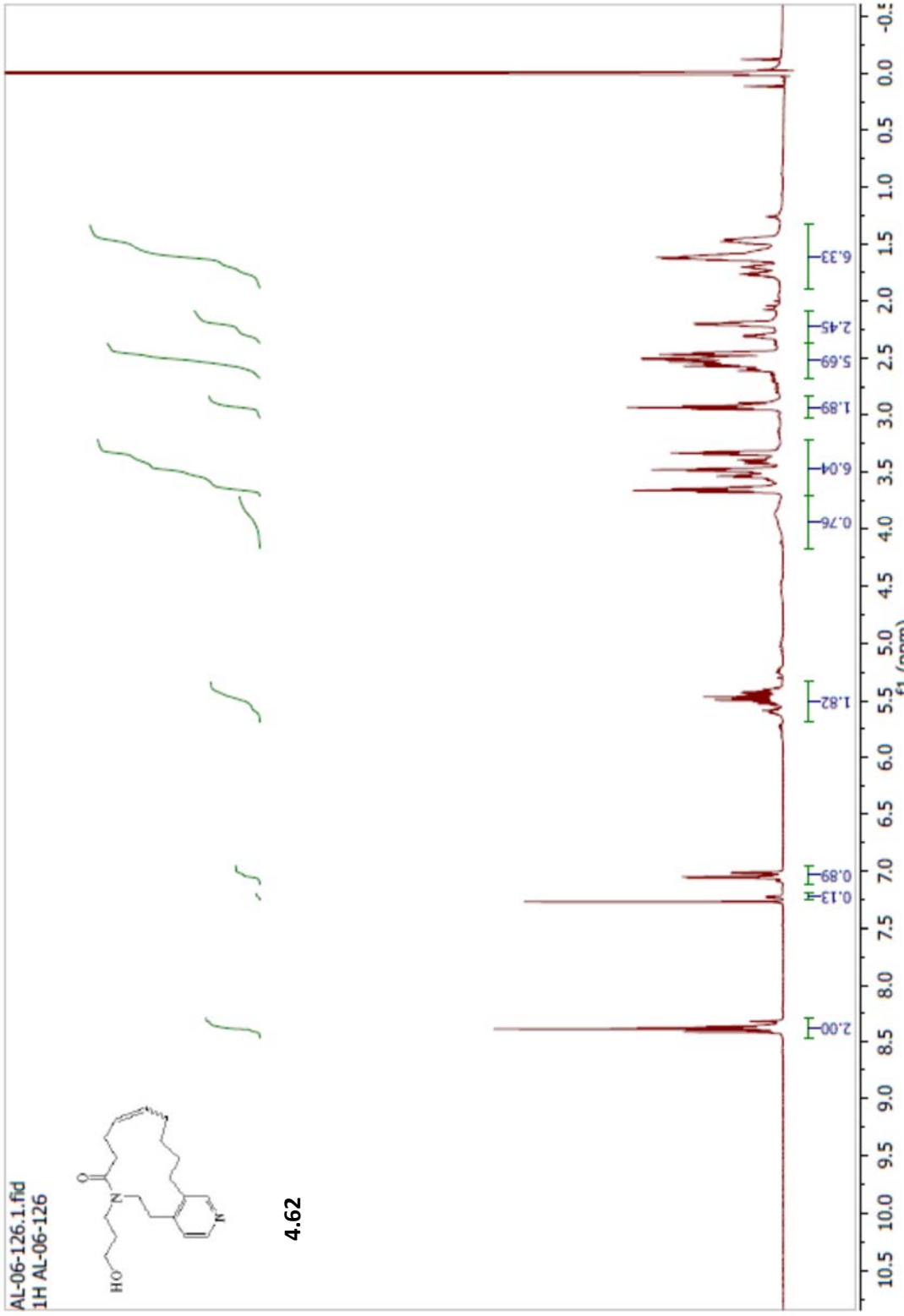

AL-06-118.1.fid
1H AL-06-118
4.60
0.53
0.49
0.36
0.38
0.42
0.58
2.06
4.47
0.88
5.22
0.95
2.18
2.20
4.65
1.79
4.26
2.05
f1 (ppm)

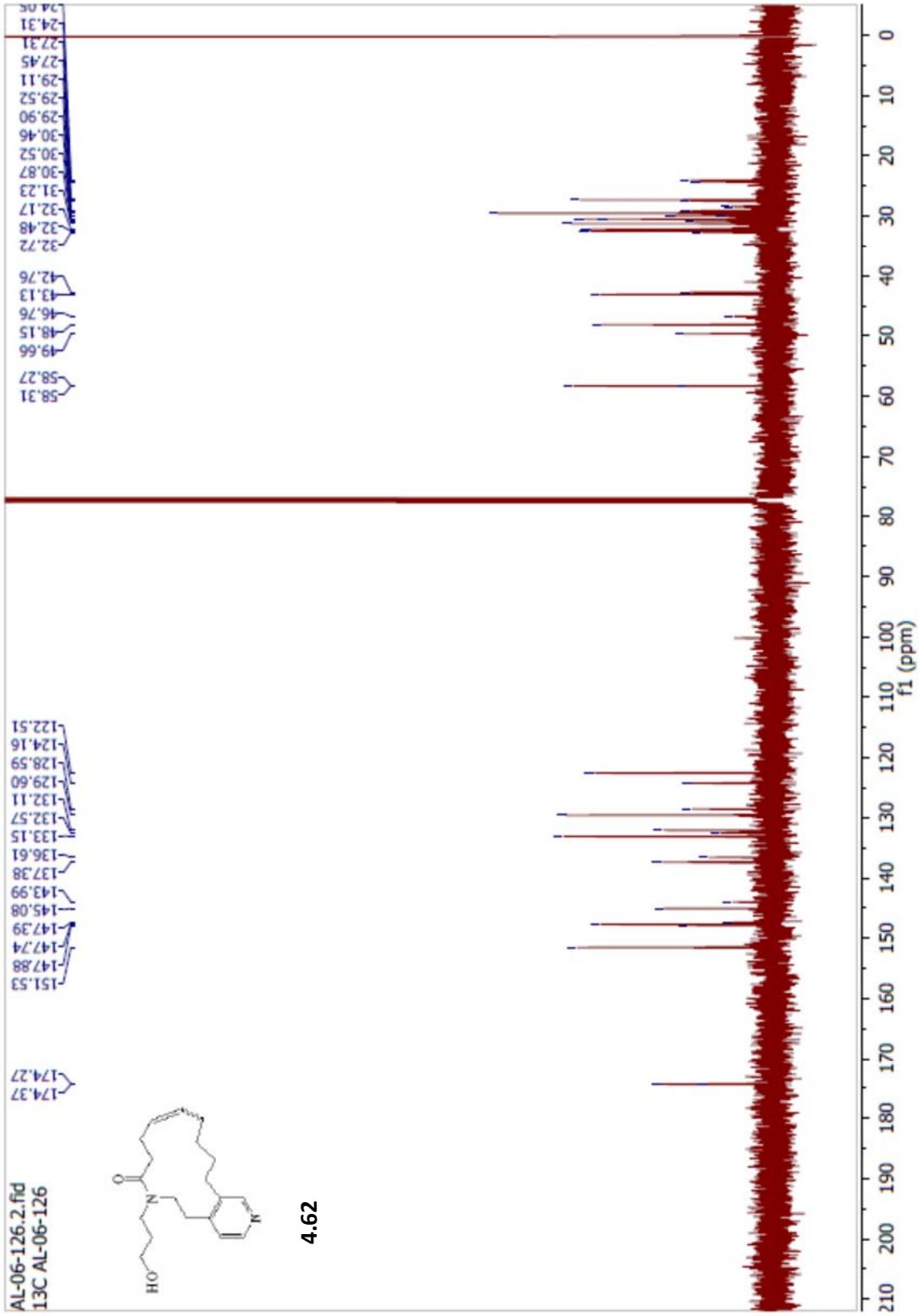

AL-06-118.2.fid
13C AL-06-118
4.60
f1 (ppm)

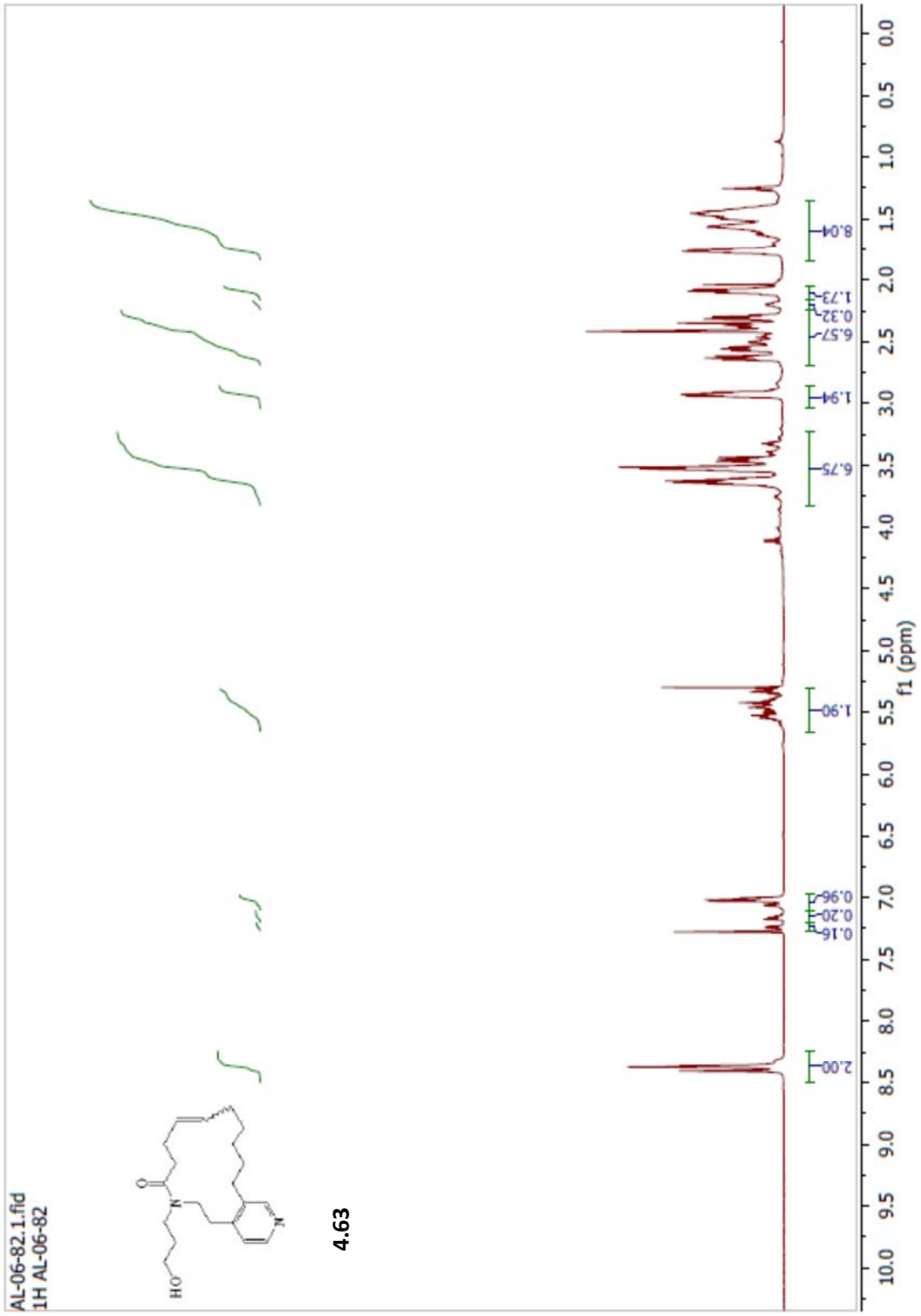


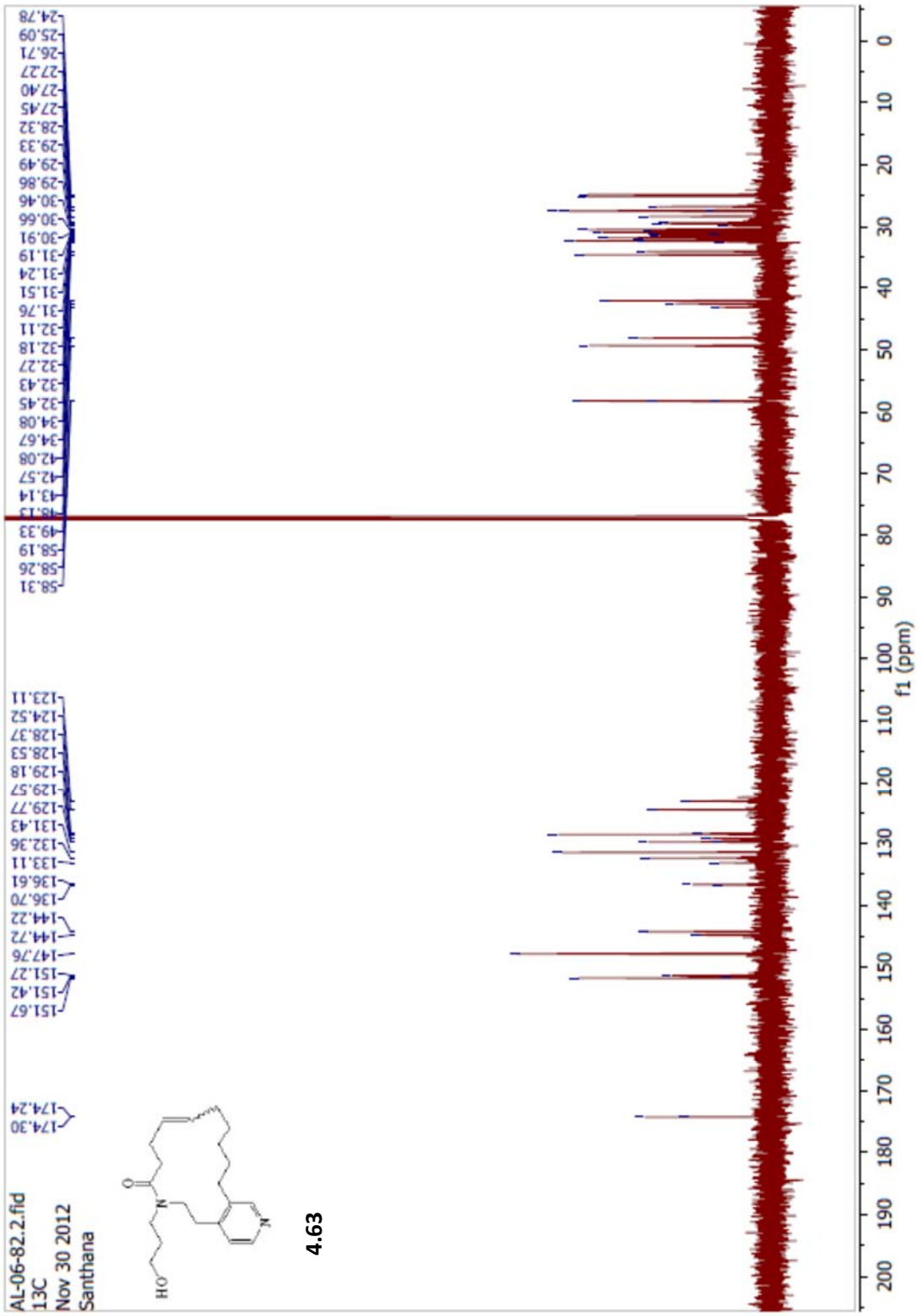
4.61

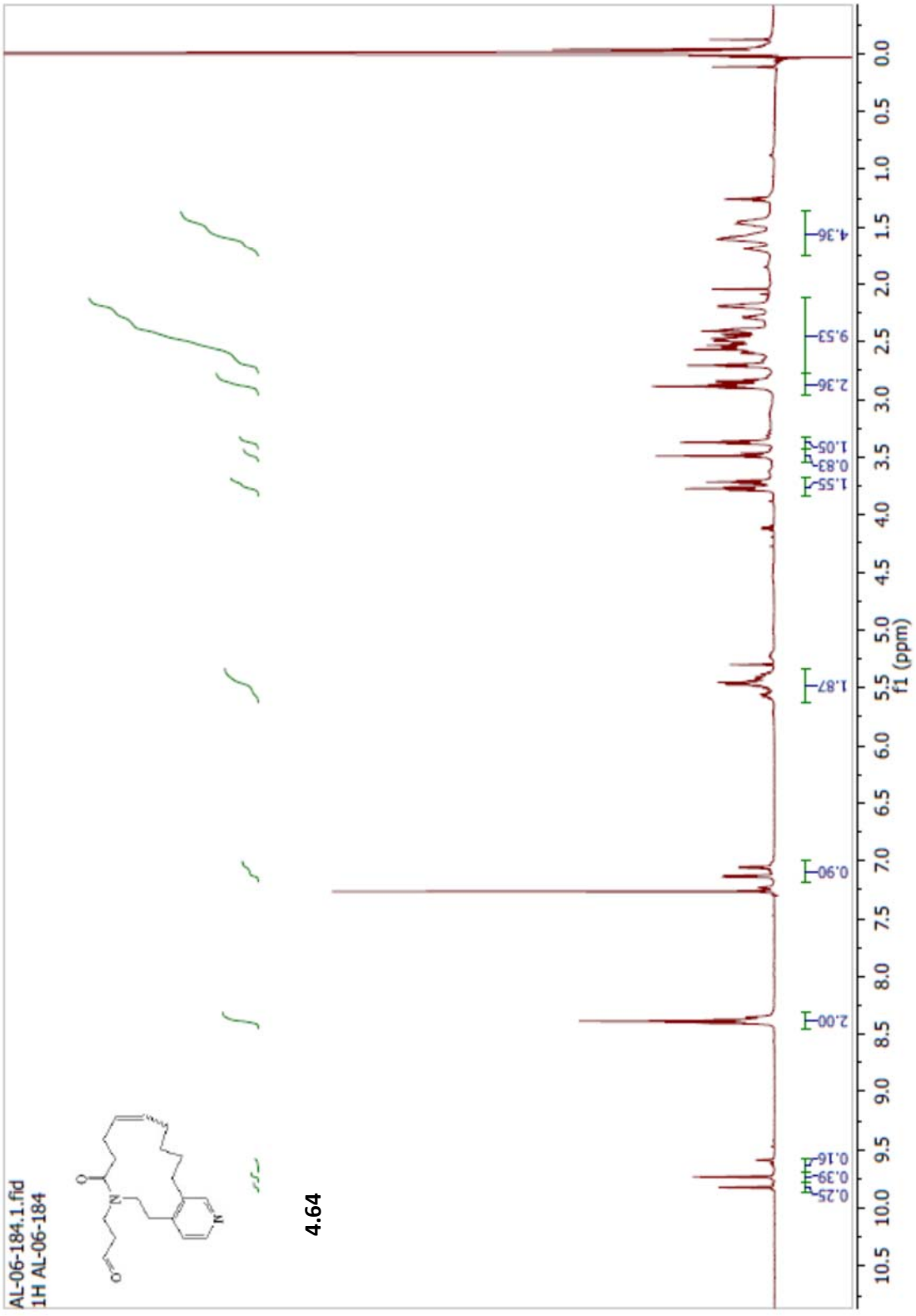

AL-06-78.2.fid
13C AL-06-78
4.61
f1 (ppm)

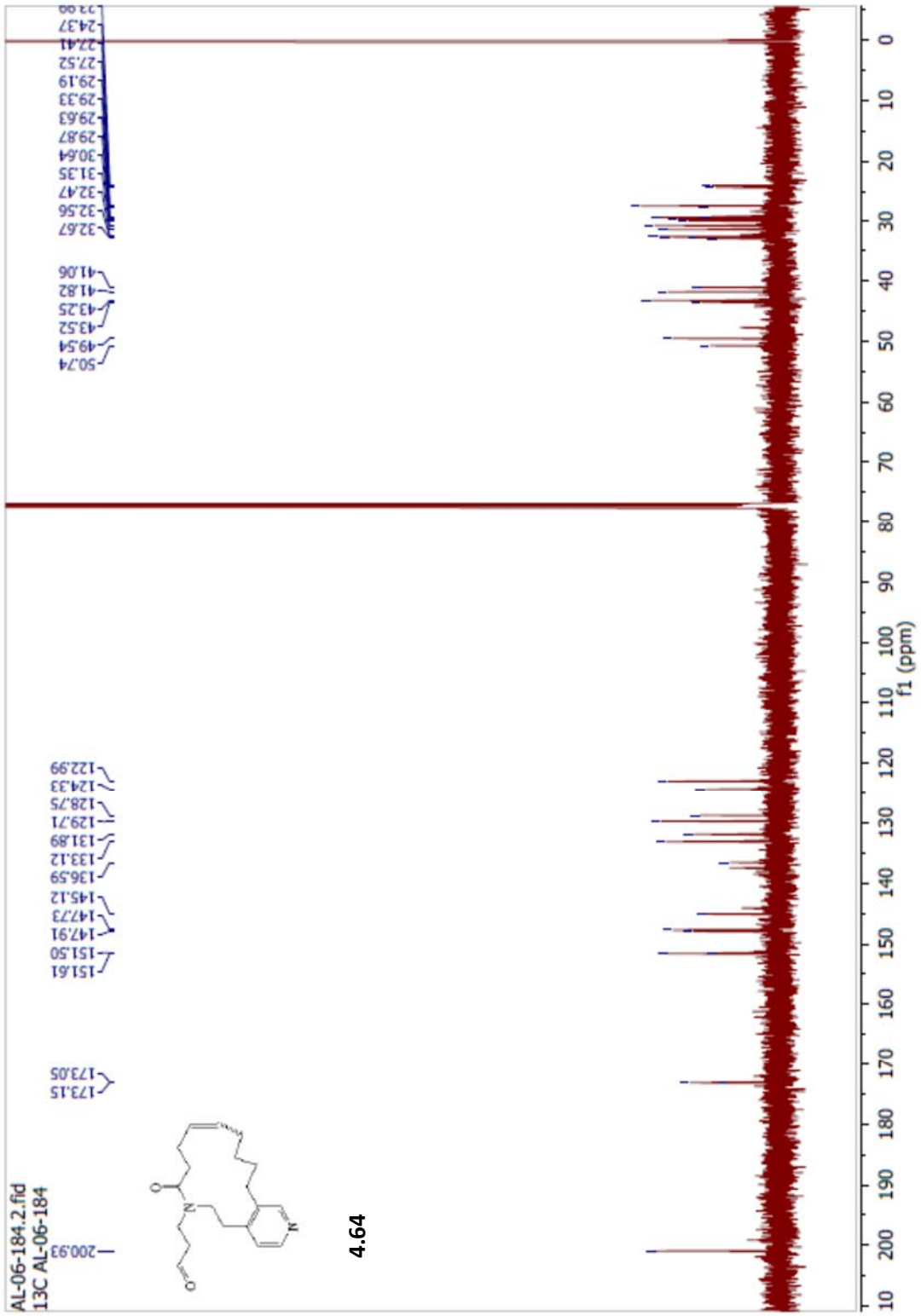

AL-06-126.1.fid
1H AL-06-126
4.62
f1 (ppm)


AL-06-126.2.fid
13C AL-06-126
4.62
f1 (ppm)

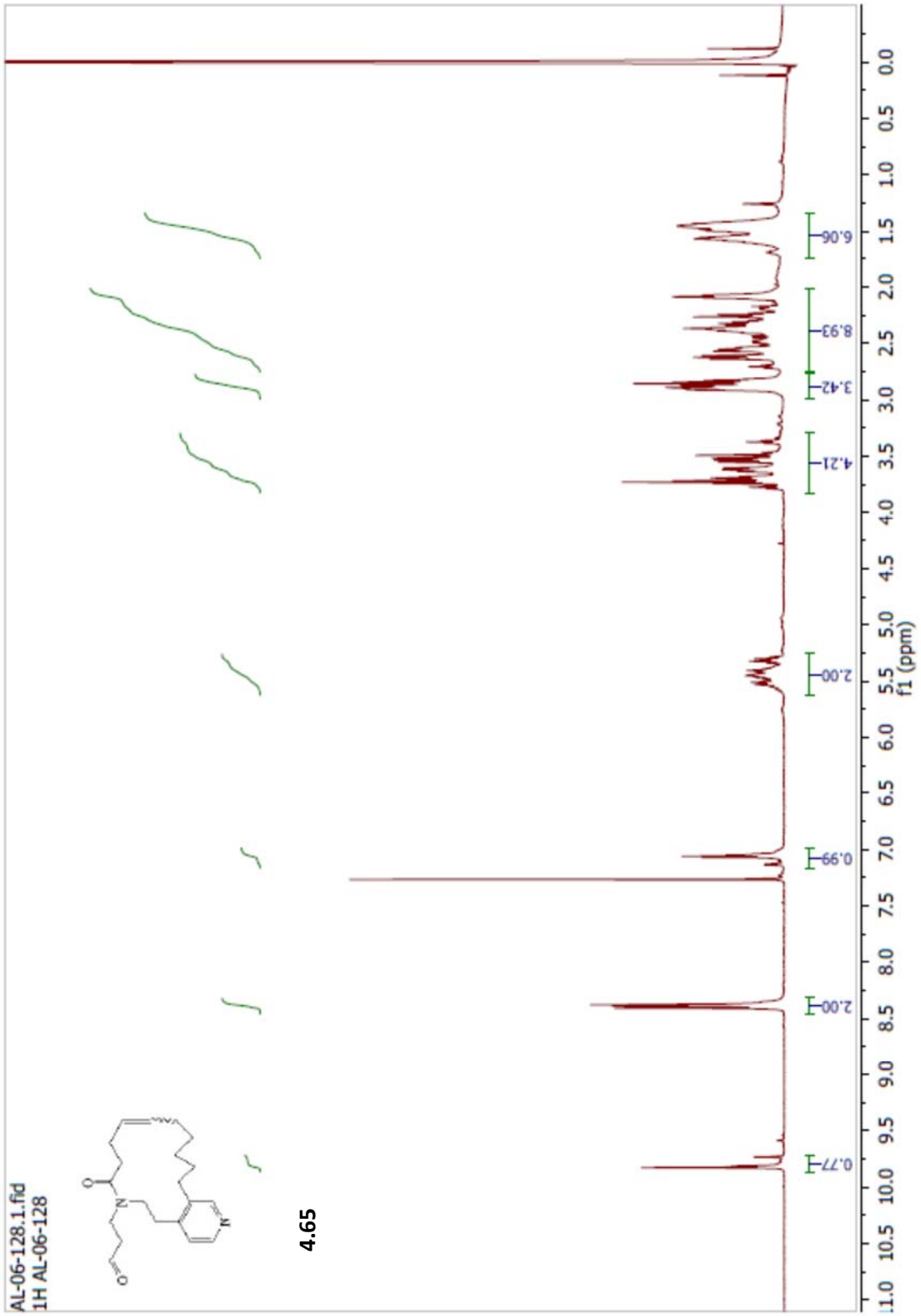

AL-06-82.1.fid
1H AL-06-82
HO
N
O
N
4.63
2.00
0.96
1.00
0.20
0.16
1.90
6.75
1.94
6.57
0.32
1.73
8.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

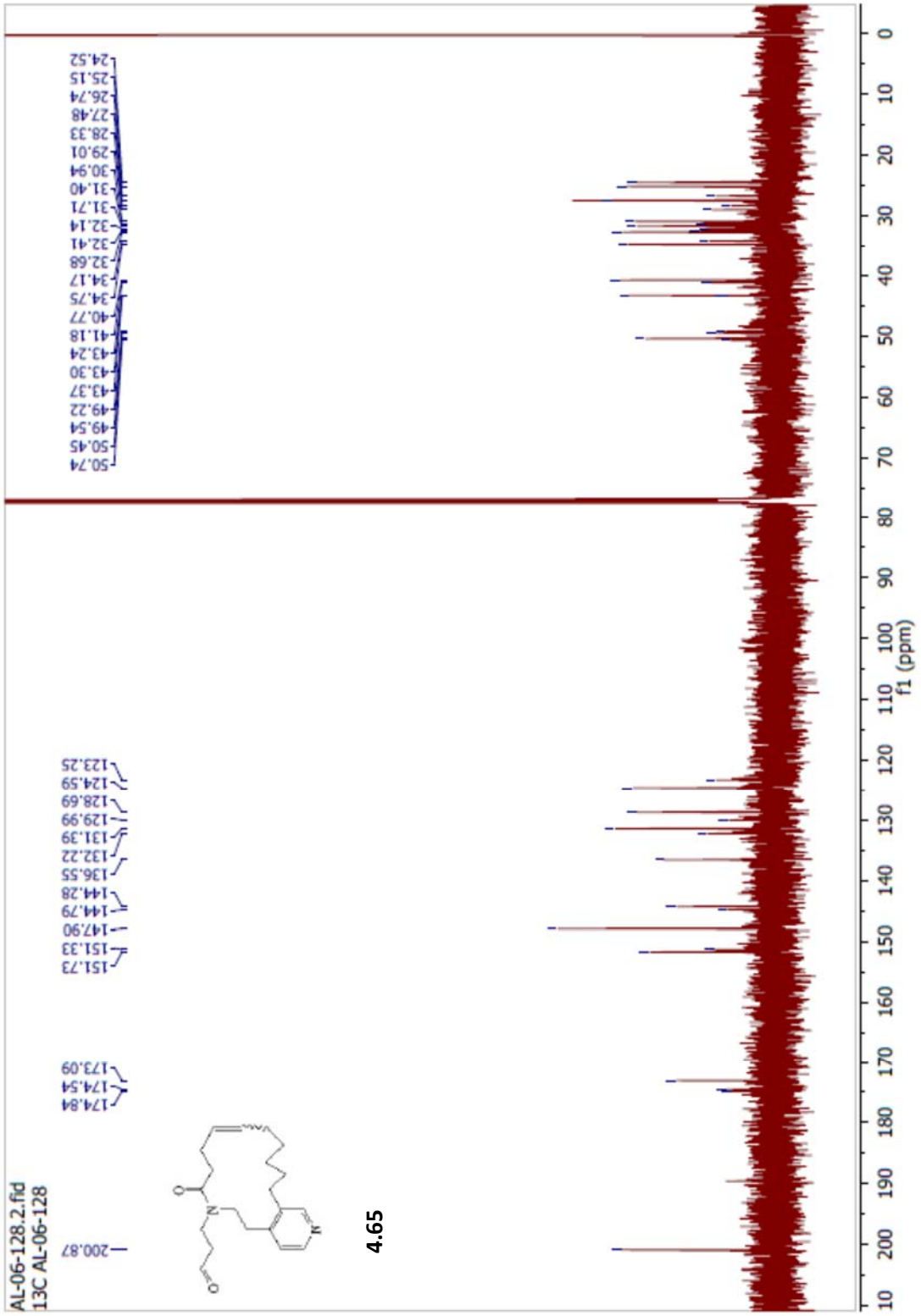

AL-06-82.2.fid
13C
Nov 30 2012
Santhana
4.63
f1 (ppm)


AL-06-184.1.fid
1H AL-06-184
4.64
f1 (ppm)

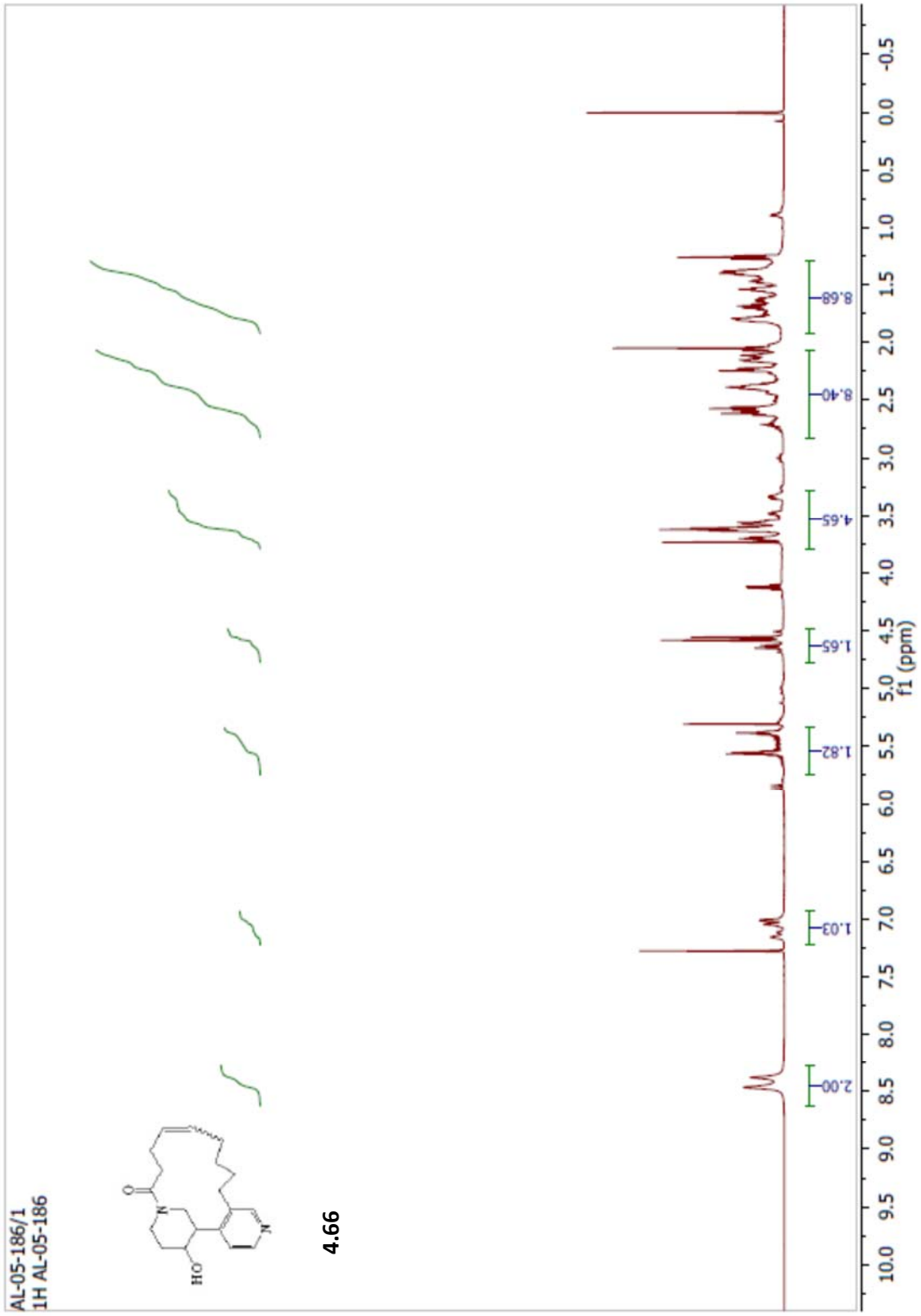

AL-06-184.2.fid
13C AL-06-184
200.93
173.15
173.05
151.61
151.50
147.91
147.73
145.12
136.59
133.12
131.89
129.71
128.75
124.33
122.99
50.74
49.54
43.52
43.25
41.82
41.06
32.67
32.56
32.47
31.35
30.64
29.87
29.63
29.33
29.19
27.52
22.41
24.37
23.98
f1 (ppm)

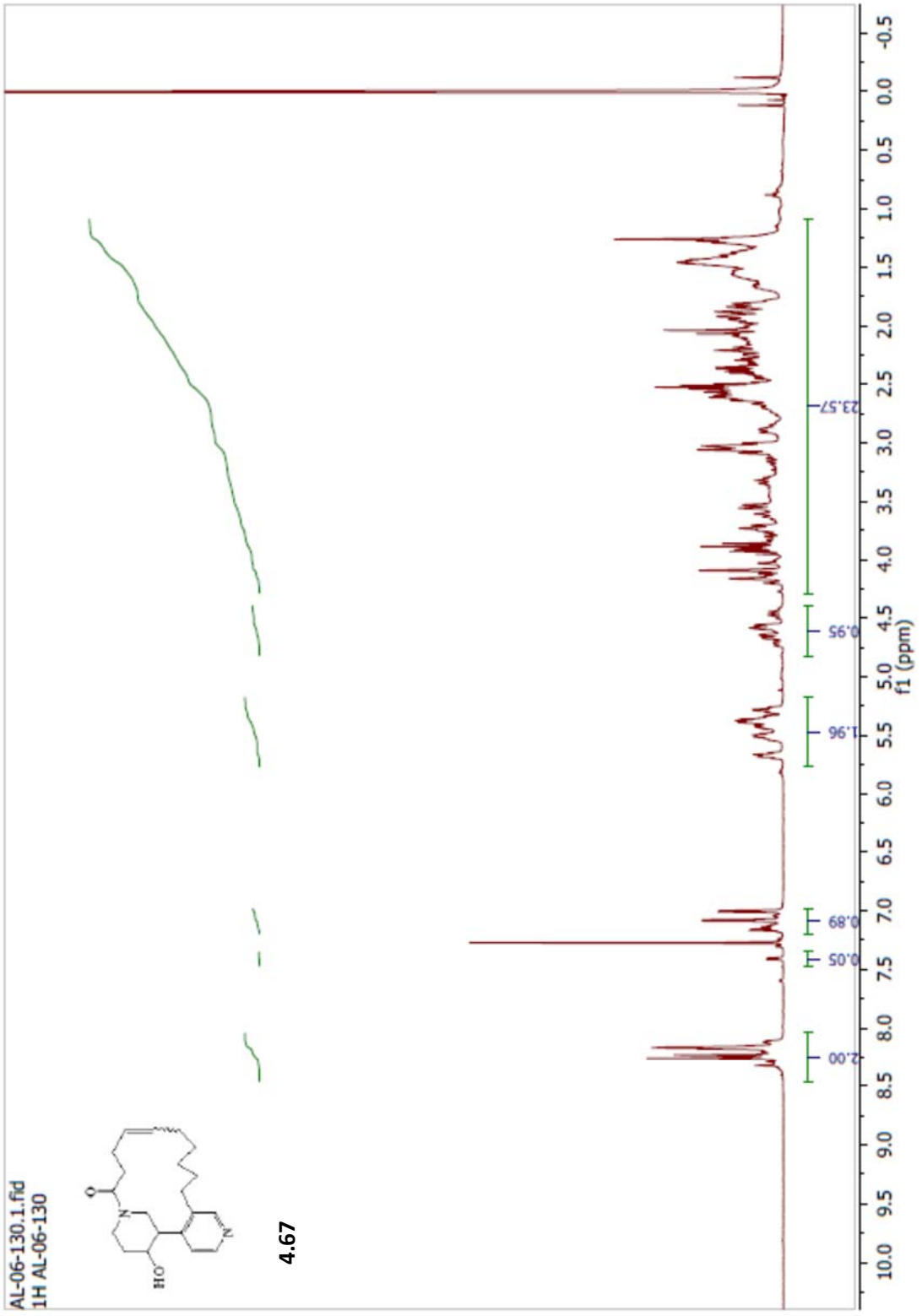
4.64

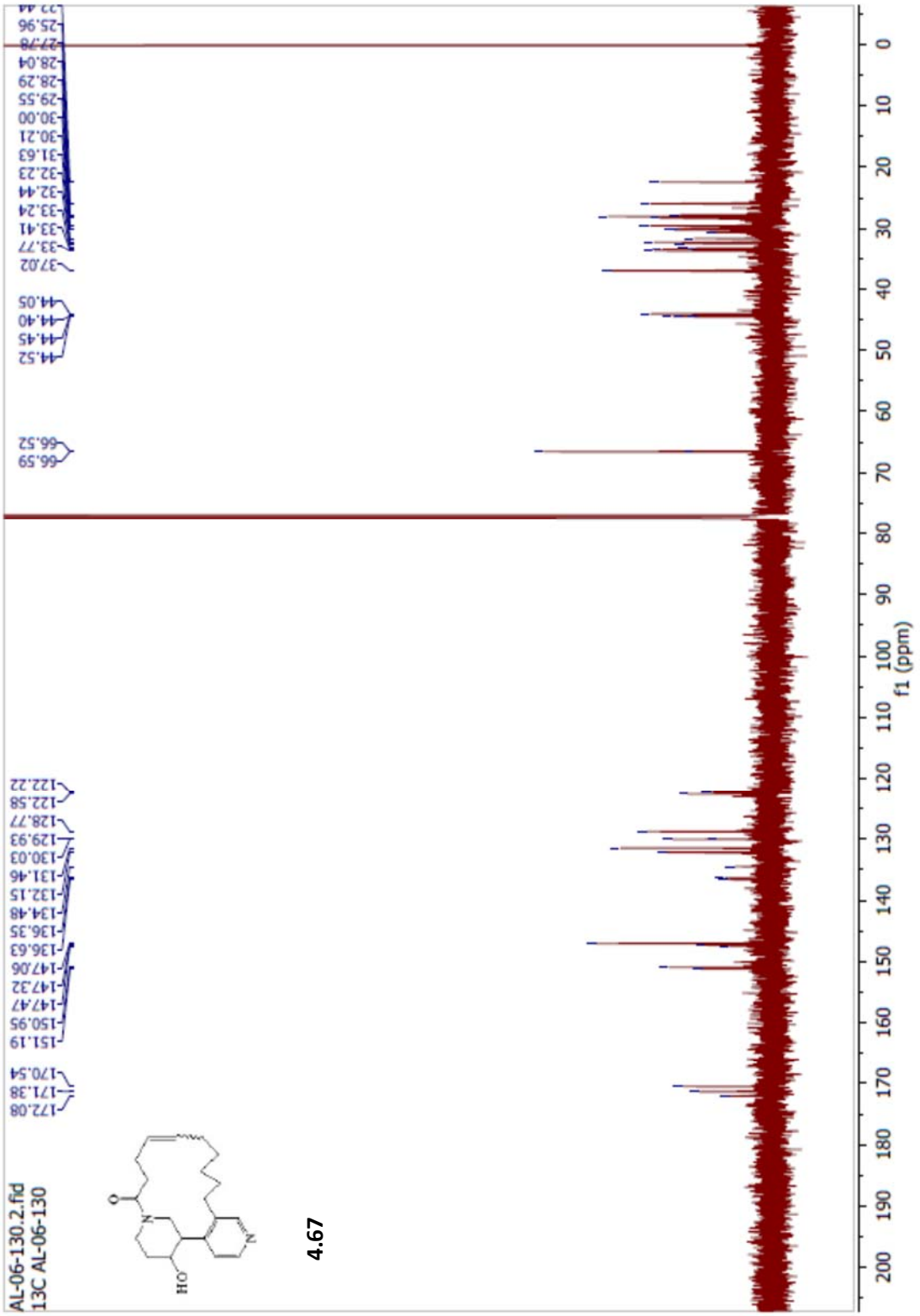

AL-06-128.1.fid
1H AL-06-128
4.65
0.77
2.00
0.99
2.00
4.21
3.42
8.93
6.06
f1 (ppm)

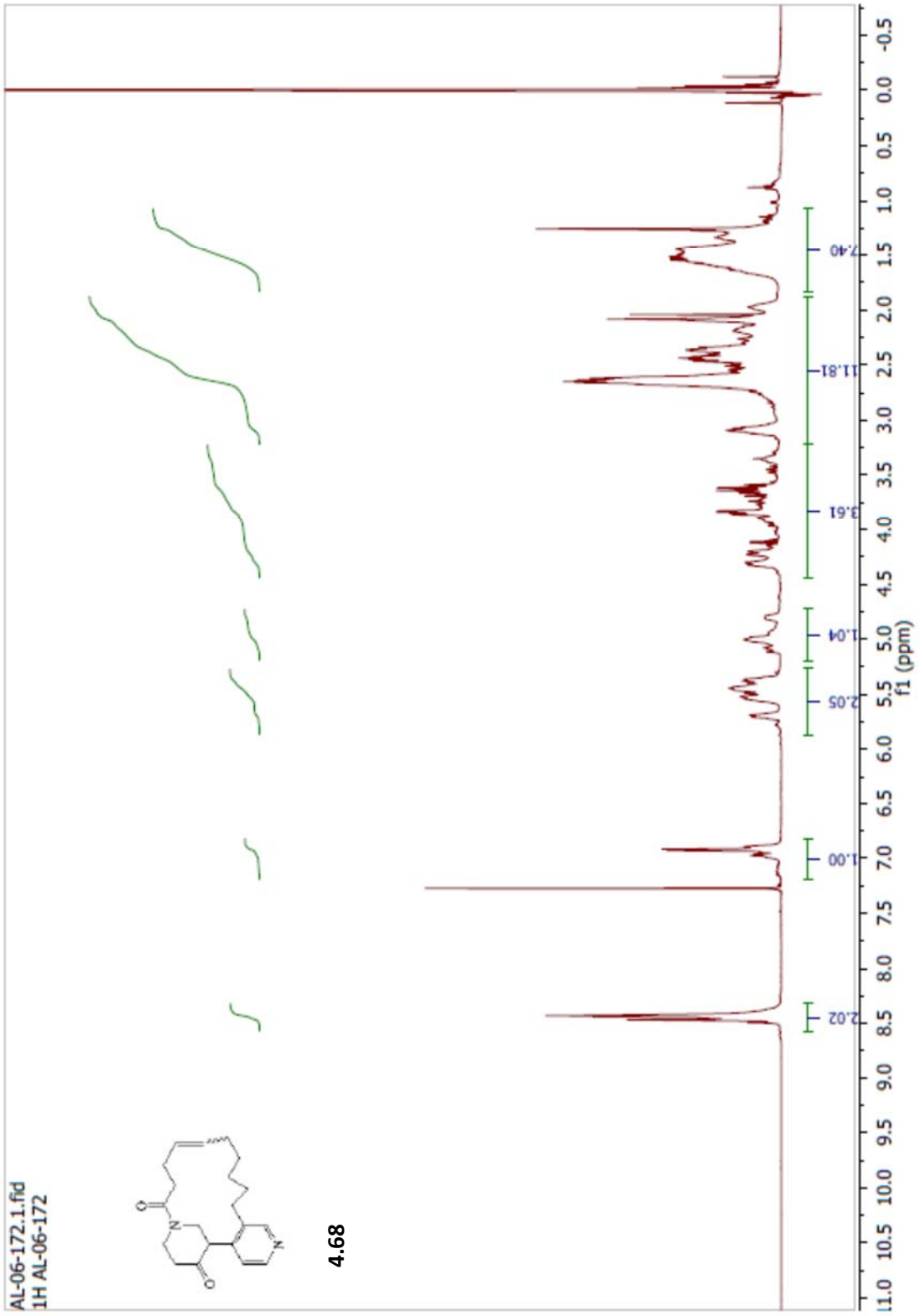

AL-06-128.2.fid
13C AL-06-128
200.87
174.84
174.54
173.09
151.73
151.33
147.90
144.79
144.28
136.55
132.22
131.39
129.99
128.69
124.59
123.25
50.74
49.54
49.45
49.22
43.37
43.30
43.24
41.18
40.77
34.75
34.17
32.68
32.41
32.14
31.71
31.40
30.94
29.01
28.33
27.48
26.74
25.15
24.52
f1 (ppm)

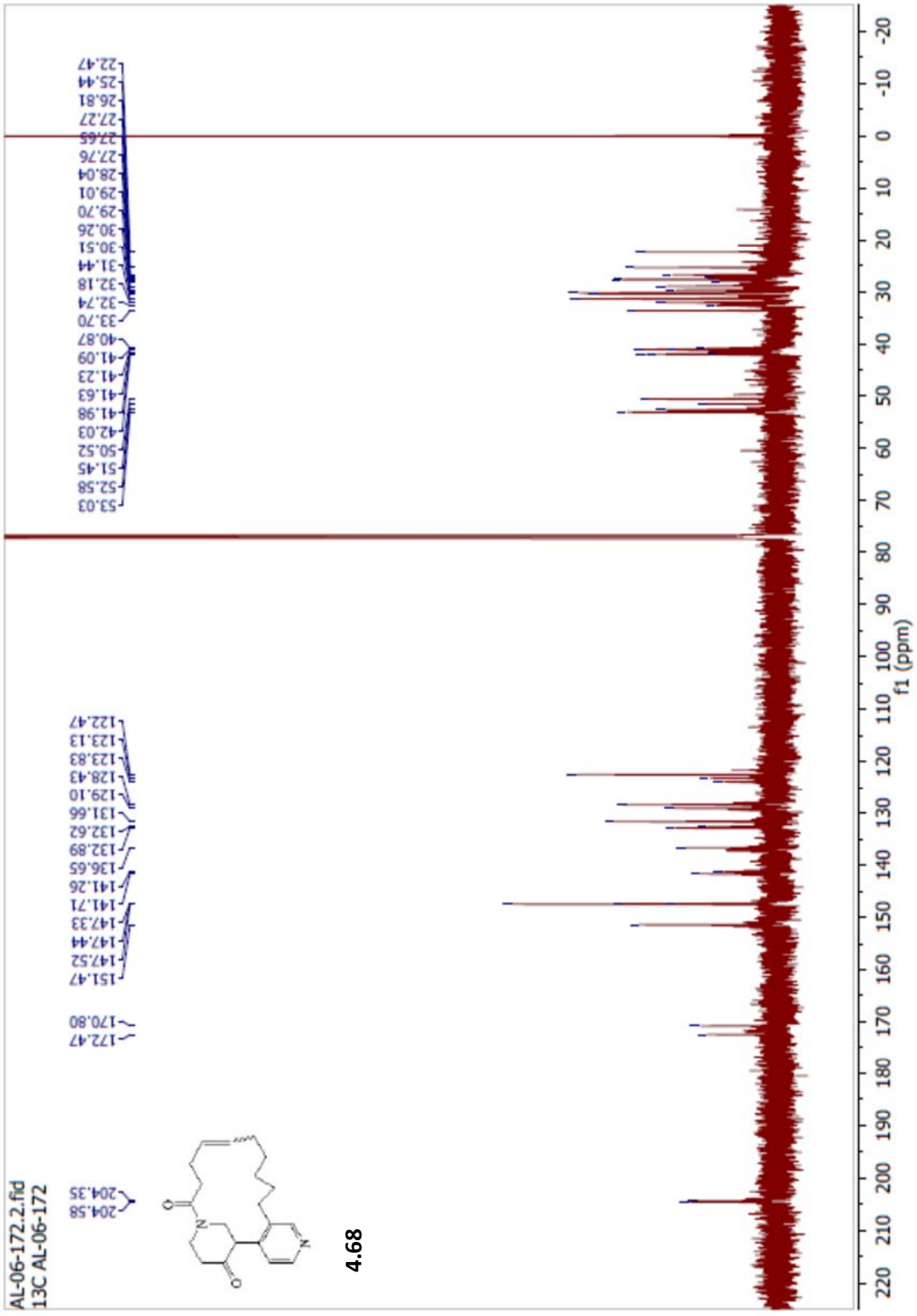
4.65


AL-05-186/1
1H AL-05-186
4.66
2.00
1.03
1.82
1.65
4.65
8.40
8.68
f1 (ppm)

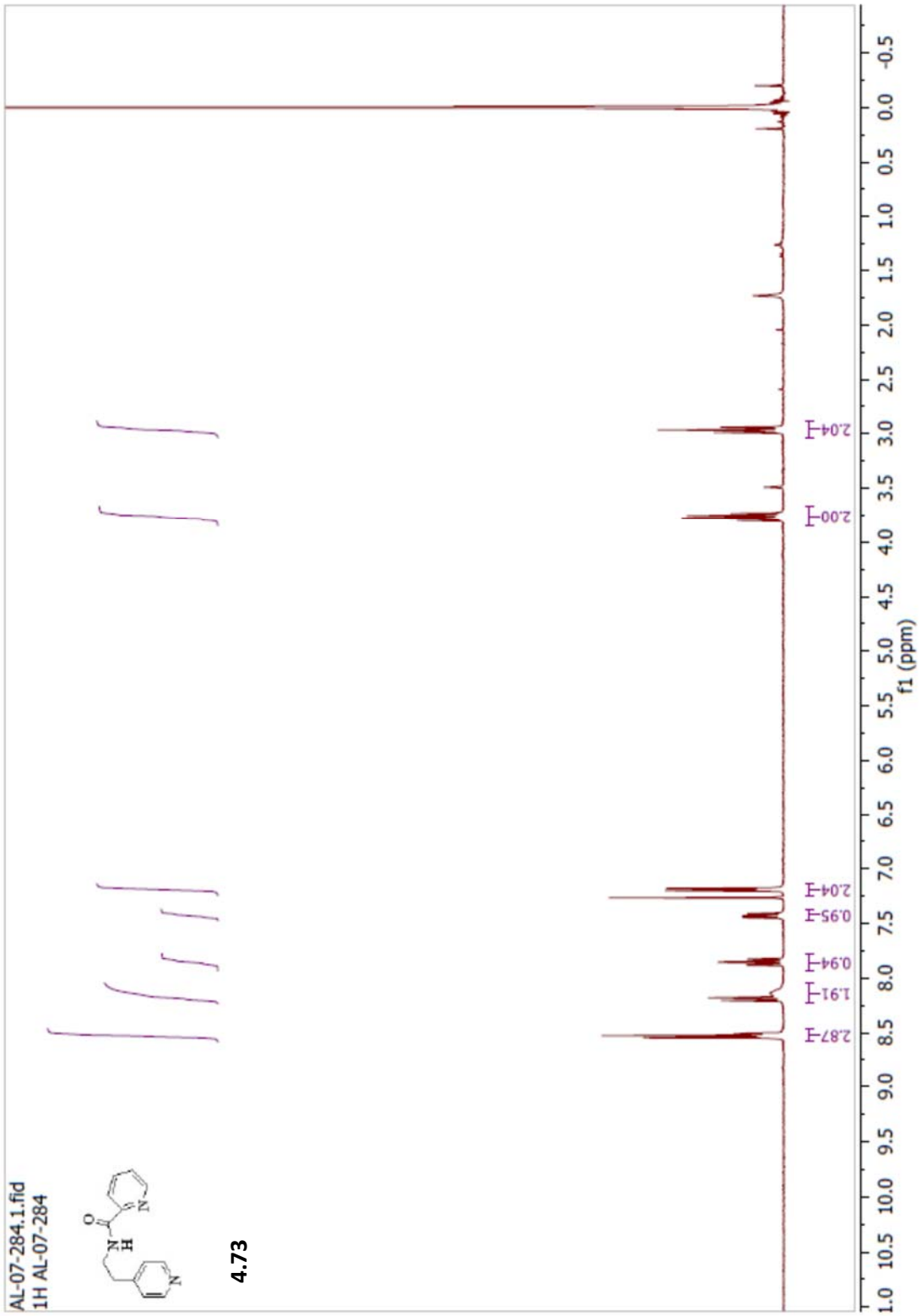

AL-06-130.1.fid
1H AL-06-130
4.67
2.00
0.05
0.89
1.96
0.95
23.57
f1 (ppm)

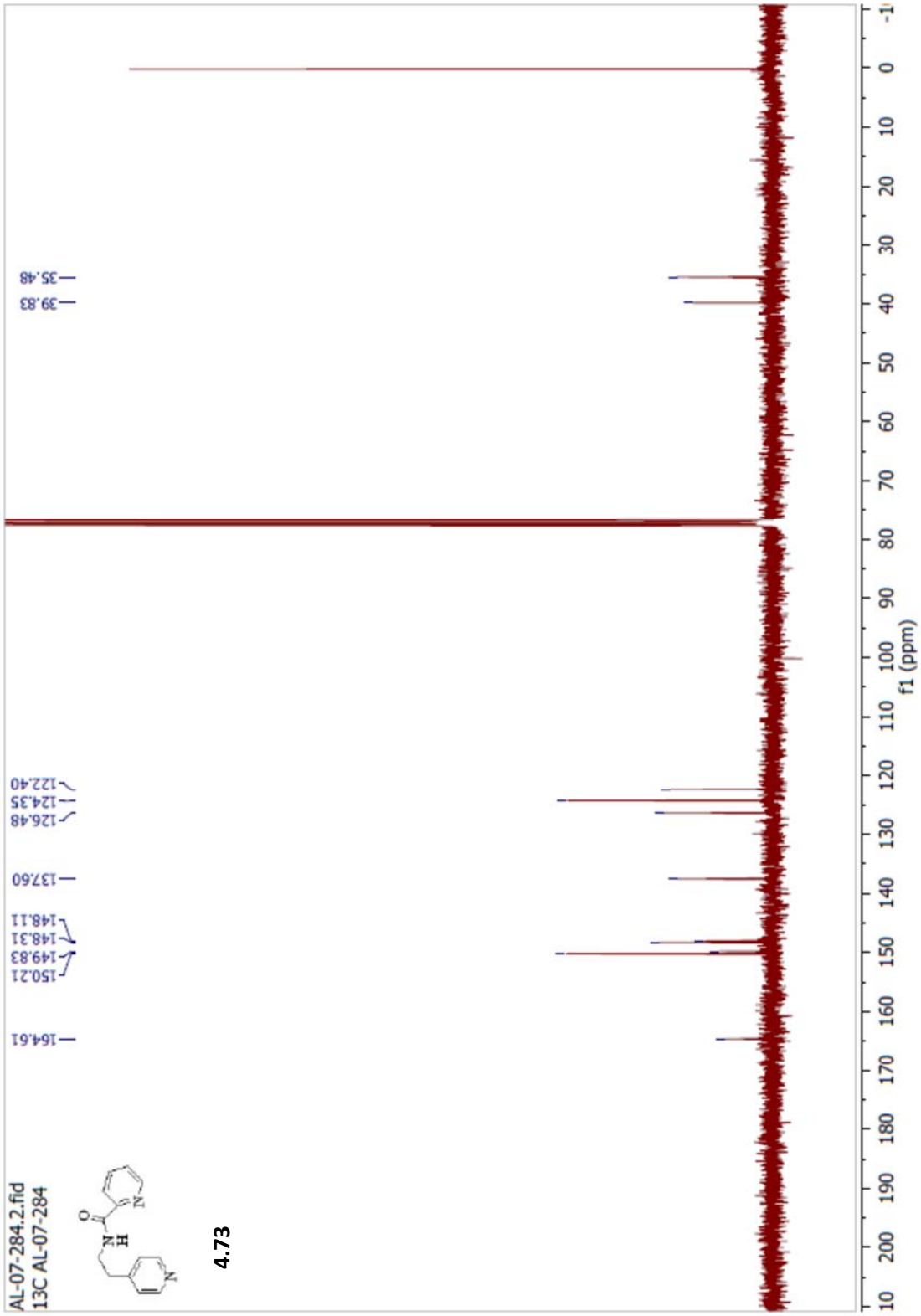

AL-06-130.2.fid
13C AL-06-130
4.67
f1 (ppm)

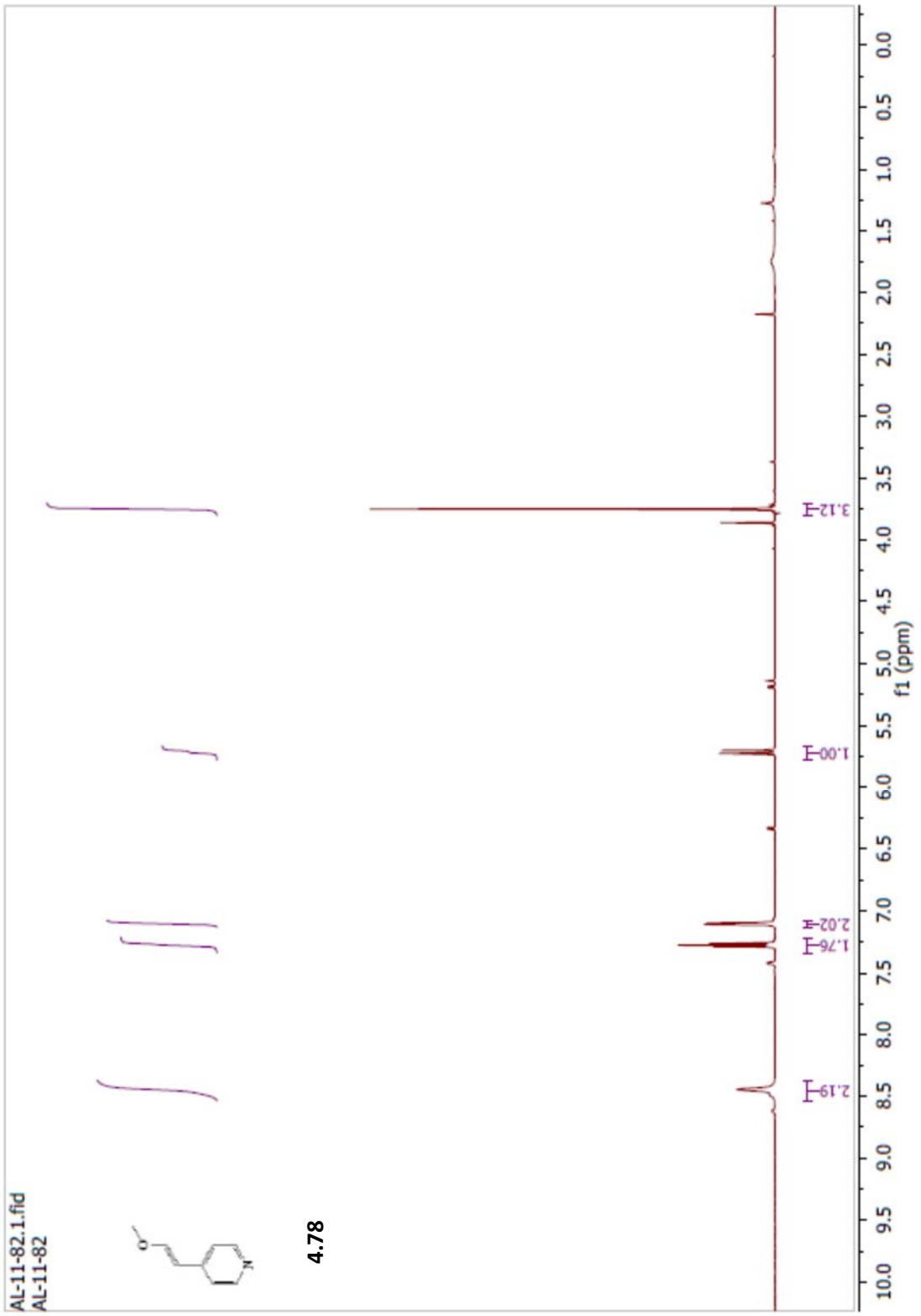

AL-06-172.1.fid
1H AL-06-172
4.68
2.02
1.00
2.05
1.04
3.61
11.81
2.40
f1 (ppm)

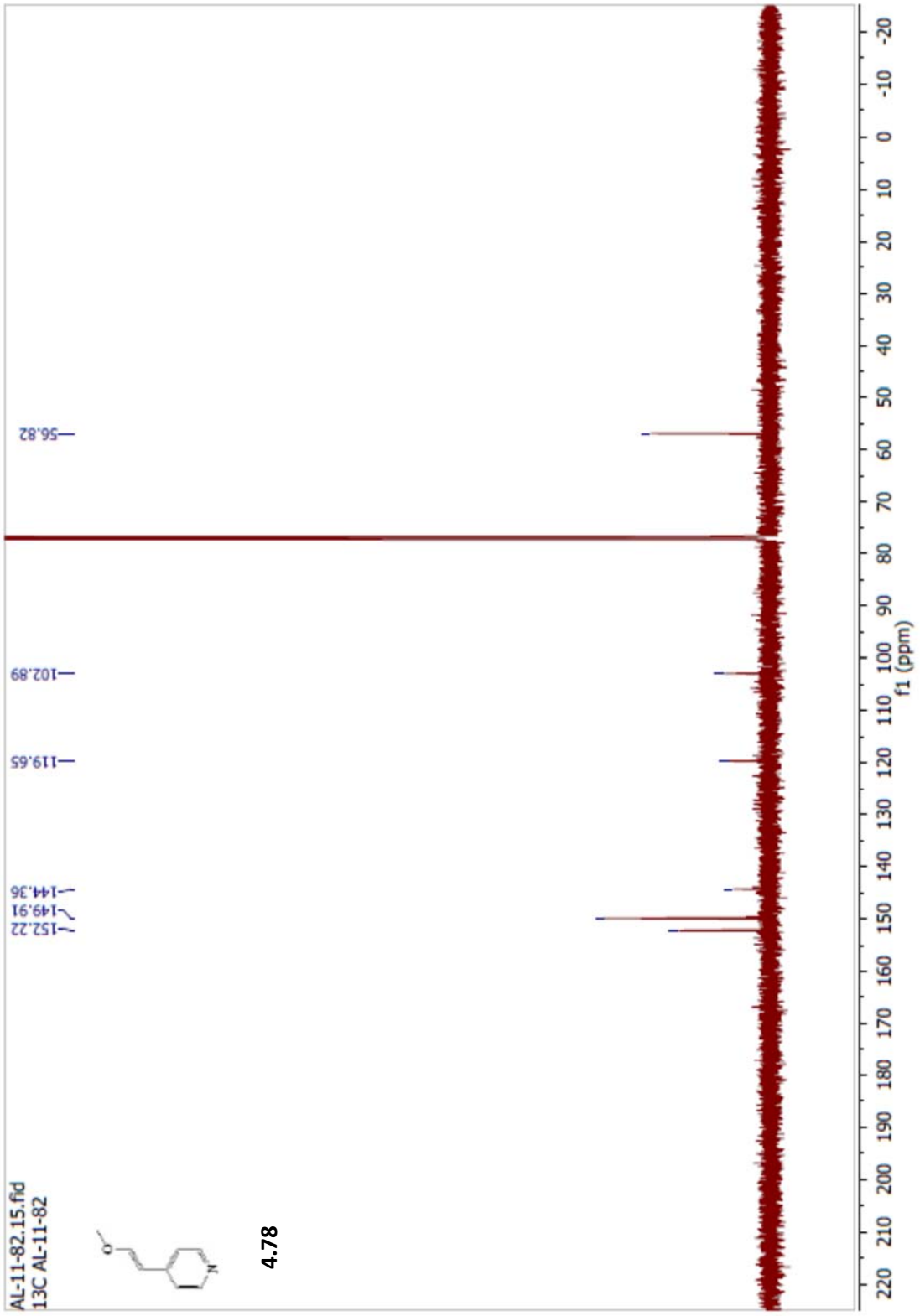

AL-06-172.2.fid
13C AL-06-172
204.58
204.35
172.47
170.80
151.47
147.52
147.44
147.33
141.71
141.26
136.65
132.89
132.62
131.66
129.10
128.43
123.83
123.13
122.47
53.03
52.58
51.45
50.52
42.03
41.98
41.63
41.23
41.09
40.87
33.70
32.74
32.18
31.44
30.51
30.26
29.70
29.01
28.04
27.76
27.65
27.27
26.81
25.44
22.47
f1 (ppm)

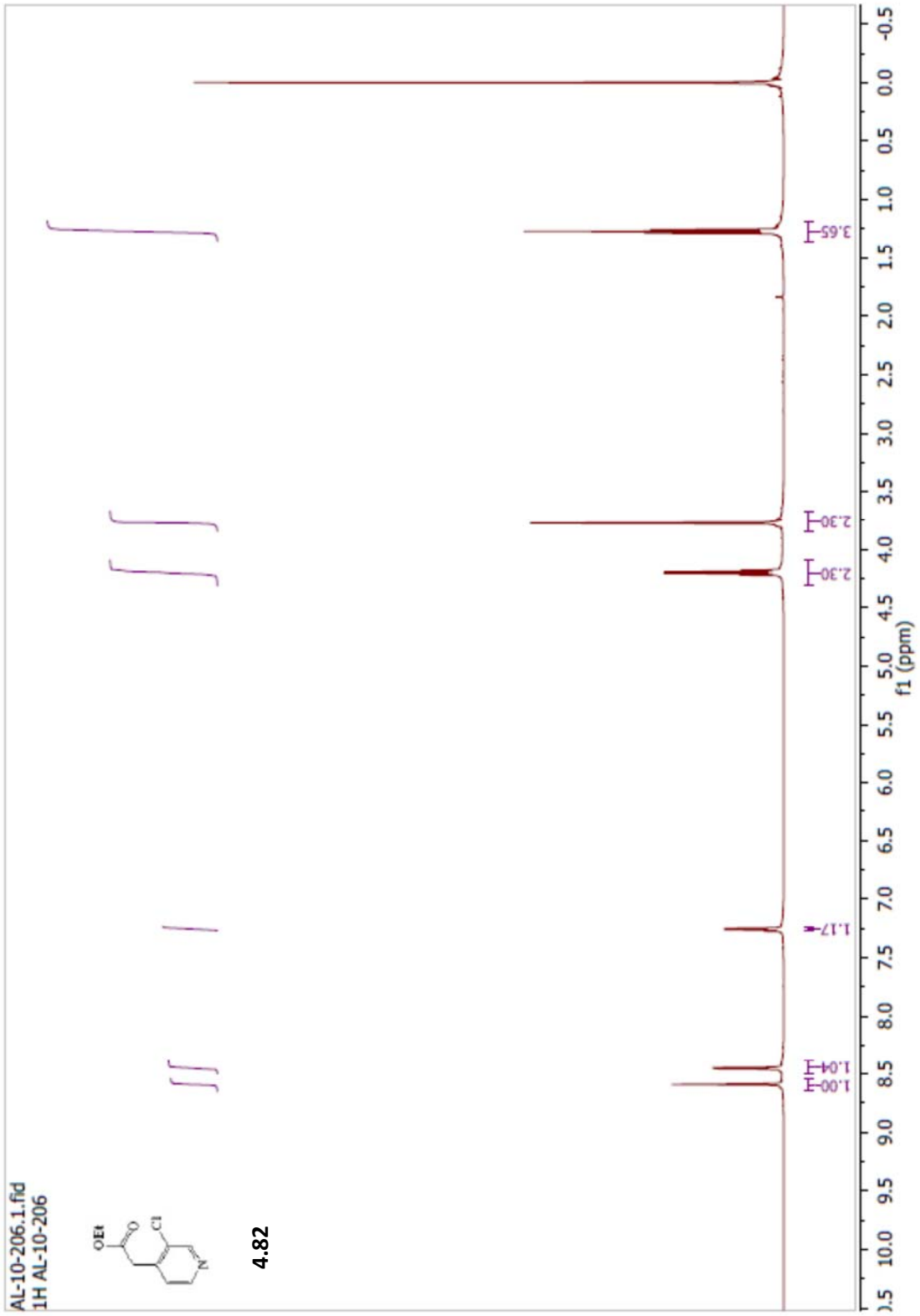
4.68

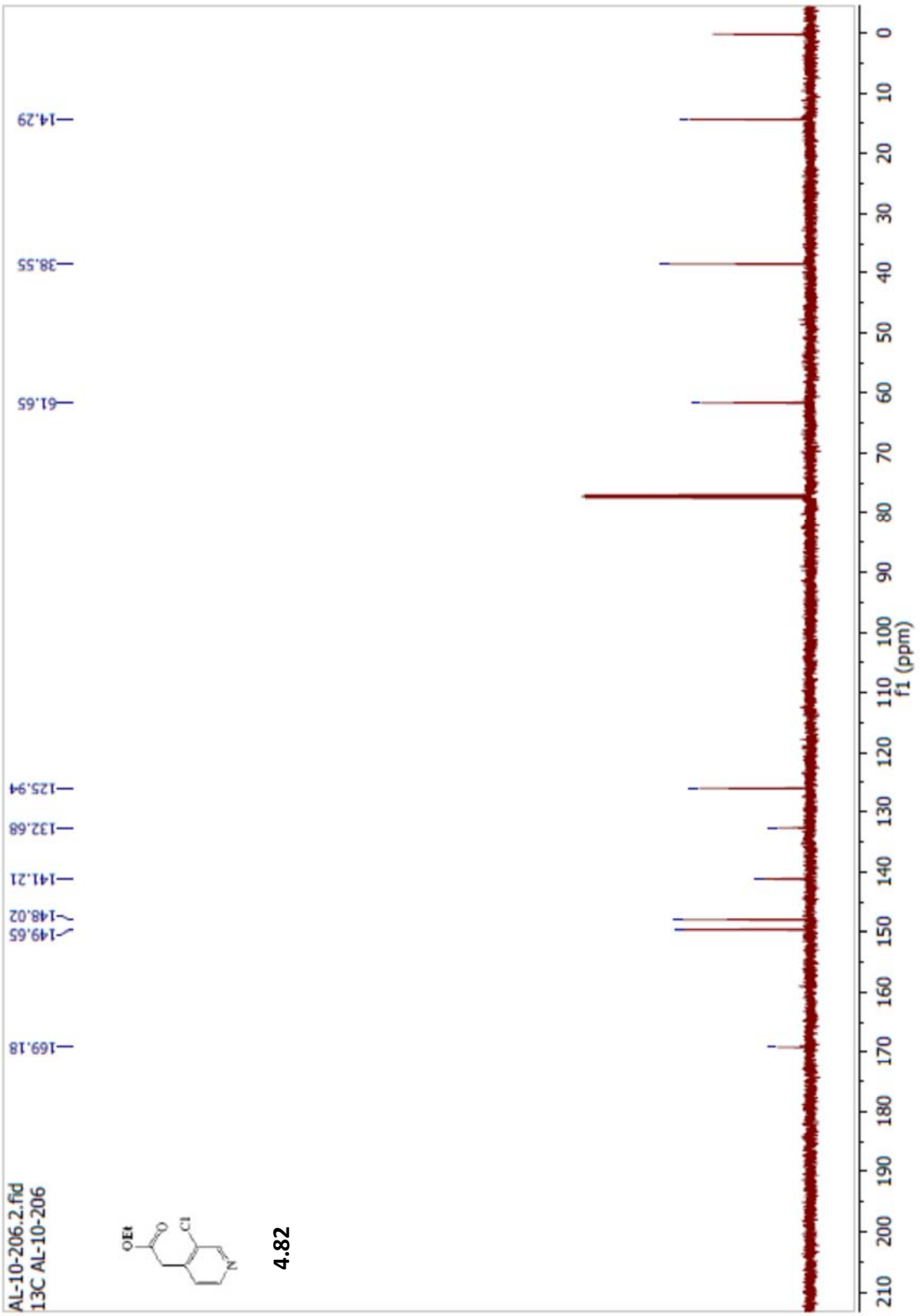

AL-07-284.1.fid
1H AL-07-284
4.73
2.87
1.91
0.94
0.95
2.04
2.00
2.04
f1 (ppm)

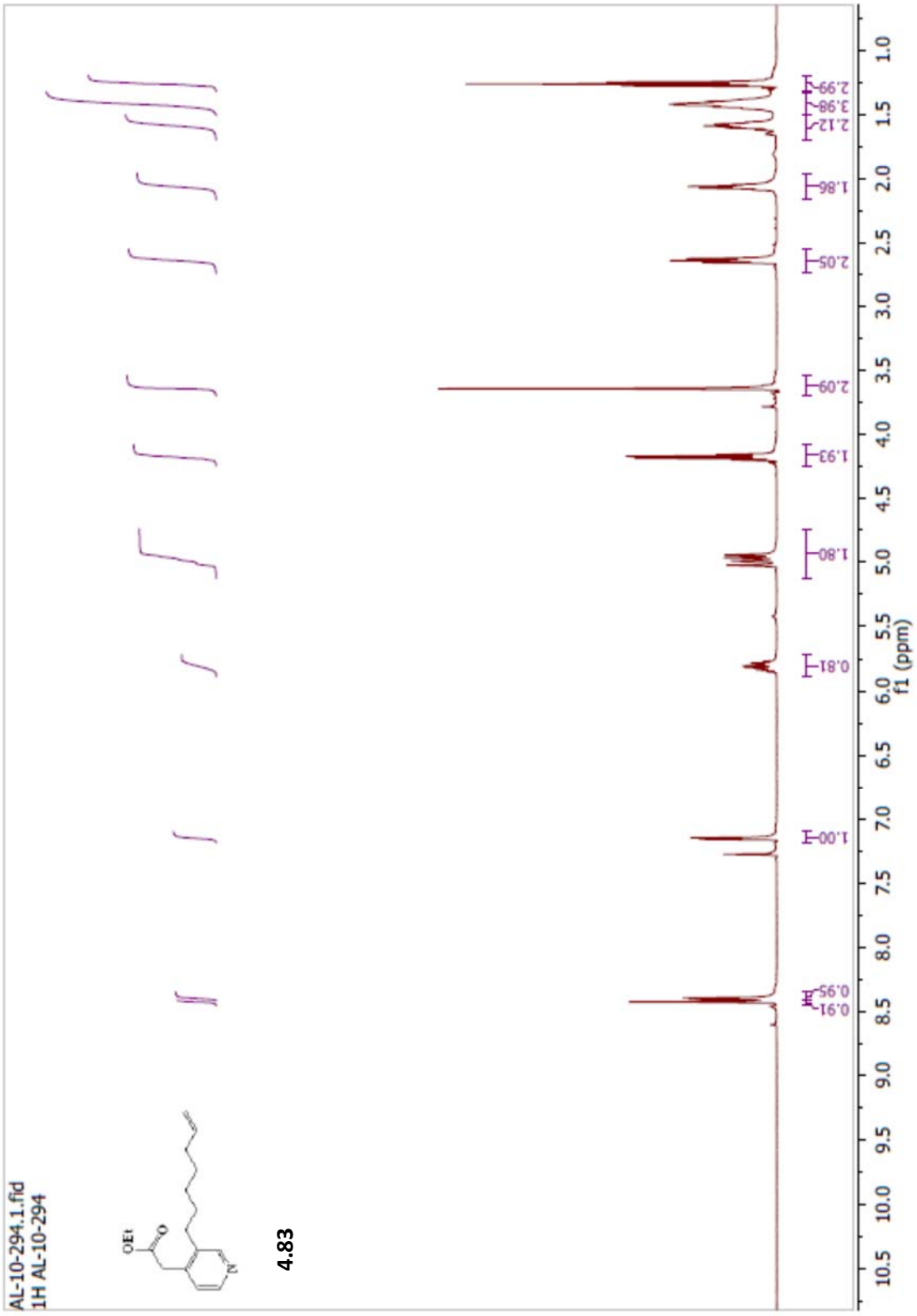

AL-07-284.2.fid
13C AL-07-284
4.73
164.61
150.21
149.83
148.31
148.11
137.60
126.48
124.35
122.40
39.83
35.48
f1 (ppm)

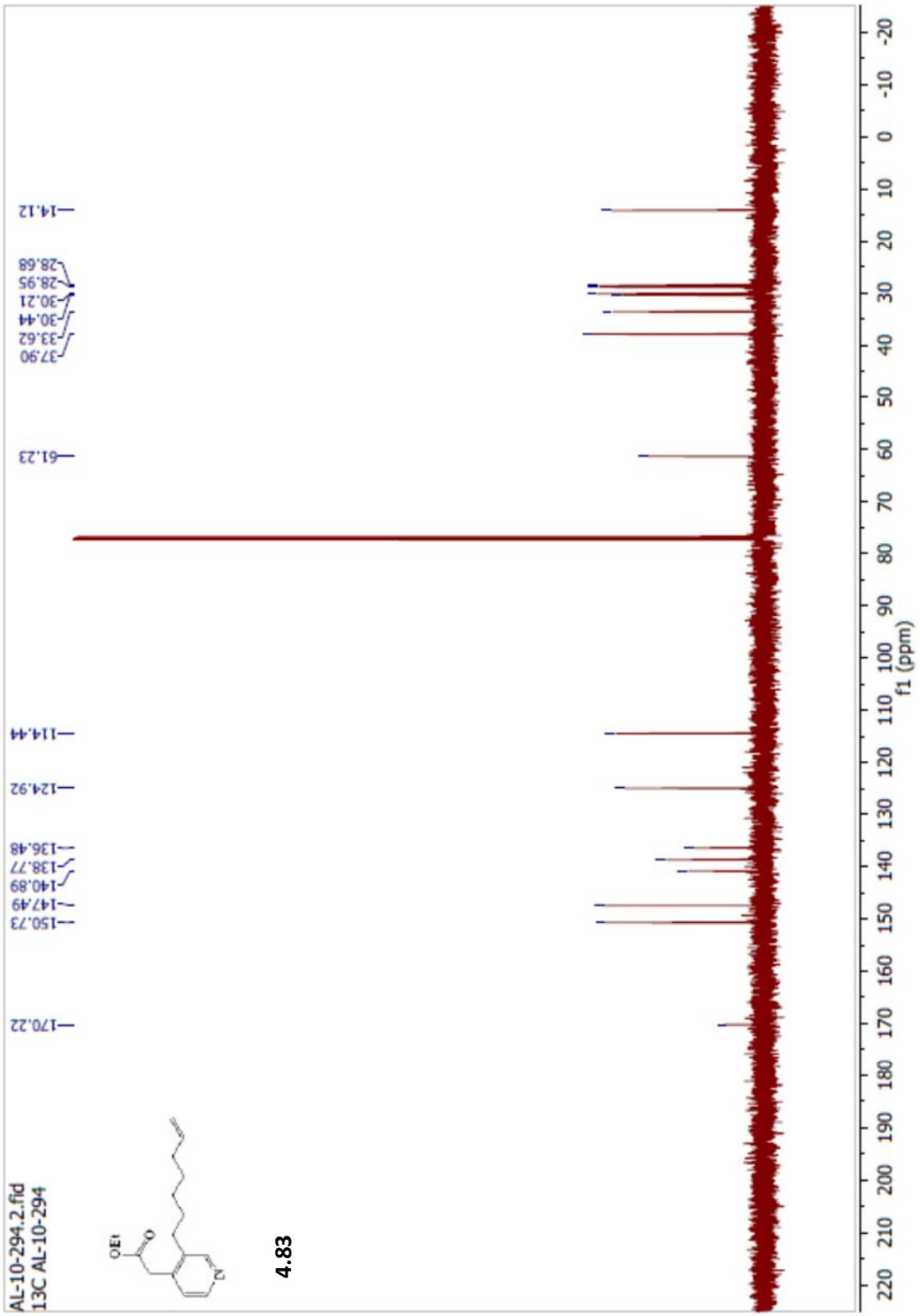

AL-11-82.1.fid
AL-11-82
4.78
3.12
1.00
2.02
1.76
2.19
f1 (ppm)

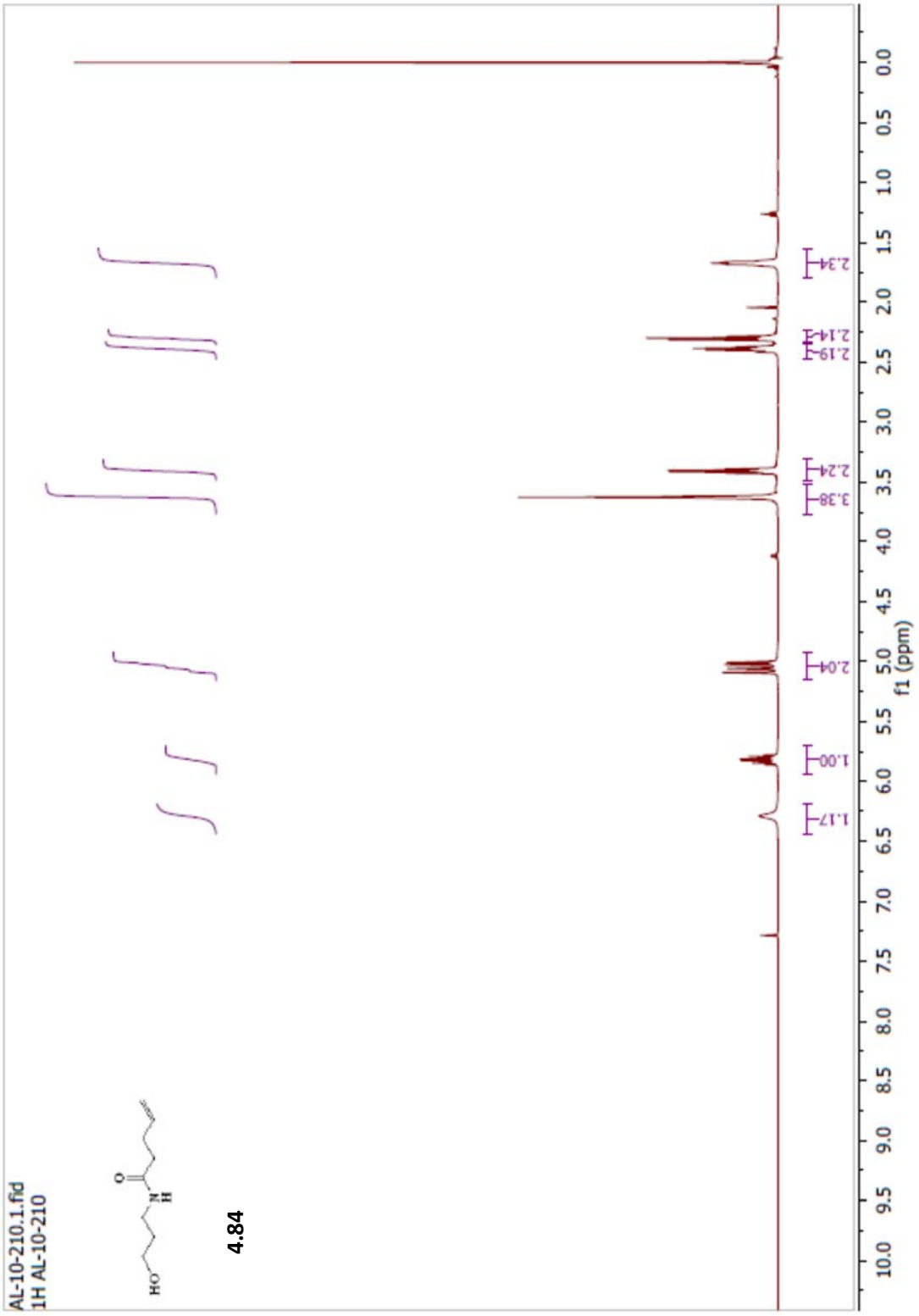

AL-11-82.15.fid
13C AL-11-82
4.78
56.82
102.89
119.65
144.36
149.91
152.22
f1 (ppm)

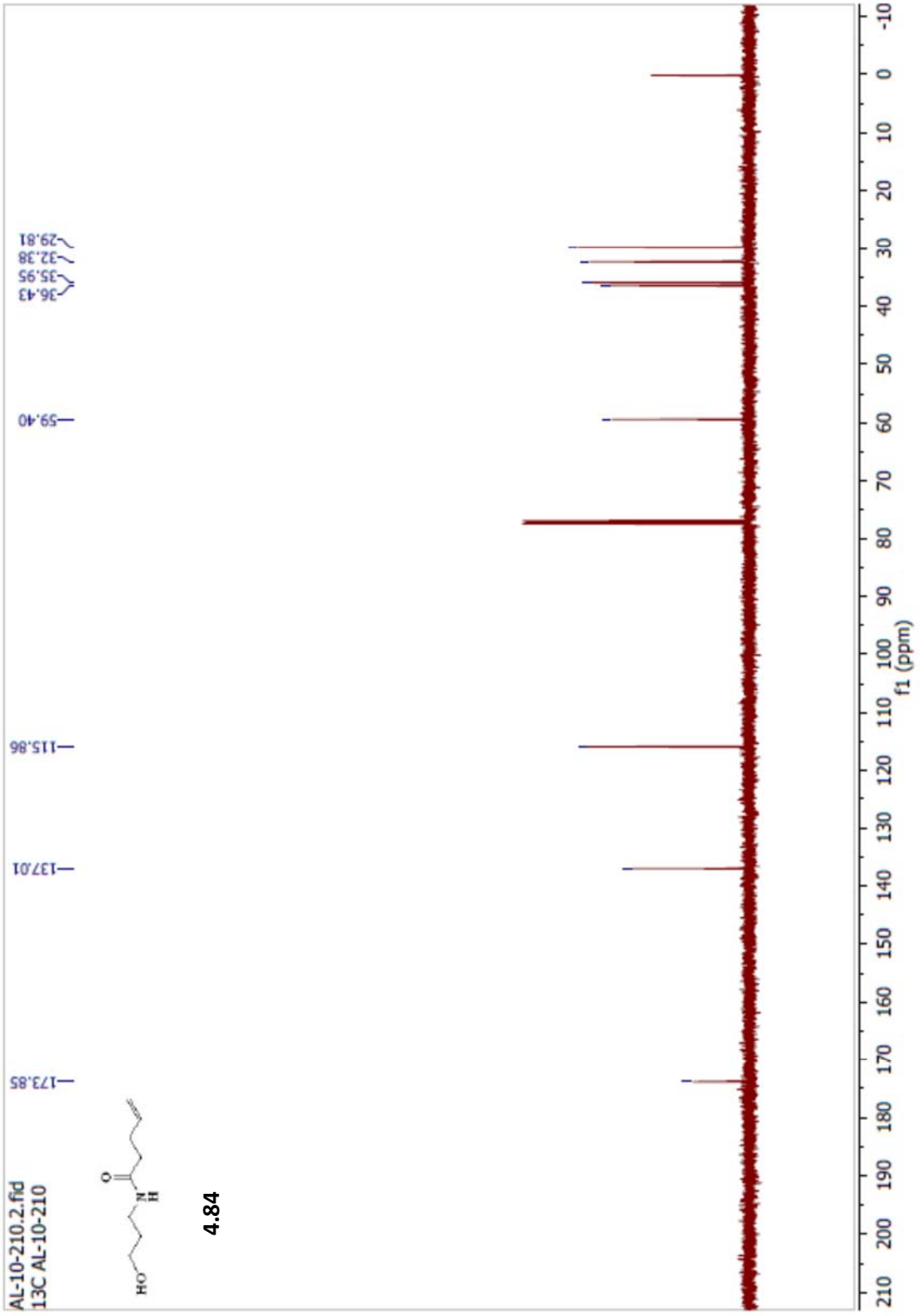

AL-10-206.1.fid
1H AL-10-206
OEt
O
Cl
N
4.82
1.00
1.04
1.17
2.30
2.30
3.65
f1 (ppm)

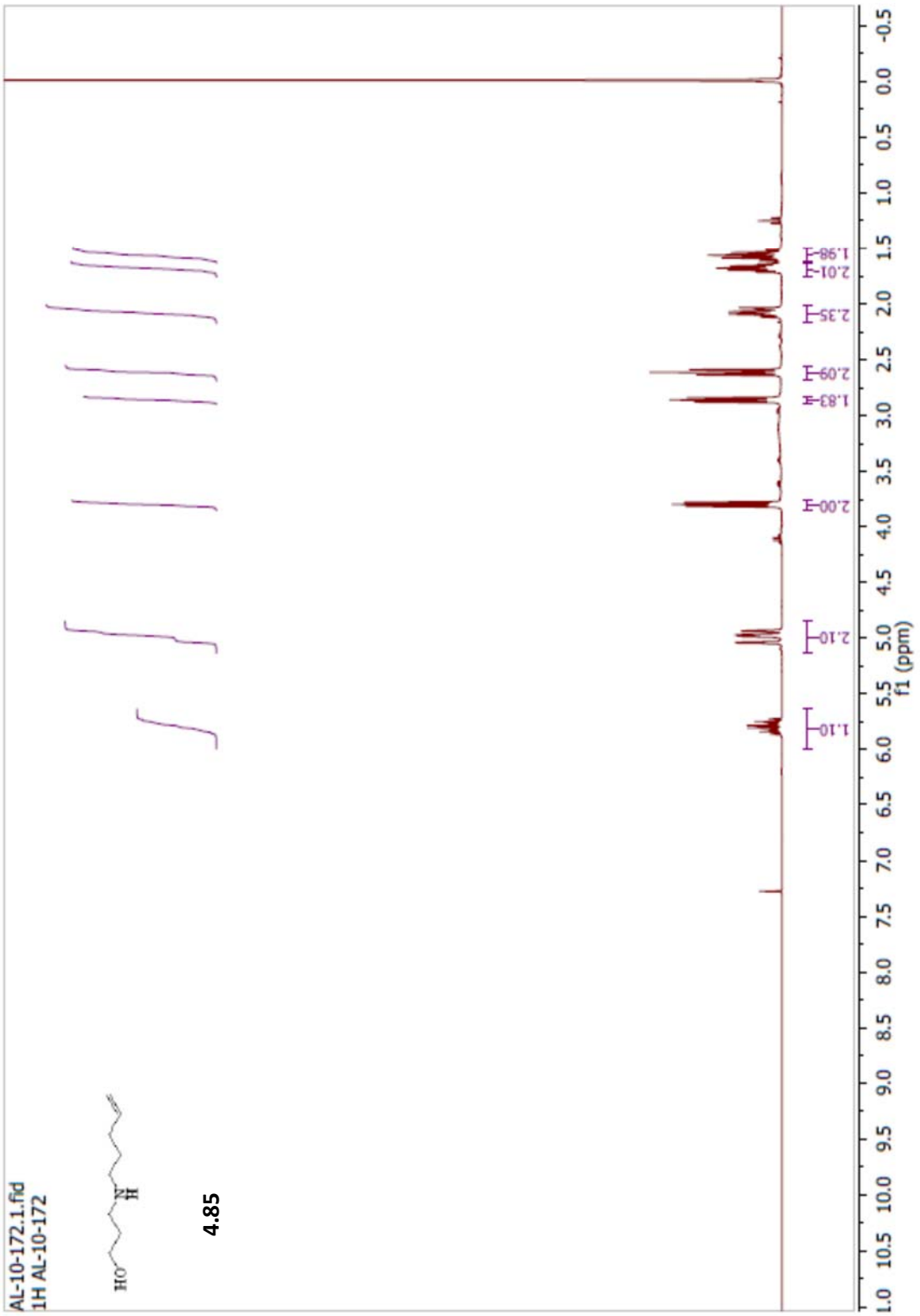

AL-10-206.2.fid
13C AL-10-206
14.29
38.55
61.65
125.94
132.68
141.21
148.02
149.65
169.18
OEt
O
Cl
N
4.82
f1 (ppm)

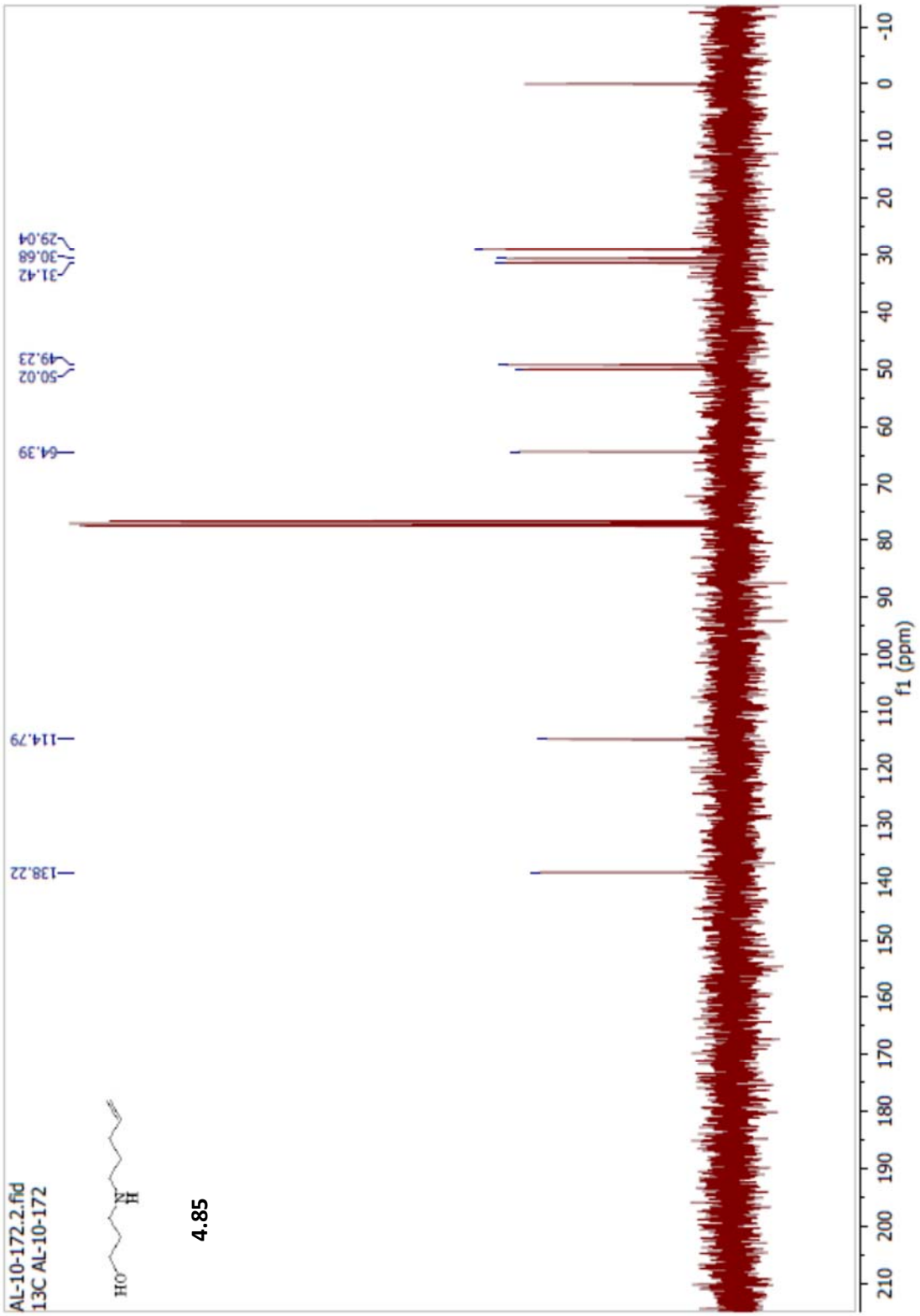

AL-10-294.1.fid
1H AL-10-294
OEt
O
N
4.83
0.91
0.95
1.00
0.81
1.80
1.93
2.09
2.05
1.86
2.12
3.98
2.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

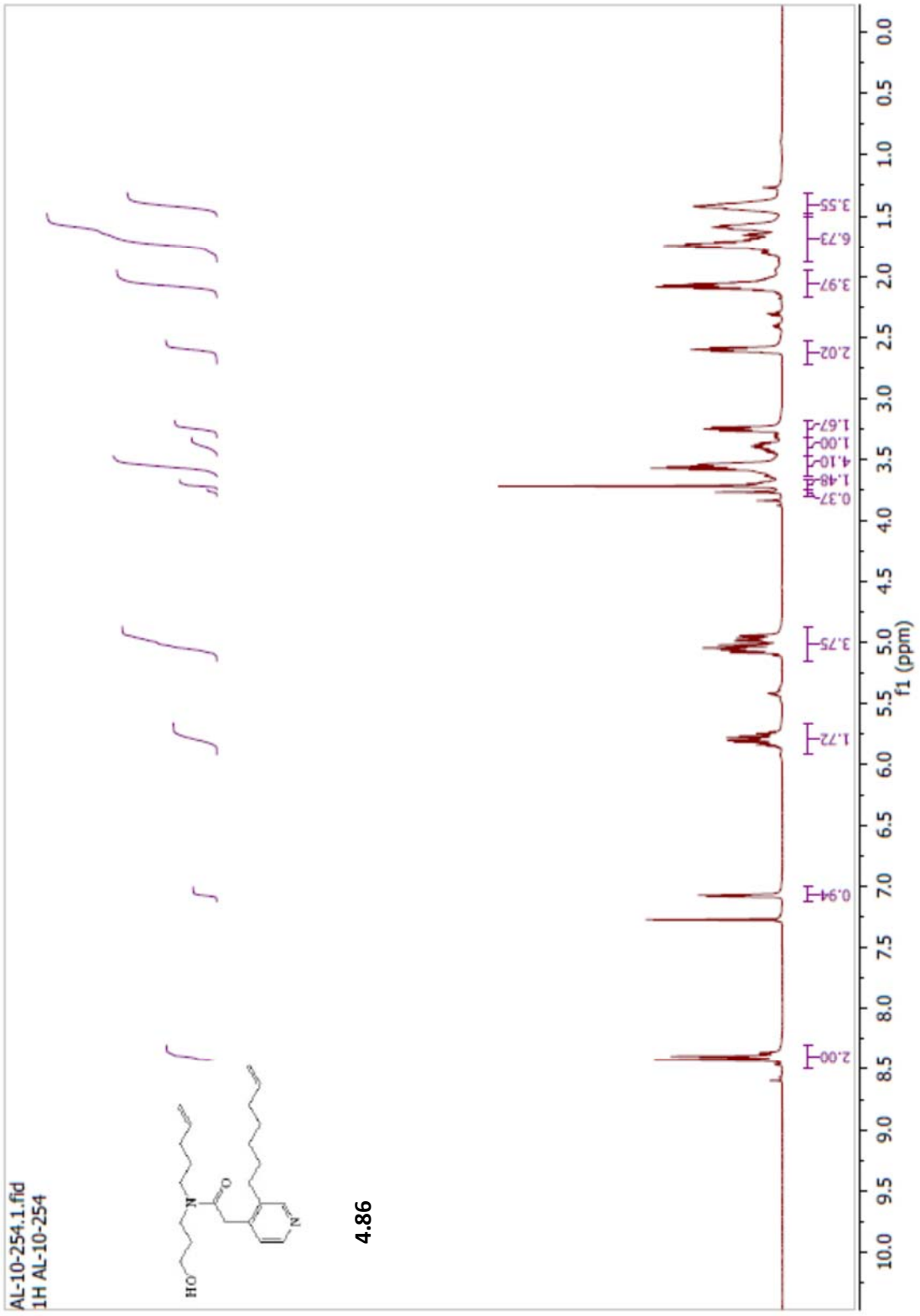

AL-10-294.2.fid
13C AL-10-294
4.83
170.22
150.73
147.49
140.89
138.77
136.48
124.92
114.44
61.23
37.90
33.62
30.44
30.21
28.95
28.68
14.12
f1 (ppm)

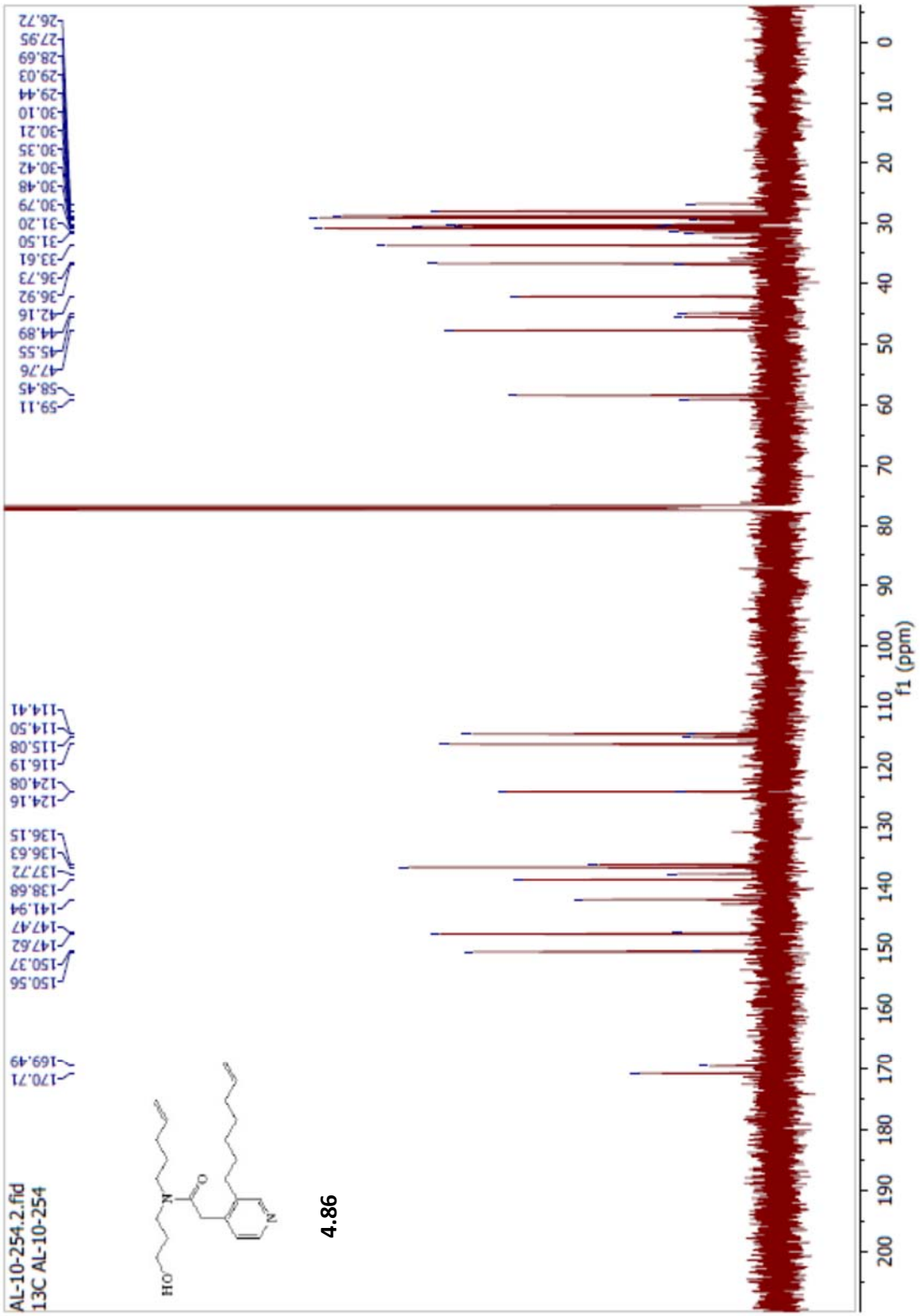

AL-10-210.1.fid
1H AL-10-210
4.84
HO
O
N
H
1.17
1.00
2.04
3.38
2.24
2.19
2.14
2.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

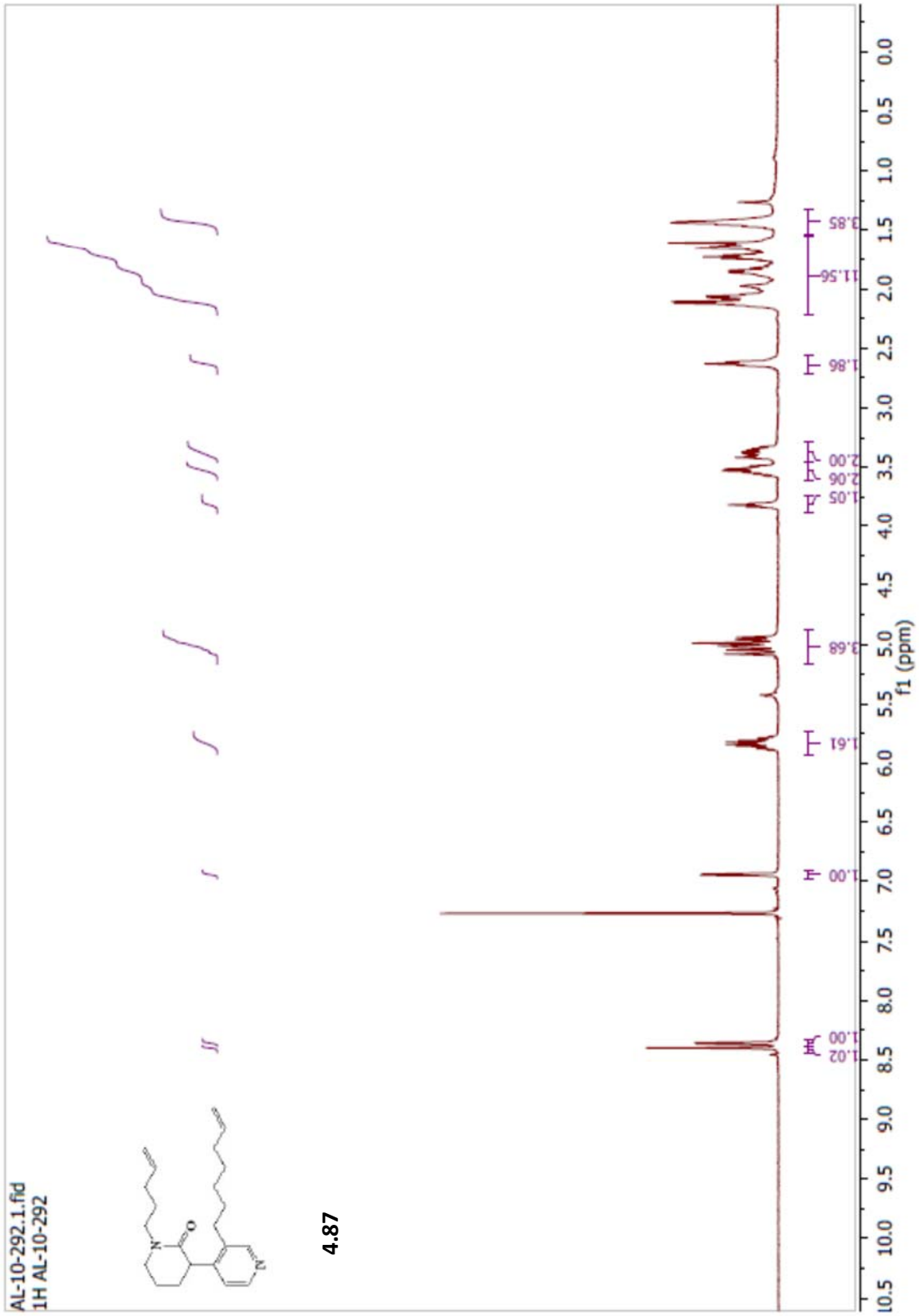

AL-10-210.2.fid
13C AL-10-210
4.84
173.85
137.01
115.86
59.40
36.43
35.95
32.38
29.81
f1 (ppm)

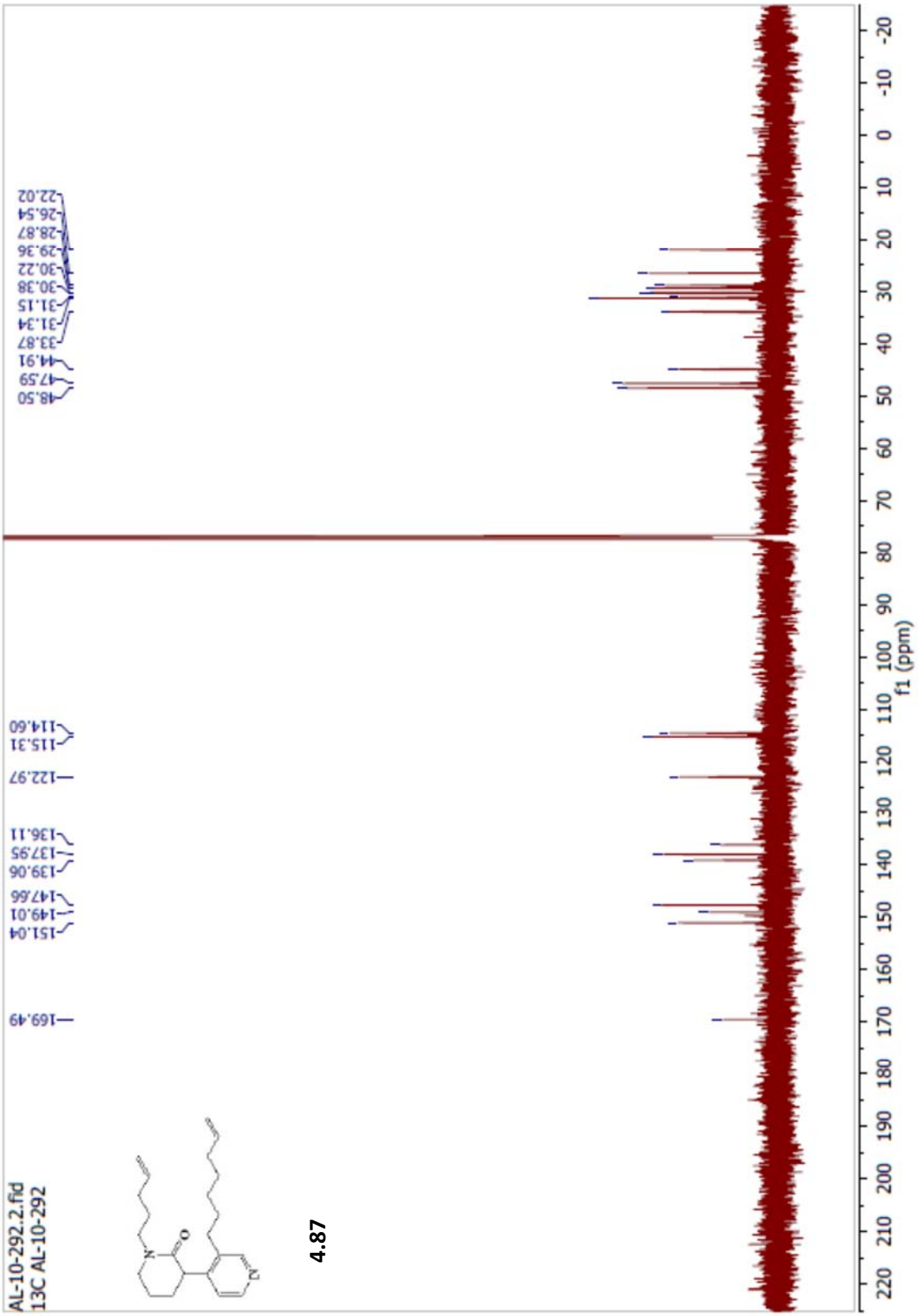

AL-10-172.1.fid
1H AL-10-172
HO
N
H
4.85
1.98
2.01
2.35
2.09
1.83
2.00
2.10
1.10
f1 (ppm)


AL-10-172.2.fid
13C AL-10-172
4.85
138.22
114.79
64.39
50.02
49.23
31.42
30.68
29.04
f1 (ppm)

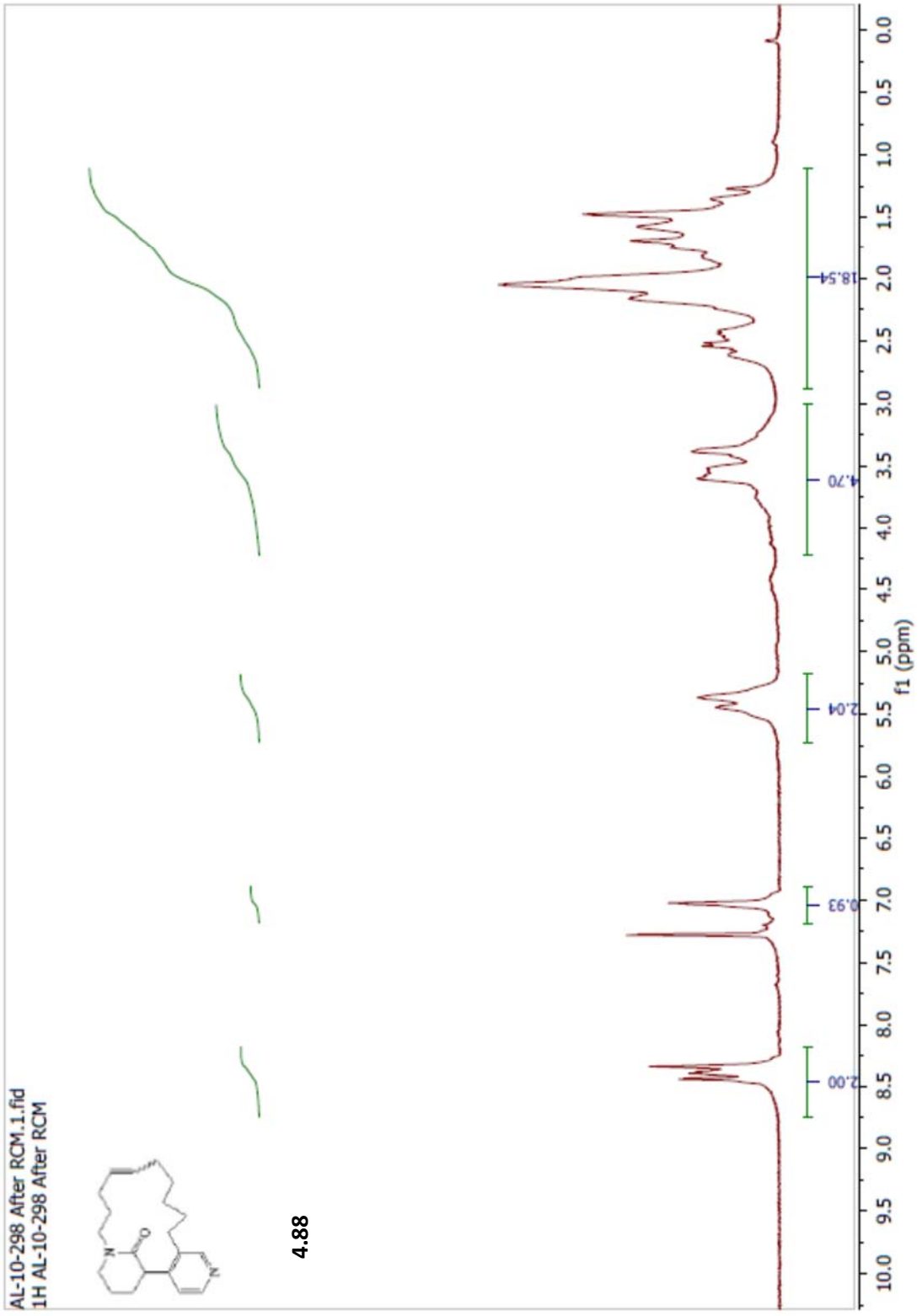

AL-10-254.1.fid
1H AL-10-254
4.86
2.00
0.94
1.72
3.75
0.37
1.48
4.10
1.00
1.67
2.02
3.97
6.73
3.55
f1 (ppm)

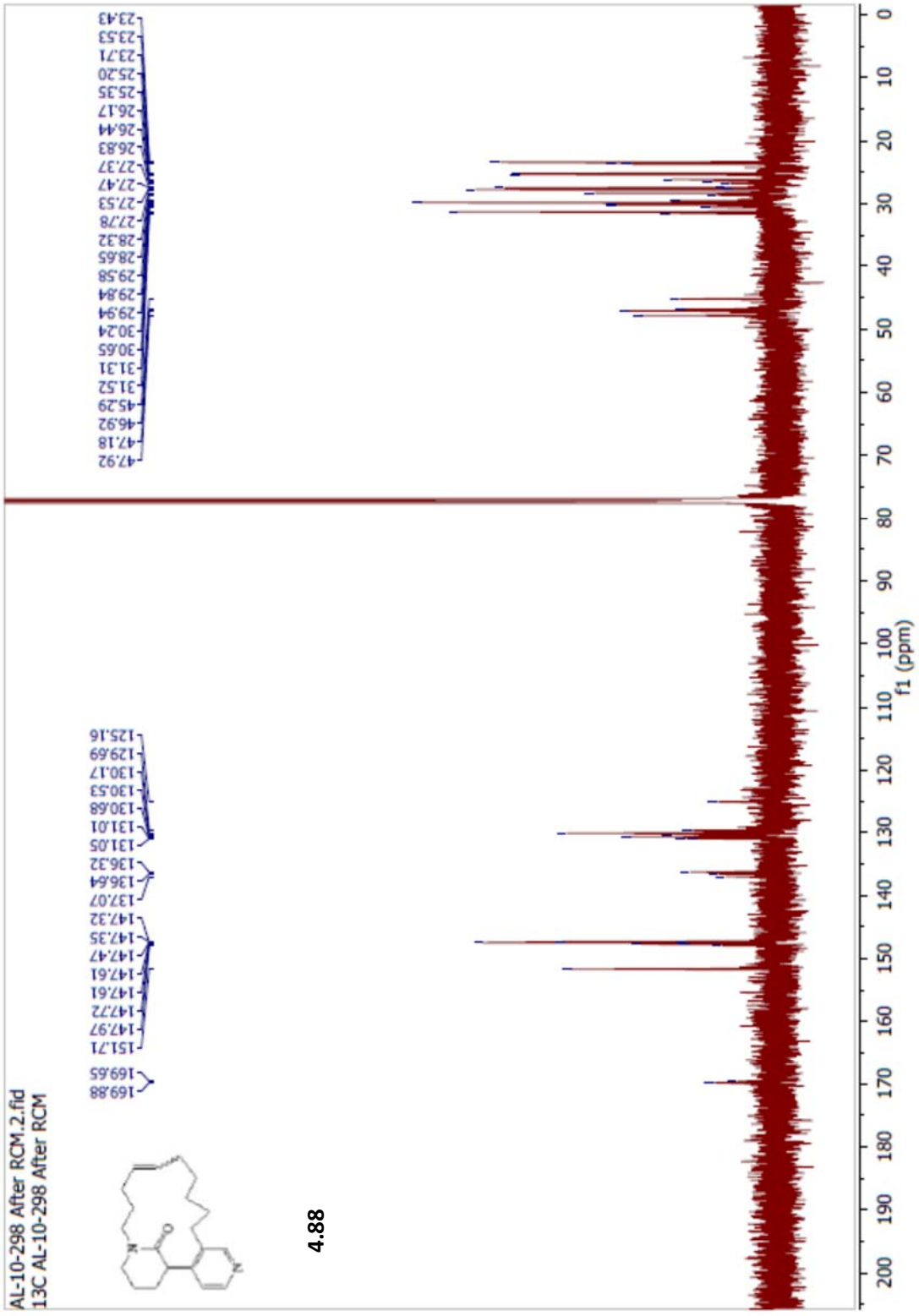

AL-10-254.2.fid
13C AL-10-254
4.86
f1 (ppm)


AL-10-292.1.fid
1H AL-10-292
4.87
1.02
1.00
1.00
1.61
3.68
1.05
2.06
2.00
1.86
11.56
3.85
f1 (ppm)

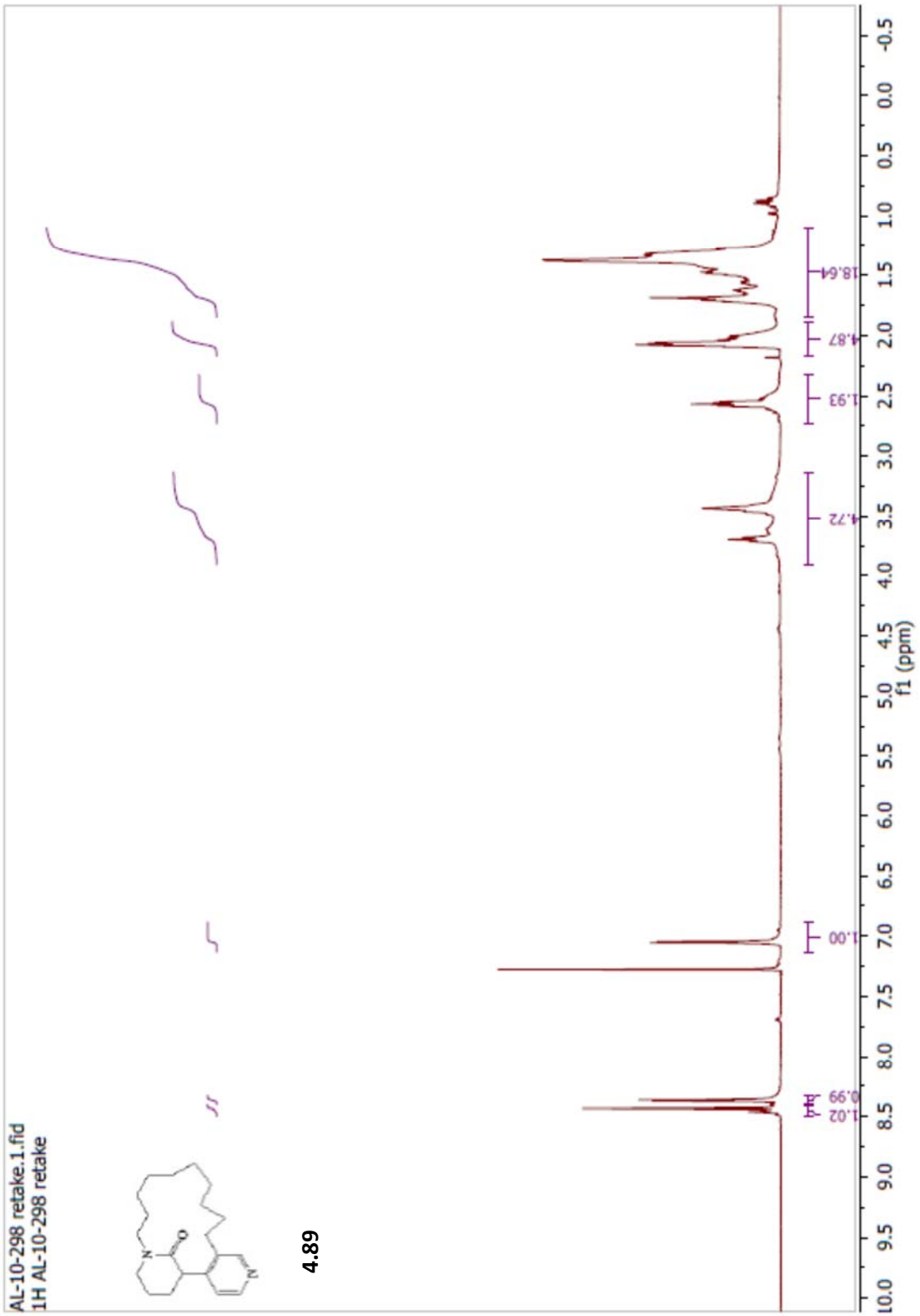

AL-10-292.2.fid
13C AL-10-292
169.49
151.04
149.01
147.66
139.06
137.95
136.11
122.97
115.31
114.60
48.50
47.59
44.91
33.87
31.34
31.15
30.38
30.22
29.36
28.87
26.54
22.02
f1 (ppm)

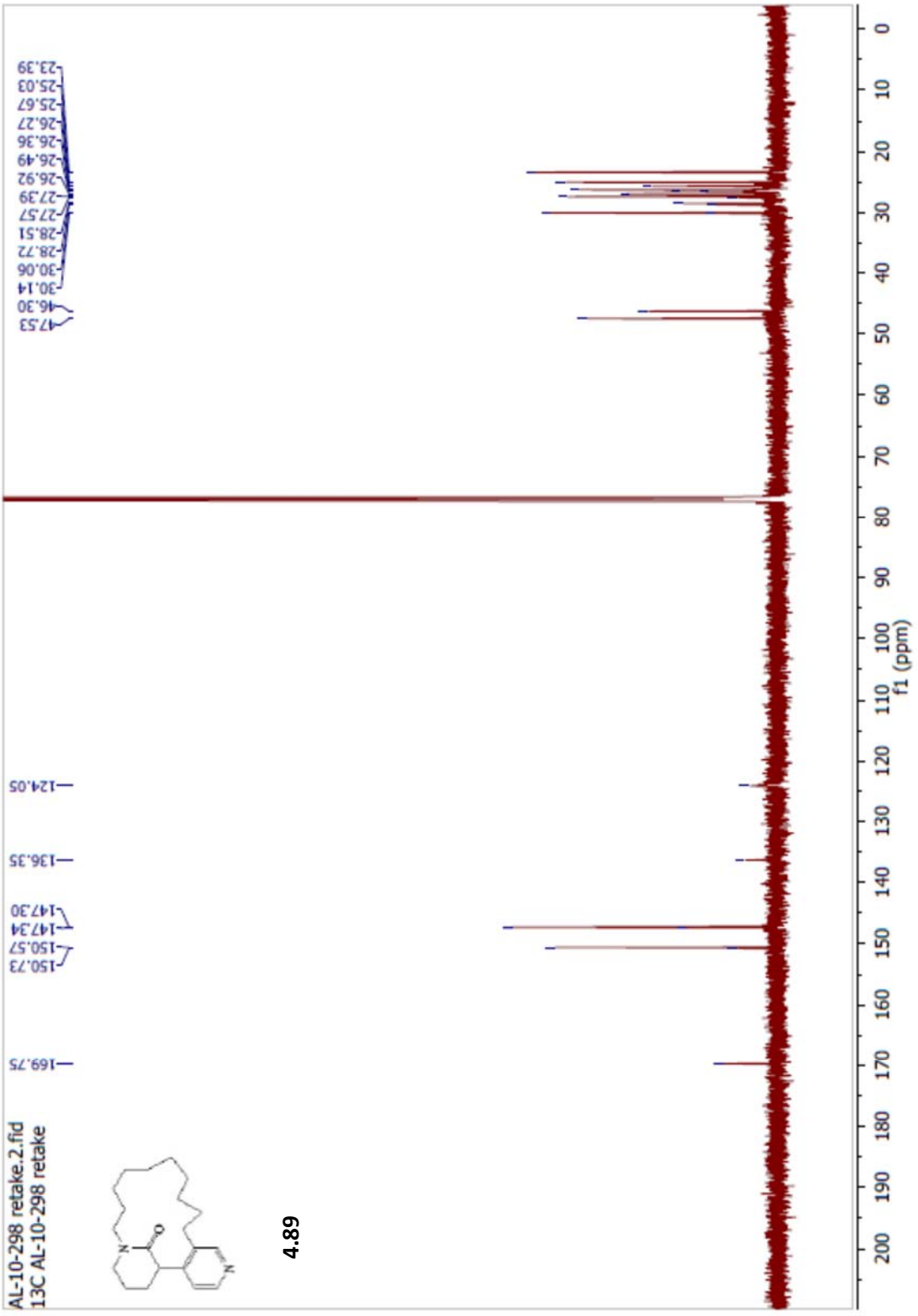
4.87

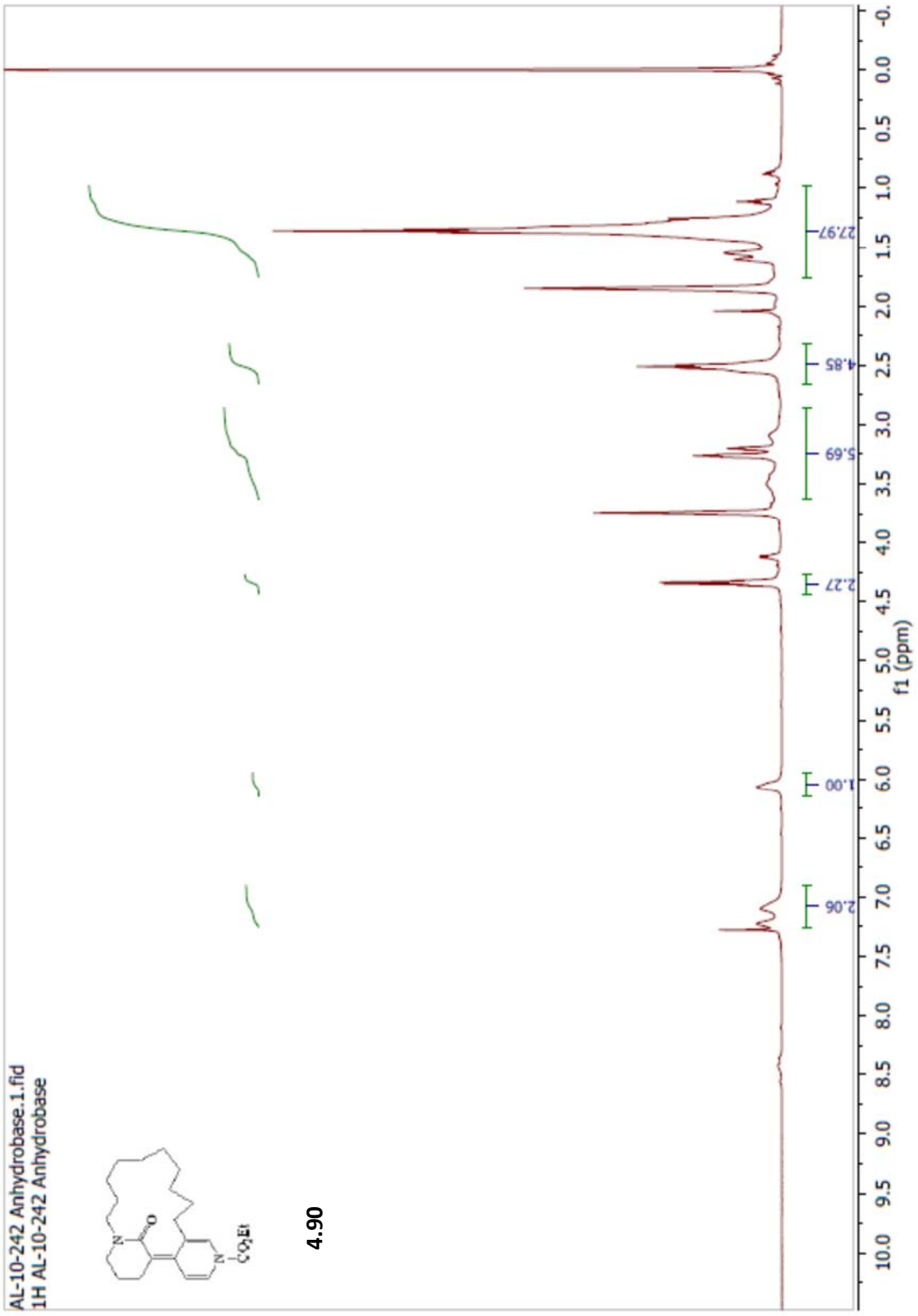

AL-10-298 After RCM.1.fid
1H AL-10-298 After RCM
4.88
2.00
0.93
2.04
4.70
18.54
f1 (ppm)

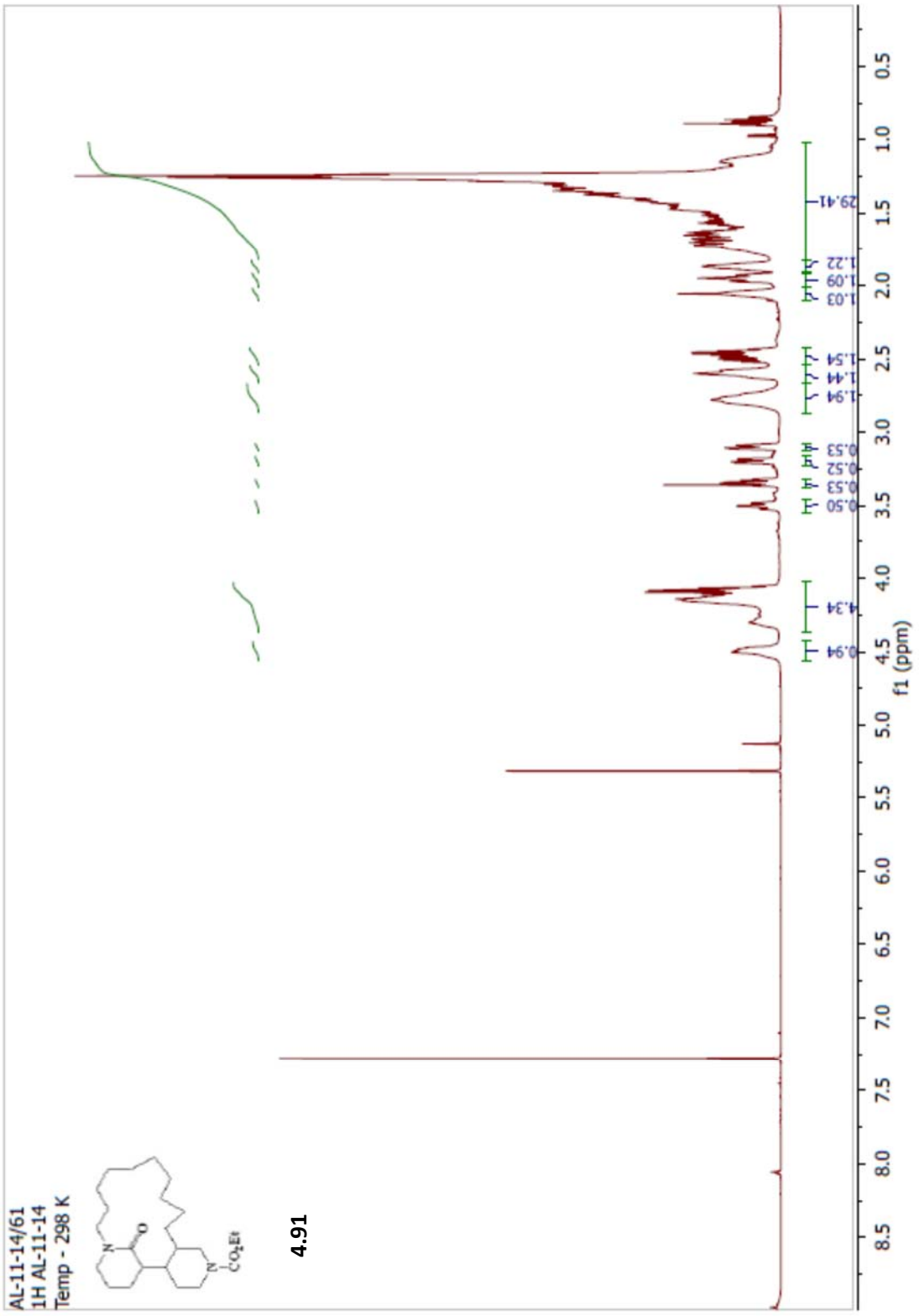

AL-10-298 After RCM.2.fid
13C AL-10-298 After RCM
169.88
169.65
151.71
147.97
147.72
147.61
147.61
147.47
147.35
147.32
137.07
136.64
136.32
131.05
131.01
130.68
130.53
130.17
129.69
125.16
47.92
47.18
46.92
45.29
31.52
31.31
30.65
30.24
29.94
29.84
29.58
28.65
28.32
27.78
27.53
27.47
27.37
26.83
26.44
26.17
25.35
25.20
23.71
23.53
23.43
f1 (ppm)

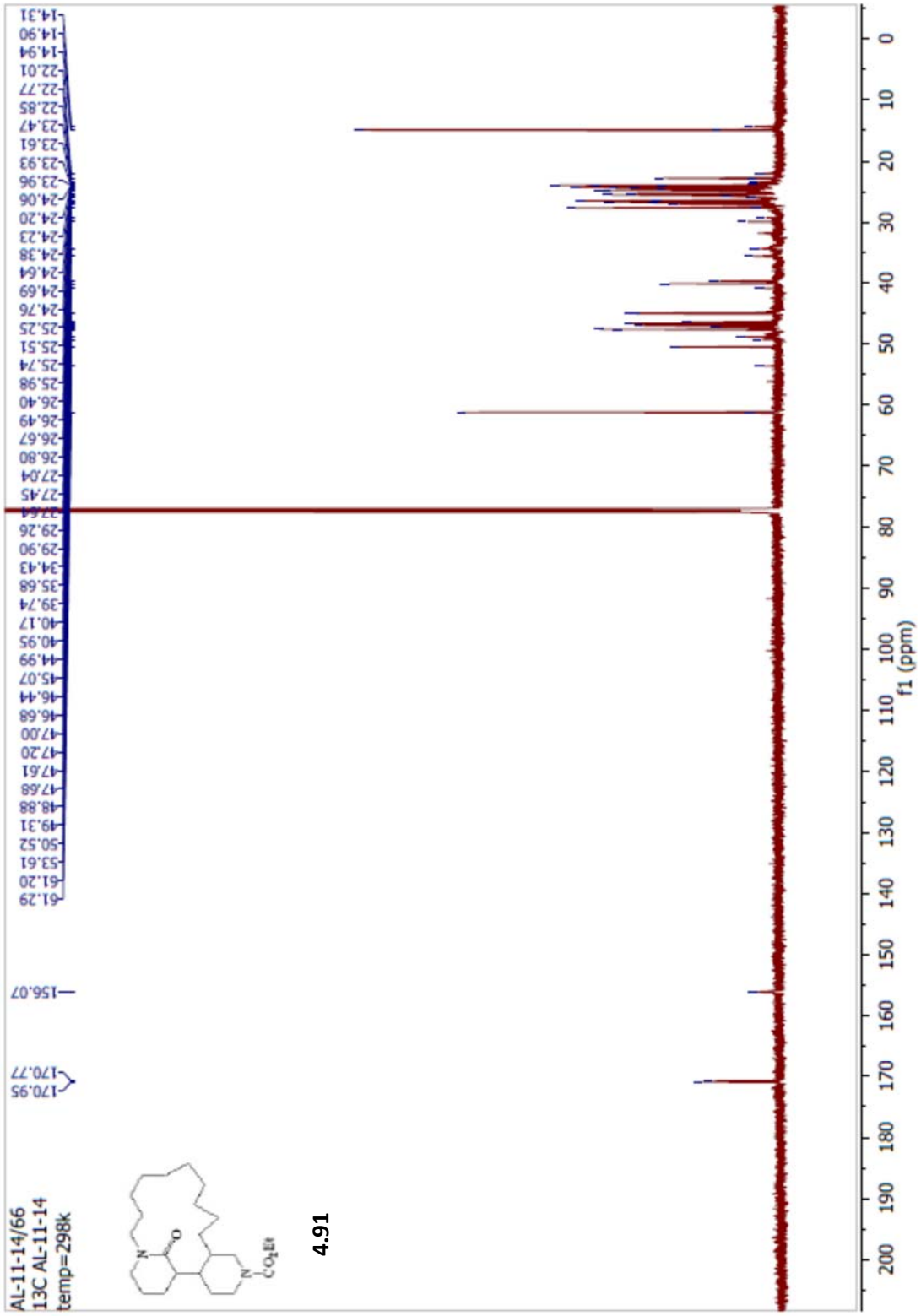
4.88

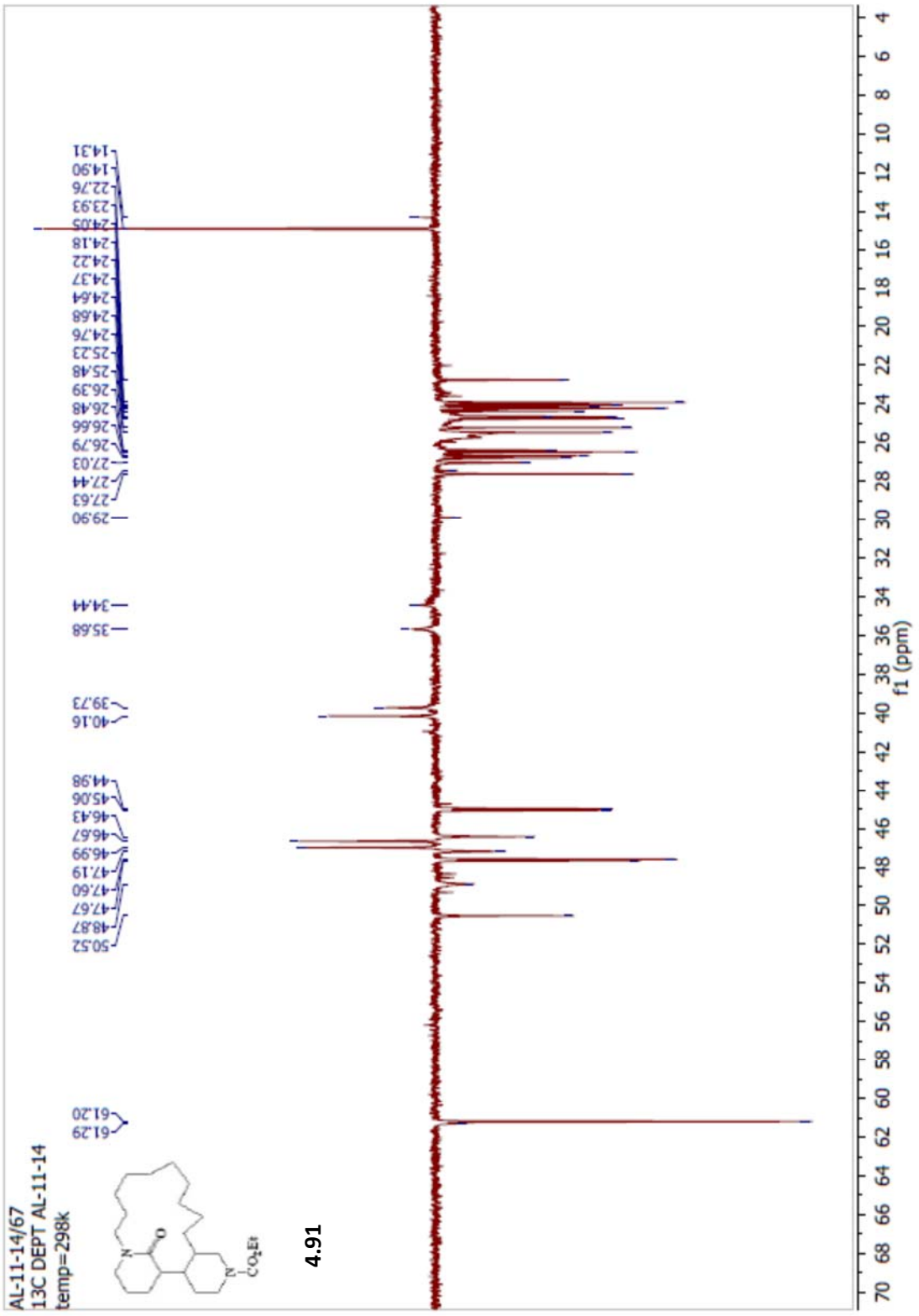

AL-10-298 retake.1.fid
1H AL-10-298 retake
4.89
1.02
0.99
1.00
4.72
1.93
4.87
18.64
f1 (ppm)


AL-10-298 retake.2.fid
13C AL-10-298 retake
4.89
169.75
150.73
150.57
147.34
147.30
136.35
124.05
47.53
46.30
30.14
30.06
28.72
28.51
27.57
27.39
26.92
26.49
26.36
26.27
25.67
25.03
23.39
f1 (ppm)

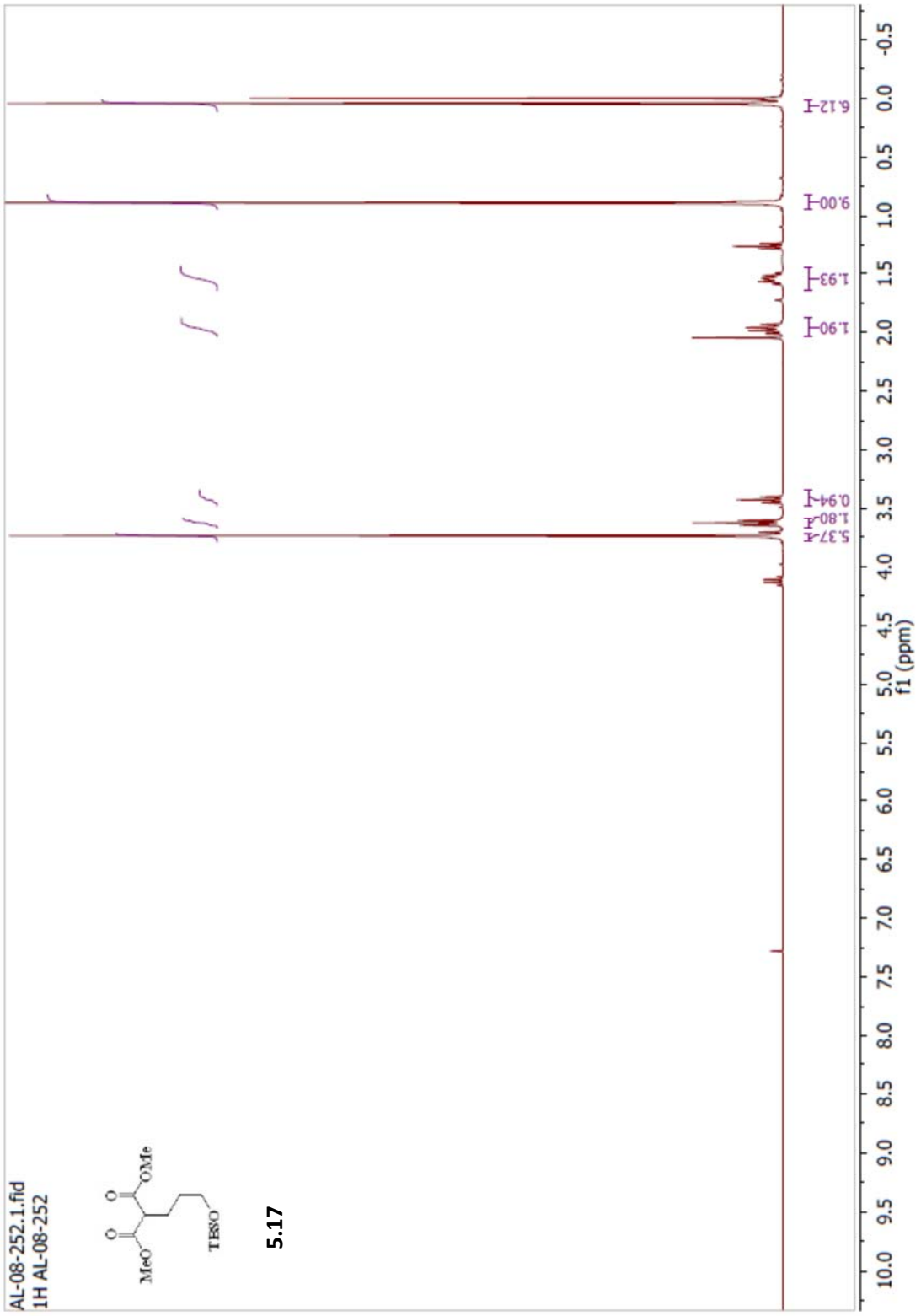

AL-10-242 Anhydrobase.1.fid
1H AL-10-242 Anhydrobase
4.90
27.97
4.85
5.69
2.27
1.00
2.06
f1 (ppm)

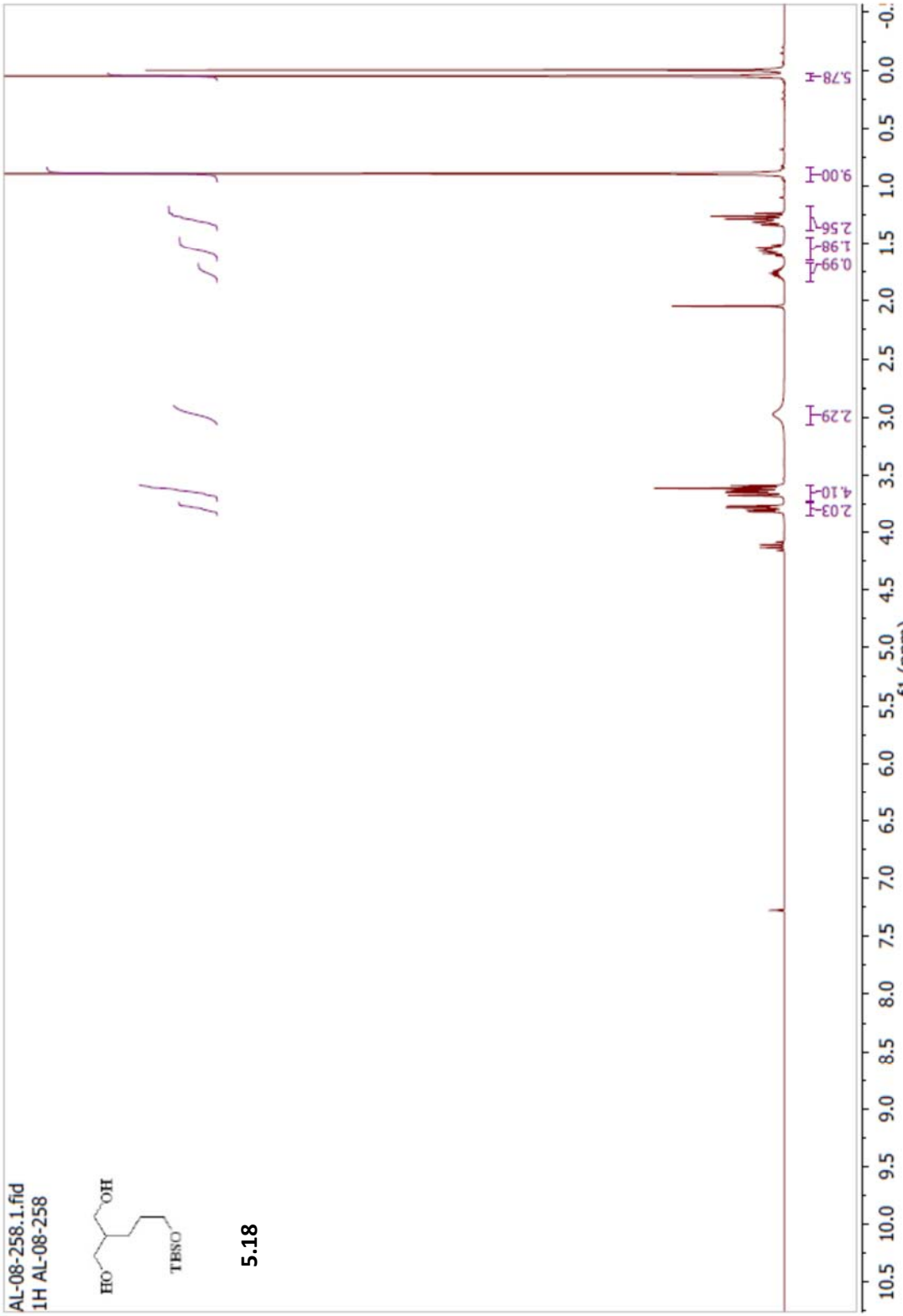

AL-11-14/61
1H AL-11-14
Temp - 298 K
4.91
f1 (ppm)

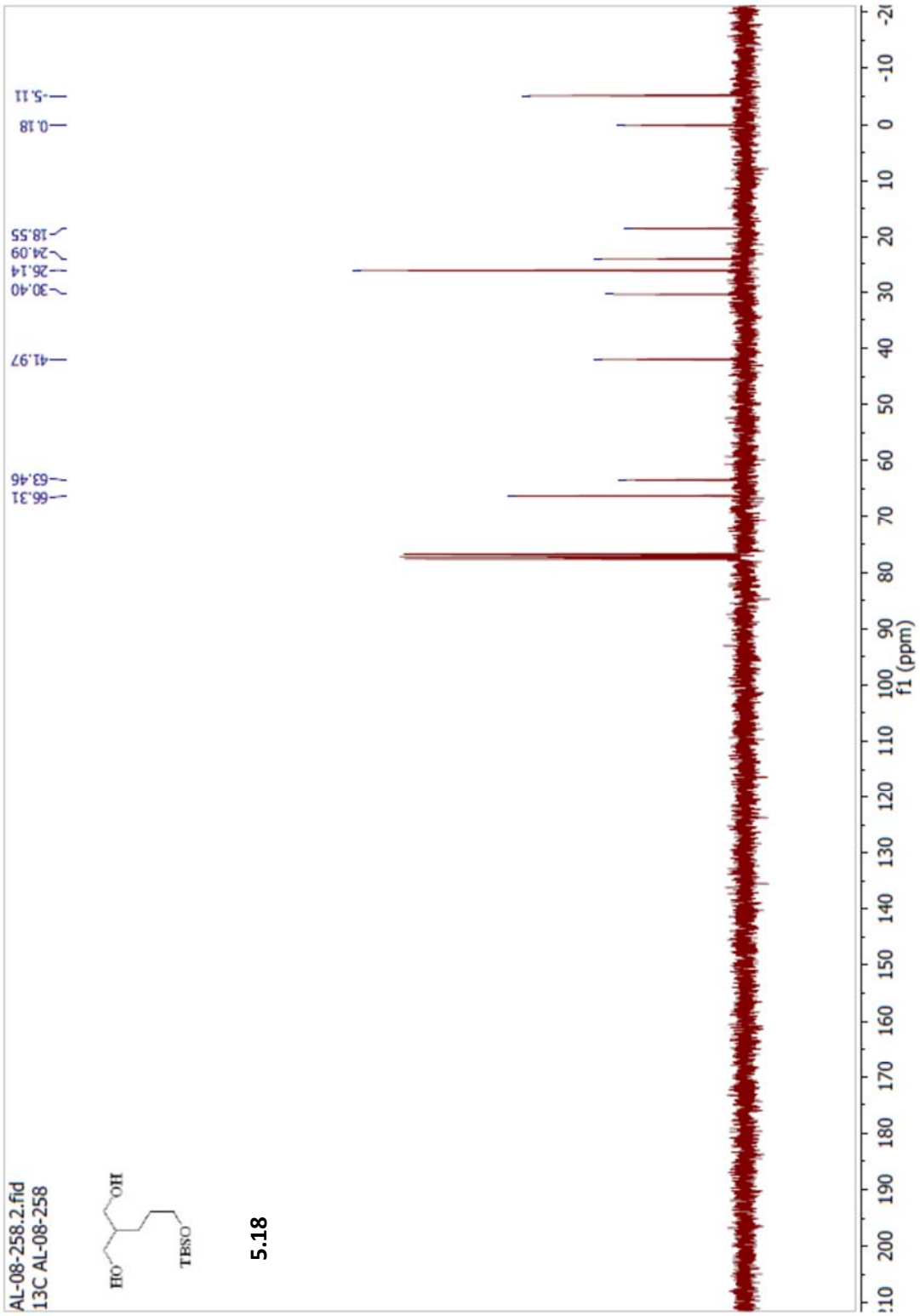

AL-11-14/66
13C AL-11-14
temp=298k
4.91
f1 (ppm)

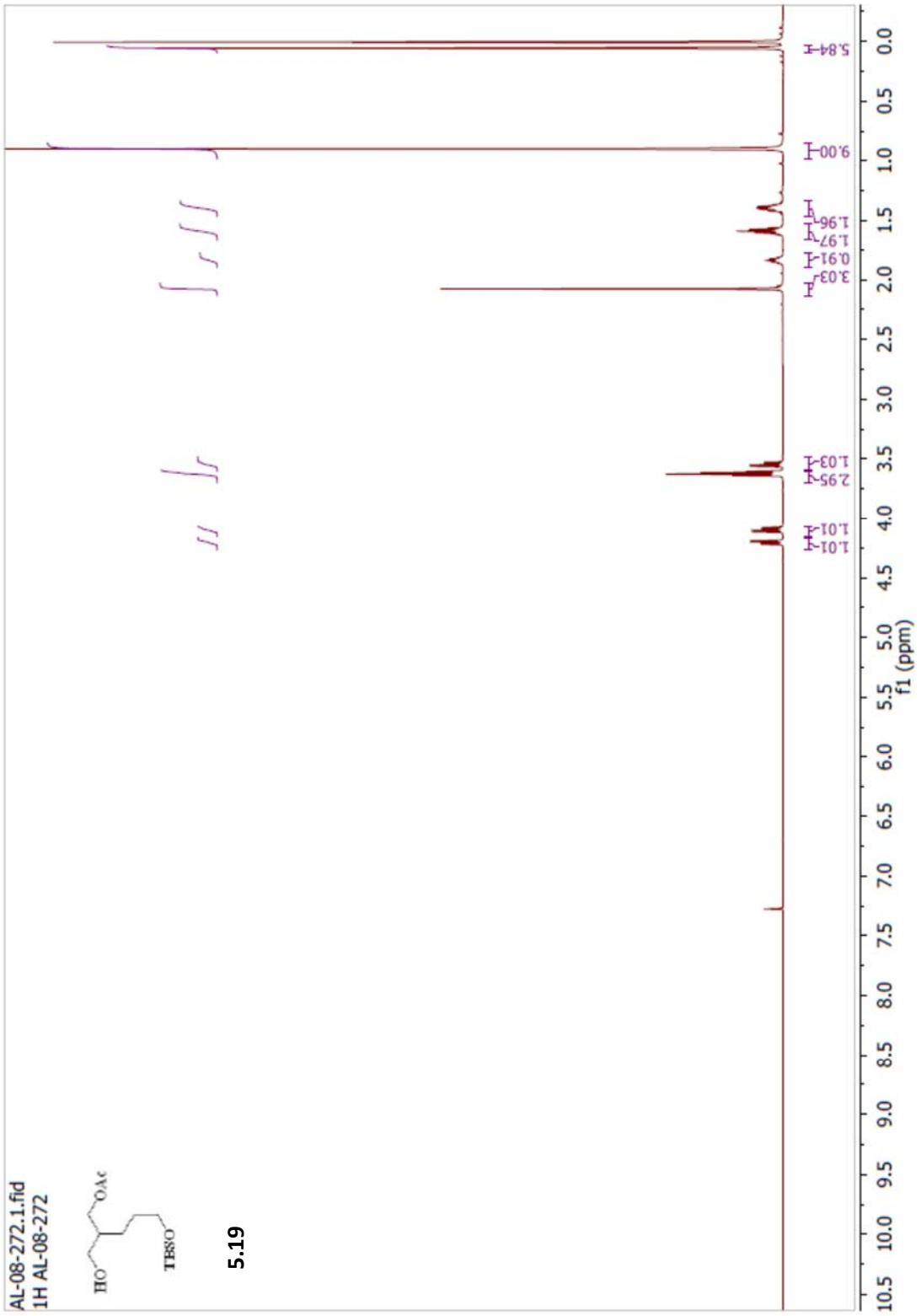

AL-11-14/67
13C DEPT AL-11-14
temp=298k
61.29
61.20
50.52
48.87
47.67
47.60
47.19
46.99
46.67
46.43
45.06
44.98
39.73
40.16
35.68
34.44
29.90
27.63
27.44
27.03
26.79
26.66
26.48
26.39
25.48
25.23
24.76
24.68
24.64
24.37
24.22
24.18
24.05
23.93
22.76
14.90
14.31
f1 (ppm)

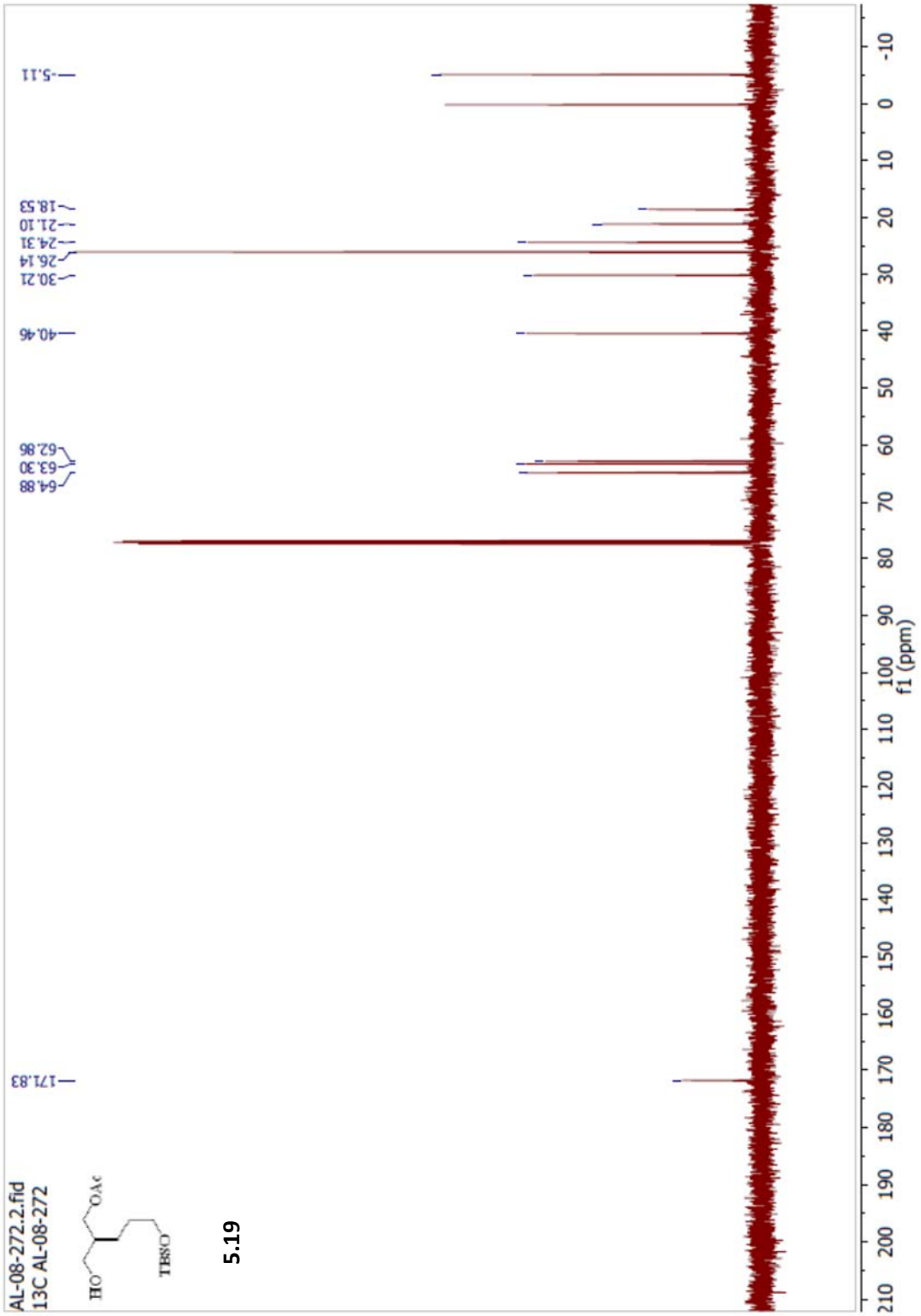
4.91

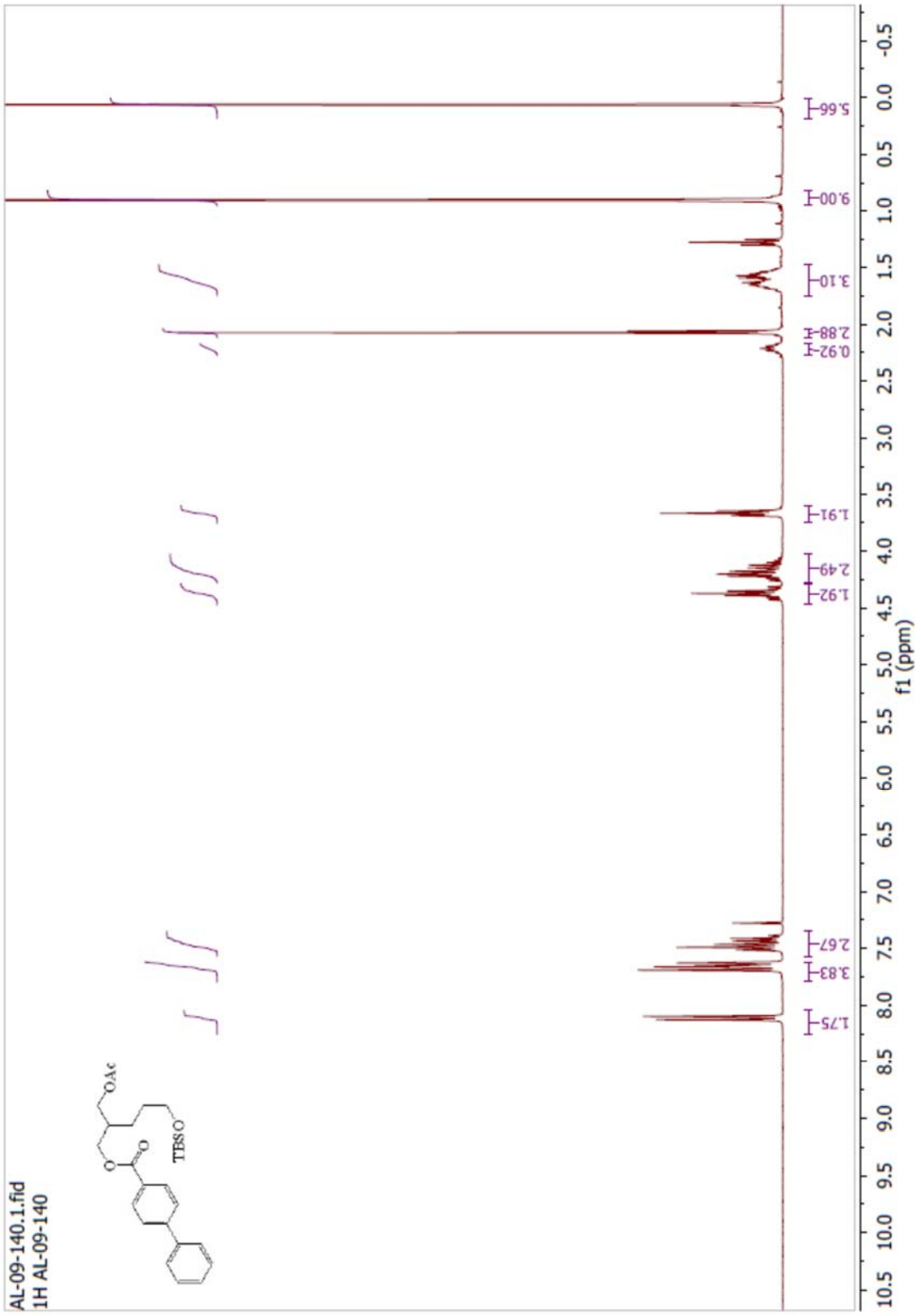

AL-08-252.1.fid
1H AL-08-252
MeO
OMe
TBSO
5.17
6.12
9.00
1.93
1.90
5.37
1.80
0.94
f1 (ppm)

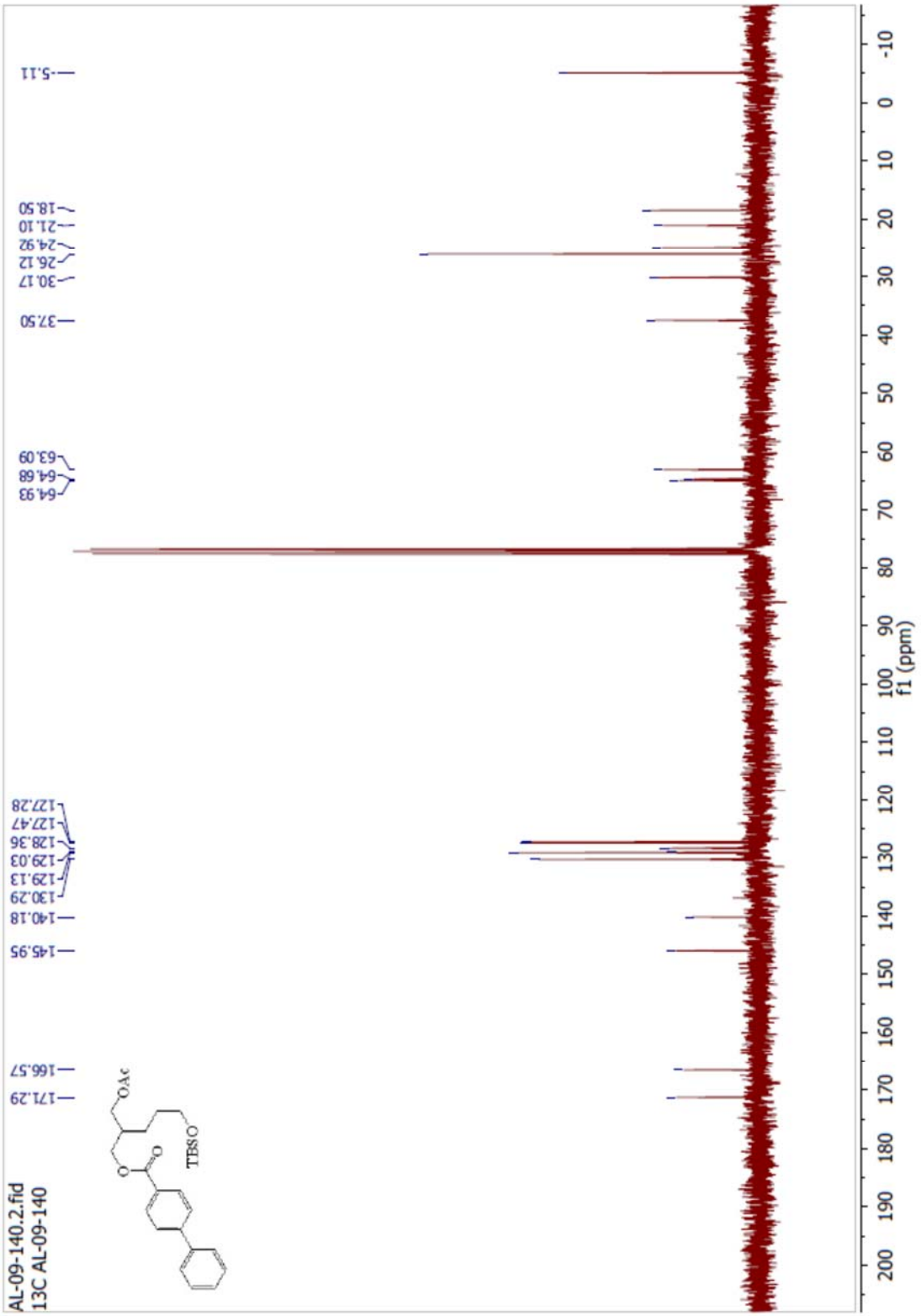

AL-08-258.1.fid
1H AL-08-258
HO
OH
TBSO
5.18
5.78
9.00
2.56
1.98
0.99
2.29
4.10
2.03
f1 (ppm)

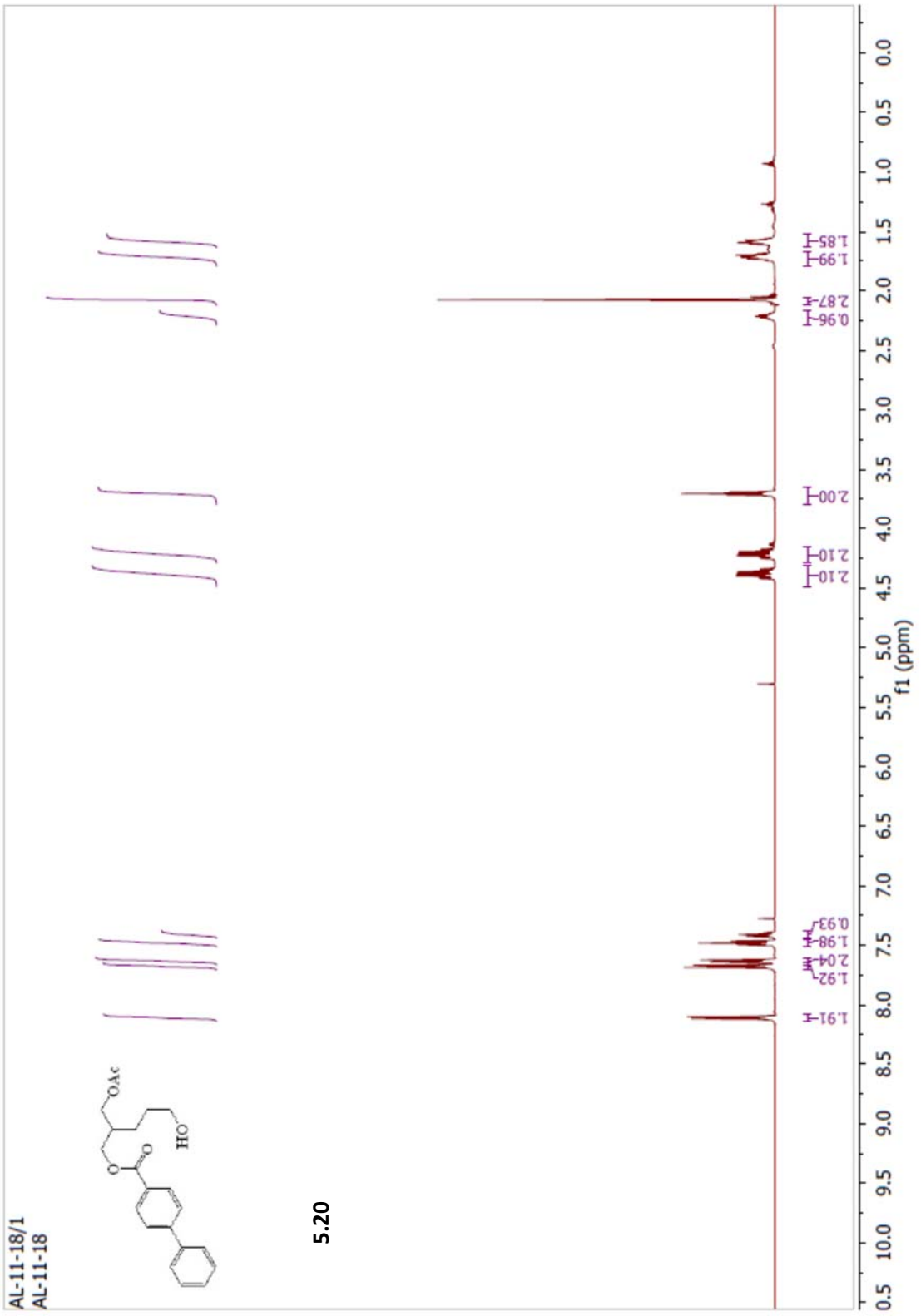

AL-08-258.2.fid
13C AL-08-258
HO
OH
TBSO
5.18
-5.11
0.18
18.55
24.09
26.14
30.40
41.97
63.46
66.31
f1 (ppm)

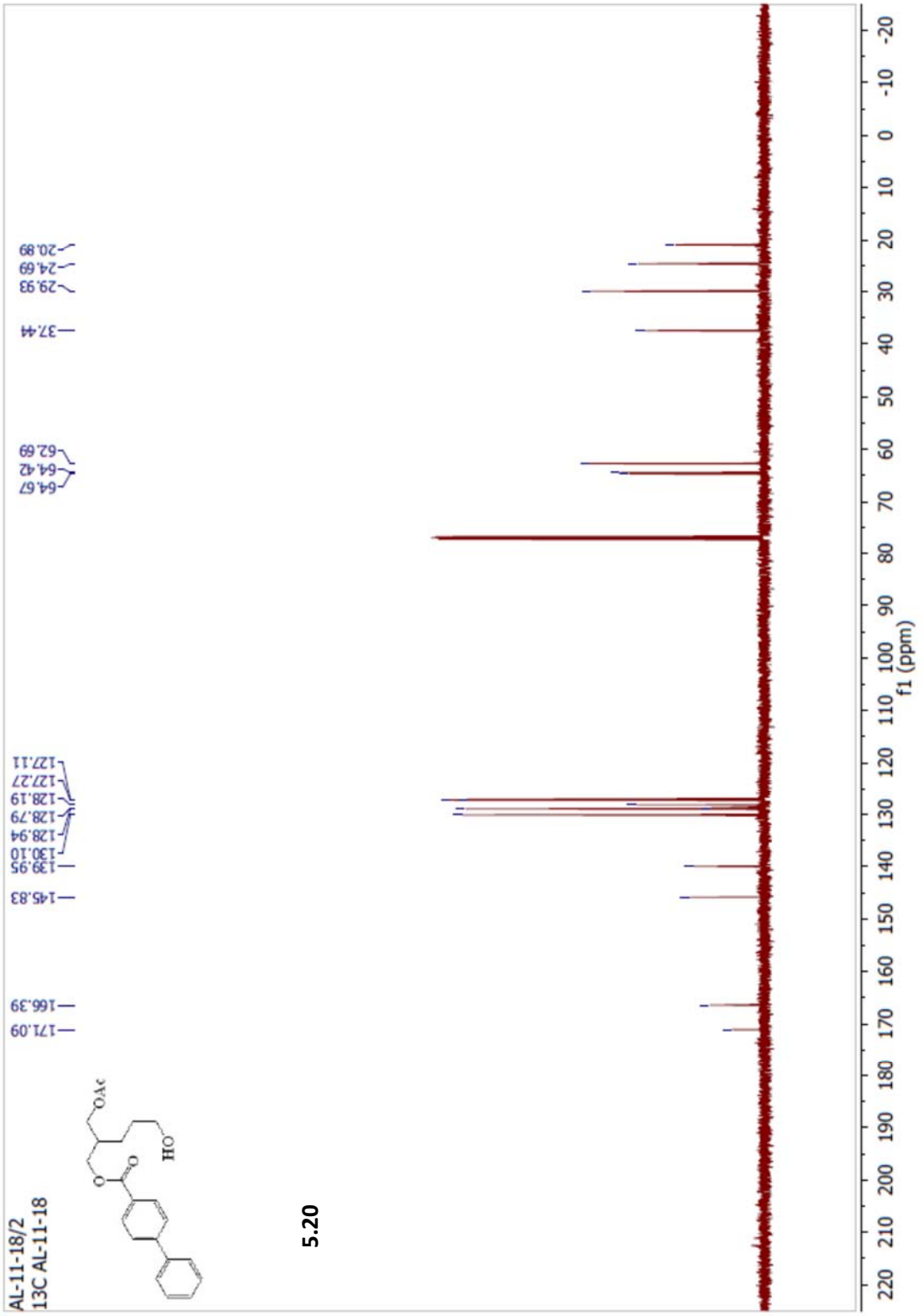

AL-08-272.1.fid
1H AL-08-272
HO
OAc
TBSO
5.19
5.84
9.00
1.96
1.97
0.91
3.03
2.95
1.03
1.01
1.01
f1 (ppm)

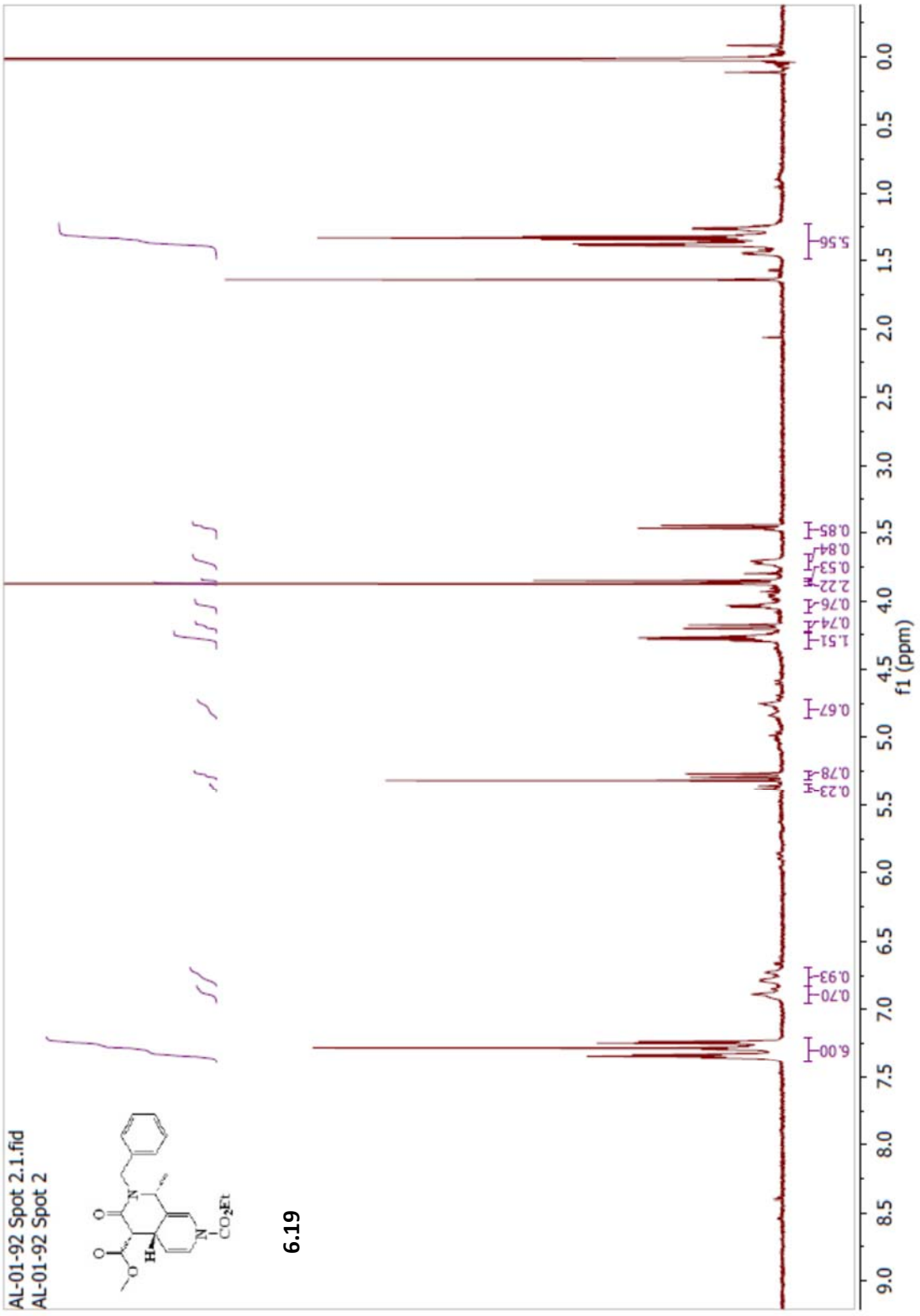

AL-08-272.2.fid
13C AL-08-272
HO
OAc
TBSO
5.19
171.83
64.88
63.30
62.86
40.46
30.21
26.14
24.31
21.10
18.53
-5.11
f1 (ppm)

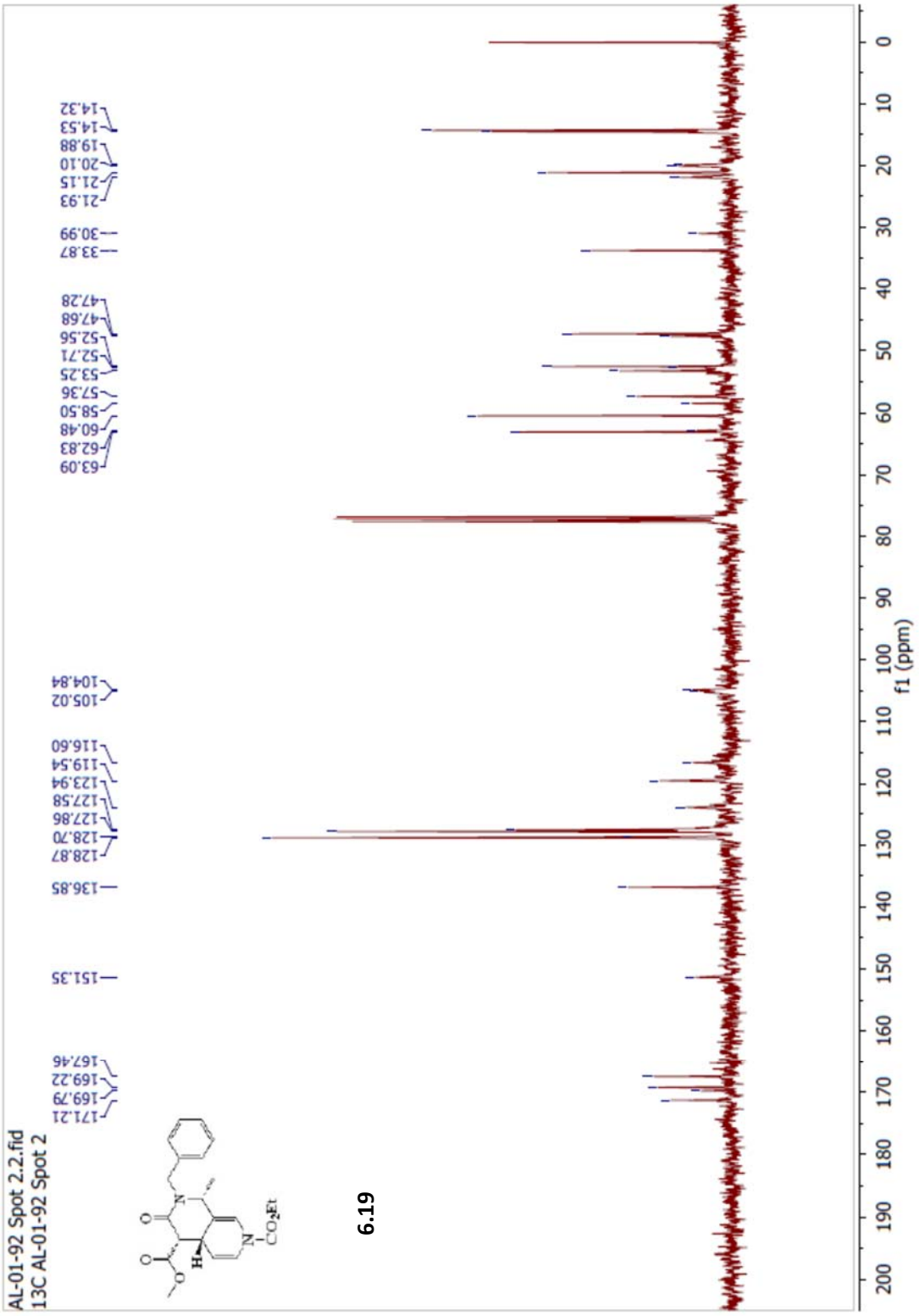

AL-09-140.1.fid
1H AL-09-140
OAc
O
O
TBSO
5.66
9.00
3.10
2.88
0.92
1.91
2.49
1.92
2.67
3.83
1.75
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


AL-09-140.2.fid
13C AL-09-140
OAc
TBSO
O
O
-5.11
18.50
21.10
24.92
26.12
30.17
37.50
63.09
64.68
64.93
127.28
127.47
128.36
129.03
129.13
130.29
140.18
145.95
166.57
171.29
f1 (ppm)

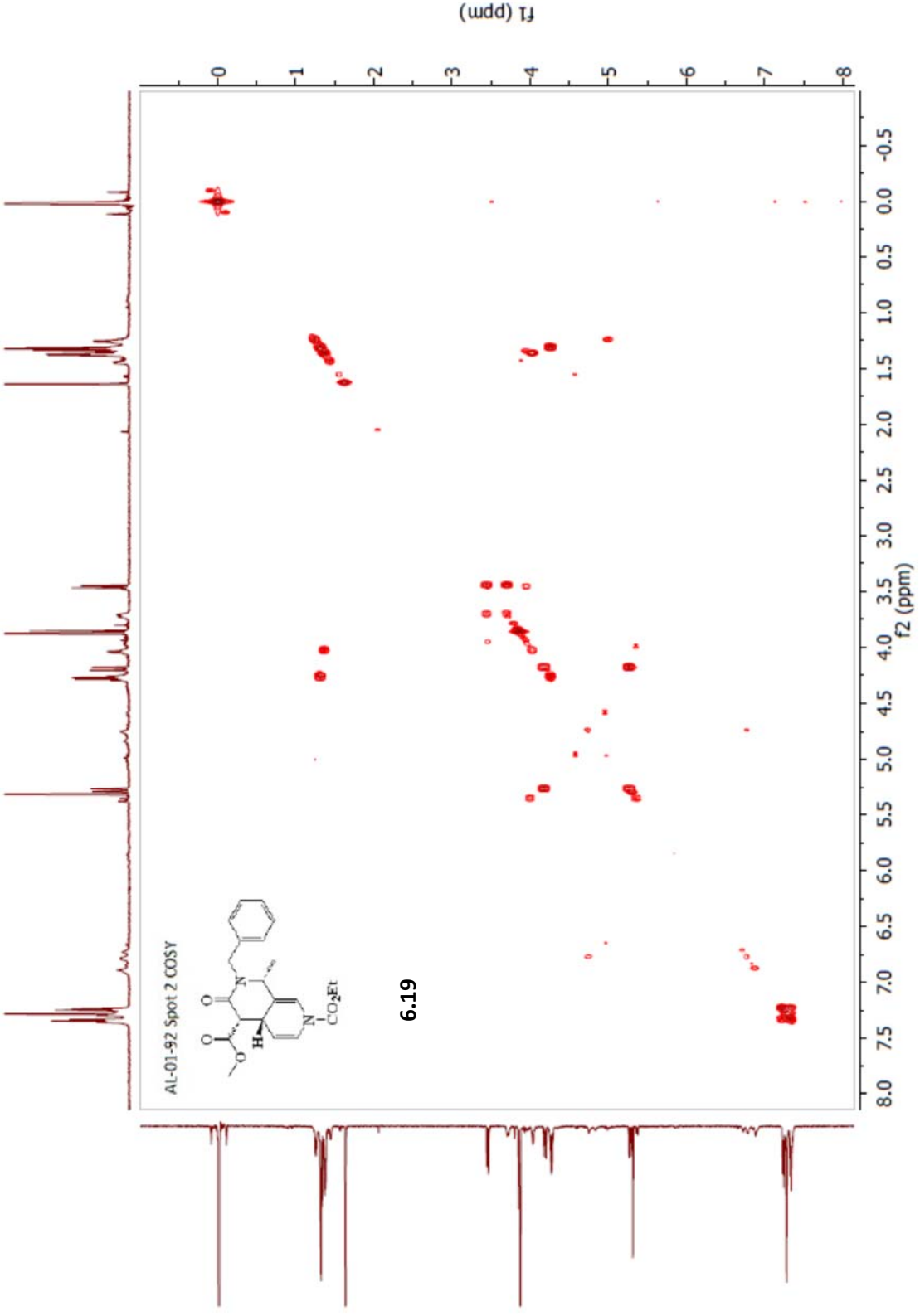

AL-11-18/1
AL-11-18
5.20
OAc
HO
O
O
1.91
1.92
2.04
1.98
0.93
2.00
2.10
2.10
0.96
2.87
1.99
1.85
f1 (ppm)

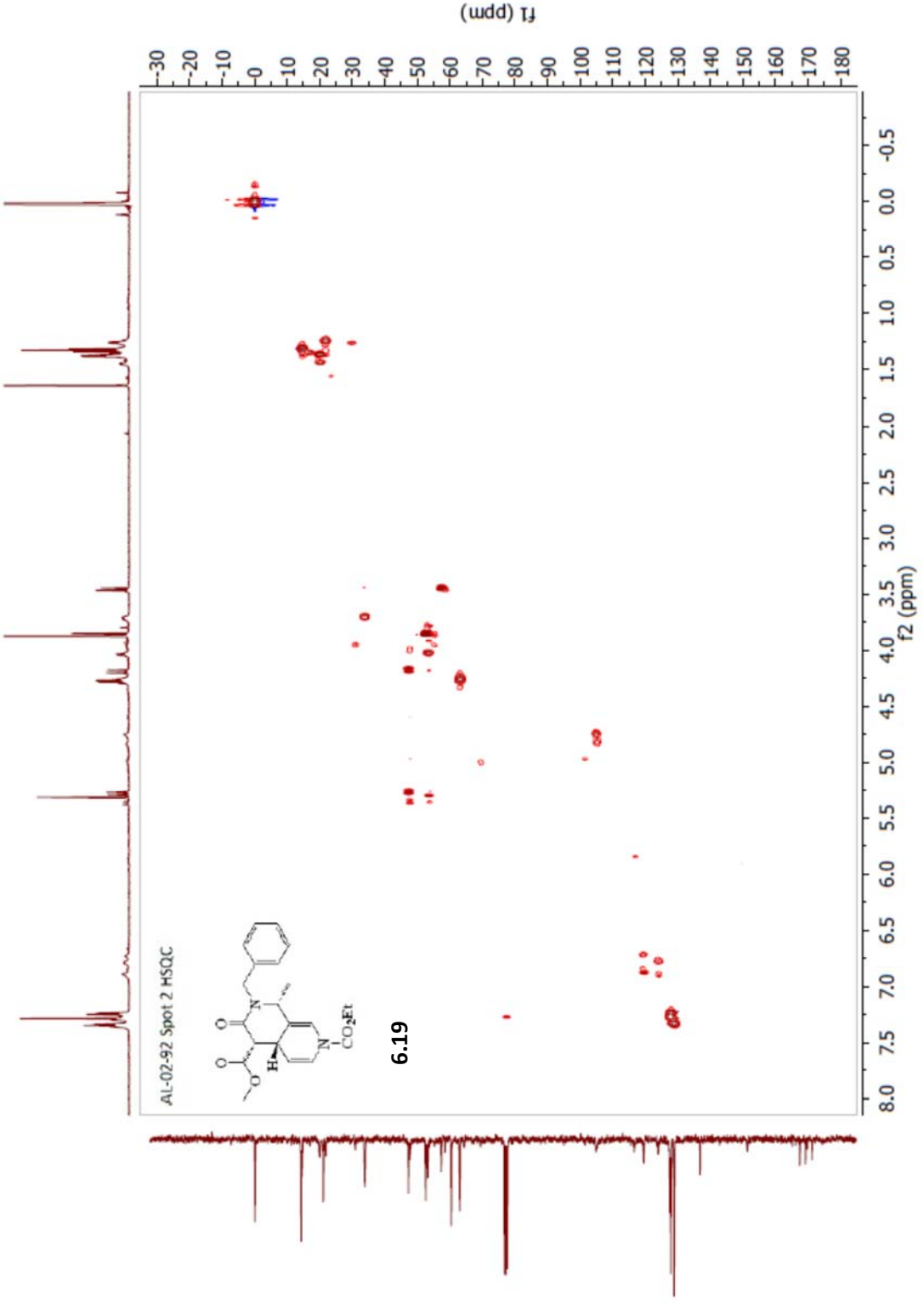

AL-11-18/2
13C AL-11-18
5.20
OAc
HO
O
O
171.09
166.39
145.83
139.95
130.10
128.94
128.79
128.19
127.27
127.11
64.67
64.42
62.69
37.44
29.93
24.69
20.89
f1 (ppm)

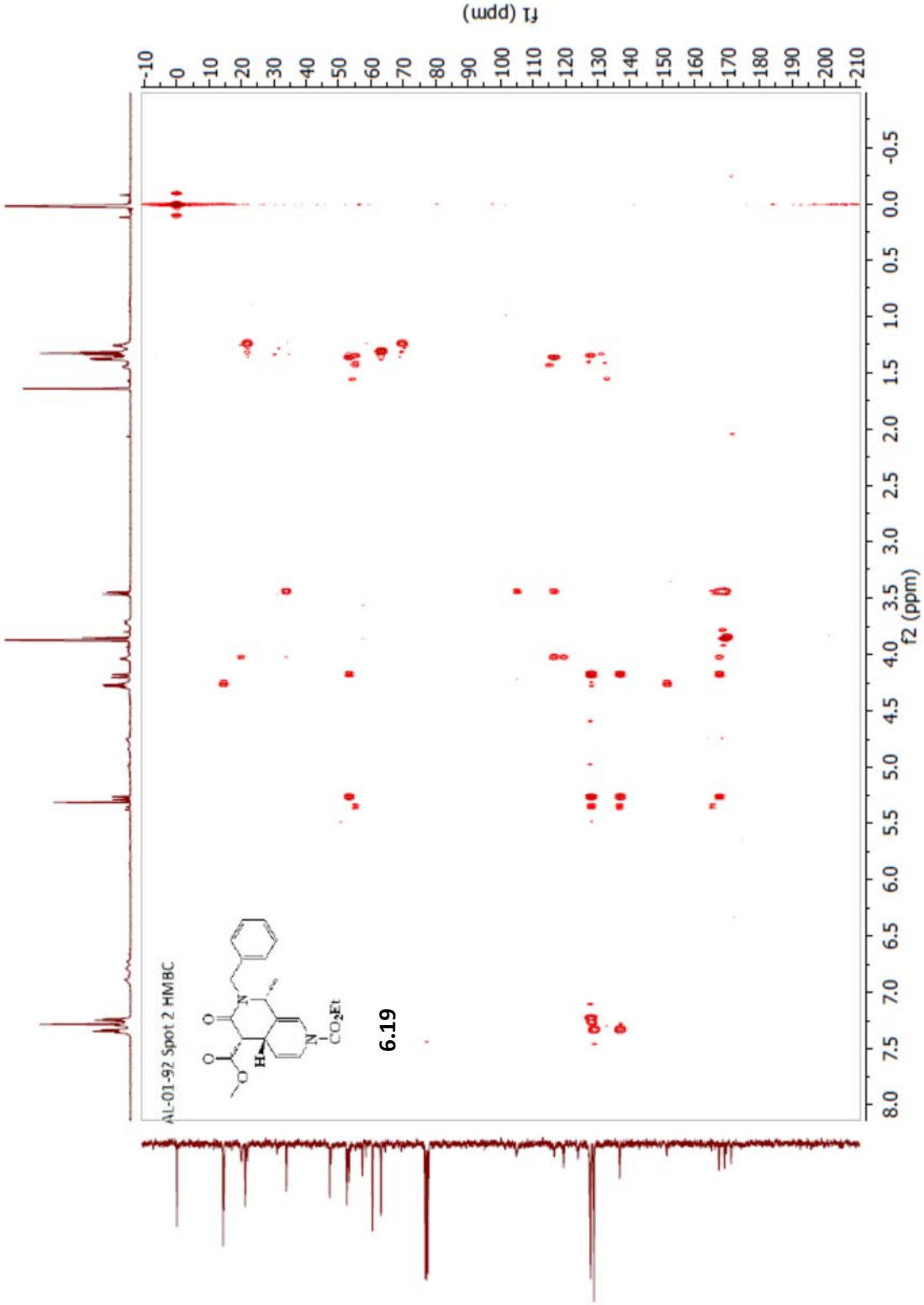

AL-01-92 Spot 2.1.fid
AL-01-92 Spot 2
6.19
f1 (ppm)

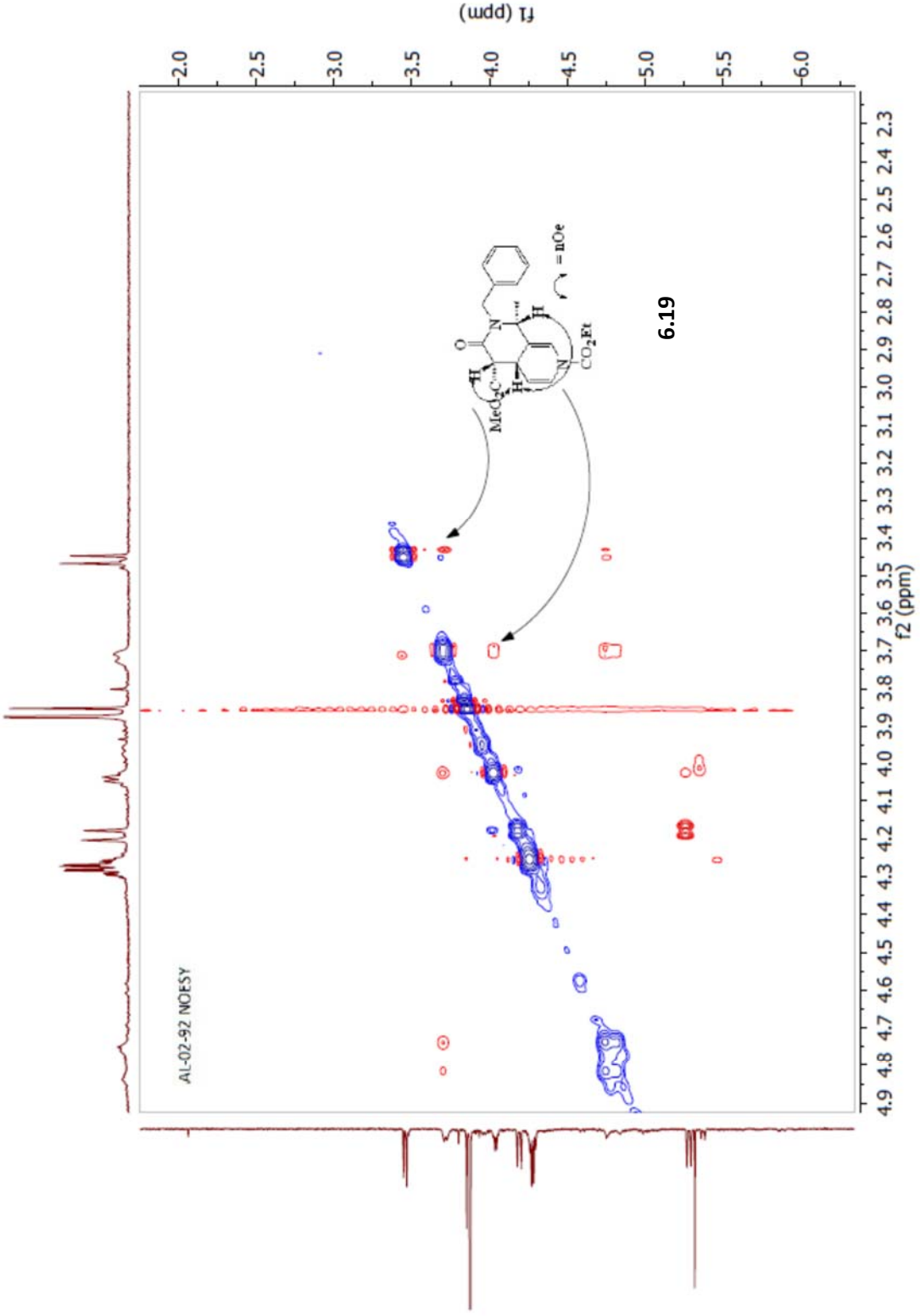

AL-01-92 Spot 2.2.fid
13C AL-01-92 Spot 2
171.21
169.79
169.22
167.46
151.35
136.85
128.87
128.70
127.86
127.58
123.94
119.54
116.60
105.02
104.84
63.09
62.83
60.48
58.50
57.36
53.25
52.71
52.56
47.68
47.28
33.87
30.99
21.93
21.15
20.10
19.88
14.53
14.32
f1 (ppm)

6.19


AL-01-92 Spot 2 COSY
f2 (ppm)
f1 (ppm)
6.19


AL-02-92 Spot 2 HSQC
6.19
f1 (ppm)
f2 (ppm)


AL-01-92 Spot 2 HMBC
6.19
f2 (ppm)
f1 (ppm)


AL-02-92 NOESY
f1 (ppm)
f2 (ppm)
6.19
= nOe
CO2Et

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