TRANSITION METAL-CATALYZED METHODOLOGIES FOR THE SYNTHESIS OF COMPLEX AMIDE BUILDING BLOCKS

Thesis by

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For Jessie

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ABSTRACT

Amides are ubiquitous functional groups that play a critical role in the composition and function of many biologically active molecules. Herein, this thesis presents three novel methodologies toward the construction of small molecules bearing amide functionality. In the first chapter, a convergent Ni-catalyzed N–N cross-coupling for the synthesis of hydrazides is described. This reaction constitutes the first example of a transition metal-catalyzed N–N bond forming reaction compatible with a wide array of aliphatic amine nucleophiles. In the second chapter, an enantioselective α-vinylation of γ-lactams is presented. In the third chapter, a novel, enantioselective spirocyclization of Pd-enolates intercepted under decarboxylative allylic alkylation conditions is disclosed. Finally, in the last appendices, we present a revised and expedient route toward the bis-THIQ natural product scaffold and describe the synthesis of some non-natural analogs.

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CHAPTER 3

An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
ºC	degrees Celsius
Å	Angstrom
Aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bz	benzoyl
c	concentration for specific rotation measurements
calc'd	calculated
cm^{-1}	wavenumer(s)
d	doublet
D	deuterium
dba	dibenzylideneacetone
DMF	*N,N*-dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent(s)

ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
G	grams
GC	gas chromatography
h	hours
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IPA	isopropanol
IR	infrared (spectroscopy)
J	coupling constant (NMR), exchange coupling constant (diradicals)
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LDA	lithium diisopropylamide
m/z	mass to charge ratio
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minutes
mol	mole(s)
n-Bu	*n*-butyl

NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
Ph	phenyl
PHOX	phosphinooxazoline
ppm	parts per million
R	generic for any atom or functional groups
SCF	self-consistent field
SFC	supercritical fluid chromatography
THIQ	tetrahydroisoquinoline

CHAPTER 1

Development of a Nickel-Catalyzed N–N Cross-Coupling for the Synthesis of Hydrazides †

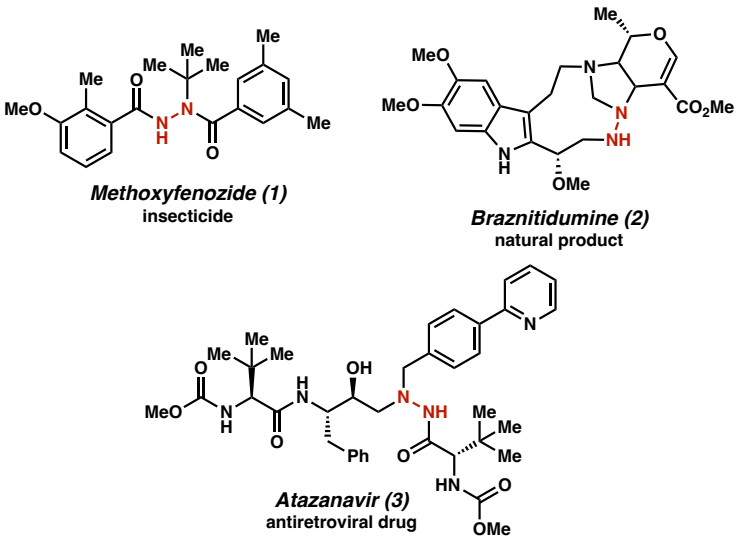
1.1 INTRODUCTION

Nitrogen–nitrogen bonds are prevalent motifs in biologically active small molecules and natural products and feature prominently in pharmaceutical and agricultural compounds (Figure 1.1).[1-5] Moreover, a variety of druglike heterocyclic scaffolds can be accessed from hydrazines and hydrazides.[2,6] The synthesis of N–N containing compounds typically entails a linear, stepwise process of hydrazine protection and derivatization, which hampers rapid access to highly-substituted products.[2] Improved methods for the convergent cross-coupling of two complex nitrogen-containing compounds would not only simplify the preparation of known hydrazines and hydrazides, but also accelerate access to

† This work was performed in collaboration with Dr. Vaishnavi N. Nair, Kimberly R. Sharp, Dr. Trevor D. Lohrey, Dr. Sara E. Dibrell, Dr. Tejas K. Shah, Dr. Martin J. Walsh, Dr Sarah E. Reisman and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Nair, V. N.; Sharp, K. S.; Lohrey, T. D.; Dibrell, S. E.; Shah, T. K.; Walsh, M. J.; Reisman, S. E.; Stoltz, B. M. Development of a Nickel-Catalyzed N–N Coupling for the Synthesis of Hydrazides. *J. Am. Chem. Soc*. **2023**, *145*, 15071–15077. © 2023 American Chemical Society.

new chemical space. For these reasons, new N–N bond forming reactions are of high value to the synthetic chemistry community.

Figure 1.1 *Compounds featuring N–N bonds.*



1.2 N–N BOND FORMING STRATEGIES

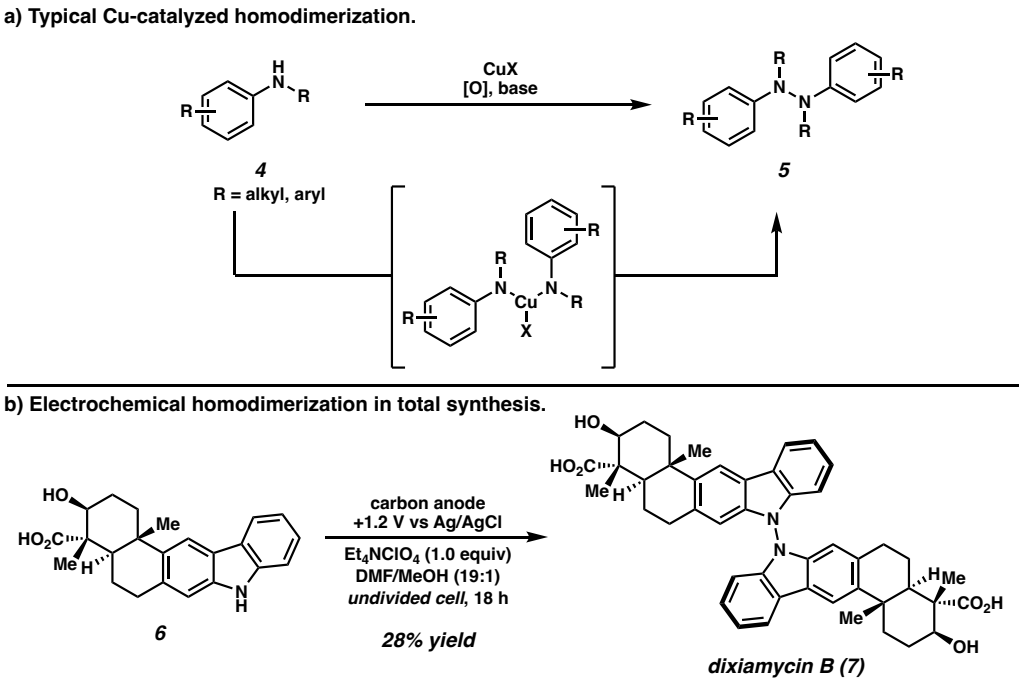
N–N cross-couplings can generally be broken into three categories: oxidative, reductive, and electrophilic. A brief discussion of the existing methodologies disclosed at the time we began this investigation is disclosed *vide infra.*

1.2.1 Oxidative N–N Cross-Couplings

Due to the difficult of chemically differentiating two amine coupling partners, oxidative N–N bond forming strategies are largely limited to the homodimerization of anilines or carbazoles.[2] Aside from the use of stoichiometric oxidizing reagents[7]—such as Ag_2O, $KMnO_4$, or $Na_2Cr_2O_7$—copper-catalyzed or electrochemical methods are the predominate technologies for N–N dimerization (Figure 1.2).[8,9] Cu-catalyzed dehydrogenative dimerizations typically invoke a Cu(I)/Cu(III) catalytic cycle and

necessitate the inclusion of an exogenous oxidant (Figure 1.2a).[8] The first electrochemical oxidative N–N dimerization was disclosed in 2014 from Baran and coworkers for the total synthesis of dixiamycin B (Figure 1.2b).[9a] Since this seminal report, several other electrochemical N–N couplings have been developed.[9b,c]

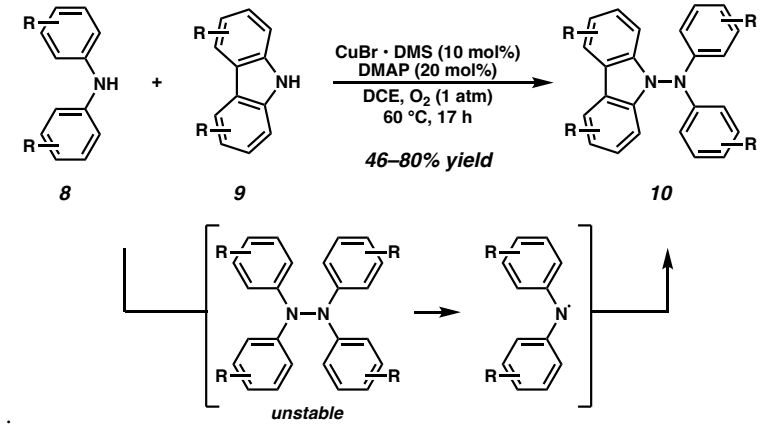
Figure 1.2 *Cu-catalyzed and electrochemical N–N homodimerizations.*



Despite the inherent challenges, cross-selective oxidative N–N couplings have also been achieved.[10] In 2018, Stahl and coworkers published an impressive Cu-catalyzed cross-selective coupling of biaryl anilines and carbazoles (Figure 1.3).[10a] Mechanistically, they propose the cross-selectivity originates from the kinetic dimerization of biaryl anilines to form tetra-arylhydrazines. Under the reaction conditions, these tetra-arylhydrazine intermediates were found to be unstable and underwent homolytic cleavage to deliver reactive aminyl radicals that could then undergo bond formation with a carbazole, delivering the thermodynamically preferred cross-coupled product. These assertions are

supported by ^{1}H NMR and EPR studies, which confirm the formation and disappearance of a tetra-arylhydrazine derived from dimerization of **8** and the presence of aminyl radicals in the reaction mixture, respectively.

Figure 1.3 *Cross-selective oxidative N–N couplings.*



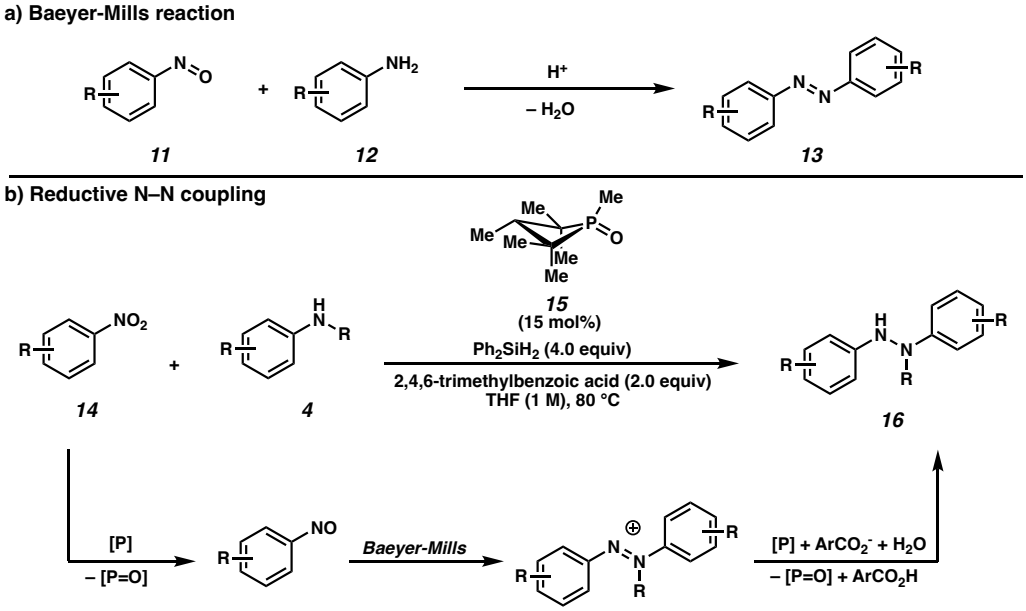
Outside of this mechanistic paradigm, other cross-selective N–N couplings typically rely upon stoichiometric biasing to achieve high yields of heterocoupled hydrazine. The development of more robust cross-selective oxidative couplings remains an ongoing challenge, and with the exception of one report,[11] these transformations are limited to diarylamine and carbazole coupling partners.

1.2.2 Reductive N–N Cross-Couplings

Reductive N–N cross-coupling strategies are derived from the Baeyer-Mills reaction, first developed in 1874, in which an amine is condensed with an aryl nitroso in the presence of catalytic acid to afford an azo product (Figure 1.4a).[12a] In collaboration with Merck, the Radosevich group developed a method expanding upon the Baeyer–Mills reaction,[12b] whereby commercially available aryl nitro compounds can be reduced *in situ* to the corresponding nitroso, followed by a Baeyer–Mills condensation and further reduction of the azo by the phosphine catalyst to generate hydrazine products in a one-pot

transformation (Figure 1.4b). Reduction of the phosphine oxide catalyst to turnover the catalytic cycle is mediated by stoichiometric amounts of a silane additive. While reductive N–N coupling strategies are generally more amenable to the synthesis of nonsymmetrical hydrazine derivatives, to date, this strategy is still limited to aryl substrates.

Figure 1.4 *Reductive N–N cross-coupling.*

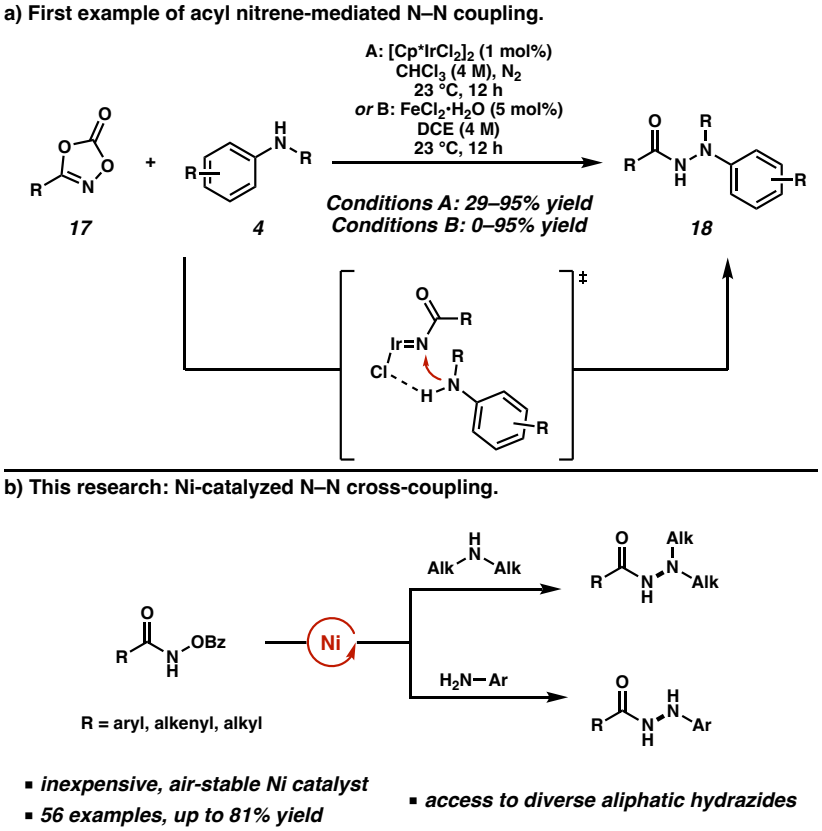


1.2.3 Electrophilic N–N Cross-Couplings

Electrophilic N–N forming strategies encompass reactions utilizing either umpolung aminating reagents, like chloramines,[13] or nitrenoid precursors, such as dioxazolones, hydroxamic esters and azides.[14] Transition metal-catalyzed nitrene insertion chemistry has gained significant attention as a potential tool for N–N bond formation. In 2021, the Chang group reported the first N–N coupling for the formation of hydrazides utilizing either iron or iridium catalysis (Figure 1.5a).[15] Mechanistically, Chang proposed the reaction initiates via decarboxylation of the dioxazolone to form a metal-bound acyl nitrene that is subject to outer-sphere attack by a secondary aniline to deliver the hydrazide product. Only primary and secondary aliphatic dioxazolones and secondary aniline

nucleophiles were demonstrated to be compatible with this chemistry. Moreover, reaction concentrations of 4 M were required to abate undesired acyl nitrene rearrangement. Although the required reaction concentrations prove environmentally friendly, they greatly limit the scope of this transformation with respect to the solubility of more challenging coupling partners.

Figure 1.5 *Acyl nitrene-mediated N–N bond formation.*



While the method developed by Chang and Chen enables efficient coupling of a wide array of aliphatic electrophiles and secondary anilines, other classes of amine nucleophiles—most notably aliphatic amines—remain incompatible. As part of an industrial-academic collaboration aimed at developing new modular approaches for N–N coupling, we pursued the development of a new acyl nitrene-mediated N–N cross-coupling

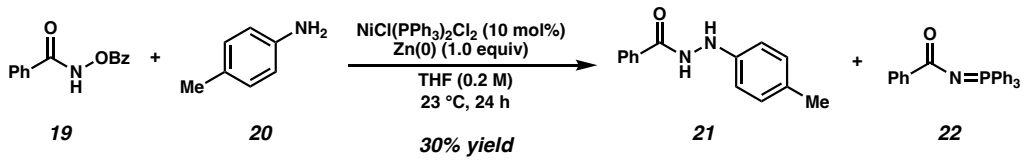
with the goal of accessing diverse hydrazides from both aryl and aliphatic coupling partners (Figure 1.5b).

1.3 REACTION OPTIMIZATION

1.3.1 Initial Reaction Discovery

After a wide survey of potential transition metal catalysts, we were pleased to discover that reaction with N-(benzoyloxy)benzamide **19** and p-toluidine (**20**) in the presence of Zn(0) and catalytic $Ni(PPh_3)_2Cl_2$ resulted in a 30% yield of the desired hydrazide product **21** (Table 1.1). Iminophosphorane **22** was observed as a side product of this reaction, which is suggestive of the intermediacy of a nitrenoid species.[16] Surprisingly, we observed no urea formation, indicating robust stabilization of the hydroxamate against Lossen-type rearrangement.[17]

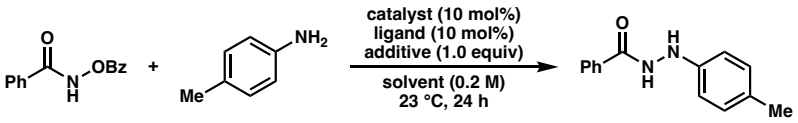
Figure 1.6 *Initial reaction discovery.*



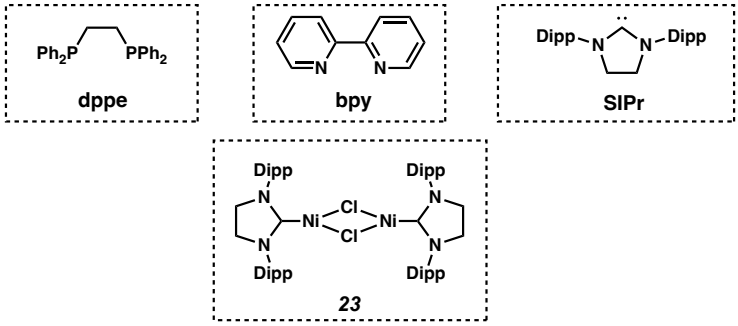
In the absence of Zn, poor conversion was observed, providing a similar 30% yield of **21** only after extended reaction time and with significant unconsumed starting material (Table 1.1). We postulate that Ni(II) may be effecting the desired transformation via an alternative mechanism, such as Lewis acid activation. Use of $Ni(cod)_2$ yielded no reaction, suggesting that a Ni(0) species is not capable of initiating the catalytic cycle. Use of bidentate ligands dppe or bpy resulted in a complete loss of reactivity; however, strongly σ-donating N-heterocyclic carbene (NHC) SIPr afforded a 32% yield of **21** with no observed nitrene transfer to the ligand. Use of alternative NHC ligands resulted in

diminished yields. Given the stark difference in reactivity observed between monodentate and bidentate ligands, we hypothesized that the catalyst must be coordinatively unsaturated to effect the desired chemistry.

Table 1.1 *Initial reaction optimization.*[a]



entry	catalyst	ligand	additive	yield (%)
1	$Ni(PPh_3)_2Cl_2$	—	Zn	30
2	$Ni(PPh_3)_2Cl_2$	—	—	30[b]
3	$Ni(cod)_2$	PPh_3	—	0
4	$NiCl_2$·glyme	dppe	Zn	0
5	$NiCl_2$·glyme	bpy	Zn	0
6	$NiCl_2$·glyme	SIPr	Zn	32
7	*23*	—	—	0
8	*23*	—	Zn	0
9	$NiCl_2$·glyme	SIPr	$PhSiH_3$	34-82[c]



[a] Reactions performed on 0.05 mmol scale. [b] 72 h. [c] Excess **19** (1.5 equiv). [d] Dipp = 2,6-diisopropylphenyl.

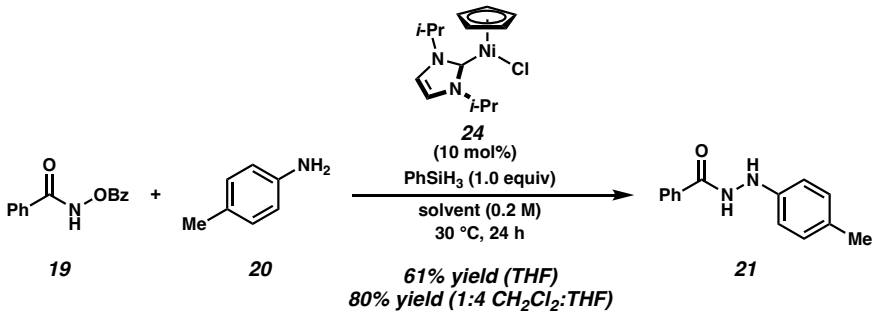
Having identified a more suitable ligand, we reexamined the role of Zn as an additive. Previous reports have demonstrated the ability of Ni(I) dimer **23** to form a bridged Ni-nitrene; we considered the possibility that Zn-mediated reduction may be forming a similar species in situ.[18] Unfortunately, examination of **23** both with and without Zn resulted in no reactivity, leading us to hypothesize a mononuclear Ni(I) complex as the active catalyst.[19] While further exploration of reductants ultimately revealed that phenylsilane improved reactivity, yields were highly variable across batches of starting

materials and reagents. Despite an extensive effort to assess the purity of our reagents, we were ultimately unable to identify the cause of irreproducibility.

1.3.2 Revised Catalyst Framework

Aiming to achieve more consistent results, we explored well-defined Ni complexes and were intrigued by reports of NHC-ligated Ni(II) half-sandwich catalysts, which have recently been utilized for catalytic oxidative N–N coupling of ammonia to dinitrogen.[20-23] These easily synthesized and air-stable complexes have been implicated to undergo hydride-mediated reduction to Ni(I),[20,21] and the cyclopentadienyl (Cp) ligand has been suggested to undergo surprisingly facile equilibration among η^5, η^3, and η^1 binding modes, which we imagined could satisfy the previously observed requirement for a coordinatively unsaturated catalyst.[20,22]

Figure 1.7 *Revised catalyst.*[a]



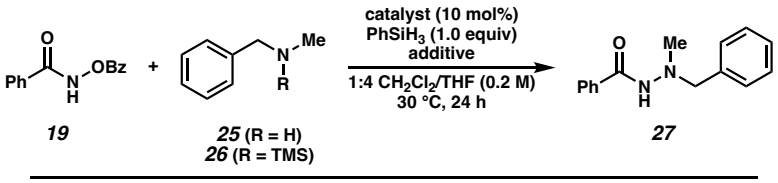
[a] Reactions performed on 0.05 mmol scale.

Excitingly, use of **24** generated a 61% yield of the desired product, which was found to be reproducible across all batches of starting materials, catalyst, and silane (Figure 1.7). Further exploration of solvent effects revealed that a 1:4 mixture of CH_2Cl_2/THF further improved the yield to 80%.

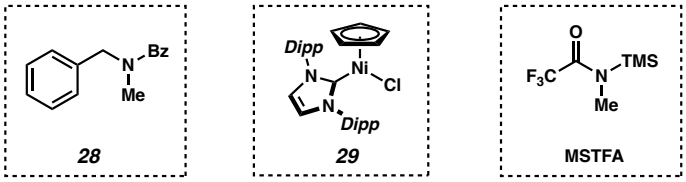
1.3.3 Aliphatic Amine Nucleophiles

Having identified optimal conditions for aryl amine nucleophiles, we sought to expand the scope of the transformation to aliphatic amines. Reaction with unprotected secondary aliphatic amine **25** resulted in significant *O*-to-*N* benzoyl transfer from the hydroxamate to the amine, yielding product **28** and minimal formation of the desired hydrazide (Table 1.2).

Table 1.2 *Optimization of aliphatic amine nucleophiles.*[a]



entry	catalyst	nucleophile	additive	yield (%)
1	*24*	*25*	–	6[b]
2	*24*	*26*	–	27[b]
3	*24*	*26* (1.1 equiv)	–	43
4	*24*	*26* (1.5 equiv)	–	57
5	*29*	*26* (1.5 equiv)	–	69
6	*29*	*25* (1.5 equiv)	MSTFA (1.5 equiv)	59



[a] Reactions performed on 0.05 mmol scale. [b] Excess **19** (1.5 equiv). [c] Dipp = 2,6-diisopropylphenyl.

Surmising that silylation of these more challenging nucleophiles might serve as a transient protection strategy until either transmetallation with the catalyst or benzoate-mediated desilylation, we explored reactivity with silylamine **26**.[24] To our satisfaction, reaction of **26** with excess **19** afforded the desired product **27** in 27% yield. Use of excess amine was found to improve the product distribution, with 1.5 equiv **26** resulting in a 57% yield. Gratifyingly, use of IPr-substituted catalyst **29** afforded a 69% yield of the desired hydrazide **27**, minimizing formation of undesired side-product **28**. We posit the *O*-to-*N*

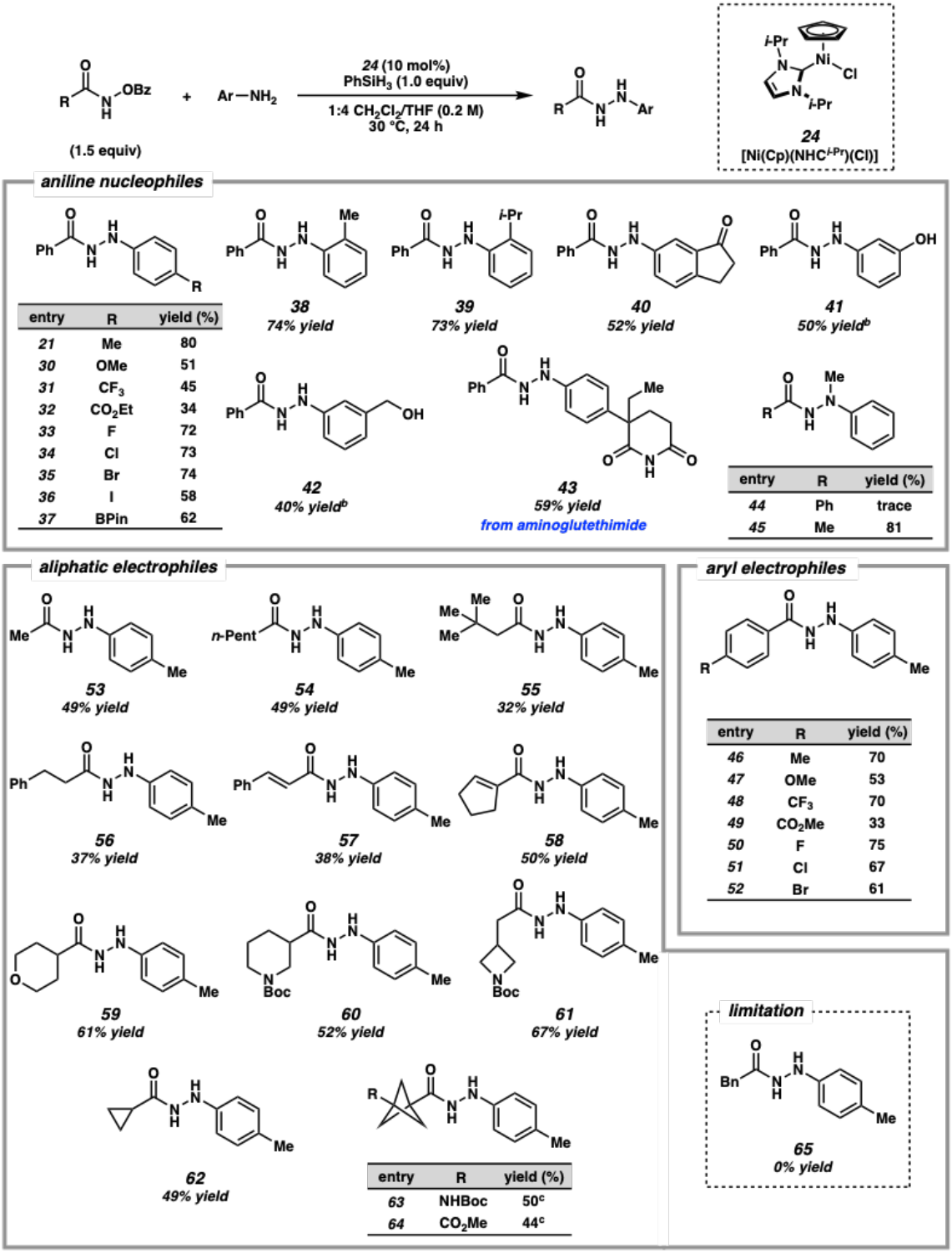
benzoyl transfer may be accelerated within the coordination sphere of the catalyst, and that increasing steric hinderance around the metal center may block this competing pathway. Although satisfied with the efficiency of these conditions utilizing pre-silylated amines, a more operationally expedient route was developed via *in situ* silylation of amine **25** with MSTFA, affording 59% yield of product in a single synthetic step.

1.4 SUBSTRATE SCOPE

With optimized conditions in hand, we examined the scope of compatible coupling partners. An electron-rich aniline derivative provided the desired product in good yields (**30**), while electron-deficient amines gave slightly diminished yields (**31** and **32**). Halide substituents on the arene (**33**–**36**) were well tolerated under the reaction conditions and showed no signs of protodehalogenation. Functional handles for further derivatization, such as an aryl iodide (**36**) and boronic ester (**37**), remained intact under the reaction conditions. Sterically hindered *ortho*-substituted aniline derivatives afforded products **38** and **39** in good yields. Amines bearing unprotected ketone (**40**) and hydroxyl (**41** and **42**) moieties were also found to be compatible. Moreover, aminoglutethimide, a drug used in the treatment of Cushing's disease,[25] was efficiently derivatized to the corresponding hydrazine (**43**), highlighting the potential use of this method for late-stage functionalization of complex molecules.

Although exploration of a secondary aniline in the reaction with **19** yielded only trace hydrazide (**44**), we observed an 81% yield of product when using *N*-(benzoyloxy)acetamide as an electrophile (**45**). We postulate the difference in reactivity between aryl and aliphatic hydroxamates with secondary anilines may reveal the balance

Figure 1.8 *Scope of aniline nucleophiles with various hydroxamates.*[a]



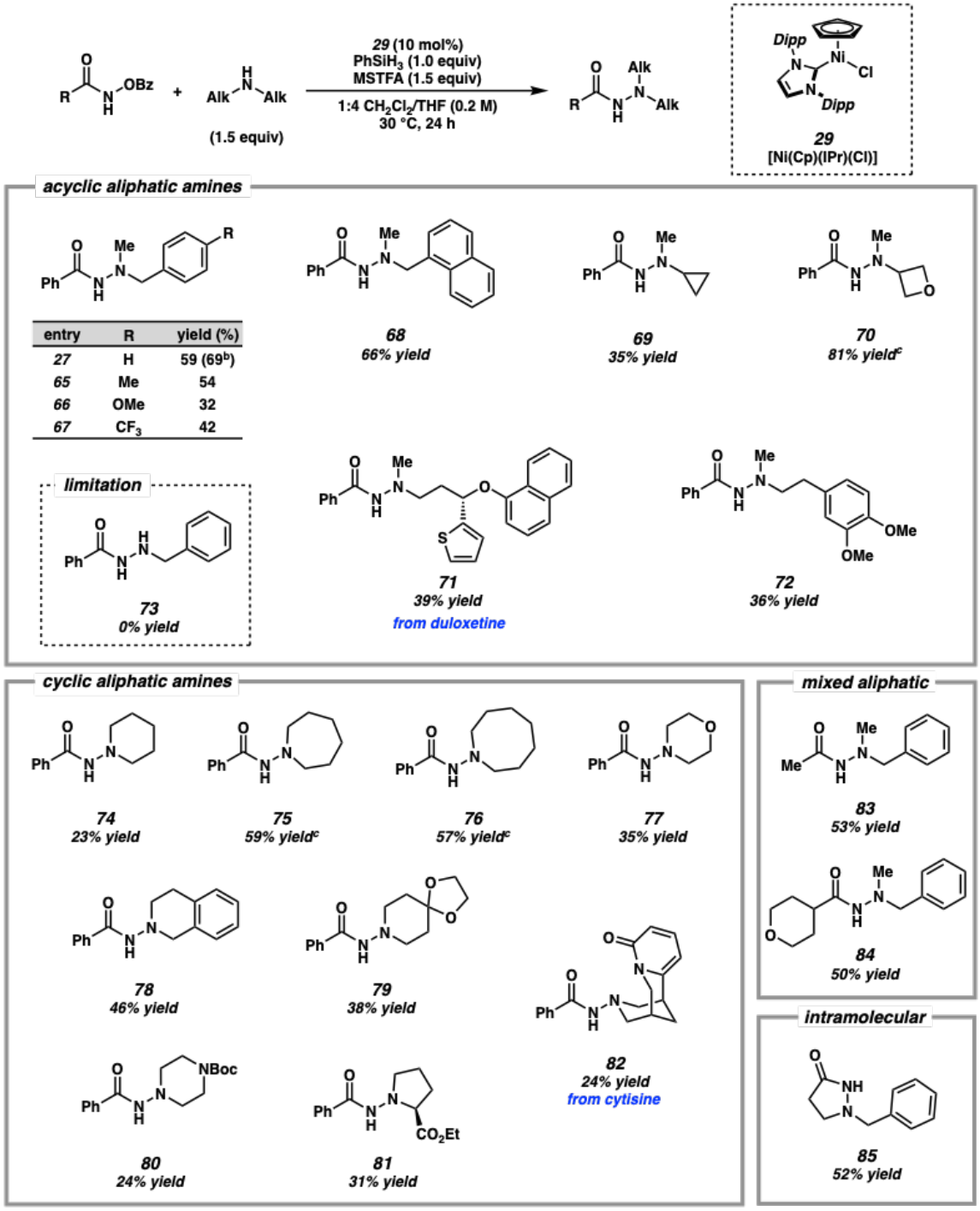
[a] Reactions performed on 0.2 mmol scale. [b] Protected as TBS ether for isolation. [c] 72 h.

between steric and electronic constraints for this transformation—although secondary anilines are more nucleophilic than primary anilines,[21] the increased steric bulk may bar their reactivity with more encumbered aryl electrophiles.

Hydroxamates with a variety of electron-donating and electron-withdrawing *para*-substituents on the aryl ring furnished the N–N products with moderate to high yields (**46**–**52**). Additionally, primary, secondary, and tertiary aliphatic hydroxamates were compatible with this chemistry (**53**–**56**). We were pleased to observe styrenyl and alkenyl functional groups did not participate in undesired C-H insertion, hydroamidation, reduction, or aziridination processes, affording moderate yields of products **57** and **58**, respectively.[19,2729] Additionally, several saturated heterocyclic compounds, such tetrahydropyran-, piperidine-, and azetidine-derived hydroxamates (**59–61**) afforded products in 52–67% yields. Hydroxamates featuring phenyl isostere [1.1.1]-bicyclopentane (BCP) derivatives were also compatible in this transformation (**63** and **64**).[30] Surprisingly, a benzylic hydroxamate remained inert under the reaction conditions (**65**).

N-methylbenzylamine derivatives with both electron-donating and electron-withdrawing substituents on the aryl ring afforded modest yields of the desired products (Figure 1.9, **65**–**67**). Replacement of the benzyl group with a variety of acyclic and cyclic moieties (**68**–**72**), including a formamide isostere (**70**), resulted in efficient product formation.[31] Reaction with duloxetine, an antidepressant, yielded the corresponding hydrazide derivative **71** in synthetically useful yield.[32] Although broadly useful with secondary aliphatic amines, primary aliphatic amines remain incompatible with this transformation, instead yielding undesired amine acylation arising from *O*-to-*N* benzoyl transfer and only trace product (**73**).

Figure 1.9. *Scope of aliphatic amine nucleophiles and mixed aliphatic substrates.*[a]

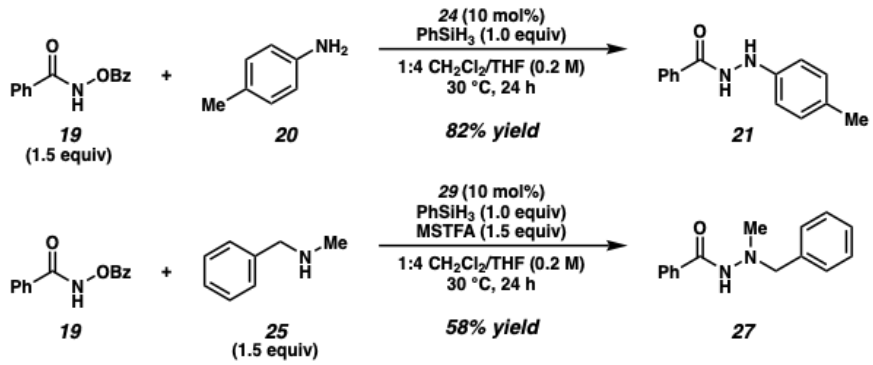


[a] Reactions performed on 0.2 mmol scale. [b] Silylamine **26** used. [c] 48 h.

Cyclic aliphatic amines were competent coupling partners in this chemistry (**74**–**82**), albeit affording products in diminished yields due to the greater propensity of these

nucleophiles to generate *O*-to-*N* benzoyl transfer side products. Cytisine, a smoking cessation agent, was able to be derivatized to the corresponding hydrazide in a synthetically useful yield (**82**),[33] and we were able to access fully aliphatic hydrazides (**83** and **84**), including saturated heterocycle **85** resulting from intramolecular bond formation. Lastly, both sets of conditions were demonstrated to be scalable, with hydrazides **21** and **27** obtained in near identical yields from 2.0 mmol scale reactions (Figure 1.10).

Figure 1.10. *Large-scale reactions.*[a]



[a] Reactions performed on 2.0 mmol scale.

1.5 REACTION MECHANISM

To investigate the role of the silane additive, Ni(I) half sandwich **87** was independently synthesized, and its catalytic competence was examined.[22] Reaction in the presence and absence of phenylsilane afforded similar product yields with near identical reaction times, supporting the notion that the active catalyst is a Ni(I) species formed via reduction with silane (Figure 1.11).[20,34] With this evidence in hand, we suggest the following mechanism (Figure 1.12): phenylsilane can reduce **24** or **29** to a Ni(I) species via formation of a Ni(II) hydride. Reaction with a hydroxamate starting material can form a putative Ni-nitrenoid with net loss of benzoic acid, which may be enabled by transient

slippage of the Cp ligand.[20,22] The Ni-nitrenoid can then undergo outer sphere N–N bond formation with an amine, which following proton transfer yields a metal bound hydrazide. Dissociation of product regenerates the active catalyst.

Figure 1.11. *Mechanistic experiments.*

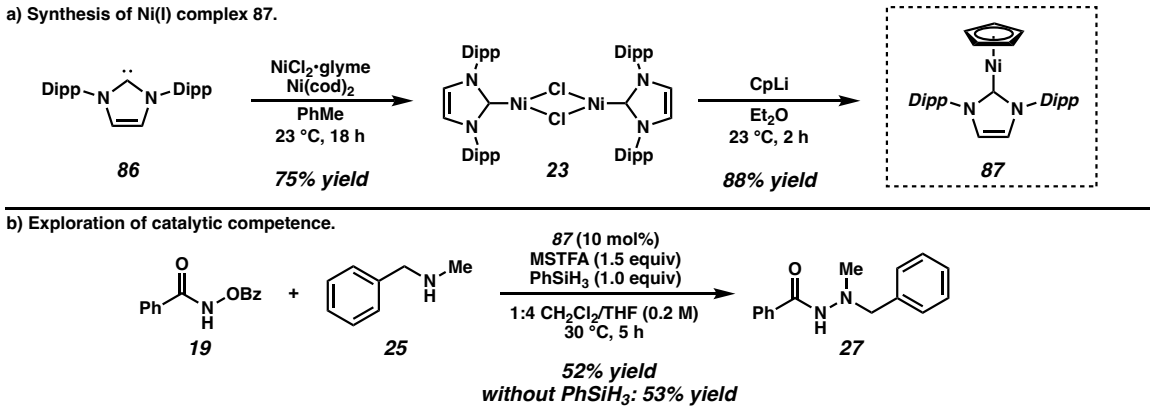
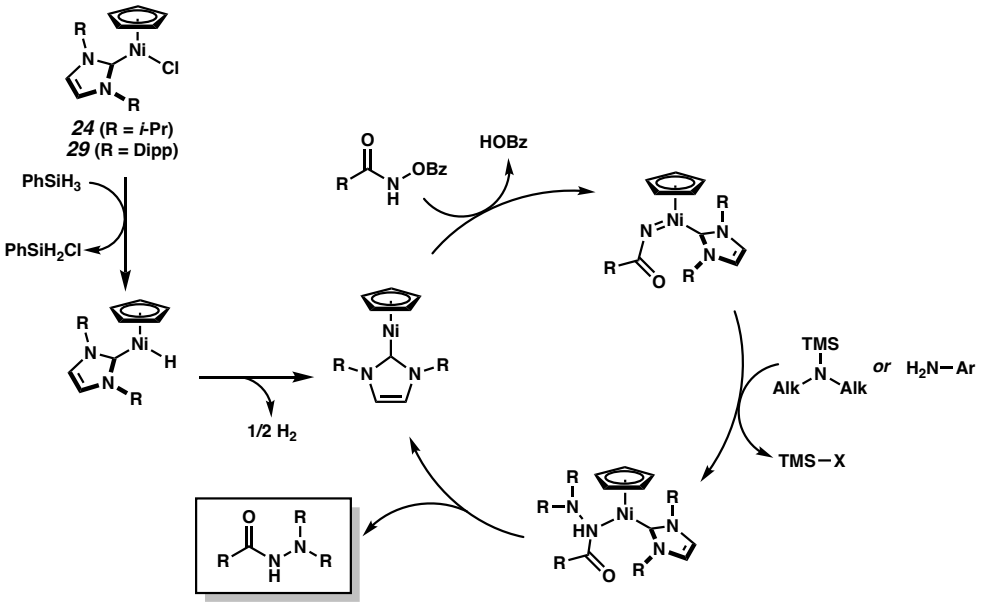


Figure 1.12. *Potential catalytic cycle.*



1.6 CONCLUSIONS

In summary, we have developed a Ni-catalyzed N–N cross-coupling enabling the convenient formation of complex hydrazides. This transformation is effected by an easily

synthesized and air-stable Ni(II) half-sandwich precatalyst. *In situ* silylation enables unprecedented access to secondary aliphatic amines in transition-metal catalyzed N–N coupling methodology. This reaction tolerates an impressive breadth of functionality, including handles for further derivatization. Preliminary mechanistic investigation suggests a mononuclear Ni(I) species as the active catalyst.

1.7 EXPERIMENTAL SECTION

1.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[35] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64; ^{19}F NMR (282 MHz, CD_3OD) δ -165.37).[36] ^{11}B NMR spectra were recorded on a Bruker 400 MHz spectrometer

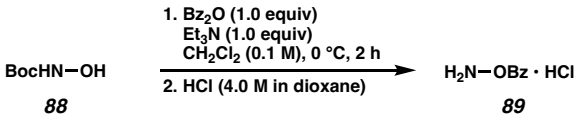
(128 MHz) and referenced to an external standard (boron trifluoride diethyl etherate; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.0).[37] Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR, ^{11}B and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a ThermoScientific Nicolet iS50 FT-IR spectrometer, or a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$).

1.7.1.1 Preparation of Known Compounds

Reagents were purchased from commercial sources and used as received unless otherwise stated. *N*-(benzoyloxy)-*N*-methylbenzamide (**112**),[38] *N*-(pivaloyloxy)benzamide (**113**),[39] *N*-acetoxybenzamide (**114**),[40] *N*-methoxybenzamide (**115**),[41] *N*-hydroxybenzamide (**116**),[42] 3-phenyl-1,4,2-dioxazol-5-one (**117**),[43] *tert*-butyl (3-((benzoyloxy)amino)-3-oxopropyl)(benzyl)carbamate (**110**),[44] [Ni(Cp)(IPr)(Cl)] (**29**),[45] [Ni(Cp)(IPr)] (**87**),[46] [Ni(Cp)(SIPr)(Cl)] (**125**),[47] [Ni(Cp)($NHC^{Me,n\text{-}Bu}$)(Cl)] (**126**),[48] and [Ni(Cp)(IMes)(Cl)] (**124**)[49] were prepared according to literature procedures.

1.7.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

1.7.2.1 Synthesis of Hydroxamate Starting Materials



_O_-benzoylhydroxylamine hydrochloride (89)

To *N*-Boc-hydroxylamine (13.3 g, 100 mmol, 1.0 equiv) and triethylamine (14 mL, 100 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) at 0 °C was added benzoic anhydride (22.6 g, 100 mmol, 1.0 equiv) portionwise over five minutes. The reaction was continued at 0 °C for 2 hours, then diluted with saturated $NaHCO_3$, transferred to a separatory funnel, and extracted with dichloromethane three times. The combined organics were washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide crude *tert*-butyl-(benzoyloxy)carbamate. The crude material was then dissolved in 4 M HCl in dioxane (200 mL, 8 equiv) and stirred for 1 hour. The precipitated product was filtered from solution, washed with diethyl ether, and dried under vacuum to afford **89** (17 g, 98% yield) as a white solid.

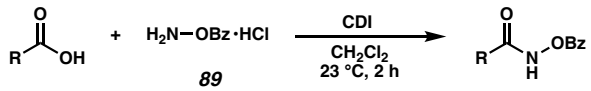
^{1}H NMR (400 MHz, CD_3OD): δ 8.11–8.02 (m, 2H), 7.82–7.71 (m, 1H), 7.66–7.49 (m, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 164.5, 136.5, 131.0, 130.4, 126.2.

IR (neat film): 1739, 1647, 1450, 1371, 1273, 1243, 1084, 1059, 907, 862, 705 cm^{-1}.

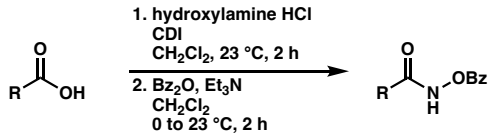
HRMS (ESI+): m/z calc'd for $C_7H_8NO_2$ $[M+H]^+$: 138.0550, found 138.0556.

Preparation of Hydroxamate Starting Materials: General Procedure A



To a round bottom flask containing carboxylic acid (1.0 equiv) dissolved in dichloromethane (0.2 M) was added 1,1'-carbonyldiimidazole (1.1 equiv). The reaction mixture was stirred for 30 minutes, and then *O*-benzoylhydroxylamine hydrochloride (**89**) (1.1 equiv) was added. The reaction was continued for an additional 2 hours, or until reaction reached completion as determined by monitoring with TLC. The crude mixture was diluted with water and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel flash chromatography to provide the desired hydroxamic ester.

Preparation of Hydroxamate Starting Materials: General Procedure B

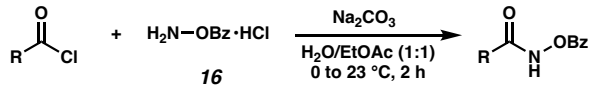


To a round bottom flask containing carboxylic acid (1.0 equiv) dissolved in dichloromethane (0.2 M) was added 1,1'-carbonyldiimidazole (1.1 equiv). The reaction mixture was stirred for 30 minutes, and then hydroxylamine hydrochloride (1.1 equiv) was added. The reaction was continued for an additional 2 hours, or until reaction reached completion as determined by TLC. The crude mixture was diluted with water and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

The crude hydroxamic acid was dissolved in dichloromethane (0.2 M), and triethylamine (1.0 equiv) was added. The reaction mixture was cooled to 0 °C, and benzoic anhydride (1.0 equiv) was added portionwise over 5 minutes. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.

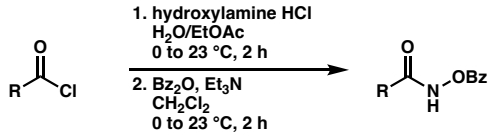
Preparation of Hydroxamate Starting Materials: General Procedure C



To a round bottom flask containing *O*-benzoylhydroxylamine hydrochloride (**16**) (1.5 equiv) and sodium carbonate (2.0 equiv) was added water and ethyl acetate (1:1, 0.2 M). The biphasic mixture was cooled to 0 °C, and the acid chloride (1.0 equiv) was added dropwise. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.

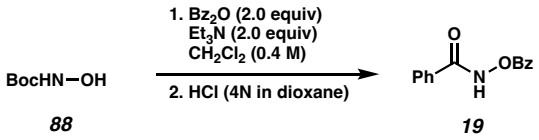
Preparation of Hydroxamate Starting Materials: General Procedure D



To a round bottom flask containing hydroxylamine hydrochloride (1.5 equiv) and sodium carbonate (2.0 equiv) was added water and ethyl acetate (1:1, 0.2 M). The biphasic mixture was cooled to 0 °C, and the acid chloride (1.0 equiv) was added dropwise. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

The crude hydroxamic acid was dissolved in dichloromethane (0.2 M), and triethylamine (1.0 equiv) was added. The reaction mixture was cooled to 0 °C, and benzoic anhydride (1.0 equiv) was added portionwise over 5 minutes. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

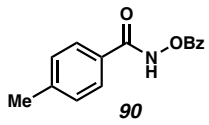
Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.



N-(benzoyloxy)benzamide (19)

To *N*-Boc-hydroxylamine (26.6 g, 200 mmol, 1.0 equiv) and triethylamine (56 mL, 400 mmol, 2.0 equiv) in CH_2Cl_2 (0.4 M) was added benzoic anhydride (90.5 g, 400 mmol, 2.0 equiv) portionwise over five minutes. The reaction was stirred at 23 °C for 2 hours, then diluted with saturated $NaHCO_3$, transferred to a separatory funnel, and extracted with dichloromethane three times. The combined organics were washed with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4, filtered through a short silica pad (~2 inches), and concentrated to provide crude *tert*-butyl benzoyl(benzoyloxy)carbamate. The crude material was then dissolved in 4 M HCl in dioxane (400 mL, 8 equiv) and stirred for 1 hour. The precipitated product was filtered from solution, washed with diethyl ether, and dried under vacuum to afford **19** (37.6 g, 78% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.21 – 8.13 (m, 2H), 7.92 – 7.85 (m, 2H), 7.80 – 7.64 (m, 1H), 7.62 – 7.55 (m, 1H), 7.54 – 7.40 (m, 4H); all characterization data match those reported in the literature.[47]



90

***N*-(benzoyloxy)-4-methylbenzamide (90)**

Prepared according to general procedure D using 4-methylbenzoyl chloride (15.0 mmol). Purification by column chromatography (10–25 % EtOAc in hexanes) yielded **90** (1.025 g, 27% yield) as a white solid.

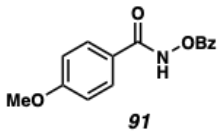
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.20 – 8.13 (m, 2H), 7.82 – 7.74 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.46 (m, 2H), 7.33 – 7.25 (m, 2H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 165.5, 143.6, 134.4, 130.2, 129.6, 128.8, 128.1,

127.7, 126.8, 21.7.

IR (neat film): 3174, 2957, 1766, 1651, 1483, 1236, 1041, 1019, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{13}NO_3Na$ $[M+Na]^+$: 278.0788, found 278.0788.



91

***N*-(benzoyloxy)-4-methoxybenzamide (91)**

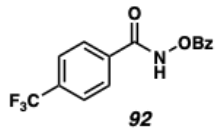
Prepared according to general procedure D using 4-methoxybenzoyl chloride (2.0 mmol). Purification by column chromatography (10–25 % EtOAc in hexanes) yielded **91** (341 mg, 63% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.20 – 8.13 (m, 2H), 7.90 – 7.80 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.44 (m, 2H), 7.01 – 6.93 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 165.6, 163.4, 134.4, 130.2, 129.7, 128.9, 126.8, 123.1, 114.3, 55.6.

IR (neat film): 3198, 2937, 1769, 1647, 1605, 1489, 1261, 1238, 1023, 707 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{13}NO_4Na$ $[M+Na]^+$: 294.0737, found 294.0739.



92

***N*-(benzoyloxy)-4-(trifluoromethyl)benzamide (92)**

Prepared according to general procedure A using N-hydroxy-4-(trifluoromethyl)benzamide (3.0 mmol). Purification by column chromatography (10–50% EtOAc in hexanes) yielded **92** (400 mg, 43% yield) as a white solid.

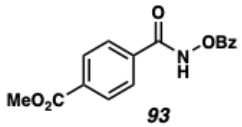
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.20 – 8.13 (m, 2H), 8.00 (d, J = 7.7 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H), 7.71 – 7.63 (m, 1H), 7.57 – 7.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 134.6, 134.2, 134.1, 130.5, 130.1, 128.8, 128.1, 126.3, 125.9 (q, J = 3.8 Hz), 123.5 (q, J = 272.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -63.3.

IR (neat film): 3144, 1775, 1659, 1326, 1237, 1123, 1067, 1016, 855, 704 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{15}H_9F_3NO_3$ $[M–H]^-$: 308.0540, found 308.0536.



93

Methyl 4-((benzoyloxy)carbamoyl)benzoate (93)

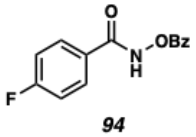
Prepared according to general procedure C from the corresponding acid chloride (3.84 mmol). Purification by column chromatography (2.5% to 10% EtOAc in CH_2Cl_2) provided **93** (525 mg, 46% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (brs, 1H), 8.17 – 8.13 (m, 4H), 7.94 (d, J = 8.6 Hz, 2H), 7.69 – 7.65 (m, 1H), 7.54 – 7.50 (m, 2H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.7, 165.3, 134.8, 134.6, 134.0, 130.2, 130.2, 129.0, 127.8, 126.5, 52.7.

IR (neat film): 3142, 2964, 1776, 1717, 1654, 1282, 1252, 1108, 1018, 911, 734, 704, 592, 417 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{16}H_{12}NO_5$ $[M–H]^-$: 298.0721, found 298.0720.



94

***N*-(benzoyloxy)-4-fluorobenzamide (94)**

Prepared according to general procedure D using 4-fluorobenzoyl chloride (10.0 mmol). A solid precipitated upon benzoylation; filtration yielded **94** (1.84 g, 71% yield).

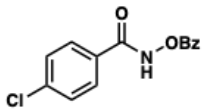
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.20 – 8.10 (m, 2H), 7.95 – 7.83 (m, 2H), 7.66 (ddt, *J* = 8.0, 7.1, 1.3 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.23 – 7.10 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.5 (d, *J* = 254.0 Hz), 165.4, 134.6, 130.2 (d, *J* = 9.2 Hz), 130.2, 128.9, 127.1 (d, *J* = 3.2 Hz), 126.6, 116.2 (d, *J* = 21.9 Hz).

^{19}F NMR (282 MHz, CD_3OD): δ -108.8.

IR (neat film): 3189, 1767, 1659, 1602, 1490, 1236, 1045, 849, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{10}FNO_3Na$ $[M+Na]^+$: 282.0537, found 282.0537.



95

***N*-(benzoyloxy)-4-chlorobenzamide (95)**

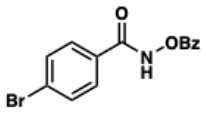
Prepared according to general procedure C using 4-chlorobenzoyl chloride (2.0 mmol). Purification by trituration with 30% EtOAc in hexanes yielded **95** (194 mg, 35% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.19 – 8.12 (m, 2H), 7.87 – 7.78 (m, 2H), 7.71 – 7.62 (m, 1H), 7.56 – 7.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 165.4, 139.4, 134.6, 130.2, 129.3, 129.3, 129.1, 128.9, 126.5.

IR (neat film): 3161, 1765, 1654, 1597, 1482, 1238, 1094, 1045, 1003, 844, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{10}ClNO_3Na$ $[M+Na]^+$: 298.0241, found 298.0237.



96

***N*-(benzoyloxy)-4-bromobenzamide (96)**

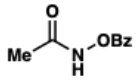
Prepared according to general procedure C using 4-bromobenzoyl chloride (2.0 mmol). Purification by trituration with 30% EtOAc in hexanes yielded **96** (235.5 mg, 37% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.19 – 8.12 (m, 2H), 7.79 – 7.71 (m, 2H), 7.70 – 7.60 (m, 3H), 7.56 – 7.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 165.4, 134.6, 132.3, 130.2, 129.8, 129.2, 128.9, 127.9, 126.5.

IR (neat film): 3150, 2972, 1764, 1652, 1589, 1478, 1237, 1044, 1011, 841, 702 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{14}H_9BrNO_3$ $[M–H]^-$: 317.9771, found 317.9764.

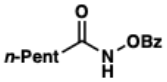


97

N-(benzoyloxy)acetamide (97)

Prepared according to general procedure C using acetyl chloride (3 mmol), providing **97** (335 mg, 61% yield) as a white solid after work up.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.14 – 8.07 (m, 2H), 7.64 (m, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 2.14 (s, 3H); all characterization data match those reported in the literature.[47]



98

N-(benzoyloxy)hexanamide (98)

Prepared according to general procedure D using hexanoyl chloride (6.0 mmol). Purification by column chromatography (10–20% EtOAc in hexanes) yielded **98** (810 mg, 57% yield) as a white solid.

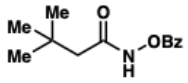
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.10 (d, *J* = 7.1 Hz, 2H), 7.68 – 7.59 (m,

1H), 7.49 (t, *J* = 7.8 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.43 – 1.27 (m, 4H), 0.97 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 165.1, 134.3, 130.1, 128.8, 126.7, 33.1, 31.4, 24.9, 22.4, 14.0.

IR (neat film): 3162, 2957, 2930, 2870, 1767, 1663, 1237, 1075, 1053, 986, 702 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1281, found 236.1289.



99

***N*-(benzoyloxy)-3,3-dimethylbutanamide (99)**

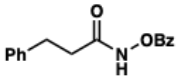
Prepared according to general procedure B using 3,3-dimethylbutanoic acid (1.0 mmol). Purification by column chromatography (30–50% EtOAc in hexanes) yielded **99** (136 mg, 58% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.15 – 8.05 (m, 2H), 7.68 – 7.58 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 2.21 (s, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 165.2, 134.4, 130.3, 130.1, 128.8, 128.6, 126.7, 31.2, 29.9.

IR (neat film): 3167, 2955, 2869, 1768, 1660, 1452 1234, 1064, 997, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1281, found 236.1288.

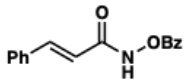


100

***N*-(benzoyloxy)-3-phenylpropanamide (100)**

Prepared according to general procedure C using 3-phenylpropanoyl chloride (2 mmol). Purification by column chromatography (2% EtOAc in CH_2Cl_2) provided **100** (419 mg, 78% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.12 – 8.06 (m, 2H), 7.69 – 7.59 (m, 1H), 7.53 – 7.44 (m, 2H), 7.36 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H); all characterization data match those reported in the literature.[48]



101

***N*-(benzoyloxy)cinnamamide (101)**

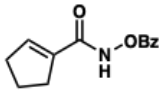
Prepared according to general procedure C using cinnamoyl chloride (5 mmol). Purification by column chromatography (2% EtOAc in CH_2Cl_2) provided **101** (643 mg, 48% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.11 (m, 2H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.58 – 7.44 (m, 4H), 7.39 (dd, *J* = 4.6, 1.8 Hz, 3H), 6.57 (d, *J* = 15.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 144.4, 134.5, 134.3, 130.6, 130.2, 129.1, 128.9, 128.3, 126.7, 115.4.

IR (neat film): 3163, 2971, 1768, 1667, 1631, 1577, 1507, 1338, 1075, 972, 756 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{13}NO_3Na$ $[M+Na]^+$: 290.0788, found 290.0783.



102

***N*-(benzoyloxy)cyclopent-1-ene-1-carboxamide (102)**

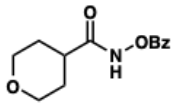
Prepared according to general procedure D from the corresponding acid chloride (2.23 mmol). Purification by column chromatography (0–50% EtOAc in hexanes) provided **102** (144 mg, 28% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (brs, 1H), 8.14 – 8.11 (m, 2H), 7.65 – 7.61 (m, 1H), 7.51 – 7.45 (m, 2H), 6.77 – 6.75 (m, 1H), 2.65 (ddt, *J* = 7.8, 6.9, 2.4 Hz, 2H), 2.53 (dtd, *J* = 9.6, 5.2, 2.6 Hz, 2H), 2.05 – 1.97 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 164.5, 141.8, 135.7, 134.3, 133.6, 130.2, 130.1, 128.8, 128.6, 126.8, 33.5, 31.4, 23.2.

IR (neat film): 3176, 2959, 1767, 1662, 1490, 1239, 1044, 1018, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{13}NNaO_3$ $[M+Na]^+$: 254.0788, found 254.0788.



103

***N*-(benzoyloxy)tetrahydro-2*H*-pyran-4-carboxamide (103)**

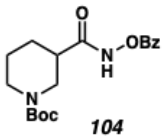
Prepared according to general procedure A from the corresponding carboxylic acid (4.00 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **103** (718 mg, 72% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (brs, 1H), 8.09 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.66 – 7.61 (m, 1H), 7.51 – 7.45 (m, 2H), 4.03 (ddd, *J* = 11.6, 4.3, 2.4 Hz, 2H), 3.44 (td, *J* = 11.6, 2.4 Hz, 2H), 2.61 – 2.53 (m, 1H), 1.95 (dtd, *J* = 13.5, 11.4, 4.4 Hz, 2H), 1.85 – 1.78 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 165.2, 134.5, 130.1, 128.9, 126.6, 67.1, 39.6, 28.9.

IR (neat film): 3180, 2953, 2846, 1773, 1665, 1506, 1239, 1119, 1039, 980 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1074, found 250.1069.



104

***Tert*-butyl 3-((benzoyloxy)carbamoyl)piperidine-1-carboxylate (104)**

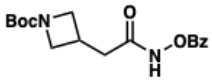
Prepared according to general procedure A using 1-(*tert*-butoxycarbonyl)piperidine-3carboxylic acid (1 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **104** (170 mg, 49% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.06 (m, 2H), 7.67 – 7.58 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 3.92 – 3.28 (m, 3H), 2.56 (s, 1H), 2.15 (d, *J* = 12.3 Hz, 1H), 1.89 (s, 1H), 1.76 – 1.65 (m, 2H), 1.63 – 1.48 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 164.8, 155.4, 134.1, 130.1, 128.7, 126.9, 80.5, 45.0, 40.3, 28.5, 27.5, 23.9.

IR (neat film): 3182, 2976, 1766, 1659, 1450, 1239, 1147, 1054, 729, 702 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{18}H_{23}N_2O_5$ $[M–H]^-$: 347.1612, found 347.1611.



105

***Tert*-butyl 3-(2-((benzoyloxy)amino)-2-oxoethyl)azetidine-1-carboxylate (105)**

Prepared according to general procedure A from the corresponding carboxylic acid (4.00 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **105** (814 mg, 61% yield) as a white solid.

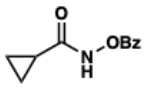
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (brs, 1H), 8.09 – 8.05 (m, 2H), 7.64 – 7.60 (m, 1H), 7.49 – 7.44 (m, 2H), 4.11 (dd, *J* = 8.5, 8.5 Hz, 2H), 3.67 (dd, *J* = 8.9, 5.3 Hz, 2H), 3.04 – 2.91 (m, 1H), 2.63 (d, *J* = 7.7 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 156.5, 134.5, 130.1, 128.9, 126.6, 79.8, 54.4, 37.2,

28.5, 25.5.

IR (neat film): 3164, 2975, 1767, 1698, 1670, 1414, 1241, 1155, 1060, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{22}N_2NaO_5$ $[M+Na]^+$: 357.1437, found 357.1431.



106

***N*-(benzoyloxy)cyclopropanecarboxamide (106)**

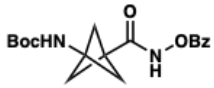
Prepared according to general procedure C from the corresponding acid chloride (6.28 mmol). Purification by column chromatography (5–10% EtOAc in CH_2Cl_2) provided **106** (445 mg, 34% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.51 – 7.47 (m, 2H), 1.63 (s, 1H), 1.13 – 1.09 (m, 2H), 0.93 – 0.88 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 134.4, 130.1, 128.8, 126.8, 11.9, 8.4.

IR (neat film): 3155, 2984, 2901, 1766, 1657, 1515, 1398, 1240, 1053, 705, 600 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{11}NNaO_3$ $[M+Na]^+$: 228.0631, found 228.0631.



107

***Tert*-butyl (3-((benzoyloxy)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate (107)**

Prepared according to general procedure A from the corresponding carboxylic acid (2.00 mmol). Purification by column chromatography (15–20% EtOAc in CH_2Cl_2) provided **107** (391 mg, 56% yield) as a white solid.

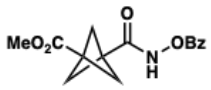
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (brs, 1H), 8.10 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 2H), 5.00 (brs, 1H), 2.38 (s, 6H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 165.0, 154.8, 134.5, 130.1, 128.9, 126.6, 80.2,

54.3, 46.0, 34.8, 28.5.

IR (neat film): 3648, 3327, 2981, 1775, 1689, 1499, 1368, 1251, 1168, 1011, 943 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{23}N_2O_5$ $[M+H]^+$: 347.1601, found 347.1604.



108

Methyl 3-((benzoyloxy)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (108)

Prepared according to general procedure A from the corresponding carboxylic acid (1.00 mmol). Purification by column chromatography (10–30% EtOAc in CH_2Cl_2) provided **108** (121 mg, 42% yield) as a white solid.

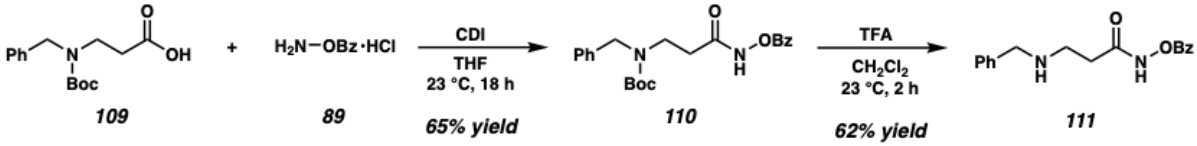
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 7.5, 1.1 Hz, 2H), 7.66 – 7.62 (m, 1H),), 7.50 – 7.46 (m, 2H), 3.70 (s, 3H), 2.40 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.4, 166.7, 164.9, 134.5, 130.1, 128.9, 126.5, 52.9, 52.1, 38.0, 37.2.

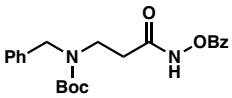
IR (neat film): 3150, 3001, 1769, 1732, 1673, 1502, 1452, 1240, 1219, 1037, 1018, 839, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{16}NO_5$ $[M+H]^+$: 290.1025, found 290.1036.

*Preparation of N-(benzoyloxy)-3-(benzylamino)propenamide (**111**)*



Note: subsequent reactions for substrate preparation are unoptimized.



110

***Tert*-butyl (3-((benzoyloxy)amino)-3-oxopropyl)(benzyl)carbamate (110)**

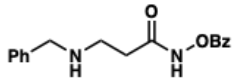
Prepared according to general procedure A, using 3-(benzyl(*tert*-butoxycarbonyl)amino)propanoic acid[42] (**109**) (715 mg, 2.56 mmol). Purification by column chromatography (20–40% EtOAc in hexanes) provided **110** (660 mg, 65% yield) as a clear oil, characterized as a mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.04 (m, 2H), 7.66 – 7.57 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 8.8, 5.9 Hz, 2H), 7.28 – 7.14 (m, 3H), 4.48 (s, 2H, major rotamer), 4.42 (s, 2H, minor rotamer), 4.44 (s, 2H), 3.58 (m, 2H), 2.63 (m, 2H), 1.51 (s, 9H, minor rotamer), 1.46 (s, 9H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 164.7, 156.5, 152.4, 138.1, 134.2, 130.1, 128.8, 128.7, 127.5, 81.0, 51.3, 42.8, 32.9, 28.5, 27.7.

IR (neat film): 3164, 2979, 2320, 1767, 1690, 1459, 1429, 1241, 1161, 889, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{22}H_{27}N_2O_5$ $[M+H]^+$: 399.1914, found 399.1923.



111

N-(benzoyloxy)-3-(benzylamino)propenamide (111)

To a 20-mL scintillation vial containing *tert*-butyl (3-((benzoyloxy)amino)-3oxopropyl)(benzyl)carbamate (**110**) (655 mg, 1.64 mmol, 1 equiv) was added CH_2Cl_2 (3 mL, 0.5 M), followed by trifluoroacetic acid (1 mL). The reaction was stirred at 23 °C for two hours, then added to a separatory funnel and washed with saturated sodium bicarbonate, dried with Na_2SO_4, filtered and concentrated to afford **111** (304 mg, 62% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.37 (d, *J* = 3.1 Hz, 3H), 4.17 (s, 2H), 3.31 – 3.26 (m, 2H), 2.87 – 2.81 (m, 2H).

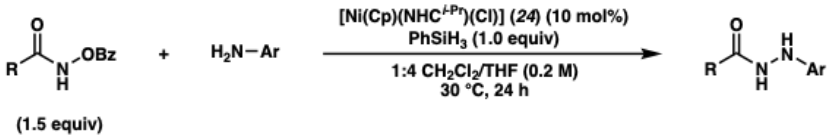
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 165.9, 134.6, 130.3, 130.0, 129.9, 129.5, 128.8, 126.3, 52.1, 44.0, 29.8.

IR (neat film): 3164, 2979, 1848, 2320, 1767, 1690, 1429, 1366, 1241, 1161, 1003, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: 299.1390, found 299.1387.

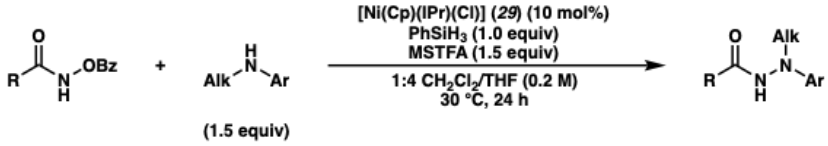
1.7.2.2 Synthesis of Hydrazide Products

Preparation of Aniline-Derived Hydrazides: General Procedure E

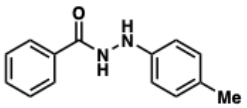


In a nitrogen-filled glovebox, a 2-dram vial is charged with hydroxamic ester (0.30 mmol, 1.5 equiv). A solution of amine (0.20 mmol, 1.0 equiv) in THF (0.8 mL) is added, followed by a solution of **24** (0.020 mmol, 10 mol%) and phenylsilane (0.20 mmol, 1.0 equiv) in dichloromethane (0.20 mL). The reaction is sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 30 °C for 24 h unless otherwise noted. After 24 h, the reaction is quenched with sat. $NaHCO_3$ (2 mL), extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by either silica gel flash chromatography or C18 reverse phase chromatography to provide the desired hydrazide product.

Preparation of Aliphatic Amine-Derived Hydrazides: General Procedure F



In a nitrogen-filled glovebox, a 2-dram vial is charged with aliphatic amine (0.30 mmol, 1.5 equiv). THF (0.80 mL) is added to the reaction vial, followed sequentially by MSTFA (0.30 mmol, 1.5 equiv), a solution of **29** (0.020 mmol, 10 mol%) and phenylsilane (0.20 mmol, 1.0 equiv) in dichloromethane (0.20 mL), and then solid hydroxamate (0.20 mmol, 1.0 equiv). The reaction is sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 30 °C for 24 h unless otherwise noted. After 24 h, the reaction is quenched with sat. $NaHCO_3$ (2 mL), extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by either silica gel flash chromatography or C18 reverse phase chromatography to provide the desired hydrazide product.



21

_N_'-(_p_-tolyl)benzohydrazide (21)

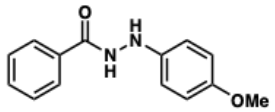
Prepared according to general procedure E using **19** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **21** (36 mg, 80% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.82 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 145.6, 132.5, 132.4, 131.1, 129.9, 128.9, 127.3, 114.3, 20.7.

IR (neat film): 3246, 3062, 3007, 2919, 2864, 1642, 1511, 1323, 1241, 930, 817, 731, 700 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1179, found 227.1179.



30

***N*'-(4-methoxyphenyl)benzohydrazide (30)**

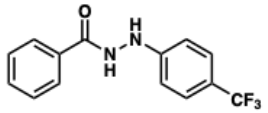
Prepared according to general procedure E using **19** (0.3 mmol) and 4-methoxyaniline (0.2 mmol). Purification by column chromatography (2% acetone in CH_2Cl_2) provided **30** (24.9 mg, 51% yield) as a gray solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.90 – 7.73 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.94 – 6.86 (m, 2H), 6.85 – 6.76 (m, 2H), 6.31 (s, 1H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 155.0, 141.7, 132.5, 132.4, 128.9, 127.2, 116.0, 114.8, 55.8.

IR (neat film): 3260, 1651, 1508, 1235, 1150, 1036, 826, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$: 243.1128, found 243.1134.



31

_N_'-(4-(trifluoromethyl)phenyl)benzohydrazide (31)

Prepared according to general procedure E using **19** (0.3 mmol) and 4-(trifluoromethyl)aniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **31** (25.1 mg, 45% yield) as a gray solid.

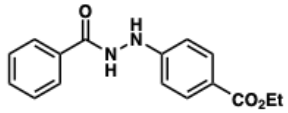
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.85 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.53 – 7.37 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.56 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 151.0, 132.8, 131.9, 129.1, 127.3, 126.8 (q, *J* = 3.8 Hz), 125.9, 123.3 (q, *J* = 32.7 Hz), 113.2.

^{19}F (282 MHz, $CDCl_3$): δ -61.6.

IR (neat film): 3270, 1652, 1617, 1521, 1477, 1324, 1263, 1157, 1110, 1063, 832, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$: 281.0896, found 281.0900.



32

Ethyl 4-(2-benzoylhydrazineyl)benzoate (32)

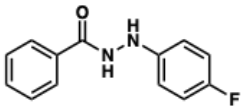
Prepared according to general procedure E using **19** (0.3 mmol) and ethyl 4-aminobenzoate (0.2 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **32** (19.1 mg, 34% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 3.2 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.85 – 7.71 (m, 2H), 7.65 – 7.52 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.88 – 6.80 (m, 2H), 6.63 (d, *J* = 3.3 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 166.7, 152.1, 132.6, 132.0, 131.4, 129.0, 127.4, 123.0, 112.5, 60.7, 14.5.

IR (neat film): 3281, 2982, 1667, 1604, 1511, 1476, 1259, 1170, 1105, 1025, 900, 844, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$: 285.1234, found 285.1238.



33

***N*'-(4-fluorophenyl)benzohydrazide (33)**

Prepared according to general procedure E using **19** (0.3 mmol) and 4-fluoroaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **33** (33.1 mg, 72% yield) as a white solid.

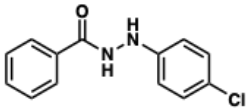
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.76 (m, 3H), 7.71 – 7.55 (m, 1H), 7.53 – 7.39 (m, 2H), 7.01 – 6.87 (m, 4H), 6.31 – 6.26 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 158.2 (d, J = 238.8 Hz), 144.2 (d, J = 2.2 Hz), 132.6, 132.2, 129.0, 127.2, 115.9 (d, J = 22.8 Hz), 115.4 (d, J = 7.9 Hz).

^{19}F (282 MHz, $CDCl_3$): δ -123.2.

IR (neat film): 3255, 1648, 1503, 1324, 1211, 1102, 912, 833, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{10}FN_2O$ $[M–H]^–$: 231.0928, found 229.0782.



34

***N*'-(4-chlorophenyl)benzohydrazide (34)**

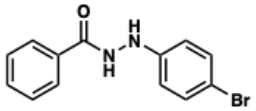
Prepared according to general procedure E using **19** (0.3 mmol) and 4-chloroaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **34** (36.1 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.80 (m, 3H), 7.66 – 7.56 (m, 1H), 7.54 – 7.45 (m, 2H), 7.25 – 7.17 (m, 2H), 6.96 – 6.84 (m, 2H), 6.33 – 6.27 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 146.8, 132.6, 132.1, 129.3, 129.0, 127.3, 126.4, 115.2.

IR (neat film): 3240, 1731, 1646, 1596, 1489, 1325, 1244, 1109, 913, 851, 693, 650 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}ClN_2O$ $[M+H]^+$: 247.0633, found 247.0634.



35

N'-(4-bromophenyl)benzohydrazide (35)

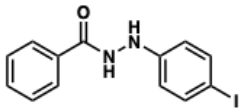
Prepared according to general procedure E using **19** (0.3 mmol) and 4-bromoaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **35** (35.4 mg, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.89 – 7.79 (m, 2H), 7.66 – 7.53 (m, 1H), 7.52 – 7.43 (m, 2H), 7.33 (dt, *J* = 8.9, 2.4 Hz, 2H), 6.85 – 6.76 (m, 2H), 6.34 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 132.6, 132.2, 132.1, 129.0, 127.3, 115.6, 113.6.

IR (neat film): 3241, 1646, 1594, 1486, 1245, 1109, 913, 834, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}BrN_2O$ $[M+H]^+$: 291.0128, found 291.0127.



36

***N*'-(4-iodophenyl)benzohydrazide (36)**

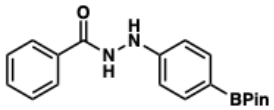
Prepared according to general procedure E using **19** (0.3 mmol) and 4-iodoaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **36** (39.2 mg, 58% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.83 (d, *J* = 7.1 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.54 – 7.32 (m, 4H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.32 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 148.1, 138.1, 132.7, 132.1, 129.1, 127.3, 116.1, 83.5.

IR (neat film): 3234, 1728, 1647, 1590, 1525, 1482, 1243, 1176, 913, 822, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}IN_2O$ $[M+H]^+$: 338.9989, found 338.9973.



37

***N*'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzohydrazide (37)**

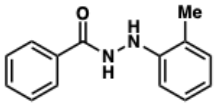
Prepared according to general procedure E using **19** (0.3 mmol) and 4-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)aniline (0.2 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **37** (41.8 mg, 62% yield) as a white solid.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 150.8, 136.4, 132.5, 132.4, 129.0, 127.3, 112.8, 83.6, 29.9, 25.0.

^{11}B NMR (128 MHz): δ 31.41.

IR (neat film): 3284, 1728, 1655, 1511, 1474, 1299, 1246, 1155, 1011, 898, 801, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{24}BN_2O_3$ $[M+H]^+$: 338.1911, found 338.1908.



38

***N*'-(*o*-tolyl)benzohydrazide (38)**

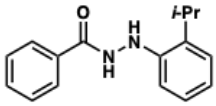
Prepared according to general procedure E using **19** (0.3 mmol) and *o*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **38** (33.5 mg, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.0 Hz, 2H), 7.80 (s, 1H), 7.65 – 7.54 (m, 1H), 7.54 – 7.34 (m, 2H), 7.17 – 7.10 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.87 (td, *J* = 7.4, 1.3 Hz, 1H), 6.28 – 6.23 (m, 1H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 145.9, 132.5, 132.4, 130.8, 129.0, 127.2, 127.1, 123.7, 121.4, 112.4, 17.2.

IR (neat film): 3277, 3058, 1642, 1516, 1488, 1249, 1114, 899, 745, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1179, found 227.1173.



39

***N*'-(2-isopropylphenyl)benzohydrazide (39)**

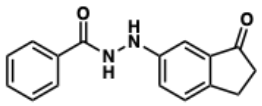
Prepared according to general procedure E using **19** (0.3 mmol) and 2-isopropylaniline (0.2 mmol). Purification by column chromatography (20% EtOAc in hexanes) provided **39** (37.3 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 1.5 Hz, 1H), 7.16 – 7.07 (m, 1H), 7.03 – 6.90 (m, 2H), 6.52 (d, *J* = 4.6 Hz, 1H), 3.14 (hept, *J* = 6.7 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 144.6, 134.3, 132.4, 132.4, 129.0, 127.2, 126.7, 125.5, 121.8, 113.0, 27.3, 22.7.

IR (neat film): 3344, 3285, 3057, 2959, 1643, 1537, 1312, 1239, 1037, 904, 749 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1494.



40

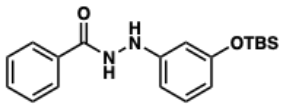
***N*'-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)benzohydrazide (40)**

Prepared according to general procedure E using **19** (0.3 mmol) and 6-amino-2,3-dihydro1H-inden-1-one (0.2 mmol). Purification by column chromatography (5% acetone in CH_2Cl_2) provided **40** (27.5 mg, 52% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.96 – 7.80 (m, 2H), 7.67 – 7.54 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.21 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 3.23 – 2.93 (m, 2H), 2.82 – 2.59 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 207.3, 167.9, 148.7, 148.2, 138.2, 132.6, 132.0, 129.0, 127.4, 127.3, 122.1, 106.9, 37.0, 25.3.

IR (neat film): 3280, 2958, 2924, 1701, 1601, 1489, 1293, 1177, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1128, found 267.1128.



41

***N*'-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)benzohydrazide (41)**

Prepared according to a modified version of general procedure E using **19** (0.3 mmol) and 3-aminophenol (0.2 mmol). Prior to purification, the crude mixture was dissolved in dichloromethane (1 mL, 0.2 M), and imidazole (41 mg, 0.6 mmol) and TBSCl (45 mg, 0.3

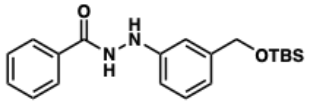
mmol) were added. The reaction was stirred at 23 °C for two hours, then diluted with water, extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (20% EtOAc in hexanes), providing **41** (28.2 mg, 50% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 3.6 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.74 – 7.53 (m, 1H), 7.51 – 7.43 (m, 3H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.69 – 6.51 (m, 1H), 6.49 – 6.35 (m, 2H), 6.29 (d, *J* = 3.9 Hz, 1H), 0.96 (s, 9H), 0.17 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 156.8, 149.5, 132.4, 132.3, 130.1, 128.9, 127.3, 113.2, 107.0, 105.9, 25.8, 18.3, -4.3.

IR (neat film): 3277, 2955, 2923, 2857, 1651, 1600, 1485, 1288, 1253, 1204, 1149, 997, 836, 779, 688 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{27}N_2O_2Si$ $[M+H]^+$: 343.1836, found 343.1846.



42

***N*'-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)benzohydrazide (42)**

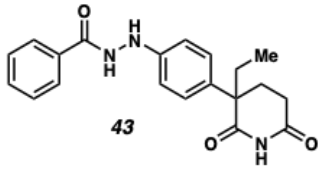
Prepared according to a modified version of general procedure E using **19** (0.3 mmol) and (3-aminophenyl)methanol (0.2 mmol). Prior to purification, the crude mixture was dissolved in dichloromethane (1 mL, 0.2 M), and imidazole (41 mg, 0.6 mmol) and TBSCl (45 mg, 0.3 mmol) were added. The reaction was stirred at 23 °C for two hours, then diluted with water, extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (20% EtOAc in hexanes), providing **42** (28.2 mg, 40% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.88 – 7.81 (m, 2H), 7.61 – 7.52 (m, 1H), 7.48 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.87 – 6.73 (m, 2H), 6.36 (d, *J* = 3.6 Hz, 1H), 4.69 (s, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 148.2, 143.0, 132.5, 132.4, 129.2, 129.0, 127.3, 119.1, 112.5, 111.3, 64.9, 26.1, 18.5, -5.1.

IR (neat film): 3299, 2954, 2928, 2856, 1640, 1596, 1533, 1471, 1255, 1107, 836, 781, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{20}H_{29}N_2O_2Si$ $[M+H]^+$: 357.1993, found 357.1992.



***N*'-(4-(3-ethyl-2,6-dioxopiperidin-3-yl)phenyl)benzohydrazide (43)**

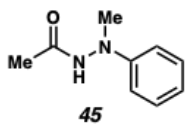
Prepared according to general procedure E using **19** (0.3 mmol) and aminoglutethimide (0.2 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **43** (51.7 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 – 7.85 (m, 1H), 7.69 – 7.56 (m, 1H), 7.54 – 7.45 (m, 1H), 7.20 – 7.11 (m, 1H), 6.95 – 6.78 (m, 1H), 2.63 – 2.44 (m, 1H), 2.42 – 2.25 (m, 1H), 2.24 – 2.07 (m, 1H), 2.00 – 1.80 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 178.1, 175.5, 170.3, 149.5, 134.1, 133.2, 131.8, 129.7, 128.5, 128.2, 114.4, 51.6, 33.9, 30.3, 28.0, 9.4.

IR (neat film): 3210, 2967, 1690, 1611, 1515, 1353, 1268, 1197, 835, 713 cm^{-1}.

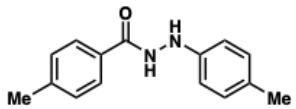
HRMS (ESI+): m/z calc'd for $C_{20}H_{22}N_3O_3$ $[M+H]^+$: 352.1656, found 352.1664.



_N_'-methyl-_N_'-phenylacetohydrazide (45)

Prepared according to general procedure E using **19** (0.3 mmol) and *N*-methyl aniline (0.2 mmol). Purification by column chromatography (25% acetone in hexanes) provided **45** (26.5 mg, 81% yield) as a white solid, characterized as a mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (brs, 1H, major rotamer), 7.30 (m, 2H, major rotamer), 7.24 (m, 2H, minor rotamer), 6.98 (brs, 1H, minor rotamer), 6.94 (m, 1H, major rotamer), 6.86 (m, 3H), 6.82 (d, 2H, minor rotamer), 3.18 (s, 3H, minor rotamer), 3.16 (s, 3H, major rotamer), 2.08 (s, 3H, major rotamer), 2.05 (s, 3H, minor rotamer); all characterization data match those reported in the literature.[50]



46

4-methyl-_N_'-(*p*-tolyl)benzohydrazide (46)

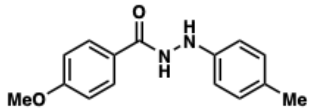
Prepared according to general procedure E using **90** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **46** (33.6 mg, 70% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 4.1 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 9.7 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 4.2 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 145.9, 142.9, 129.9, 129.7, 129.6, 127.2, 114.2, 21.7, 20.7.

IR (neat film): 3354, 3243, 2981, 2918, 1648, 1613, 1539, 1512, 1250, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found 241.1335.



47

4-methoxy-*N′*-(*p*-tolyl)benzohydrazide (47)

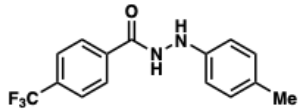
Prepared according to general procedure E using **91** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (20–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **47** (27.1 mg, 53% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.20 – 8.13 (m, 2H), 7.90 – 7.80 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.44 (m, 2H), 7.01 – 6.93 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 162.8, 145.8, 130.8, 129.7, 129.0, 124.6, 114.1, 114.0, 55.5, 20.6.

IR (neat film): 3280, 1648, 1607, 1511, 1254, 1178, 1029, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$: 257.1285, found 257.1287.



48

***N*'-(*p*-tolyl)-4-(trifluoromethyl)benzohydrazide (48)**

Prepared according to general procedure E using **92** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **48** (41.0 mg, 70% yield) as a white solid.

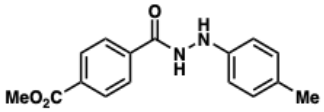
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.91 (m, 3H), 7.74 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.28 (d, J = 4.3 Hz, 1H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, ($(CD_3)_2CO$): δ 166.3, 148.0, 138.0, 133.4 (q, J = 32.2 Hz), 130.1, 129.8, 129.0, 126.4 (q, J = 3.6 Hz), 125.0 (q, J = 270.2 Hz), 114.3, 20.5.

^{19}F NMR (282 MHz, CD_3OD): δ -64.5.

IR (neat film): 3264, 1650, 1512, 1328, 1168, 1128, 860, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{14}F_3N_2O$ $[M+H]^+$: 295.1053, found 295.1057.



49

Methyl 4-(2-(*p*-tolyl)hydrazine-1-carbonyl)benzoate (49)

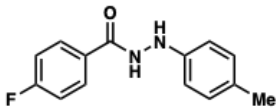
Prepared according to general procedure E using **93** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (1% MeOH in CH_2Cl_2) provided **49** (18.8 mg, 33% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.94 – 7.86 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 1H), 3.96 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 166.3, 145.5, 136.4, 133.5, 131.3, 130.2, 129.9, 127.3, 114.3, 52.6, 20.7.

IR (neat film): 3289, 2952, 1724, 1658, 1513, 1436, 1280, 1110, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$: 285.1234, found 284.1235.



50

4-fluoro-*N*'-(*p*-tolyl)benzohydrazide (50)

Prepared according to general procedure E using **94** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **50** (36.7 mg, 75% yield) as a white solid.

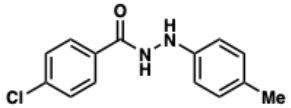
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.80 (m, 3H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 165.3 (d, *J* = 253.2 Hz), 145.7, 131.2, 129.9, 129.6 (d, *J* = 9.0 Hz), 128.7 (d, *J* = 3.2 Hz), 116.1 (d, *J* = 22.0 Hz), 114.2, 20.7.

^{19}F NMR (282 MHz, CD_3OD): δ -109.9.

IR (neat film): 3341, 3234, 3070, 1648, 1511, 1232, 856, 815, 668 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}FN_2O$ $[M+H]^+$: 245.1085, found 245.1088.



51

4-chloro-*N*'-(*p*-tolyl)benzohydrazide (51)

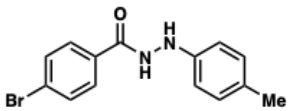
Prepared according to general procedure E using **95** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **51** (34.9 mg, 67% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.81 – 7.74 (m, 2H), 7.49 – 7.41 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.28 – 6.22 (m, 1H), 2.27 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 145.6, 138.7, 131.3, 130.9, 129.9, 129.3, 128.7, 114.2, 20.7.

IR (neat film): 3341, 3237, 1647, 1510, 1093, 852, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}ClN_2O$ $[M+H]^+$: 261.0789, found 261.0791.



52

4-bromo-*N*'-(*p*-tolyl)benzohydrazide (52)

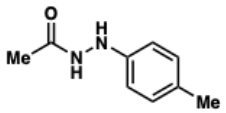
Prepared according to general procedure E using **96** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **52** (37.5 mg, 61% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.24 (d, *J* = 4.3 Hz, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 145.6, 132.3, 131.3, 131.3, 129.9, 128.8, 127.2, 114.3, 20.7.

IR (neat film): 3246, 1647, 1589, 1511, 1009, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}BrN_2O$ $[M+H]^+$: 305.0284, found 305.0279.



53

***N*'-(*p*-tolyl)acetohydrazide (53)**

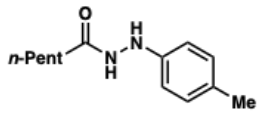
Prepared according to general procedure E using **97** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (5–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **53** (16.1 mg, 49% yield) as a white solid, characterized as a mixture of 2:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.03 (d, *J* = 7.8 Hz, 2H, major rotamer), 6.74 (d, *J* = 8.0 Hz, 2H, major rotamer), 6.67 (d, *J* = 7.9 Hz, 2H, minor rotamer), 6.13 (s, 1H, major rotamer), 5.74 (s, 1H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer), 2.11 (s, 3H, minor rotamer), 2.04 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 145.6, 144.8, 130.8, 130.1, 129.8, 114.0, 112.7, 21.1, 20.7, 20.6, 19.3.

IR (neat film): 3261, 3025, 2922, 1658, 1510, 1371, 1244, 996, 813, 714, 600 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1022, found 165.1022.



54

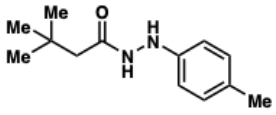
_N_'-(_p_-tolyl)hexanehydrazide (54)

Prepared according to general procedure E using **98** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) followed by preparative thin layer chromatography (50% EtOAc in hexanes) provided **54** (12.9 mg, 29% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 145.8, 145.0, 130.9, 130.8, 130.1, 129.8, 114.0, 112.7, 34.6, 31.7, 31.6, 25.3, 22.6, 22.5, 20.7, 14.1.

IR (neat film): 3261, 3025, 2958, 2925, 2859, 1645, 1615, 1514, 975, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1645.



55

3,3-dimethyl-_N_'-(_p_-tolyl)butanehydrazide (55)

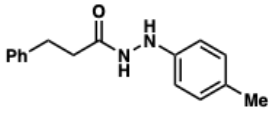
Prepared according to general procedure E using **99** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (1% MeOH in CH_2Cl_2) followed by preparative thin layer chromatography (10% EtOAc in CH_2Cl_2) provided **55** (14.1 mg, 32% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 2H, minor rotamer), 7.03 (d, *J* = 8.7 Hz, 2H, major rotamer), 6.77 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.3 Hz, 2H, minor rotamer), 2.63 – 1.72 (m, 5H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 145.9, 130.8, 130.1, 129.8, 114.1, 112.9, 48.2, 42.8, 31.2, 30.0, 20.7.

IR (neat film): 3266, 3025, 2953, 2867, 1659, 1513, 1476, 1366, 1237, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1649.



56

3-phenyl-*N*'-(*p*-tolyl)propanehydrazide (56)

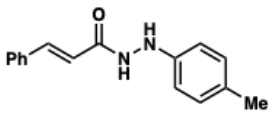
Prepared according to general procedure E using **100** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **56** (18.7 mg, 37% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 4.0 Hz, 1H, major rotamer), 7.35 – 7.14 (m, 5H), 7.02 (d, *J* = 8.2 Hz, 2H, minor rotamer), 6.97 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.61 – 6.49 (m, 2H), 6.04 (d, *J* = 4.1 Hz, 1H, major rotamer), 5.47 (s, 1H, minor rotamer), 2.97 (m, 2H), 2.75 (m, 2H, minor rotamer), 2.53 (t, *J* = 7.5 Hz, 2H, major rotamer), 2.30 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 172.3, 145.5, 144.7, 141.2, 140.5, 130.8, 130.7, 130.0, 129.7, 128.8, 128.6, 128.6, 128.6, 128.5, 126.6, 126.3, 113.8, 112.7, 36.3, 33.1, 31.5, 30.8, 20.7, 20.6.

IR (neat film): 3257, 3026, 2920, 1655, 1510, 1453, 1239, 994, 812, 698 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1493.



57

***N*'-(*p*-tolyl)cinnamohydrazide (57)**

Prepared according to general procedure E using **101** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with

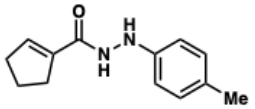
0.1% TFA, C18 column) provided **57** (19.2 mg, 38% yield) as a white solid, characterized as a ratio of 2:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 15.9 Hz, 1H, minor rotamer), 7.72 (d, *J* = 15.7 Hz, 1H, major rotamer), 7.67 (d, *J* = 4.2 Hz, 1H), 7.51 (m, 5H, minor rotamer), 7.38 – 7.37 (m, 3H, major rotamer), 7.34 (m, 2H, major rotamer), 7.15 (d, *J* = 15.9 Hz, 1H, minor rotamer), 7.08 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.04 (d, *J* = 8.1 Hz, 2H, major rotamer), 6.80 (d, *J* = 8.2 Hz, 2H, major rotamer), 6.74 (d, *J* = 8.1 Hz, 2H, minor rotamer), 6.48 (d, *J* = 15.7 Hz, 1H, major rotamer), 6.28 (d, *J* = 4.3 Hz, 1H), 5.77 (s, 1H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 166.3, 145.6, 145.1, 144.6, 142.9, 135.1, 134.6, 131.1, 130.9, 130.2, 130.2, 130.1, 129.9, 129.0, 128.9, 128.4, 128.1, 117.6, 115.4, 114.2, 113.2, 20.7.

IR (neat film): 3227, 3025, 2917, 1661, 1626, 1510, 1449, 1349, 1217, 1177, 977, 810, 726, 650 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335, found 253.1335.



58

***N*'-(*p*-tolyl)cyclopent-1-ene-1-carbohydrazide (58)**

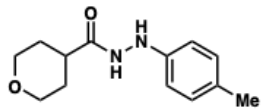
Prepared according to general procedure E using **102** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (15% EtOAc in CH_2Cl_2) provided **58** (21.6 mg, 50% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (brs, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.67 – 6.64 (m, 1H), 6.19 (brs, 1H), 2.60 (ddt, *J* = 10.3, 7.4, 2.3 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.26 (s, 3H), 2.06 – 1.97 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 145.8, 140.1, 137.1, 130.8, 129.8, 114.2, 33.3, 31.4, 23.4, 20.7.

IR (neat film): 3276, 2953, 2853, 1652, 1614, 1512, 1470, 1294, 1122, 813, 658 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{17}N_2O$ $[M+H]^+$: 217.1335, found 217.1330.



59

***N*'-(*p*-tolyl)tetrahydro-2*H*-pyran-4-carbohydrazide (59)**

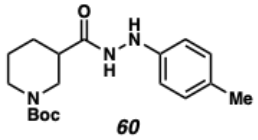
Prepared according to general procedure E using **103** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (30–50% EtOAc in CH_2Cl_2) provided **59** (28.6 mg, 61% yield) as a white solid, characterized as a ratio of 4:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H, minor rotamer), 7.49 (d, *J* = 4.3 Hz, 1H, major rotamer), 7.08 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.03 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.72 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.6 Hz, 2H, minor rotamer), 6.13 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.67 (s, 1H, minor rotamer), 4.03 (ddd, *J* = 10.7, 4.0, 1.9 Hz, 2H, major rotamer), 3.97 (ddd, *J* = 12.0, 4.5, 2.4 Hz, 2H, minor rotamer), 3.47 –3.35 (m, 2 x 2H), 3.08 (tt, *J* = 11.5, 3.9 Hz, 1H, minor rotamer), 2.44 (tt, *J* = 11.4, 4.2 Hz, 1H, major rotamer), 2.28 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.93 – 1.81 (m, 2 x 2H), 1.81 – 1.73 (m, 2 x 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.1, 174.4, 145.7, 131.3, 131.0, 130.2, 113.9, 112.9, 67.3, 67.2, 67.1, 42.4, 40.6, 36.4, 29.1, 28.6, 28.6, 20.7, 20.6.

IR (neat film): 3285, 2954, 2848, 1743, 1682, 1513, 1277, 1243, 1135, 1087, 815 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{19}N_2O_2$ $[M+H]^+$: 235.1441, found 235.1437.



60

***Tert*-butyl 3-(2-(*p*-tolyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (60)**

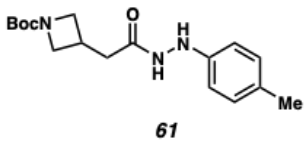
Prepared according to general procedure E using **104** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **60** (34.5 mg, 52% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 – 6.98 (m, 2H), 6.76 – 6.65 (m, 2H), 3.94 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.74 (s, 1H), 3.28 (t, *J* = 10.3 Hz, 1H), 3.06 (s, 1H), 2.40 (s, 1H), 2.32 – 2.19 (m, 3H), 1.89 (s, 2H), 1.74 – 1.61 (m, 1H), 1.46 (s, 9H), 1.43 – 1.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.4, 173.1, 154.8, 145.8, 145.0, 130.7, 130.1, 129.8, 113.9, 112.9, 80.3, 79.7, 77.5, 77.4, 77.2, 76.8, 45.7, 41.3, 34.0, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 28.6, 28.5, 27.6, 27.4, 25.0, 24.2, 22.8, 20.7, 20.6, 14.3.

IR (neat film): 3266, 2922, 2857, 1660, 1512, 1424, 1364, 1242, 1148, 909, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{28}N_3O_3$ [M+H]+: 332.1980, found 332.1980.



61

***Tert*-butyl 3-(2-oxo-2-(2-(*p*-tolyl)hydrazineyl)ethyl)azetidine-1-carboxylate (61)**

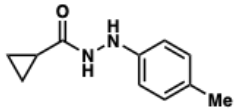
Prepared according to general procedure E using **105** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0–5% MeOH in CH_2Cl_2) provided **61** (42.8 mg, 67% yield) as a white solid, characterized as a ratio of 1.8:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 4.1 Hz, 1H, major rotamer), 7.07 (d, *J* = 8.6 Hz, 2H, minor rotamer), 7.02 (d, *J* = 8.1 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.66 (d, *J* = 8.4 Hz, 2H, minor rotamer), 6.09 (d, *J* = 4.2 Hz, 1H, major rotamer), 5.76 (s, 1H, minor rotamer), 4.07 (dd, *J* = 8.5, 8.5 Hz, 2 x 2H), 3.62 (dd, *J* = 8.8, 5.4 Hz, 2H, major rotamer), 3.56 (dd, *J* = 8.8, 5.2 Hz, 2H, minor rotamer), 2.96 – 2.88 (m, 1H, major rotamer), 2.86 – 2.83 (m, 1H, minor rotamer), 2.75 (d, *J* = 7.8 Hz, 2H, minor rotamer), 2.53 (d, *J* = 7.8 Hz, 2H, major rotamer), 2.28 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.43 (s, 9H, major rotamer); 1.41 (s, 9H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 171.0, 156.5, 156.4, 145.6, 144.7, 131.1, 130.9, 130.2, 129.9, 113.9, 112.6, 79.7, 79.5, 54.5, 41.7, 38.4, 36.0, 28.5, 25.6, 24.9, 24.6, 20.7, 20.6.

IR (neat film): 3278, 2976, 1675, 1513, 1408, 1145, 814, 731 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{26}N_3O_3$ $[M+H]^+$: 320.1969, found 320.1973.



62

***N*'-(*p*-tolyl)cyclopropanecarbohydrazide (62)**

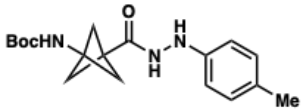
Prepared according to general procedure E using **106** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (25% EtOAc in CH_2Cl_2) provided **62** (18.6 mg, 49% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 6.99 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 2.22 (s, 3H), 1.66 (tt, *J* = 7.9, 4.7 Hz, 1H), 0.92 – 0.87 (m, 2H), 0.85 – 0.77 (m, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 176.5, 147.7, 130.6, 130.4, 114.3, 113.7, 20.6, 13.1, 9.9, 8.4, 7.3.

IR (neat film): 3295, 2414, 2358, 1622, 1606, 1513, 1462, 1100, 952, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{14}N_2NaO$ $[M+Na]^+$: 213.0998, found 213.1001.



63

***Tert*-butyl (3-(2-(*p*-tolyl)hydrazine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)carbamate (63)**

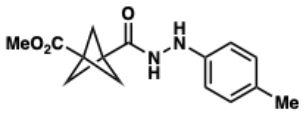
Prepared according to general procedure E using **107** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (10–40% EtOAc in CH_2Cl_2) provided **63** (33.1 mg, 50% yield) as a white solid, characterized as a ratio of 7.3:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 4.3 Hz, 1H, major rotamer), 7.05 (d, *J* = 4.1 Hz, 2H, minor rotamer), 7.02 (d, *J* = 7.8 Hz, 2H, major rotamer), 6.71 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.63 (d, *J* = 8.4 Hz, 2H, minor rotamer), 6.07 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.62 (s, 1H, minor rotamer), 5.05 (s, 1H, major rotamer), 4.94 (s, 1H, minor rotamer), 2.33 (s, 6H, minor rotamer), 2.30 (s, 6H, major rotamer), 2.27 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.45 (s, 9H, major rotamer) 1.40 (s, 9H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 169.2, 145.4, 144.9, 131.0, 130.8, 130.1, 129.8, 114.1, 112.8, 80.1, 54.7, 54.1, 53.9, 46.4, 45.6, 35.7, 28.5, 28.5, 20.7, 20.6.

IR (neat film): 3278, 2980, 2920, 1694, 1513, 1366, 1251, 1168, 1051, 814, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{26}N_3O_3$ $[M+H]^+$: 332.1969, found 332.1972.



64

Methyl 3-(2-(*p*-tolyl)hydrazine-1-carbonyl)bicyclo[1.1.1]pentane-1-carboxylate (64)

Prepared according to general procedure E using **108** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (10–30% EtOAc in CH_2Cl_2) provided **64**

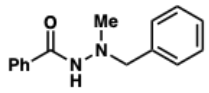
(11 mg, 44% yield) as a white solid, characterized as a ratio of 5:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 4.3 Hz, 1H, major rotamer), δ 7.07 (d, *J* = 8.4 Hz, 2H, minor rotamer), 7.04 (d, *J* = 8.6 Hz, 2H, major rotamer), 6.89 (s, 1H, minor rotamer), 6.73 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.66 (d, *J* = 8.4 Hz, 2H, minor rotamer), 5.99 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.62 (s, 1H, minor rotamer), 3.71 (s, 3H, major rotamer), 3.63 (s, 3H, minor rotamer), 2.36 (s, 6H, major rotamer), 2.34 (s, 6H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 172.3, 169.6, 168.8, 146.2, 145.3, 131.2, 130.2, 129.9, 114.2, 112.8, 53.5, 52.6, 52.1, 51.9, 38.6, 38.1, 37.5, 20.7, 20.6.

IR (neat film): 3274, 1732, 1658, 1513, 1312, 1277, 1063, 910, 814, 711 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{19}N_2O$ $[M+H]^+$: 275.1390, found 275.1389.



27

***N*'-benzyl-*N*'-methylbenzohydrazide (27)**

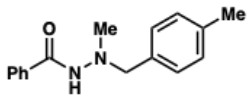
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (0–30% EtOAc in CH_2Cl_2) provided **27** (28.4 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.57 (m, 2H), 7.49 – 7.44 (m, 1H), 7.39 – 7.28 (m, 7H), 6.90 (s, 1H), 4.11 (s, 2H), 2.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 135.9, 134.0, 131.7, 129.7, 128.7, 128.6, 127.9, 127.0, 62.6, 44.7.

IR (neat film): 3235, 3061, 2848, 1645,1542, 1448, 1306, 1108, 1006, 921, 742 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found 241.1338.



65

***N*'-methyl-*N*'-(4-methylbenzyl)benzohydrazide (65)**

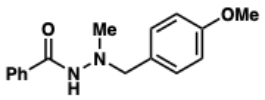
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methyl-1-(*p*tolyl)methanamine (0.3 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **65** (27.5 mg, 54% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.59 (m, 2H), 7.49 – 7.44 (m, 1H), 7.40 – 7.35 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.86 (brs, 1H), 4.06 (s, 2H), 2.77 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 137.6, 134.0, 132.6, 131.6, 129.7, 129.3, 128.7, 127.0, 62.3, 44.6, 21.3.

IR (neat film): 3228, 2848, 1648, 1578, 1448, 1306, 1108, 1004, 802, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1495.



66

***N*'-(4-methoxybenzyl)-*N*'-methylbenzohydrazide (66)**

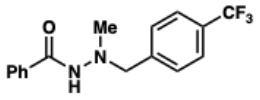
Prepared according to general procedure F, using **19** (0.2 mmol) and 1-(4-methoxyphenyl)*N*-methylmethanamine (0.3 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **66** (17.4 mg, 32% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.57 (m, 2H), 7.51 – 7.41 (m, 1H), 7.40 – 7.32 (m, 2H), 7.32 – 7.21 (m, 2H), 6.92 – 6.81 (m, 3H), 4.04 (s, 2H), 3.79 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 159.3, 134.0, 131.6, 130.9, 128.7, 127.8, 127.0, 113.9, 61.9, 55.4, 44.6.

IR (neat film) 3223, 2953, 2836, 1768, 1651, 1511, 1449, 1240, 1174, 1035, 909, 853, 701 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1441, found 271.1446.



67

***N*'-(4-methoxybenzyl)-*N*'-methylbenzohydrazide (67)**

Prepared according to general procedure F, using **19** (0.2 mmol) and *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (0.3 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **67** (25.7 mg, 42% yield) as a white solid.

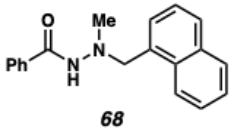
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (m, 4H), 7.48 (dd, *J* = 20.8, 7.7 Hz, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.05 (s, 1H), 4.18 (s, 2H), 2.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 140.9, 133.7, 131.8, 123.0 (q, *J* = 32.3 Hz), 129.5, 128.8, 125.5 (q, *J* = 3.5 Hz), 124.3 (q, *J* = 272.0 Hz), 122.9, 120.2, 62.0, 45.0.

^{19}F (282 MHz, $CDCl_3$): δ -62.5.

IR (neat film): 3214, 1640, 1538, 1324, 1165, 1115, 1066, 1019, 913, 858, 817, 724, 691, 648 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{16}F_3N_2O$ $[M+H]^+$: 309.1108, found 309.1121.



68

***N*'-methyl-*N*'-(naphthalen-1-ylmethyl)benzohydrazide (68)**

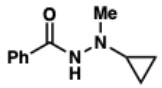
Prepared according to general procedure F, using **19** (0.2 mmol) and *N*-methyl-1-(naphthalen-1-yl)-methanamine (0.3 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **68** (36.6 mg, 66% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.53 – 7.50 (m, 1H), 7.49 – 7.32 (m, 5H), 7.07 (s, 1H), 4.58 (s, 2H), 2.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 134.0, 134.0, 132.6, 132.6, 131.6, 128.8, 128.7, 128.6, 128.3, 127.0, 126.5, 126.0, 125.3, 124.8, 60.2, 44.5.

IR (neat film): 3218, 3056, 1640, 1538, 1324, 1165, 1114, 1067, 907, 799, 725 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{19}N_2O$ $[M+H]^+$: 291.1492, found 291.1479.



69

***N*'-cyclopropyl-*N*'-methylbenzohydrazide (9h)**

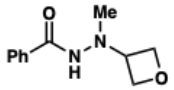
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methyl-cyclopropanamine (0.3 mmol). Purification by column chromatography (0–30% EtOAc in CH_2Cl_2) provided **69** (16.4 mg, 43% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.42 (ddd, *J* = 8.4, 6.5, 1.5 Hz, 2H), 7.23 (s, 1H), 2.84 (s, 3H), 2.49 (tt, *J* = 6.7, 3.4 Hz, 1H), 0.79 – 0.67 (m, 2H), 0.60 – 0.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 134.1, 131.7, 128.7, 127.1, 45.3, 39.8, 6.8.

IR (neat film): 3238, 3061, 2954, 1647, 1578, 1541, 1490, 1448, 1300, 1142, 1018, 915, 888, 712, 693 cm^{-1}.

HRMS (ESI+) m/z calc'd for $C_{11}H_{15}N_2O$ $[M+H]^+$: 191.1179, found 191.118.



70

_N_'-methyl-_N_'-(oxetan-3-yl)benzohydrazide (70)

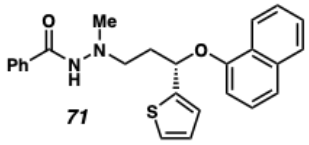
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (20–33% acetone in CH_2Cl_2) provided **70** (33.4 mg, 81% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.51 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.42 (dd, *J* = 7.6, 7.4 Hz, 2H), 7.30 (s, 1H), 4.71 (dd, *J* = 6.6, 2.1 Hz, 4H), 4.32 (dt, *J* = 6.6, 6.3 Hz, 1H), 2.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 133.4, 132.0, 128.8, 127.2, 74.8, 60.5, 41.9.

IR (neat film): 3229, 2953, 2878, 1648, 1536, 1490, 1289, 1069, 975, 921, 898 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128, found 207.1129.



71

(_S_)-_N_'-methyl-_N_'-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)benzohydrazide (71)

Prepared according to general procedure F, using **19** (0.2 mmol) and duloxetine (0.3 mmol). Purification by column chromatography (10% EtOAc in hexanes) provided **71** (32.7 mg, 39% yield) as a white solid.

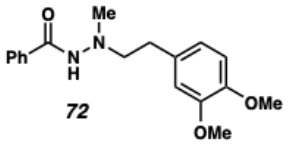
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 6.3, 3.4 Hz, 1H), 7.78 (dd, *J* = 6.1, 3.3 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.53 – 7.43 (m, 3H), 7.43 – 7.35 (m, 3H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.10 (d, *J* = 2.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.92

(dd, *J* = 5.1, 3.5 Hz, 1H), 6.79 (s, 1H), 6.03 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.21 – 2.89 (m, 2H), 2.72 (s, 3H), 2.57 – 2.23 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 153.4, 145.2, 134.7, 133.8, 131.7, 128.7, 127.6, 127.1, 126.7, 126.3, 126.0, 125.3, 124.9, 124.8, 122.2, 120.7, 107.4, 74.2, 55.9, 46.7, 36.8.

IR (neat film): 3220, 3054, 2957, 1643, 1578, 1396, 1264, 1235, 1094, 908, 727 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{25}H_{25}N_2O_2S$ $[M+H]^+$: 417.1631, found 417.1647.



***N*'-(3,4-dimethoxyphenethyl)-*N*'-methylbenzohydrazide (72)**

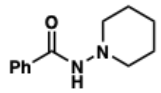
Prepared according to general procedure F using **19** (0.2 mmol) and 2-(3,4dimethoxyphenyl)-*N*-methylethan-1-amine (0.3 mmol). Purification by reverse phase flash chromatography (10%–100% MeCN in H_2O with 0.1% TFA, C18 column), and basic workup of the resulting TFA salt of **72** with saturated $NaHCO_3$ solution, provided **72** (22.6 mg, 36% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.0 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.42 (dd, *J* = 8.2, 6.7 Hz, 2H), 6.79 – 6.73 (m, 4H, N–H & aromatic C–H), 3.84 (s, 3H), 3.83 (s, 3H), 3.10 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.87 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 149.1, 147.6, 133.8, 132.4, 131.8, 128.7, 127.1, 120.6, 112.2, 111.4, 61.1, 56.0, 56.0, 46.4, 33.7.

IR (neat film): 3240, 2927, 2851, 1648, 1515, 1464, 1261, 1236, 1156, 1141, 1028, 805, 715, 695 cm^{-1}.

HRMS (ESI+) m/z calc'd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 315.1703, found 315.1692.



74

***N*-(piperidin-1-yl)benzamide (74)**

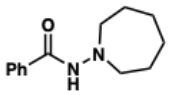
Prepared according to general procedure F using **19** (0.2 mmol) and piperidine (0.3 mmol). Purification by column chromatography (0–25% acetone in hexanes) provided **74** (9.4 mg, 23% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.1 Hz, 2H), 7.49 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.41 (dd, *J* = 7.7, 7.3 Hz, 1H), 6.79 (s, 1H), 2.87 (t, *J* = 5.4 Hz, 4H), 1.80 – 1.75 (m, 4H), 1.48 – 1.43 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 134.2, 131.6, 128.7, 127.1, 57.3, 25.5, 23.4.

IR (neat film): 3191, 3031, 2938, 2811, 1653, 1638, 1570, 1472, 1316, 1143, 1085, 918, 725 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335, found 205.1342.



75

***N*-(azepan-1-yl)benzamide (75)**

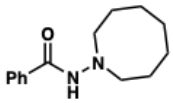
Prepared according to general procedure F using **19** (0.2 mmol) and azepane (0.3 mmol). Purification by column chromatography (25% EtOAc in CH_2Cl_2) provided **75** (25.8 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.41 (dd, *J* = 7.6, 7.1 Hz, 2H), 7.30 (s, 1H), 3.20 – 3.14 (m, 4H), 1.78 – 1.72 (m, 4H), 1.68 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 134.2, 131.6, 128.7, 127.1, 58.3, 27.2, 26.4.

IR (neat film): 3191, 3031, 2811, 1653, 1638, 1570, 1316, 1143, 1085, 1038, 918, 725, 695 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492, found 219.1499.



76

***N*-(azocan-1-yl)benzamide (76)**

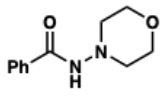
Prepared according to general procedure F using **19** (0.2 mmol) and azocane (0.3 mmol). Purification by column chromatography (10–15% EtOAc in CH_2Cl_2) provided **76** (26.5 mg, 57% yield) as a white solid, characterized as a ratio of 7.8:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 6.9 Hz, 2H, major rotamer), 7.66 (d, *J* = 7.3 Hz, 2H, minor rotamer), 7.51 – 7.46 (m, 2 x 1H), 7.45 – 7.39 (m, 2 x 2H), 3.15 (t, *J* = 5.3 Hz, 4H, major rotamer), 2.90 – 2.85 (m, 4H, minor rotamer), 1.73 – 1.64 (m, 10H, major rotamer), 1.53 – 1.50 (m, 10H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 134.3, 131.6, 128.7, 128.3, 127.7, 127.1, 58.9, 56.4, 27.1, 27.0, 26.5, 26.3, 25.5.

IR (neat film): 3251, 2910, 1649, 1545, 1308, 1167, 1015, 927, 891, 649 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648, found 233.1655.



77

***N*-morpholinobenzamide (77)**

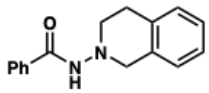
Prepared according to general procedure F, using **19** (0.2 mmol) and morpholine (0.3 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **77** (14.5 mg, 35% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 7.83 – 7.76 (m, 2H), 7.59 – 7.51 (m, 1H), 7.46 (dd, *J* = 8.2, 6.7 Hz, 2H), 3.85 – 3.78 (m, 4H), 2.95 – 2.88 (m, 4H).

^{13}C NMR (101 MHz, CD_3OD): δ 168.4, 134.6, 132.9, 129.6, 128.4, 67.5, 56.3.

IR (neat film): 2954, 2848, 2320, 1631, 1577, 1432, 1381, 1264, 1108, 1104, 889 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128, found 207.1128.



78

***N*-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (78)**

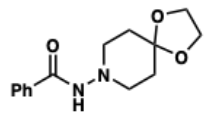
Prepared according to general procedure F, using **19** (0.2 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.3 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **78** (23.2 mg, 46% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.21 (s, 1H), 7.19 – 7.10 (m, 3H), 7.07 – 6.98 (m, 1H), 4.20 (s, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 6.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 133.9, 133.1, 133.0, 131.8, 128.8, 128.8, 127.2, 127.0, 126.9, 126.2, 57.4, 52.9, 27.8.

IR (neat film): 3191, 3029, 2927, 1644, 1558, 1313, 940, 905, 738, 707 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335, found 253.1343.



79

_N_-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzamide (79)

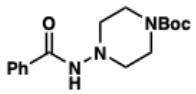
Prepared according to general procedure F using **19** (0.2 mmol) and 1,4-dioxa-8azaspiro[4.5]decane (0.3 mmol). Purification by reverse phase flash chromatography (10%–100% MeCN in H_2O with 0.1% TFA, C18 column), and basic workup of the resulting TFA salt of **79** with saturated $NaHCO_3$ solution, provided **79** (19.9 mg, 38% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.1 Hz, 2H), 7.51 – 7.45 (m, 1H), 7.41 (dd, *J* = 8.2, 6.6 Hz, 2H), 6.87 (brs, 1H), 3.95 (s, 4H), 3.01 (t, *J* = 5.6 Hz, 4H), 1.92 (t, *J* = 5.7 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 133.9, 131.7, 128.7, 127.2, 106.2, 64.5, 54.1, 34.2.

IR (neat film): 3224, 2930, 1648, 1549, 1294, 1223, 1144, 1071, 1037, 963, 846 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390, found 263.1400.



80

***Tert*-butyl 4-benzamidopiperazine-1-carboxylate (80)**

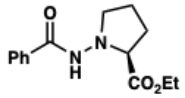
Prepared according to general procedure F, using **19** (0.2 mmol) and *tert*-butyl piperazine1-carboxylate (0.3 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **80** (14.5 mg, 24% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.82 – 7.76 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.68 (t, *J* = 5.1 Hz, 4H), 3.31 (t, *J* = 5.1 Hz, 4H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 154.4, 132.8, 132.0, 129.1, 127.4, 81.1, 54.4, 42.5, 28.5.

IR (neat film): 2980, 2319, 1650, 1428, 1263, 1173, 1138, 998, 889, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{24}N_3O_3$ $[M+H]^+$: 306.1812, found 306.1813.



81

Ethyl benzamido-(*L*)-prolinate (81)

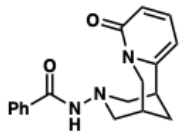
Prepared according to general procedure F using **19** (0.2 mmol) and ethyl (*L*)-prolinate (0.3 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **81** (16.3 mg, 31% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.73 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.44 – 7.39 (m, 2H), 4.24 – 4.13 (m, 3H, N–H & CH_2), 3.50 (td, *J* = 8.0, 5.6 Hz, 1H), 3.24 (td, *J* = 8.2, 5.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.08 – 1.96 (m, 2H), 1.95 – 1.86 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 166.5, 133.7, 131.8, 128.7, 127.1, 63.7, 61.0, 53.1, 28.3, 22.0, 14.3.

IR (neat film): 3248, 2980, 1733, 1652, 1579, 1539, 1375, 1294, 1184, 1026, 929, 860, 801, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390, found 263.1401; $[\alpha]_D^{21.7}$ – 53.62 (*c* 1.26, $CHCl_3$).



82

***N*-((1*S*,5*S*)-8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3(4*H*)-yl)benzamide (82)**

Prepared according to general procedure F, using **19** (0.2 mmol) and cytisine (0.3 mmol).

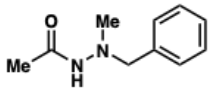
Purification by reverse phase flash chromatography (0–95% MeCN in H_2O with 0.1% TFA, C18 column) provided **82** (15 mg, 24% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.61 (m, 2H), 7.54 – 7.37 (m, 3H), 7.37 – 7.27 (m, 1H), 7.16 (m, 1H, major rotamer), 6.87 (s, 1H, minor rotamer), 6.74 (d, *J* = 8.9 Hz, 1H, major rotamer), 6.65 (d, *J* = 9.0 Hz, 1H, minor rotamer), 6.30 (d, *J* = 7.0 Hz, 1H, major rotamer), 6.12 (d, *J* = 7.0 Hz, 1H, minor rotamer), 4.24 (d, *J* = 15.7 Hz, 1H, major rotamer), 4.06 – 3.92 (m, 2H), 3.91 – 3.74 (m, 1H, minor rotamer), 3.13 (d, *J* = 25.9 Hz, 3H), 2.81 (dd, *J* = 17.0, 10.4 Hz, 1H, minor rotamer), 2.60 (s, 1H, major rotamer), 2.54 (s, 1H, minor rotamer), 2.07 – 1.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 164.1, 151.6, 140.6, 139.9, 133.2, 132.1, 131.6, 128.8, 127.9, 127.6, 126.9, 116.8, 115.9, 108.2, 107.3, 63.3, 59.8, 59.6, 50.9, 50.1, 36.1, 35.4, 28.5, 28.2, 24.7, 24.6.

IR (neat film): 3234, 2948, 1644, 1546, 1192, 1143, 907, 802, 729, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{20}N_3O_2$ $[M+H]^+$: 310.1550, found 310.1554.



83

***N*'-benzyl-*N*'-methylacetohydrazide (83)**

Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (25–50% acetone in hexanes) provided **83** (18.9 mg, 53% yield) as a white solid, characterized as a ratio of 2.7:1 rotamers.

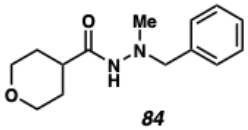
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 2 x 5H), 6.45 (s, 1H, major rotamer), 6.30

(s, 1H, minor rotamer), 3.97 (s, 2H, minor rotamer), 3.74 (s, 2H, major rotamer), 2.67 (s, 3H, minor rotamer), 2.54 (s, 3H, major rotamer), 1.94 (s, 3H, minor rotamer), 1.82 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5, 168.4, 135.8, 135.8, 129.8, 129.5, 128.6, 128.5, 128.0, 127.8, 65.1, 62.6, 46.3, 44.8, 21.7, 19.9.

IR (neat film): 3212, 3062, 2954, 2849, 1652, 1547, 1495, 1446, 1368, 1325, 1297, 1112, 997, 891, 746, 698, 526 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1179, found 179.1176.



84

***N*'-benzyl-*N*'-methyltetrahydro-2*H*-pyran-4-carbohydrazide (84)**

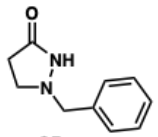
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (25–50% acetone in hexanes) provided **84** (24.8 mg, 50% yield) as a white solid, characterized as a 1.3:1 ratio of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 2 x 5H), 6.27 (s, 1H, minor rotamer), 6.03 (s, 1H, major rotamer), 3.99 (s, 2H, major rotamer), 3.96 – 3.91 (m, 2H, major rotamer), 3.91 – 3.85 (m, 2H, minor rotamer), 3.80 (d, J = 12.3 Hz, 1H, minor rotamer), 3.66 (d, J = 12.2 Hz, 1H, minor rotamer), 3.45 – 3.38 (m, 2H, minor rotamer), 3.32 (td, J = 11.7, 2.3 Hz, 2H, major rotamer), 2.95 (tt, J = 11.7, 3.9 Hz, 1H), 2.72 (s, 3H, minor rotamer), 2.58 (s, 3H, major rotamer), 2.11 (tt, J = 11.5, 3.9 Hz, 1H, minor rotamer), 1.78 – 1.49 (m, 2 x 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.8, 172.6, 136.2, 135.6, 130.0, 129.6, 128.7, 128.5, 128.2, 127.8, 67.4, 67.3, 65.5, 62.4, 47.1, 44.9, 41.0, 36.9, 29.1, 29.0, 28.0.

IR (neat film): 3225, 3061, 2951, 2846, 1660, 1533, 1445, 1297, 1127, 1088, 1016, 984, 859, 741, 700 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$: 249.1598, found 249.1600.



85

1-benzylpyrazolidin-3-one (85)

Prepared according to general procedure F, using *N*-(benzoyloxy)-3(benzylamino)propenamide (**19**) (0.2 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **85** (18.4 mg, 52% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.47 – 7.33 (m, 5H), 4.14 (s, 2H), 3.59 – 3.55 (m, 2H), 2.54 (t, J = 8.1 Hz, 2H).

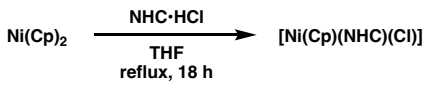
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 131.3, 130.4, 129.6, 129.4, 63.0, 50.7, 29.5.

IR (neat film): 3030, 2848, 2319, 1678, 1630, 1576, 1429, 1263, 1197, 1132, 889, 712, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{10}H_{13}N_2O$ $[M+H]^+$: 177.1022, found 177.1016.

1.7.2.3 Synthesis of Ni Half-Sandwich Catalyst

*Preparation of [Ni(Cp)(NHC$^{i\text{-}Pr}$)(Cl)] (**24**): General Procedure G*



A procedure was adapted from the literature.[43]

In a nitrogen-filled glovebox, nickelocene (1.13 g, 1.0 equiv) and 1,3-diisopropyl-1*H*imidazol-3-ium chloride (1.13 g, 1.0 equiv) were weighed into a Schlenk tube and dissolved in THF (50 mL, 0.12 M). The tube was sealed, removed from the glovebox, and the green solution was heated to reflux overnight, during which the solution turned from dark green to maroon. After 18 hours, the reaction mixture was passed through a Celite plug eluting with CH_2Cl_2, concentrated, and purified with silica gel chromatography (0–25% EtOAc in CH_2Cl_2), collecting only the maroon fractions, to provide **24** (1.41 g, 75% yield) as a dark red solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 2H), 6.42 (p, *J* = 6.8 Hz, 2H), 5.22 (s, 5H), 1.53 (dd, *J* = 41.1, 6.8 Hz, 12H).

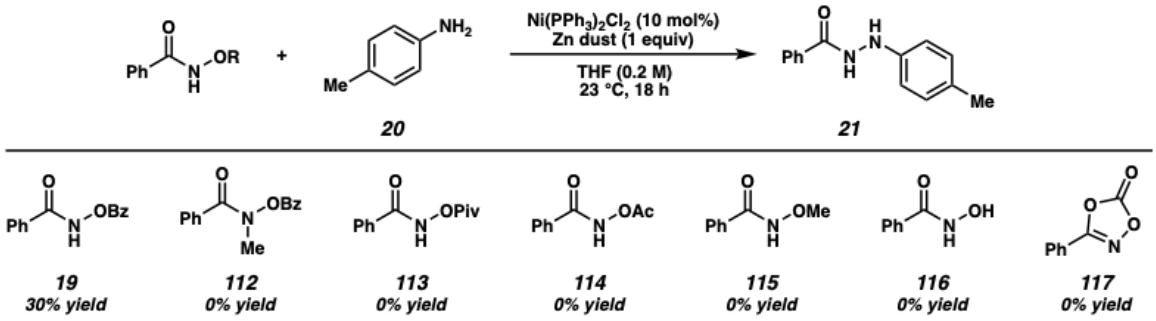
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.1, 118.5, 91.8, 53.7, 23.9, 23.6.

IR (neat film): 3088, 2974, 2933, 2875, 1424, 1213, 777, 728, 694 cm^{-1}.

HRMS (FD): m/z calc'd for $C_{14}H_{21}N_2ClNi$ $[M]^{+\bullet}$: 310.07467, found 310.07478.

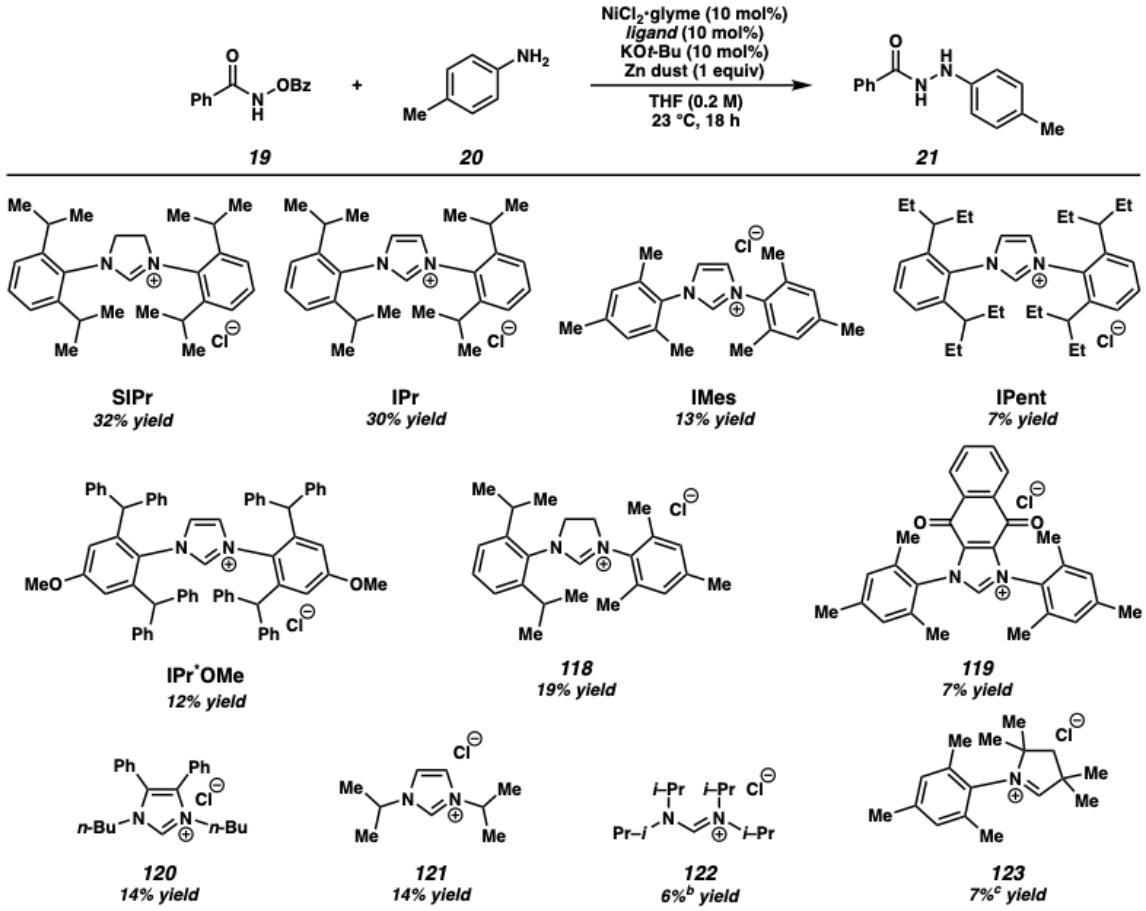
1.7.3 ADDITIONAL OPTIMIZATION DATA

Table 1.3. *Initial evaluation of alternative electrophiles.*[a].



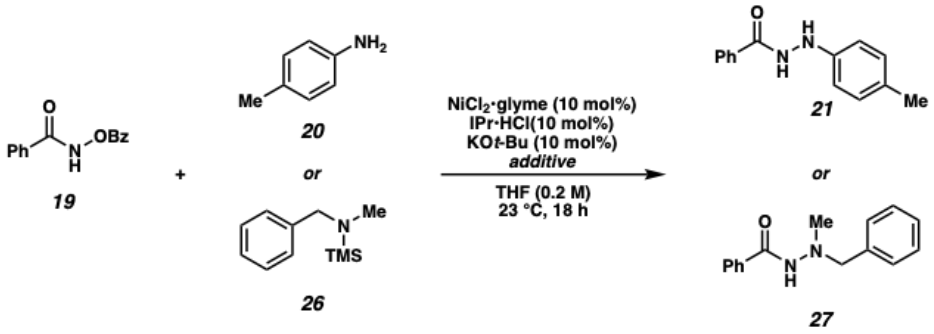
[a] Yields determined by LC/MS integration against internal standard.

Table 1.4. *Initial evaluation of NHC ligands.*[a]



[a] Yields determined by LC/MS integration against internal standard. [b] KHMDS used instead of KO*t*-Bu.[c] LDA used instead of KO*t*Bu.

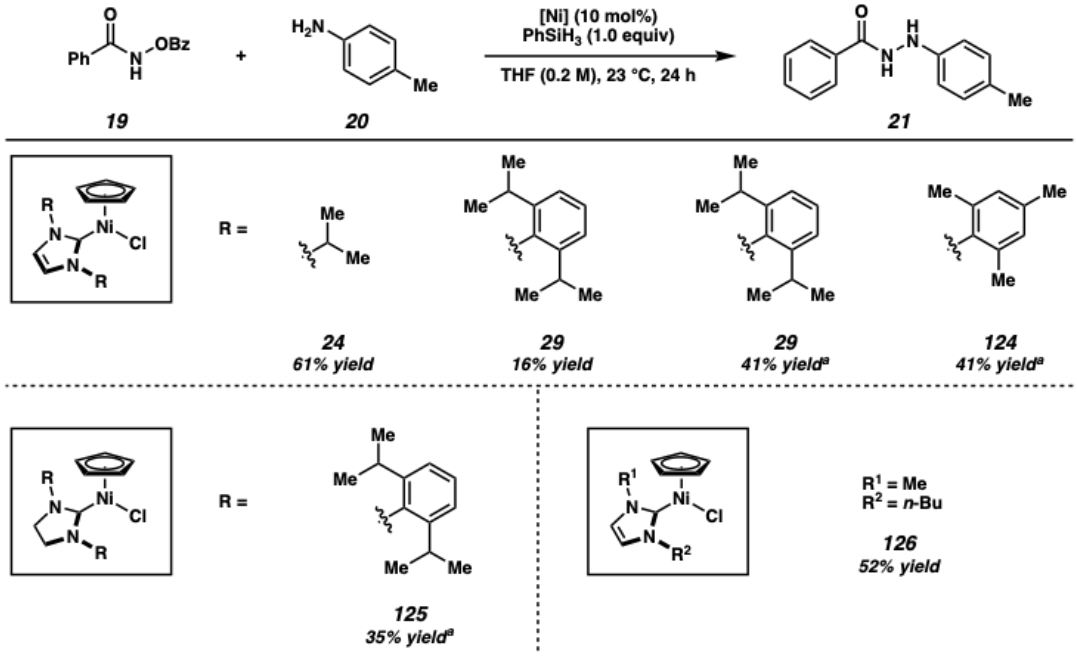
Table 1.5. *Evaluation of additives.*[a]



Entry	Additive	Equiv	Nucleophile	Deviation	Yield (%)[a]
1	Zn dust	1 equiv	2	–	30
2	Mn dust	1 equiv	2	–	7
3	B_2Pin_2	1 equiv	2	–	54
4	B_2Pin_2	1 equiv	8b	–	0
5	Et_3SiH	1 equiv	2	–	37
6	Et_3SiH	1 equiv	8b	–	36
7	$Me(OEt)_2SiH$	1 equiv	2	–	33
8	PMHS	5 equiv	2	SIPr instead of IPr	53
9	$PhSiH_3$	1 equiv	2	–	68
10	$PhSiH_3$	1 equiv	8b	–	65

[a] Yields determined by LC/MS integration against internal standard.

Table 1.6. *Evaluation of half-sandwich complexes with aryl amines.*



[a] Reaction time 72 h.

Table 1.7 *Evaluation of half-sandwich complexes with aliphatic amines.*

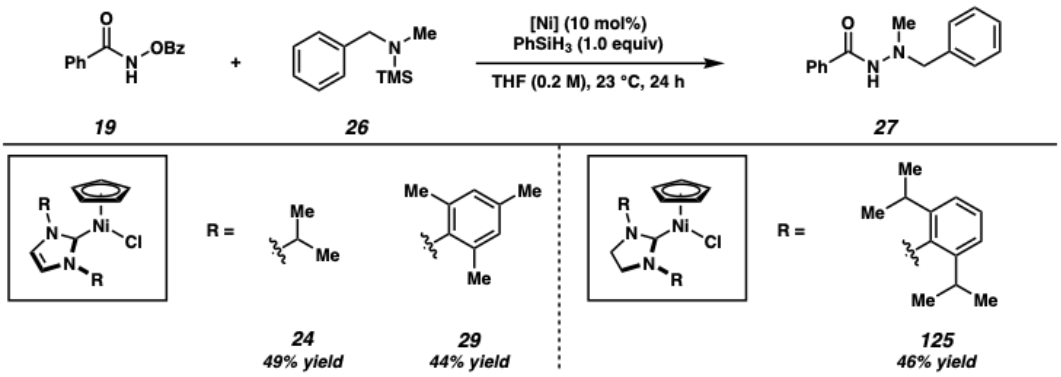
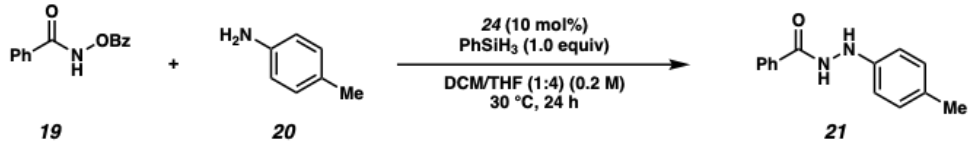
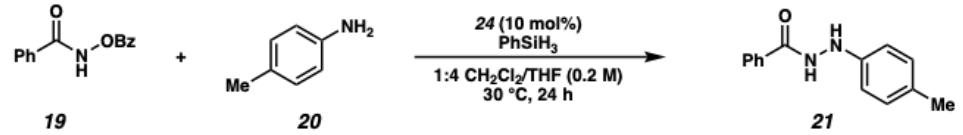


Table 1.8 *Control studies.*



Entry	Devation	Yield (%)
1	No [Ni]	0
2	No $PhSiH_3$	24
3	No [Ni] or $PhSiH_3$	0
4	under air	54

Table 1.9 *Examination of reduced silane loadings.*



entry	$PhSiH_3$ (mol%)	yield (%)
1	10	49[a]
2	20	71
3	50	81

[a] Yield determined by ^1H NMR integration against internal standard.

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APPENDIX 1

Spectra Relevant to Chapter 1: Development of a Ni-Catalyzed N–N Cross-Coupling for the Synthesis of Hydrazides

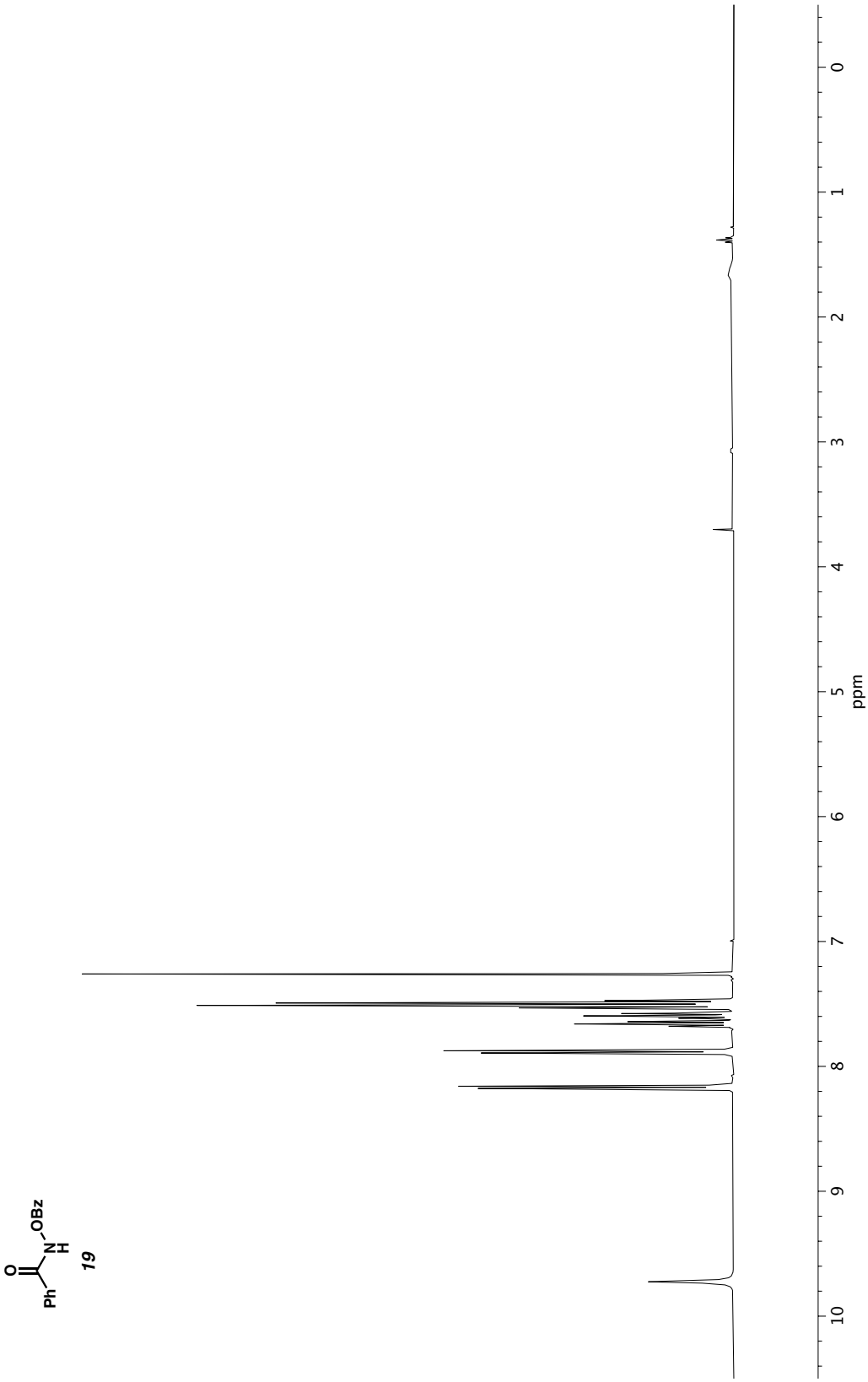


Figure A1.1 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19***.

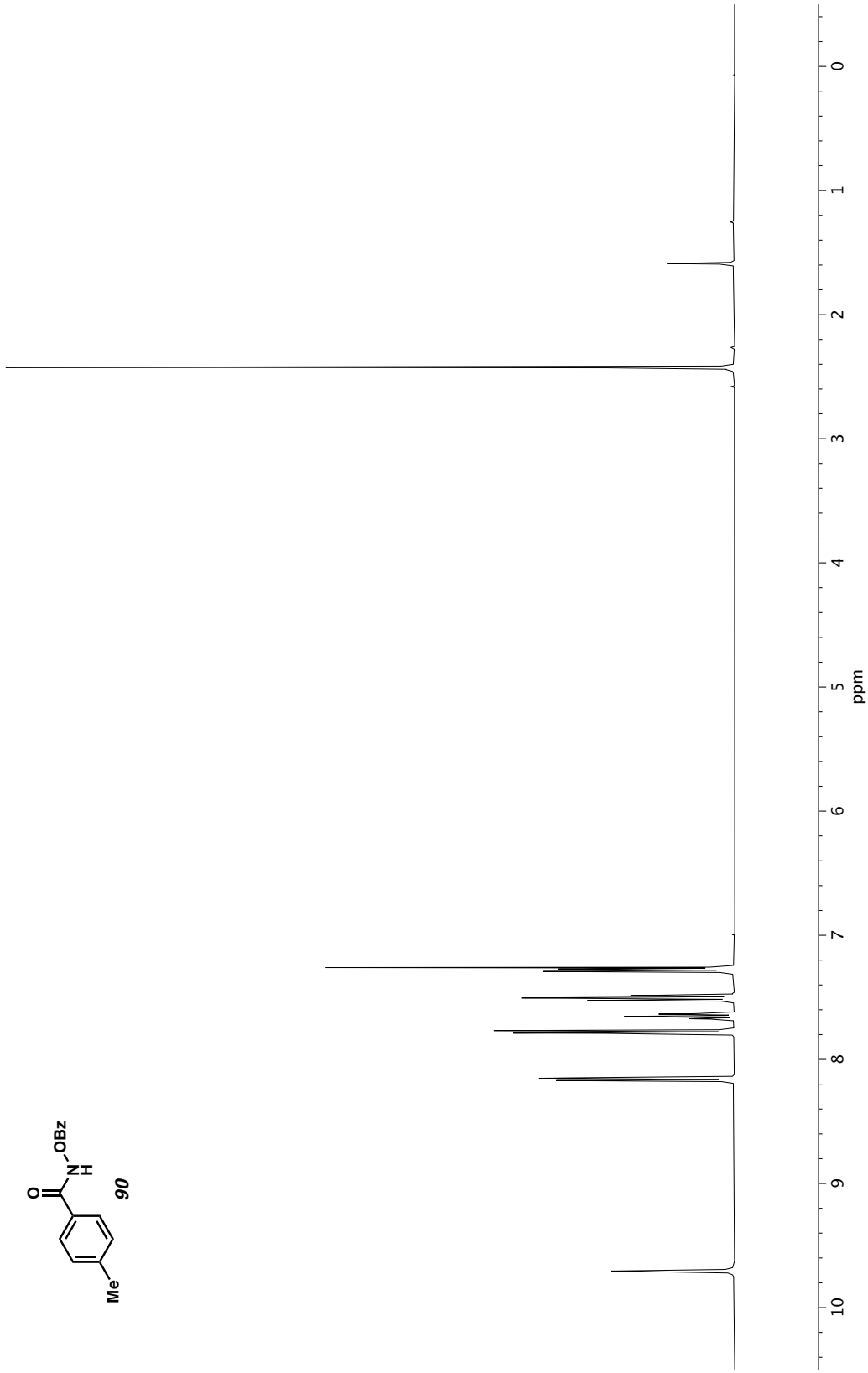


Figure A1.2 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***90***.

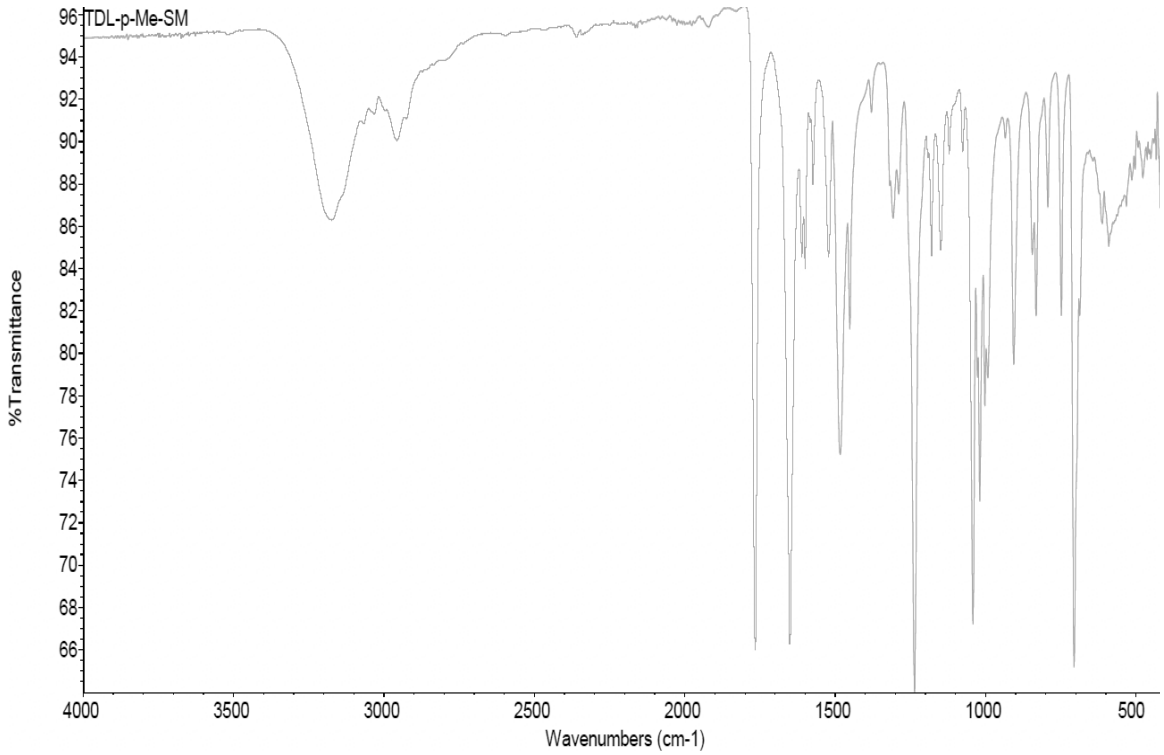


Figure A1.3 *Infrared spectrum (Thin Film) of compound* ***90****.*

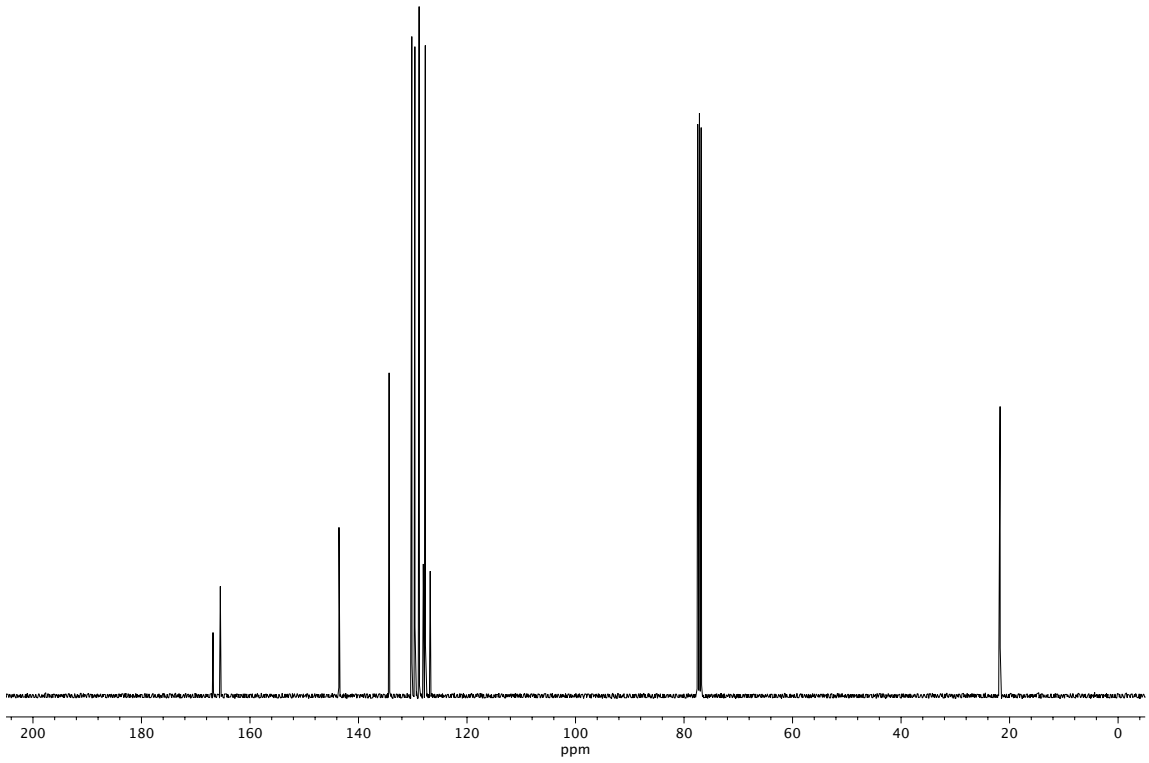


Figure A1.4 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***90****.*

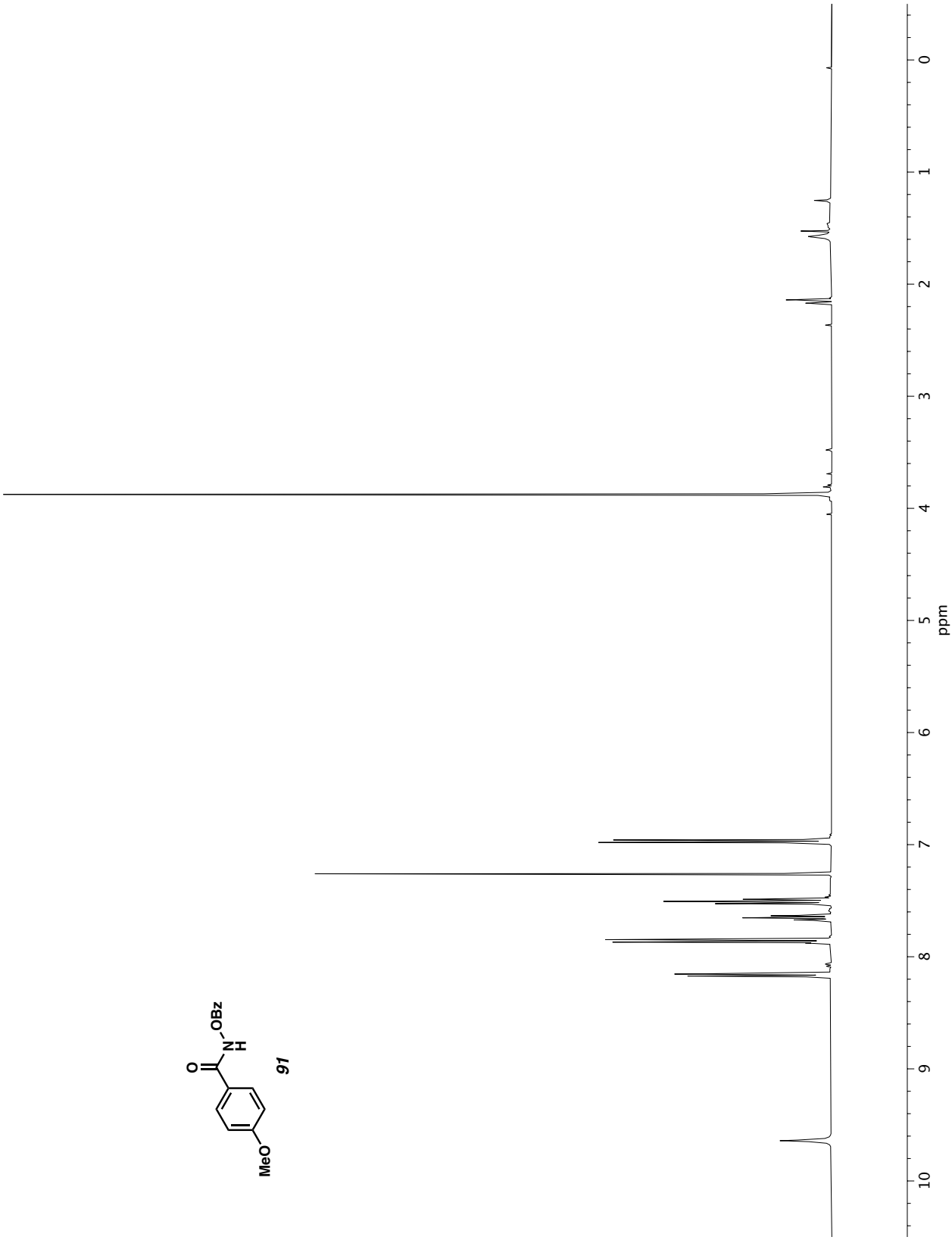


Figure A1.5 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***91***.

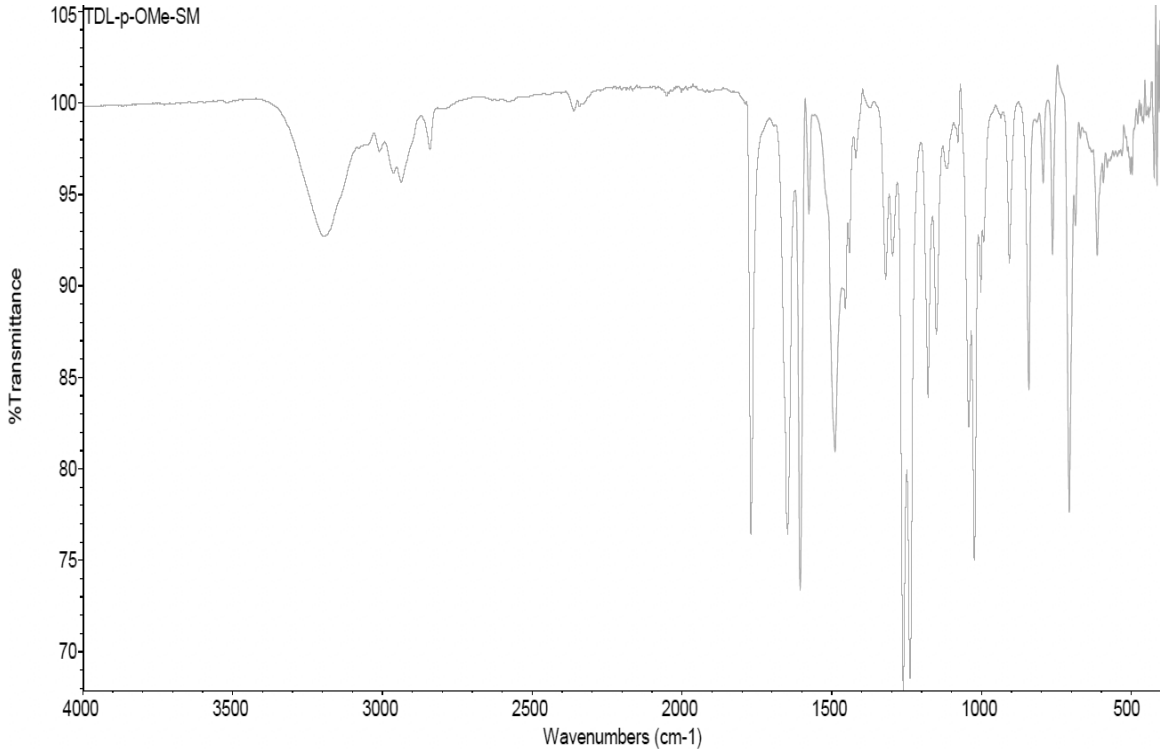


Figure A1.6 *Infrared spectrum (Thin Film) of compound* ***91***.

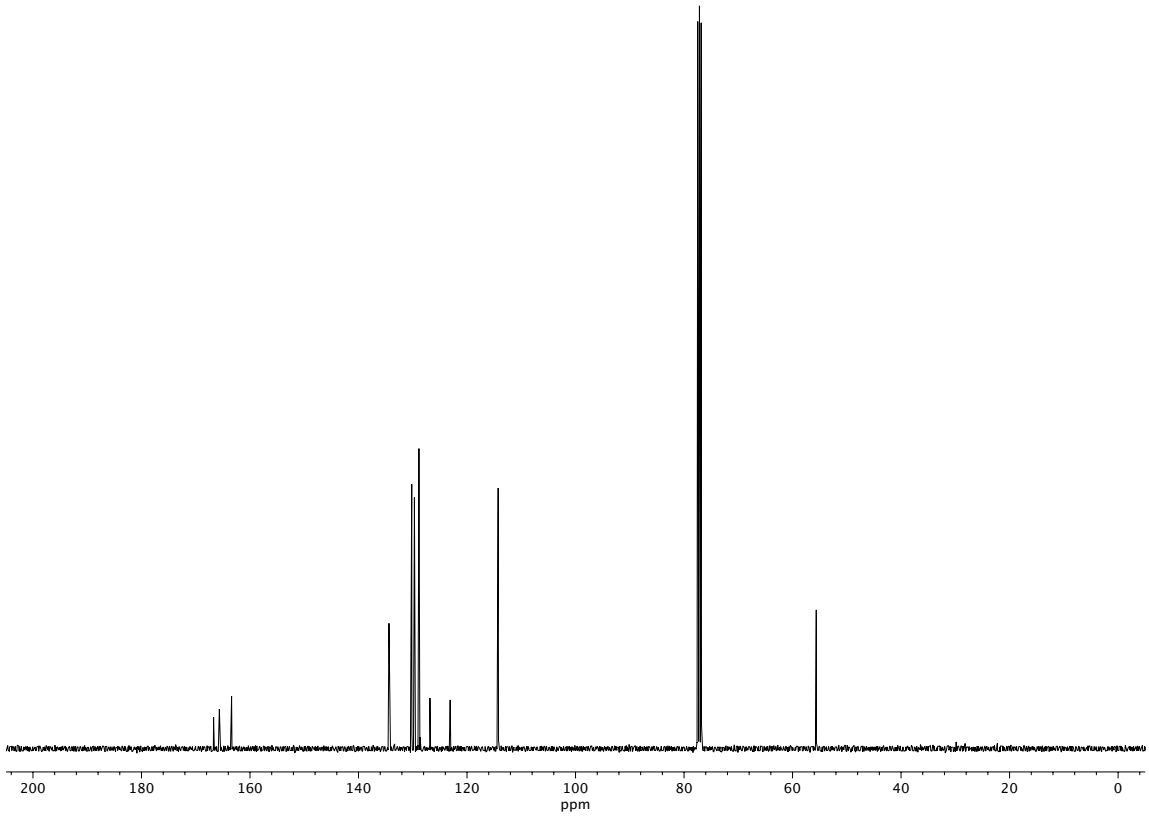


Figure A1.7 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***91***.

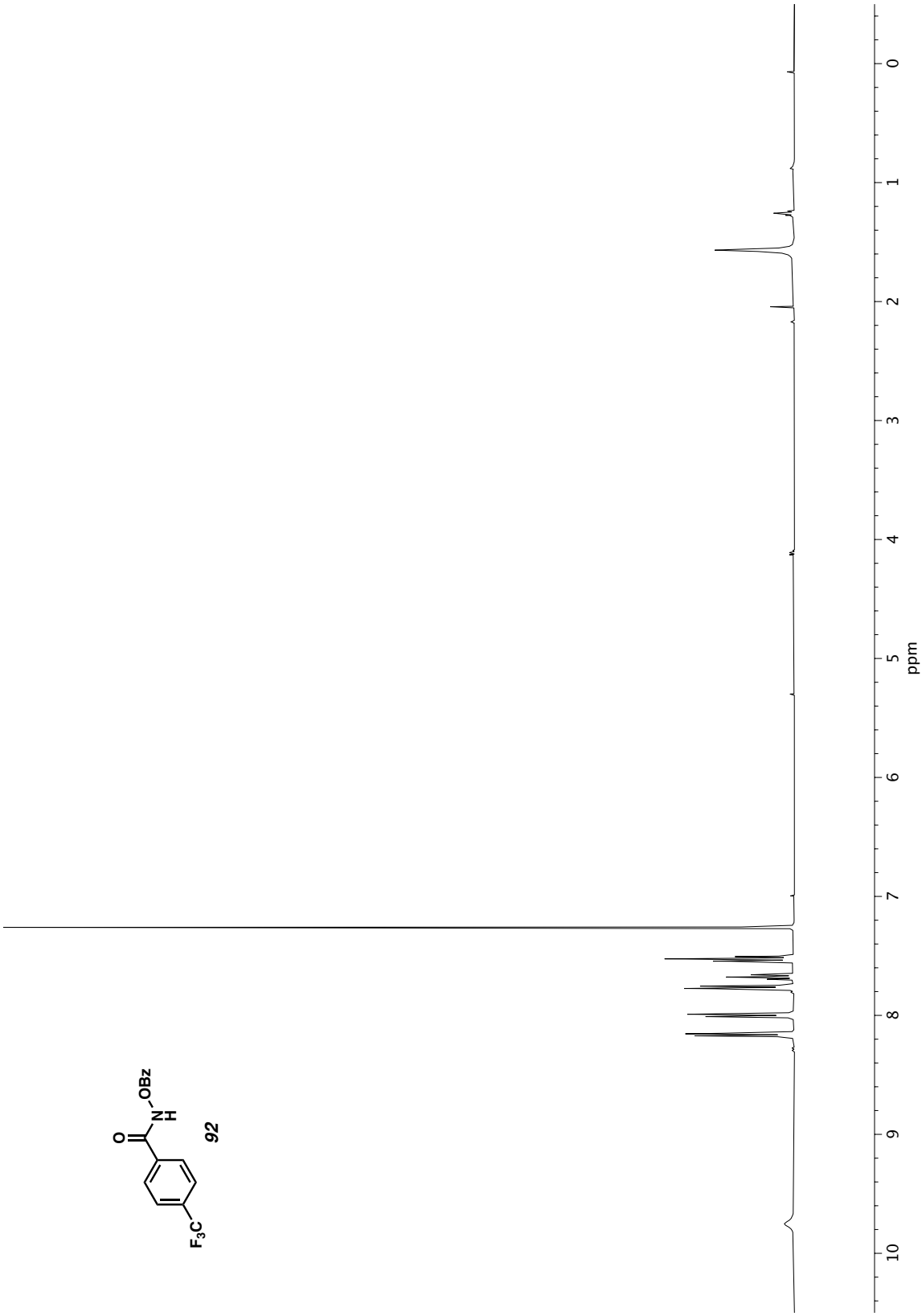


Figure A1.8 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***92***.

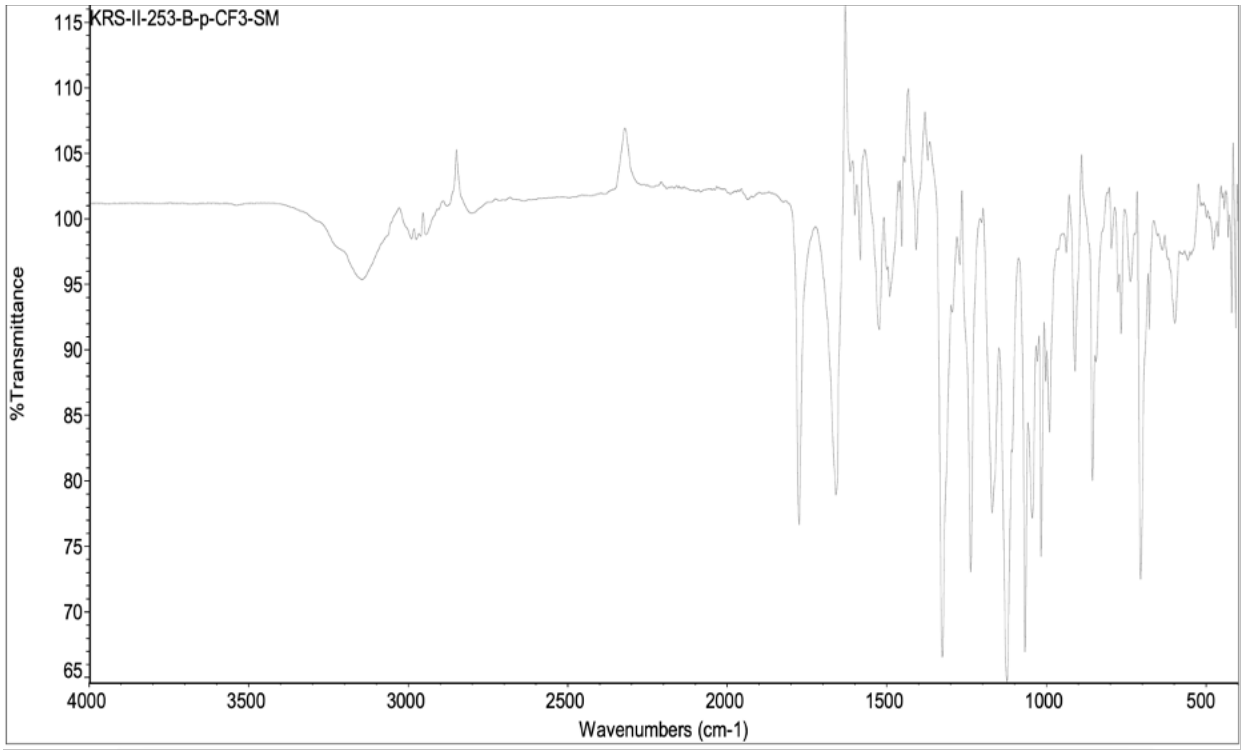


Figure A1.9 *Infrared spectrum (Thin Film) of compound* ***92***.

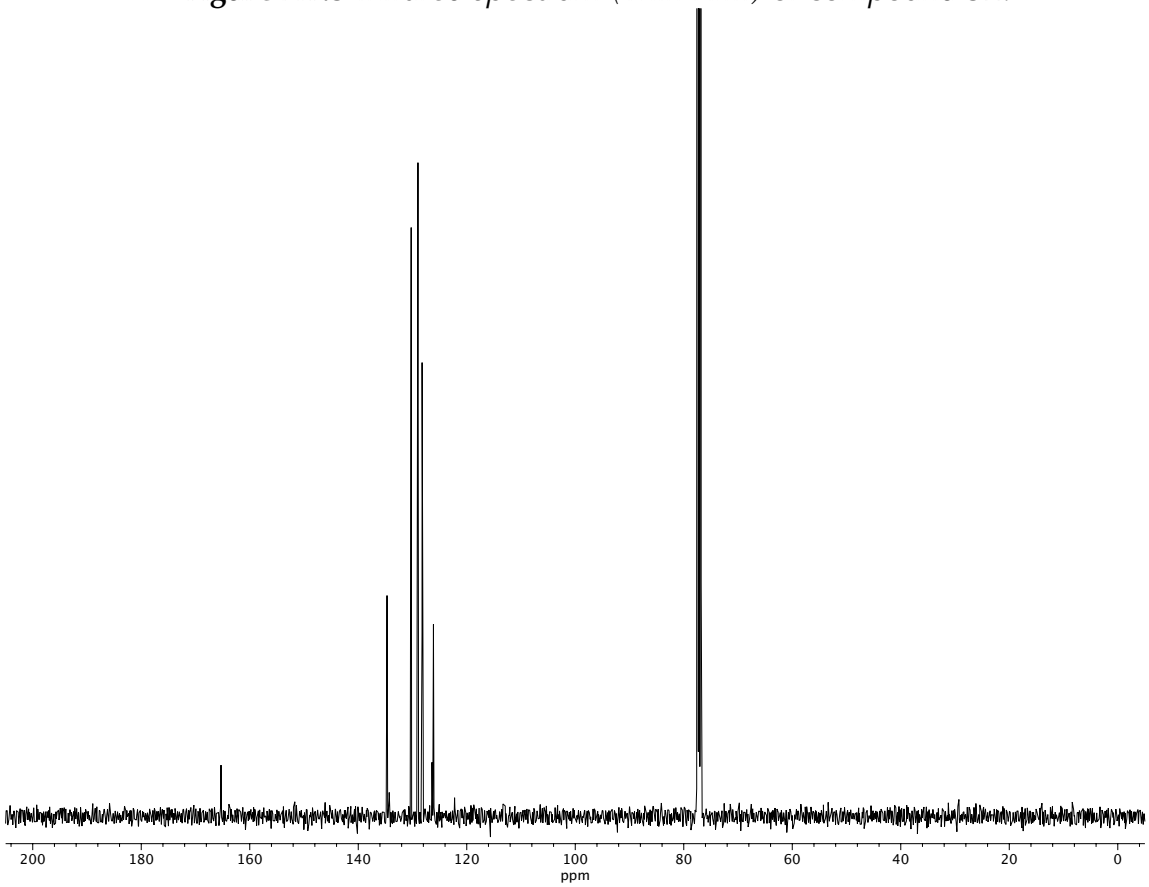


Figure A1.10 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***92***.

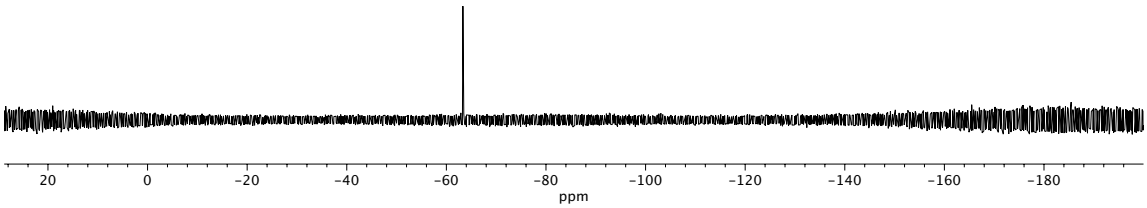


Figure A1.11 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***92****.*

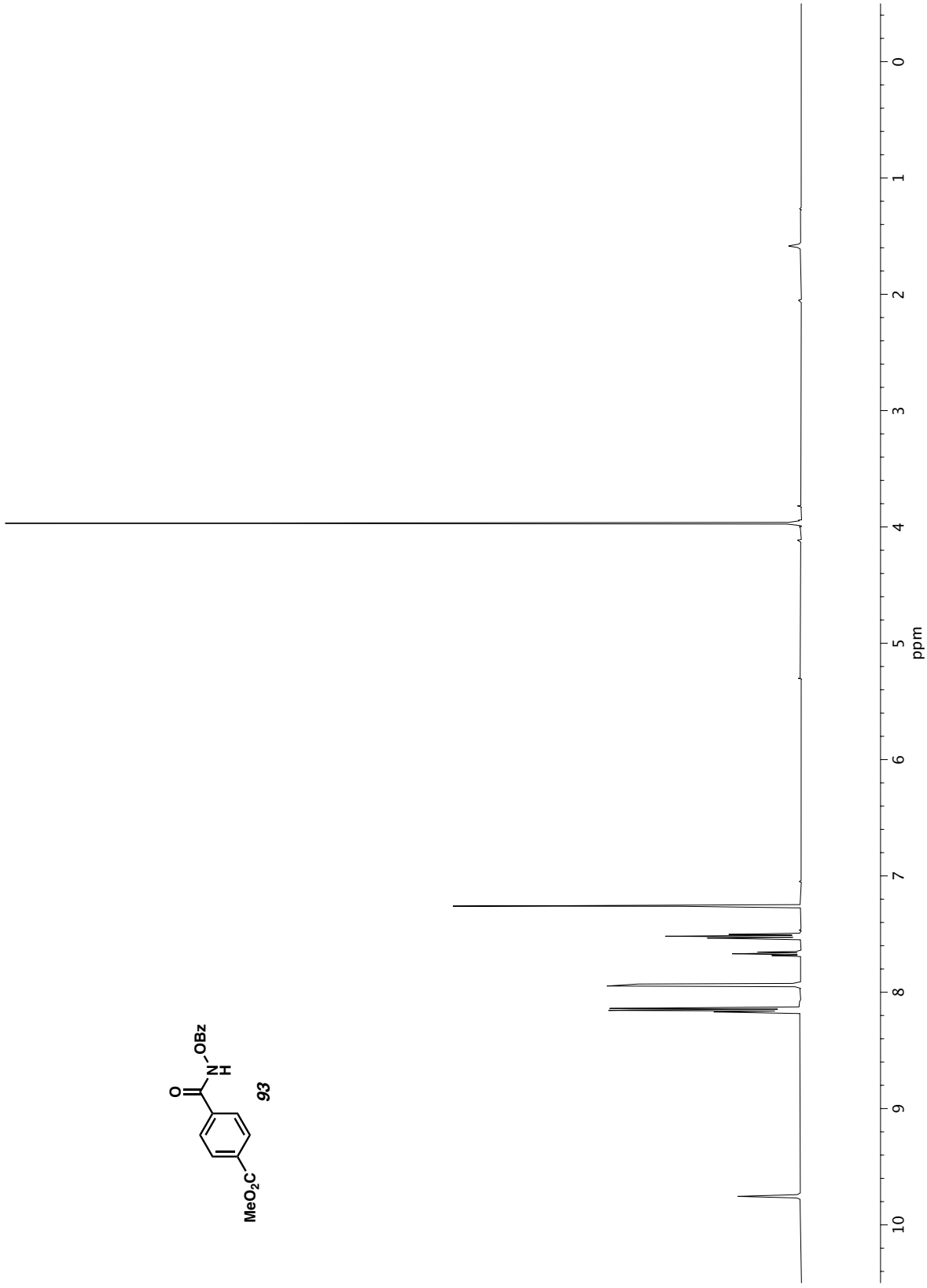


Figure A1.12 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***93***.

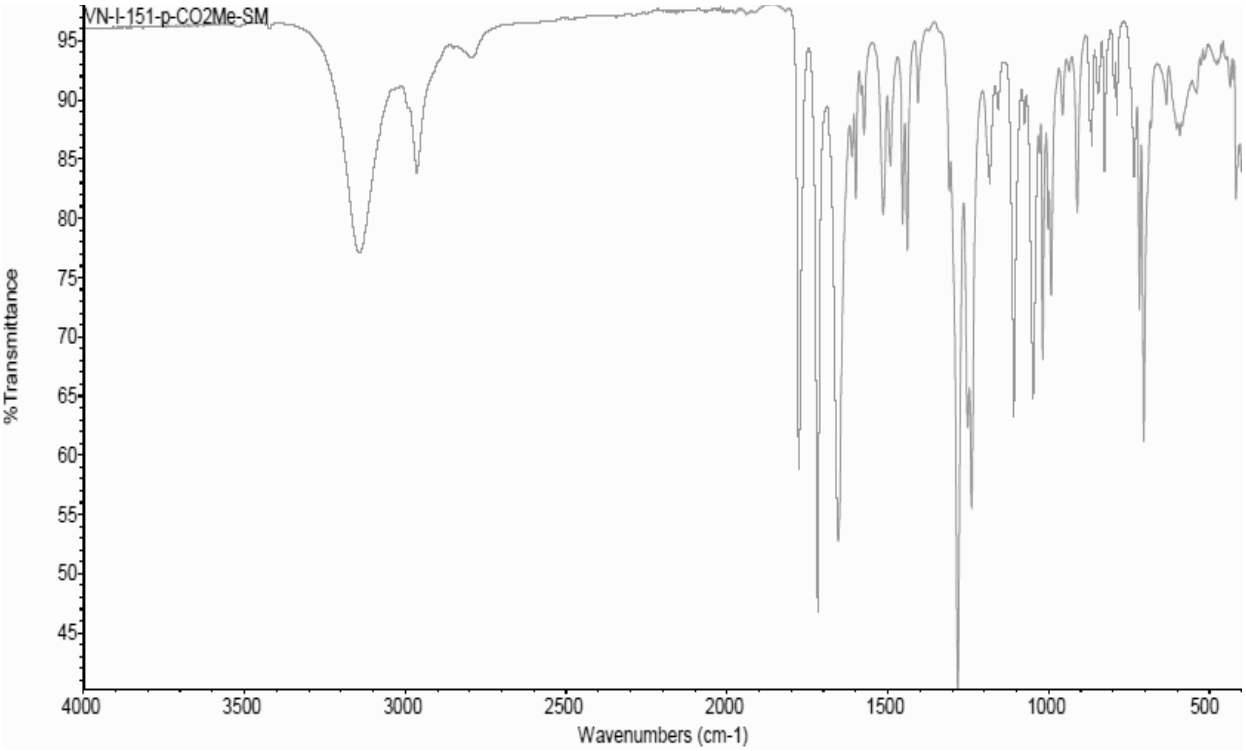


Figure A1.13 *Infrared spectrum (Thin Film) of compound* ***93***.

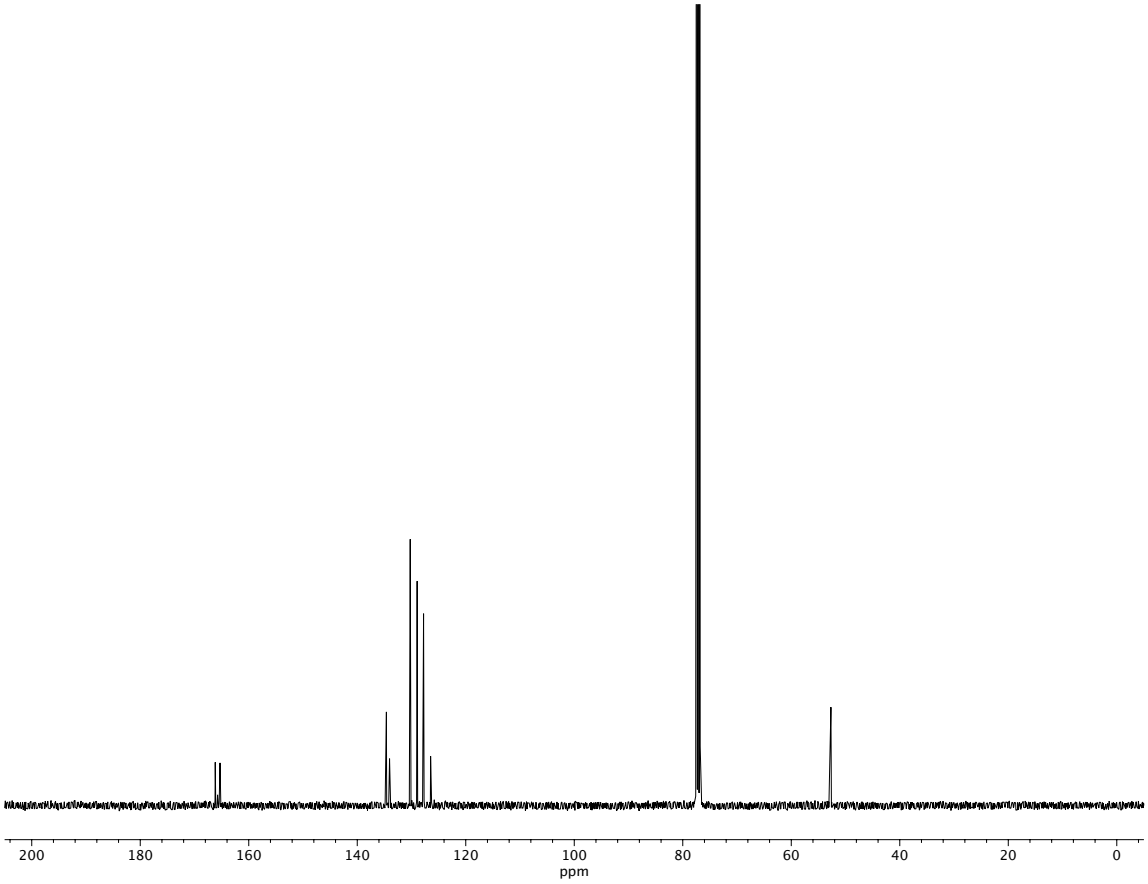


Figure A1.14 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***93***.

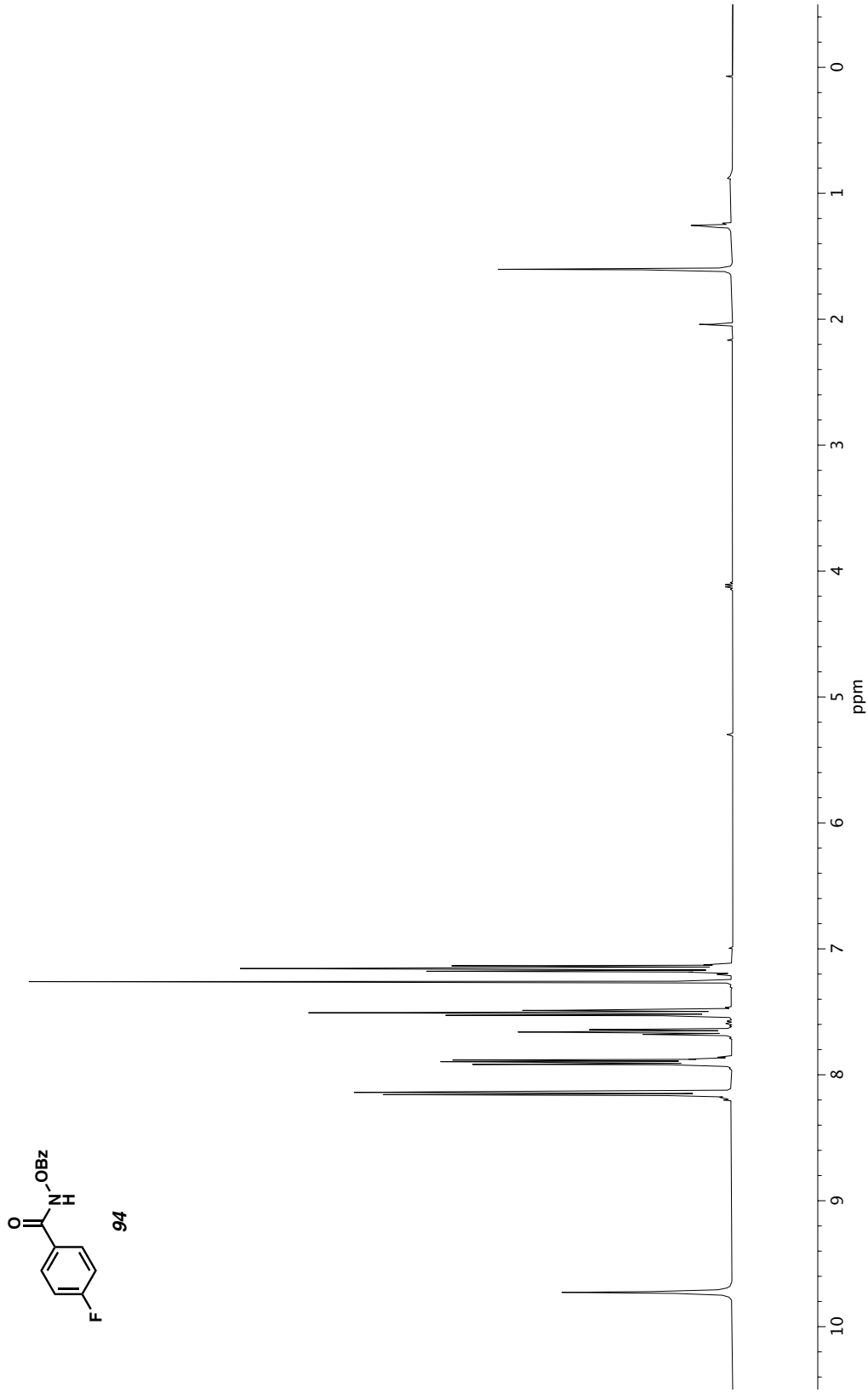


Figure A1.15 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***94***.

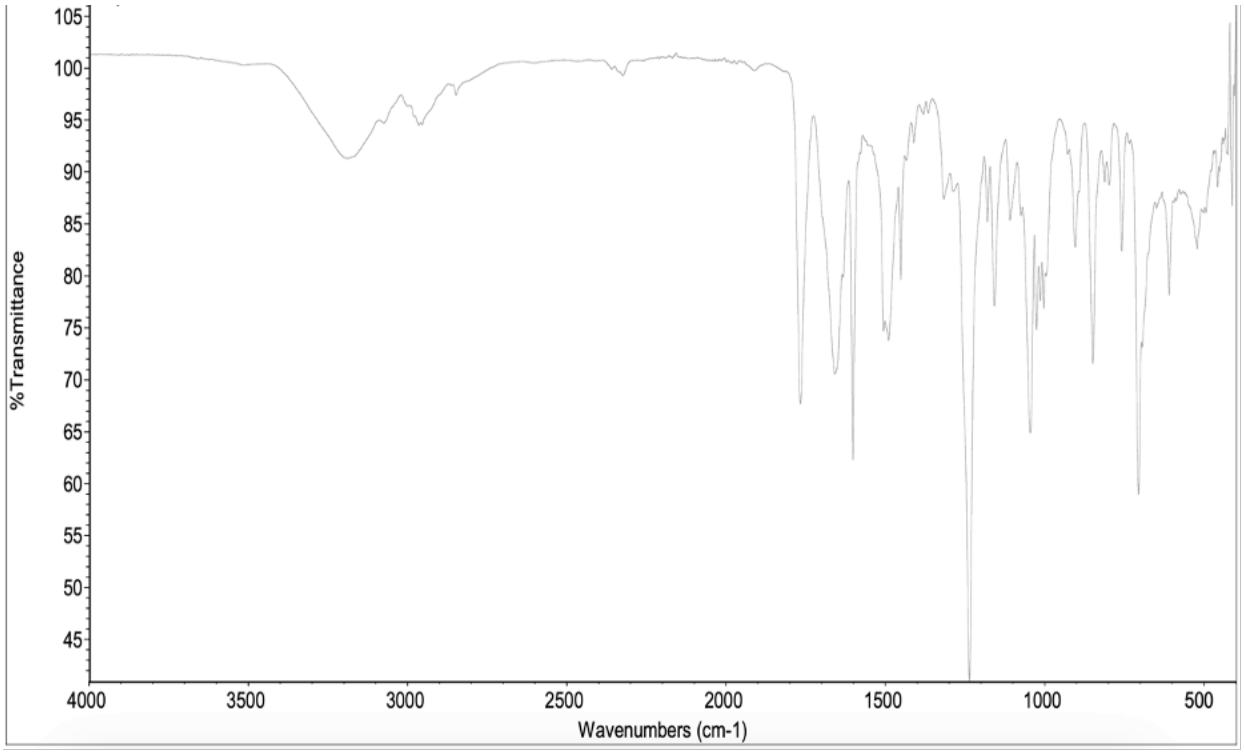


Figure A1.16 *Infrared spectrum (Thin Film) of compound* ***94***.

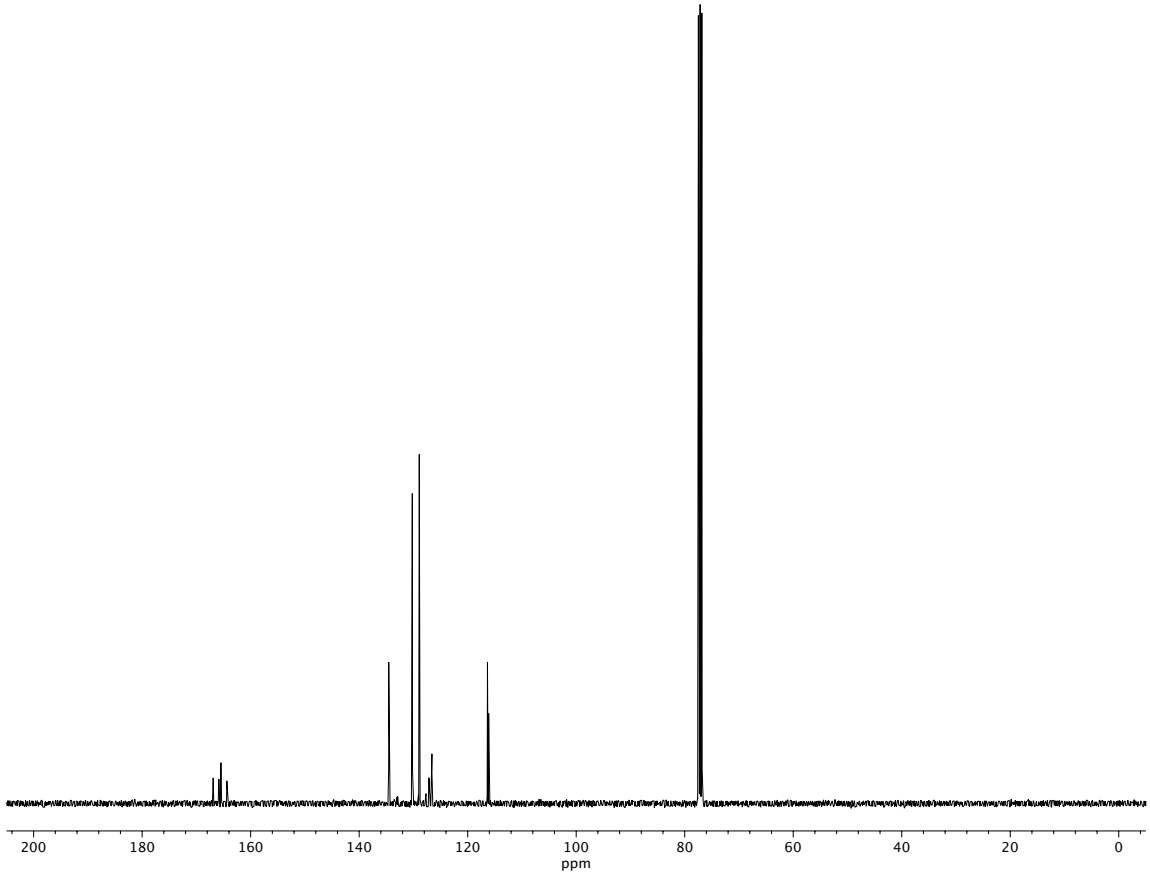


Figure A1.17 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***94***.

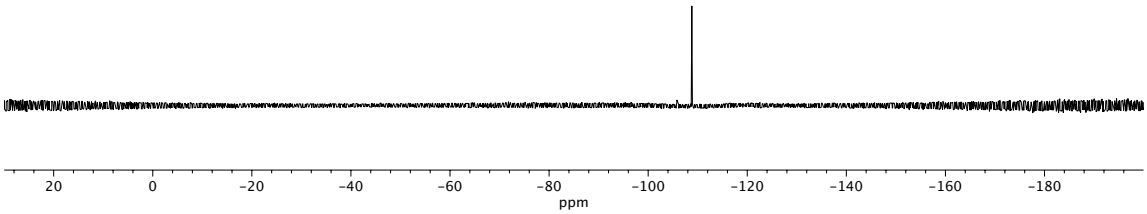


Figure A1.18 *^{19}F NMR (282 MHz, CD_3OD) of compound* ***94***.

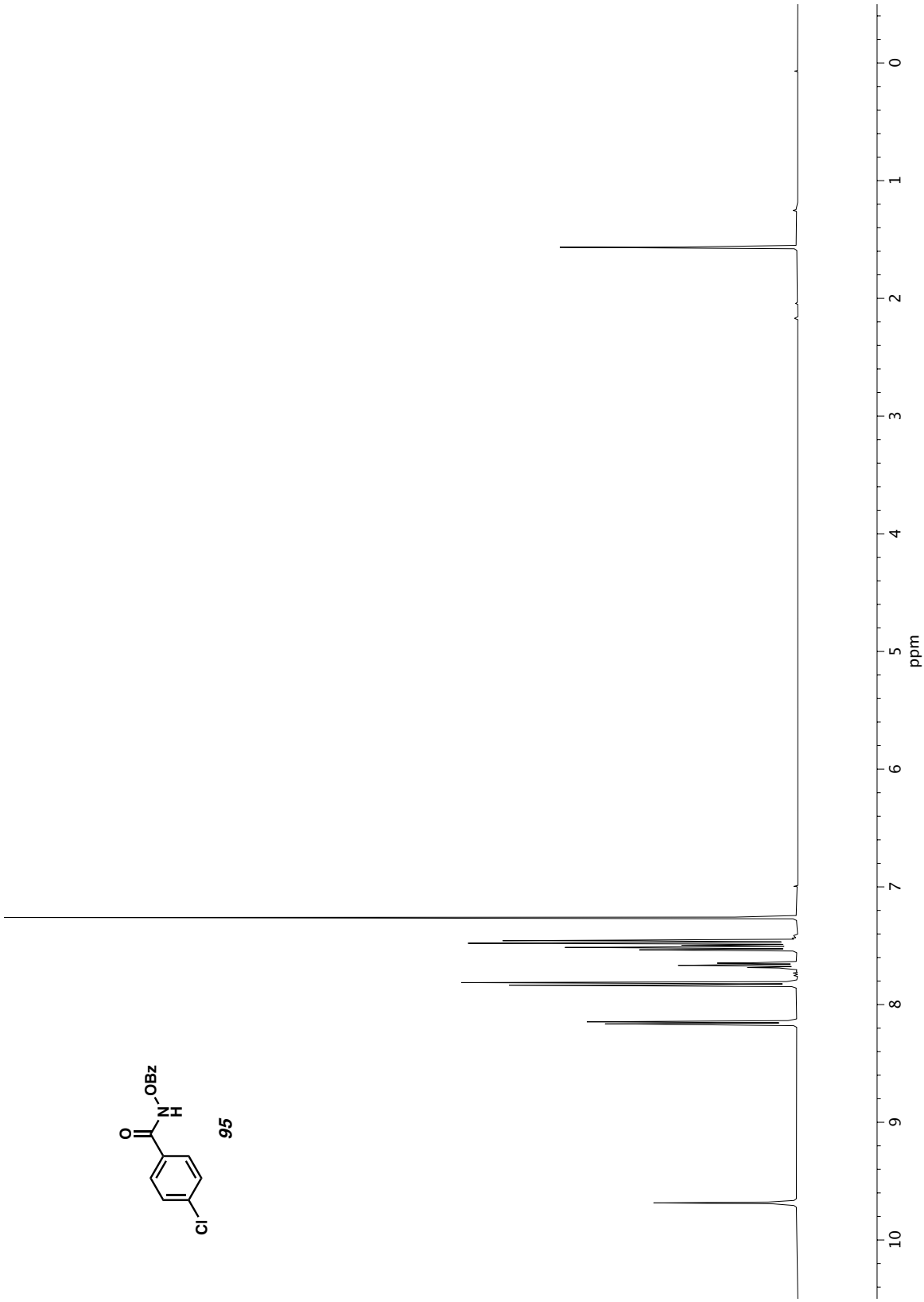


Figure A1.19 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***95***.

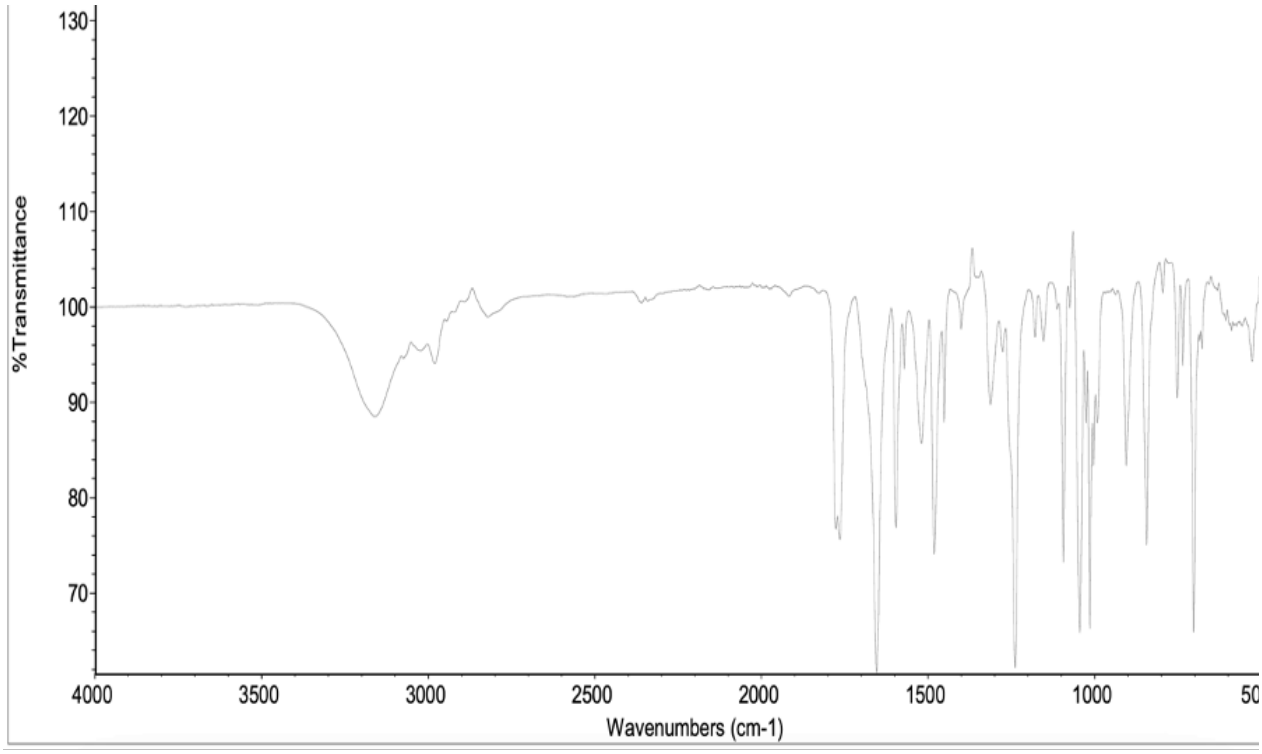


Figure A1.20 *Infrared spectrum (Thin Film) of compound* ***95***.

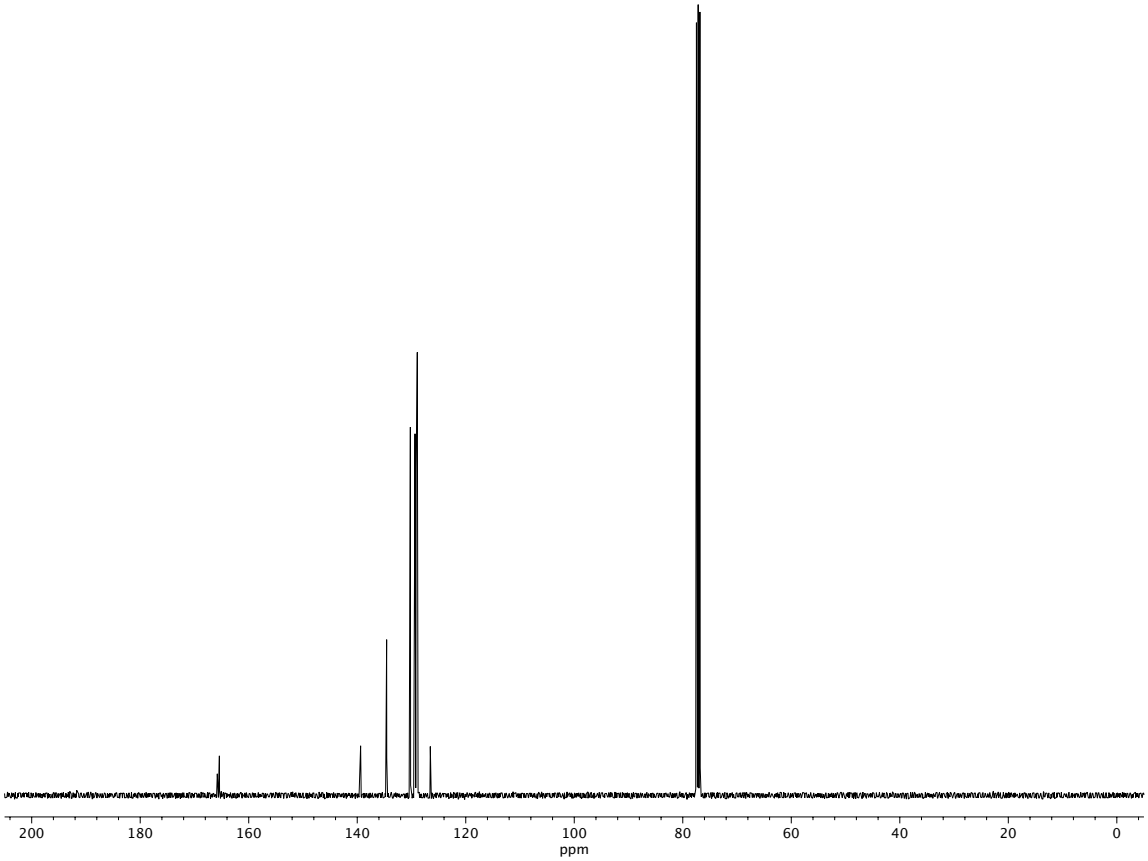


Figure A1.21 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***95***.

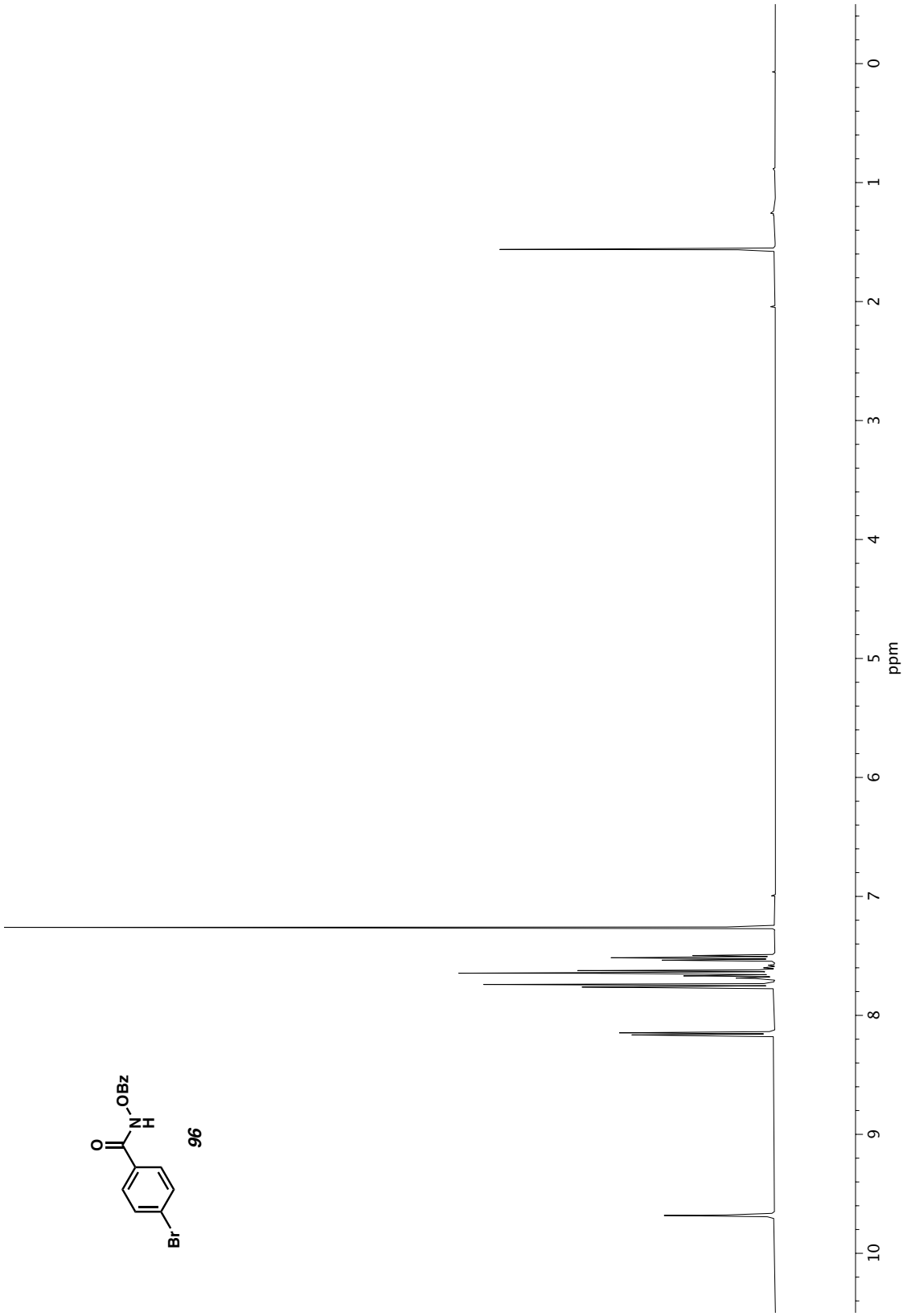


Figure A1.22 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***96***.

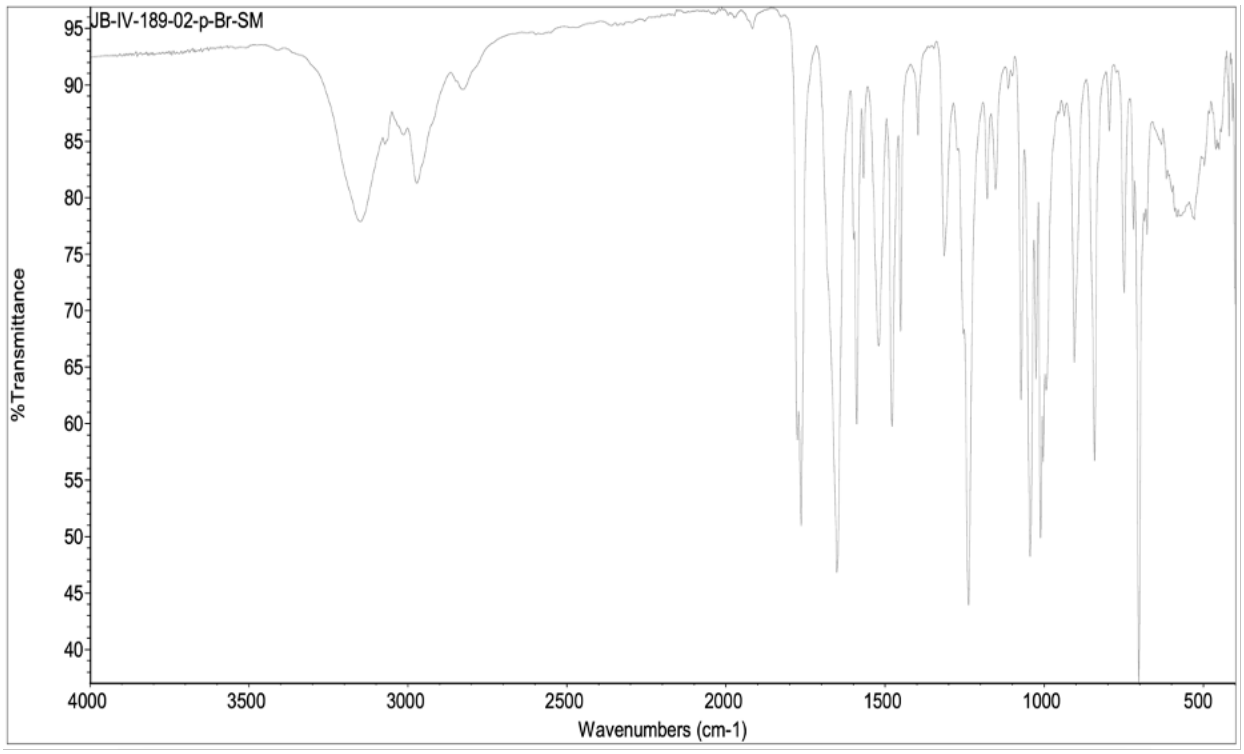


Figure A1.23 *Infrared spectrum (Thin Film) of compound* ***96***.

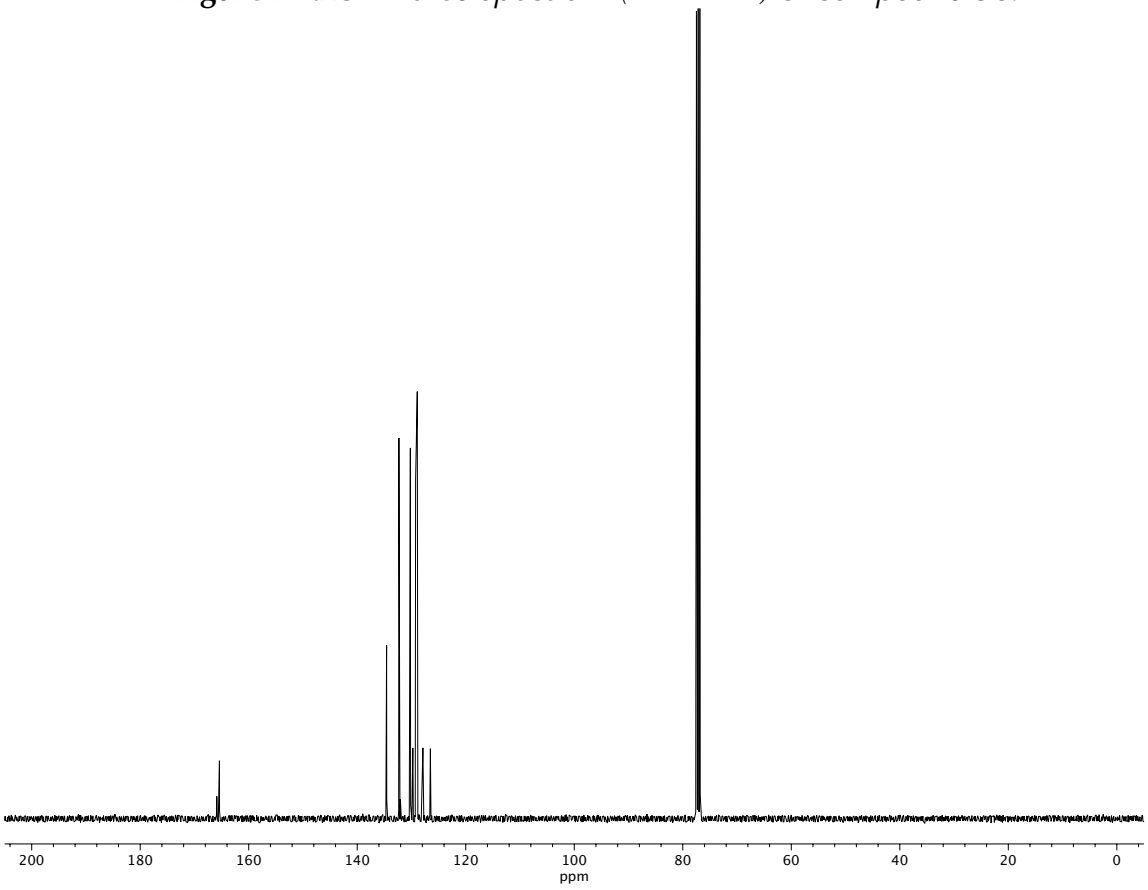


Figure A1.24 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***96***.

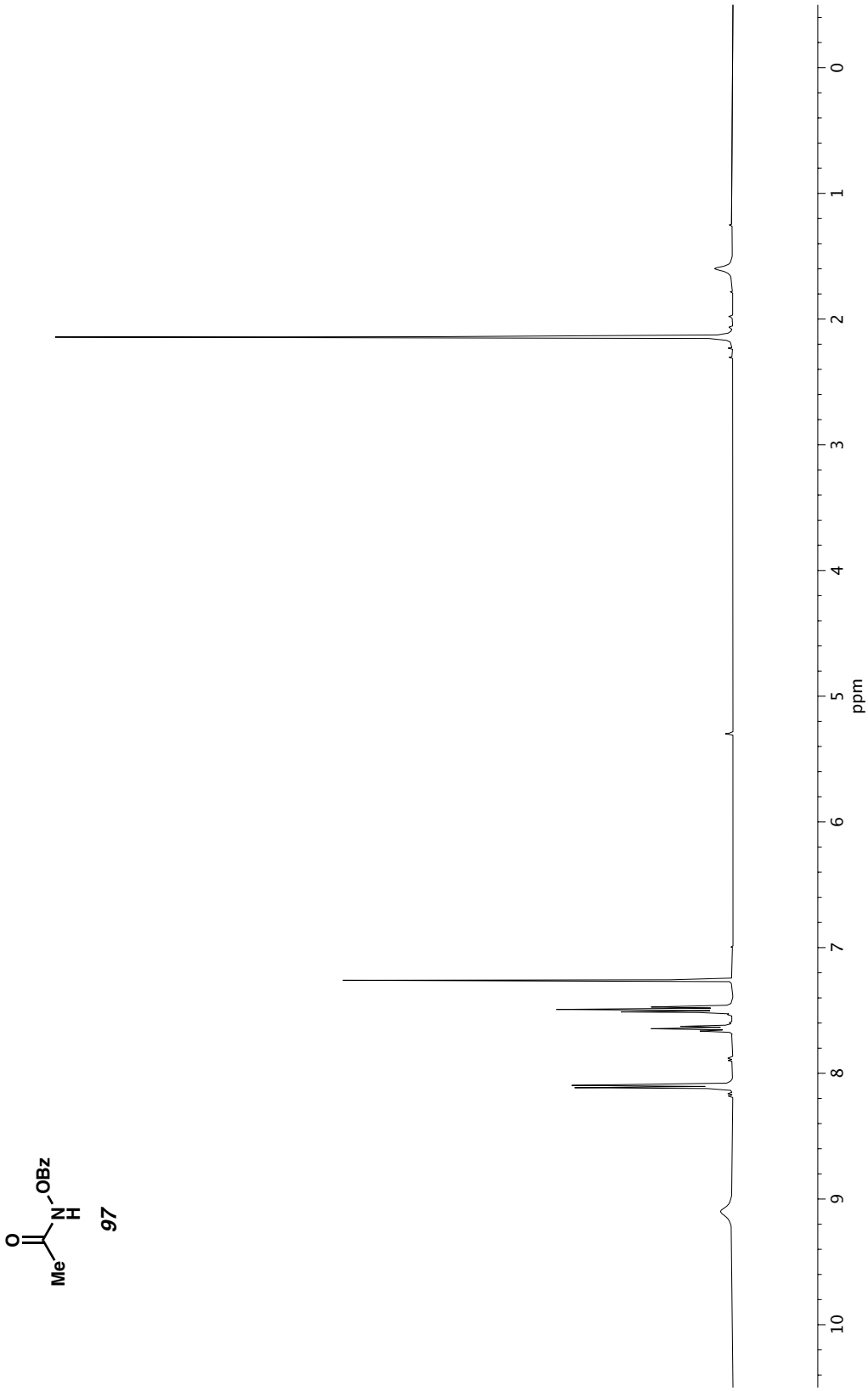


Figure A1.25 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***97****.*

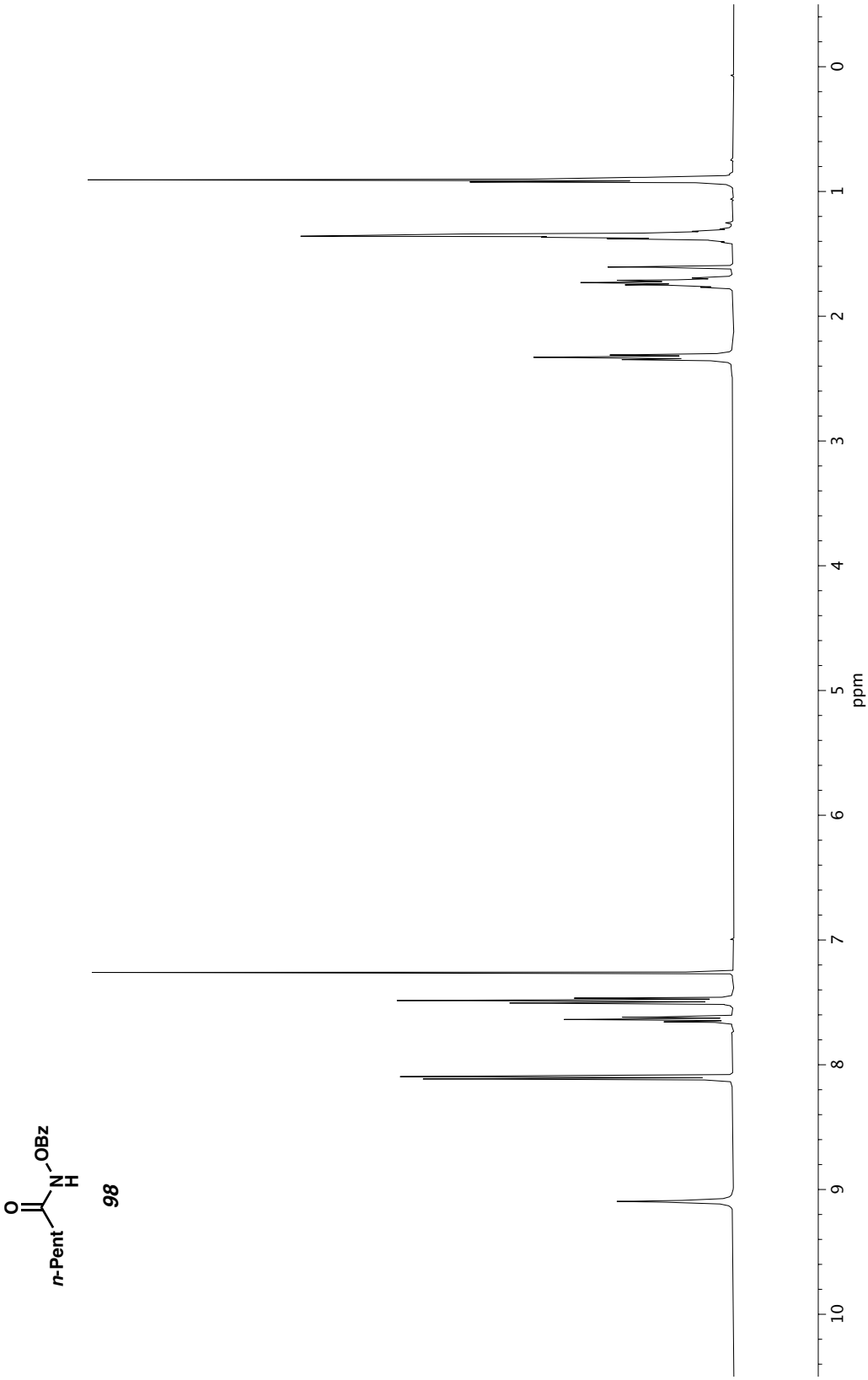


Figure A1.26 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***98****.*

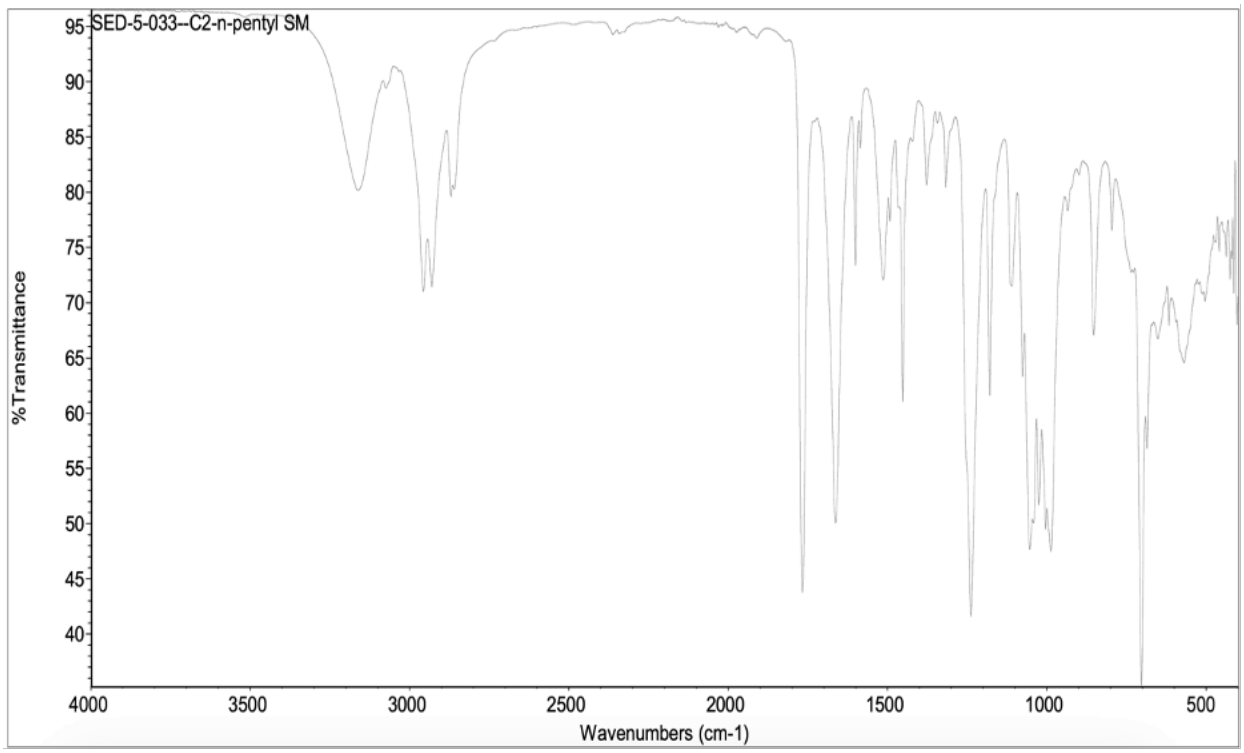


Figure A1.27 *Infrared spectrum (Thin Film) of compound* ***98***.

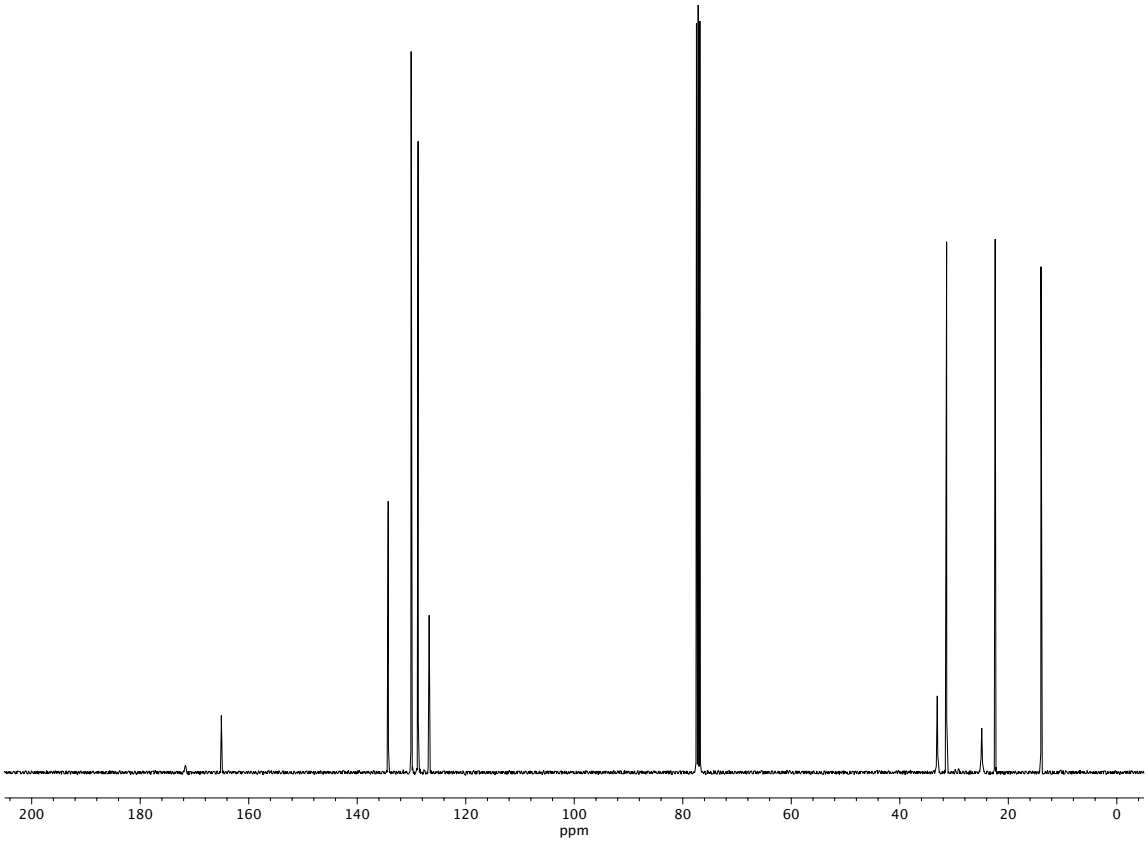


Figure A1.28 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***98***.

Figure A1.29 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***99***.

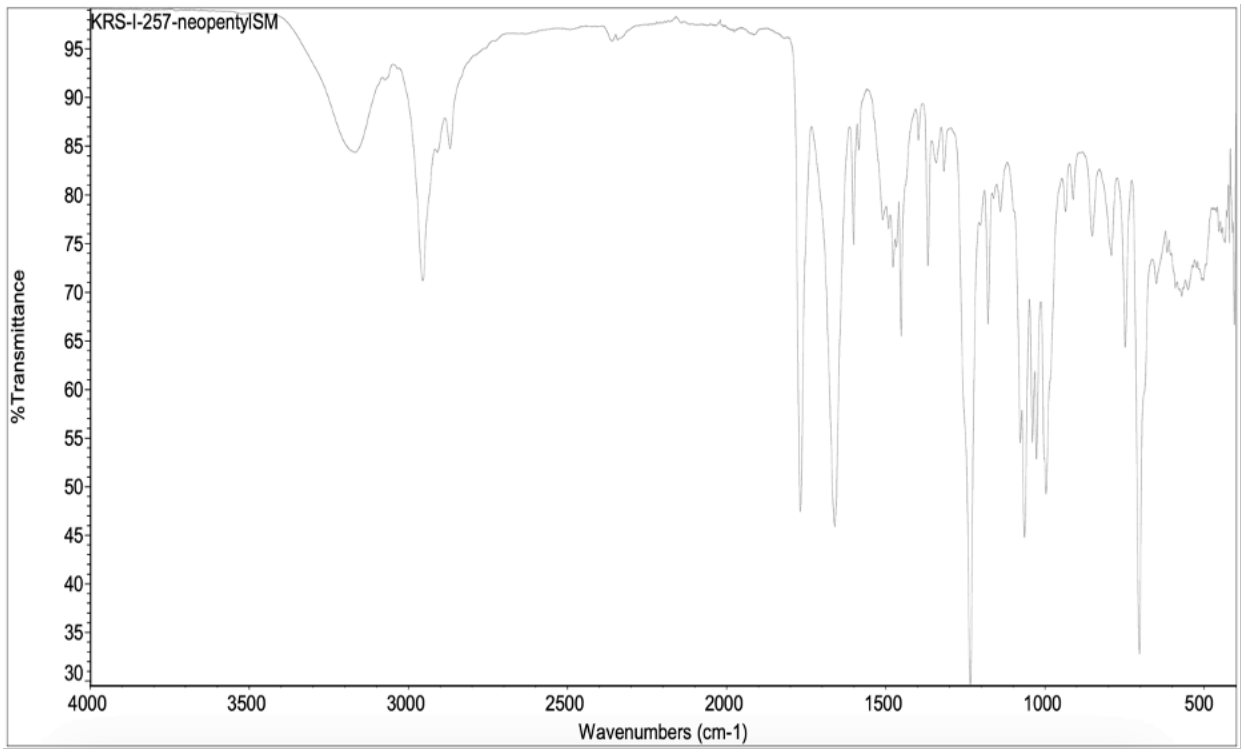


Figure A1.30 *Infrared spectrum (Thin Film) of compound* ***99***.

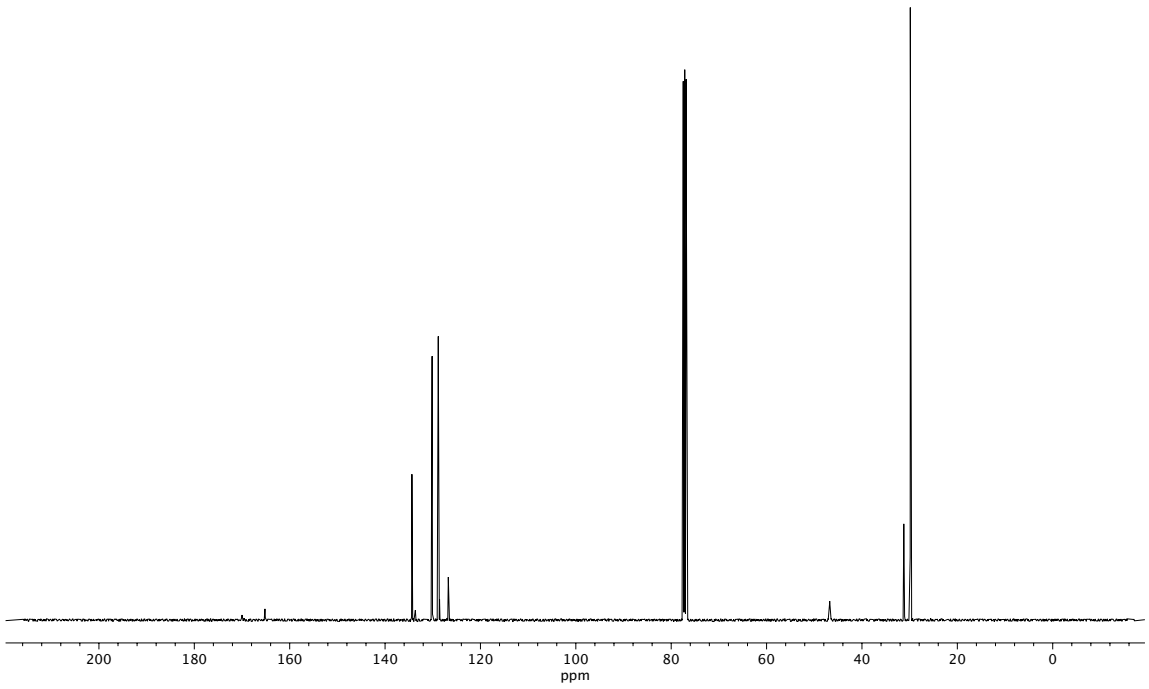


Figure A1.31 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***99***.

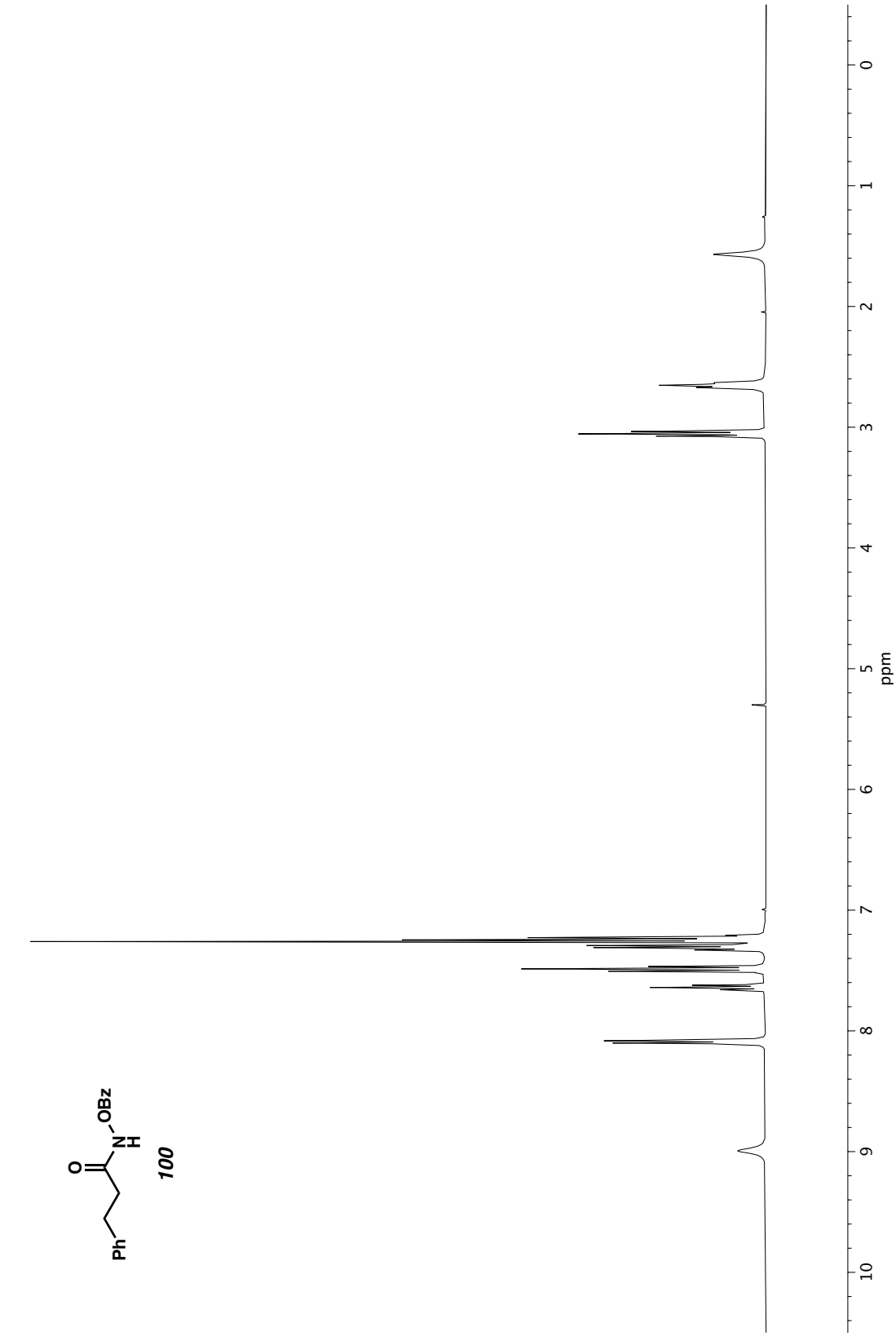


Figure A1.32 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***100***.

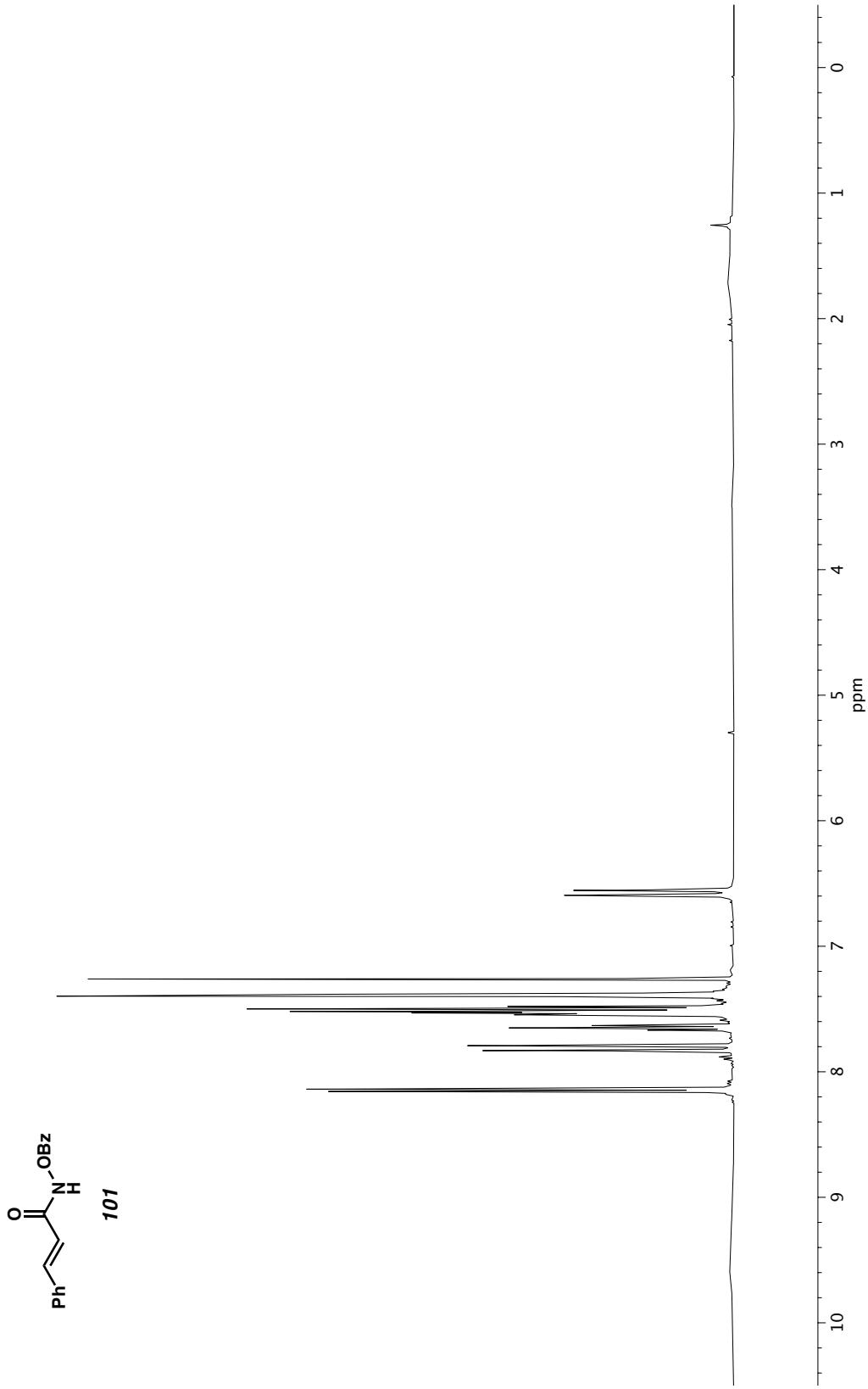


Figure A1.33 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***101***.

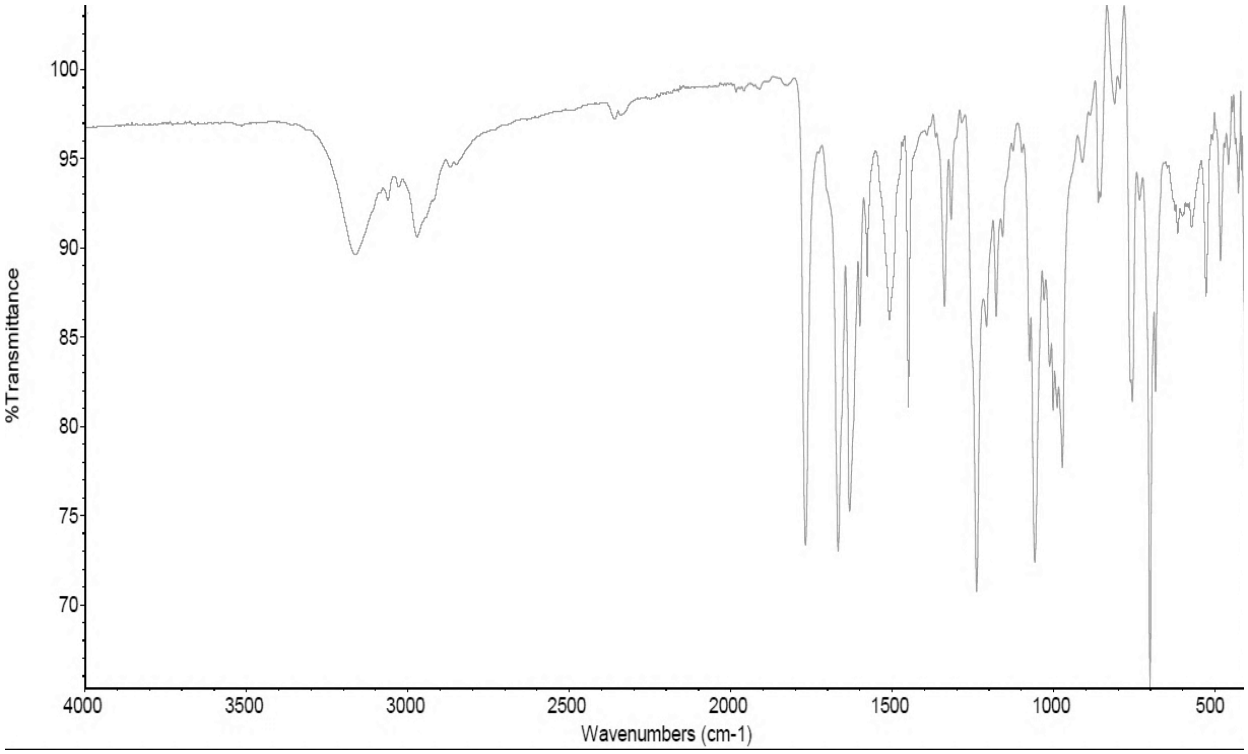


Figure A1.34 *Infrared spectrum (Thin Film) of compound* ***101***.

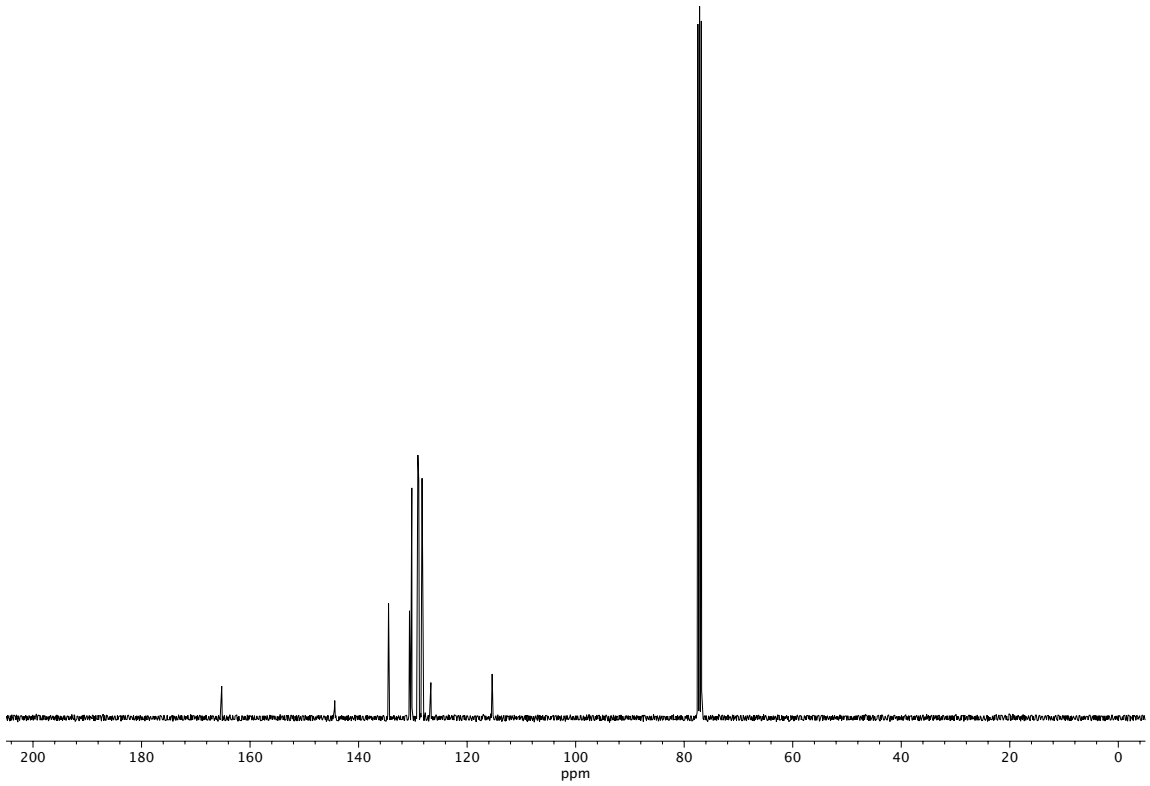


Figure A1.35 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***101***.

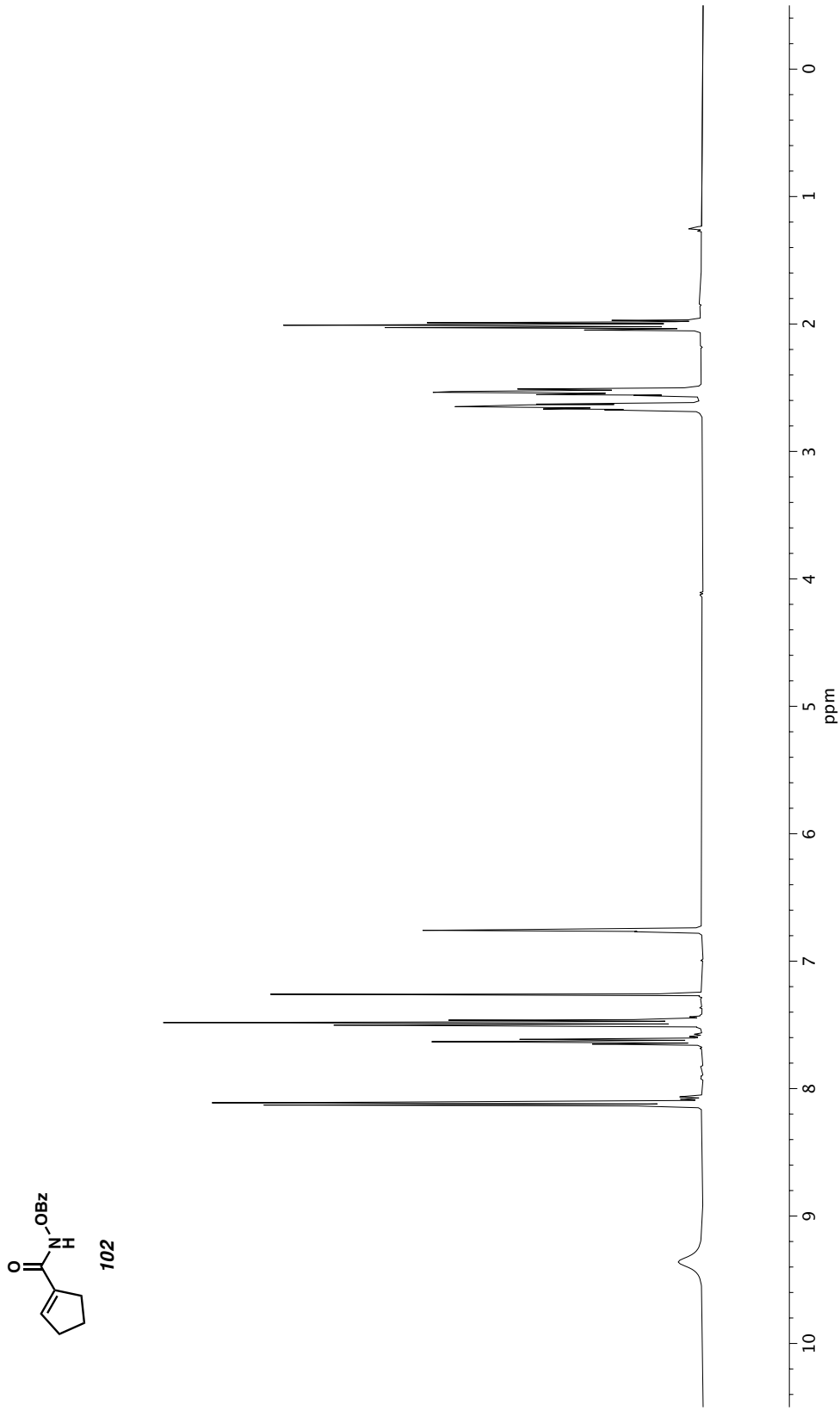


Figure A1.36 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***102***.

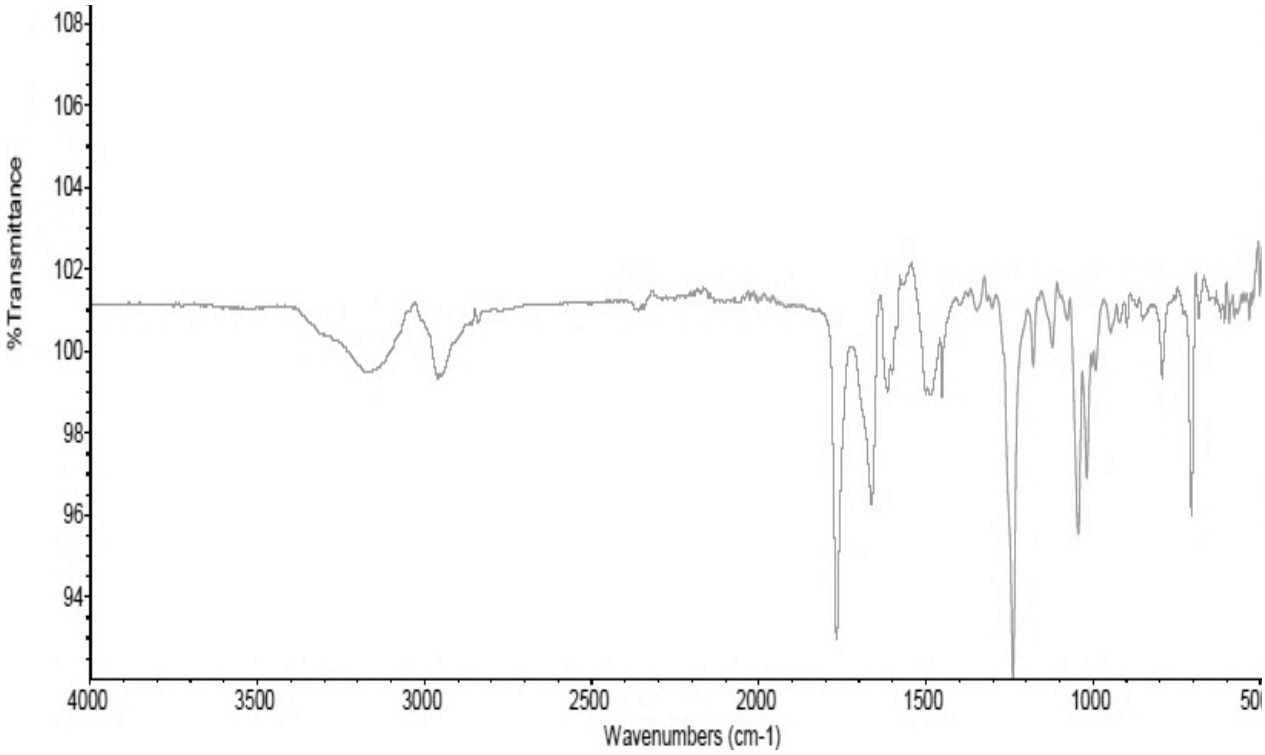


Figure A1.37 *Infrared spectrum (Thin Film) of compound* ***102***.

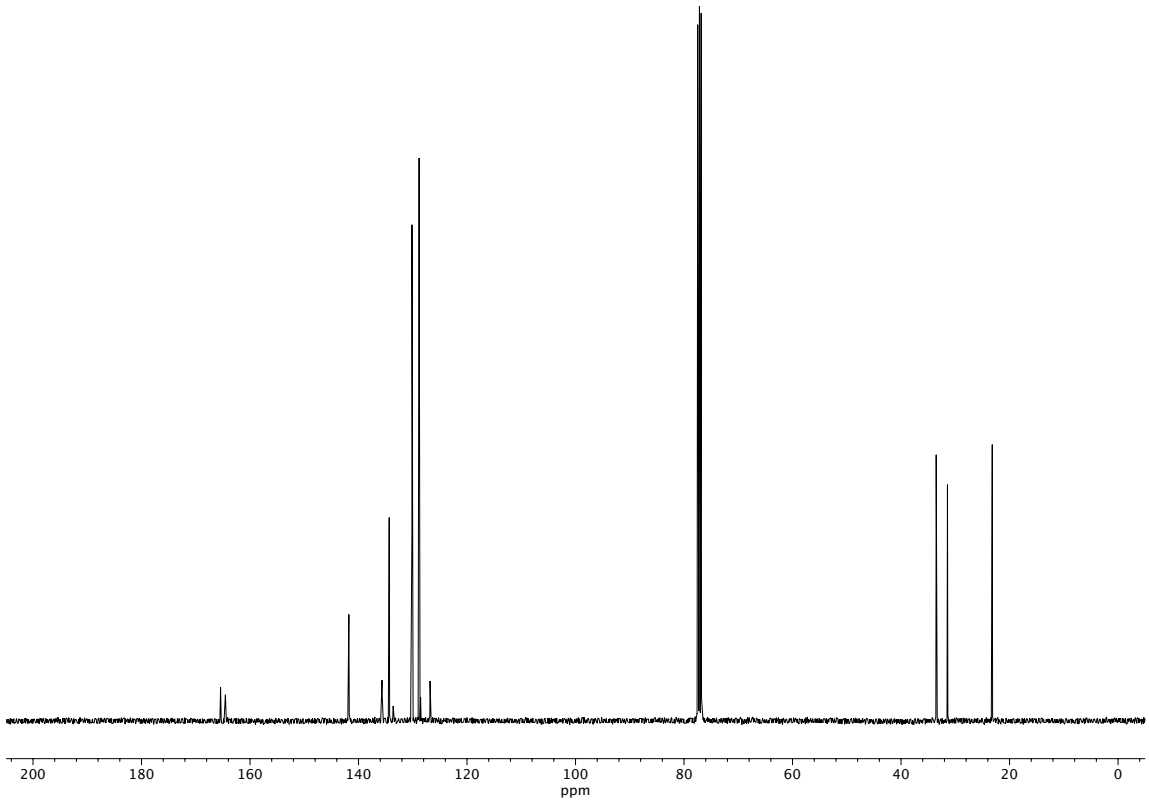


Figure A1.38 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***102***.

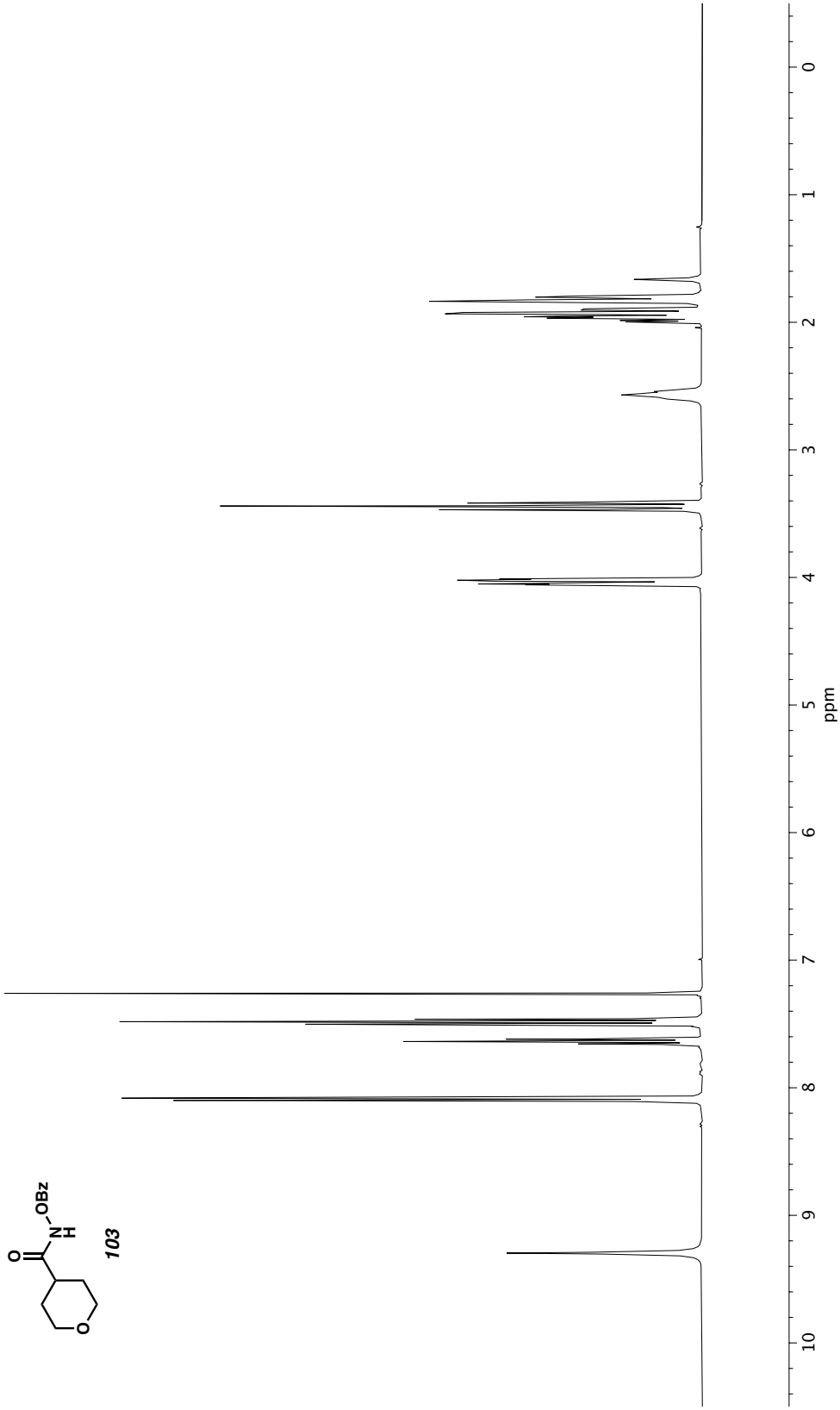


Figure A1.39 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***103.***

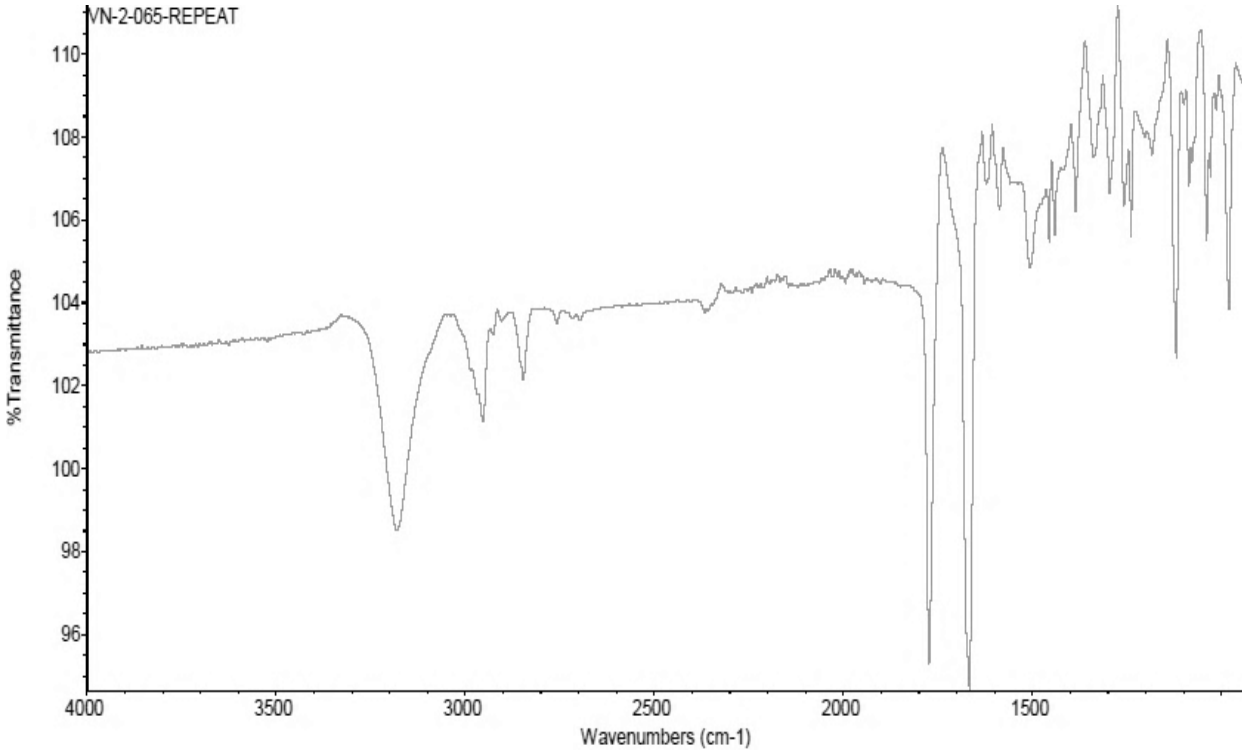


Figure A1.40 *Infrared spectrum (Thin Film) of compound* ***103***.

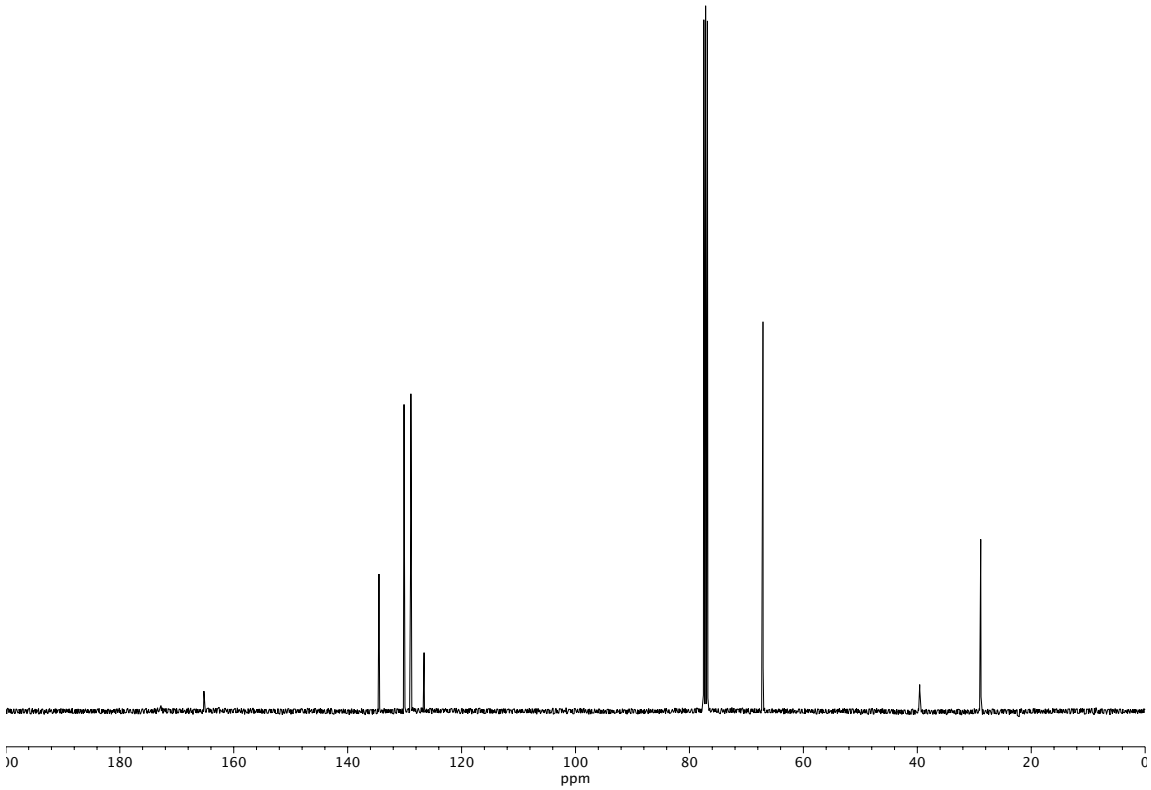


Figure A1.41 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***103***.

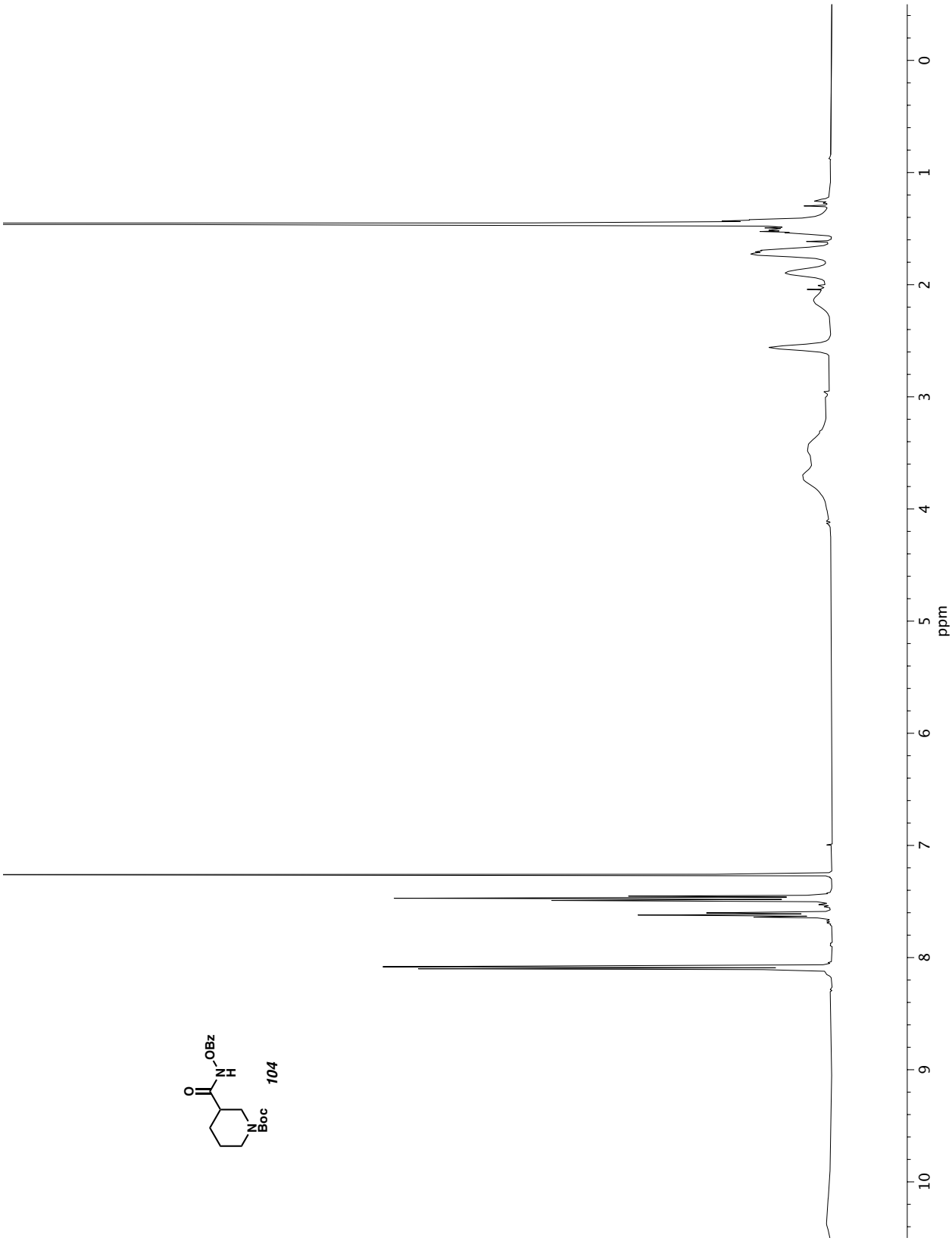


Figure A1.42 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***104****.*

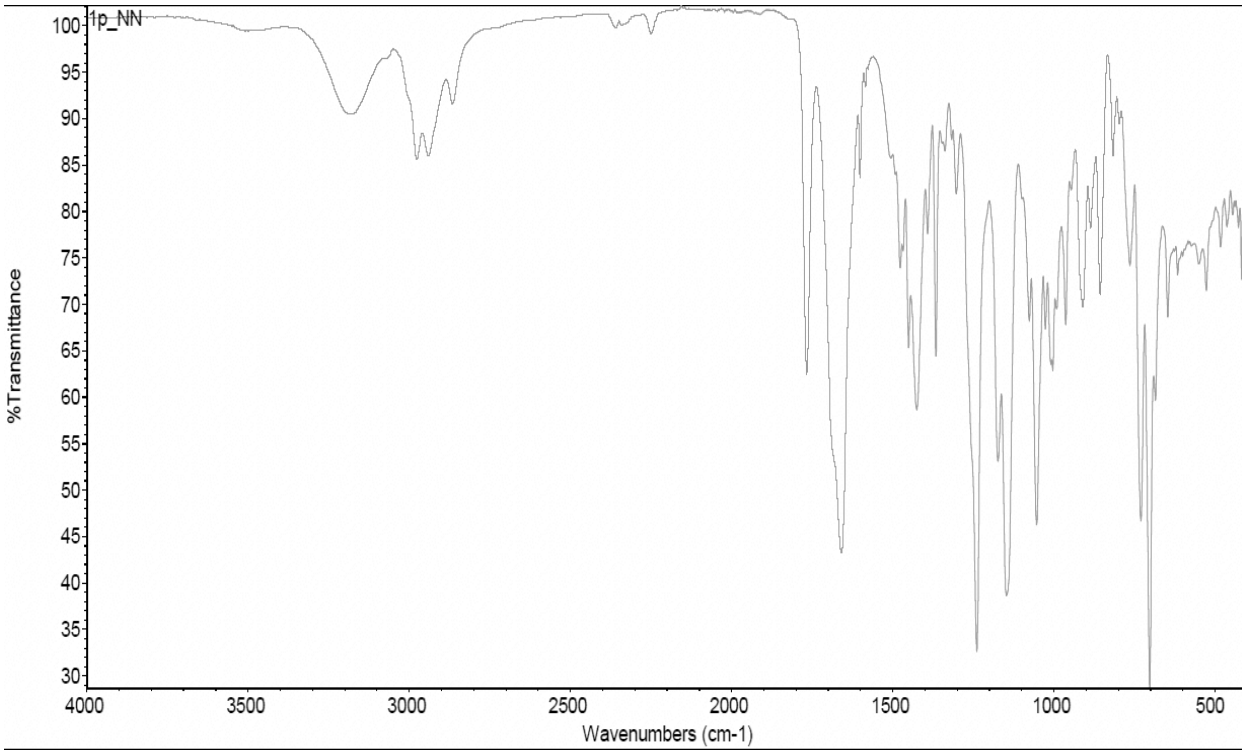


Figure A1.43 *Infrared spectrum (Thin Film) of compound* ***104****.*

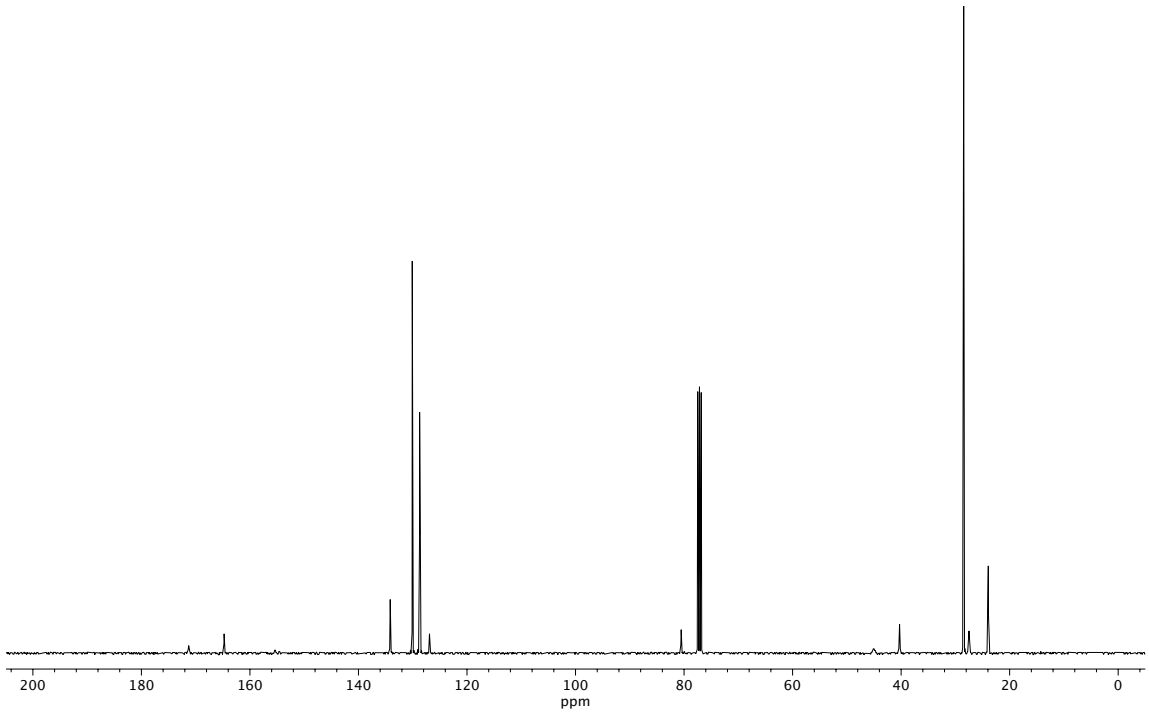


Figure A1.44 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***104****.*

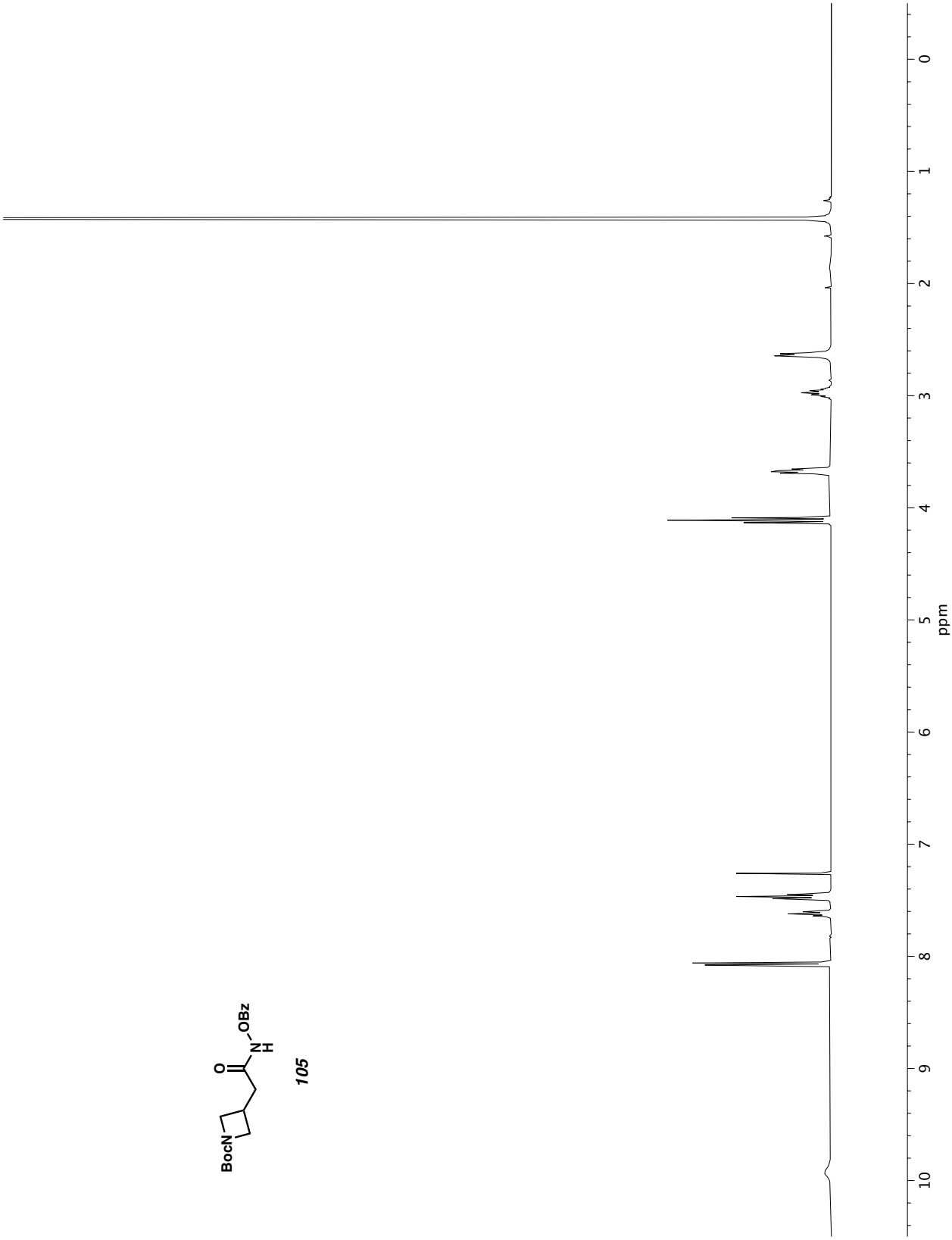


Figure A1.45 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***105***.

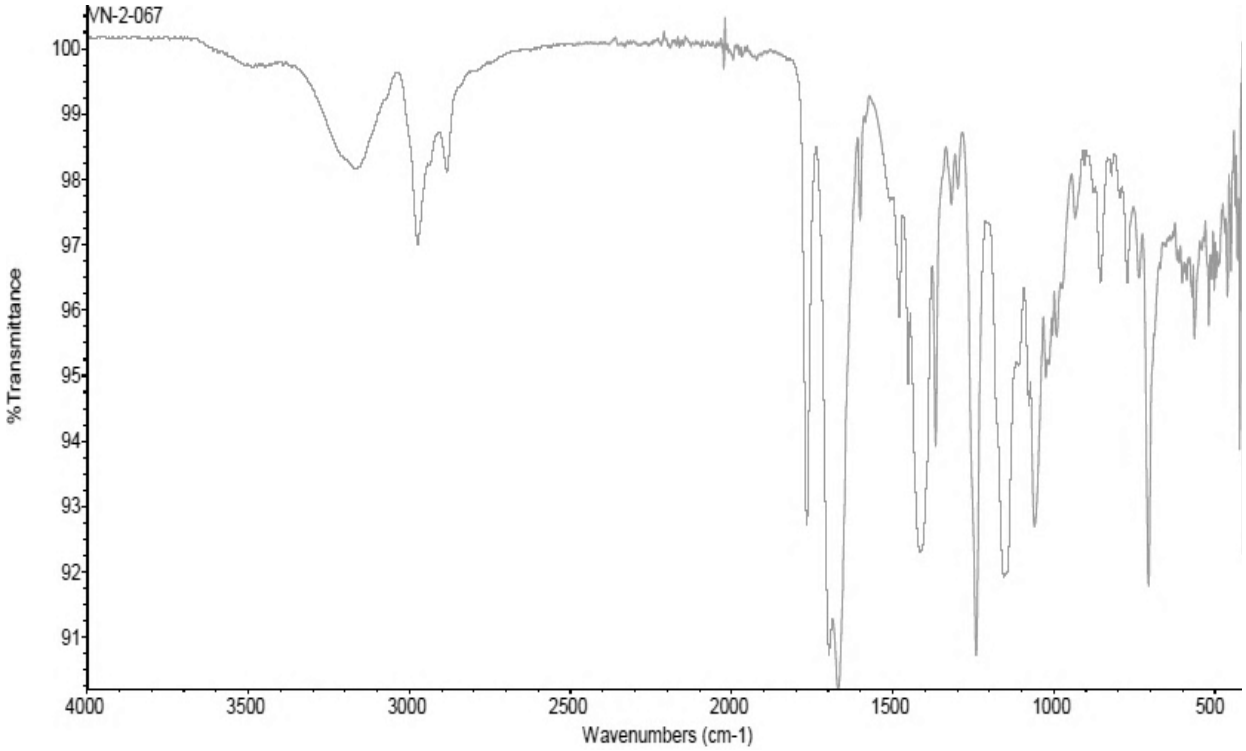


Figure A1.46 *Infrared spectrum (Thin Film) of compound* ***105***.

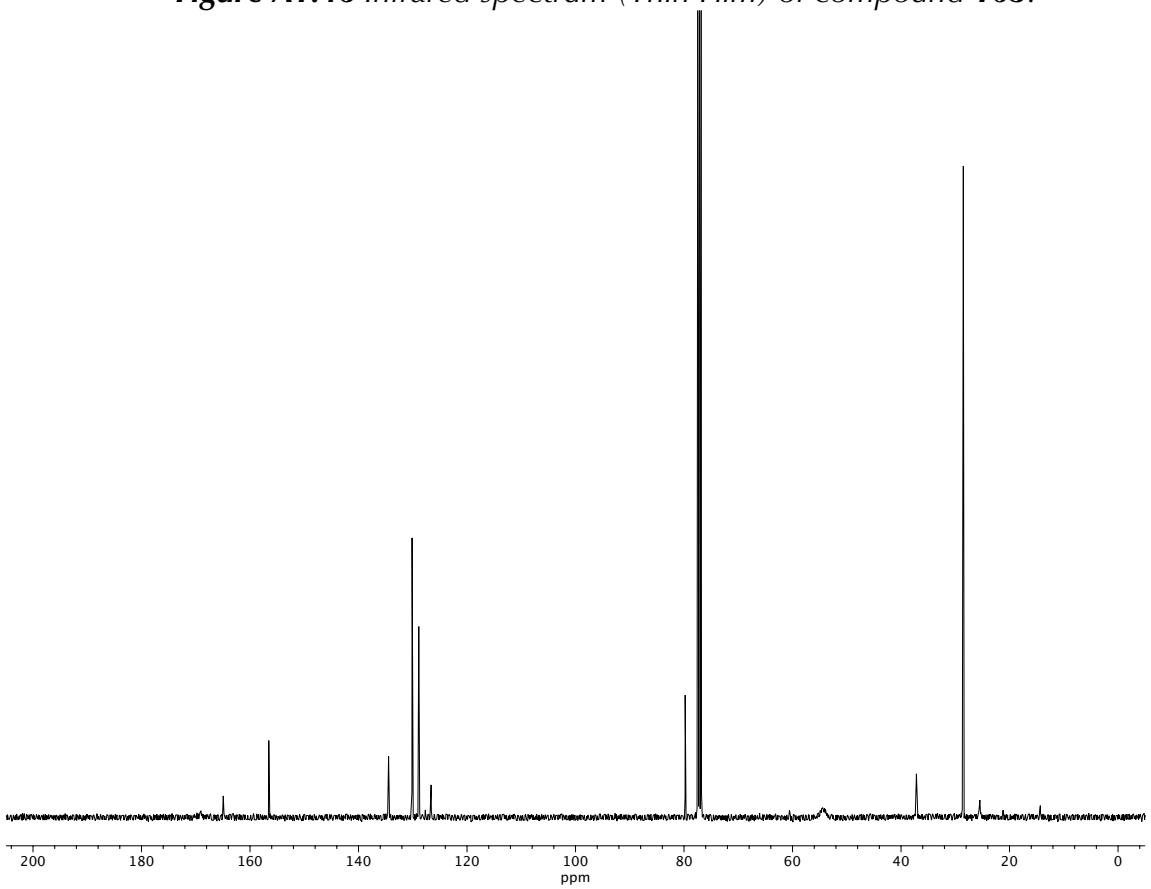


Figure A1.47 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***105***.

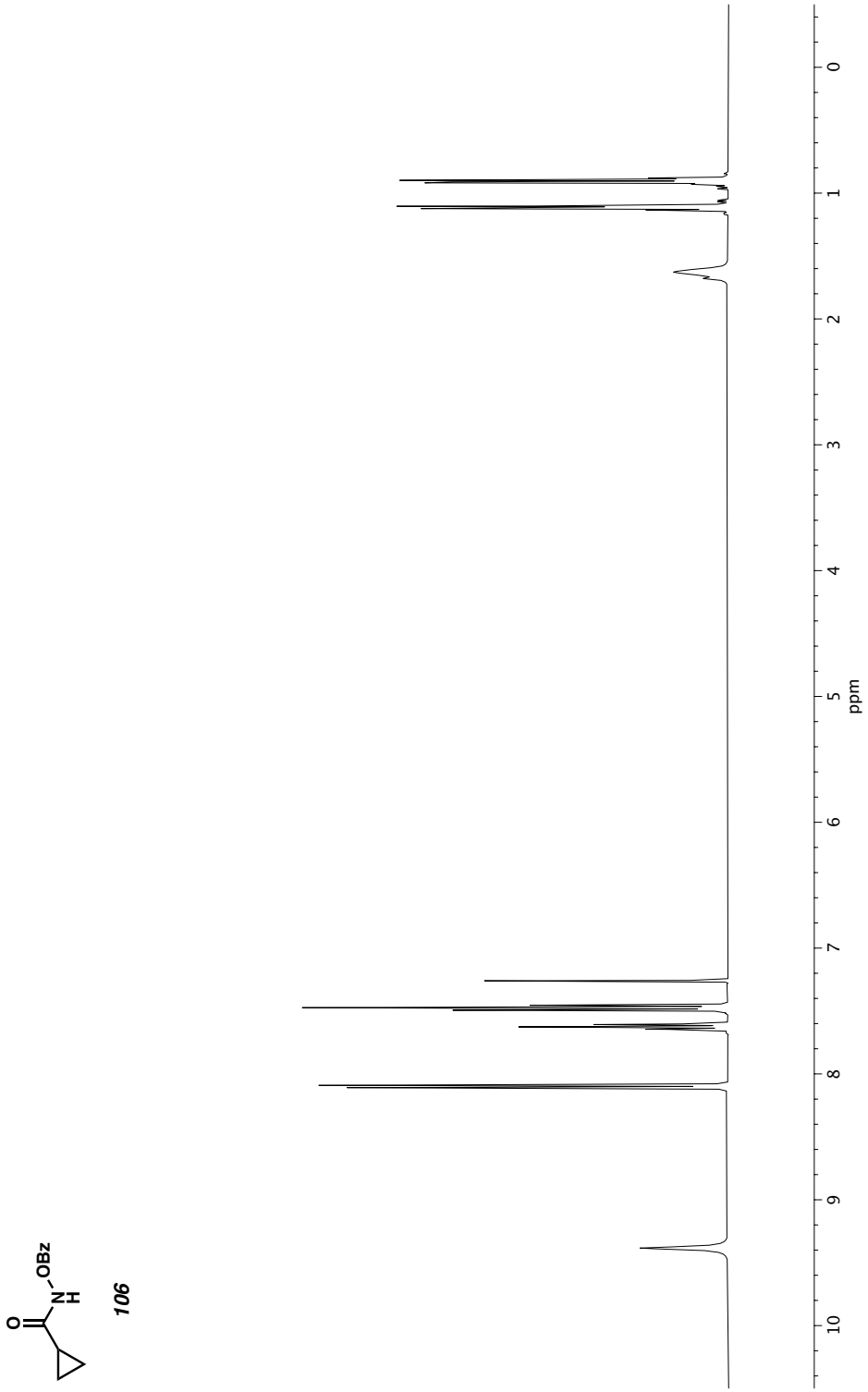


Figure A1.48 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***106****.*

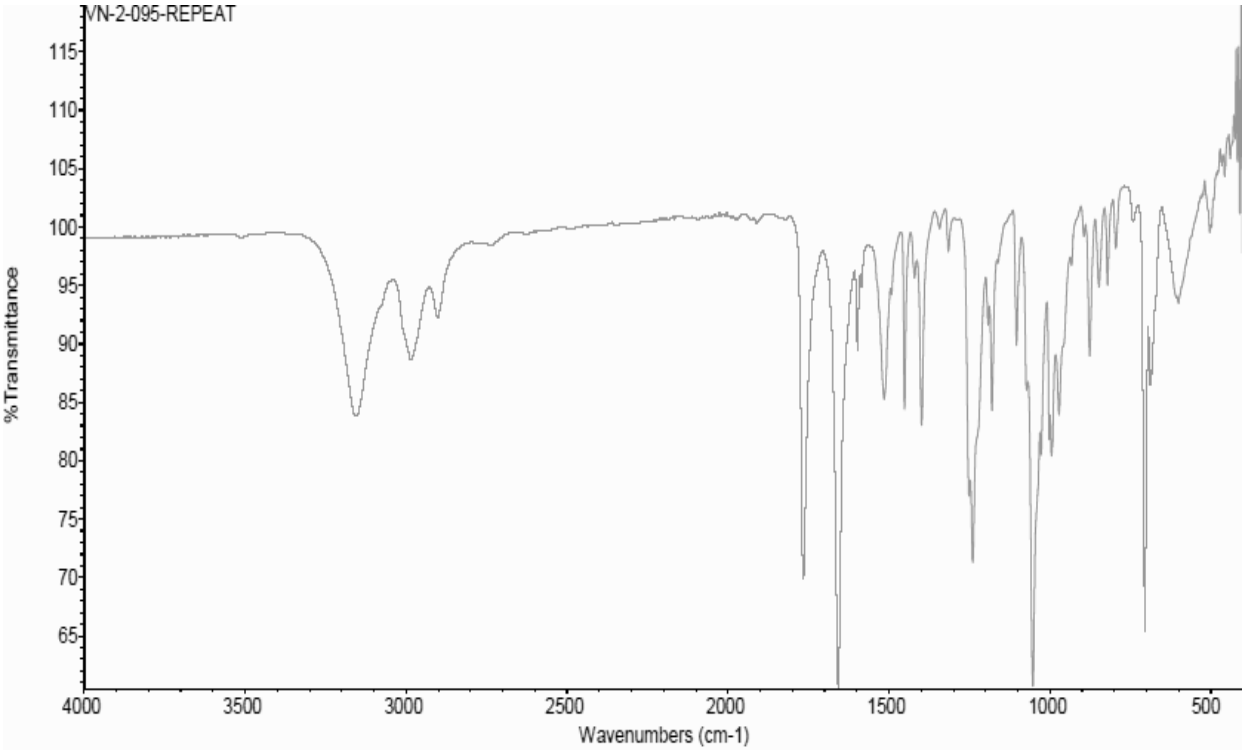


Figure A1.49 *Infrared spectrum (Thin Film) of compound* ***106***.

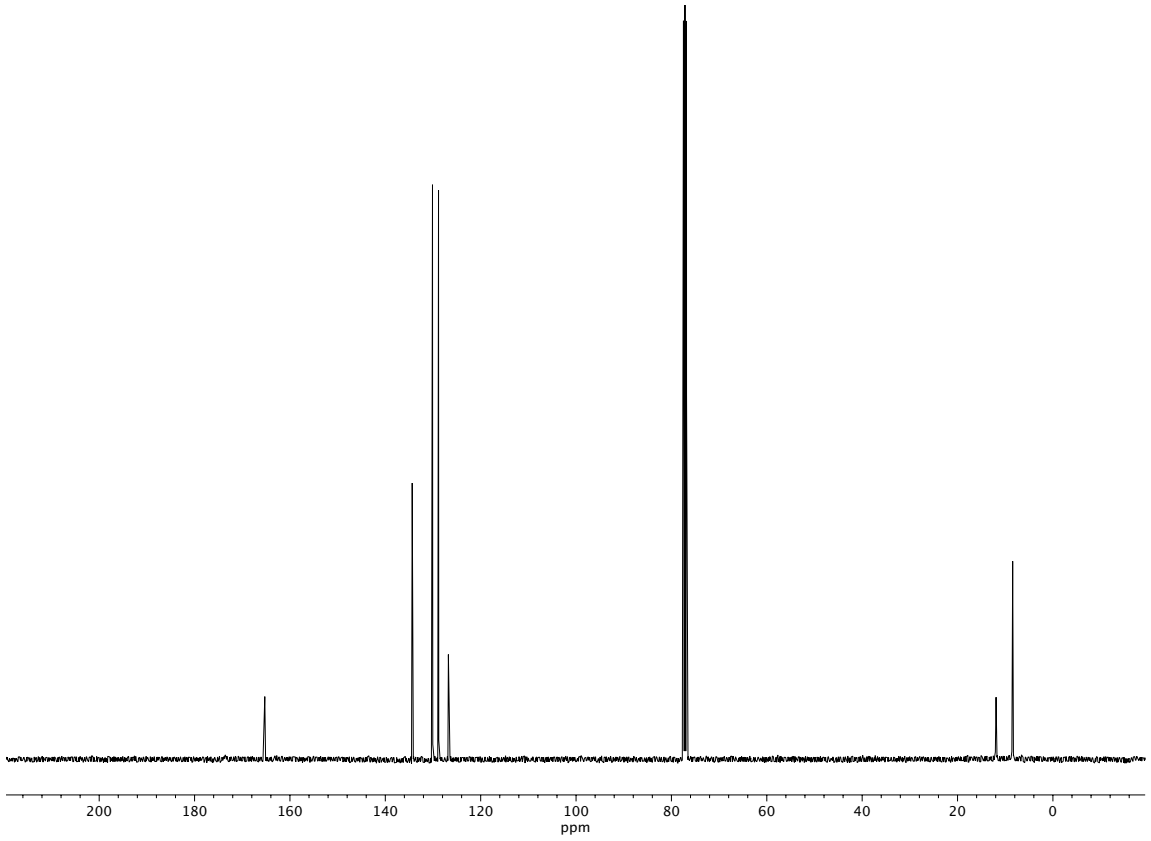


Figure A1.50 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***106***.

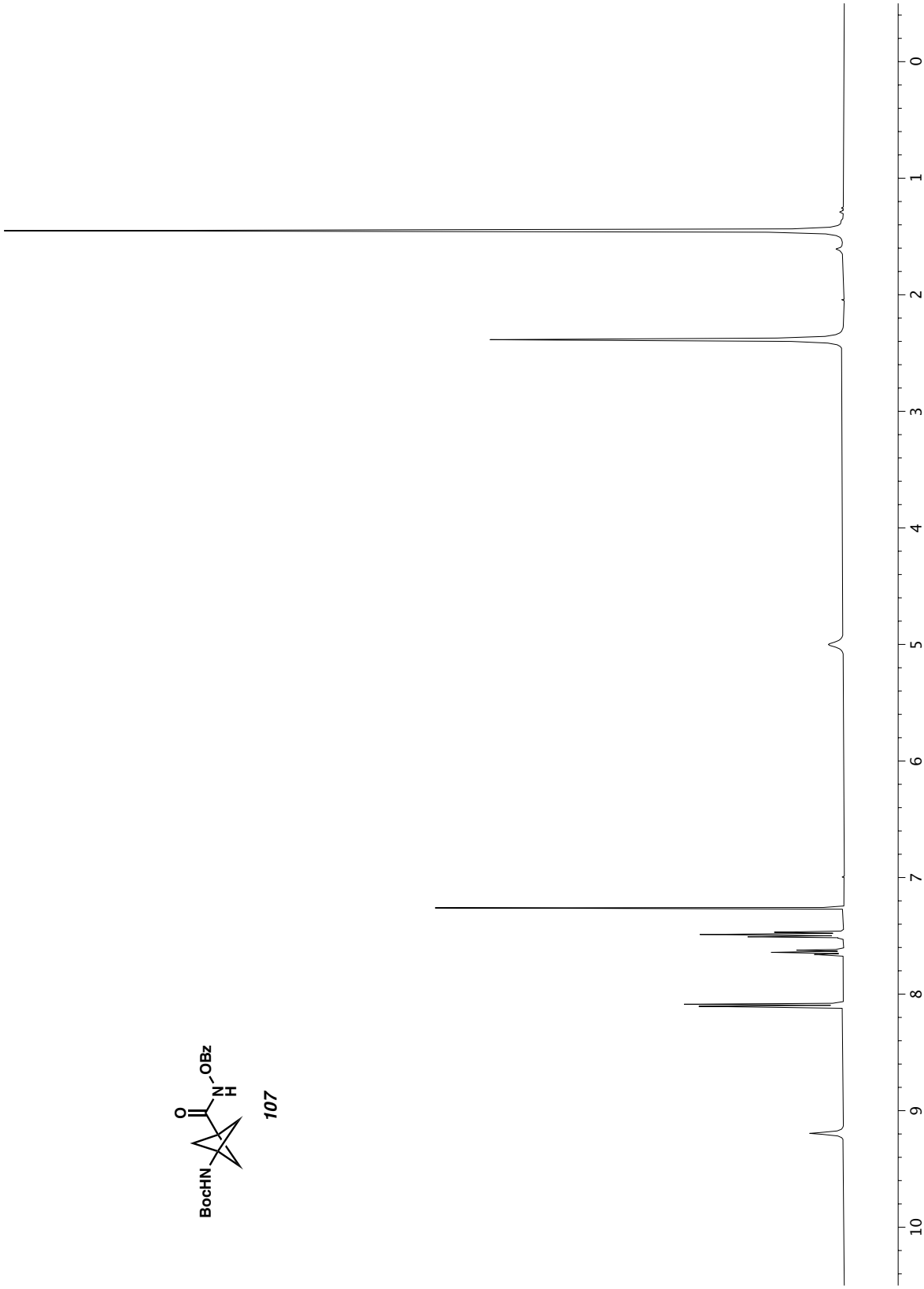


Figure A1.51 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***107****.*

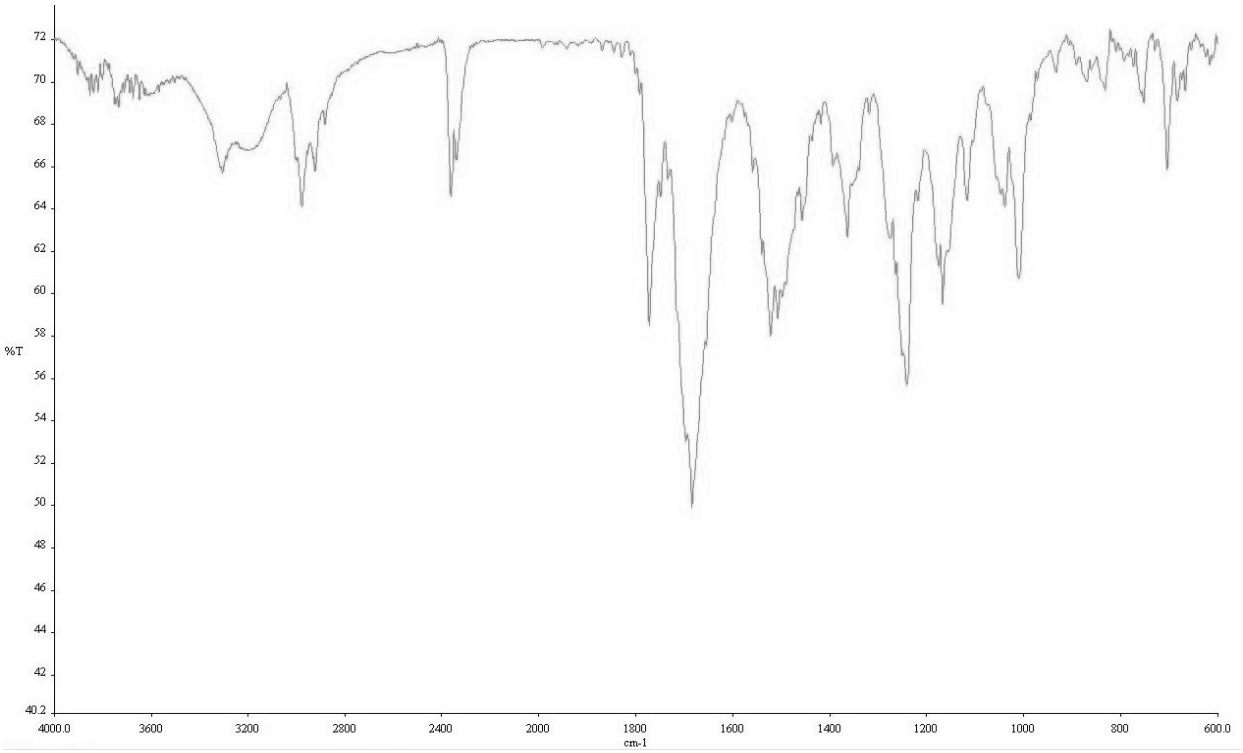


Figure A1.52 *Infrared spectrum (Thin Film, NaCl) of compound* ***107****.*

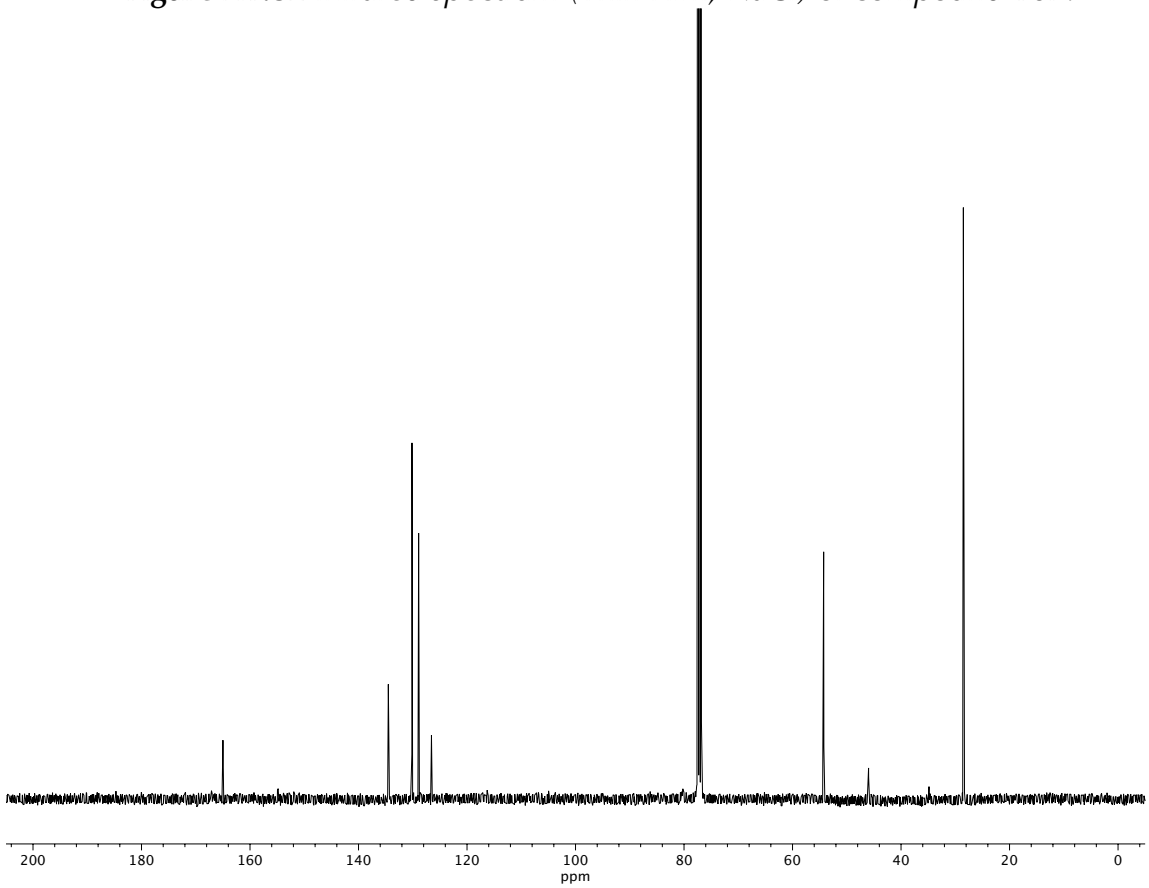


Figure A1.53 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***107****.*

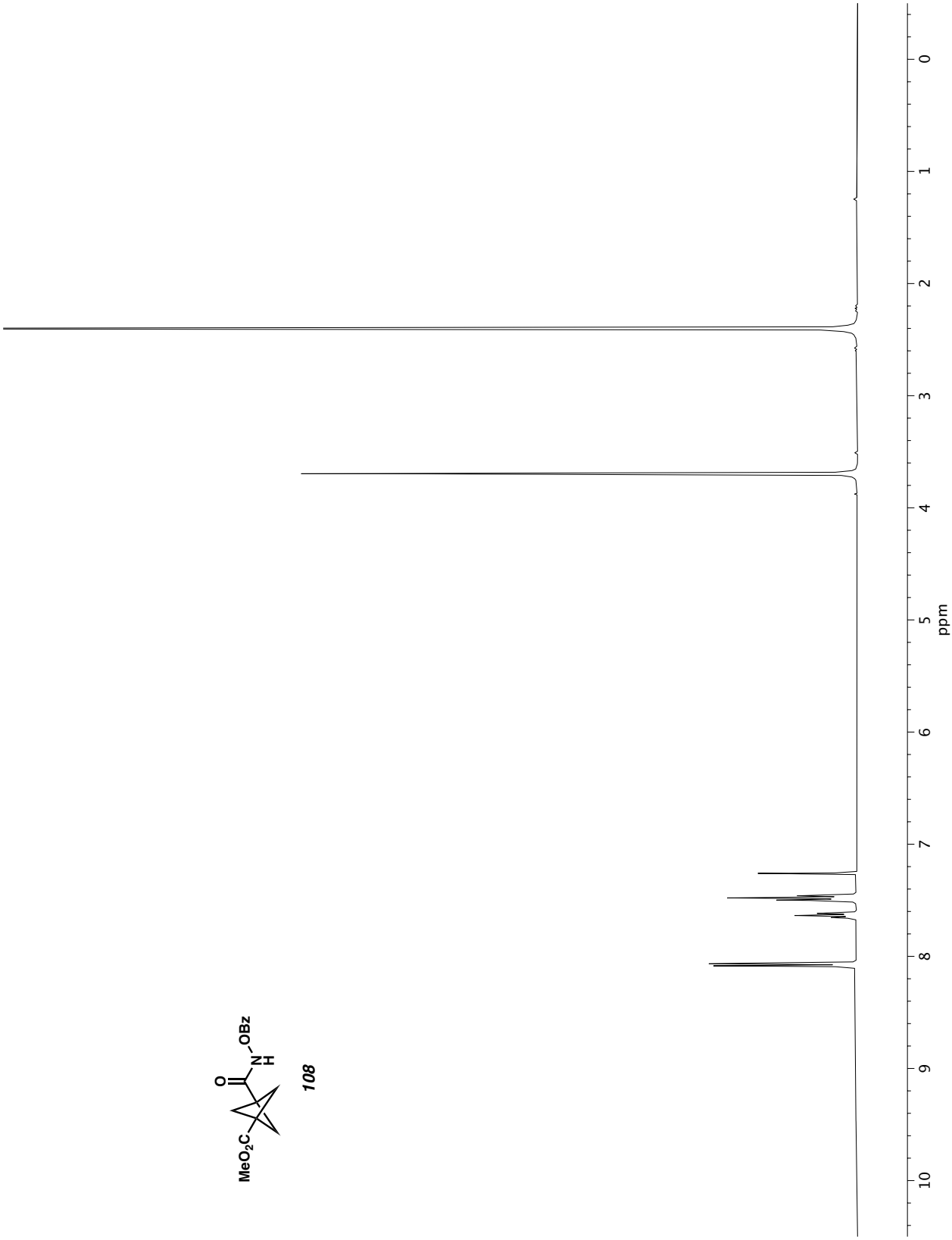


Figure A1.54 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***108***.

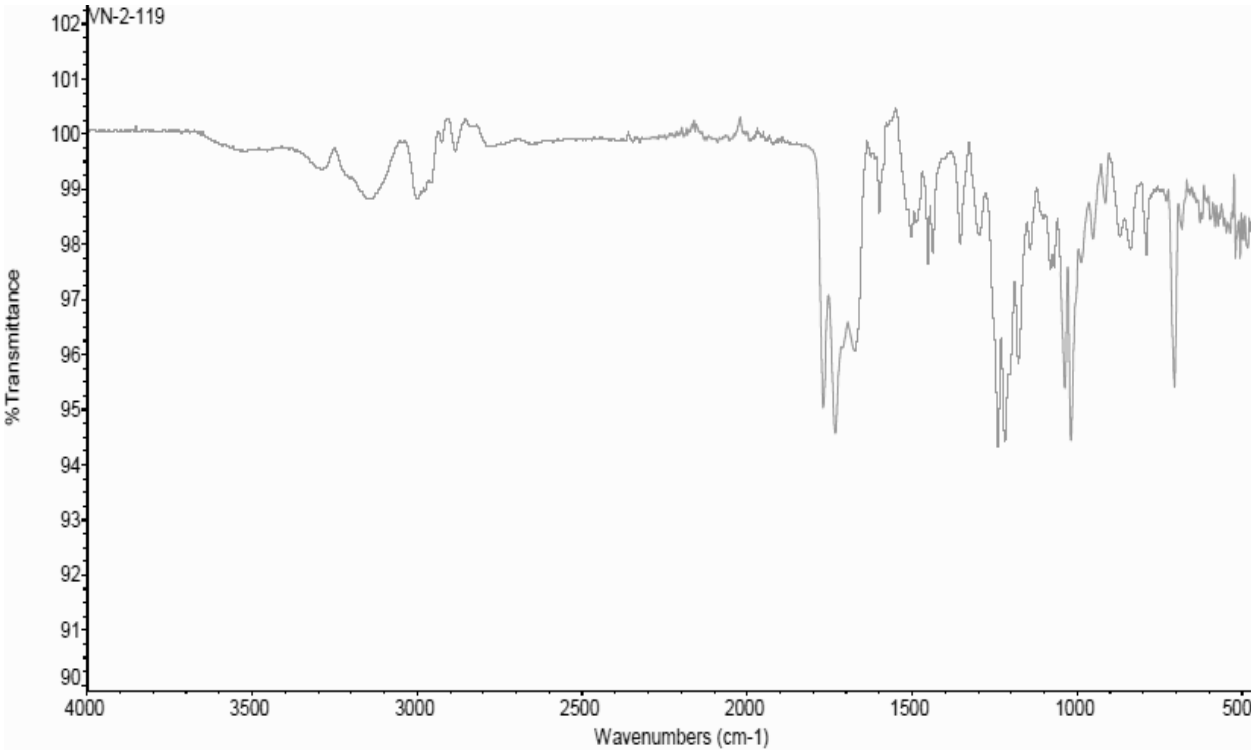


Figure A1.55 *Infrared spectrum (Thin Film) of compound* ***108***.

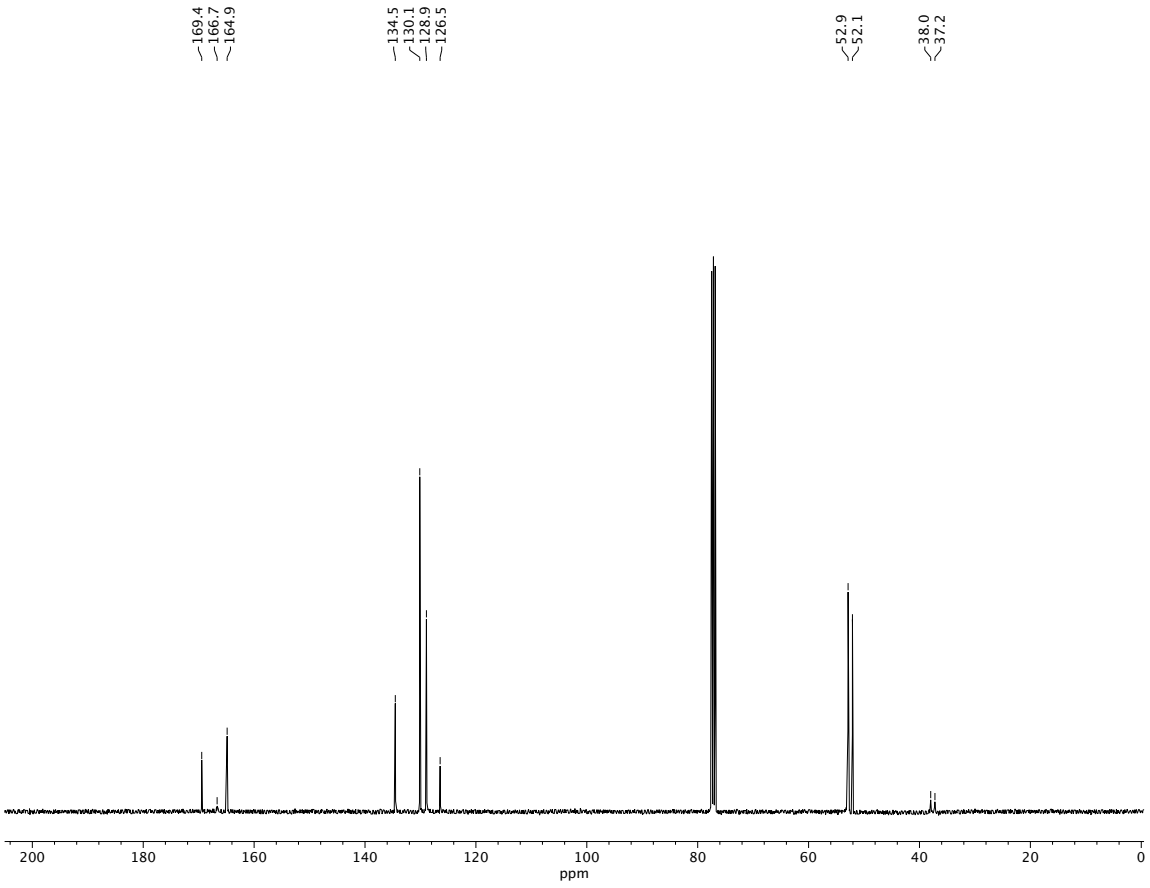


Figure A1.56 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***108***.

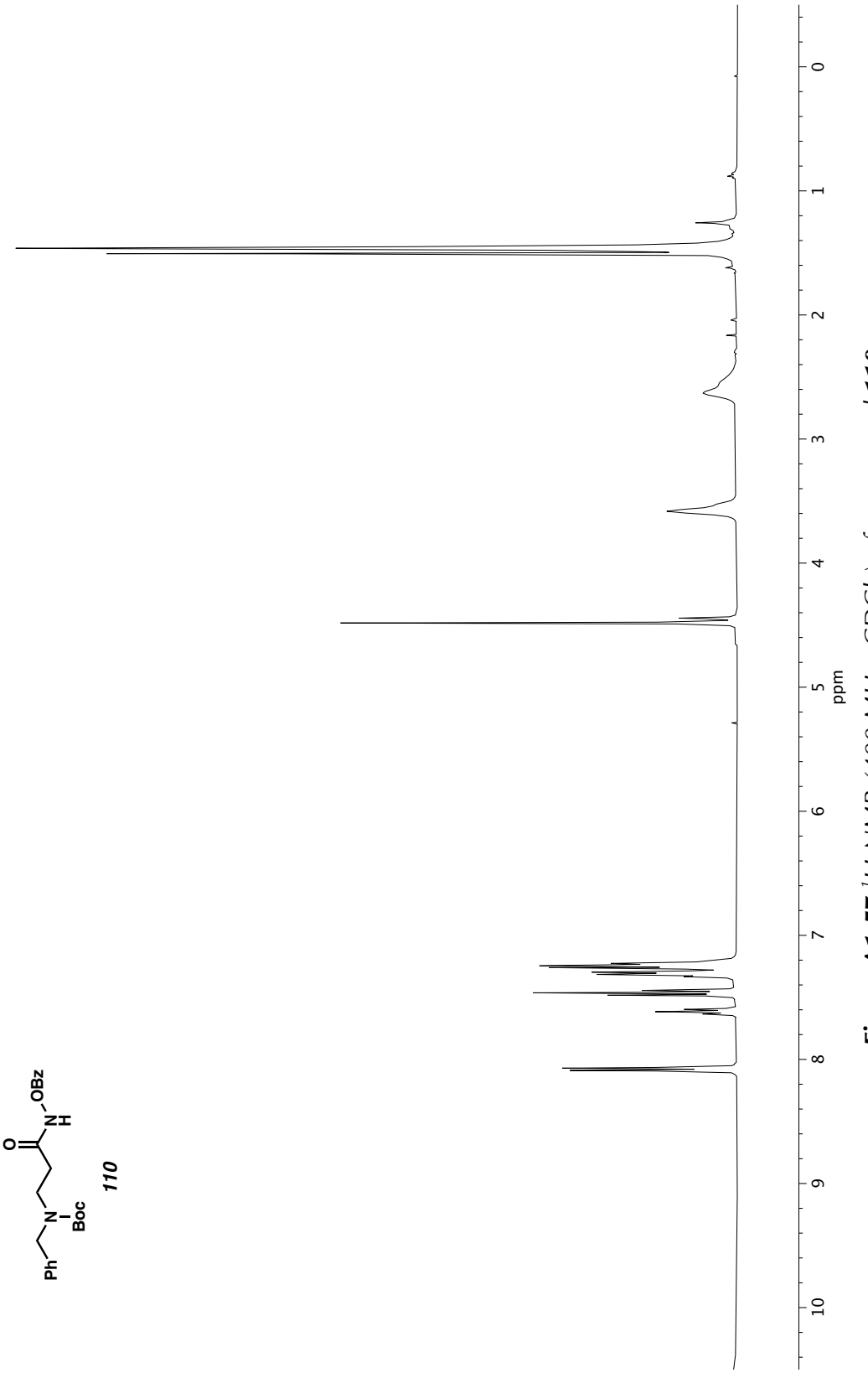


Figure A1.57 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***110***.

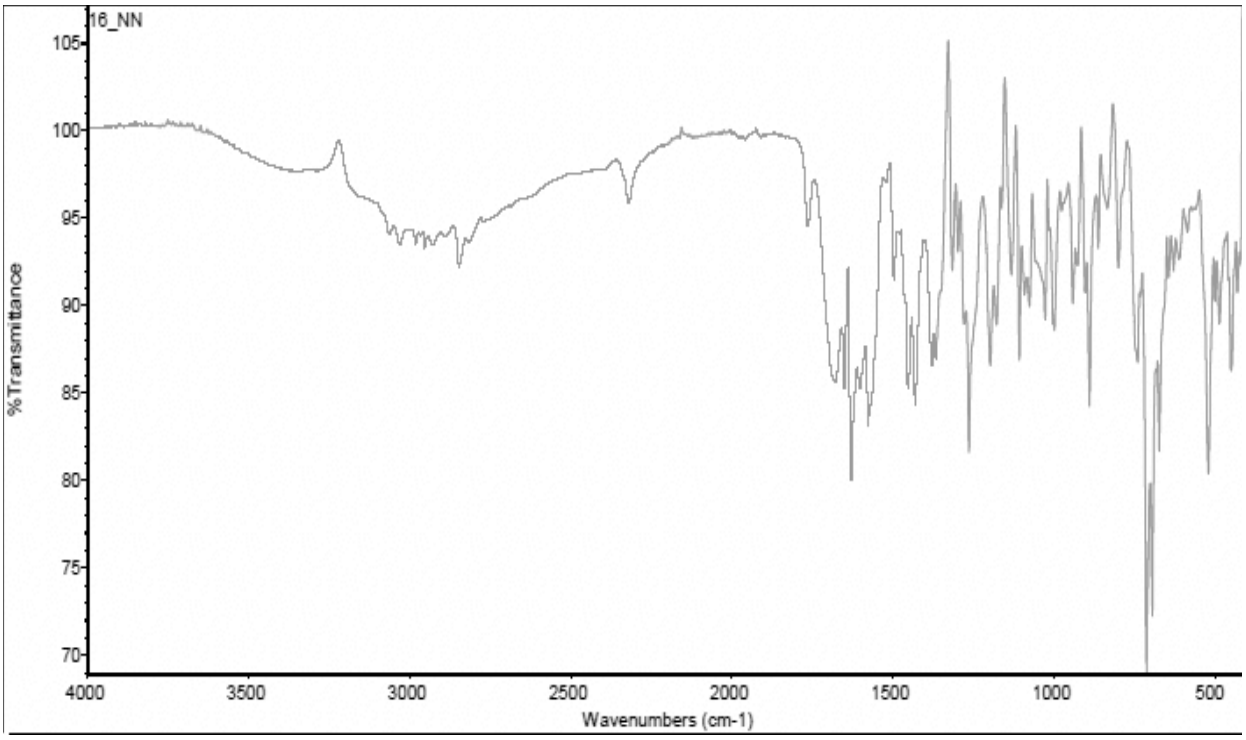


Figure A1.58 *Infrared spectrum (Thin Film) of compound* ***110***.

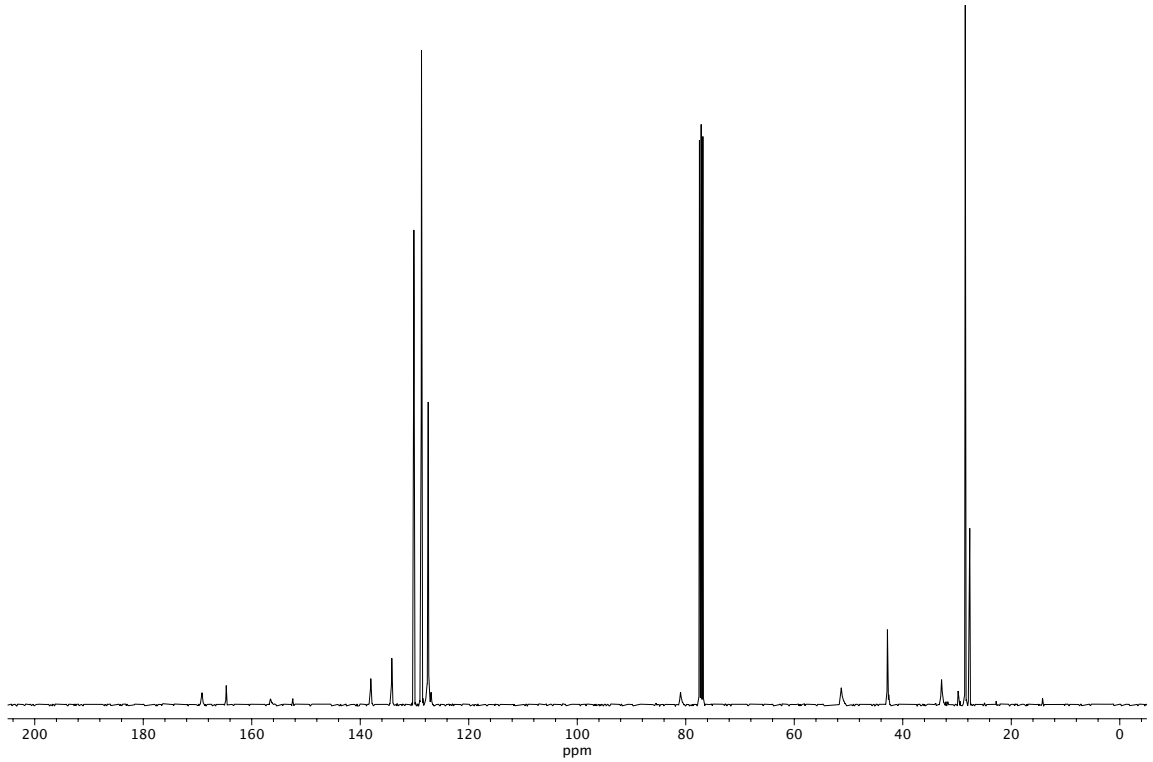


Figure A1.59 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***110***.

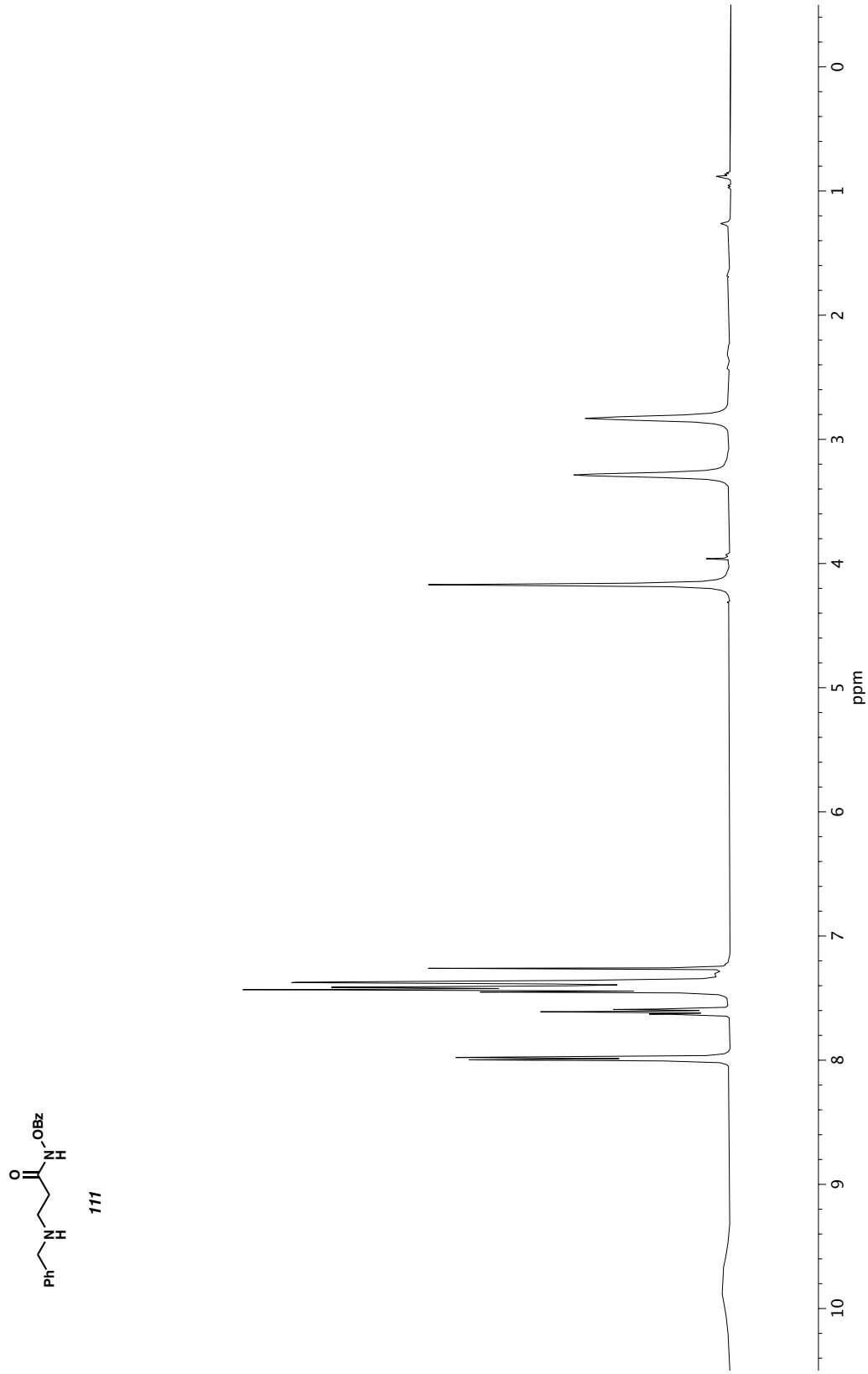


Figure A1.60 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***111***.

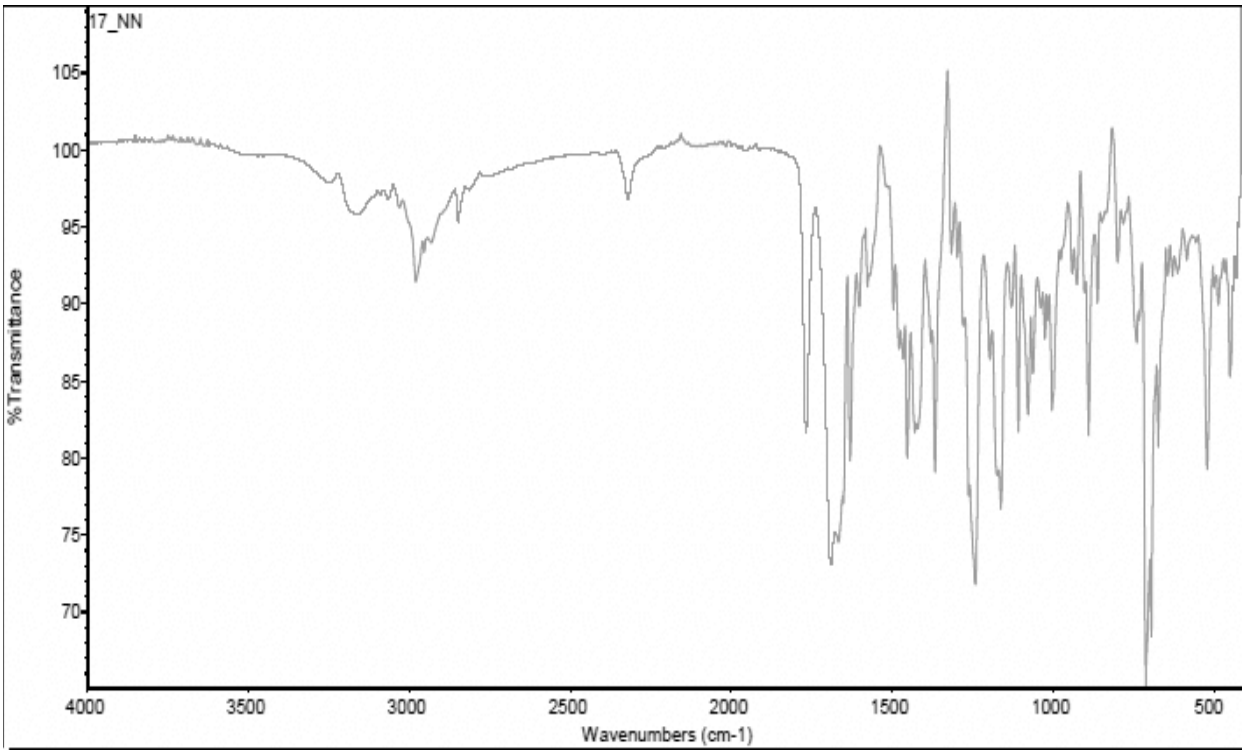


Figure A1.61 *Infrared spectrum (Thin Film) of compound* ***111***.

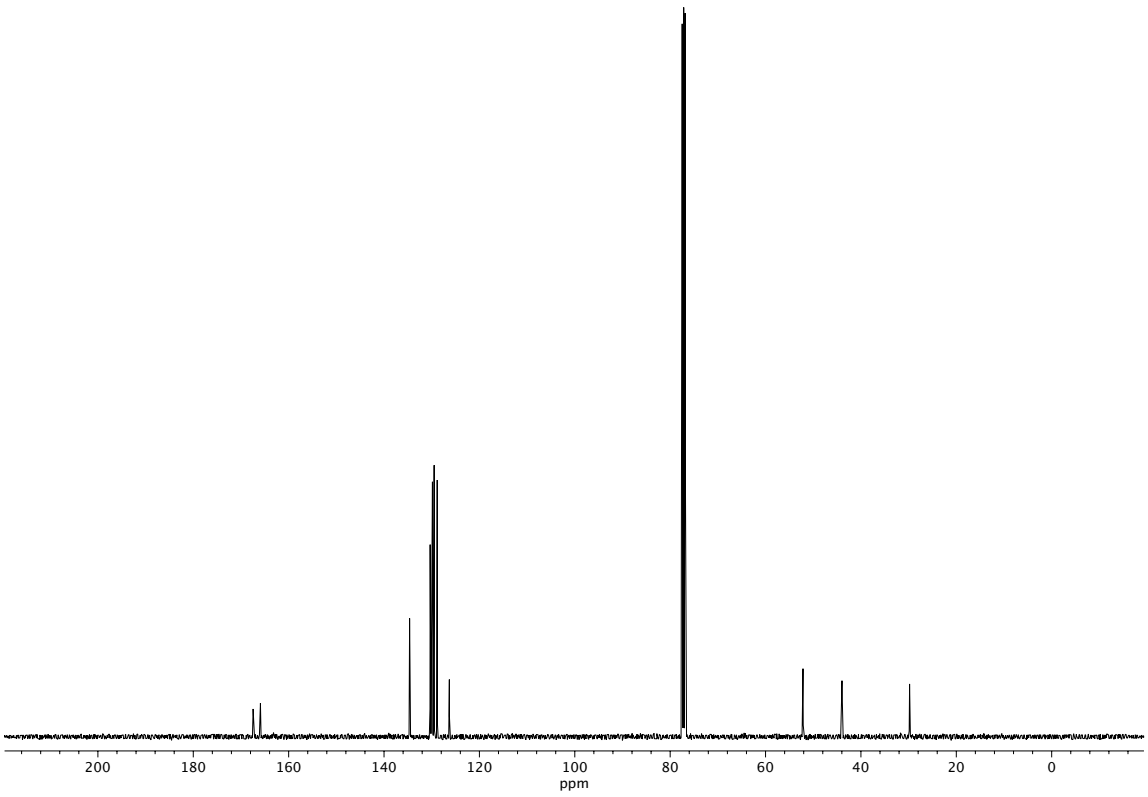


Figure A1.62 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***111***.

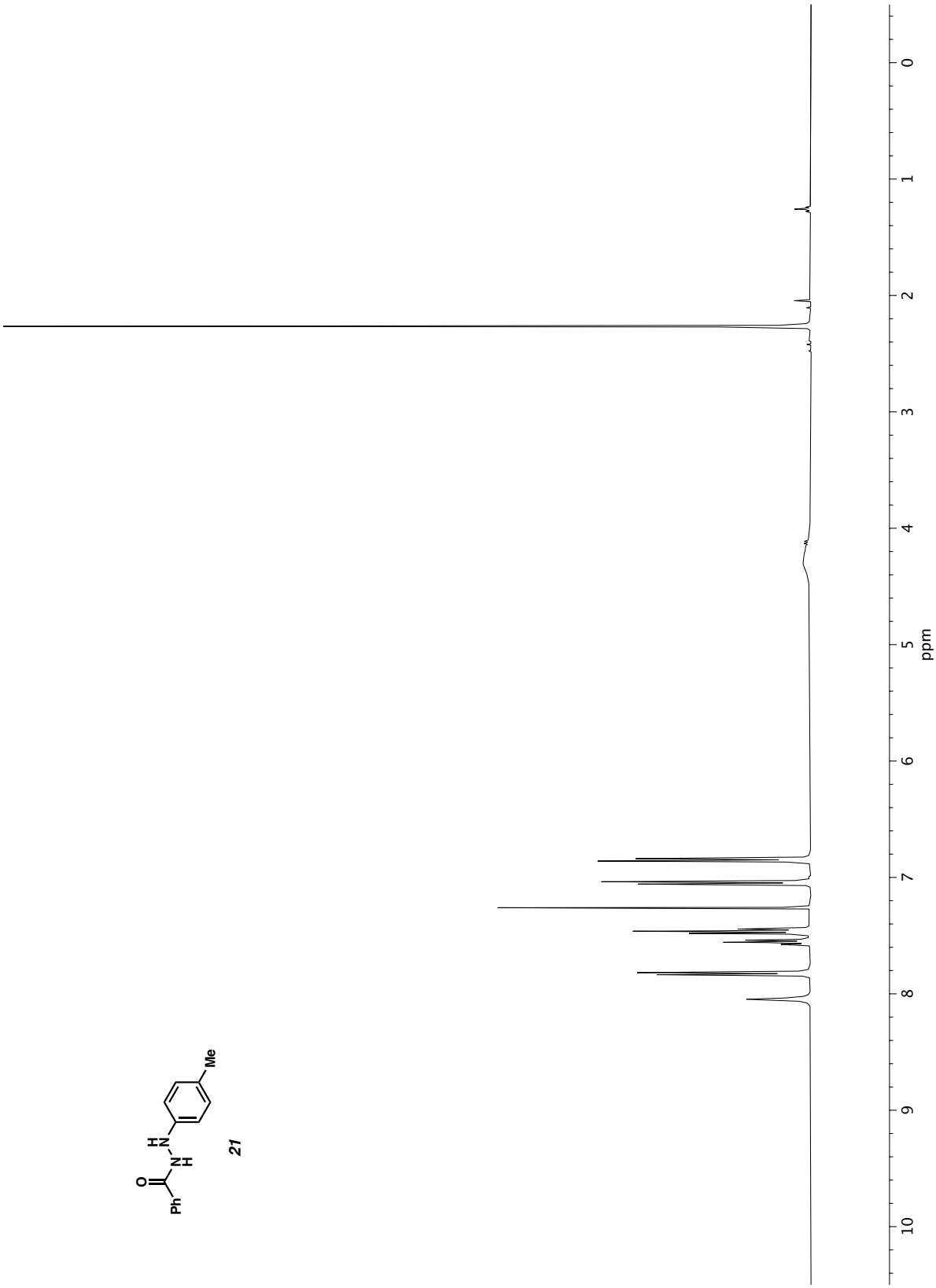


Figure A1.63 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***21***.

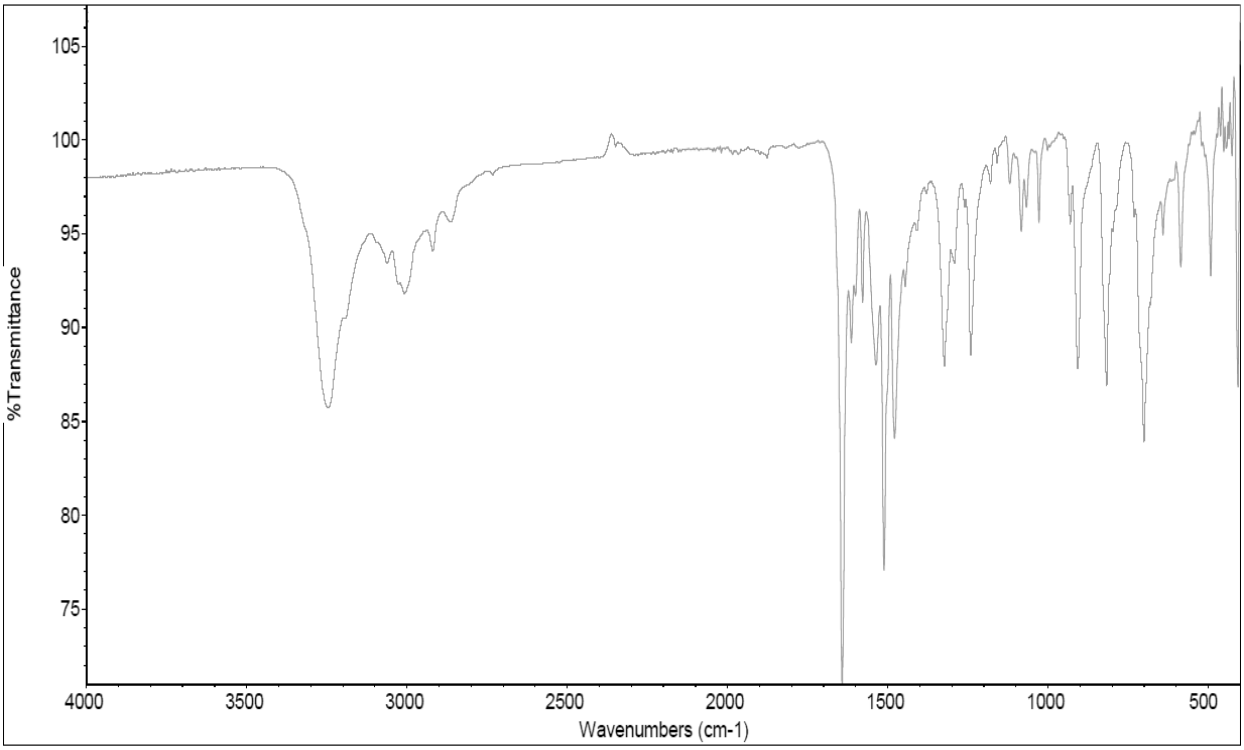


Figure A1.64 *Infrared spectrum (Thin Film) of compound* ***21***.

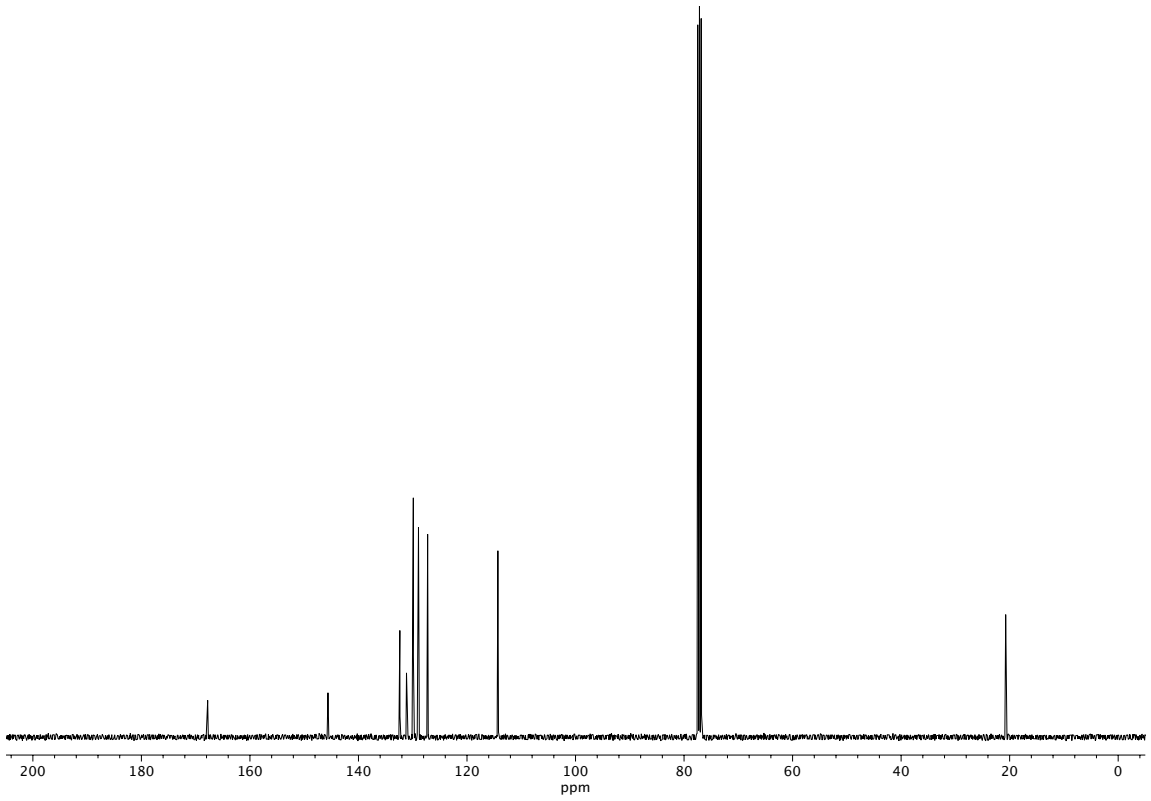


Figure A1.65 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***21***.

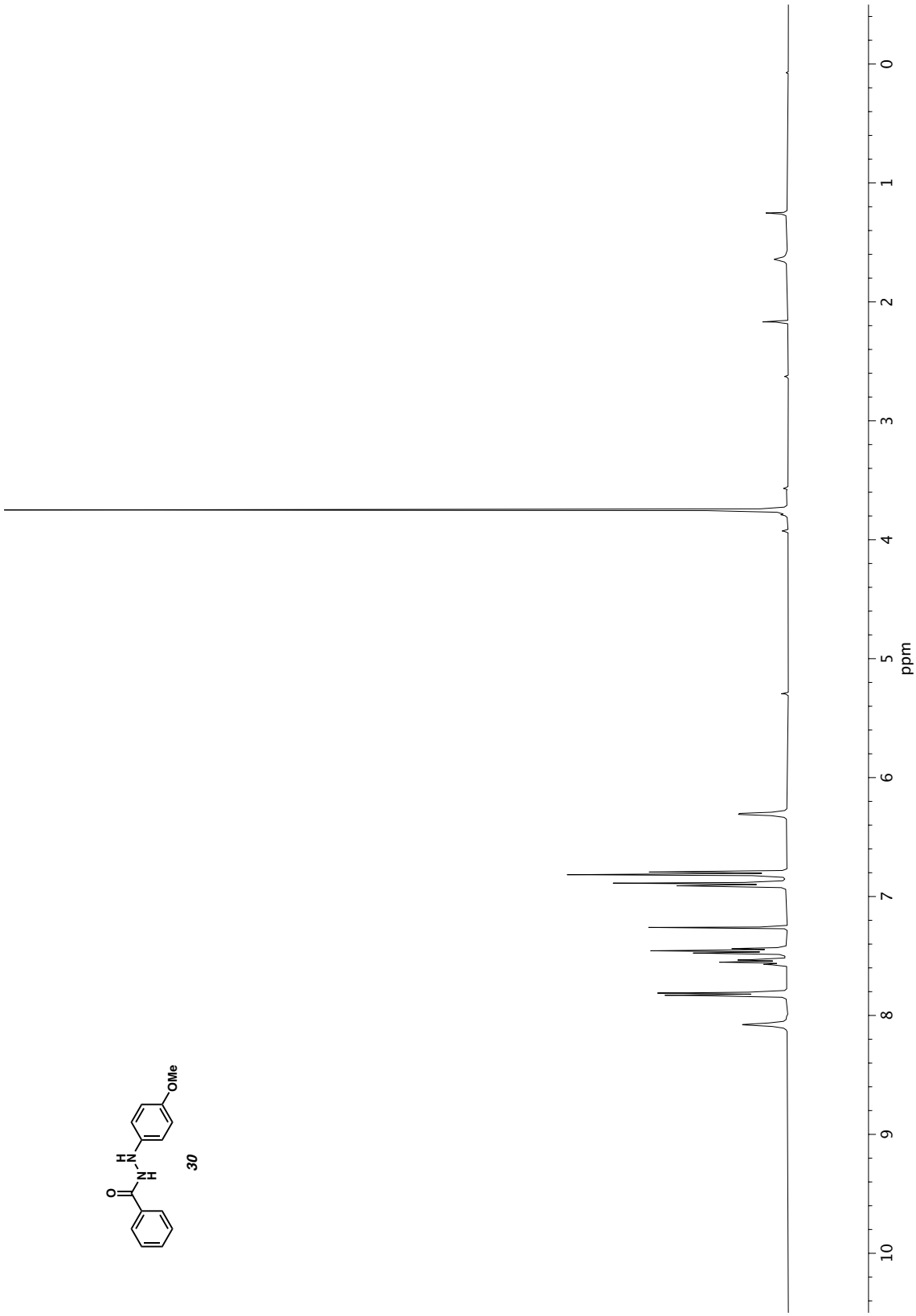


Figure A1.66 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***30***.

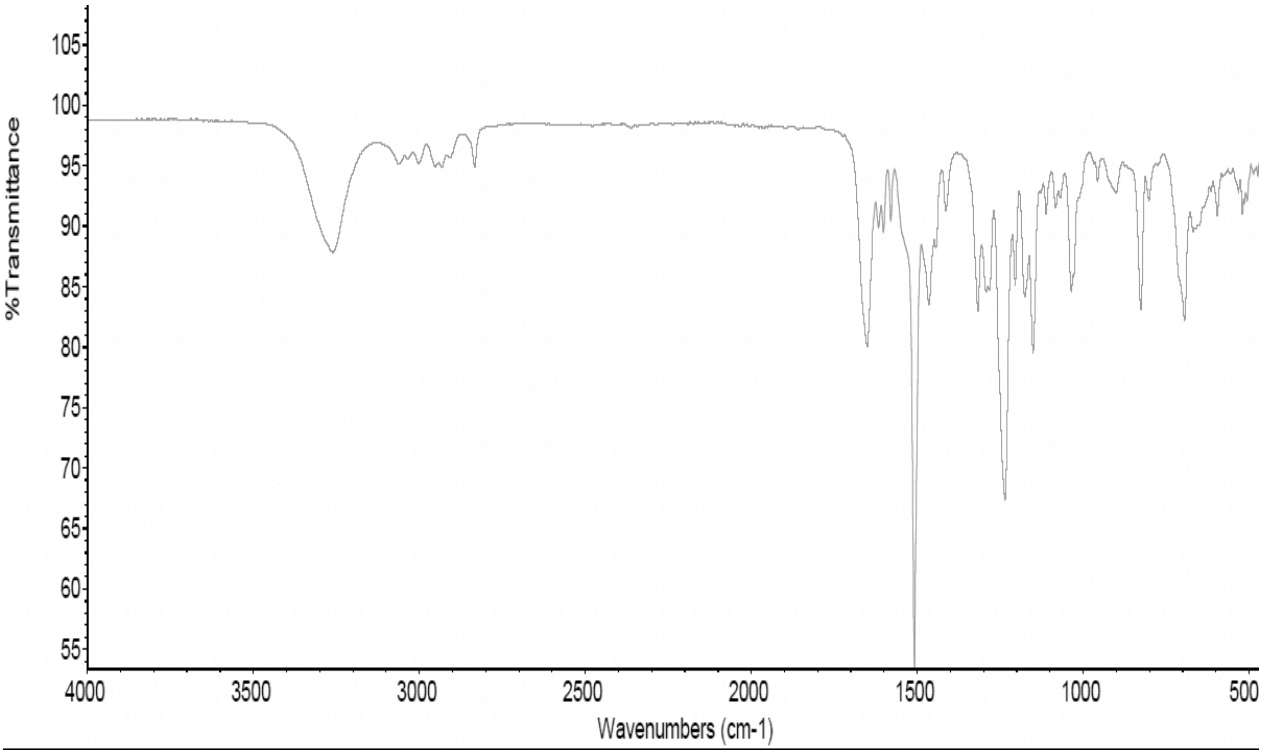


Figure A1.67 *Infrared spectrum (Thin Film) of compound* ***30***.

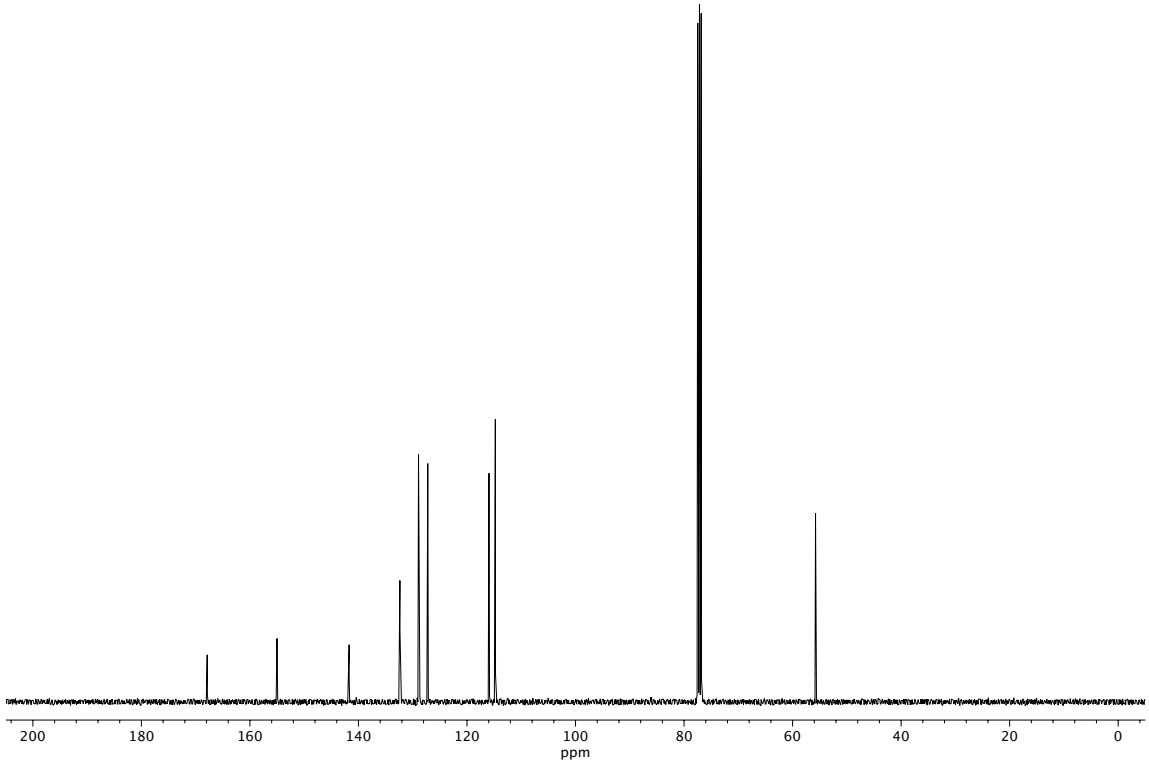


Figure A1.68 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***30***.

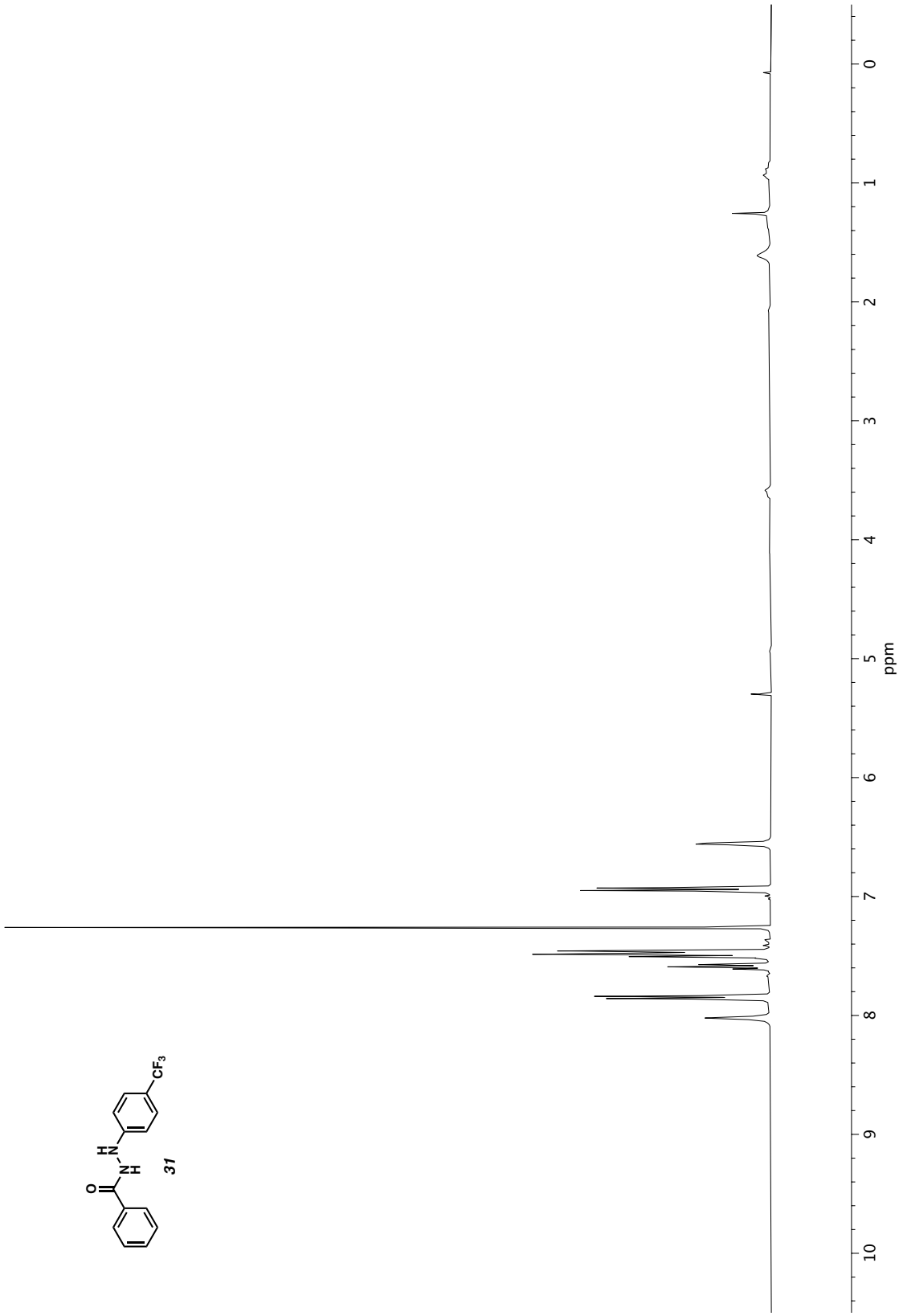


Figure A1.69 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***31***.

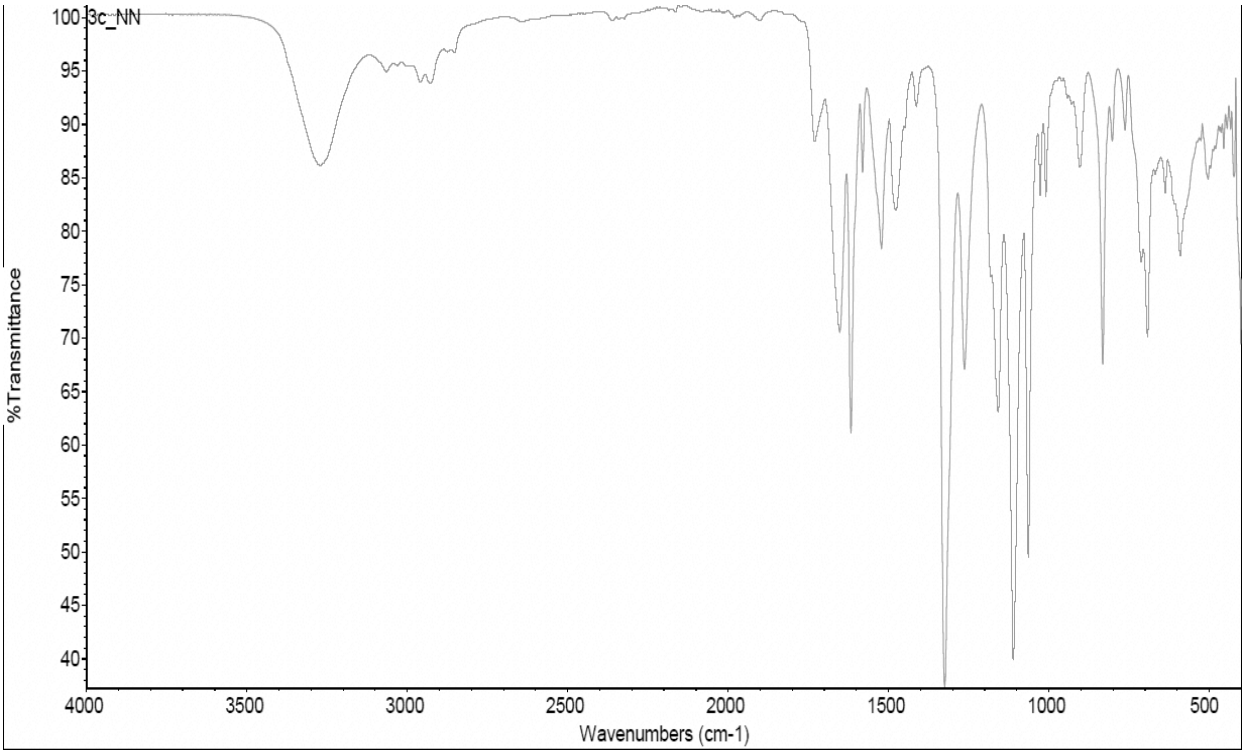


Figure A1.70 *Infrared spectrum (Thin Film) of compound* ***31***.

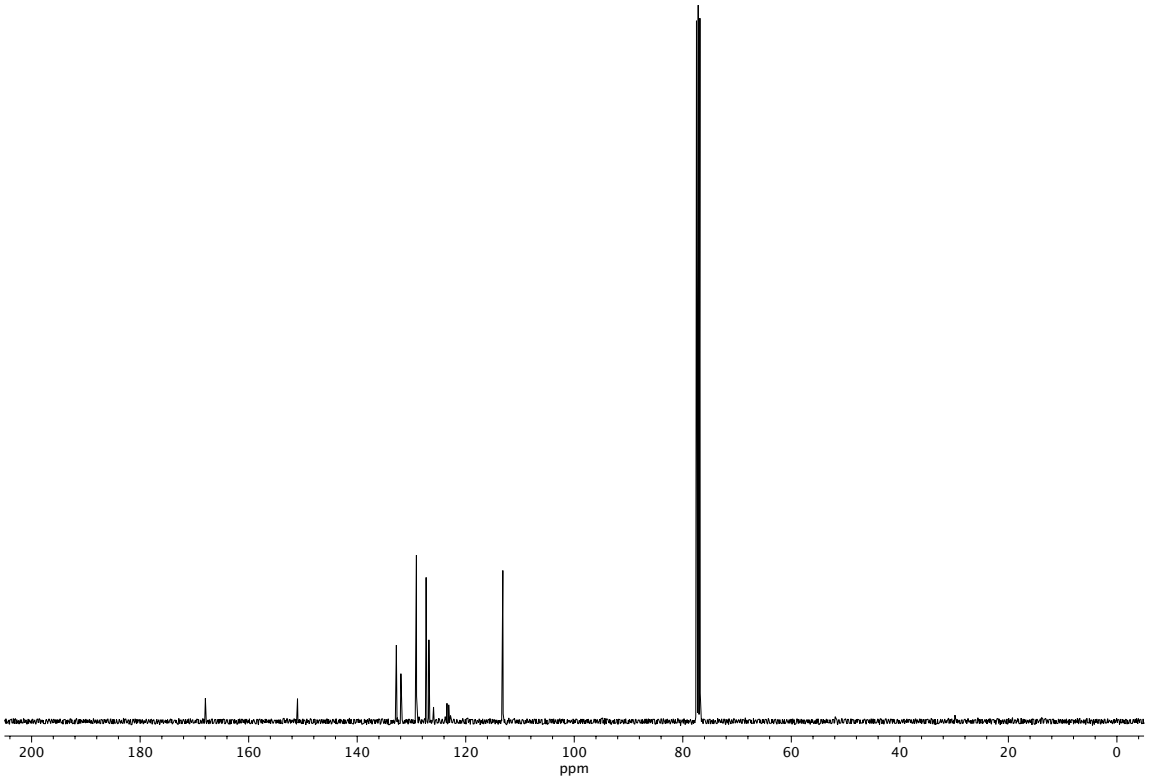


Figure A1.71 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***31***.

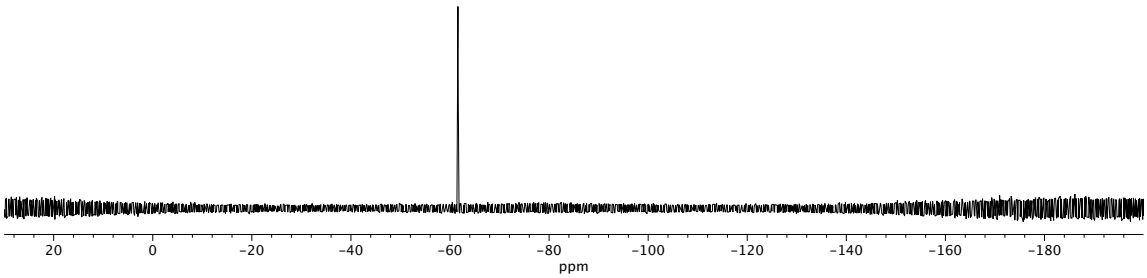


Figure A1.72 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***31***.

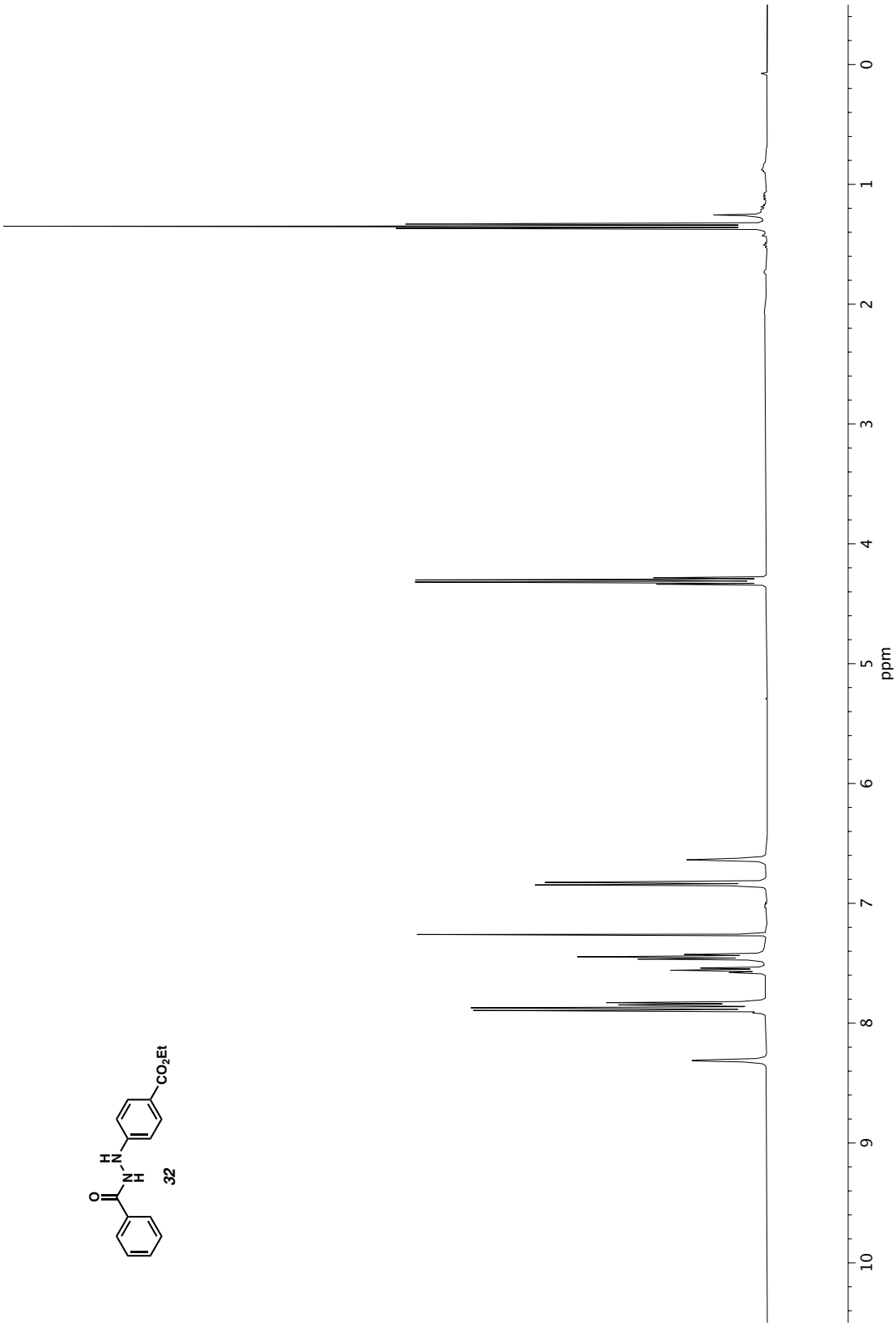


Figure A1.73 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***32***.

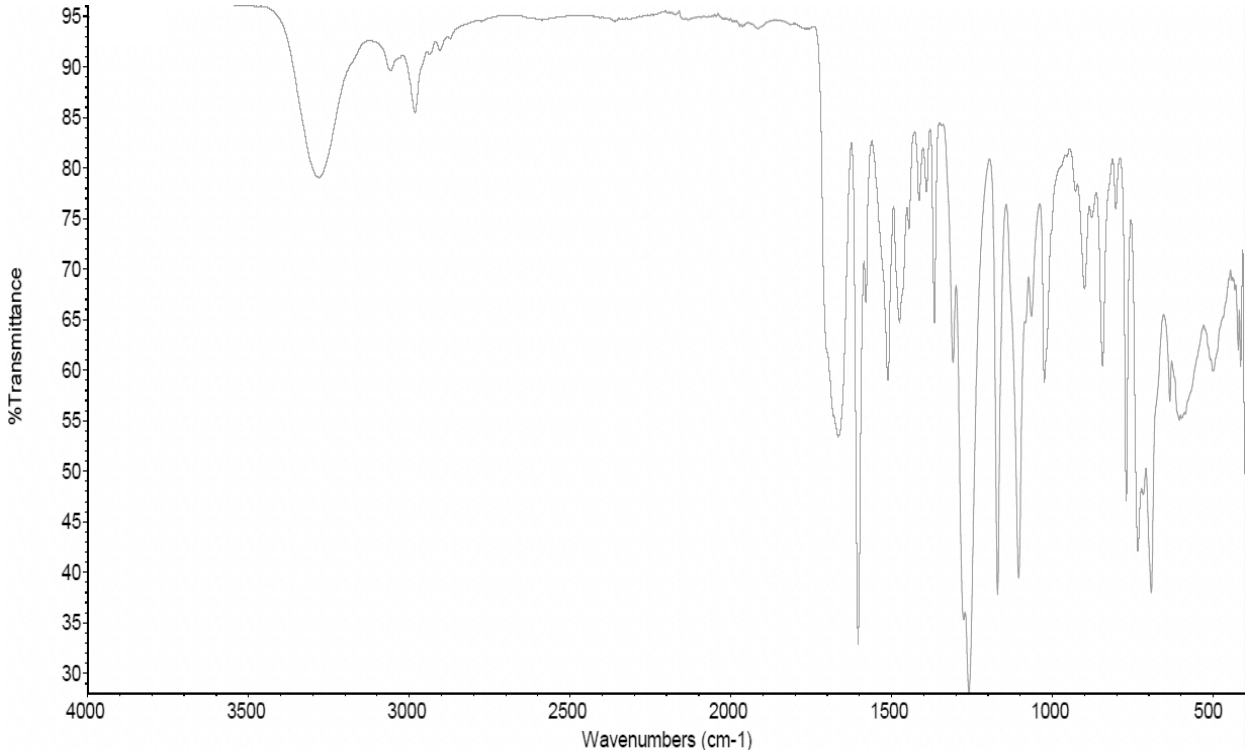


Figure A1.74 *Infrared spectrum (Thin Film) of compound* ***32***.

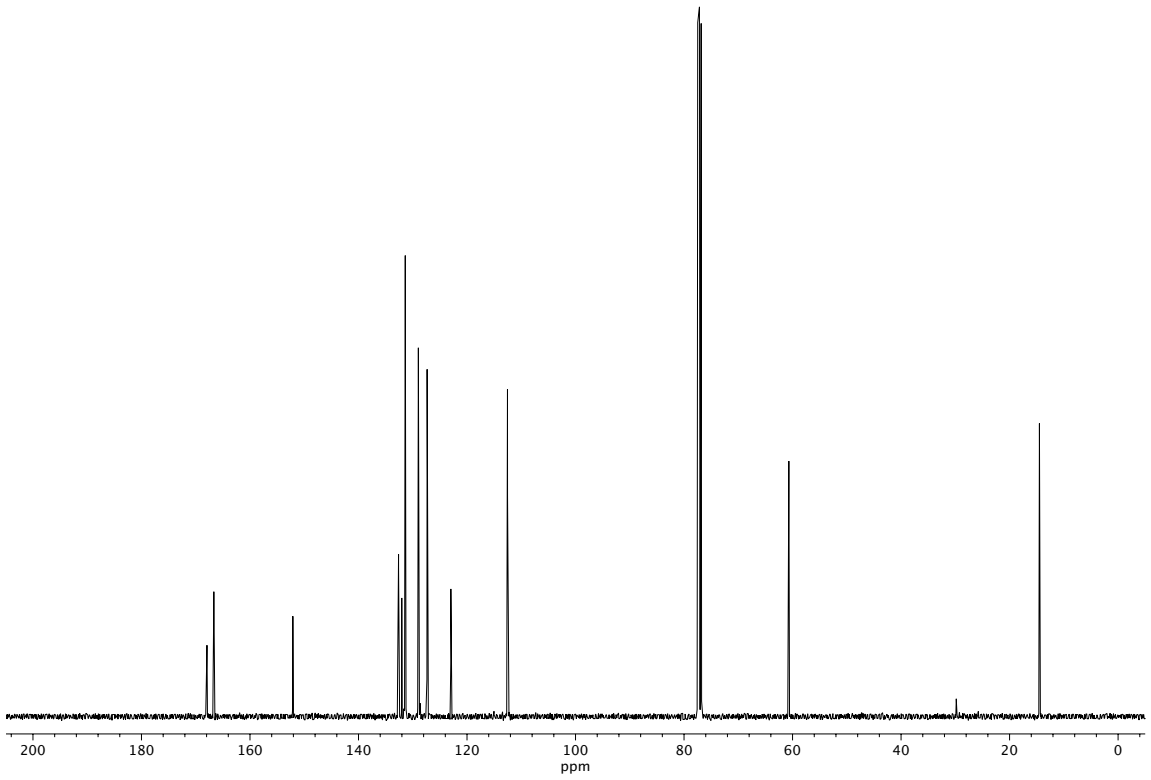


Figure A1.75 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***32***.

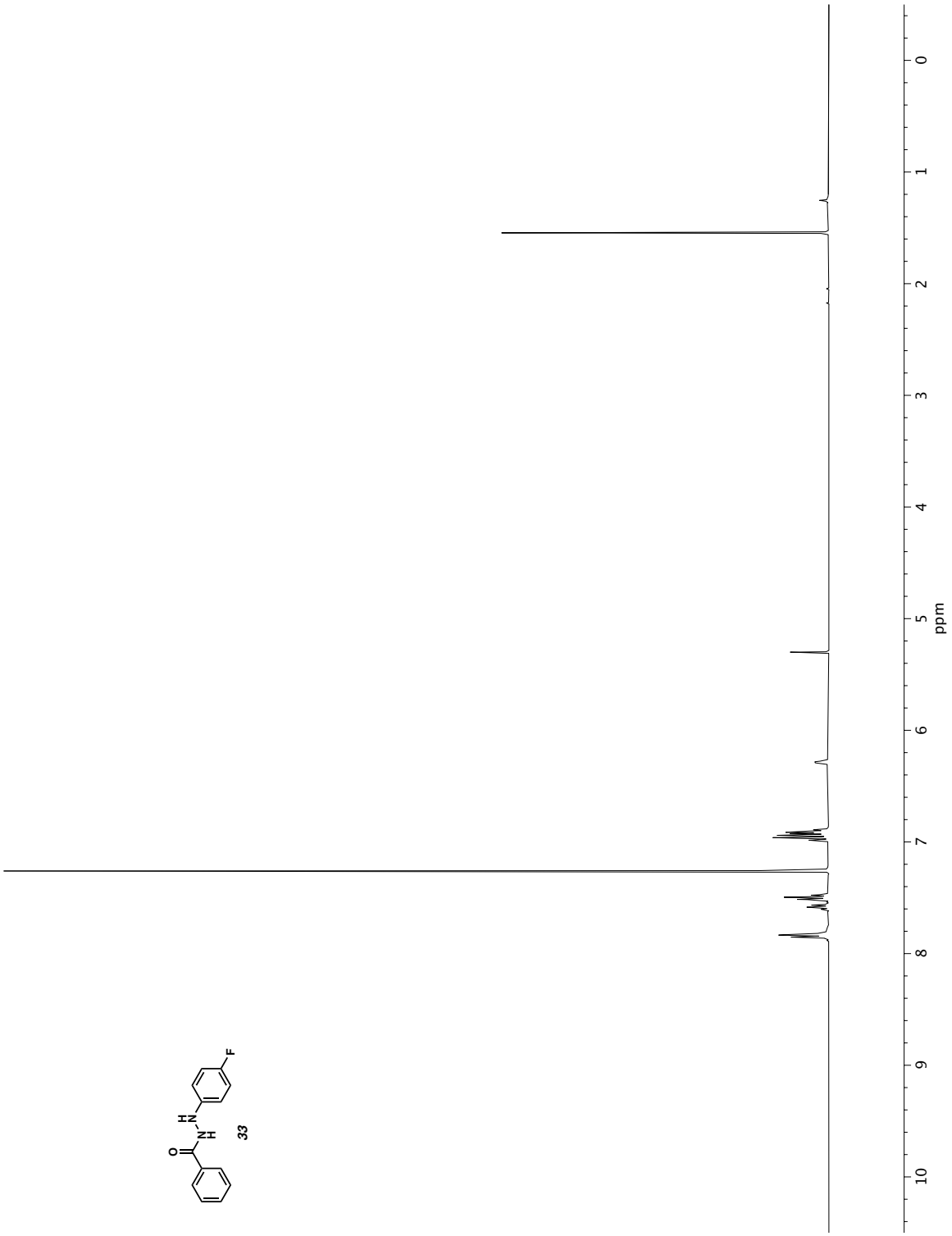


Figure A1.76 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***33***.

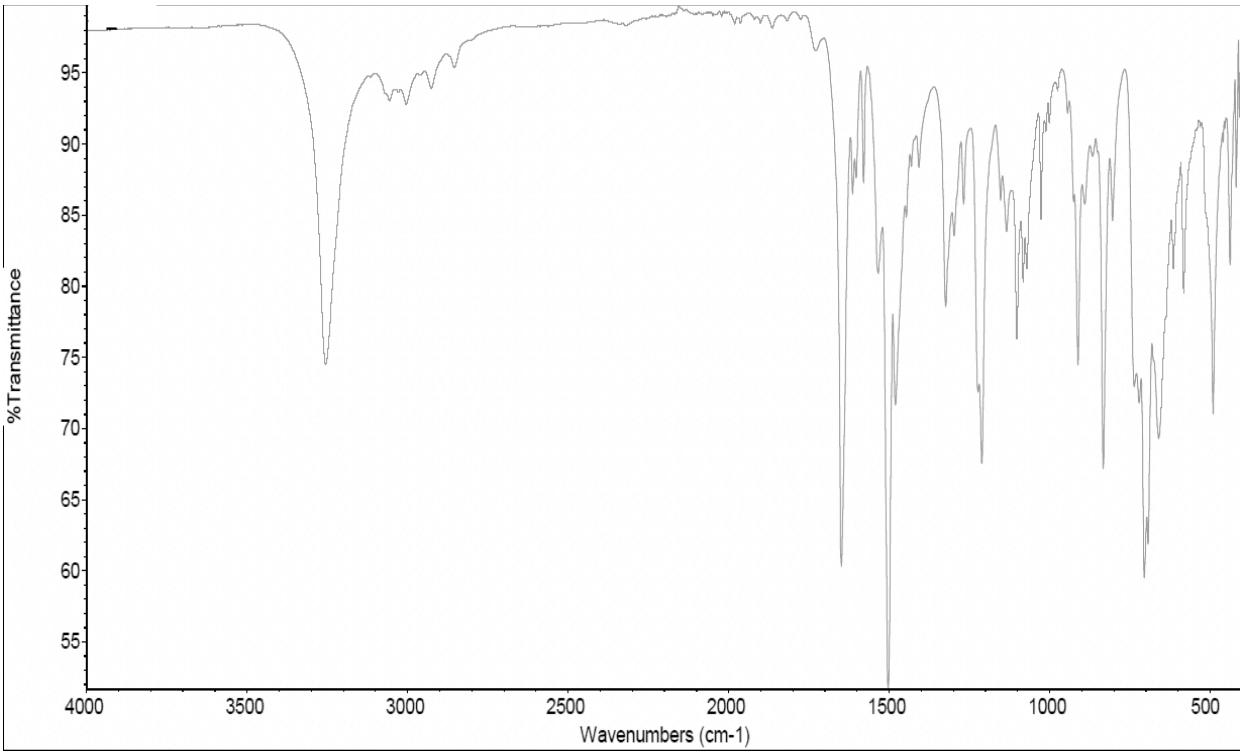


Figure A1.77 *Infrared spectrum (Thin Film) of compound* ***33***.

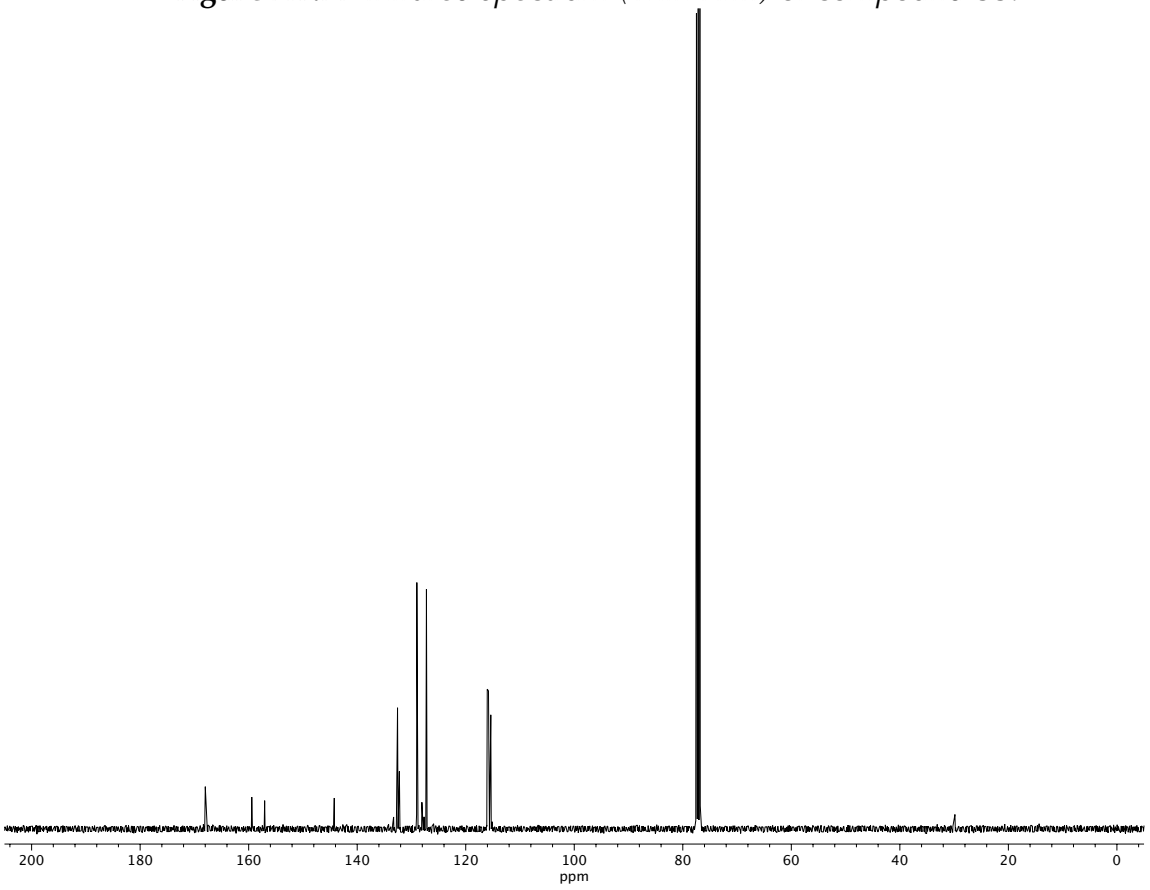


Figure A1.78 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***33***.

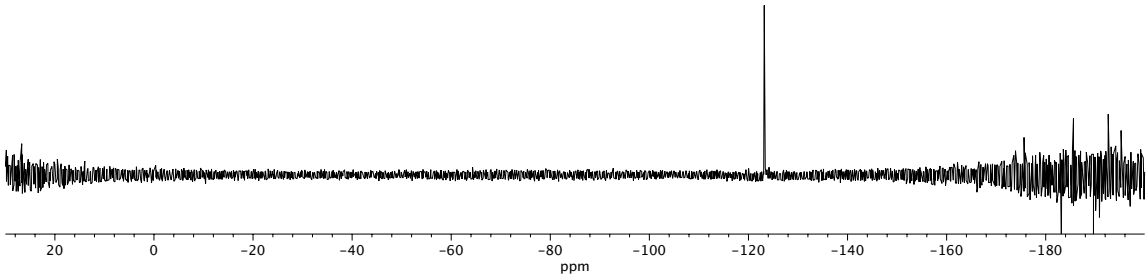


Figure A1.79 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***33***.

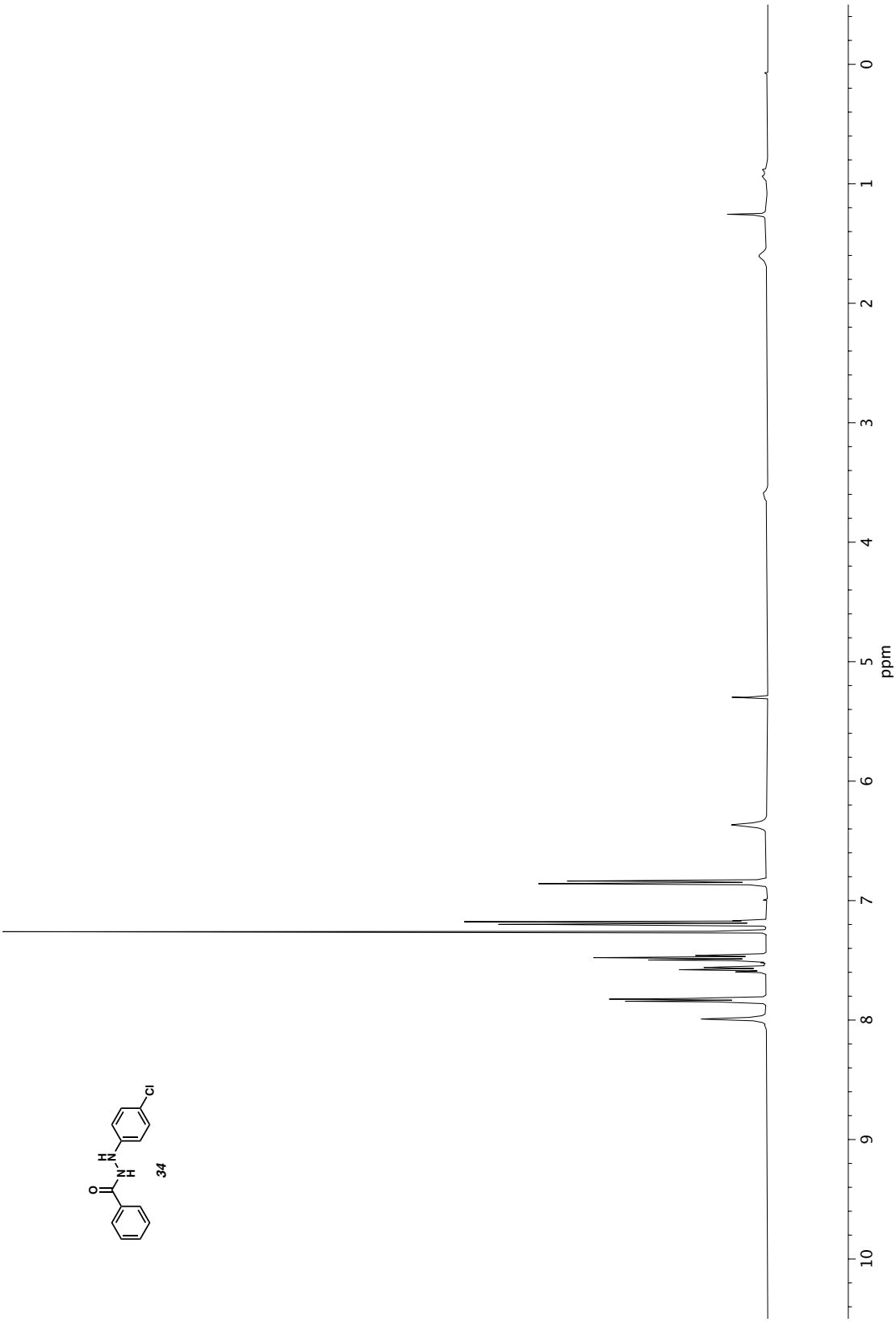


Figure A1.80 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***34***.

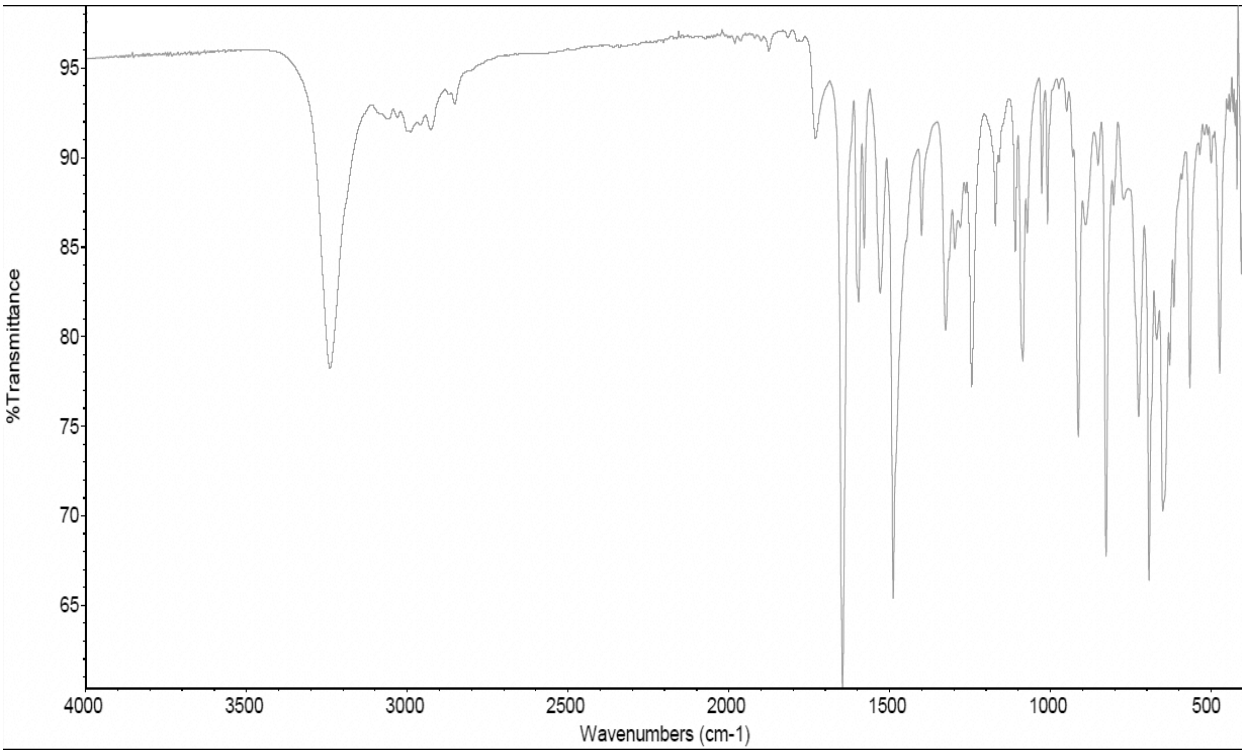


Figure A1.81 *Infrared spectrum (Thin Film) of compound* ***34***.

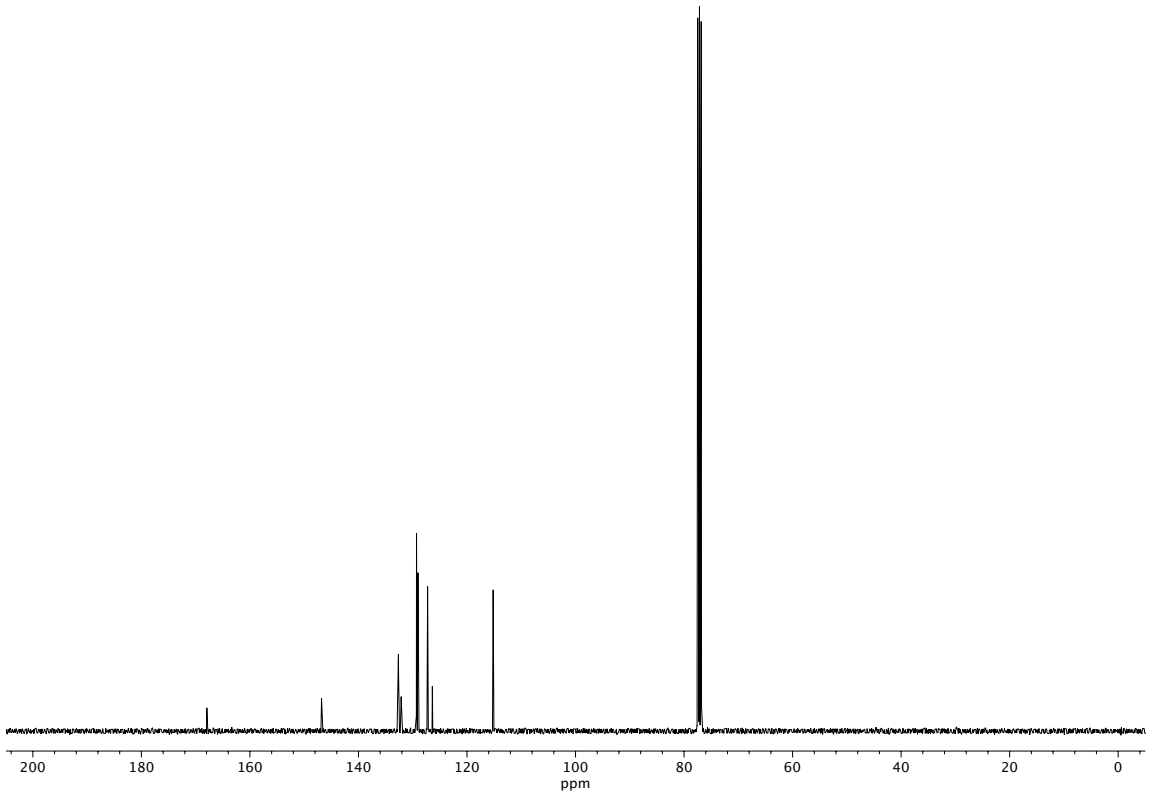


Figure A1.82 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***34***.

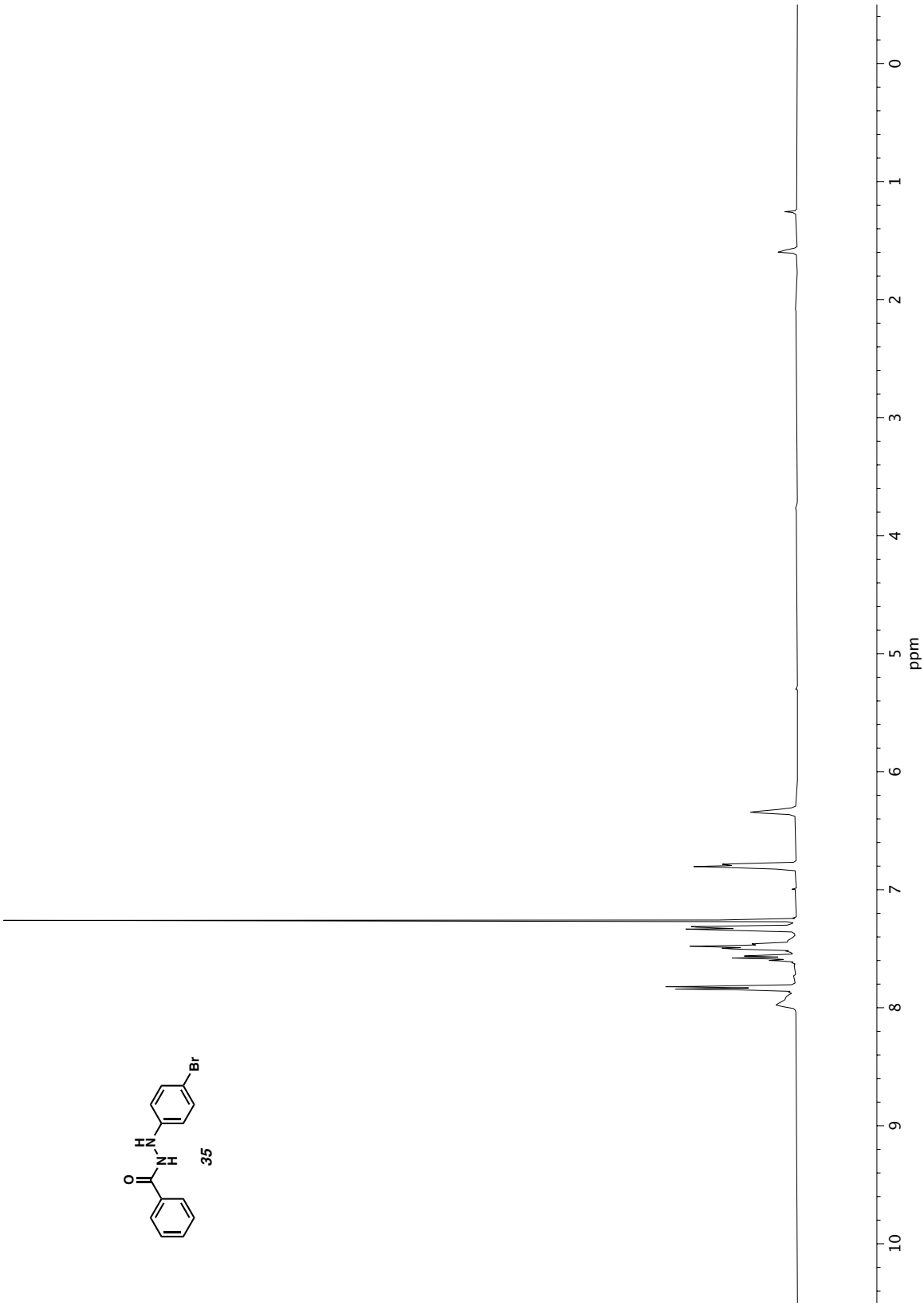


Figure A1.83 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **35**.*

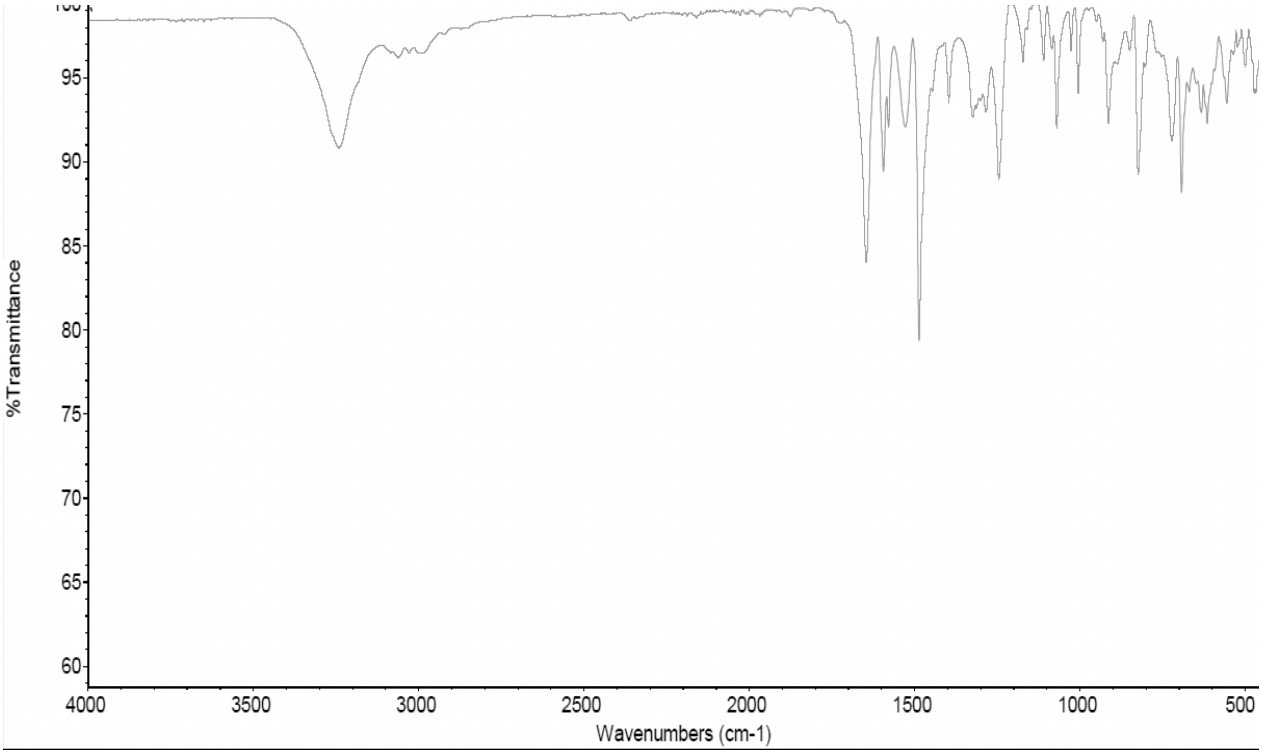


Figure A1.84 *Infrared spectrum (Thin Film) of compound* ***35***.

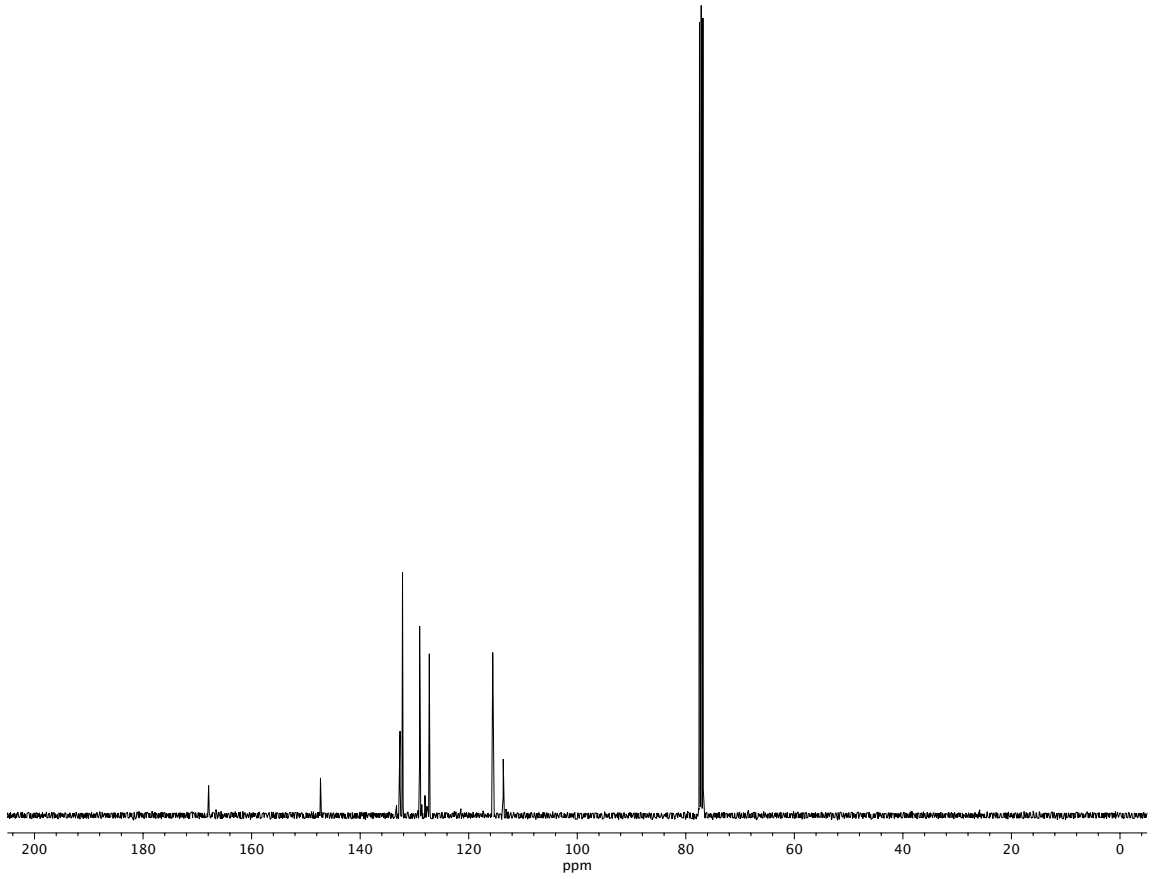


Figure A1.85 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***35***.

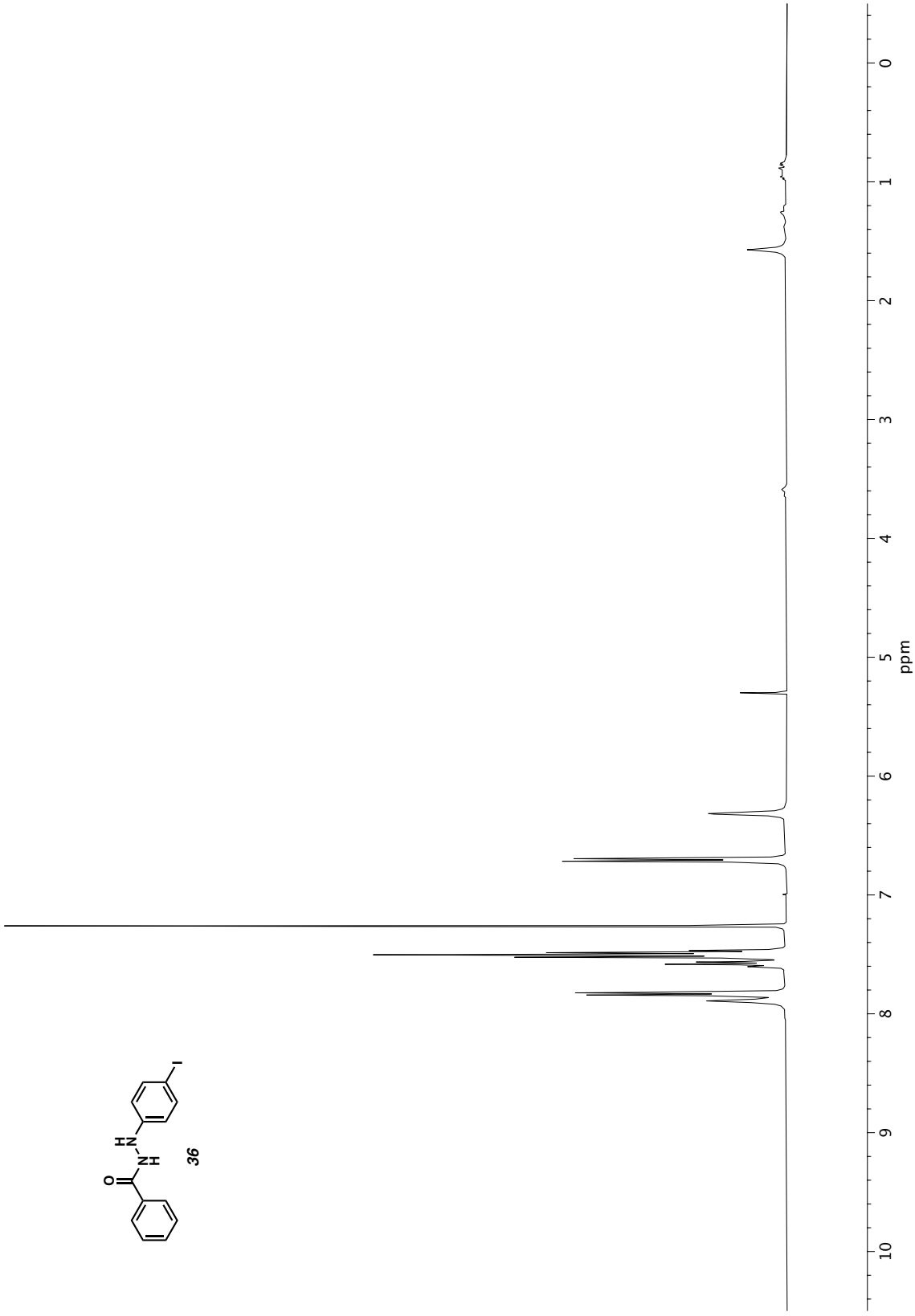


Figure A1.86 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***36***.

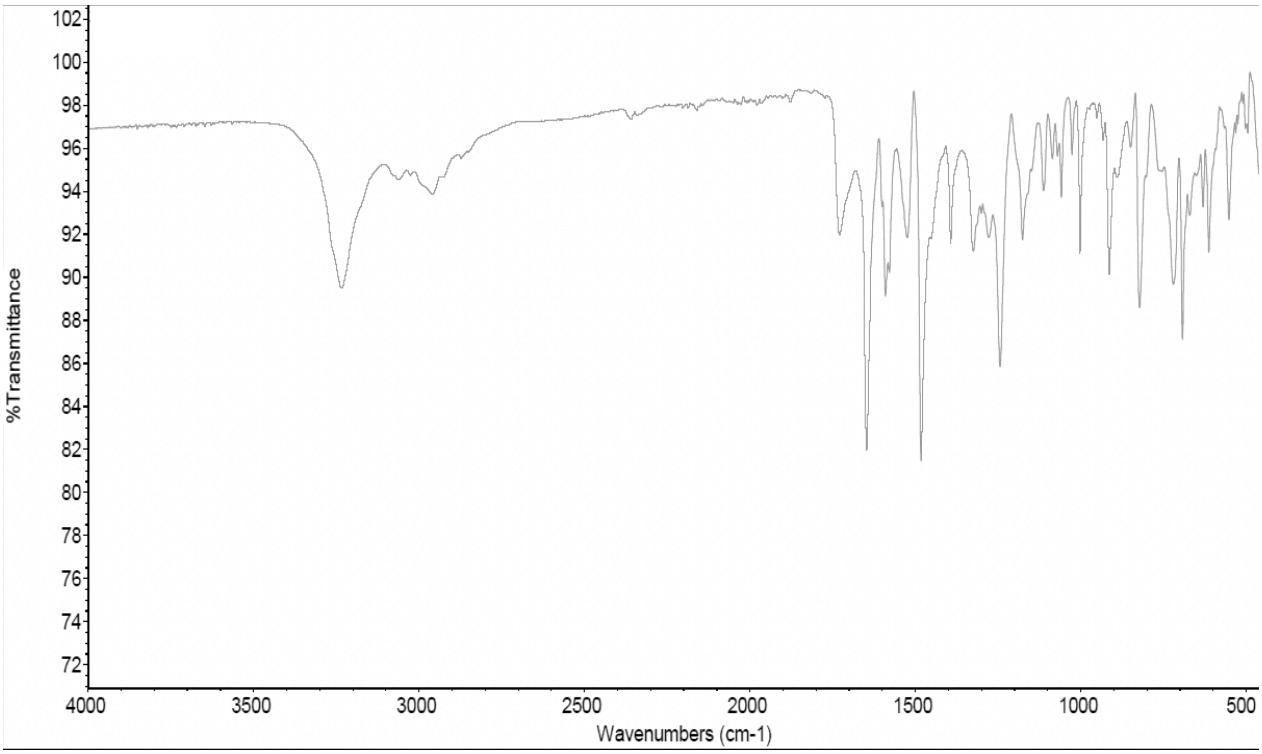


Figure A1.87 *Infrared spectrum (Thin Film) of compound* ***36***.

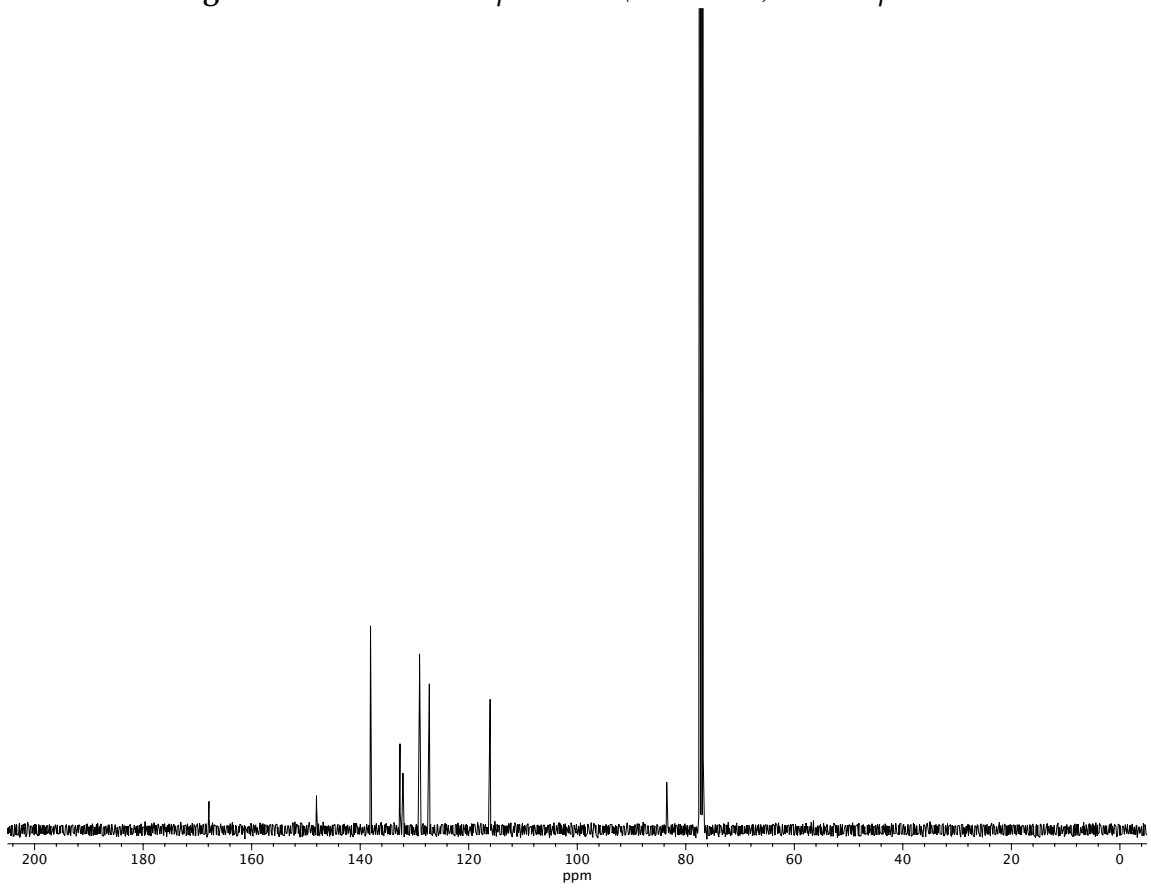


Figure A1.88 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***36***.

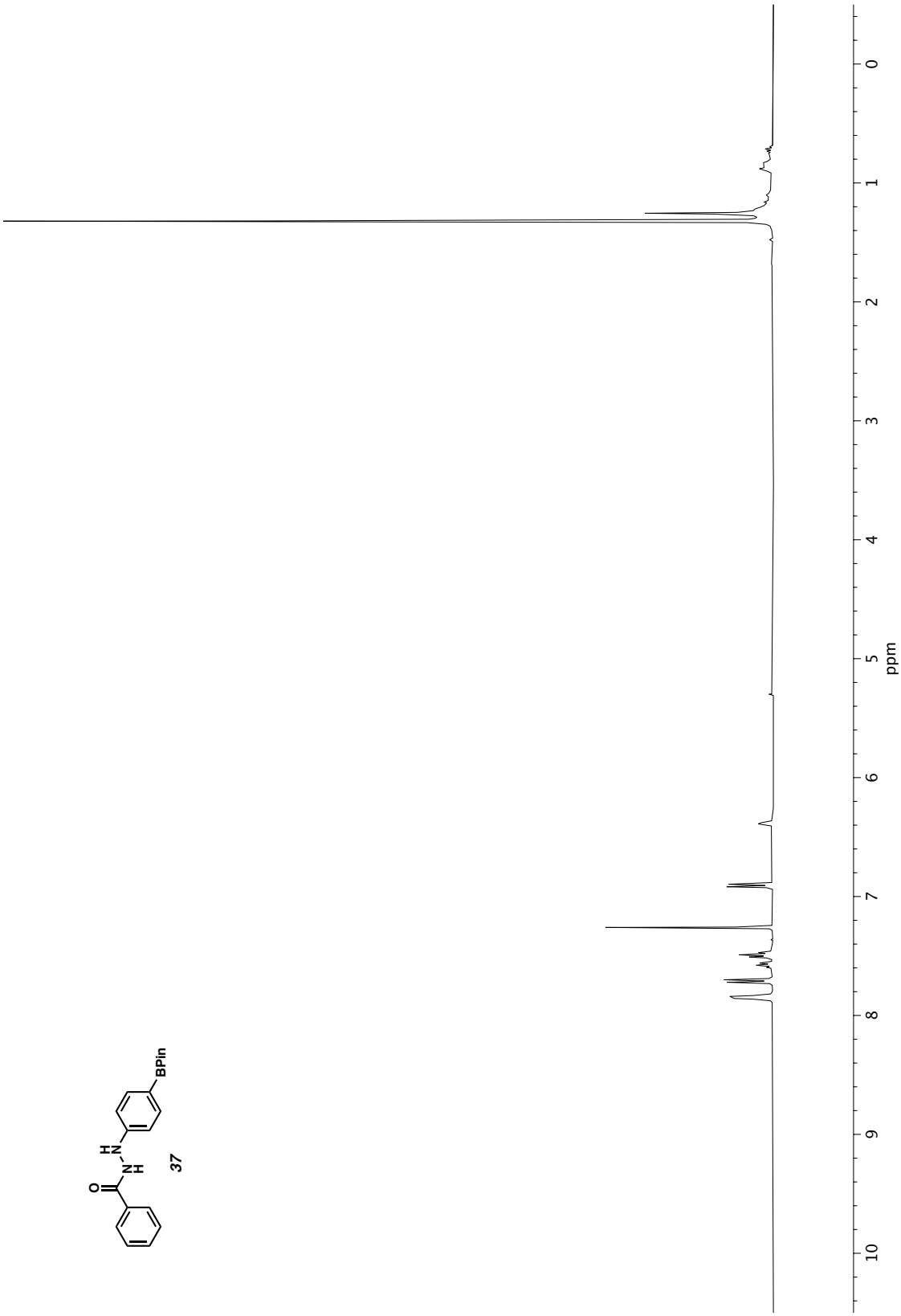


Figure A1.89 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***37****.*

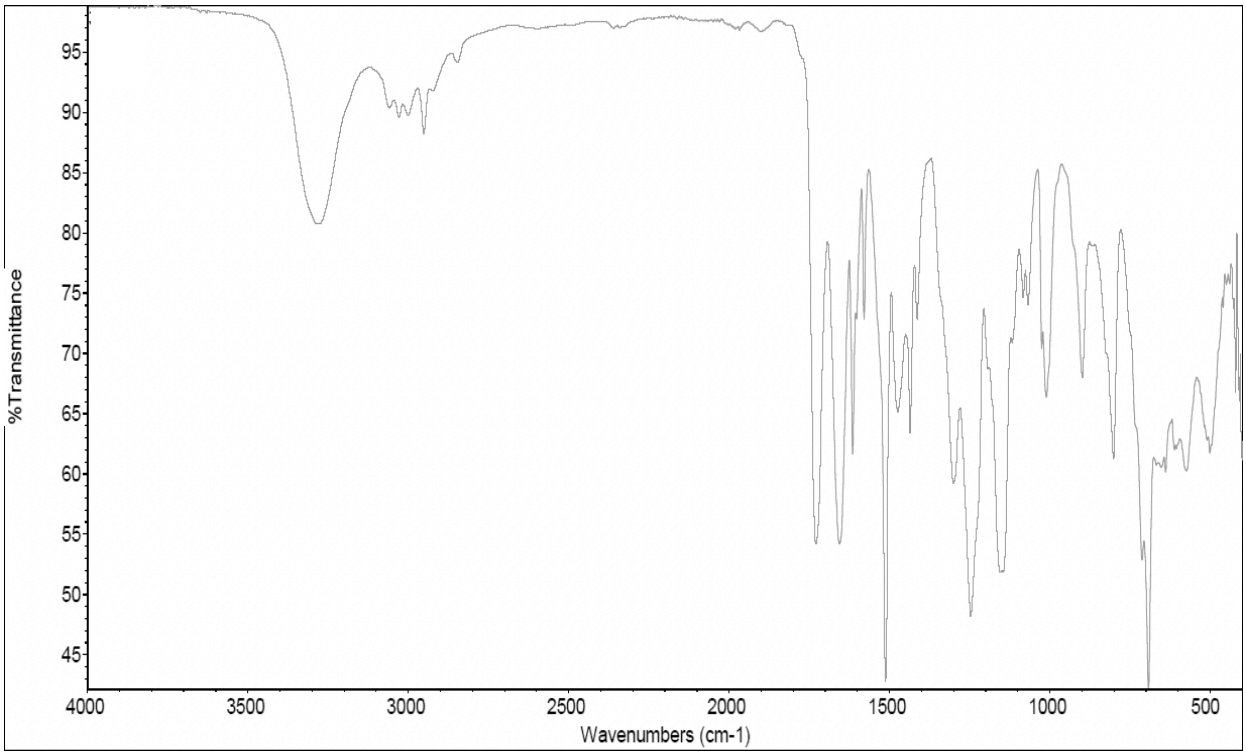


Figure A1.90 *Infrared spectrum (Thin Film) of compound **37**.*

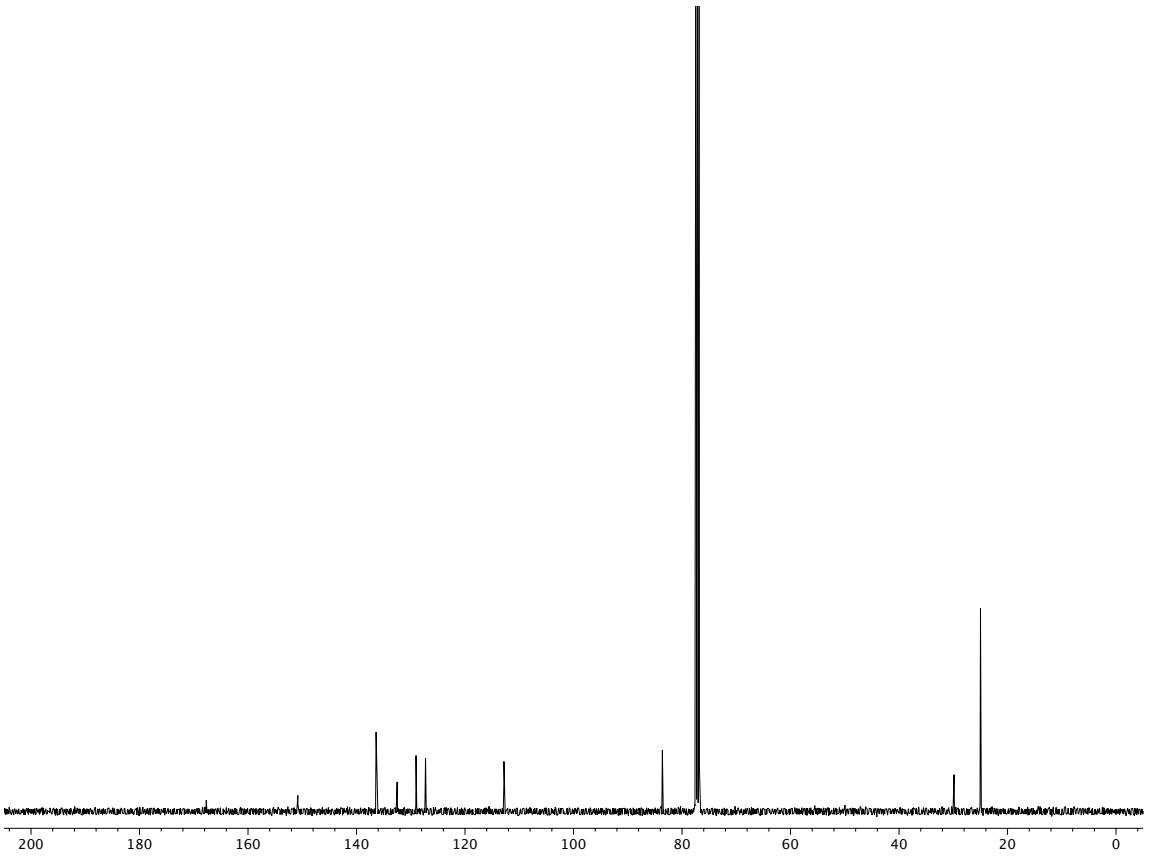


Figure A1.91 *^{13}C NMR (101 MHz, $CDCl_3$) of compound **37**.*

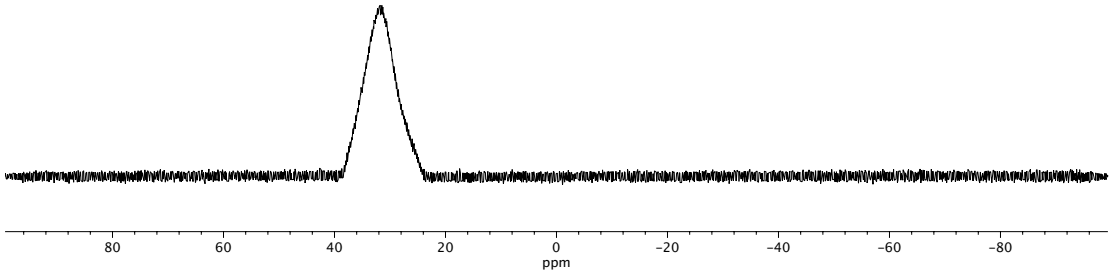


Figure A1.92 *^{11}B NMR (128 MHz, $CDCl_3$) of compound **37**.*

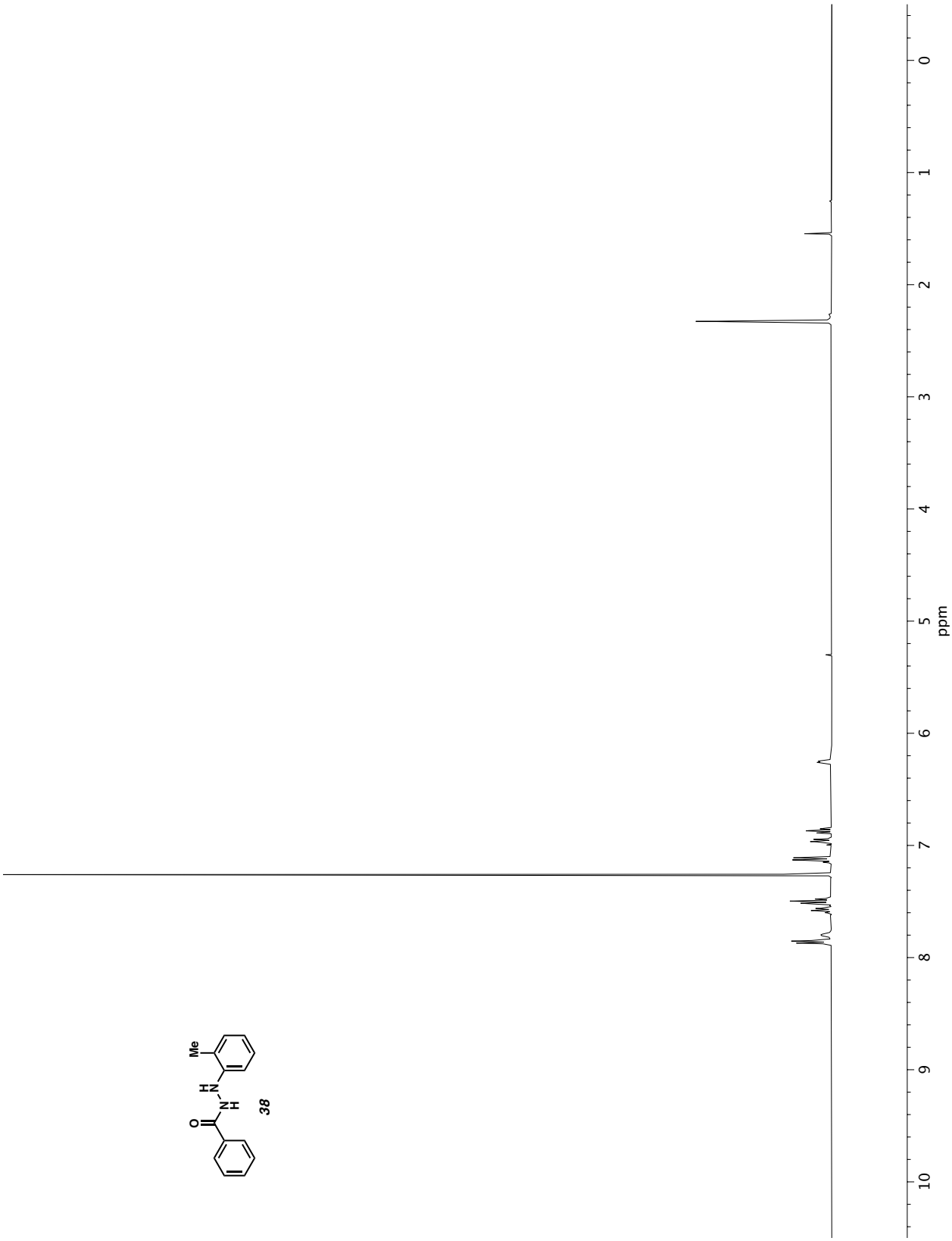


Figure A1.93 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **38**.*

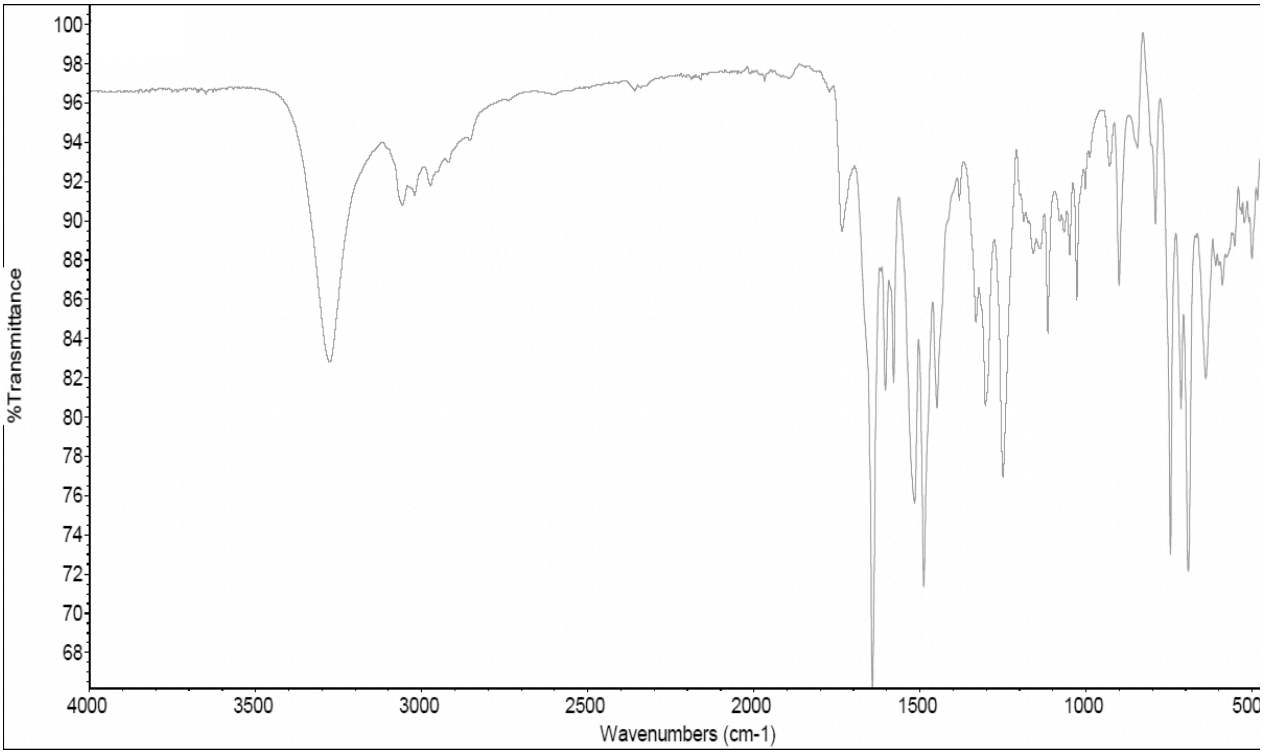


Figure A1.94 *Infrared spectrum (Thin Film) of compound* ***38****.*

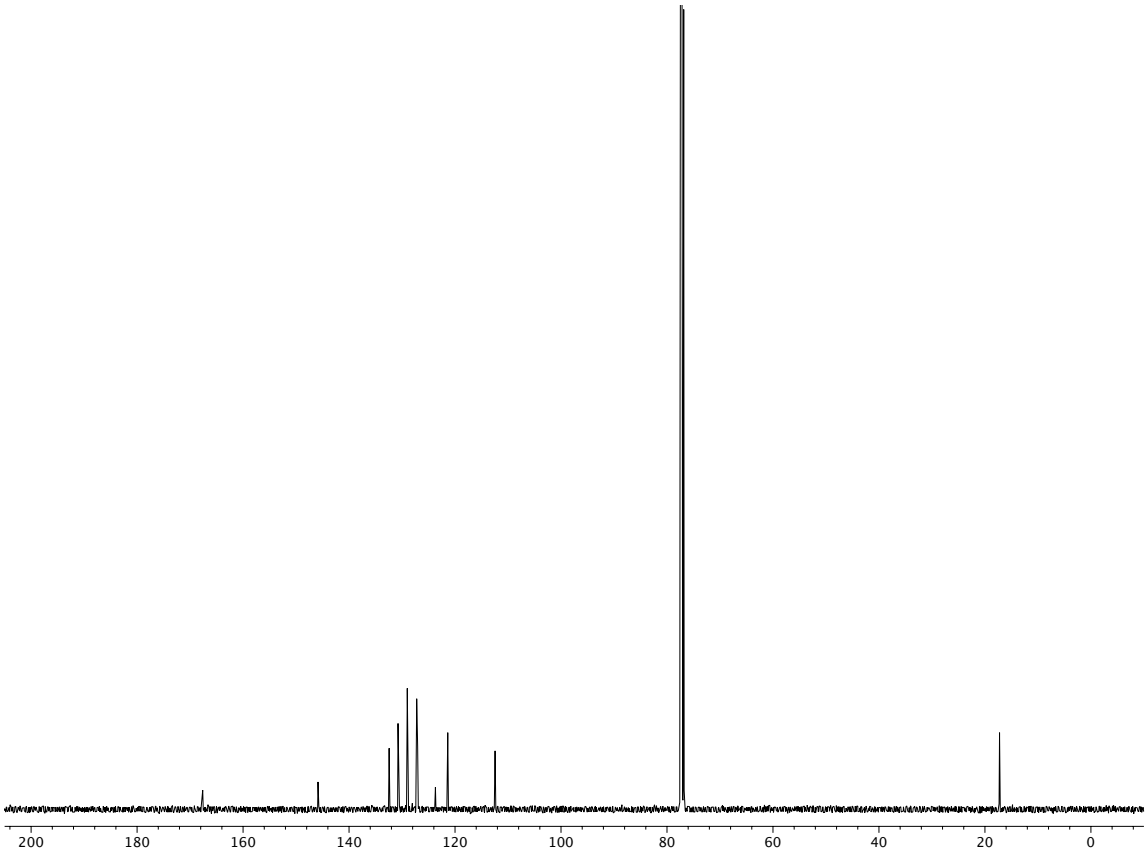


Figure A1.95 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***38****.*

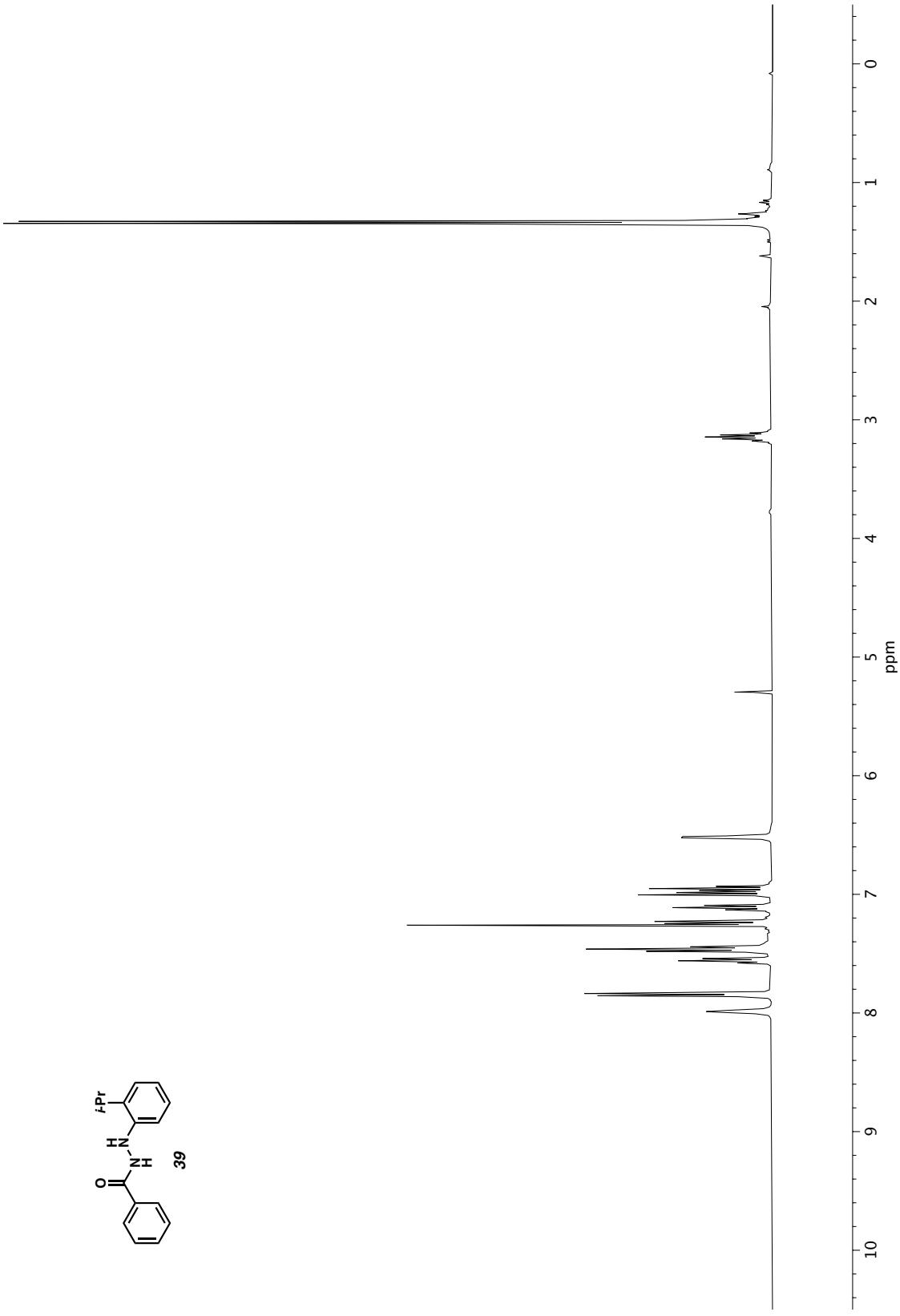


Figure A1.96 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***39***.

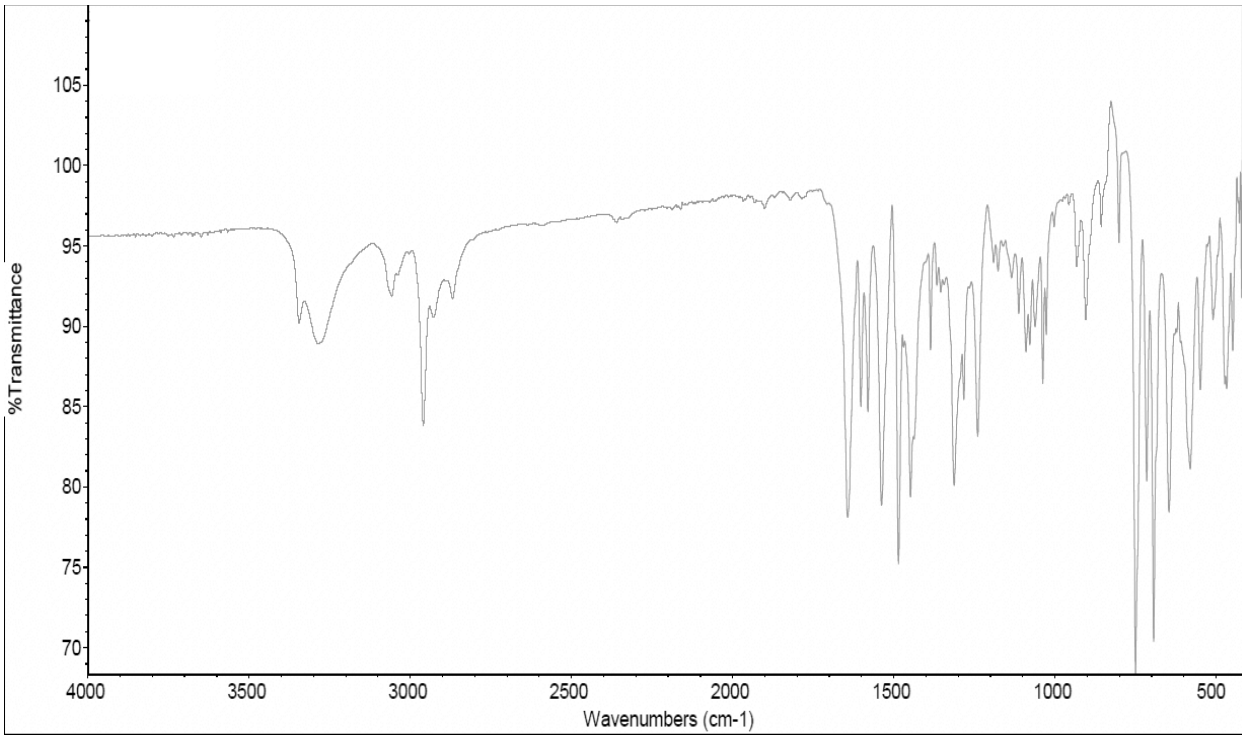


Figure A1.97 *Infrared spectrum (Thin Film) of compound* ***39***.

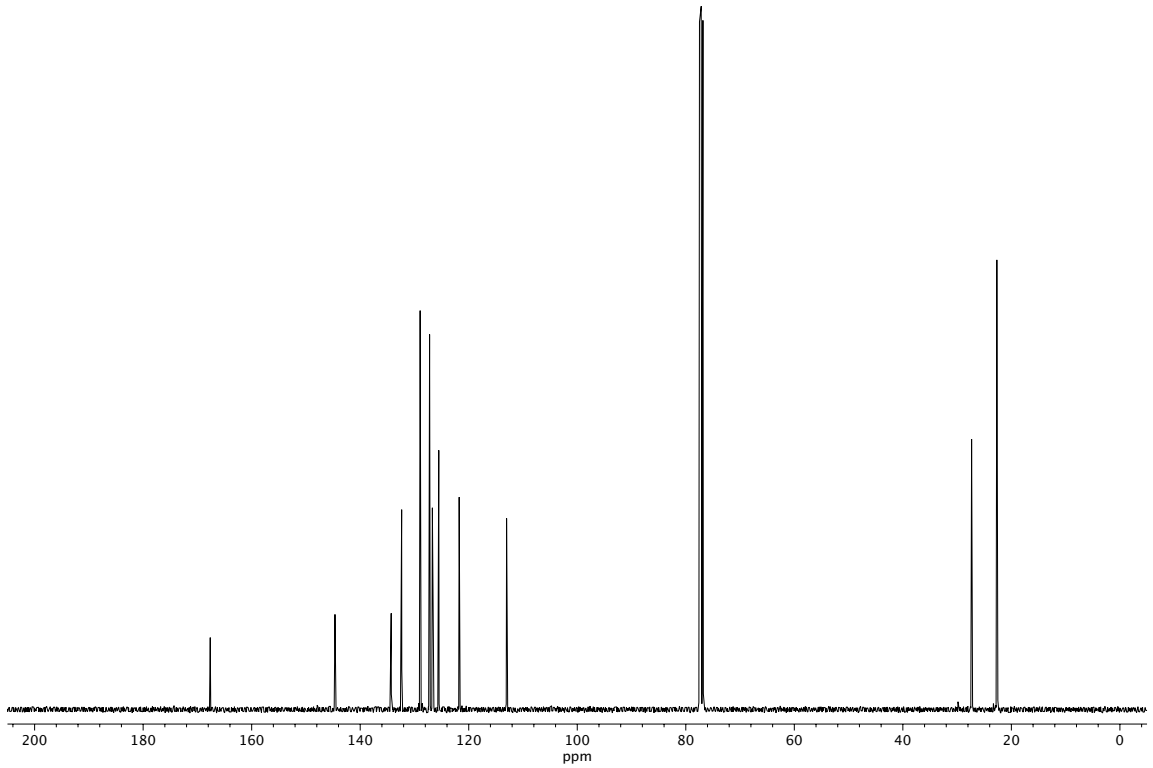


Figure A1.98 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***39***.

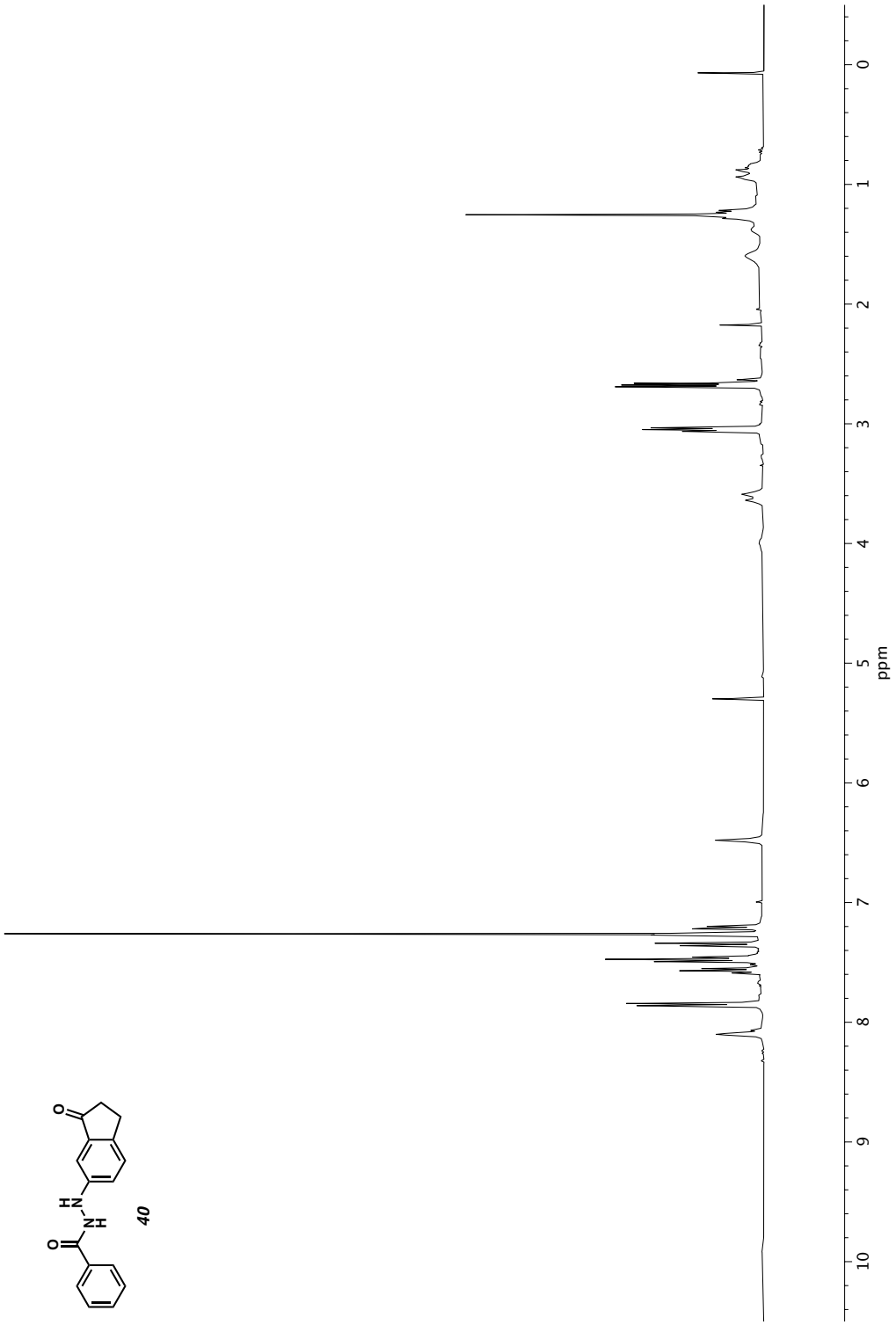


Figure A1.99 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***40***.

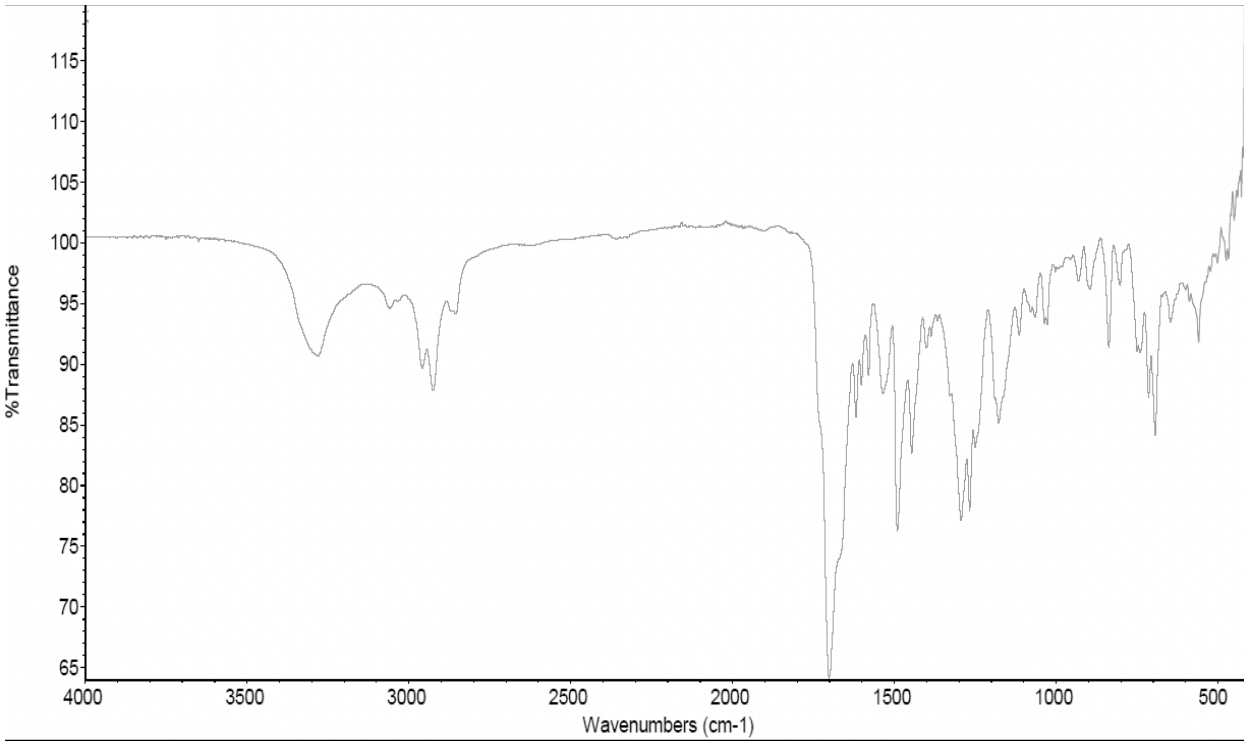


Figure A1.100 *Infrared spectrum (Thin Film) of compound* ***40***.

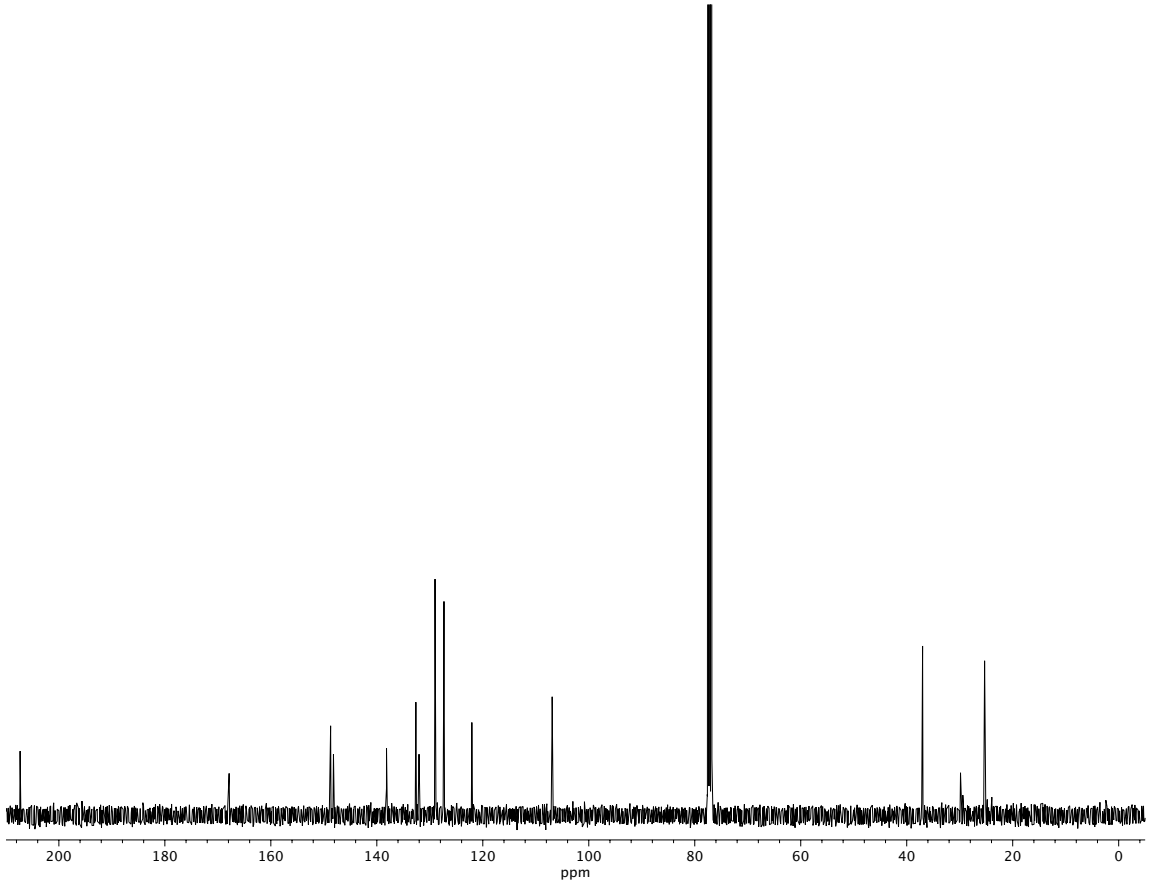


Figure A1.101 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***40***.

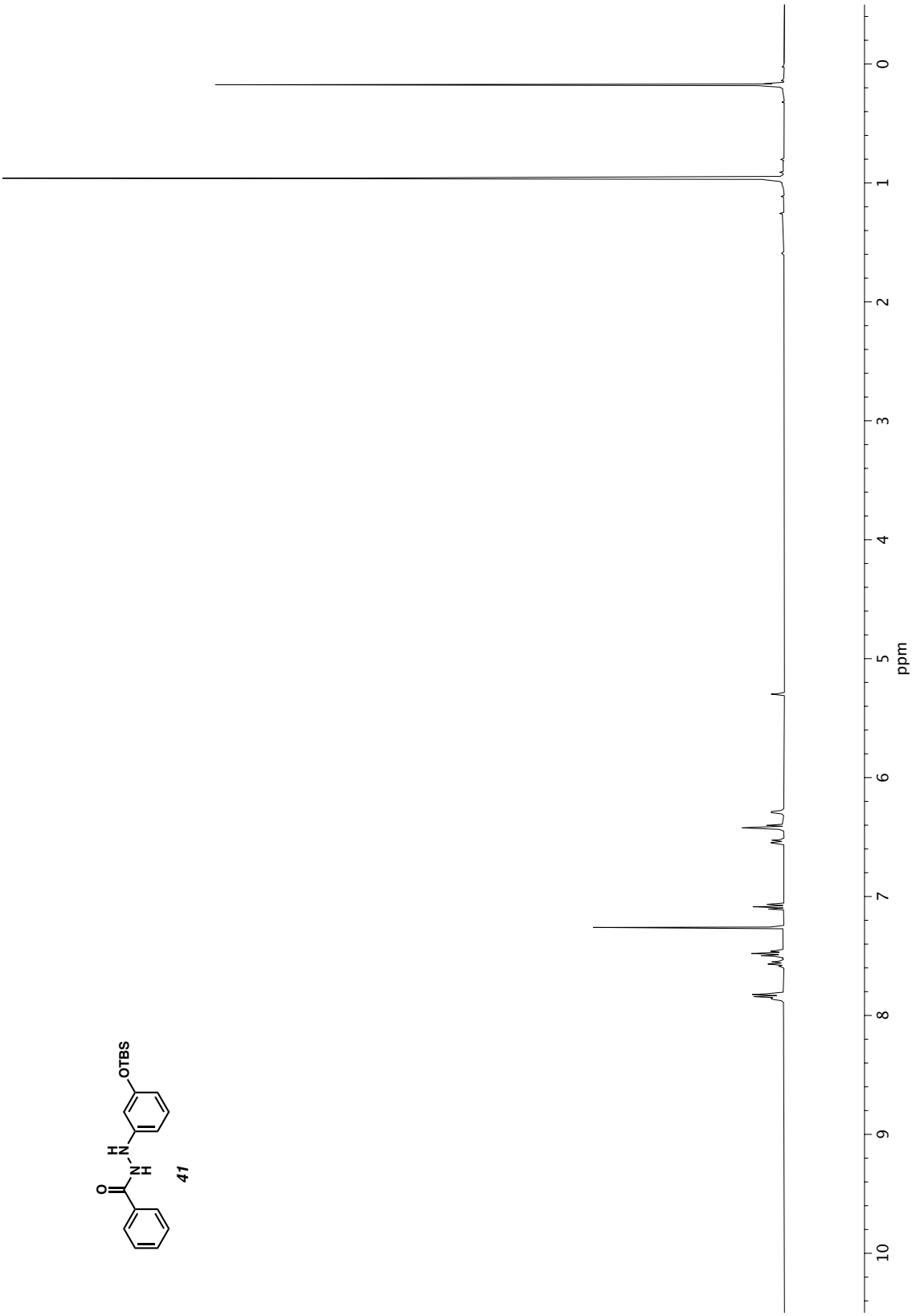


Figure A1.102 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***41***.

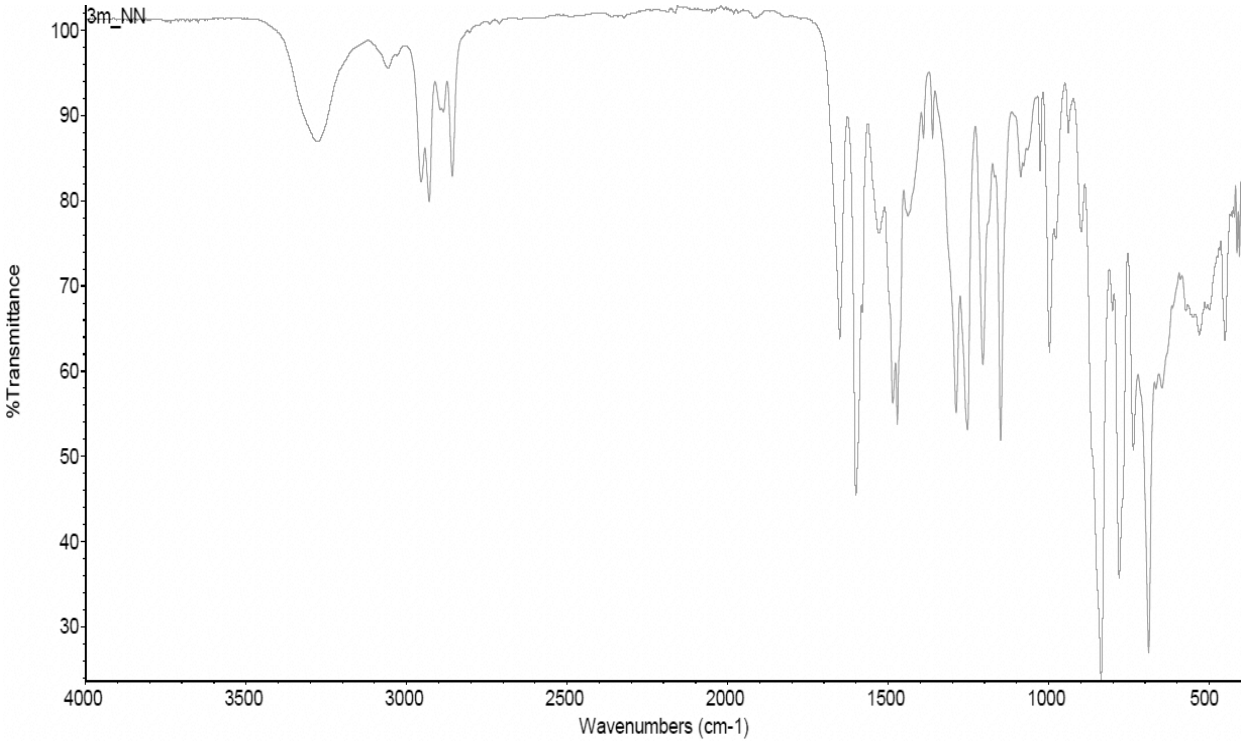


Figure A1.103 *Infrared spectrum (Thin Film) of compound* ***41***.

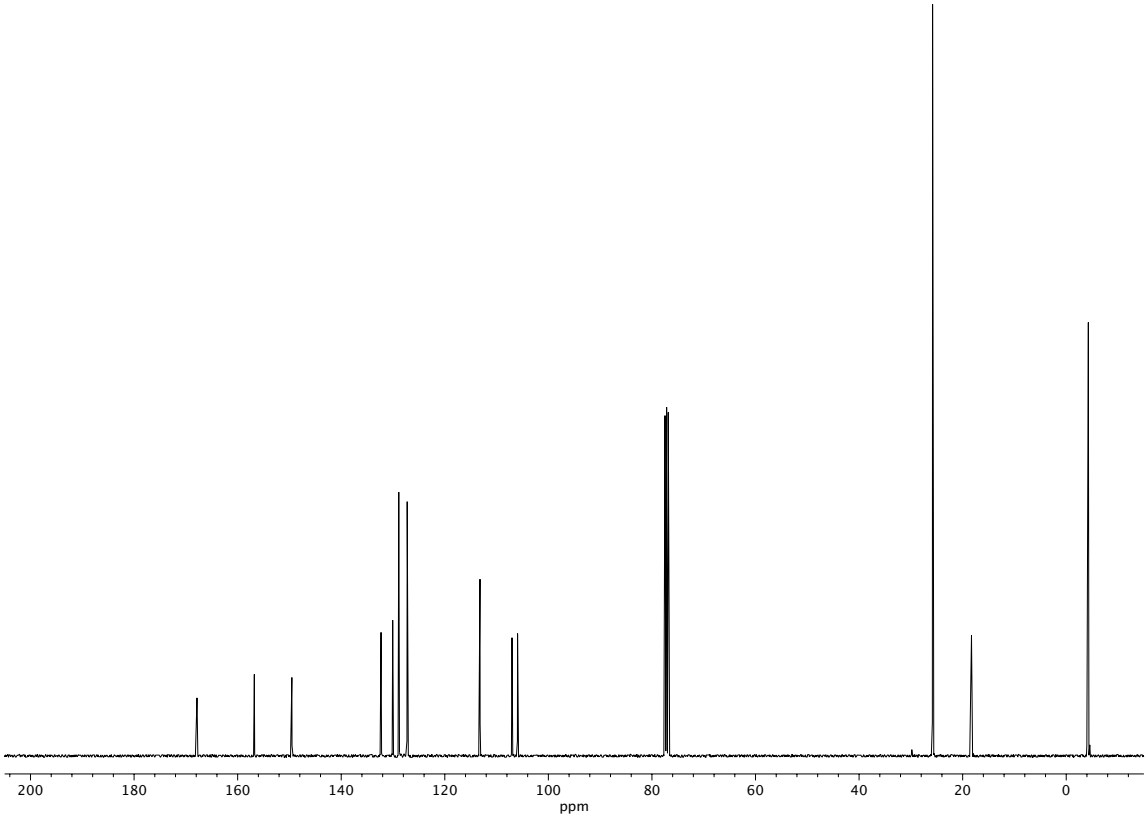


Figure A1.104 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***41***.

Figure A1.105 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***42***.

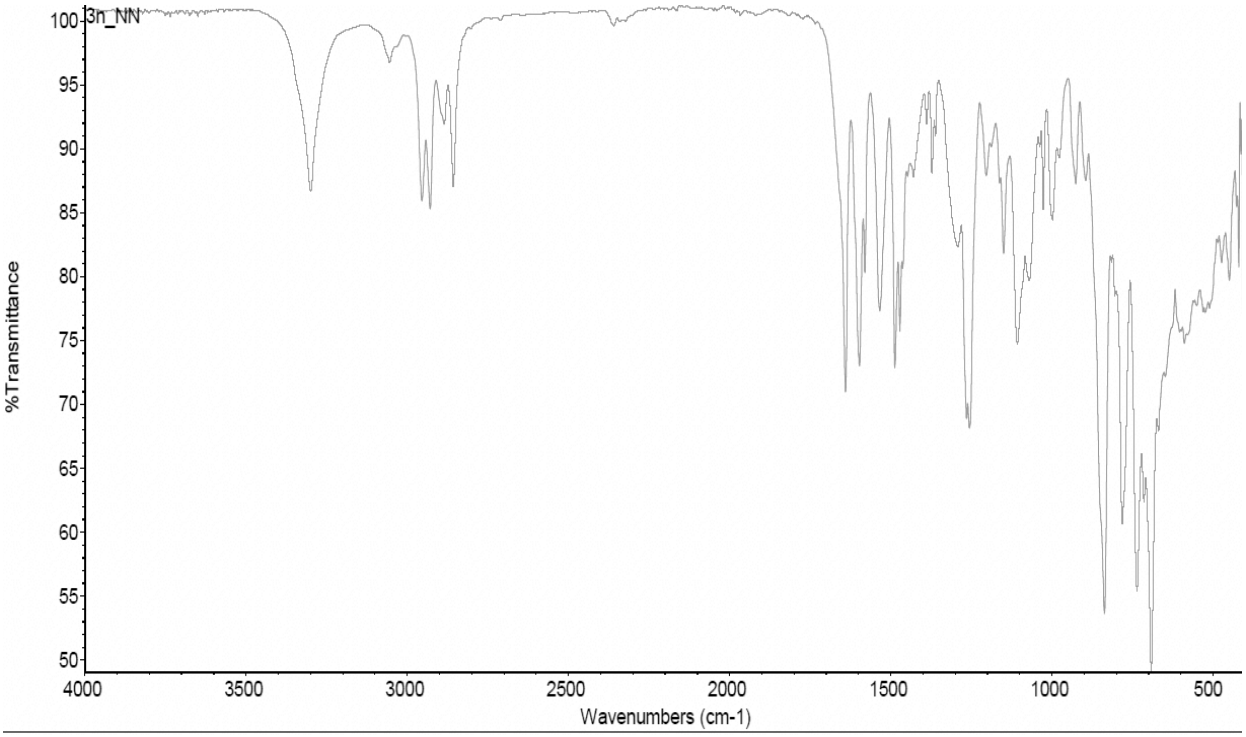


Figure A1.106 *Infrared spectrum (Thin Film) of compound* ***42***.

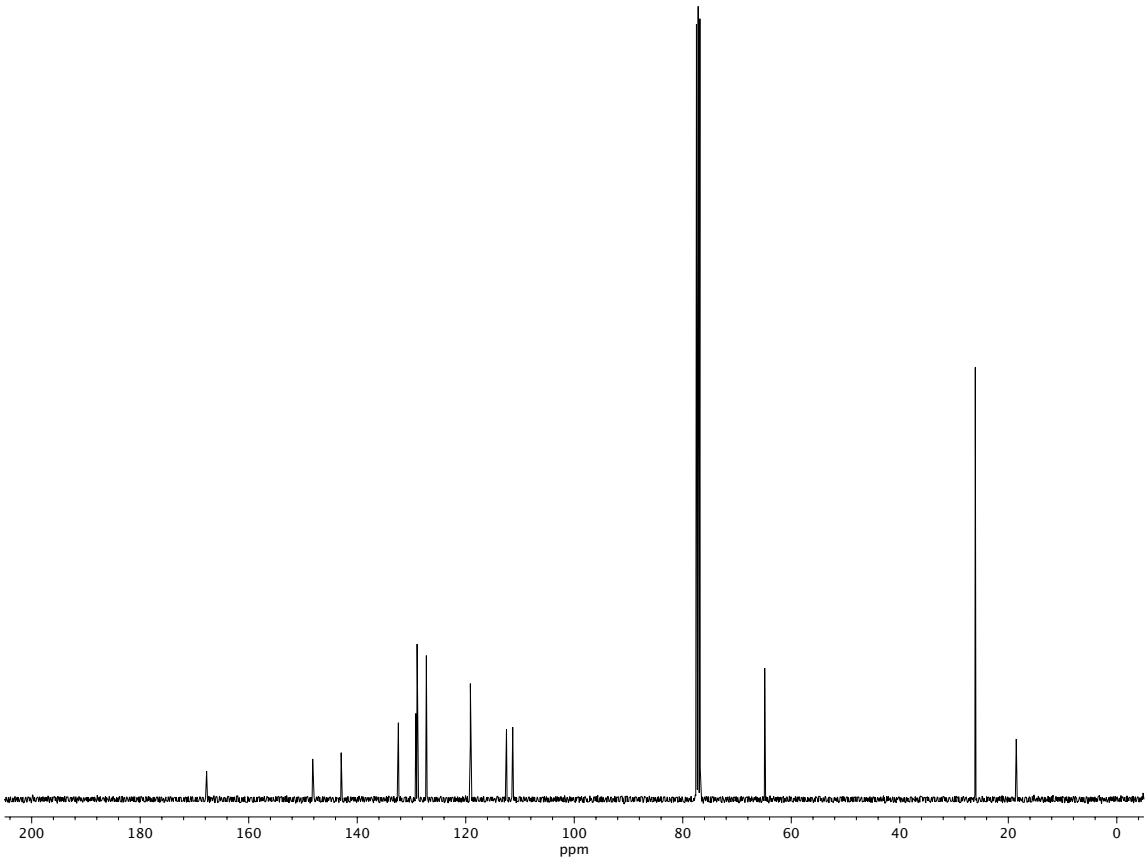


Figure A1.107 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***42***.

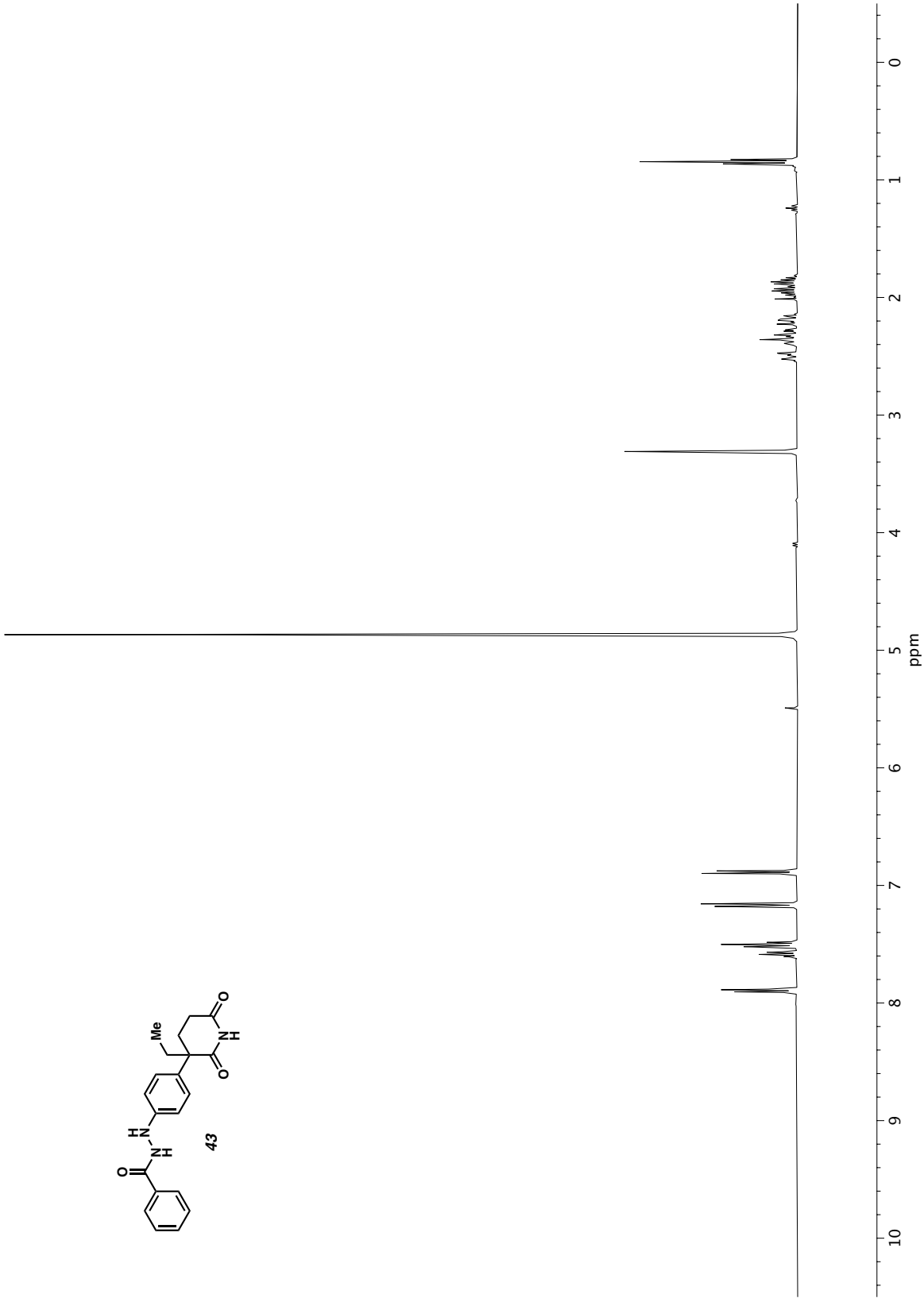


Figure A1.108 *^1H NMR (400 MHz, CD_3OD) of compound* ***43***.

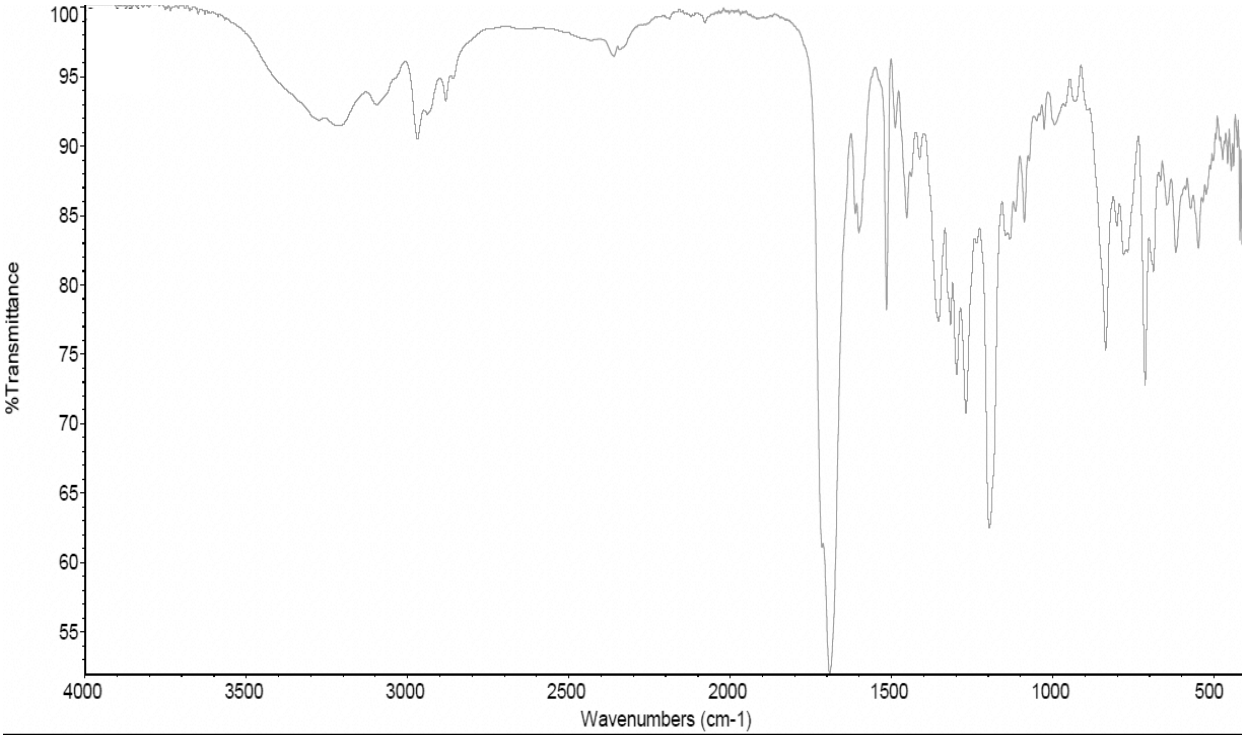


Figure A1.109 *Infrared spectrum (Thin Film) of compound* ***43***.

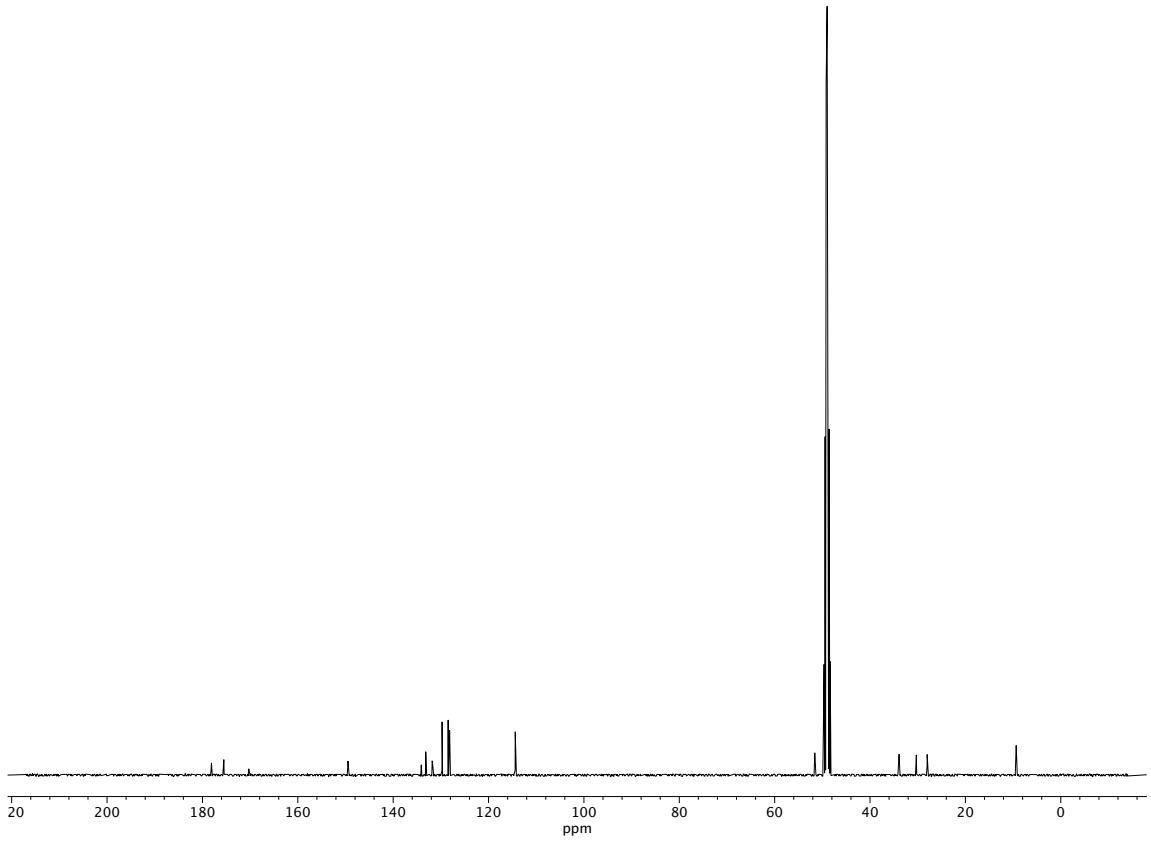


Figure A1.110 *^{13}C NMR (101 MHz, CD_3OD) of compound* ***43***.

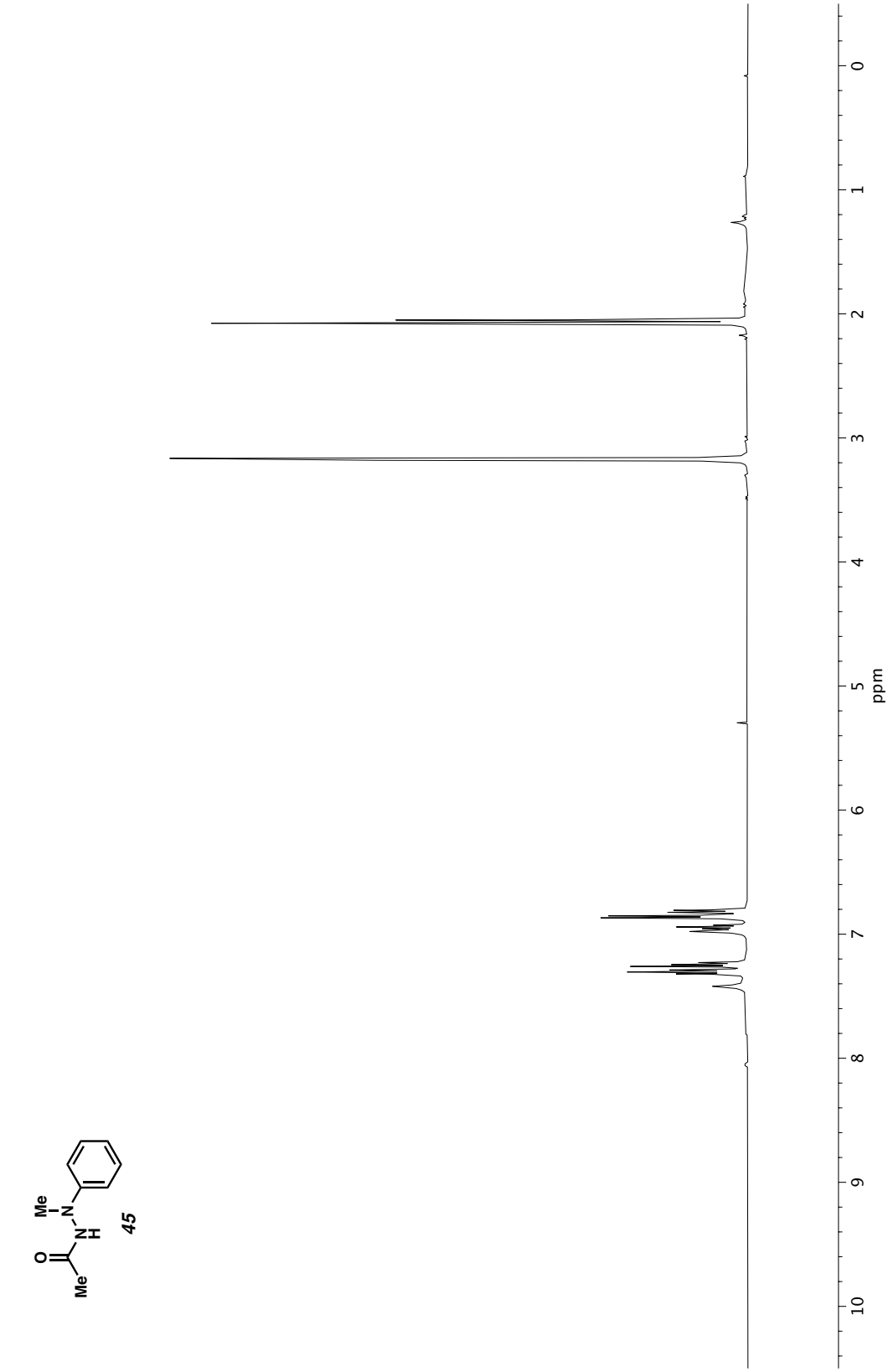


Figure A1.111 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***45***.

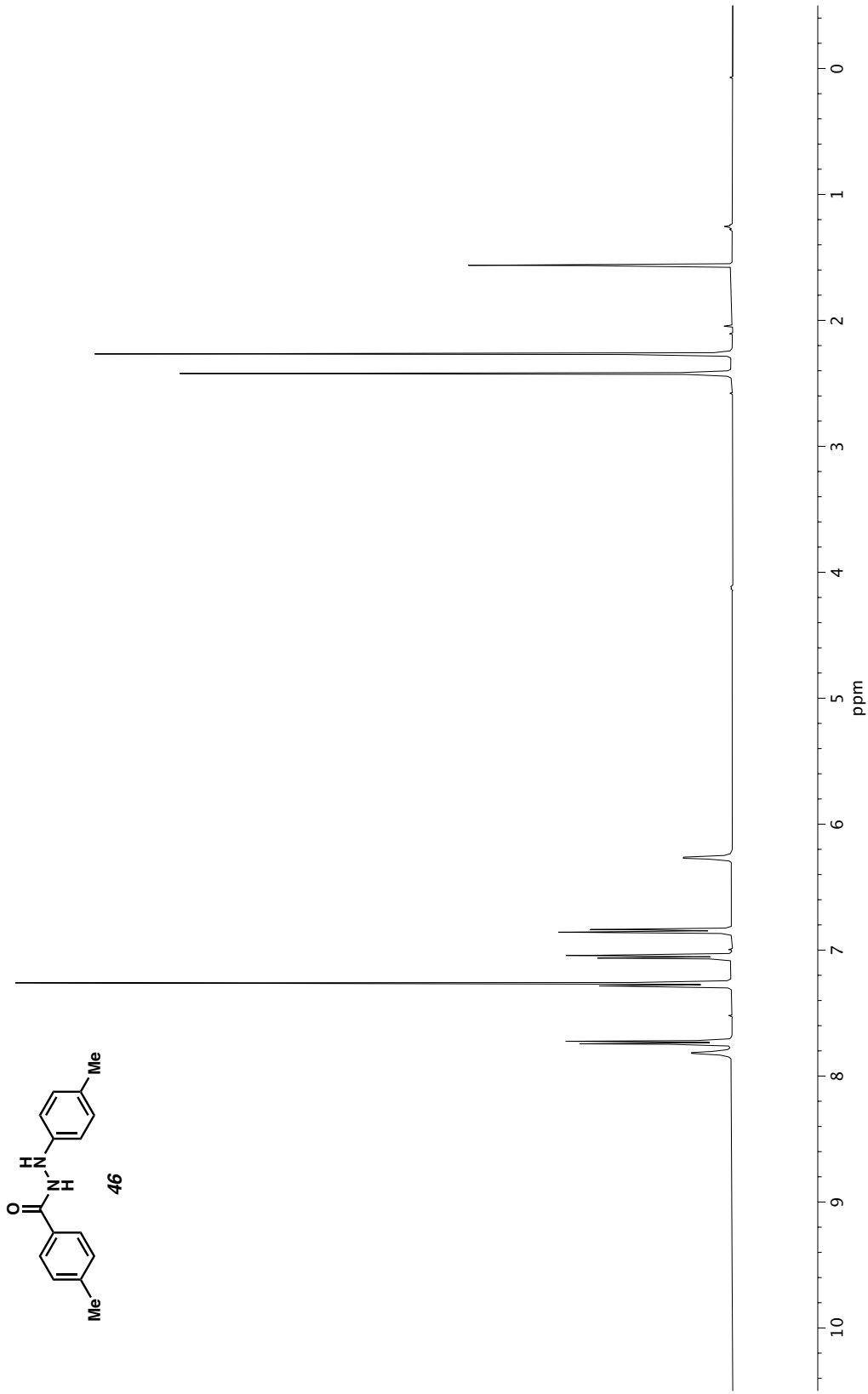


Figure A1.112 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***46***.

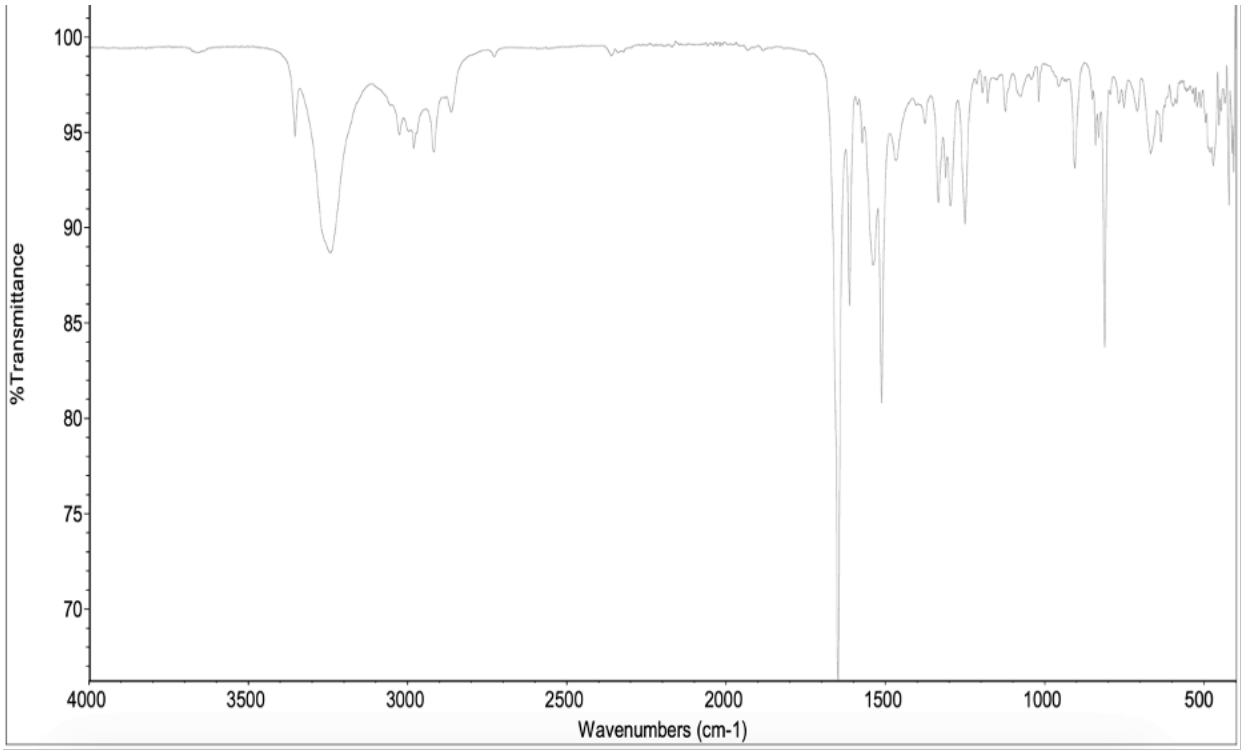


Figure A1.113 *Infrared spectrum (Thin Film) of compound* ***46****.*

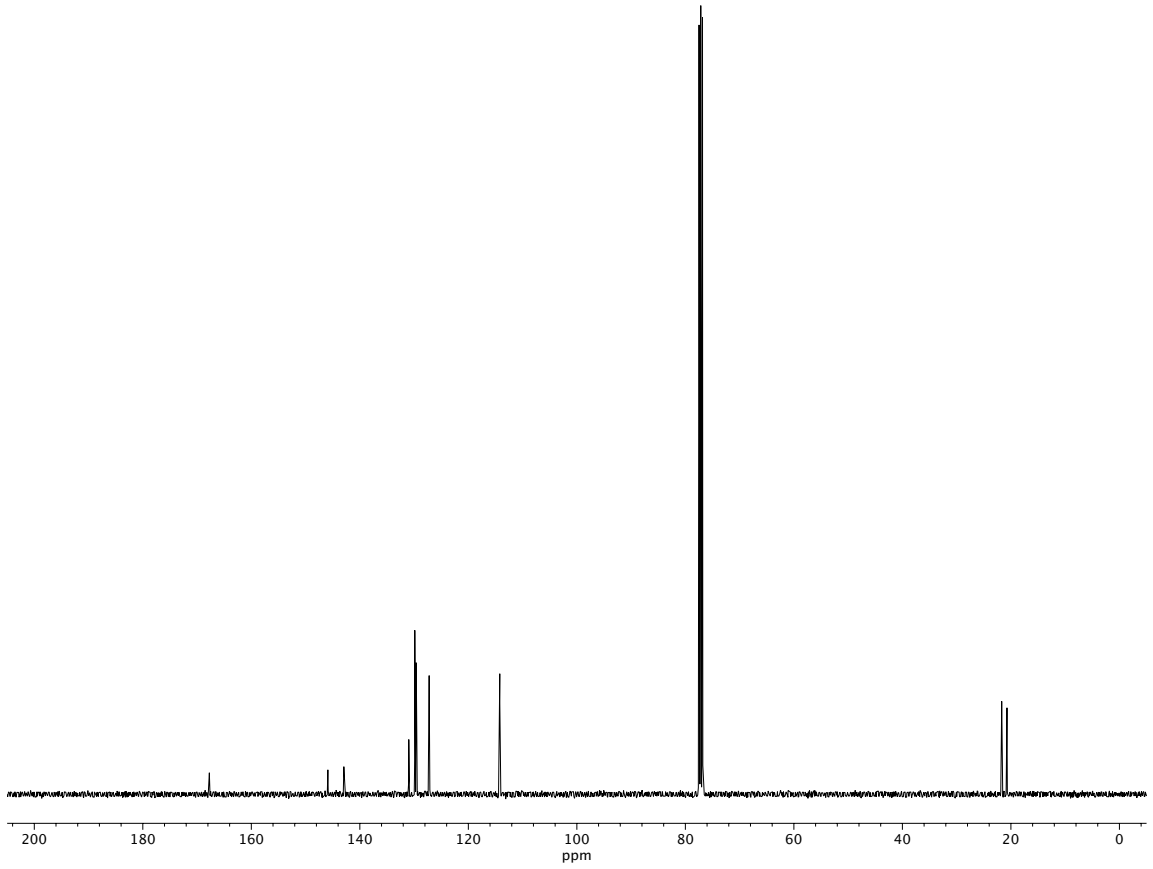


Figure A1.114 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***46****.*

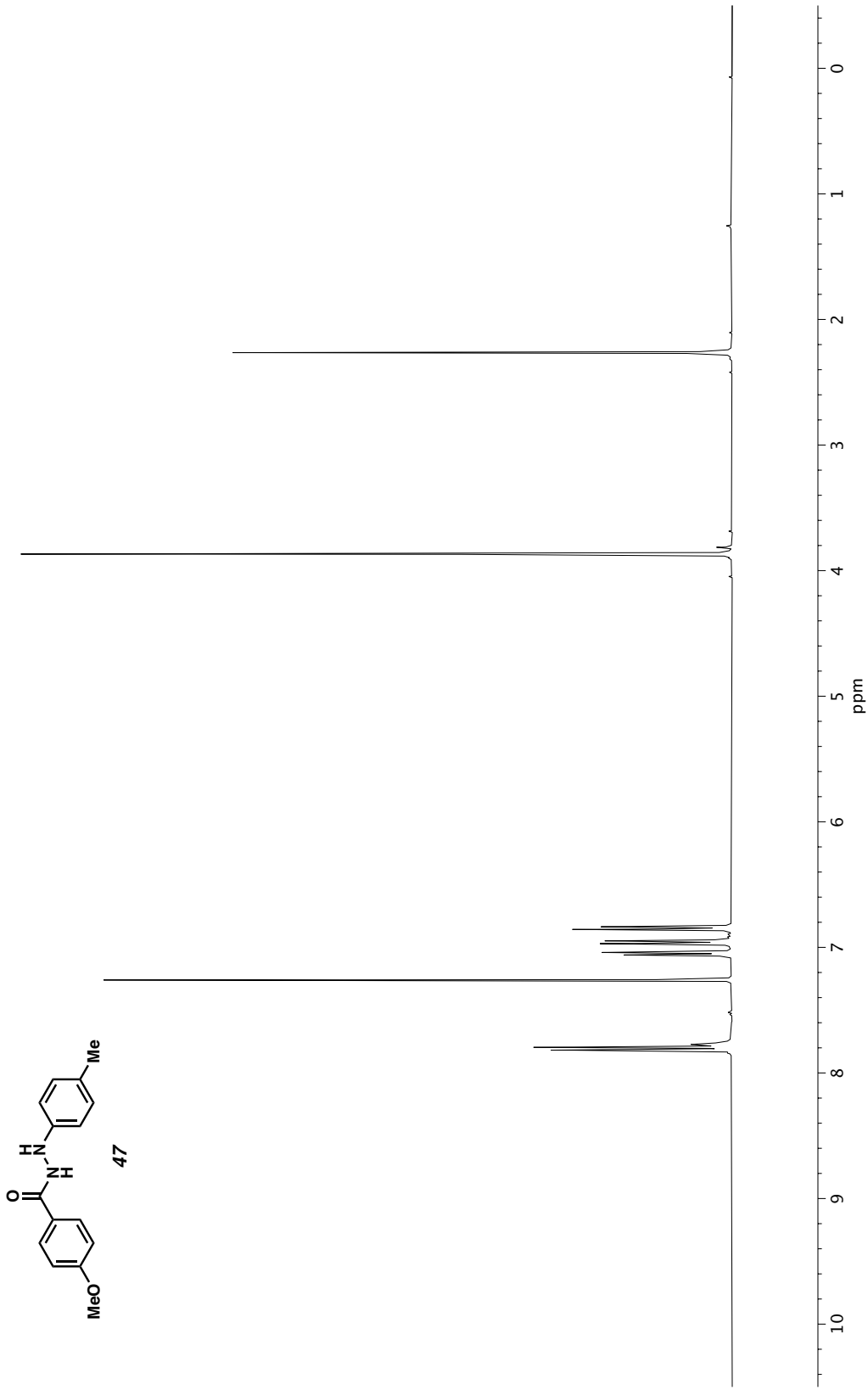


Figure A1.115 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***47****.*

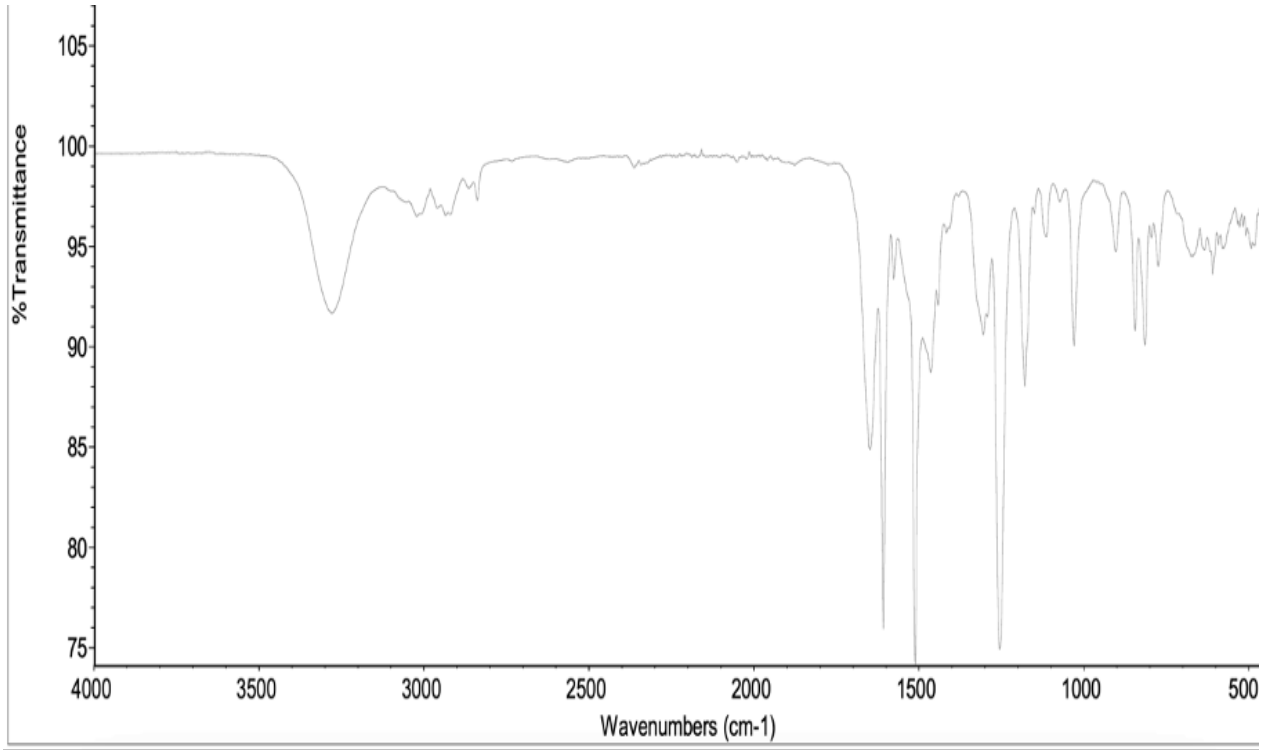


Figure A1.116 *Infrared spectrum (Thin Film) of compound* ***47****.*

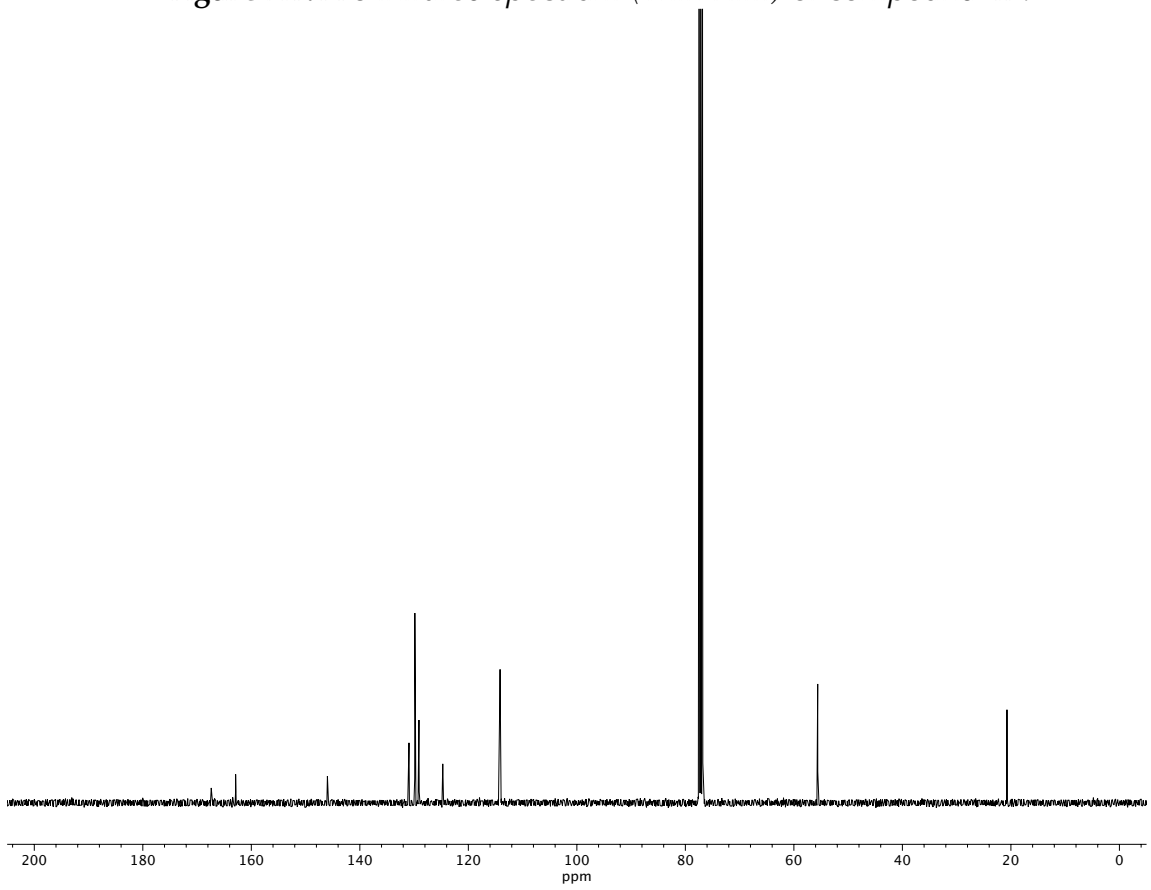


Figure A1.117 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***47****.*

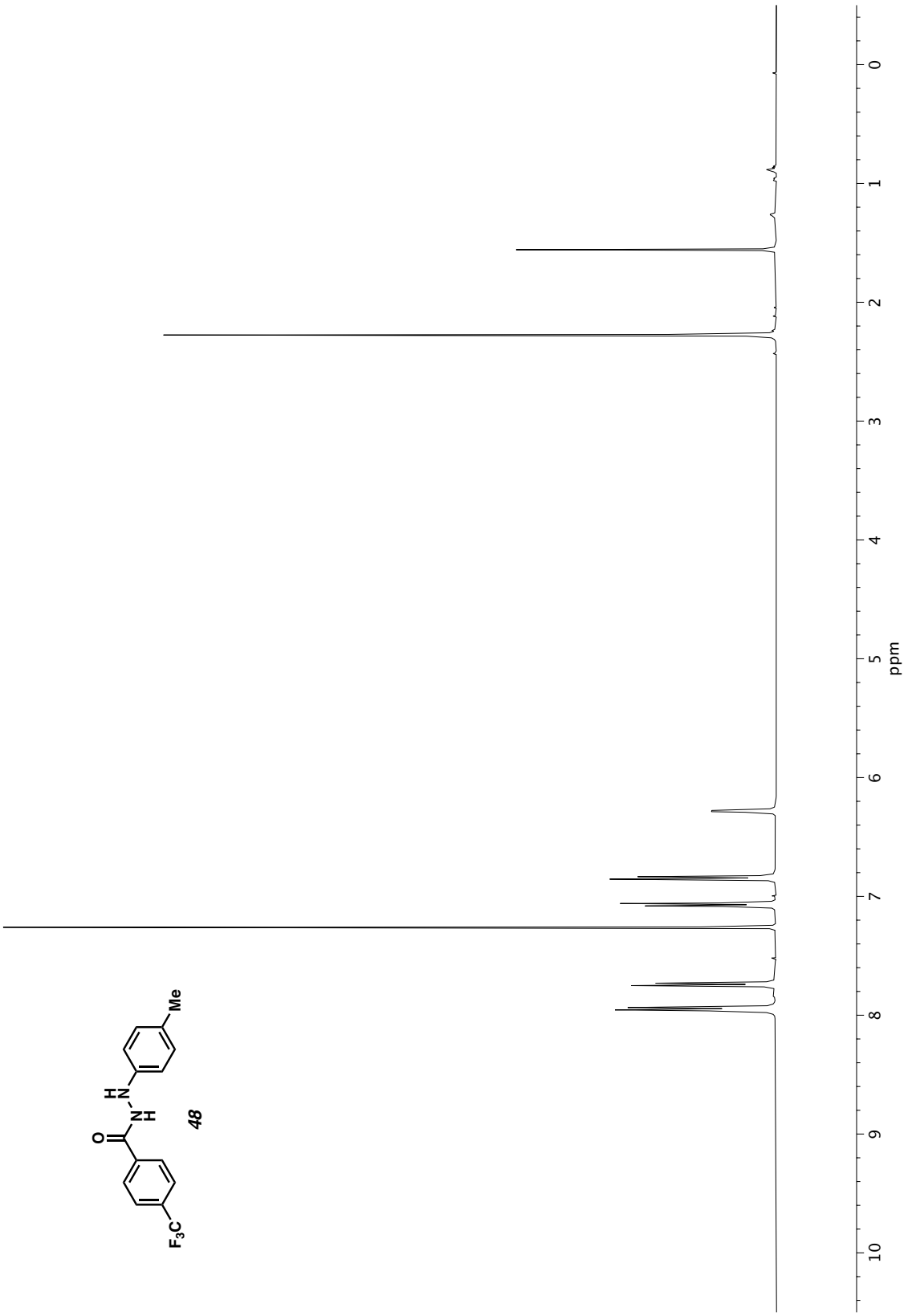


Figure A1.118 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***48****.*

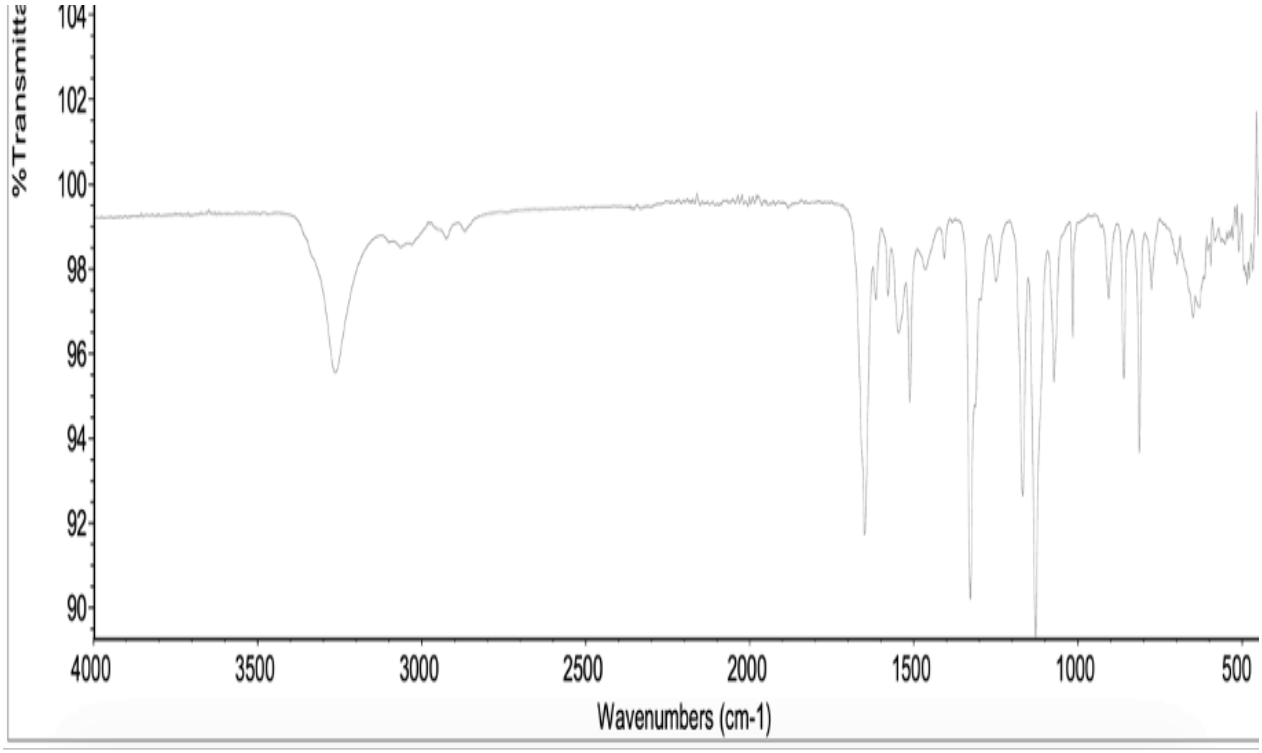


Figure A1.119 *Infrared spectrum (Thin Film) of compound* ***48****.*

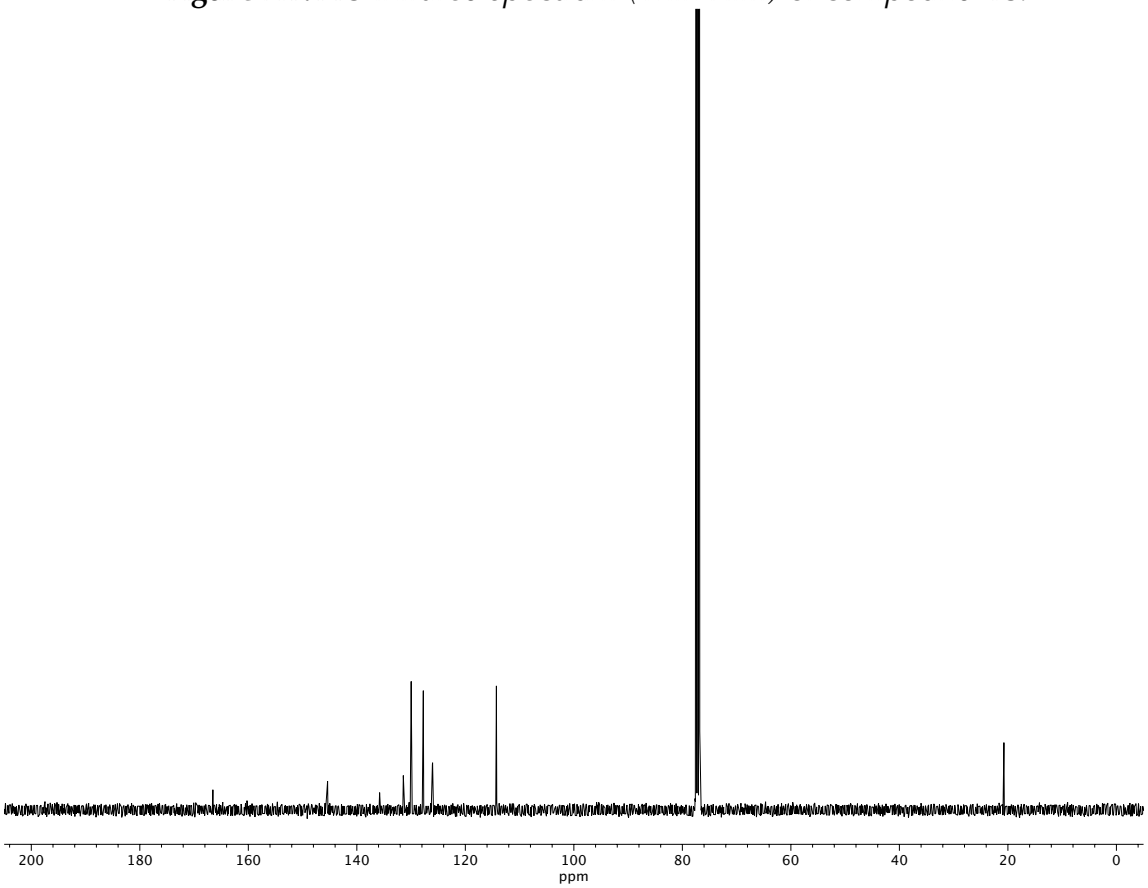


Figure A.1.120 *^{13}C NMR (101 MHz, $(CD_3)_2CO$) of compound* ***48****.*

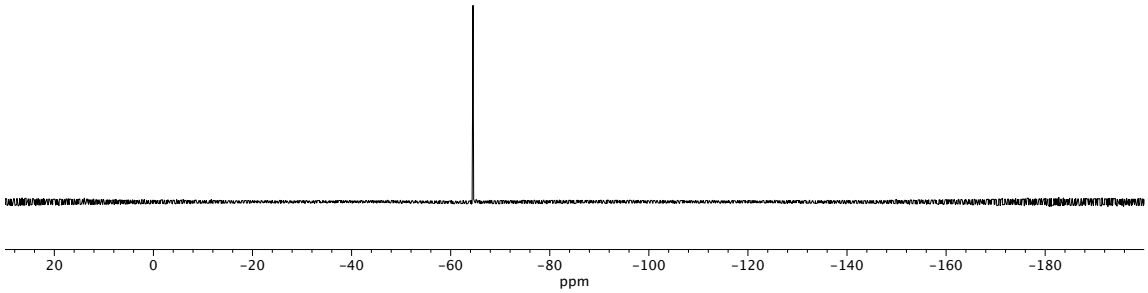


Figure A1.121 *^{19}F NMR (282 MHz, CD_3OD) of compound **48**.*

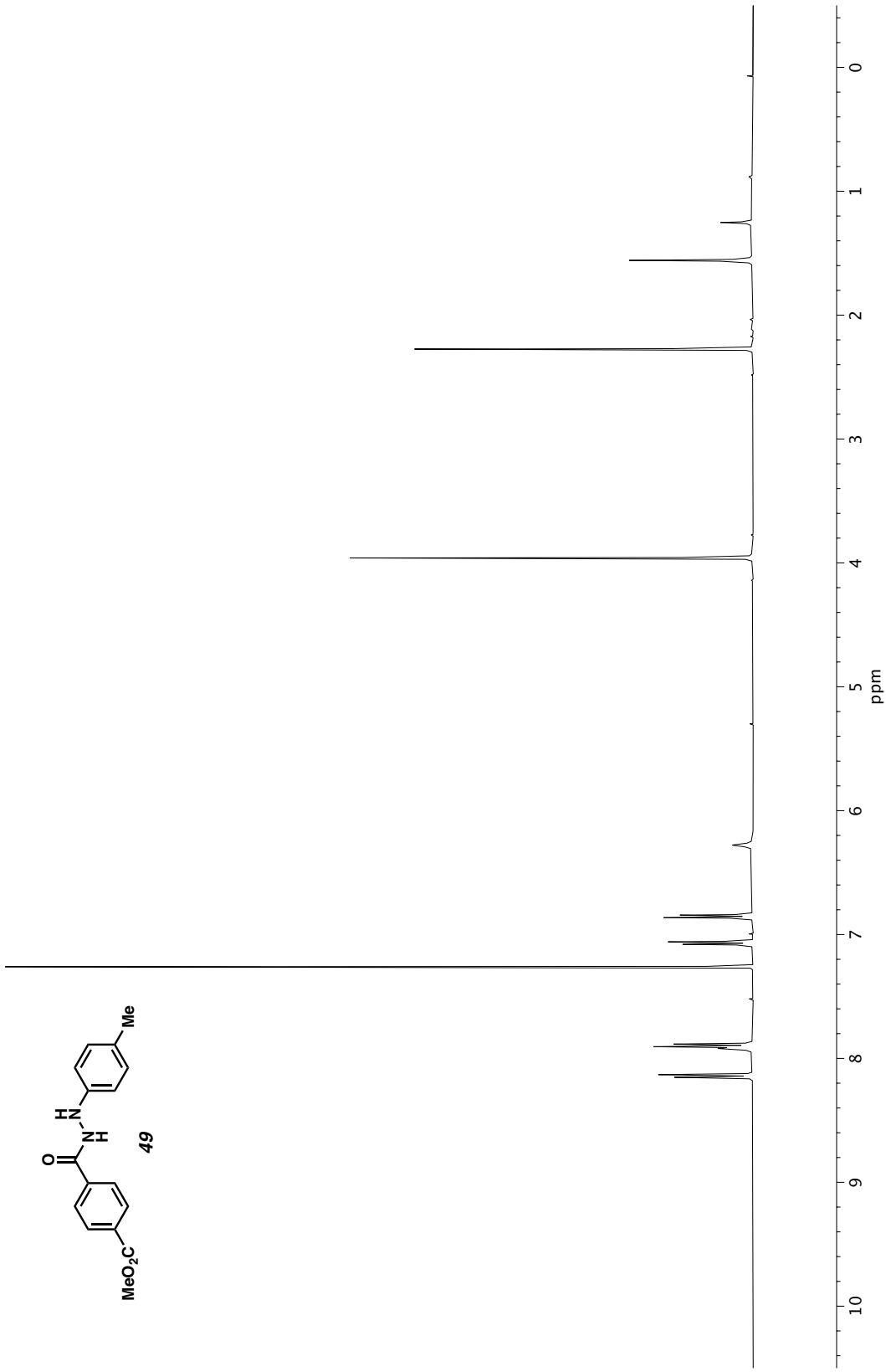


Figure A1.122 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***49***.

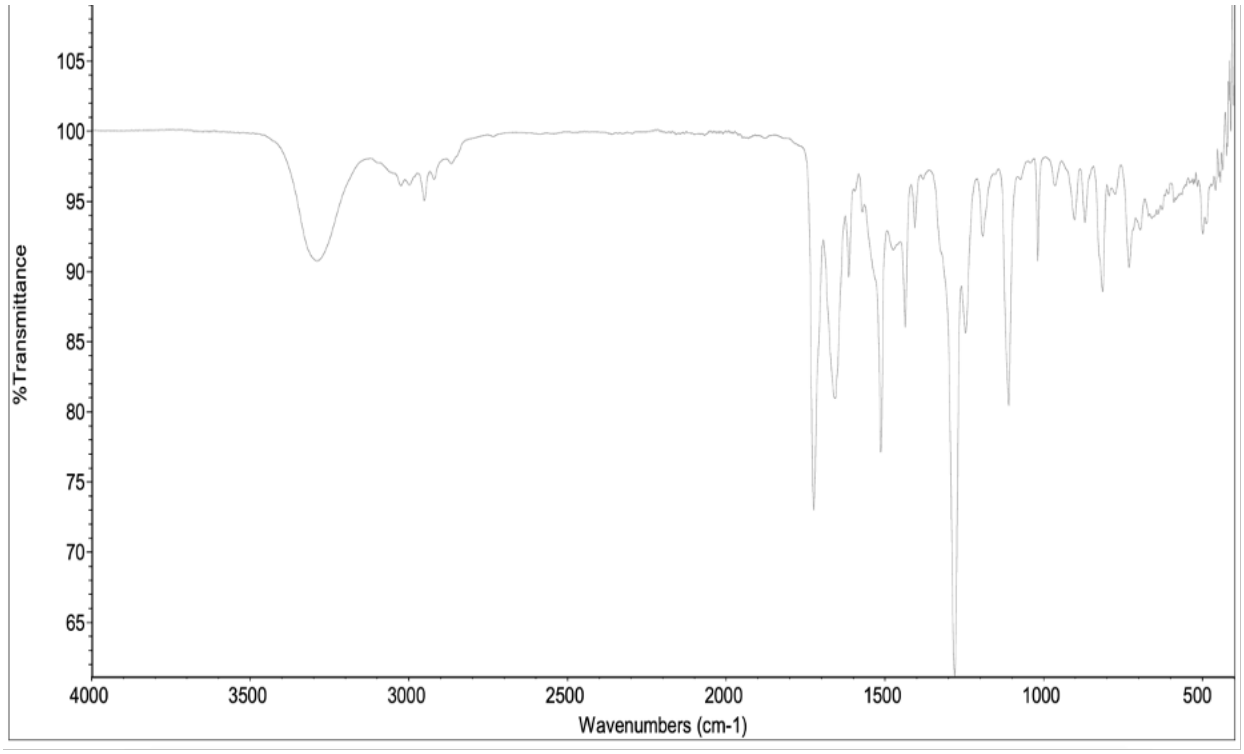


Figure A1.123 *Infrared spectrum (Thin Film) of compound* ***49***.

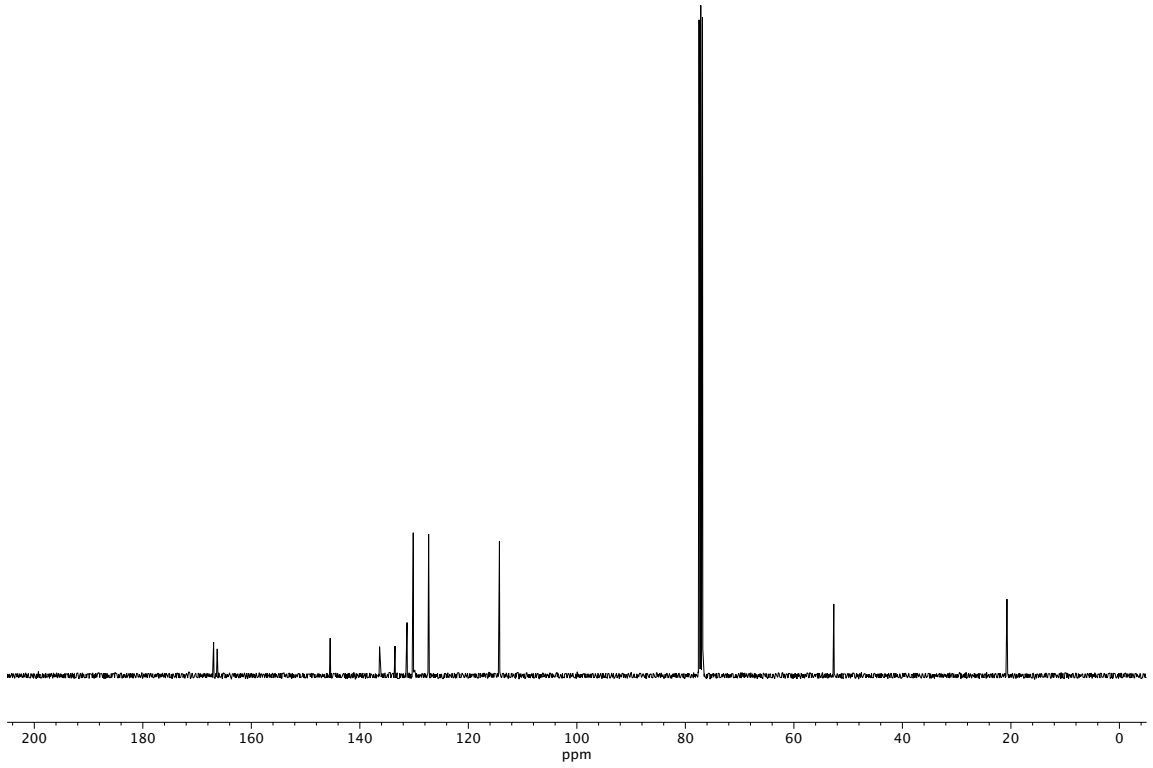


Figure A1.124 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***49***.

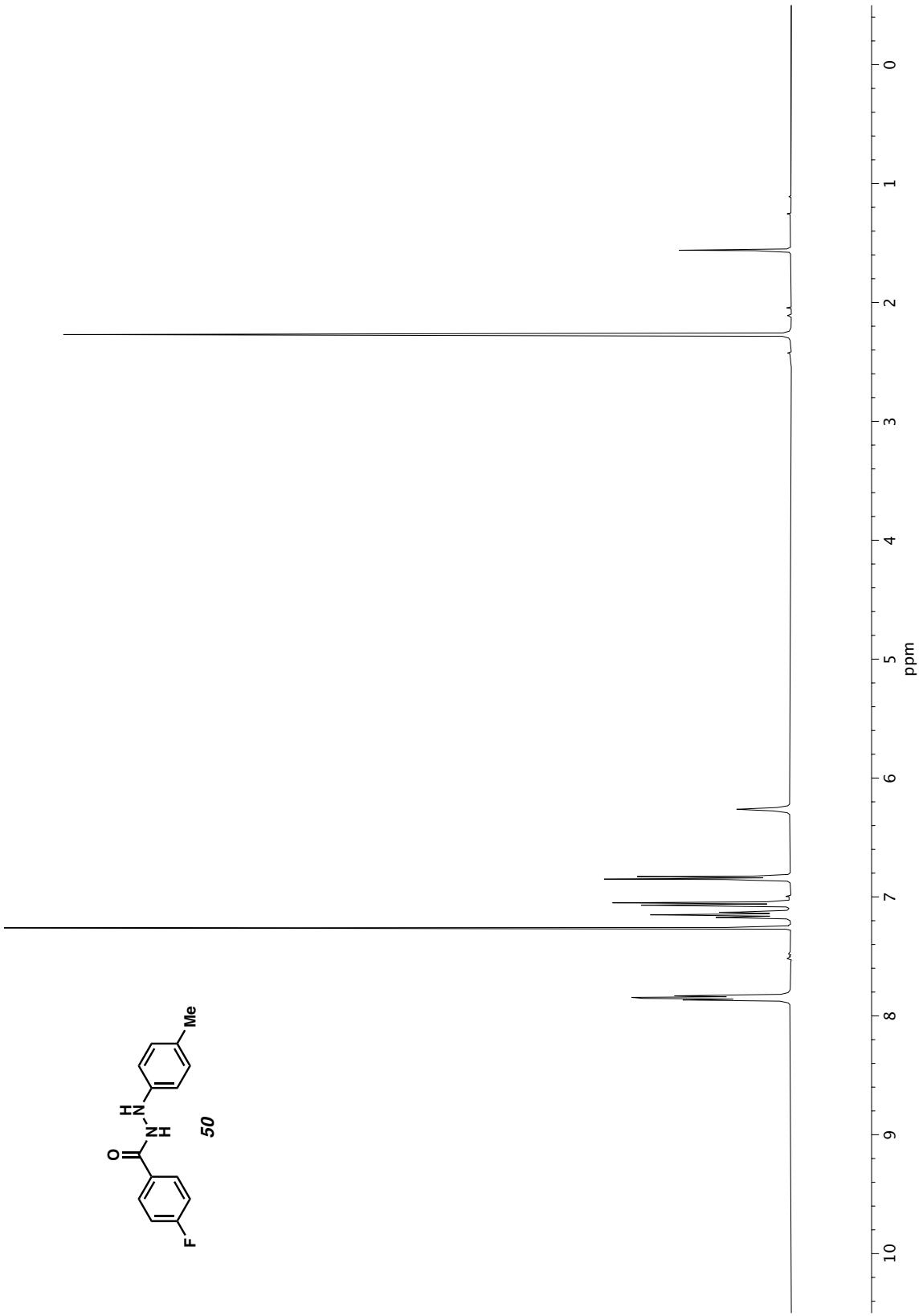


Figure A1.125 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***50***.

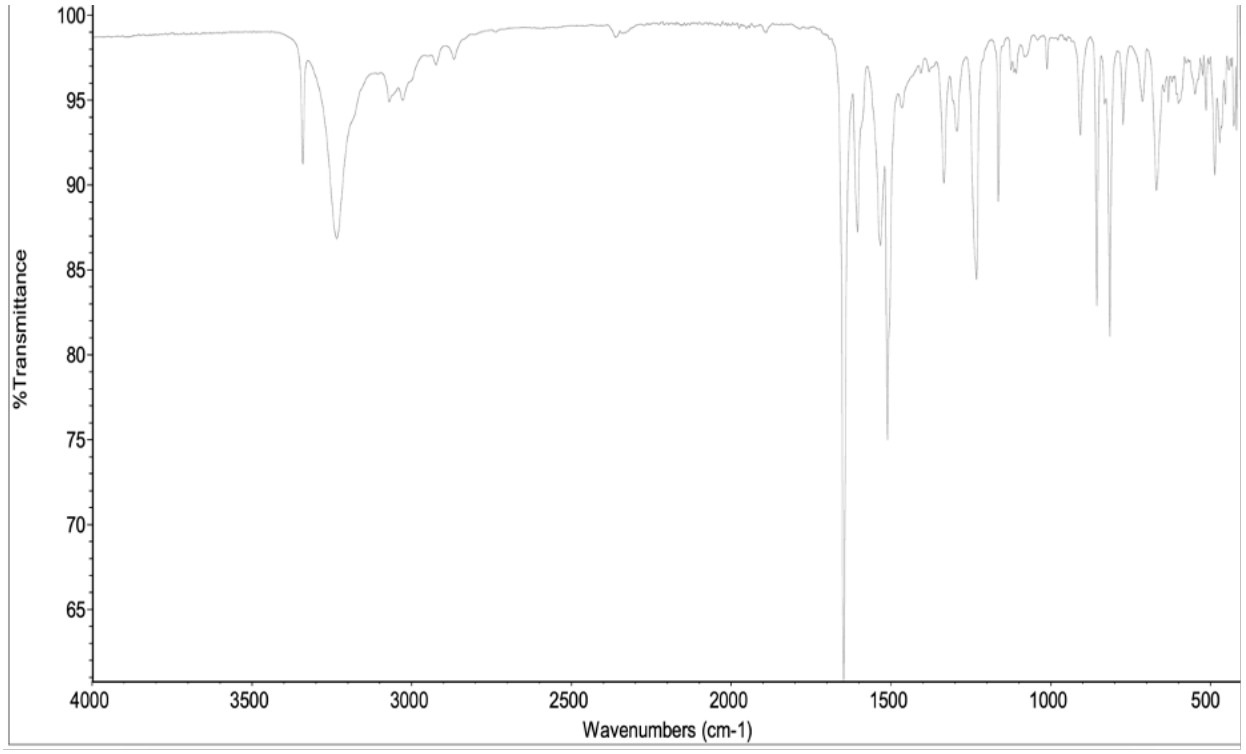


Figure A1.126 *Infrared spectrum (Thin Film) of compound* ***50****.*

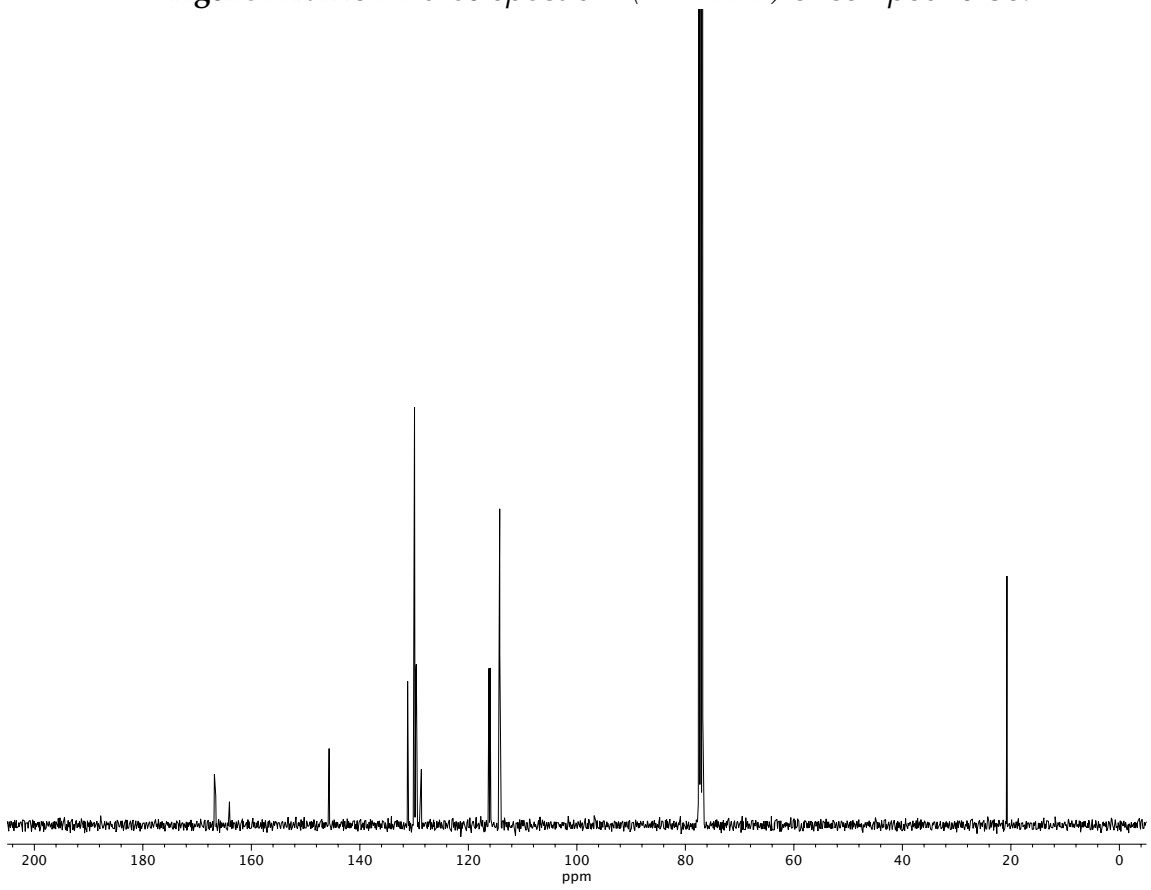


Figure A1.127 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***50****.*

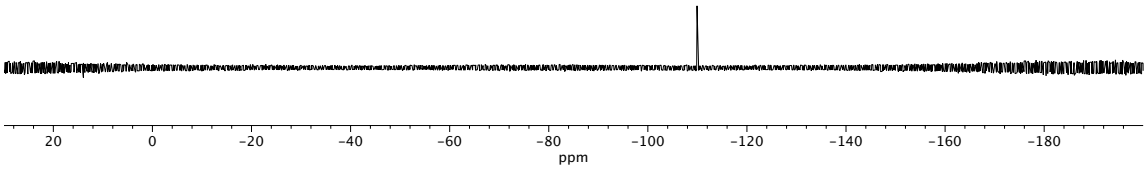


Figure A1.128 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***50****.*

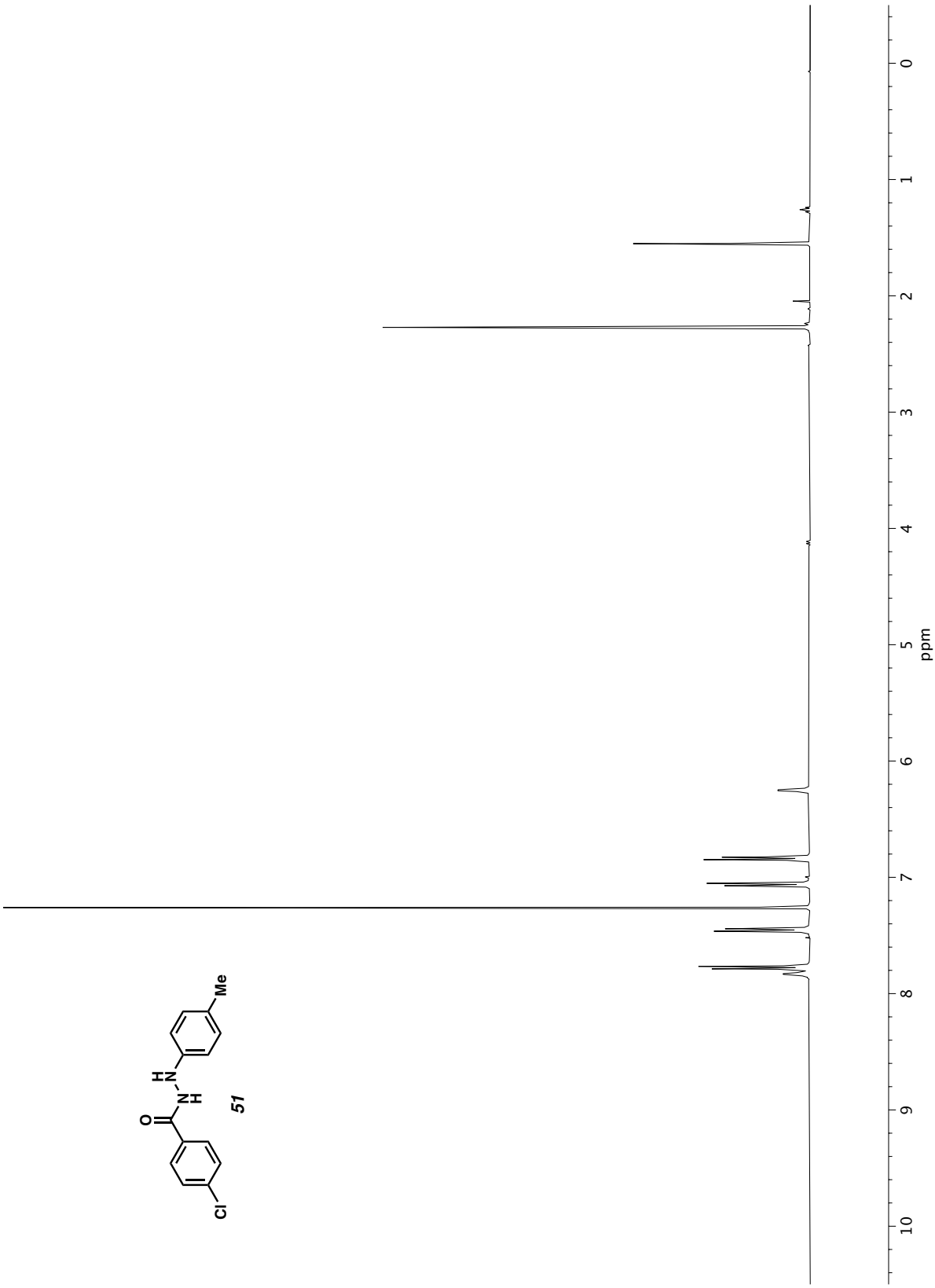


Figure A1.129 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***51****.*

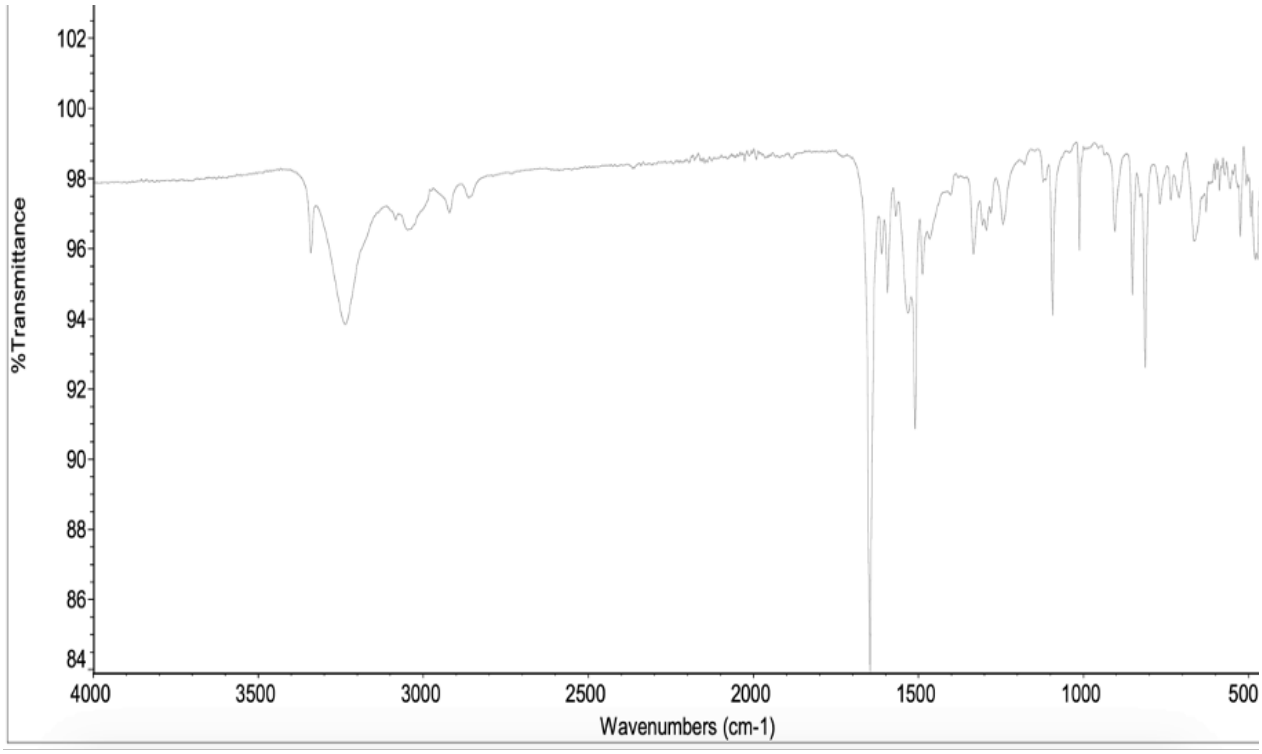


Figure A1.130 *Infrared spectrum (Thin Film) of compound* ***51***.

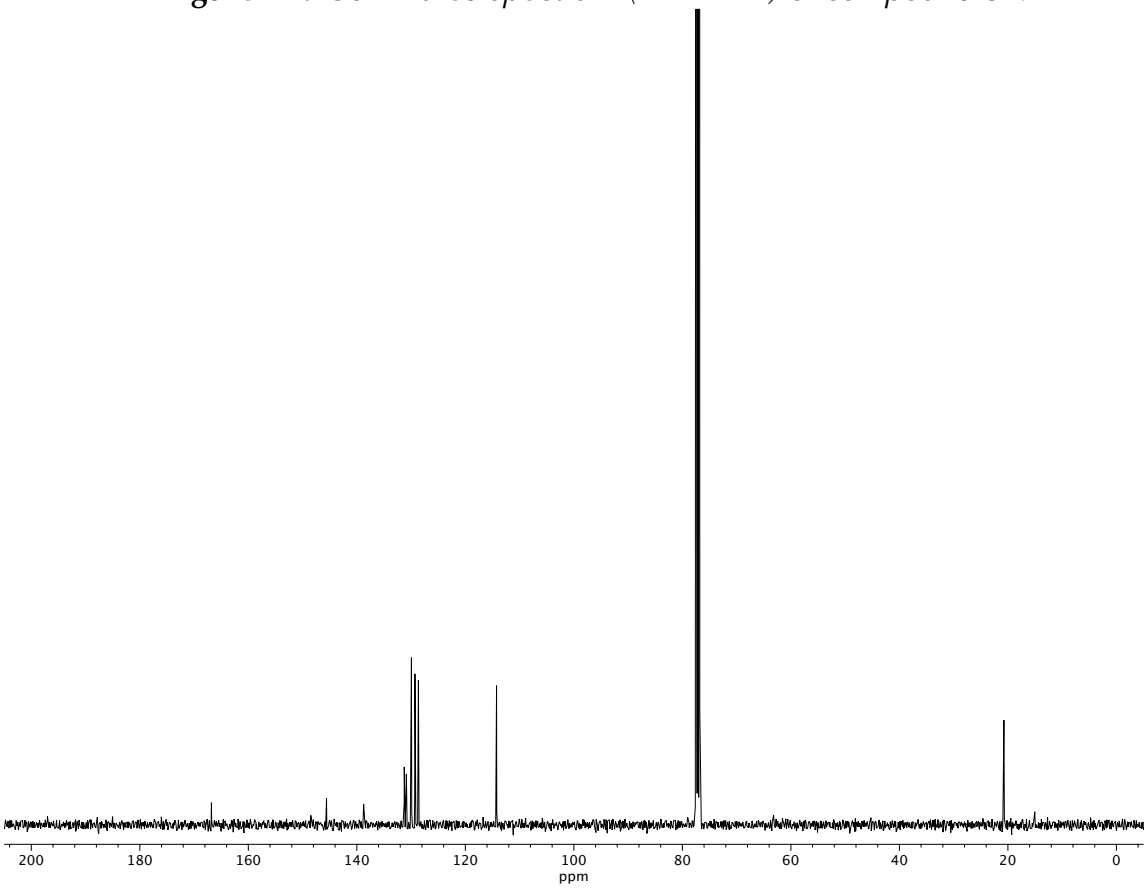


Figure A1.131 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***51***.

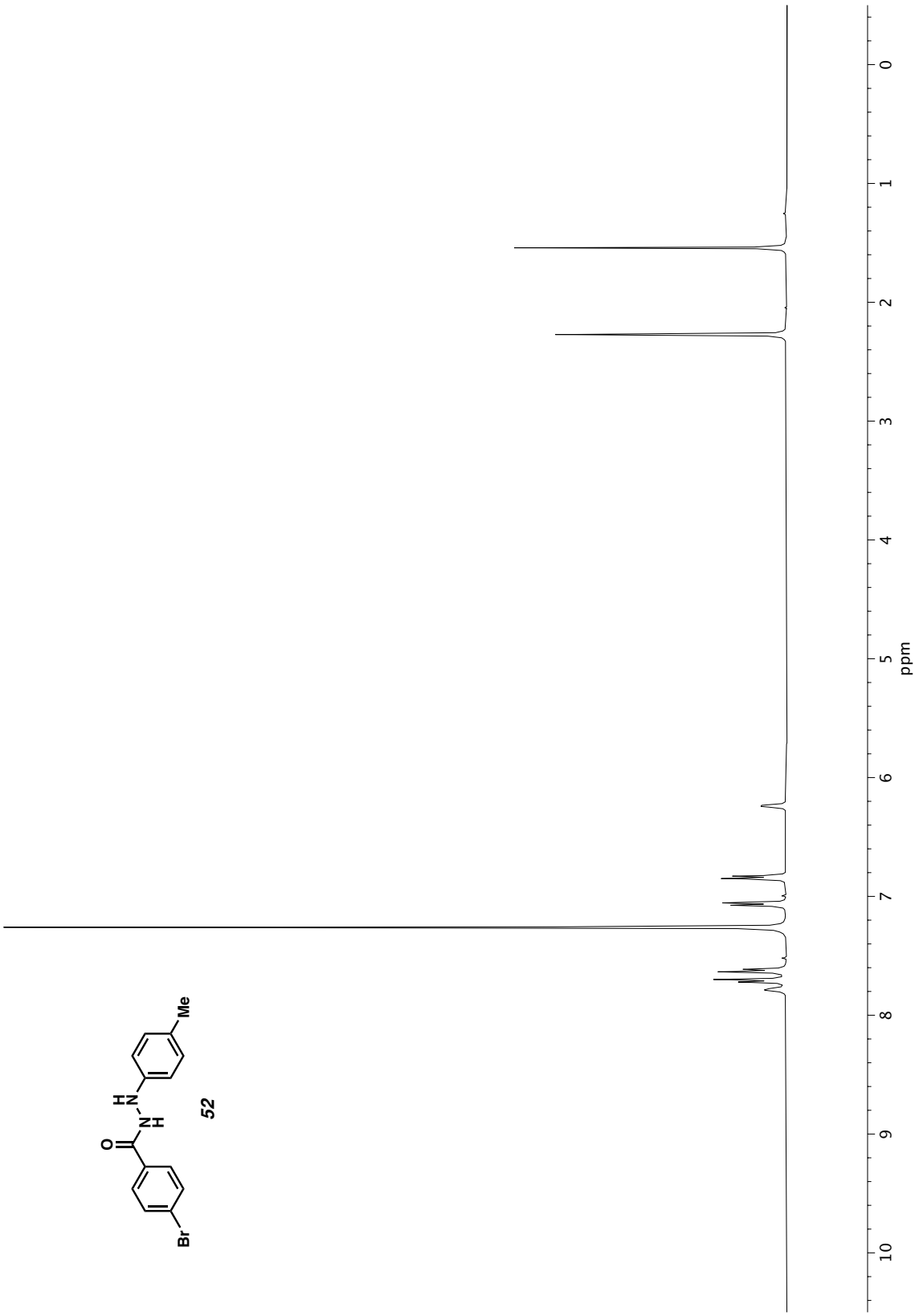


Figure A1.132 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***52****.*

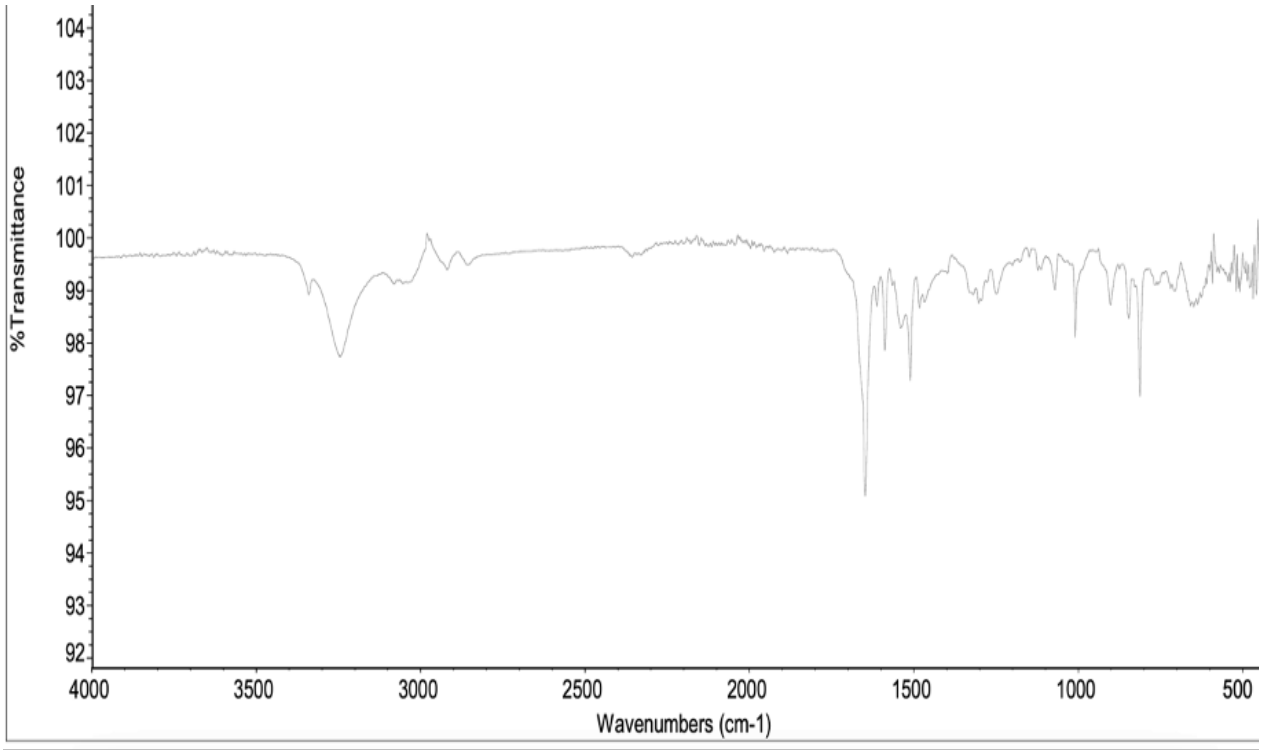


Figure A1.133 *Infrared spectrum (Thin Film) of compound* ***52***.

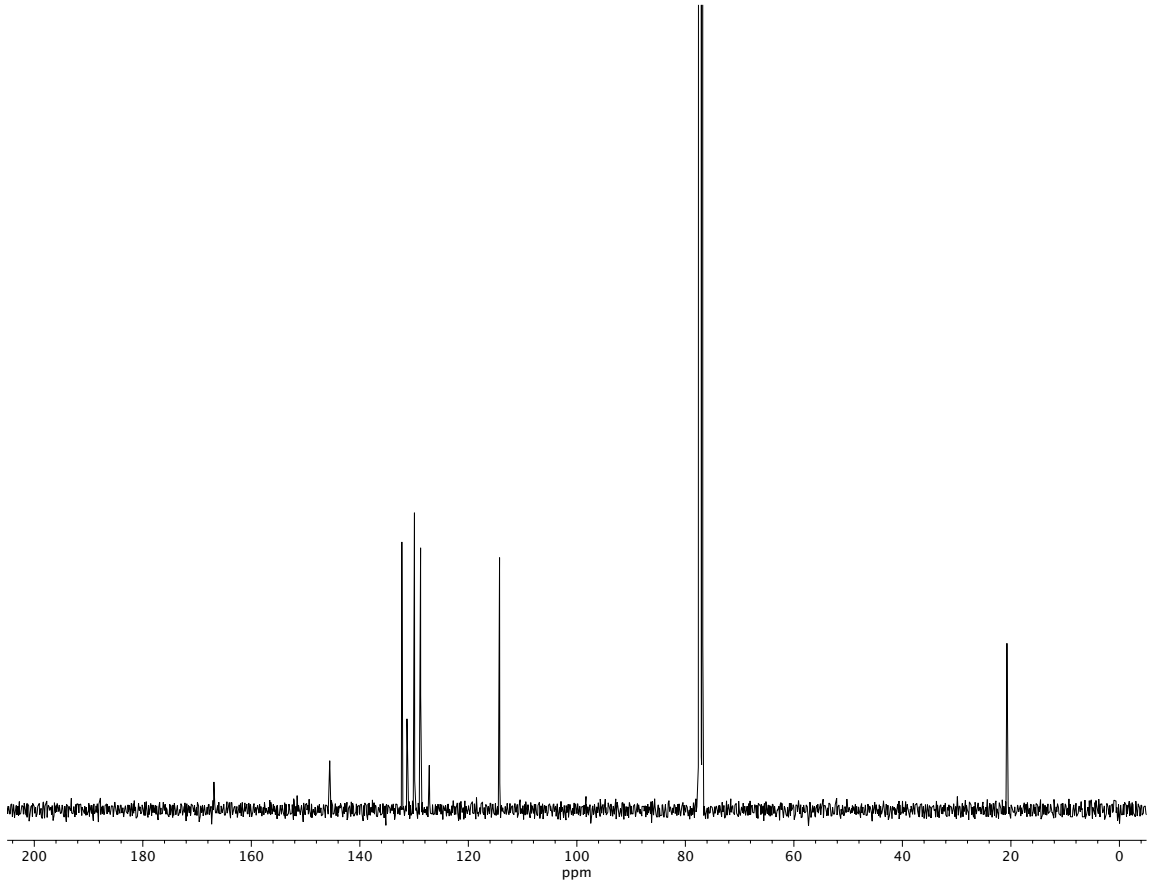


Figure A1.134 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***52***.

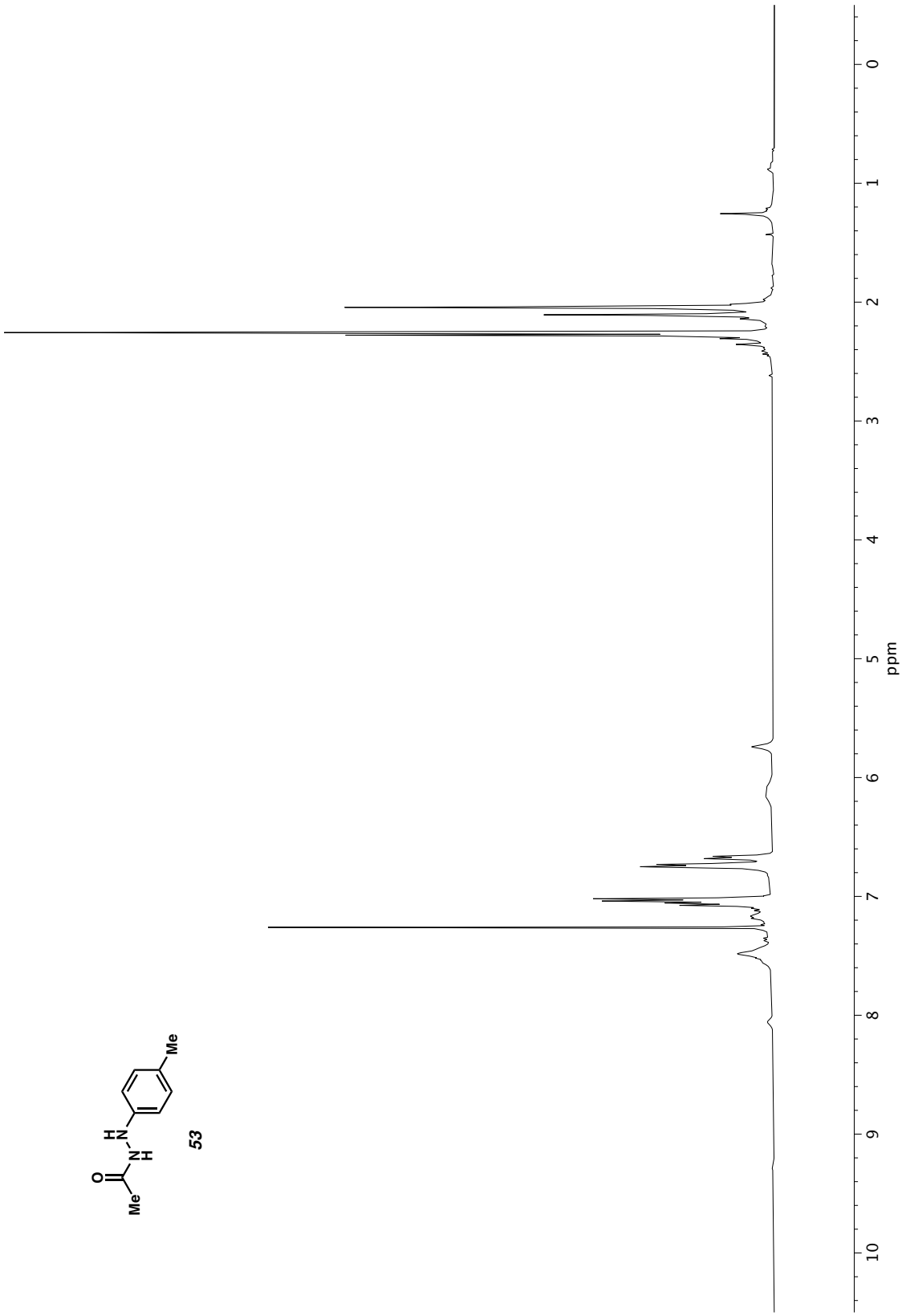


Figure A1.135 *^1H NMR (400 MHz, $CDCl_3$) of compound **53**.*

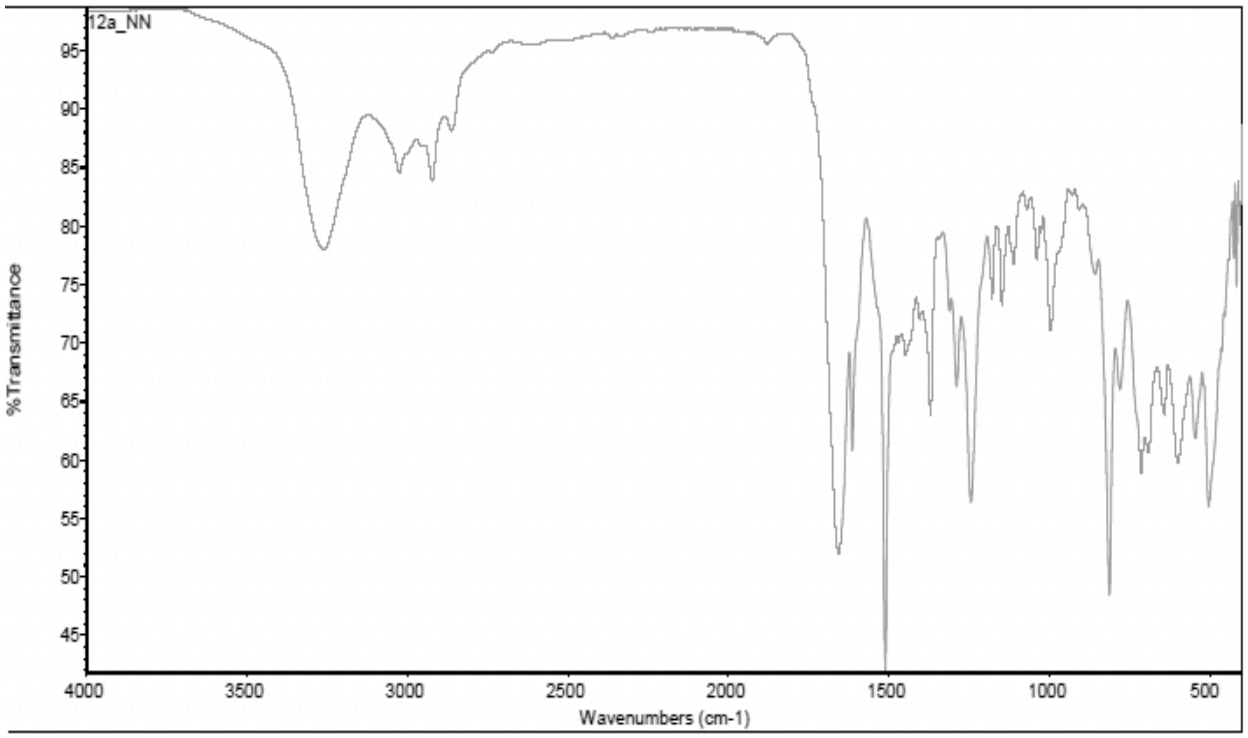


Figure A1.136 *Infrared spectrum (Thin Film) of compound* ***53***.

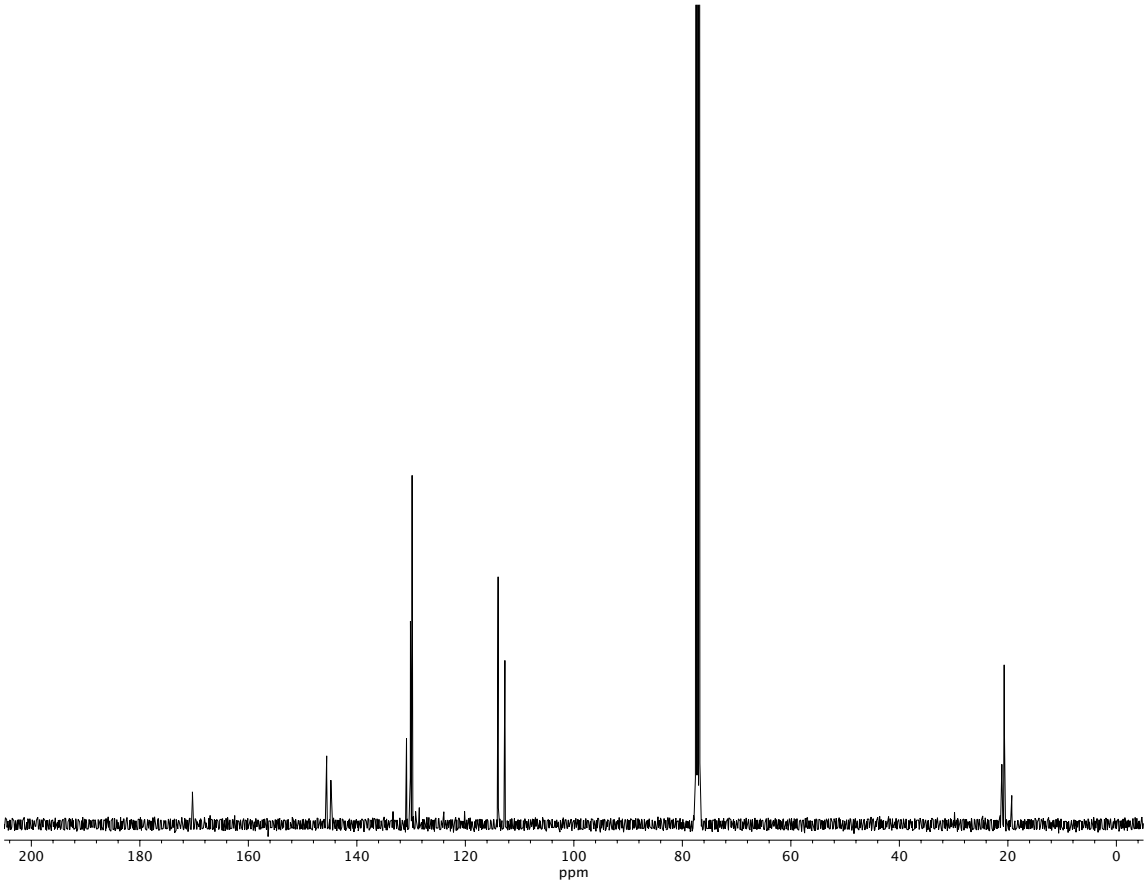


Figure A1.137 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***53***.

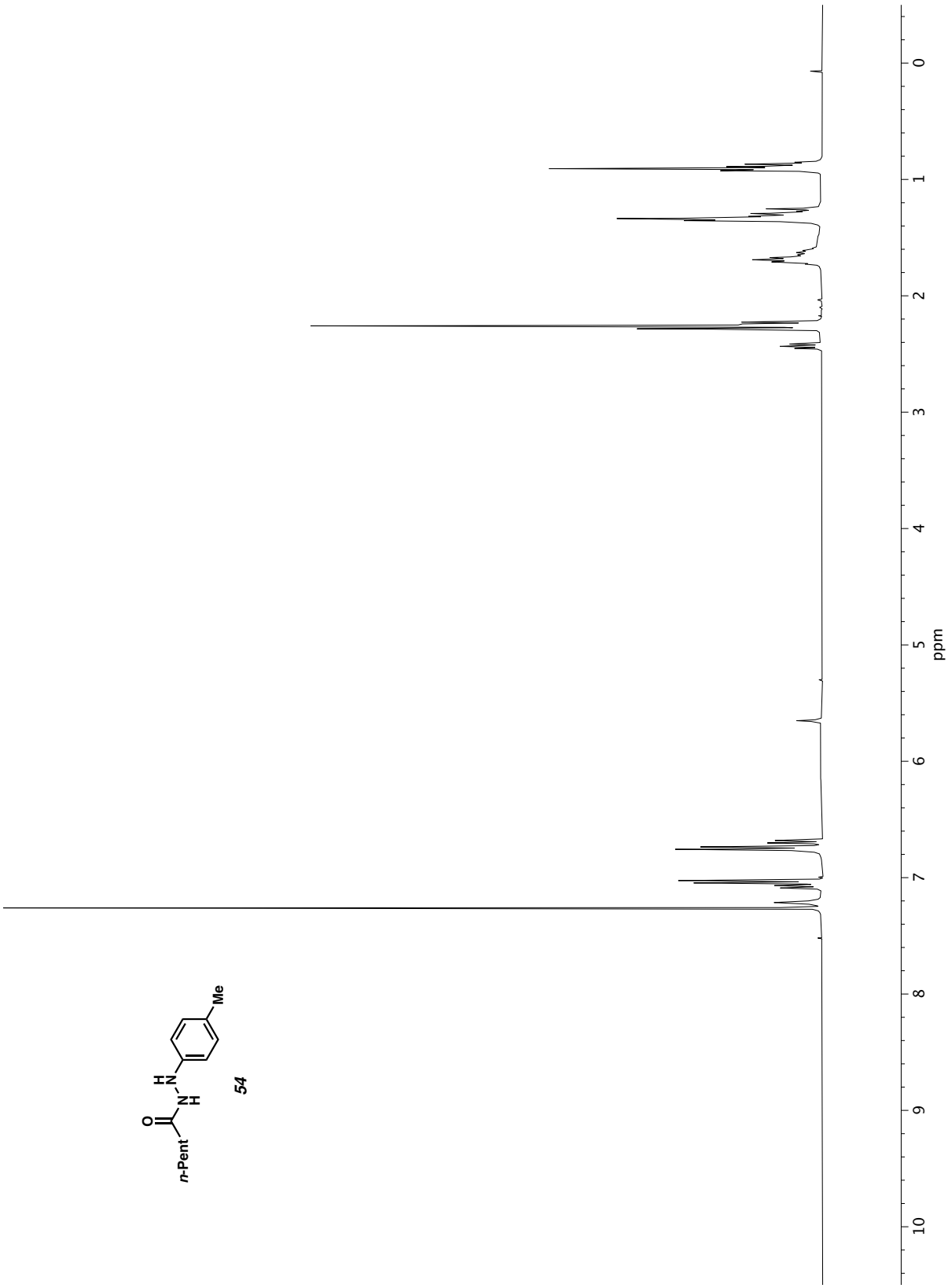


Figure A1.138 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***54****.*

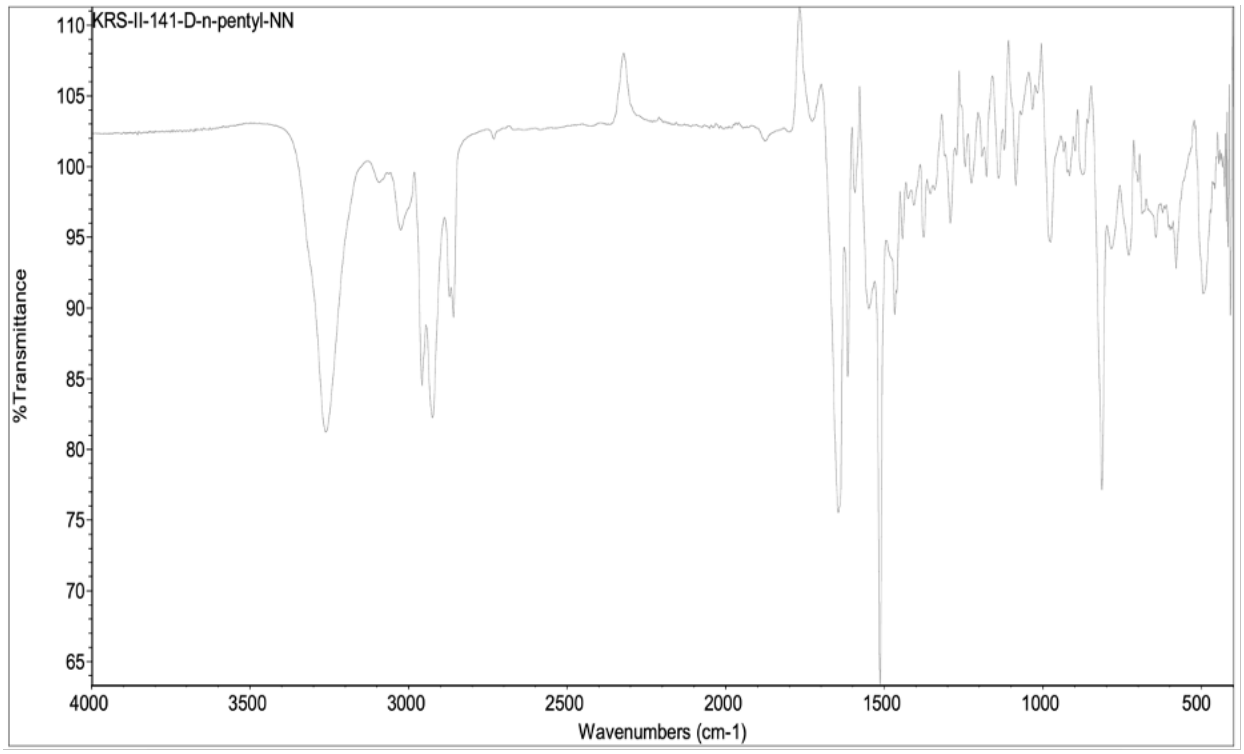


Figure A1.139 *Infrared spectrum (Thin Film) of compound* ***54****.*

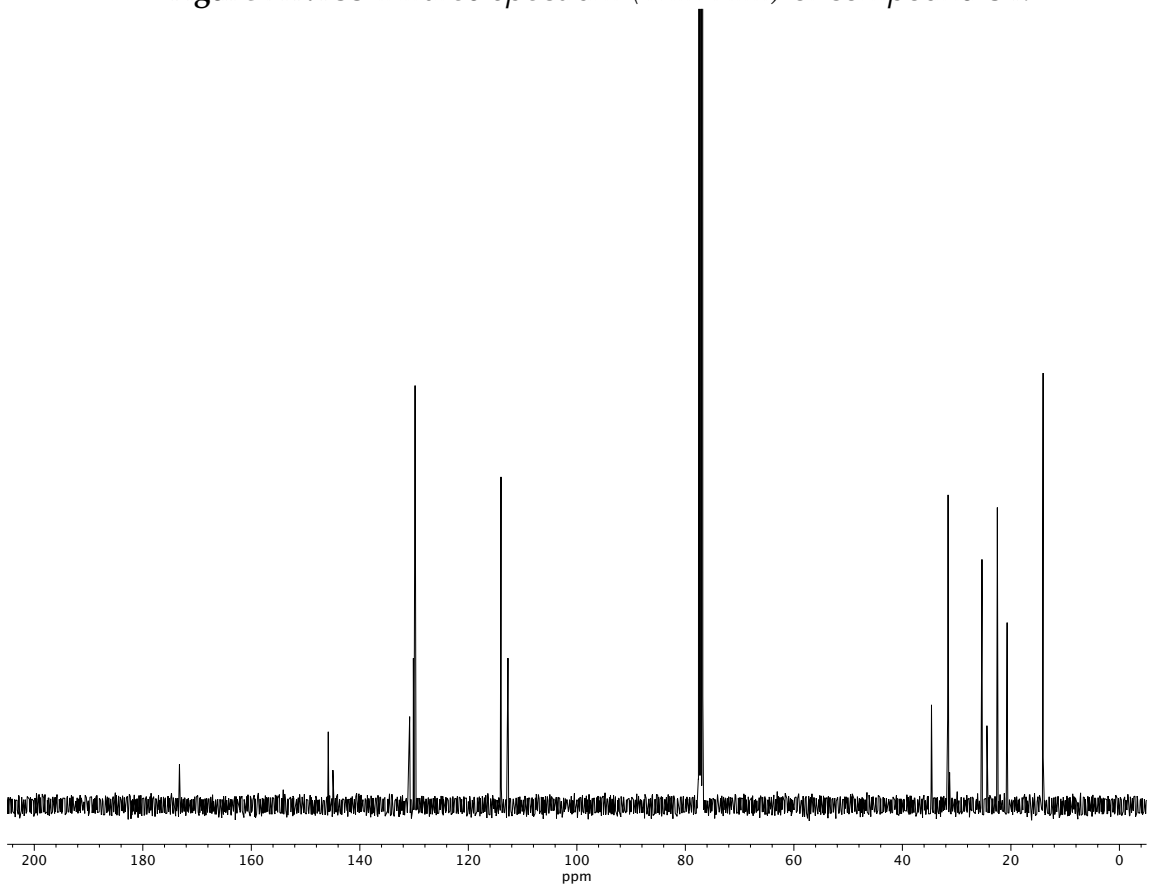


Figure A1.140 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***54****.*

Figure A1.141 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***55***.

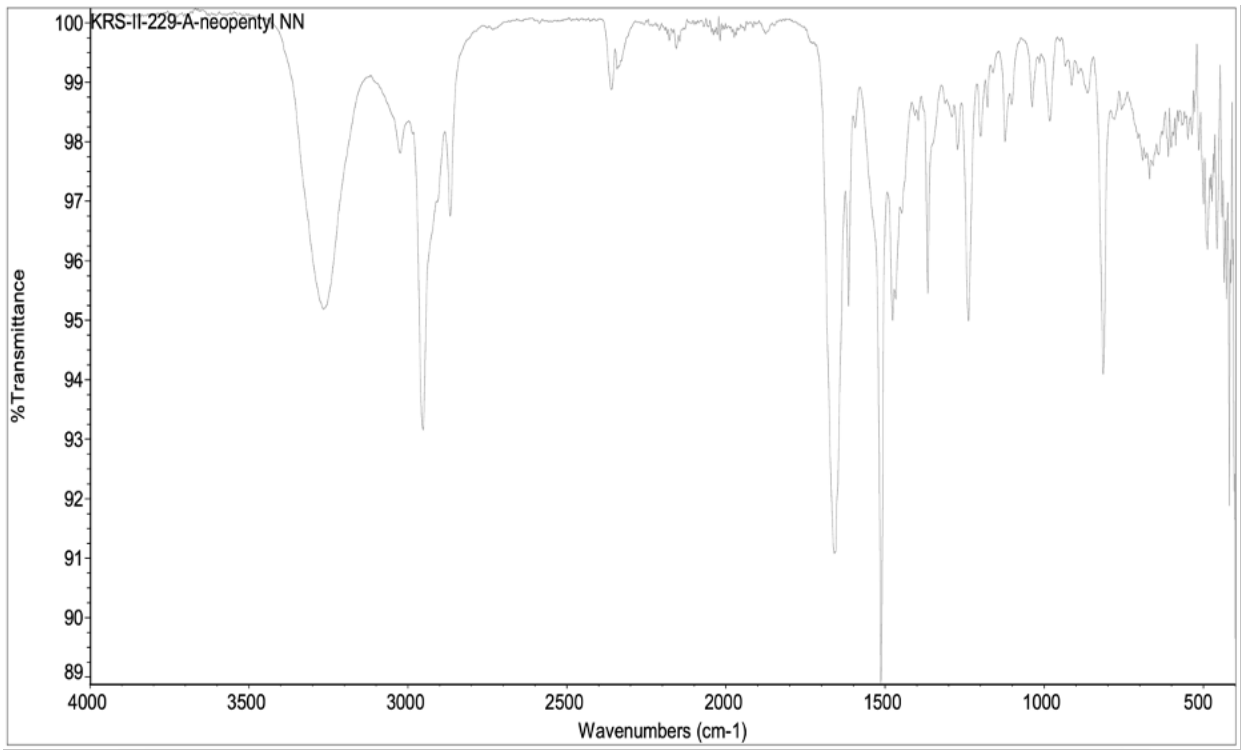


Figure A1.142 *Infrared spectrum (Thin Film) of compound* ***55****.*

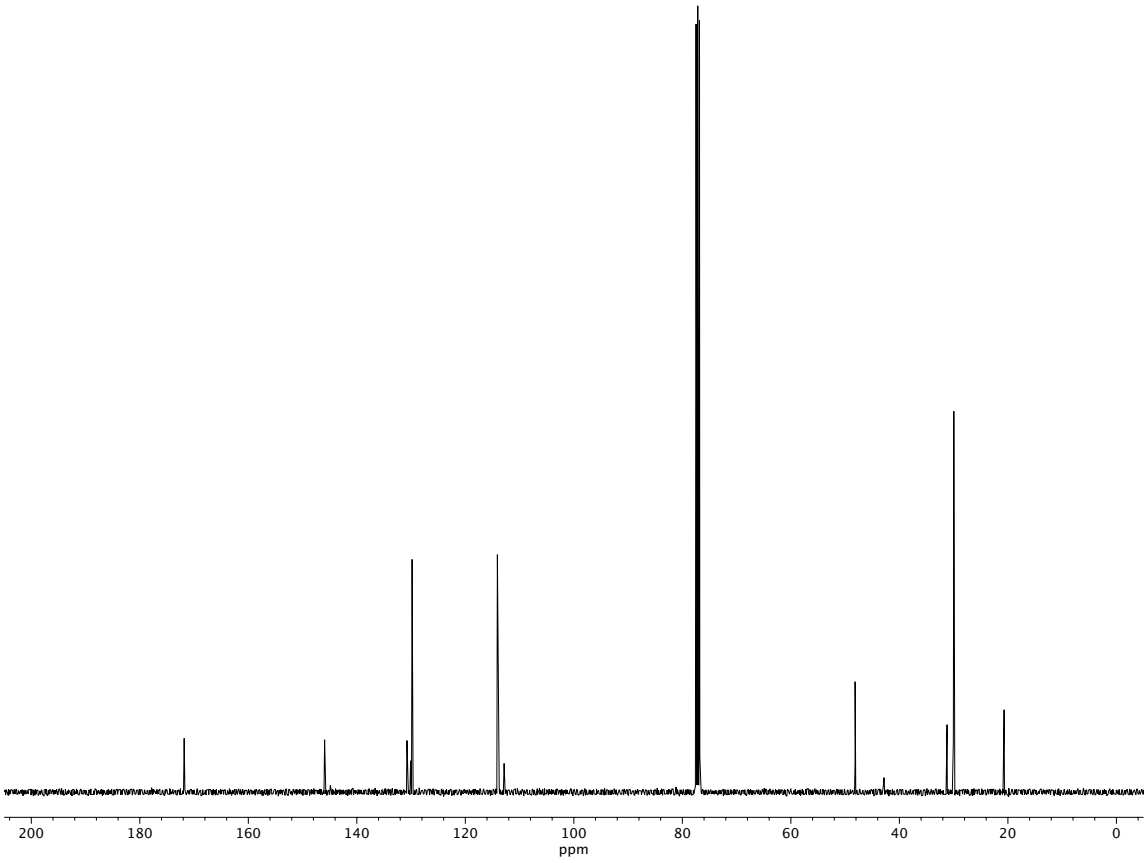


Figure A1.143 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***55****.*

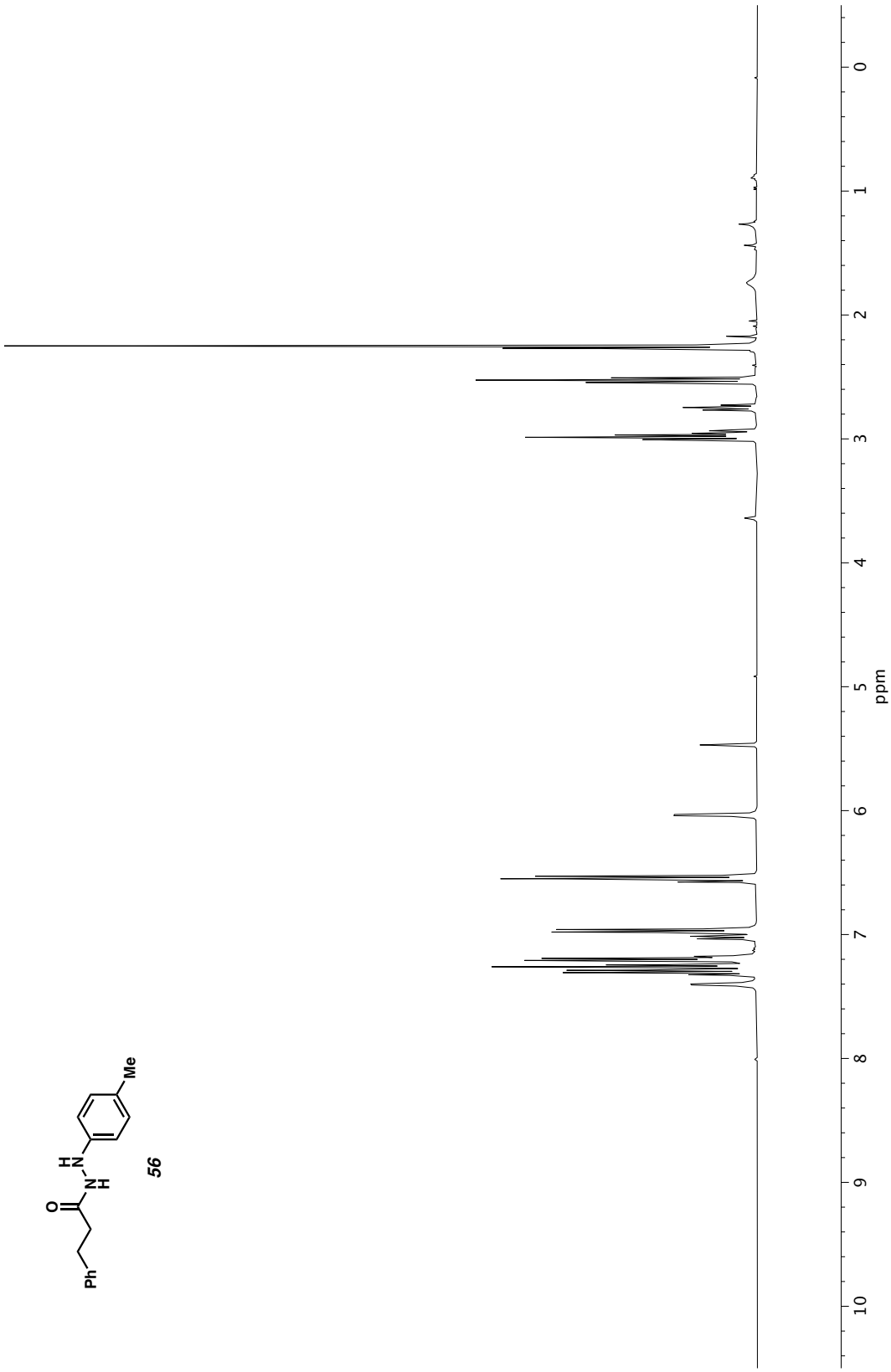


Figure A1.144 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **56**.*

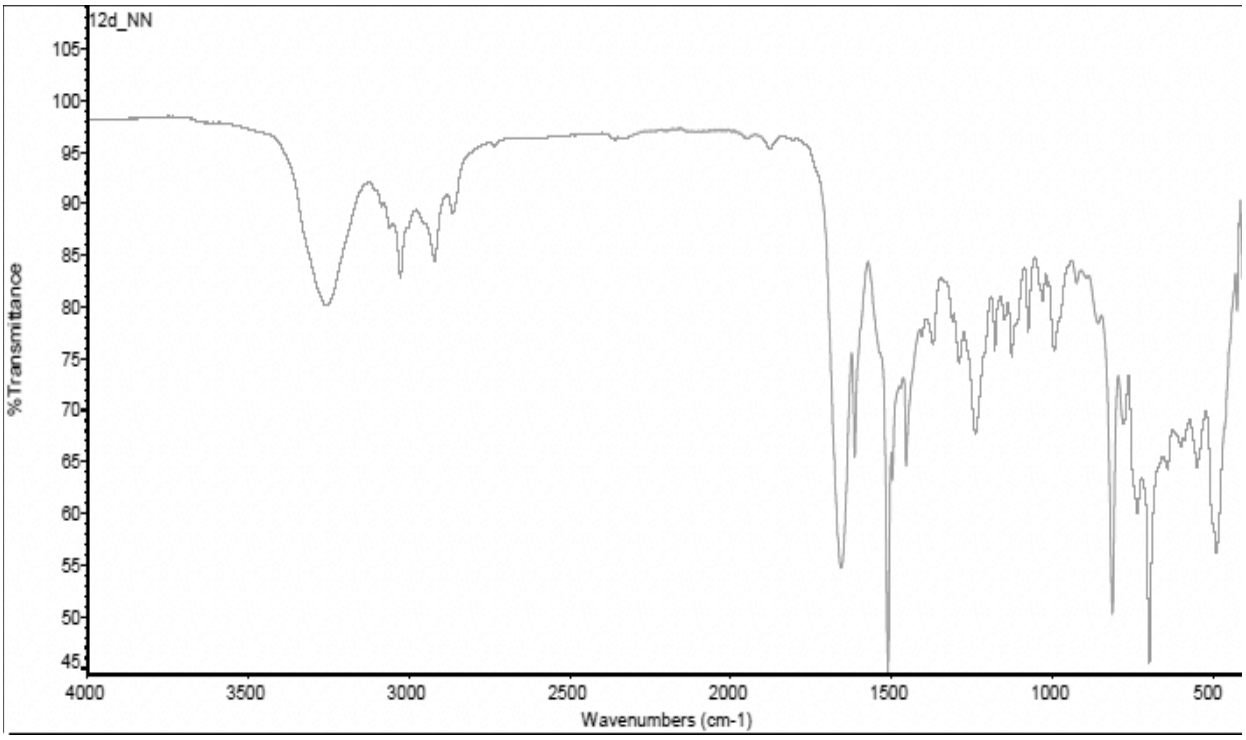


Figure A1.145 *Infrared spectrum (Thin Film) of compound* ***56****.*

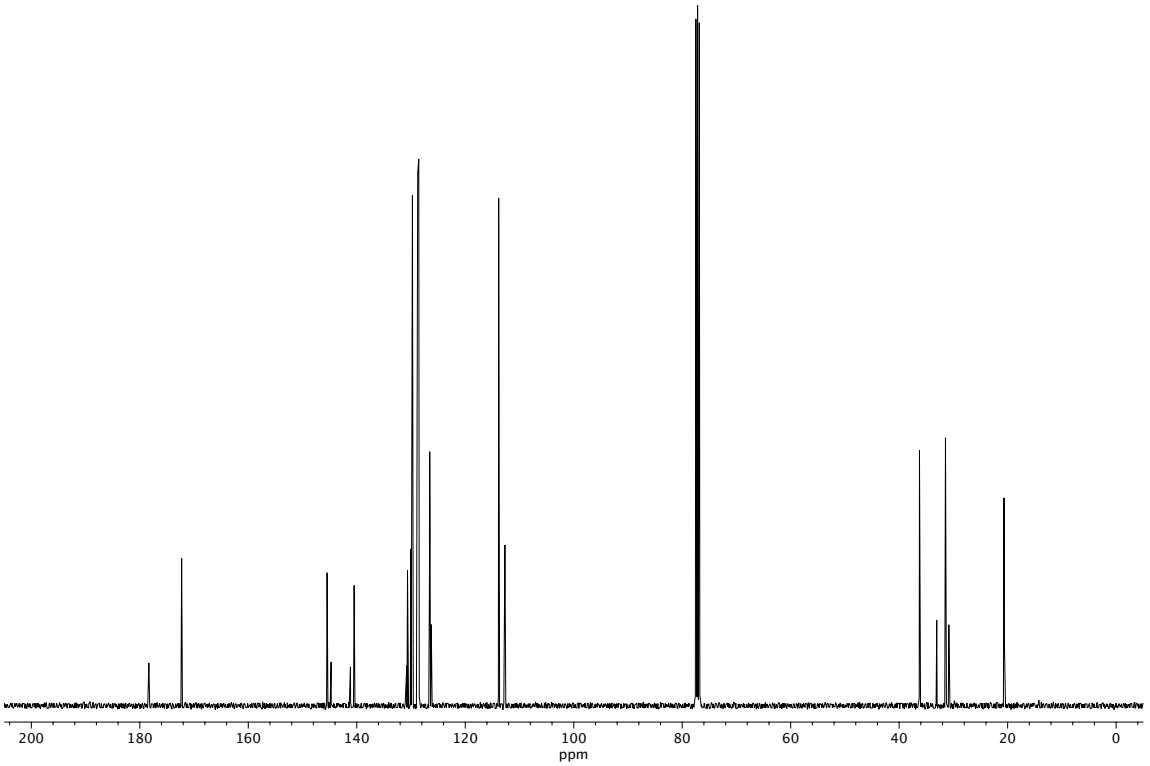


Figure A1.146 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***56****.*

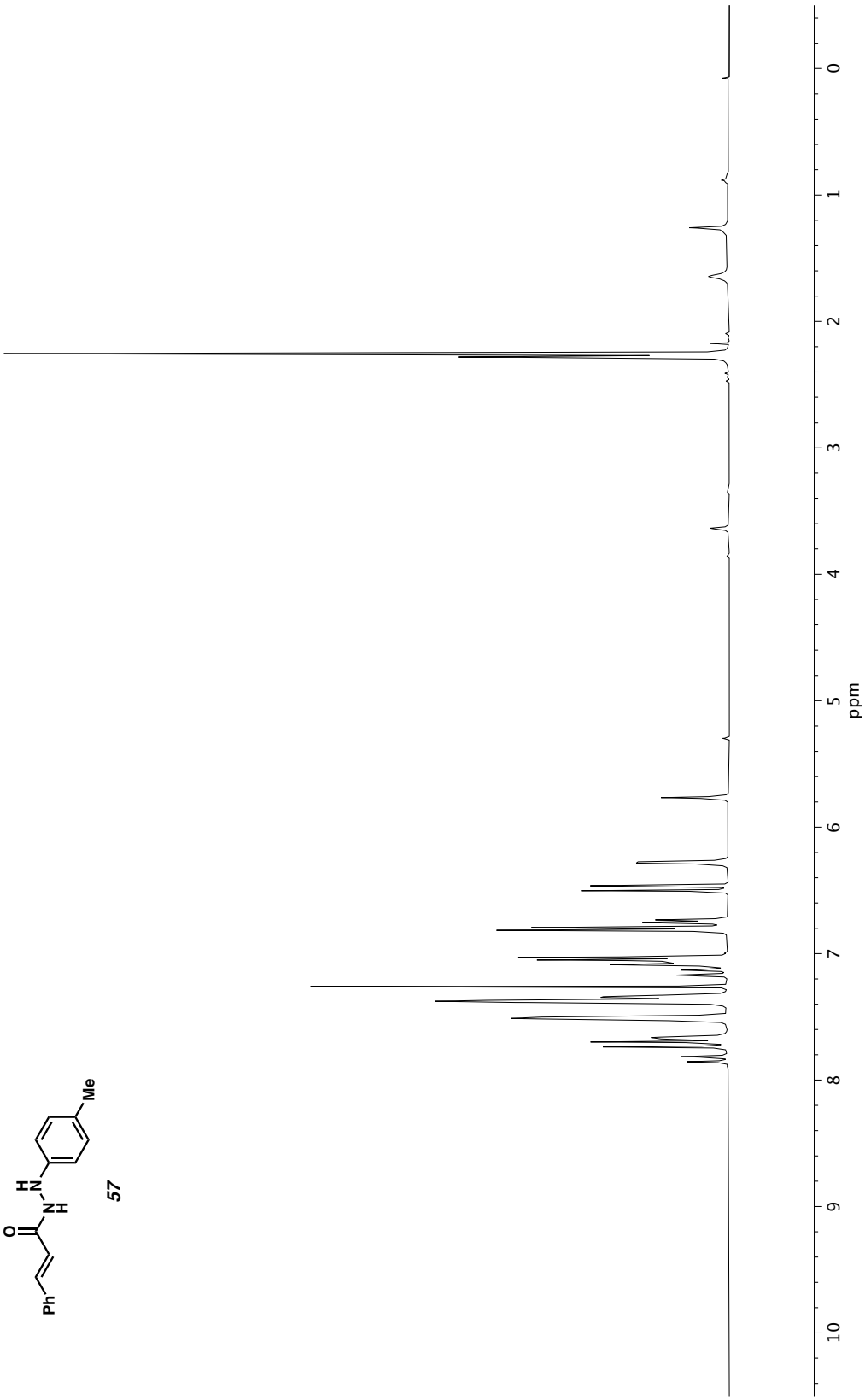


Figure A1.147 *^1H NMR (400 MHz, $CDCl_3$) of compound **57**.*

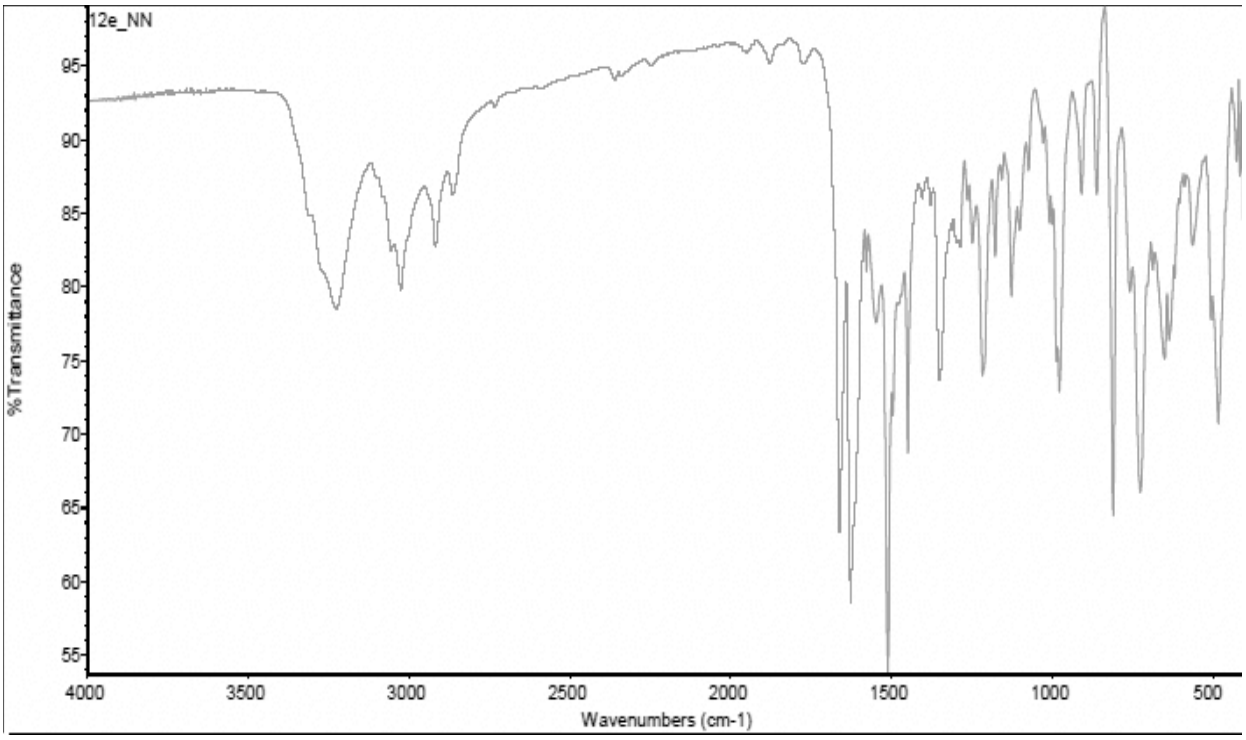


Figure A1.148 *Infrared spectrum (Thin Film) of compound* ***57****.*

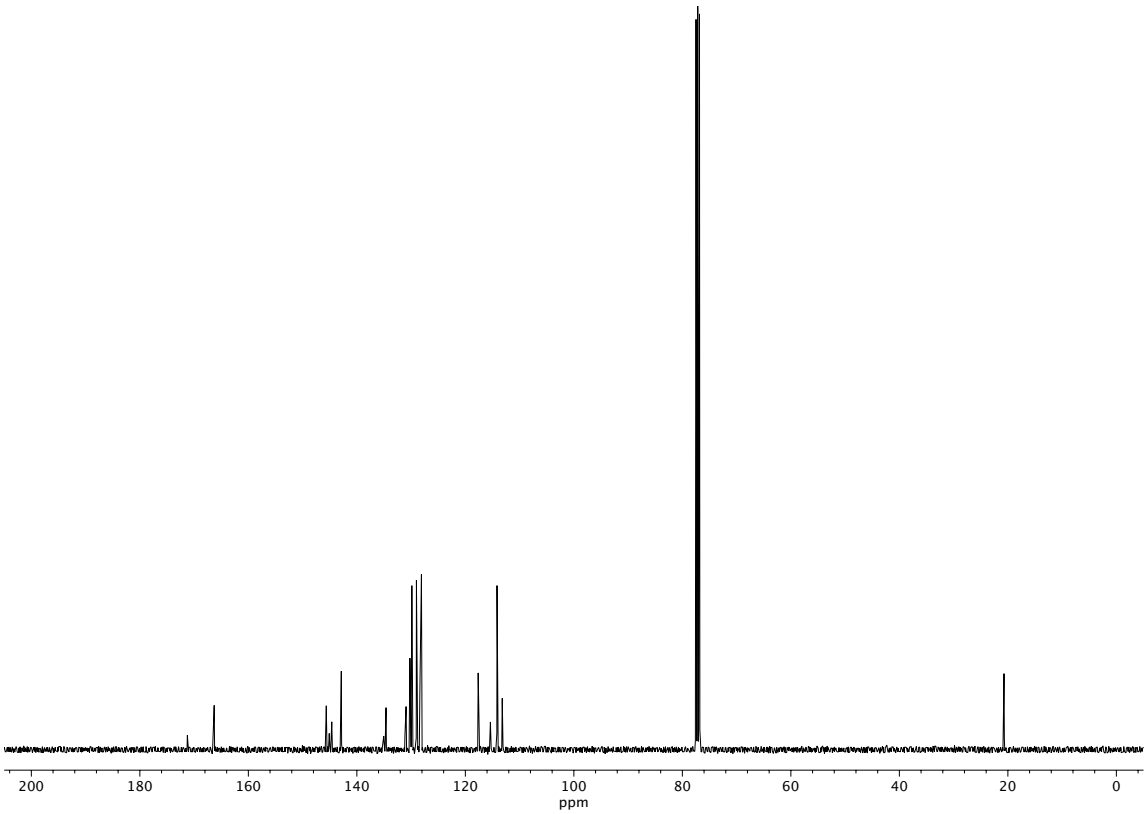


Figure A1.149 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***57****.*

Figure A1.150 *^1H NMR (400 MHz, $CDCl_3$) of compound **58**.*

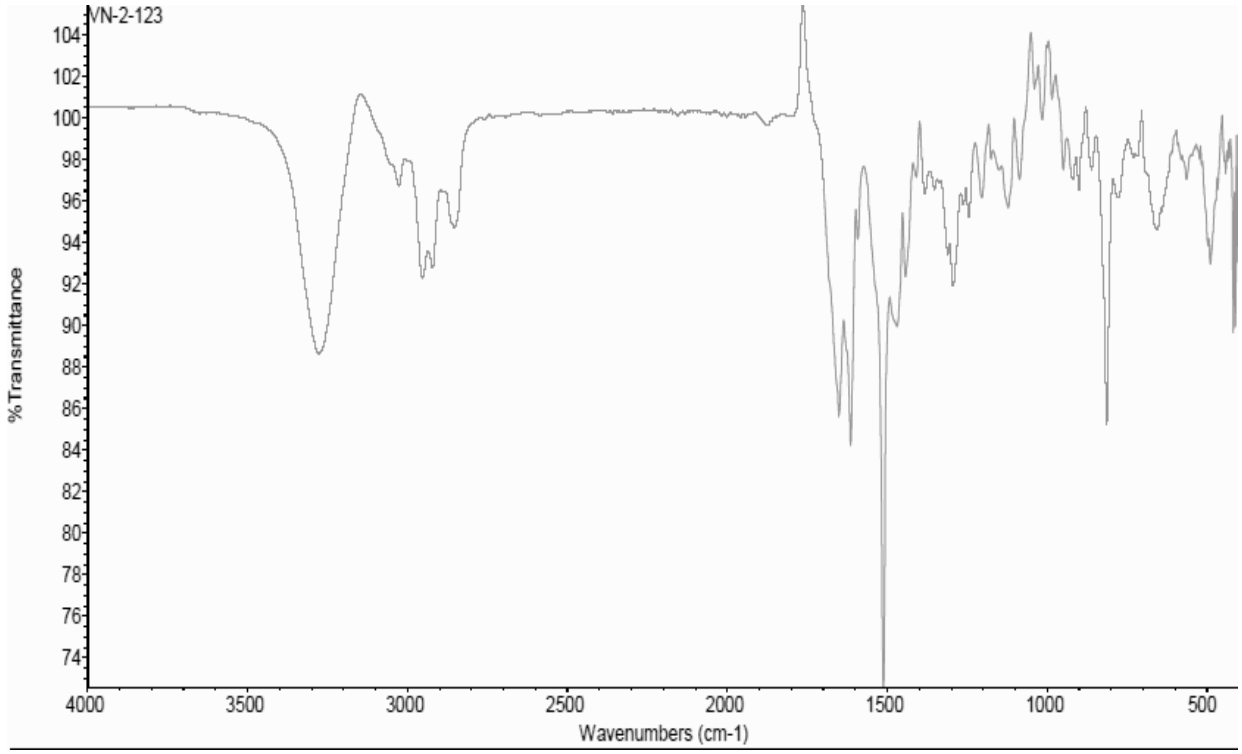


Figure A1.151 *Infrared spectrum (Thin Film) of compound* ***58****.*

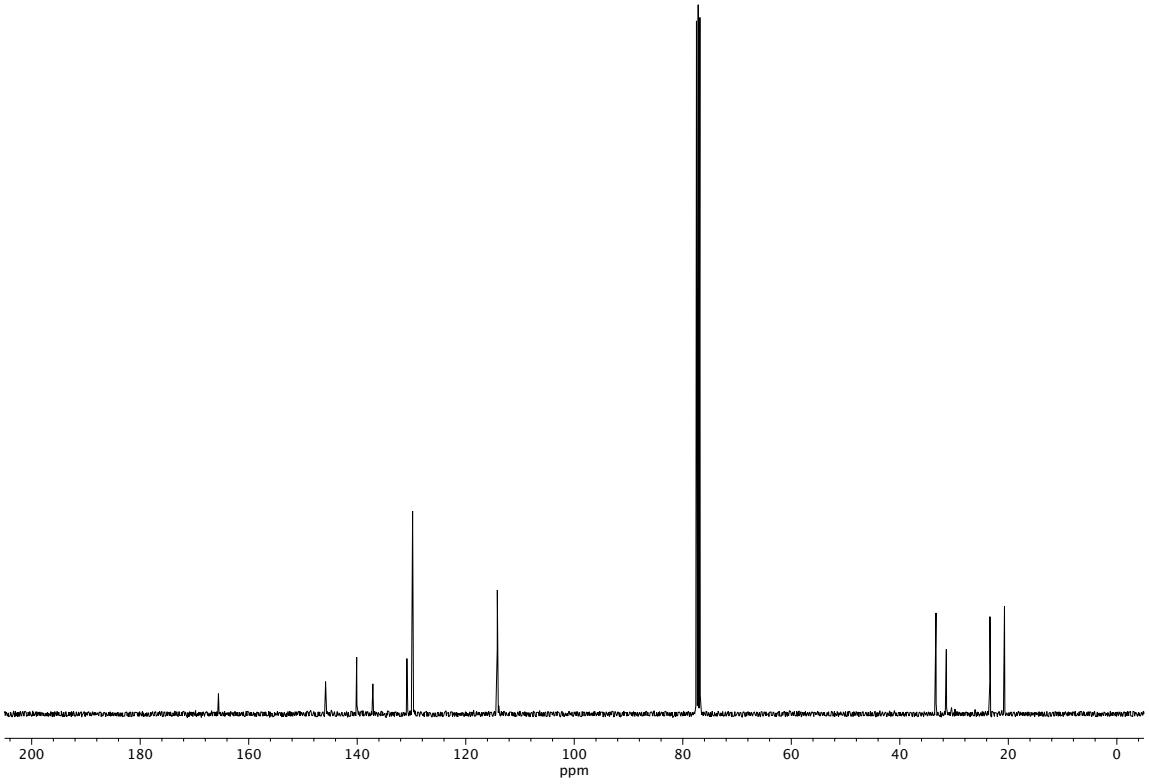


Figure A1.152 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***58****.*

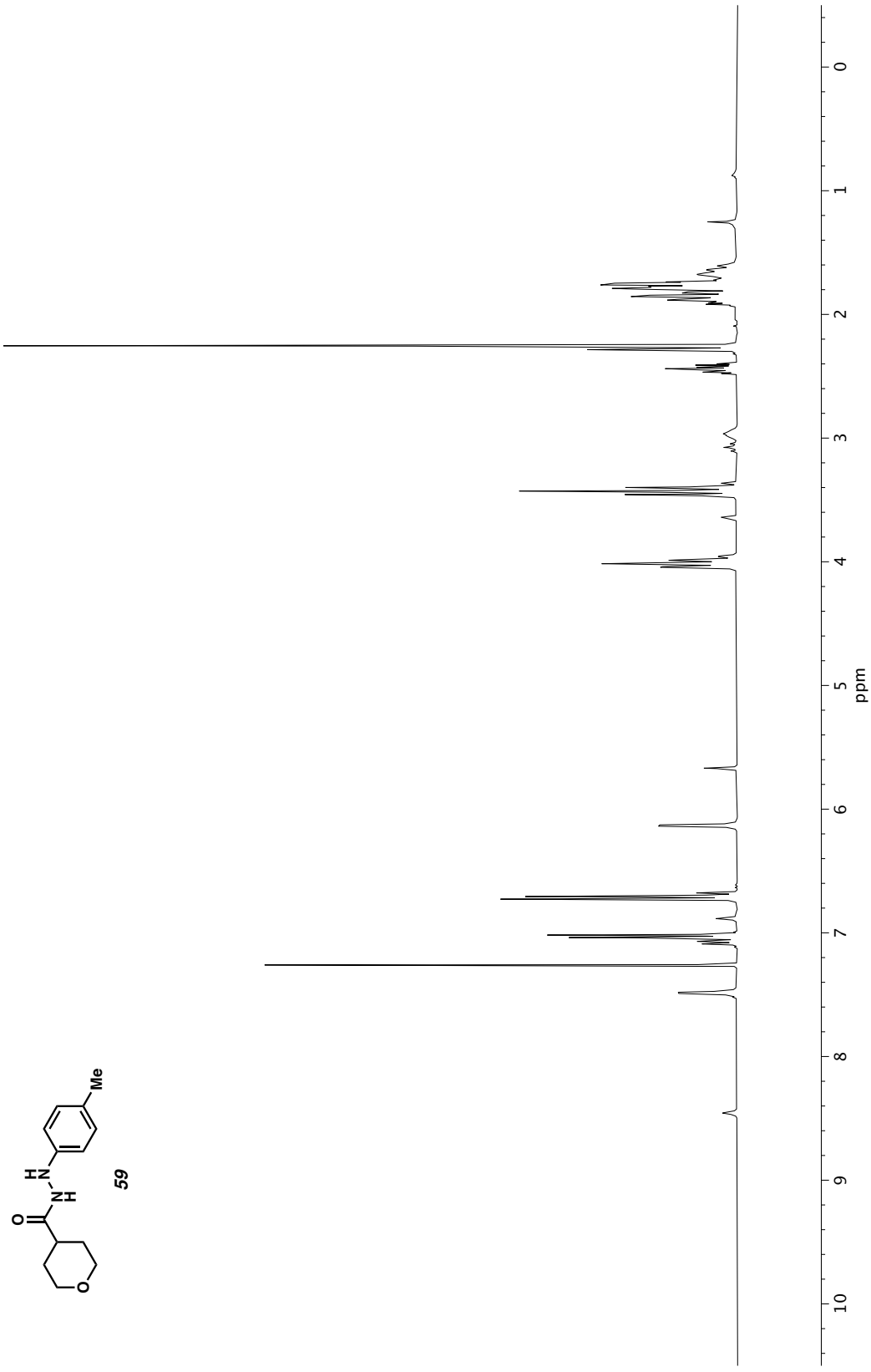


Figure A1.153 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **59**.*

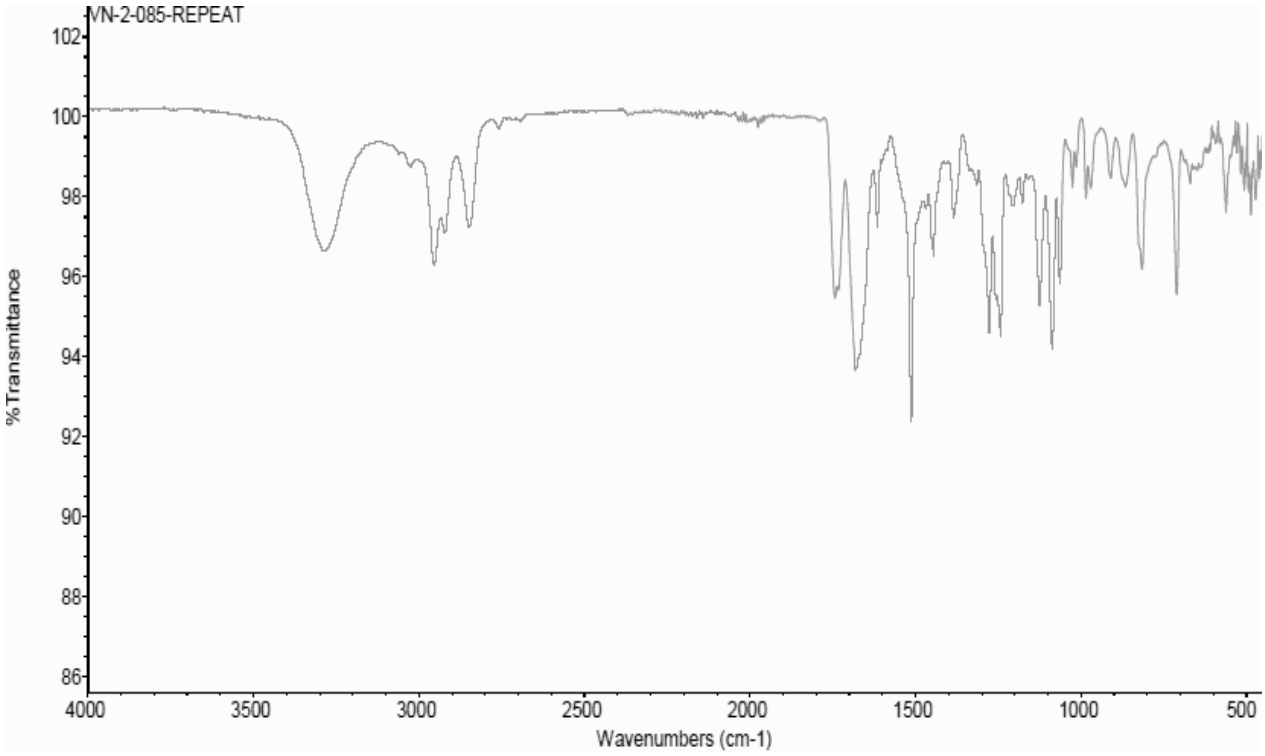


Figure A1.154 *Infrared spectrum (Thin Film) of compound* ***59***.

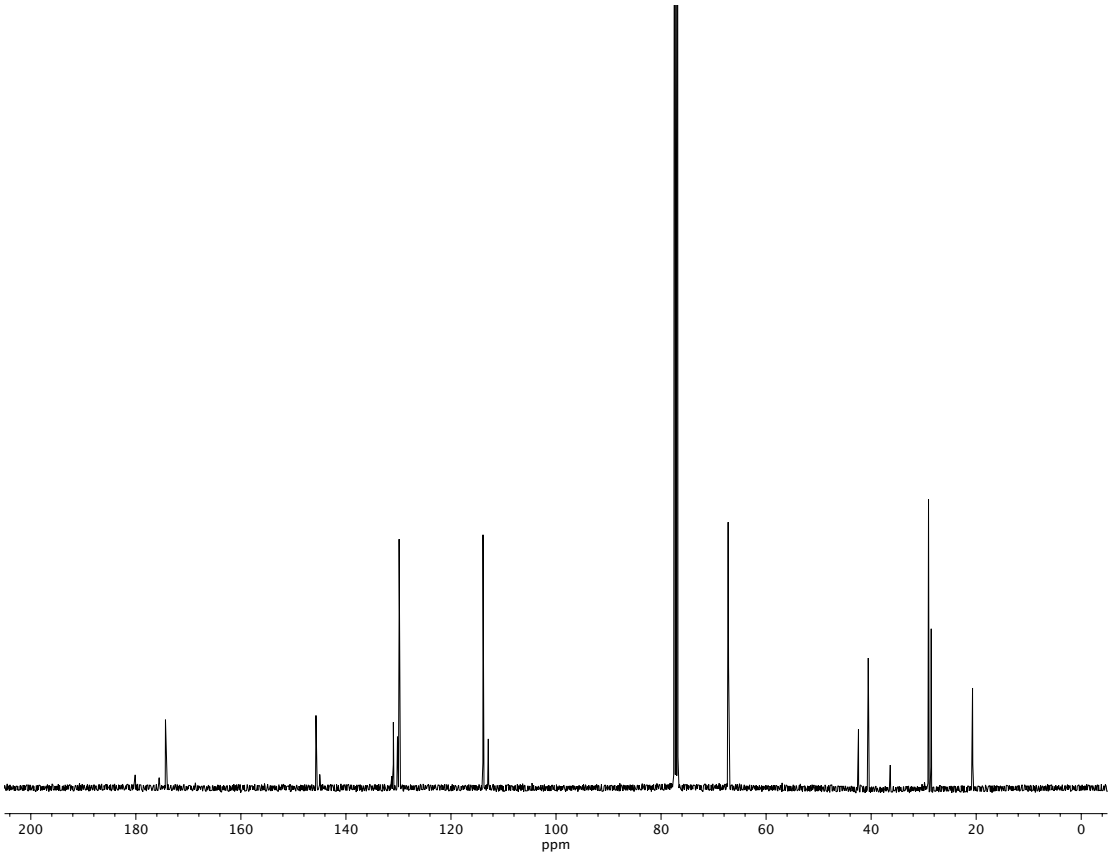


Figure A1.155 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***59***.

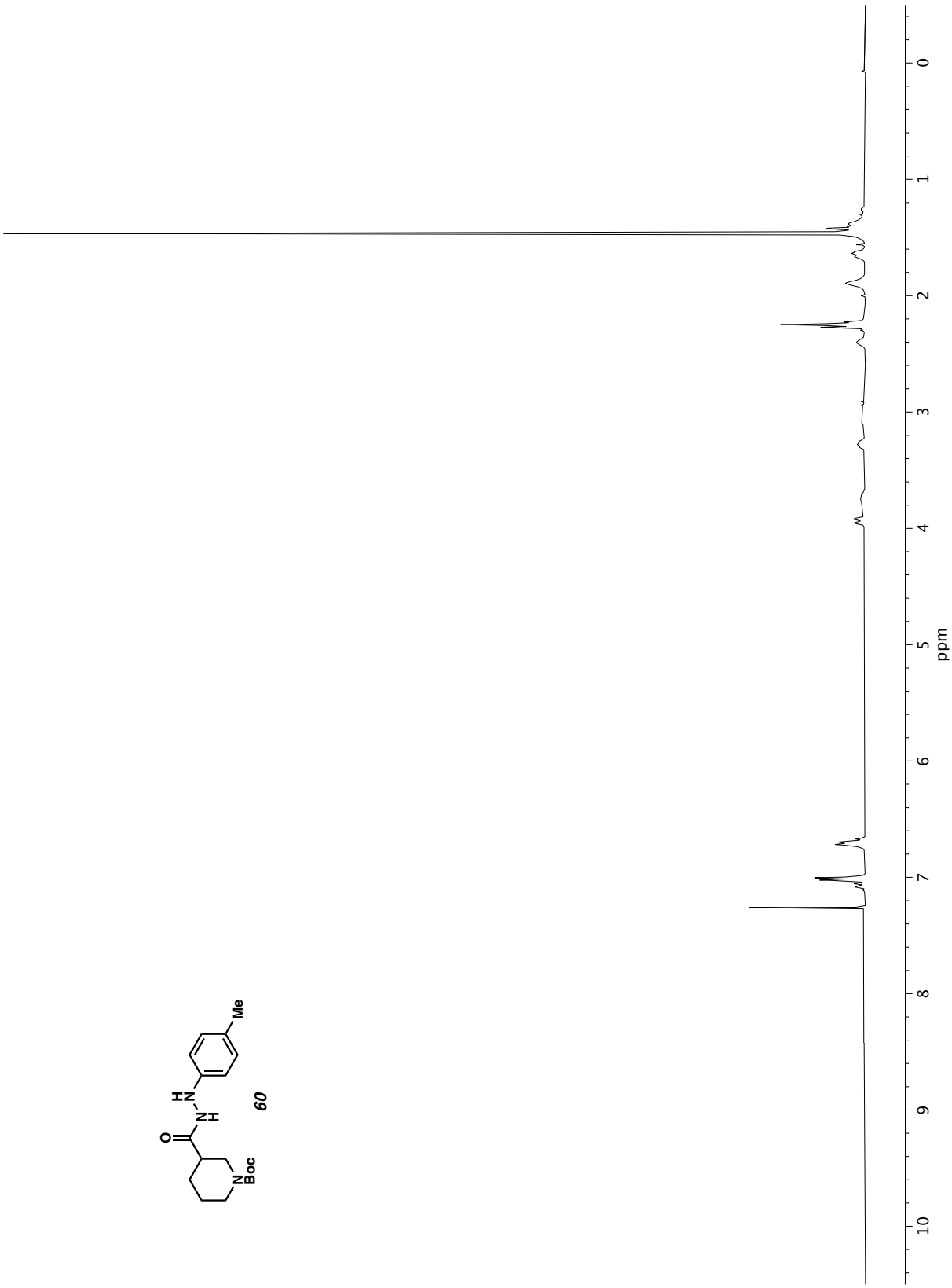


Figure A1.156 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***60***.

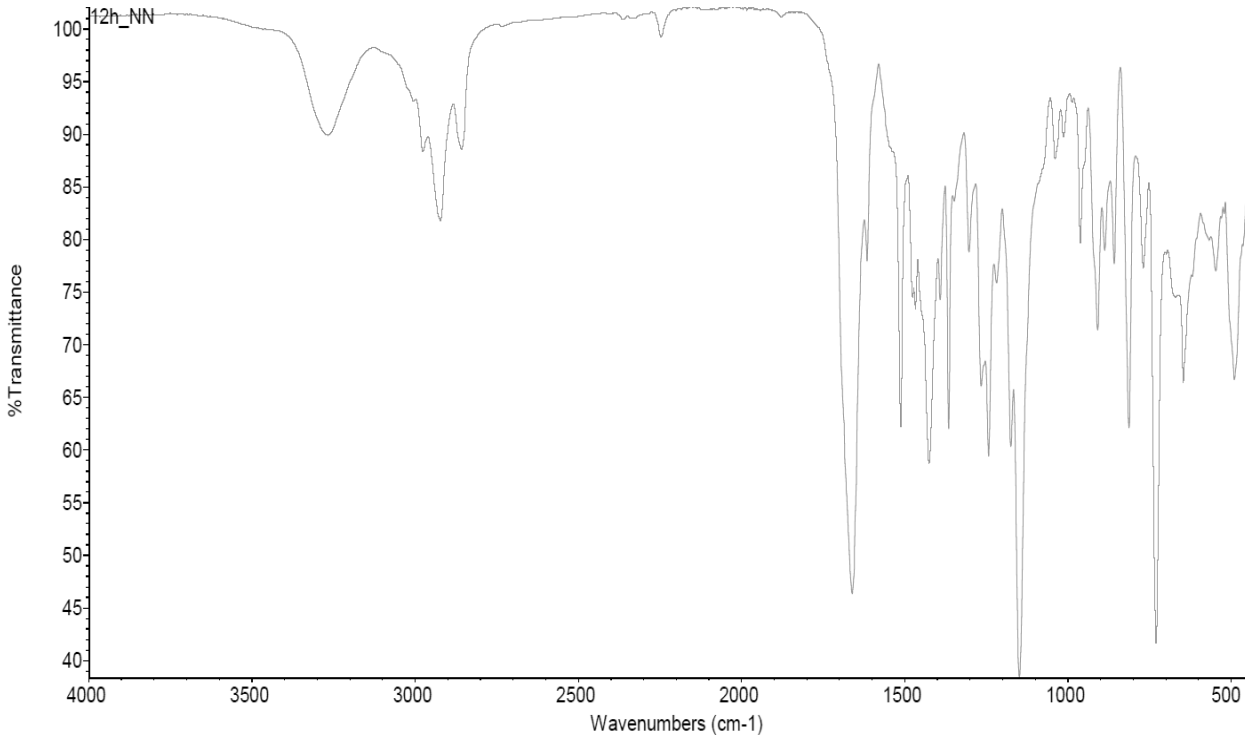


Figure A1.157 *Infrared spectrum (Thin Film) of compound* ***60****.*

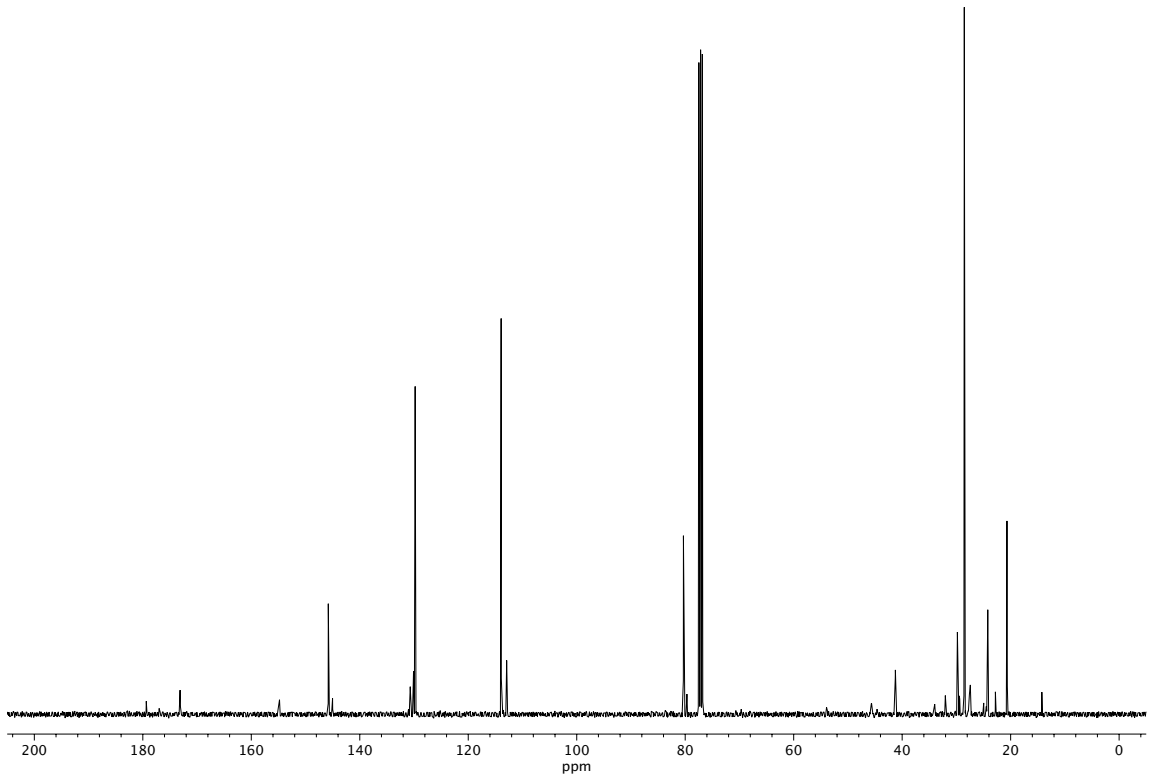


Figure A1.158 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***60****.*

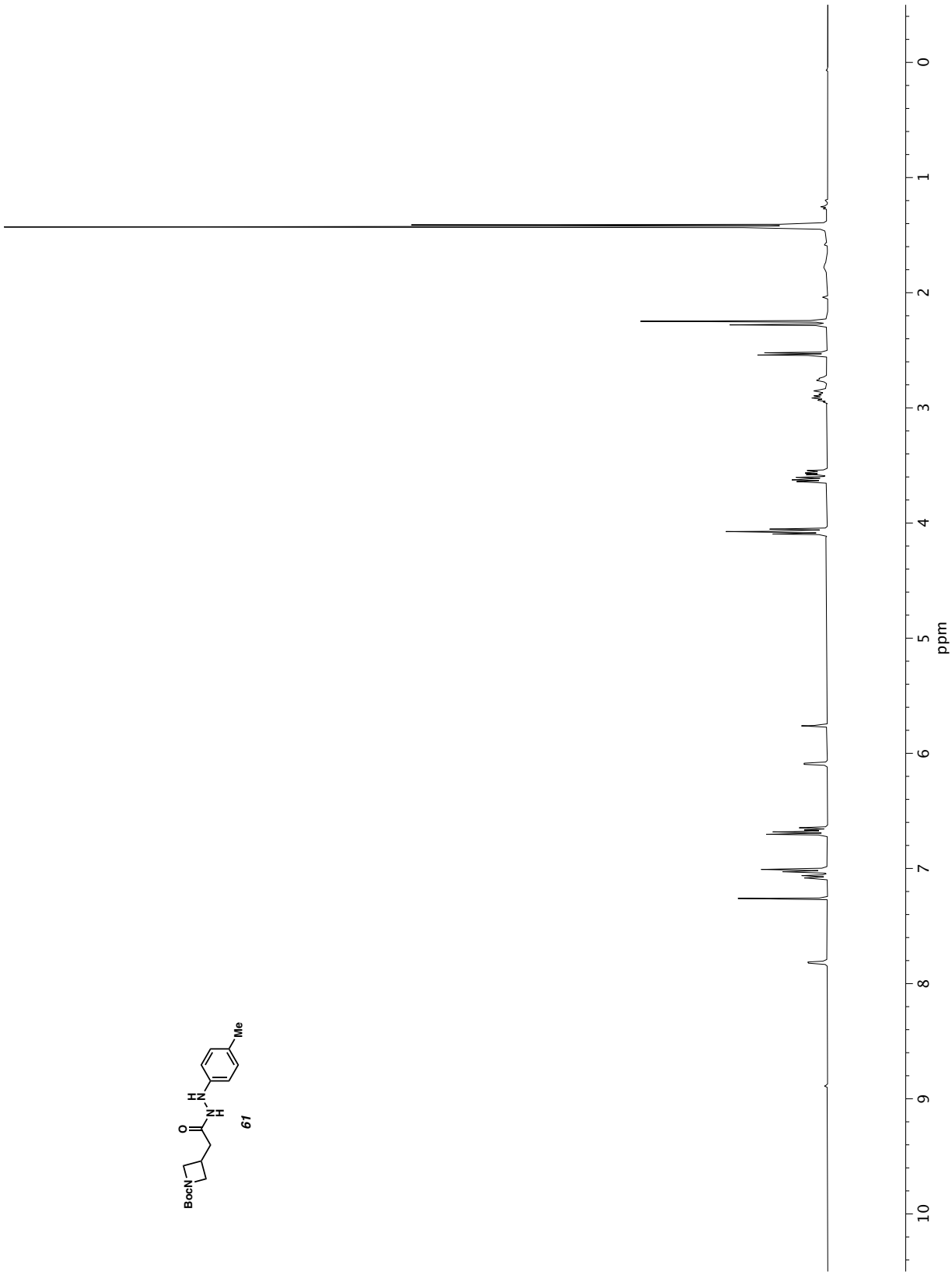


Figure A1.159 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***61****.*

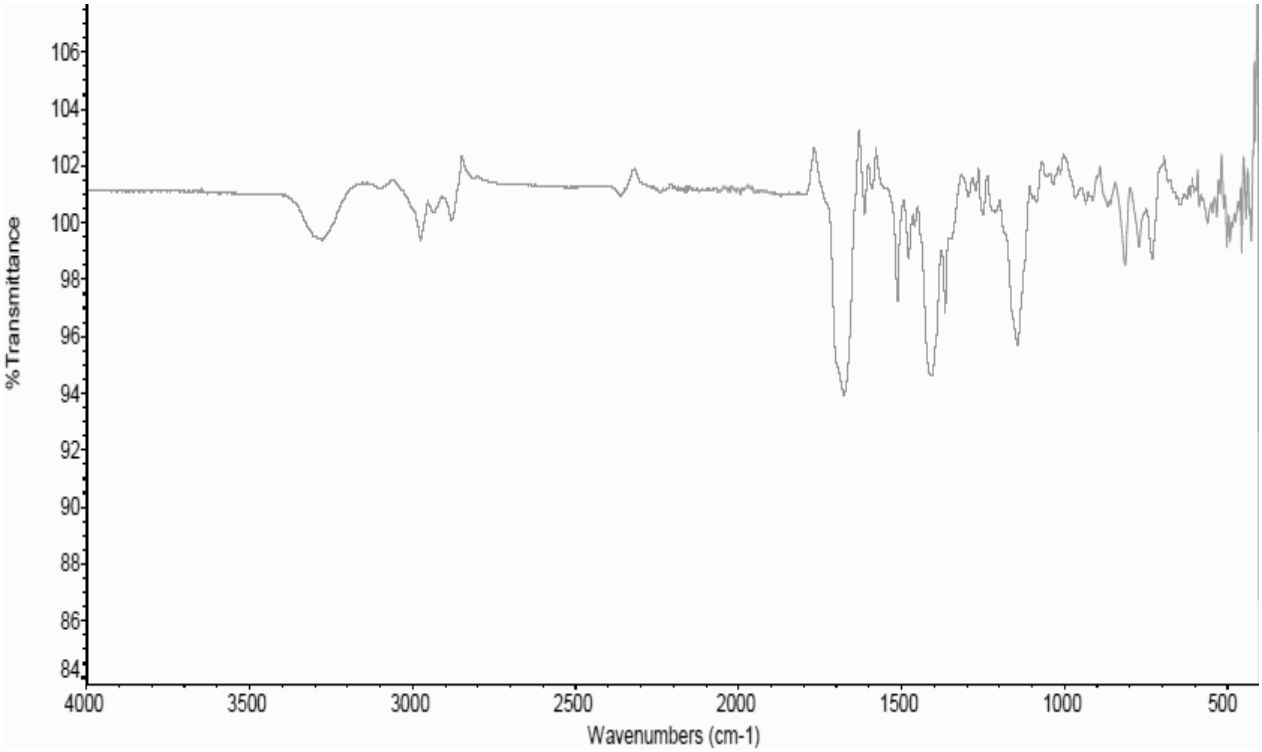


Figure A1.160 *Infrared spectrum (Thin Film) of compound* ***61***.

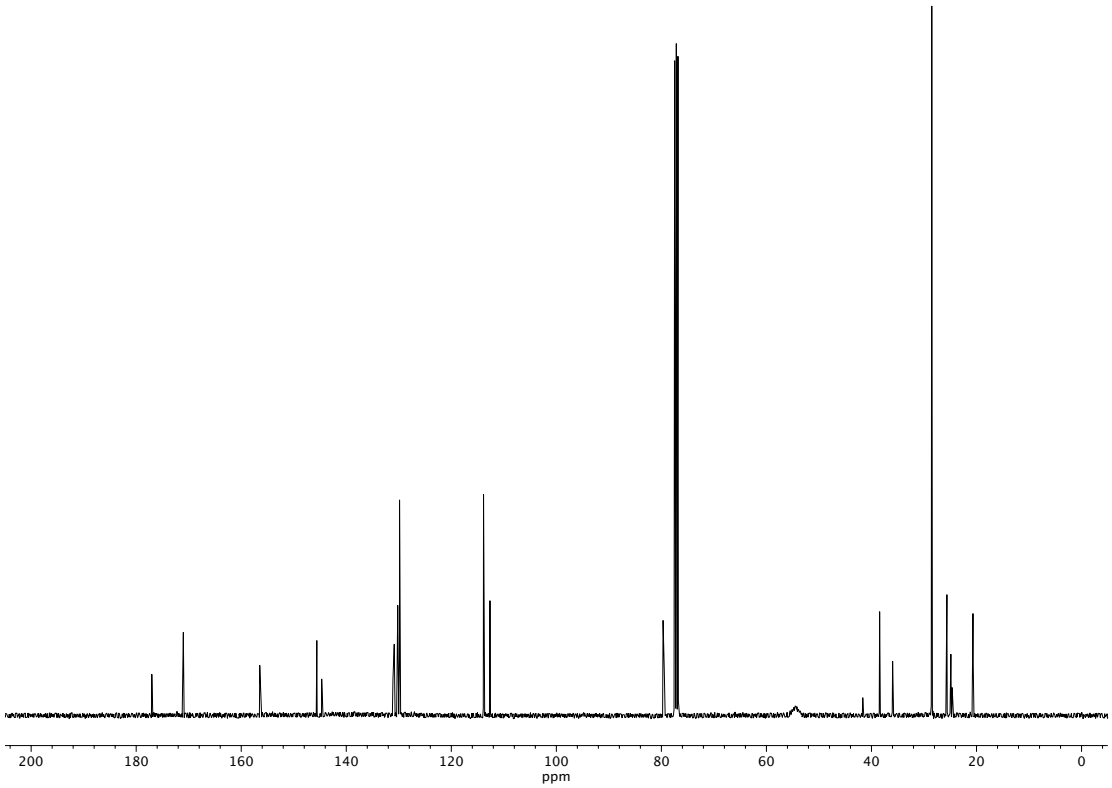


Figure A1.161 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***61***.

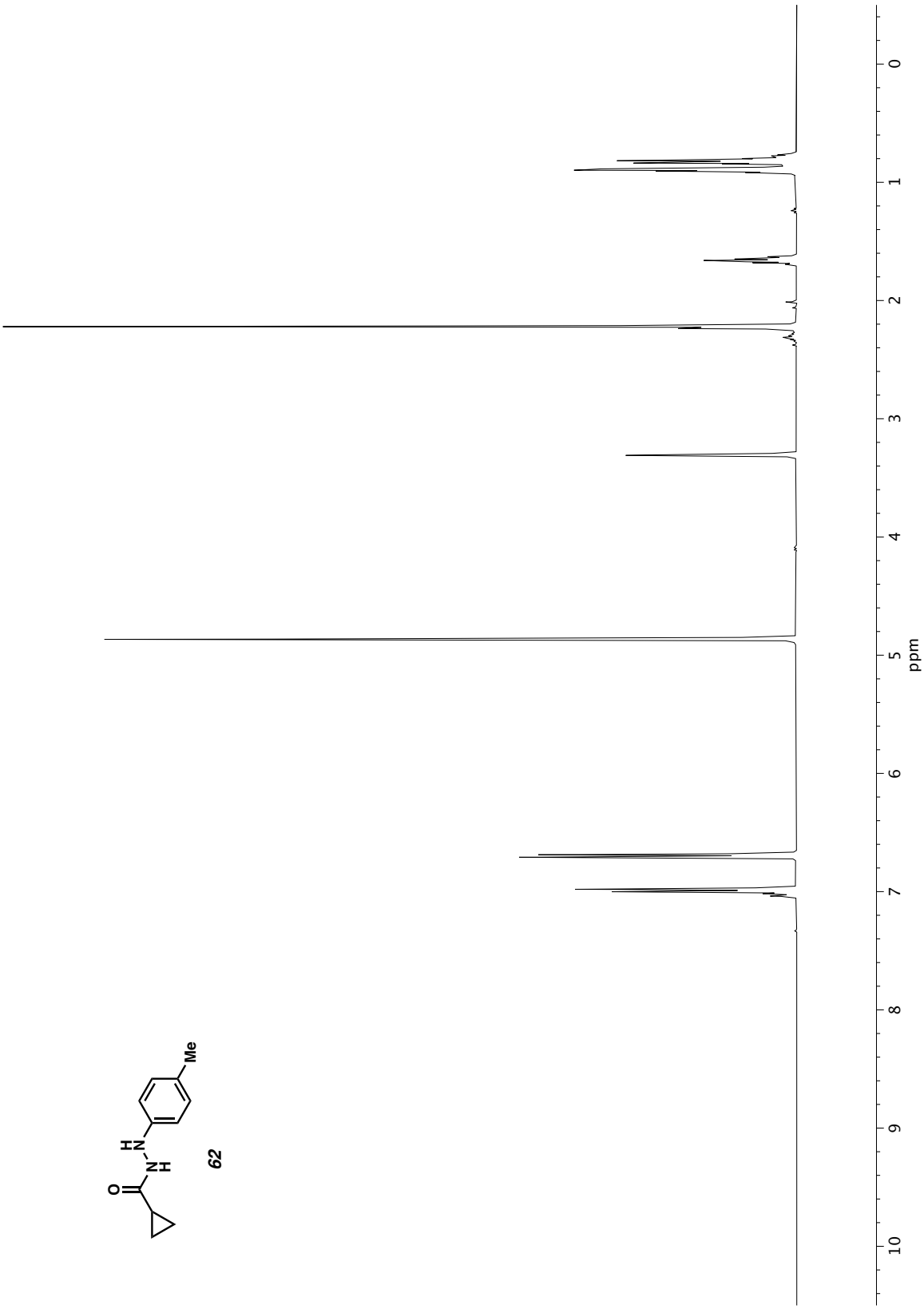


Figure A1.162 *^{1}H NMR (400 MHz, CD_3OD) of compound* ***62***.

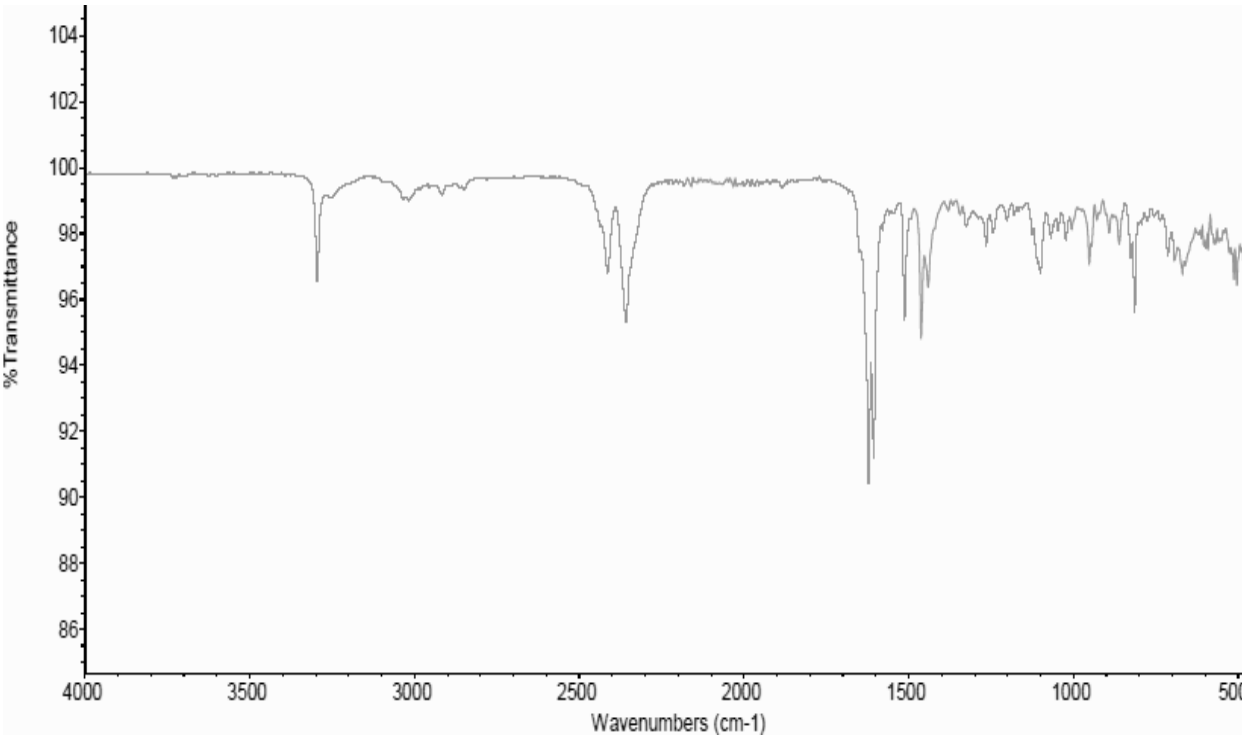


Figure A1.163 *Infrared spectrum (Thin Film) of compound* ***62***.

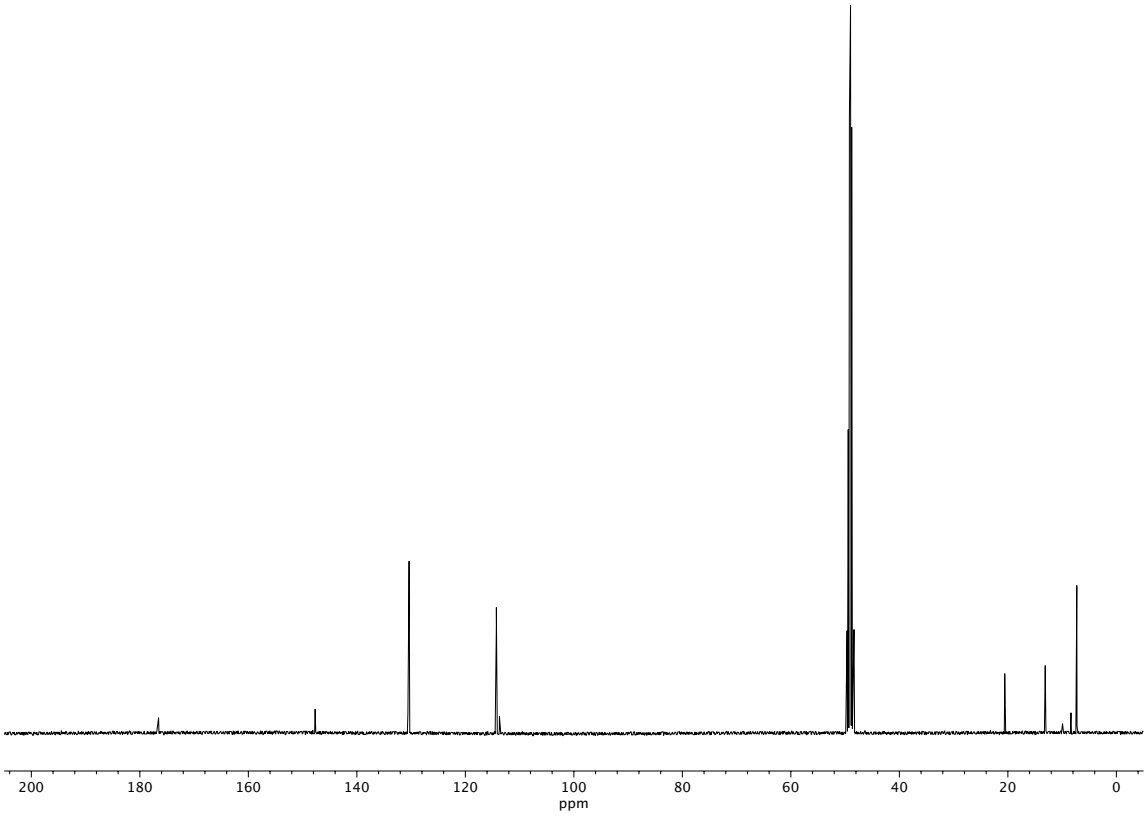


Figure A1.164 *^{13}C NMR (101 MHz, CD_3OD) of compound* ***62***.

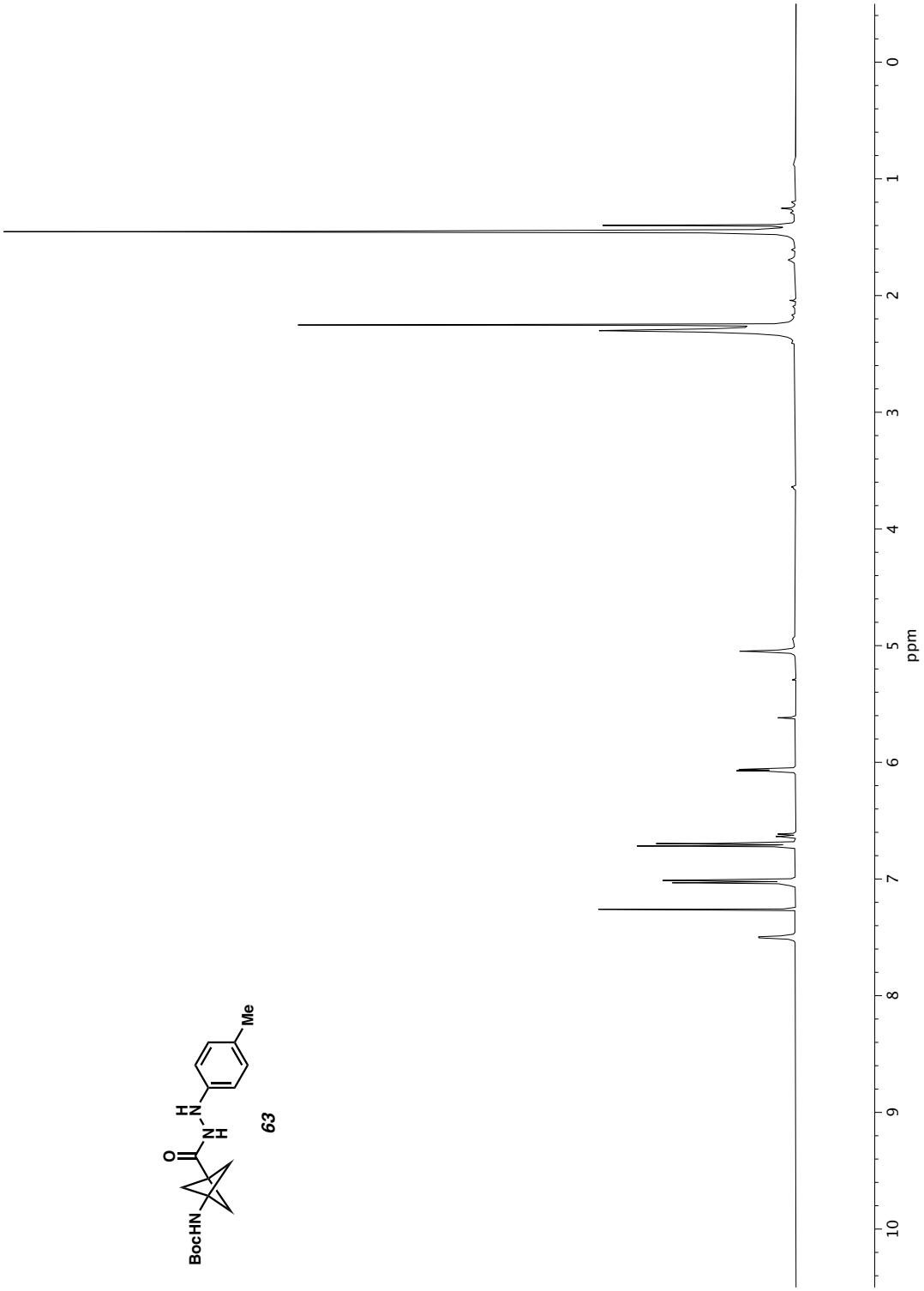


Figure A1.165 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***63***.

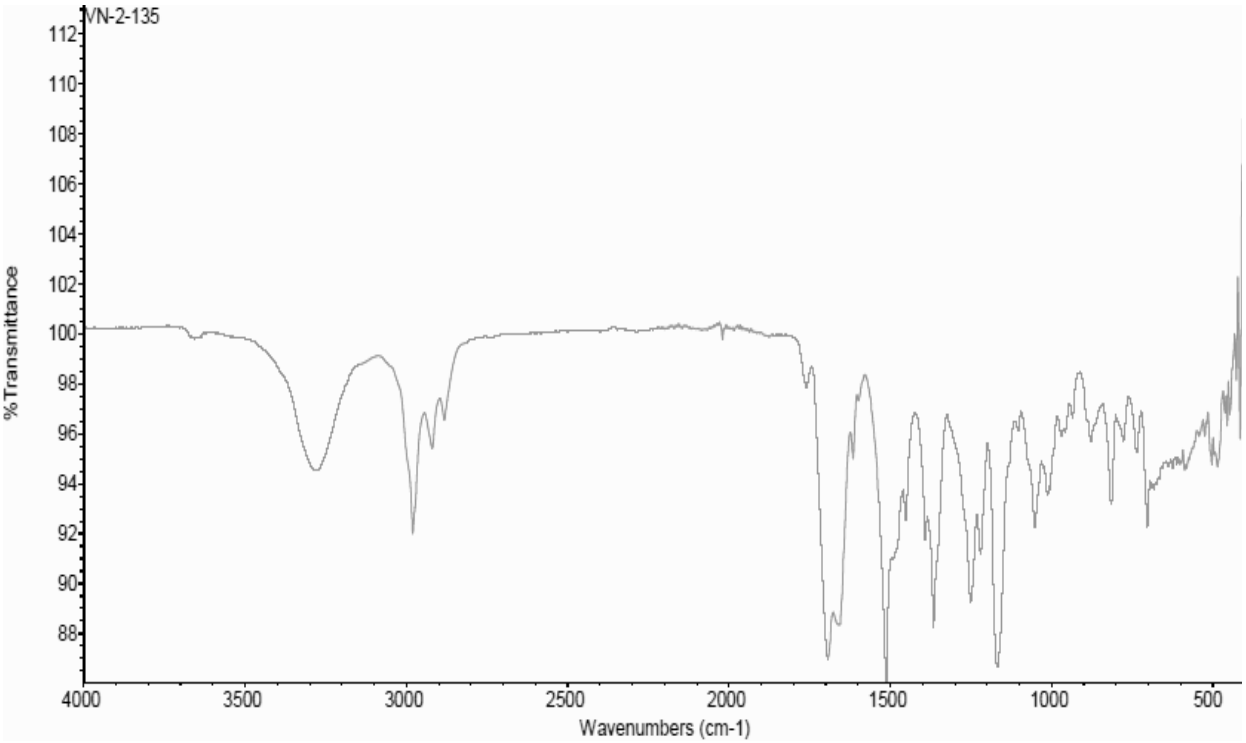


Figure A1.166 *Infrared spectrum (Thin Film) of compound* ***63***.

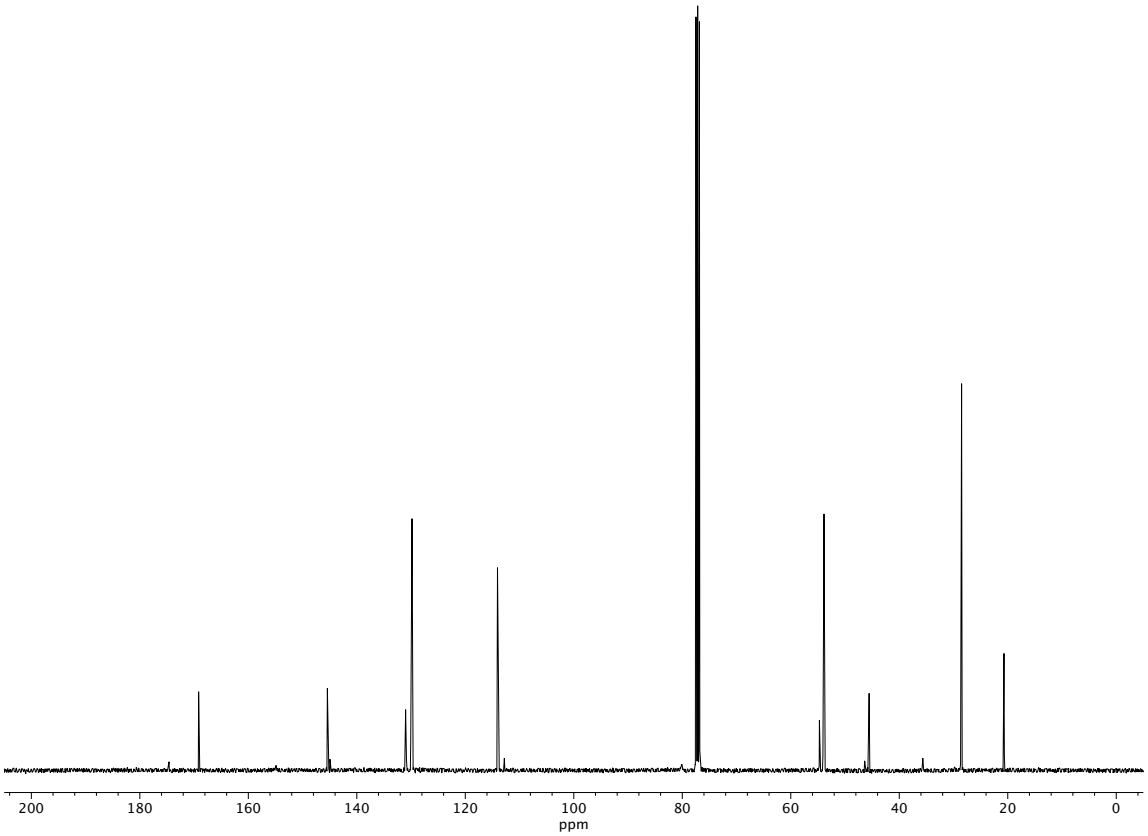


Figure A1.167 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***63***.

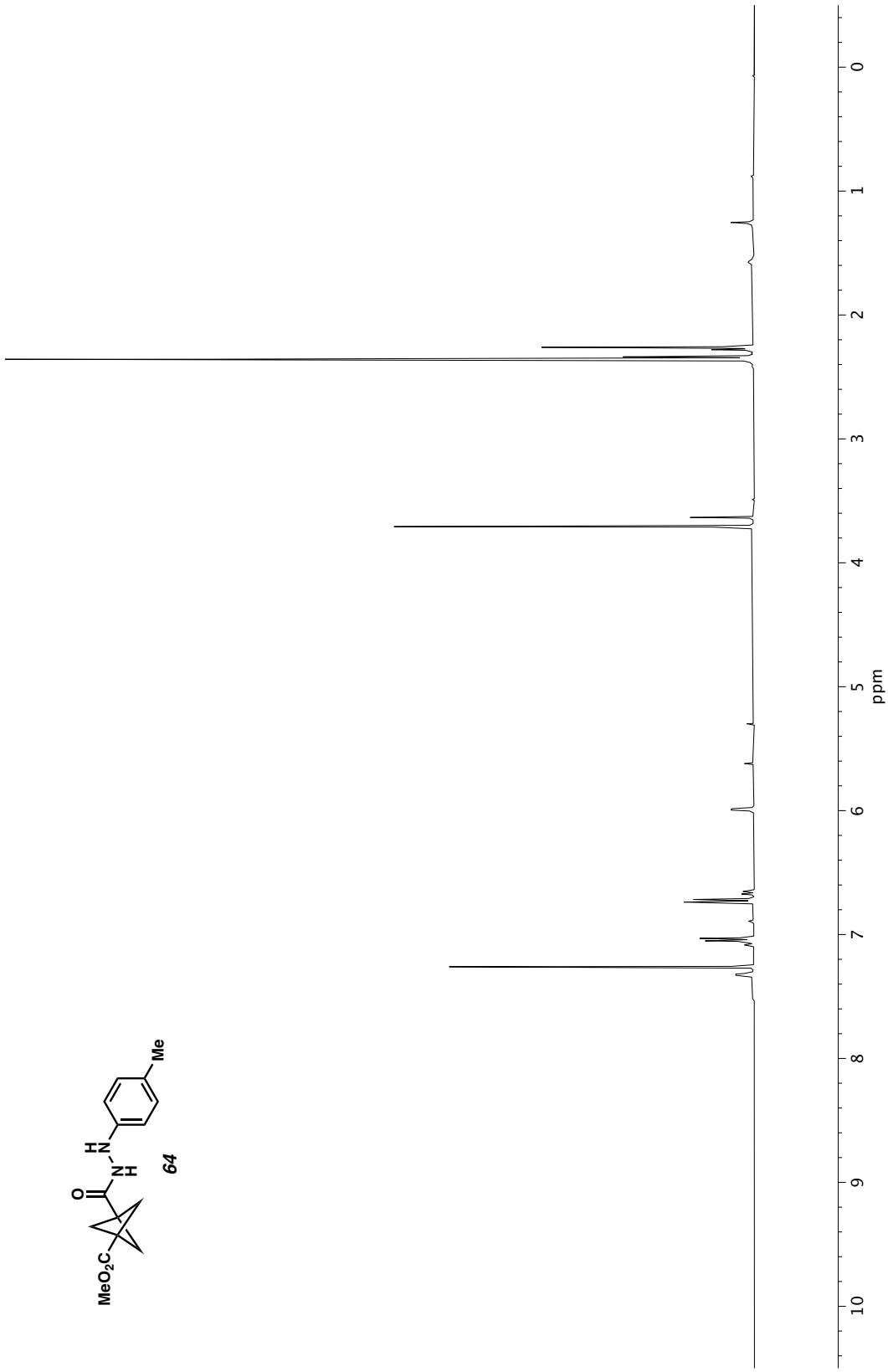


Figure A1.168 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***64****.*

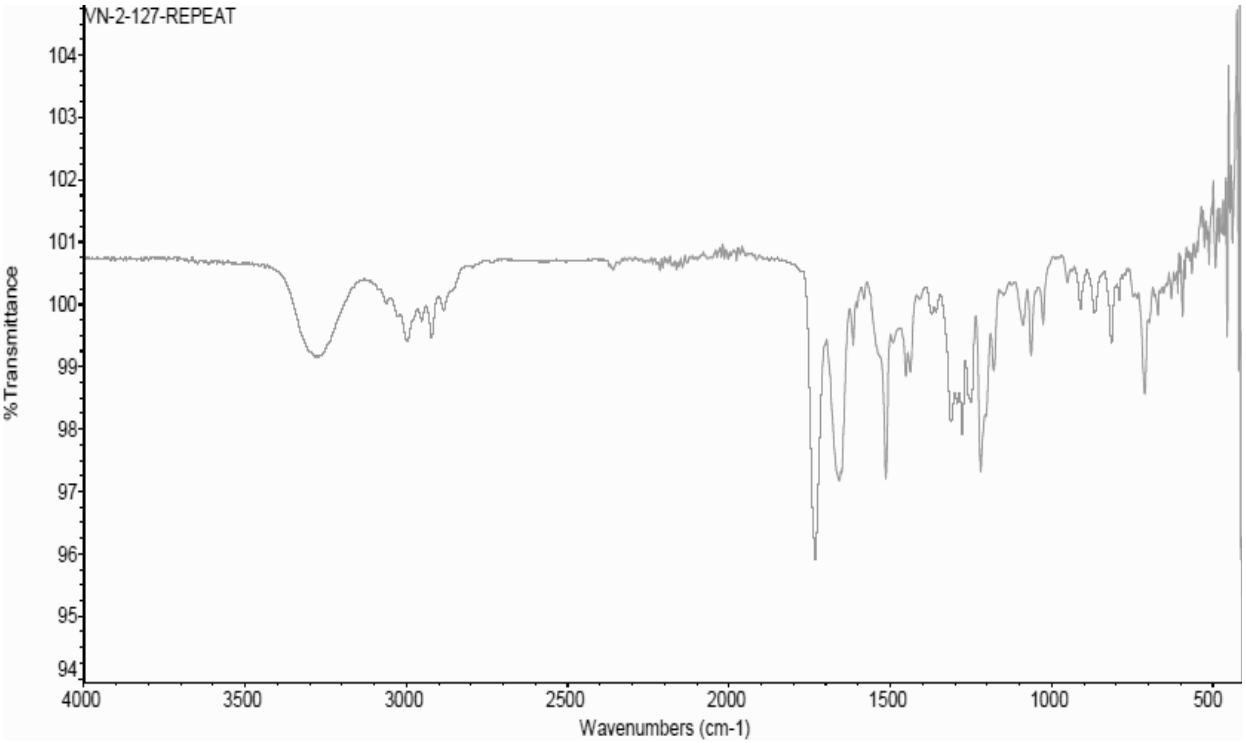


Figure A1.169 *Infrared spectrum (Thin Film) of compound* ***64****.*

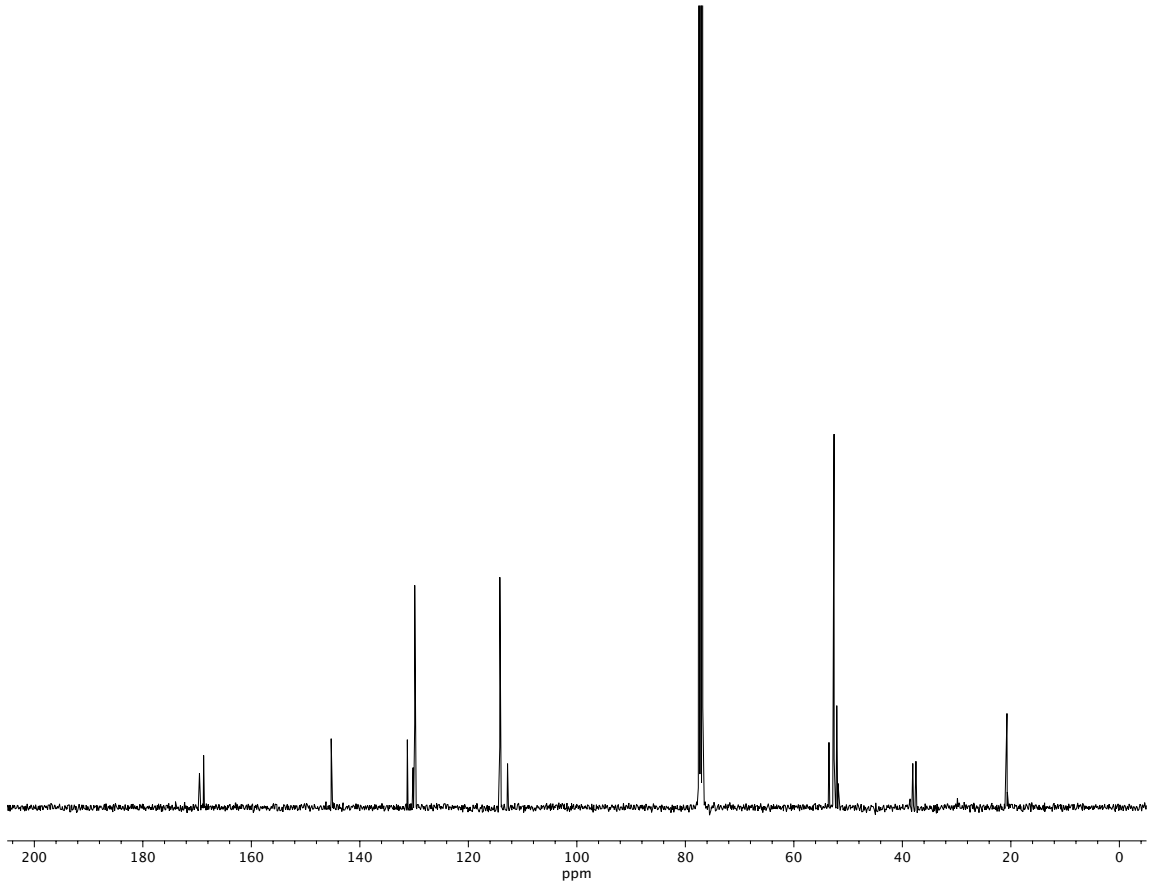


Figure A1.170 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***64****.*

Figure A1.171 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***27****.*

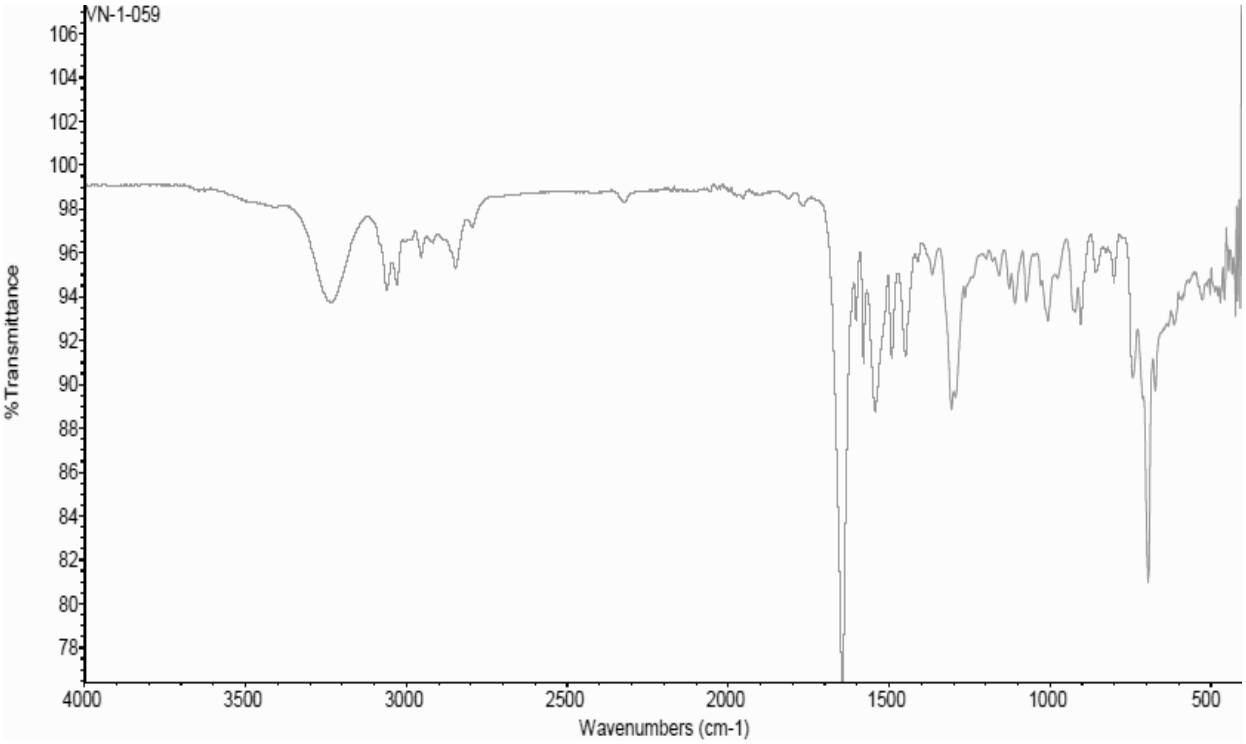


Figure A1.172 *Infrared spectrum (Thin Film) of compound* ***27****.*

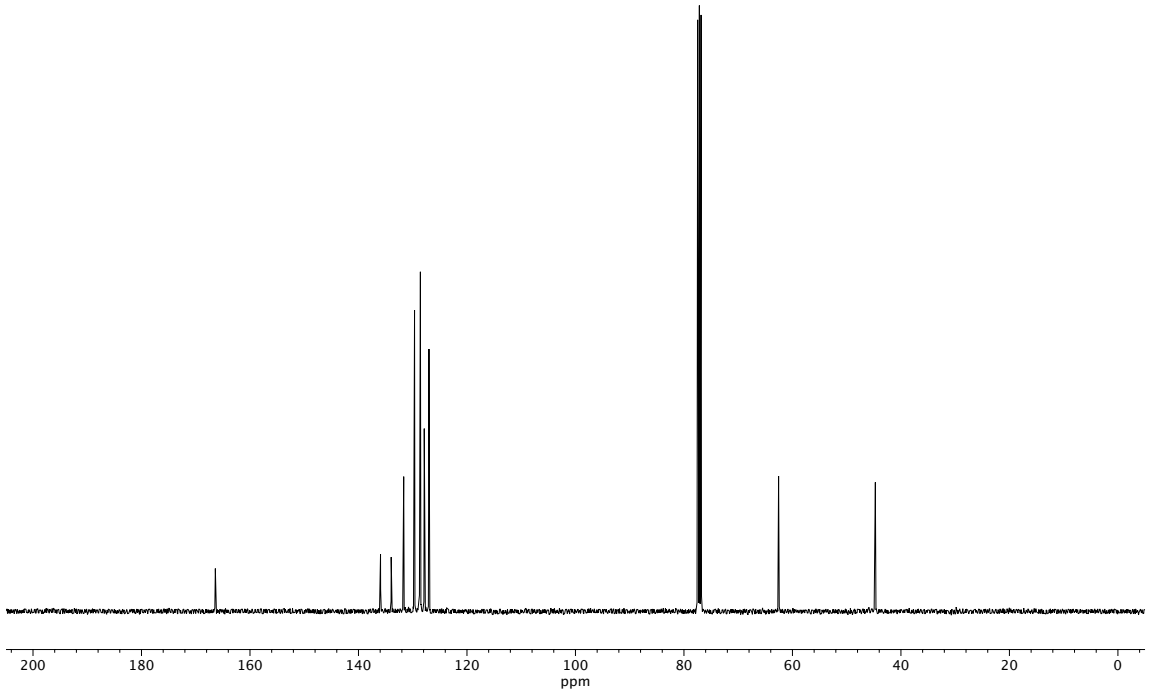


Figure A1.173 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***27****.*

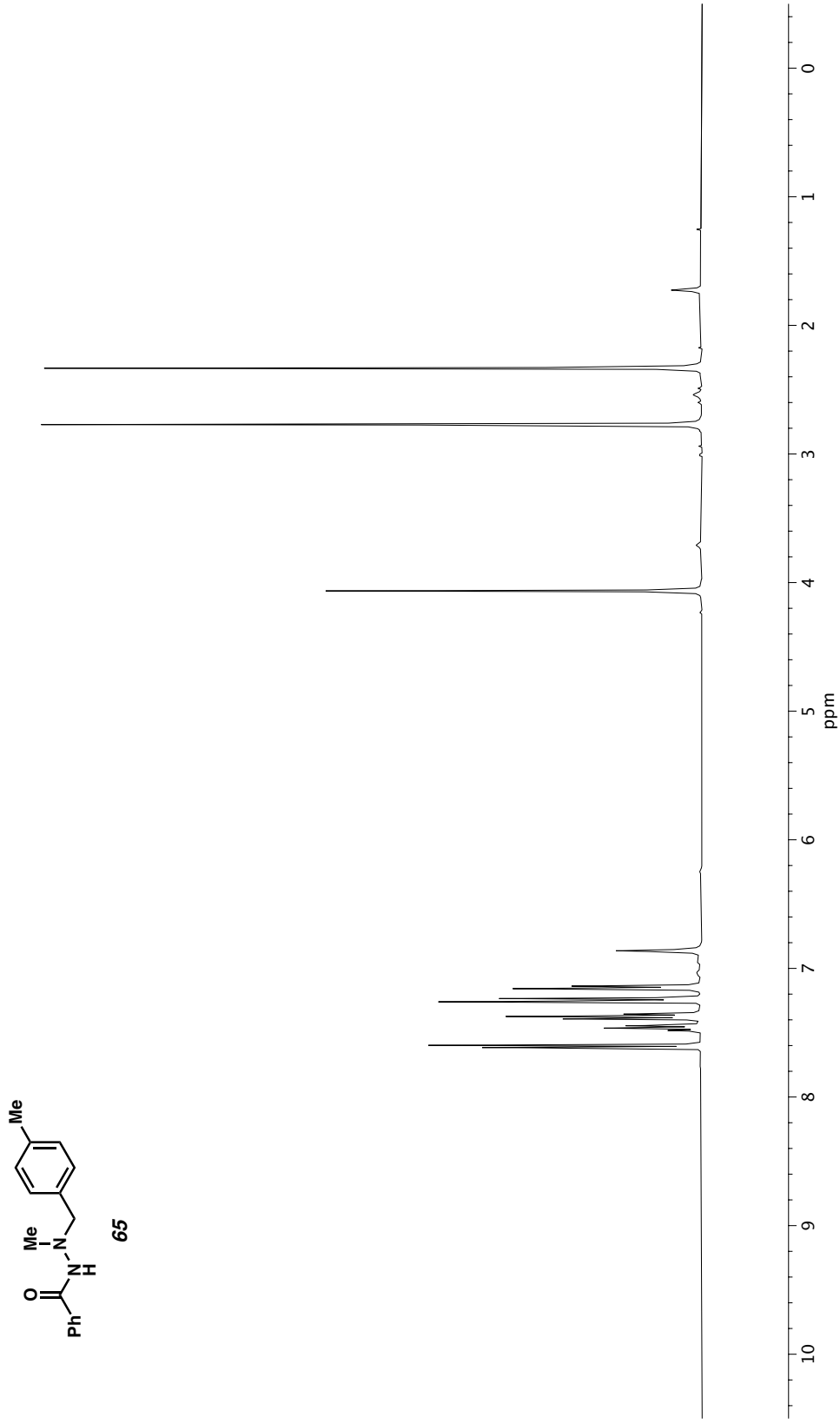


Figure A1.174 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***65***.

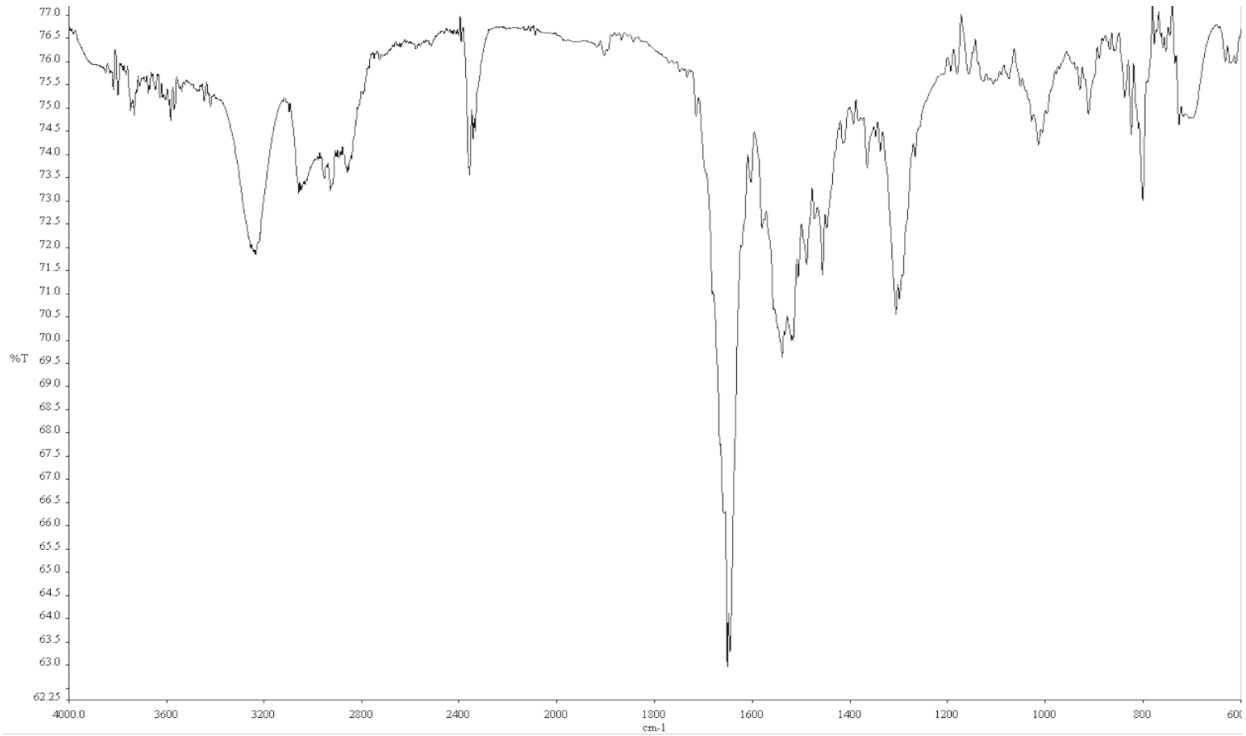


Figure A1.175 *Infrared spectrum (Thin Film, NaCl) of compound* ***65***.

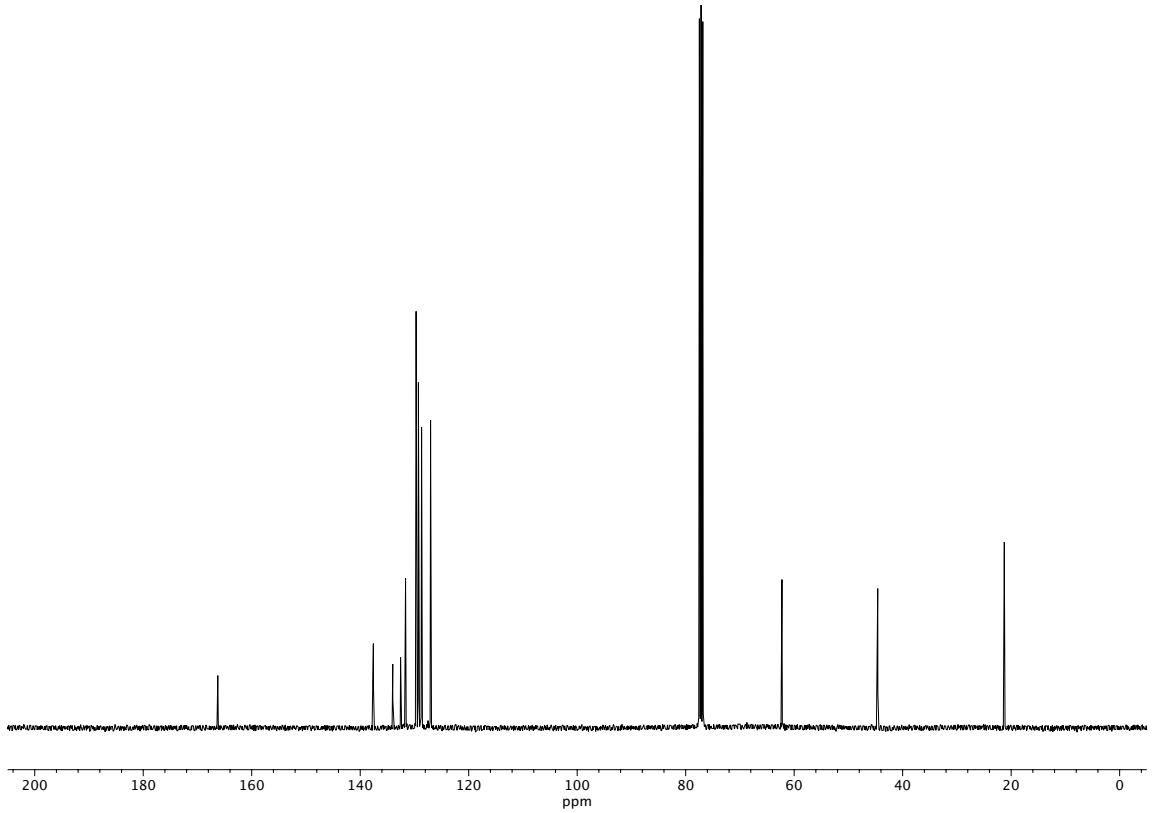


Figure A1.176 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***65***.

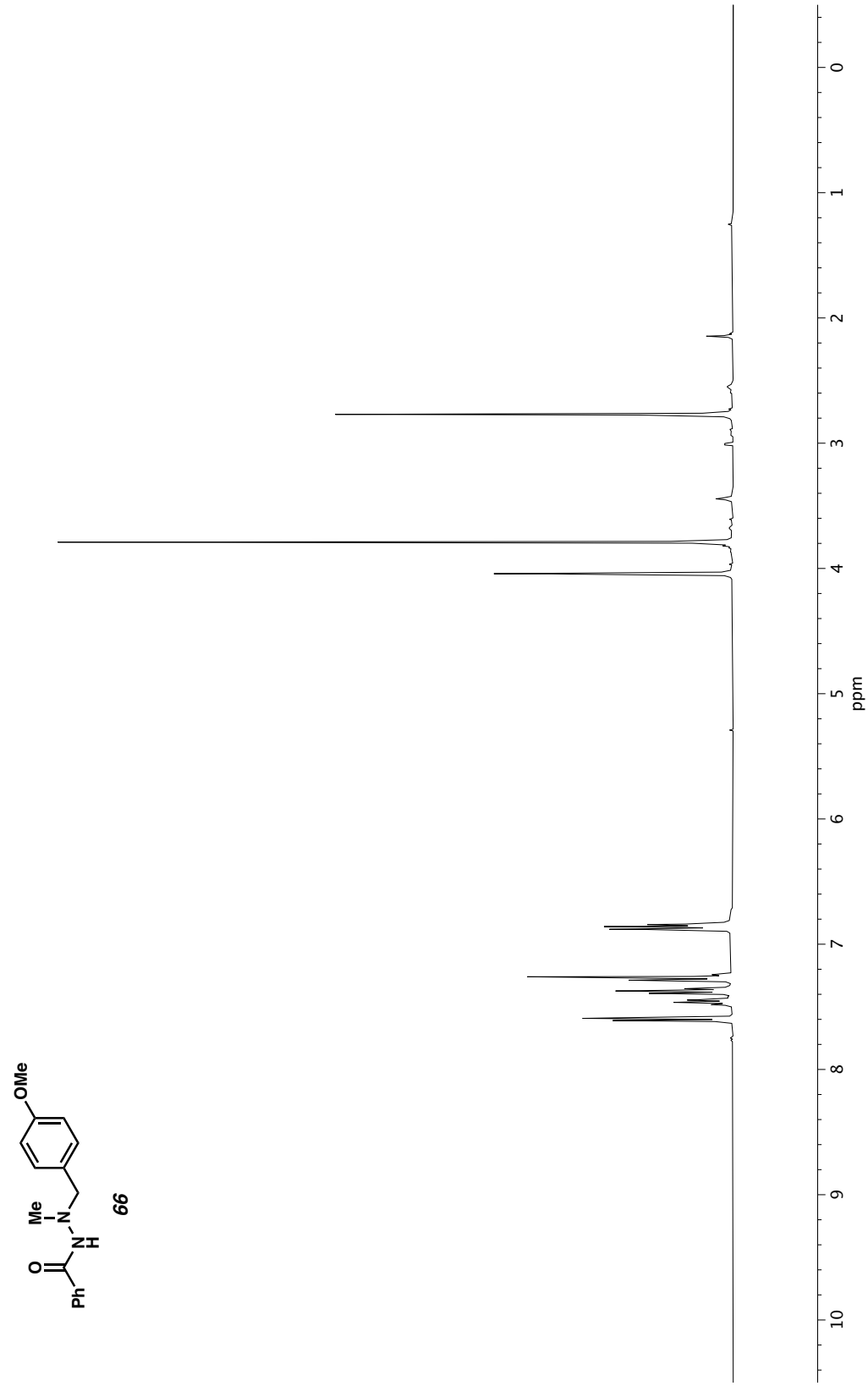


Figure A1.177 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***66***.

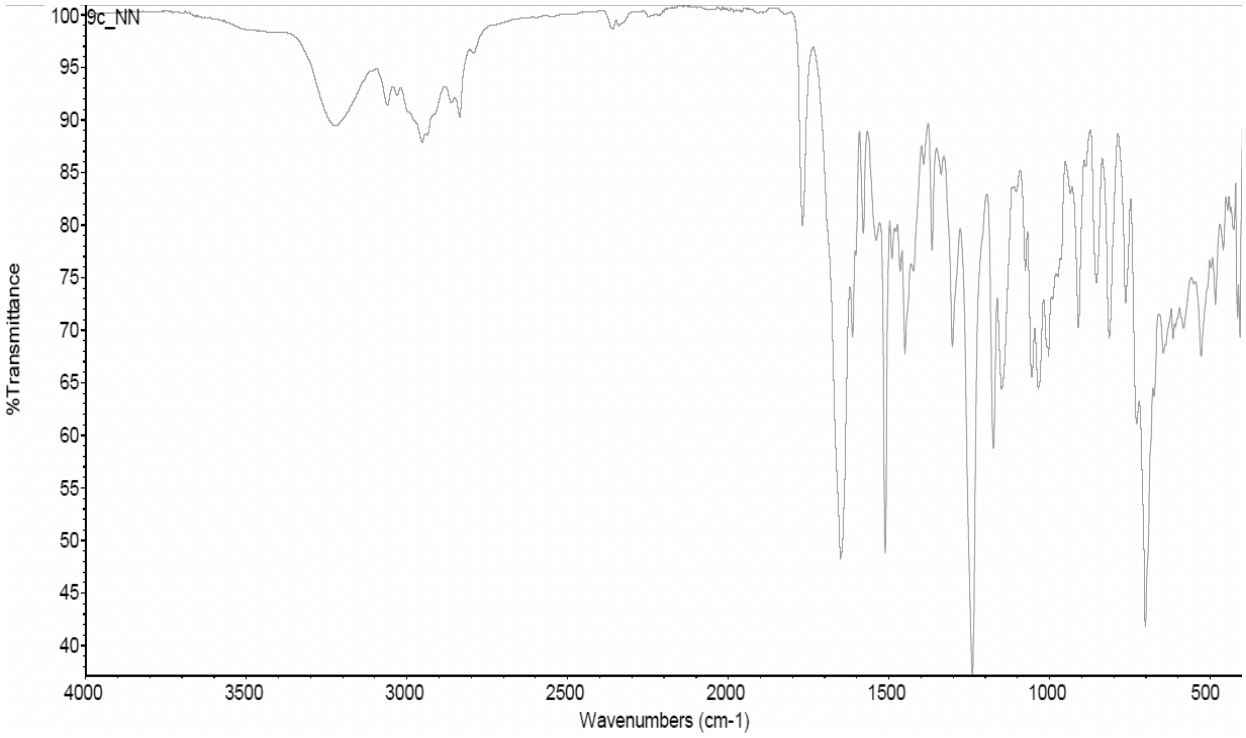


Figure A1.178 *Infrared spectrum (Thin Film) of compound* ***66***.

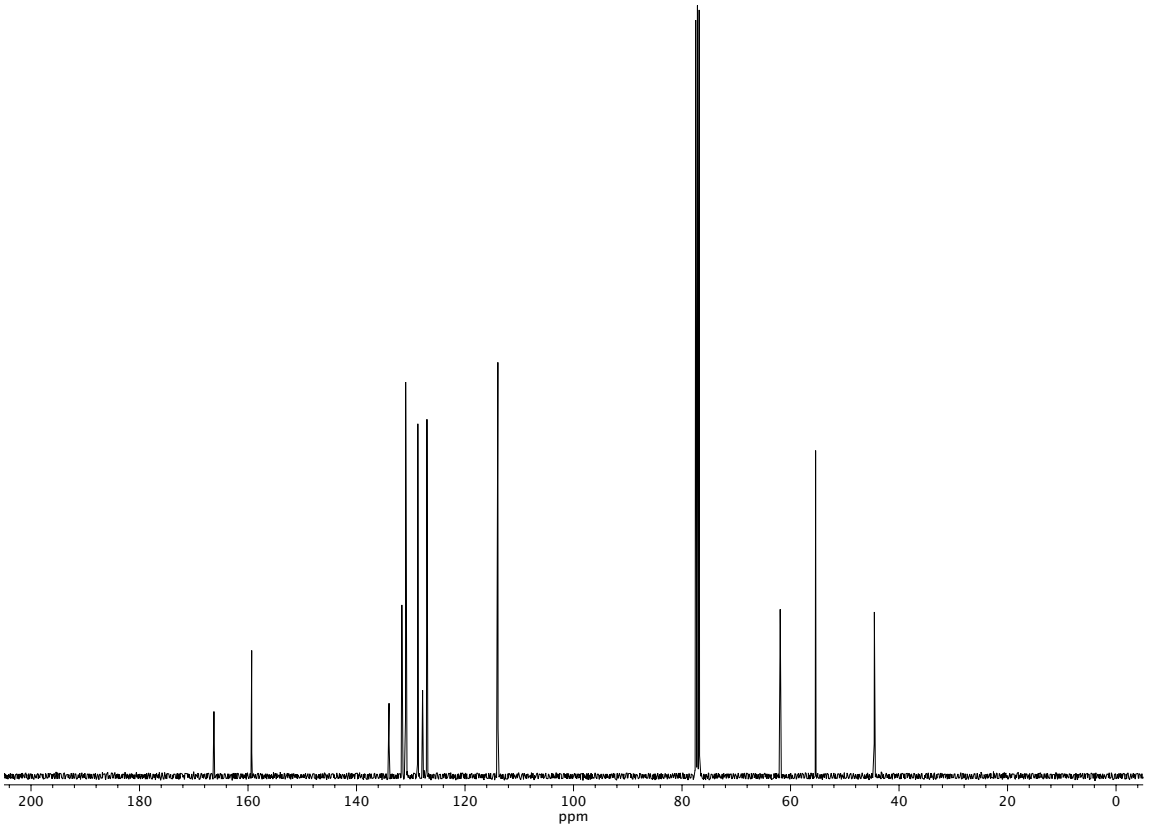


Figure A1.179 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***66***.

Figure A1.180 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **67**.*

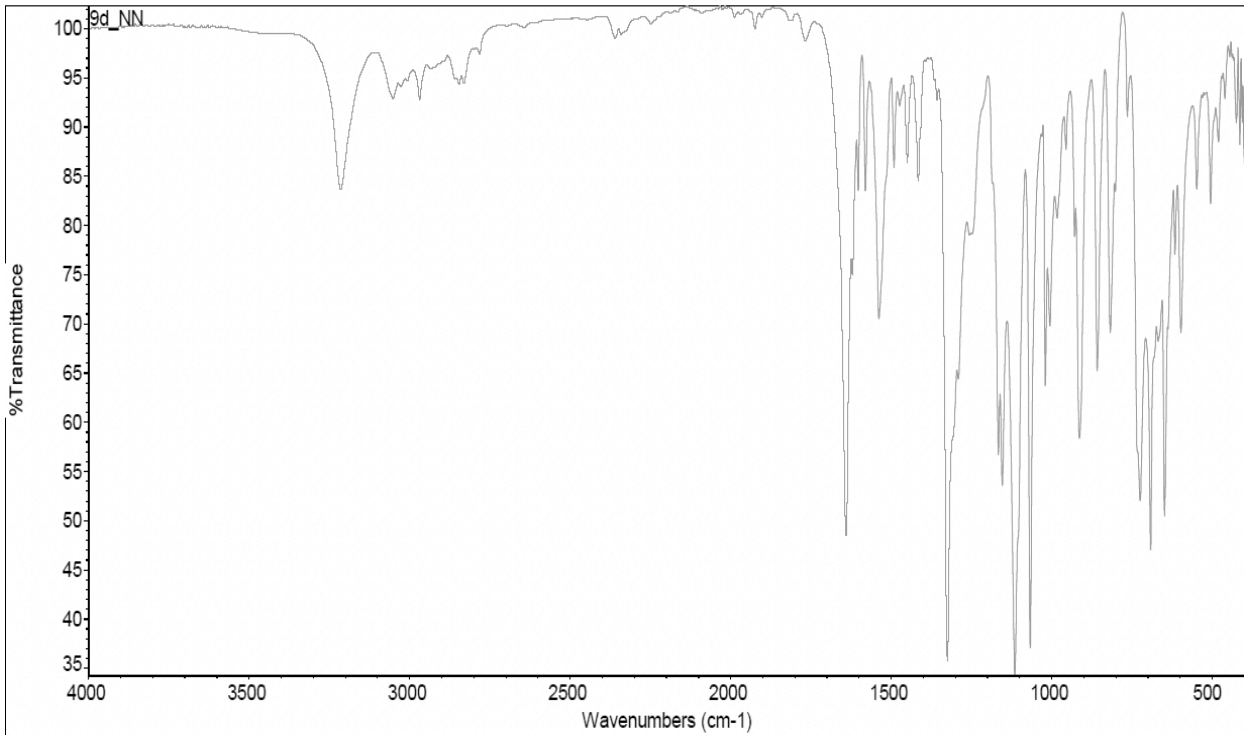


Figure A1.181 *Infrared spectrum (Thin Film) of compound* ***67****.*

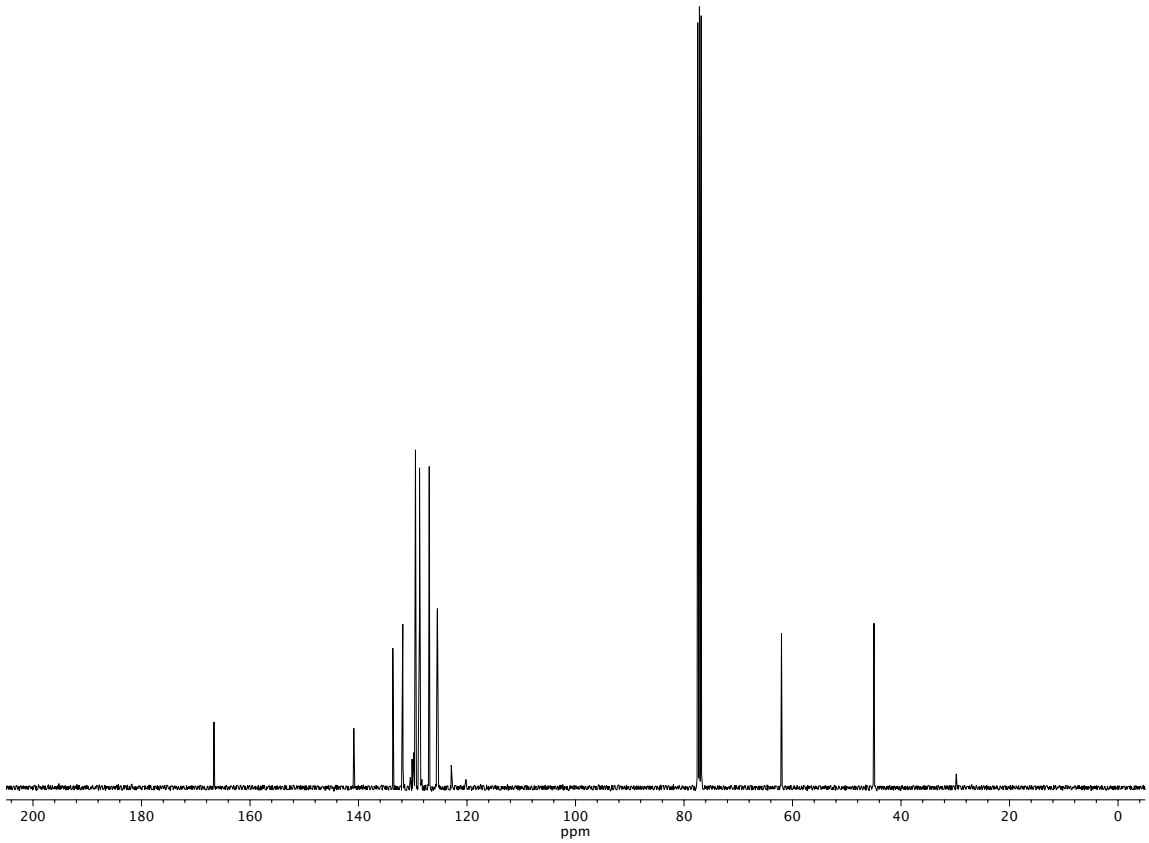


Figure A1.182 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***67****.*

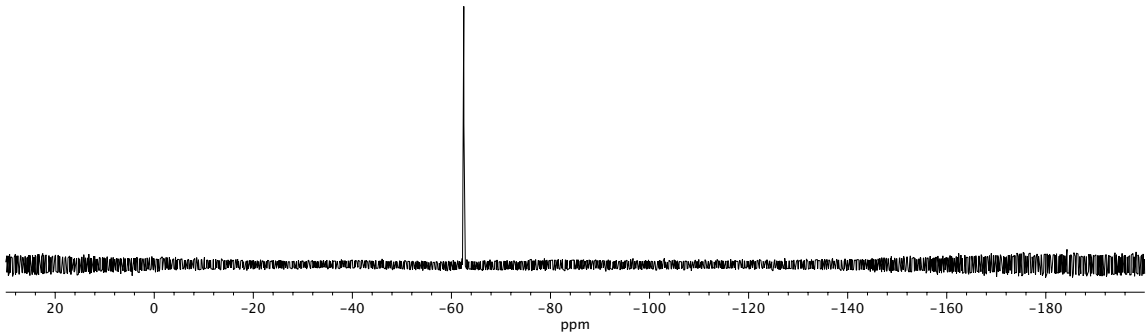


Figure A1.183 *^{19}F NMR (282 MHz, $CDCl_3$) of compound **67**.*

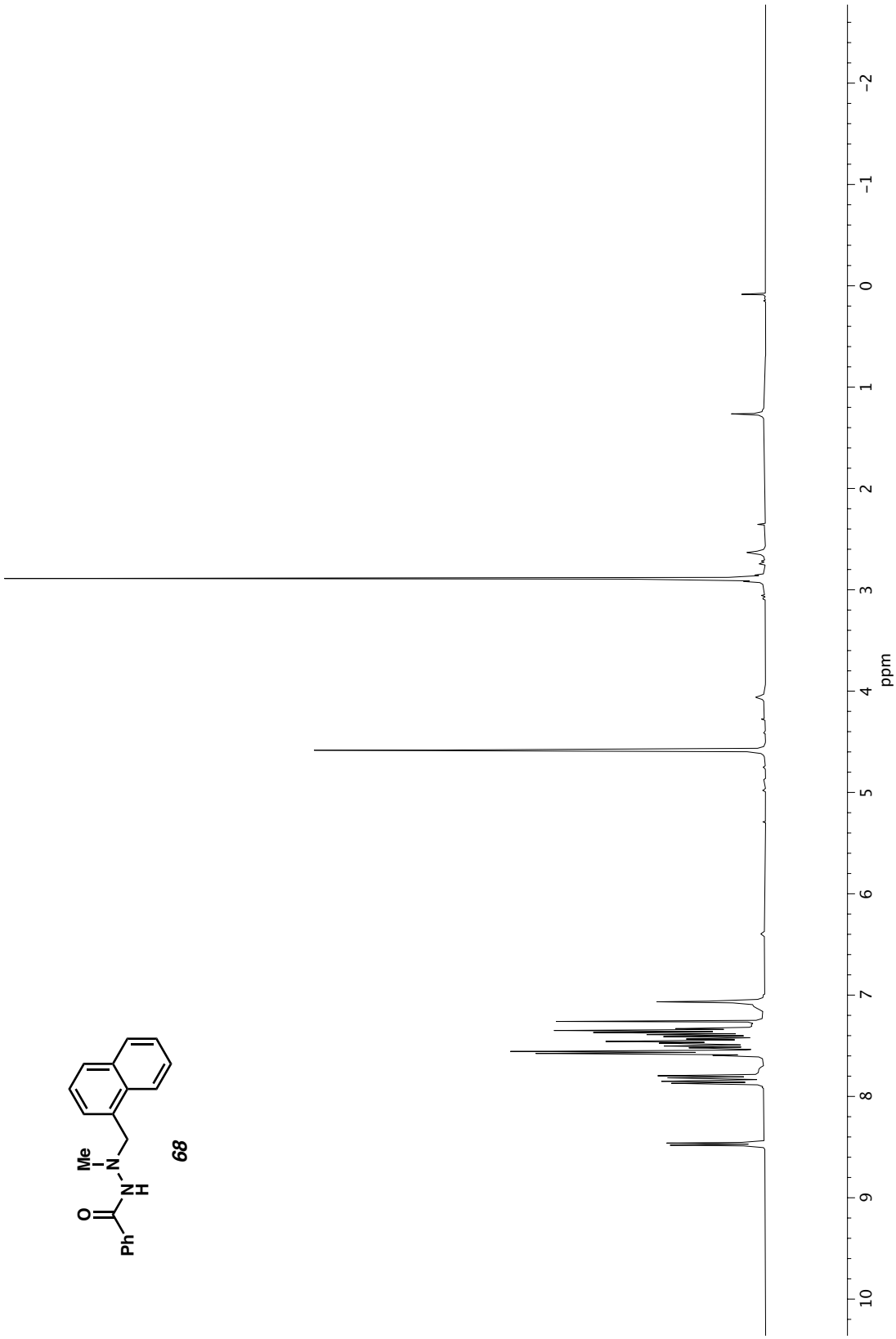


Figure A1.184 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***68****.*

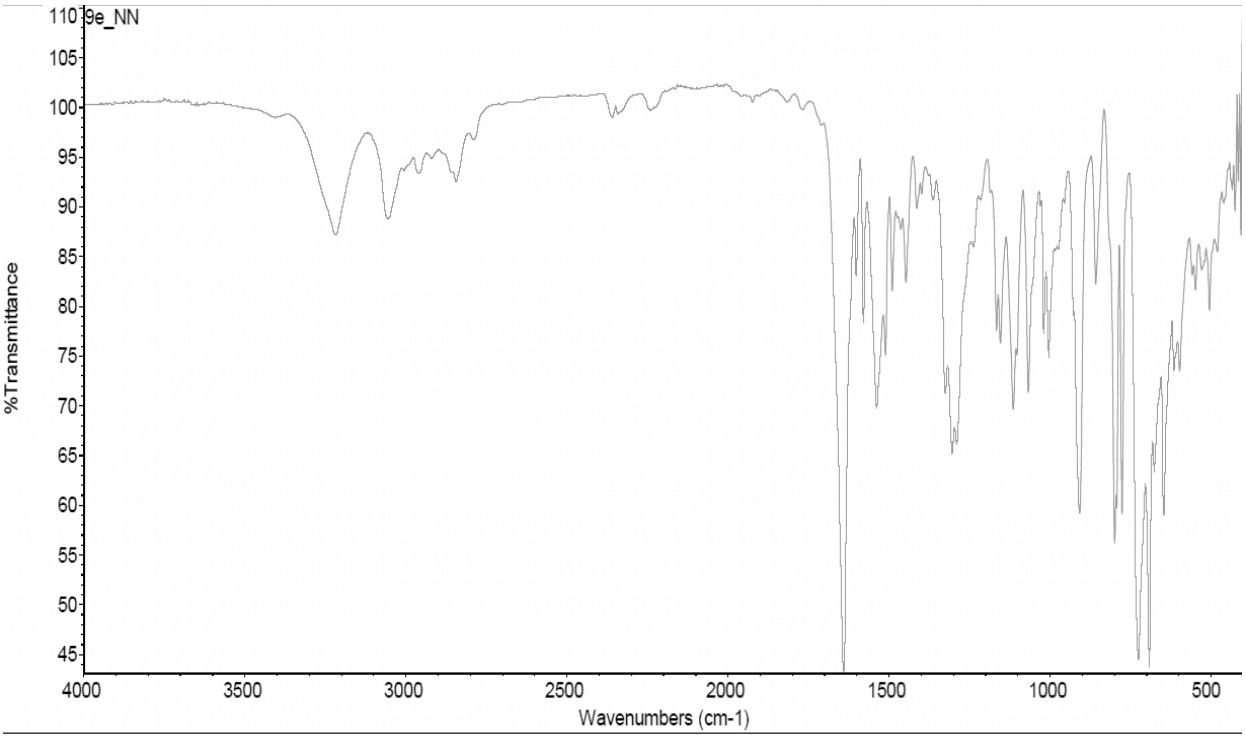


Figure A1.185 *Infrared spectrum (Thin Film) of compound* ***68***.

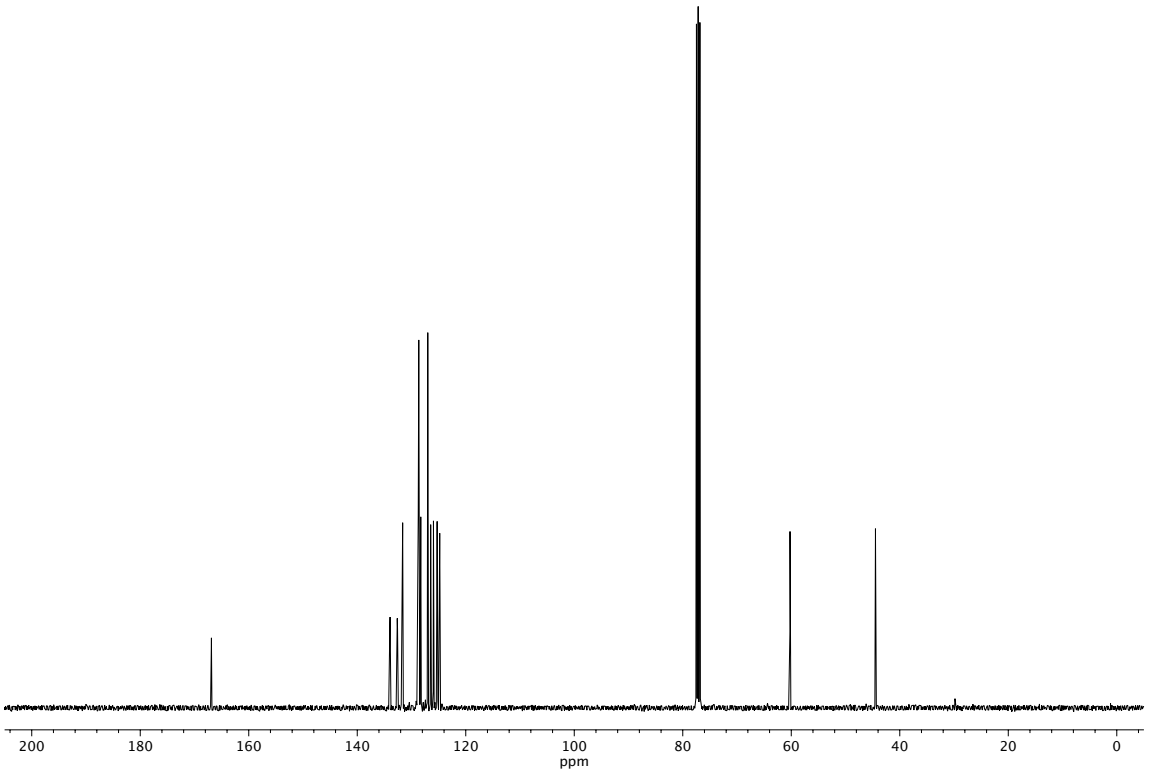


Figure A1.186 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***68***.

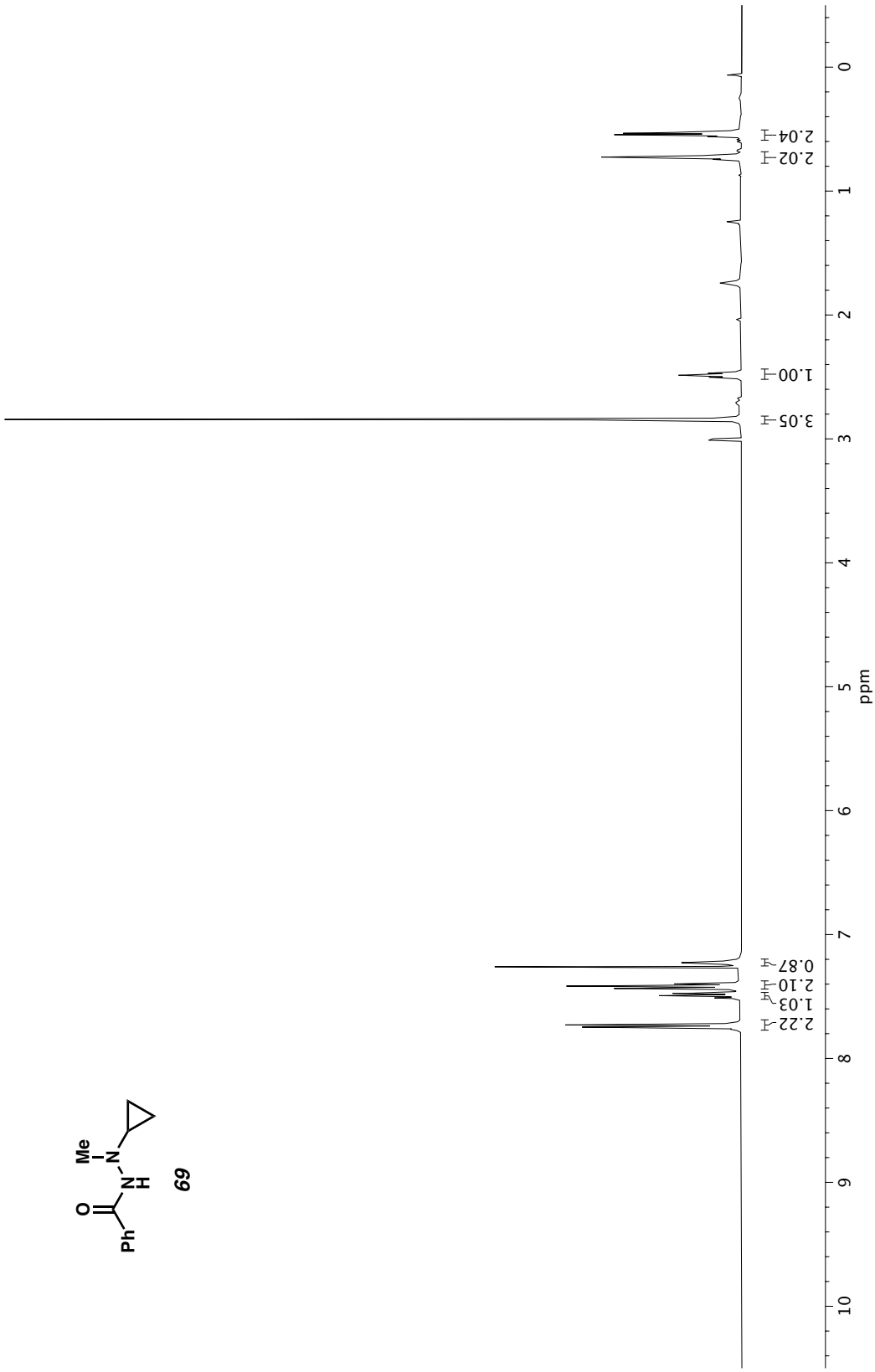


Figure A1.187 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***69***.

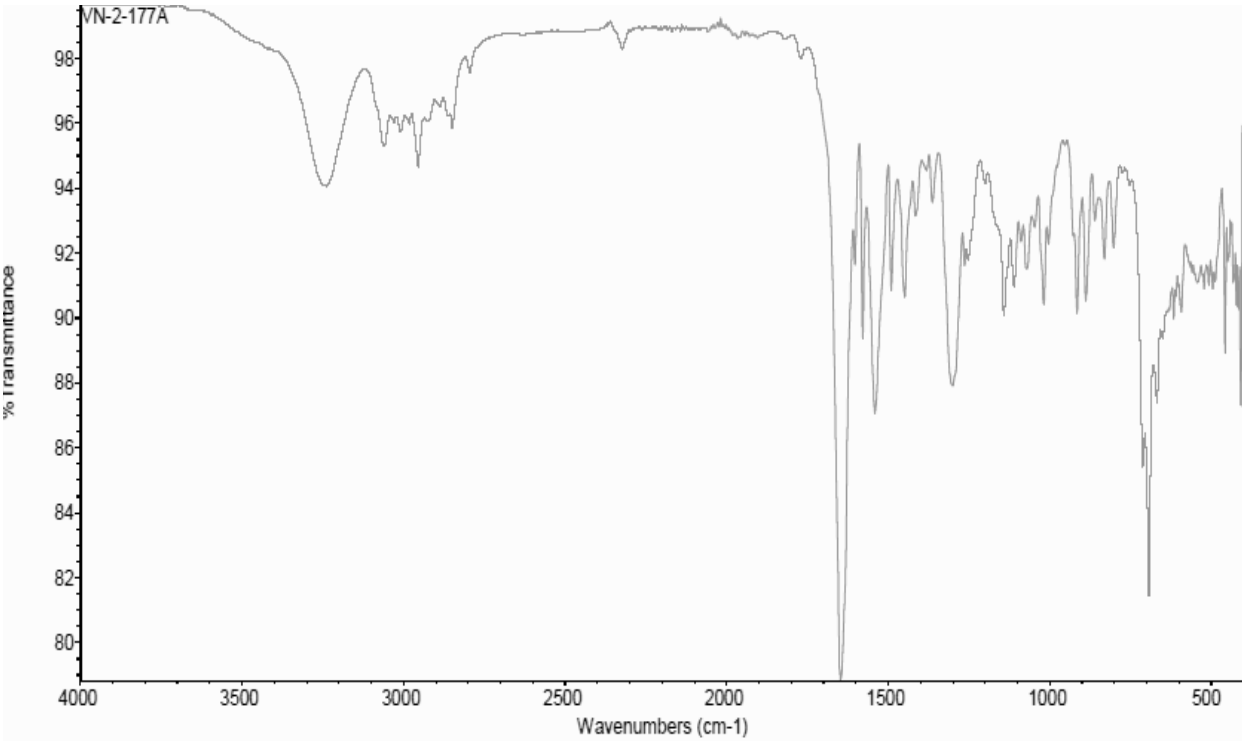


Figure A1.188 *Infrared spectrum (Thin Film) of compound* ***69****.*

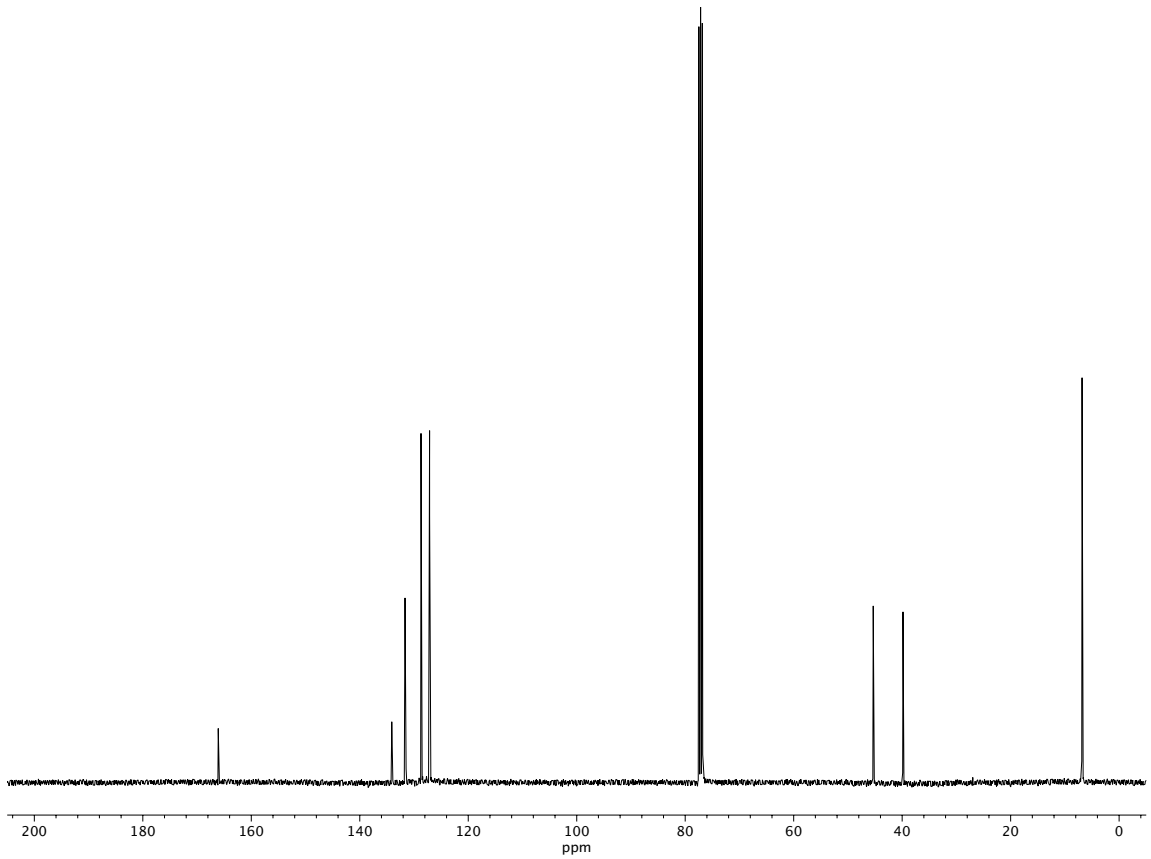


Figure A1.189 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***69****.*

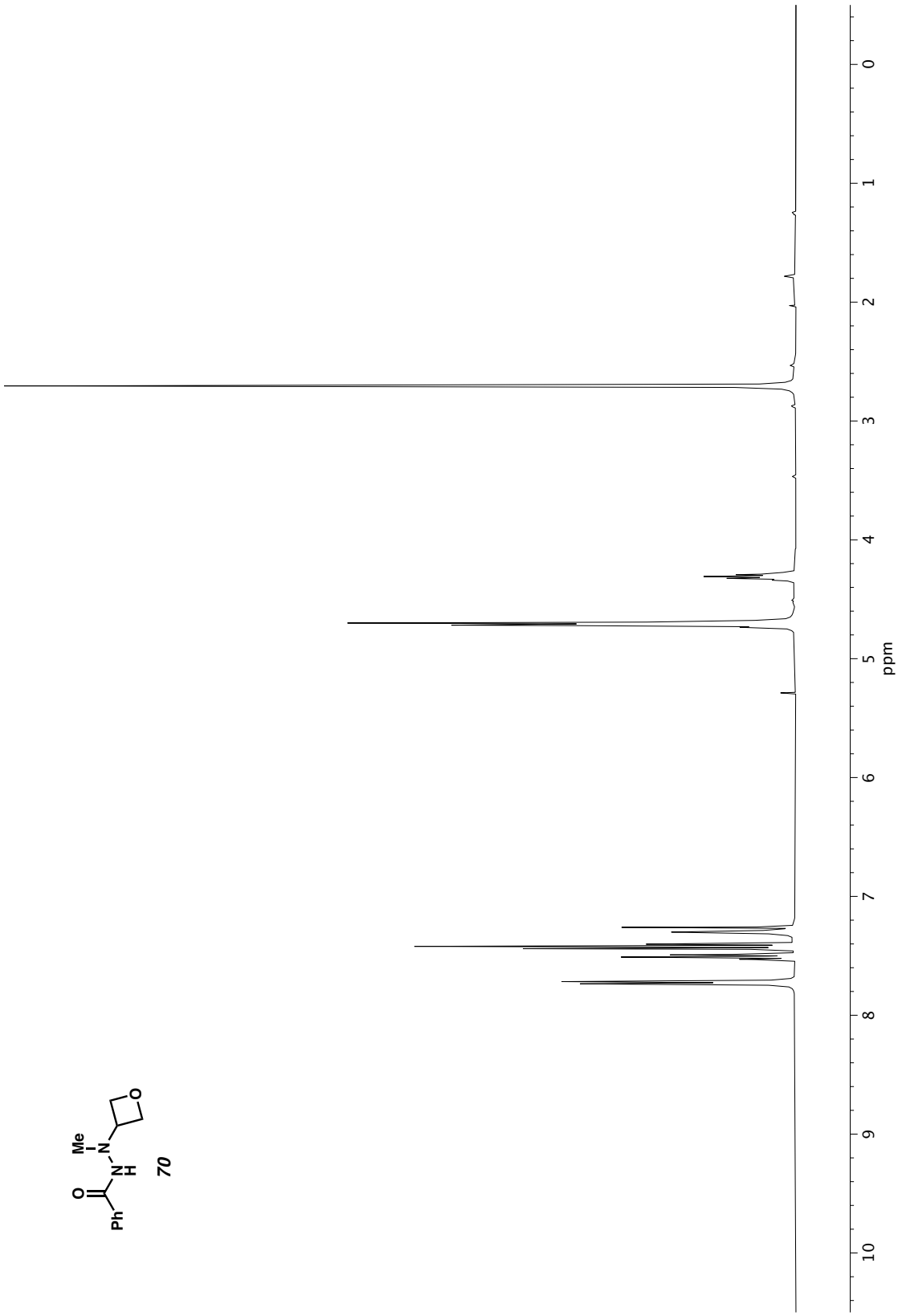


Figure A1.190 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **70**.*

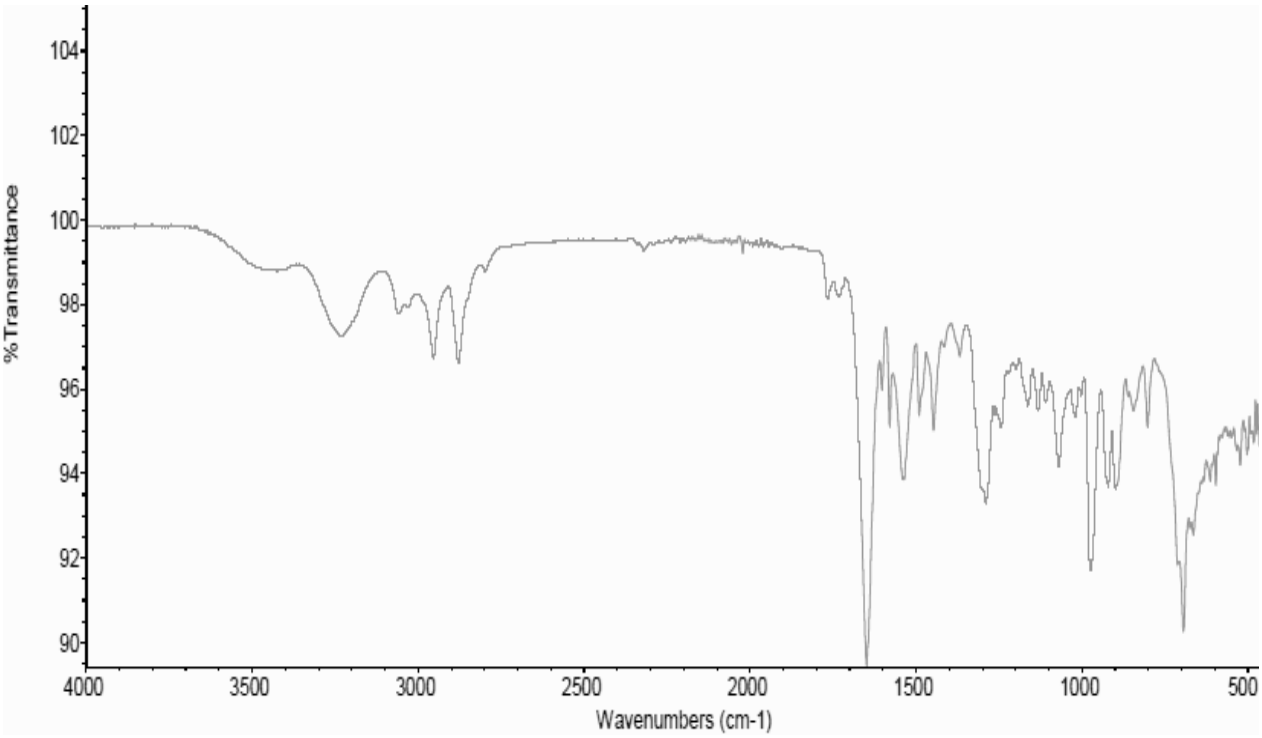


Figure A1.191 *Infrared spectrum (Thin Film) of compound* ***70****.*

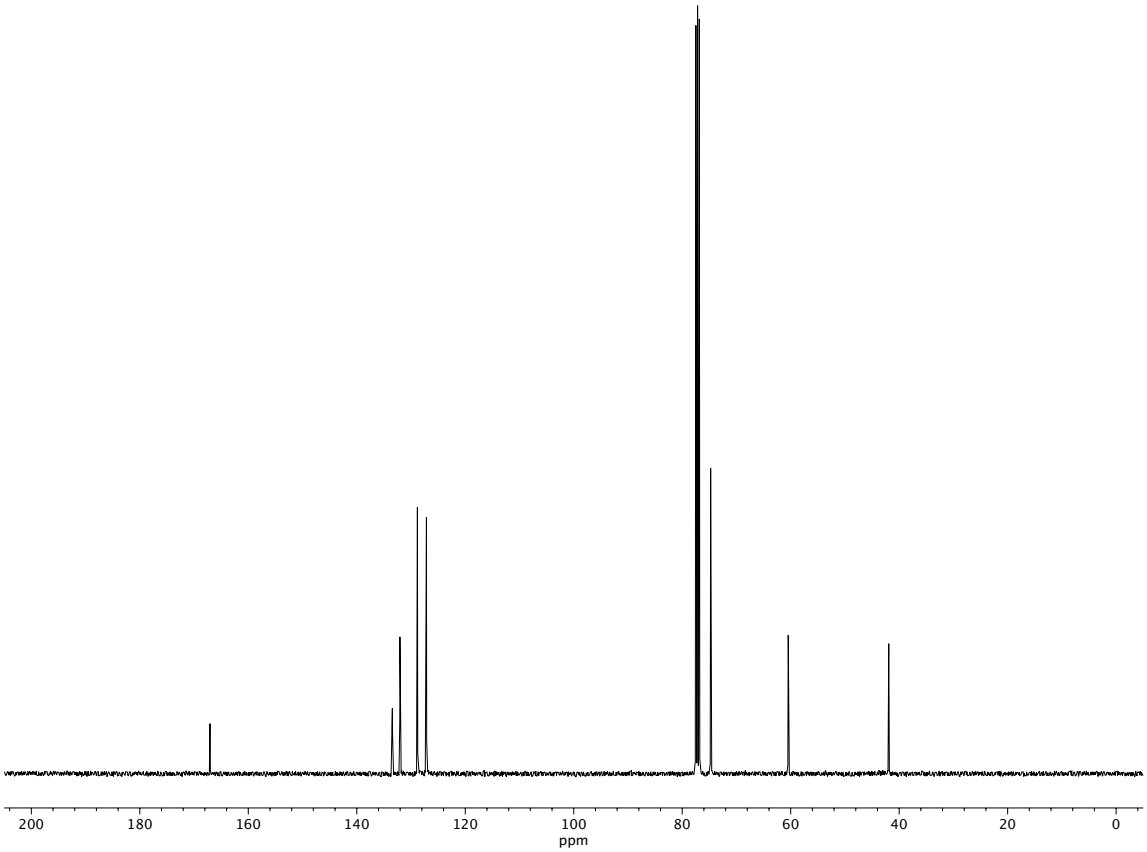


Figure A1.192 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***70****.*

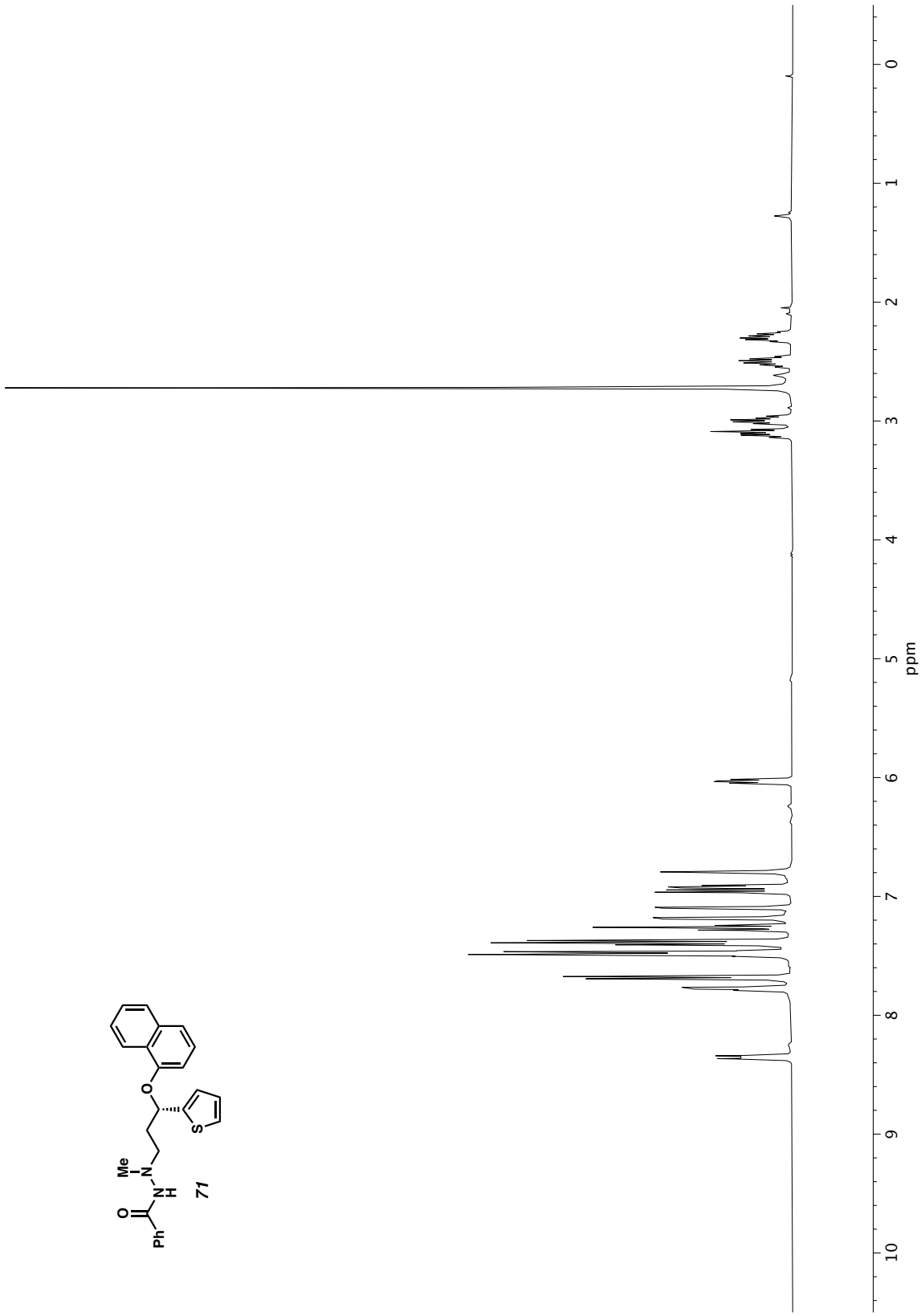


Figure A1.193 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **71**.*

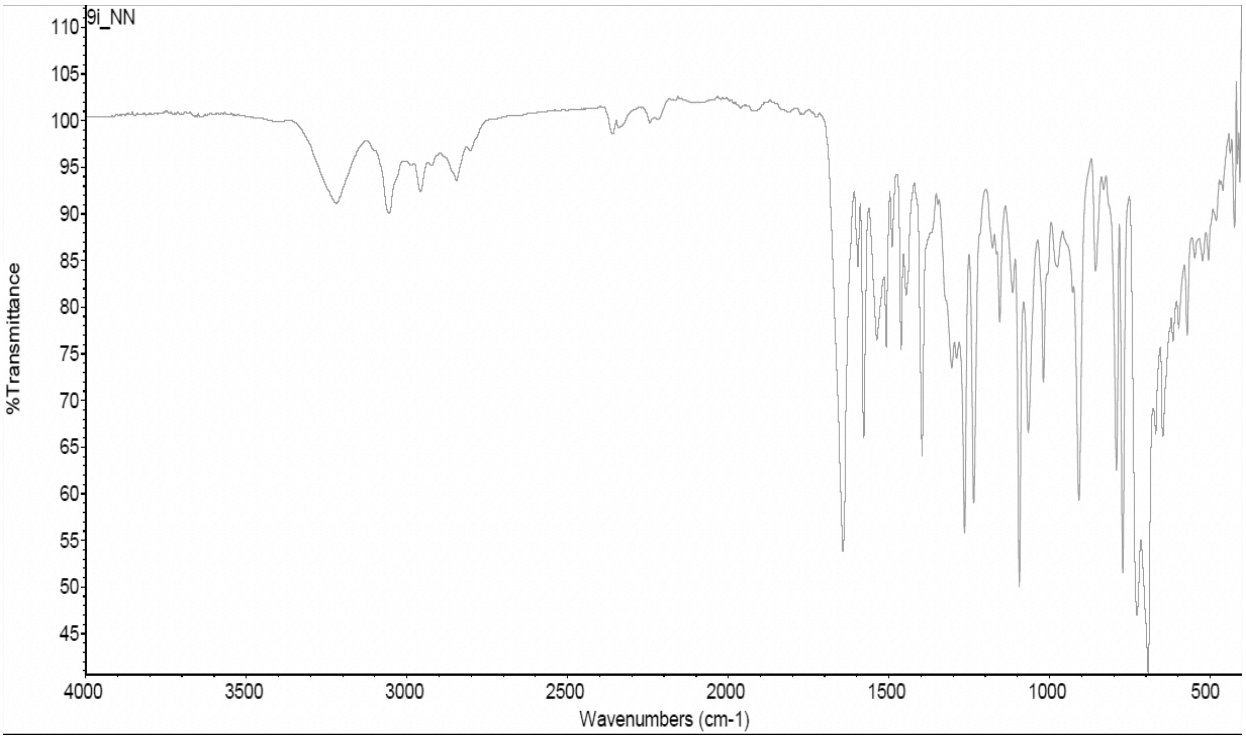


Figure A1.194 *Infrared spectrum (Thin Film) of compound* ***71***.

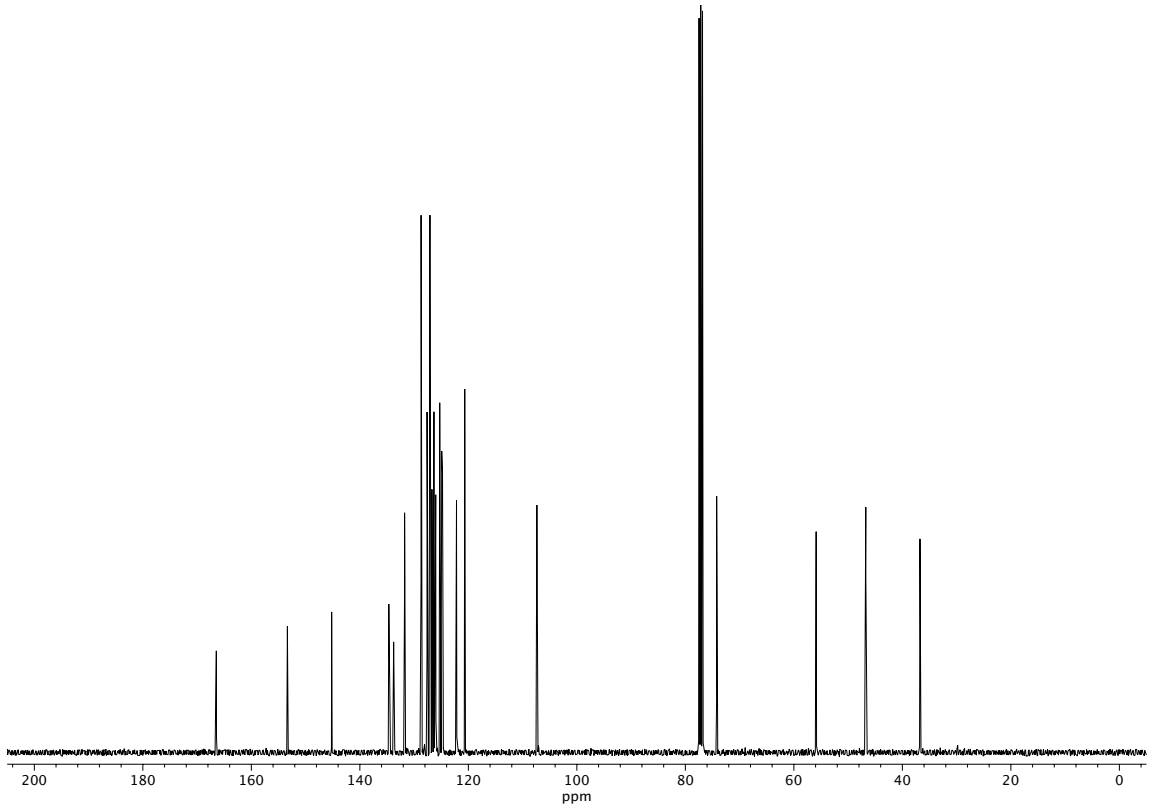


Figure A1.195 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***71***.

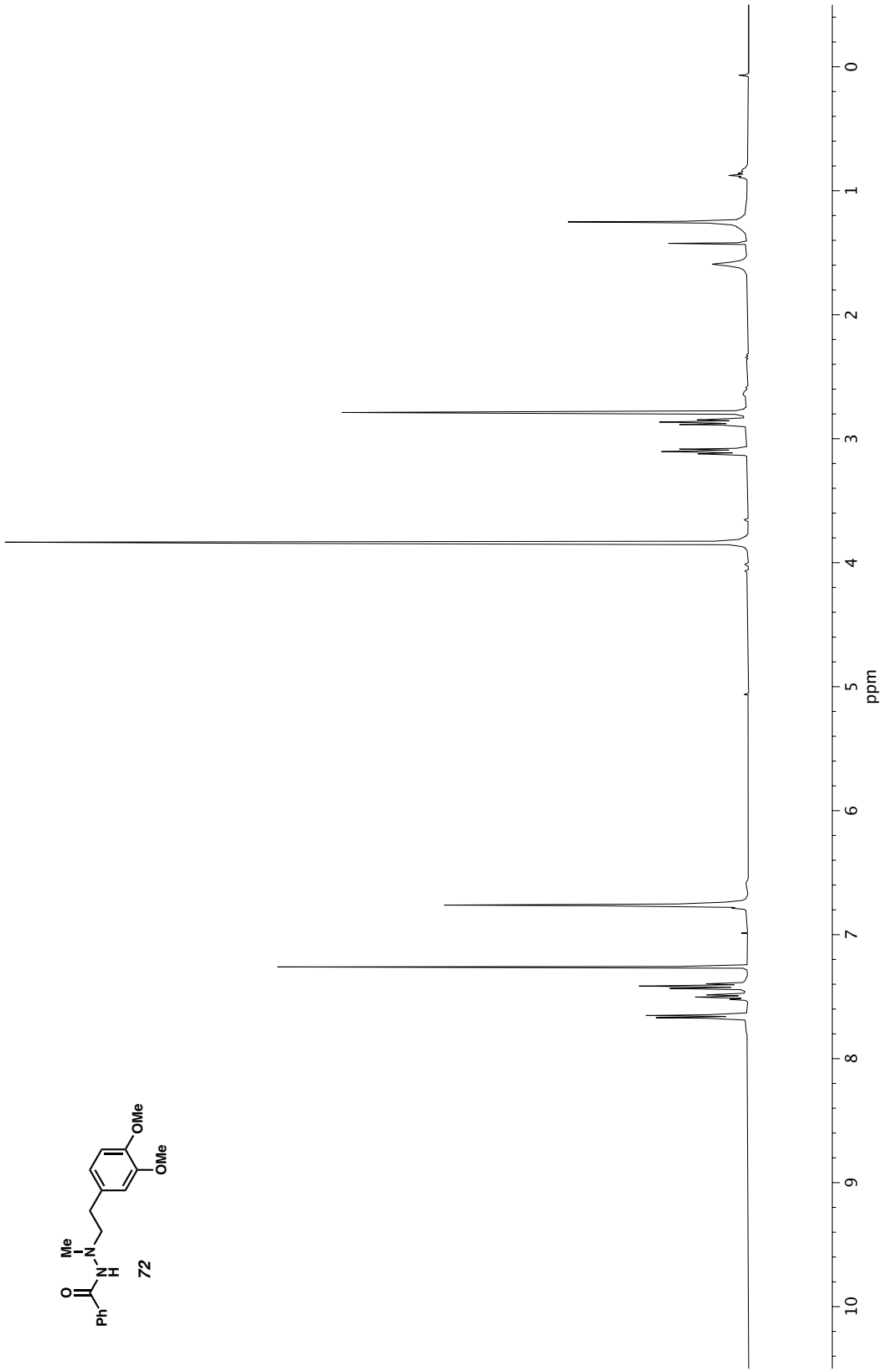


Figure A1.196 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***72****.*

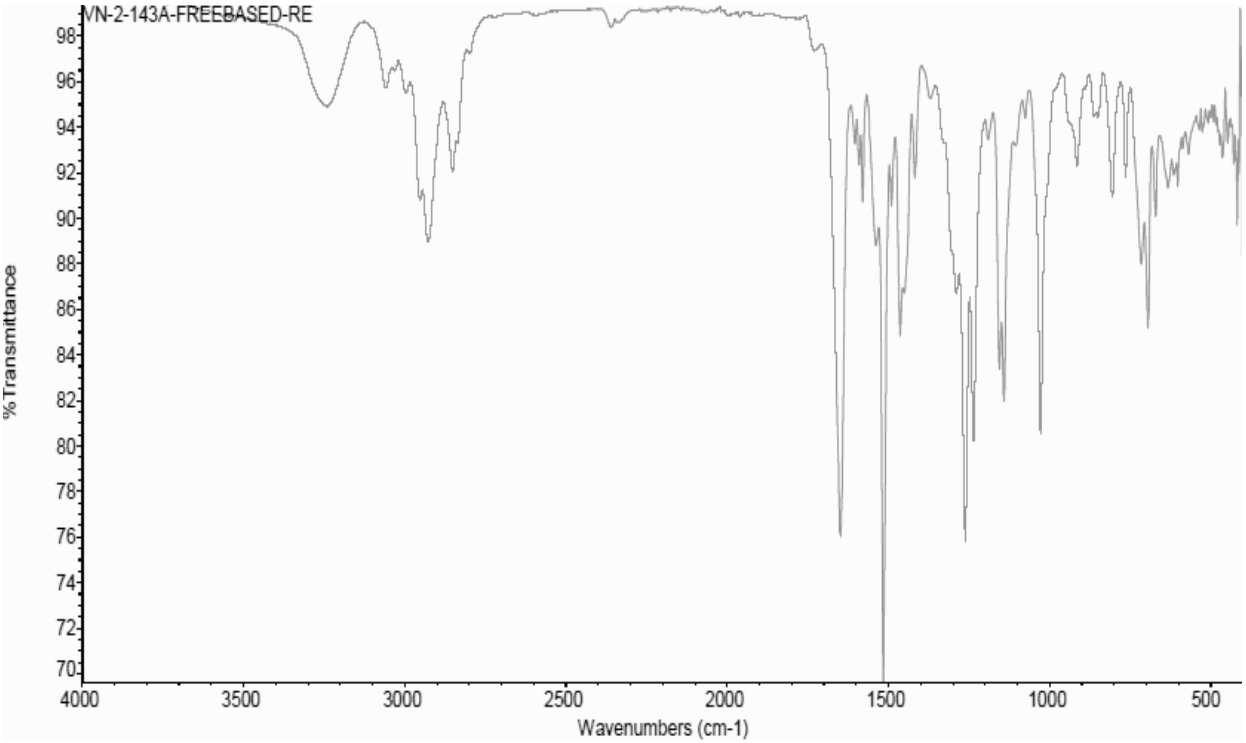


Figure A1.197 *Infrared spectrum (Thin Film) of compound* ***72***.

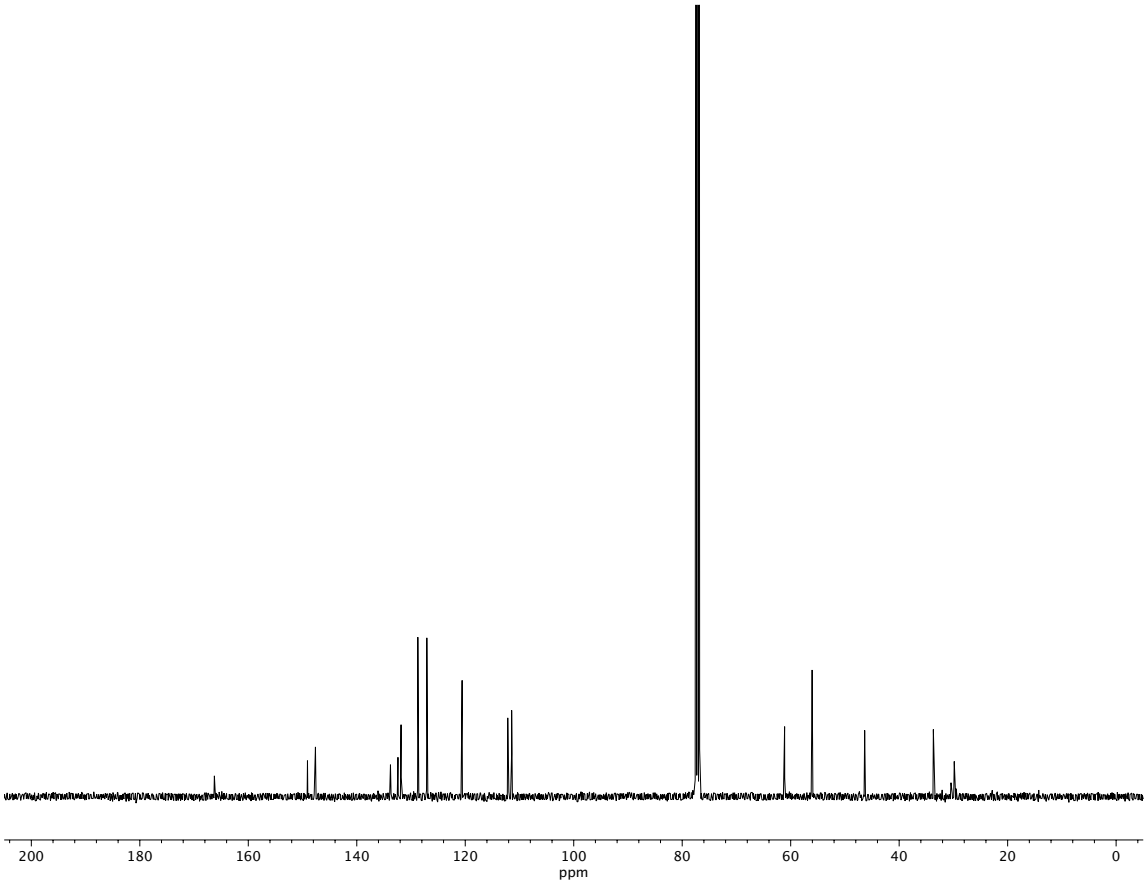


Figure A1.198 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***72***.

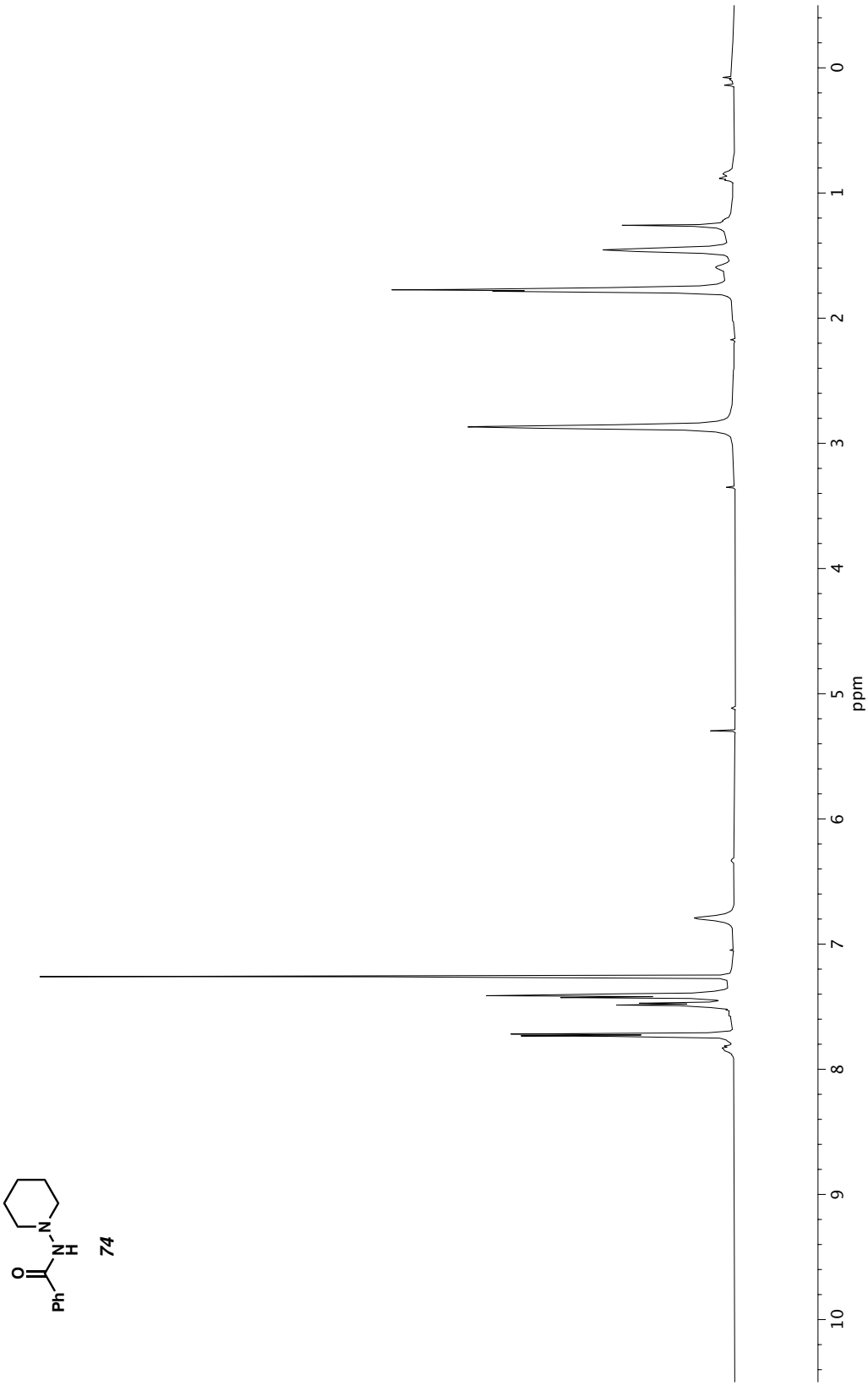


Figure A1.199 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **74**.*

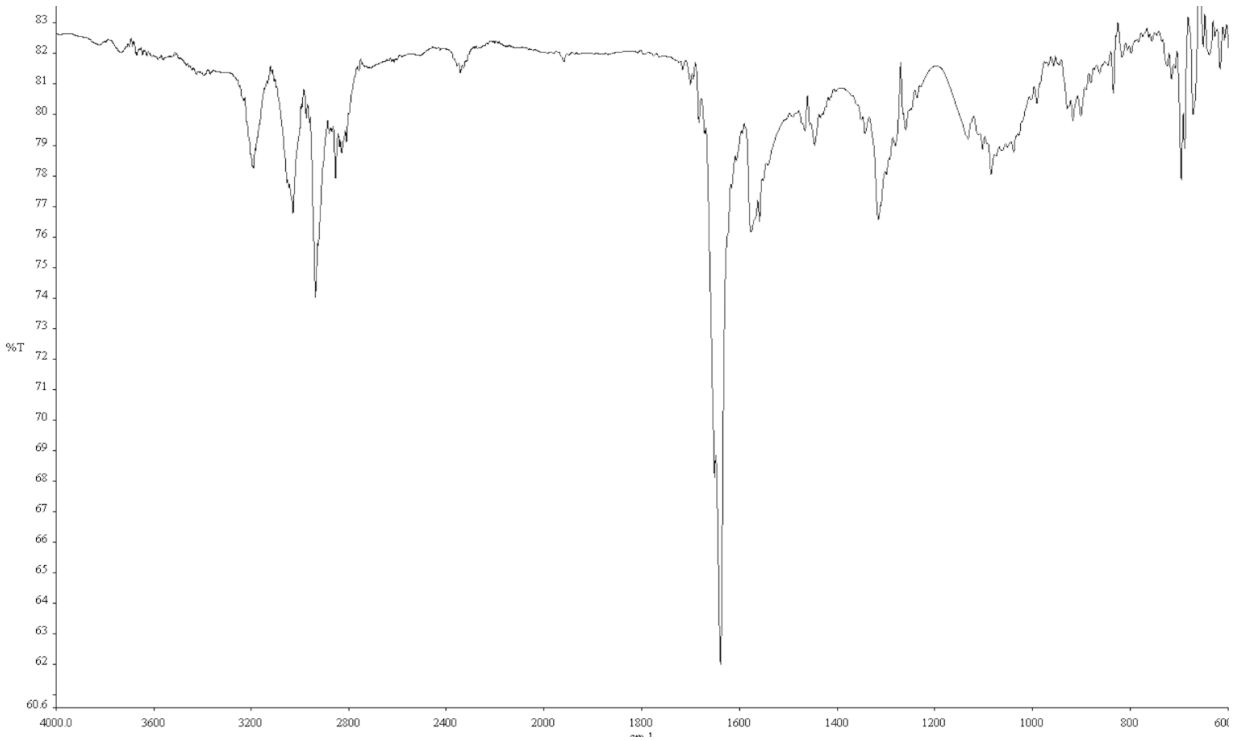


Figure A1.200 *Infrared spectrum (Thin Film, NaCl) of compound* ***74****.*

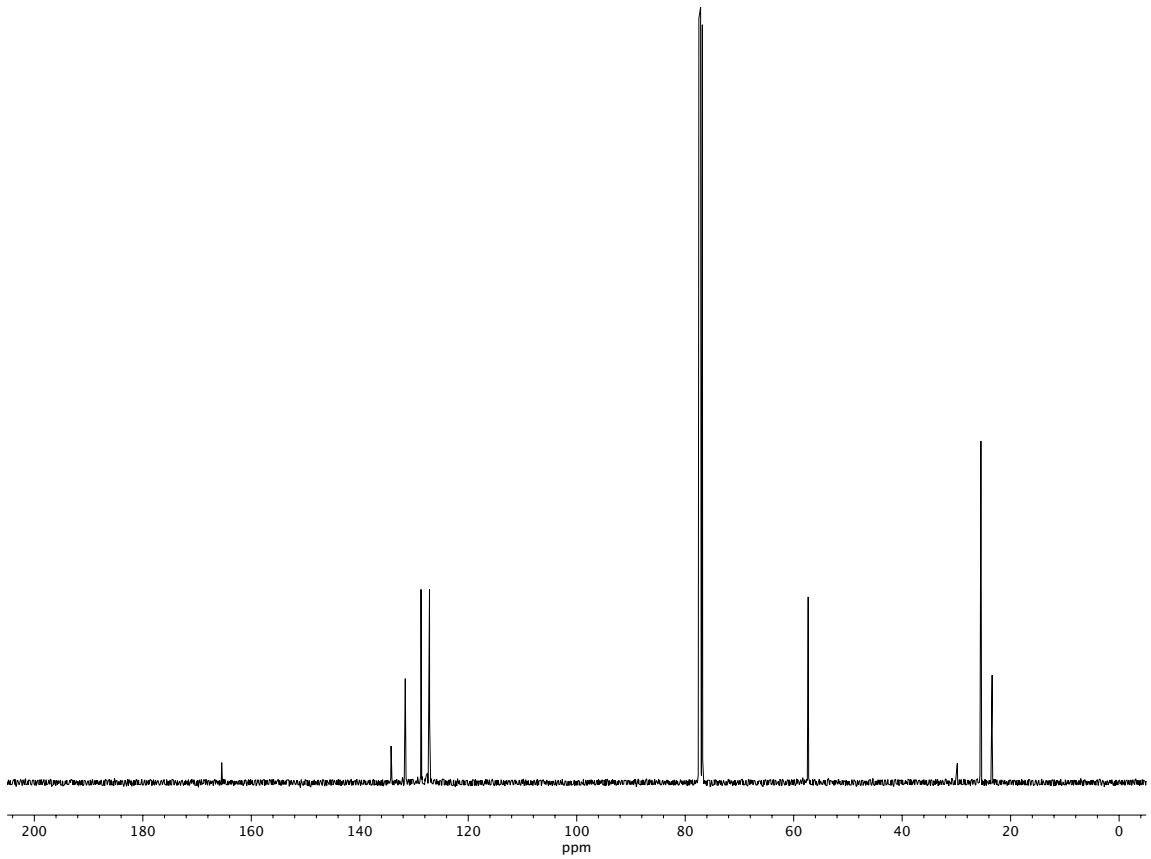


Figure A1.201 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***74****.*

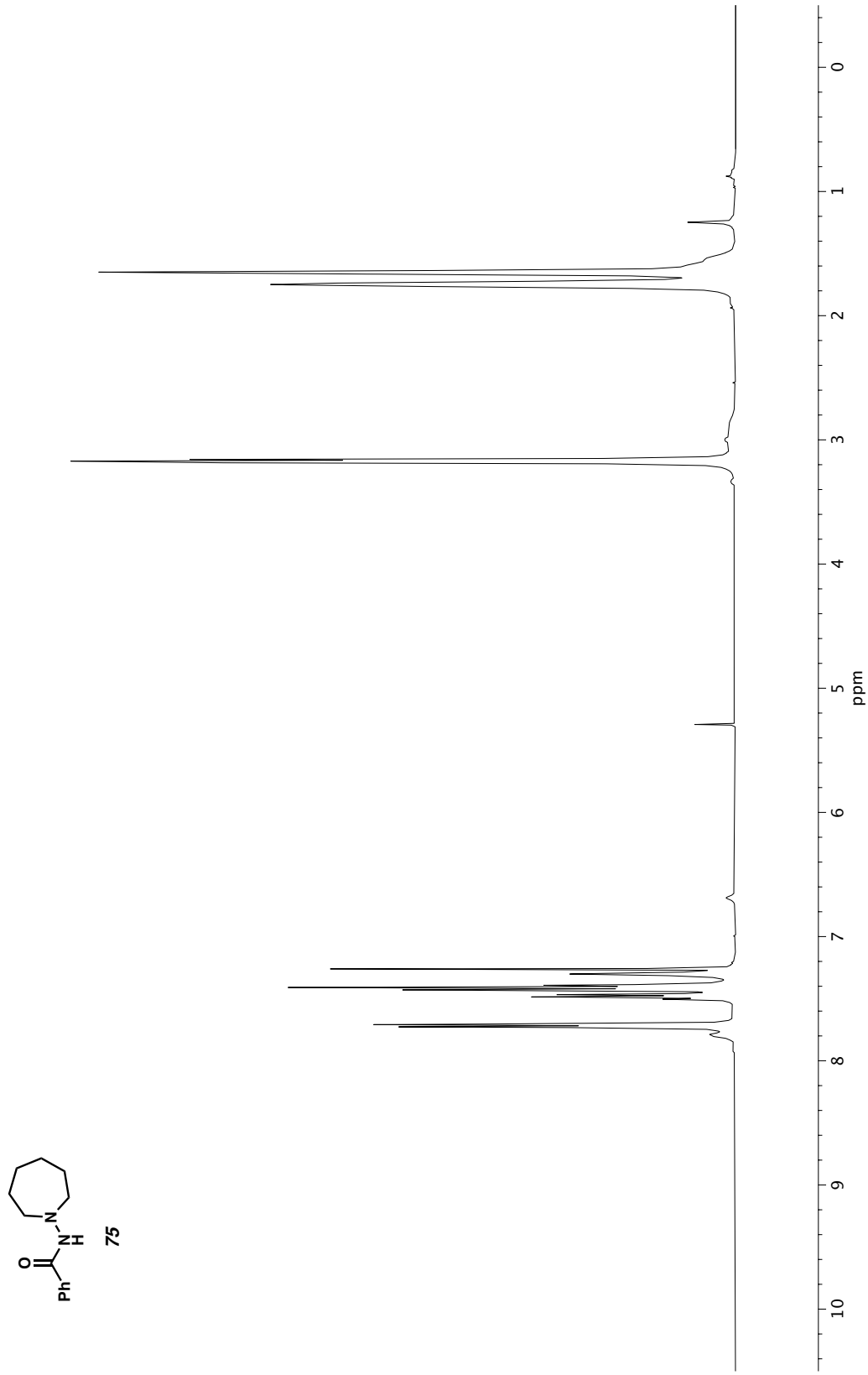


Figure A1.202 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **75**.*

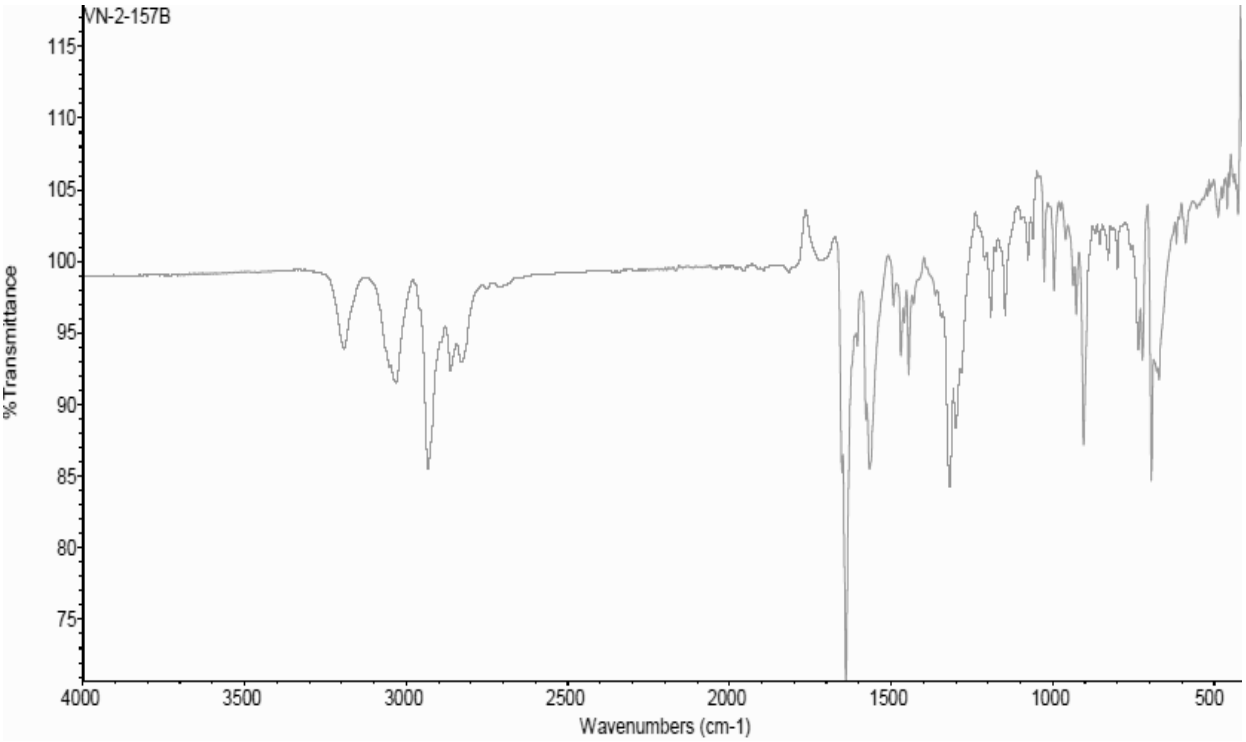


Figure A1.203 *Infrared spectrum (Thin Film) of compound* ***75***.

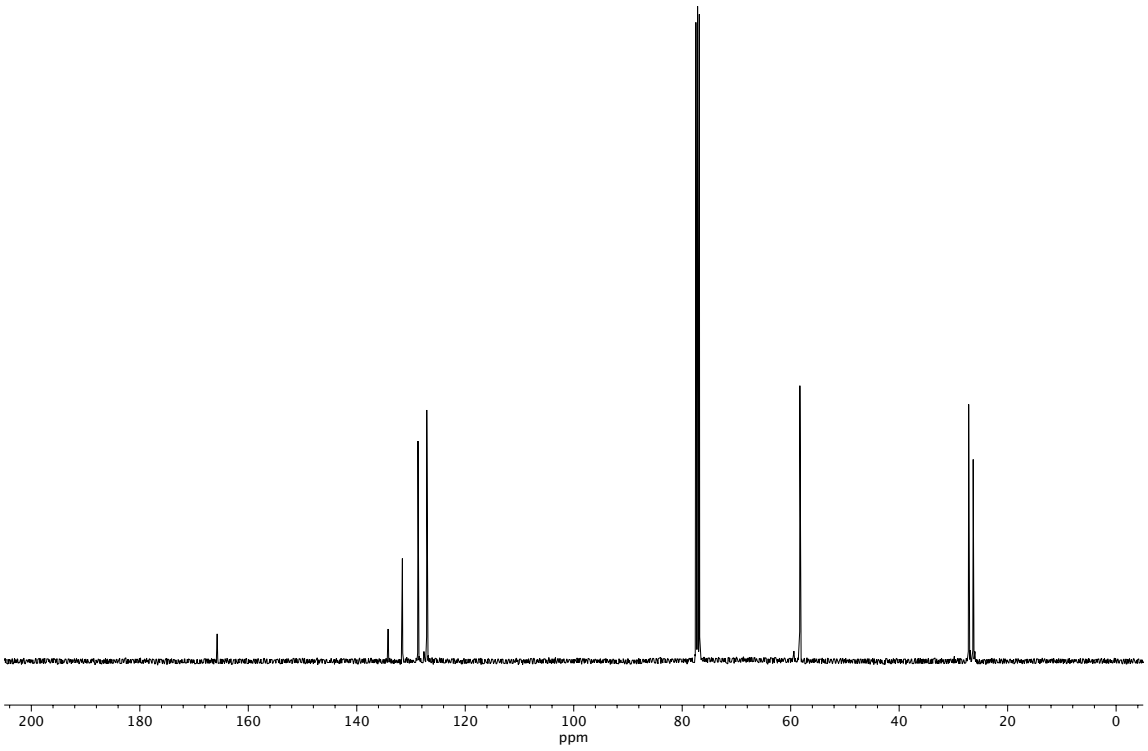


Figure A1.204 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***75***.

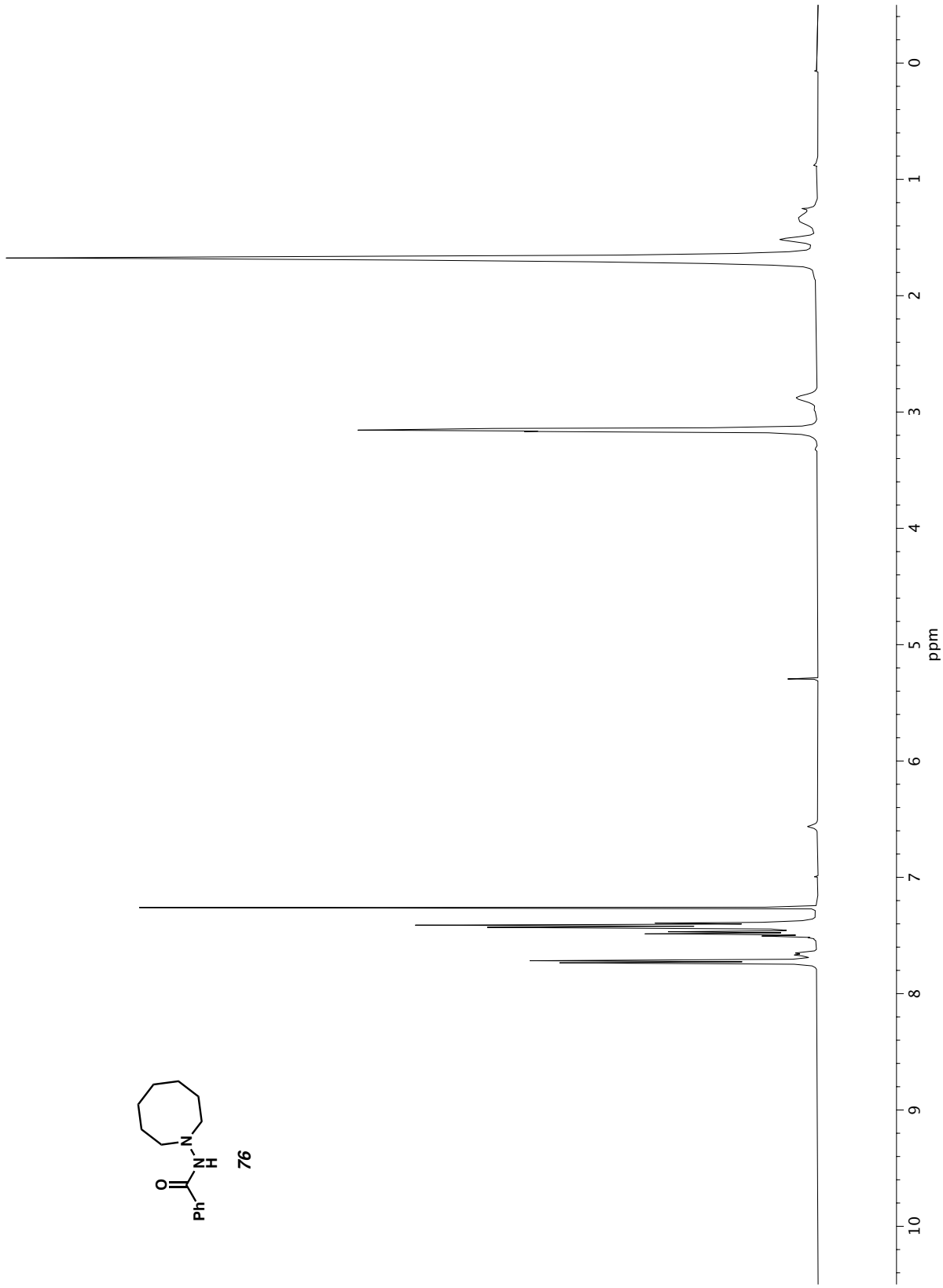


Figure A1.205 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***76***.

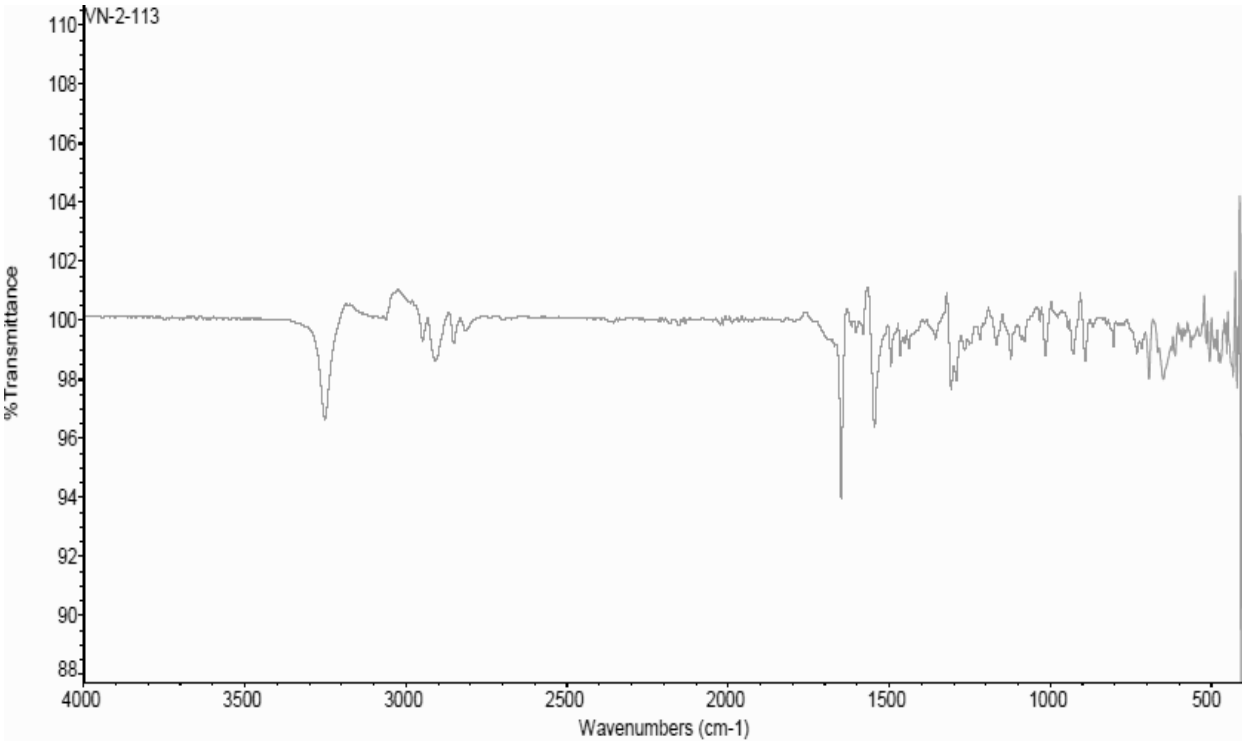


Figure A1.206 *Infrared spectrum (Thin Film) of compound* ***76***.

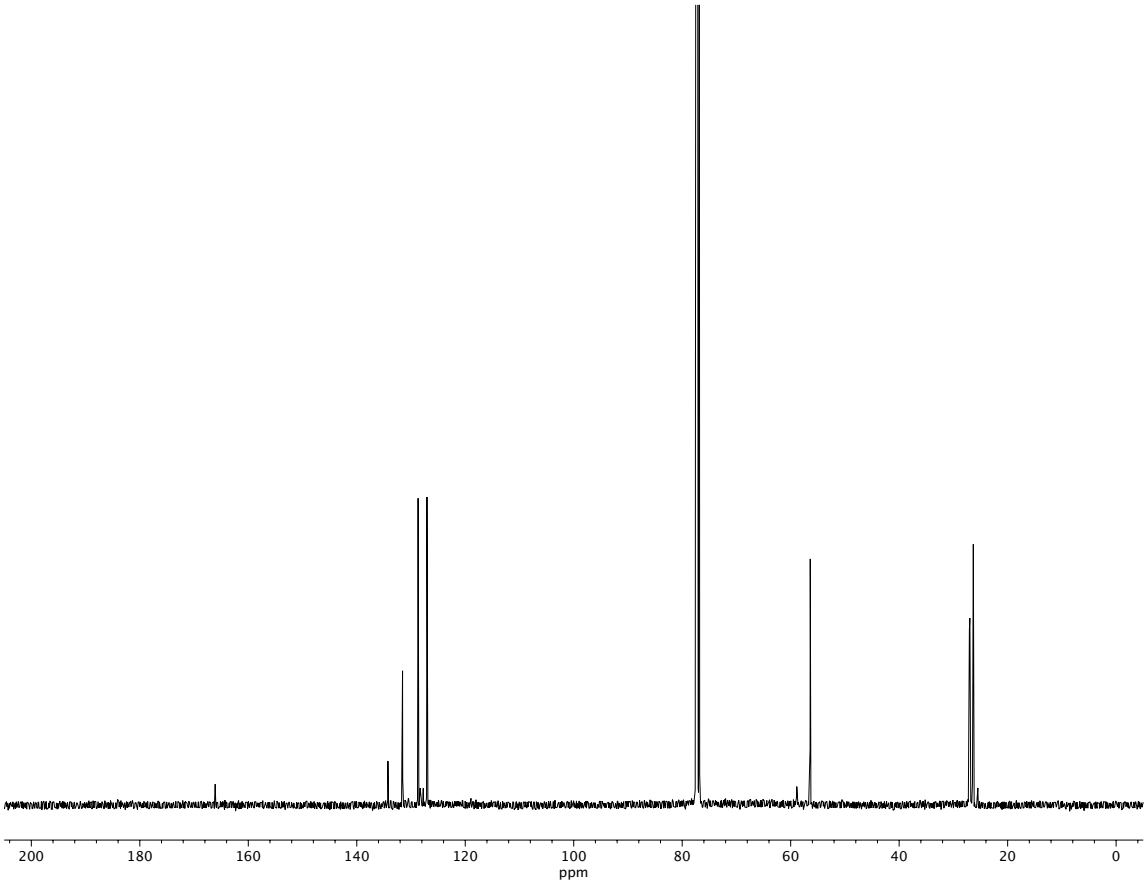


Figure A1.207 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***76***.

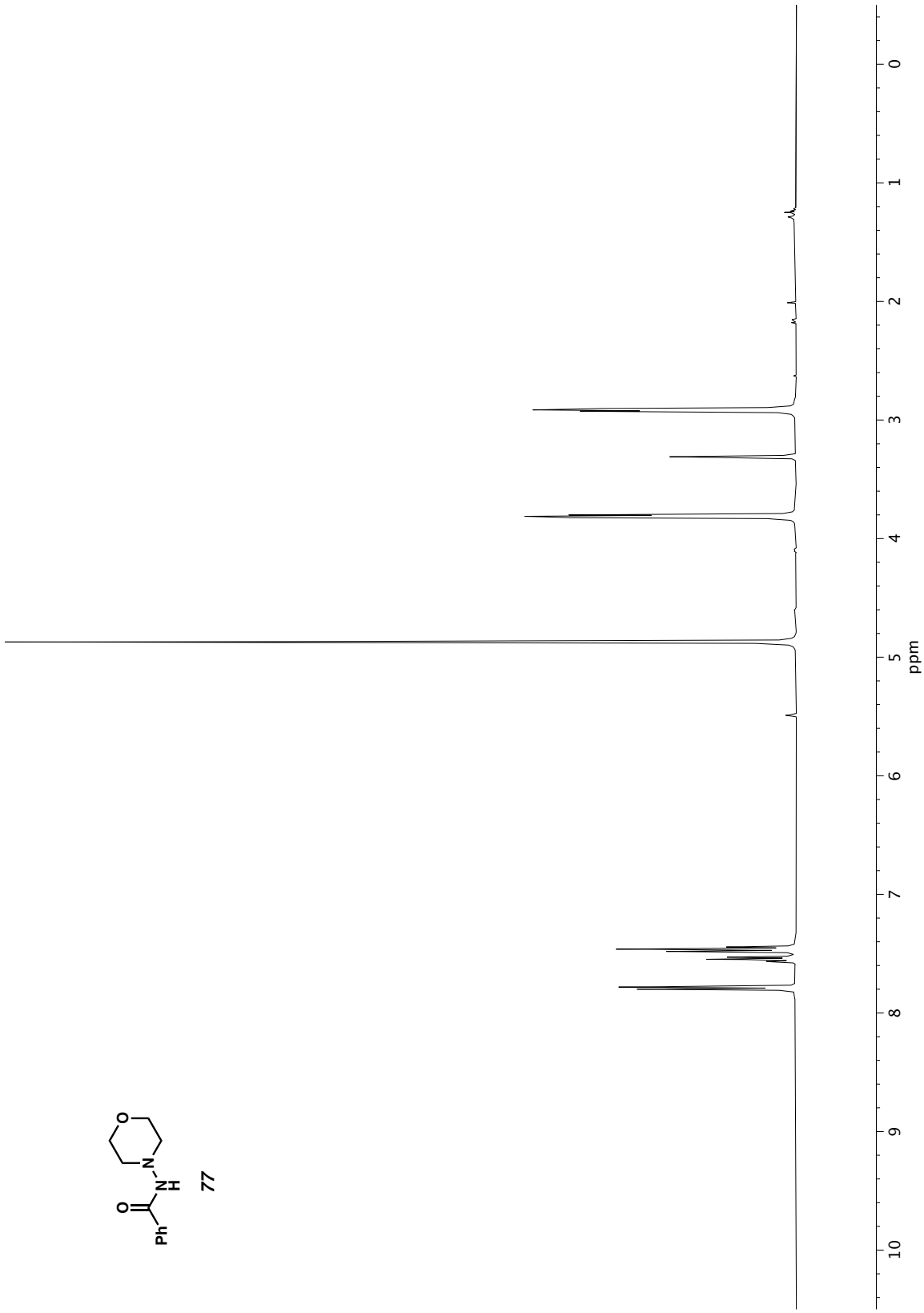


Figure A1.208 *^1H NMR (400 MHz, CD_3OD) of compound **77**.*

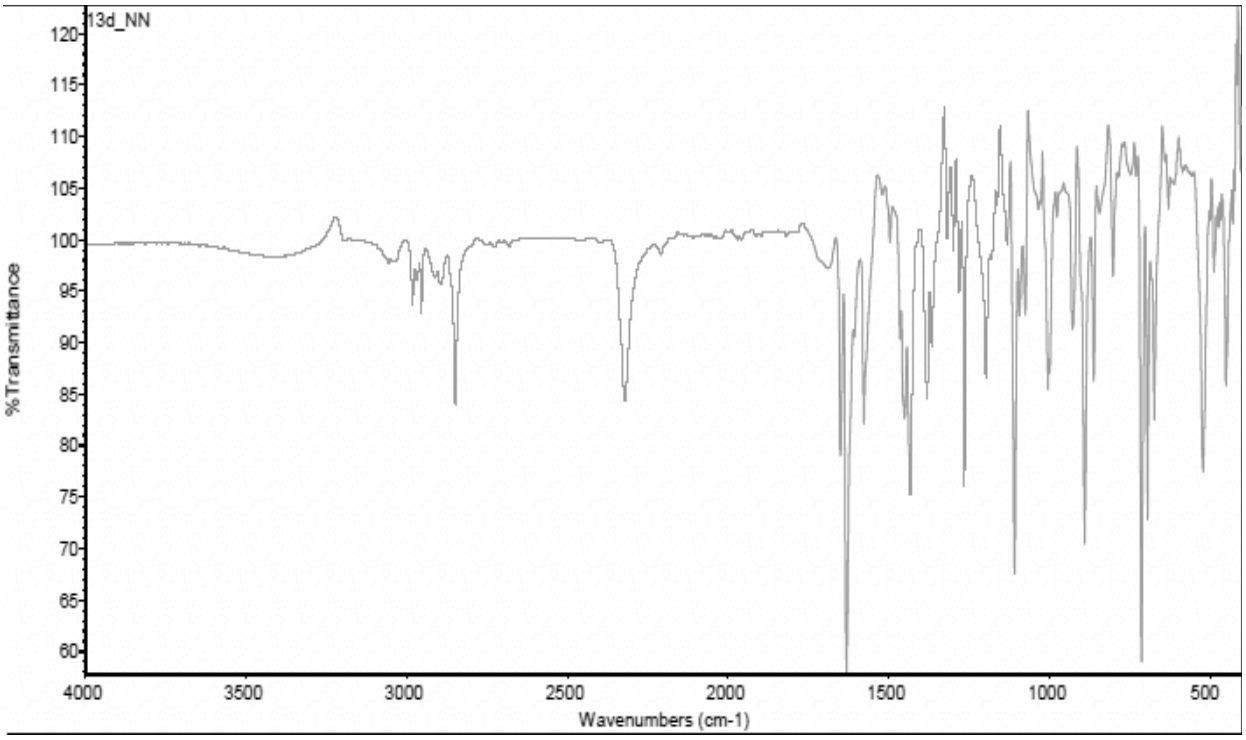


Figure A1.209 *Infrared spectrum (Thin Film) of compound **77**.*

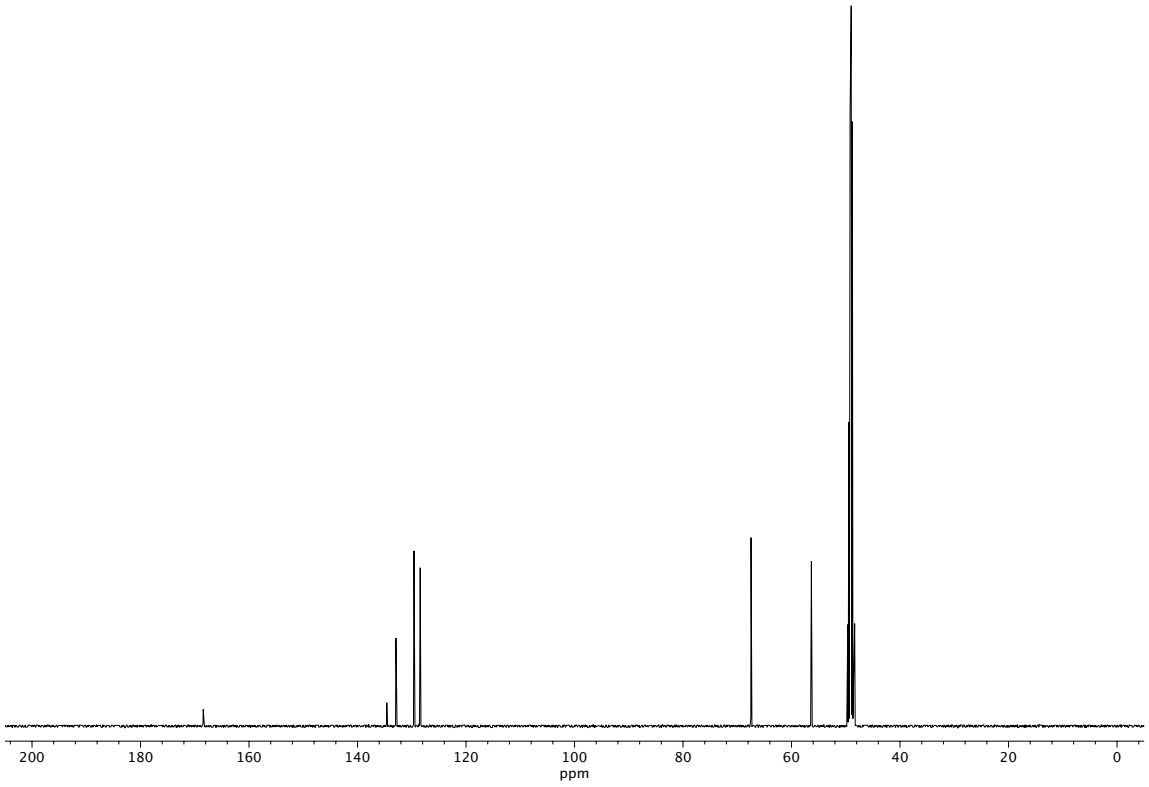


Figure A1.210 *^{13}C NMR (101 MHz, CD_3OD) of compound **77**.*

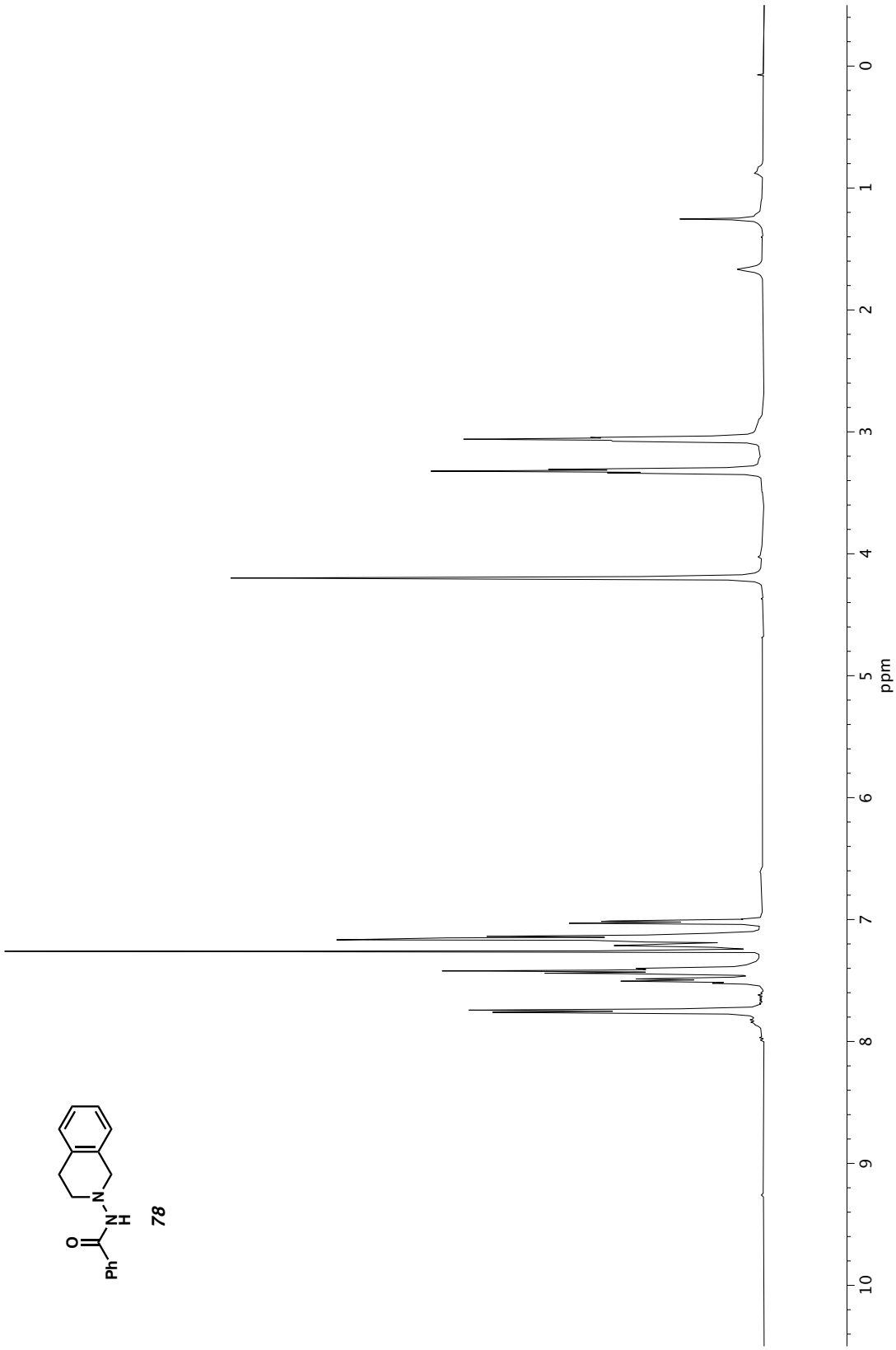


Figure A1.211 *^1H NMR (400 MHz, $CDCl_3$) of compound **78**.*

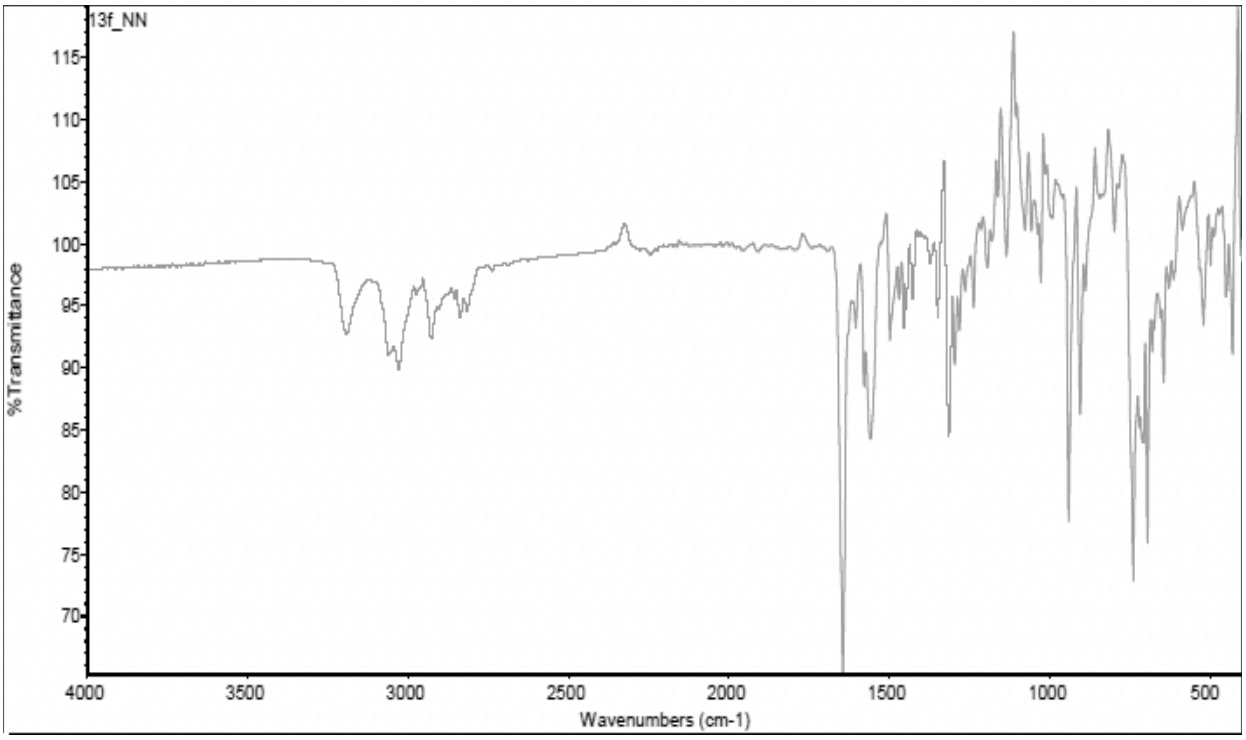


Figure A1.212 *Infrared spectrum (Thin Film) of compound* ***78****.*

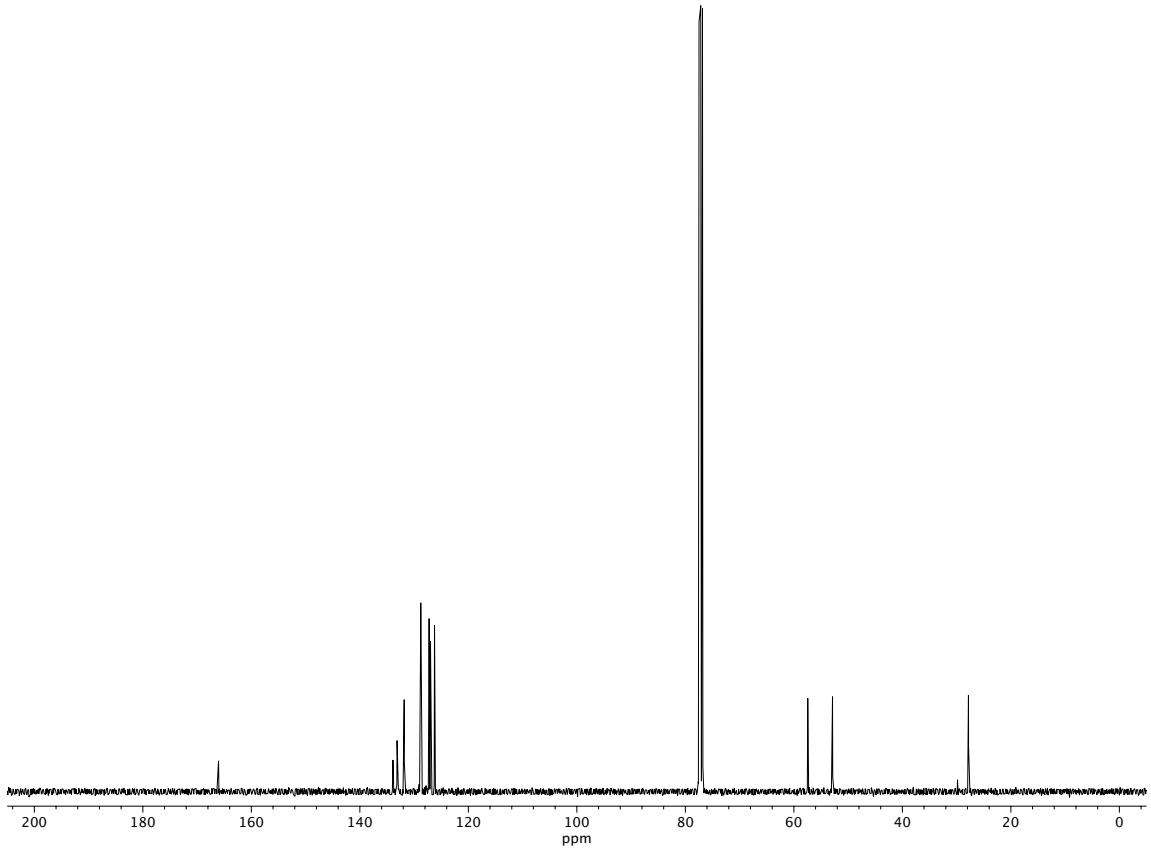


Figure A1.213 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***78****.*

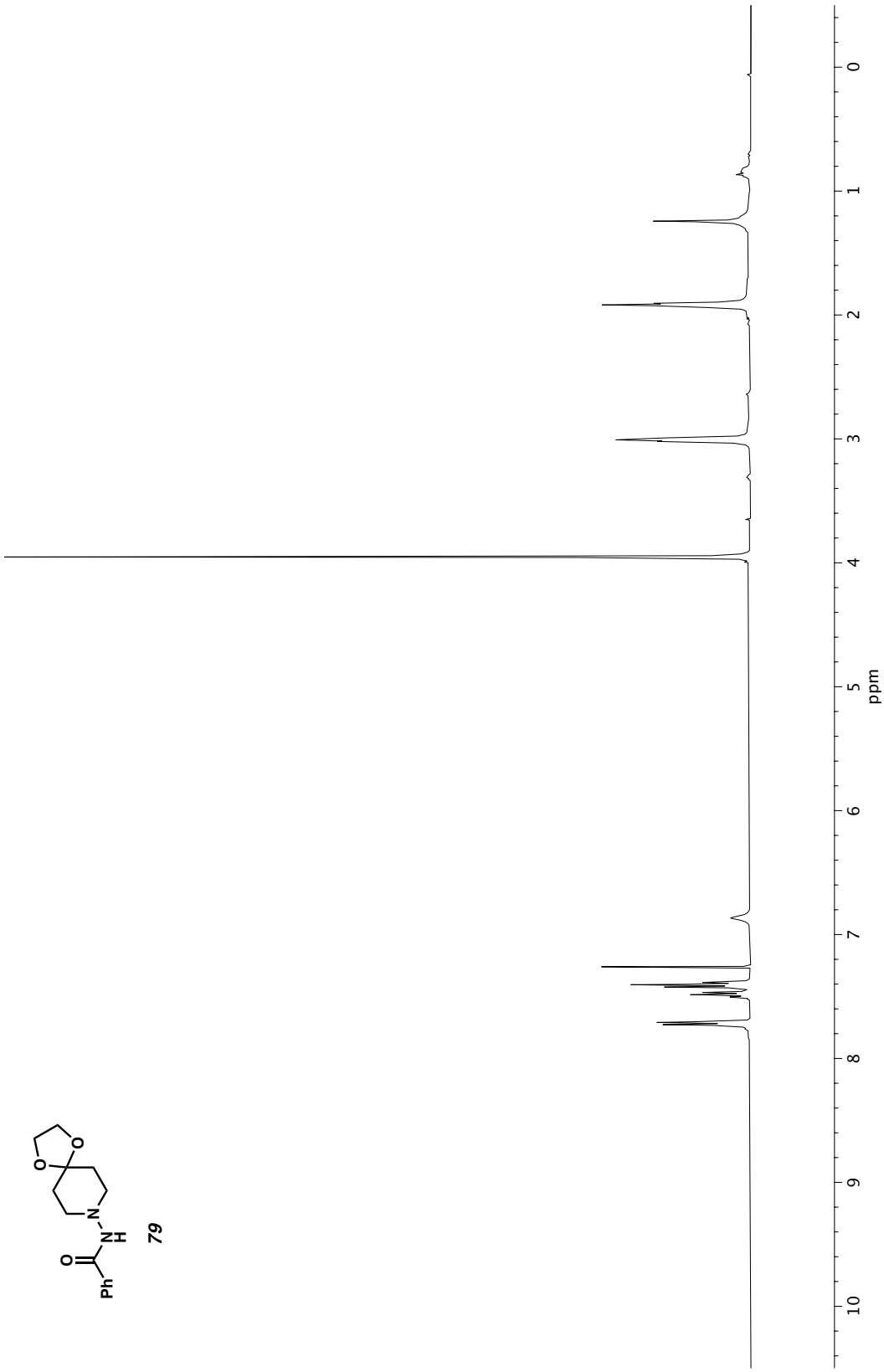


Figure A1.214 *^1H NMR (400 MHz, $CDCl_3$) of compound **79**.*

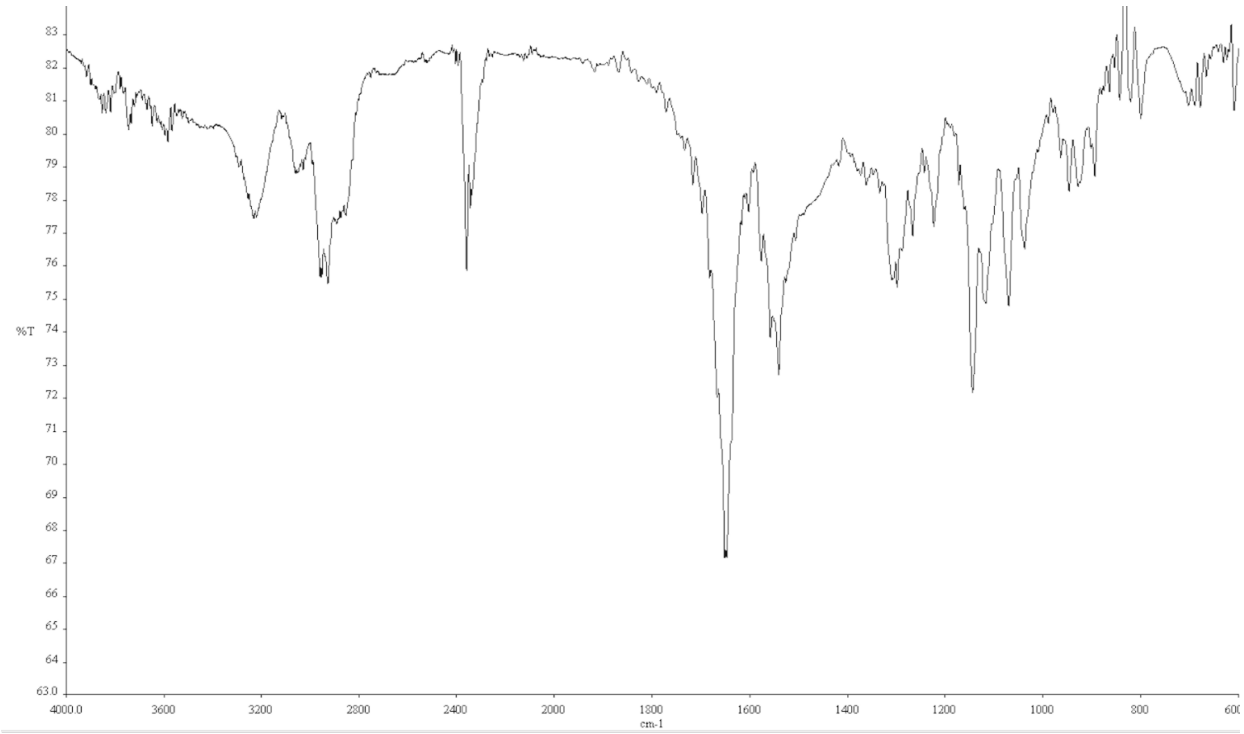


Figure A1.215 *Infrared spectrum (Thin Film) of compound* ***79***.

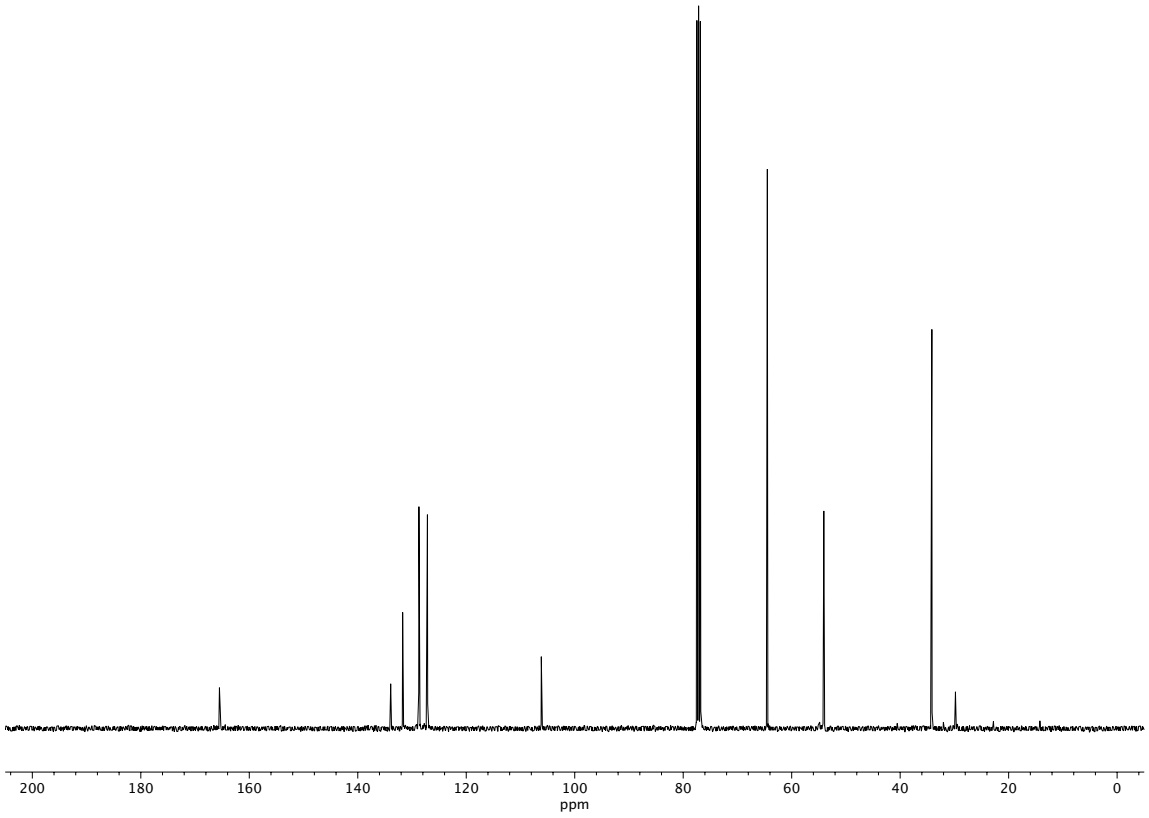


Figure A1.216 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***79***.

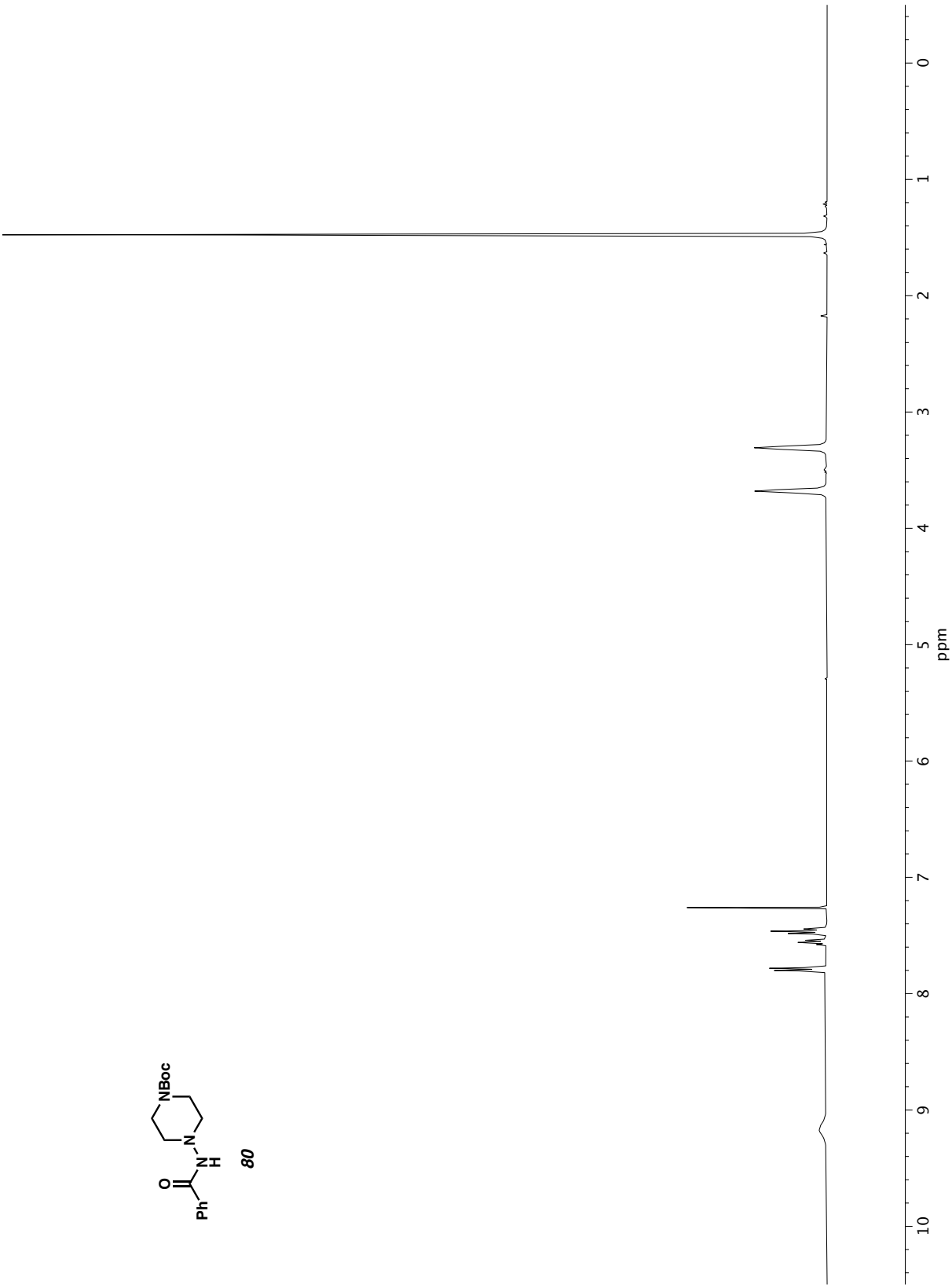


Figure A1.217 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***80***.

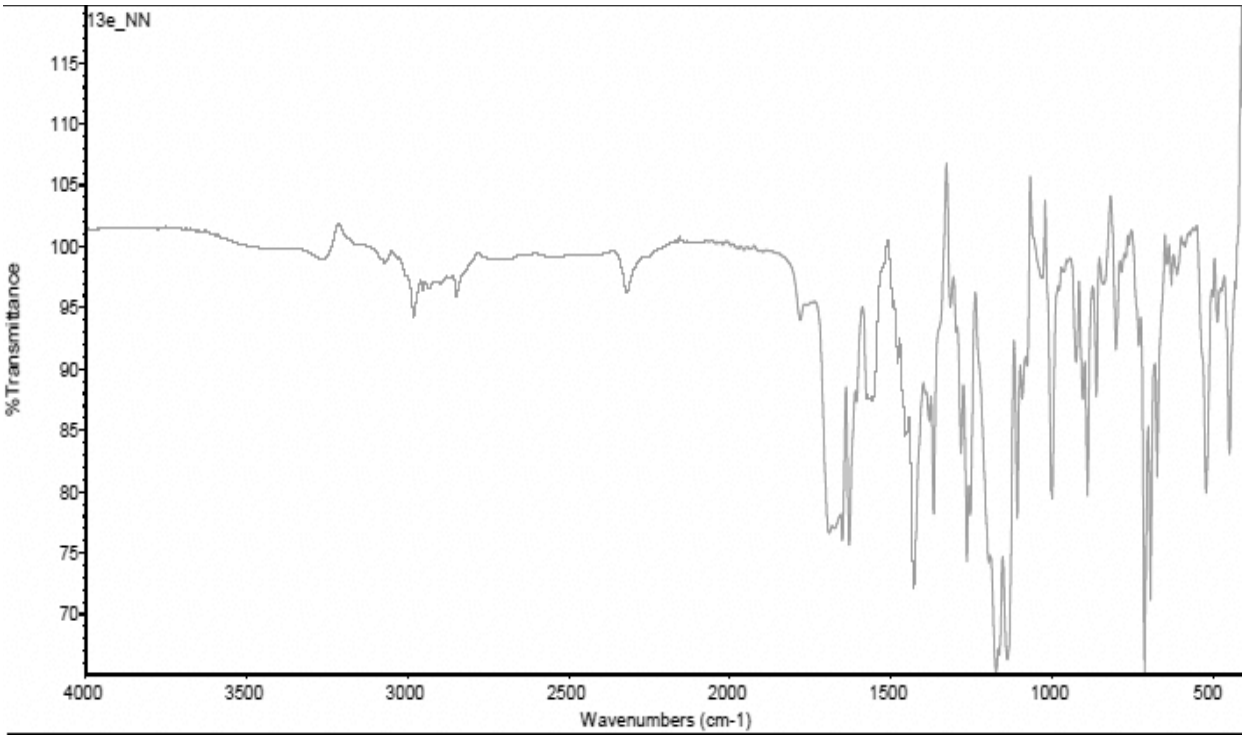


Figure A1.218 *Infrared spectrum (Thin Film) of compound* ***80***.

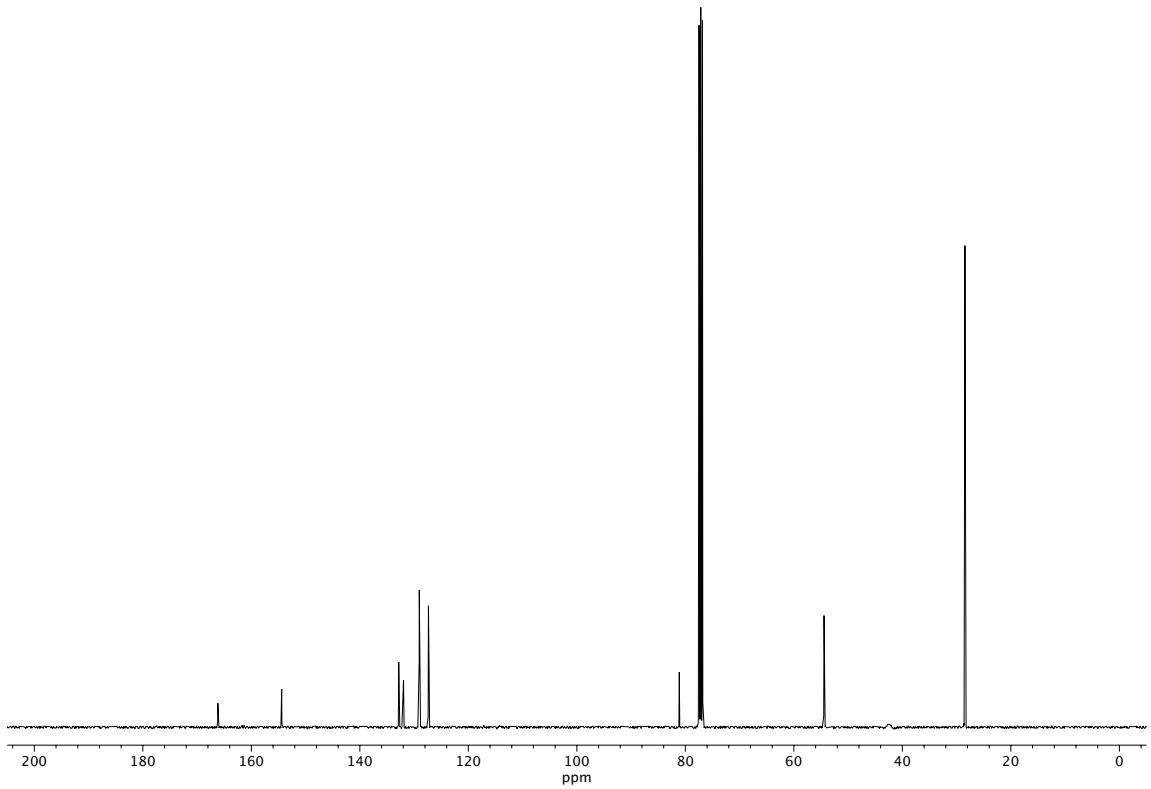
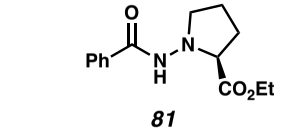


Figure A1.219 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***80***.



81

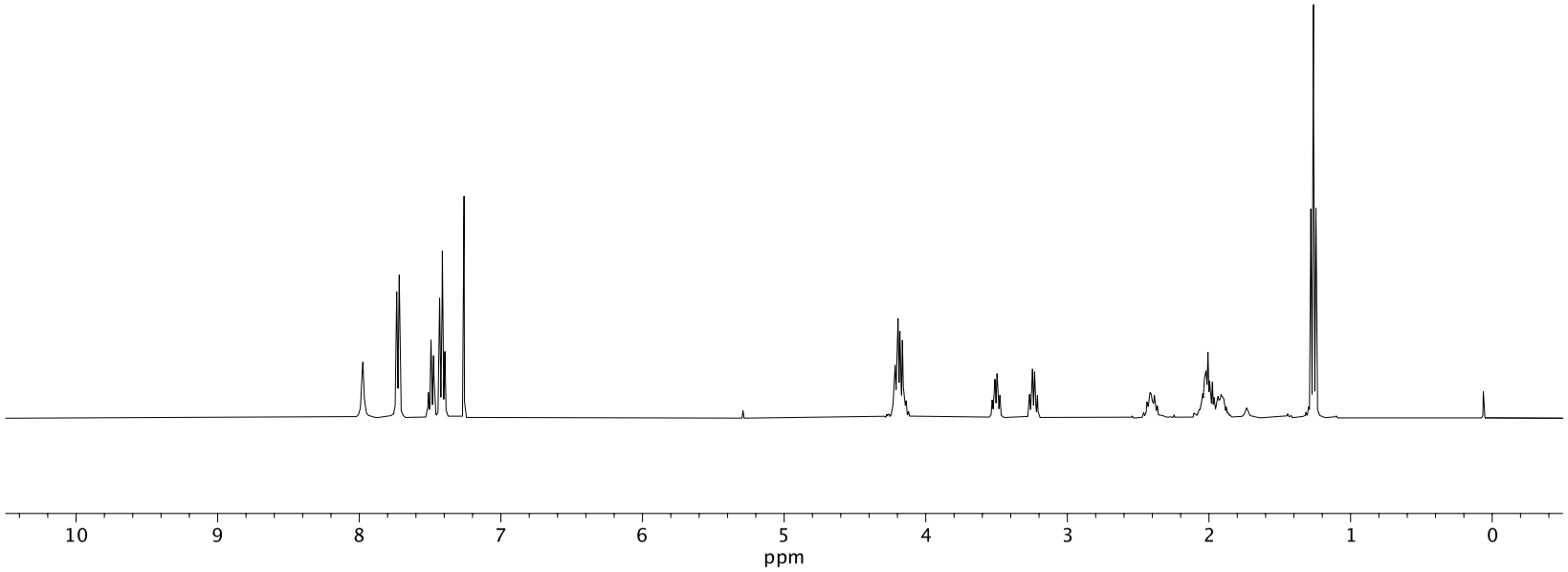


Figure A1.220 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***81***.

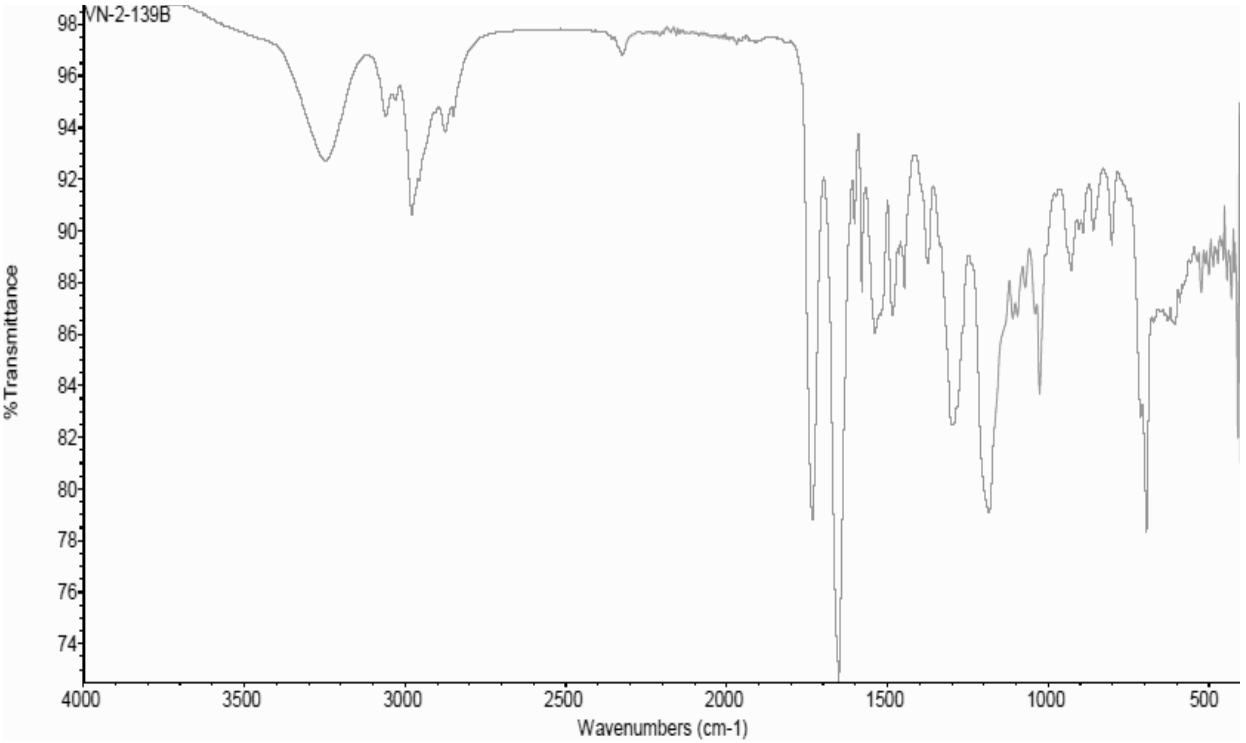


Figure A1.221 *Infrared spectrum (Thin Film) of compound* ***81***.

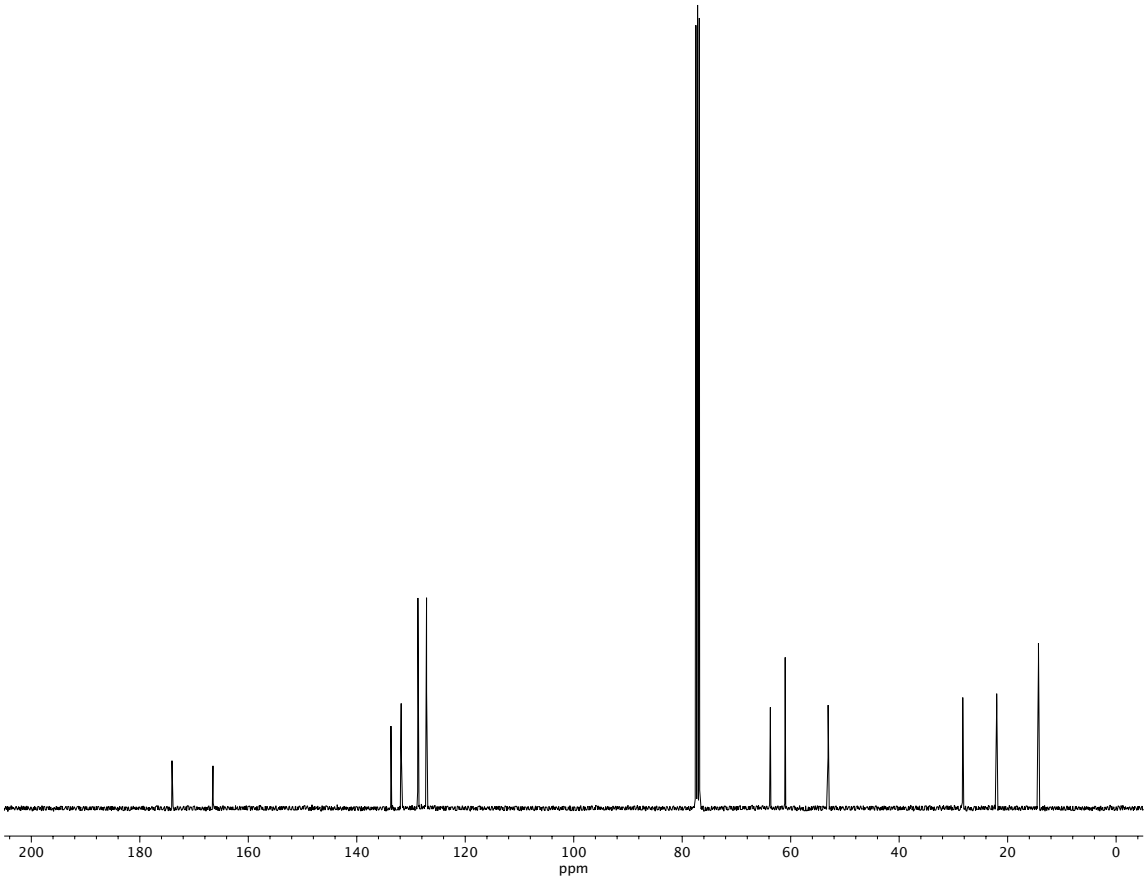


Figure A1.222 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***81***.

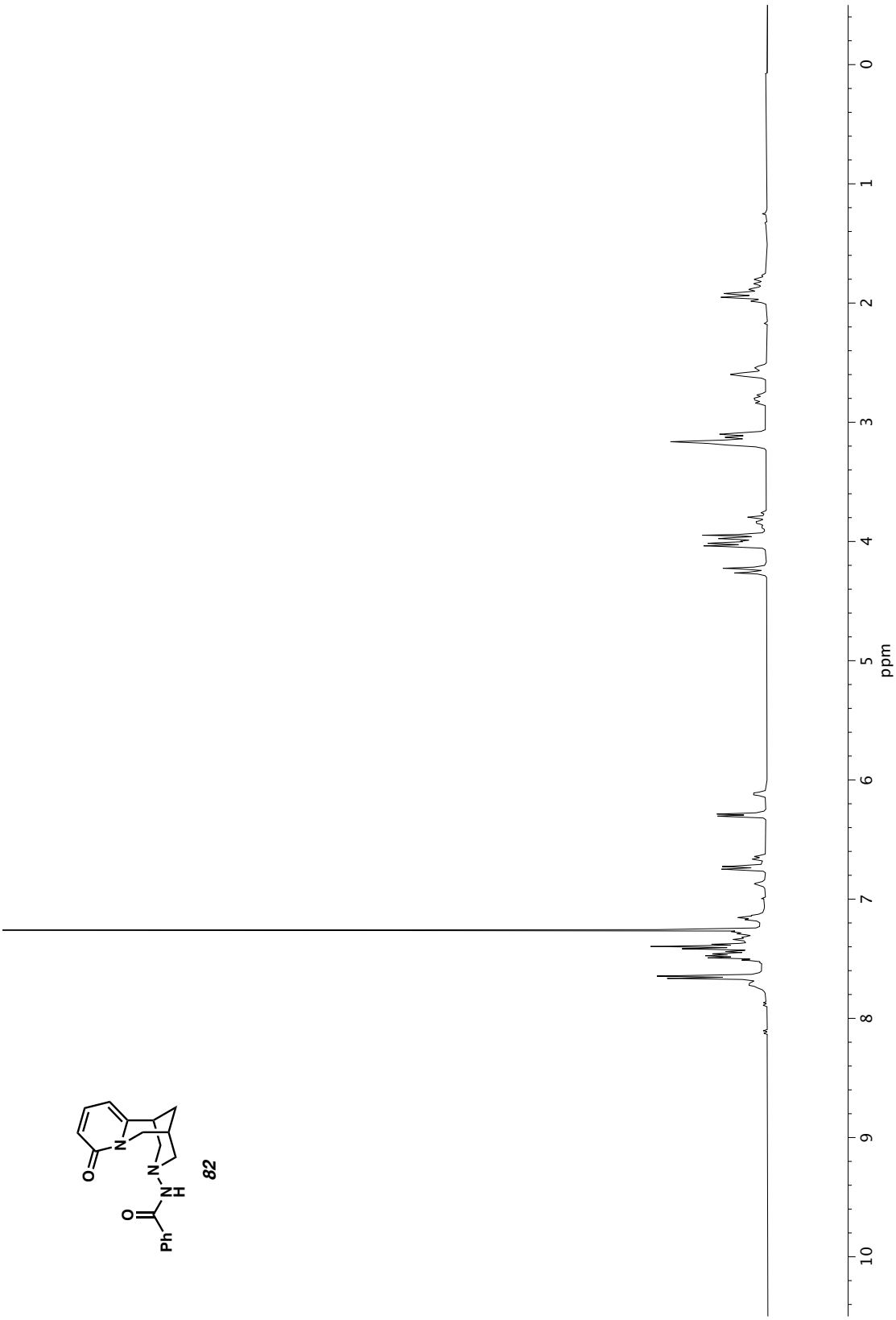


Figure A1.223 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***82***.

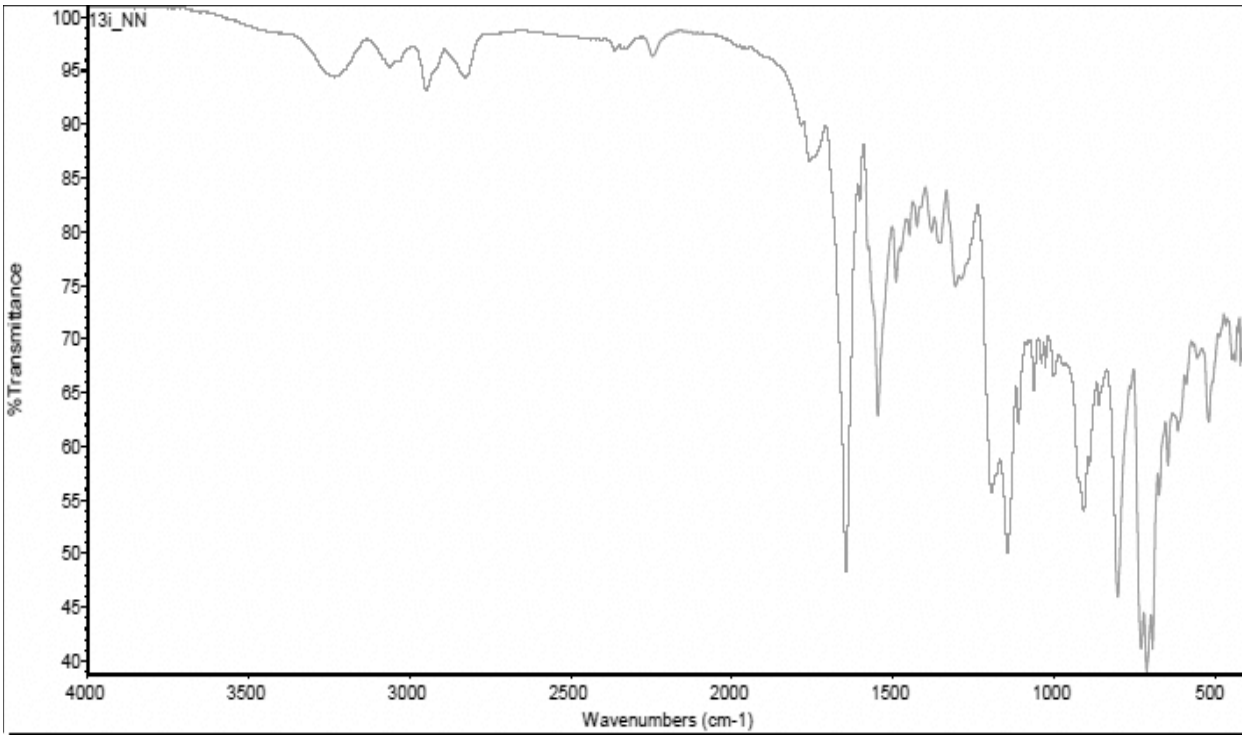


Figure A1.224 *Infrared spectrum (Thin Film) of compound* ***82***.

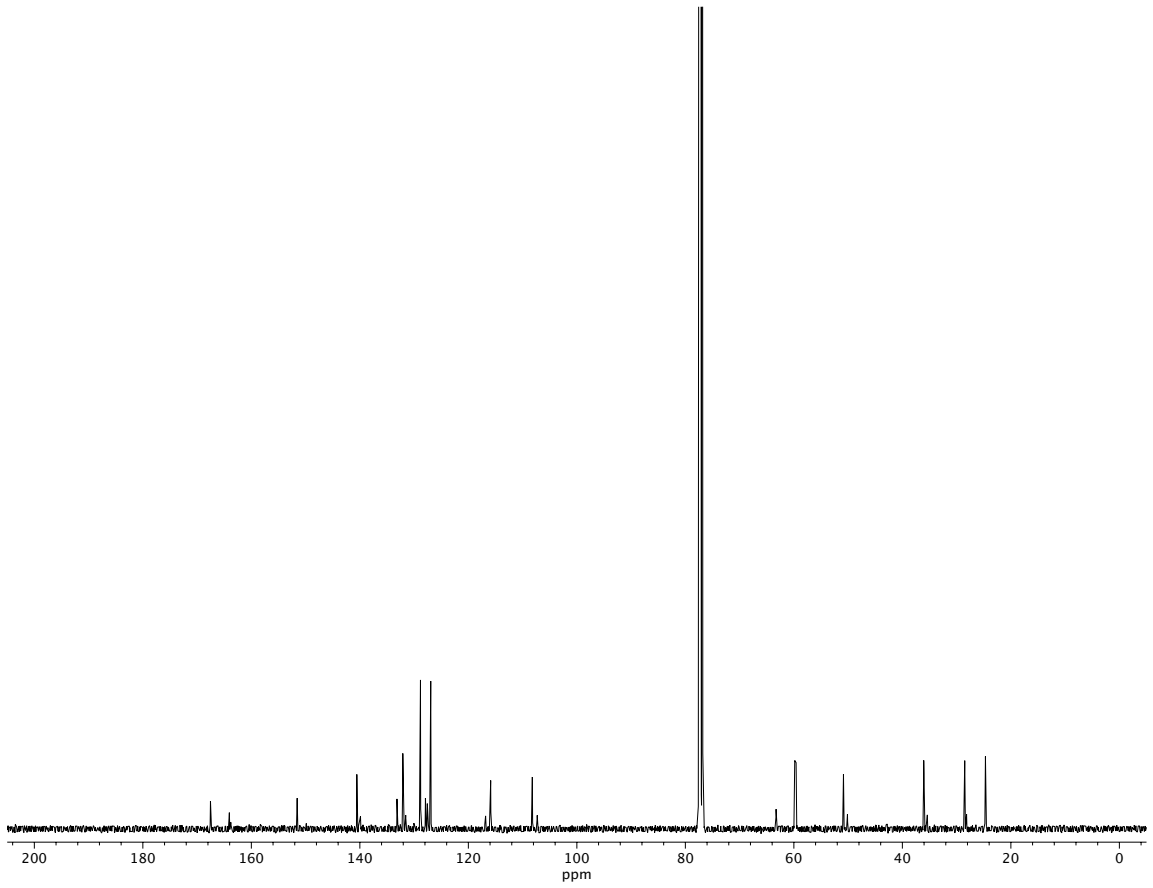


Figure A1.225 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***82***.

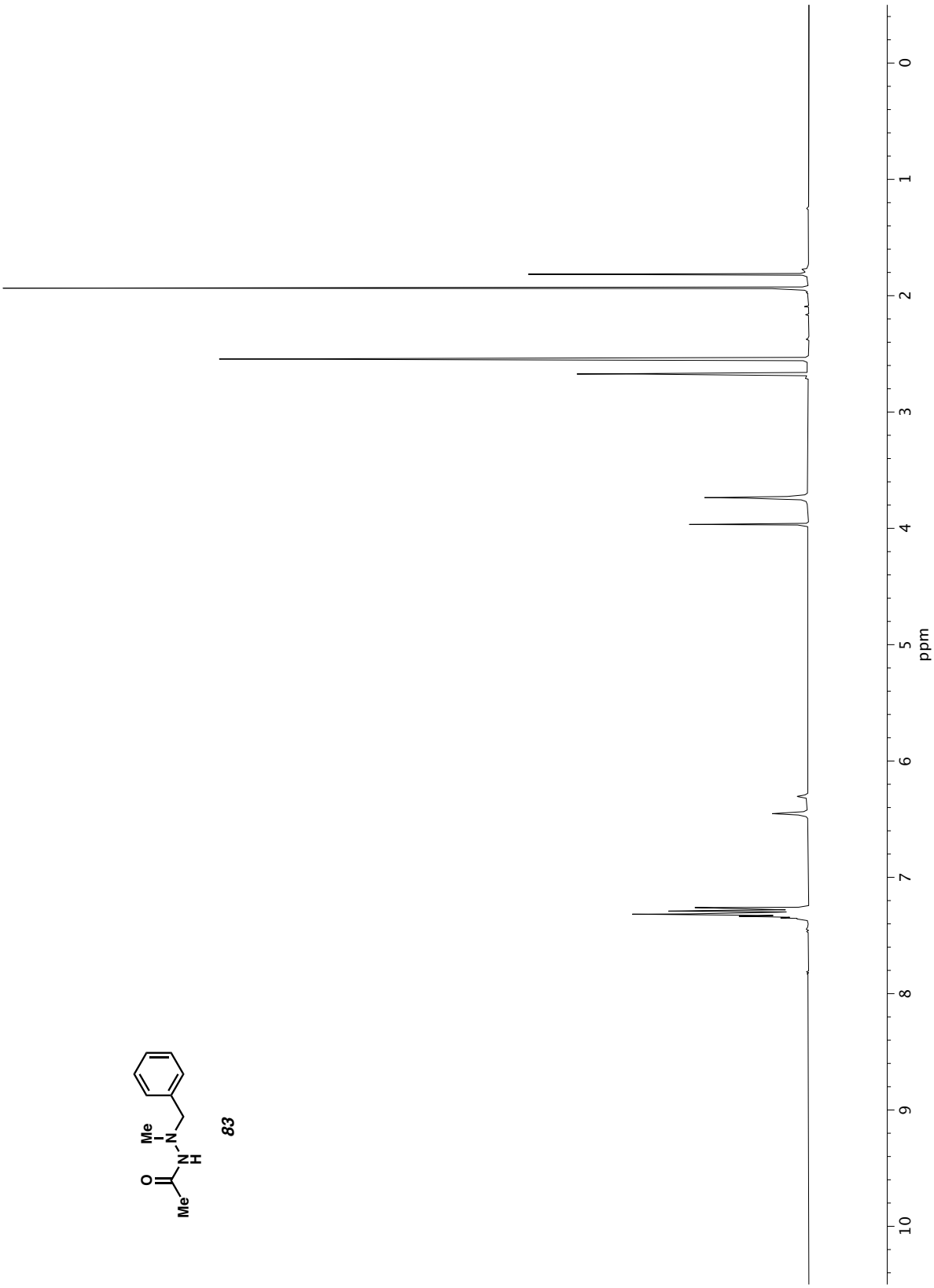


Figure A1.226 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***83***.

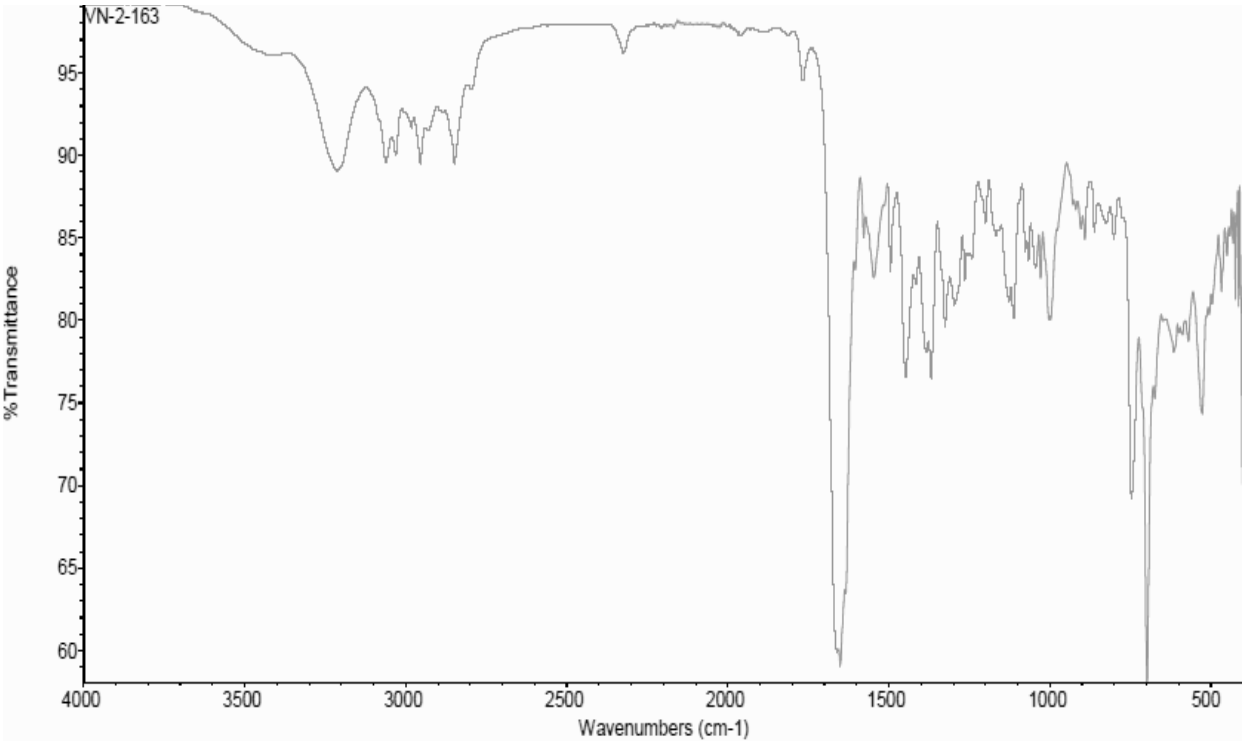


Figure A1.227 *Infrared spectrum (Thin Film) of compound* ***83***.

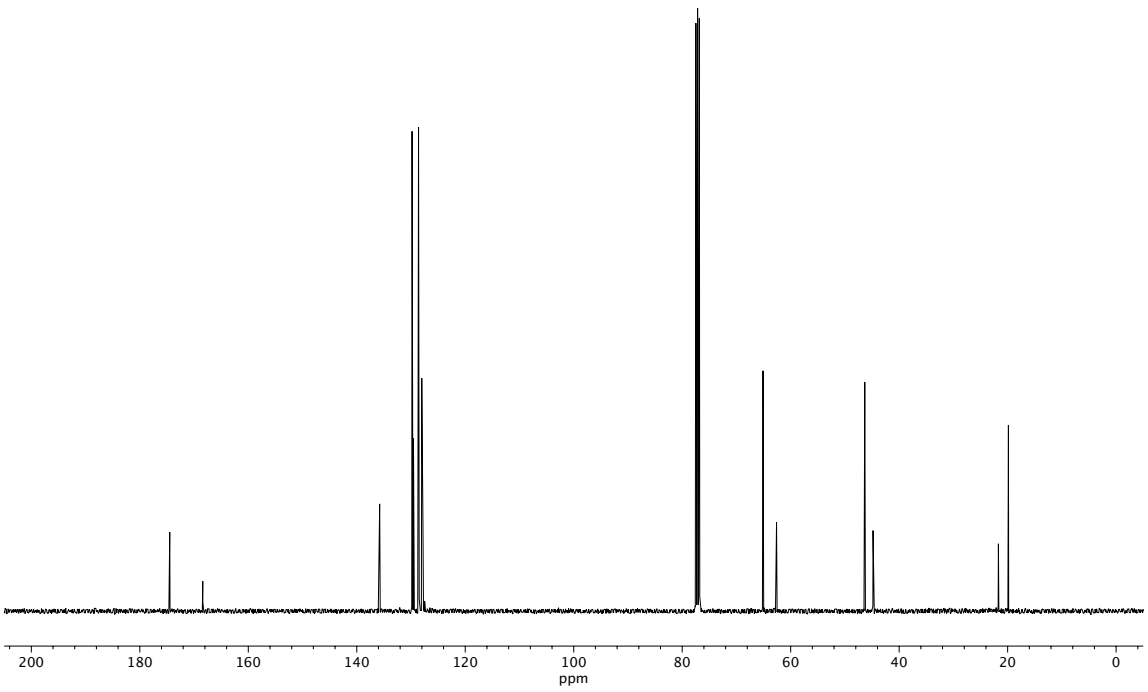


Figure A1.228 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***83***.

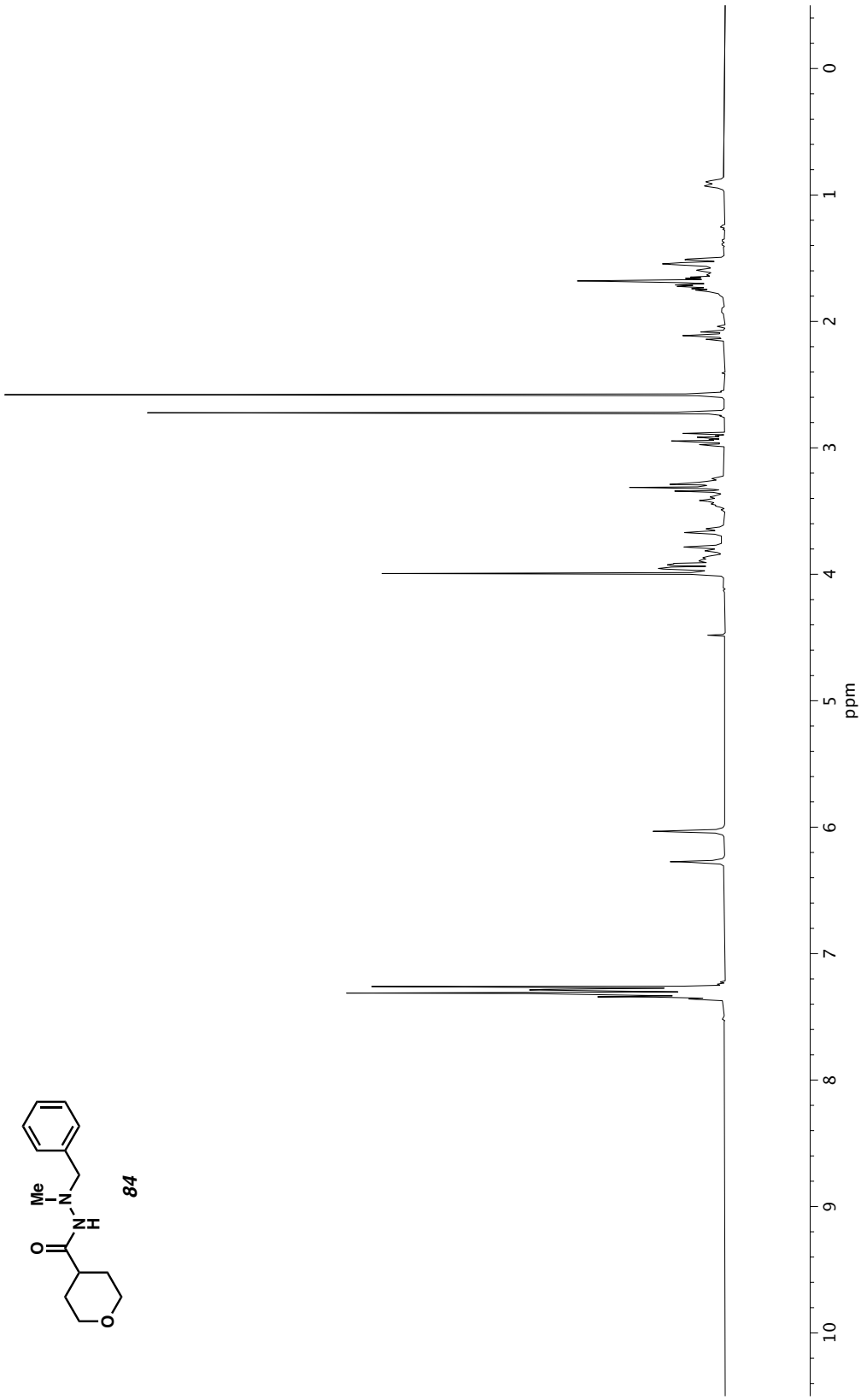


Figure A1.229 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***84****.*

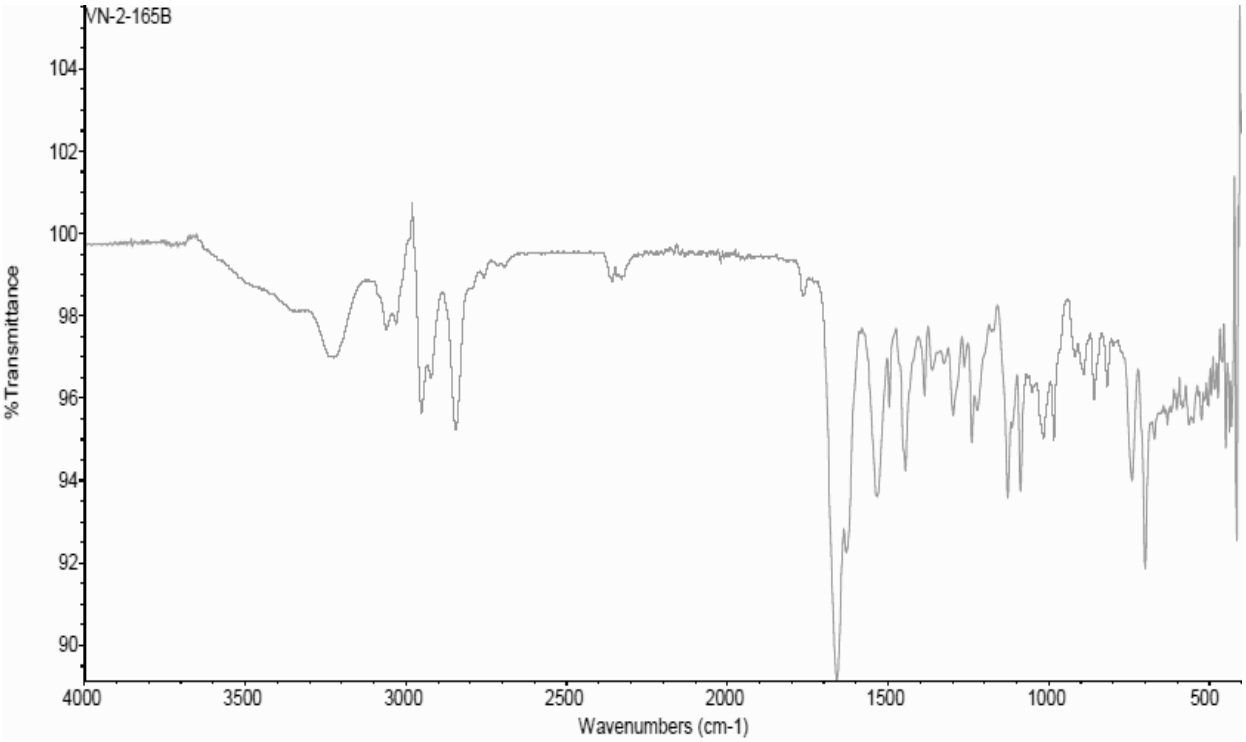


Figure A1.230 *Infrared spectrum (Thin Film) of compound* ***84***.

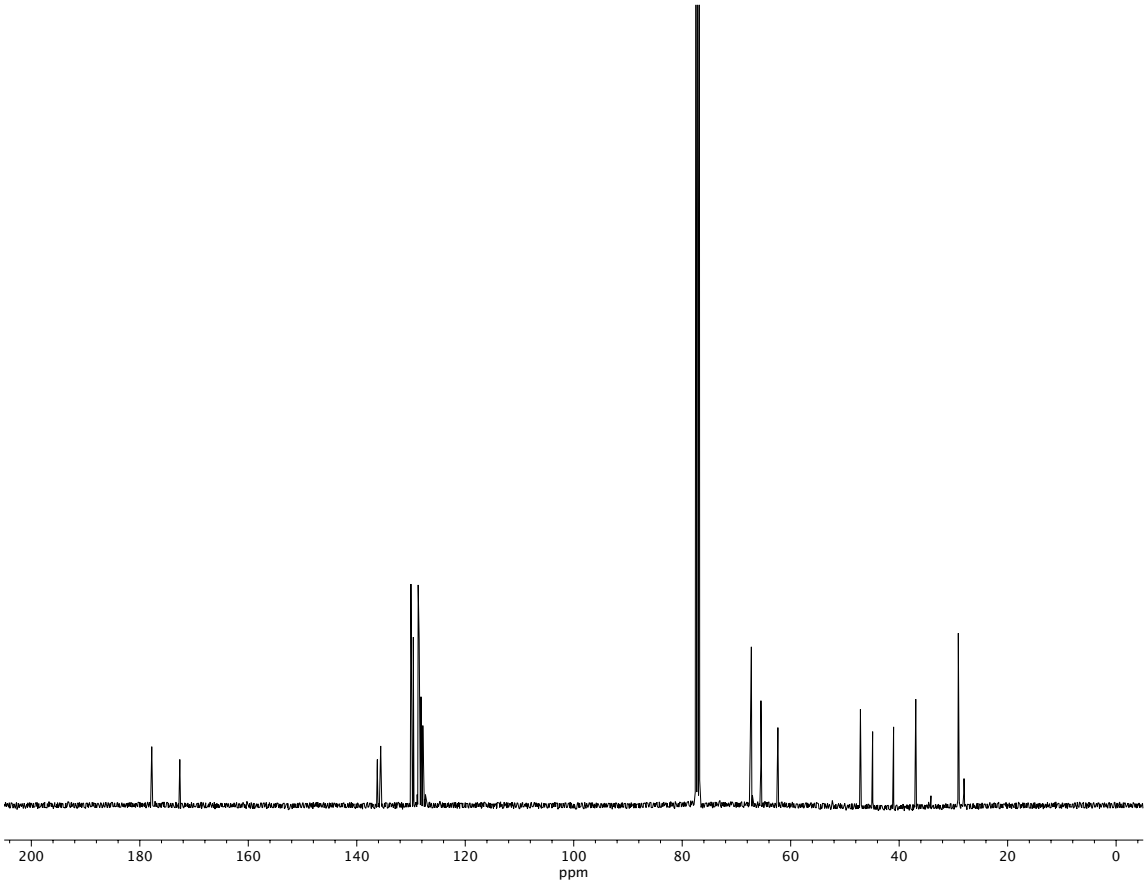


Figure A1.231 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***84***.

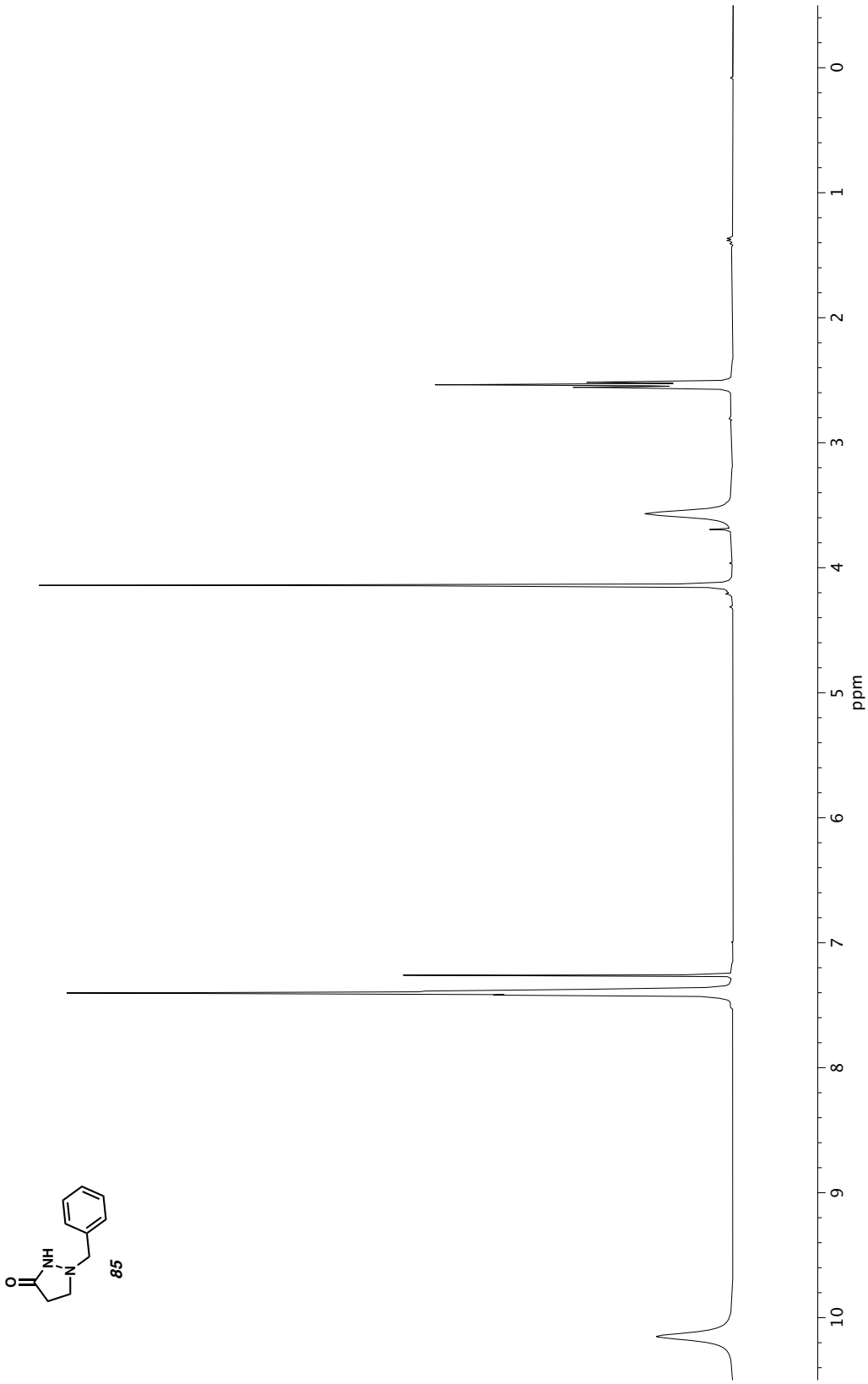


Figure A1.232 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***85***.

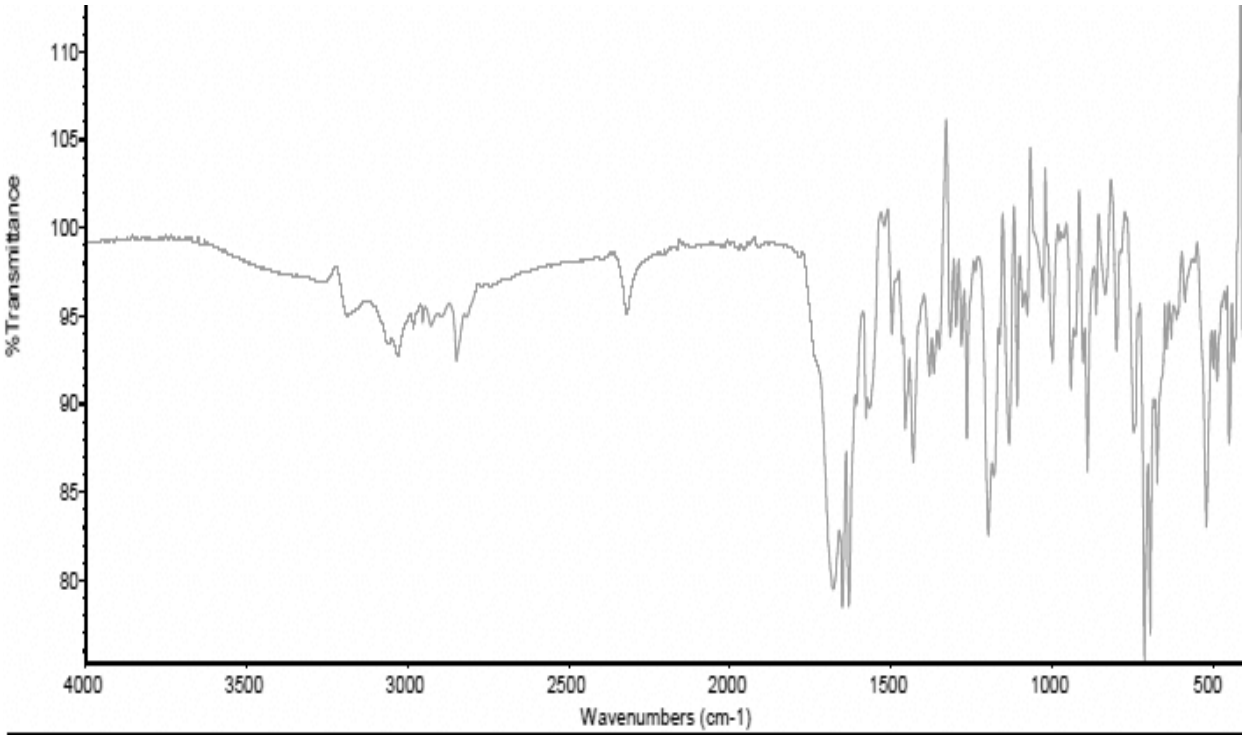


Figure A1.233 *Infrared spectrum (Thin Film) of compound* ***85***.

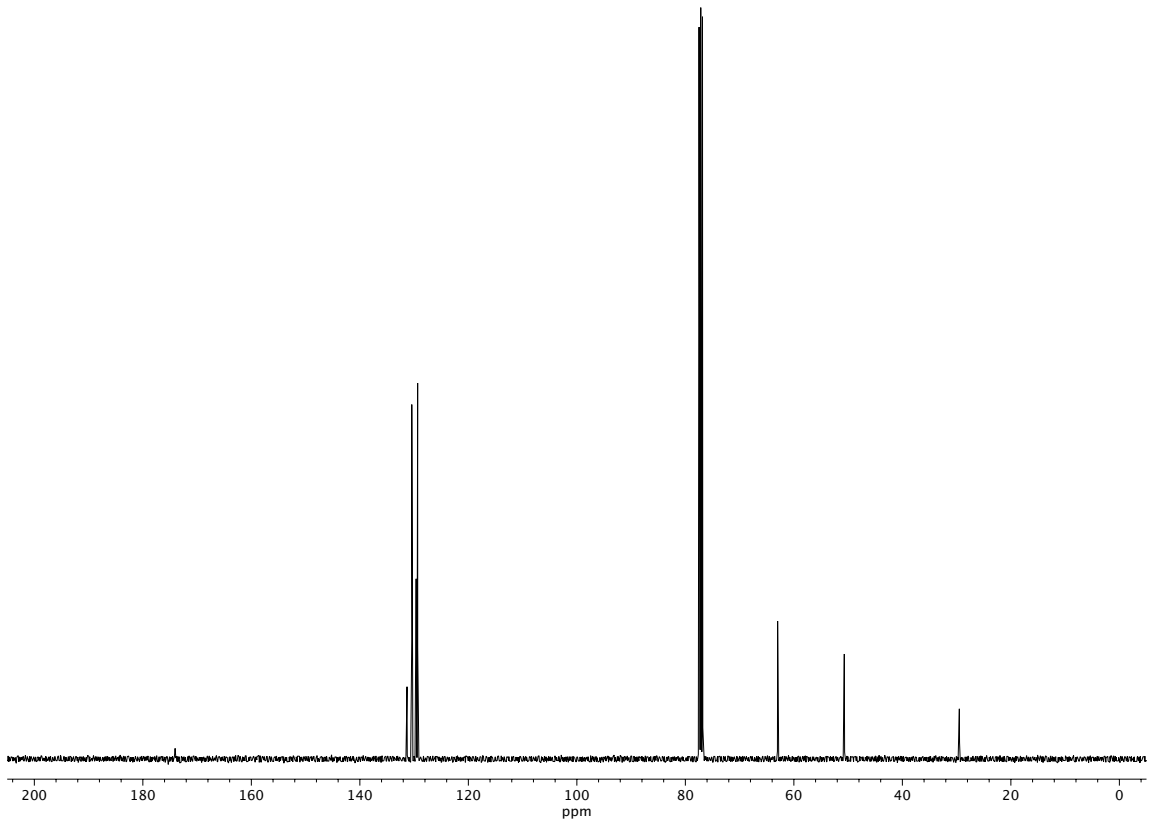


Figure A1.234 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***85***.

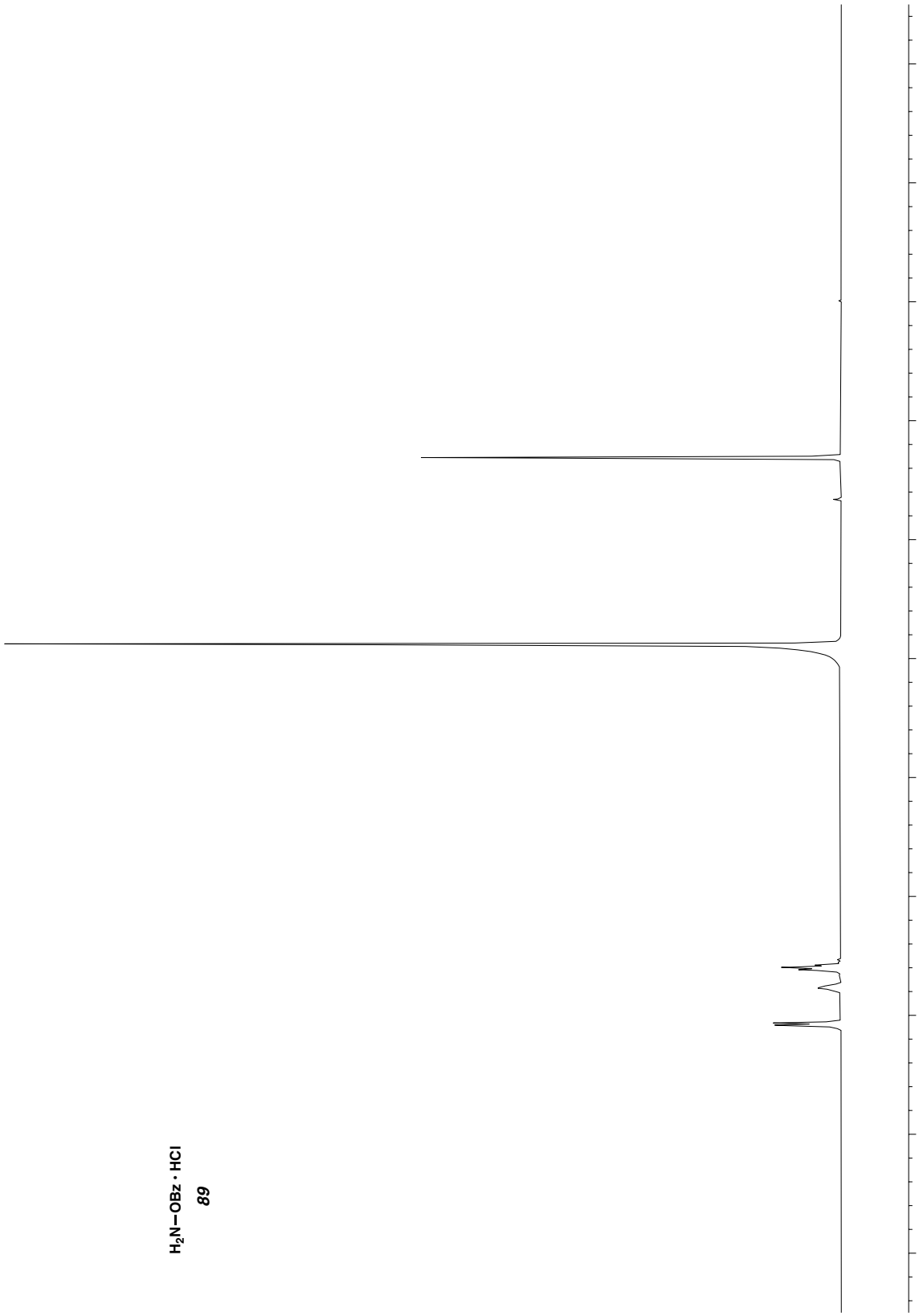


Figure A1.235 *^{1}H NMR (400 MHz, CD_3OD) of compound* ***89***.

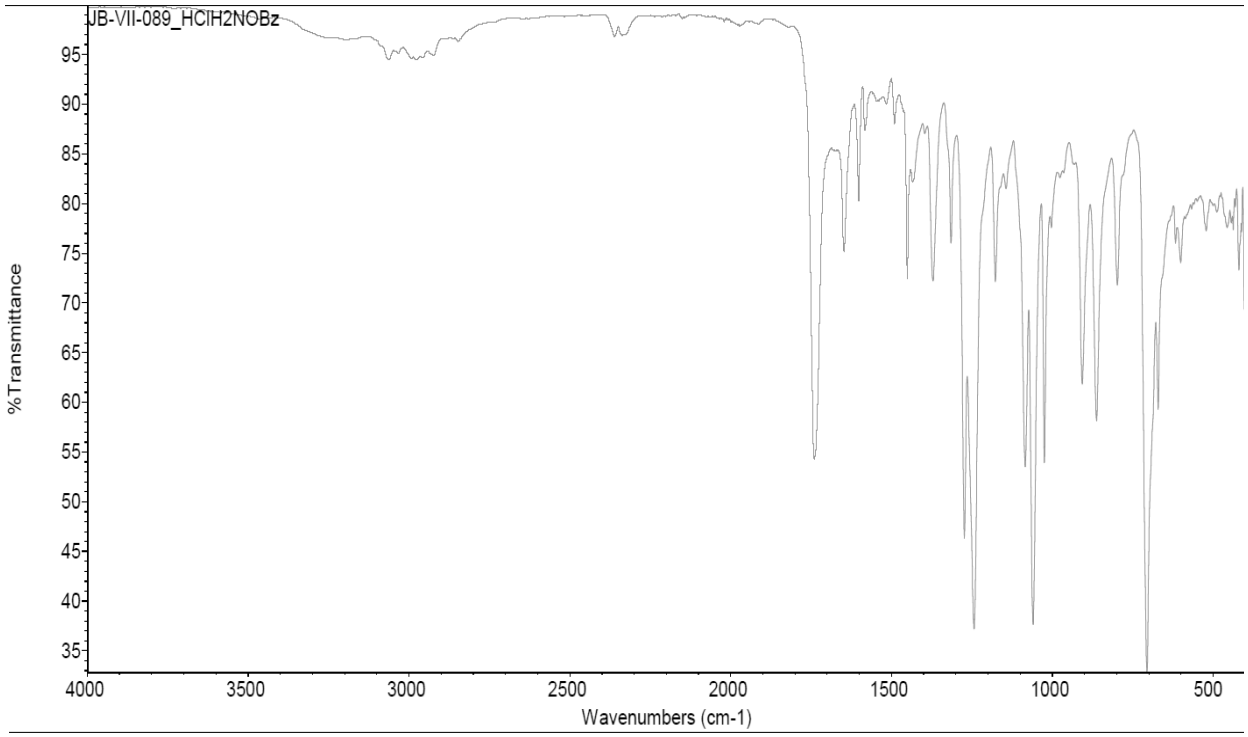


Figure A1.236 *Infrared spectrum (Thin Film) of compound* ***89***.

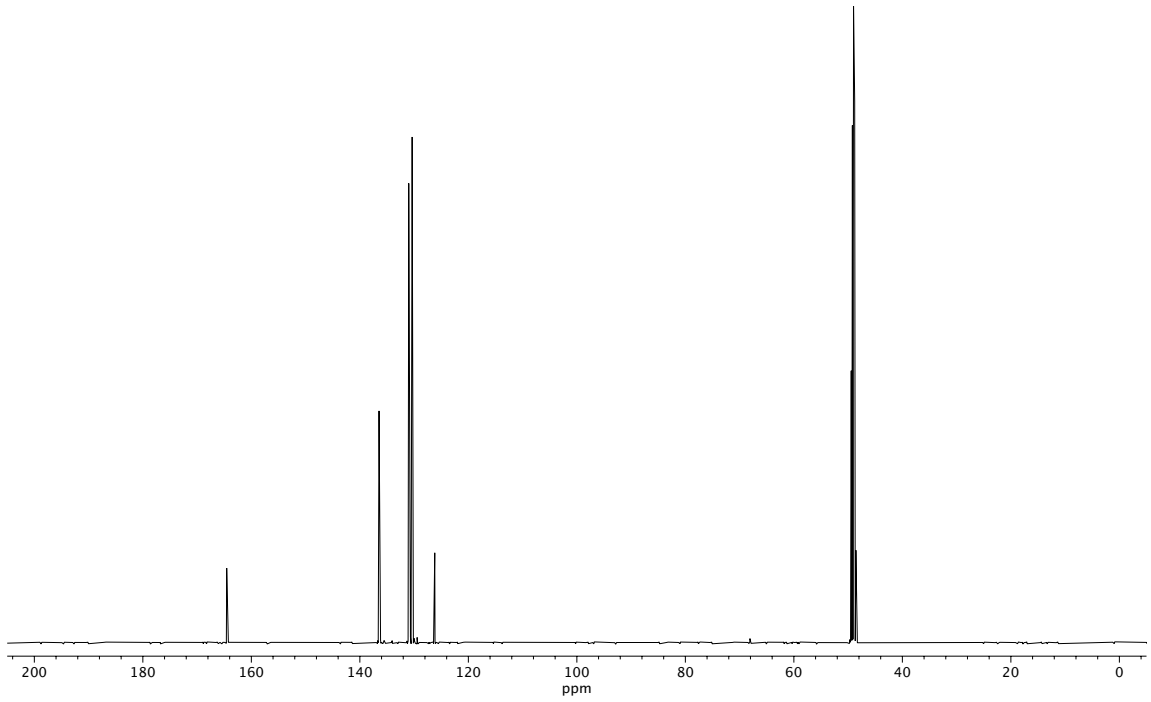


Figure A1.237 *^{13}C NMR (101 MHz, CD_3OD) of compound* ***89***.

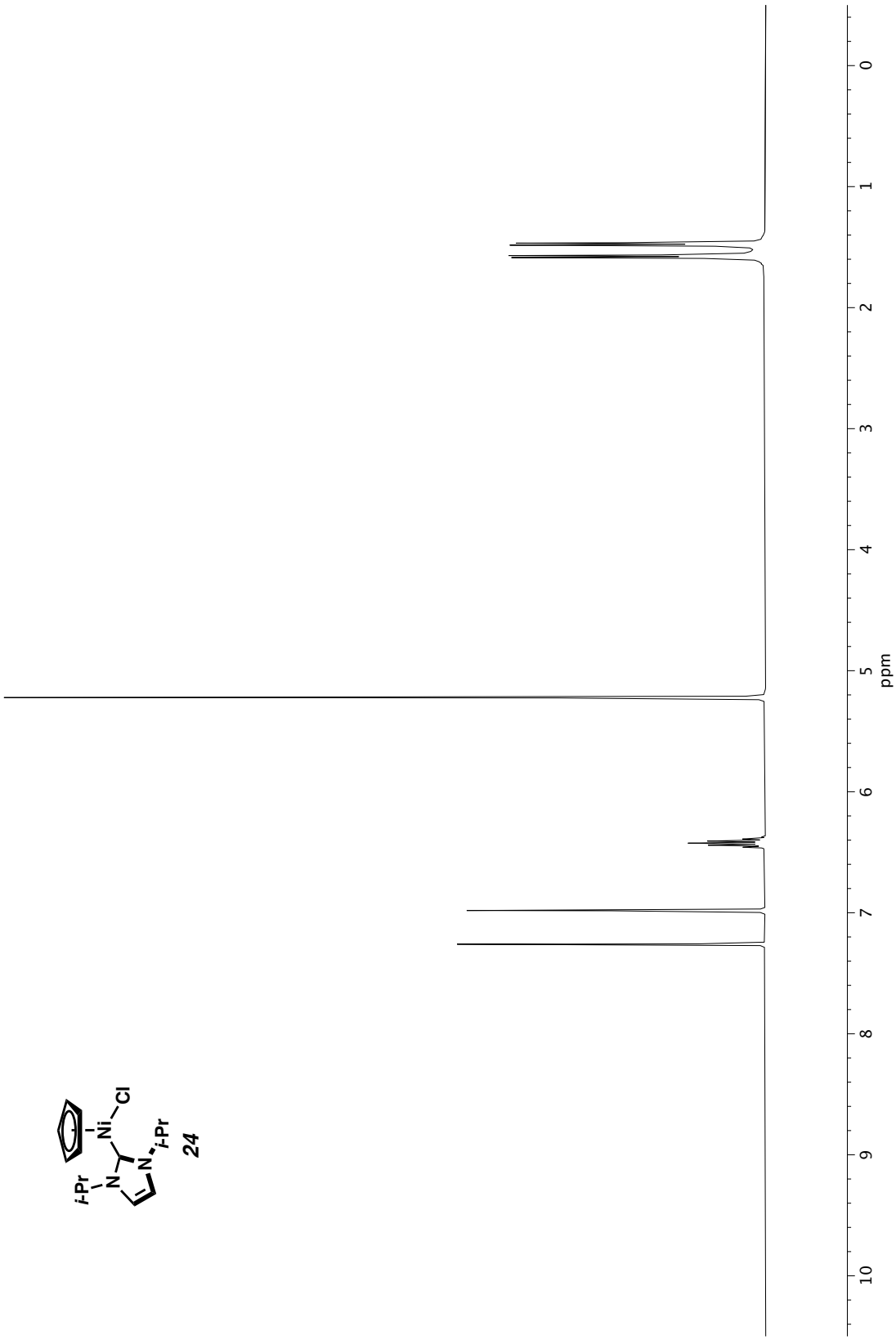


Figure A1.238 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***24****.*

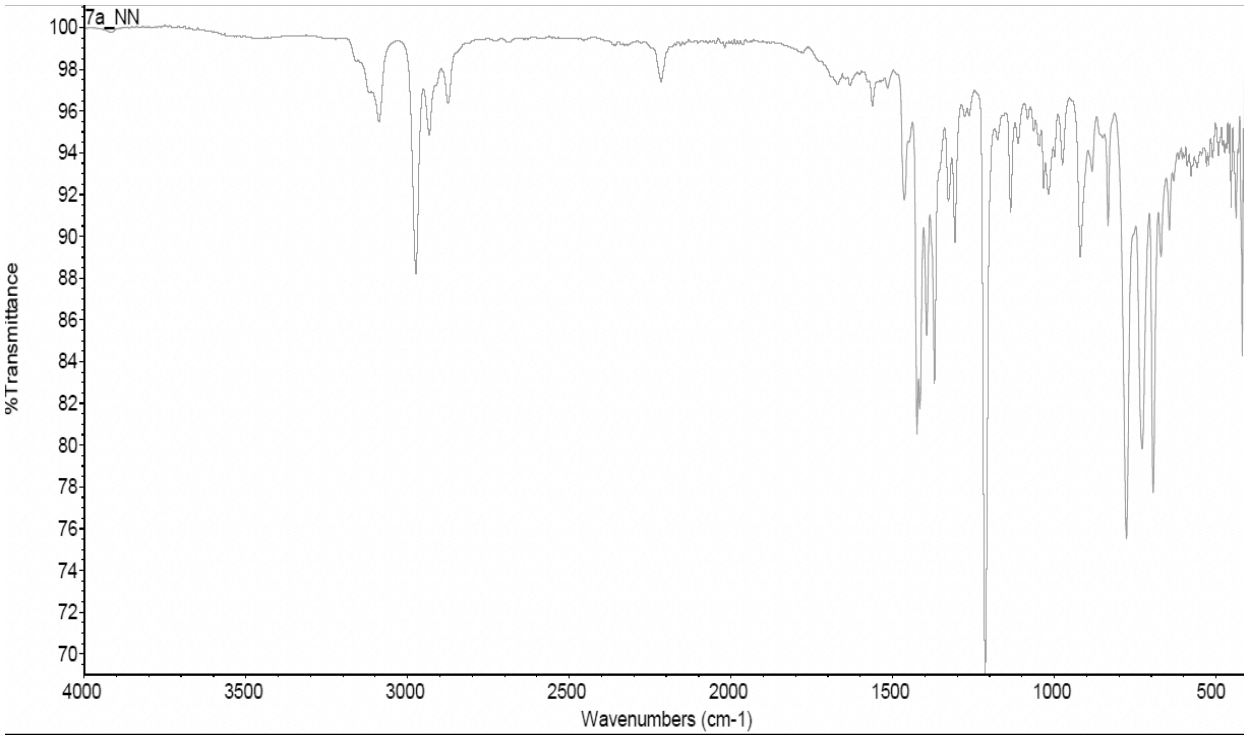


Figure A1.239 *Infrared spectrum (Thin Film) of compound* ***24****.*

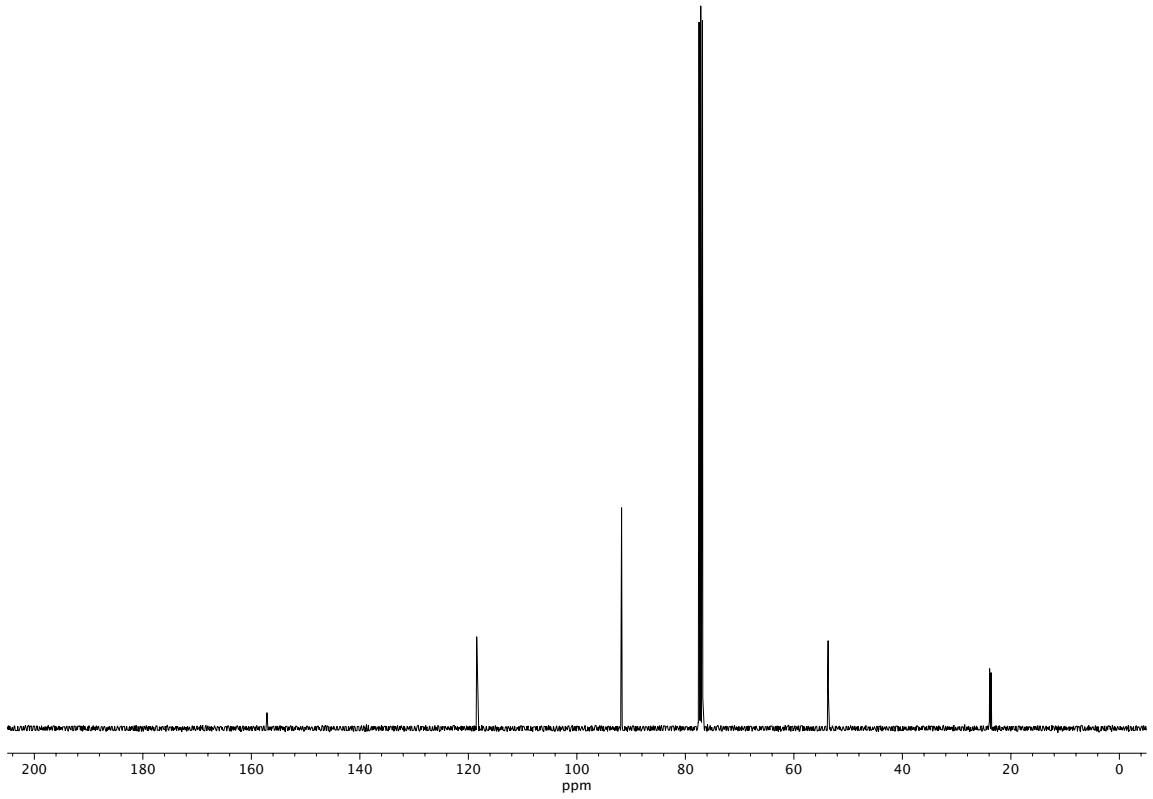


Figure A1.240 *^{13}C NMR (101 MHz, $CDCl_3$) of compound* ***24****.*

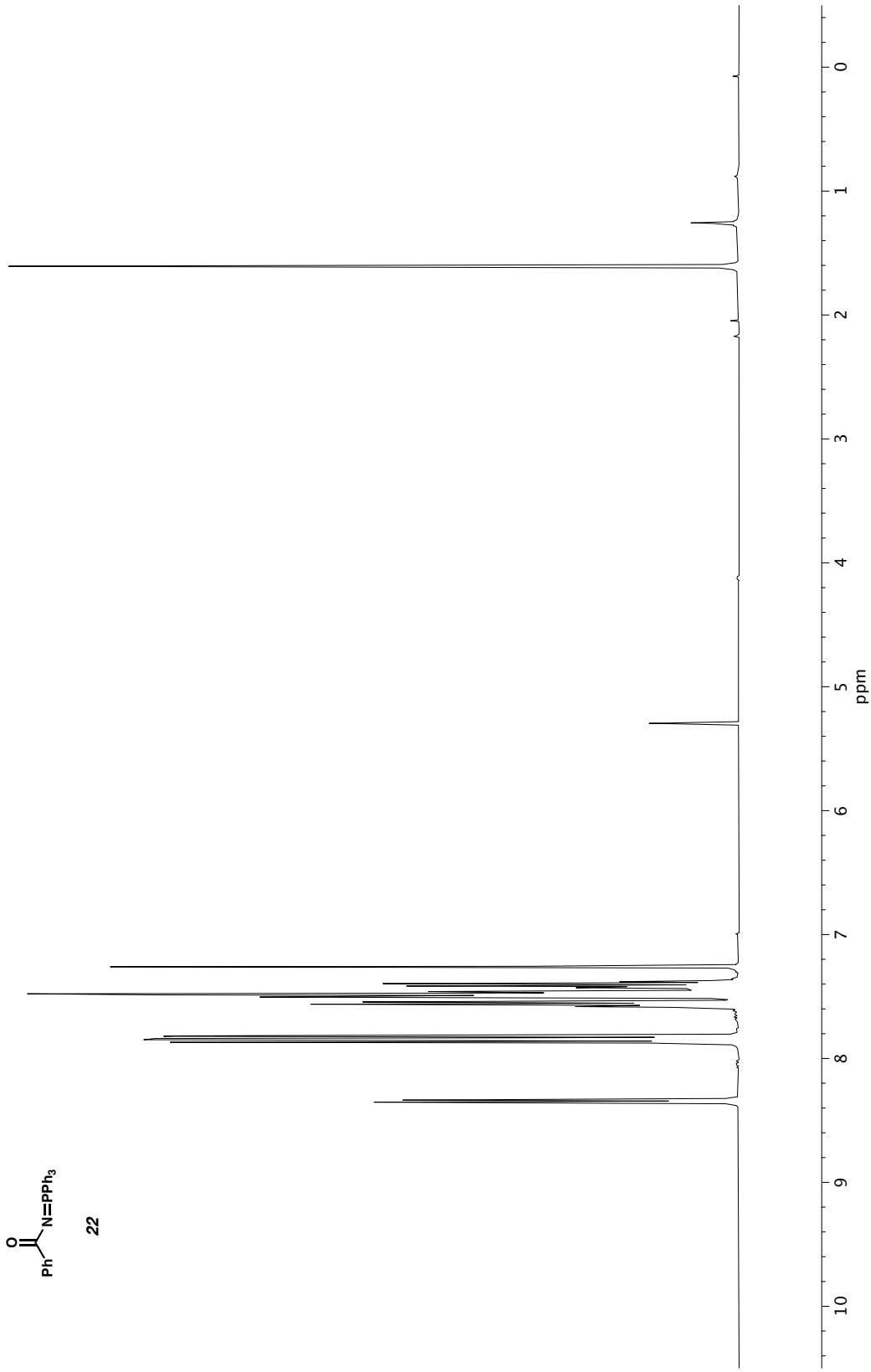


Figure A1.241 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***22****.*

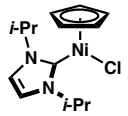
APPENDIX 2

X-Ray Crystallographic Reports Relevant to Chapter 1: Development of a Ni-Catalyzed N–N Cross-Coupling for the Synthesis of Hydrazides

A2.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A2.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF CATALYST 24



24

Ni catalyst **24** was recrystallized from a mixture of dichloromethane and hexanes at 23 °C to provide crystals suitable for X-ray analysis.

Figure A2.1 *X-ray crystal structure of Ni-catalyst* ***24***.

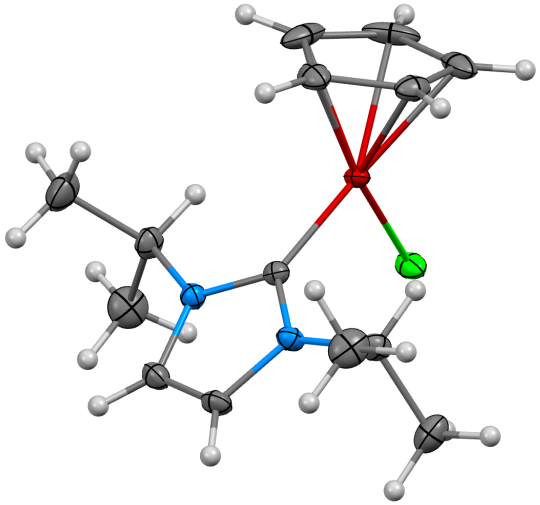


Table A2.1 *Crystal data and structure refinement for Ni-catalyst* ***24***.

Identification code	V22313.	
Empirical formula	C14 H21 Cl N2 Ni	
Formula weight	311.49	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 11.858(3) Å	a= 90°.
	b = 9.642(3) Å	b= 90°.
	c = 13.085(3) Å	g = 90°.
Volume	1496.1(7) Å3	
Z	4	
Density (calculated)	1.383 Mg/m3	
Absorption coefficient	1.460 mm-1	
F(000)	656	
Crystal size	0.300 x 0.200 x 0.150 mm3	
Theta range for data collection	2.624 to 36.319°.	
Index ranges	-17<=h<=19, -16<=k<=15, -21<=l<=21	
Reflections collected	26205	
Independent reflections	7121 [R(int) = 0.0409]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.7471 and 0.6003
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	7121 / 1 / 167
Goodness-of-fit on F^2	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0201, wR2 = 0.0436
R indices (all data)	R1 = 0.0226, wR2 = 0.0442
Absolute structure parameter	0.025(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.343 and -0.248 e.Å-3

Table A2.2 *Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for* ***24****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
Cl(1)	5916(1)	5176(1)	5298(1)	20(1)
Ni(1)	4391(1)	6328(1)	5714(1)	12(1)
C(1)	3144(1)	7582(2)	6257(1)	22(1)
C(2)	4136(2)	8409(2)	6256(1)	30(1)
C(3)	4904(1)	7761(2)	6901(1)	34(1)
C(4)	4363(2)	6596(2)	7373(1)	28(1)
C(5)	3277(1)	6521(2)	7006(1)	21(1)
C(6)	3706(1)	5849(1)	4476(1)	13(1)
N(1)	2998(1)	4782(1)	4277(1)	15(1)
C(9)	2612(1)	3758(1)	5030(1)	18(1)
C(10)	3162(1)	2362(2)	4821(1)	26(1)
C(11)	1332(1)	3683(2)	5024(1)	28(1)
C(7)	2765(1)	4714(1)	3238(1)	18(1)
C(8)	3325(1)	5759(2)	2794(1)	18(1)
N(2)	3898(1)	6450(1)	3559(1)	15(1)
C(12)	4622(1)	7671(2)	3411(1)	19(1)
C(13)	5529(1)	7372(2)	2620(1)	30(1)
C(14)	3894(2)	8921(2)	3141(1)	32(1)

Table A2.3 *Bond lengths [Å] and angles [°] for* ***24****.*

Cl(1)-Ni(1)	2.1913(6)
Ni(1)-C(6)	1.8699(12)
Ni(1)-C(1)	2.0372(14)
Ni(1)-C(2)	2.1488(15)
Ni(1)-C(5)	2.1529(14)
Ni(1)-C(3)	2.1654(14)
Ni(1)-C(4)	2.1859(15)
C(1)-C(2)	1.421(2)
C(1)-C(5)	1.425(2)
C(1)-H(1)	0.9500
C(2)-C(3)	1.389(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.434(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.376(2)
C(4)-H(4)	0.9500
C(5)-H(5)	0.9500
C(6)-N(2)	1.3520(16)
C(6)-N(1)	1.3536(17)
N(1)-C(7)	1.3888(15)
N(1)-C(9)	1.4676(17)
C(9)-C(11)	1.519(2)

C(9)-C(10)	1.520(2)
C(9)-H(9)	1.0000
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(7)-C(8)	1.339(2)
C(7)-H(7)	0.9500
C(8)-N(2)	1.3810(17)
C(8)-H(8)	0.9500
N(2)-C(12)	1.4697(18)
C(12)-C(13)	1.521(2)
C(12)-C(14)	1.524(2)
C(12)-H(12)	1.0000
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(6)-Ni(1)-C(1)	97.68(6)

C(6)-Ni(1)-C(2)	117.07(7)
C(1)-Ni(1)-C(2)	39.57(7)
C(6)-Ni(1)-C(5)	115.80(6)
C(1)-Ni(1)-C(5)	39.66(6)
C(2)-Ni(1)-C(5)	64.81(6)
C(6)-Ni(1)-C(3)	154.22(7)
C(1)-Ni(1)-C(3)	64.85(6)
C(2)-Ni(1)-C(3)	37.56(8)
C(5)-Ni(1)-C(3)	63.53(6)
C(6)-Ni(1)-C(4)	151.99(6)
C(1)-Ni(1)-C(4)	64.72(6)
C(2)-Ni(1)-C(4)	63.92(7)
C(5)-Ni(1)-C(4)	36.98(6)
C(3)-Ni(1)-C(4)	38.47(7)
C(6)-Ni(1)-Cl(1)	91.02(4)
C(1)-Ni(1)-Cl(1)	170.50(4)
C(2)-Ni(1)-Cl(1)	132.16(5)
C(5)-Ni(1)-Cl(1)	138.18(4)
C(3)-Ni(1)-Cl(1)	105.67(5)
C(4)-Ni(1)-Cl(1)	108.60(4)
C(2)-C(1)-C(5)	108.18(14)
C(2)-C(1)-Ni(1)	74.46(9)
C(5)-C(1)-Ni(1)	74.55(8)

C(2)-C(1)-H(1)	125.9
C(5)-C(1)-H(1)	125.9
Ni(1)-C(1)-H(1)	117.1
C(3)-C(2)-C(1)	106.82(14)
C(3)-C(2)-Ni(1)	71.87(9)
C(1)-C(2)-Ni(1)	65.98(8)
C(3)-C(2)-H(2)	126.6
C(1)-C(2)-H(2)	126.6
Ni(1)-C(2)-H(2)	127.1
C(2)-C(3)-C(4)	108.75(14)
C(2)-C(3)-Ni(1)	70.57(9)
C(4)-C(3)-Ni(1)	71.54(9)
C(2)-C(3)-H(3)	125.6
C(4)-C(3)-H(3)	125.6
Ni(1)-C(3)-H(3)	123.9
C(5)-C(4)-C(3)	107.98(15)
C(5)-C(4)-Ni(1)	70.20(8)
C(3)-C(4)-Ni(1)	69.99(9)
C(5)-C(4)-H(4)	126.0
C(3)-C(4)-H(4)	126.0
Ni(1)-C(4)-H(4)	125.4
C(4)-C(5)-C(1)	107.80(15)
C(4)-C(5)-Ni(1)	72.82(9)

C(1)-C(5)-Ni(1)	65.79(7)
C(4)-C(5)-H(5)	126.1
C(1)-C(5)-H(5)	126.1
Ni(1)-C(5)-H(5)	126.8
N(2)-C(6)-N(1)	105.02(10)
N(2)-C(6)-Ni(1)	126.20(10)
N(1)-C(6)-Ni(1)	128.58(9)
C(6)-N(1)-C(7)	110.34(11)
C(6)-N(1)-C(9)	125.17(10)
C(7)-N(1)-C(9)	124.27(11)
N(1)-C(9)-C(11)	109.90(12)
N(1)-C(9)-C(10)	109.92(11)
C(11)-C(9)-C(10)	112.69(12)
N(1)-C(9)-H(9)	108.1
C(11)-C(9)-H(9)	108.1
C(10)-C(9)-H(9)	108.1
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(9)-C(11)-H(11A)	109.5

C(9)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(9)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(8)-C(7)-N(1)	106.91(11)
C(8)-C(7)-H(7)	126.5
N(1)-C(7)-H(7)	126.5
C(7)-C(8)-N(2)	106.98(11)
C(7)-C(8)-H(8)	126.5
N(2)-C(8)-H(8)	126.5
C(6)-N(2)-C(8)	110.75(11)
C(6)-N(2)-C(12)	123.90(11)
C(8)-N(2)-C(12)	125.35(11)
N(2)-C(12)-C(13)	110.56(12)
N(2)-C(12)-C(14)	109.47(14)
C(13)-C(12)-C(14)	113.10(13)
N(2)-C(12)-H(12)	107.8
C(13)-C(12)-H(12)	107.8
C(14)-C(12)-H(12)	107.8
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5

C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(12)-C(14)-H(14A)	109.5
C(12)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(12)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table A2.4 *Anisotropic displacement parameters ($Å^2$ x 10^3) for* ***24****. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2}U^{11}+...+2hka^*b^*U^{12}]$.*

	U11	U22	U33	U23	U13	U12
Cl(1)	18(1)	24(1)	17(1)	-5(1)	-2(1)	8(1)
Ni(1)	12(1)	12(1)	12(1)	-3(1)	-1(1)	0(1)
C(1)	22(1)	25(1)	19(1)	-6(1)	-1(1)	10(1)
C(2)	45(1)	13(1)	33(1)	-7(1)	21(1)	-3(1)
C(3)	19(1)	43(1)	38(1)	-31(1)	5(1)	-8(1)
C(4)	33(1)	35(1)	18(1)	-12(1)	-7(1)	17(1)
C(5)	24(1)	18(1)	20(1)	-4(1)	8(1)	-2(1)
C(6)	13(1)	12(1)	14(1)	-2(1)	0(1)	0(1)
N(1)	15(1)	15(1)	14(1)	-2(1)	-1(1)	-2(1)
C(9)	19(1)	17(1)	18(1)	-1(1)	1(1)	-6(1)
C(10)	23(1)	18(1)	36(1)	5(1)	1(1)	1(1)
C(11)	20(1)	28(1)	37(1)	1(1)	9(1)	-3(1)
C(7)	18(1)	19(1)	16(1)	-5(1)	-4(1)	-1(1)
C(8)	18(1)	21(1)	13(1)	-2(1)	-2(1)	1(1)
N(2)	15(1)	14(1)	14(1)	1(1)	-1(1)	-1(1)
C(12)	21(1)	16(1)	21(1)	4(1)	0(1)	-4(1)
C(13)	23(1)	34(1)	33(1)	3(1)	6(1)	-6(1)
C(14)	39(1)	19(1)	37(1)	7(1)	1(1)	2(1)

Table A2.5 *Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x10^3) for* ***24****.*

	x	y	z	U(eq)
H(1)	2504	7714	5832	26
H(2)	4252	9244	5885	36
H(3)	5661	8044	7010	40
H(4)	4696	5983	7855	34
H(5)	2716	5878	7214	25
H(9)	2857	4077	5722	22
H(10A)	2912	2013	4155	39
H(10B)	2946	1703	5356	39
H(10C)	3984	2471	4817	39
H(11A)	1020	4601	5178	42
H(11B)	1079	3017	5541	42
H(11C)	1072	3383	4348	42
H(7)	2297	4054	2906	21
H(8)	3328	5982	2087	21
H(12)	5006	7871	4076	23
H(13A)	6021	6628	2869	45
H(13B)	5977	8211	2503	45
H(13C)	5174	7084	1978	45
H(14A)	3517	8757	2486	48

H(14B)	4371	9748	3089	48
H(14C)	3327	9062	3676	48

Table A2.6 *Torsion angles [°] for* ***24****.*

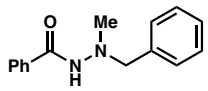
C(5)-C(1)-C(2)-C(3)	6.91(15)
Ni(1)-C(1)-C(2)-C(3)	-60.61(10)
C(5)-C(1)-C(2)-Ni(1)	67.52(9)
C(1)-C(2)-C(3)-C(4)	-4.82(16)
Ni(1)-C(2)-C(3)-C(4)	-61.68(10)
C(1)-C(2)-C(3)-Ni(1)	56.87(10)
C(2)-C(3)-C(4)-C(5)	0.89(17)
Ni(1)-C(3)-C(4)-C(5)	-60.19(10)
C(2)-C(3)-C(4)-Ni(1)	61.08(10)
C(3)-C(4)-C(5)-C(1)	3.42(16)
Ni(1)-C(4)-C(5)-C(1)	-56.63(9)
C(3)-C(4)-C(5)-Ni(1)	60.05(10)
C(2)-C(1)-C(5)-C(4)	-6.44(16)
Ni(1)-C(1)-C(5)-C(4)	61.02(10)
C(2)-C(1)-C(5)-Ni(1)	-67.46(10)
C(1)-Ni(1)-C(6)-N(2)	97.07(12)
C(2)-Ni(1)-C(6)-N(2)	60.65(13)
C(5)-Ni(1)-C(6)-N(2)	134.16(11)
C(3)-Ni(1)-C(6)-N(2)	52.1(2)
C(4)-Ni(1)-C(6)-N(2)	145.46(13)
Cl(1)-Ni(1)-C(6)-N(2)	-79.08(11)
C(1)-Ni(1)-C(6)-N(1)	-88.92(13)

C(2)-Ni(1)-C(6)-N(1)	-125.34(12)
C(5)-Ni(1)-C(6)-N(1)	-51.83(14)
C(3)-Ni(1)-C(6)-N(1)	-133.93(14)
C(4)-Ni(1)-C(6)-N(1)	-40.5(2)
Cl(1)-Ni(1)-C(6)-N(1)	94.94(12)
N(2)-C(6)-N(1)-C(7)	0.68(15)
Ni(1)-C(6)-N(1)-C(7)	-174.32(10)
N(2)-C(6)-N(1)-C(9)	175.41(12)
Ni(1)-C(6)-N(1)-C(9)	0.41(19)
C(6)-N(1)-C(9)-C(11)	126.81(14)
C(7)-N(1)-C(9)-C(11)	-59.17(17)
C(6)-N(1)-C(9)-C(10)	-108.62(14)
C(7)-N(1)-C(9)-C(10)	65.40(17)
C(6)-N(1)-C(7)-C(8)	-0.59(16)
C(9)-N(1)-C(7)-C(8)	-175.38(13)
N(1)-C(7)-C(8)-N(2)	0.25(16)
N(1)-C(6)-N(2)-C(8)	-0.52(15)
Ni(1)-C(6)-N(2)-C(8)	174.64(10)
N(1)-C(6)-N(2)-C(12)	179.55(12)
Ni(1)-C(6)-N(2)-C(12)	-5.29(19)
C(7)-C(8)-N(2)-C(6)	0.17(16)
C(7)-C(8)-N(2)-C(12)	-179.90(13)
C(6)-N(2)-C(12)-C(13)	125.09(14)

C(8)-N(2)-C(12)-C(13)	-54.83(19)
C(6)-N(2)-C(12)-C(14)	-109.67(15)
C(8)-N(2)-C(12)-C(14)	70.42(17)

Symmetry transformations used to generate equivalent atoms:

A2.3 X-RAY CRYSTAL STRUCTURE ANALYSIS OF N–N PRODUCT 27



27

Compound **27** was crystallized from a mixture of dichloromethane and hexanes at 23 °C to provide crystals suitable for X-ray analysis.

Figure A2.2 *X-ray crystal structure of N–N product* ***27***.

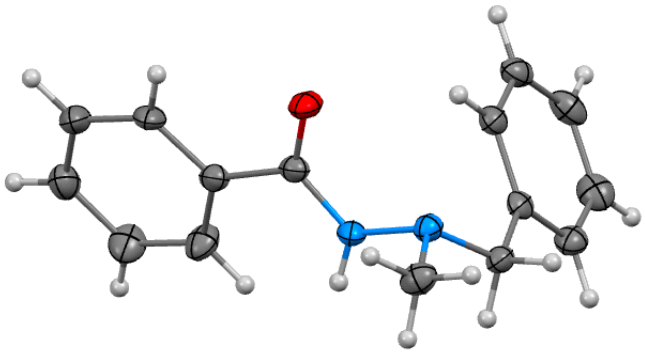


Table A2.7 *Crystal data and structure refinement for N–N product* ***27***.

Empirical formula	$C_{15}H_{16}N_2O$
Formula weight	240.30
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	Pbcn
Unit cell dimensions	a = 15.570(2) Å a= 90°.
	b = 9.7681(14) Å b= 90°.
	c = 17.1374(19) Å g = 90°.
Volume	2606.4(6) Å3
Z	8
Density (calculated)	1.225 Mg/m^3
Absorption coefficient	0.617 mm^{-1}
F(000)	1024
Crystal size	0.400 x 0.050 x 0.030 mm3
Theta range for data collection	5.162 to 74.603°.
Index ranges	-19<=h<=19, -11<=k<=12, -21<=l<=21
Reflections collected	30984
Independent reflections	2675 [R(int) = 0.1106]
Completeness to theta =	67.679° 100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.5363

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2675 / 1 / 167
Goodness-of-fit on F2	1.067
Final R indices	[I>2sigma(I)] R1 = 0.0458, wR2 = 0.1156
R indices (all data)	R1 = 0.0615, wR2 = 0.1218
Extinction coefficient	n/a
Largest diff. peak and hole	0.300 and -0.203 e.Å-3

Table A2.8 *Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^{2}x10^3) for* ***27****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	2972(1)	5181(1)	1190(1)	28(1)
C(1)	3078(1)	3941(1)	1271(1)	22(1)
C(2)	3967(1)	3334(1)	1260(1)	23(1)
C(3)	4637(1)	4196(2)	1050(1)	28(1)
C(4)	5477(1)	3729(2)	1049(1)	33(1)
C(5)	5659(1)	2393(2)	1264(1)	32(1)
C(6)	4994(1)	1517(2)	1454(1)	36(1)
C(7)	4147(1)	1978(2)	1453(1)	32(1)
N(1)	2426(1)	3063(1)	1382(1)	22(1)
N(2)	1575(1)	3578(1)	1401(1)	22(1)
C(8)	1093(1)	2874(1)	2012(1)	23(1)
C(9)	1413(1)	3151(1)	2828(1)	21(1)
C(10)	1924(1)	4272(2)	3017(1)	24(1)
C(11)	2170(1)	4496(2)	3787(1)	28(1)
C(12)	1904(1)	3623(2)	4378(1)	31(1)
C(13)	1389(1)	2512(2)	4192(1)	33(1)
C(14)	1155(1)	2271(2)	3425(1)	27(1)
C(15)	1172(1)	3377(2)	635(1)	30(1)

Table A2.9 *Bond lengths [Å] and angles [°] for* ***27****.*

O(1)-C(1)	1.2301(18)
C(1)-N(1)	1.3419(19)
C(1)-C(2)	1.505(2)
C(2)-C(3)	1.389(2)
C(2)-C(7)	1.394(2)
C(3)-C(4)	1.384(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.385(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.382(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.393(2)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
N(1)-N(2)	1.4177(17)
N(1)-H(1N)	0.865(15)
N(2)-C(8)	1.4608(19)
N(2)-C(15)	1.468(2)
C(8)-C(9)	1.509(2)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.392(2)

C(9)-C(14)	1.395(2)
C(10)-C(11)	1.392(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.386(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.387(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.384(2)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
O(1)-C(1)-N(1)	122.94(13)
O(1)-C(1)-C(2)	120.61(13)
N(1)-C(1)-C(2)	116.44(12)
C(3)-C(2)-C(7)	119.07(14)
C(3)-C(2)-C(1)	117.12(13)
C(7)-C(2)-C(1)	123.80(13)
C(4)-C(3)-C(2)	120.70(14)
C(4)-C(3)-H(3)	119.7
C(2)-C(3)-H(3)	119.7
C(3)-C(4)-C(5)	120.22(15)

C(3)-C(4)-H(4)	119.9
C(5)-C(4)-H(4)	119.9
C(6)-C(5)-C(4)	119.50(15)
C(6)-C(5)-H(5)	120.2
C(4)-C(5)-H(5)	120.2
C(5)-C(6)-C(7)	120.56(15)
C(5)-C(6)-H(6)	119.7
C(7)-C(6)-H(6)	119.7
C(6)-C(7)-C(2)	119.90(15)
C(6)-C(7)-H(7)	120.1
C(2)-C(7)-H(7)	120.1
C(1)-N(1)-N(2)	118.91(12)
C(1)-N(1)-H(1N)	121.7(13)
N(2)-N(1)-H(1N)	118.1(13)
N(1)-N(2)-C(8)	109.28(11)
N(1)-N(2)-C(15)	109.39(12)
C(8)-N(2)-C(15)	110.99(11)
N(2)-C(8)-C(9)	114.23(11)
N(2)-C(8)-H(8A)	108.7
C(9)-C(8)-H(8A)	108.7
N(2)-C(8)-H(8B)	108.7
C(9)-C(8)-H(8B)	108.7
H(8A)-C(8)-H(8B)	107.6

C(10)-C(9)-C(14)	118.66(14)
C(10)-C(9)-C(8)	123.04(13)
C(14)-C(9)-C(8)	118.25(13)
C(11)-C(10)-C(9)	120.07(14)
C(11)-C(10)-H(10)	120.0
C(9)-C(10)-H(10)	120.0
C(12)-C(11)-C(10)	120.88(15)
C(12)-C(11)-H(11)	119.6
C(10)-C(11)-H(11)	119.6
C(11)-C(12)-C(13)	119.13(15)
C(11)-C(12)-H(12)	120.4
C(13)-C(12)-H(12)	120.4
C(14)-C(13)-C(12)	120.23(15)
C(14)-C(13)-H(13)	119.9
C(12)-C(13)-H(13)	119.9
C(13)-C(14)-C(9)	121.01(15)
C(13)-C(14)-H(14)	119.5
C(9)-C(14)-H(14)	119.5
N(2)-C(15)-H(15A)	109.5
N(2)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
N(2)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5

H(15B)-C(15)-H(15C) 109.5

Symmetry transformations used to generate equivalent atoms:

Table A2.10 *Anisotropic displacement parameters ($Å^2$ x 10^3) for* ***27****. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.*

	U11	U22	U33	U23	U13	U12
O(1)	25(1)	16(1)	44(1)	2(1)	1(1)	-1(1)
C(1)	26(1)	18(1)	22(1)	-2(1)	1(1)	-2(1)
C(2)	26(1)	20(1)	22(1)	-2(1)	1(1)	-2(1)
C(3)	29(1)	14(1)	42(1)	-5(1)	4(1)	-1(1)
C(4)	26(1)	24(1)	50(1)	-9(1)	7(1)	-5(1)
C(5)	25(1)	32(1)	38(1)	-4(1)	1(1)	4(1)
C(6)	34(1)	26(1)	48(1)	12(1)	2(1)	6(1)
C(7)	29(1)	26(1)	42(1)	11(1)	4(1)	-2(1)
N(1)	22(1)	15(1)	28(1)	-1(1)	3(1)	0(1)
N(2)	21(1)	19(1)	27(1)	1(1)	0(1)	0(1)
C(8)	20(1)	20(1)	29(1)	0(1)	1(1)	-2(1)
C(9)	18(1)	17(1)	29(1)	0(1)	1(1)	5(1)
C(10)	22(1)	21(1)	30(1)	-1(1)	2(1)	2(1)
C(11)	25(1)	23(1)	37(1)	-8(1)	-3(1)	4(1)
C(12)	36(1)	31(1)	27(1)	-4(1)	-4(1)	11(1)
C(13)	41(1)	27(1)	31(1)	7(1)	2(1)	7(1)
C(14)	27(1)	20(1)	33(1)	2(1)	1(1)	1(1)
C(15)	33(1)	28(1)	28(1)	4(1)	-2(1)	-5(1)

Table A2.11 *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for* ***27****.*

	x	y	z	U(eq)
H(3)	4519	5115	904	34
H(4)	5930	4327	901	40
H(5)	6236	2081	1281	38
H(6)	5115	593	1587	44
H(7)	3693	1369	1583	39
H(1N)	2497(13)	2187(16)	1346(11)	26
H(8A)	1119	1877	1914	27
H(8B)	483	3156	1979	27
H(10)	2106	4885	2619	29
H(11)	2525	5258	3911	34
H(12)	2073	3784	4902	37
H(13)	1196	1914	4592	39
H(14)	813	1495	3303	32
H(15A)	504	3863	236	45
H(15B)	584	3736	647	45
H(15C)	1158	2398	512	45

Table A2.12. *Torsion angles [°] for* ***27****.*

O(1)-C(1)-C(2)-C(3)	-8.6(2)
N(1)-C(1)-C(2)-C(3)	172.17(14)
O(1)-C(1)-C(2)-C(7)	170.86(15)
N(1)-C(1)-C(2)-C(7)	-8.3(2)
C(7)-C(2)-C(3)-C(4)	-1.6(2)
C(1)-C(2)-C(3)-C(4)	177.89(15)
C(2)-C(3)-C(4)-C(5)	-0.4(3)
C(3)-C(4)-C(5)-C(6)	2.1(3)
C(4)-C(5)-C(6)-C(7)	-1.9(3)
C(5)-C(6)-C(7)-C(2)	-0.1(3)
C(3)-C(2)-C(7)-C(6)	1.9(3)
C(1)-C(2)-C(7)-C(6)	-177.62(16)
O(1)-C(1)-N(1)-N(2)	0.6(2)
C(2)-C(1)-N(1)-N(2)	179.75(12)
C(1)-N(1)-N(2)-C(8)	-139.83(13)
C(1)-N(1)-N(2)-C(15)	98.48(14)
N(1)-N(2)-C(8)-C(9)	65.32(15)
C(15)-N(2)-C(8)-C(9)	-173.95(12)
N(2)-C(8)-C(9)-C(10)	19.30(19)
N(2)-C(8)-C(9)-C(14)	-163.31(12)
C(14)-C(9)-C(10)-C(11)	0.1(2)
C(8)-C(9)-C(10)-C(11)	177.50(13)

C(9)-C(10)-C(11)-C(12)	-0.7(2)
C(10)-C(11)-C(12)-C(13)	0.2(2)
C(11)-C(12)-C(13)-C(14)	0.9(2)
C(12)-C(13)-C(14)-C(9)	-1.5(2)
C(10)-C(9)-C(14)-C(13)	1.0(2)
C(8)-C(9)-C(14)-C(13)	-176.55(14)

Symmetry transformations used to generate equivalent atoms:

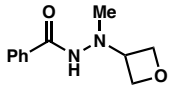
Table A2.13 *Hydrogen bonds for* ***27*** *[Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.865(15)	2.108(17)	2.9018(16)	152.2(18)
C(8)-H(8A)...O(1)#1	0.99	2.51	3.3207(18)	139.2

Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,y-1/2,z

A2.3 X-RAY CRYSTAL STRUCTURE ANALYSIS OF N–N PRODUCT 70



70

Compound **70** was crystallized from a mixture of dichloromethane and hexanes at 23 °C to provide crystals suitable for X-ray analysis.

Figure A2.3 *X-ray crystal structure of N–N product* ***70***.

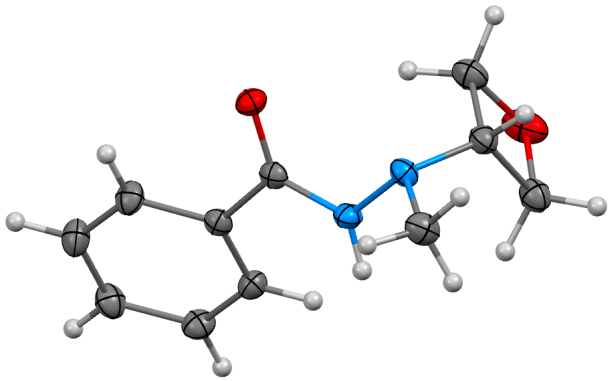


Figure A2.14 *Crystal data and structure refinement for N–N product* ***70****.*

Empirical formula	$C_{11}H_{14}N_2O_2$	
Formula weight	206.24	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Tetragonal	
Space group	$I4_1/a$	
Unit cell dimensions	a = 18.1243(9) Å	a= 90°.
	b = 18.1243(9) Å	b= 90°.
	c = 12.9625(14) Å	g = 90°.
Volume	4258.1(6) $Å^3$	
Z	16	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.734 mm^{-1}	
F(000)	1760	
Crystal size	0.050 x 0.050 x 0.050 mm^3	
Theta range for data collection	4.193 to 74.554°.	
Index ranges	-22<=h<=22, -20<=k<=22, -16<=l<=16	
Reflections collected	27679	
Independent reflections	2186 [R(int) = 0.0683]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.6823	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2186 / 1 / 140
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.0874
R indices (all data)	R1 = 0.0503, wR2 = 0.0983
Extinction coefficient	n/a
Largest diff. peak and hole	0.232 and -0.186 e.$Å^{-3}$

Table A2.15 *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for* ***70****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	1333(1)	5983(1)	2099(1)	21(1)
C(1)	1354(1)	5592(1)	2881(1)	17(1)
C(2)	1169(1)	5909(1)	3918(1)	18(1)
C(3)	1221(1)	6672(1)	4038(1)	23(1)
C(4)	1040(1)	6999(1)	4975(1)	27(1)
C(5)	795(1)	6565(1)	5790(1)	25(1)
C(6)	728(1)	5807(1)	5671(1)	23(1)
C(7)	913(1)	5479(1)	4736(1)	20(1)
N(1)	1530(1)	4871(1)	2853(1)	19(1)
N(2)	1680(1)	4541(1)	1886(1)	19(1)
C(11)	2394(1)	4169(1)	1901(1)	26(1)
C(8)	1080(1)	4064(1)	1554(1)	22(1)
C(9)	322(1)	4426(1)	1440(1)	28(1)
O(2)	-19(1)	3873(1)	2086(1)	34(1)
C(10)	688(1)	3530(1)	2307(1)	26(1)

Table A2.16 *Bond lengths [Å] and angles [°] for* ***70****.*

O(1)-C(1)	1.2381(17)
C(1)-N(1)	1.3451(18)
C(1)-C(2)	1.5001(19)
C(2)-C(7)	1.3942(19)
C(2)-C(3)	1.3948(19)
C(3)-C(4)	1.391(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.391(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.387(2)
C(5)-H(5)	0.9500
C(6)-C(7)	1.391(2)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
N(1)-N(2)	1.4161(16)
N(1)-H(1N)	0.884(14)
N(2)-C(8)	1.4537(18)
N(2)-C(11)	1.4598(18)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(8)-C(9)	1.530(2)

C(8)-C(10)	1.548(2)
C(8)-H(8)	1.0000
C(9)-O(2)	1.4452(19)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
O(2)-C(10)	1.4525(19)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
O(1)-C(1)-N(1)	122.79(12)
O(1)-C(1)-C(2)	120.54(12)
N(1)-C(1)-C(2)	116.66(12)
C(7)-C(2)-C(3)	119.48(13)
C(7)-C(2)-C(1)	122.82(12)
C(3)-C(2)-C(1)	117.61(12)
C(4)-C(3)-C(2)	120.23(13)
C(4)-C(3)-H(3)	119.9
C(2)-C(3)-H(3)	119.9
C(5)-C(4)-C(3)	119.83(13)
C(5)-C(4)-H(4)	120.1
C(3)-C(4)-H(4)	120.1
C(6)-C(5)-C(4)	120.25(14)
C(6)-C(5)-H(5)	119.9
C(4)-C(5)-H(5)	119.9

C(5)-C(6)-C(7)	119.94(13)
C(5)-C(6)-H(6)	120.0
C(7)-C(6)-H(6)	120.0
C(6)-C(7)-C(2)	120.24(13)
C(6)-C(7)-H(7)	119.9
C(2)-C(7)-H(7)	119.9
C(1)-N(1)-N(2)	118.68(11)
C(1)-N(1)-H(1N)	123.8(11)
N(2)-N(1)-H(1N)	117.3(11)
N(1)-N(2)-C(8)	111.75(11)
N(1)-N(2)-C(11)	110.71(11)
C(8)-N(2)-C(11)	113.10(11)
N(2)-C(11)-H(11A)	109.5
N(2)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
N(2)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
N(2)-C(8)-C(9)	116.40(12)
N(2)-C(8)-C(10)	121.88(12)
C(9)-C(8)-C(10)	85.18(11)
N(2)-C(8)-H(8)	110.3
C(9)-C(8)-H(8)	110.3

C(10)-C(8)-H(8)	110.3
O(2)-C(9)-C(8)	91.79(11)
O(2)-C(9)-H(9A)	113.3
C(8)-C(9)-H(9A)	113.3
O(2)-C(9)-H(9B)	113.3
C(8)-C(9)-H(9B)	113.3
H(9A)-C(9)-H(9B)	110.7
C(9)-O(2)-C(10)	91.91(10)
O(2)-C(10)-C(8)	90.77(11)
O(2)-C(10)-H(10A)	113.5
C(8)-C(10)-H(10A)	113.5
O(2)-C(10)-H(10B)	113.5
C(8)-C(10)-H(10B)	113.5
H(10A)-C(10)-H(10B)	110.8

Symmetry transformations used to generate equivalent atoms:

Table A2.17 *Anisotropic displacement parameters ($Å^2$ x 10^3) for* ***70****. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2\ a^{*2}U^{11}+...+2\ h\ k\ a^*\ b^*\ U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	21(1)	19(1)	4(1)	2(1)	0(1)
C(1)	13(1)	21(1)	18(1)	1(1)	0(1)	-2(1)
C(2)	14(1)	21(1)	20(1)	0(1)	-1(1)	0(1)
C(3)	25(1)	20(1)	24(1)	1(1)	5(1)	-4(1)
C(4)	31(1)	20(1)	29(1)	-4(1)	5(1)	-4(1)
C(5)	27(1)	27(1)	21(1)	-5(1)	4(1)	-2(1)
C(6)	25(1)	25(1)	21(1)	3(1)	4(1)	0(1)
C(7)	21(1)	18(1)	21(1)	1(1)	1(1)	1(1)
N(1)	22(1)	20(1)	14(1)	1(1)	0(1)	1(1)
N(2)	19(1)	22(1)	16(1)	-3(1)	1(1)	0(1)
C(11)	23(1)	31(1)	23(1)	-3(1)	1(1)	5(1)
C(8)	24(1)	23(1)	19(1)	-1(1)	-1(1)	-1(1)
C(9)	23(1)	34(1)	27(1)	0(1)	-4(1)	-2(1)
O(2)	22(1)	56(1)	25(1)	5(1)	1(1)	-4(1)
C(10)	26(1)	28(1)	24(1)	-1(1)	1(1)	-4(1)

Table A2.18 *Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for* ***70****.*

	x	y	z	U(eq)
H(3)	1382	6969	3477	28
H(4)	1082	7518	5057	32
H(5)	674	6788	6431	30
H(6)	555	5513	6227	28
H(7)	865	4961	4654	24
H(1N)	1591(9)	4596(9)	3409(12)	23
H(11A)	2781	4526	2076	39
H(11B)	2495	3958	1219	39
H(11C)	2387	3775	2417	39
H(8)	1218	3800	904	26
H(9A)	299	4929	1736	33
H(9B)	136	4424	722	33
H(10A)	715	3007	2093	31
H(10B)	847	3589	3033	31

Table A2.19 *Torsion angles [°] for* ***70****.*

O(1)-C(1)-C(2)-C(7)	155.11(13)
N(1)-C(1)-C(2)-C(7)	-23.97(18)
O(1)-C(1)-C(2)-C(3)	-21.46(19)
N(1)-C(1)-C(2)-C(3)	159.47(12)
C(7)-C(2)-C(3)-C(4)	1.8(2)
C(1)-C(2)-C(3)-C(4)	178.47(13)
C(2)-C(3)-C(4)-C(5)	-0.9(2)
C(3)-C(4)-C(5)-C(6)	-0.4(2)
C(4)-C(5)-C(6)-C(7)	0.7(2)
C(5)-C(6)-C(7)-C(2)	0.2(2)
C(3)-C(2)-C(7)-C(6)	-1.4(2)
C(1)-C(2)-C(7)-C(6)	-177.95(12)
O(1)-C(1)-N(1)-N(2)	-1.58(19)
C(2)-C(1)-N(1)-N(2)	177.47(11)
C(1)-N(1)-N(2)-C(8)	-106.43(13)
C(1)-N(1)-N(2)-C(11)	126.53(13)
N(1)-N(2)-C(8)-C(9)	58.61(16)
C(11)-N(2)-C(8)-C(9)	-175.65(12)
N(1)-N(2)-C(8)-C(10)	-42.83(17)
C(11)-N(2)-C(8)-C(10)	82.91(16)
N(2)-C(8)-C(9)-O(2)	-127.65(13)
C(10)-C(8)-C(9)-O(2)	-4.30(11)

C(8)-C(9)-O(2)-C(10)	4.57(11)
C(9)-O(2)-C(10)-C(8)	-4.51(11)
N(2)-C(8)-C(10)-O(2)	122.50(13)
C(9)-C(8)-C(10)-O(2)	4.27(11)

Symmetry transformations used to generate equivalent atoms:

Table A2.20 *Hydrogen bonds for* ***70*** *[Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.884(14)	2.075(14)	2.9435(15)	167.0(16)
C(8)-H(8)...O(2)#2	1.00	2.42	3.2099(18)	135.0
C(10)-H(10A)...O(2)#2	0.99	2.63	3.3047(19)	125.2
C(10)-H(10B)...O(1)#1	0.99	2.41	3.3735(18)	165.6

Symmetry transformations used to generate equivalent atoms:

#1 -y+3/4,x+1/4,z+1/4 #2 y-1/4,-x+1/4,-z+1/4

CHAPTER 2

Formation of All-Carbon Quaternary Centers via Enantioselective Pd-Catalyzed α-Vinylation of γ-Lactams †

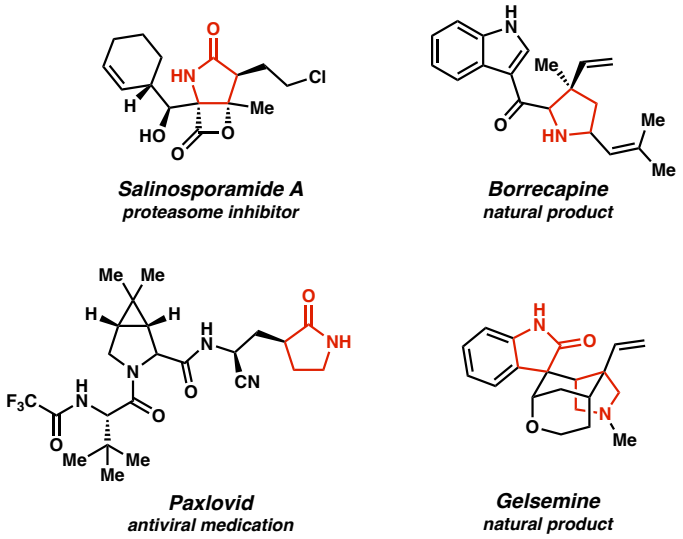
2.1 INTRODUCTION

γ-lactams are heterocyclic motifs that are overrepresented in pharmaceuticals and natural products alike (Figure 2.1).[1,2] The direct vinylation of these materials remains an unsolved problem in organic synthesis, limiting the ability of these structures to be elaborated to more complex scaffolds with potential biological applications. Our group has previously disclosed a novel, Pd-catalyzed strategy toward the α-arylation of PMP-protected γ-lactams containing pre-existing substitution at the α-position.[3] As such, we successfully achieved the first asymmetric α-arylation of γ-lactams forming enantioenriched all-carbon quaternary centers. We imagined that this success could be

† This work was performed in collaboration with Farbod A. Moghadam, Dr. Melinda Chan, Dr. Carina Jette, Dr. Shunya Sakurai, and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Moghadam, F. A.; Barbor, J. P.; Chan, M.; Jette, C. I.; Sakurai, S.; Stoltz, B. M. Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams. *Org. Lett.* **2024**, *26*, 7551–7554. © 2024 American Chemical Society.

translated to the more unprecedented vinylation of these nucleophiles, so we commenced with an optimization campaign aimed to effect a Pd-catalyzed vinylation.

Figure 2.1 *Selected examples of γ-lactams of pharmaceutical relevance and natural products.*

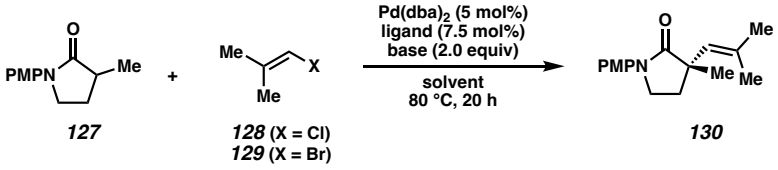


2.2 REACTION OPTIMIZATION

Utilizing the same catalytic conditions disclosed in our prior report, initial optimization efforts illustrated the superiority of vinyl chloride electrophiles and lithium bases (Table 2.1). We observed a severe counterion effect, as use of NaHMDS or KHMDS afforded no desired product, whereas LiHMDS afforded a 46% yield of the desired **130** with an excellent 90% ee. Exploration of similar lithium bases, like LiTMP, garnered diminished results. Similarly, vinyl chlorides were found to be essential for both yield and enantioselectivity, as use of the corresponding vinyl bromide **129** delivered **130** in a diminished 27% yield and 77% ee. Use of the more sterically encumbered ligand **132** did not improve the reaction further. Although initially excited to find that use of CPME resulted in a slight improvement of the ee to 92%, we found that dioxane was ultimately

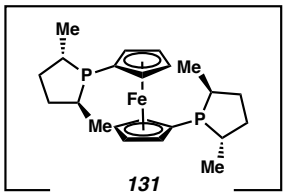
the optimal solvent for this transformation, and dilution of the reaction to 0.05 M allowed for an improved 58% yield and 93% ee.

Table 2.1 *Reaction optimization.*

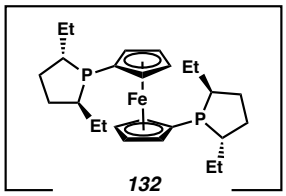


127 ***128*** **(X = Cl)** ***129*** **(X = Br)** ***130***

Entry	Ligand	X	Base	Solvent	Yield (%)	ee (%)
1	131	Cl	NaHMDS	dioxane	0	–
2	131	Cl	KHMDS	dioxane	0	–
3	131	Cl	LiHMDS	dioxane	46	90
4	131	Cl	LiTMP	dioxane	29	ND
5	131	Br	LiHMDS	dioxane	27	77
6	132	Cl	LiHMDS	dioxane	43	88
7[b]	131	Cl	LiHMDS	THF	19	ND
8[b]	131	Cl	LiHMDS	CPME	43	92
9[c]	131	Cl	LiHMDS	CPME	38	ND
10[c]	131	Cl	LiHMDS	dioxane	58	93



131
(*S*,*S*)-Me-Ferrocelane



132
(*S*,*S*)-Et-Ferrocelane

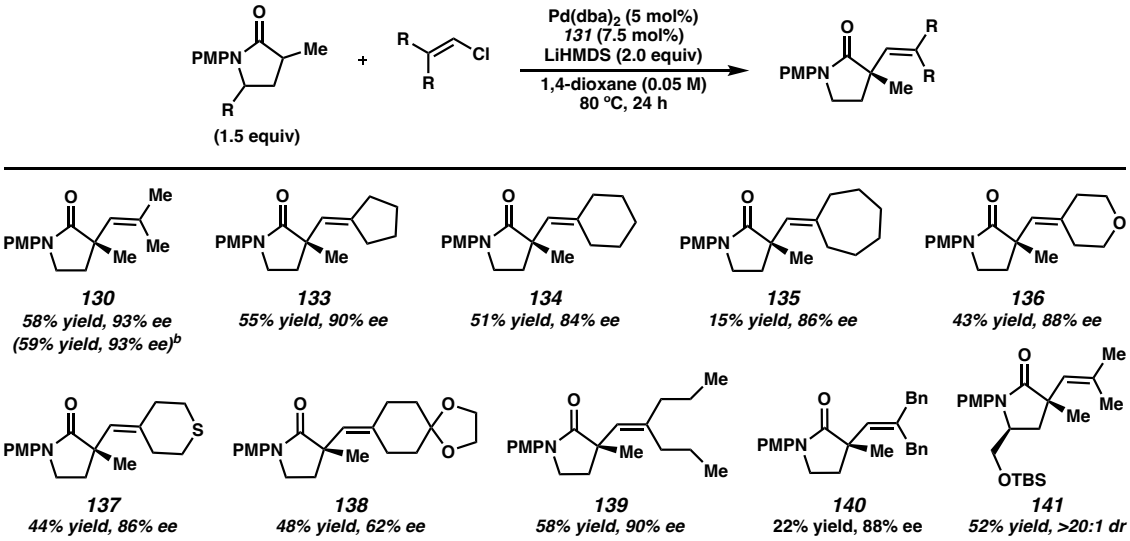
[a] Reactions performed at 0.1 mmol scale and 0.1 M. Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. [b] Reaction performed at 70 ºC for 48h. [c] Reaction performed at 0.05 M concentration.

2.3 SUBSTRATE SCOPE

With optimized conditions in hand, we sought to investigate the range of compatible substitution patterns on the vinyl halide coupling partner (Table 2.2). Vinyl electrophiles featuring a cyclopentyl, cyclohexyl and cycloheptyl substitution at the 2,2-position afforded products with high enantioselectivity, although **135** was generated in diminished yield likely due to increased steric hindrance. Additionally, saturated heterocyclic moieties, such as a pyran and thiopyran, were well tolerated. Although acyclic

substrate **139** could also be obtained in comparable yield and ee, **140** was isolated in diminished yield. Substitution at the α-position was limited to methyl, but we were pleased to find that pre-existing substitution at the γ-position of the lactam resulted in a predictable matched/mismatched situation. Enhancement of diastereoselectivity and higher reaction efficiency was observed for product **141**, whereas lower yield and diastereoselectivity was observed for its epimer **154**.[4] We were also able to implement our method at a 3 mmol scale, thereby obtaining over 450 mg of **130** in similar yield and ee.

Table 2.2 *Substrate scope.*[a]



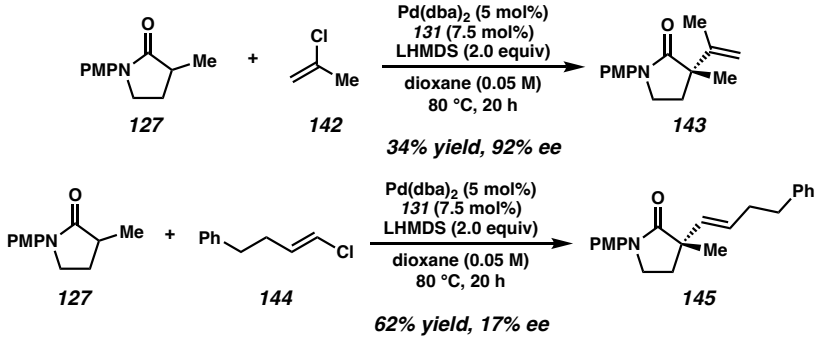
[a] Reactions performed at 0.1 mmol scale. [b] Reaction performed on 3.0 mmol scale. [c] Yields determined by ^{1}H NMR with CH_2Br_2 internal standard.

2.4 PRELIMINARY MECHANISTIC INSIGHTS

While exploring the scope of this transformation, we found that use of 1,1-disubstituted or *trans*-1,2-disubstituted electrophiles resulted in either a diminished yield or enantioselectivity, respectively (Scheme 2.1). Hypothesizing that reductive elimination is both inner-sphere and enantiodetermining,[5,6] we posit that the diminished yield of the

1,1-disubstituted electrophiles originates from steric congestion at the metal center, which may deter transmetalation of the lithium enolate to palladium. Conversely, we propose that the greatly minimized interactions between the ligand and *trans*-1,2-disubstituted electrophiles result in high conversion but with poor enantiocontrol.

Scheme 2.1 *Reaction with 1,1- and 1,2-disubstituted electrophiles.*



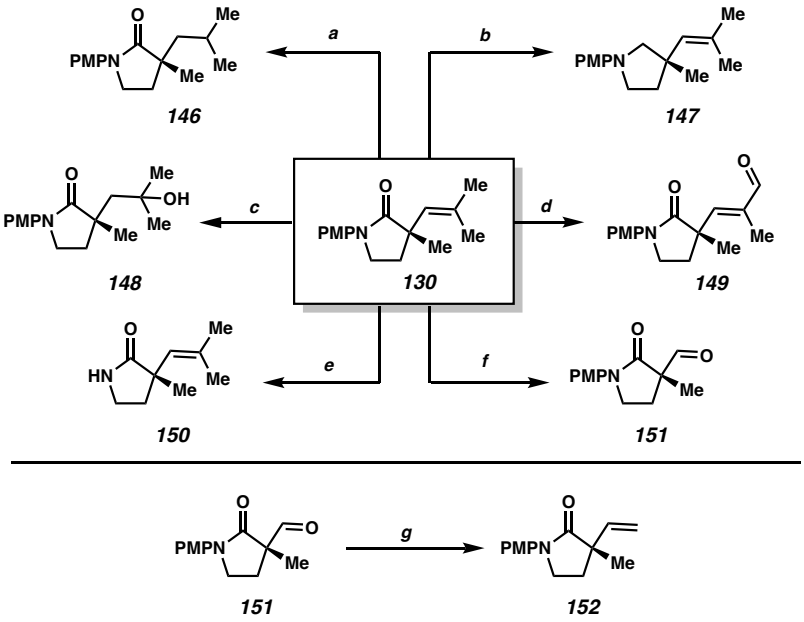
2.5 PRODUCT DERIVATIZATIONS

These enantioenriched heterocycles, adorned with highly substituted quaternary centers, exhibit significant potential for pharmaceutical and total synthetic applications.[7] As a result, we embarked on a series of derivatizations of product **130** to generate differentially substituted pyrrolidinone derivatives (Scheme 2.2). Our initial strategy involved the hydrogenation of product **130** to yield α-quaternary lactam **146**. Given the inherent challenges associated with enantioselective α-alkylation of lactams using conventional methods, we postulate that this alternative approach offers great synthetic value.

Reduction of the lactam with lithium aluminum hydride yielded β-quaternary pyrrolidine **147**. This derivative contains a heterocycle of significant pharmaceutical importance,[8] as pyrrolidines are ubiquitous in various existing drug molecules and natural

products.[9] Hydration of the vinyl group with *p*-TsOH produces tertiary alcohol **148**.[10] Allylic oxidation with SeO_2 results in the formation of aldehyde **149**. Additionally, the deprotection of the PMP group with ceric ammonium nitrate (CAN) reveals unprotected lactam **150**. Finally, **130** can undergo oxidative cleavage to yield the corresponding aldehyde **151** through ozonolysis. From **151**, a Wittig reaction can be conducted to generate vinylated lactam **152** with no substitution at the terminal position.[11]

Scheme 2.2 *Product derivatizations.*



[a] H_2, Pd/C (10 mol%), MeOH, 12h, 74 % yield. [b] LAH (5 equiv), Et_2O, 0–18 °C, 21 h, 84 % yield. [c] PTSA, AcOH, 70 °C, 12h, 59 % yield. [d] SeO_2, 1,4-dioxane, reflux, 15 min, 49% yield. [e] CAN, H_2O, 60 ºC, 32h, 40% yield. [f] O_3, PPh_3 CH_2Cl_2, 15min, 89% yield. [g] KO*t*-Bu, methyltriphenylphosphonium bromide, THF, 0 ºC to reflux, 12h, 84% yield.

2.6 CONCLUSIONS

In conclusion, our study showcases an enantioselective vinylation method for γ-lactams yielding α-quaternary centers in up to 58% yield and 94% ee. Notably, the reaction exhibits distinct preferences among different classes of electrophiles. Particularly, we observed that trisubstituted vinyl chlorides outperformed other vinyl halides under these

conditions in terms of both yield and ee. Moreover, these highly substituted γ-lactams hold significant synthetic potential, offering diverse functional handles for the synthesis of complex drug molecules or natural products.

2.7 EXPERIMENTAL SECTION

2.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[12] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz, Bruker 400 MHz, or Varian Mercury 300 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited

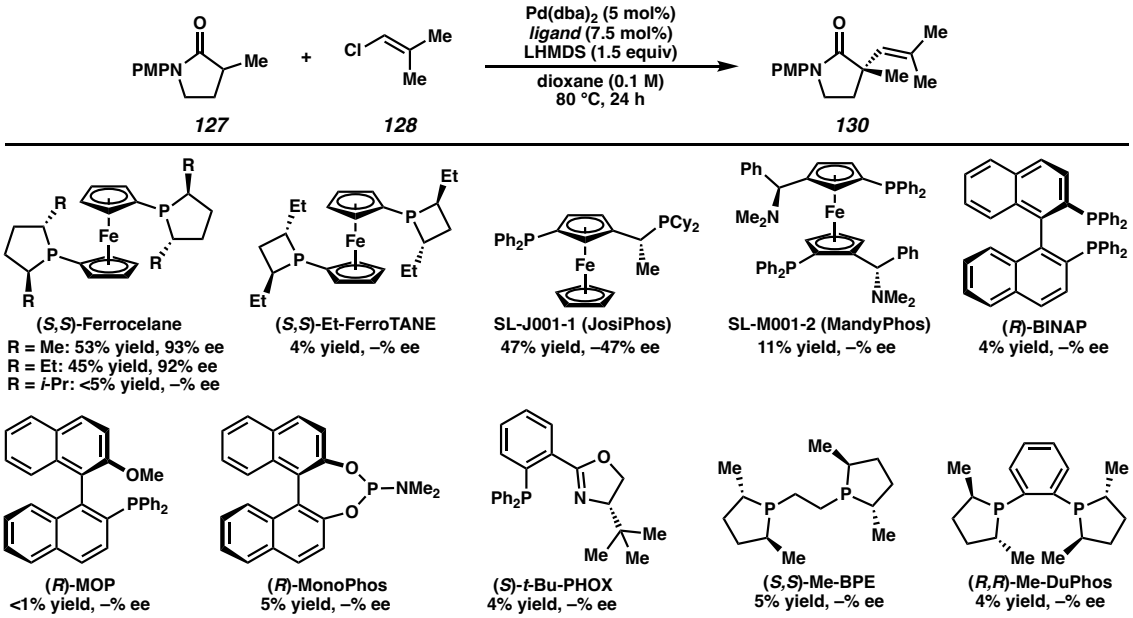
on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESIAPCI+), or obtained from Caltech mass spectrometry laboratory. Reagents were purchased from commercial sources and used as received unless otherwise stated.

2.7.1.1 Preparation of Known Compounds

Compound **127** was prepared according to a literature procedure,[3] and **128** and **129** were purchased from Sigma Aldrich.

2.7.2 ADDITONAL OPTIMIZATION DATA

Table 2.3 *Ligand evaluation.*[a]

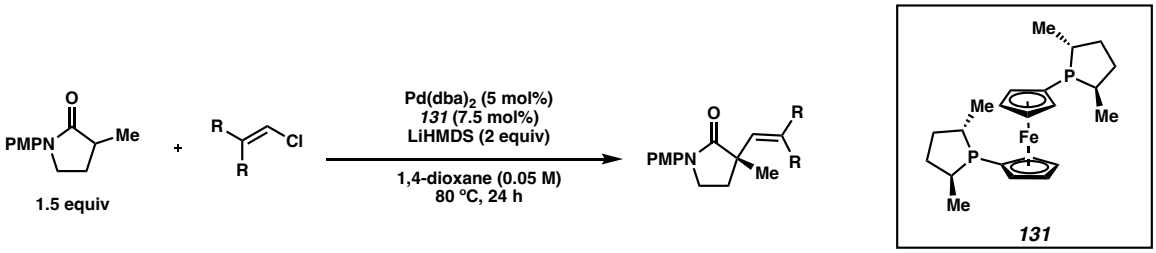


[a] Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excess (ee) was determined by chiral SFC analysis of the isolated product.

2.7.3 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

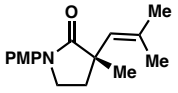
2.7.3.1 Pd-Catalyzed Vinylation Reactions

Preparation of α-Vinyl Lactams: General Procedure A



In a nitrogen-filled glovebox, a catalyst solution of $Pd(dba)_2$ (9.6 mg/mL) and **131** (10.4 mg/mL) in 1,4-dioxane was stirred for 20 min at 40 °C. In a vial, the lactam was dissolved in 1,4-dioxane (1.5 equiv, 0.09 M), and subsequently LHMDS (2.0 equiv) was

added. A 2-dram vial was charged with neat vinyl chloride (0.1 mmol, 1.0 equiv) and a magnetic stir bar. After the catalyst pre-stir was complete, 0.4 mL of the catalyst solution was added to the vinyl chloride, followed by 1.6 mL of the nucleophile/base mixture. The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 80 °C in a metal heating block for 24 h unless noted otherwise. After 24 h, 3 mL 0.5 M HCl or sat. NH_4Cl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography to provide the desired vinylation product.



130

***(S)*-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (130)**

Prepared according to general procedure A using vinyl chloride **128** (0.1 mmol) and lactam **127**. Purification by silica gel chromatography (0-30% EtOAc/Hexanes) provided 15 mg (58%, 94% ee) of a yellow oil. The reaction was also performed using 3 mmol vinyl chloride to obtain 456 mg (59%, 94% ee) of a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.46 (t, *J* = 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.63 (m, 2H), 2.32 – 2.12 (m, 2H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.36 (s, 3H).

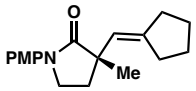
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.8, 156.5, 134.6, 133.3, 128.5, 121.6, 114.1, 55.6, 46.3, 45.7, 34.3, 27.1, 24.4, 19.2.

IR (Neat Film, NaCl): 2965, 1694, 1513, 1400, 1297, 1250, 1170, 1089, 1063, 1033, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1649.

Optical rotation: $[\alpha]_D^{25}$ –79.9 (*c* 1.0, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, t_R (min): minor = 3.37, major = 5.18.



133

(*S*)-3-(cyclopentylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (133)

Prepared according to general procedure A using **155**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **133** as a white solid (15.6 mg, 55% yield, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.53 (p, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.75 – 3.51 (m, 2H), 2.26 (m, 5H), 2.15 – 1.87 (m, 1H), 1.88 – 1.60 (m, 2H), 1.60 – 1.42 (m, 2H), 1.35 (s, 3H).

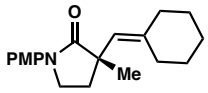
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.5, 145.1, 133.3, 123.7, 121.5, 114.1, 55.6, 47.1, 45.8, 35.5, 34.0, 28.9, 27.3, 25.8, 23.9.

IR (neat film, NaCl): 3835, 3732, 2951, 2866, 2360, 1693, 1511, 1455, 1395, 1298, 1248, 1181, 1084, 1035, 833, 662 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found 286.1815.

Optical rotation: $[\alpha]_D^{25}$ –56.8 (c 0.75, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 4.69, major = 7.78.



134

(*S*)-3-(cyclohexylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (134)

Prepared according to general procedure A using **156**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **134** as a white solid (15.3 mg, 51% yield, 84% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 5.36 – 5.31 (m, 1H), 3.69 (s, 3H), 3.67 – 3.34 (m, 2H), 2.12 (m, 2H), 2.08 – 1.94 (m, 4H), 1.55 – 1.32 (m, 6H), 1.25 (s, 3H).

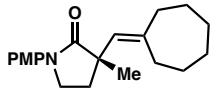
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.4, 142.7, 133.2, 125.4, 121.5, 114.0, 55.5, 45.9, 45.6, 37.7, 34.6, 30.2, 28.7, 27.6, 26.5, 24.7.

IR (neat film, NaCl): 3835, 3745, 2925, 2851, 2359, 1693, 1513, 1443, 1396, 1298, 1248, 1179, 1088, 1035, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{19}H_{26}NO_2$ $[M+H]^+$: 300.1958, found 300.1972.

Optical rotation: $[\alpha]_D^{25}$ –64.5 (c 1.0, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.21, major = 9.35.



135

(*S*)-3-(cycloheptylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (135)

Prepared according to general procedure A using **157**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **135** as a white solid (4.7 mg, 15% yield, 86% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.52 (p, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.32 (m, 2H), 2.86 – 1.98 (m, 6H), 1.84 – 1.40 (m, 8H), 1.36 (s, 3H).

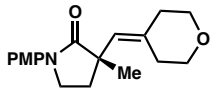
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.5, 144.2, 133.3, 128.8, 121.6, 121.6, 114.2, 55.6, 46.3, 45.8, 38.5, 34.1, 31.0, 29.9, 29.7, 29.3, 27.0, 24.4.

IR (neat film, NaCl): 3834, 3732, 2923, 2849, 2341, 1693, 1511, 1395, 1298, 1247, 1087, 1035, 827 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2115, found 314.2029.

Optical rotation: $[\alpha]_D^{25}$ – 39.4 (c 0.5, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.32, major = 9.13.



136

(*S*)-3-(tetrahydropyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (136)

Prepared according to general procedure A using **158**. Purification by column chromatography (0–30% EtOAc/Hexanes) yielded **136** as a colorless oil (13.2 mg, 43%, 88% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.57 (m, 6H), 2.34 (tt, *J* = 5.8, 1.2 Hz, 2H), 2.29 – 2.17 (m, 4H), 1.37 (s, 3H).

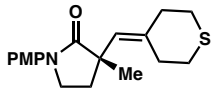
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.6, 137.5, 133.1, 127.5, 121.6, 114.2, 69.8, 68.4, 55.6, 46.0, 45.7, 37.5, 34.9, 31.3, 24.8.

IR (neat film, NaCl): 2958, 2839, 1691, 1511, 1462, 1396, 1286, 1269, 1246, 1087, 1032, 831 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1750.

Optical rotation: $[\alpha]_D^{25}$ – 41.4 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 8.03, major = 11.15.



137

(*S*)-3-(tetrahydro-thiopyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (137)

Prepared according to general procedure A using **159**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **137** as a colorless oil (13.5 mg, 44%, 86% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 9.1 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 5.55 (t, *J* = 1.0 Hz, 1H), 3.80 (s, 2H), 3.78 – 3.68 (m, 1H), 2.76 – 2.48 (m, 4H), 2.44 (td, *J* = 5.4, 2.5 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.36 (s, 2H).

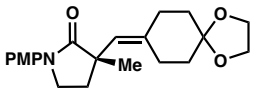
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.6, 139.6, 133.05, 129.0, 121.6, 114.2, 55.6, 45.9, 45.7, 39.4, 34.8, 32.2, 31.2, 29.9, 24.8.

IR (neat film, NaCl): 2953, 1689, 1511, 1428, 1398, 1297, 1247, 1180, 1087, 1034, 821 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1522, found 318.1520.

Optical rotation: $[\alpha]_D^{25}$ –58.3 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OJ-3 column, λ = 254 nm, tR (min): minor = 7.45, major = 6.32.



138

(*S*)-3-((1,4-dioxaspiro[4.5]decan-8-ylidene)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (138)

Prepared according to general procedure A using **160**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **138** (48% yield, 74% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.7 Hz, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 – 3.60 (m, 2H), 2.40 – 2.29 (m, 2H), 2.31 – 2.16 (m, 4H), 1.71 (td, *J* = 6.7, 3.9 Hz, 3H), 1.68 – 1.62 (m, 1H), 1.60 (s, 1H), 1.37 (s, 3H).

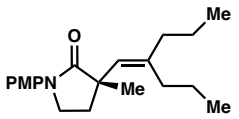
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.7, 156.6, 140.0, 133.2, 127.2, 121.6, 114.2, 114.1, 108.7, 77.5, 77.4, 77.2, 76.8, 64.5, 64.5, 55.6, 46.1, 45.7, 36.4, 35.3, 34.7, 34.5, 26.7, 24.7.

IR (thin film, NaCl): 3465, 2950, 2886, 2320, 2009, 1902, 1693, 1681, 1513, 1433, 1401, 1298, 1276, 1248, 1226, 1181, 1171, 1120, 1082, 1032, 944, 906, 826, 738, 728 cm^{-1}.

HRMS (ESI): m/z calc'd $C_{21}H_{27}NO_4Na$ $[M+Na]^+$: 380.1832, found: 380.1843.

Optical rotation: $[a]_D^{25}$ + 4.5 ° (*c* 0.52, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.53, major = 5.02.



139

(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-propylpent-1-en-1-yl)pyrrolidin-2-one (139)

Prepared according to general procedure A using **161**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **139** (58% yield, 92% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.50 (t, *J* = 1.0 Hz, 1H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.78 – 3.67 (m, 2H), 2.34 – 2.25 (m, 1H), 2.25 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.94 (m, 3H), 1.48 – 1.38 (m, 4H), 1.36 (s, 3H), 0.93 – 0.84 (m, 6H).

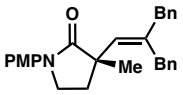
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.4, 142.4, 133.2, 128.5, 121.4, 114.0, 77.4, 77.2, 77.0, 76.7, 55.5, 46.2, 45.6, 38.8, 34.5, 33.0, 24.7, 21.3, 21.1, 14.6, 13.8.

IR (thin film, NaCl): 2958, 2930, 2870, 1694, 1513, 1469, 1454, 1423, 1398, 1299, 1288, 1248, 1181, 1168, 1122, 1087, 1036, 836, 823, 805, 634 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{20}H_{29}NO_2Na$ $[M+Na]^+$: 338.2091, found: 338.2100.

Optical rotation: $[a]_D^{25}$ – 2.5 ° (*c* 0.35, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 2.88, major = 3.73.



140

(S)-3-(2-benzyl-3-phenylprop-1-en-1-yl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (140)

Prepared according to general procedure A using **162**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **140** (22% yield, 88% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 9.1 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.17 – 7.10 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.02 (t, *J* = 1.0 Hz, 1H), 3.86 (s, 3H), 3.84 – 3.74 (m, 2H), 3.54 – 3.38 (m, 2H), 3.27 (t, *J* = 1.6 Hz, 2H), 2.43 (dt, *J* = 12.5, 8.2 Hz, 1H), 2.30 (ddd, *J* = 12.5, 7.2, 3.6 Hz, 1H), 1.52 (s, 3H).

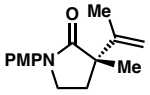
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.5, 139.8, 139.5, 139.0, 132.9, 132.8, 129.0, 128.9, 128.5, 128.3, 128.2, 126.1, 121.6, 114.1, 77.4, 77.2, 77.0, 76.7, 55.5, 46.4, 45.7, 43.3, 35.9, 34.1, 24.8.

IR (thin film, NaCl): 3059, 3025, 2930, 2835,m 2340, 1682, 1600, 1520, 1493, 1453, 1398, 1298, 1240, 1181, 1120, 1088, 1031, 829, 734, 702 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{28}H_{29}NO_2Na$ $[M+Na]^+$: 434.2091, found: 434.2102.

Optical rotation: $[a]_D^{25}$ – 12.4 ° (*c* 0.56, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.63, major = 7.11.



143

(S)-1-(4-methoxyphenyl)-3-methyl-3-(prop-1-en-2-yl)pyrrolidin-2-one (143)

Prepared according to general procedure A using **142**. The crude product was purified by silica gel chromatography (0–30% EtOAc/Hexanes) to afford vinylated lactam **143** (8.3 mg, 34% yield, 92% ee) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.93 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.76 – 3.44 (m, 2H), 2.32 (ddd, *J* = 12.7, 7.0, 4.4 Hz, 1H), 1.94 (dt, *J* = 12.7, 7.8 Hz, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.39 (s, 3H).

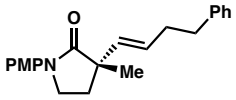
^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 156.6, 145.4, 133.1, 121.7, 114.2, 114.1, 111.9, 55.6, 51.2, 45.9, 31.9, 22.5, 19.8.

IR (thin film, NaCl): 2933, 1738, 1693, 1643, 1512, 1455, 1396, 1297, 1248, 1181, 1088, 1034, 892, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1498, found 246.1495.

Optical rotation: $[a]_D^{25}$ – 125.8 ° (*c* 1, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.77, major = 4.09.



145

(S,E)-1-(4-methoxyphenyl)-3-methyl-3-(4-phenylbut-1-en-1-yl)pyrrolidin-2-one (145)

Prepared according to general procedure A using **144**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **145** (20.6 mg, 62% yield, 19% ee) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 – 7.38 (m, 2H), 7.22 – 7.12 (m, 2H), 7.12 – 6.99 (m, 3H), 6.89 – 6.73 (m, 2H), 5.57 – 5.38 (m, 2H), 3.72 (s, 3H), 3.63 – 3.49 (m, 2H), 2.66 –

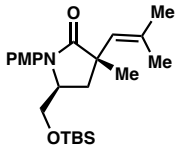
2.53 (m, 2H), 2.35 – 2.19 (m, 2H), 2.07 (ddd, J = 12.4, 6.3, 5.0 Hz, 1H), 1.89 (dt, J = 12.5, 7.7 Hz, 1H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 156.5, 141.9, 133.1, 133.1, 129.0, 128.7, 128.4, 125.9, 121.5, 114.1, 55.6, 47.8, 45.6, 35.9, 34.5, 32.7, 23.6.

IR (thin film, NaCl): 2928, 1693, 1513, 1461, 1395, 1297, 1249, 1181, 1091, 1032, 974, 830, 798, 739, 700 cm^{-1}.

HRMS (FD+): m/z calc'd $C_{22}H_{25}NO_2$ $[M]^{+\bullet}$, 335.1885, found 335.1890.

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 254 nm, tR (min): minor = 7.77, major = 9.64.



141

(3S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (141)

Prepared according to general procedure A using **128**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **141** (21 mg, 52% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 6.92 – 6.86 (m, 2H), 5.41 (h, *J* = 1.4 Hz, 1H), 4.09 (dddd, *J* = 8.6, 5.8, 4.4, 2.8 Hz, 1H), 3.80 (s, 3H), 3.62 – 3.45 (m, 2H), 2.41 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.13 (dd, *J* = 12.9, 5.7 Hz, 1H), 1.70 (dd, *J* = 3.6, 1.4 Hz, 6H), 1.47 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), -0.09 (d, *J* = 13.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.9, 157.8, 134.1, 130.7, 129.8, 126.5, 114.3, 62.6, 58.5, 55.6, 45.3, 37.5, 27.1, 27.0, 26.0, 19.1, 18.4, 1.2, -5.5, -5.5.

IR (thin film, NaCl): 2932, 2857, 1693, 1513, 1467, 1401, 1247, 1104, 1043, 826 cm^{-1}.

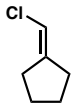
HRMS (MM:ESI-APCI+): m/z calc'd $C_{23}H_{38}NO_3Si$ $[M+H]^+$: 404.2615, found 404.2626.

Optical rotation: $[a]_D^{25}$ – 36.8 ° (*c* 1, $CHCl_3$).

2.7.3.2 Preparation of Vinyl Chloride Starting Materials

Preparation of Vinyl Chloride Substrates: General Procedure B

To a stirred suspension of (chloromethyl)triphenylphosphonium chloride (2.60 g, 7.50 mmol, 1.5 equiv) in diethyl ether (60 mL) was added sodium bis(hexamethylsilyl)amide (1.38 g, 7.50 mmol, 1.5 equiv) in diethyl ether (15 mL) at –78 °C or 0 ºC, and the resulting mixture was stirred at this temperature for 1 h. Then, ketone (5 mmol, 1.0 equiv) was added dropwise, and the reaction was allowed to slowly warm to room temperature and stirred overnight. After 18 h, the reaction was quenched with water (50 mL), transferred to a separatory funnel, and extracted with diethyl ether (20 mL) three times. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired vinyl chloride.



155

(chloromethylene)cyclopentane (155)

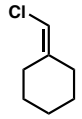
Prepared according to general procedure B using cyclopentanone. Purification by column chromatography (100% Hexanes) yielded **155** as a clear oil (209 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (p, *J* = 2.4 Hz, 1H), 2.42 – 2.23 (m, 4H), 1.80 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.9, 108.0, 32.6, 30.7, 27.4, 25.8.

IR (neat film, NaCl): 3817, 3645, 2955, 2359, 1650, 1455, 772, 653 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9Cl $[M]^{+\bullet}$: 116.0400, found 116.0393.



156

(chloromethylene)cyclohexane (156)

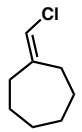
Prepared according to general procedure B using cyclohexanone. Purification by silica gel chromatography (100% Hexanes) yielded **156** as a clear oil (419 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (p, J = 1.2 Hz, 1H), 2.32 (m, 2H), 2.13 (m, 2H), 1.55 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.3, 108.5, 34.2, 28.6, 28.0, 26.8, 26.5.

IR (neat film, NaCl): 3817, 3732, 3064, 2937, 2356, 1636, 1541, 1455, 1336, 1293, 1231, 986, 786 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_7H_{11}Cl$ $[M]^{+\bullet}$: 130.0549, found 130.0558.



157

(chloromethylene)cycloheptane (157)

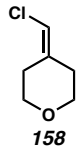
Prepared according to general procedure B using cycloheptanone. Purification by silica gel chromatography (100% Hexanes) yielded **157** as a colorless oil (557 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (p, *J* = 1.5 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.30 – 2.22 (m, 2H), 1.70 – 1.55 (m, 4H), 1.53 – 1.43 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 111.7, 35.2, 30.9, 30.2, 29.4, 29.0, 26.2.

IR (neat film, NaCl): 3380, 2921, 2859, 2360, 1674, 1506, 1069, 682 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_8H_{13}Cl$ $[M]^{+\bullet}$: 144.0712, found 144.0706.



158

4-(chloromethylene)tetrahydro-2H-pyran (158)

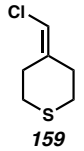
Prepared according to general procedure B using tetrahydro-4*H*-pyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **158** (136 mg, 45%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (t, *J* = 1.3 Hz, 1H), 3.69 (dt, *J* = 7.5, 5.5 Hz, 4H), 2.46 (ddd, *J* = 6.5, 5.3, 1.3 Hz, 2H), 2.27 (ddd, *J* = 6.2, 5.0, 1.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2, 110.6, 68.8, 68.0, 34.3, 29.5.

IR (thin film, NaCl): 3069, 2961, 2907, 2848, 2747, 2704, 2360, 1954, 1645, 1466, 1432, 1380, 1356, 1323, 1296, 1228, 1165, 1099, 1021, 1000, 923, 859, 822, 792, 749 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9ClO $[M]^{+\bullet}$: 132.0342, found 132.0348.



159

4-(chloromethylene)tetrahydro-2H-thiopyran (159)

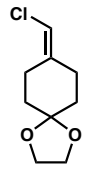
Prepared according to general procedure B using tetrahydro-4*H*-thiopyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **159** (189 mg, 81%) as a colorless, malodorous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (d, *J* = 1.1 Hz, 1H), 2.71 – 2.62 (m, 6H), 2.51 – 2.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.3, 111.7, 36.0, 30.5, 30.4, 29.4.

IR (thin film, NaCl): 3065, 2949, 2907, 2829, 2360, 1649, 1626, 1425, 1337, 1323, 1291, 1270, 1223, 1171, 991, 975, 938, 822, 797 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9ClS $[M]^{+\bullet}$: 148.0114, found 148.0123.



160

8-(chloromethylene)-1,4-dioxaspiro[4.5]decane (160)

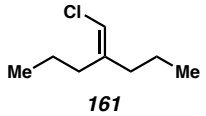
Prepared according to general procedure B using 1,4-dioxaspiro[4.5]decan-8-one. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **160** (79% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 4H), 2.53 – 2.43 (m, 2H), 2.30 (td, *J* = 6.5, 1.3 Hz, 2H), 1.76 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.6, 110.0, 108.6, 77.5, 77.2, 76.8, 64.6, 35.6, 34.5, 30.9, 25.4.

IR (thin film, NaCl): 3068, 2950, 2930, 2883, 2685, 2728, 2685, 1718, 1654, 1634, 1443, 1366, 1341, 1295, 1272, 1246, 1225, 1186, 1100, 1080, 1034, 962, 943, 908, 828, 797, 770., 748, 678 cm^{-1}.

HRMS (FI+): m/z calc'd $C_9H_{13}ClO_2$ $[M]^{+\bullet}$: 188.0604, found: 188.0619.



161

4-(chloromethylene)heptane (161)

Prepared according to general procedure B using 4-heptanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **161** (27% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 – 5.73 (m, 1H), 2.21 – 2.14 (m, 2H), 2.03 (td, *J* = 7.6, 1.3 Hz, 2H), 1.58 – 1.34 (m, 4H), 0.91 (dt, *J* = 16.5, 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.7, 112.1, 77.5, 77.2, 76.8, 37.0, 32.2, 21.0, 20.5, 14.1, 13.9.

IR (thin film, NaCl): 3066, 2980, 2933, 2872, 1911, 1630, 1465, 1456, 1379, 1319, 1169, 1109, 836, 791, 766 cm^{-1}.

HRMS (FI+): m/z calc'd $C_8H_{15}Cl$ $[M]^{+\bullet}$: 146.0862, found: 146.0872.

162

(2-(chloromethylene)propane-1,3-diyl)dibenzene (162)

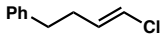
Prepared according to general procedure B using 1,3-diphenyl-2-propanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **162** (68% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.27 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.07 – 6.01 (m, 1H), 3.56 (s, 2H), 3.32 (d, *J* = 1.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 138.3, 138.0, 129.1, 128.9, 128.6, 128.5, 126.6, 126.4, 114.9, 77.4, 77.0, 76.7, 40.4, 35.6.

IR (thin film, NaCl): 3088, 3062, 3020, 2916, 2845, 2355, 1947, 1872, 1809, 1633, 1601, 1494, 1453, 1433, 1310, 1296, 1178, 1075, 1029, 960, 906, 870, 829,787, 740, 703, 634 cm^{-1}.

HRMS (FI+): m/z calc'd $C_{16}H_{15}Cl$ $[M]^{+\bullet}$: 242.0862, found: 242.0889.



144

(*E*)-(4-chlorobut-3-en-1-yl)benzene (144)

Inspired by a literature protocol, 4-phenyl-1-butyne (523 mg, 4.02 mmol) was dissolved in hexanes (1 M) in a two-neck flask. Under a N_2 atmosphere, neat DIBAL-H (0.788 mL, 1.1 equiv) was added slowly at ambient temperature. The reaction was heated to 50ºC for 2.5 h before being slowly chilled to 18 ºC, at which point Et_2O (2 M) was added. At –78ºC, solid NCS (1.08 g, 2 equiv) was quickly added through one neck of the flask. The reaction was allowed to warm to 18 ºC. After 16h, the reaction mixture was poured into a flask containing 30 mL pentane and 15 mL 6 M HCl with ice. The organic layer was extracted with Et_2O three times, after which it was washed with 10 mL 1 M NaOH then sat. $Na_2S_2O_3$ (10 mL). The organic layer was then dried with Na_2SO_4, filtered, and concentrated, at which point purification by silica gel chromatography (100% Hexanes) yielded the desired vinyl chloride **144** (205 mg, 25% yield).

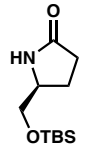
Characterization data in agreement with the literature.[13]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, J = 8.0, 6.8 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.07 – 5.79 (m, 2H), 2.71 (dd, J = 8.7, 6.7 Hz, 2H), 2.45 – 2.26 (m, 2H).

2.7.3.3 Preparation of New Lactam Starting Materials

Following a literature protocol, enantiopure 5-(hydroxymethyl)pyrrolidin-2-one was dissolved in CH_2Cl_2 (0.86 M). Iteratively, TBSCl (1.2 equiv) and imidazole (1.5 equiv) were added. The reaction was stirred for 4h, after which it was quenched with H_2O and separated into layers. The aqueous phase was extracted with CH_2Cl_2 two more times, and

the combined organic extracts were dried with Na_2SO_4. The product was isolated as a colorless oil (quant.) and used in the next step without additional purification.

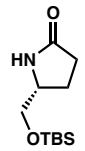


163

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one (163)

Prepared according to a literature procedure. Characterization data was in agreement with the literature.[14]

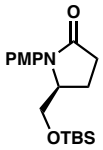
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (s, 1H), 3.92 – 3.70 (m, 1H), 3.63 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.44 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.35 (ddd, *J* = 8.6, 7.2, 2.8 Hz, 2H), 2.25 – 2.09 (m, 1H), 1.73 (dddd, *J* = 13.2, 9.3, 7.7, 5.5 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).



164

(*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one (164)

Refer to **163** for ^{1}H NMR data.



165

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (165)

In a flask equipped with a magnetic stir bar, CuI (0.5 mmol, 10 mol%) was combined with anhydrous K_2CO_3 (10 mmol, 2 equiv). The vial was purged and backfilled with N_2 three times. At this point, 5 mL of toluene was added, followed by N, N'-

dimethylethylenediamine (1 mmol, 20 mol%), intermediate **165** or **166** (6 mmol, 1.2 equiv), and p-Br anisole (5 mmol). The reaction mixture was allowed to react at 100 ºC for 24h. The crude reaction mixture was concentrated and purified by silica gel chromatography (0-100% EtOAc/Hexanes) to afford the product as a yellow oil (1.10 g, 66% yield).

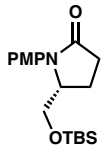
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.12 (dtd, *J* = 8.6, 3.6, 2.5 Hz, 1H), 3.80 (3, 2H), 3.68 – 3.43 (m, 2H), 2.68 (ddd, *J* = 16.9, 10.1, 8.1 Hz, 1H), 2.49 (ddd, *J* = 16.9, 10.2, 4.6 Hz, 1H), 2.26 (ddt, *J* = 12.8, 10.1, 8.3 Hz, 1H), 2.09 (dddd, *J* = 12.7, 10.1, 4.6, 3.5 Hz, 1H), 0.86 (s, 9H), -0.04 (d, *J* = 11.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 157.9, 130.5, 126.5, 114.5, 63.0, 62.0, 55.6, 31.6, 25.9, 21.5, 18.3, -5.47, -5.51.

IR (thin film, NaCl): 2934, 1694, 1513, 1248, 1090, 834, 682 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{18}H_{30}NO_3Si$ $[M+H]^+$: 336.1989, found 336.1999.

Optical rotation: $[\alpha]_D^{25}$ –48.0º (c 1.0, $CHCl_3$).

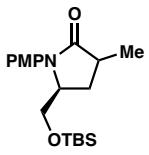


166

(*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (166)

Refer to Compound **165** for ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

Optical rotation: $[\alpha]_D^{25}$ 47.9º (c 1.0, $CHCl_3$).



167

(*5S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (167)

A solution of LDA was prepared by the slow addition of n-BuLi (1.44 mL, 2.5 M in hexanes) to a solution of diisopropylamine (3.61 mmol) in THF (0.9 M) at -78ºC. After letting the mixture stir for 1h at this temperature, substrate **165** or **166** was added slowly as a solution in THF (0.3 M). 30 min later, MeI (3.61 mmol) was added slowly to the reaction mixture, and it was allowed to warm up to 18 ºC. After 16h, the reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The crude compound was concentrated and purified by silica gel chromatography (10-60% EtOAc/Hexanes) to afford the product as a dark solid (703 mg, 61% yield).

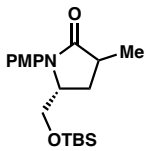
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.15 – 4.01 (m, 1H), 3.81 (s, 3H), 3.68 – 3.43 (m, 2H), 2.81 (td, *J* = 9.1, 7.1 Hz, 1H), 2.33 (ddd, *J* = 12.7, 9.0, 2.0 Hz, 1H), 1.90 (dt, *J* = 12.6, 9.1 Hz, 1H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 11.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5, 157.5, 131.0, 125.7, 114.4, 63.0, 59.9, 55.6, 36.8, 30.9, 25.9, 18.3, 17.1, -5.45, -5.48.

IR (thin film, NaCl): 2928, 1693, 1513, 1463, 1272, 1246, 1171, 1107, 1041, 832, 776, 681 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{19}H_{32}NO_3Si$ $[M+H]^+$: 350.2146, found 350.2143.

Optical rotation: $[\alpha]_D^{25}$ –30.0º (c 1.0, $CHCl_3$).



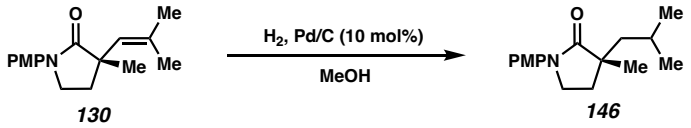
153

(*5R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (153)

Refer to Compound **167** for ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

Optical rotation: $[\alpha]_D^{25}$ 32.3º (c 1.0, $CHCl_3$).

2.7.2.4 Derivatization of Lactam Products



130 *146*

(*R*)-3-isobutyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (146)

A flamed-dried one-dram vial was charged with a stir bar and starting material **130** (15 mg, 0.058mmol, 1 equiv) in MeOH (0.421uL, 0.1M), followed by Pd/C (10%) (6.23mg, 0.058 mmol, 1 equiv). Reaction mixture was purged with N_2 for 5 minutes and then with H_2, and the mixture was stirred overnight with a H_2 balloon. Upon complete consumption of starting material as determined by TLC (30% EtOAc in Hexanes), the reaction was quenched by filtering through a pad of celite with DCM. The filtrate was concentrated in vacuo, and the crude product was purified by prep TLC (25% EtOAc/Hexanes) to afford lactam **146** (7.6 mg, 74% yield) as a pale yellow oil.

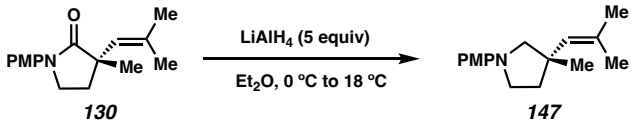
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.44 (m, 2H), 7.04 – 6.81 (m, 2H), 3.80 (s, 3H), 3.77 – 3.65 (m, 2H), 2.17 (ddd, *J* = 12.7, 8.4, 7.0 Hz, 1H), 1.92 (ddd, *J* = 12.6, 7.8, 4.7 Hz, 1H), 1.79 (dqd, *J* = 8.3, 6.6, 4.6 Hz, 1H), 1.68 – 1.58 (m, 2H), 1.49 (dd, *J* = 14.1, 8.3 Hz, 1H), 1.21 (s, 3H), 0.94 (dd, *J* = 17.5, 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.6, 156.5, 133.3, 121.6, 114.1, 55.6, 46.2, 45.7, 45.2, 31.3, 25.2, 25.0, 23.8, 23.4.

IR (thin film, NaCl): 3358, 2953, 2930, 2869, 2837, 2058, 1885, 1700, 1610, 1518, 1461, 1453, 1394, 1366, 1313, 1290, 1252, 1233, 1184, 1168, 1121, 1036, 1011, 830, 805, 743, 722.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{23}NO_2Na$ $[M+Na]^+$: 284.1621, found: 284.1628.

Optical rotation: $[\alpha]_D^{25}$ – 117.2 ° (*c* 0.20, $CHCl_3$).



130 *147*

(*S*)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidine (147)

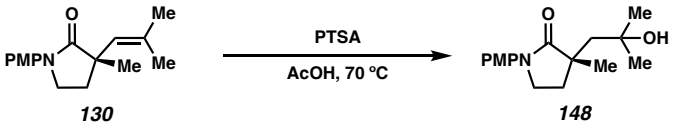
Following our previous report,[15] solid LAH was added to a solution of lactam **130** in Et_2O (0.1 M) at 0 ºC. The solution was stirred at this temperature for 5 min and then was allowed to warm to 18 ºC. After 21 h, the reaction was quenched with H_2O. Extractions were performed with EtOAc seven times, and the crude product was subjected to silica gel chromatography (0-40% EtOAc/Hexanes) to afford the desired product (**147**) as a white solid (22.5 mg, 84% yield).

^{1}H NMR (400 MHz, CDCl3): δ 6.85 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 5.34 (s, 1H), 3.76 (s, 3H), 3.35 – 3.13 (m, 4H), 2.10 – 2.00 (m, 1H), 1.92 (s, 1H), 1.73 (d, J = 1.3 Hz, 3H), 1.70 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, CDCl3): δ 132.7, 132.0, 115.2, 112.14, 61.46, 56.24, 47.11, 42.40, 39.67, 27.21, 25.77, 19.41.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{24}NO$ $[M+H]^+$: 245.1780, found 245.1784.

Optical rotation: $[a]_D^{25}$ 5.5° (*c* 1.0, $CHCl_3$).



130 ***148***

(*S*)-3-(2-hydroxy-2-methylpropyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (148)

In a one-dram vial, starting material **130** (10.9mg, 0.042 mmol, 1 equiv) was combined with PTSA (4mg, 0.021 mmol, 0.5 equiv) and acetic acid (700uL, 0.06M). The reaction mixture was heated to 70 ºC overnight, and reaction was tracked by LCMS. After completion, saturated aqueous $NaHCO_3$ was added to quench the reaction, and then extracted with DCM and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified via prep TLC (50% EtOAc/Hexanes) to afford alcohol **148** (6.3 mg, 59% yield) as a colorless oil.

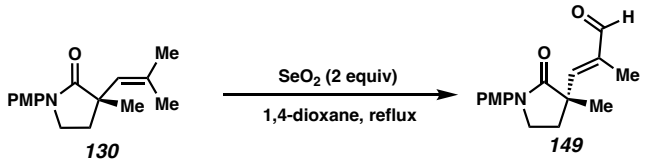
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.22 (ddd, *J* = 12.1, 8.7, 5.3 Hz, 1H), 3.12 (ddd, *J* = 12.1, 8.8, 6.7 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.78 (m, 3H), 1.47 (s, 3H), 1.39 (d, *J* = 5.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.6, 152.5, 142.3, 115.0, 114.4, 81.3, 77.5, 77.4, 77.2, 76.8, 55.9, 46.4, 44.1, 41.0, 38.7, 30.4, 30.2, 26.6.

IR (thin film, NaCl): 3369, 2968, 2930, 2834, 2339, 1754, 1681, 1513, 1455, 1401, 1377, 1265, 1249, 182, 1171, 1115, 1098, 1035, 942, 824.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1771.

Optical rotation: $[\alpha]_D^{25}$ 4.1950 ° (*c* 0.60, $CHCl_3$).



130 ***149***

(*S,E*)-3-(1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl)-2-methylacrylaldehyde (149)

To a solution of **130** (26 mg, 0.1 mmol) in dioxane (0.2 M) was added SeO_2 (22 mg, 0.2 mmol), and the reaction was heated to reflux. After 15 minutes, starting material was consumed by TLC. The crude reaction was concentrated and passed through a silica plug (ca. 1" silica), eluting with 35% EtOAc/Hexanes, to afford the desired aldehyde **149** as a tan solid (13.4 mg 49% yield).

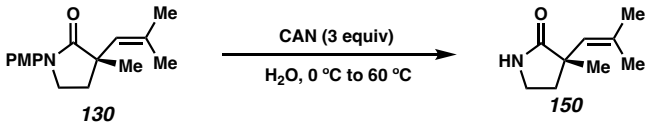
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 1.4 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 4H), 3.78 – 3.35 (m, 1H), 2.43 – 2.31 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.8, 175.4, 157.0, 156.1, 139.7, 132.5, 121.8, 114.3, 55.6, 47.5, 45.8, 32.5, 22.9, 10.1.

IR (neat film, NaCl): 3834, 3732, 2958, 2359, 1688, 1512, 1396, 1299, 1249, 1178, 1090, 1031, 833 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_{16}H_{19}NO_3$ $[M]^{+\bullet}$: 273.1365, found 273.1393.

Optical rotation: $[\alpha]_D^{25}$ –60.6º (c 1.0, $CHCl_3$).



130 *150*

(*S*)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (150)

A solution of CAN (82 mg, 0.15 mmol) in deionized H_2O (0.05 M) was added dropwise to a solution of **130** (26 mg, 0.1 mmol) at 0 °C, and the reaction was allowed to slowly warm to room temperature. After 12 hours, starting material remained by TLC. CAN (82 mg, 0.15 mmol) added, and the reaction was allowed to continue at 23 °C. After 2 h, the reaction

was heated to 60 °C and continued for 18 hours, at which point starting material was consumed by TLC. The reaction was cooled, diluted with ethyl acetate and water, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, the combined organics were dried with Na_2SO_4, filtered and concentrated. The material was purified with silica gel chromatography (5–10% MeOH/CH_2Cl_2) to afford the desired lactam **150** as a white solid (6.2 mg, 40% yield).

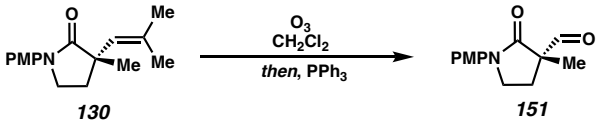
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 – 5.97 (bs, 1H), 5.38 (p, *J* = 1.4 Hz, 1H), 3.32 (ddd, *J* = 8.2, 5.5, 0.9 Hz, 2H), 2.39 – 1.87 (m, 2H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.8, 134.7, 128.1, 44.0, 39.0, 36.8, 27.0, 24.4, 19.1.

IR (neat film, NaCl): 3835, 3732, 3229, 2964, 2927, 2358, 1697, 1454, 1281, 1062, 832 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_9H_{16}NO$ $[M+H]^+$: 154.1226, found 154.1230.

Optical rotation: $[\alpha]_D^{25}$ –15.7 (c 0.5, $CHCl_3$).

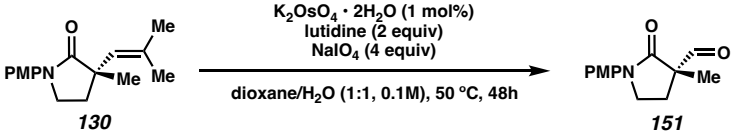


130 *151*

(*S*)-1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carbaldehyde (151)

Procedure A: A flamed-dried one-dram vial was charged with stir bar, and starting material **151** (50mg, 0.2 mmol, 1 equiv) was added with CH_2Cl_2 (482uL, 0.4M). The reaction mixture was cooled to – 78 ºC in a dry-ice bath, and ozone (1 atm) was bubbled through until all starting material was consumed as indicated by TLC. Then, O_2 gas was bubbled through to quench the residual ozone, and PPh_3 (101.2mg, 0.4 mmol, 2 equiv) was added and reaction was warmed to room temperature. The crude mixture was concentrated

in vacuo and purified by silica gel chromatography (30% EtOAc/Hexanes) to afford aldehyde **151** (40 mg, 89% yield) as a white solid.



Procedure B: A one-dram vial was charged with a stir bar and compound **130**. To this vial, 2,6-lutidine (2 equiv) and K_2OsO_4 • 2 H_2O was added as a solution in dioxane/H_2O. To the stirring mixture, NaIO4 was added and the temperature was increased to 50 ºC. After 24 h, the crude mixture was filtered through a pad of celite, eluting with CH_2Cl_2 and EtOAc. H_2O was added and CH_2Cl_2 was used to perform an extraction. The organic layer was washed with brine and dried with Na_2SO_4. The crude compound was purified via silica gel chromatography to afford compound **151**.[16]

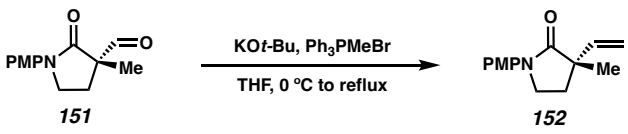
Optical rotation: $[a]_D^{25}$ – 26.8 ° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, *J* = 0.7 Hz, 1H), 7.56 – 7.43 (m, 2H), 6.96 – 6.83 (m, 2H), 3.93 – 3.67 (m, 5H), 2.75 (ddd, *J* = 12.9, 8.0, 4.8 Hz, 1H), 1.91 (dddd, *J* = 13.1, 8.6, 6.7, 0.7 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5, 171.3, 157.1, 132.2, 121.9, 114.3, 58.0, 55.6, 46.0, 25.9, 18.8.

IR (thin film, NaCl): 2932, 2358, 1731, 1682, 1520, 1455, 1402, 1297, 1248, 1170, 1092, 1032, 825 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found 234.1121.



(*S*)-1-(4-methoxyphenyl)-3-methyl-3-vinylpyrrolidin-2-one (152)

A one-dram vial was flame dried and charged with stir bar. The Ph_3PCH_2Br (51mg, 0.145mmol, 2.5 equiv) was added in THF (300uL, 0.1M) and cooled to 0 ºC. Reaction mixture was then charged with KO*t*-Bu (14mg, 0.128 mmol, 2.2 equiv) and stirred at 0 ºC for 20 minutes. Starting material **130** (13.2 mg, 0.057 mmol, 1 equiv) was added with the remaining THF (about 100 μL) and slowly warmed to room temperature and heated to reflux overnight. Second day all starting material was consumed by TLC (50% EtOAc/Hexanes) and reaction was quenched with NH_4Cl and extracted with EtOAc (3x) and washed with brine. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant crude product was the purified by pipette column chromatography (15% EtOAc/Hexanes) to afford vinylated lactam **152** (11 mg, 84% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.48 (m, 2H), 6.95 – 6.80 (m, 2H), 5.97 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.24 – 5.11 (m, 2H), 3.80 (s, 3H), 3.73 (ddt, *J* = 7.8, 5.0, 2.5 Hz, 2H), 2.26 (ddd, *J* = 12.3, 7.0, 5.0 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0, 156.6, 140.6, 133.1, 121.6, 114.2, 114.0, 55.6, 48.6, 45.6, 32.0, 23.1.

IR (Neat film, NaCl): 3360, 3077, 2962, 2927, 2060, 1693, 1512, 1504, 1455, 1394, 1315, 1299, 1246, 1182, 1170, 1124, 1111, 1090, 1034, 1005, 924, 913, 883, 825, 807, 731, 636 cm^{-1}.

HRMS (MM:ESI-APCI+): *m/z* calc'd for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151, found 254.1155.

Optical rotation: $[a]_D^{25}$ – 0.6 ° (*c* 0.35, $CHCl_3$).

2.8 REFERENCES AND NOTES

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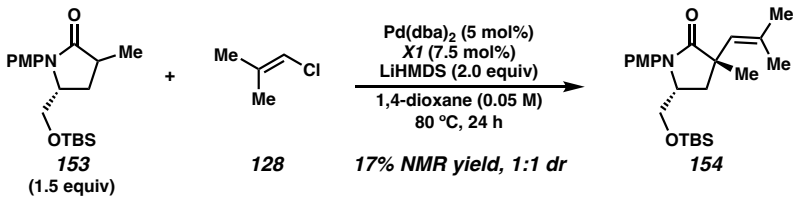
(4) In a matched/mismatched case, we observed poor efficiency of the reaction to deliver compound **154**:



(5) (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (b) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004***, 14*, 3398–3416. (c) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.

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(11) Synthesis of product **152** from vinyl chloride directly would be prohibitive, as this would require a toxic gas as the electrophile and would be unlikely to exhibit asymmetric induction in a Pd-catalyzed system.

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APPENDIX 3

Spectra Relevant to Chapter 2: Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams

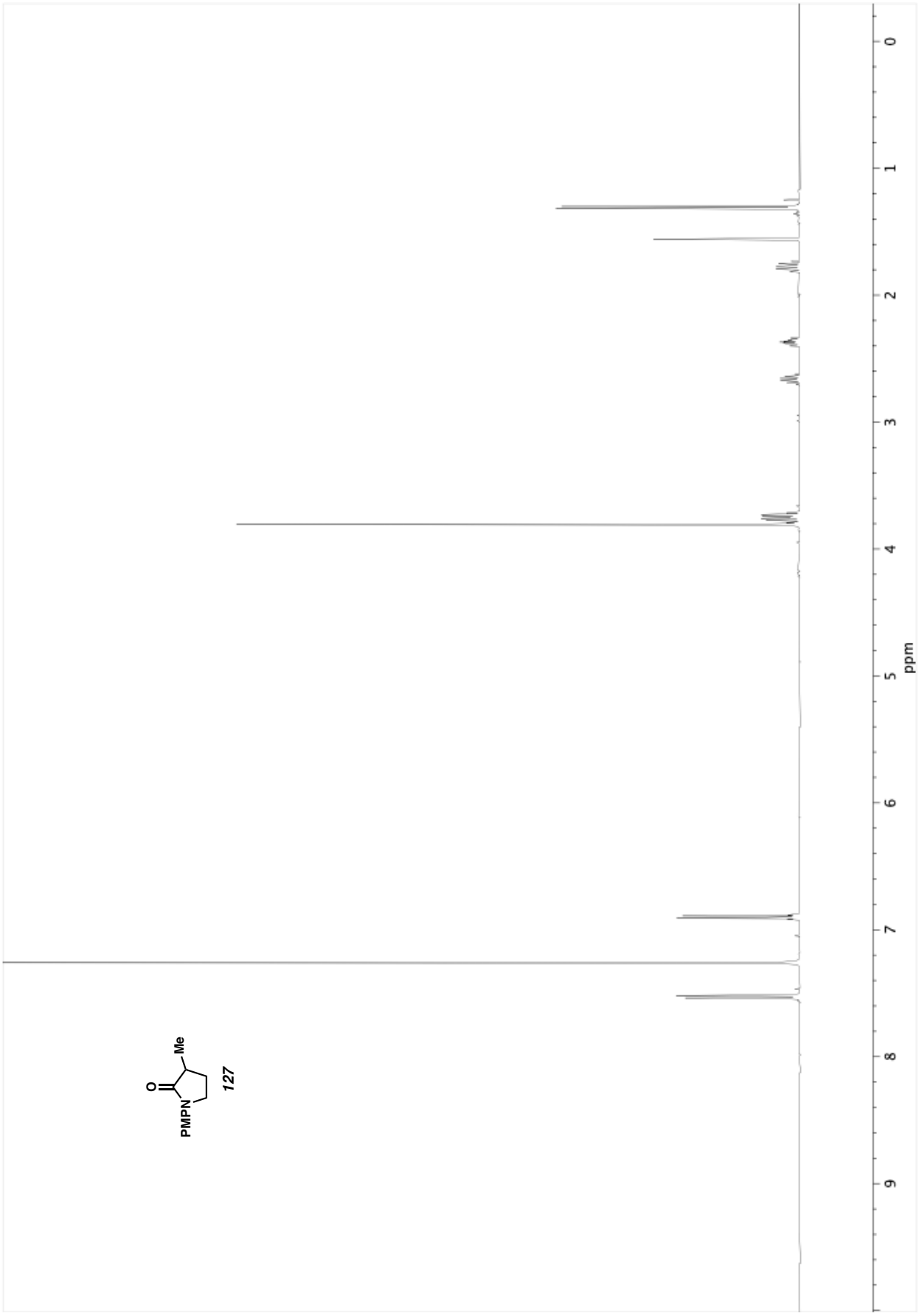


Figure A3.1 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***127.***

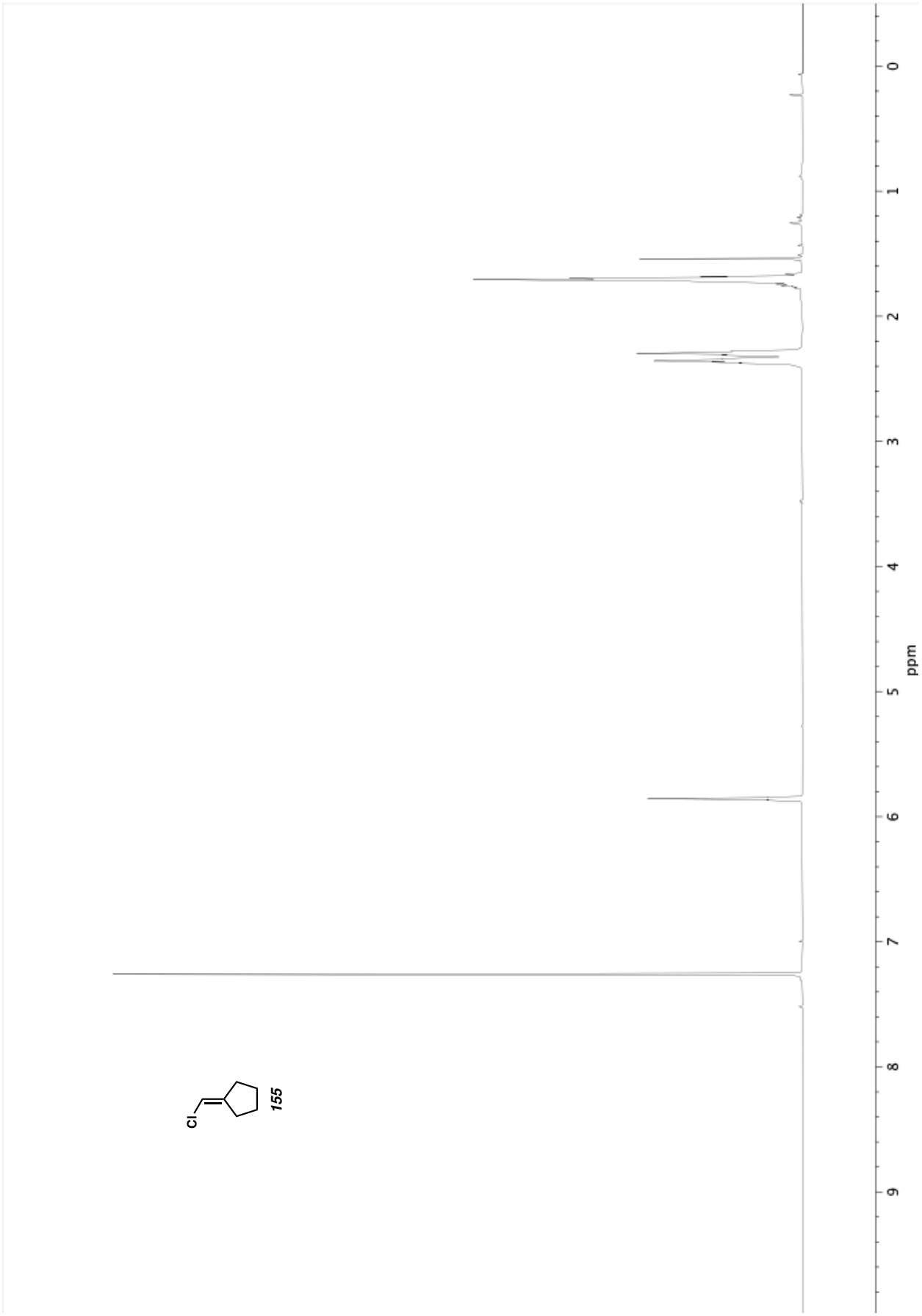


Figure A3.2 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***155****.*

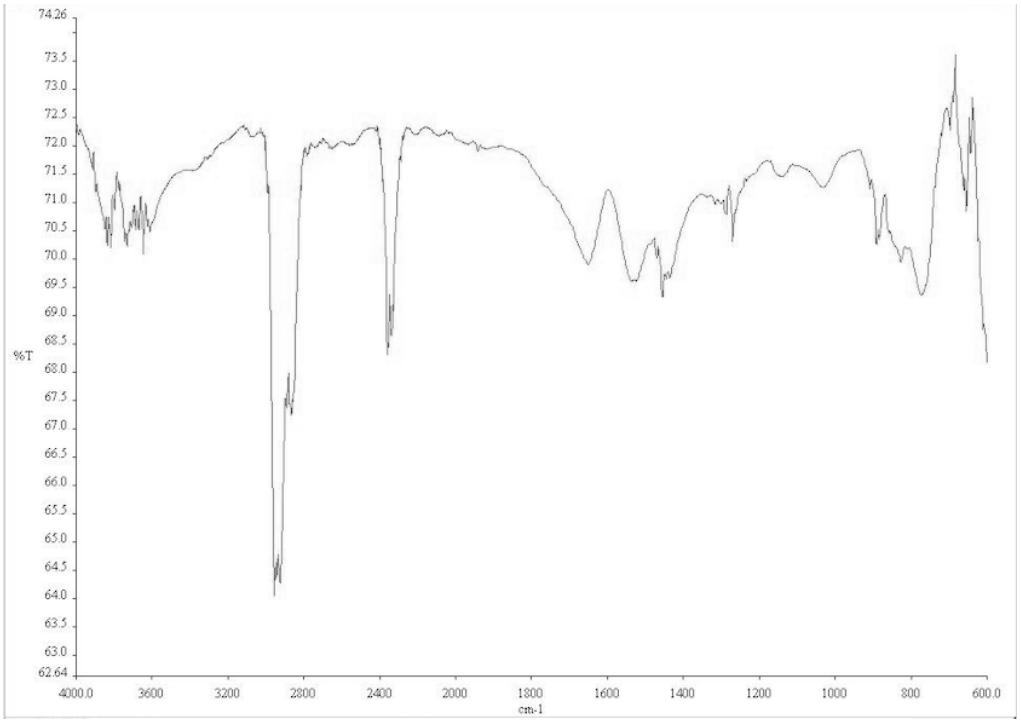


Figure A3.3 *Infrared spectrum (Thin Film, NaCl) of* ***155****.*

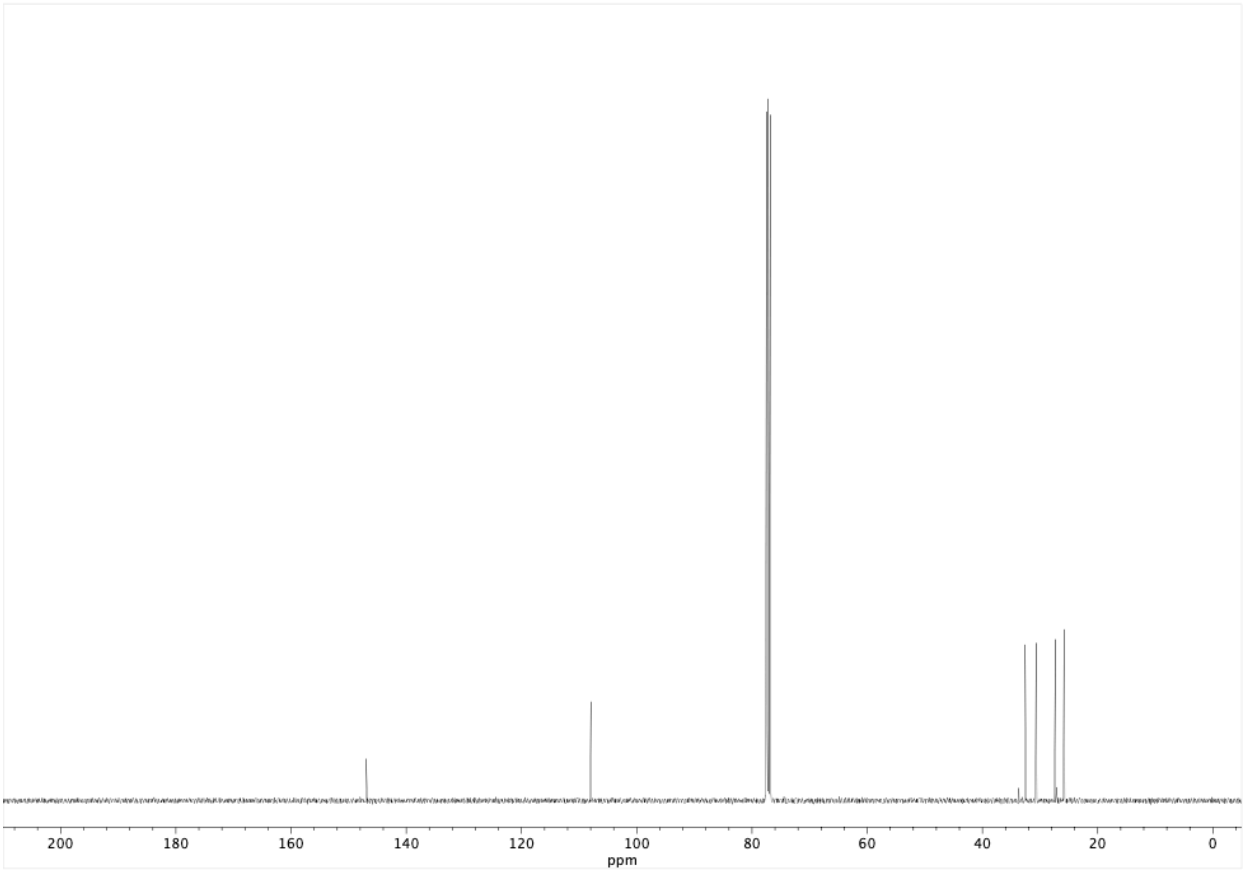


Figure A3.4 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***155.***

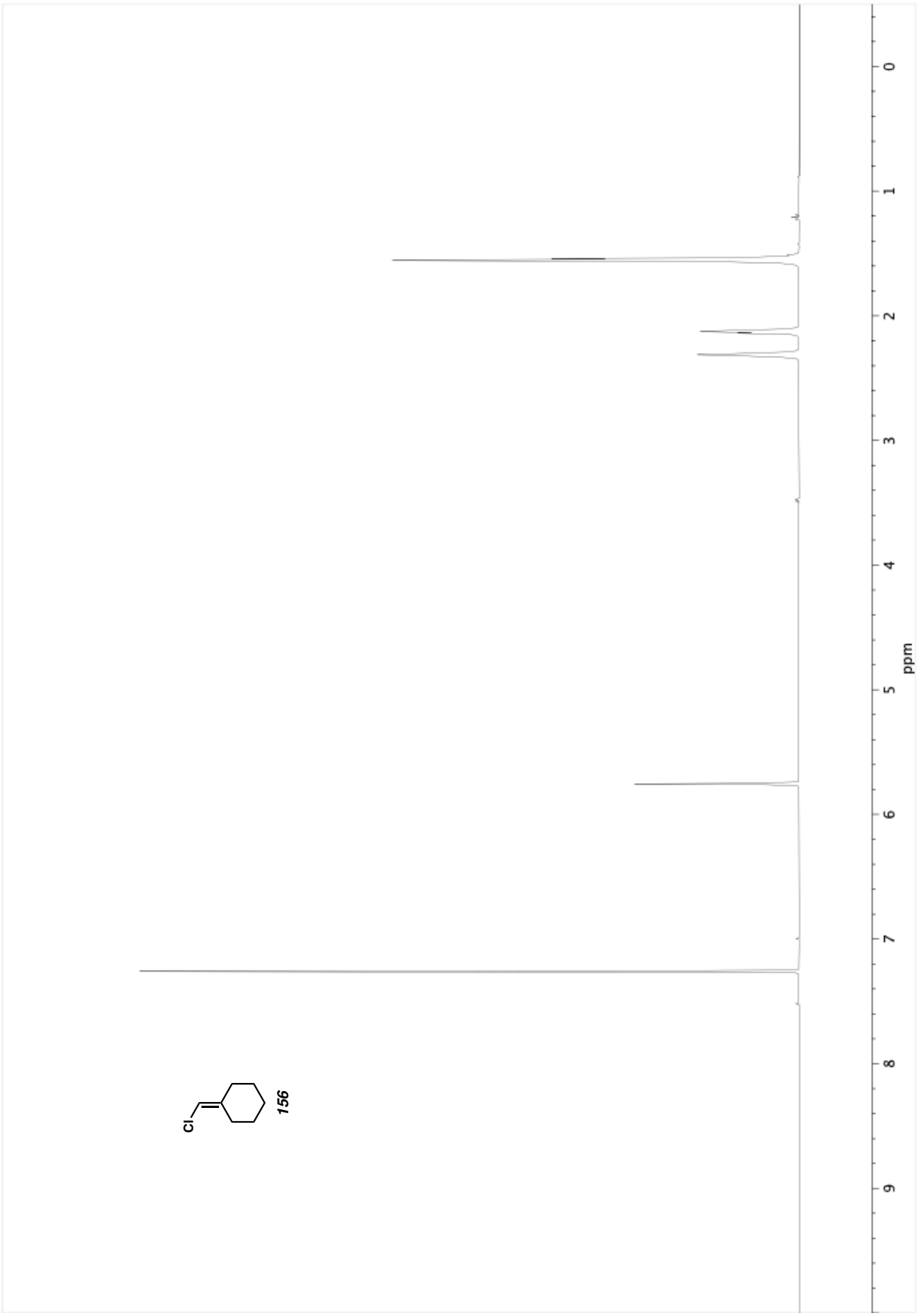


Figure A3.5 *^1H NMR (400 MHz, $CDCl_3$) of* ***156****.*

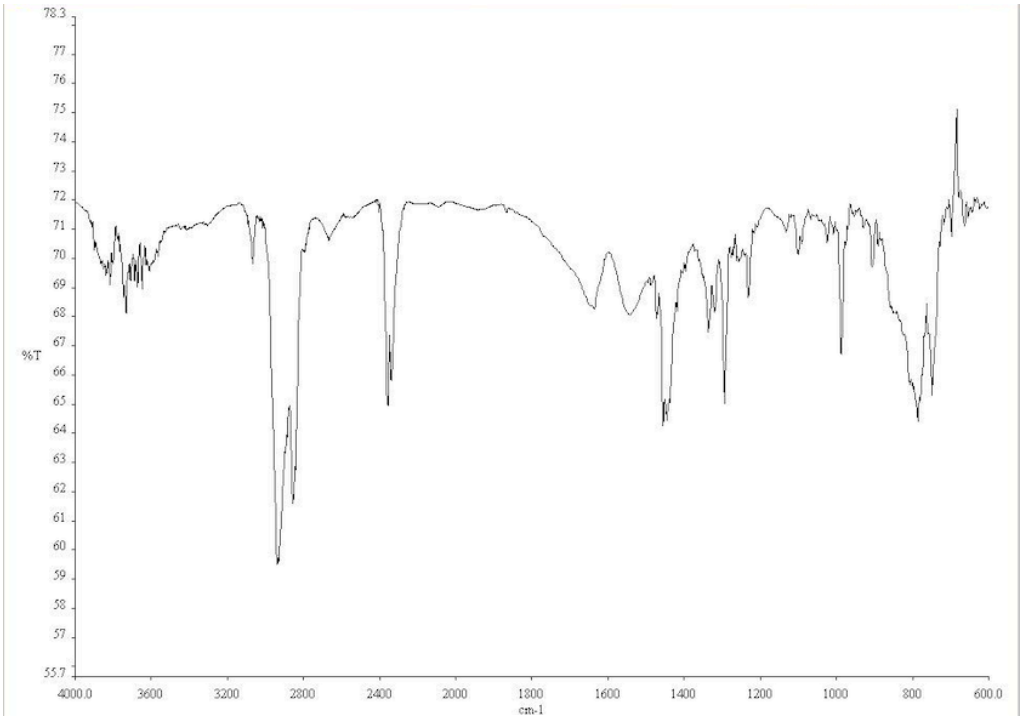


Figure A3.6 *Infrared spectrum (Thin Film, NaCl) of* ***156****.*

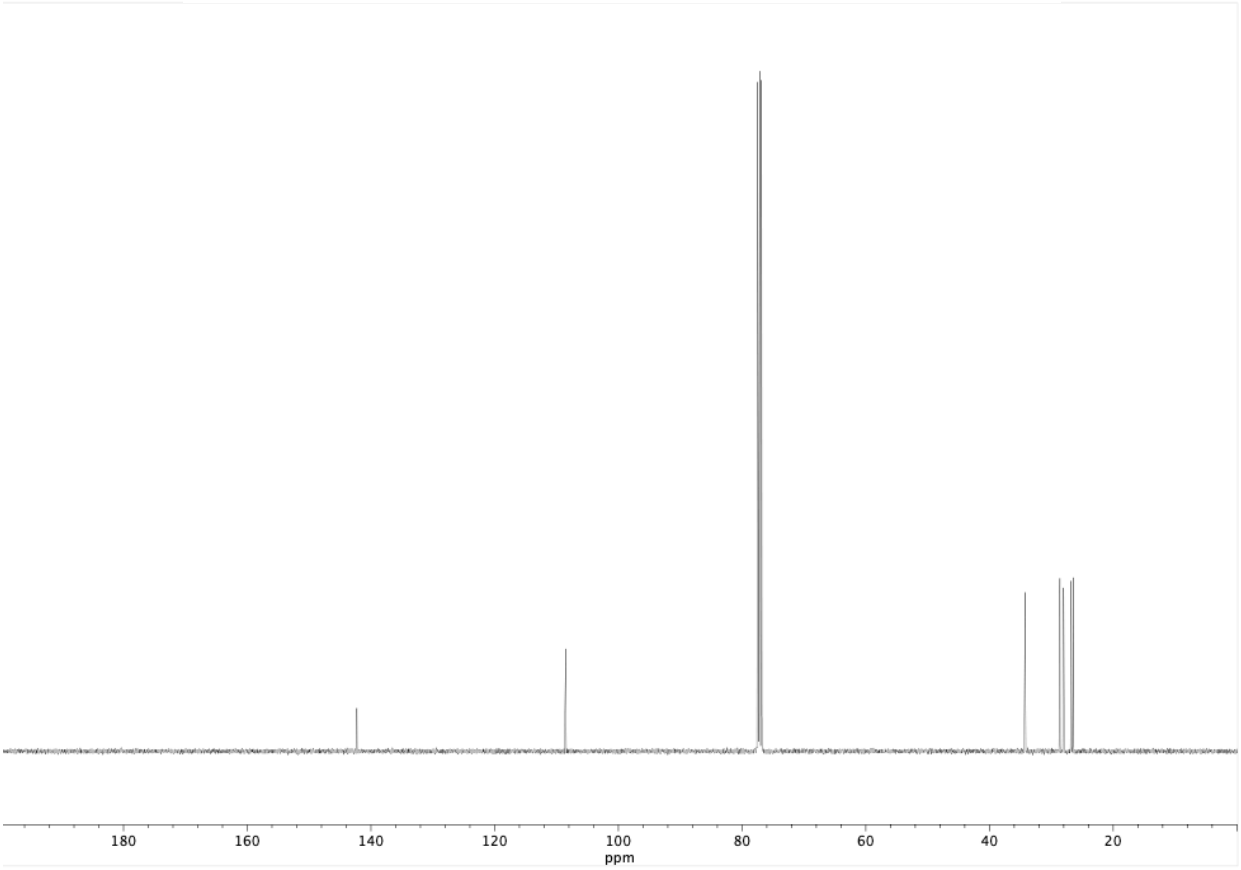


Figure A3.7 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***156.***

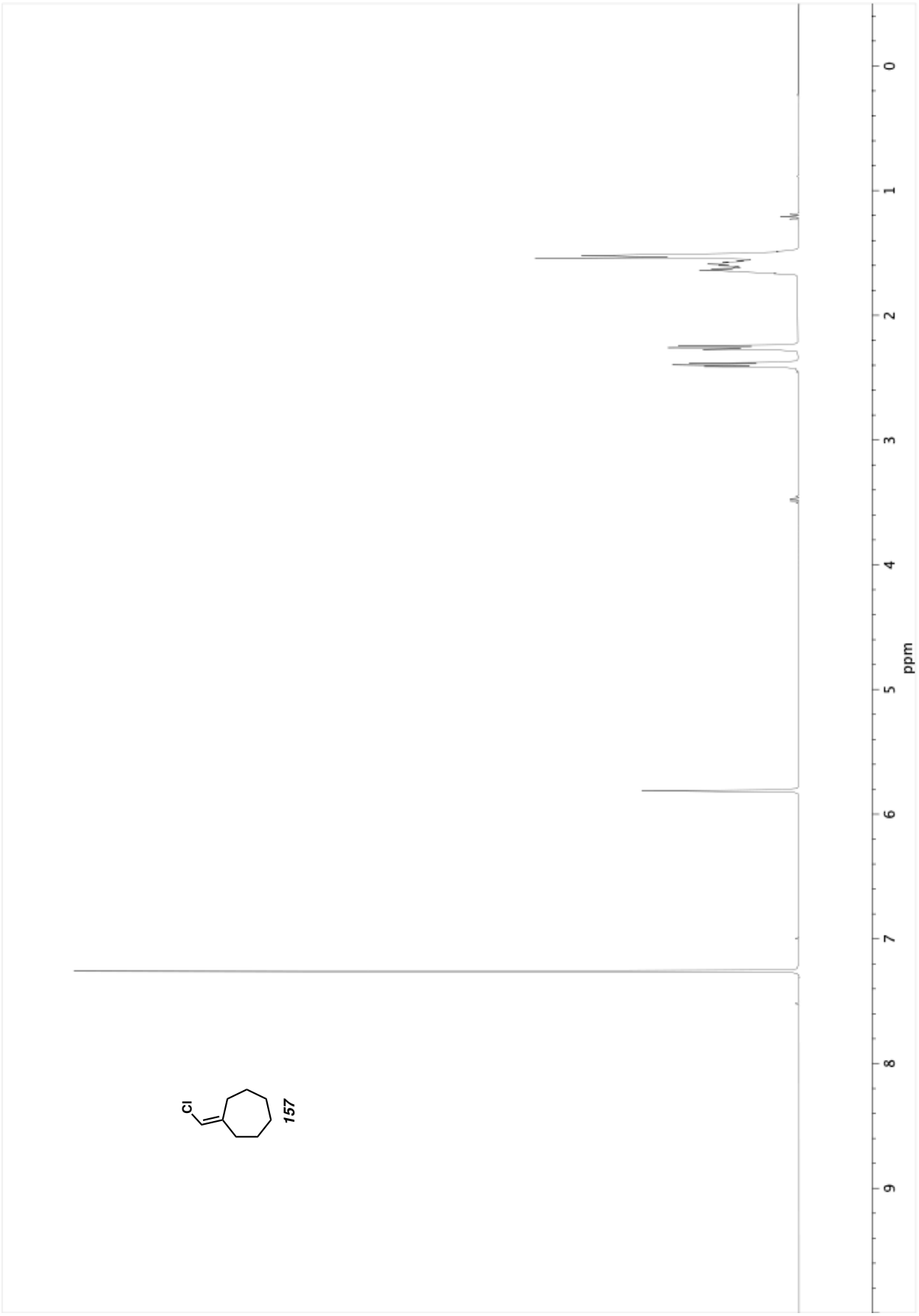


Figure A3.8 *^1H NMR (400 MHz, $CDCl_3$) of* ***157.***

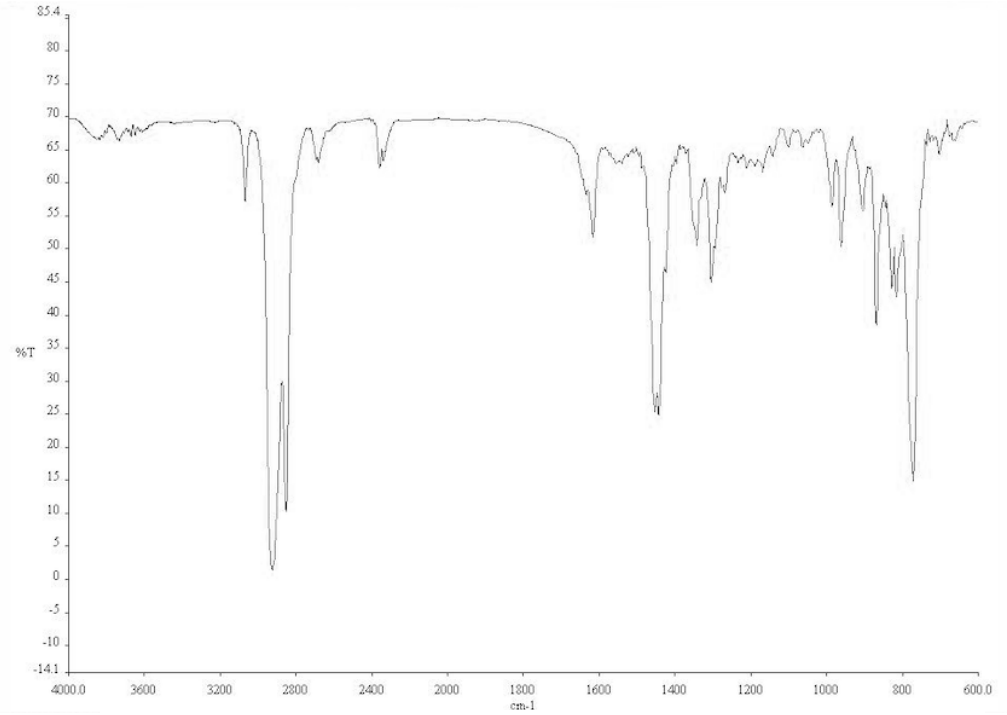


Figure A3.9 *Infrared spectrum (Thin Film, NaCl) of* ***157****.*

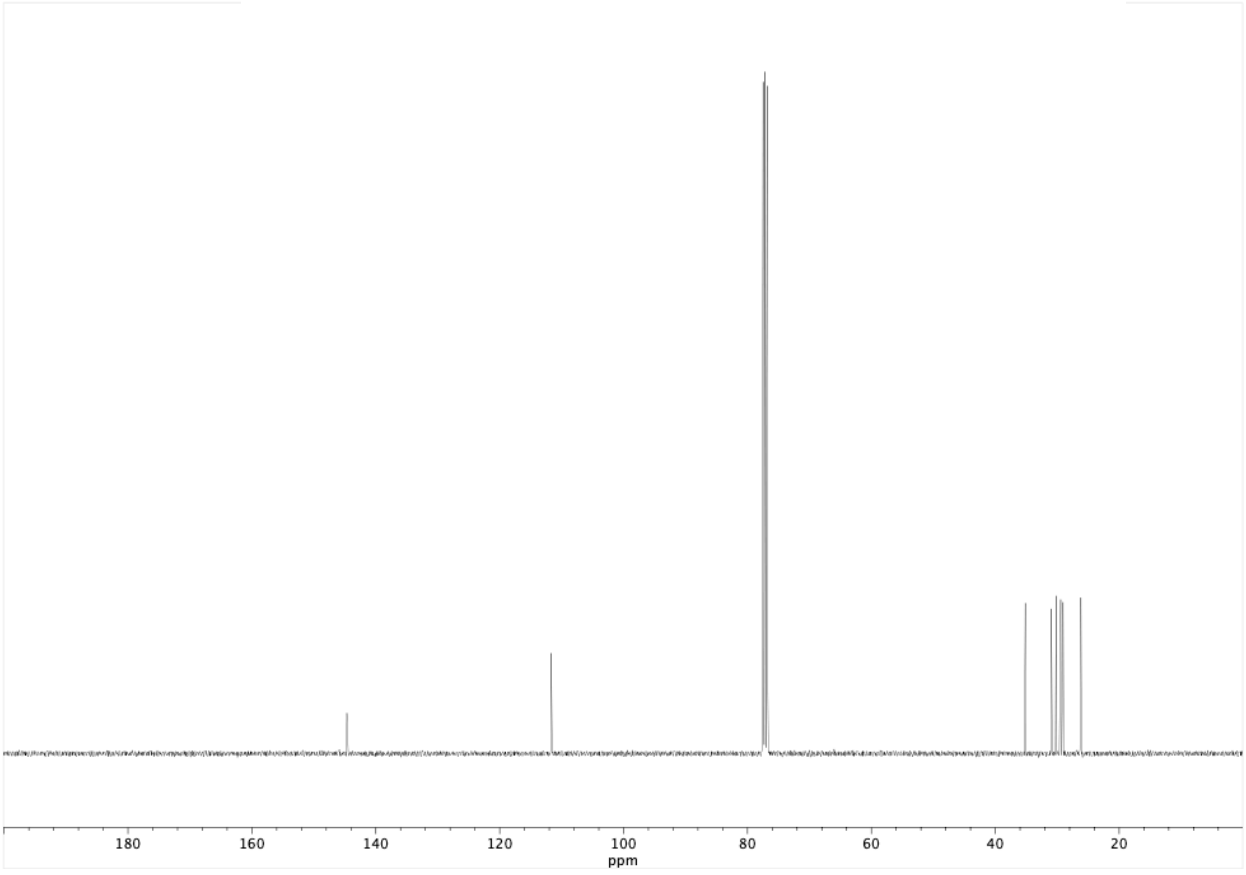


Figure A3.10 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***157****.*

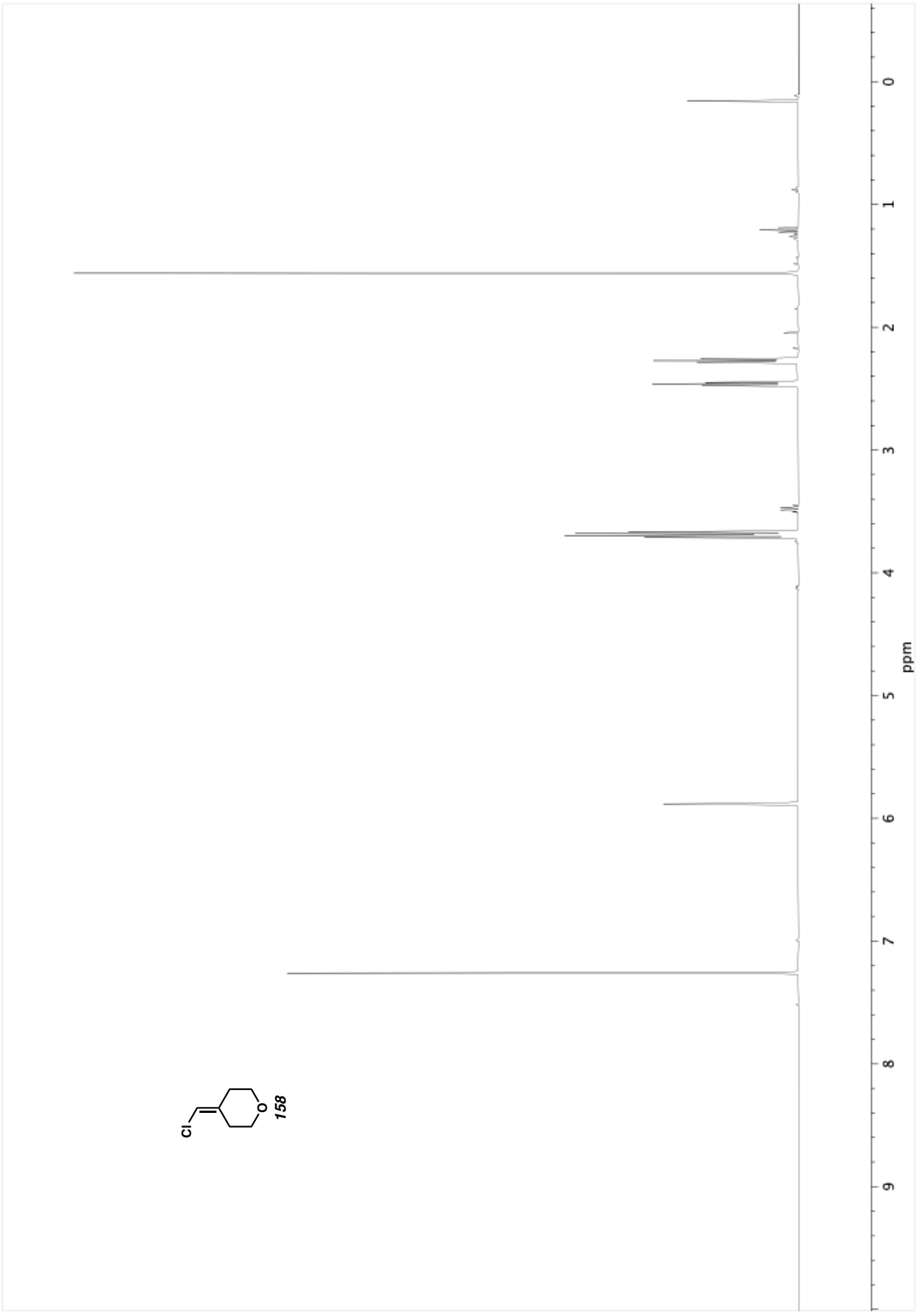


Figure A3.11 *^1H NMR (400 MHz, $CDCl_3$) of* ***158.***

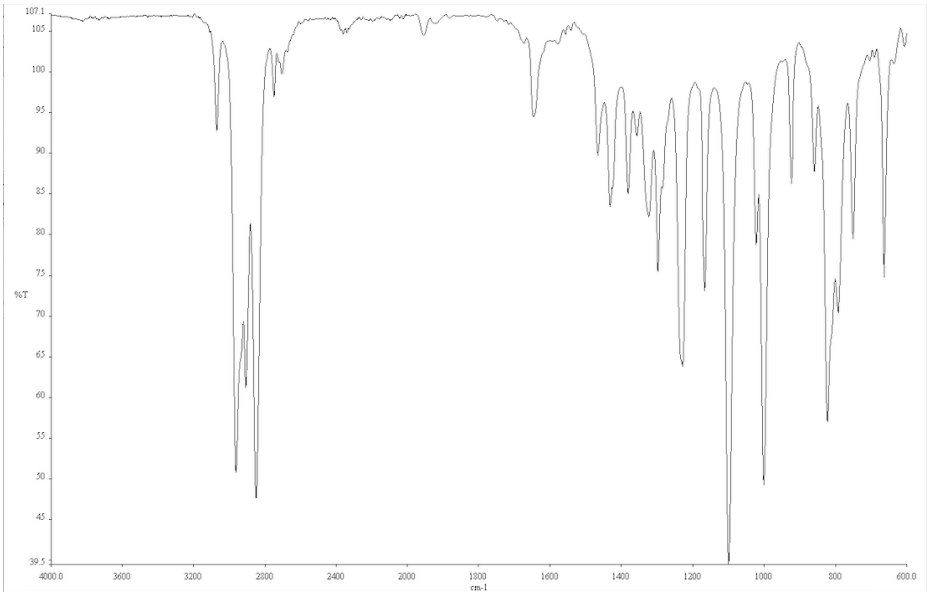


Figure A3.12 *Infrared spectrum (Thin Film, NaCl) of* ***158****.*

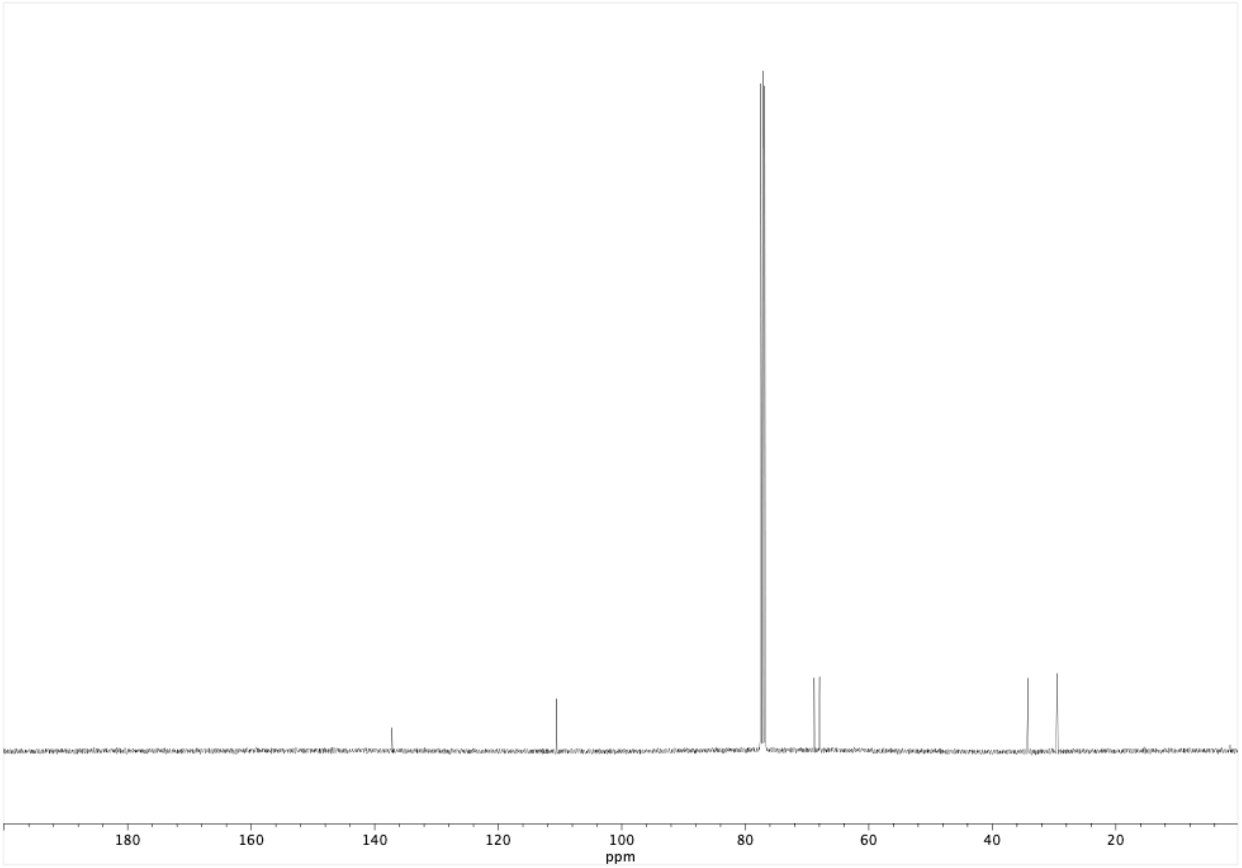


Figure A3.13 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***158****.*

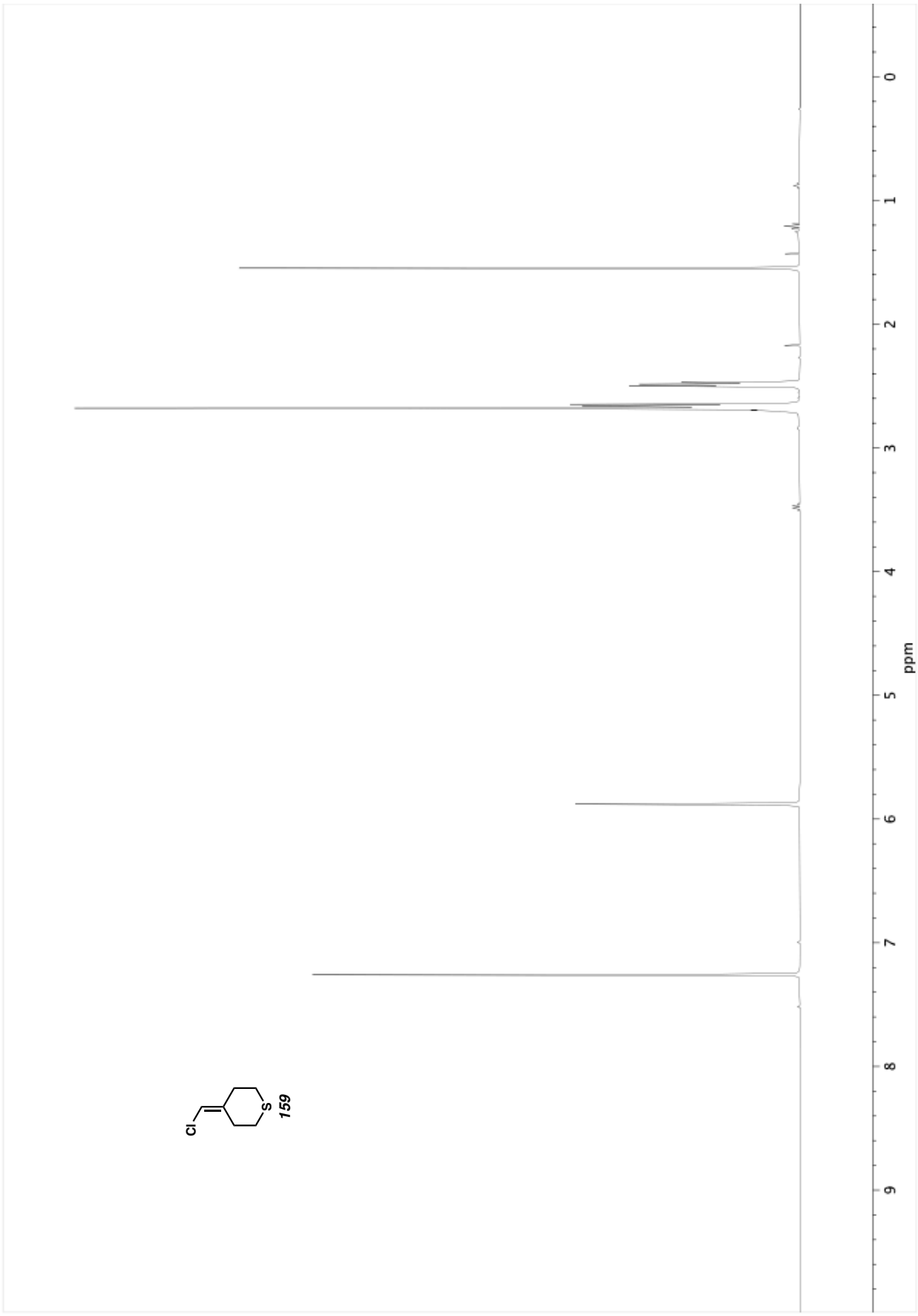


Figure A3.14 *^{1}HNMR (400 MHz, $CDCl_3$) of* ***159.***

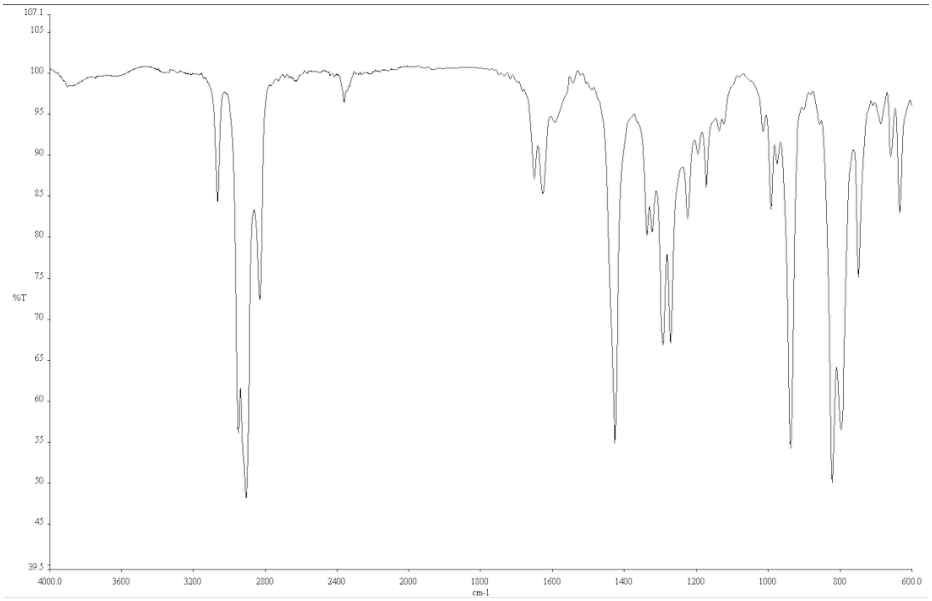


Figure A3.15 *Infrared spectrum (Thin Film, NaCl) of* ***159.***

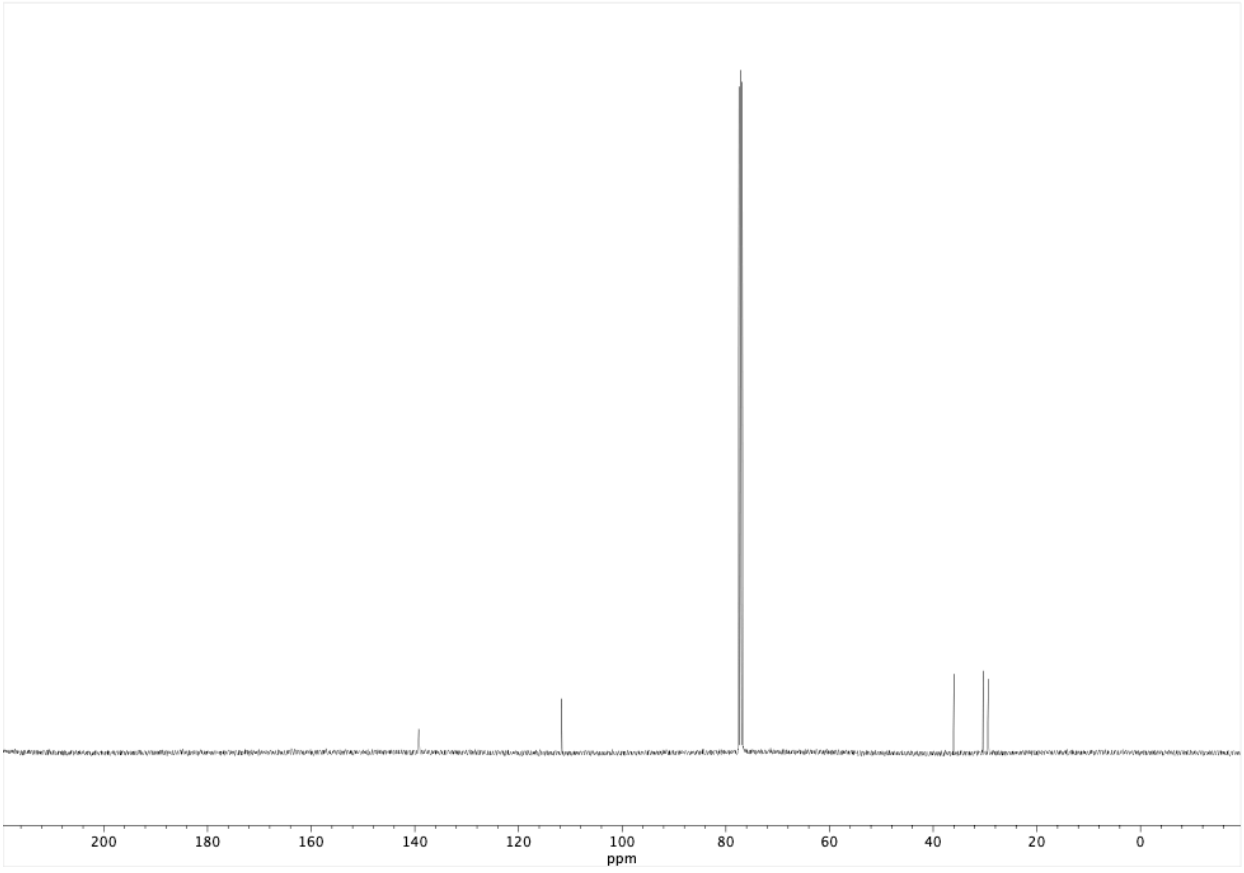


Figure A3.16 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***159.***

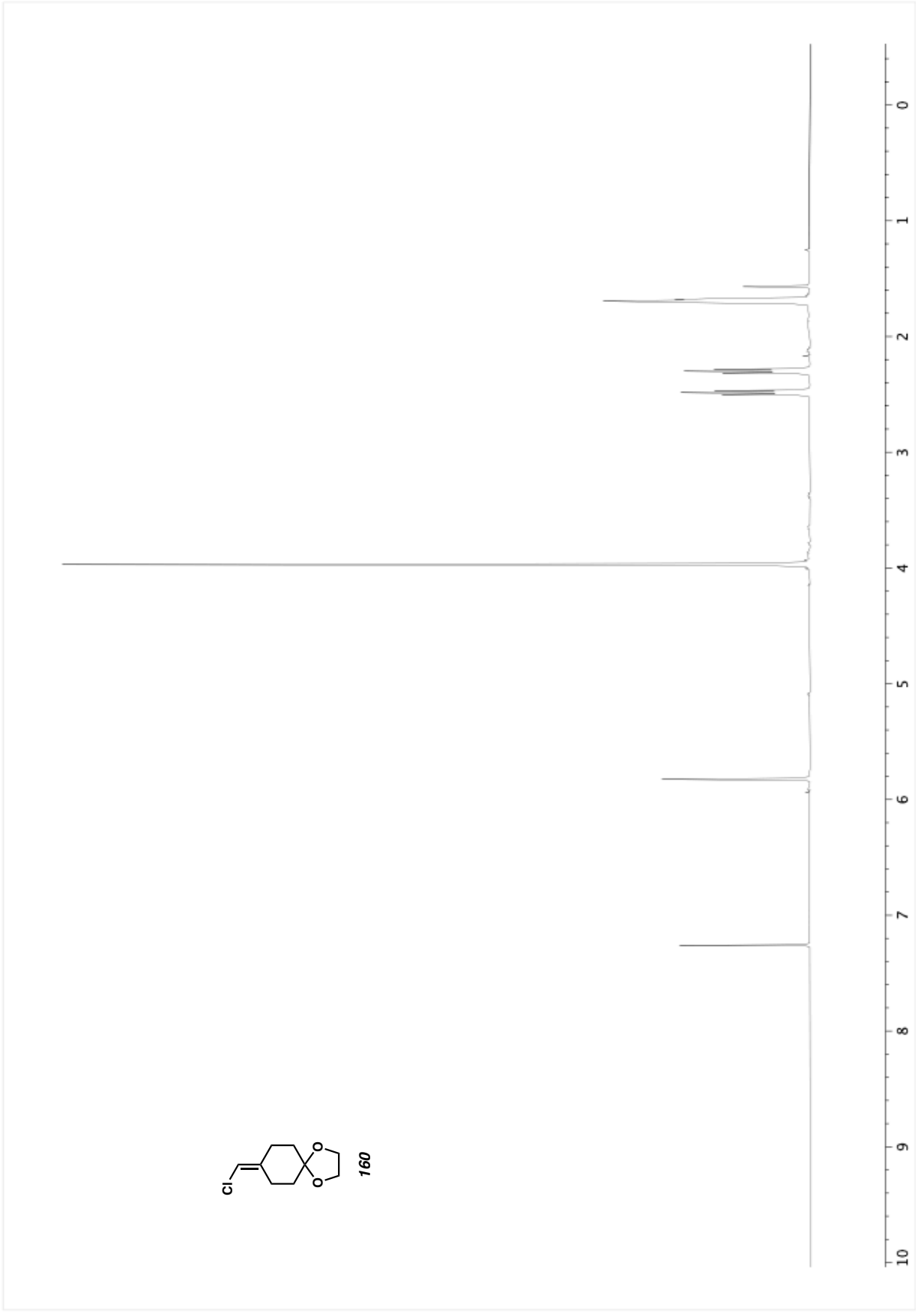


Figure A3.17 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***160***.

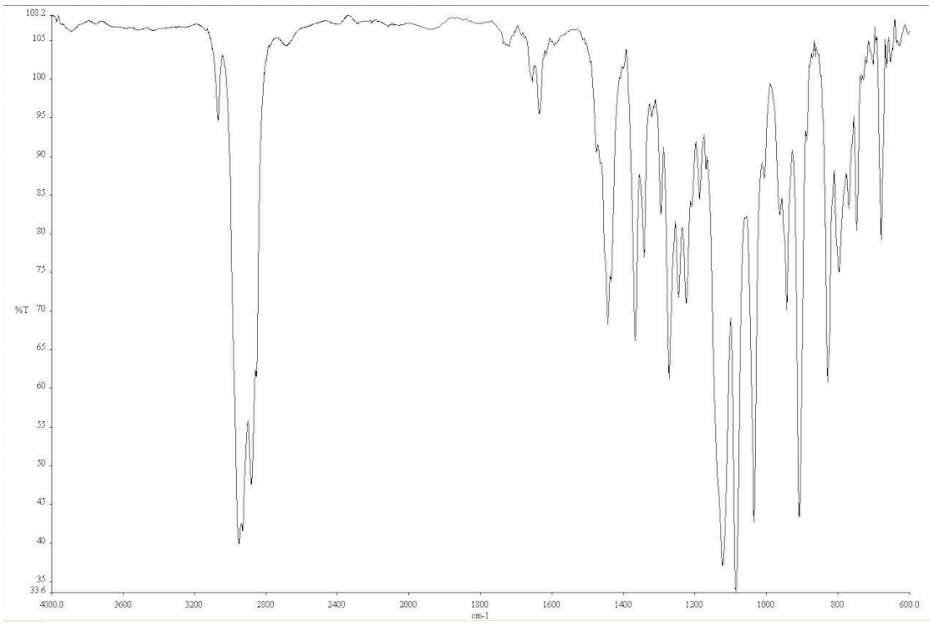


Figure A3.18 *Infrared spectrum (Thin Film, NaCl) of* ***160****.*

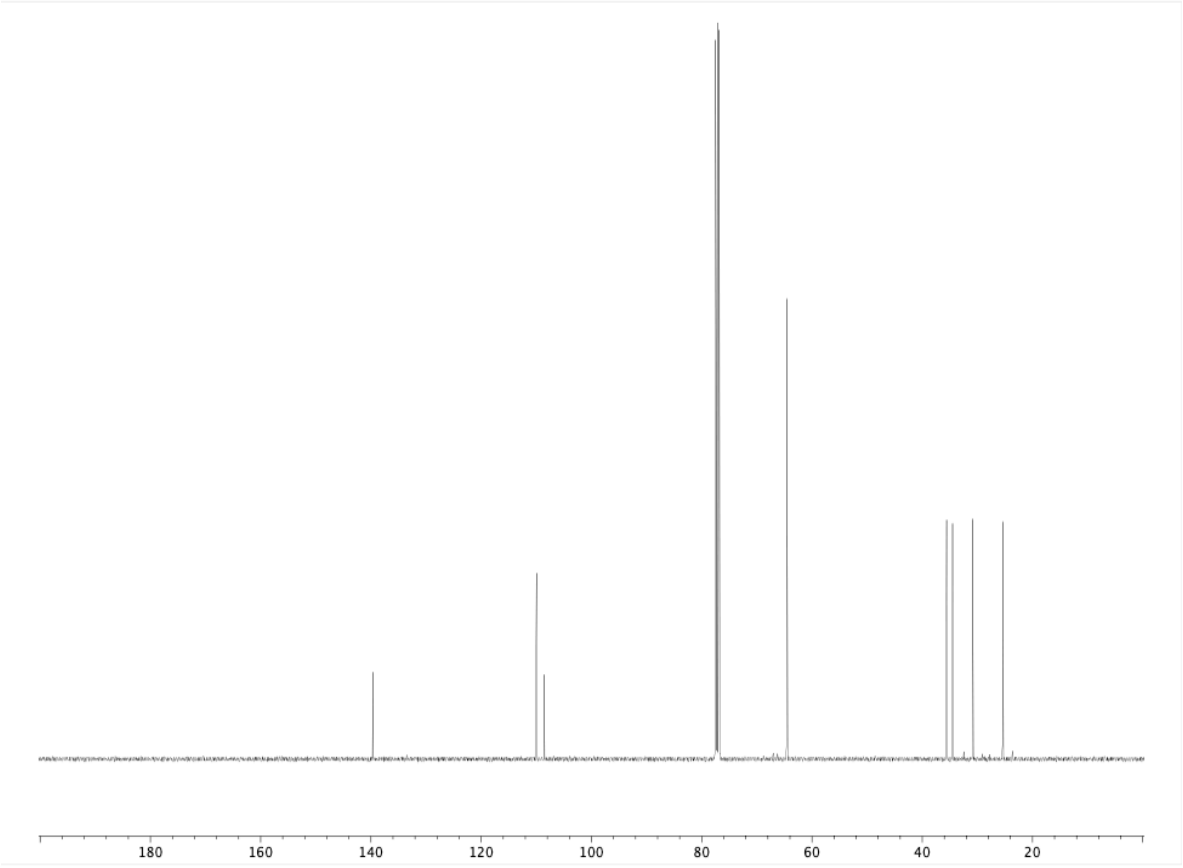


Figure A3.19 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***160****.*

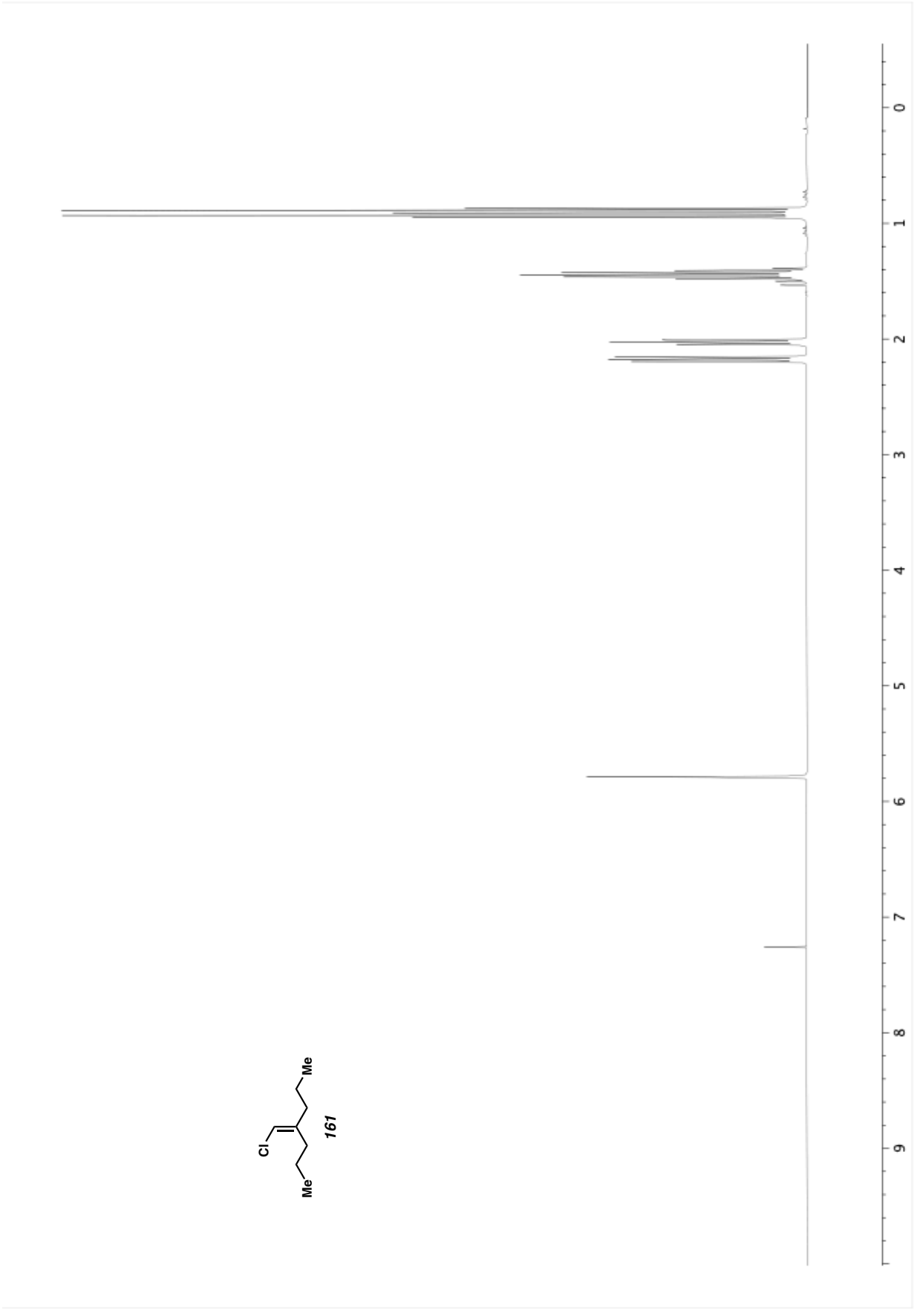


Figure A3.20 *^1H NMR (400 MHz, $CDCl_3$) of* ***161****.*

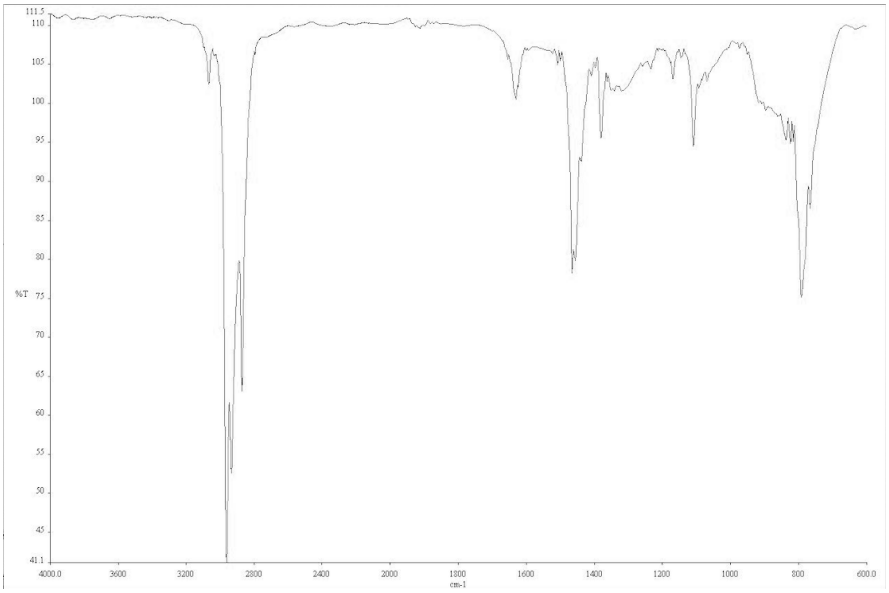


Figure A3.21 *Infrared spectrum (Thin Film, NaCl) of* ***161***.

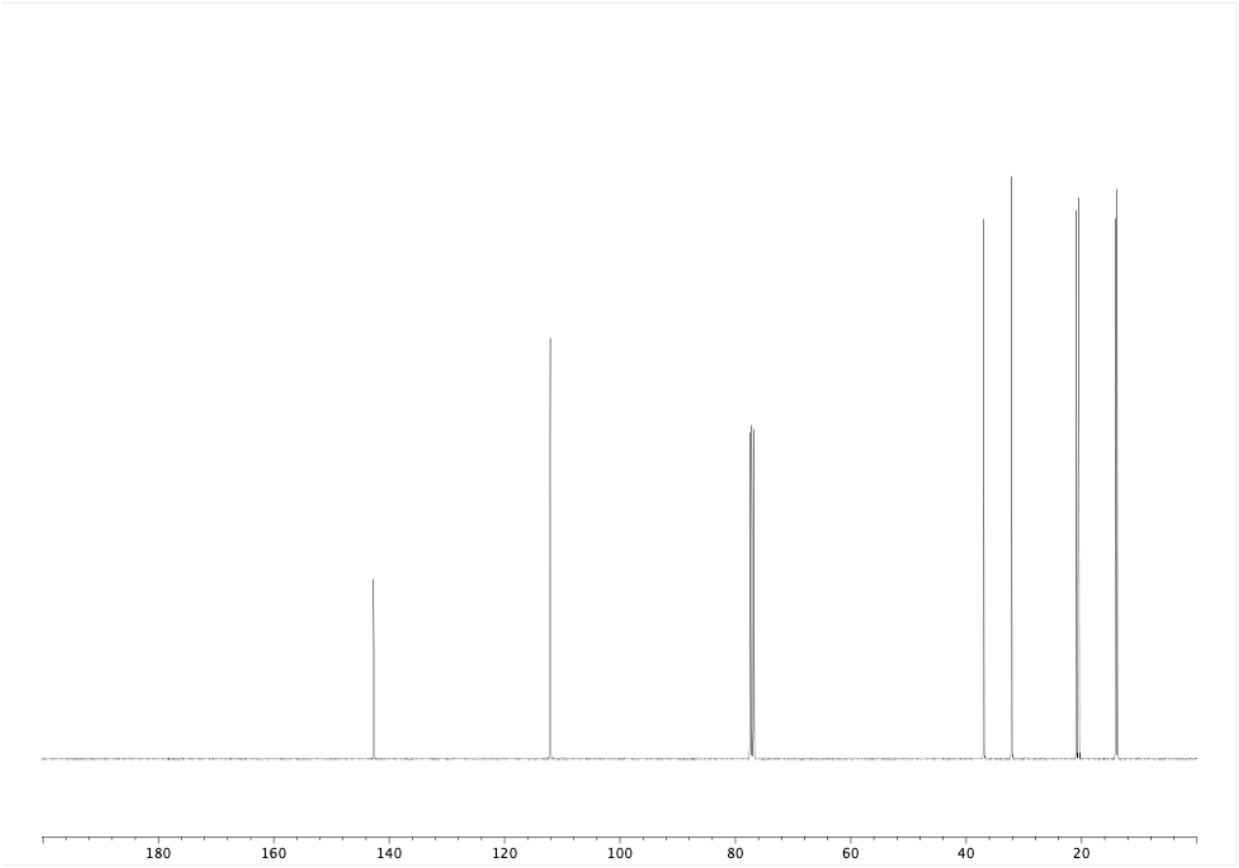


Figure A3.22 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***161***.

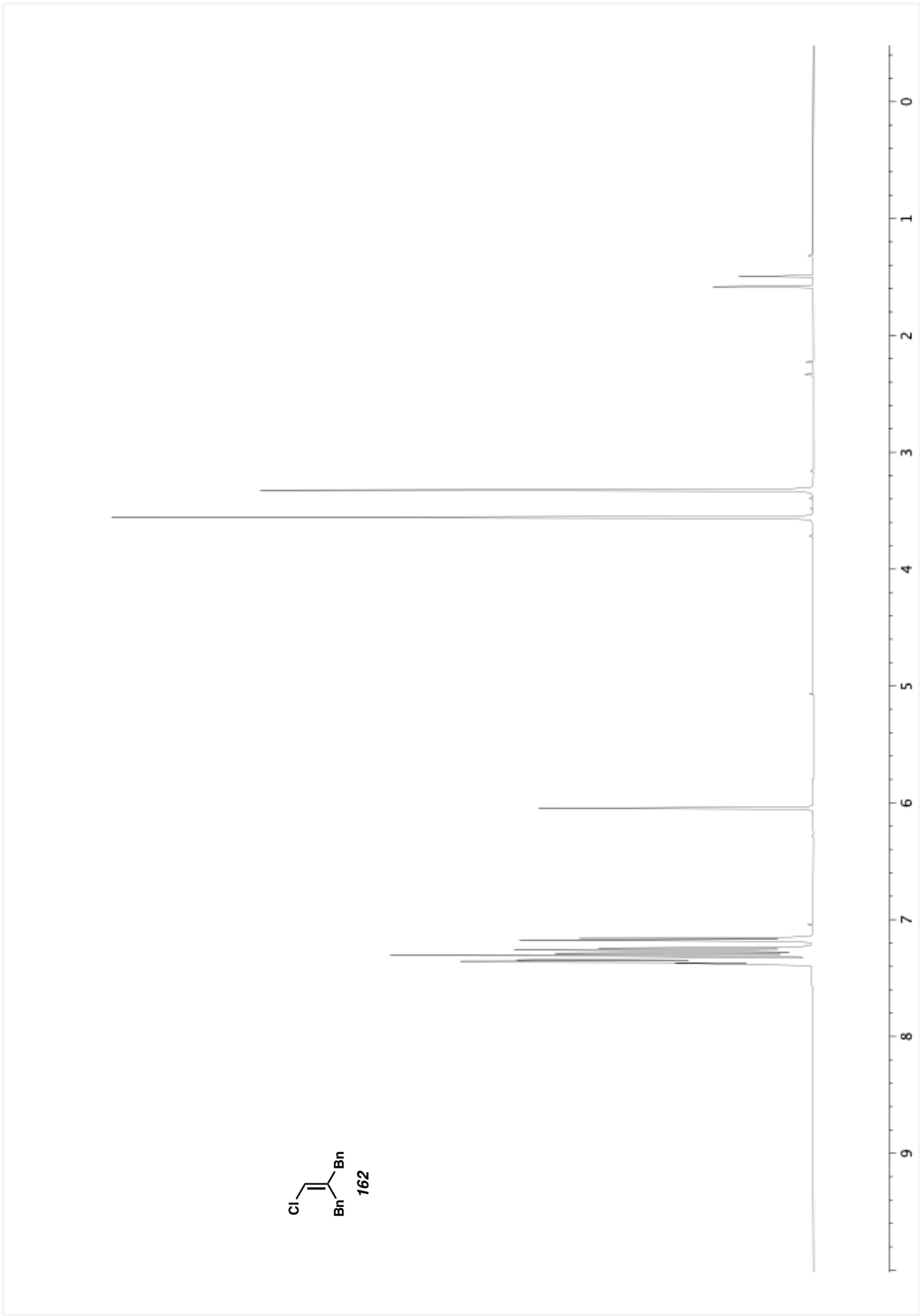


Figure A3.23 *^1H NMR (400 MHz, $CDCl_3$) of* ***162****.*

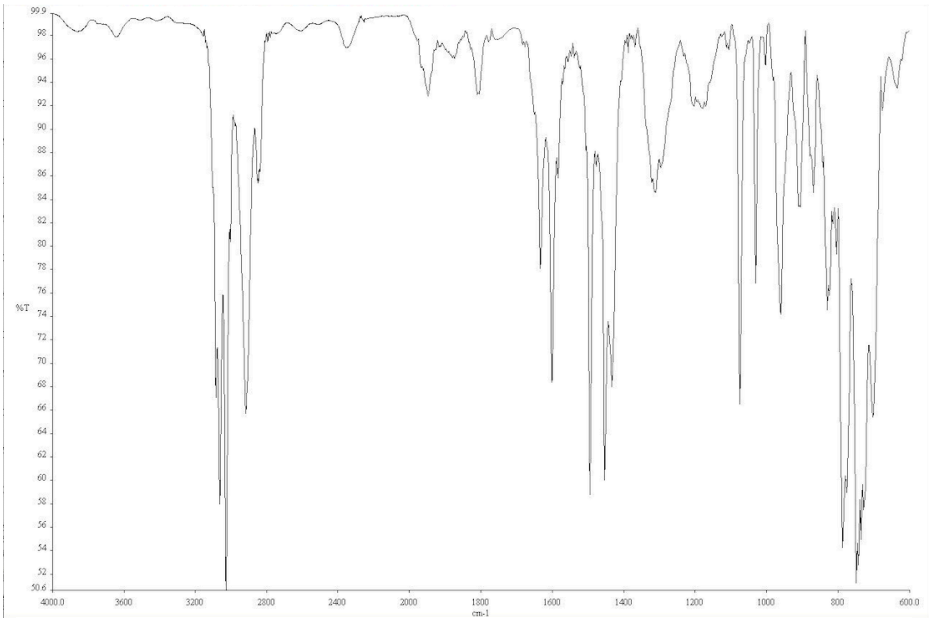


Figure A3.24 *Infrared spectrum (Thin Film, NaCl) of* ***162.***

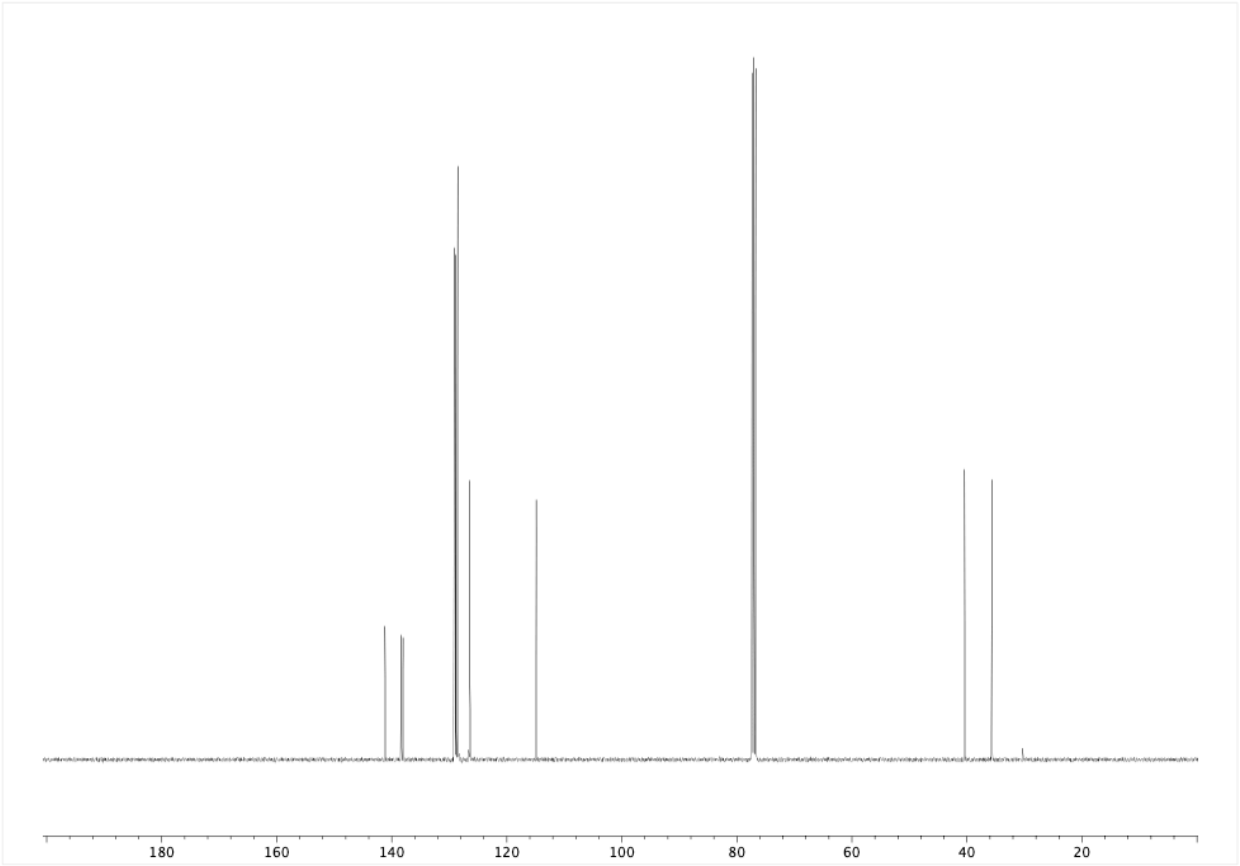


Figure A3.25 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***162****.*

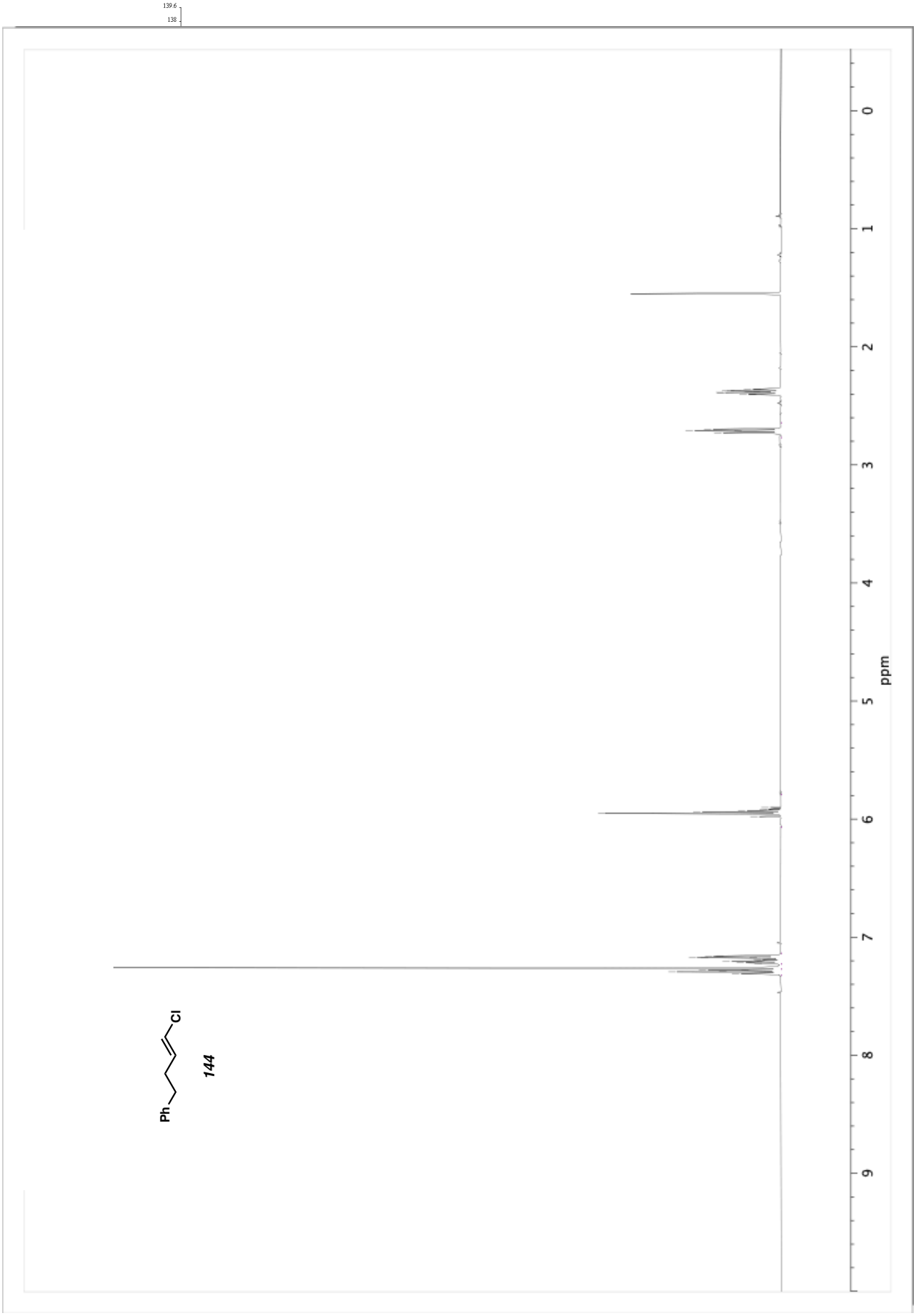


Figure A3.26 *^1H NMR (400 MHz, $CDCl_3$) of* ***144****.*

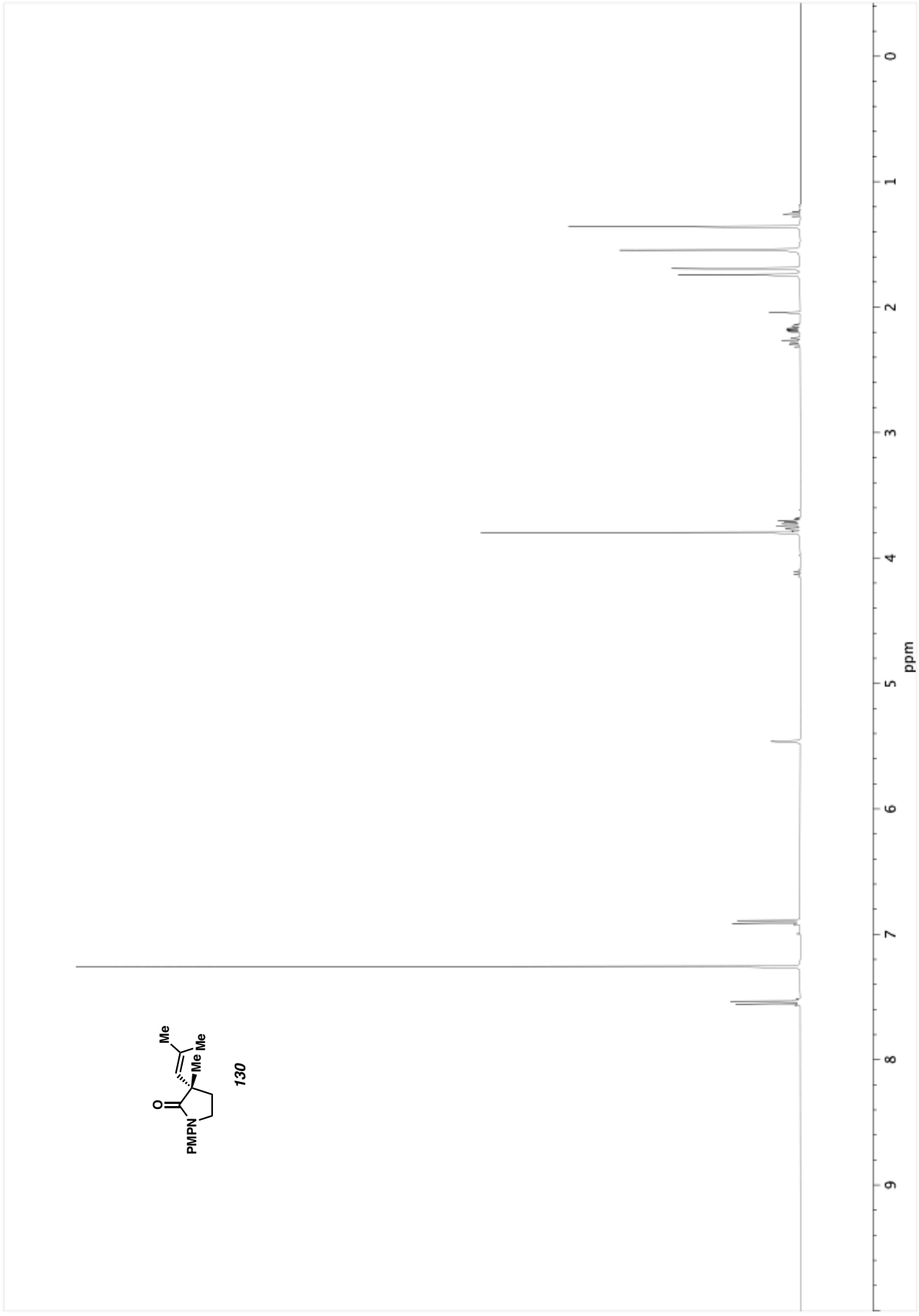


Figure A3.27 *^1H NMR (400 MHz, $CDCl_3$) of* ***130***.

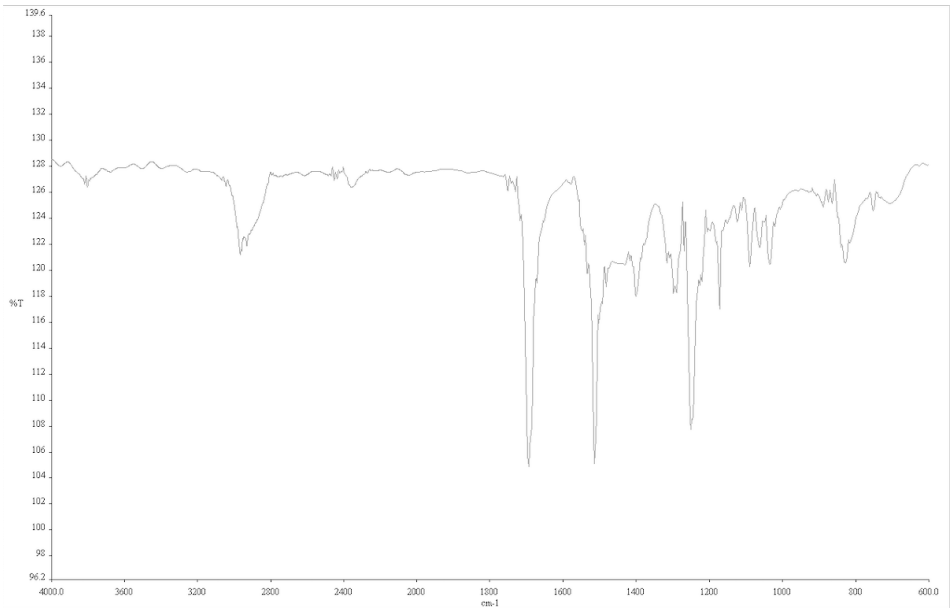


Figure A3.28 *Infrared spectrum (Thin Film, NaCl) of* ***130****.*

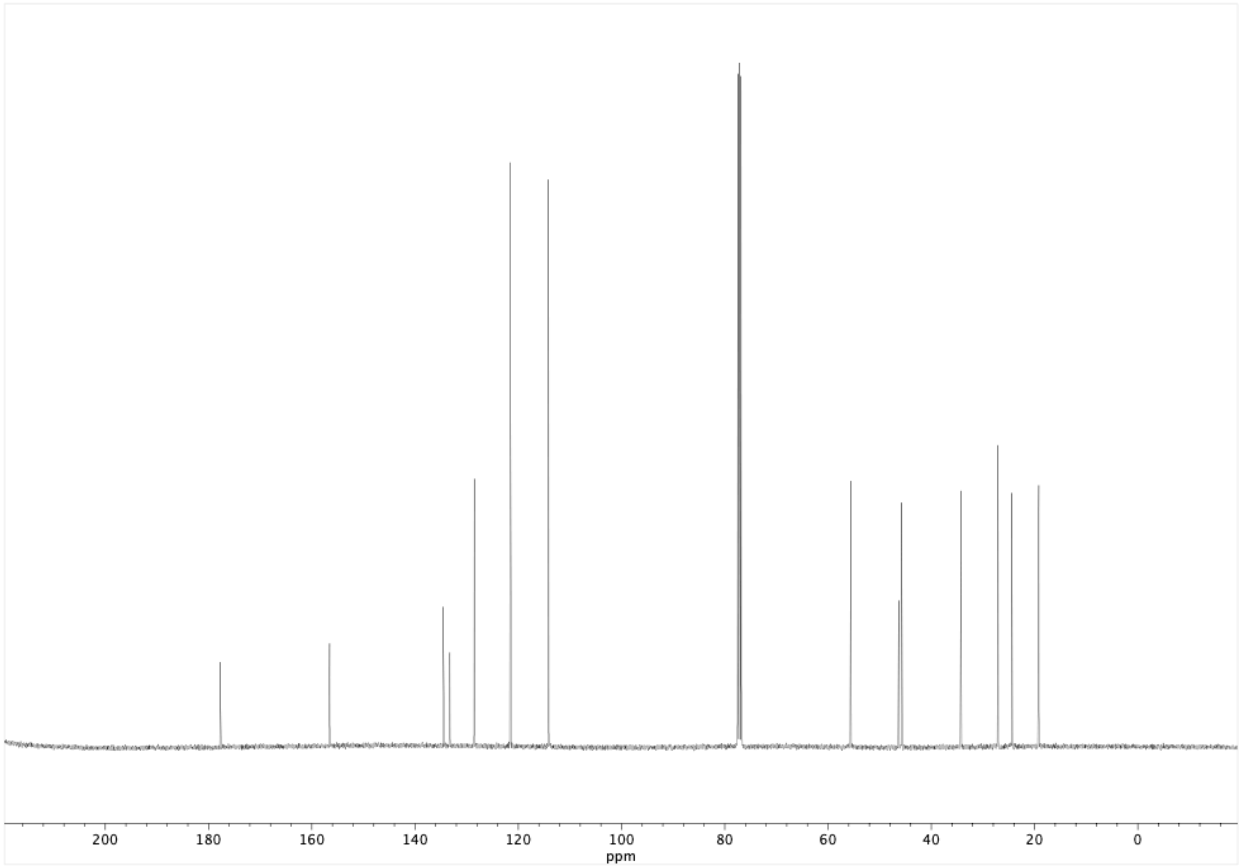


Figure A3.29 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***130****.*

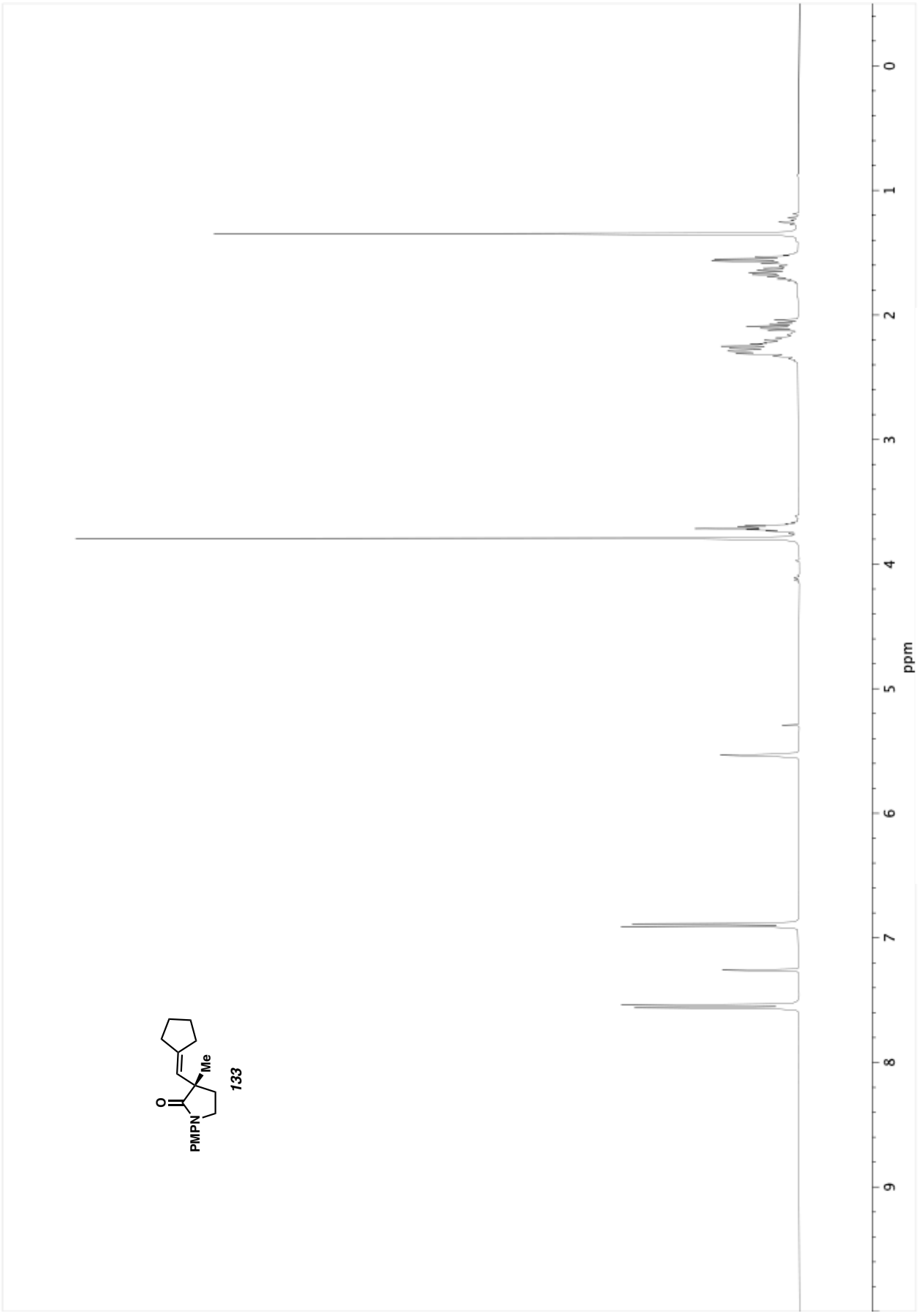


Figure A3.30 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***133***.

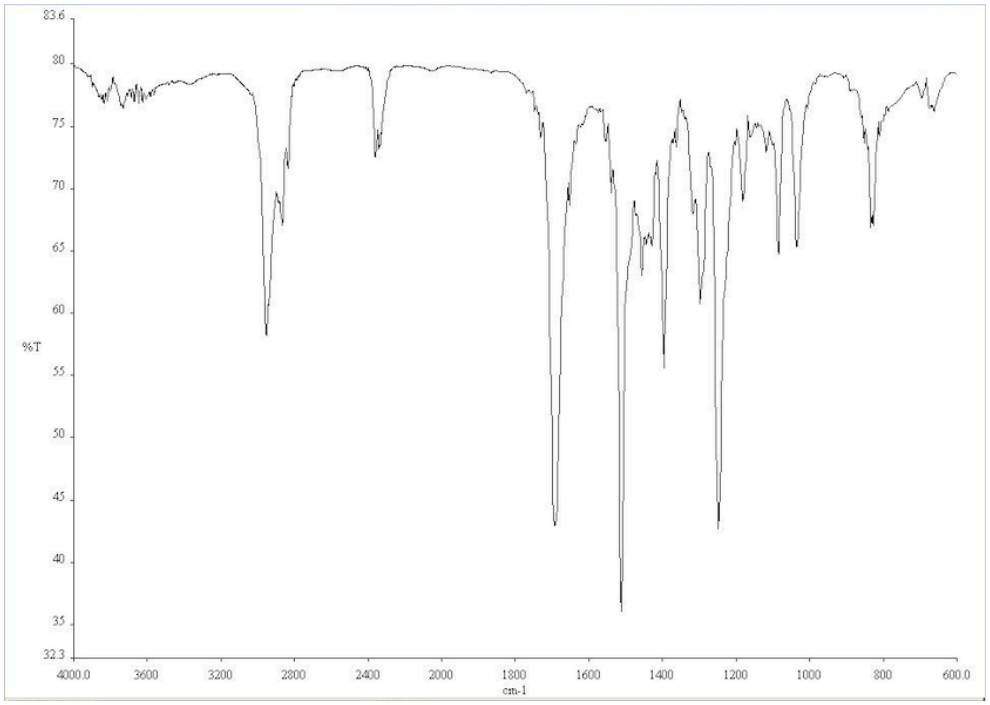


Figure A3.31 *Infrared spectrum (Thin Film, NaCl) of* ***133***.

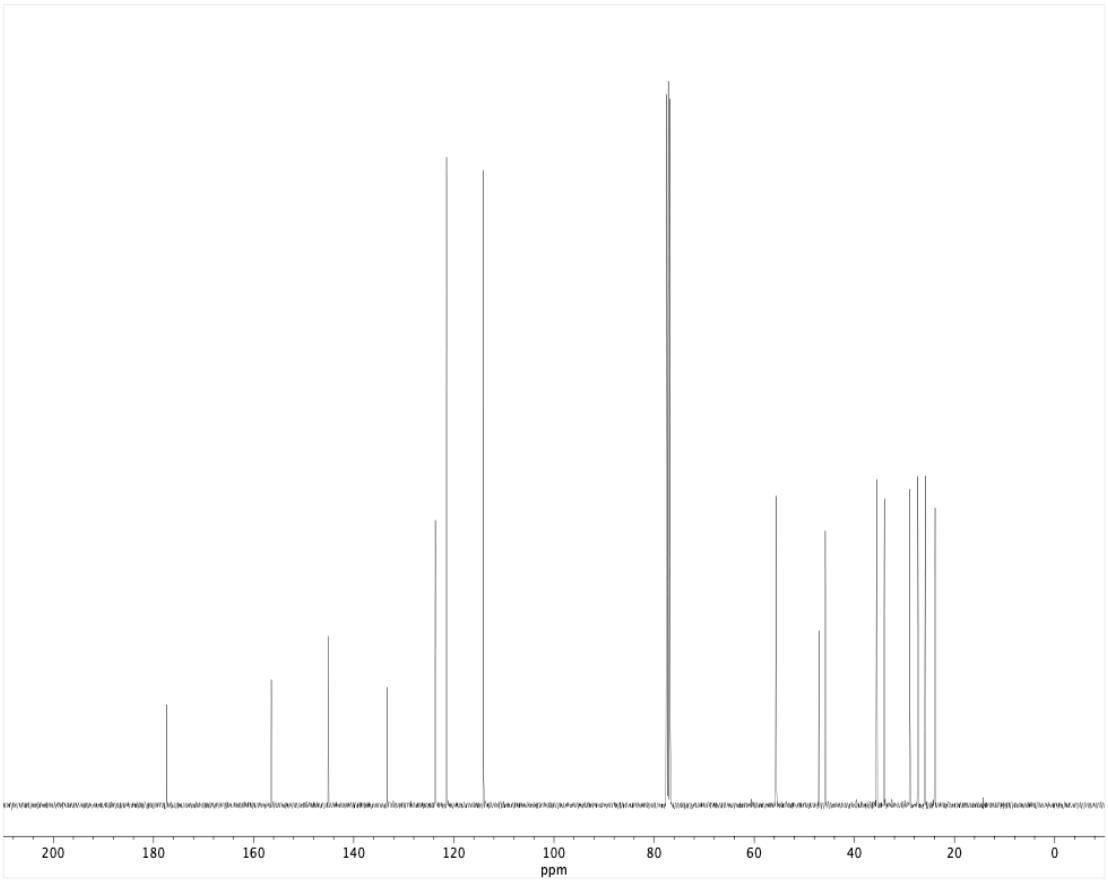


Figure A3.32 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***133***.

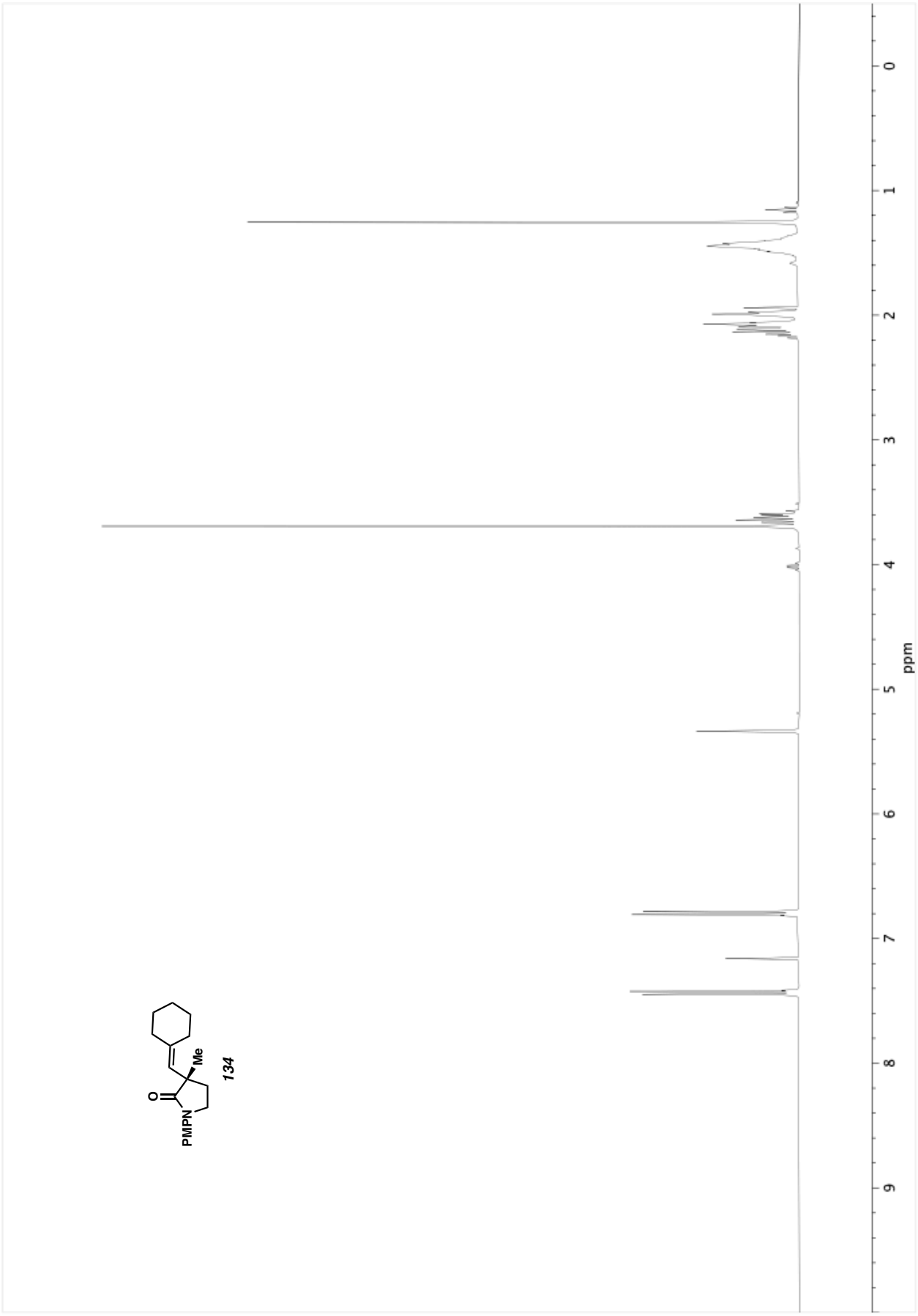


Figure A3.33 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***134****.*

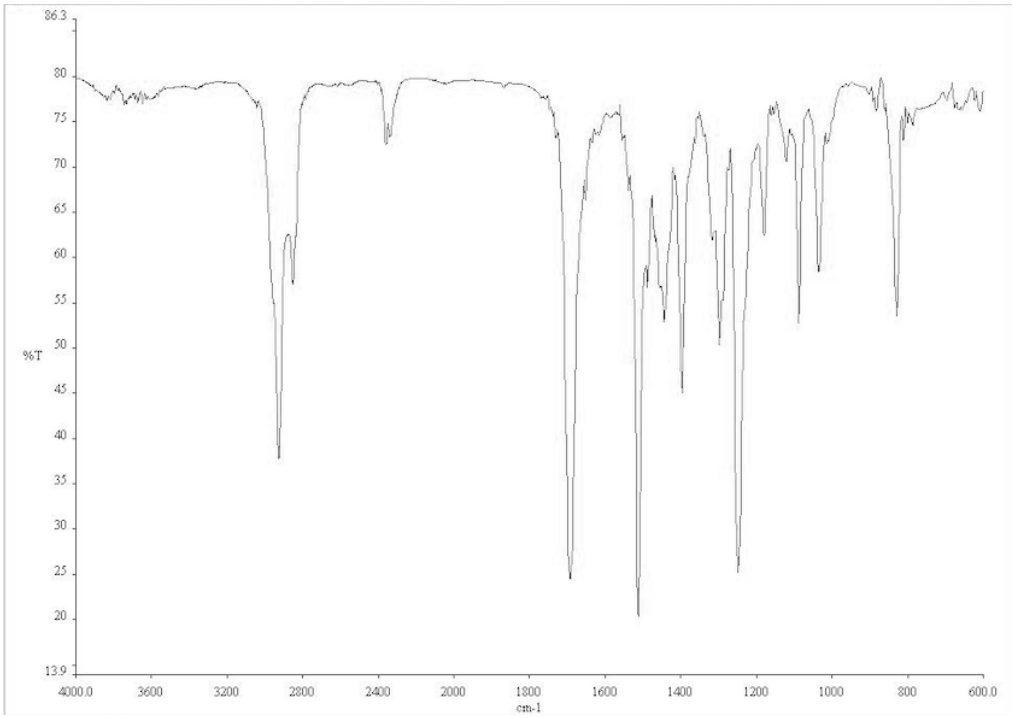


Figure A3.34 *Infrared spectrum (Thin Film, NaCl) of* ***134****.*

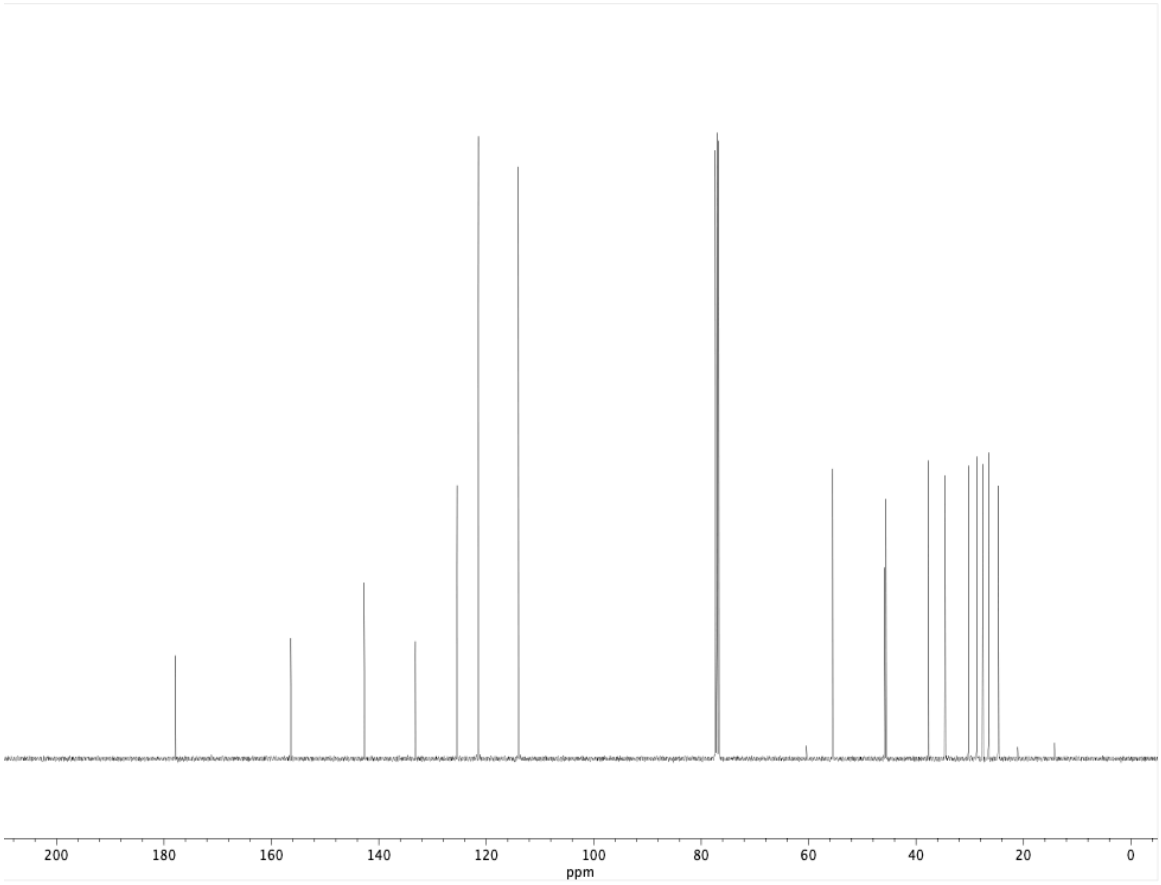


Figure A3.35 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***134.***

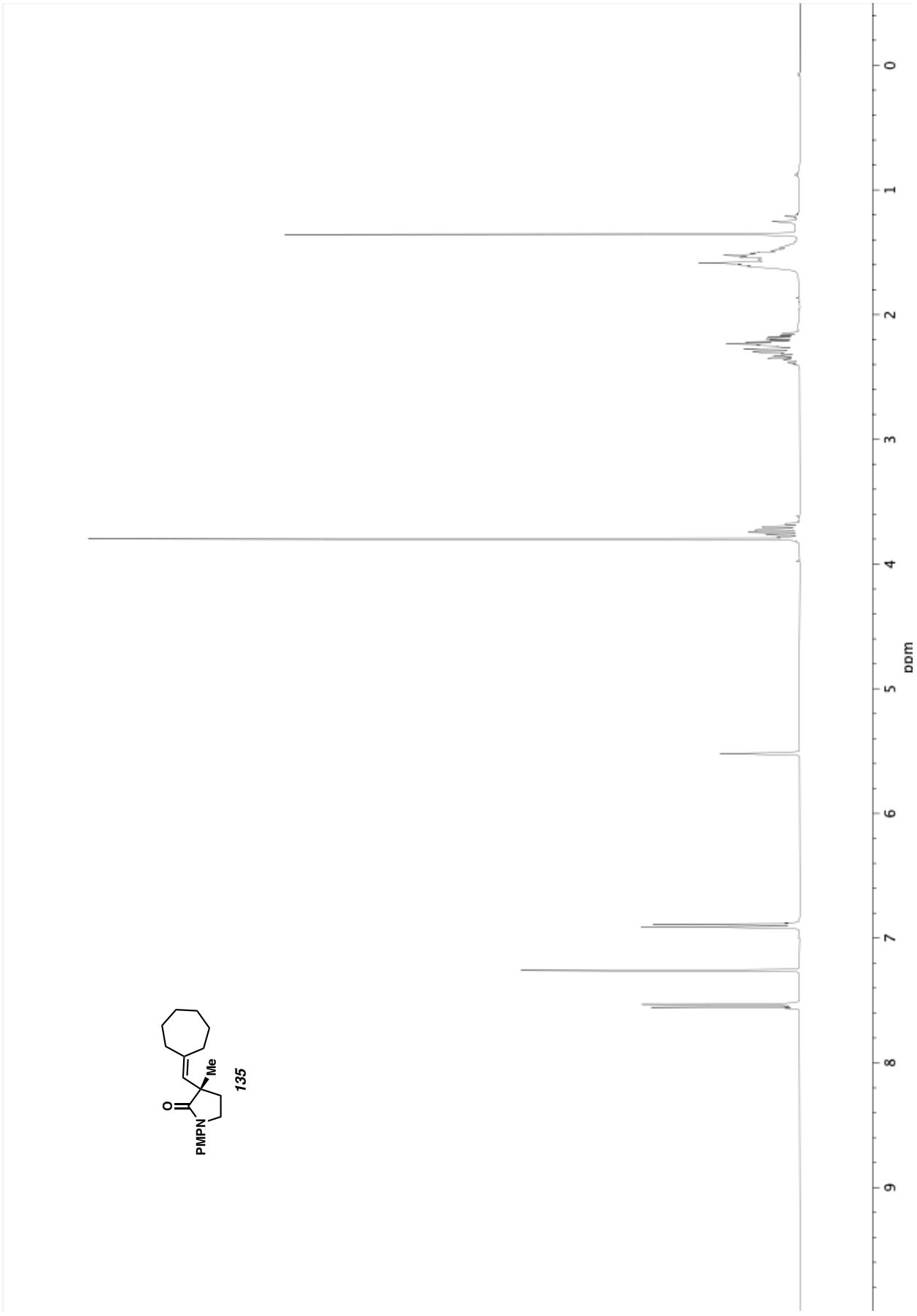


Figure A3.36 *^1H NMR (400 MHz, $CDCl_3$) of* ***135***.

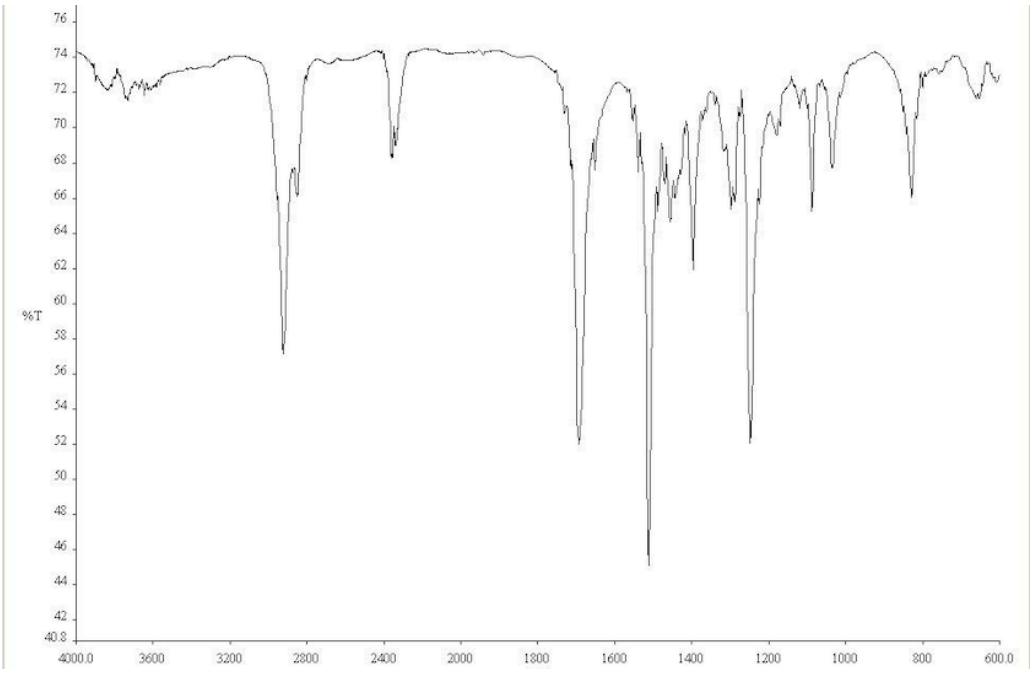


Figure A3.37 *Infrared spectrum (Thin Film, NaCl) of* ***135****.*

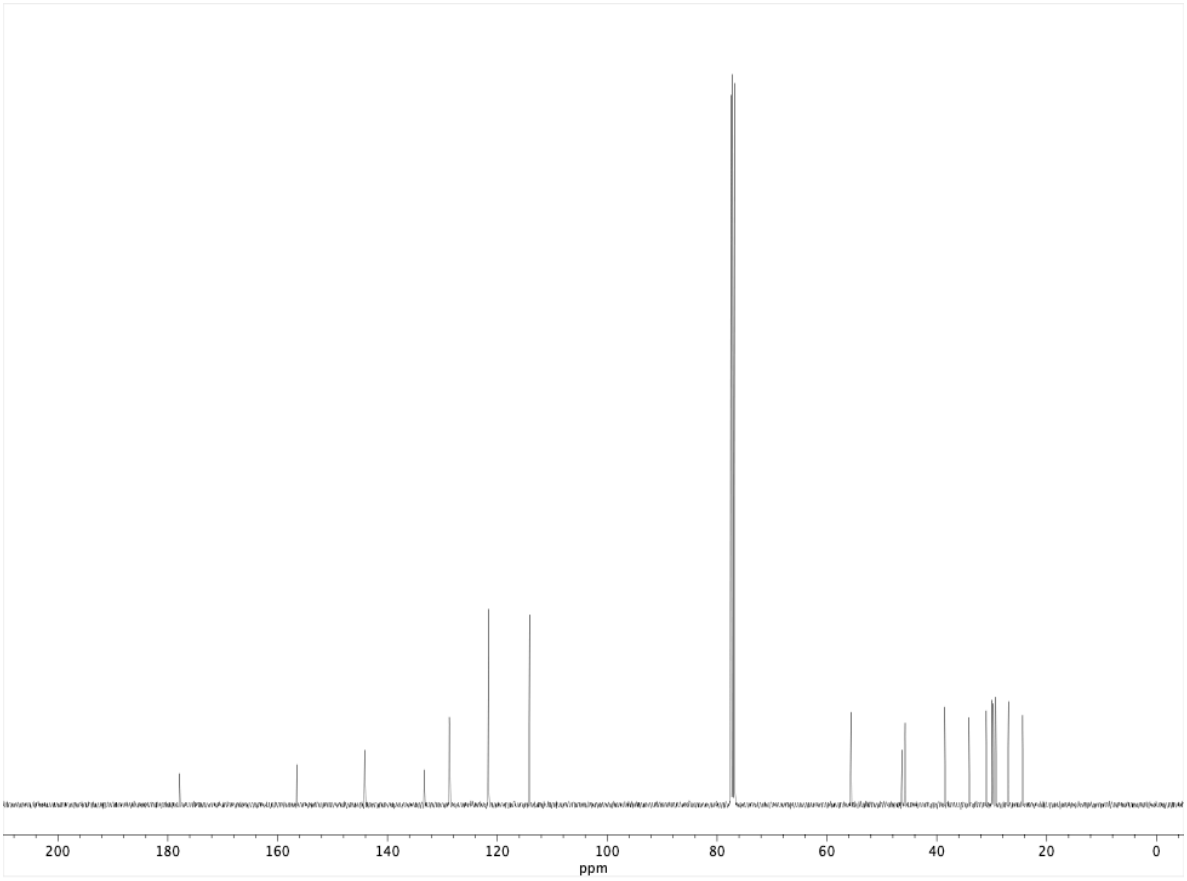


Figure A3.38 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***135****.*

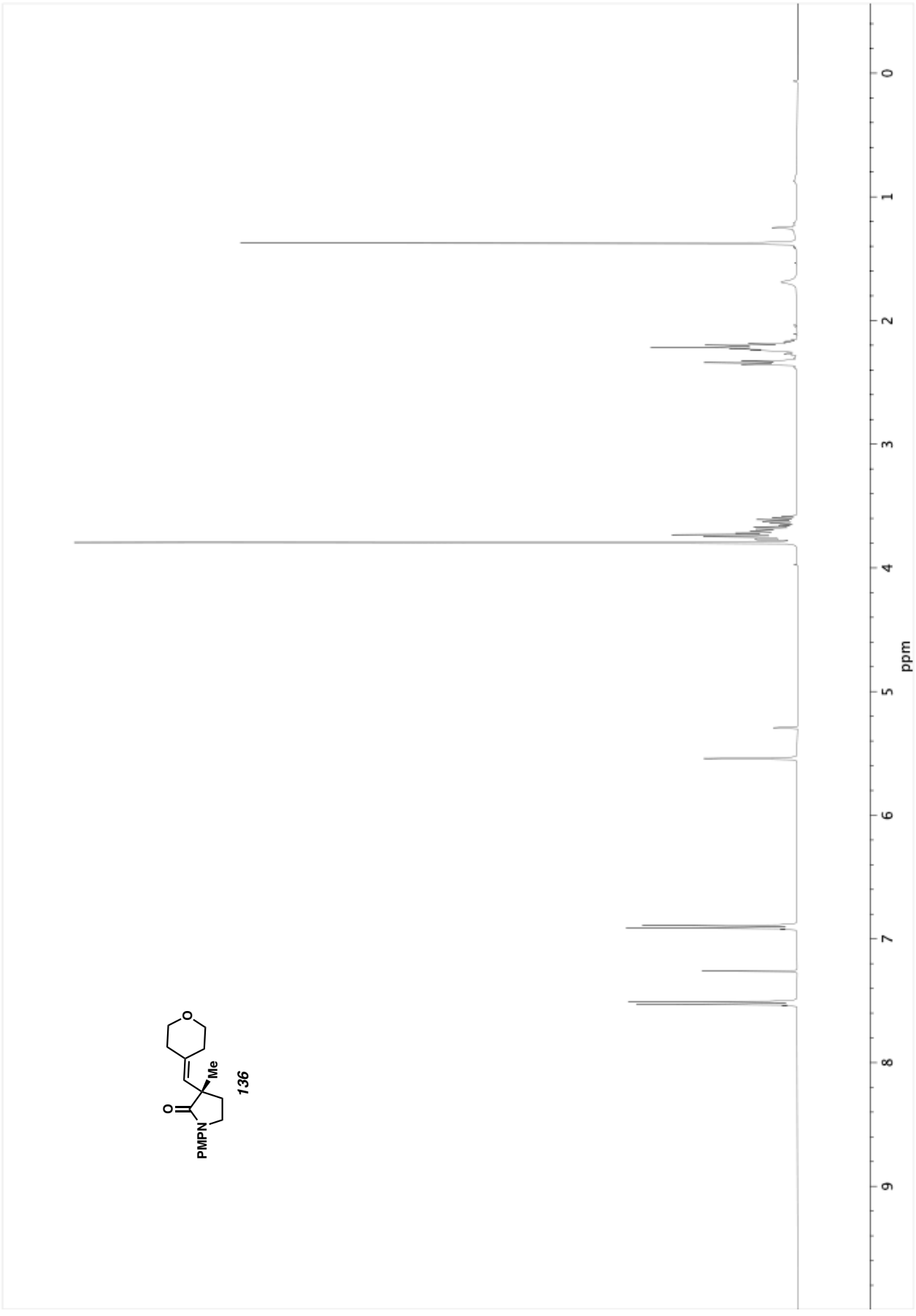


Figure A3.39 *^1H NMR (400 MHz, $CDCl_3$) of* ***136****.*

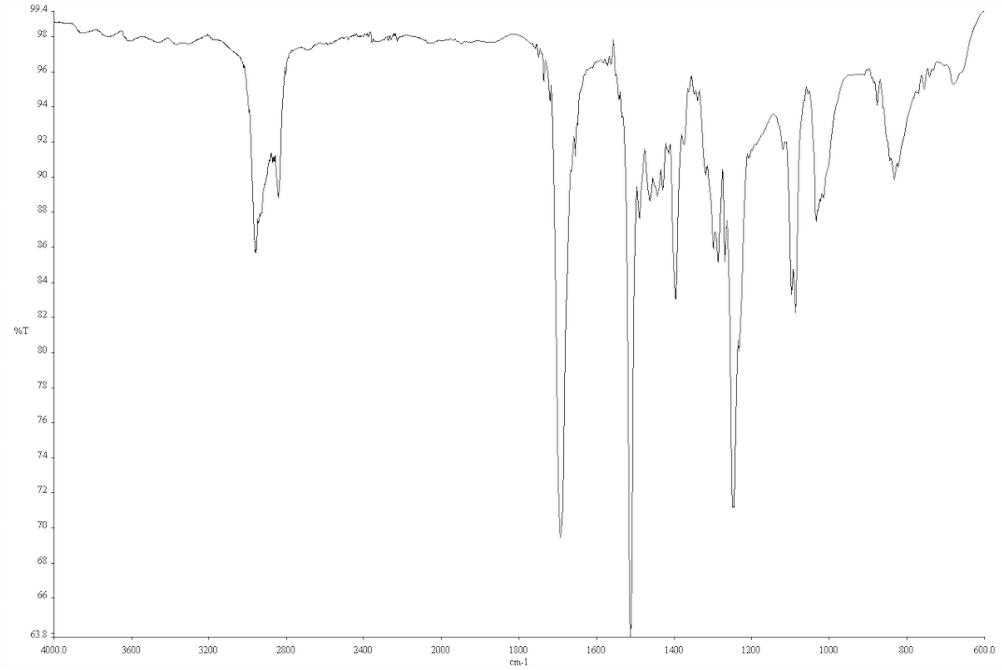


Figure A3.40 *Infrared spectrum (Thin Film, NaCl) of* ***136****.*

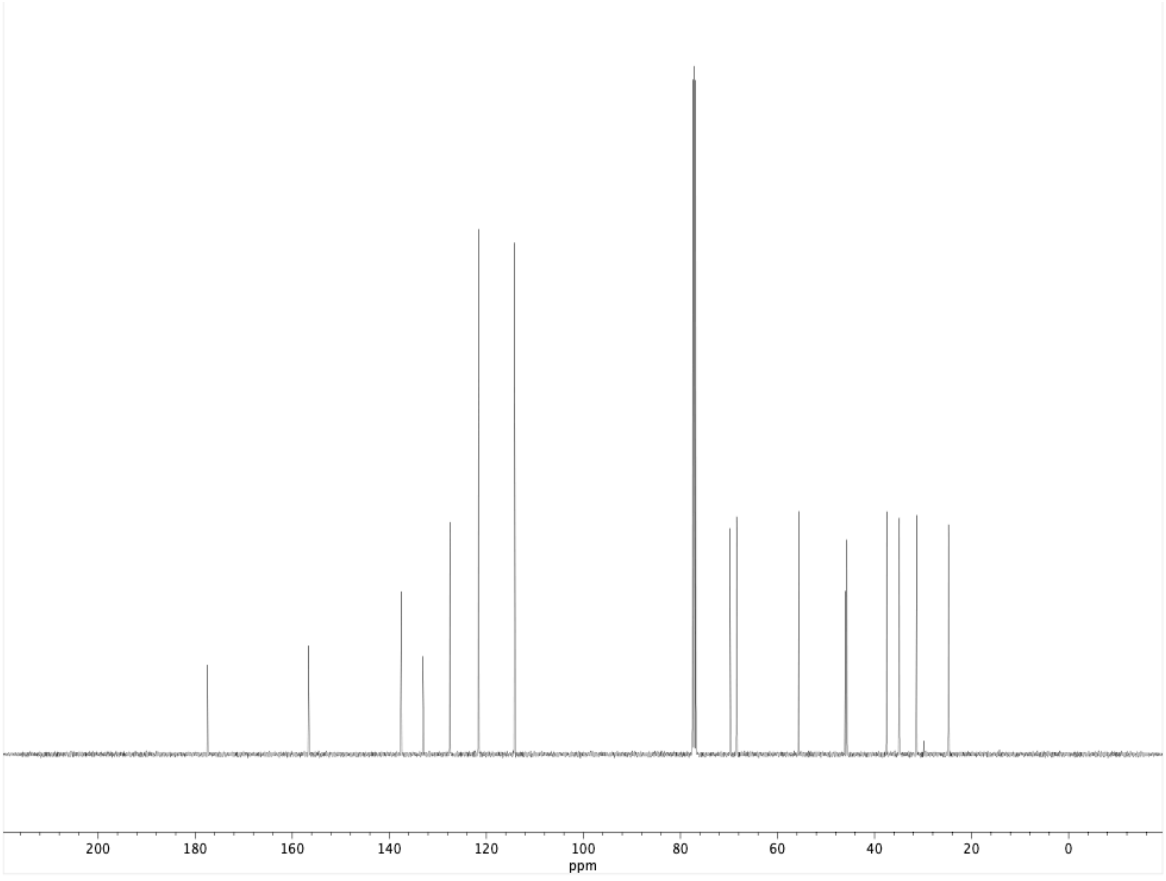


Figure A3.41 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***136****.*

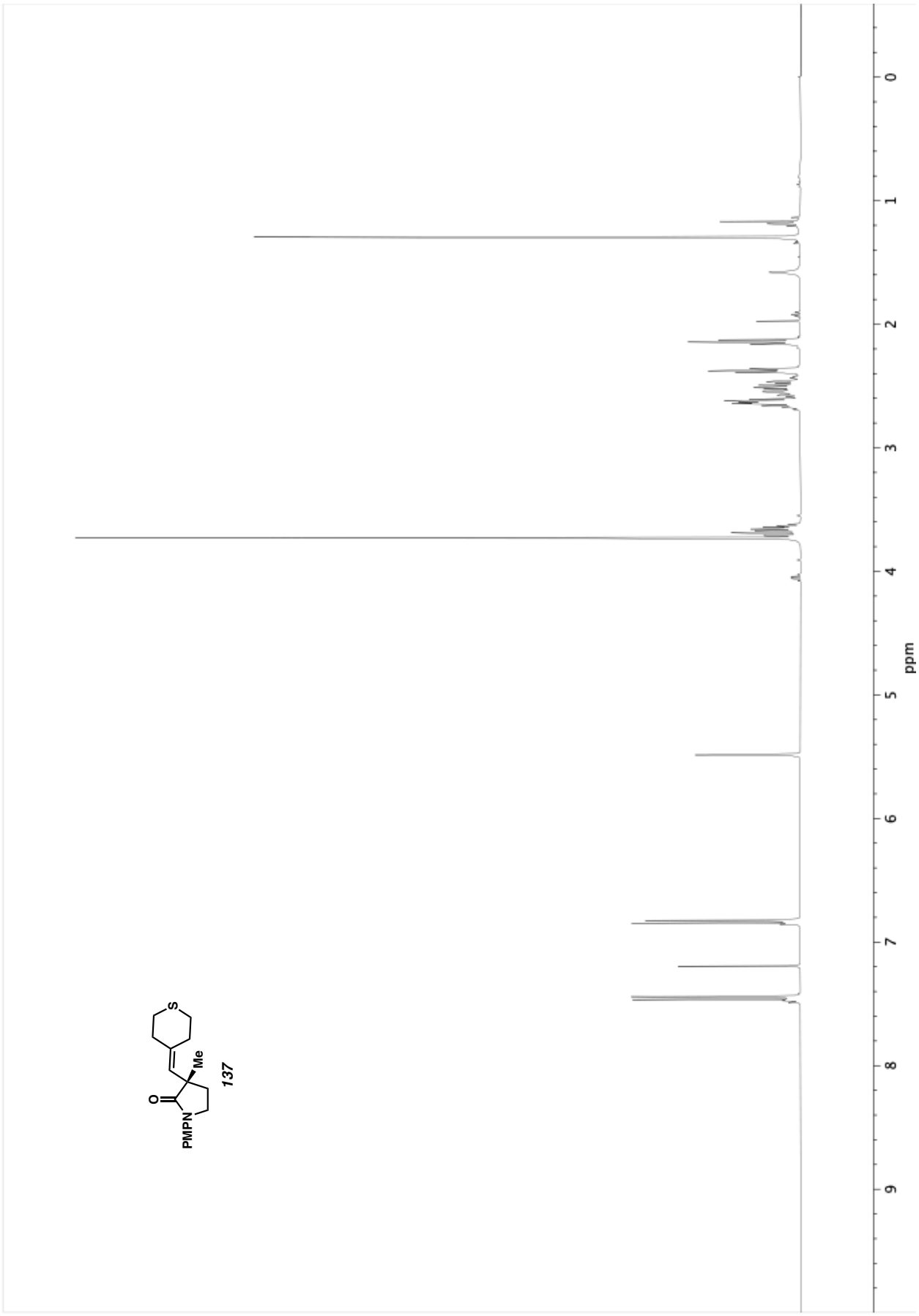


Figure A3.42. *^1H NMR (400 MHz, $CDCl_3$) of* ***137****.*

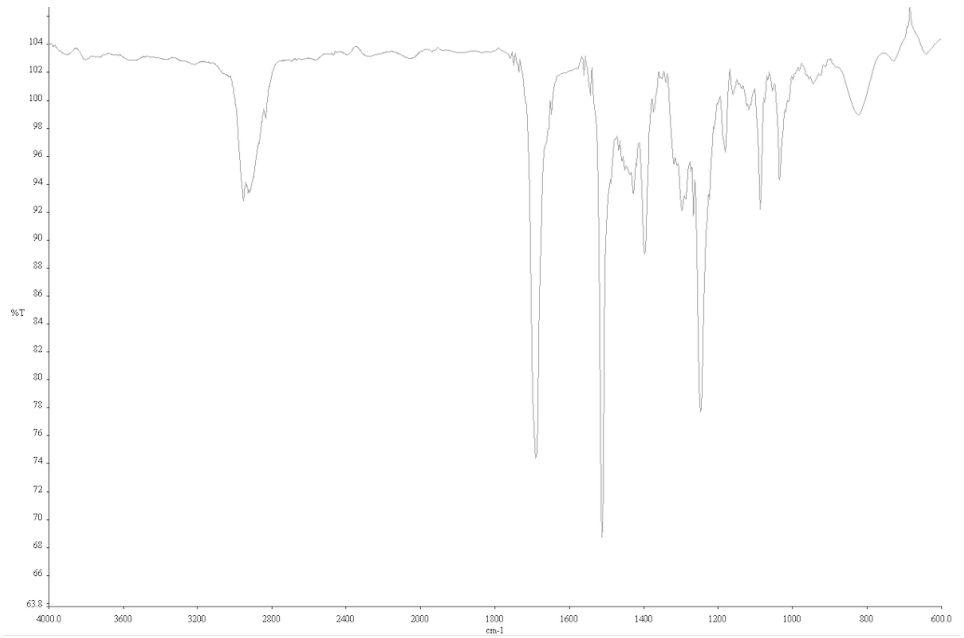


Figure A3.43 *Infrared spectrum (Thin Film, NaCl) of* ***137****.*

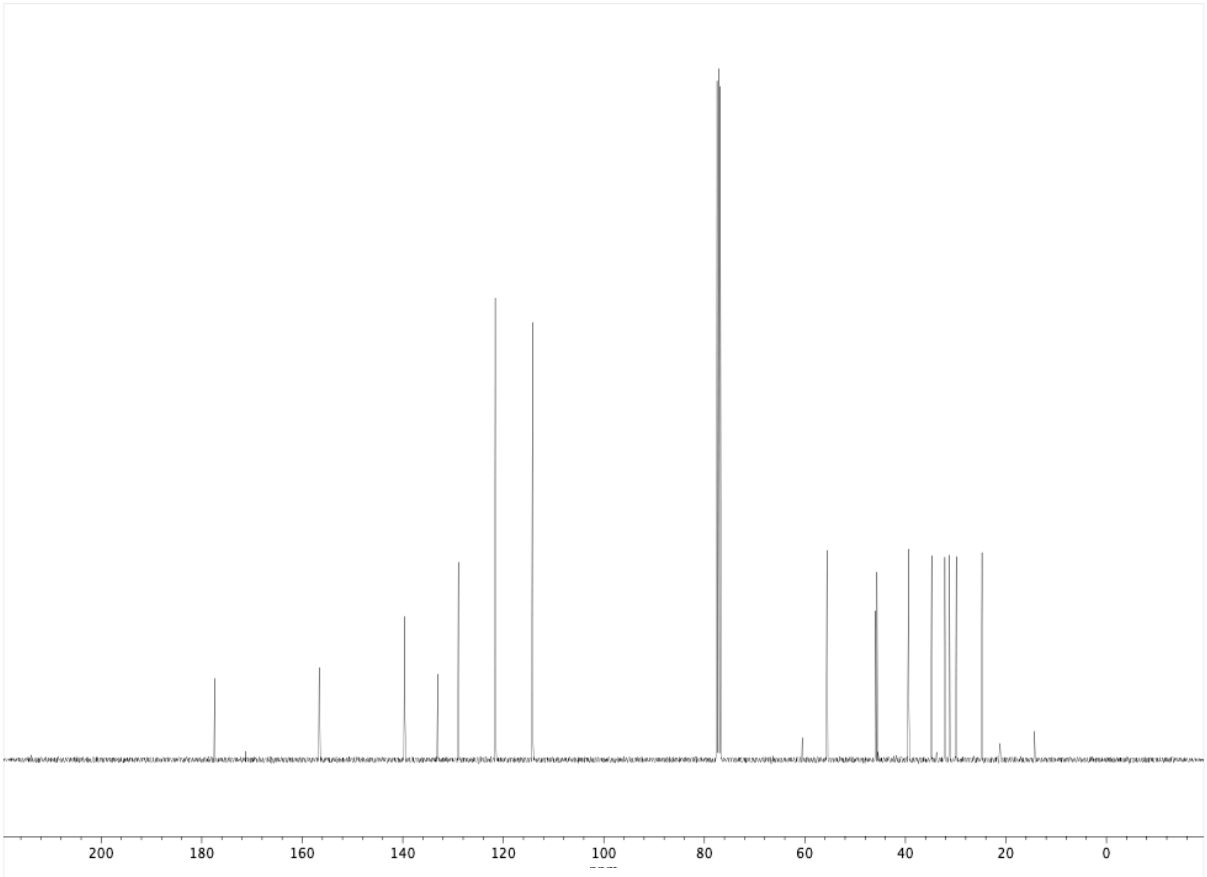


Figure A3.44 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***137****.*

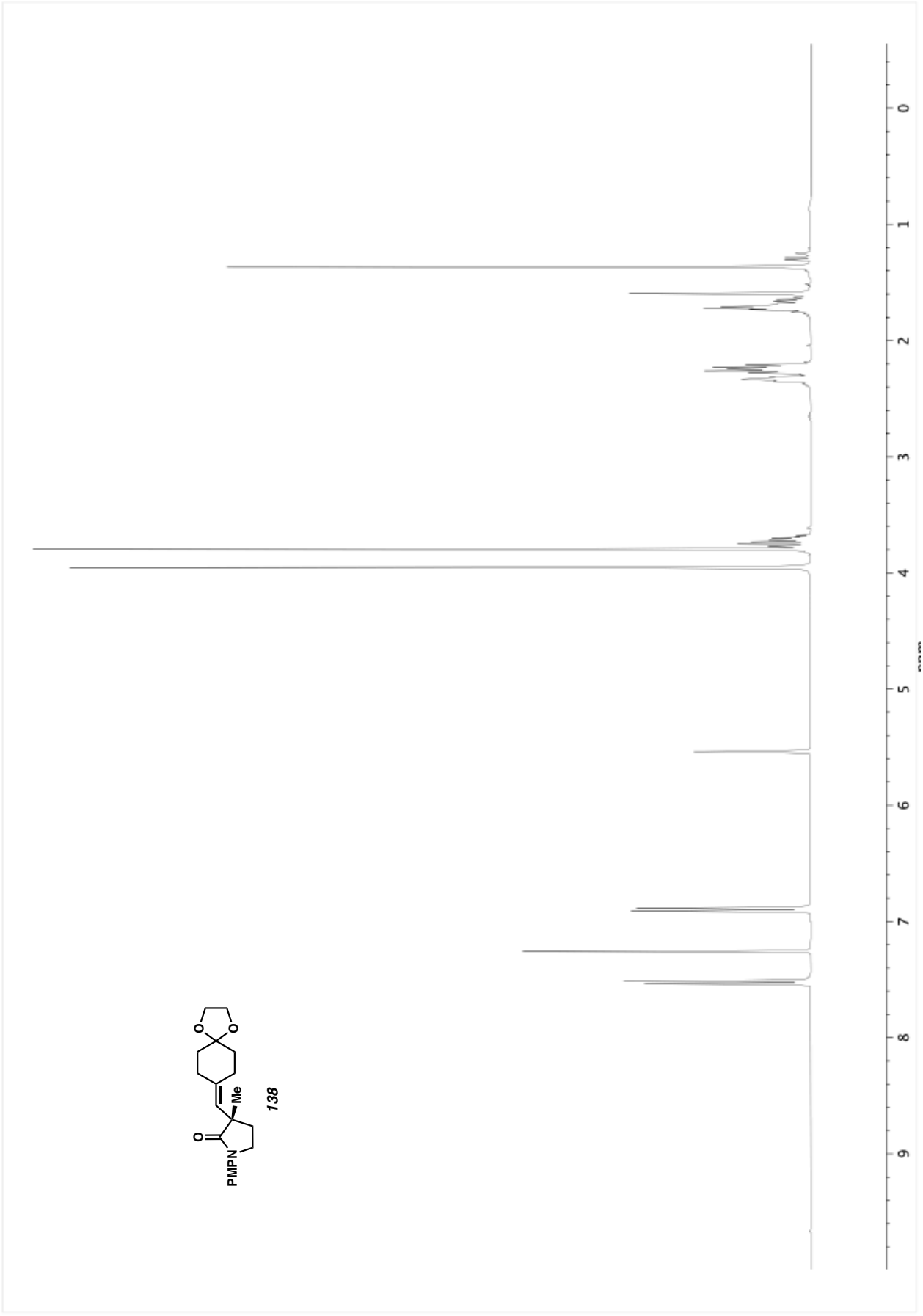


Figure A3.45 *^1H NMR (400 MHz, $CDCl_3$) of **138**.*

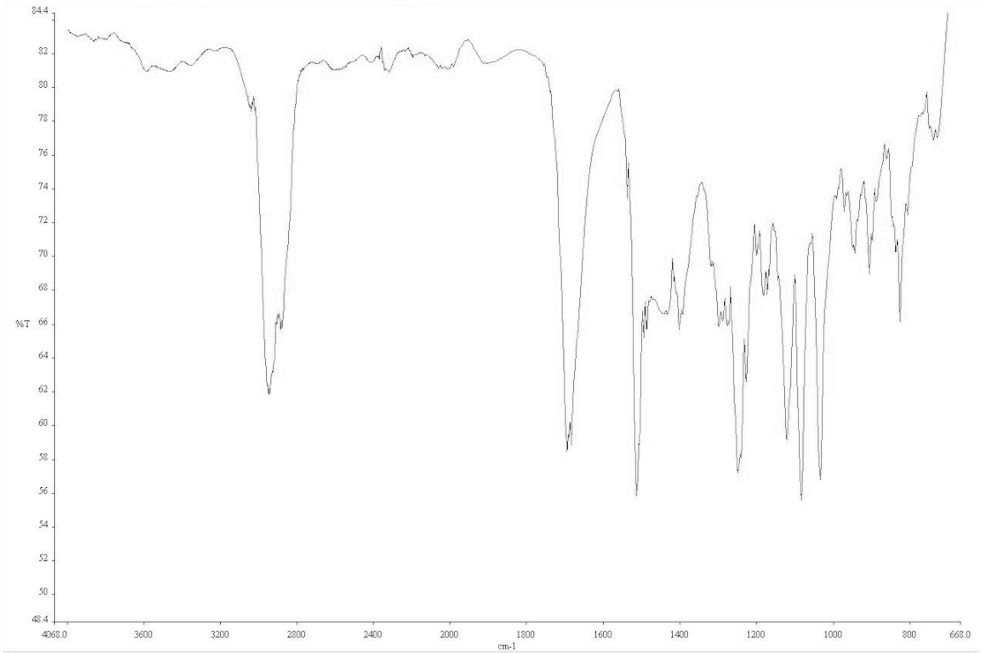


Figure A3.46 *Infrared spectrum (Thin Film, NaCl) of* ***138.***

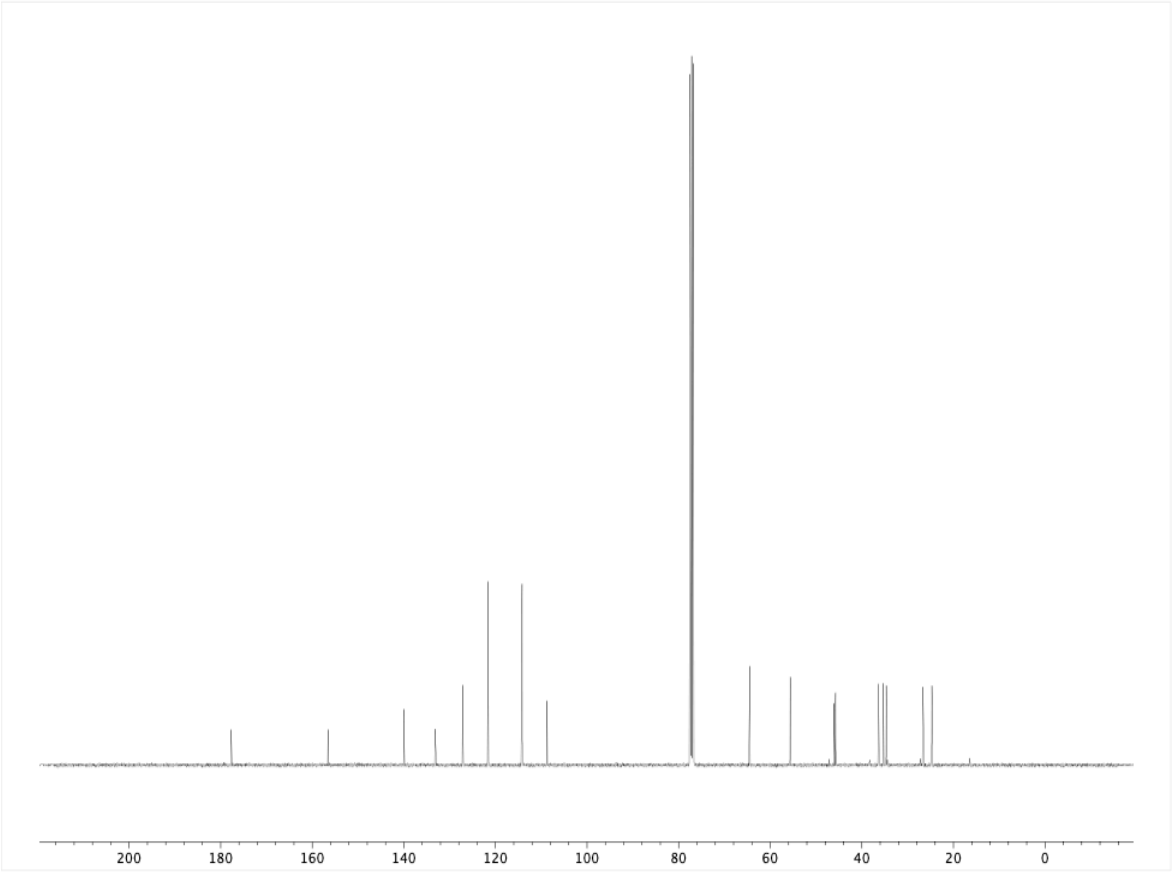


Figure A3.47 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***138****.*

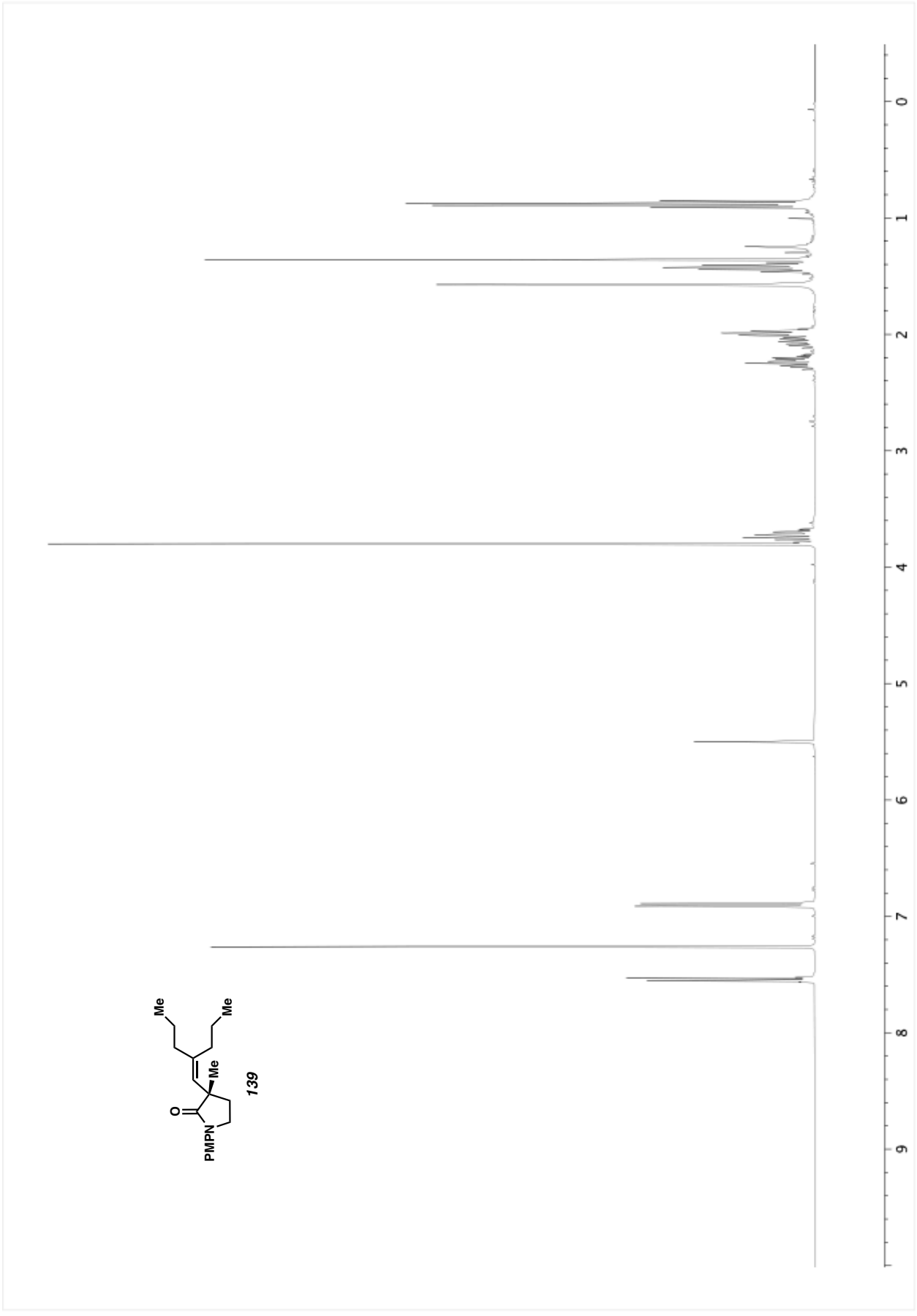


Figure A3.48 *^1H NMR (400 MHz, $CDCl_3$) of* ***139.***

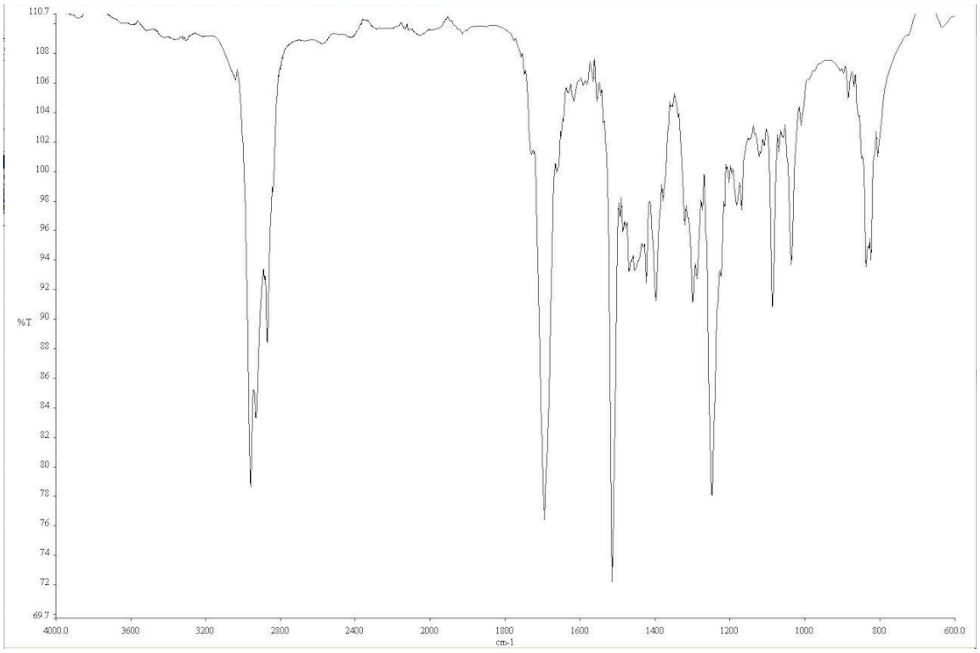


Figure A3.49 *Infrared spectrum (Thin Film, NaCl) of* ***139***.

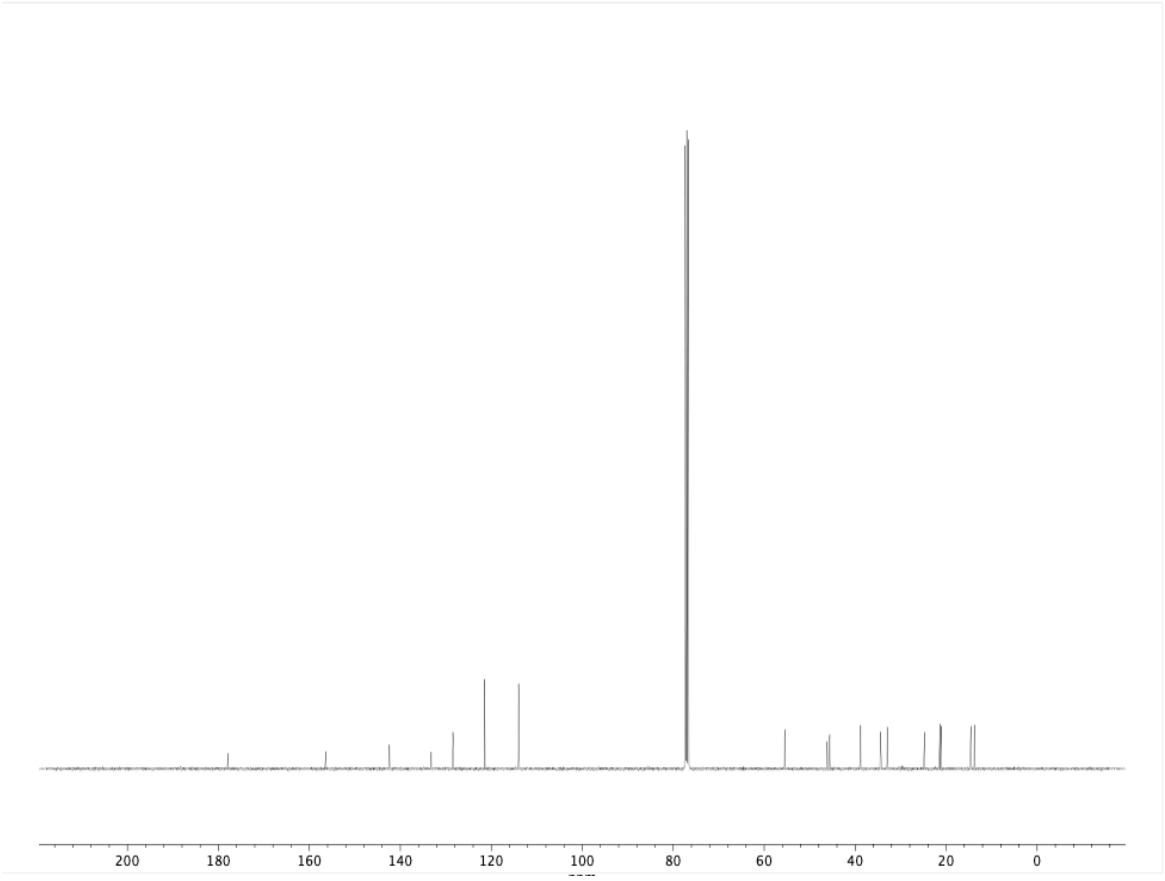


Figure A3.50 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***139***.

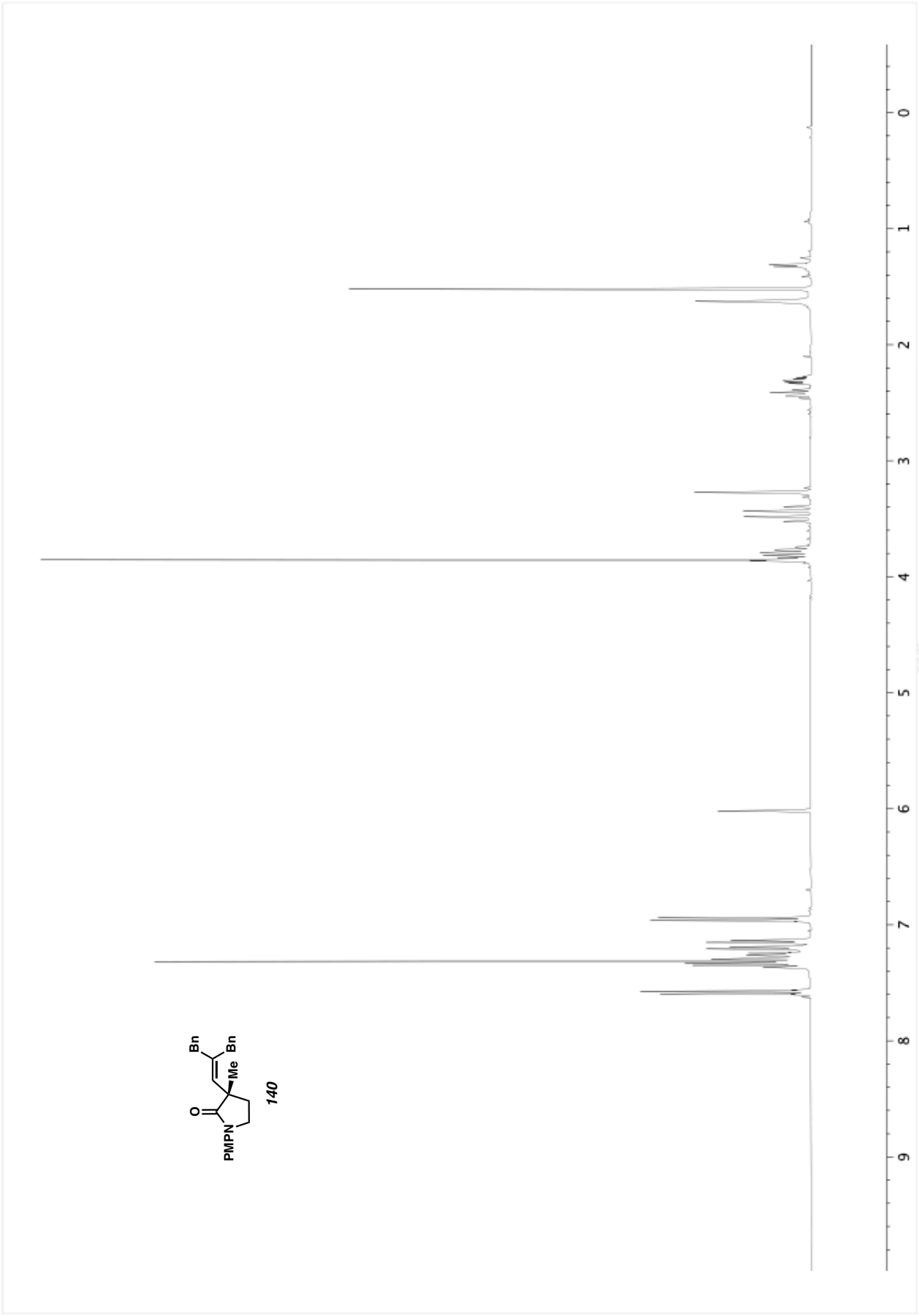


Figure A3.51 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***140****.*

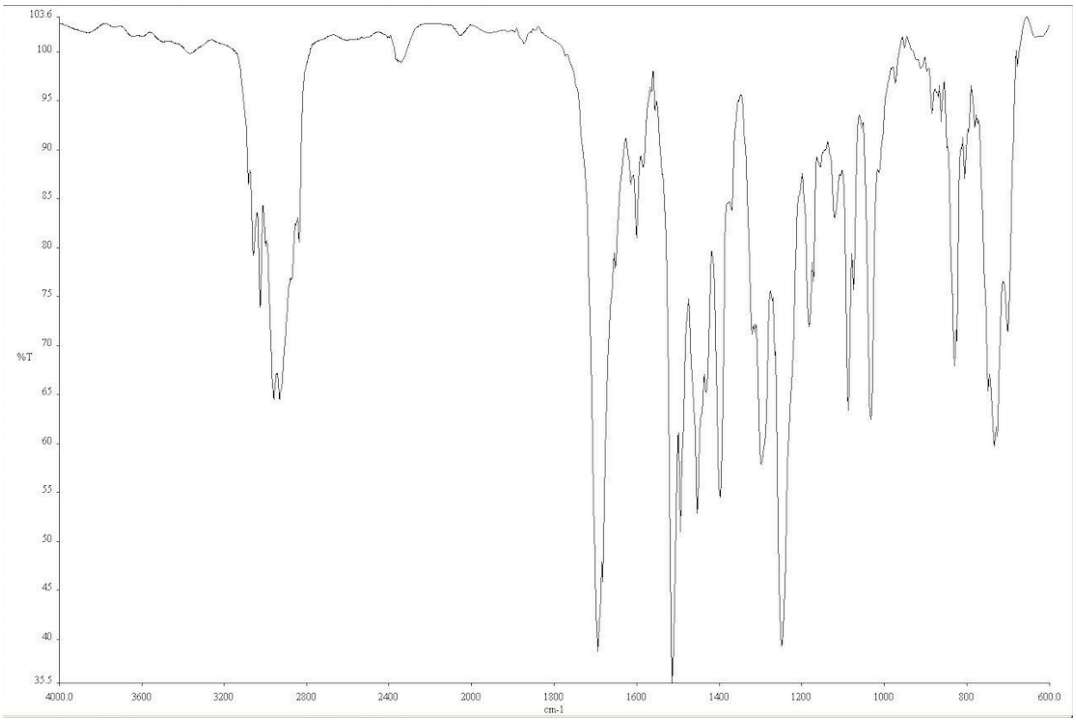


Figure A3.52 *Infrared spectrum (Thin Film, NaCl) of* ***140***.

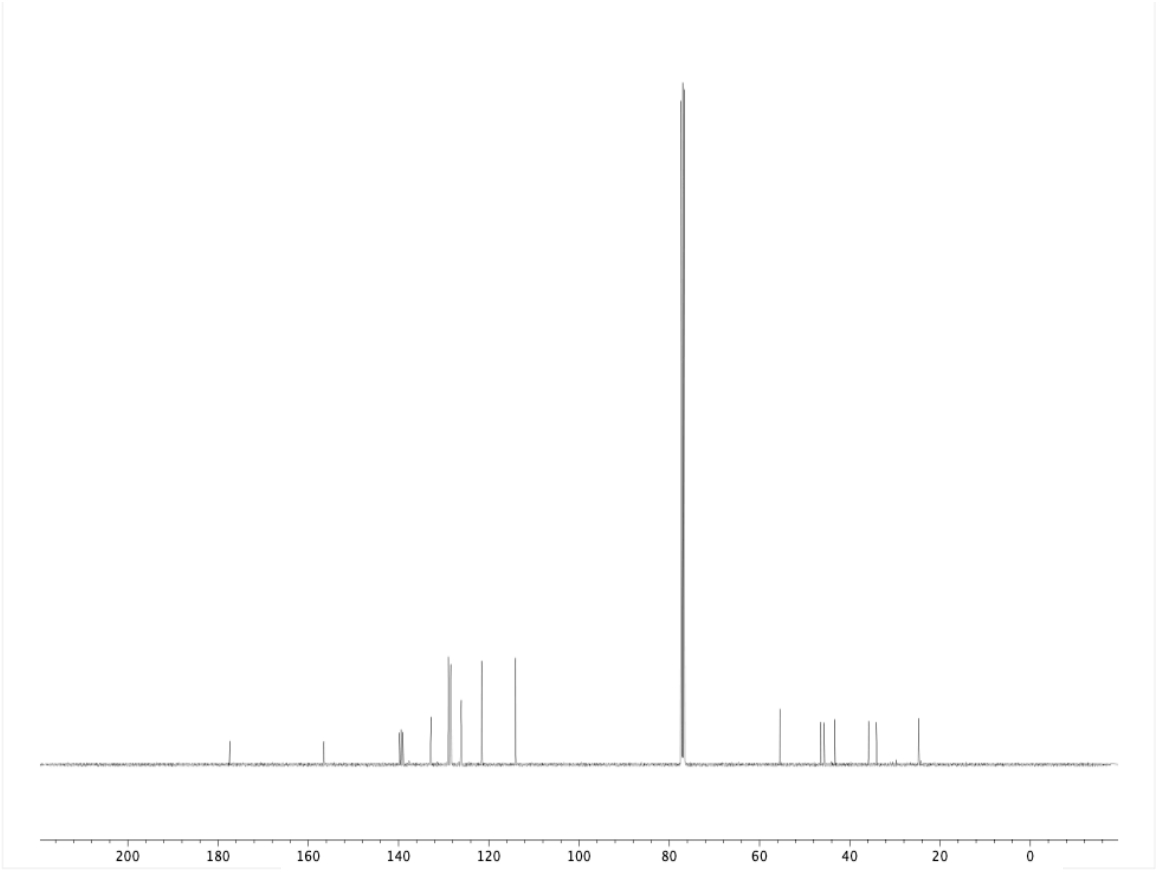


Figure A3.53 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***140***.

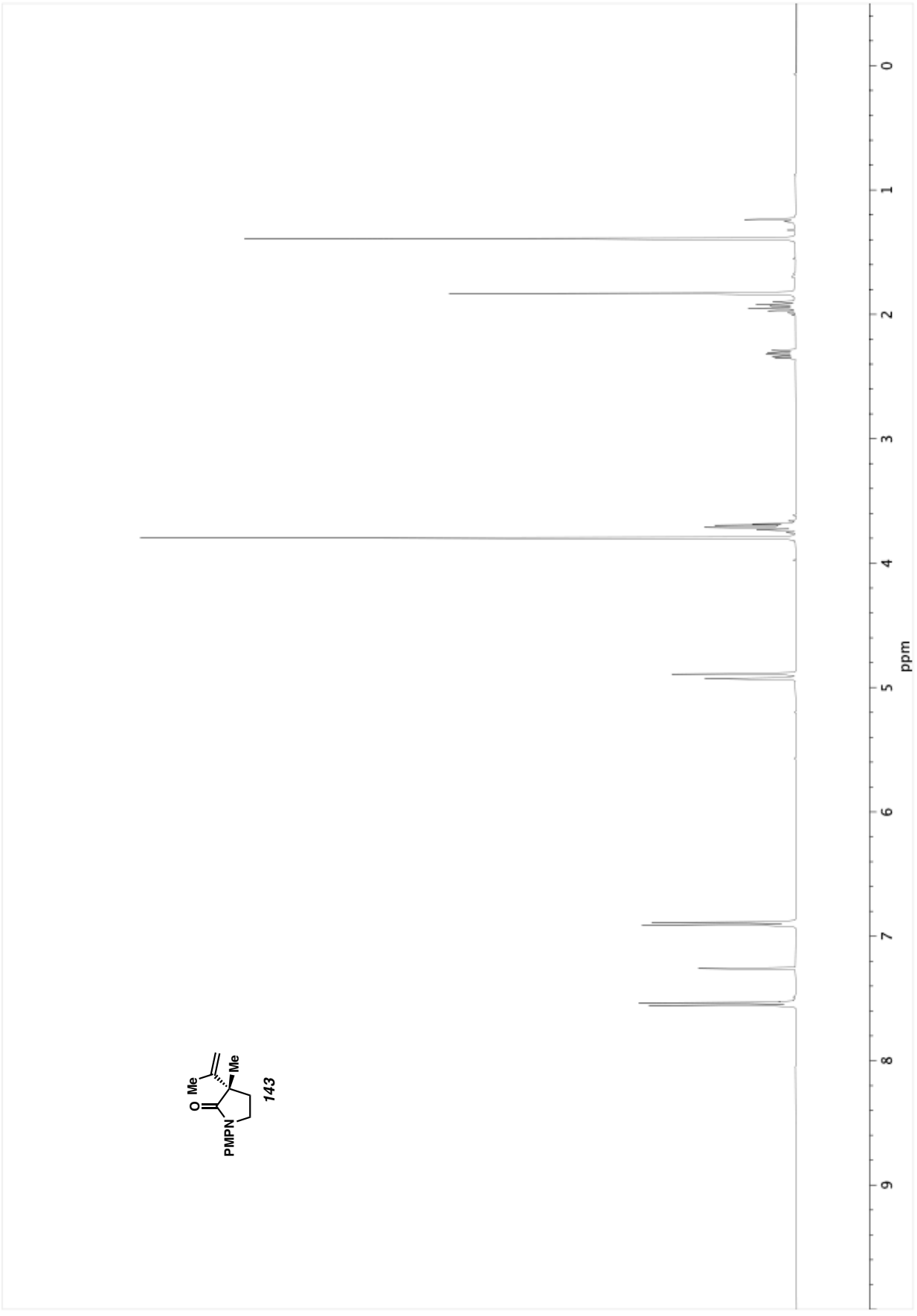


Figure A3.54 *^1H NMR (400 MHz, $CDCl_3$) of* ***143****.*

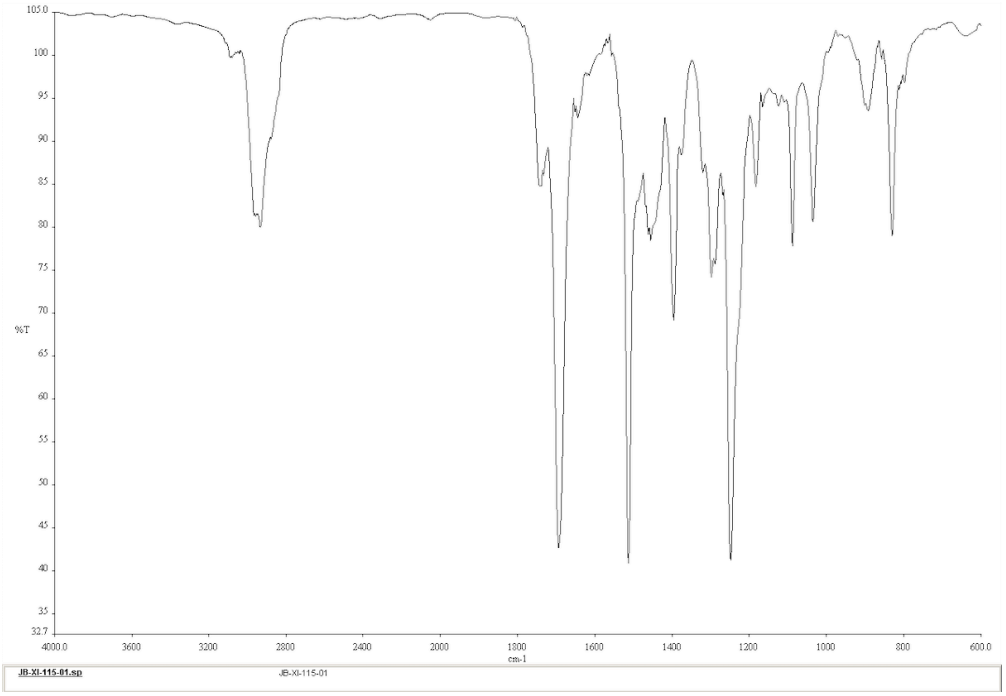


Figure A3.55 *Infrared spectrum (Thin Film, NaCl) of* ***143***.

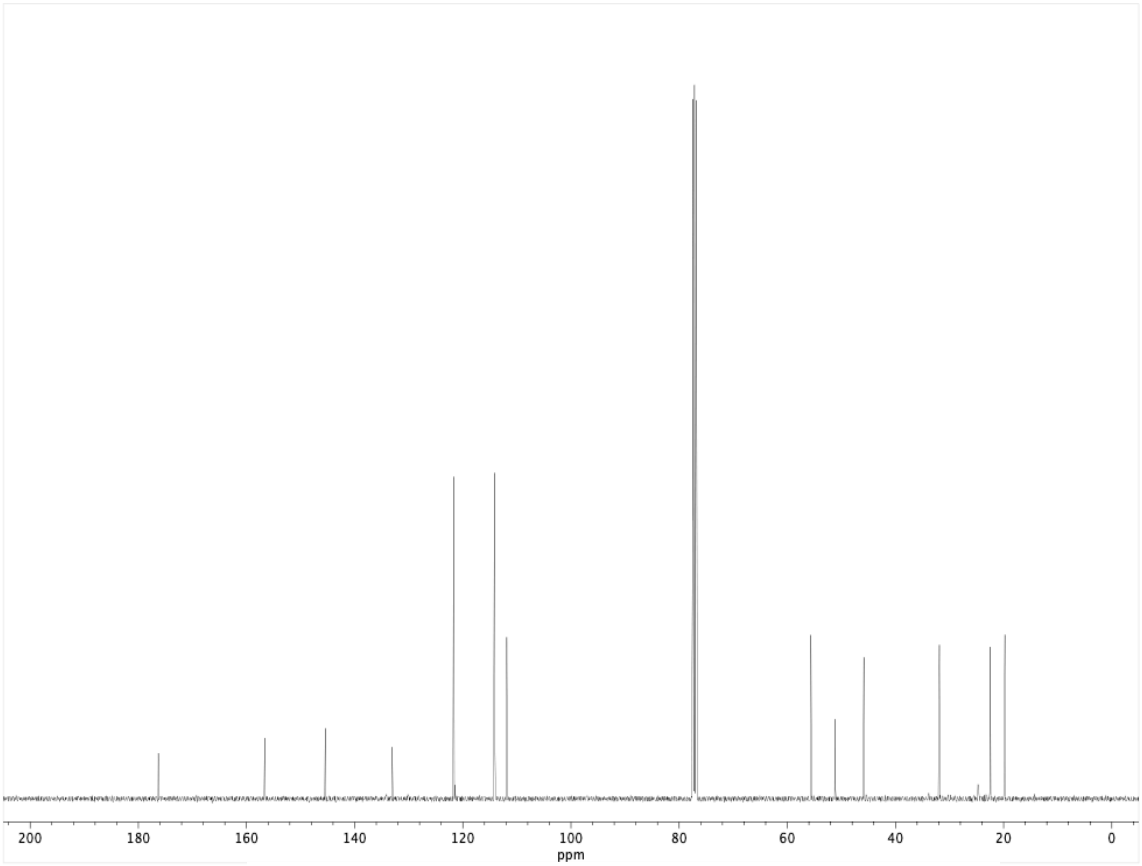


Figure A3.56 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***143***.

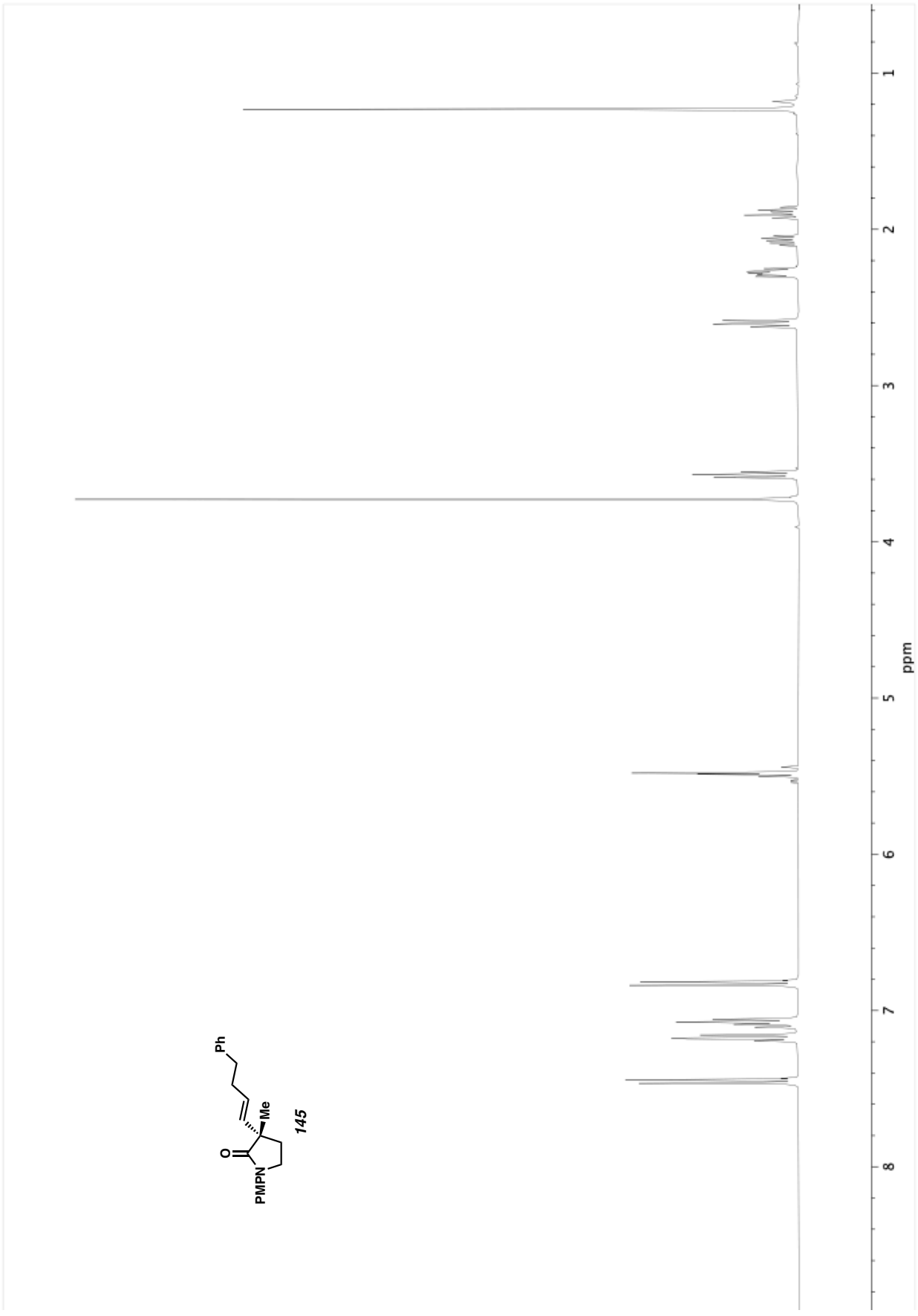


Figure A3.57 *^1H NMR (400 MHz, $CDCl_3$) of* ***145****.*

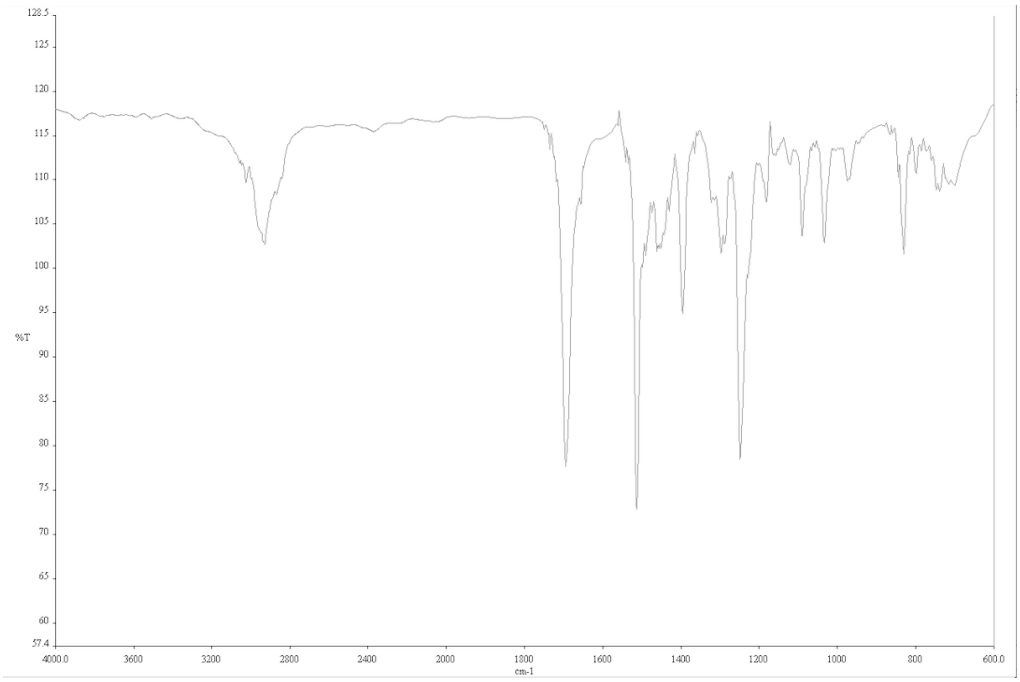


Figure A3.58 *Infrared spectrum (Thin Film, NaCl) of* ***145****.*

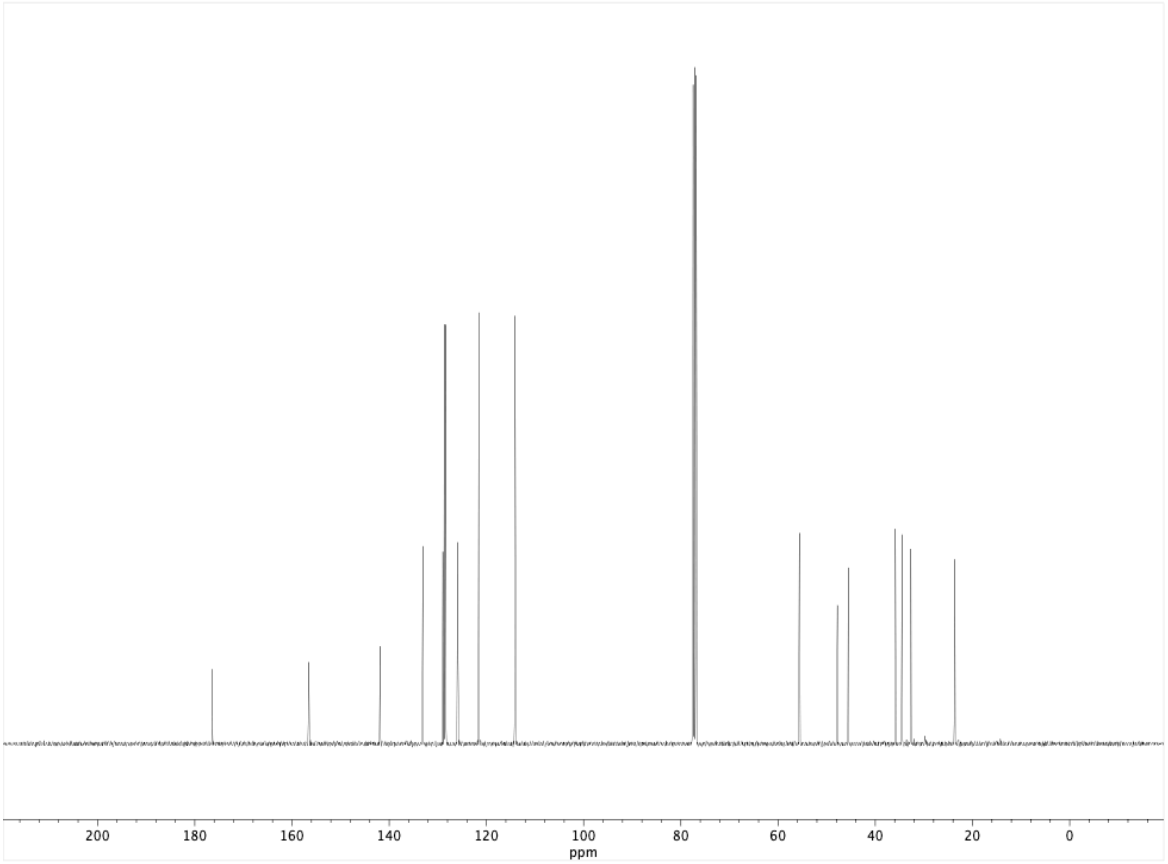


Figure A3.59 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***145****.*

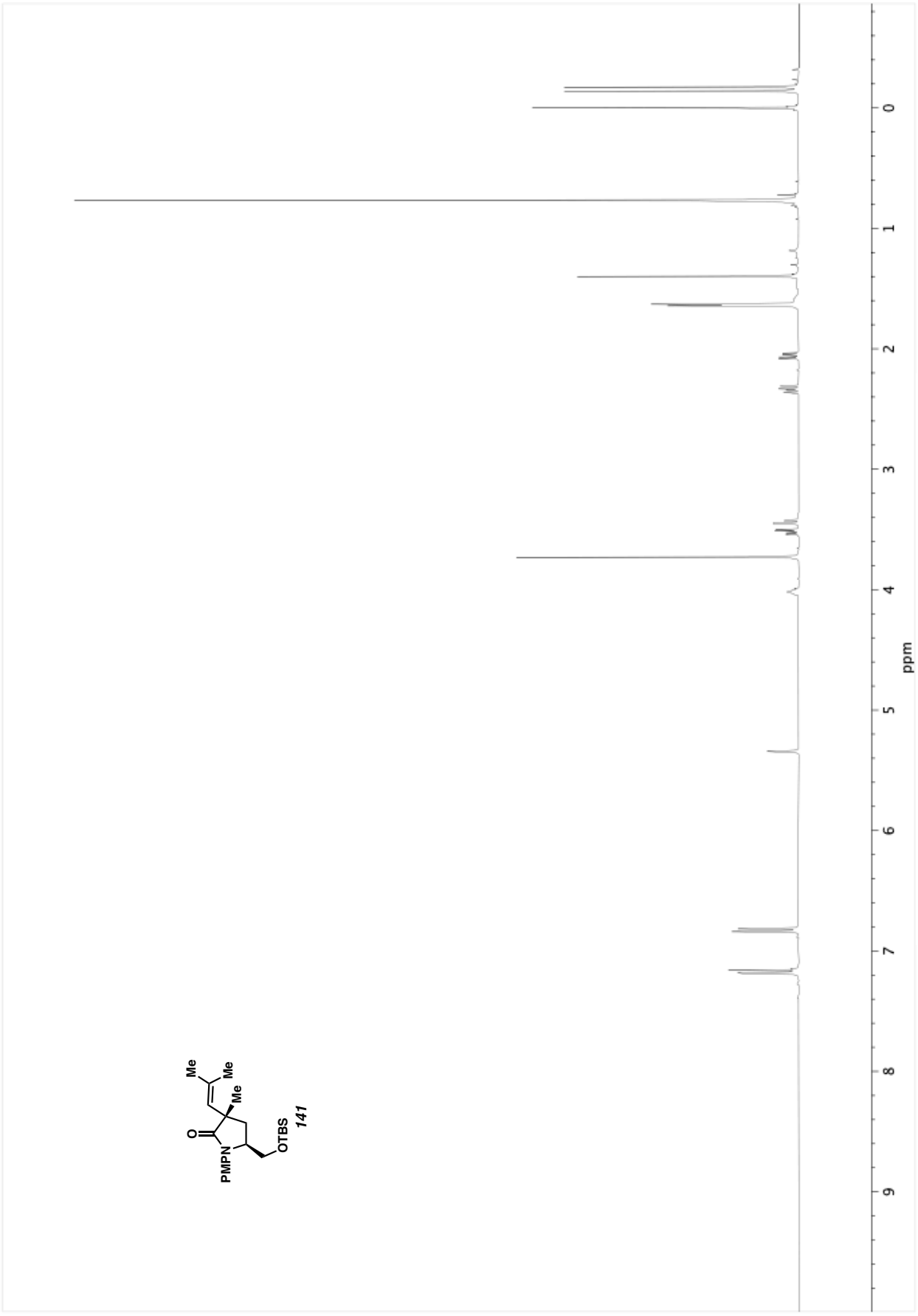


Figure A3.60 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***141****.*

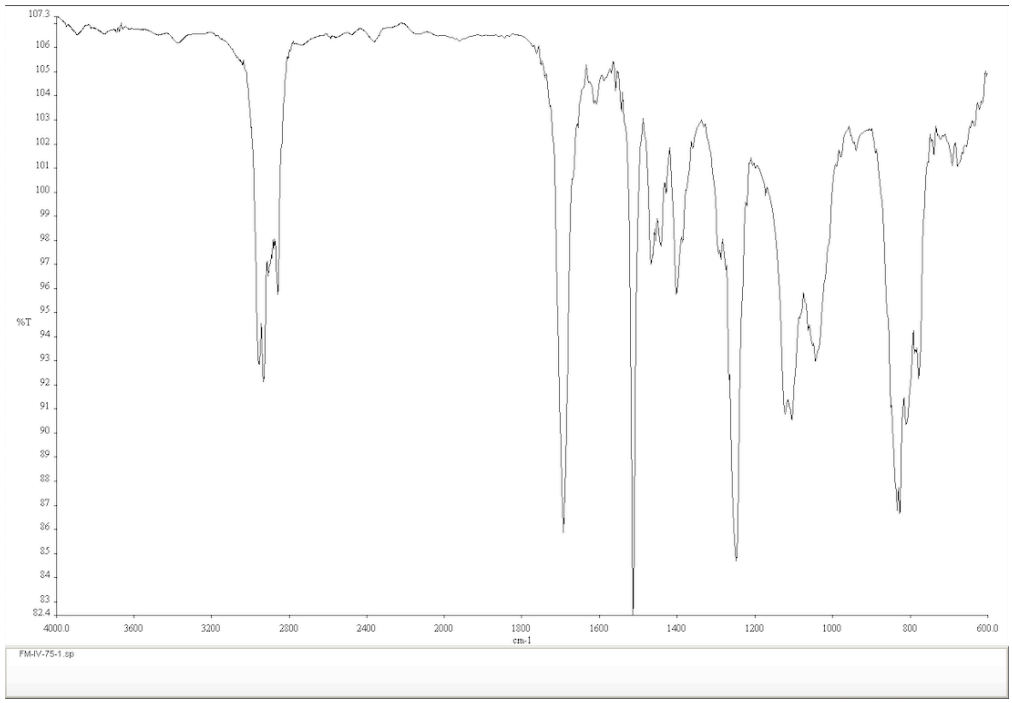


Figure A3.61 *Infrared spectrum (Thin Film, NaCl) of* ***141***.

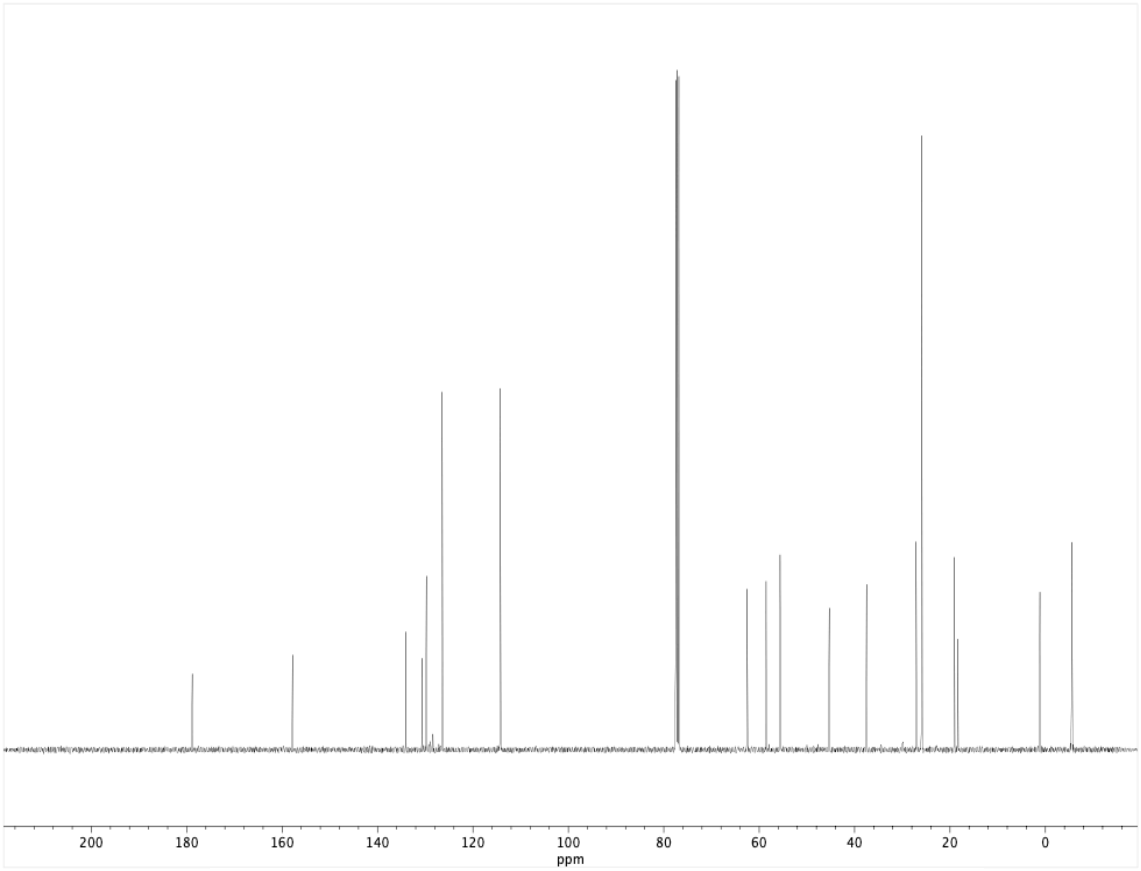


Figure A3.62 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***141***.

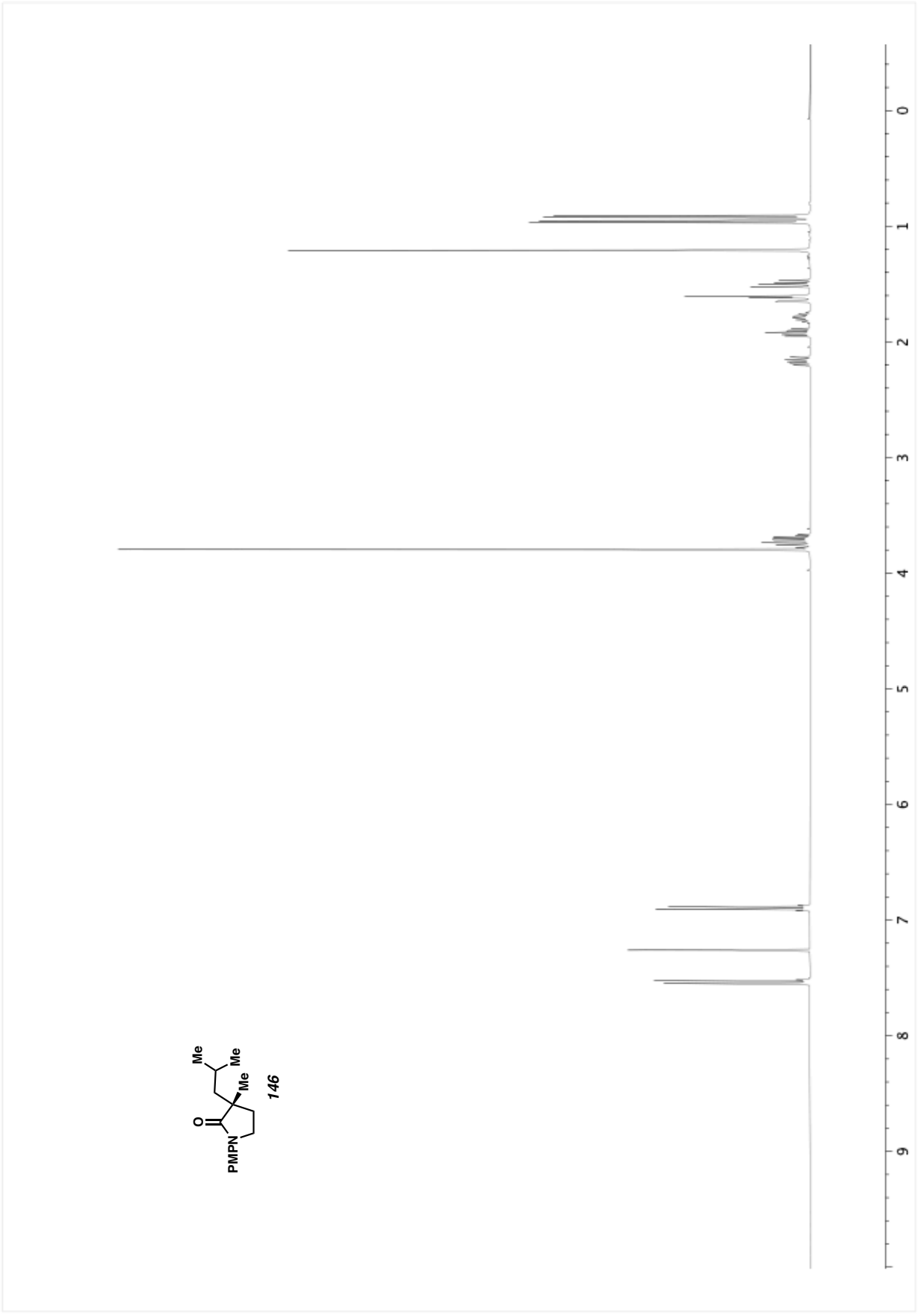


Figure A3.63 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***146****.*

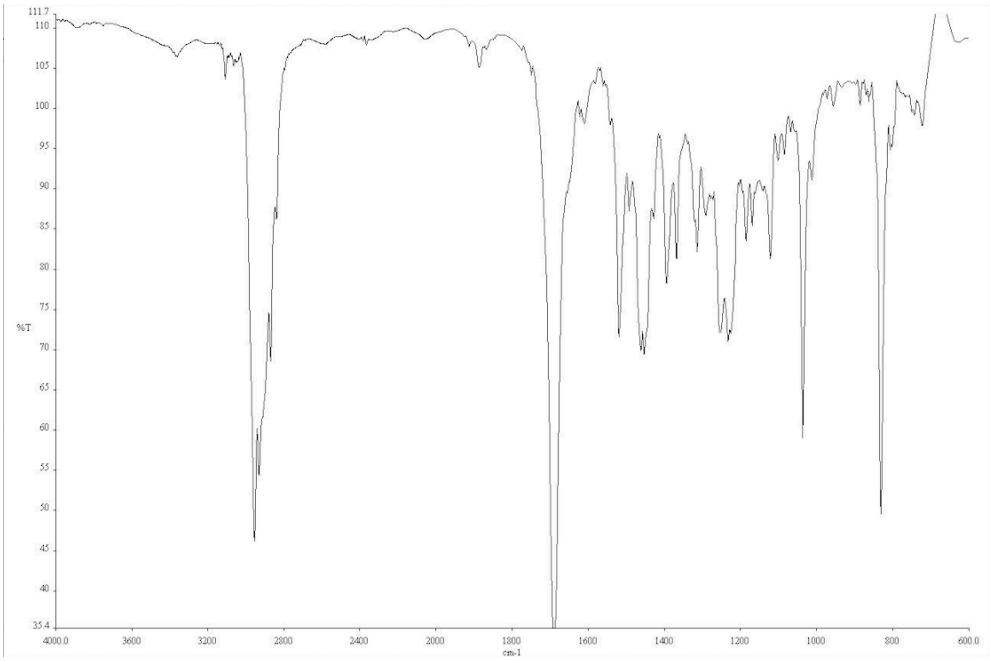


Figure A3.64 *Infrared spectrum (Thin Film, NaCl) of* ***146***.

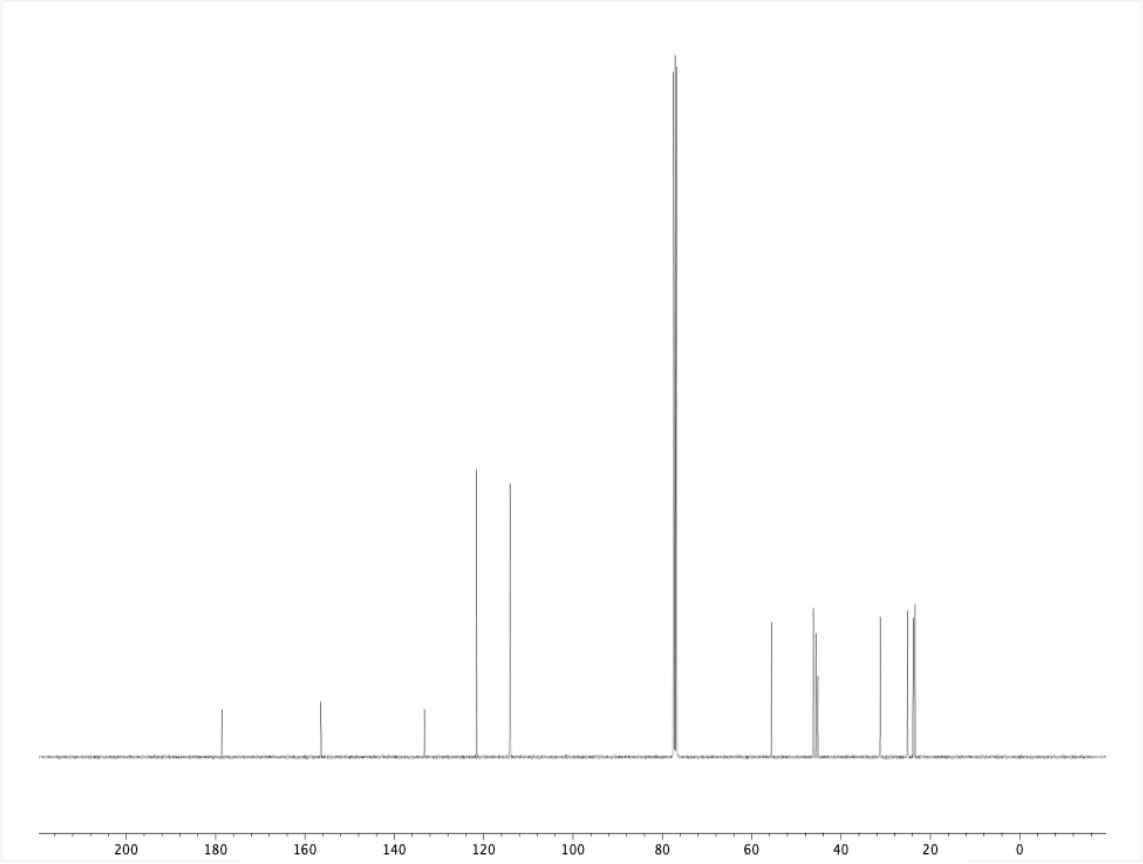


Figure A3.65 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***146***.

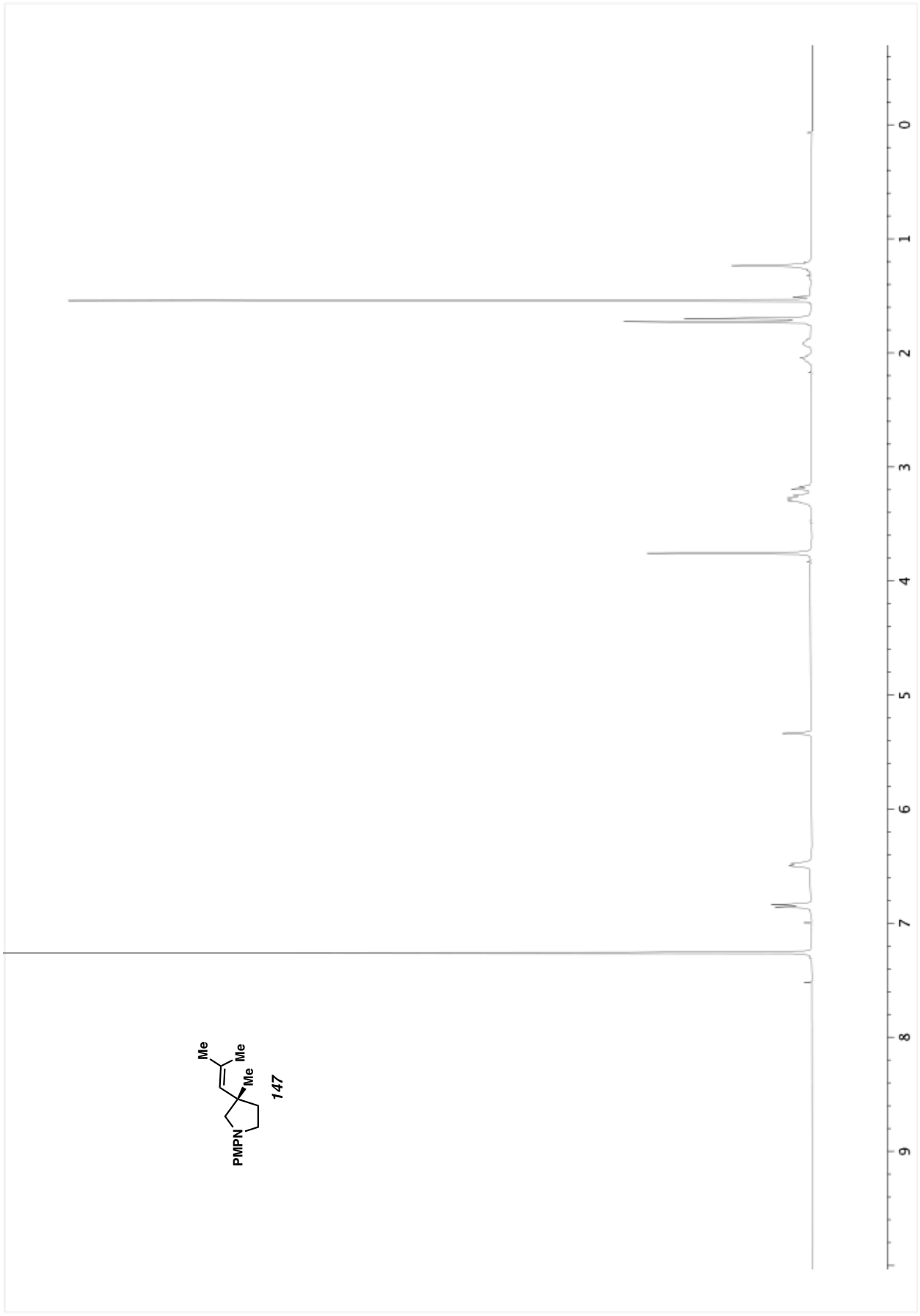


Figure A3.66 *^1H NMR (400 MHz, $CDCl_3$) of* ***147.***

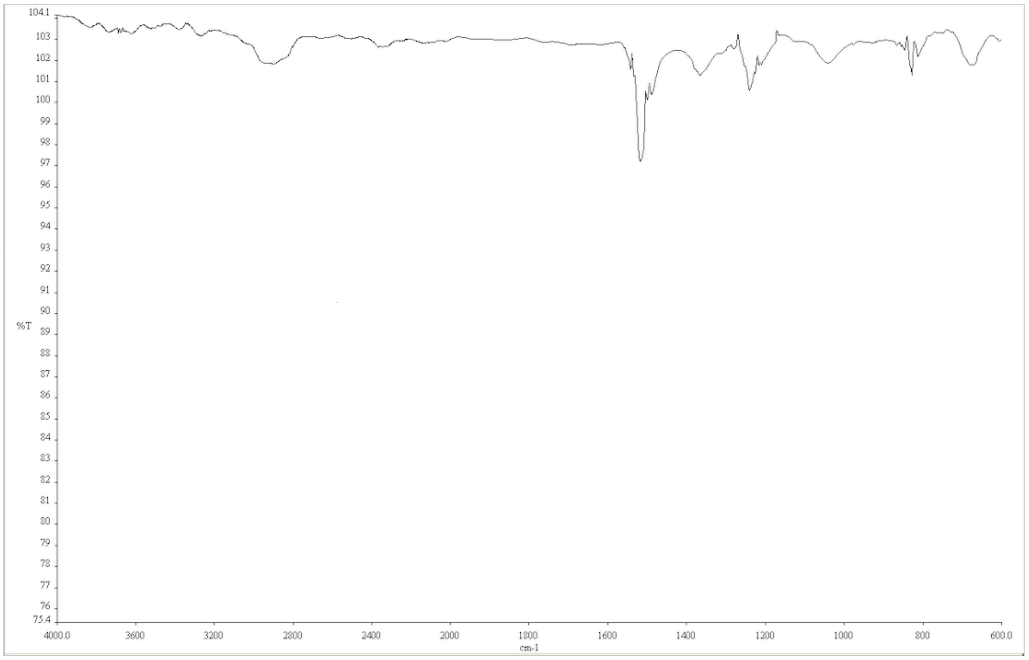


Figure A3.67 *Infrared spectrum (Thin Film, NaCl) of* ***147****.*

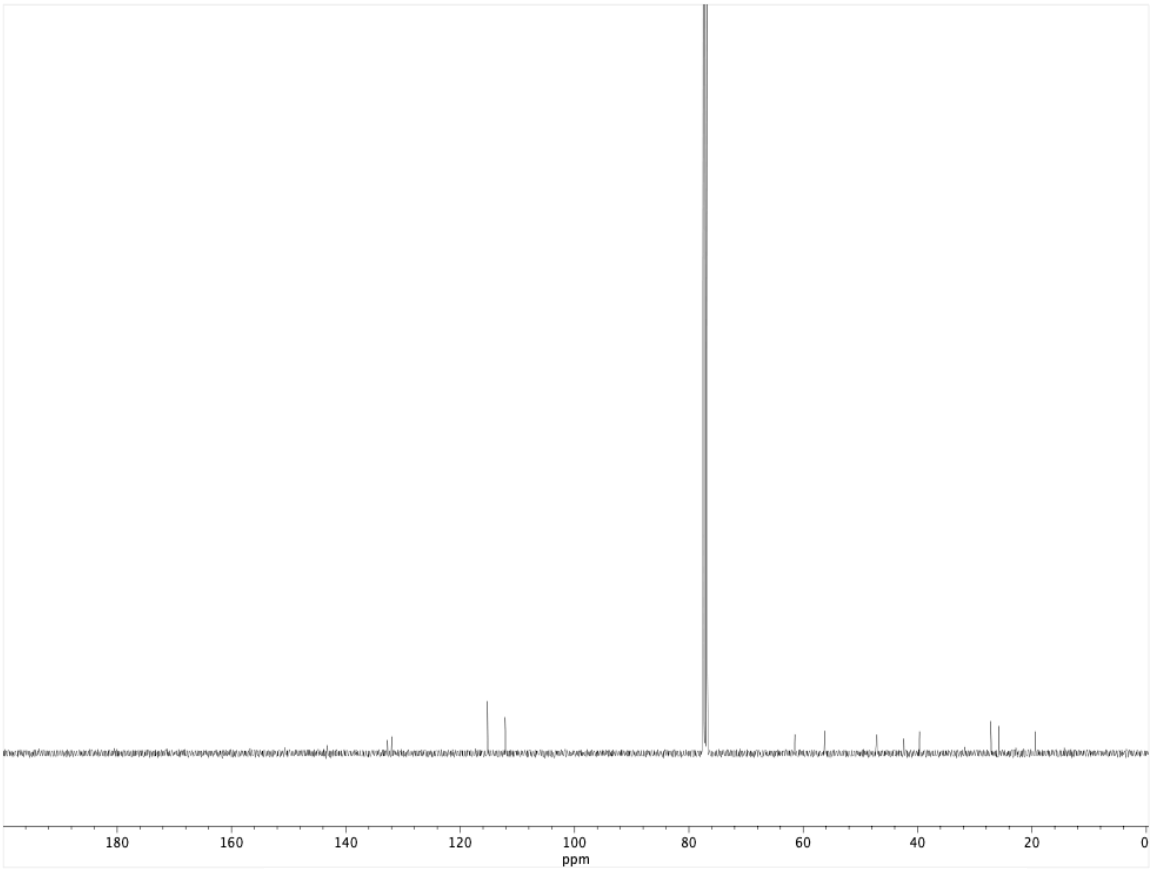


Figure A3.68 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***147****.*

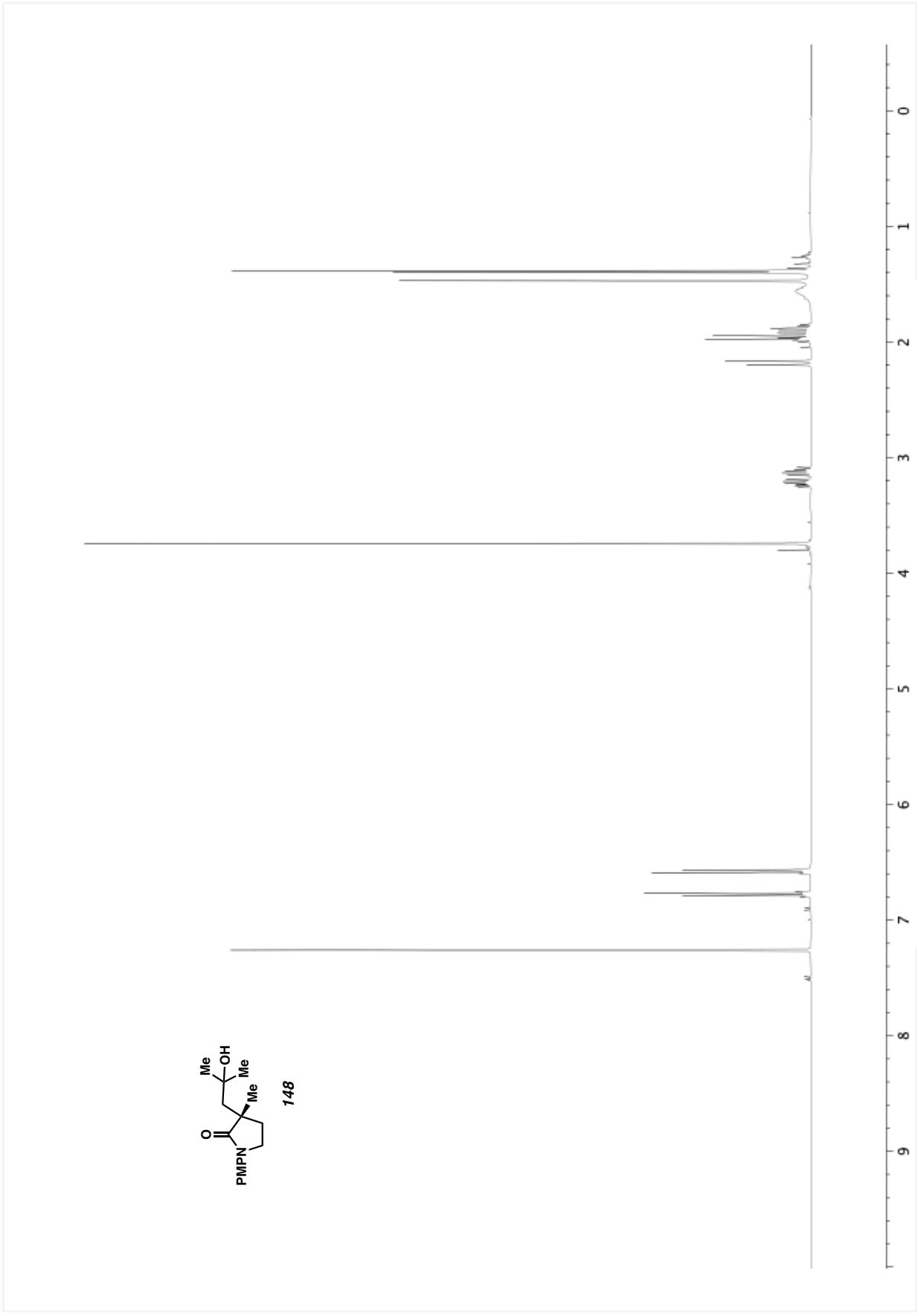


Figure A3.69 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***148****.*

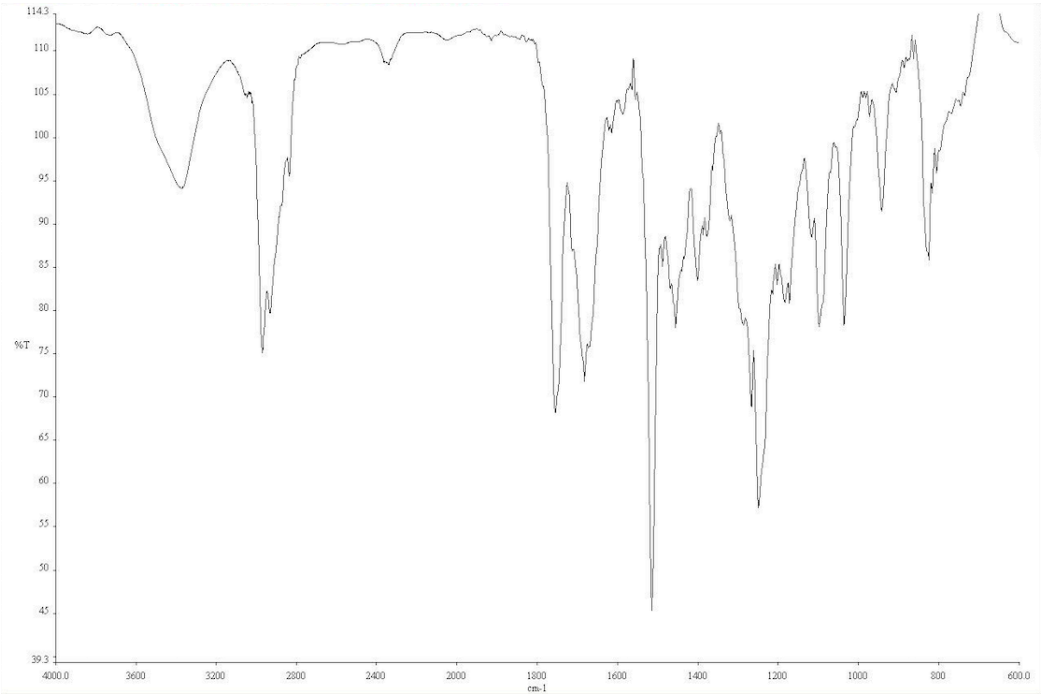


Figure A3.70 *Infrared spectrum (Thin Film, NaCl) of* ***148****.*

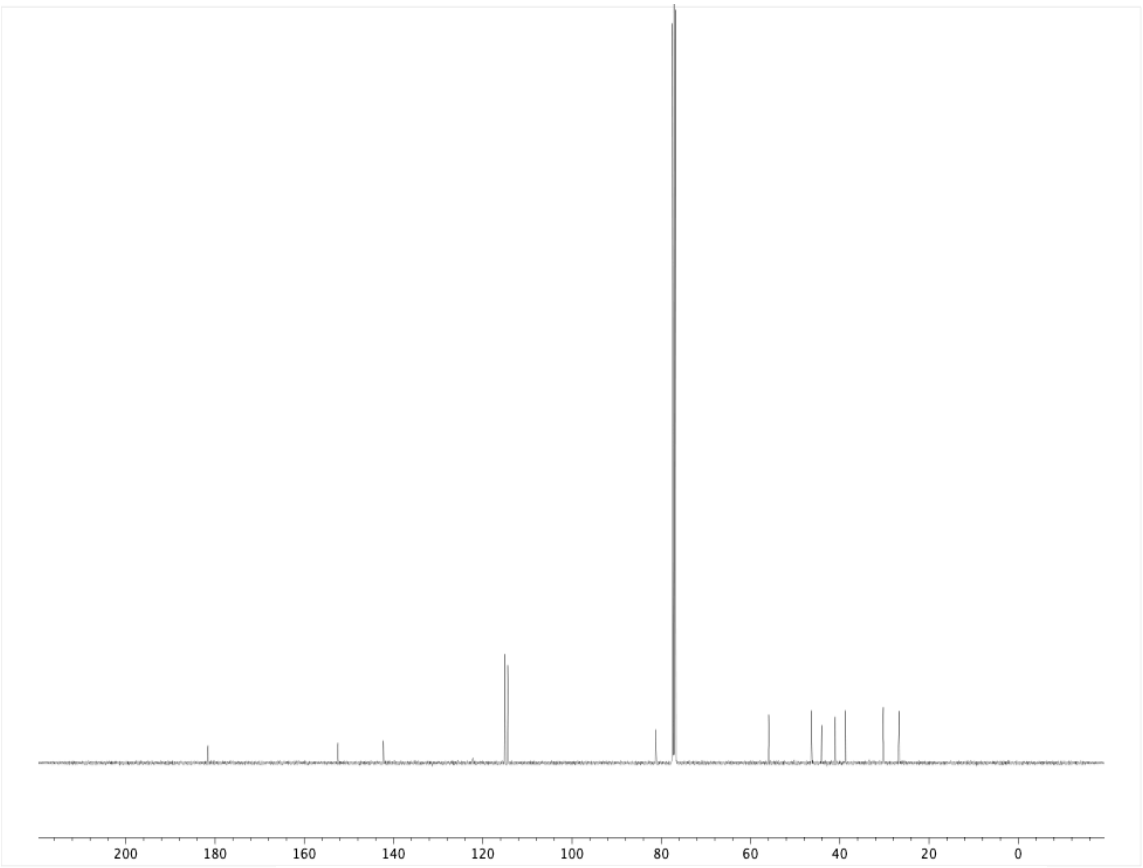


Figure A3.71 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***148****.*

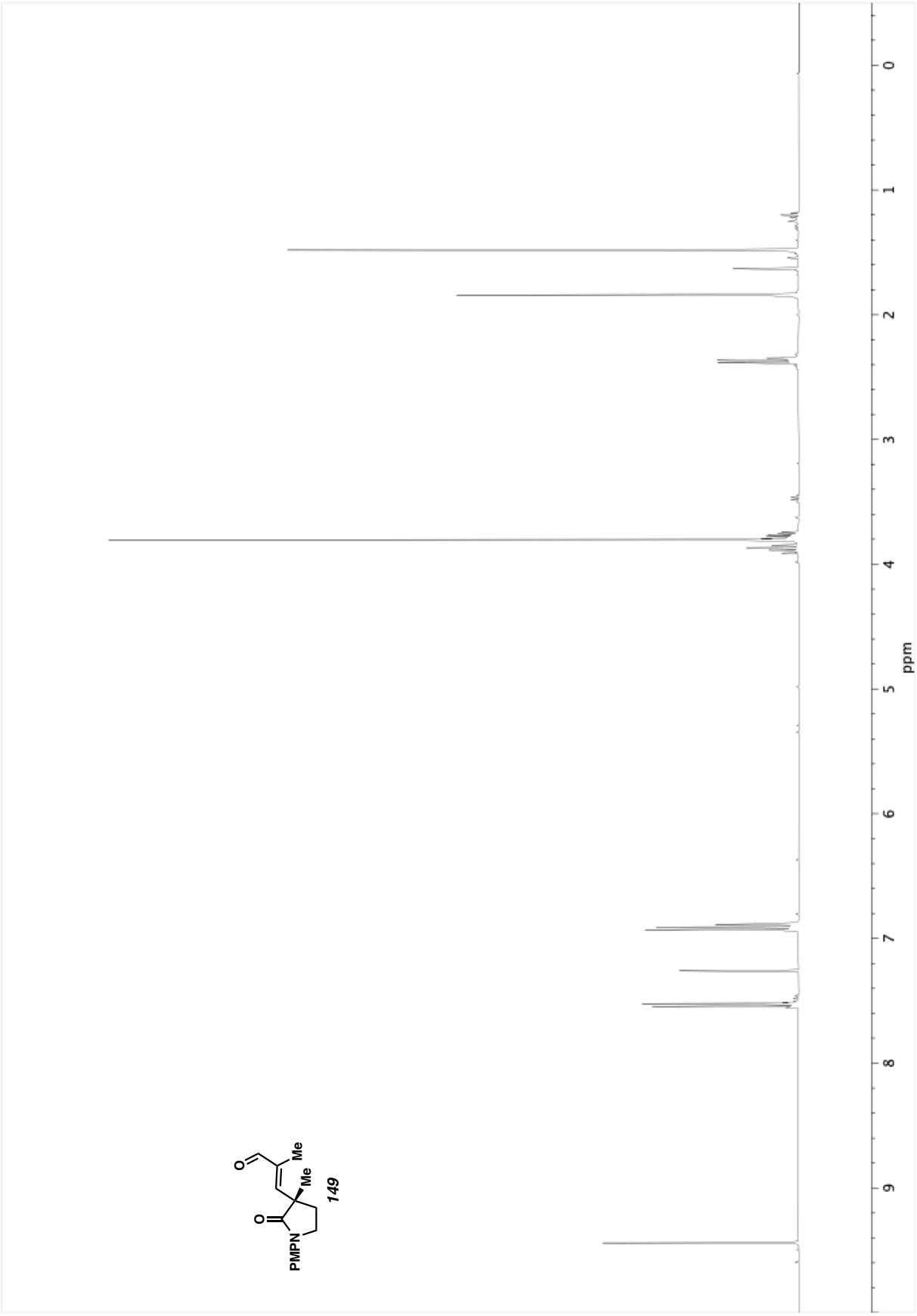


Figure A3.72 *^1H NMR (400 MHz, $CDCl_3$) of* ***149****.*

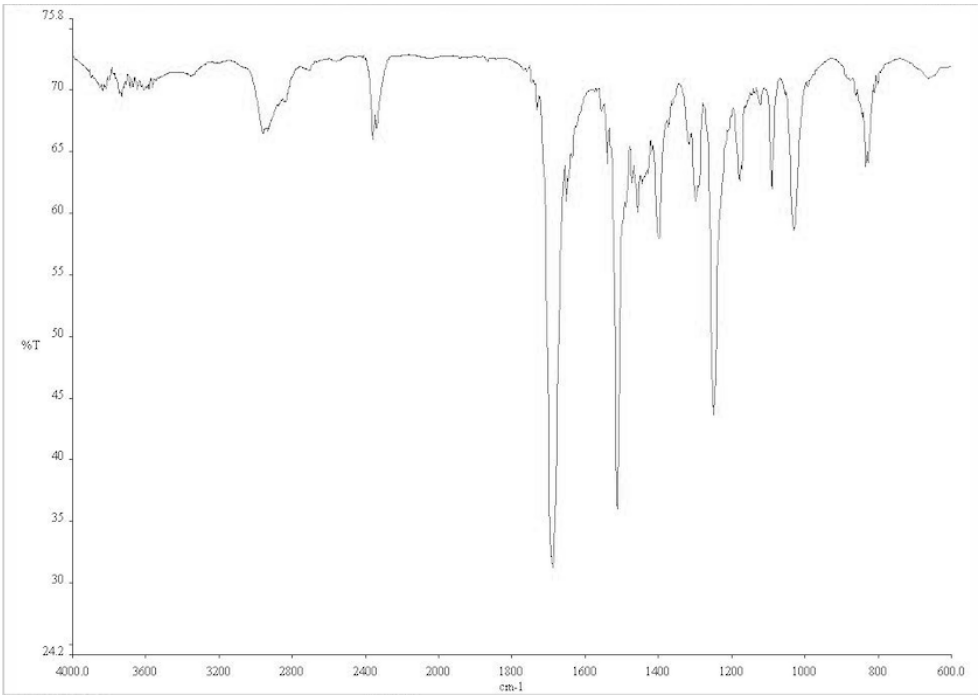


Figure A3.73 *Infrared spectrum (Thin Film, NaCl) of* ***149****.*

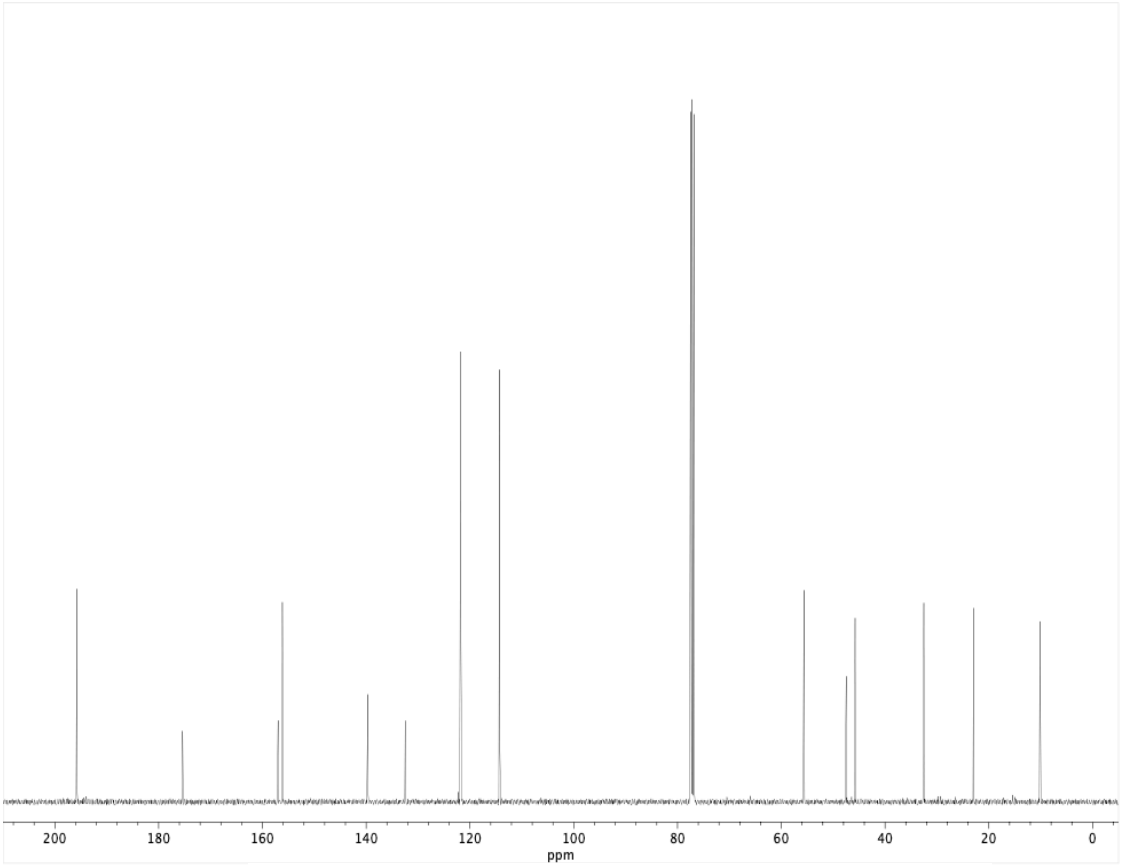


Figure A3.74 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***149****.*

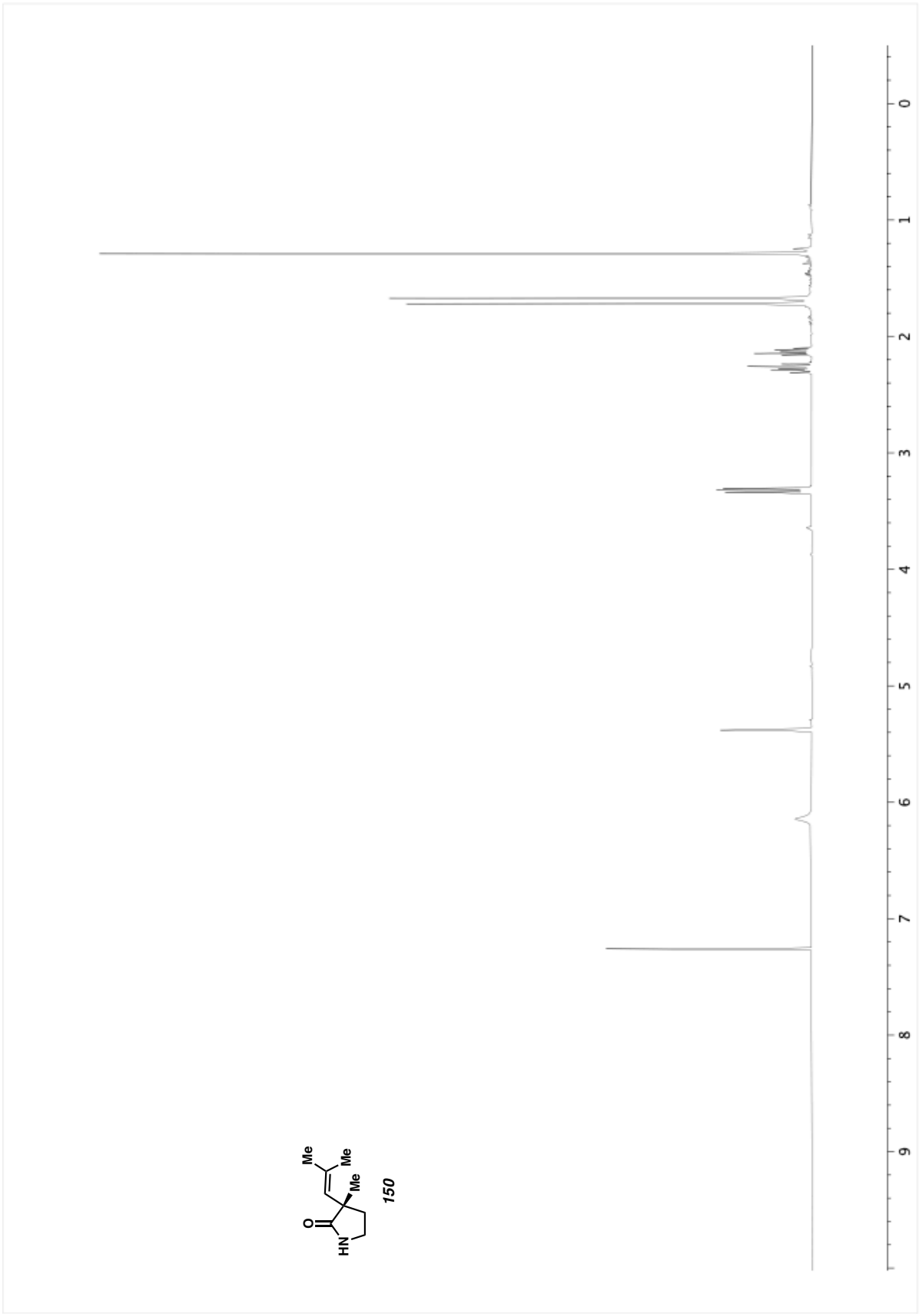


Figure A3.75 *^1H NMR (400 MHz, $CDCl_3$) of* ***150.***

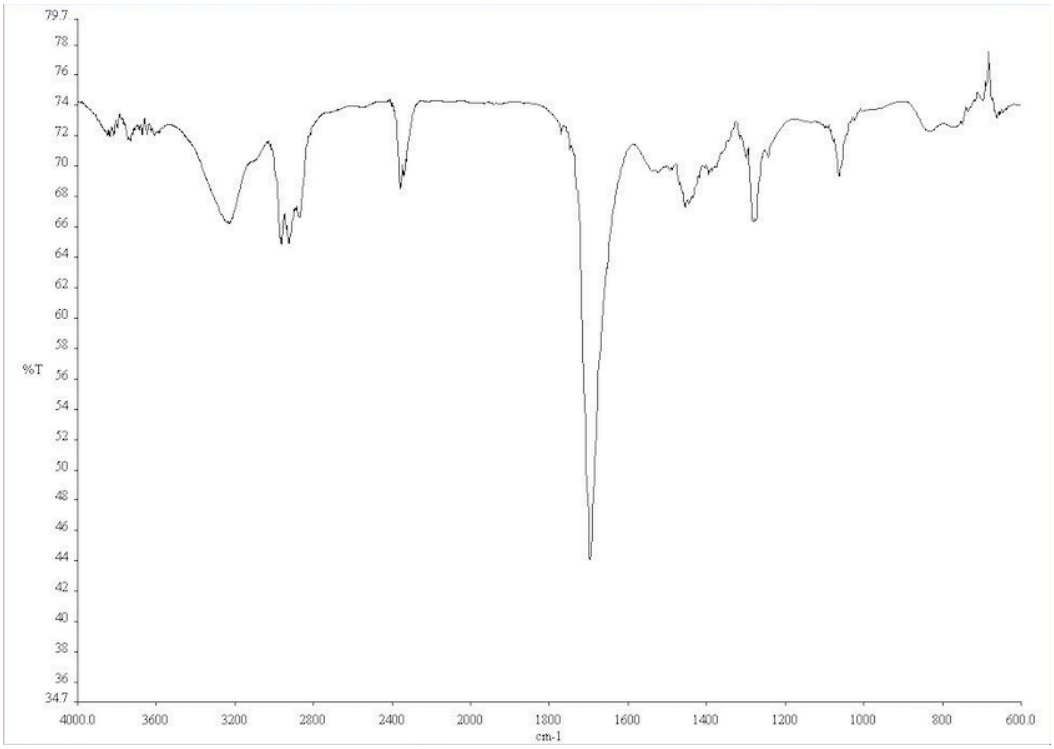


Figure A3.76 *Infrared spectrum (Thin Film, NaCl) of* ***150***.

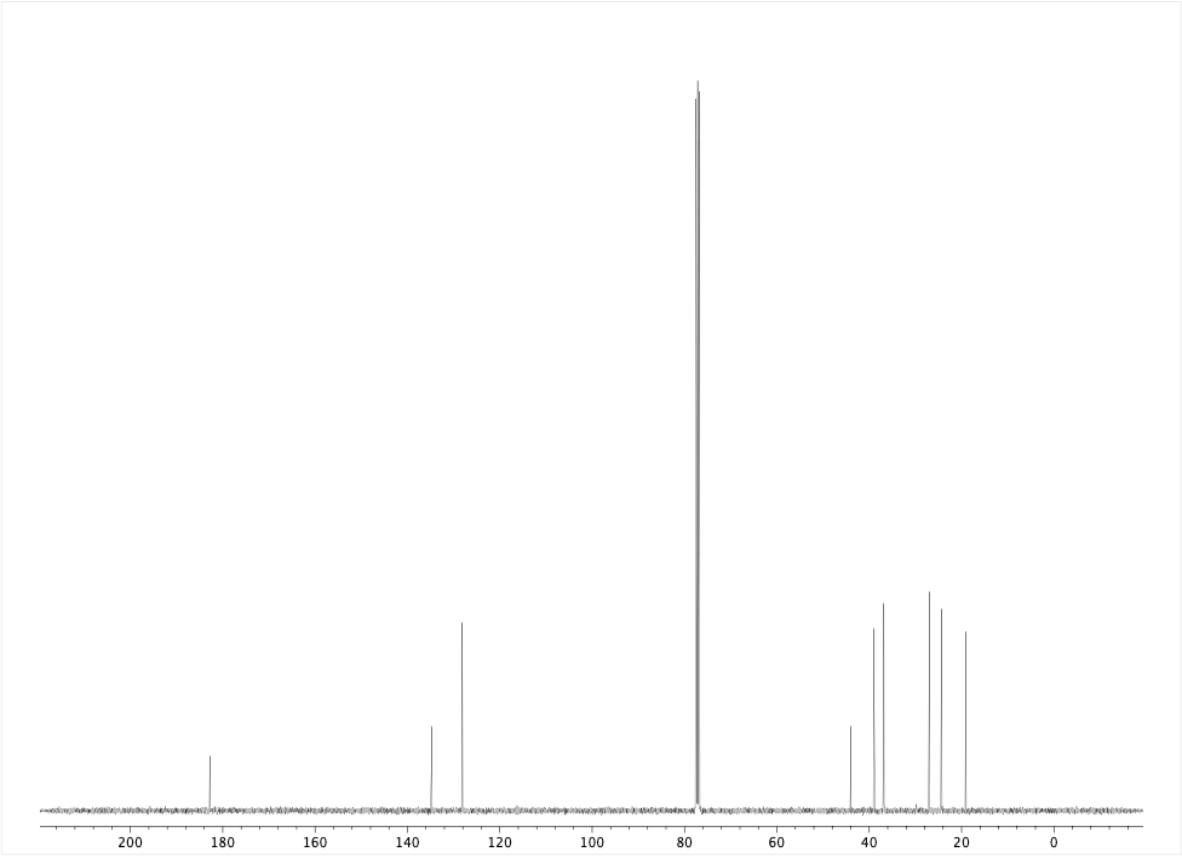


Figure A3.77 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***150***.

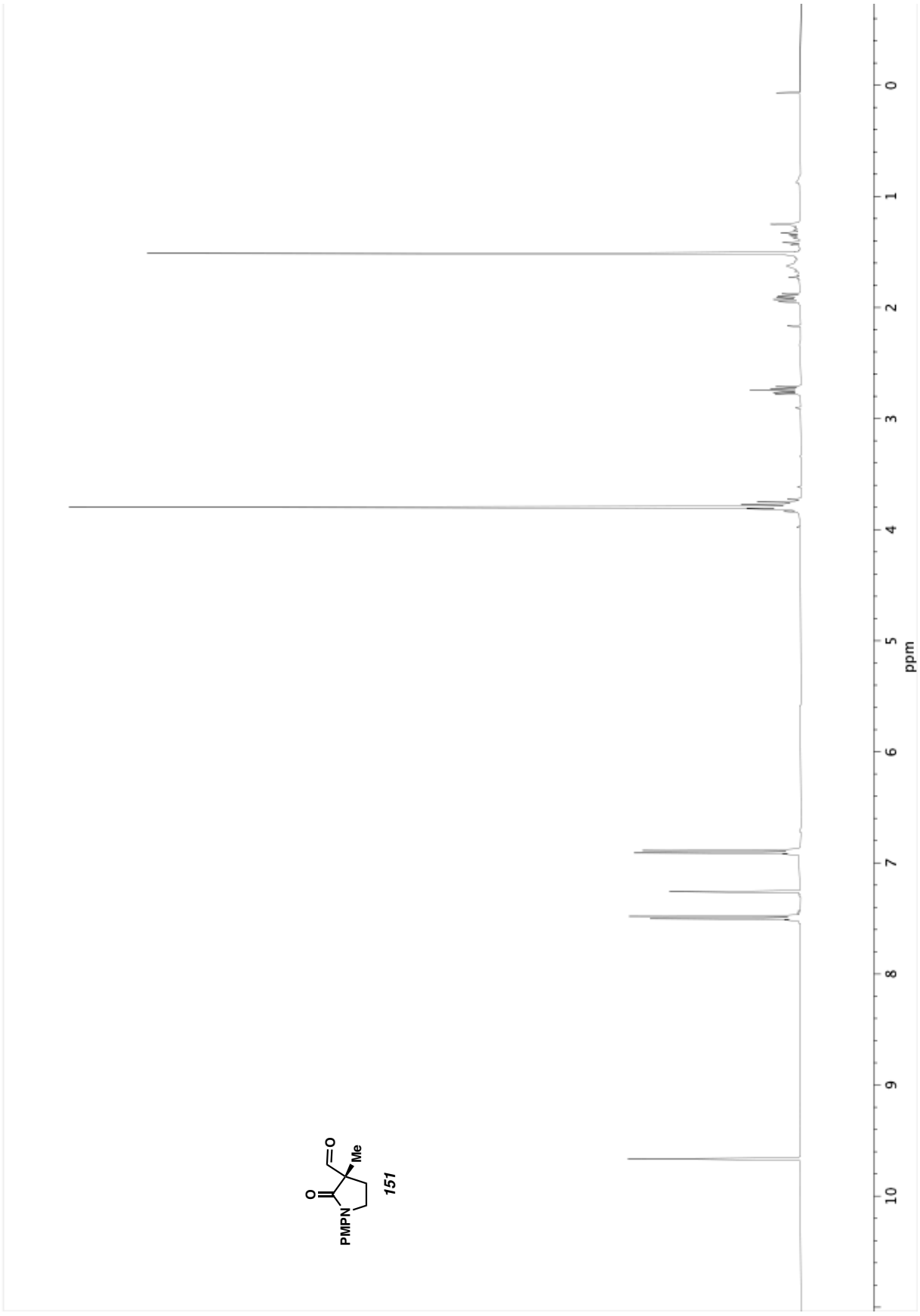


Figure A3.78 *^1H NMR (400 MHz, $CDCl_3$) of* ***151****.*

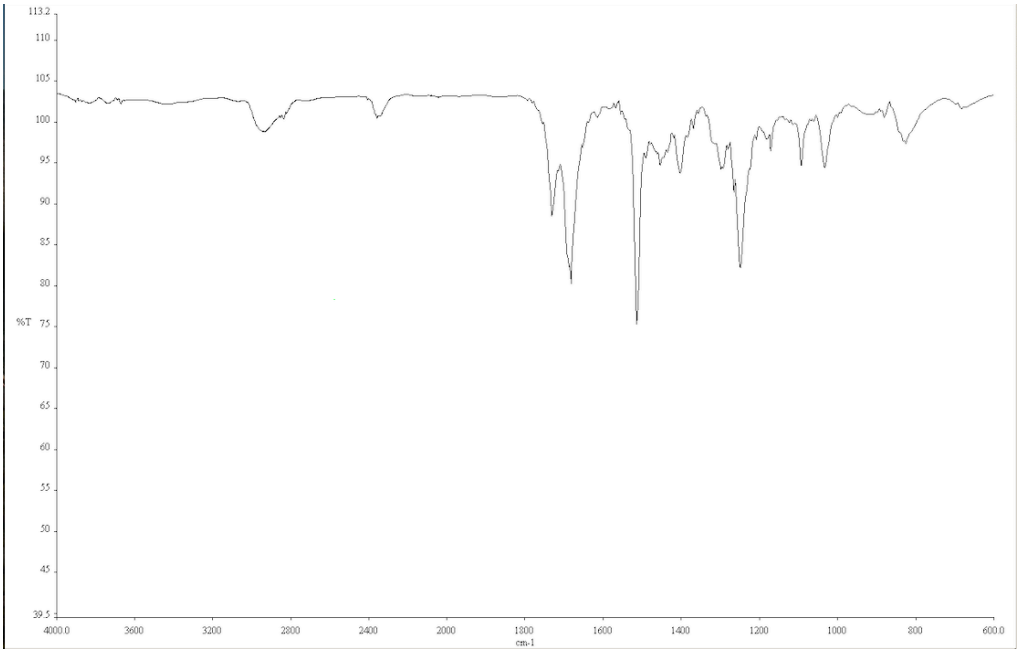


Figure A3.79 *Infrared spectrum (Thin Film, NaCl) of* ***151***.

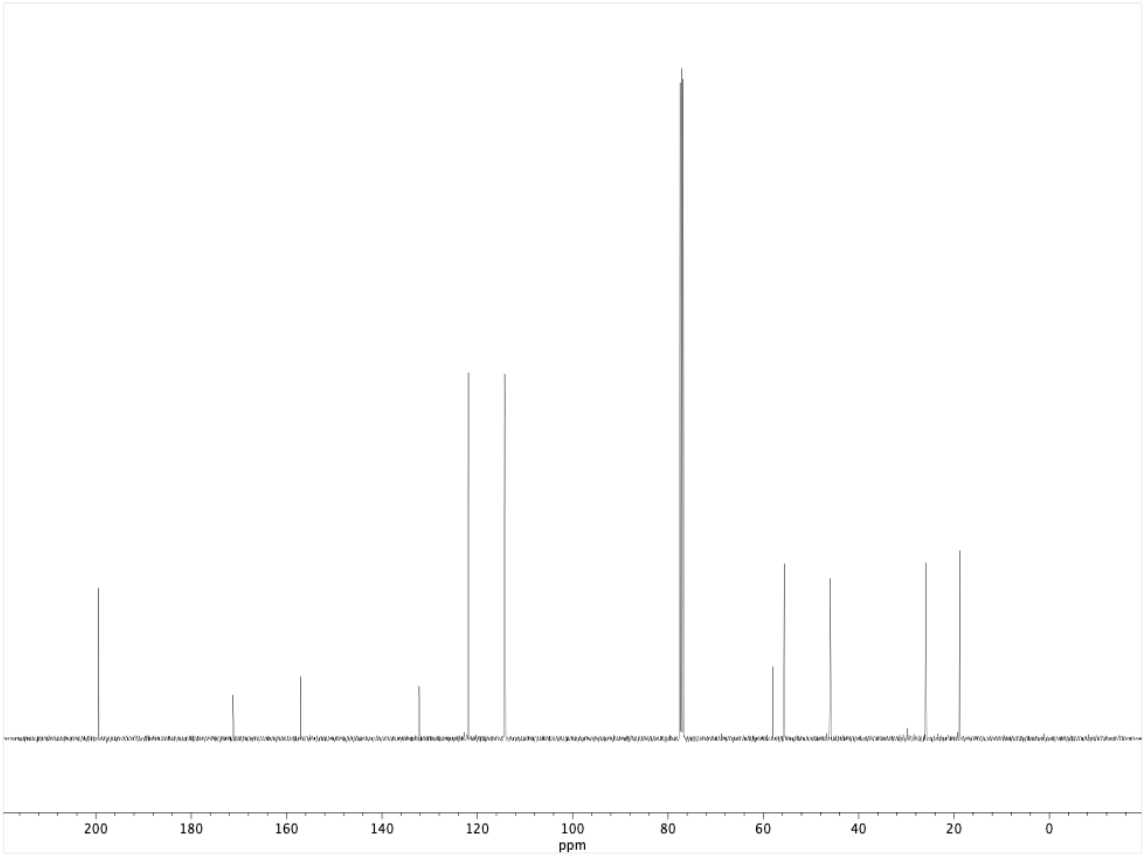


Figure A3.80 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***151***.

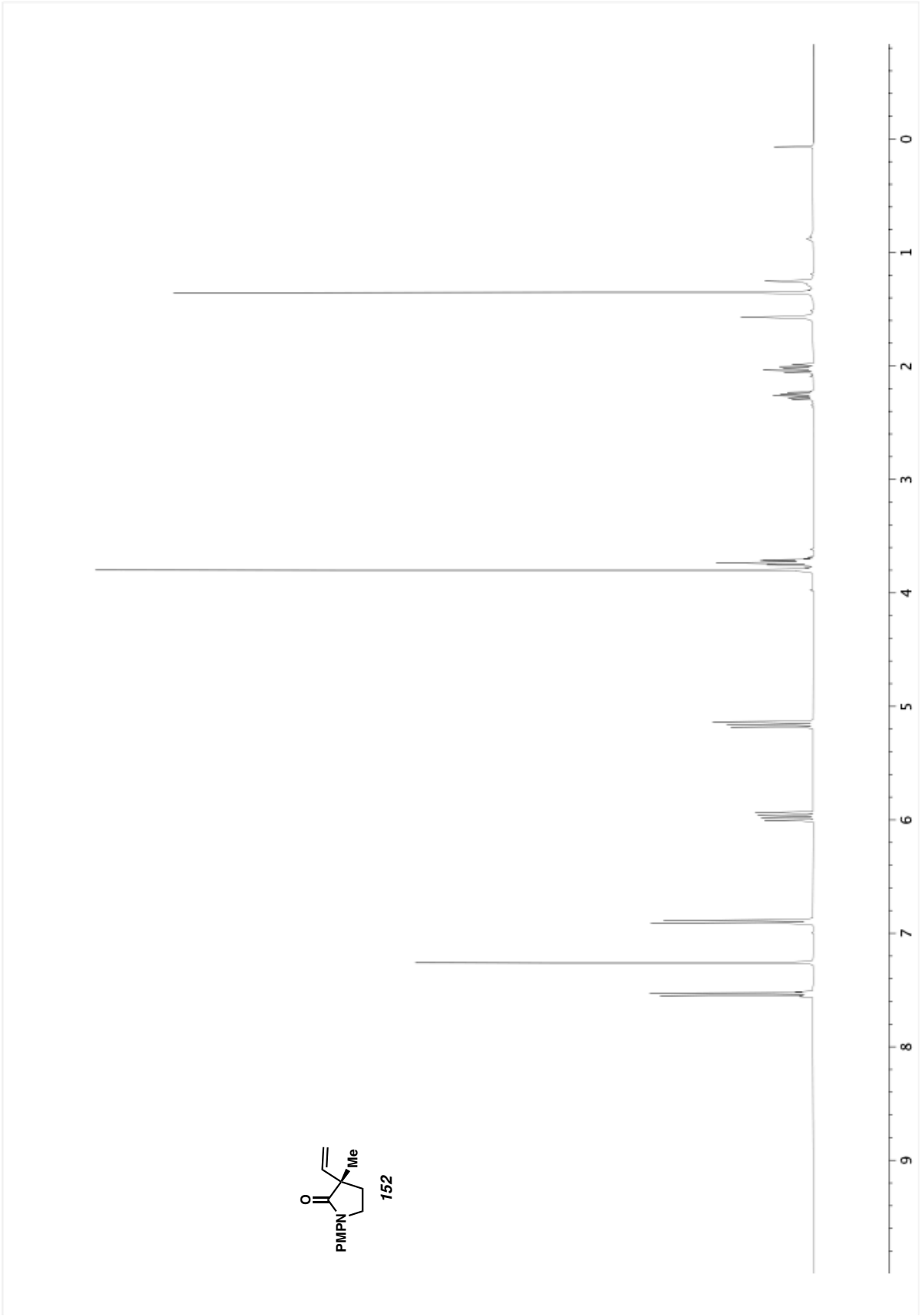


Figure A3.81 *^1H NMR (400 MHz, $CDCl_3$) of* ***152.***

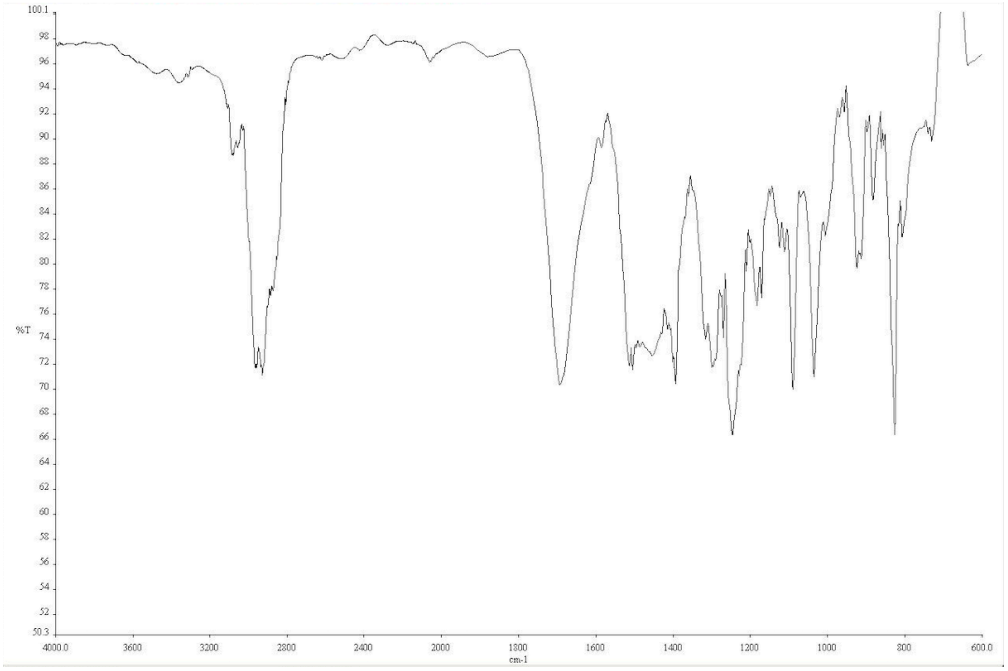


Figure A3.82 *Infrared spectrum (Thin Film, NaCl) of* ***152***.

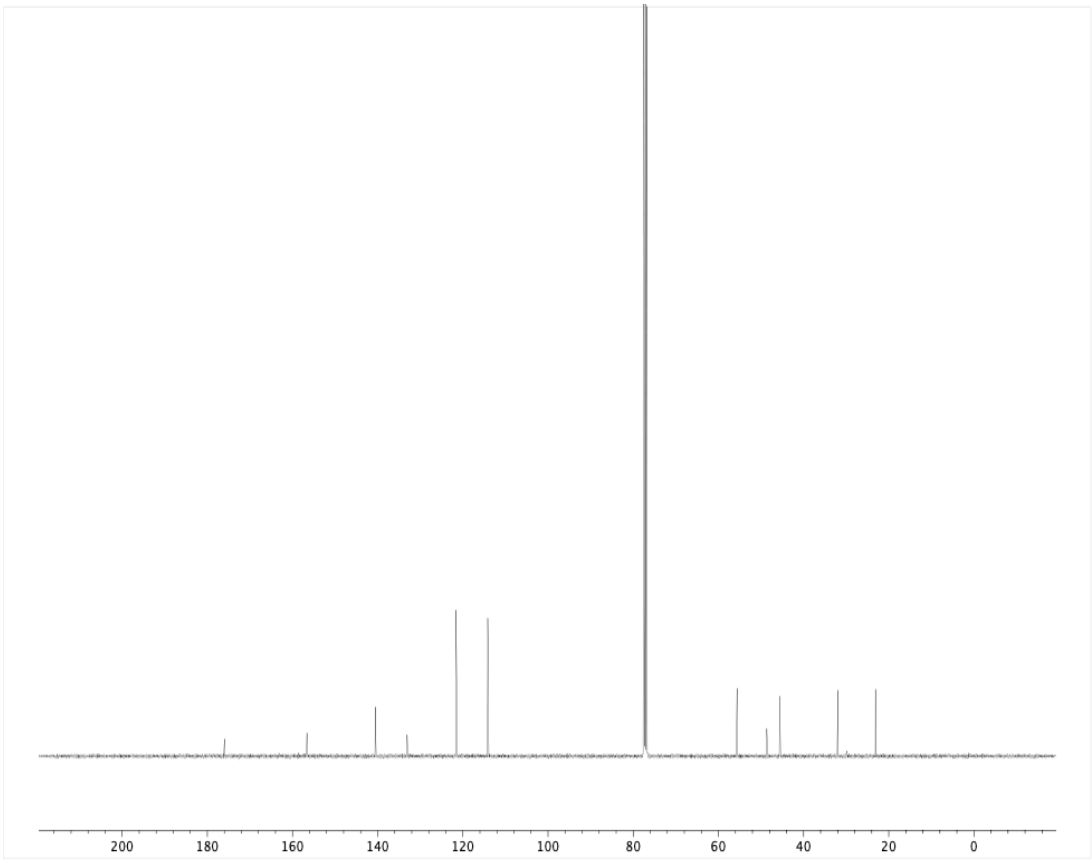


Figure A3.83 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***152***.

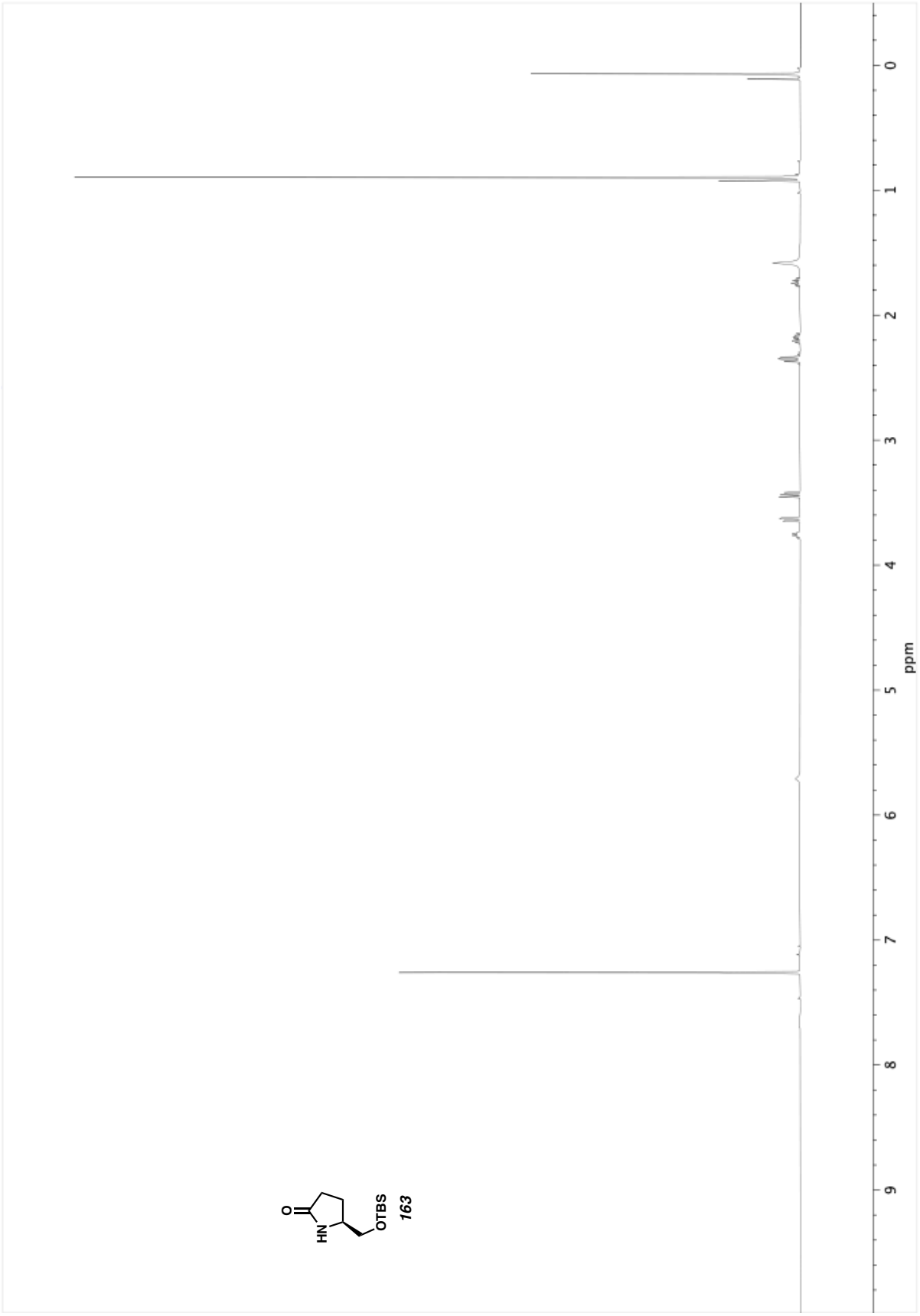


Figure A3.84 *^{1}H NMR (400 MHz, $CDCl_3$) of* ***163.***

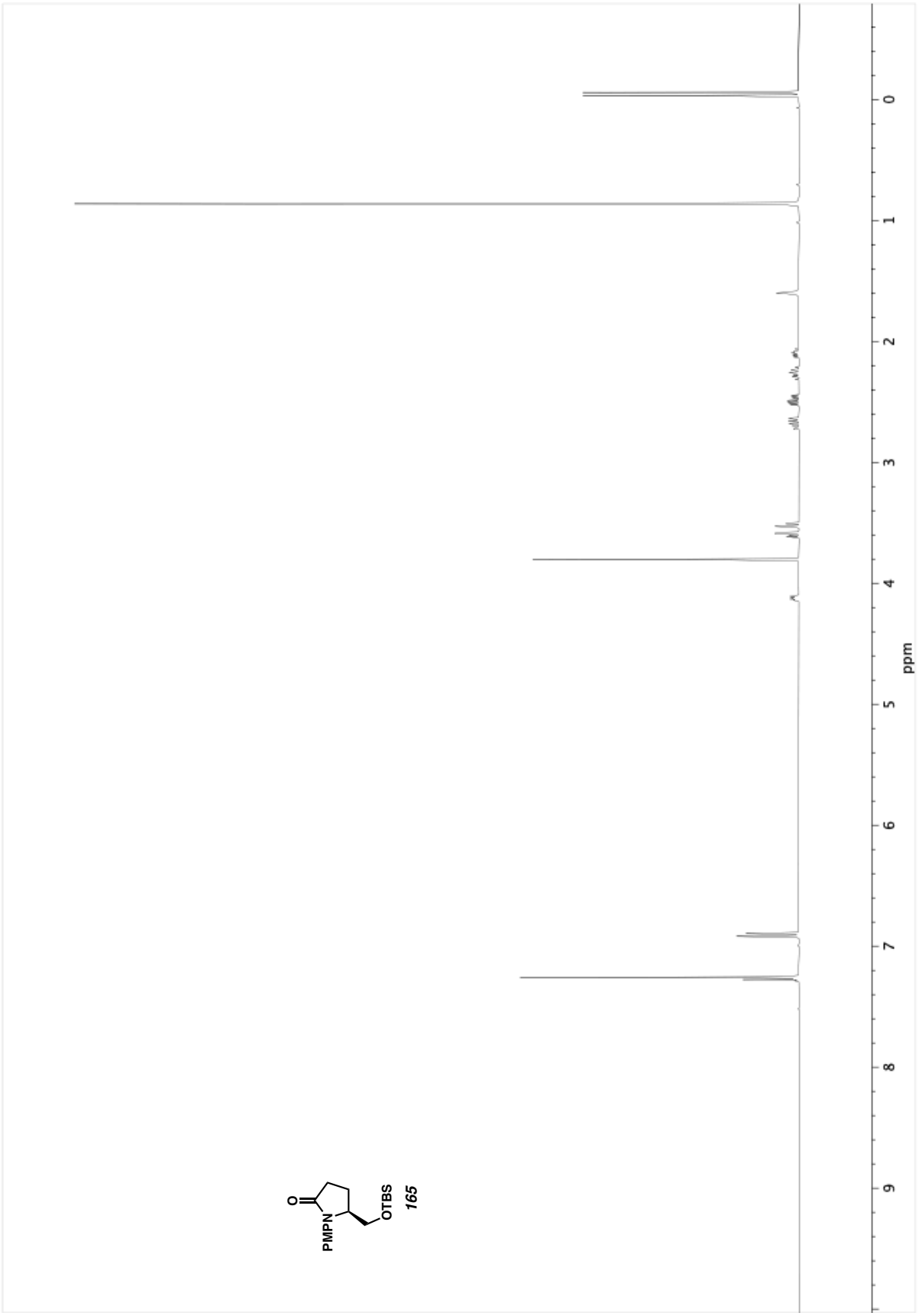


Figure A3.85 *^1H NMR (400 MHz, $CDCl_3$) of* ***165.***

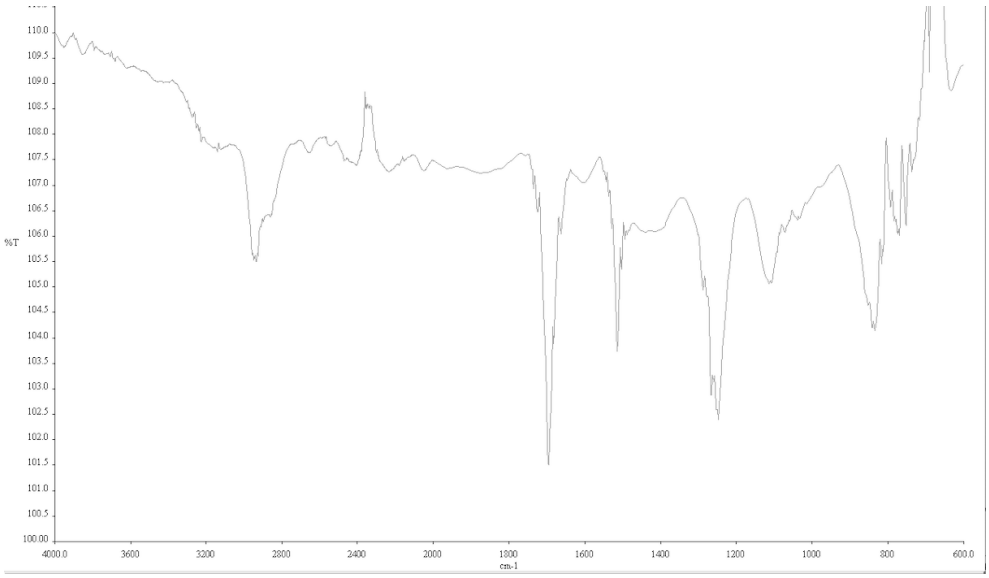


Figure A3.86 *Infrared spectrum (Thin Film, NaCl) of* ***165****.*

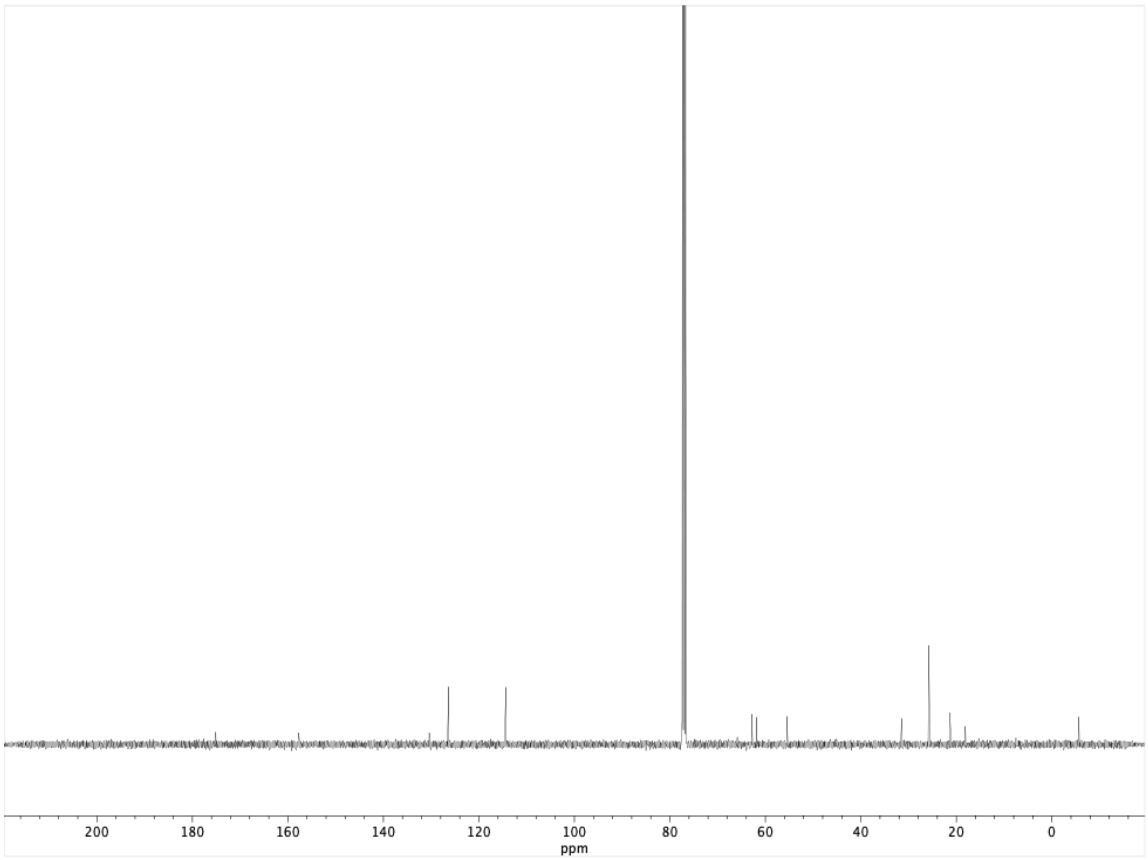


Figure A3.87 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***165****.*

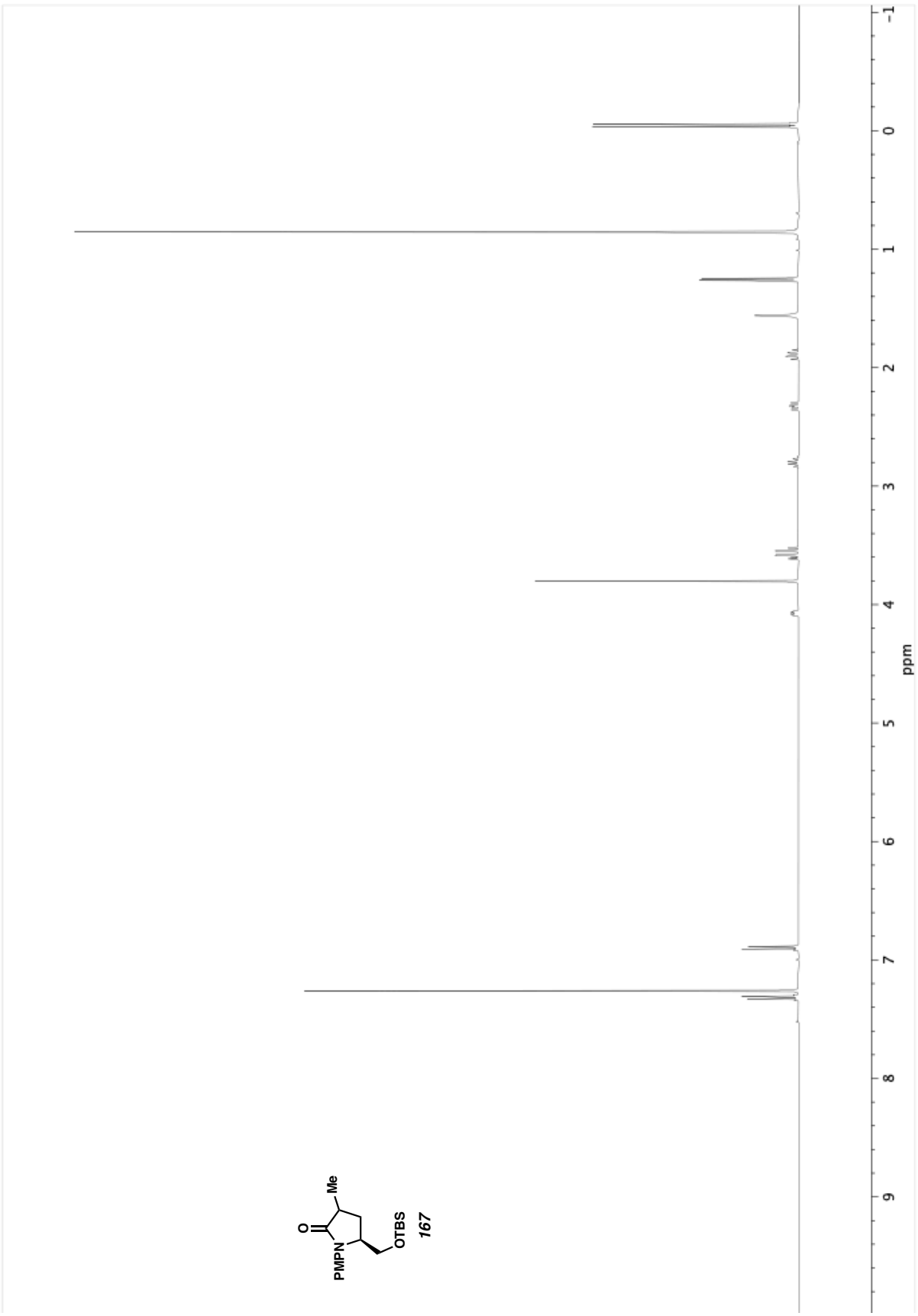


Figure A3.88 *^1H NMR (400 MHz, $CDCl_3$) of* ***167.***

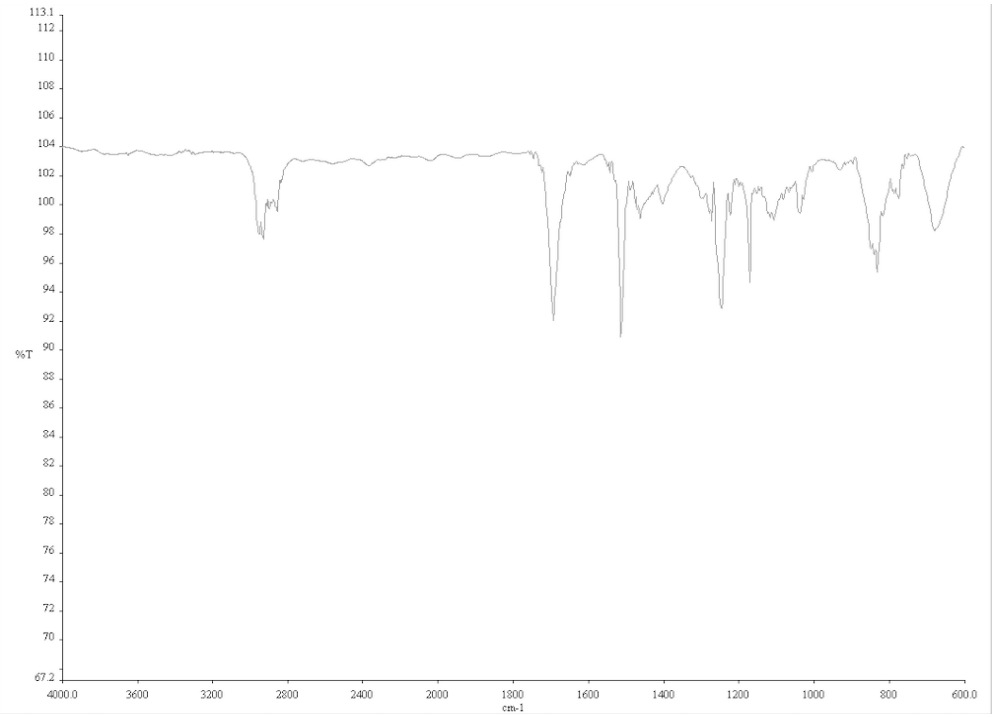


Figure A3.89 *Infrared spectrum (Thin Film, NaCl) of* ***167****.*

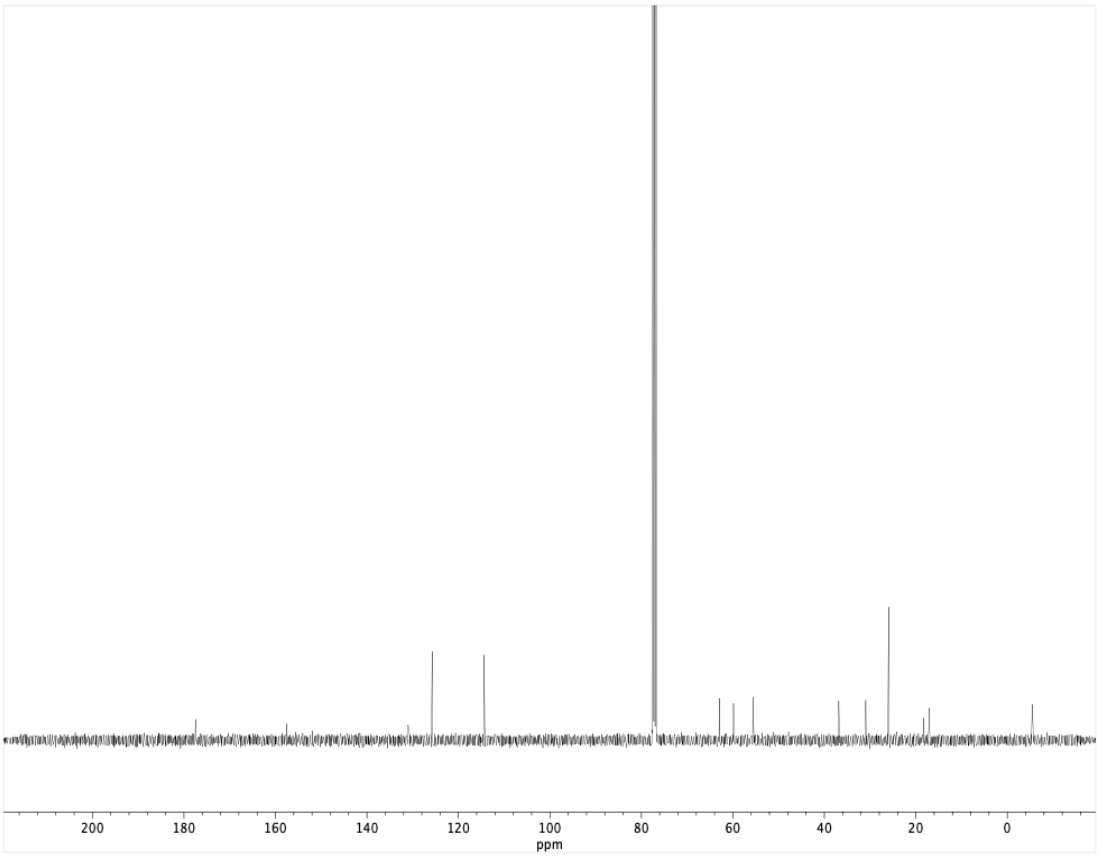


Figure A3.90 *^{13}C NMR (100 MHz, $CDCl_3$) of* ***167****.*

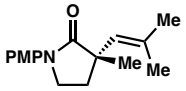
APPENDIX 4

X-Ray Crystallographic Reports Relevant to Chapter 2: Formation of All-Carbon Quaternary Centers via Enantioselective Pd-Catalyzed α-Vinylation of γ-Lactams

A4.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A4.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF PRODUCT 130



130

Vinylated lactam **130** was recrystallized from slow evaporation in hexanes at 23 °C to provide crystals suitable for X-ray analysis.

Figure A4.1 *X-ray crystal structure of lactam* ***130***.

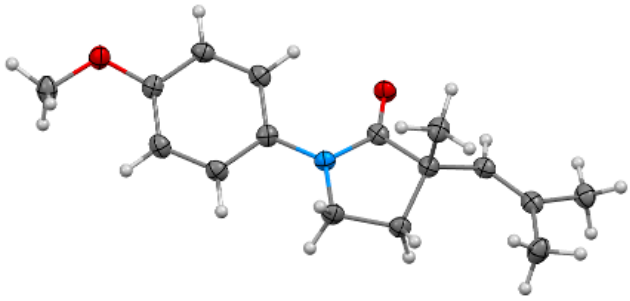


Table A4.1. *Crystal data and structure refinement for lactam* ***130****.*

Identification code	V24190	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3874(10) Å	a= 90°.
	b = 9.1155(13) Å	b= 90°.
	c = 20.860(3) Å	g = 90°.
Volume	1404.7(3) Å3	
Z	4	
Density (calculated)	1.226 Mg/m3	
Absorption coefficient	0.636 mm-1	
F(000)	560	
Crystal size	0.150 x 0.100 x 0.005 mm3	
Theta range for data collection	4.239 to 74.536°.	
Index ranges	-9<=h<=9, -11<=k<=10, -26<=l<=26	
Reflections collected	21524	
Independent reflections	2879 [R(int) = 0.1102]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.6287	

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2879 / 0 / 176
Goodness-of-fit on F2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0947
R indices (all data)	R1 = 0.0574, wR2 = 0.1004
Absolute structure parameter	0.0(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.173 and -0.182 e.Å-3

Table A4.2 *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***130****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
C(1)	4790(4)	5751(3)	3452(1)	21(1)
O(1)	4177(3)	6906(2)	3656(1)	26(1)
C(2)	6222(4)	4815(3)	3796(1)	21(1)
C(5)	5146(4)	3885(3)	4282(1)	28(1)
C(6)	7569(4)	5786(3)	4137(1)	22(1)
C(7)	9203(4)	5434(3)	4356(1)	24(1)
C(8)	10344(4)	6545(3)	4705(1)	27(1)
C(9)	10082(4)	3964(3)	4275(2)	32(1)
C(3)	6944(4)	3841(3)	3251(1)	24(1)
C(4)	5384(4)	3742(3)	2771(1)	25(1)
N(1)	4290(3)	5050(2)	2897(1)	21(1)
C(10)	2709(4)	5361(3)	2530(1)	21(1)
C(11)	2486(4)	4690(3)	1933(1)	24(1)
C(12)	900(4)	4883(3)	1582(1)	25(1)
C(13)	-480(4)	5762(3)	1821(1)	23(1)
O(2)	-2108(3)	6022(2)	1528(1)	28(1)
C(16)	-2465(5)	5246(3)	947(1)	31(1)
C(14)	-238(4)	6463(3)	2410(1)	25(1)
C(15)	1327(4)	6257(3)	2761(1)	24(1)

Table A4.3 *Bond lengths [Å] and angles [°] for* ***130****.*

C(1)-O(1)	1.222(3)
C(1)-N(1)	1.373(3)
C(1)-C(2)	1.538(4)
C(2)-C(6)	1.509(4)
C(2)-C(3)	1.538(4)
C(2)-C(5)	1.542(4)
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-C(7)	1.329(4)
C(6)-H(6)	0.9500
C(7)-C(9)	1.499(4)
C(7)-C(8)	1.506(4)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(3)-C(4)	1.529(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900

C(4)-N(1)	1.464(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
N(1)-C(10)	1.425(4)
C(10)-C(15)	1.394(4)
C(10)-C(11)	1.396(4)
C(11)-C(12)	1.393(4)
C(11)-H(11)	0.9500
C(12)-C(13)	1.389(4)
C(12)-H(12)	0.9500
C(13)-O(2)	1.370(4)
C(13)-C(14)	1.397(4)
O(2)-C(16)	1.427(3)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(14)-C(15)	1.381(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
O(1)-C(1)-N(1)	126.5(3)
O(1)-C(1)-C(2)	124.8(2)
N(1)-C(1)-C(2)	108.7(2)
C(6)-C(2)-C(1)	110.3(2)

C(6)-C(2)-C(3)	117.3(2)
C(1)-C(2)-C(3)	102.3(2)
C(6)-C(2)-C(5)	110.6(2)
C(1)-C(2)-C(5)	104.9(2)
C(3)-C(2)-C(5)	110.3(2)
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(7)-C(6)-C(2)	128.2(2)
C(7)-C(6)-H(6)	115.9
C(2)-C(6)-H(6)	115.9
C(6)-C(7)-C(9)	124.8(3)
C(6)-C(7)-C(8)	120.8(3)
C(9)-C(7)-C(8)	114.4(3)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5

C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(4)-C(3)-C(2)	104.8(2)
C(4)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8
C(4)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.9
N(1)-C(4)-C(3)	104.5(2)
N(1)-C(4)-H(4A)	110.8
C(3)-C(4)-H(4A)	110.8
N(1)-C(4)-H(4B)	110.8
C(3)-C(4)-H(4B)	110.8
H(4A)-C(4)-H(4B)	108.9
C(1)-N(1)-C(10)	125.6(2)
C(1)-N(1)-C(4)	112.4(2)
C(10)-N(1)-C(4)	121.2(2)
C(15)-C(10)-C(11)	118.6(3)
C(15)-C(10)-N(1)	122.1(2)

C(11)-C(10)-N(1)	119.3(2)
C(12)-C(11)-C(10)	120.9(3)
C(12)-C(11)-H(11)	119.6
C(10)-C(11)-H(11)	119.6
C(13)-C(12)-C(11)	120.1(3)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
O(2)-C(13)-C(12)	125.7(2)
O(2)-C(13)-C(14)	115.2(2)
C(12)-C(13)-C(14)	119.1(3)
C(13)-O(2)-C(16)	117.1(2)
O(2)-C(16)-H(16A)	109.5
O(2)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(2)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(14)-C(13)	120.7(3)
C(15)-C(14)-H(14)	119.7
C(13)-C(14)-H(14)	119.7
C(14)-C(15)-C(10)	120.7(3)
C(14)-C(15)-H(15)	119.6
C(10)-C(15)-H(15)	119.6

Symmetry transformations used to generate equivalent atoms:

Table A4.4 *Anisotropic displacement parameters ($Å^2$ x 10^3) for* ***130****. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.*

	U11	U22	U33	U23	U13	U12
C(1)	25(1)	17(1)	22(1)	1(1)	2(1)	-4(1)
O(1)	30(1)	19(1)	27(1)	-4(1)	-3(1)	4(1)
C(2)	23(1)	18(1)	24(1)	1(1)	-1(1)	-1(1)
C(5)	27(2)	28(1)	28(1)	6(1)	-2(1)	-4(1)
C(6)	26(1)	16(1)	24(1)	-1(1)	2(1)	-2(1)
C(7)	27(2)	22(1)	23(1)	1(1)	2(1)	-5(1)
C(8)	29(1)	25(1)	28(1)	-2(1)	-2(1)	-5(1)
C(9)	30(2)	25(1)	40(2)	0(1)	-8(1)	3(1)
C(3)	25(1)	18(1)	28(1)	-2(1)	-2(1)	3(1)
C(4)	26(1)	18(1)	30(1)	-3(1)	-1(1)	4(1)
N(1)	24(1)	16(1)	23(1)	0(1)	-1(1)	2(1)
C(10)	25(1)	15(1)	23(1)	3(1)	0(1)	-1(1)
C(11)	29(1)	17(1)	25(1)	-1(1)	0(1)	2(1)
C(12)	33(2)	18(1)	24(1)	-1(1)	-2(1)	-1(1)
C(13)	24(1)	17(1)	27(1)	3(1)	-3(1)	-1(1)
O(2)	29(1)	26(1)	29(1)	-3(1)	-6(1)	2(1)
C(16)	37(2)	24(1)	31(1)	-2(1)	-10(1)	-2(1)
C(14)	28(2)	20(1)	26(1)	-1(1)	3(1)	1(1)
C(15)	29(2)	18(1)	24(1)	-1(1)	0(1)	-1(1)

Table A4.5 *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for* ***130***.

	x	y	z	U(eq)
H(5A)	5974	3226	4510	42
H(5B)	4233	3304	4055	42
H(5C)	4546	4534	4591	42
H(6)	7202	6773	4203	27
H(8A)	9672	7468	4744	41
H(8B)	11465	6717	4466	41
H(8C)	10637	6174	5134	41
H(9A)	9147	3206	4240	47
H(9B)	10851	3759	4648	47
H(9C)	10824	3966	3886	47
H(3A)	8025	4289	3050	28
H(3B)	7271	2855	3414	28
H(4A)	5844	3745	2326	29
H(4B)	4667	2839	2841	29
H(11)	3427	4093	1765	29
H(12)	761	4413	1179	30
H(16A)	-1567	5522	623	46
H(16B)	-3679	5496	793	46
H(16C)	-2394	4189	1027	46

H(14)	-1161	7088	2572	30
H(15)	1463	6731	3163	29

Table A4.6 *Torsion angles [°] for* ***130****.*

O(1)-C(1)-C(2)-C(6)	-36.0(4)
N(1)-C(1)-C(2)-C(6)	146.0(2)
O(1)-C(1)-C(2)-C(3)	-161.5(3)
N(1)-C(1)-C(2)-C(3)	20.4(3)
O(1)-C(1)-C(2)-C(5)	83.2(3)
N(1)-C(1)-C(2)-C(5)	-94.8(3)
C(1)-C(2)-C(6)-C(7)	-162.8(3)
C(3)-C(2)-C(6)-C(7)	-46.2(4)
C(5)-C(2)-C(6)-C(7)	81.6(4)
C(2)-C(6)-C(7)-C(9)	3.0(5)
C(2)-C(6)-C(7)-C(8)	-178.0(3)
C(6)-C(2)-C(3)-C(4)	-147.2(2)
C(1)-C(2)-C(3)-C(4)	-26.3(3)
C(5)-C(2)-C(3)-C(4)	84.9(3)
C(2)-C(3)-C(4)-N(1)	23.5(3)
O(1)-C(1)-N(1)-C(10)	-14.5(4)
C(2)-C(1)-N(1)-C(10)	163.5(2)
O(1)-C(1)-N(1)-C(4)	175.9(3)
C(2)-C(1)-N(1)-C(4)	-6.1(3)
C(3)-C(4)-N(1)-C(1)	-11.2(3)
C(3)-C(4)-N(1)-C(10)	178.7(2)
C(1)-N(1)-C(10)-C(15)	-11.4(4)

C(4)-N(1)-C(10)-C(15)	157.3(2)
C(1)-N(1)-C(10)-C(11)	172.0(2)
C(4)-N(1)-C(10)-C(11)	-19.3(4)
C(15)-C(10)-C(11)-C(12)	-1.4(4)
N(1)-C(10)-C(11)-C(12)	175.3(3)
C(10)-C(11)-C(12)-C(13)	0.5(4)
C(11)-C(12)-C(13)-O(2)	-179.0(3)
C(11)-C(12)-C(13)-C(14)	1.0(4)
C(12)-C(13)-O(2)-C(16)	4.4(4)
C(14)-C(13)-O(2)-C(16)	-175.7(2)
O(2)-C(13)-C(14)-C(15)	178.3(3)
C(12)-C(13)-C(14)-C(15)	-1.7(4)
C(13)-C(14)-C(15)-C(10)	0.9(4)
C(11)-C(10)-C(15)-C(14)	0.7(4)
N(1)-C(10)-C(15)-C(14)	-175.9(3)

Symmetry transformations used to generate equivalent atoms:

CHAPTER 3

An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates†

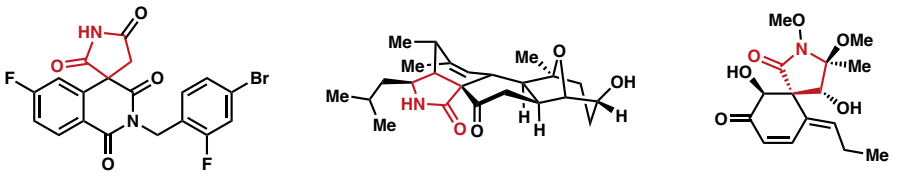
3.1 INTRODUCTION

Since their first description by von Baeyer over 120 years ago,[1] spirocyclic compounds have found widespread utility as chiral ligands,[2] pharmaceuticals,[3] and optoelectronic materials.[4] Spirocyclic frameworks are also found within nature and feature in a variety of bioactive natural products.[5] Due to their inherently high fraction of sp^3 carbon atoms (Fsp^3) and their ability to project functionality along multiple distinct spatial vectors, spiranes are of increased interest in modern medicinal chemistry campaigns.[3] While the development of new stereoselective methods for the construction of spirocyclic compounds remains an ongoing challenge, many new asymmetric technologies have been developed for the synthesis of spirocyclic oxindoles.[5] In comparison, there are far fewer asymmetric methods for the synthesis of saturated spirocyclic γ-lactams, despite the

† This work was performed in collaboration with Dr. Kaylin N. Flesch, Dr. Melinda Chan, Hannah R. Ang, and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Barbor, J. P.; Flesch, K. N.; Chan, M.; Ang, H.R.; Stoltz, B. M. An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates. *Angew. Chem. Int. Ed.* **2025**, e202502583. © 2025 Wiley-VCH.

prevalence of this motif in a range of biologically active small molecules and natural products (Figure 3.1).[6,7]

Figure 3.1 *Natural products and pharmaceutical compounds bearing a spirocyclic lactam.*

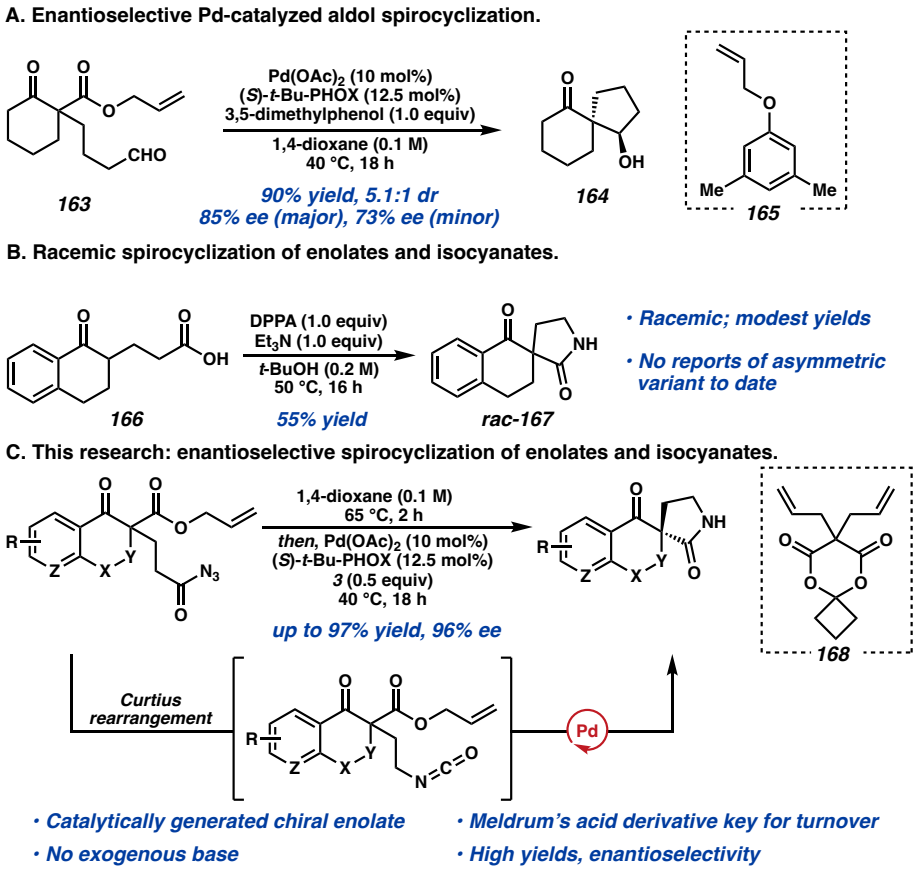


In 2020, our group disclosed an enantioselective Pd-catalyzed aldol cyclization, enabling the general asymmetric construction of spiranes bearing a 1,3-dioxygenation pattern (Scheme 3.1a).[8] Following decarboxylative enolate formation, chiral Pd enolates can undergo an intramolecular aldol cyclization, which upon further oxidation delivers a variety of 1,3-diketospiranes in good yields and enantioselectivity. Bronsted acidic additives, namely phenols, were found to be essential for catalyst turnover, serving as a proton-donor for the putative Pd-alkoxide and facilitating Pd reduction by trapping the allyl group. Following this report, we sought to expand this strategy toward other classes of electrophiles and hypothesized that we may be able to achieve similar success with isocyanates, enabling access to chiral spirocyclic lactams.

An uncatalyzed and racemic variant of our targeted reaction was reported by Xue and coworkers in 2015 (Scheme 3.1b).[9] Upon treatment with DPPA and triethylamine, δ-keto acids could undergo a Curtius rearrangement and subsequent nucleophilic cyclization, delivering spirocyclic lactams in modest to good yields. Within the context of catalysis, isocyanates are well-precedented to undergo a variety of polymerization reactions in the presence of transition metal catalysts,[10] and there is a well-established body of literature pertaining to the reactions of isocyanates with Pd π-allyl intermediates.[11] However, there

appears to be a general lack of research into controlled, stereoselective additions of metal enolates and isocyanates. In fact, we have been unable to find any general reports detailing the stereoselective addition of an enolate to an isocyanate,[12] which we attribute to the unforgiving propensity of isocyanates to decompose or self-condense and their inherent incompatibility with many strong bases.[10c] Given the mild, base-free, and regiospecific nature under which we can generate chiral Pd enolates from allyl β-keto esters, we envisioned that this decarboxylative enolate formation would be an appropriate manifold for the development of a general asymmetric spirocyclization of Pd enolates and isocyanates (Scheme 3.1c).

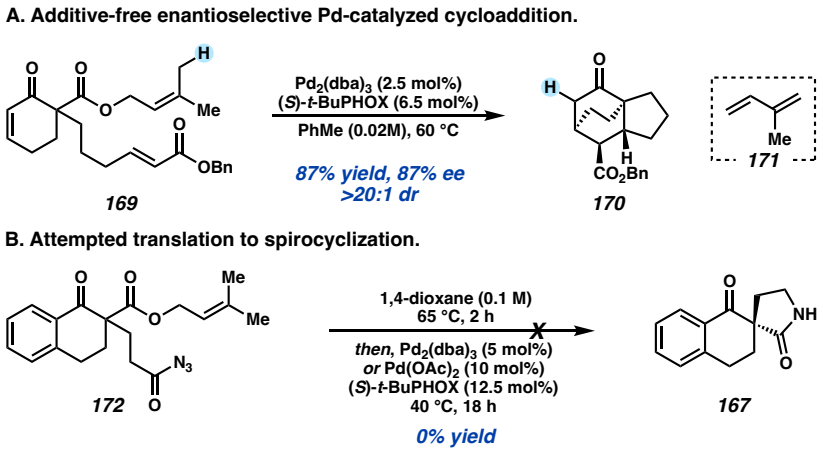
Scheme 3.1 *Construction of spiranes via enolate addition.*



3.2 REACTION DESIGN AND OPTIMIZATION

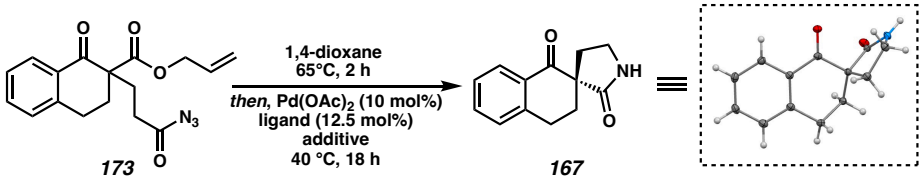
Inspired by a recent disclosure from our group, we decided to first explore reactivity with a prenyl β-keto ester. In 2023, our group reported an asymmetric decarboxylative Pd-catalyzed [4+2] cycloaddition.[13] Rather than adding an exogenous additive, we found that use of a prenylated β-keto ester enabled proton-transfer from the prenyl group following cycloaddition, generating isoprene and turning over the catalytic cycle (Scheme 3.2a). Unfortunately, subjecting prenylated starting material **172** to a Curtius rearrangement followed by treatment with a Pd/PHOX catalyst resulted in a complex mixture of undesired byproducts (Scheme 3.2b).

Scheme 3.2 *Attempted additive-free spirocyclization.*

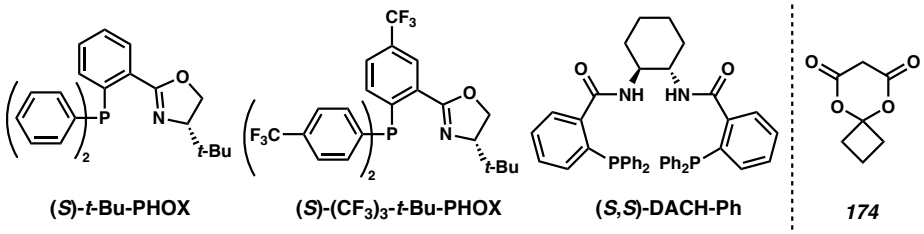


Alternatively, Curtius rearrangement of allyl β-keto ester **173** followed by treatment with a Pd/PHOX catalyst generated the desired product **167** in 89% ee, albeit in a modest 10% yield (Table 3.1, entry 1). Akin to the previously developed aldol spirocyclization, we did not observe reductive elimination of the allyl group onto the amidate following cyclization.[8] Unable to force reductive elimination of the allyl, we decided to explore alternative strategies to achieve turnover.

Table 3.1 *Reaction optimization.*[a]



entry	ligand	additive	result
1	(*S*)-*t*-Bu-PHOX	–	10% yield, 89% ee
2	(*S*)-*t*-Bu-PHOX	phenol (1.0 equiv)	17% yield, 39% ee
3	(*S*)-*t*-Bu-PHOX	Meldrum's acid (0.5 equiv)	59% yield, 93% ee
4	(*S*)-*t*-Bu-PHOX	Meldrum's acid (1.0 equiv)	19% yield, 85% ee
5	(*S*)-*t*-Bu-PHOX	dimedone (0.5 equiv)	43% yield, 31% ee
6	(*S*)-*t*-Bu-PHOX	acacH (0.5 equiv)	32% yield, 58% ee
7	(*S*)-*t*-Bu-PHOX	*174* (0.5 equiv)	99(93[b])% yield, 96% ee
8	(*S*)-$(CF_3)_3$-*t*-Bu-PHOX	*174* (0.5 equiv)	89% yield, 83% ee
9	(*S*,*S*)-DACH-Ph	*174* (0.5 equiv)	99% yield, 10% ee
10[c]	(*S*)-*t*-Bu-PHOX	*174* (0.5 equiv)	85% yield, 98% ee



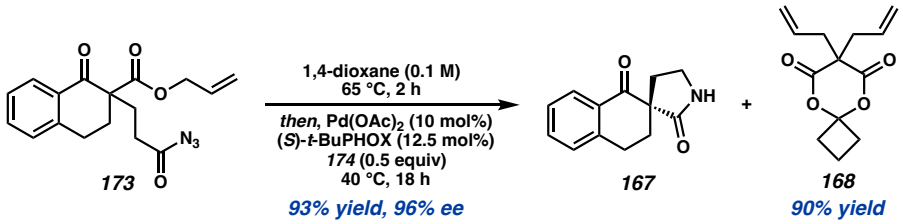
[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 0.2 mmol scale, isolated yield. [c] 1.0 mmol scale, isolated yield.

Drawing inspiration from the previously developed aldol spirocyclization, we decided to explore phenol as an additive.[8] Predictably, inclusion of phenol in this reaction generated significant amounts of carbamate side products, with only a marginally improved 17% yield of our desired product (Table 3.1, entry 2).[14,15] Pursuing alternative additives that may be less reactive toward the isocyanate, we decided to assess the use of Meldrum's acid, as we have previously demonstrated that this additive can be used for enantioselective protonation.[16]

Gratifyingly, inclusion of 50 mol% of Meldrum's acid delivered a 59% yield of product **167** in 93% ee, highlighting that cyclization to form the γ-lactam kinetically outcompetes protonation of the enolate (Table 3.1, entry 3). Increasing equivalents of

Meldrum's acid resulted in lower conversion (Table 3.1, entry 4). Use of similar 1,3-dicarbonyl compounds, like dimedone or acacH, also resulted in poorer reaction performance, with the ee of the product dropping significantly (Table 3.1, entries 5 and 6); however, use of Meldrum's acid derivative **174** resulted in near quantitative yield of the desired product and excellent 96% ee (Table 3.1, entry 7).[16] (*S*)-*t*-Bu-PHOX was found to be the optimal ligand for this transformation, with a more electron-deficient PHOX ligand or DACH-Ph affording diminished ee (Table 3.1, entry 8, 9). Additionally, we were pleased to find that the reaction also performs well on scale, with a 1.0 mmol scale reaction generating an 85% yield of product with 98% ee (Table 3.1, entry 10). From a 0.2 mmol scale reaction of our model substrate, 90% of **174** added to the reaction could be reisolated as the diallylated byproduct (**168**), confirming the ultimate fate of **174** and the allyl group (Scheme 3.3).

Scheme 3.3. *Isolation of reaction byproduct.*

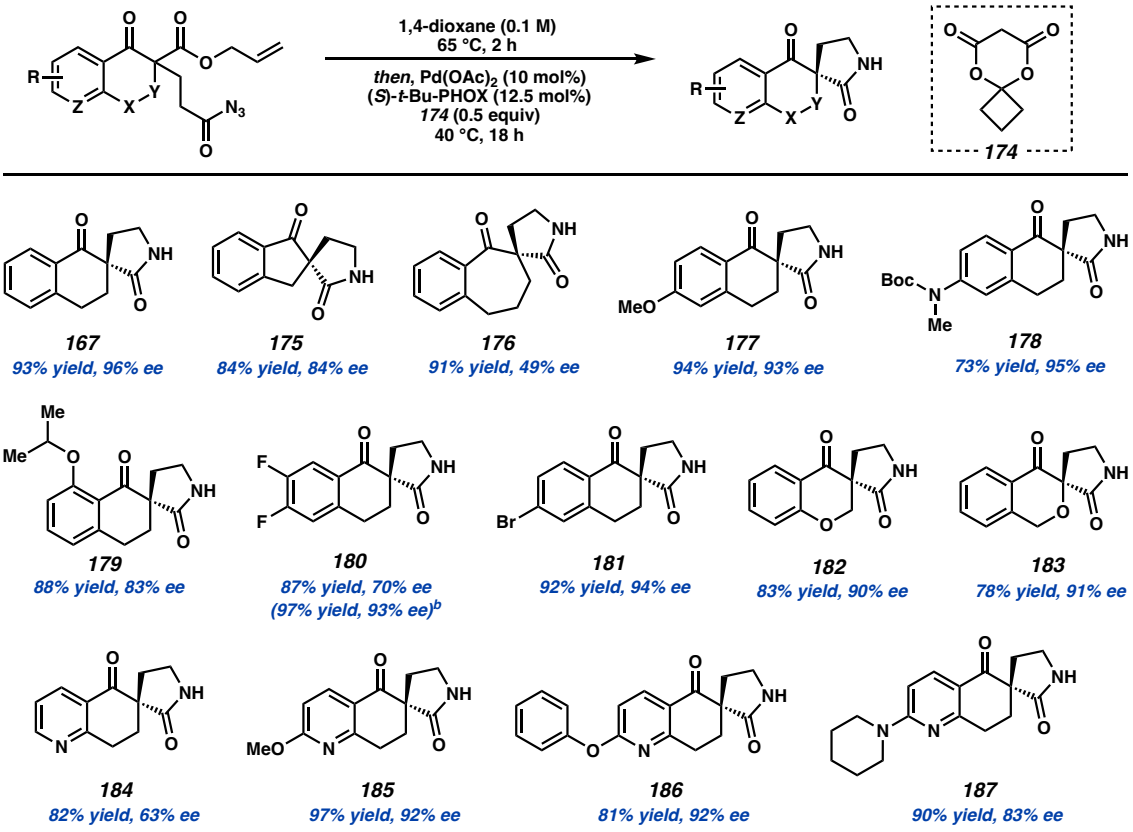


3.3 SUBSTRATE SCOPE

With optimized reaction conditions in hand, we explored the scope of the transformation (Table 3.2). Ring contraction from the model system to an indanone derived substrate (**175**) was well tolerated. Ring-expanded benzosuberone product **176** was formed in an excellent 91% yield, albeit in a diminished 49% ee. Electron donating groups para to the ketone performed well (**177** and **178**). Additionally, incorporation of an *ortho*-isopropyl

ether (**179**) was successful, demonstrating that this reaction can accommodate a moderate amount of steric bulk near the ketone. Gratifyingly, a compound bearing an aryl bromide can withstand the reaction conditions without any evidence of protodehalogenation, generating **181** in 92% yield and 94% ee. Heterocyclic chromanone **182** and isochromanone **183** were also competent substrates. Saturated ketone, α,β-unsaturated ketone, or *N*-benzoylated lactam starting materials all furnished product in good to excellent yield but suffered from low enantioselectivity under these reaction conditions.

Table 3.2 *Substrate scope.*[a]



[a] Reactions performed on 0.2 mmol scale, isolated yield. [b] Reaction performed on 0.05 mmol scale with (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, isolated yield.

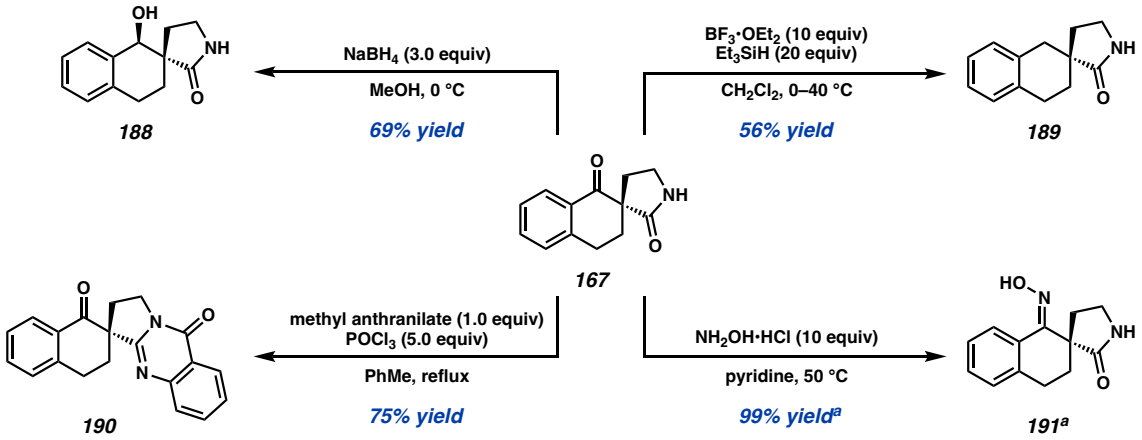
Although di-fluorinated (**180**) and pyridine-containing (**184**) compounds were able to be synthesized in excellent yields, the ee of these products was notably diminished.

Increasing electron density by substitution of the pyridine derivative with a methoxy (**185**), phenoxy (**186**), or piperidine (**187**) enabled the synthesis of these complex heterocyclic spiranes in excellent yields and enantioselectivities. Given the overall trends of the scope of this reaction, we postulate that it is necessary for substrates to be electron rich to obtain products with high ee using (*S*)-*t*-Bu-PHOX. Excitingly, **180** could be synthesized in 97% yield and 93% ee with the more electron-deficient (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, indicating that further tuning of the catalyst can potentially improve the performance of this reaction across electronically diverse substrates.[17]

3.4 PRODUCT DERIVATIZATIONS

To highlight the utility of these spirocyclic compounds, we explored various transformations to further diversify the products obtained from the reaction (Scheme 3.4).

Scheme 3.4 *Product derivatizations.*



[a] Oxime geometry not determined.

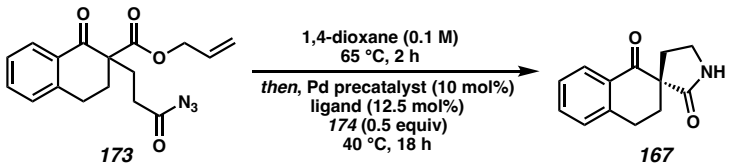
Diastereoselective reduction of the ketone with $NaBH_4$ to alcohol **188** can be achieved in 69% yield and >20:1 dr. Selective ketone reduction with BF_3•Et_2O and Et_3SiH yielded lactam **189** in 56% yield. Owing to the fact that this reaction affords unprotected lactam

products, **167** could directly undergo a heterocyclic annulation to deliver pentacyclic pyrimidone **190** in 75% yield. Furthermore, oxime **191** can be selectively formed as a single stereoisomer in 99% yield.

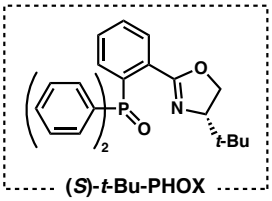
3.5 MECHANISTIC STUDIES

Throughout the development of this reaction, we observed a stark correlation between the choice of Pd-precatalyst and enantioselectivity (Table 3.3).

Table 3.3 *Investigation of reaction dependence on Pd-precatalyst.*[a]



entry	Pd precatalyst	ligand	additive	yield (%)	ee (%)
1	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	99	96
2[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	—	99	15
3[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	$[NBu_4]OAc$ (20 mol%)	94	3
4	$Pd(dba)_2$	(*S*)-*t*-Bu-PHOX	—	97	15
5	[Pd((*S*)-*t*-BuPHOX)dba]	—	—	98	11
6	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX/ (*S*)-*t*-Bu-PHOX=O (1:1)	—	39	83
7[c]	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	94	84
8	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX (40 mol%)	—	19	90
9	$Pd(TFA)_2$	(*S*)-*t*-Bu-PHOX	—	9	76
10	$Pd(TFA)_2$ (8 mol%)/ $Pd_2(dba)_3$ (1 mol%)	(*S*)-*t*-Bu-PHOX	—	96	74



[a] Reactions performed on 0.05 mmol scale and yields determined by ^1H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 5 mol% $Pd_2(dba)_3$. [c] O_2 balloon.

Interestingly, use of $Pd_2(dba)_3$ in place of $Pd(OAc)_2$ under otherwise identical reaction conditions affords a similarly excellent yield of product but with a severely diminished 15%

ee (Table 3.3, entries 1 and 2). To further probe this effect, we first explored the impact of the ancillary ligands for each of these precatalysts.

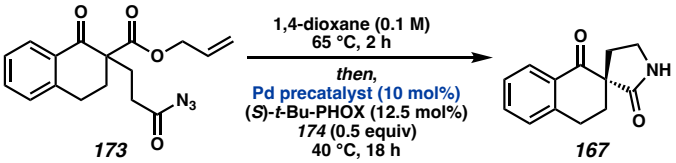
Addition of acetate in the form of [N(*n*-Bu)$_4$]OAc to a reaction utilizing Pd$_2$(dba)$_3$ did not restore ee (Table 3.3, entry 3); likewise, alteration of the amount of dibenzylideneacetone (dba) did not have any significant impact on reaction performance (Table 3.3, entries 4 and 5), indicating that neither of these ancillary ligands alter the enantioselectivity of the reaction. Because reduction of Pd(OAc)$_2$ to Pd(0) with a phosphine ligand necessitates the formation of the corresponding phosphine oxide with adventitious water,[18] we were curious if the oxidized variant of our ligand played a supporting role in the reaction mechanism. Yet, utilizing a 1:1 ratio of (*S*)-*t*-Bu-PHOX to the oxidized derivative, (*S*)-*t*-Bu-PHOX=O, resulted in diminished product ee and significant unreacted starting material (Table 3.3, entry 6), eliminating the possibility that (*S*)-*t*-Bu-PHOX=O might serve some beneficial function as a supporting ligand.

We were surprised that use of such a small excess of PHOX ligand with Pd(OAc)$_2$ afforded product in both high yield and ee, as typically, full reduction of Pd(OAc)$_2$ to Pd(0) requires three to four times the amount of phosphine relative to Pd(II),[18] and previous research within our group has demonstrated that a 1:4 ratio of Pd(OAc)$_2$ to PHOX ligand is required for high enantioselectivity in allylic alkylation reactions utilizing Pd(OAc)$_2$.[19] To probe whether this reaction might be a Pd(II)-only mechanism, we performed an experiment with an O$_2$ balloon (Table 3.2, entry 7). While we only obtained a 19% yield of product, indicating that the reaction is likely not a Pd(II)-only mechanism, we observed a similar 90% ee. Conversely, increasing equivalents of (*S*)-*t*-BuPHOX in an effort to force the reduction of Pd(OAc)$_2$ to Pd(0) resulted in diminished ee (Table 3.3, entry 8).

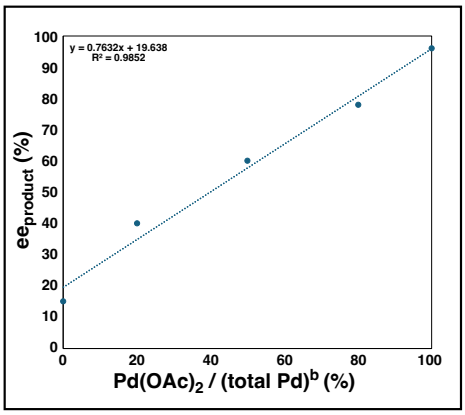
We decided to survey alternative Pd(II) precatalysts that might also be effective, and we found that while $Pd(TFA)_2$ alone affords only a 9% yield of product, enantioselectivity was improved to 76% ee as compared to the nearly racemic $Pd_2(dba)_3$ reactions (Table 3.3, entry 9). Curiously, replacing a small amount of the total palladium loading with $Pd_2(dba)_3$ restored the yield to 96% while maintaining 74% ee (Table 3.3, entry 10).

Table 3.4 *Exploration of mixed precatalysts.*[a]

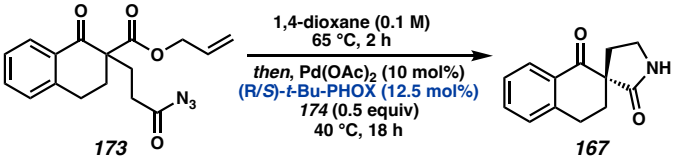
A. Exploration of mixed precatalysts.



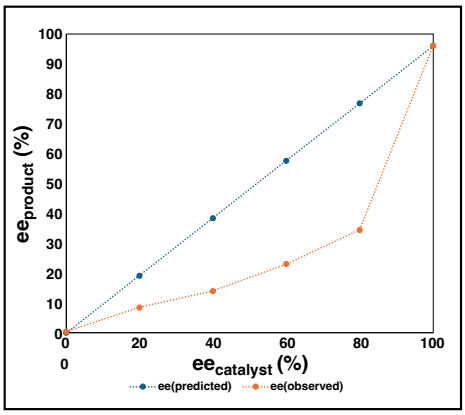
entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	yield (%)	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96



B. Nonlinearity experiment.



entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



[a] Reactions performed on 0.05 mmol scale and yields determined by ^1H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] Total Pd is the molar amount of Pd by combination of $Pd(OAc)_2$ and $Pd_2(dba)_3$.

To explore this effect further, we mixed varying amounts of $Pd(OAc)_2$ and $Pd_2(dba)_3$, keeping the total Pd concentration at 10 mol%, and we observed a nearly linear

relationship between increased $Pd(OAc)_2$ loading and product ee (Table 3.4a). In a more traditional nonlinearity experiment,[20] we observed a negative nonlinear effect (Table 3.4b). Taken together, we posit that it is mechanistically important for some amount of Pd(II) to be present in the reaction mixture to obtain product with high ee, and these findings implicate the formation of catalytically relevant higher-order species. These results suggest a remarkable mechanistic departure from previously studied decarboxylative Pd enolate reactions and warrant further investigation to determine if this pathway is more generalizable.

3.6 CONCLUSIONS

In conclusion, we have developed a novel asymmetric cyclization of isocyanates and Pd enolates for the synthesis of spirocyclic γ-lactams. To the best of our knowledge, this transformation is the first example of an asymmetric enolate addition to an isocyanate. This reaction tolerates a variety of functional groups, including aryl bromides and electron-rich heterocyclic motifs. The importance of the Pd(II) precatalyst was explored through preliminary mechanistic investigations, which revealed both a negative non-linear effect and strong correlation between the presence of Pd(II) in the reaction and high enantioselectivity. In the future, we intend to perform additional mechanistic studies, both kinetic and computational, to obtain a deeper understanding of this unusual catalytic cycle. Ultimately, we aim to leverage these findings for the development of new reactions derived from this decarboxylative Pd enolate formation.

3.7 EXPERIMENTAL SECTION

3.7.1 Materials and Methods

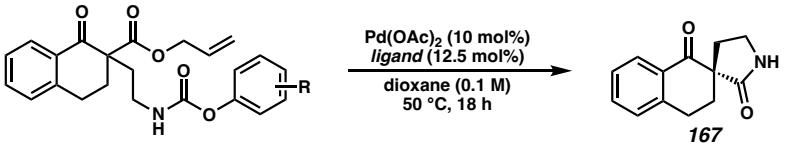
Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[21] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64.[22] Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm

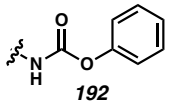
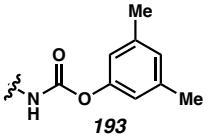
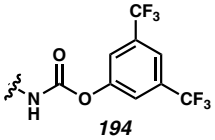
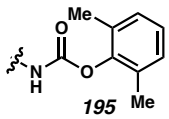
path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system or an Agilent 1260 Infinity II supercritical CO_2 analytical chromatography system utilizing utilizing Chiralpak (IC-3, AD-3, ID- 3, IF-3, IG-3, IH-3) or Chiralcel (OD-3, OJ-3) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$). The Caltech Chemistry Division Mass Spectrometry laboratory acknowledges DOW Chemical Company (DOW Next Generation Instrumentation Grant) and the NSF CRIF program for providing funds that enabled the purchase of this instrumentation.

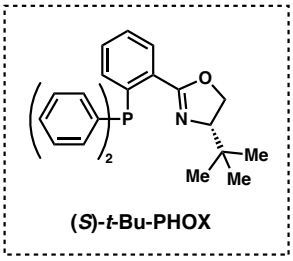
Reagents were purchased from commercial sources and used as received unless otherwise stated. Compound **174** was prepared according to a literature procedure.[23]

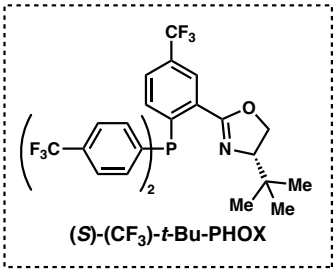
3.7.2 ADDITIONAL OPTIMIZATION DATA

Table 3.5 *Assessment of alternative carbamate electrophiles.*[a]



substrate	(*S*)-*t*-Bu-PHOX	(*S*)-(CF$_3$)-*t*-Bu-PHOX
 192	15% yield 46% ee	0% yield
 193	trace yield ND ee	0% yield
 194	16% yield 32% ee	64% yield 14% ee
 195	trace yield ND ee	0% yield

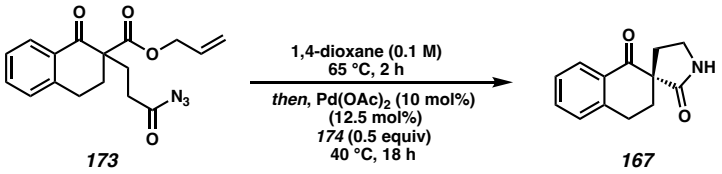




[a] Yields determined by ^{1}H NMR integration against an internal standard.

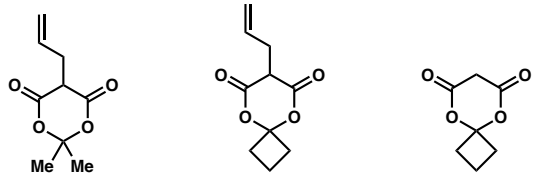
Note: adding various bases to encourage blocked isocyanate reactivity was unsuccessful;[24] in a few instances, we observed improved enantioselectivity that was found to be irreproducible.

Table 3.6 *Assessment of alternative additives.*[a]



173 167

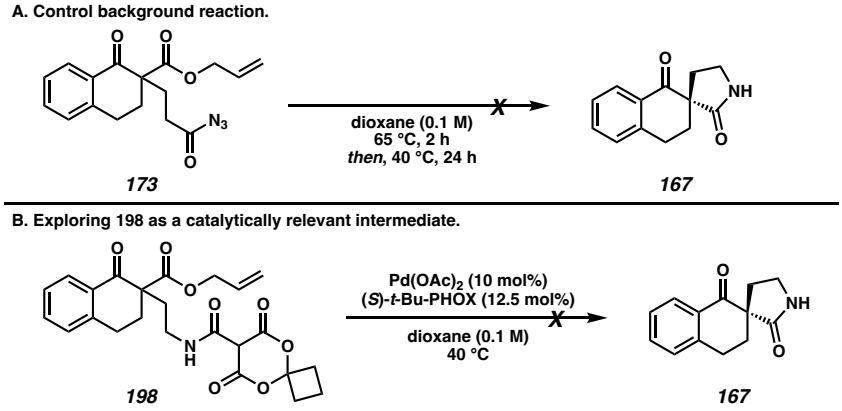
entry	additive	result
1	acac	32% yield, 58% ee
2	dimethyl malonate	0% yield, ND ee
3	methylsulfonylacetone	0% yield, ND ee
4	*197* (1.0 equiv)	98% yield, 54% ee
5	*198* (1.0 equiv)	91% yield, 57% ee
6	*199* (1.0 equiv)	93% yield, 92% ee



196 197 174

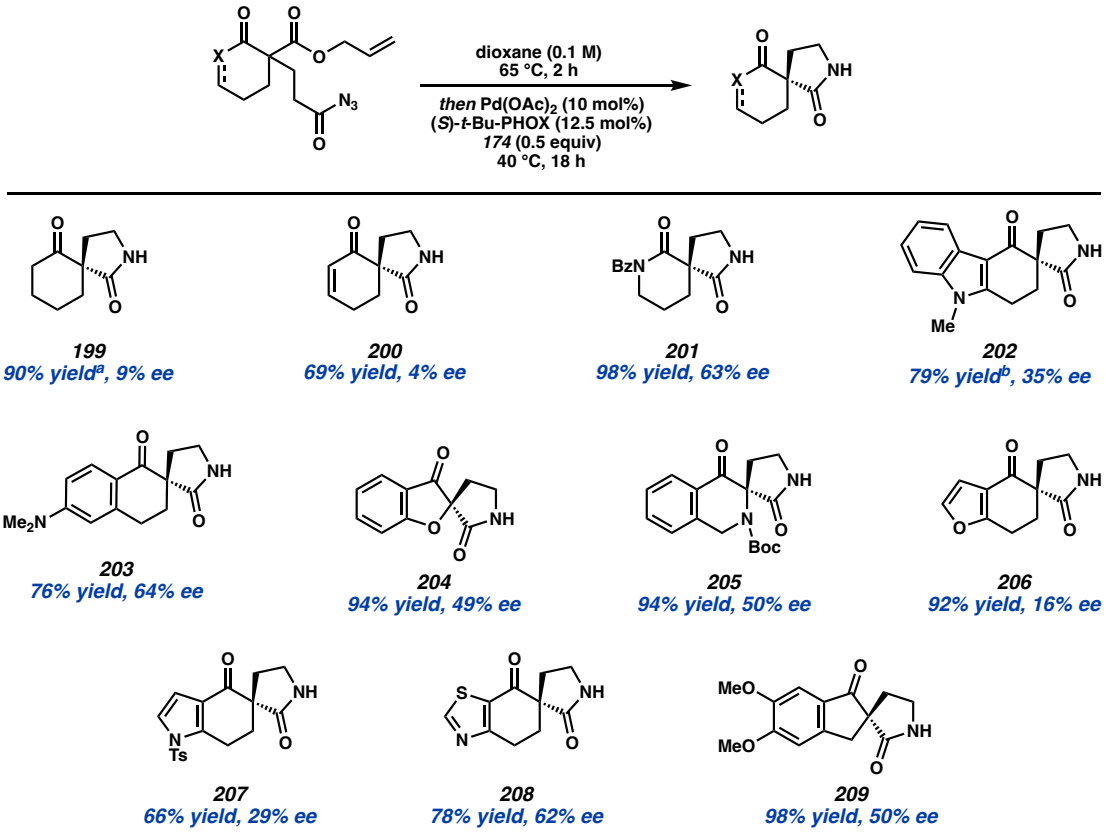
[a] Yields determined by ^{1}H NMR integration against an internal standard.

Scheme 3.5 *Control reactions.*



173 167 198 167

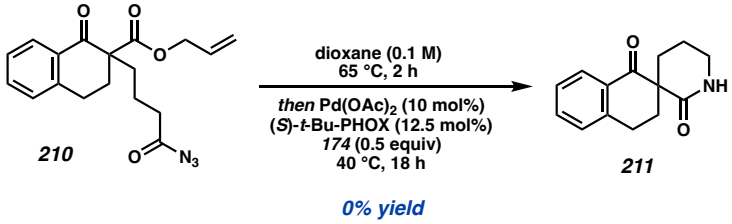
Scheme 3.6 *Failed substrates.*



[a] Yield determined by ^{1}H NMR integration against internal standard (1,3,5-trimethoxybenzene); **199** was found to be volatile.

[b] Reaction performed at 50 °C.

Scheme 3.7 *Failed δ-lactam synthesis.*[a]



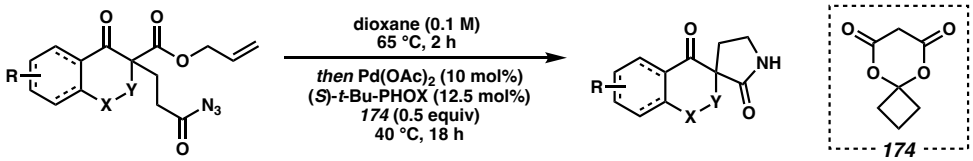
[a] Reaction performed on 0.05 mmol scale.

Note: only protonation of the enolate was observed; resulting isocyanate unstable to purification, confirmed identity via IR.

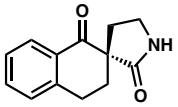
3.7.3 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

3.7.3.1 Pd-Catalyzed Decarboxylative Spirocyclization

General Procedure A: *Asymmetric Pd-Catalyzed Decarboxylative Spirocyclization*



In a nitrogen-filled glovebox, an oven-dried 2-dram vial was charged with a stir bar, acyl azide (0.2 mmol), and dioxane (0.8 mL, 0.25 M). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 65 °C. After 2 h, the solution was cooled and pumped into the glovebox. To a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (0.02 mmol, 10 mol%) and (*S*)-*t*-Bu-PHOX (0.025 mmol, 12.5 mol%) was taken up in dioxane (0.8 mL, 0.25 M) and stirred at 23 °C for 20 minutes. The reaction vial is charged with a solution of **174** (0.1 mmol, 0.5 equiv) in dioxane (0.4 mL, 0.5 M) and the Pd stock solution (0.8 mL), sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixture was then cooled, concentrated under reduced pressure, and purified on silica gel chromatography to afford the spirocyclic product.



167

3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (167)

Prepared from **173** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a light yellow solid (40.0 mg, 0.19 mmol, 93% yield, 96% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.29 (m, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.42 (s, 1H), 3.51 (dt, *J* = 9.7, 7.5 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.29 (ddd, *J* = 16.8, 6.5, 4.7 Hz, 1H), 2.96 (ddd, *J* = 16.9, 9.4, 4.7 Hz, 1H), 2.61 (m, 2H), 2.19 – 2.02 (m, 2H).

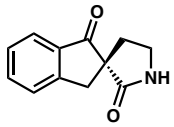
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 177.1, 144.0, 134.0, 131.1, 128.8, 128.3, 127.0, 55.1, 39.5, 32.0, 31.4, 25.7.

IR (neat film, NaCl): 3238, 1701, 1570, 1598, 1360, 1290, 1229, 1071 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found 216.1018.

Optical Rotation: $[\alpha]_D^{24}$ = 82.20 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27.



175

spiro[indene-2,3'-pyrrolidine]-1,2'(3*H*)-dione (175)

Prepared from **212** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as a light yellow solid (33.8 mg, 0.17 mmol, 84% yield, 81% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (td, *J* = 7.4, 1.3 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.43 – 7.34 (m, 1H), 6.65 (s, 1H), 3.81 – 3.68 (m, 2H), 3.41 (tdd, *J* = 9.1, 3.0, 1.1 Hz, 1H), 2.99 (d, *J* = 17.1 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.6, 3.0 Hz, 1H), 2.25 (ddd, *J* = 12.8, 8.8, 7.9 Hz, 1H).

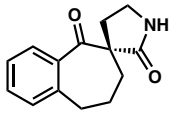
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 176.7, 153.8, 135.5, 135.1, 127.9, 126.5, 124.8, 58.0, 40.0, 37.8, 32.7.

IR (neat film, NaCl): 3246, 1693, 1278 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_2$ $[M+H]^+$: 202.0863, found 202.0859.

Optical Rotation: $[\alpha]_D^{24}$ = 114.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.76, t_R (min): minor = 4.05.



176

8,9-dihydrospiro[benzo[7]annulene-6,3'-pyrrolidine]-2',5(7*H*)-dione (176)

Prepared from **213** following General Procedure A. Purification by flash column chromatography (0–100% ethyl acetate/hexanes) afforded the title compound as an off-white solid (41.5 mg, 0.18 mmol, 91% yield, 49% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.17 (s, 1H), 3.77 – 3.55 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.5, 3.9, 1.0 Hz, 1H), 2.90 (ddd, *J* = 14.3, 6.2, 4.1 Hz, 1H), 2.75 (ddd, *J* = 14.3, 10.5, 6.8 Hz, 1H), 2.59 (dddd, *J* = 12.0, 8.0, 4.0, 1.6 Hz, 1H), 2.31 – 2.12 (m, 2H), 2.07 – 1.85 (m, 2H), 1.77 (dddd, *J* = 14.7, 5.4, 3.8, 1.2 Hz, 1H).

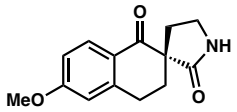
^{13}C NMR (100 MHz, $CDCl_3$): δ 209.8, 177.8, 139.8, 137.7, 132.2, 128.6, 128.0, 127.2, 58.2, 39.8, 39.8, 31.8, 31.1, 29.8, 29.7, 22.1.

IR (neat film, NaCl): 3228, 2942, 1698, 1671, 1597, 1448, 1348, 1280, 1254, 1066, 960 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176, found 230.1174.

Optical Rotation: $[\alpha]_D^{24}$ = 36.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.07, t_R (min): minor = 4.03.



177

6-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (177)

Prepared from **214** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (46.0 mg, 0.188 mmol, 94% yield, 93% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.14 (s, 1H), 3.86 (s, 3H), 3.61 – 3.46 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.4, 3.5, 1.0 Hz, 1H), 3.27 (ddd, *J* = 16.8, 6.7, 4.7 Hz, 1H), 2.91 (ddd, *J* = 16.7, 9.3, 4.6 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.14 – 2.01 (m, 2H).

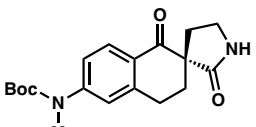
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 177.3, 164.1, 146.6, 130.8, 124.7, 113.7, 112.6, 55.6, 54.7, 39.5, 32.2, 31.6, 26.1.

IR (neat film, NaCl): 3320, 2921, 1695, 1661, 1598, 1230 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found 246.1123.

Optical Rotation: $[\alpha]_D^{24}$ = 71.93 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.15, t_R (min): minor = 8.66.



178

***tert*-butyl (*S*)-(1,2'-dioxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-6-yl)(methyl)carbamate (178)**

Prepared from **216** following General Procedure A. Purification by flash column chromatography (20% acetone/CH_2Cl_2) afforded the title compound as an off-white solid (51.0 mg, 0.15 mmol, 73% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 5.70 (s, 1H), 3.57 – 3.49 (m, 1H), 3.40 (dddd, *J* = 9.3, 8.3, 3.4, 1.0 Hz, 1H), 3.30 (s, 4H), 2.94 (ddd, *J* = 16.8, 9.2, 4.7 Hz, 1H), 2.66 – 2.56 (m, 2H), 2.15 – 2.04 (m, 2H), 1.49 (s, 9H).

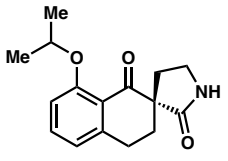
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 176.8, 154.2, 148.7, 144.7, 128.9, 127.5, 123.8, 123.1, 81.4, 54.7, 39.4, 36.9, 32.2, 31.6, 28.4, 25.9.

IR (Neat Film, NaCl): 3228, 2940, 1702, 1670, 1601, 1352, 1152 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 345.1800, found 345.1800.

Optical Rotation: $[\alpha]_D^{21}$ 64.12 (c 1.0, $CHCl_3$).

SFC conditions: 25% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 5.10, major = 3.38.



179

(*S*)-8-isopropoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (179)

Prepared from **217** following General Procedure A. Purification by flash column chromatography (0–40% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.1 mg, 0.18 mmol, 88% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.5, 7.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.80 – 6.66 (m, 1H), 6.42 (s, 1H), 4.55 (p, *J* = 6.1 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.42 – 3.30 (m, 1H), 3.19 (ddd, *J* = 16.4, 6.4, 4.5 Hz, 1H), 2.87 (ddd, *J* = 15.9, 10.1, 4.4 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.7, 3.1 Hz, 1H), 2.58 – 2.43 (m, 1H), 2.10 – 1.92 (m, 2H), 1.37 (dd, *J* = 9.7, 6.0 Hz, 6H).

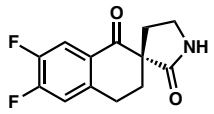
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 177.7, 159.8, 146.6, 134.3, 121.8, 120.5, 113.9, 113.8, 71.8, 56.6, 56.6, 39.6, 32.8, 31.5, 26.9, 22.2, 22.1.

IR (neat film, NaCl): 3217, 2977, 2931, 2361, 2246, 1698, 1592, 1462, 1271, 1207, 1113, 919, 730 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1434.

Optical Rotation: $[\alpha]_D^{24}$ = 127.86 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 210 nm, t_R (min): major = 2.81, t_R (min): minor = 3.46.



180

6,7-difluoro-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (180)

Prepared from **218** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (43.5 mg, 0.17 mmol, 87% yield, 68% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 10.6, 8.3 Hz, 1H), 7.05 (dd, *J* = 10.4, 7.1 Hz, 1H), 6.06 (s, 1H), 3.68 – 3.47 (m, 1H), 3.41 (dddd, *J* = 9.4, 8.3, 3.9, 1.0 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.03 – 2.85 (m, 1H), 2.68 (ddd, *J* = 12.9, 7.8, 3.9 Hz, 1H), 2.58 (ddd, *J* = 13.2, 8.1, 4.8 Hz, 1H), 2.16 – 2.04 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 176.4, 157.5 – 151.6 (dd, *J* = 259.0, 13.5 Hz), 149.7 (dd, *J* = 249.7, 13.2 Hz), 141.9 (dd, *J* = 7.4, 3.6 Hz), 128.2, 117.3 (d, *J* = 17.5 Hz), 117.0 (dd, *J* = 17.8, 2.2 Hz), 54.3, 39.4, 31.9, 31.5, 25.2.

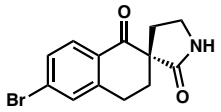
^{19}F NMR (282 MHz, $CDCl_3$): δ -128.25, -138.98.

IR (neat film, NaCl): 3248, 1698, 1674, 1616, 1509, 1355, 1330, 1283 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{12}F_2NO_2$ $[M+H]^+$: 252.0831, found 252.0830.

Optical Rotation: $[\alpha]_D^{24}$ = 68.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 280 nm, t_R (min): major = 4.28, t_R (min): minor = 4.61.



181

(*S*)-6-bromo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (181)

Prepared from **219** following General Procedure A. Purification by flash column chromatography (0–20% acetone/dichloromethane) afforded the title compound as an off-white solid (54.3 mg, 0.18 mmol, 92% yield, 94% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.86 (m, 1H), 7.53 – 7.41 (m, 2H), 6.52 (s, 1H), 3.56 – 3.45 (m, 1H), 3.45 – 3.19 (m, 2H), 2.91 (ddd, *J* = 17.0, 8.7, 4.7 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.15 – 2.01 (m, 2H).

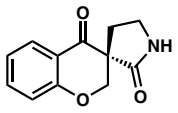
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 176.7, 145.8, 131.8, 130.5, 130.0, 129.9, 129.3, 54.9, 39.5, 31.9, 31.3, 25.5.

IR (neat film, NaCl): 3233, 2930, 2893, 2362, 1701, 1672, 1586, 1430, 1353, 1289, 1226, 1079, 911, 735 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{13}NO_2Br$ $[M+H]^+$: 294.0124, found 294.0125.

Optical Rotation: $[\alpha]_D^{24}$ = 85.81 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.28, t_R (min): minor = 7.28.



182

(*R*)-spiro[chromane-3,3'-pyrrolidine]-2',4-dione (182)

Prepared from **220** following General Procedure A. Purification by flash column chromatography (75% EtOAc/hexanes) afforded the title compound as an off-white solid (35.9 mg, 0.17 mmol, 83% yield, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.89 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.53 (dtd, *J* = 9.6, 7.6, 0.7 Hz, 1H), 3.44 (dddd, *J* = 9.6, 8.6, 3.2, 1.1 Hz, 1H), 2.52 (ddd, *J* = 13.4, 7.6, 3.2 Hz, 1H), 2.30 (ddd, *J* = 13.4, 8.5, 7.7 Hz, 1H).

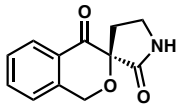
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 173.7, 161.5, 136.6, 128.0, 122.0, 119.7, 118.1, 72.4, 54.4, 39.4, 30.0.

IR (Neat Film, NaCl): 3247, 2902, 1704, 1680, 1605, 1477, 1301 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{12}H_{11}NO_3$ $[M+H]^+$: 218.0812, found 218.0811.

Optical Rotation: $[\alpha]_D^{21}$ 62.22 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 4.59, major = 4.22.



183

(*R*)-spiro[isochromane-3,3'-pyrrolidine]-2',4-dione (183)

Prepared from **221** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (34.1 mg, 0.16 mmol, 78% yield, 91% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.19 (s, 1H), 5.98 (s, 1H), 5.63 (d, *J* = 15.3 Hz, 1H), 4.88 (d, *J* = 15.3 Hz, 1H), 3.52 (td, *J* = 6.6, 1.0 Hz, 2H), 2.91 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.30 (dt, *J* = 13.3, 6.4 Hz, 1H).

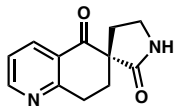
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 173.3, 141.6, 134.6, 128.6, 127.9, 127.1, 124.5, 83.9, 64.4, 39.2, 32.3.

IR (neat film, NaCl): 3252, 2954, 2901, 2246, 1706, 1684, 1603, 1441, 1284, 1222, 1123, 1055, 886, 755 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0812, found 218.0807.

Optical Rotation: $[\alpha]_D^{24}$ = 50.98 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.27, t_R (min): minor = 3.65.



184

7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (184)

Prepared from **222** following General Procedure A. Purification by flash column chromatography (0–30% acetone/dichloromethane) afforded the title compound as an off-white solid (35.3 mg, 0.16 mmol, 82% yield, 63% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.59 (s, 1H), 3.67 – 3.46 (m, 2H), 3.42 (dddd, *J* = 9.5, 8.3, 4.1, 1.0 Hz, 1H), 3.12 (ddd, *J* = 17.7, 8.4, 5.0 Hz, 1H), 2.78 – 2.43 (m, 2H), 2.33 – 2.02 (m, 2H).

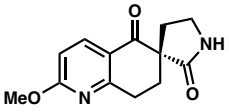
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 176.4, 163.3, 154.0, 136.0, 126.9, 122.5, 54.8, 54.8, 46.1, 39.4, 31.6, 30.3, 30.3, 28.9.

IR (neat film, NaCl): 2930, 2603, 2496, 1645, 1396, 1035 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0972, found 217.0971.

Optical Rotation: $[\alpha]_D^{24}$ = 81.71 (c 0.42, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack ID-3 column, λ = 280 nm, t_R (min): major = 2.61, t_R (min): minor = 3.55.



185

2'-methoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (185)

Prepared from **223** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.0 mg, 0.195 mmol, 97% yield, 92% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.34 (s, 1H), 3.99 (s, 3H), 3.51 (dddd, *J* = 9.5, 7.8, 7.1, 0.8 Hz, 1H), 3.45 – 3.30 (m, 2H), 2.97 (ddd, *J* = 17.8, 8.4, 5.0 Hz, 1H), 2.70 – 2.53 (m, 2H), 2.16 – 2.01 (m, 2H).

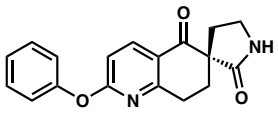
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 176.8, 166.6, 163.7, 138.6, 121.4, 110.4, 54.4, 54.2, 39.5, 31.8, 30.5, 28.9.

IR (neat film, NaCl): 3305, 2942, 1700, 1669, 1591, 1412, 1347, 1329, 1266, 1235, 1013, 906, 734 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1077, found 247.1073.

Optical Rotation: $[\alpha]_D^{24}$ = 92.99 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 2.76, t_R (min): minor = 3.56.



186

(*S*)-2'-phenoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (186)

Prepared from **224** following General Procedure A. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as an off-white solid (50.1 mg, 0.16 mmol, 81% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.7 Hz, 1H), 7.41 (tt, *J* = 7.6, 2.2 Hz, 2H), 7.30 – 7.19 (m, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 3.62 – 3.45 (m, 1H), 3.43 – 3.18

(m, 2H), 2.93 (ddd, *J* = 17.9, 8.2, 5.0 Hz, 1H), 2.66 (ddd, *J* = 12.9, 7.9, 4.1 Hz, 1H), 2.57 (ddd, *J* = 13.5, 8.2, 5.1 Hz, 1H), 2.07 (dddd, *J* = 18.4, 8.3, 7.2, 4.5 Hz, 2H).

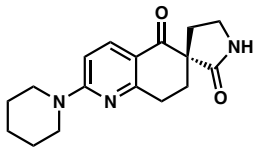
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 176.6, 166.1, 164.1, 153.3, 139.8, 129.9, 125.5, 122.7, 121.6, 109.8, 54.5, 39.5, 31.7, 30.4, 28.8.

IR (neat film, NaCl): 3227, 2939, 1698, 1672, 1509, 1488, 1452, 1346, 1260, 1201, 934, 909, 774, 727 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$: 309.1234, found 309.1243.

Optical Rotation: $[\alpha]_D^{24}$ = 86.14 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.58, t_R (min): minor = 4.53.



187

(*S*)-2'-(piperidin-1-yl)-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (187)

Prepared from **225** following General Procedure A. Purification by flash column chromatography (0–75% ethyl acetate/hexanes) afforded the title compound as an off-white solid (53.6 mg, 0.18 mmol, 90% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.25 (s, 1H), 3.70 (dd, *J* = 6.3, 4.4 Hz, 4H), 3.57 – 3.44 (m, 1H), 3.37 (dddd, *J* = 9.4, 8.4, 3.7, 1.0 Hz, 1H), 3.21 (ddd, *J* = 17.4, 6.6, 4.9 Hz, 1H), 2.86 (ddd, *J* = 17.3, 9.3, 4.9 Hz, 1H), 2.64 – 2.50 (m, 2H), 2.13 – 1.97 (m, 2H), 1.80 – 1.66 (m, 2H), 1.63 (m, 4H).

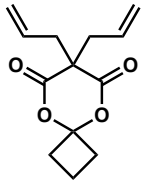
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 177.6, 164.4, 159.9, 137.3, 116.5, 105.0, 54.2, 45.8, 39.6, 32.2, 30.6, 29.2, 25.8, 24.8.

IR (neat film, NaCl): 3226, 2932, 2855, 2239, 1697, 1653, 1587, 1496, 1345, 1239, 1126, 1021, 913, 728 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{22}N_3O_2$ $[M+H]^+$: 300.1707, found 300.1709.

Optical Rotation: $[\alpha]_D^{24}$ = 77.89 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 230 nm, t_R (min): major = 3.52, t_R (min): minor = 9.73.



168

7,7-diallyl-5,9-dioxaspiro[3.5]nonane-6,8-dione (168)

Isolated from a reaction with **173** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a clear oil (21.0 mg, 0.09 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (ddt, *J* = 17.3, 10.1, 7.4 Hz, 2H), 5.23 – 5.13 (m, 4H), 2.72 – 2.66 (m, 4H), 2.65 – 2.57 (m, 4H), 1.89 (tt, *J* = 9.8, 7.2 Hz, 2H).

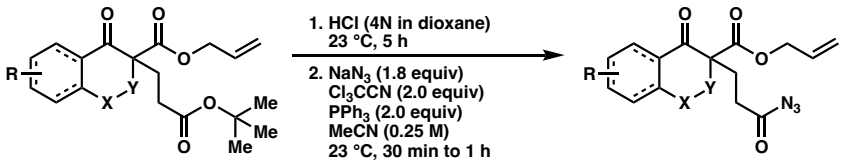
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 130.6, 121.4, 104.5, 53.6, 41.4, 37.7, 10.7.

IR (neat film, NaCl): 2956, 1782, 1750, 1285, 1246, 1157, 995, 929 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{13}H_{16}O_4$ $[M]^{+\bullet}$: 236.1043, found 236.1041.

3.7.3.2 Preparation of Acyl Azide Starting Materials

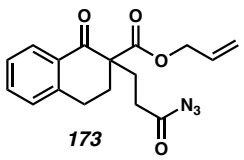
General Procedure B: Synthesis of Acyl Azides



To a flask containing ester intermediate was added HCl (4N in dioxane) at 23 °C. The resultant solution was stirred for 5 h, or until full consumption of starting material by TLC analysis. The crude mixture was concentrated under reduced pressure, then dissolved in ethyl acetate, washed with water twice, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

Acyl azides were synthesized according to a modified literature procedure.[25] To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. The product was purified by silica gel chromatography.

Note: occasionally, upon addition of trichloroacetonitrile, the reaction gently exotherms, in which case the reaction flask was cooled with an ice bath at 0 °C until completion of the dropwise addition.



173

allyl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (173)

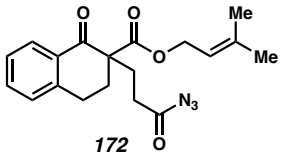
Prepared from **226** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (642 mg, 1.96 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.48 (m, 1H), 7.36 – 7.28 (m, 1H), 7.25 – 7.18 (m, 1H), 5.78 (ddt, *J* = 17.5, 10.2, 5.6 Hz, 1H), 5.17 (m, 1H), 5.16 – 4.97 (m, 1H), 4.58 (ddt, *J* = 5.6, 3.4, 1.4 Hz, 2H), 3.21 – 2.84 (m, 2H), 2.73 – 2.41 (m, 3H), 2.38 – 2.17 (m, 2H), 2.11 (ddd, *J* = 13.6, 9.8, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 180.1, 171.3, 142.8, 133.9, 133.9, 132.0, 131.4, 128.9, 128.2, 128.2, 127.1, 127.1, 118.9, 118.8, 66.0, 56.7, 32.7, 31.7, 28.8, 26.0.

IR (neat film, NaCl): 3735, 2939, 2268, 2137, 1731, 1686, 1600, 1454, 1180, 929, 743 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{17}N_3O_4$ $[M]^{+\bullet}$: 327.1214, found 327.1211.



172

3-methylbut-2-en-1-yl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2- carboxylate (172)

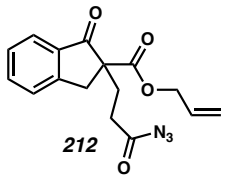
Prepared from **227** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (881 mg, 2.48 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.32 – 7.28 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.20 (ddt, *J* = 7.2, 5.9, 1.4 Hz, 1H), 4.63 – 4.48 (m, 2H), 3.14 – 2.84 (m, 2H), 2.76 – 2.38 (m, 3H), 2.36 – 2.13 (m, 2H), 2.08 (ddd, *J* = 13.5, 10.2, 4.9 Hz, 1H), 1.68 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 180.1, 171.5, 142.8, 133.7, 132.1, 130.2, 128.8, 128.1, 126.9, 117.9, 62.4, 56.6, 32.7, 31.9, 28.9, 26.0, 25.7, 18.1.

IR (neat film, NaCl): 2930, 2264, 2136, 1717, 1599, 1457, 1185, 1-71, 957, 766 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{21}N_3O_4Na$ $[M+Na]^+$: 378.1424, found 378.1412.



212

allyl 2-(3-azido-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (212)

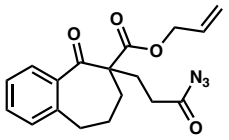
Prepared from **228** following General Procedure B. Purification by flash column chromatography (10–15% EtOAc/hexanes) afforded the title compound (191 mg, 0.50 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.4, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.42 (td, *J* = 7.4, 0.9 Hz, 1H), 5.82 (ddt, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.3 Hz, 1H), 3.06 (d, *J* = 17.3 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.51 – 2.30 (m, 2H), 2.27 (ddd, *J* = 14.0, 10.6, 4.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 179.8, 170.5, 152.6, 135.8, 135.1, 131.5, 128.3, 126.6, 125.2, 118.7, 66.3, 59.3, 37.8, 32.5, 29.5.

IR (Neat Film, NaCl): 3423, 2269, 2137, 1713, 1173 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{15}NO_4$ $[M+H]^+$: 286.1074, found 286.1067.



213

allyl 6-(3-azido-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (213)

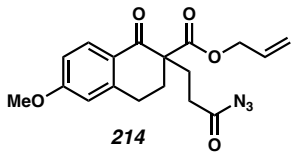
Prepared from **229** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (184 mg, 0.54 mmol, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 7.36 (m, 1H), 7.26 (m, 1H), 7.12 (m, 1H), 5.65 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.28 – 5.03 (m, 2H), 4.46 (dd, *J* = 5.9, 1.3 Hz, 1H), 2.89 (dddd, *J* = 53.8, 15.7, 8.3, 4.2 Hz, 2H), 2.67 – 2.28 (m, 4H), 2.28 – 2.13 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 180.0, 171.7, 140.0, 138.7, 131.5, 131.3, 129.3, 129.2, 126.7, 119.3, 66.2, 61.1, 33.1, 33.0, 32.5, 30.9, 23.9.

IR (neat film, NaCl): 2937, 2265, 2137, 1784, 1685, 1598, 1447, 1182, 959, 743 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_1O_4$ $[M–N_2+H]^+$: 314.3487, found 314.3478.



214

allyl 2-(3-azido-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (214)

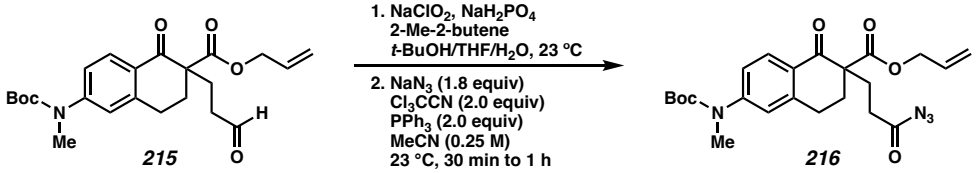
Prepared from **230** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (513 mg, 1.44 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.87 – 5.73 (m, 1H), 5.25 – 5.11 (m, 2H), 4.58 (m, 2H), 3.85 (s, 3H), 3.11 – 2.80 (m, 2H), 2.74 – 2.39 (m, 3H), 2.38 – 2.14 (m, 2H), 2.15 – 1.95 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.2, 171.5, 164.0, 145.4, 131.5, 130.7, 125.5, 118.7, 113.8, 112.6, 66.0, 56.5, 55.6, 32.7, 31.6, 28.8, 26.3.

IR (neat film, NaCl): 2940, 2268, 2137, 1726, 1675, 1599, 1442, 1352, 1256, 1187, 1076, 931 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_3O_5$ $[M+H]^+$: 330.1336, found 330.1337.



allyl 2-(3-azido-3-oxopropyl)-6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (216)

To a solution of aldehyde **215** (1.28 g, 3.07 mmol, 1 equiv) and 2-Me-2-butene (4.9 mL, 46 mmol, 15 equiv) in *t*-BuOH/THF (1:1 ratio, 30 mL, 0.1 M total) was added $NaClO_2$ (833 mg, 3 equiv, 9.2 mmol) and NaH_2PO_4 (2.21 g, 18.4 mmol, 6 equiv) in H_2O (8 mL, 0.4 M). The reaction was stirred for 2 hours at 23 ºC until starting material was consumed by TLC analysis. The reaction was quenched with 1 N HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate,

filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

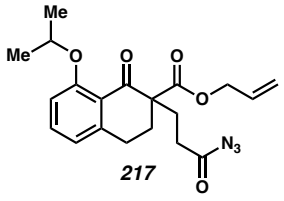
To a solution of the carboxylic acid intermediate in acetonitrile (16 mL, 0.25 M) at 23 °C was added sodium azide (242 mg, 3.7 mmol, 1.8 equiv) and triphenylphosphine (1.63 g, 6.2 mmol, 2.0 equiv). Trichloroacetonitrile (0.62 mL, 6.2 mmol, 2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (939 mg, 2.06 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.19 (dq, *J* = 9.8, 1.4 Hz, 1H), 5.15 (dq, *J* = 2.8, 1.4 Hz, 1H), 4.58 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.28 (s, 3H), 3.02 (ddd, *J* = 17.3, 10.0, 4.8 Hz, 1H), 2.91 (dt, *J* = 17.4, 5.1 Hz, 1H), 2.69 – 2.42 (m, 3H), 2.35 – 2.16 (m, 2H), 2.09 (ddd, *J* = 13.6, 9.8, 4.9 Hz, 1H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 180.1, 171.3, 154.1, 148.6, 143.4, 131.4, 128.8, 128.3, 123.8, 123.1, 118.8, 81.4, 66.0, 56.6, 36.9, 32.7, 31.6, 28.8, 28.4, 26.1.

IR (Neat Film, NaCl): 2976, 2935, 2264, 2139, 1704, 1601, 1356, 1153 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{28}N_4O_6$ $[M+H]^+$: 457.2082, found 457.2078.



217

allyl 2-(3-azido-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (217)

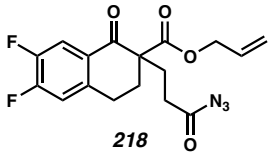
Prepared from **231** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (343 mg, 0.89 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.73 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.65 – 4.47 (m, 3H), 3.27 – 2.75 (m, 2H), 2.63 (ddd, *J* = 16.9, 10.6, 5.4 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.23 (dddd, *J* = 56.7, 14.1, 10.5, 5.4 Hz, 2H), 2.07 – 1.88 (m, 1H), 1.37 (dd, *J* = 16.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 180.3, 171.6, 159.2, 144.8, 133.8, 131.6, 123.4, 120.6, 118.5, 113.7, 71.8, 65.8, 57.7, 32.7, 31.1, 29.2, 26.6, 22.2, 22.1.

IR (neat film, NaCl): 2979, 2933, 2263, 2138, 1731, 1694, 1592, 1454, 1270, 1182, 1111, 922, 763 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{23}N_3O_5Na$ $[M+Na]^+$: 408.1530, found 408.1515.



218

allyl 2-(3-azido-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (218)

Prepared from **232** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (416 mg, 1.14 mmol, 64% yield).

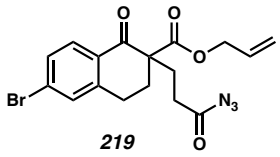
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 10.6, 8.2 Hz, 1H), 7.01 (dd, *J* = 10.3, 7.1 Hz, 1H), 5.79 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.24 – 5.11 (m, 2H), 4.65 – 4.53 (m, 2H), 3.06 – 2.84 (m, 2H), 2.71 – 2.38 (m, 3H), 2.36 – 2.15 (m, 2H), 2.10 (ddd, *J* = 13.7, 10.3, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.90, 179.93, 170.85, 153.95 (dd, *J* = 258.9, 13.6 Hz), 149.76 (dd, *J* = 250.2, 13.1 Hz), 140.37 (dd, *J* = 7.3, 3.6 Hz), 131.21, 130.04 – 126.31 (m), 119.17, 117.28 (d, *J* = 17.5 Hz), 116.94 (dd, *J* = 17.9, 2.2 Hz), 66.26, 56.18, 32.54, 31.74, 28.82, 25.57.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.23, -138.48.

IR (neat film, NaCl): 3067, 2937, 2269, 2139, 1731, 1619, 1511, 1356, 1284, 1170, 1072, 919, 786 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{16}F_2O_4$ $[M–N_3+H]^+$: 321.0933, found 321.0936.



219

allyl 2-(3-azido-3-oxopropyl)-6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (219)

Prepared from **233** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (484 mg, 1.19 mmol, 67% yield).

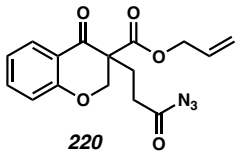
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.40 (s, 1H), 5.79 (m, *J* = 17.2, 9.9, 5.6 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.16 – 2.79 (m, 2H), 2.64 (ddd, *J* = 16.6, 10.3, 5.5 Hz, 1H), 2.55 (dt, *J* = 13.7, 4.8

Hz, 1H), 2.46 (ddd, *J* = 16.7, 10.1, 5.5 Hz, 1H), 2.26 (dddd, *J* = 40.0, 14.1, 10.2, 5.5 Hz, 2H), 2.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 180.0, 171.0, 144.5, 131.8, 131.3, 130.9, 130.6, 129.9, 129.1, 119.1, 66.2, 56.6, 32.6, 31.5, 28.8, 25.8.

IR (neat film, NaCl): 2939, 2271, 2138, 1728, 1688, 1587, 1443, 1349, 1183, 1071, 905 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{16}N_3O_4Br$ $[M]^{+\bullet}$: 405.0319, found 405.0329.



220

allyl 3-(3-azido-3-oxopropyl)-4-oxochromane-3-carboxylate (220)

A solution of **234** (507 mg, 1.41 mmol, 1 equiv) in acetone (0.5 M, 2.8 mL) was cooled to 0 ºC. Concentrated HCl (2.8 mL) was added. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with brine and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude carboxylic acid which was used directly in the next step.

To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography

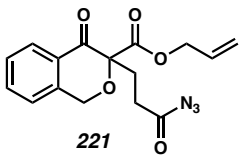
(15% EtOAc/hexanes) afforded the title compound as a clear oil (148 mg, 0.45 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.06 (td, *J* = 7.7, 1.1 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.25 – 5.17 (m, 2H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.68 – 4.59 (m, 2H), 4.31 (d, *J* = 11.7 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.31 (ddd, *J* = 14.2, 10.1, 5.8 Hz, 1H), 2.15 (ddd, *J* = 14.3, 10.3, 5.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 179.6, 169.0, 161.0, 136.5, 131.1, 128.0, 122.2, 120.1, 119.0, 117.9, 72.1, 66.5, 56.3, 32.4, 25.0.

IR (Neat Film, NaCl): 3076, 2937, 2264, 2136, 1713, 1606, 1458, 1220 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5$ $[M+H]^+$: 302.1023, found 302.1012.



221

allyl 3-(3-azido-3-oxopropyl)-4-oxoisochromane-3-carboxylate (221)

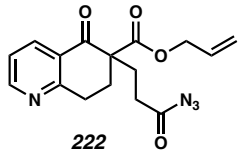
Prepared from **235** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (400 mg, 1.22 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.58 (m, 1H), 7.41 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.41 – 5.16 (m, 2H), 4.90 (d, *J* = 16.1 Hz, 1H), 4.63 (m, 2H), 2.64 – 2.38 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 179.8, 167.8, 141.0, 134.7, 131.0, 128.4, 128.0, 127.4, 124.4, 119.3, 84.1, 66.6, 64.3, 31.2.

IR (neat film, NaCl): 2948, 2270, 2139, 1741, 1701, 1603, 1449, 1287, 1210, 1051, 756 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5Na$ $[M–N_2+Na]^+$: 324.0842, found 324.0831.



222

allyl 6-(3-azido-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (222)

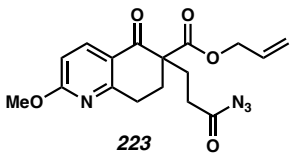
Prepared from **236** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (0.193 mg, 0.59 mmol, 27% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.34 – 8.26 (m, 1H), 7.31 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.78 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.2, 1.4 Hz, 2H), 3.29 – 3.09 (m, 2H), 2.74 – 2.56 (m, 2H), 2.47 (ddd, *J* = 16.7, 10.1, 5.4 Hz, 1H), 2.29 (dddd, *J* = 42.9, 14.1, 10.3, 5.4 Hz, 2H), 2.15 (ddd, *J* = 13.9, 9.6, 6.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 179.9, 170.8, 162.0, 154.0, 136.0, 131.2, 127.9, 122.6, 119.3, 66.3, 56.5, 32.5, 30.6, 29.3, 28.8.

IR (neat film, NaCl): 2949, 2272, 2138, 1713, 1694, 1584, 1442, 1181, 1089, 943, 759 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{16}H_{16}N_4O_4$ $[M]^{+\bullet}$: 328.1166, found 328.1154.



223

allyl 6-(3-azido-3-oxopropyl)-2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (223)

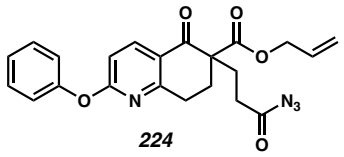
Prepared from **237** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (259 mg, 0.72 mmol, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.81 (ddt, *J* = 17.4, 10.2, 5.7 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.78 – 2.54 (m, 2H), 2.48 (ddd, *J* = 16.8, 10.1, 5.5 Hz, 1H), 2.32 (ddd, *J* = 14.1, 10.1, 5.6 Hz, 1H), 2.21 (ddd, *J* = 14.2, 10.4, 5.5 Hz, 1H), 2.14 – 1.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.1, 171.2, 166.5, 162.4, 138.5, 131.4, 122.1, 119.0, 110.6, 66.2, 56.1, 54.2, 32.6, 30.5, 29.2, 28.7.

IR (neat film, NaCl): 2945, 2267, 2139, 1727, 1592, 1480, 1329, 1267, 1183, 1072, 1020, 842, 784 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{=17}H_{19}N_2O_5$ $[M–N_2+H]^+$: 331.1288, found 331.1301.



224

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (224)

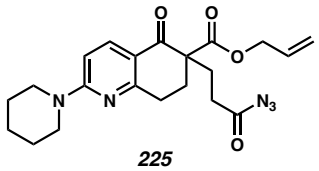
Prepared from **238** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (164 mg, 0.39 mmol, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.33 (m, 2H), 7.26 (s, 1H), 7.19 – 7.11 (m, 2H), 6.76 (d, *J* = 8.7 Hz, 1H), 5.81 (m, 1H), 5.22 (dd, *J* = 8.4, 1.4 Hz, 1H), 5.19 (m, 1H), 4.59 (m, 2H), 3.18 – 2.86 (m, 2H), 2.75 – 2.38 (m, 3H), 2.27 (dddd, *J* = 43.3, 14.1, 10.2, 5.5 Hz, 2H), 2.09 (ddd, *J* = 13.9, 9.8, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 180.0, 171.0, 166.1, 162.8, 153.3, 139.8, 131.3, 129.9, 125.6, 123.5, 121.6, 119.1, 110.0, 66.2, 56.2, 32.6, 30.5, 29.1, 28.7.

IR (neat film, NaCl): 2946, 2266, 2137, 1727, 1579, 1489, 1451, 1414, 1314, 1257, 1196, 1071, 941, 777 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{21}N_2O_5$ $[M–N_2+H]^+$: 393.1445, found 393.1446.



225

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (225)

Prepared from **239** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 2.87 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.53 (d, *J* = 9.1 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.34 – 5.14 (m, 2H), 4.64 – 4.56 (m, 2H), 3.70 (m, 4H), 3.02 – 2.77 (m, 2H), 2.69 – 2.40 (m, 3H), 2.38 – 2.19 (m, 2H), 2.13 – 1.86 (m, 1H), 1.76 – 1.66 (m, 2H), 1.67 – 1.57 (m, 4H).

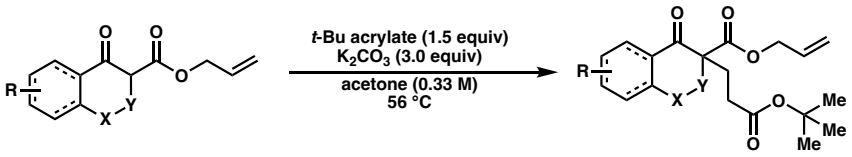
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 180.3, 171.8, 163.4, 159.8, 137.3, 131.7, 118.7, 117.1, 105.1, 66.0, 56.0, 45.8, 32.8, 30.5, 29.5, 28.8, 25.9, 24.8.

IR (neat film, NaCl): 2938, 2855, 2266, 2137, 1729, 1662, 1589, 1498, 1408, 1249, 1088, 1024, 941, 817 cm^{-1}.

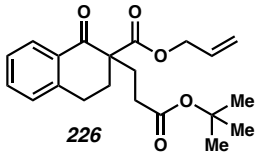
HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.2132, found 412.2113.

3.7.3.3 Preparation of *tert*-Butyl Ester Intermediates

General Procedure C: Michael Addition of tert-Butyl Acrylate



To a flask containing the allyl β-keto ester intermediate was added acetone (0.33 M), *t*-butyl acrylate (1.5 equiv) and K_2CO_3 (3.0 equiv). The reaction was heated to 56 °C for 5 h, or until complete consumption of starting material by TLC analysis. The reaction was cooled, filtered through a small Celite plug, concentrated, and purified via silica gel chromatography to afford the *tert*-butyl ester products.



226

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (226)

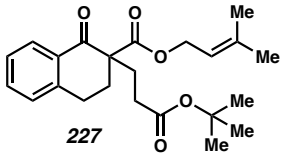
Prepared from **240** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (11.65 g, 32.5 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 1H), 7.46 (m, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 5.86 – 5.71 (m, 1H), 5.21 – 5.09 (m, 2H), 4.65 – 4.51 (m, 2H), 3.11 – 2.89 (m, 2H), 2.57 (m, 1H), 2.51 – 2.39 (m, 1H), 2.38 – 2.04 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 172.5, 171.5, 142.9, 133.7, 132.1, 131.6, 128.8, 128.2, 127.0, 118.4, 80.5, 65.8, 56.9, 31.2, 31.1, 29.0, 28.2, 25.9.

IR (neat film, NaCl): 2974, 2365, 1729, 1686, 1601, 1365, 1228, 1154, 947 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}O_5Na$ $[M+Na]^+$: 381.1672, found 381.1676.



227

3-methylbut-2-en-1-yl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (227)

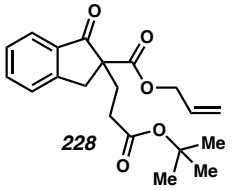
Prepared from **241** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 3.10 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.58 – 7.38 (m, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.22 (ddt, *J* = 7.2, 5.8, 1.4 Hz, 1H), 4.65 – 4.49 (m, 2H), 3.10 – 2.87 (m, 2H), 2.60 – 2.39 (m, 2H), 2.38 – 2.20 (m, 2H), 2.20 – 1.97 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 172.6, 171.8, 143.0, 139.9, 133.6, 132.3, 128.8, 128.2, 126.9, 118.2, 80.5, 62.3, 56.9, 31.5, 31.2, 29.2, 28.2, 26.0, 25.8, 18.1.

IR (neat film, NaCl): 2974, 2361, 1729, 1691, 1601, 1454, 1367, 1226, 1164, 941, 741 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$: 409.1985, found 409.1977.



228

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (228)

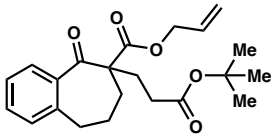
Prepared from **242** following General Procedure C. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (772 mg, 2.24 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (td, *J* = 7.2, 0.9 Hz, 1H), 5.83 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.60 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.4 Hz, 1H), 3.09 (d, *J* = 17.3 Hz, 1H), 2.38 – 2.21 (m, 4H), 1.44 (s, 2H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.1, 170.7, 152.8, 135.6, 135.3, 131.7, 128.1, 126.5, 125.0, 118.5, 80.7, 66.2, 59.7, 37.3, 31.1, 30.0, 28.2.

IR (Neat Film, NaCl): 3427, 2980, 2340, 1715, 1605, 1453, 1368, 1168 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.1516, found 367.1527.



229

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (229)

Prepared from **243** following General Procedure C. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (409 mg, 1.10 mmol, 79% yield).

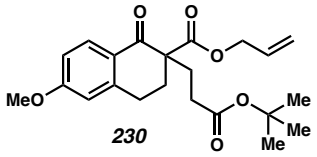
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 1H), 7.35 (m, 1H), 7.29 – 7.20 (m, 3H), 7.11 (m, 1H), 5.66 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.47 (dt, *J* = 5.7, 1.1 Hz,

2H), 3.09 – 2.61 (m, 2H), 2.58 – 2.12 (m, 5H), 2.10 – 1.95 (m, 1H), 1.92 – 1.72 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 172.4, 171.9, 140.2, 138.8, 131.5, 131.3, 129.3, 129.2, 126.6, 119.0, 80.6, 66.0, 61.4, 33.1, 32.8, 31.6, 30.9, 28.2, 24.0.

IR (neat film, NaCl): 2935, 1730, 1685, 1449, 1366, 1253, 1153, 1090, 958 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{29}O_5Na$ $[M+Na]^+$: 395.1829, found 395.1831.



230

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (230)

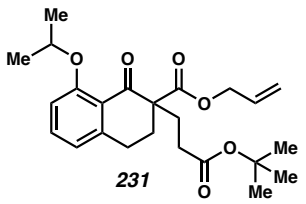
Prepared from **244** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.02 g, 2.62 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.88 – 5.74 (m, 1H), 5.24 – 5.12 (m, 2H), 4.66 – 4.53 (m, 2H), 3.85 (s, 3H), 3.07 – 2.86 (m, 2H), 2.56 (ddd, *J* = 13.6, 5.9, 4.8 Hz, 1H), 2.50 – 2.01 (m, 5H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.6, 171.7, 163.9, 145.5, 131.7, 130.7, 125.6, 118.4, 113.7, 112.5, 80.5, 65.8, 56.7, 55.6, 31.2, 29.0, 28.2, 26.3.

IR (neat film, NaCl): 2934, 1729, 1600, 1450, 1366, 1257, 1155, 1080, 934, 850, 681 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{28}O_6Na$ $[M+Na]^+$: 411.1778, found 411.1775.



231

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (231)

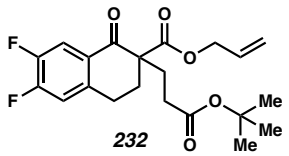
Prepared from **246** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (637 mg, 1.53 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.77 (ddt, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.22 – 5.00 (m, 2H), 4.65 – 4.47 (m, 3H), 3.20 – 2.71 (m, 2H), 2.62 – 2.20 (m, 4H), 2.20 – 2.09 (m, 1H), 2.06 – 1.88 (m, 1H), 1.43 (s, 9H), 1.36 (dd, *J* = 14.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.6, 171.8, 159.2, 145.0, 133.7, 131.7, 123.6, 120.6, 118.2, 113.7, 80.4, 71.8, 65.6, 58.0, 31.1, 30.6, 29.4, 28.2, 26.6, 22.2, 22.2.

IR (neat film, NaCl): 2976, 2932, 1780, 1693, 1592, 1453, 1367, 1270, 1154, 1112, 921, 848, 764 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{24}H_{33}O_6$ $[M+H]^+$: 417.2272, found 417.2274.



232

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (232)

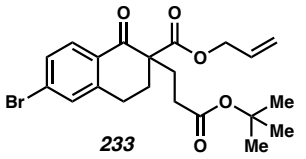
Prepared from **247** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.07 g, 2.71 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 1H), 7.00 (m, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.11 (m, 2H), 4.65 – 4.51 (m, 2H), 3.05 – 2.84 (m, 2H), 2.55 (m, 1H), 2.50 – 2.37 (m, 1H), 2.36 – 2.16 (m, 3H), 2.16 – 2.05 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.99, 172.29, 171.03, 153.83 (dd, *J* = 258.5, 13.5 Hz), 149.68 (dd, *J* = 249.9, 13.3 Hz), 140.48 (dd, *J* = 7.3, 3.6 Hz), 131.38, 129.45 – 128.95 (m), 118.83, 117.22 (d, *J* = 17.5 Hz), 116.88 (dd, *J* = 17.7, 2.2 Hz), 80.68, 66.07, 56.42, 31.26, 30.97, 28.98, 28.18, 25.53.

IR (neat film, NaCl): 3434, 2935, 2356, 1750, 1435, 1213, 1097, 991, 665 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{24}F_2O_5$ $[M+Na]^+$: 417.1484, found 417.1492.



233

allyl 6-bromo-2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (233)

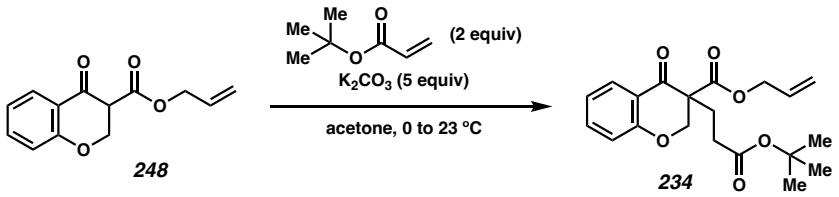
Prepared from **248** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (772 mg, 1.77 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 6.05 – 5.59 (m, 1H), 5.25 – 5.15 (m, 2H), 4.61 (dq, *J* = 5.6, 1.5 Hz, 2H), 3.11 – 2.89 (m, 2H), 2.58 (m, 1H), 2.52 – 2.39 (m, 1H), 2.41 – 2.09 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 172.4, 171.2, 144.6, 131.8, 131.5, 131.0, 130.5, 129.9, 129.0, 118.8, 80.7, 66.0, 56.8, 31.1, 31.0, 29.0, 28.2, 25.8.

IR (neat film, NaCl): 2975, 2360, 1780, 1691, 1587, 1367, 1226, 1154, 1089 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{25}BrO_5Na$ $[M+Na]^+$: 459.0778, found 459.0783.



allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (234)

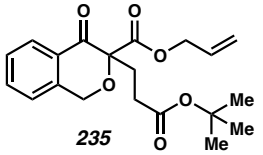
48 reactions performed in parallel and combined for purification. Yield significantly decreased at larger scale. A solution of β-ketoester **248** (20 mg, 0.09 mmol, 1 equiv) in acetone (0.3 mL, 0.3 M) was cooled to 0 ºC. To the reaction K_2CO_3 (59 mg, 0.43 mmol, 5 equiv) and *t*-Bu acrylate (25 mL, 0.17 mmol, 2 equiv) were added, and the reaction was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with acetone and concentrated. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the title compound (500 mg, 1.38 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.05 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.70 – 4.58 (m, 2H), 4.32 (d, *J* = 11.6 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.29 (ddd, *J* = 14.0, 10.1, 5.8 Hz, 1H), 2.12 (ddd, *J* = 14.1, 10.5, 5.4 Hz, 1H), 1.43 (s, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 171.9, 169.2, 161.0, 136.3, 131.3, 128.0, 122.1, 120.3, 118.8, 117.9, 80.9, 72.0, 66.4, 56.5, 30.9, 28.2, 25.5.

IR (Neat Film, NaCl): 3437, 2980, 2932, 1731, 1607, 1479, 1217 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.1465, found 383.1470.



235

allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (235)

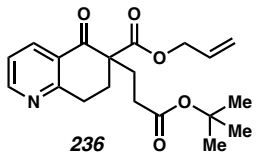
Prepared from **250** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (686 mg, 1.90 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.16 (dt, *J* = 7.7, 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.34 – 5.15 (m, 3H), 4.94 – 4.85 (m, 1H), 4.71 – 4.57 (m, 2H), 2.66 – 2.10 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 172.1, 168.1, 141.1, 134.5, 131.2, 128.5, 127.9, 127.4, 124.4, 119.1, 84.6, 80.5, 66.4, 64.2, 30.5, 29.7, 28.2.

IR (neat film, NaCl): 2973, 1781, 1603, 1364, 1230, 1169, 707 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$: 383.1465, found 383.1467.



236

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (236)

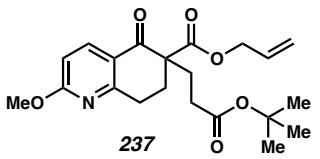
Prepared from **250** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (830 mg, 2.31 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.13 (m, 2H), 4.59 (dq, *J* = 5.7, 1.5 Hz, 2H), 3.27 – 3.09 (m, 2H), 2.62 (dt, *J* = 13.9, 5.0 Hz, 1H), 2.54 – 2.41 (m, 1H), 2.38 – 2.26 (m, 2H), 2.26 – 2.10 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 172.3, 171.0, 162.2, 153.9, 136.0, 131.4, 127.9, 122.5, 119.0, 80.7, 66.2, 56.7, 31.0, 30.2, 29.3, 29.0, 28.2.

IR (neat film, NaCl): 2977, 1729, 1697, 1584, 1456, 1367, 1229, 1171, 1155, 937 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found 360.1813.



237

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (237)

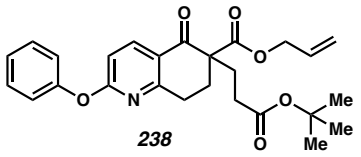
Prepared from **251** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (670 mg, 1.72 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.60 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.59 (dt, *J* = 13.8, 5.3 Hz, 1H), 2.50 – 2.02 (m, 5H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.4, 171.3, 166.4, 162.5, 138.6, 131.6, 122.2, 118.7, 110.4, 80.6, 66.0, 56.4, 54.2, 31.1, 30.1, 29.2, 28.9, 28.2.

IR (neat film, NaCl): 2977, 2365, 1780, 1683, 1480, 1415, 1329, 1265, 1154, 1020 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{28}NO_6$ $[M+H]^+$: 390.1911, found 390.1913.



238

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (238)

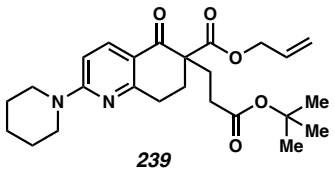
Prepared from **252** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (395 mg, 0.87 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.4, 0.8 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.82 (dddd, *J* = 11.4, 10.5, 5.2, 0.8 Hz, 1H), 5.27 – 5.15 (m, 2H), 4.60 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.62 – 2.02 (m, 6H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.4, 171.2, 166.0, 162.9, 153.3, 139.8, 131.5, 129.9, 125.5, 123.6, 121.6, 118.8, 109.9, 80.7, 66.1, 56.5, 31.0, 30.1, 29.1, 28.9, 28.2.

IR (neat film, NaCl): 2973, 2351, 1729, 1685, 1579, 1455, 1315, 1256, 1156 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{26}H_{30}NO_6$ $[M+H]^+$: 452.2068, found 452.2072.



239

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (239)

Prepared from **253** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.94 g, 4.39 mmol, 94% yield).

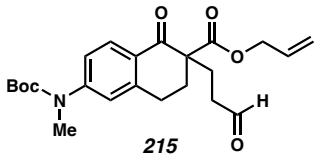
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 5.84 (ddt, *J* = 17.4, 10.7, 5.5 Hz, 1H), 5.34 – 5.13 (m, 2H), 4.59 (dd, *J* = 5.5, 1.5 Hz, 2H), 3.69 (m, 4H), 3.03 – 2.79 (m, 2H), 2.54 (ddd, *J* = 13.7, 6.1, 5.0 Hz, 1H), 2.47 – 2.21 (m, 3H), 2.22 – 2.11 (m, 1H), 2.06 (ddd, *J* = 13.9, 8.6, 5.2 Hz, 1H), 1.69 (d, *J* = 4.8 Hz, 2H), 1.66 – 1.54 (m, 6H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.6, 171.9, 163.5, 159.8, 137.4, 131.8, 118.4, 117.2, 105.0, 80.4, 65.8, 56.2, 45.8, 31.2, 30.1, 29.5, 29.0, 28.2, 25.8, 24.8.

IR (neat film, NaCl): 2937, 2855, 1729, 1663, 1589, 1496, 1406, 1249, 1154, 1085, 1022, 949, 698 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{25}H_{35}N_2O_5$ $[M+H]^+$: 443.2540, found 443.2551.

Preparation of aldehyde S13.



215

allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-2-(3-hydroxy-3λ2-propyl)-1-oxo-1,2,3,4- tetrahydronaphthalene-2-carboxylate (215)

To a solution of **245** (1.42 g, 3.95 mmol) was added acrolein (0.4 mL, 5.9 mmol, 1.5 equiv) and triethylamine (80 uL, 0.6 mmol, 0.15 equiv) in DMF (3.2 mL, 1.2 M). The reaction was stirred at 23 °C until starting material was consumed by TLC, at which point the

reaction was quenched with water and extracted with diethyl ether (x3), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (30% ethyl acetate/hexanes) afforded the title compound (1.33 g, 3.21 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.81 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.59 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.29 (s, 3H), 3.09 – 2.97 (m, 1H), 2.92 (dt, *J* = 17.4, 5.2 Hz, 1H), 2.79 – 2.68 (m, 1H), 2.65 – 2.51 (m, 2H), 2.35 – 2.18 (m, 2H), 2.11 (ddd, *J* = 13.7, 9.8, 4.9 Hz, 1H), 1.49 (s, 9H).

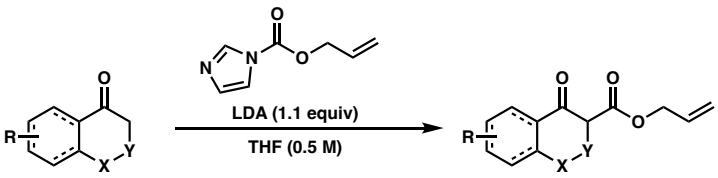
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 194.3, 171.6, 154.2, 148.6, 143.5, 131.5, 128.8, 128.4, 123.9, 123.1, 118.8, 81.5, 66.0, 56.6, 39.8, 36.9, 31.8, 28.4, 26.3, 26.2.

IR (Neat Film, NaCl): 2941, 2346, 1703, 1600, 1357, 1164 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{29}NO_6$ $[M+H]^+$: 416.2068, found 416.2067.

3.7.3.4 Preparation of β-Keto Ester Intermediates

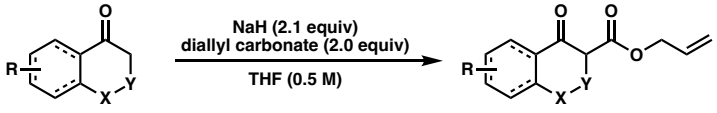
General Procedure D: Acylation of Ketones using N-Acyl Imidazole Reagent



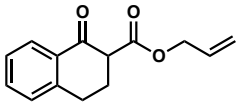
A flame dried round bottom flask was charged with *i*-Pr_2NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Then, ketone (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the N-acyl imidazole reagent (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 ºC and diluted

with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone.

General Procedure E: Acylation of Ketones using Diallyl Carbonate



A flame dried round bottom flask was charged with NaH (2.1 equiv) and THF (0.625 M). Diallyl carbonate was added, followed by a solution of ketone (1.0 equiv) in THF (2.5 M) dropwise. The solution was heated to reflux for 2 h or until complete conversion by TLC, at which point the reaction was cooled and quenched with 1 M aqueous HCl until neutral. The reaction mixture was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone.

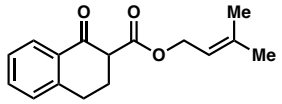


240

allyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (240)

Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (622 mg, 2.70 mmol, 54% yield). All characterization data match those reported in the literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.39 (s, 0.7H), 8.05 (dd, *J* = 7.9, 1.5 Hz, 0.3H), 7.81 (dd, *J* = 7.5, 1.6 Hz, 1=0.7H), 7.50 (m, 0.3H), 7.42 – 7.27 (m, 2H), 7.21 – 7.10 (m, 0.7H), 6.14 – 5.82 (m, 1H), 5.52 – 5.34 (m, 1H), 5.33 – 5.07 (m, 1H), 4.83 – 4.52 (m, 2H), 3.65 (dd, *J* = 10.5, 4.7 Hz, 0.3H), 3.04 (dt, *J* = 13.6, 5.0 Hz, 0.6H), 2.82 (dd, *J* = 8.9, 6.6 Hz, 1.4H), 2.65 – 2.56 (m, 1.4H), 2.55 – 2.17 (m, 0.6H).



241

3-methylbut-2-en-1-yl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (241)

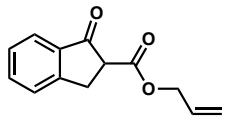
Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D, using a prenyl variant of the N-acyl imidazole reagent instead. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.15 g, 4.75 mmol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.46 (s, 0.6H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 0.4H), 7.80 (dd, *J* = 7.4, 1.7 Hz, 0.6H), 7.49 (td, *J* = 7.5, 1.5 Hz, 0.4H), 7.36 – 7.22 (m, 2H), 7.21 – 7.11 (m, 0.6H), 5.48 – 5.25 (m, 1H), 4.85 – 4.48 (m, 2H), 3.61 (dd, *J* = 10.3, 4.7 Hz, 0.4H), 3.12 – 2.93 (m, 0.8H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 1.2H), 2.57 (dd, *J* = 8.8, 6.6 Hz, 1.2H), 2.53 – 2.14 (m, 0.8H), 1.79 (s, 2.4H), 1.75 (s, 3.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 172.9, 170.4, 165.1, 143.8, 139.6, 139.6, 139.2, 134.0, 132.0, 130.6, 130.2, 128.9, 127.9, 127.5, 127.0, 126.7, 124.4, 118.8, 118.4, 118.3, 97.3, 64.7, 62.4, 61.6, 54.7, 27.9, 27.8, 26.6, 26.0, 25.9, 20.7, 18.3, 18.2.

IR (neat film, NaCl): 2938, 2342, 1739, 1643, 1453, 1392, 1268, 1210, 1082, 956, 759 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{18}O_3Na$ $[M+Na]^+$: 281.1148, found 281.1140.

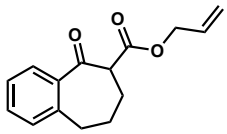


242

allyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (242)

Prepared from 2,3-dihydro-1*H*-inden-1-one following General Procedure D. Purification by flash column chromatography (5–10% EtOAc/hexanes) afforded the title compound as a clear oil (1.24 g, 5.72 mmol, 57% yield). All characterization data match those reported in the literature.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 5.94 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70 (tt, *J* = 5.9, 1.5 Hz, 2H), 3.76 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.63 – 3.52 (m, 1H), 3.39 (dd, *J* = 17.3, 8.2 Hz, 1H).



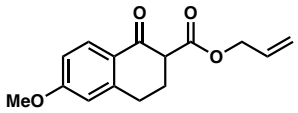
243

allyl 5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (243)

Prepared from 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (339 mg, 1.39 mmol, 28% yield). All characterization data match those reported in the literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.59 (s, 0.7H), 7.75 (dd, *J* = 7.7, 1.5 Hz, 0.3H), 7.67 – 7.58 (m, 0.7H), 7.43 (td, *J* = 7.5, 1.5 Hz, 0.3H), 7.39 – 7.29 (m, 1.7H), 7.25 – 7.03 (m, 1H), 6.22 – 5.74 (m, 1H), 5.38 (m, 1H), 5.33 – 5.20 (m,

1H), 4.74 (m, 1.4H), 4.70 – 4.59 (m, 0.6H), 3.85 (dd, *J* = 10.5, 4.4 Hz, 0.3H), 3.01 – 2.90 (m, 0.6H), 2.65 (t, *J* = 6.8 Hz, 1.4H), 2.26 – 1.99 (m, 3.7H), 1.85 (ddd, *J* = 8.9, 6.8, 5.5 Hz, 0.3H).

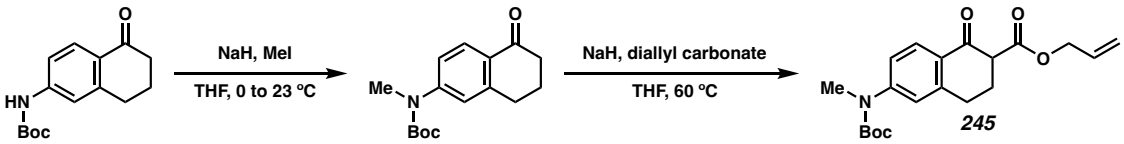


244

allyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (244)

Prepared from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (751 mg, 2.89 mmol, 58% yield). All characterization data match those reported in the literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (3:7) δ 12.44 (s, 0.3H), 8.03 (d, *J* = 8.8 Hz, 0.7H), 7.74 (d, *J* = 8.6 Hz, 0.3H), 6.82 (ddd, *J* = 16.3, 8.7, 2.6 Hz, 1H), 6.70 (dd, *J* = 5.9, 2.5 Hz, 1H), 6.07 – 5.86 (m, 1H), 5.48 – 5.12 (m, 2H), 4.86 – 4.62 (m, 2H), 3.86 (s, 2H), 3.84 (s, 1H), 3.60 (dd, *J* = 10.3, 4.7 Hz, 0.7H), 3.16 – 2.91 (m, 1.4H), 2.79 (m, 0.6H), 2.63 – 2.56 (m, 0.6H), 2.54 – 2.26 (m, 1.4H).



245

allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (245)

A solution of *tert*-butyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (466 mg, 1.8 mmol, 1 equiv) and THF (1.2 M, 1.5 mL) was cooled 0 ºC. NaH (60% dispersion in mineral oil, 86 mg, 2.1 mmol, 1.2 equiv) was added portion wise. Then MeI (0.13 mL, 2.1 mmol, 1.2 equiv) was added dropwise, and the reaction was slowly warmed to 23 ºC. Upon

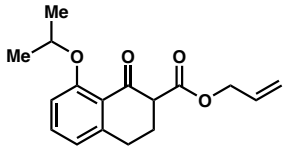
complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude *N*-Me aniline which was used directly in the next step. To NaH (60% dispersion in mineral oil, 150 mg, 3.7 mmol, 2.1 equiv) in THF (2.1 mL, 1.8 M) diallyl carbonate (0.51 mL, 3.6 mmol, 2 equiv) was added. Crude *N*-Me aniline in THF (1.5 mL, 1.2 M) was added, and the reaction was heated to 60 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was cooled to 23 ºC and diluted with a saturated solution of NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound (376 mg, 1.05 mmol, 59% yield). Mixture of enol-keto tautomers. Used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 6.06 – 5.88 (m, 2H), 5.36 (ddq, *J* = 16.8, 13.6, 1.6 Hz, 2H), 5.26 (ddq, *J* = 13.1, 10.5, 1.3 Hz, 2H), 4.73 (dt, *J* = 5.6, 1.5 Hz, 2H), 4.69 (ddt, *J* = 6.1, 4.7, 1.4 Hz, 1H), 3.62 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.30 (s, 2H), 3.28 (s, 3H), 3.10 – 2.91 (m, 2H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 2H), 2.65 – 2.57 (m, 2H), 2.57 – 2.45 (m, 1H), 2.36 (ddt, *J* = 13.5, 5.8, 4.7 Hz, 1H), 1.49 (s, 7H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 172.4, 170.1, 165.3, 154.6, 154.2, 148.8, 145.9, 144.3, 140.2, 132.4, 131.9, 128.6, 128.3, 126.8, 124.9, 124.0, 123.1, 123.0, 118.6, 118.3, 96.5, 81.5, 80.9, 66.0, 65.2, 54.6, 37.2, 36.9, 34.8, 31.7, 28.5, 28.4, 28.0, 28.0, 26.5, 22.8, 20.7, 14.3.

IR (Neat Film, NaCl): 2976, 2937, 1738, 1704, 1602, 1433, 1352, 1150 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{25}NO_5$ $[M+H]^+$: 360.1805, found 360.1806.



246

allyl 8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (246)

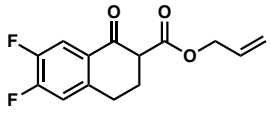
Prepared from 8-isopropoxy-3,4-dihydronaphthalen-1(2H)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (500 mg, 1.73 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.68 (s, 0.4H), 7.35 (dd, *J* = 8.4, 7.6 Hz, 0.6H), 7.22 (dd, *J* = 8.4, 7.4 Hz, 0.4H), 6.92 – 6.80 (m, 1H), 6.78 (m, 1H), 5.96 (m, H), 5.51 – 5.28 (m, 1H), 5.27 – 5.00 (m, 2H), 4.70 (ddt, *J* = 16.2, 5.6, 1.5 Hz, 2H), 4.55 (m, 1H), 3.61 (dd, *J* = 10.4, 4.9 Hz, 0.6H), 3.23 – 2.84 (m, 1H), 2.71 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.46 – 2.18 (m, 1H), 1.44 – 1.32 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 172.3, 170.4, 167.7, 159.5, 157.0, 146.1, 143.2, 134.2, 132.6, 132.1, 131.3, 122.6, 120.7, 120.6, 118.4, 118.1, 115.9, 113.7, 97.6, 72.8, 71.8, 65.8, 65.0, 56.5, 29.7, 28.8, 26.2, 22.3, 22.1, 22.1, 20.8.

IR (neat film, NaCl): 2975, 2937, 1740, 1684, 1592, 1463, 1383, 1267, 1116, 989, 922 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}O_3$ $[M+H]^+$: 274.1438, found 274.1434.



247

allyl 6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (247)

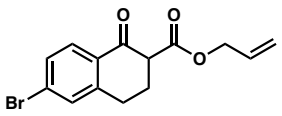
Prepared from 6,7-difluoro-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (976 mg, 3.67 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.23 (s, 0.7H), 7.74 (dd, *J* = 10.5, 8.2 Hz, 0.3H), 7.49 (dd, *J* = 11.0, 8.1 Hz, 0.7H), 6.95 (dd, *J* = 10.4, 7.2 Hz, 0.3H), 6.87 (dd, *J* = 10.4, 7.5 Hz, 0.7H), 6.02 – 5.72 (m, 1H), 5.39 – 5.21 (m, 1H), 5.22 – 5.01 (m, 1H), 4.79 – 4.46 (m, 2H), 3.51 (dd, *J* = 9.9, 4.8 Hz, 0.3H), 2.88 (dt, *J* = 17.9, 7.4 Hz, 0.6H), 2.66 (dd, *J* = 9.1, 6.5 Hz, 1.4H), 2.49 (dd, *J* = 9.1, 6.6 Hz, 1.4H), 2.45 – 2.12 (m, 0.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 172.2, 169.5, 163.5, 163.5, 163.5, 155.4, 155.3, 152.8, 152.8, 152.7, 152.6, 151.0, 150.9, 150.5, 150.4, 150.3, 150.1, 148.5, 148.4, 148.1, 148.0, 141.4, 141.4, 141.3, 141.3, 136.6, 136.5, 136.5, 136.5, 132.2, 132.1, 131.7, 128.9, 128.9, 128.8, 126.9, 126.8, 126.8, 126.8, 118.8, 118.5, 118.4, 117.5, 117.3, 117.3, 116.8, 116.8, 116.6, 116.6, 116.4, 113.9, 113.9, 113.8, 113.7, 97.1, 97.1, 68.1, 66.1, 65.4, 53.8, 50.1, 27.2, 27.1, 27.1, 27.1, 26.4, 20.5.

IR (neat film, NaCl): 2938, 2340, 1744, 1693, 1651, 1590, 1511, 1387, 1327, 1250, 1076, 926, 804 cm^{-1}.

HMRS (ESI–): *m/z* calc'd for $C_{14}H_{12}F2O_3$ $[M–H]^–$: 265.0682, found 265.0686.



248

allyl 6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (248)

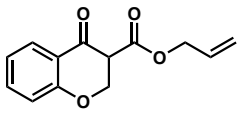
Prepared from 6-bromo-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure E. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (639 mg, 2.07 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.35 (s, 0.6H), 7.91 (d, *J* = 8.3 Hz, 0.4H), 7.65 (d, *J* = 8.3 Hz, 0.6H), 7.52 – 7.38 (m, 1.4H), 7.34 (dt, *J* = 2.0, 0.9 Hz, 0.6H), 6.17 – 5.79 (m, 1H), 5.48 – 5.33 (m, 1H), 5.33 – 5.16 (m, 1H), 4.77 – 4.50 (m, 2H), 3.63 (dd, *J* = 10.1, 4.7 Hz, 0.4H), 3.14 – 2.89 (m, 0.8H), 2.80 (m, 1.2H), 2.67 – 2.53 (m, 1.2H), 2.54 – 2.25 (m, 0.8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 172.3, 169.7, 164.6, 145.4, 141.5, 132.2, 131.9, 131.8, 131.7, 130.7, 130.6, 129.9, 129.6, 129.4, 129.1, 126.1, 125.1, 119.1, 118.8, 118.4, 97.2, 68.6, 66.1, 65.4, 54.4, 27.6, 27.5, 26.3, 20.5.

IR (neat film, NaCl): 2341, 1613, 1259, 1212, 824 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{14}H_{13}BrO_3$ $[M]^{+\bullet}$: 308.0043, found 308.0052.



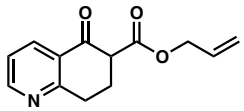
249

allyl 4-oxochromane-3-carboxylate (249)

Prepared from chroman-4-one following General Procedure D. Purification by flash column chromatography (0–5% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.47 g, 6.3 mmol, 42% yield). All characterization data match those reported in the literature.[30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (s, 0.4H), 7.93 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.7 Hz, 0.6H), 7.51 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 0.6H), 7.06 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz,

0.6H), 6.01 – 5.94 (m, 0.6H), 5.94 – 5.85 (m, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 0.6H), 5.34 – 5.28 (m, 1.6H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.99 (s, 1.2H), 4.81 (dd, *J* = 11.7, 8.4 Hz, 1H), 4.71 (m, 3.2H), 4.65 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.78 (dd, *J* = 8.4, 4.4 Hz, 1H).



250

allyl 5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (250)

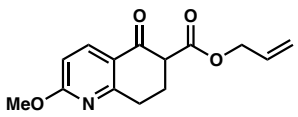
Prepared from 7,8-dihydroquinolin-5(6*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (580 mg, 2.56 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (9:1) δ 12.29 (s, 0.9H), 8.71 (dd, *J* = 4.8, 1.9 Hz, 0.1H), 8.50 (dd, *J* = 4.9, 1.8 Hz, 0.9H), 8.30 (dd, *J* = 7.9, 1.9 Hz, 0.1H), 8.03 (dd, *J* = 7.8, 1.8 Hz, 0.9H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 0.1H), 7.23 (dd, *J* = 7.8, 4.9 Hz, 0.9H), 6.00 (m, 1H), 5.39 (m, 1H), 5.30 (m, 1H), 4.75 (d, *J* = 5.6 Hz, 1.8H), 4.70 (ddd, *J* = 4.4, 2.9, 1.4 Hz, 0.2H), 3.69 (dd, *J* = 10.0, 4.8 Hz, 0.1H), 3.32 – 3.10 (m, 0.2H), 3.04 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.73 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.61 – 2.36 (m, 0.2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.2, 169.5, 163.7, 162.9, 159.5, 154.2, 150.6, 135.7, 132.1, 131.7, 131.7, 127.7, 125.9, 122.6, 122.0, 118.9, 118.6, 97.6, 66.2, 65.5, 54.0, 30.7, 30.6, 25.1, 20.0.

IR (neat film, NaCl): 2948, 1743, 1692, 1654, 1380, 1321, 1269, 1209, 1085, 980, 805 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0968, found 232.0969.



251

allyl 2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (251)

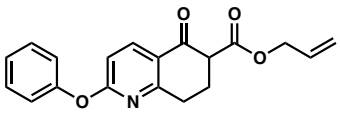
Prepared from 2-methoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.504 g, 5.76 mmol, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (15:85) δ 12.37 (s, 0.15H), 8.15 (d, *J* = 8.7 Hz, 0.85H), 7.91 (d, *J* = 8.5 Hz, 0.15H), 6.67–6.61 (m, 1H), 6.14 – 5.75 (m, 1H), 5.54 – 5.11 (m, 2H), 4.81 – 4.57 (m, 2H), 3.98 (s, 2.55H), 3.95 (s, 0.45H), 3.61 (dd, *J* = 10.1, 4.8 Hz, 0.85H), 3.19 – 2.95 (m, 1.7H), 2.94 – 2.62 (m, 0.6H), 2.57 – 2.25 (m, 1.7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 172.3, 169.9, 166.6, 165.1, 165.0, 163.3, 159.0, 138.2, 134.7, 132.3, 131.8, 122.1, 119.1, 118.7, 118.3, 110.5, 108.6, 94.5, 66.0, 65.2, 54.2, 53.9, 53.8, 30.7, 30.5, 25.2, 20.0.

IR (neat film, NaCl): 2945, 1740, 1681, 1591, 1479, 1331, 1267, 1200, 1023, 925, 834 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074, found 262.1070.



252

allyl 5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (252)

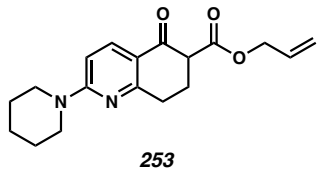
Prepared from 2-phenoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.067 g, 3.30 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.35 (s, 0.4H), 8.27 (d, *J* = 8.6 Hz, 0.6H), 8.01 (d, *J* = 8.6 Hz, 0.4H), 7.42 (m, 2H), 7.31 – 7.21 (m, 1H), 7.16 (m, 1.8H), 6.76 (d, *J* = 8.7 Hz, 0.6H), 6.68 (t, *J* = 8.6 Hz, 0.6H), 6.16 – 5.86 (m, 1H), 5.45 – 5.35 (m, 1H), 5.33 – 5.22 (m, 1H), 4.77 – 4.62 (m, 2H), 3.62 (m, 0.6H), 3.35 – 2.96 (m, 1.6H), 2.97 – 2.86 (m, 0.4H), 2.69 (m, 0.4H), 2.60 – 2.29 (m, 1.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 169.7, 166.2, 163.6, 159.5, 153.9, 153.2, 139.7, 138.4, 135.8, 132.9, 132.1, 131.8, 130.0, 125.7, 125.3, 123.5, 121.6, 121.3, 118.9, 118.5, 110.7, 109.9, 108.4, 95.8, 67.5, 66.1, 66.0, 65.4, 53.8, 30.4, 30.0, 25.1, 19.9.

IR (neat film, NaCl): 2938, 1739, 1685, 1580, 1450, 1259, 1076, 990 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1230, found 324.1229.



253

allyl 5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (253)

Prepared from 2-(piperidin-1-yl)-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.46 g, 4.64 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (5:95) δ 12.41 (s, 0.05H), 7.95 (dd, *J* = 9.1, 1.5 Hz, 0.95H), 7.72 (dd, *J* = 8.9, 1.5 Hz, 0.05H), 6.48 (dd, *J* = 9.0, 1.5 Hz, 0.95H), 6.44 (dd, *J* = 8.8, 1.5 Hz, 0.05H), 6.05 – 5.73 (m, 1H), 5.30 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.80 – 4.43 (m, 2H), 3.78 – 3.57 (m, 3.75H), 3.59

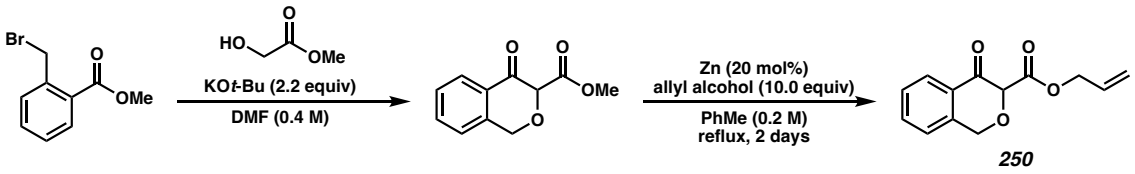
(t, *J* = 4.7 Hz, 0.25H), 3.51 (ddd, *J* = 10.3, 4.8, 1.5 Hz, 1H), 3.07 – 2.79 (m, 2H), 2.78 – 2.56 (m, 0.25H), 2.53 – 2.20 (m, 1.75H), 1.65 (m, 2H), 1.58 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 170.4, 164.1, 159.7, 136.8, 133.2, 132.5, 131.9, 118.3, 117.0, 104.8, 103.7, 92.3, 65.6, 64.7, 53.7, 45.6, 31.0, 25.7, 25.3, 24.6.

IR (neat film, NaCl): 2935, 2853, 1739, 1662, 1593, 1498, 1417, 1249, 1120, 1023 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_3Na$ $[M+Na]^+$: 337.1523, found 337.1518.

Preparation of ß-Keto Ester **250**



250

A flame dried round bottom flask under N_2 was charged with KO*t*-Bu (2.2 equiv), methyl 2-(bromomethyl)benzoate (1.0 equiv, 10 mmol) and DMF (0.4 M). After cooling to 0 °C, methyl 2-hydroxyacetate was added. The ice bath was then removed, and the reaction was allowed to continue stirring for 18 h. The reaction was quenched with 1 N HCl, extracted with EtOAc three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude methyl ester intermediate was used without further purification.

To the crude intermediate in PhMe (0.2 M) was added Zn powder (20 mol%) and allyl alcohol (5.0 equiv). The reaction was refluxed for 24 h, at which point more allyl alcohol (5.0 equiv) was added. After an additional day of refluxing, the reaction was cooled, filtered over Celite, and concentrated. The crude product was purified by flash silica gel column chromatography (0–15% ethyl acetate/hexanes) to afford the acylated ketone **250** (1.126 g, 4.84 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (1:1) δ 10.36 (s, 0.5H), 8.06 (dd, *J* = 7.9, 1.3 Hz, 0.5H), 7.73 – 7.64 (m, 0.5H), 7.60 (td, *J* = 7.6, 1.4 Hz, 0.5H), 7.49 – 7.40 (m, 0.5H), 7.40 – 7.32 (m, 1H), 7.21 (dt, *J* = 7.5, 0.9 Hz, 0.5H), 7.16 – 7.07 (m, 0.5H), 5.98 (dddt, *J* = 31.0, 17.1, 10.4, 5.9 Hz, 1H), 5.50 – 5.34 (m, 1H), 5.33 – 5.22 (m, 1.5H), 5.02 (s, 1H), 4.99 (s, 0.5H), 4.94 (s, 0.5H), 4.78 (ddt, *J* = 25.7, 5.8, 1.4 Hz, 2H).

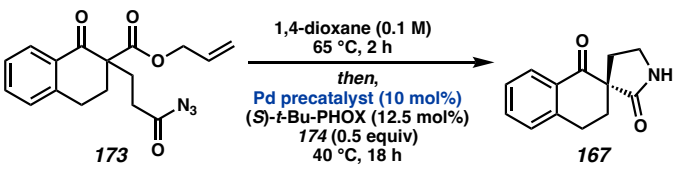
^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 167.7, 166.1, 152.7, 141.2, 134.8, 133.0, 131.7, 131.3, 130.9, 130.7, 128.7, 128.4, 128.2, 127.7, 127.2, 127.1, 124.5, 124.3, 124.0, 123.5, 122.6, 119.8, 119.7, 119.4, 80.9, 68.4, 67.9, 66.6, 66.1, 62.3.

IR (neat film, NaCl): 1752, 1701, 1400, 1273, 744 cm^{-1}.

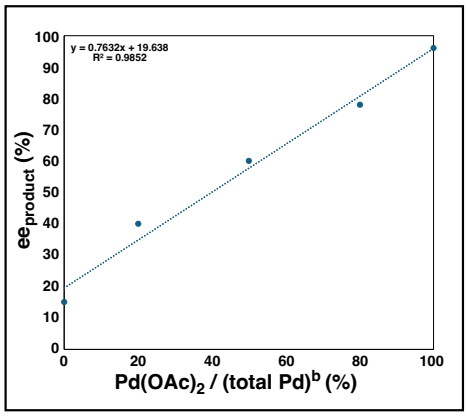
HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 262.1074, found 262.1070.

3.7.3.5 Mechanistic Experiments

Mixed Precatalyst Experiment



entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	yield (%)	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar and **173** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and each vial was heated to 65 °C for 2 h. After cooling, **174** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL) was added. In a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and (*S*)-*t*-BuPHOX (14.5 mg, 0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. In another oven-dried

2-dram vial, $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol) and (*S*)-*t*-BuPHOX (0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. To each reaction vial containing **173** and **174** was added the corresponding volume of Pd-stock solutions, such that the mol% of Pd is as represented in the table and graph above:

Vial 01: Pd_2dba_3 solution (0.20 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.16 mL, 4 mol%), $Pd(OAc)_2$ solution (0.04 mL, 2 mol%)

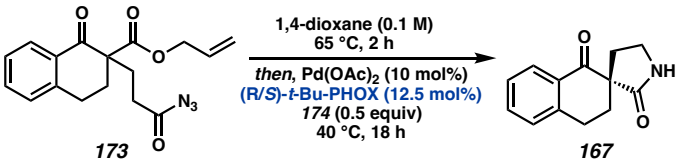
Vial 02: Pd_2dba_3 solution (0.10 mL, 2.5 mol%), $Pd(OAc)_2$ solution (0.10 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.04 mL, 1 mol%), $Pd(OAc)_2$ solution (0.16 mL, 8 mol%)

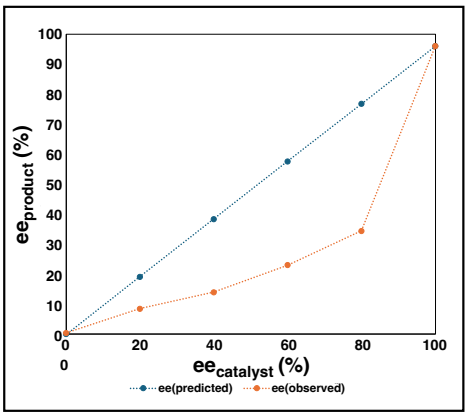
Vial 02: $Pd(OAc)_2$ solution (0.20 mL, 10 mol%)

The vials were sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixtures were then cooled, 1,3,5-trimethoxybenzene (0.33 equiv) was added to each reaction, and the crude reactions mixtures were concentrated under reduced pressure. The yield was determined by ^{1}H NMR integration against 1,3,5-trimethoxybenzene as an internal standard, and the ee was determined utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

Nonlinearity Experiment



entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar and **173** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and each vial was heated to 65 °C for 2 h. After cooling, **174** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL) was added. In five separate oven-dried 1-dram vials was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol). Stock solutions were prepared of (*S*)-*t*-BuPHOX (19.4 mg, 0.05 mmol) in dioxane (1.6 mL) and (*R*)-*t*-BuPHOX (9.7 mg, 0.025 mmol) in dioxane (0.8 mL), and the corresponding volume of (*S*)- or (*R*)-*t*-BuPHOX stock solutions was added to each vial of $Pd(OAc)_2$, such that the ee of the resulting Pd solution is as represented in the table and graph above:

Vial 01: (*R*)-*t*-BuPHOX stock solution (0.04 mL, 1.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.36 mL, 11.25 mol%)

Vial 02: (*R*)-*t*-BuPHOX stock solution (0.08 mL, 2.5 mol%), (*S*)-*t*-BuPHOX stock solution (0.32 mL, 10 mol%)

Vial 03: (*R*)-*t*-BuPHOX stock solution (0.12 mL, 3.75 mol%), (*S*)-*t*-BuPHOX stock solution (0.28 mL, 8.75 mol%)

Vial 04: (*R*)-*t*-BuPHOX stock solution (0.16 mL, 5 mol%), (*S*)-*t*-BuPHOX stock solution (0.24 mL, 7.5 mol%)

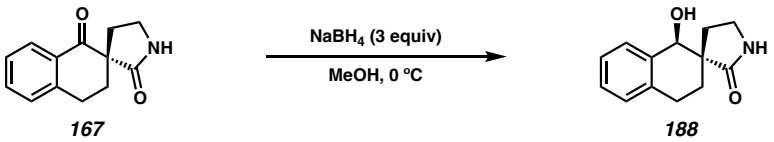
Vial 05: (*R*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%)

The vials were sealed and stirred for 20 min at 23 °C. To each reaction vial, the corresponding Pd stock solution (0.2 mL) was added. The reaction vials were sealed, from the glovebox, and heated to 40 °C for 30 min, at which point the reactions were quenched by opening to air and concentrated. The ee of each reaction product was determined

utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

3.7.3.6 Product Derivatizations

*Preparation of alcohol **188***



167 ***188***

(2*S*)-1-hydroxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (188)

A flame dried vial under N_2 was charged with **167** (1 equiv, 0.05 mmol, 10.8 mg) and MeOH (0.03 M, 1.8 mL) at 0 ºC. $NaBH_4$ (2 equiv, 0.1 mmol, 3.8 mg) was added to the reaction. After two hours, starting material was not consumed and additional $NaBH_4$ (1 equiv, 0.05 mmol, 1.9 mg) was added to the reaction. Following complete consumption of starting material as determined by TLC, the reaction was diluted with water. The reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **188** as a white solid (7.5 mg, 0.035 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 3.45 – 3.30 (m, 2H), 3.04 (ddd, *J* = 17.8, 7.1, 2.3 Hz, 1H), 2.00 (ddd, *J* = 13.1, 7.3, 3.8 Hz, 1H), 1.81 (dt, *J* = 13.2, 8.3 Hz, 1H), 1.71 (dd, *J* = 13.6, 5.9 Hz, 1H).

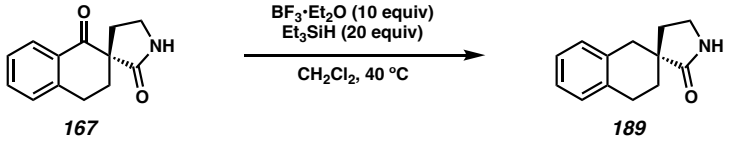
^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 135.5, 135.4, 130.6, 129.2, 128.4, 126.3, 72.9, 44.8, 39.1, 29.3, 25.0, 22.8.

IR (Neat Film, NaCl): 3300, 2929, 1684, 1456, 1285 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{13}H_{15}NO_2$ $[M+Na]^+$: 240.0995, found 240.0985.

Optical Rotation: $[\alpha]_D^{21}$ –36.0 (c 0.75, $CHCl_3$).

*Preparation of lactam **189***



167 ***189***

(R)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (189)

A flame dried vial under N_2 was charged with ketone **167** (1 equiv, 0.05 mmol, 10.8 mg) and CH_2Cl_2 (0.1 M, 0.5 mL) at 0 ºC. Et_3SiH (10 equiv, 0.5 mmol, 62 µL) then BF_3•Et_2O (20 equiv, 1 mmol, 0.16 mL) was added to the reaction. The reaction was heated to 40 ºC. Following complete consumption of starting material as determined by TLC, the reaction was cooled to 23 ºC and diluted with saturated aqueous $NaHCO_3$. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **189** as a white solid (5.6 mg, 0.028 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.05 (m, 4H), 6.18 (s, 1H), 3.37 (ddd, J = 7.6, 6.1, 0.9 Hz, 2H), 3.10 (d, J = 16.4 Hz, 1H), 2.94 (ddd, J = 17.3, 6.5, 2.7 Hz, 1H), 2.84 (dddd, J = 17.4, 12.1, 5.9, 1.6 Hz, 1H), 2.63 (dd, J = 16.4, 2.3 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.94 (dt, J = 12.7, 6.0 Hz, 1H), 1.74 (ddt, J = 13.3, 5.9, 2.5 Hz, 1H).

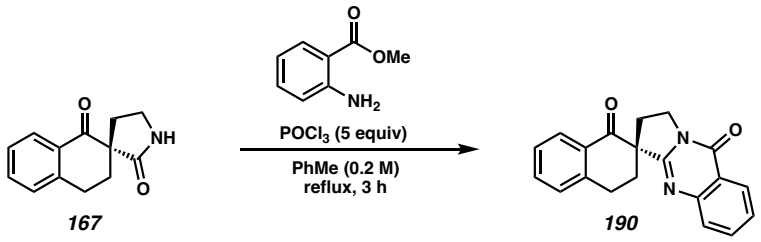
^{13}C NMR (100 MHz, $CDCl_3$): 182.4, 135.4, 134.5, 129.7, 129.0, 126.1, 126.0, 42.7, 39.0, 36.2, 31.7, 29.2, 25.8.

IR (Neat Film, NaCl): 3224, 3012, 2926, 2352, 1694, 1455, 1297 cm^{-1}.

HRMS (MM: ESI+): m/z calc'd for $C_{13}H_{15}NO$ $[M+H]^+$: 202.1226, found 202.1217.

Optical Rotation: $[\alpha]_D^{21}$ –9.2 (c 0.53, $CHCl_3$).

*Preparation of pyrimidone **190***



(*R*)-1',2',3,4-tetrahydro-1*H*,9'*H*-spiro[naphthalene-2,3'-pyrrolo[2,1-*b*]quinazoline]-1,9'-dione (190)

To a vial containing **167** (21.5 mg, 0.1 mmol) in toluene (0.5 mL, 0.2 M) added methyl anthranilate (13 uL, 0.1 mmol, 1.0 equiv) and $POCl_3$ (47 uL, 0.5 mmol, 5.0 equiv). The vial was capped and heated to 110 °C for 3 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled and poured over a cold solution of saturated $NaHCO_3$. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure. The crude material was purified on column chromatography (0–50% ethyl acetate/hexanes) to afford **190** (23.7 mg, 0.075 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.06 (dd, J = 7.9, 1.4 Hz, 1H), 7.69 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.45 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.40 – 7.29 (m, 2H), 4.37 (ddd, J = 11.8, 8.7, 2.8 Hz, 1H), 4.16 (ddd, J = 12.1, 9.0, 7.5 Hz, 1H), 3.36 (dt, J = 16.6, 4.8 Hz, 1H), 3.11 (ddd, J = 16.3, 10.8, 4.3 Hz, 1H), 2.98 (ddd, J = 13.5, 10.8, 4.5 Hz, 1H), 2.69 (ddd, J = 13.1, 7.6, 2.8 Hz, 1H), 2.34 – 2.22 (m, 2H).

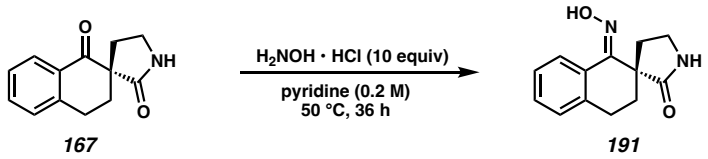
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 161.0, 159.9, 149.4, 143.8, 134.4, 134.1, 130.5, 128.9, 128.6, 127.6, 127.3, 126.7, 126.5, 121.3, 58.1, 44.0, 32.4, 30.9, 25.7.

IR (neat film, NaCl): 2928, 1673, 1614, 1468, 1320, 1221, 774, 683 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317,1285, found 317.1275.

Optical Rotation: $[\alpha]_D^{24}$ = 14.21 (c 1.0, $CHCl_3$).

*Preparation of oxime **191***



167 ***191***

(*S*,*E*)-1-(hydroxyimino)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (191)

To a vial containing **167** (21.5 mg, 0.1 mmol) in pyridine (0.5 mL, 0.2 M) added hydroxylamine HCl (70 mg, 1.0 mmol, 10 equiv). The vial was capped and heated to 50 °C for 36 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled, concentrated under reduced pressure, and then partitioned between water and ethyl acetate. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure to afford **191** (22.9 mg, 0.10 mmol, 99% yield).

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (dd, J = 8.3, 1.4 Hz, 1H), 7.30 – 7.19 (m, 1H), 7.19 – 6.95 (m, 2H), 4.60 (s, 2H), 3.62 – 3.41 (m, 2H), 2.95 – 2.77 (m, 2H), 2.65 (dddd, J = 12.7, 10.0, 7.5, 1.2 Hz, 1H), 2.22 (ddd, J = 12.7, 8.4, 3.2 Hz, 1H), 2.03 (dddd, J = 13.0, 10.3, 5.9, 1.2 Hz, 1H), 1.93 (t, J = 4.1 Hz, 1H), 1.90 (t, J = 4.1 Hz, 1H).

^{13}C NMR (100 MHz, CD_3OD): δ 182.6, 154.3, 139.7, 132.5, 129.8, 129.1, 127.4, 125.7, 40.6, 33.4, 30.9, 27.1.

IR (neat film, NaCl): 3265, 2913, 2512, 2070, 1669, 1163, 978, 830, 773, 687 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128, found 231.1126.

Optical Rotation: $[\alpha]_D^{24}$ = 50.32 (c 1.0, $CHCl_3$).

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(14) We briefly explored phenolic carbamates as alternative electrophiles to isocyanates with the hypothesis that an electron deficient variant might be sufficiently electrophilic to outcompete allylic alkylation, or that these carbamates could act as blocked isocyanates under tailored reaction conditions; ultimately, this approach yielded limited success, generating product **167** in both diminished yields and enantioselectivities.

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(16) Substoichiometric use of additive **174** (less than 0.5 equiv) delivers oligomeric byproducts arising from condensation of the unprotonated product with the isocyanate starting material.

(17) Attempts to improve the ee of substrates **176** or **184** by using (*S*)-$(CF_3)_3$-*t*-Bu-PHOX failed.

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APPENDIX 5

Spectra Relevant to Chapter 3: An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates

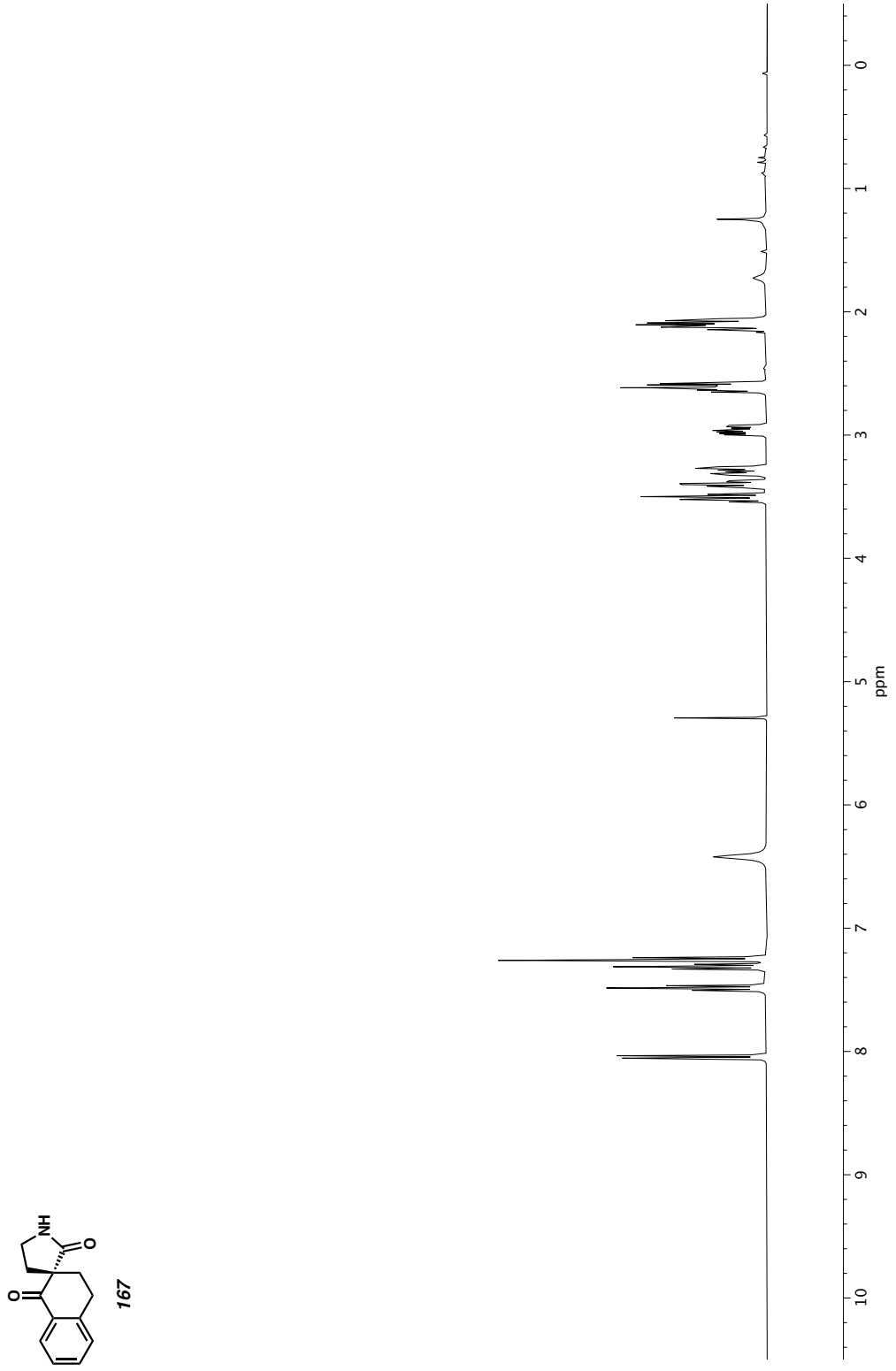


Figure A5.1 *^1H NMR (400 MHz, $CDCl_3$) of compound **167**.*

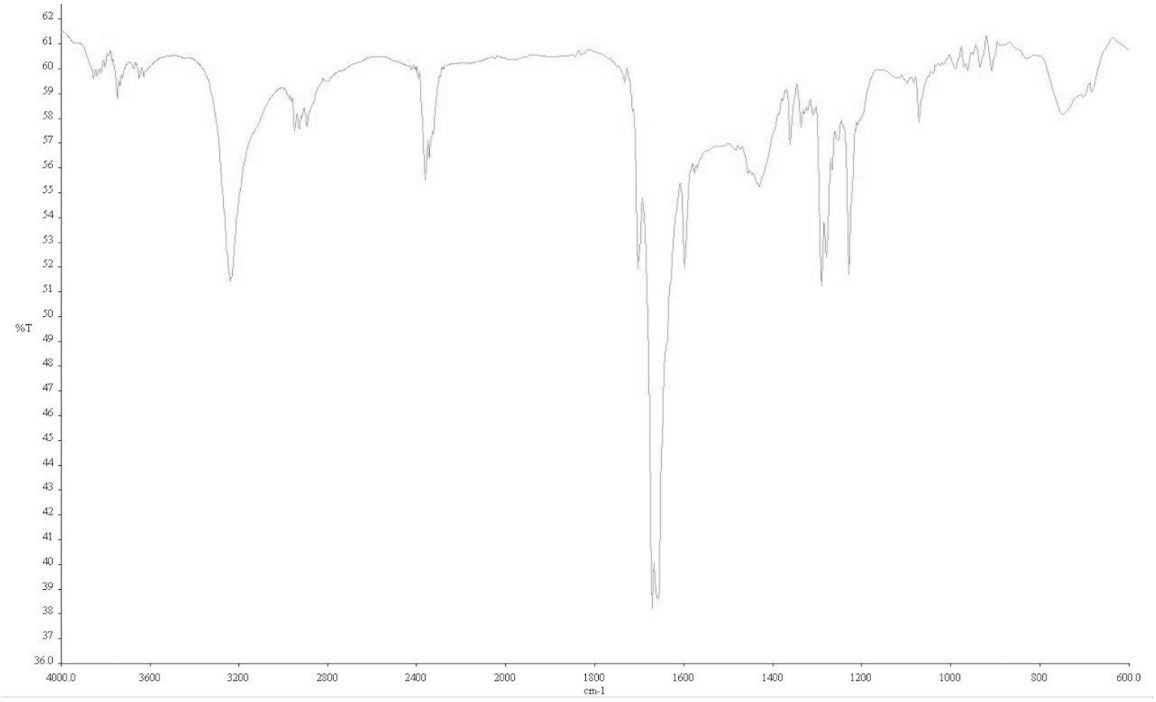


Figure A5.2 *Infrared spectrum (Thin Film, NaCl) of compound* ***167****.*

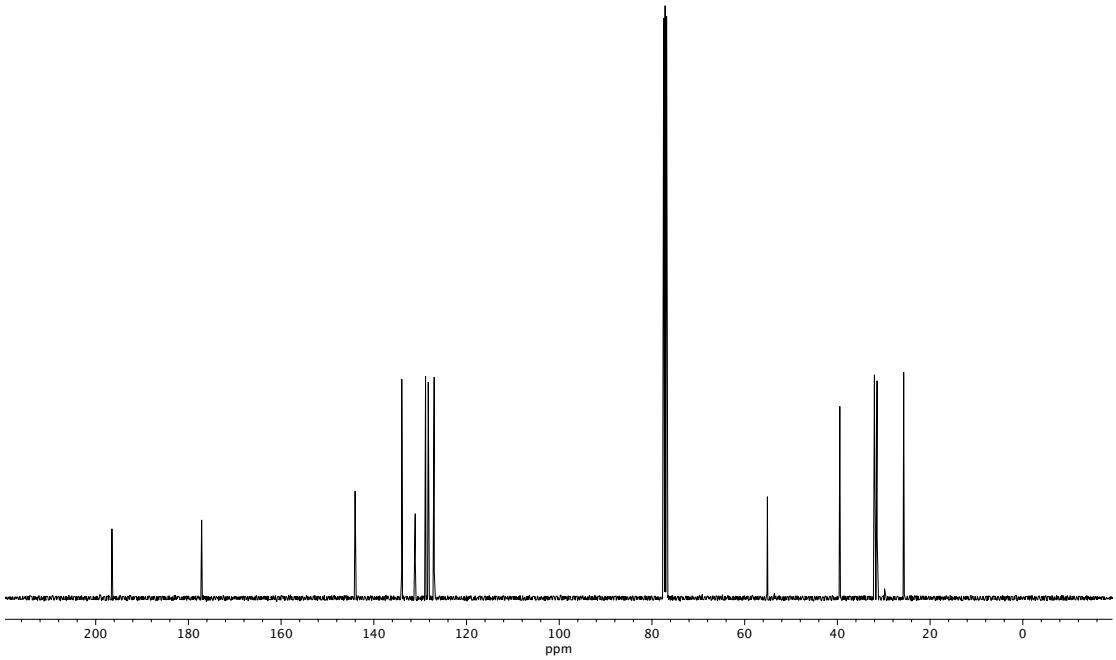
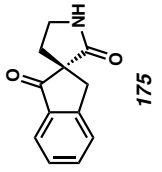


Figure A5.3 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***167****.*



175

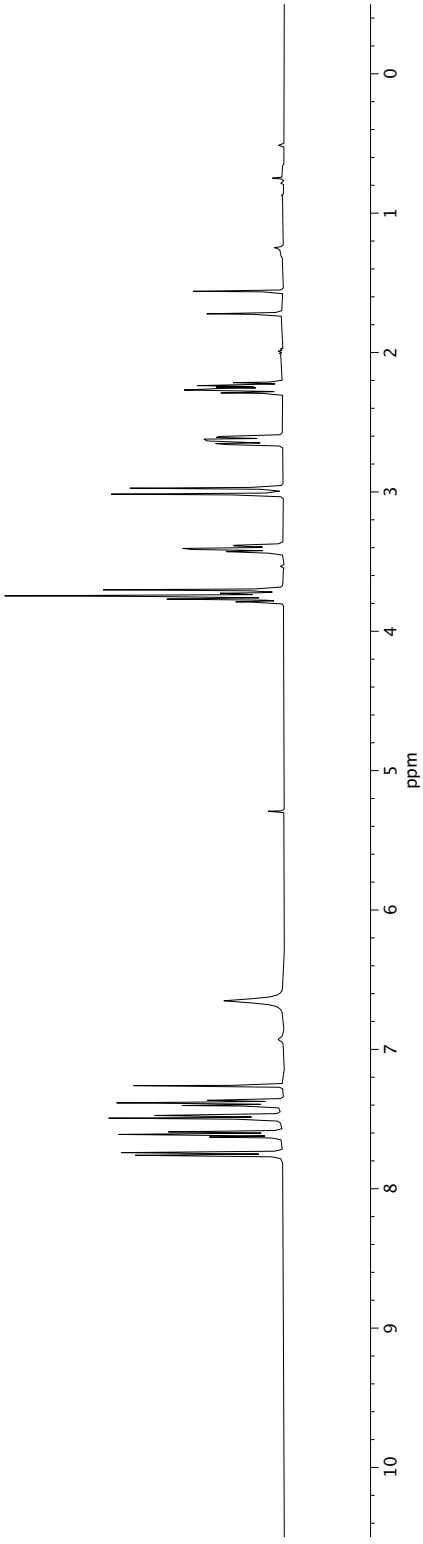


Figure A5.4 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***175****.*

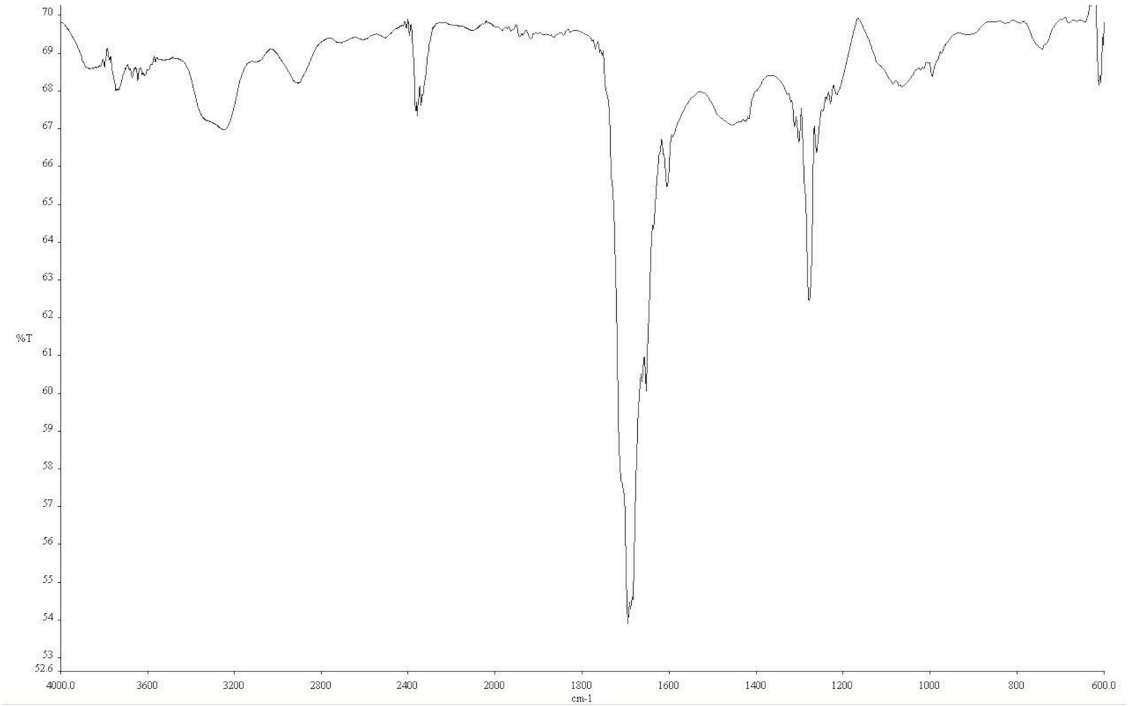


Figure A5.5 *Infrared spectrum (Thin Film, NaCl) of compound* ***175***.

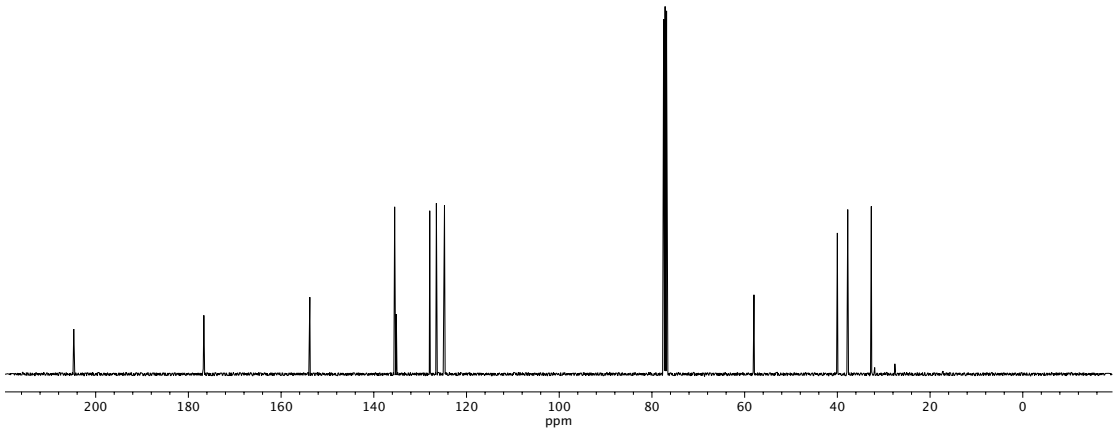
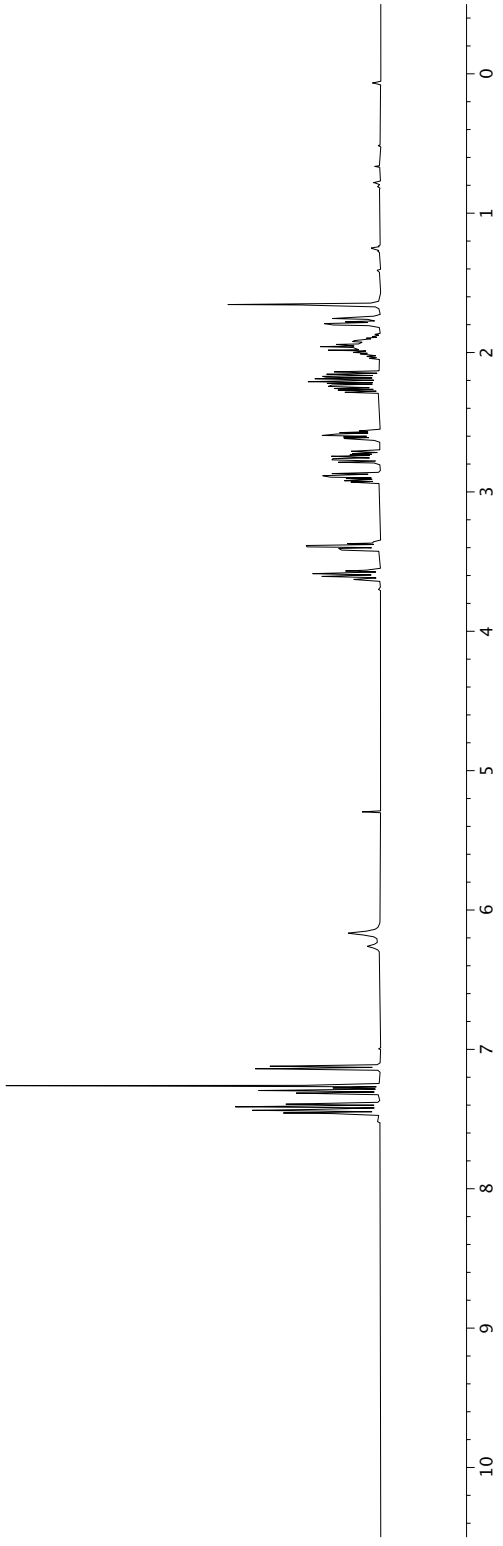
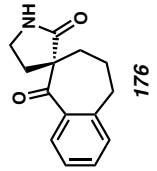


Figure A5.6 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***175***.





176

Figure A5.7 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***176****.*

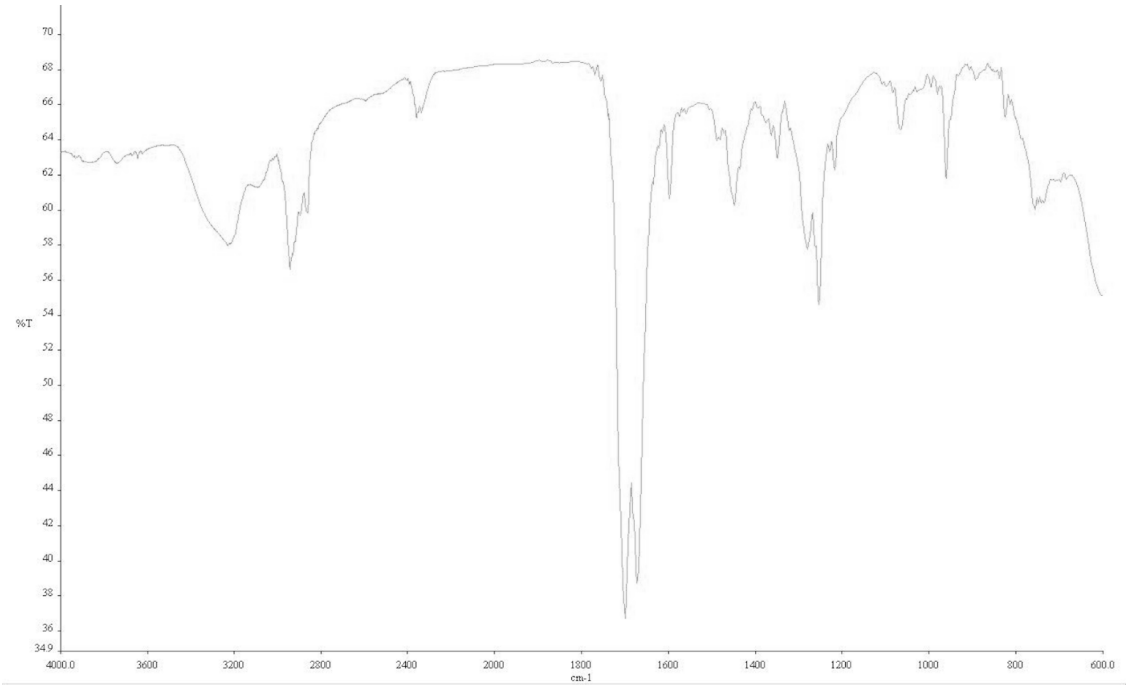


Figure A5.8 *Infrared spectrum (Thin Film, NaCl) of compound* ***176***.

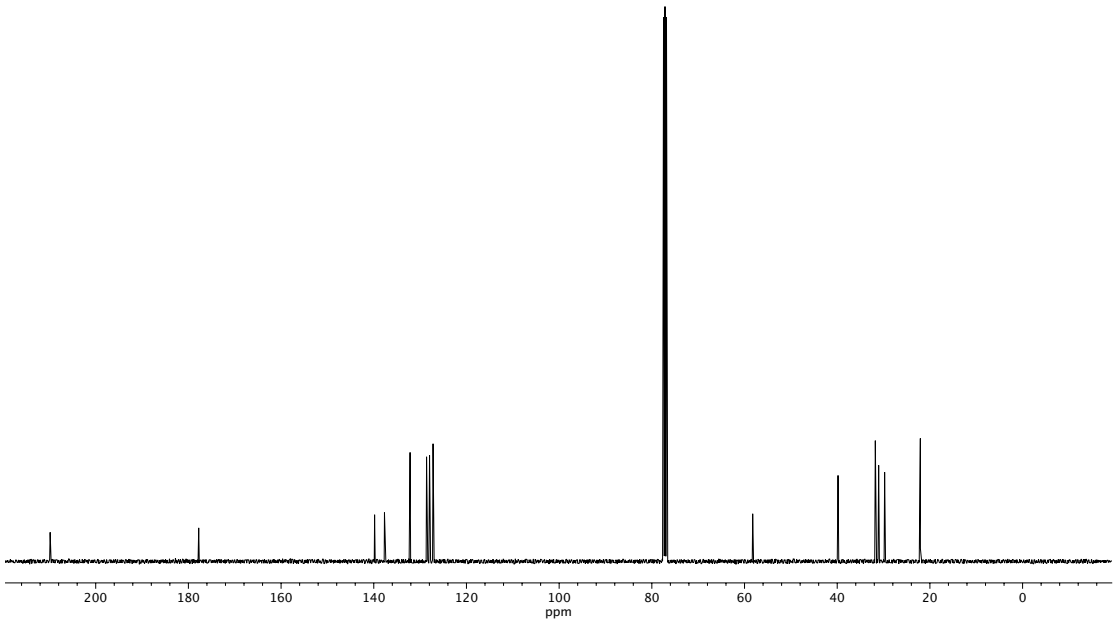
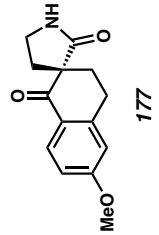


Figure A5.9 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***176***.



177

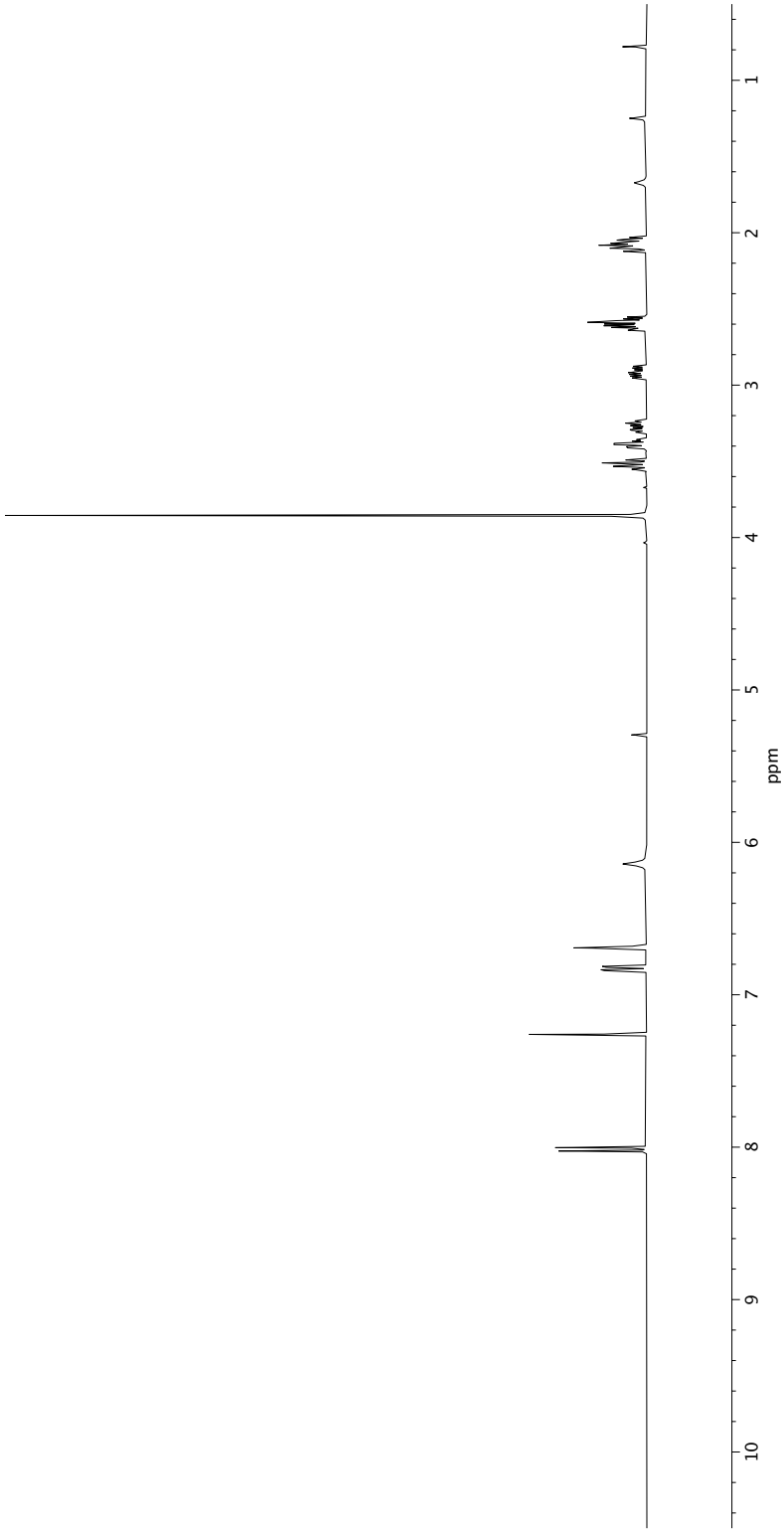


Figure A5.10 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***177****.*

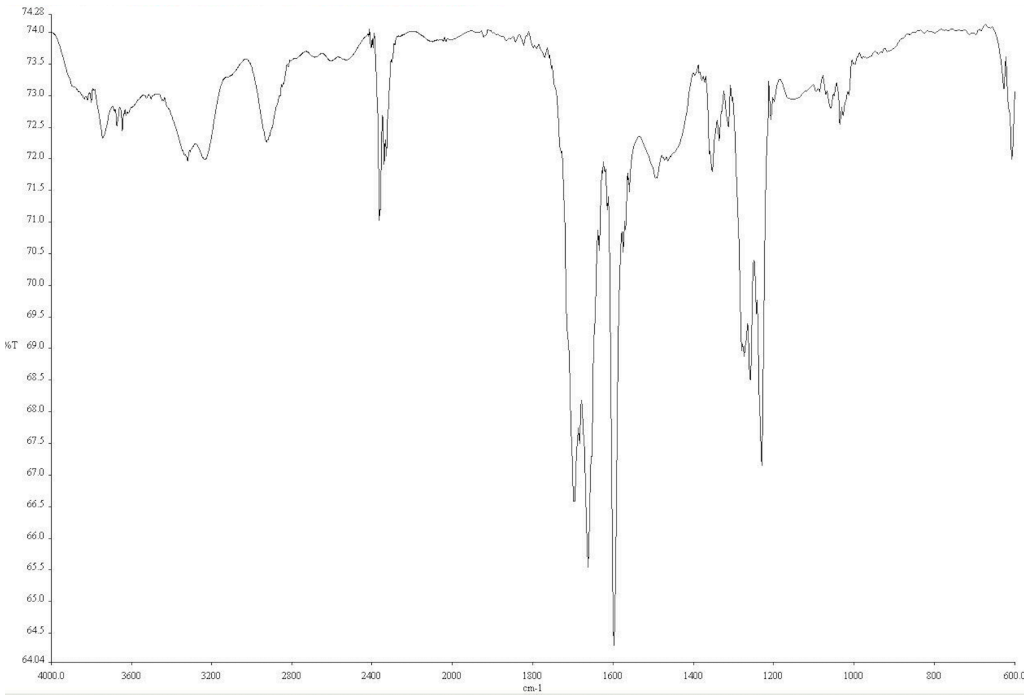


Figure A5.11 *Infrared spectrum (Thin Film, NaCl) of compound* ***177****.*

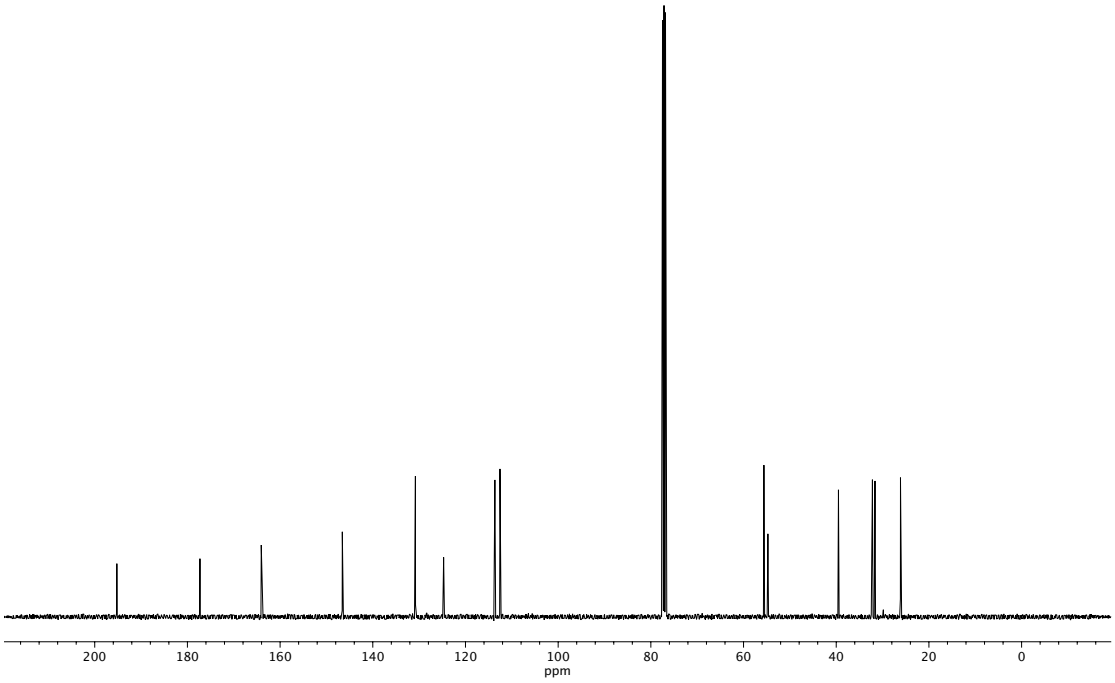


Figure A5.12 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***177****.*

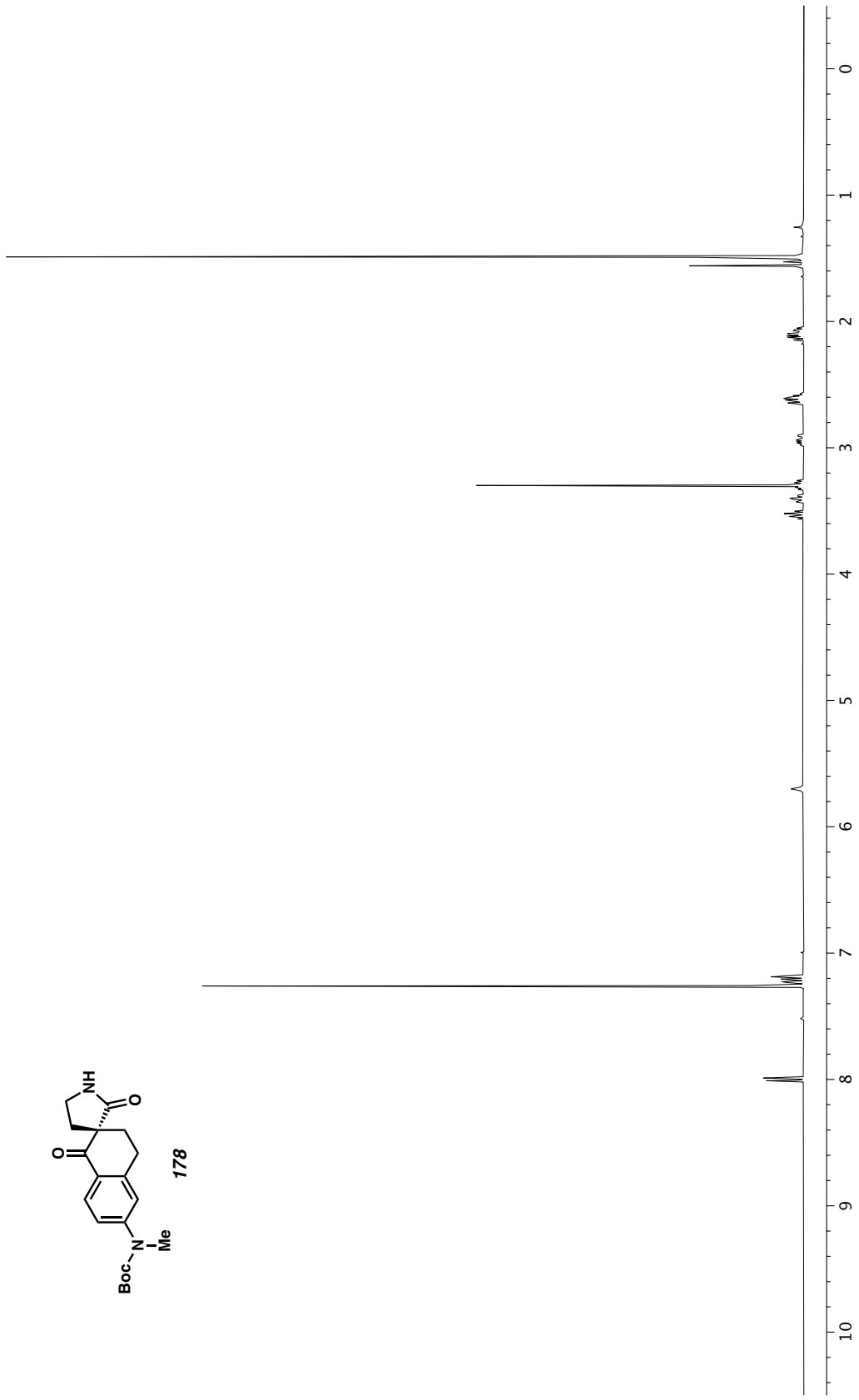


Figure A5.13 *^1H NMR (400 MHz, $CDCl_3$) of compound **178**.*

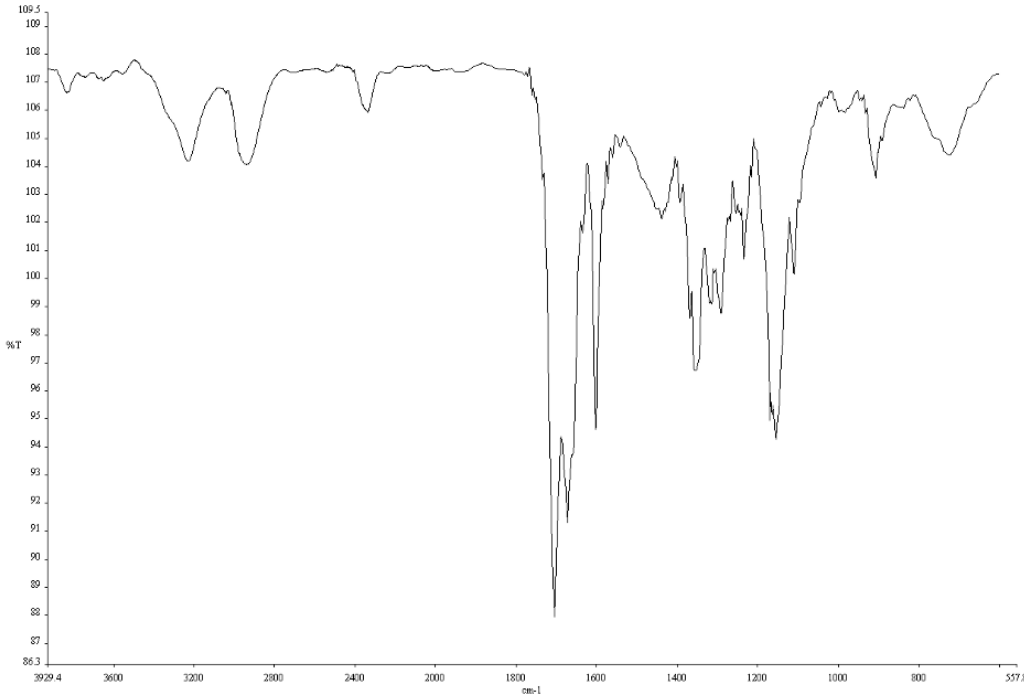


Figure A5.14 *Infrared spectrum (Thin Film, NaCl) of compound* ***178****.*

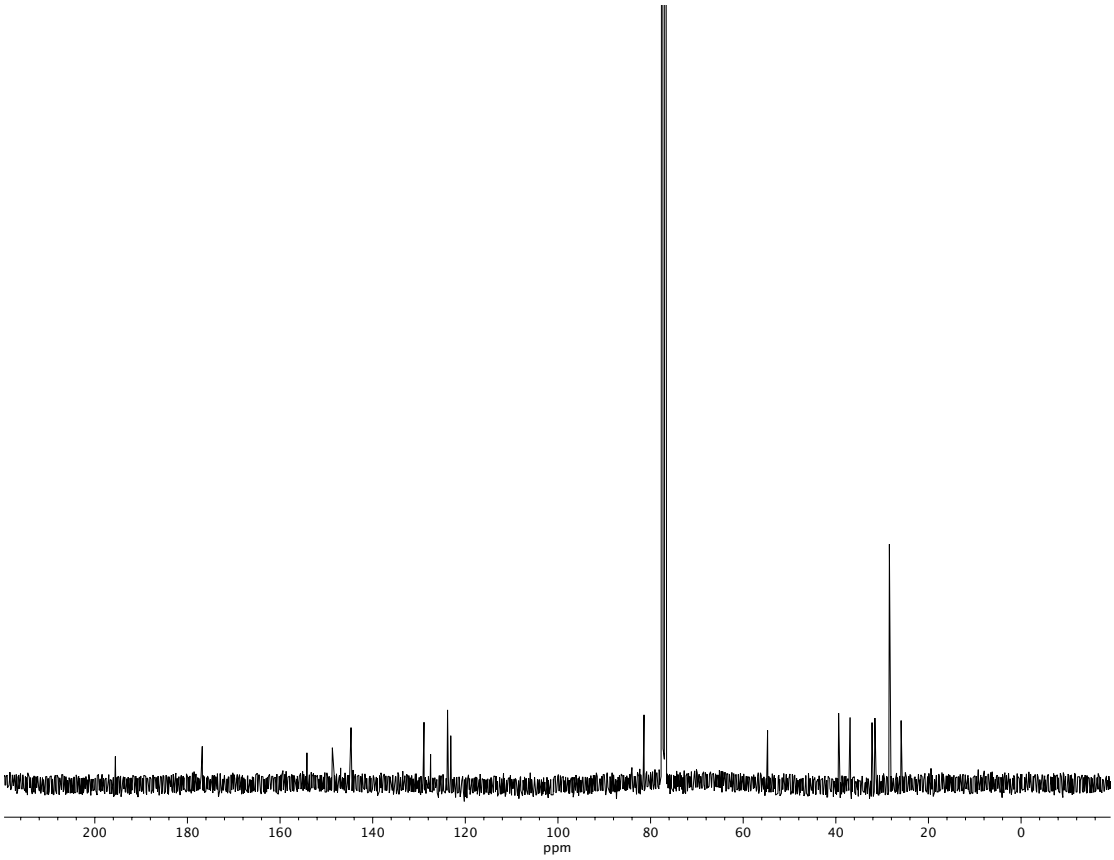


Figure A5.15 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***178****.*

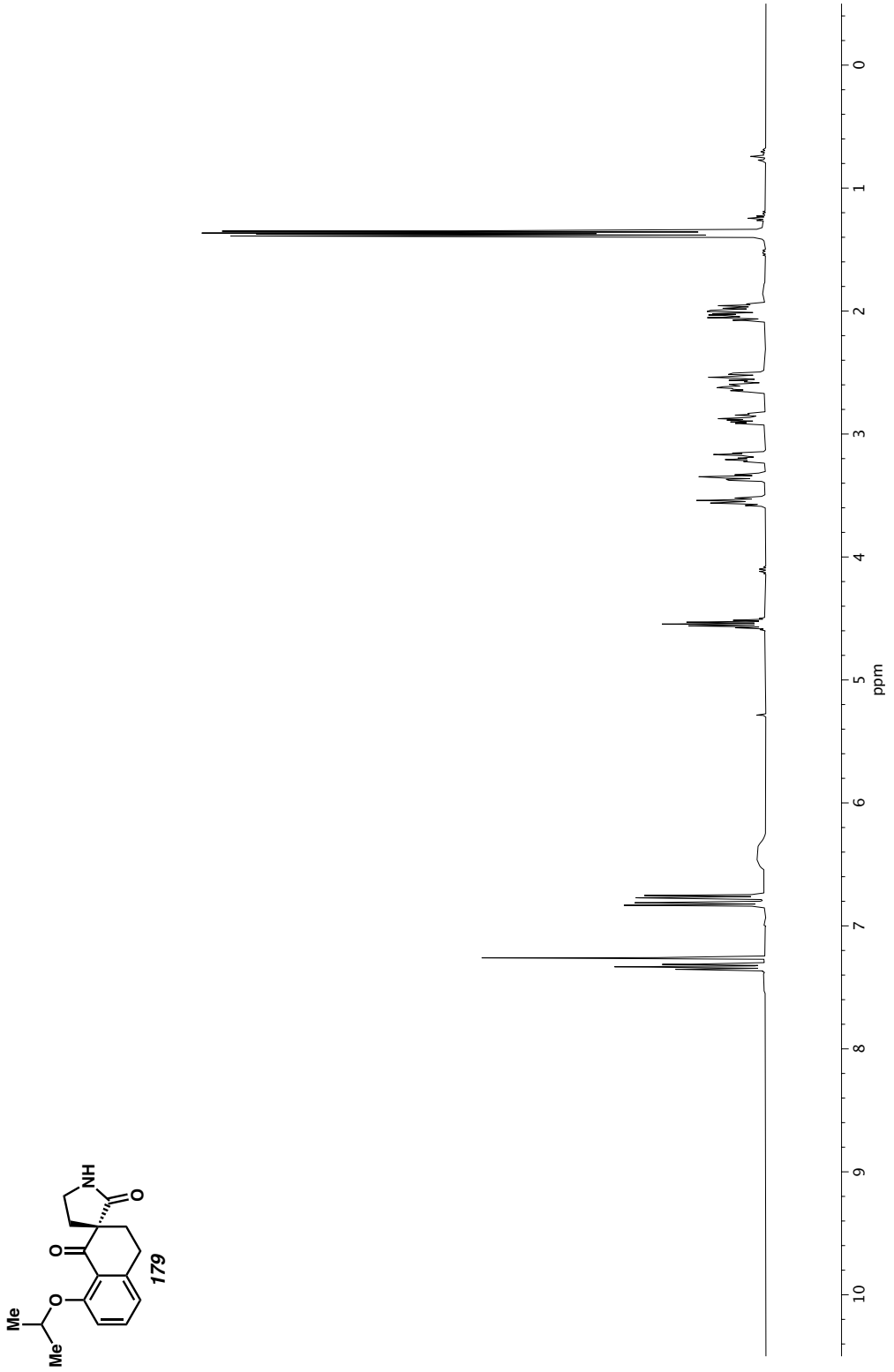


Figure A5.16 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***179****.*

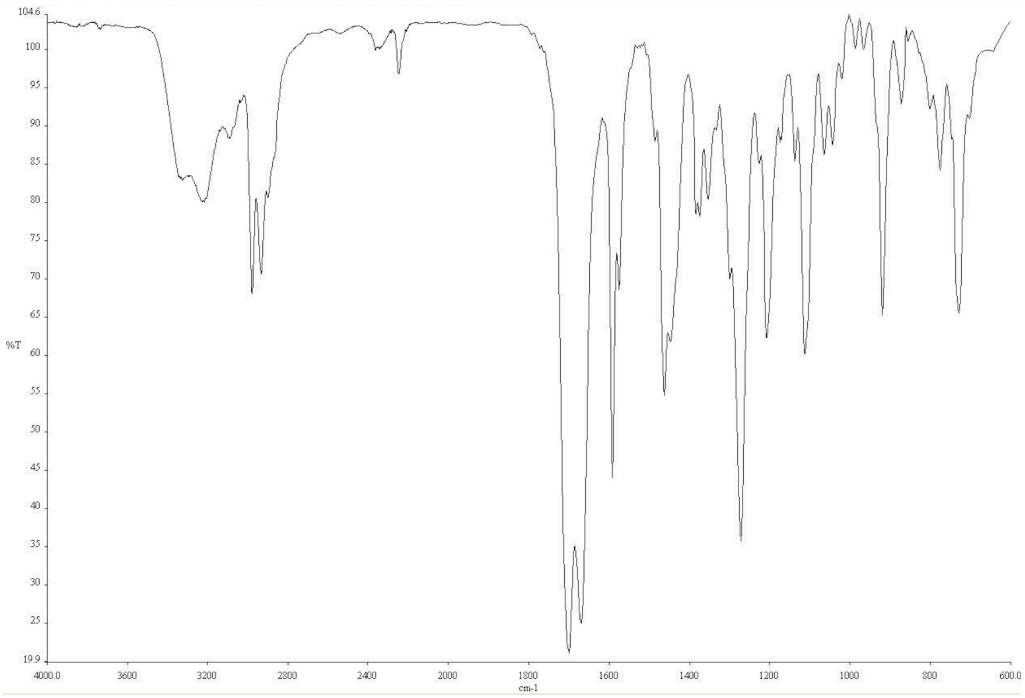


Figure A5.17 *Infrared spectrum (Thin Film, NaCl) of compound* ***179***.

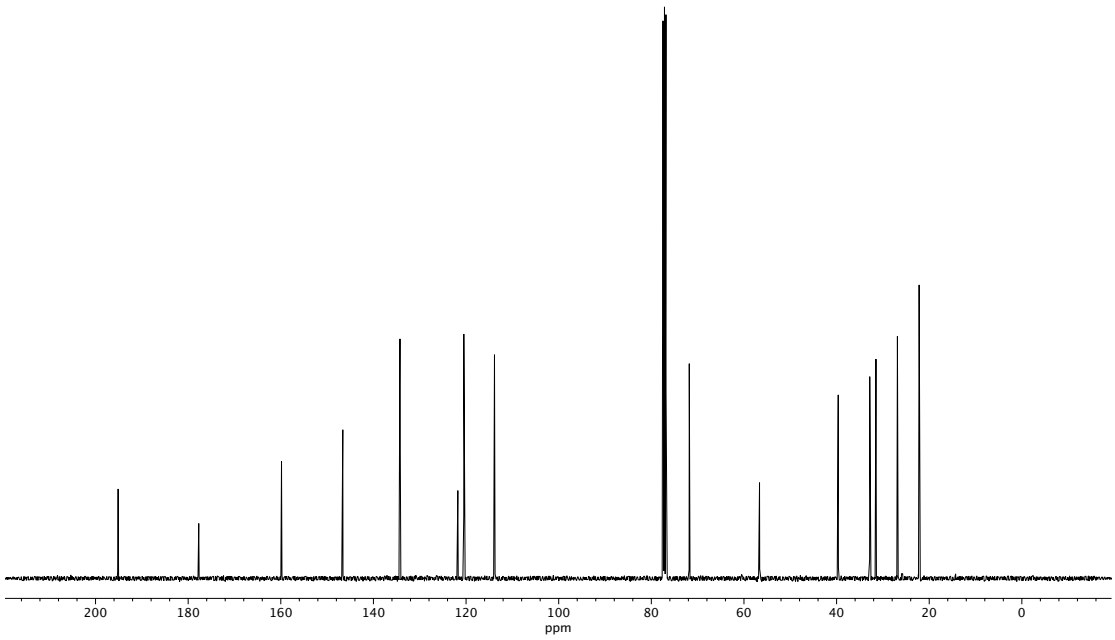


Figure A5.18 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***179***.

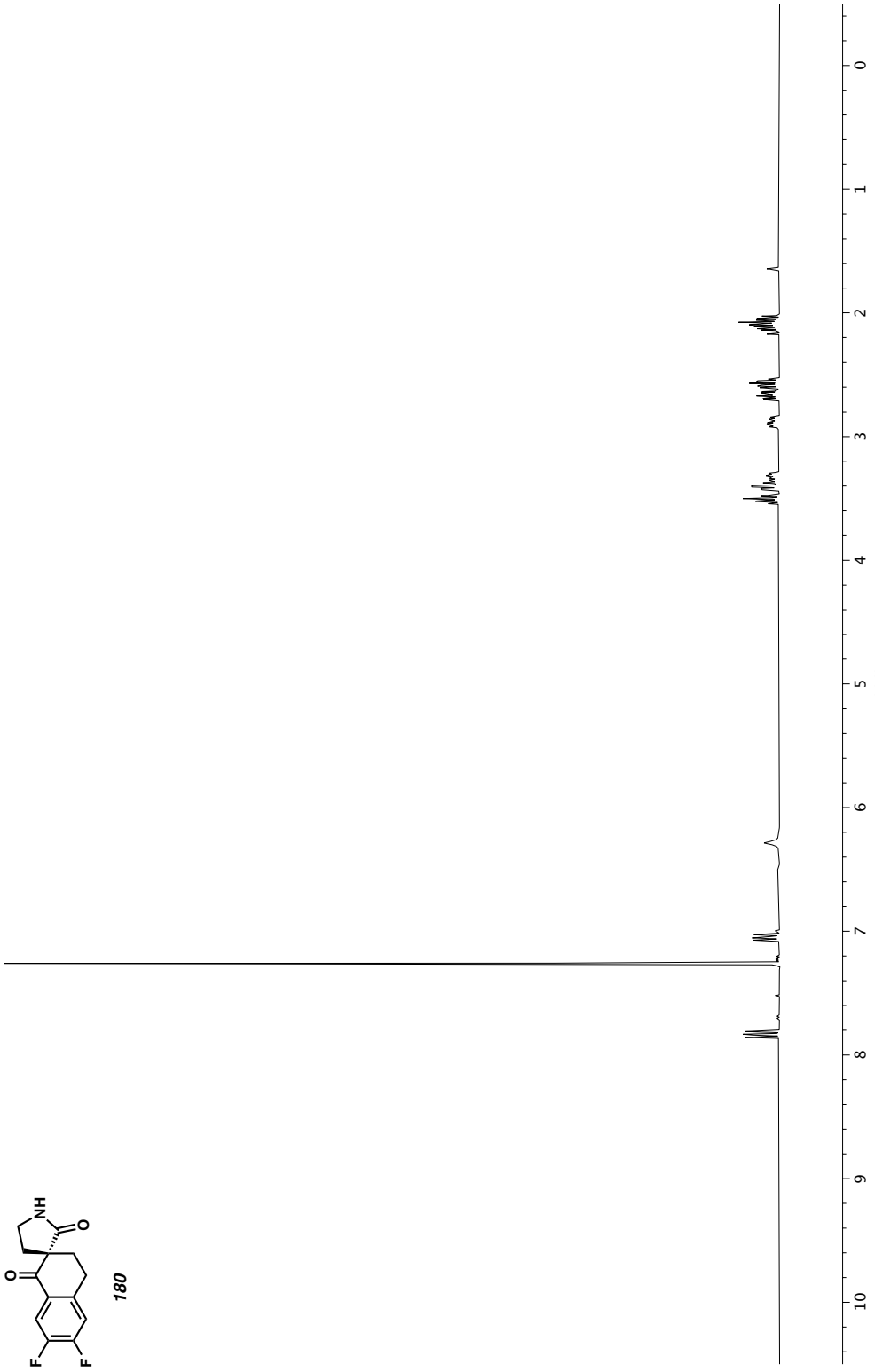


Figure A5.19 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***180****.*

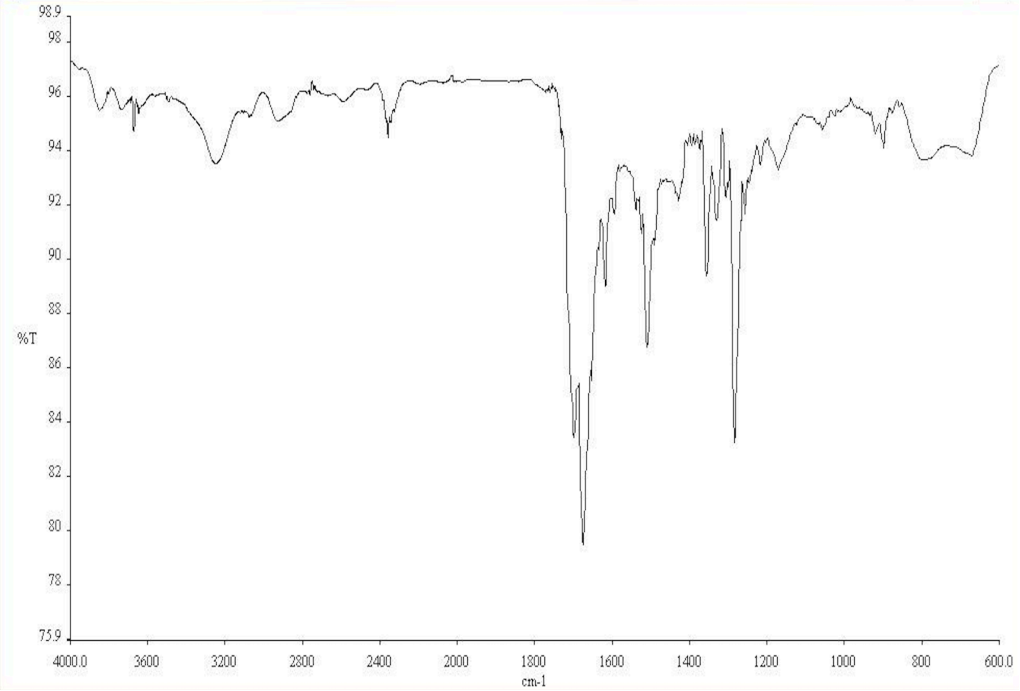


Figure A5.20 *Infrared spectrum (Thin Film, NaCl) of compound* ***180****.*

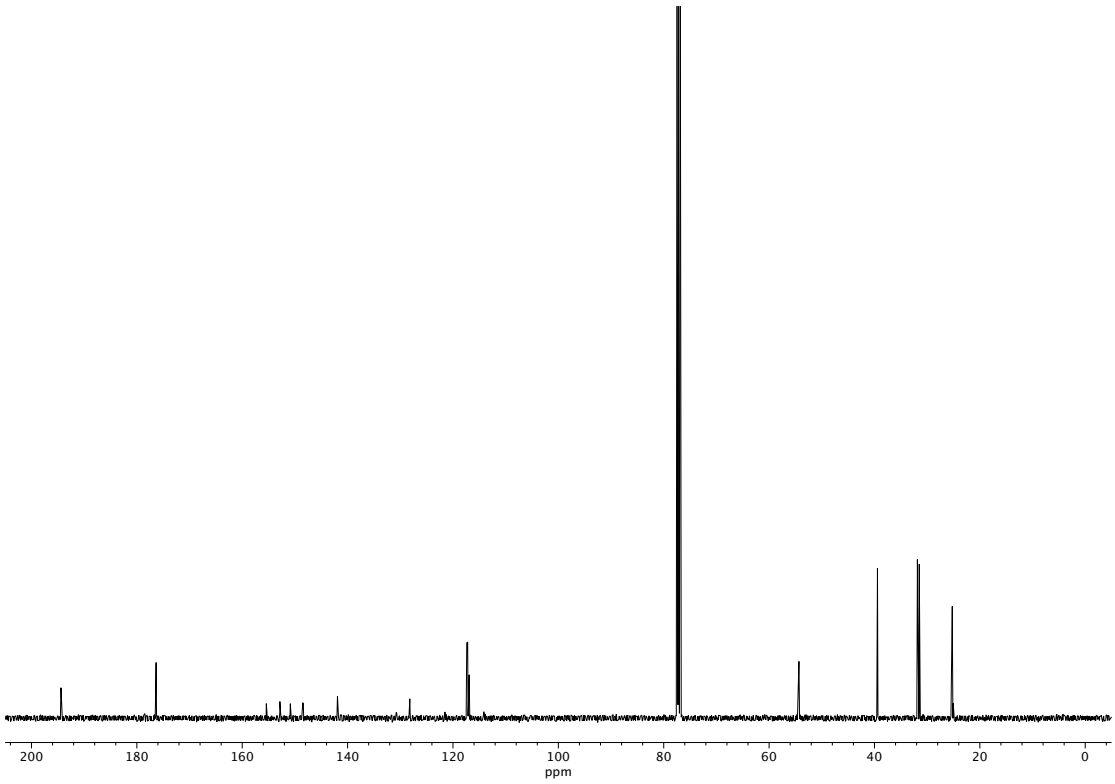


Figure A5.21 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***180****.*

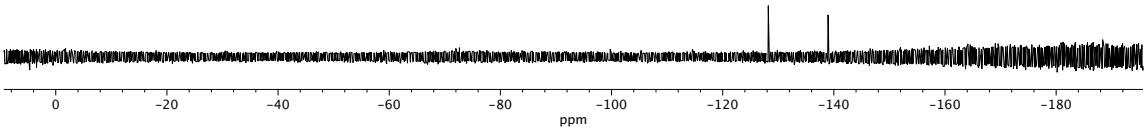


Figure A5.22 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***180***.

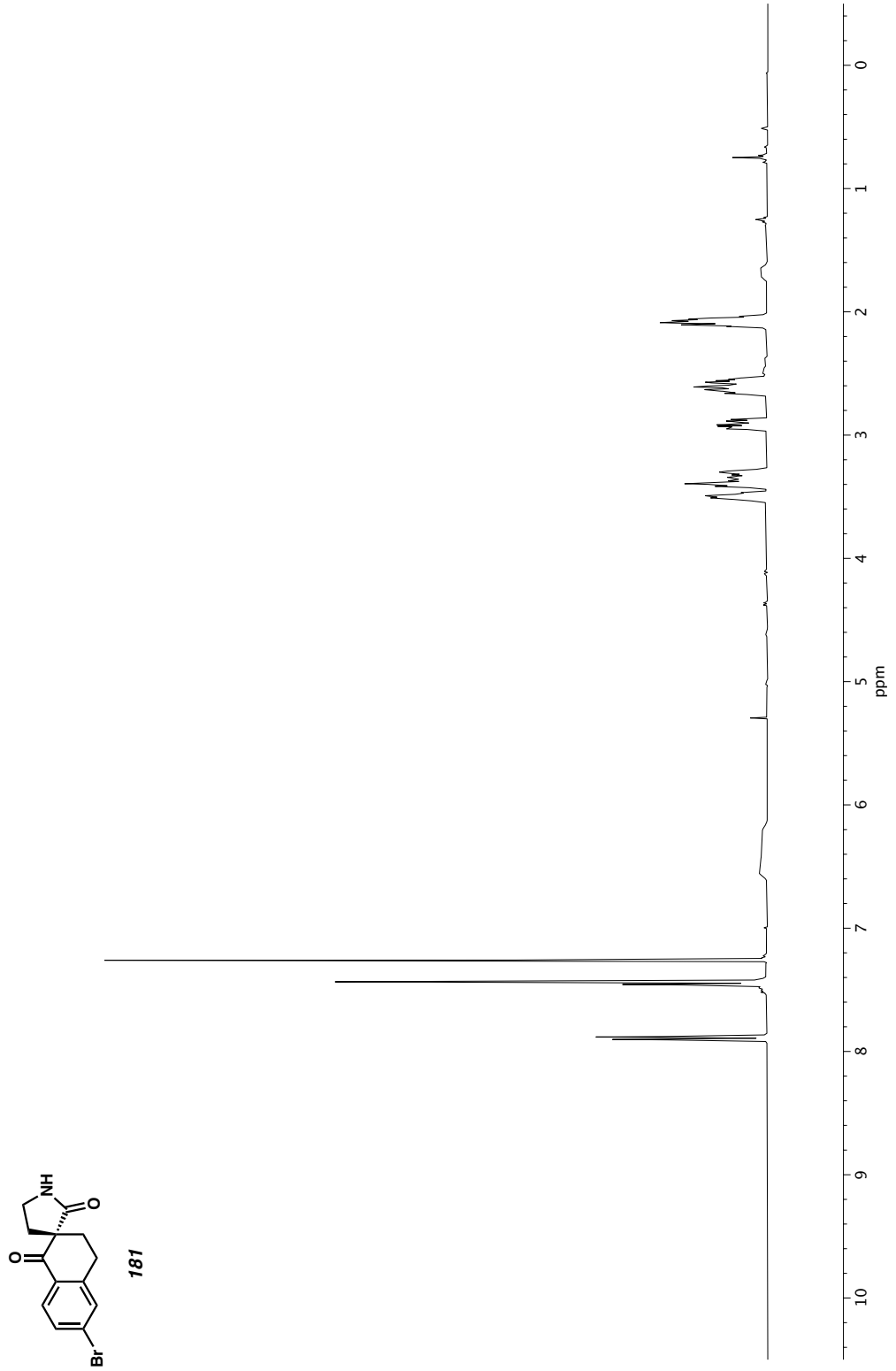


Figure A5.23 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***181****.*

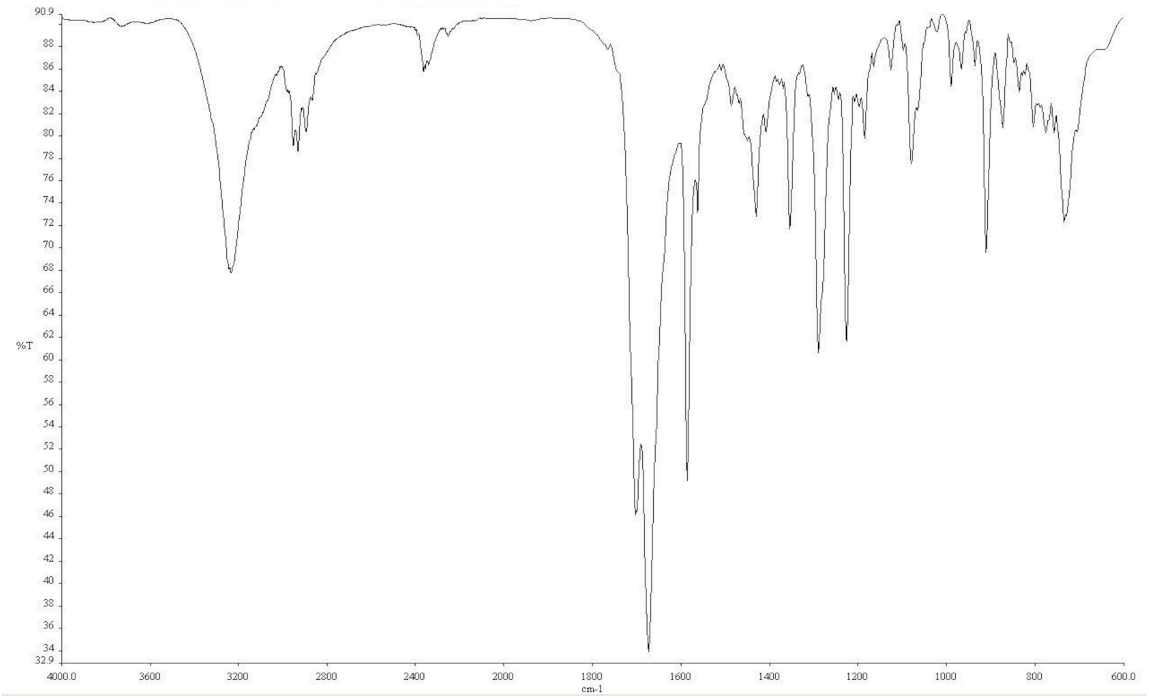


Figure A5.24 *Infrared spectrum ($CDCl_3$ solution) of compound* ***181***.

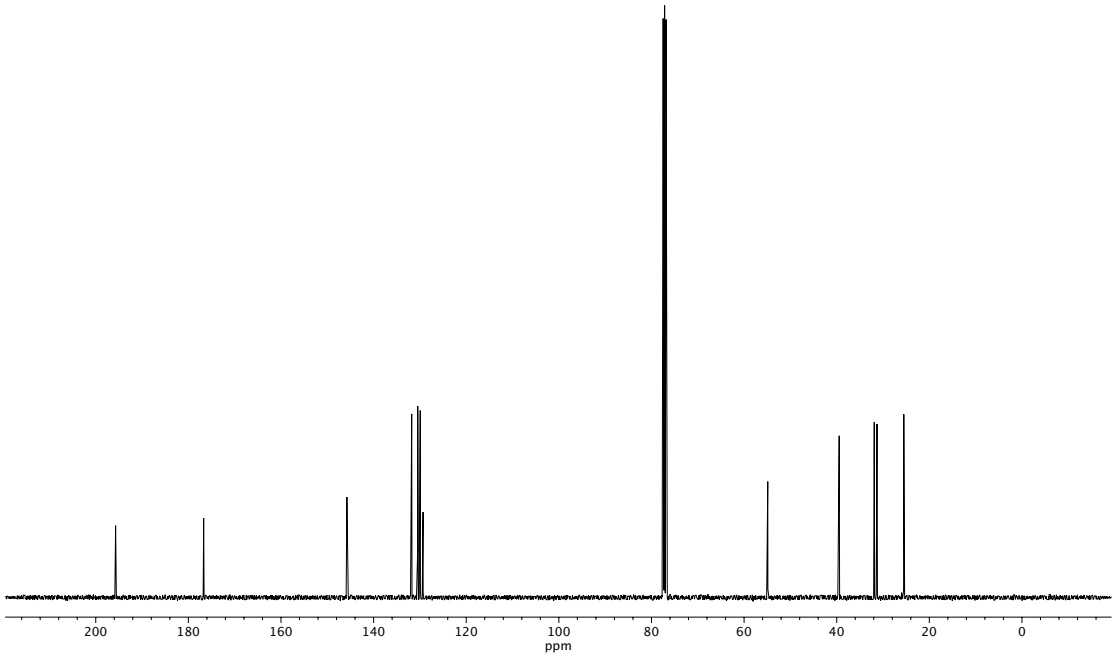


Figure A5.25 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***181***.

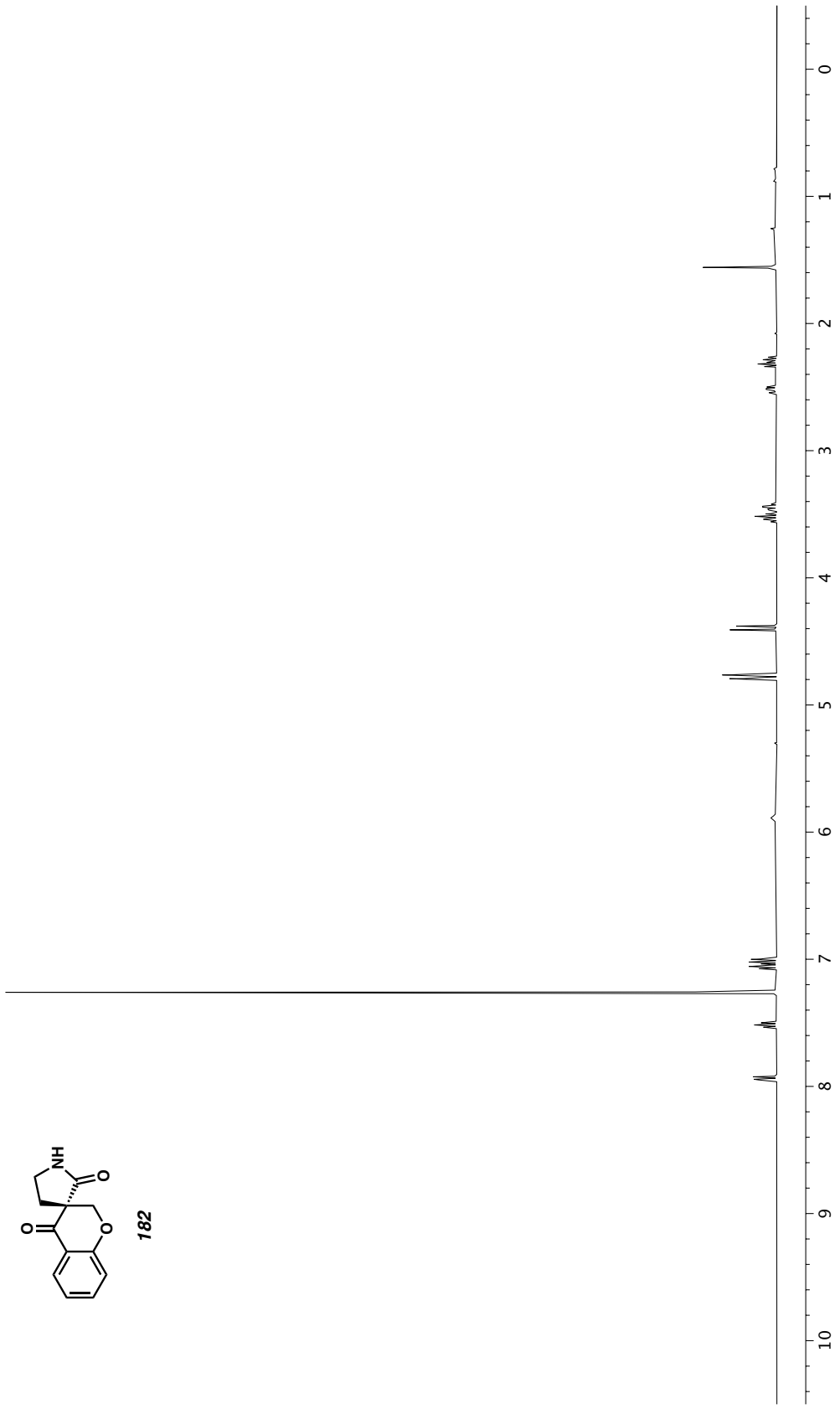


Figure A5.26 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***182***.

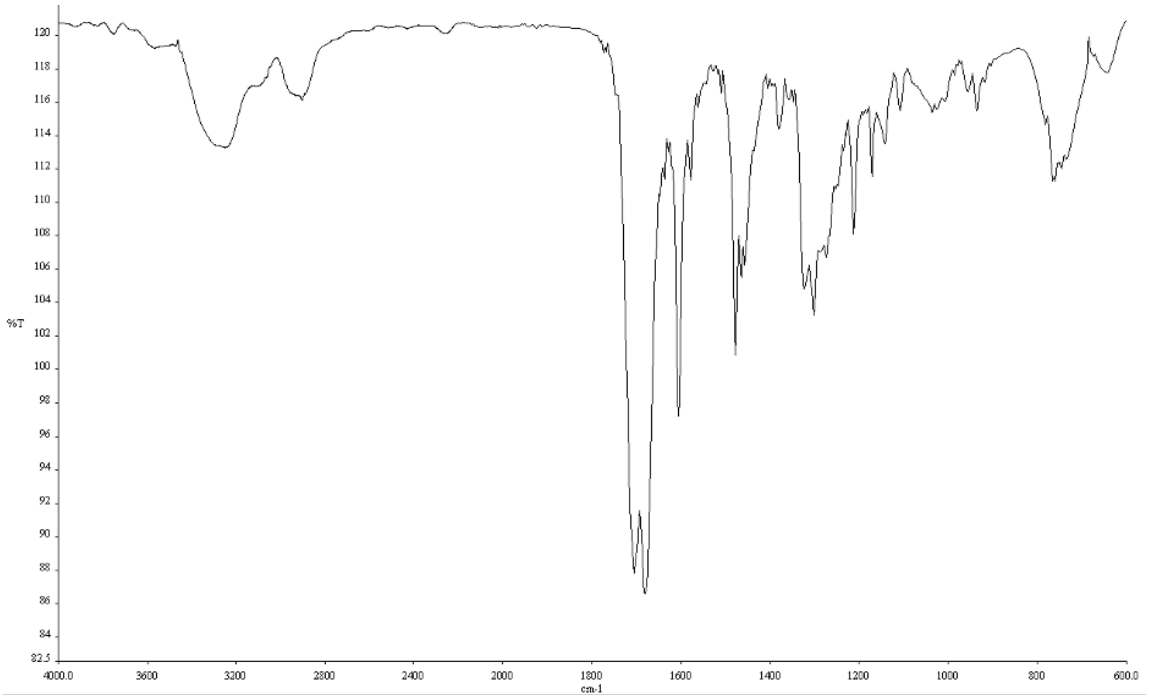


Figure A5.27 *Infrared spectrum ($CDCl_3$ solution) of compound* ***182***.

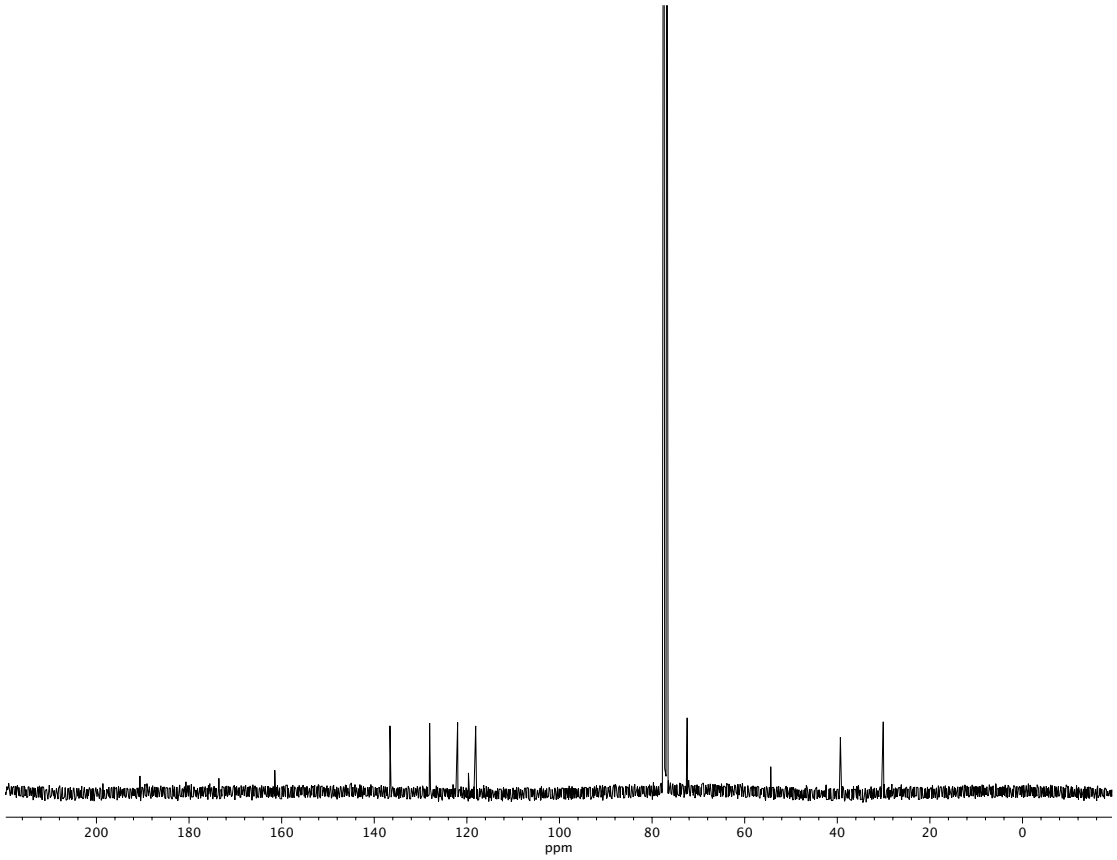


Figure A5.28 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***182***.

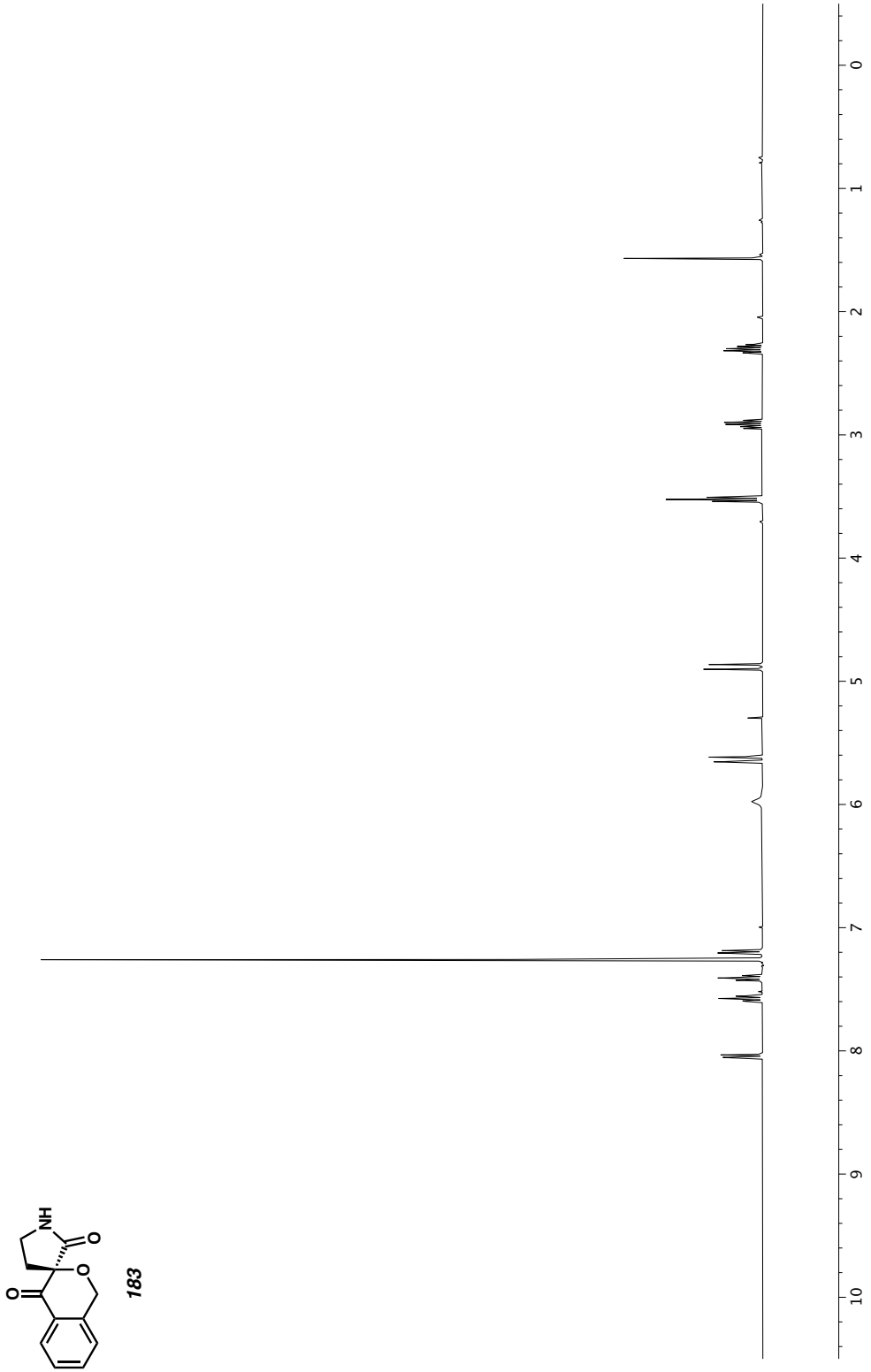


Figure A5.29 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***183****.*

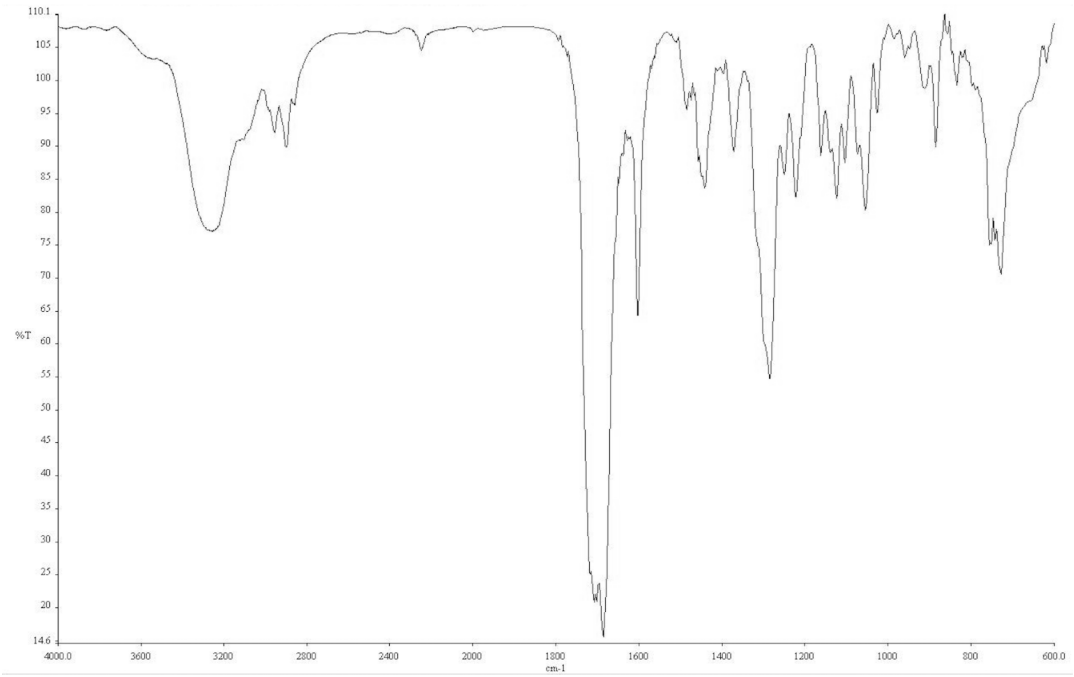


Figure A5.30 *Infrared spectrum (Thin Film, NaCl) of compound* ***183***.

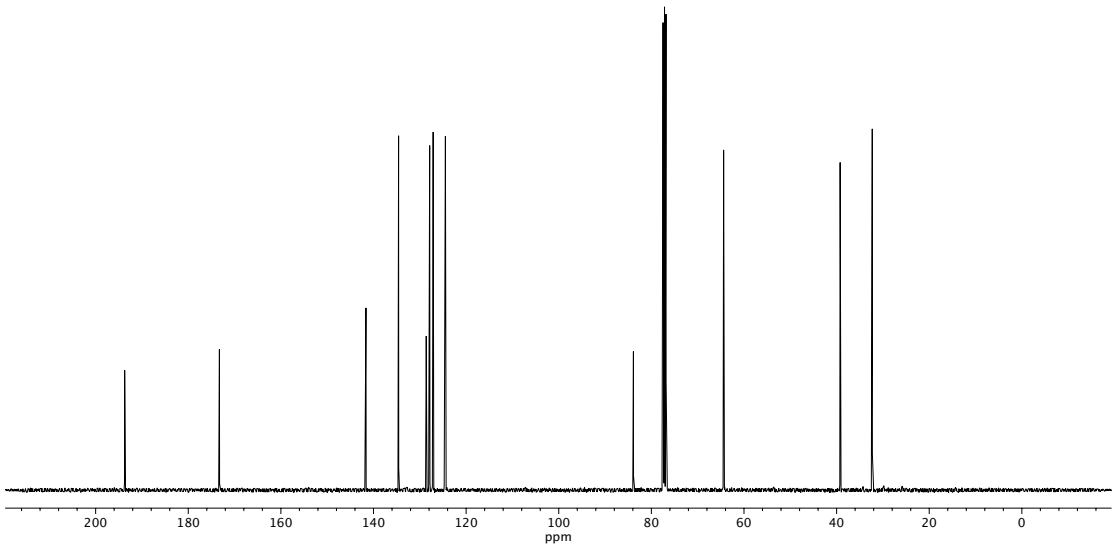
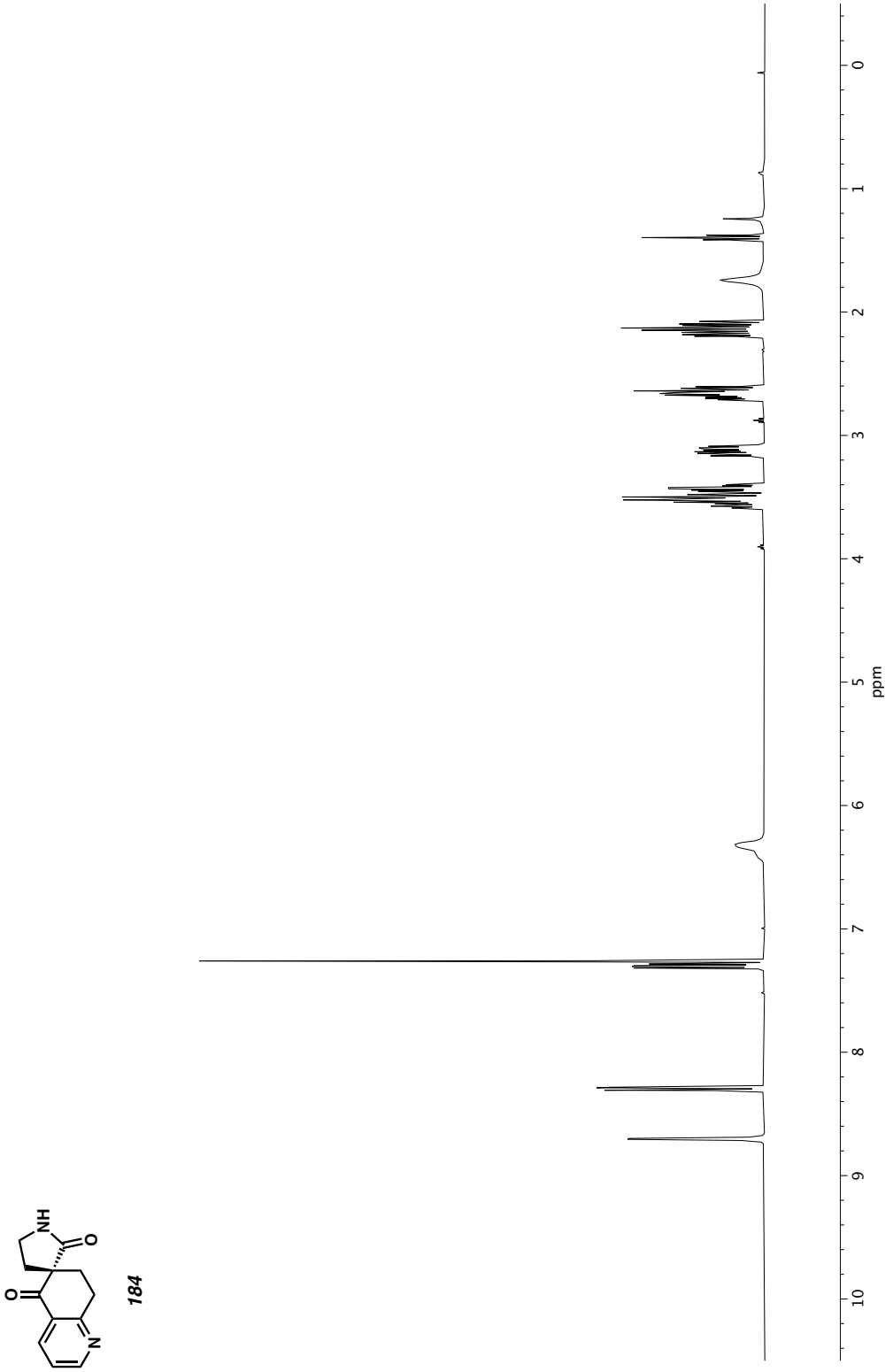


Figure A5.31 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***183***.



184

Figure A5.32 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***184****.*

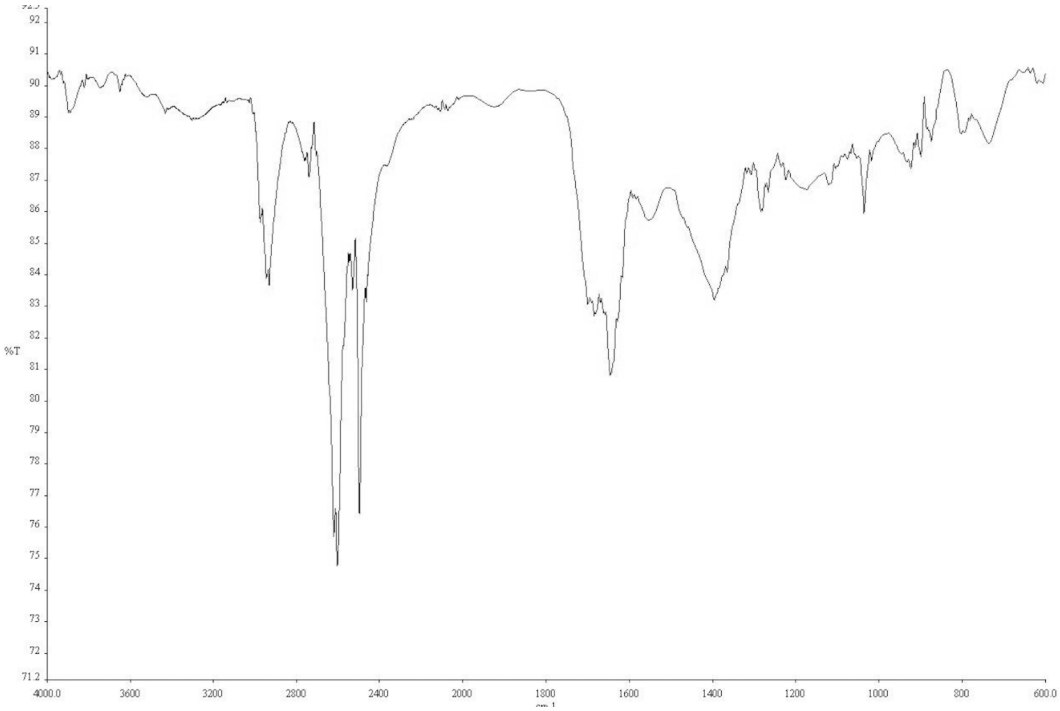


Figure A5.33 *Infrared spectrum (Thin Film, NaCl) of compound* ***184****.*

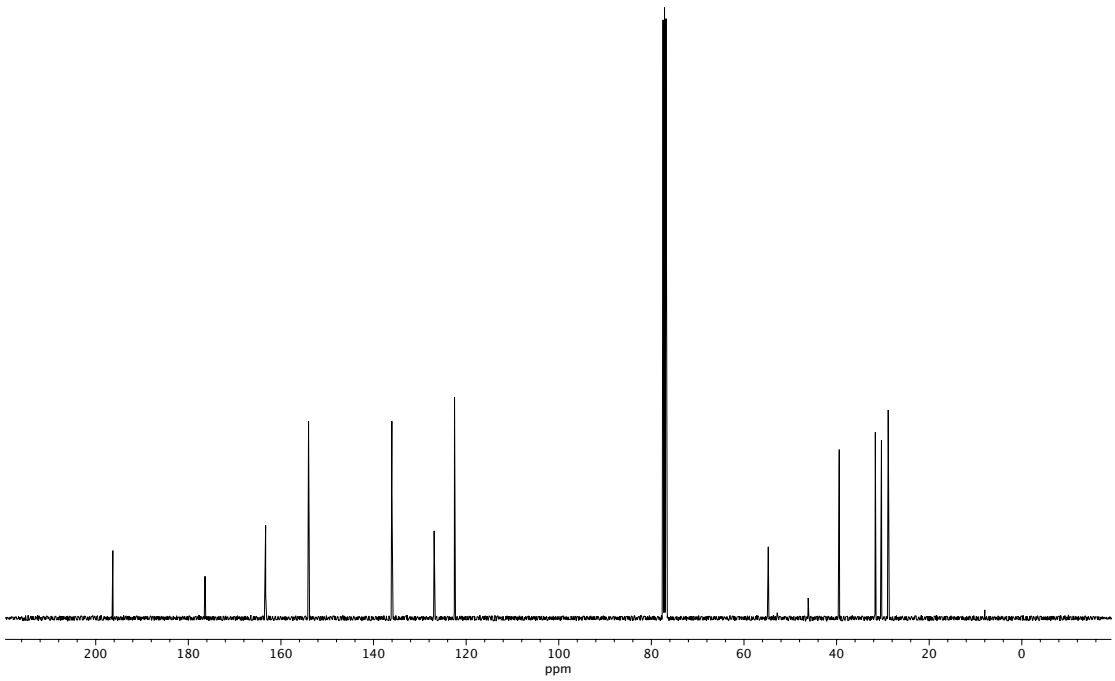


Figure A5.34 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***184****.*

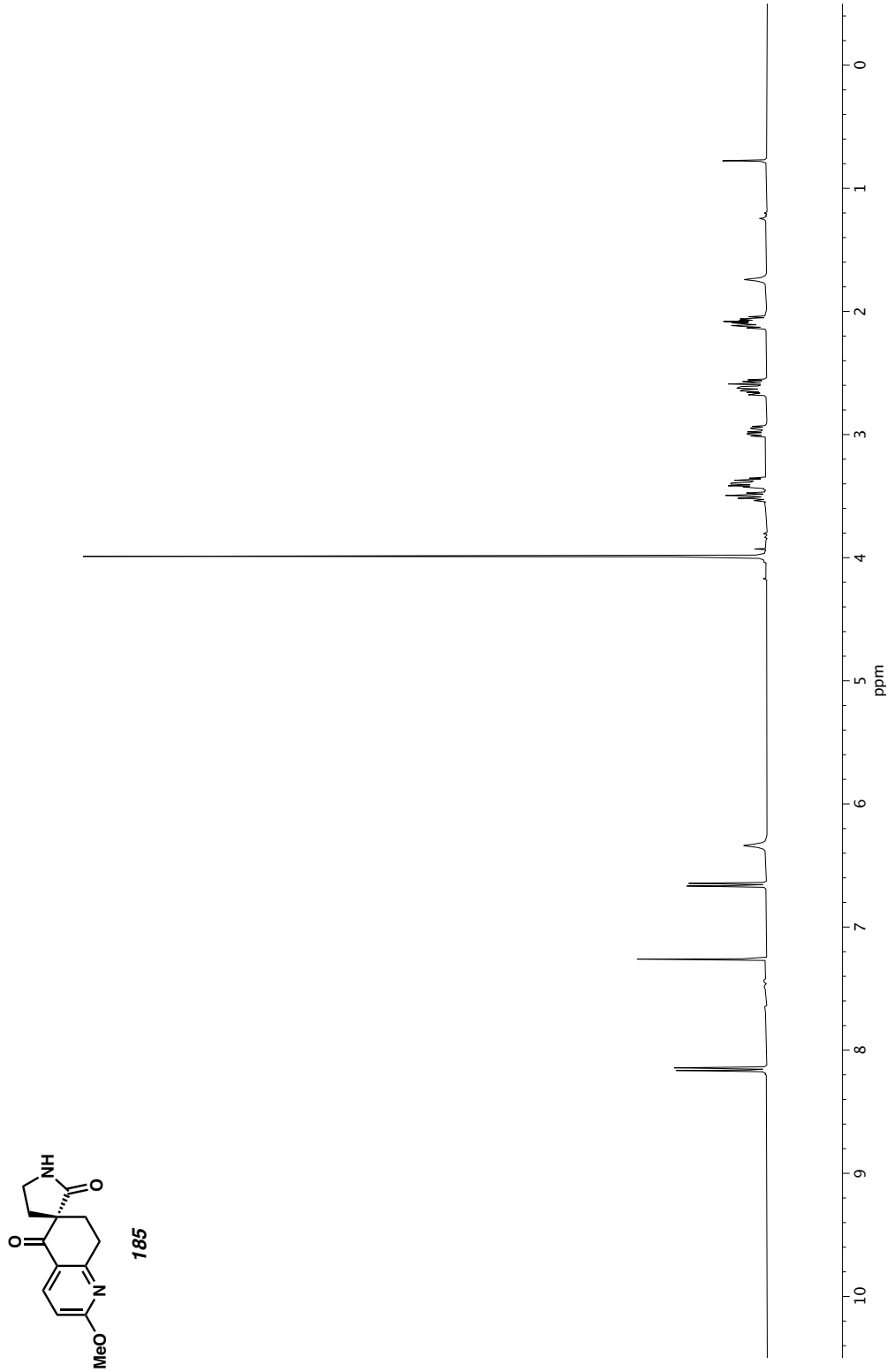


Figure A5.35 *^1H NMR (400 MHz, $CDCl_3$) of compound **185**.*

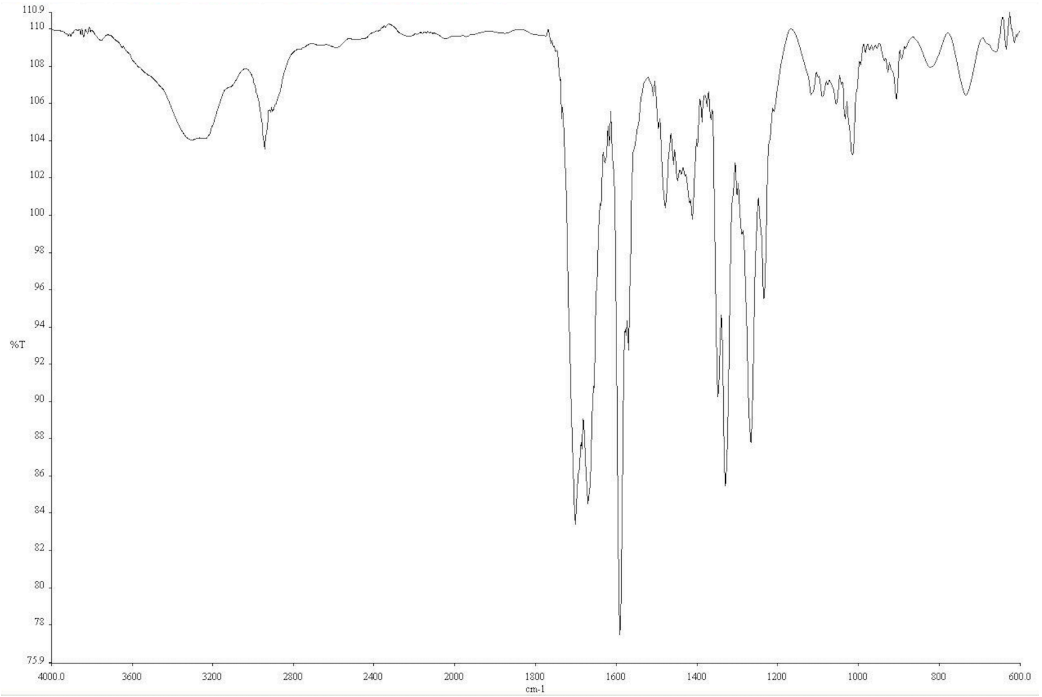


Figure A5.36 *Infrared spectrum (Thin Film, NaCl) of compound* ***185***.

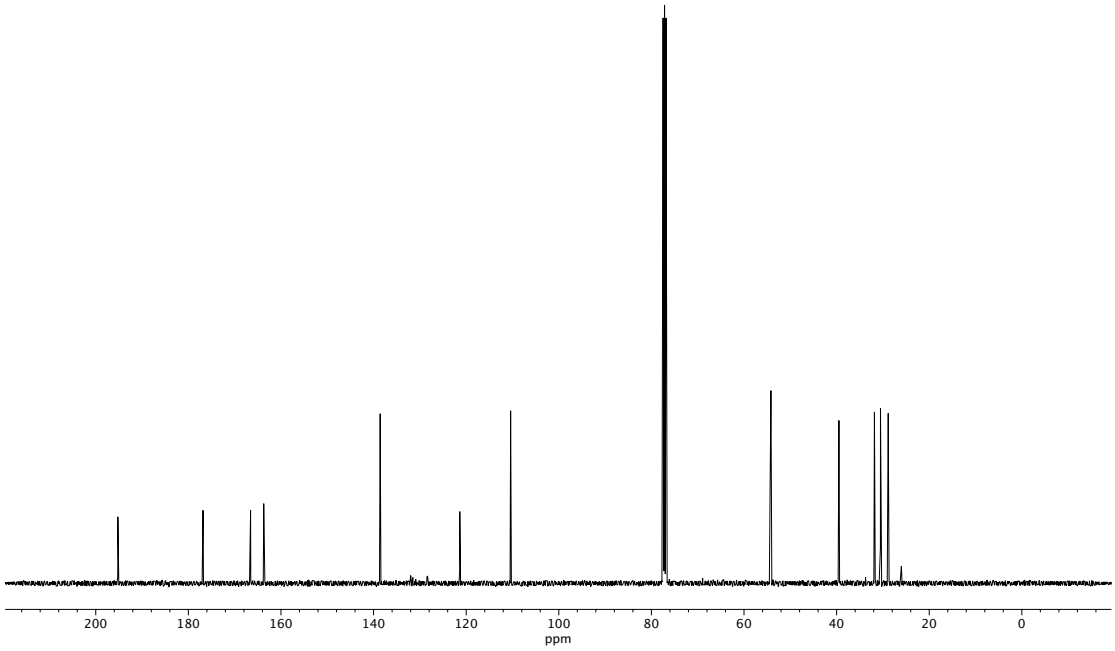


Figure A5.37 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***185***.

Figure A5.38 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***186****.*

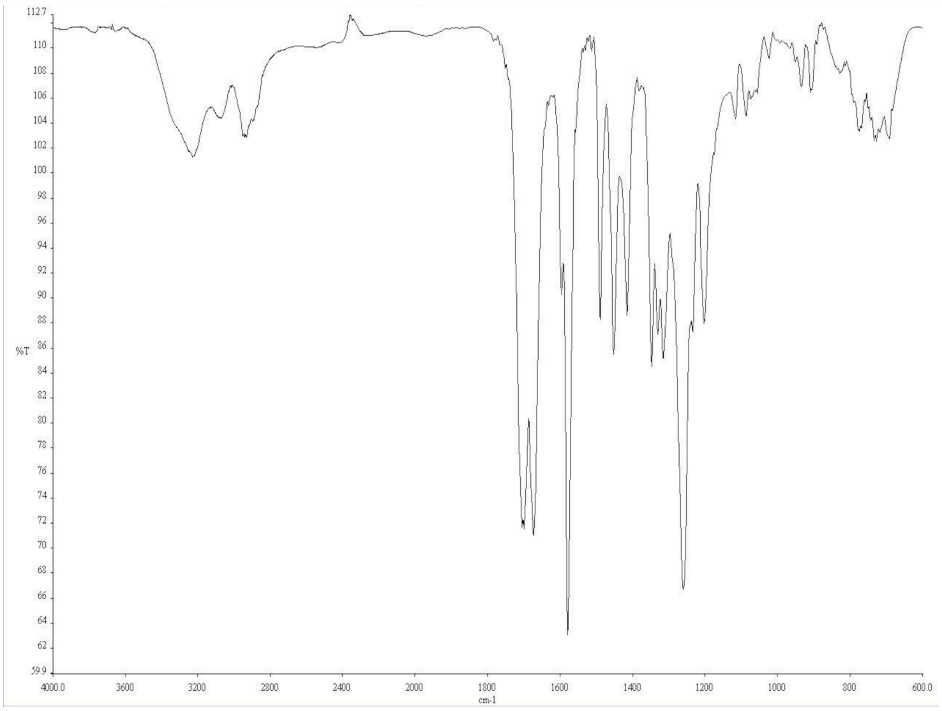


Figure A5.39 *Infrared spectrum (Thin Film, NaCl) of compound* ***186***.

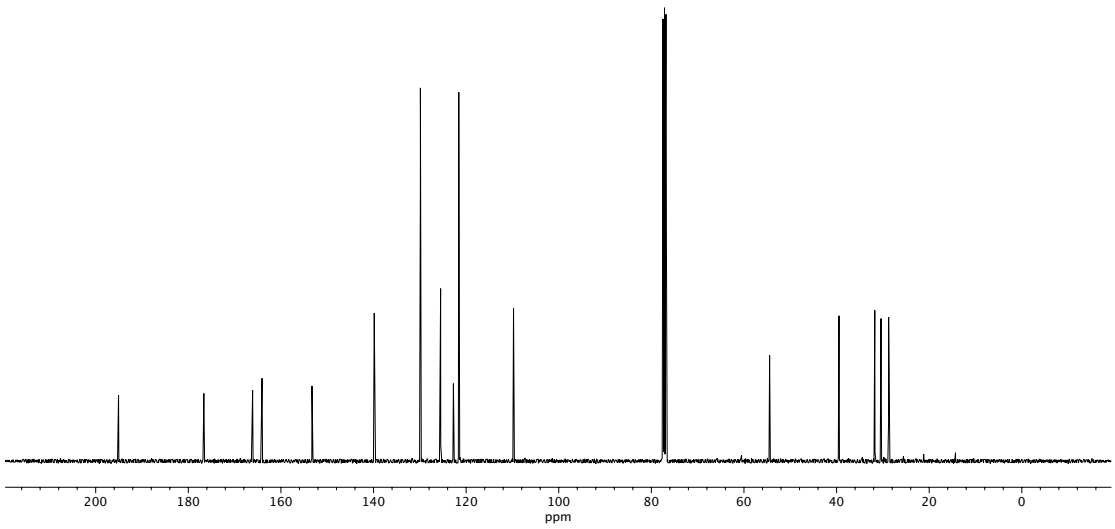


Figure A5.40 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***186***.

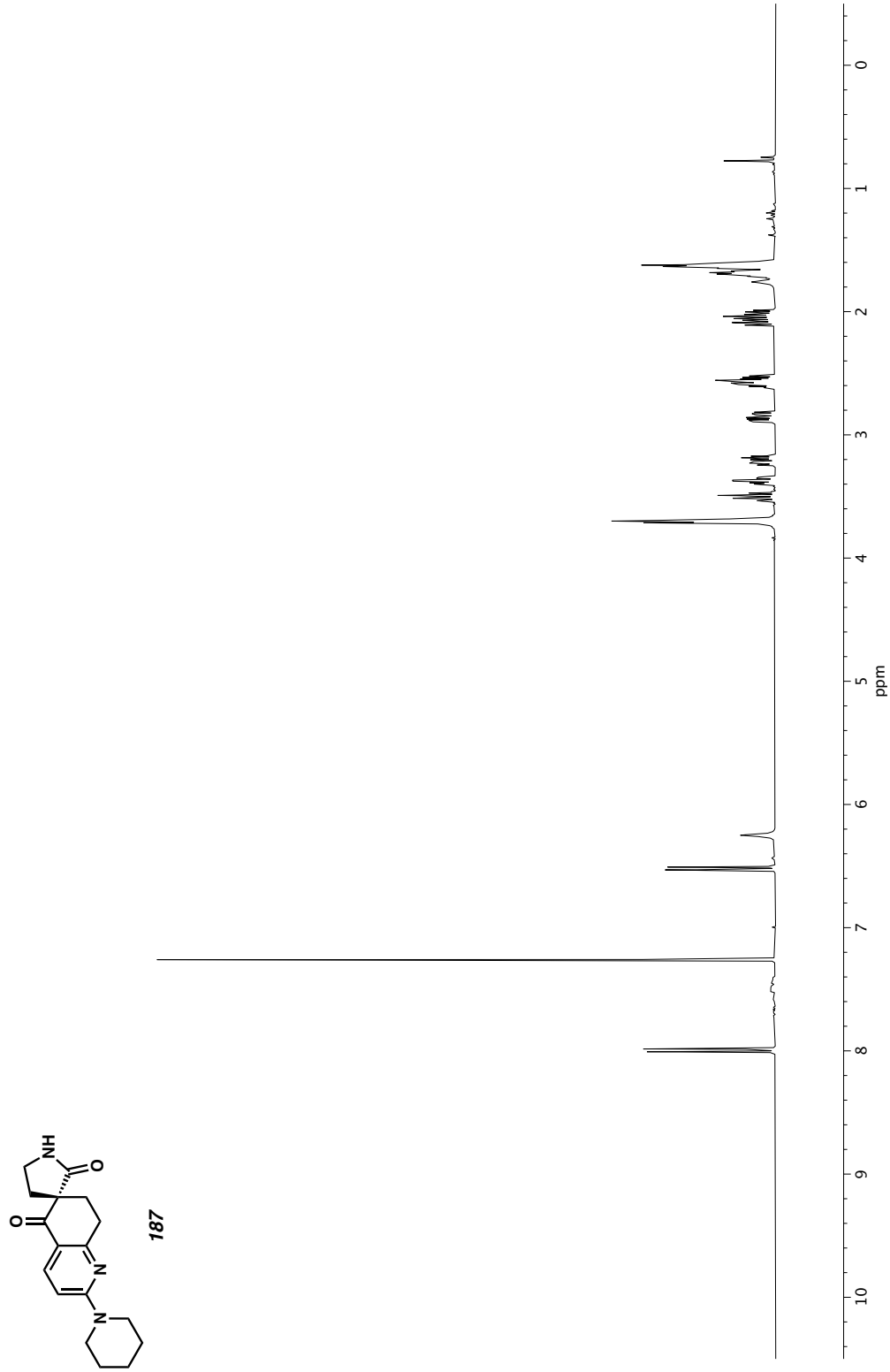


Figure A5.41 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***187****.*

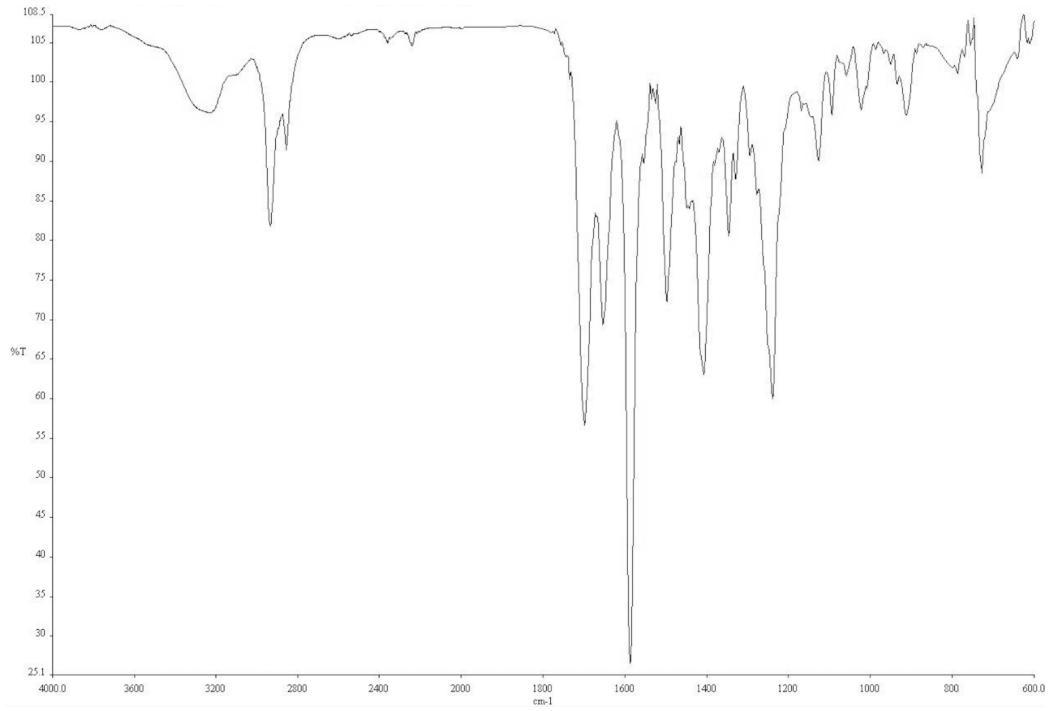


Figure A5.42 *Infrared spectrum (Thin Film, NaCl) of compound* ***187****.*

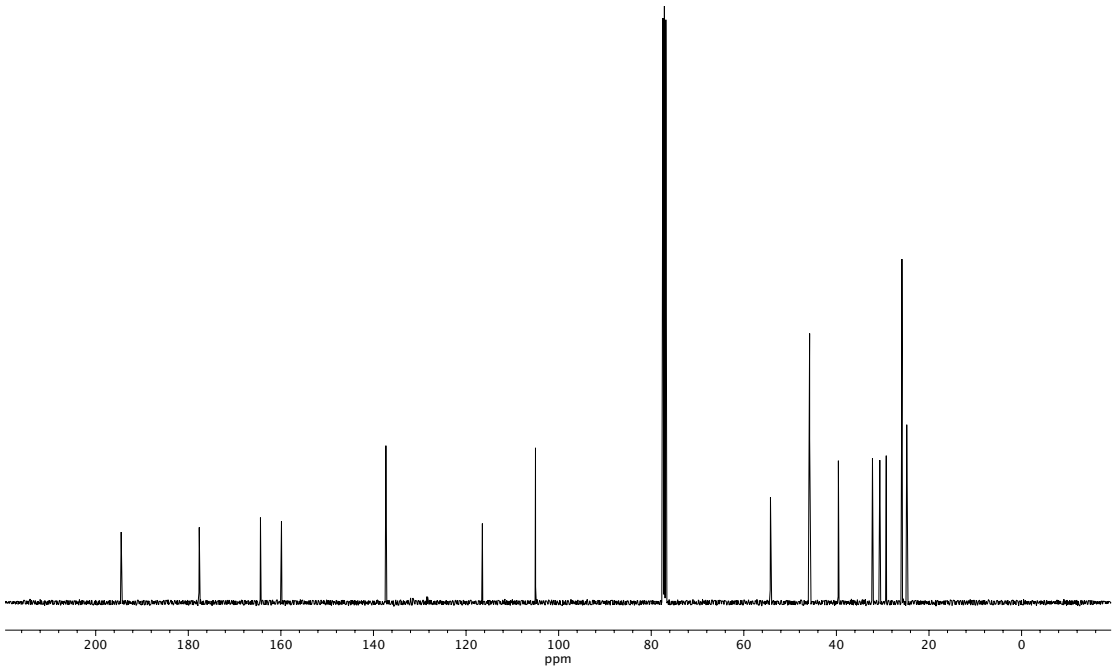
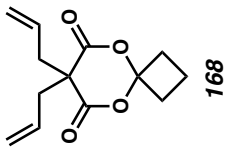


Figure A5.43 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***187****.*



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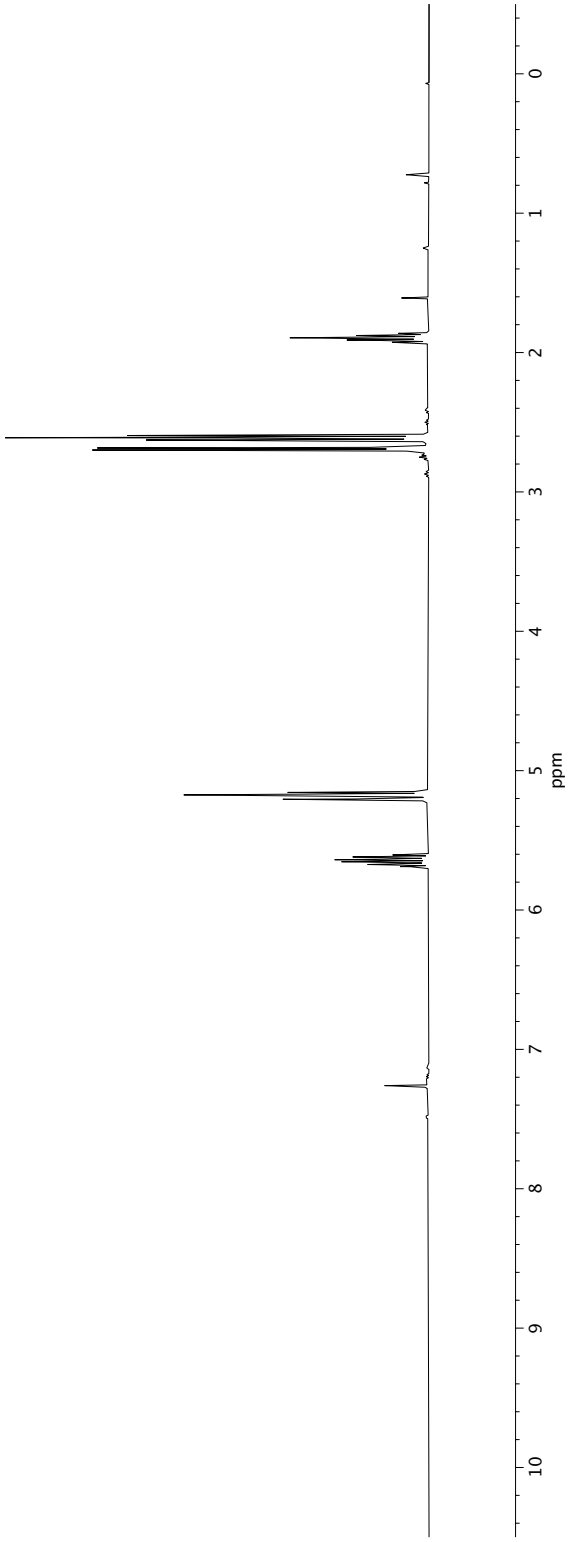

Figure A5.44 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***168****.*

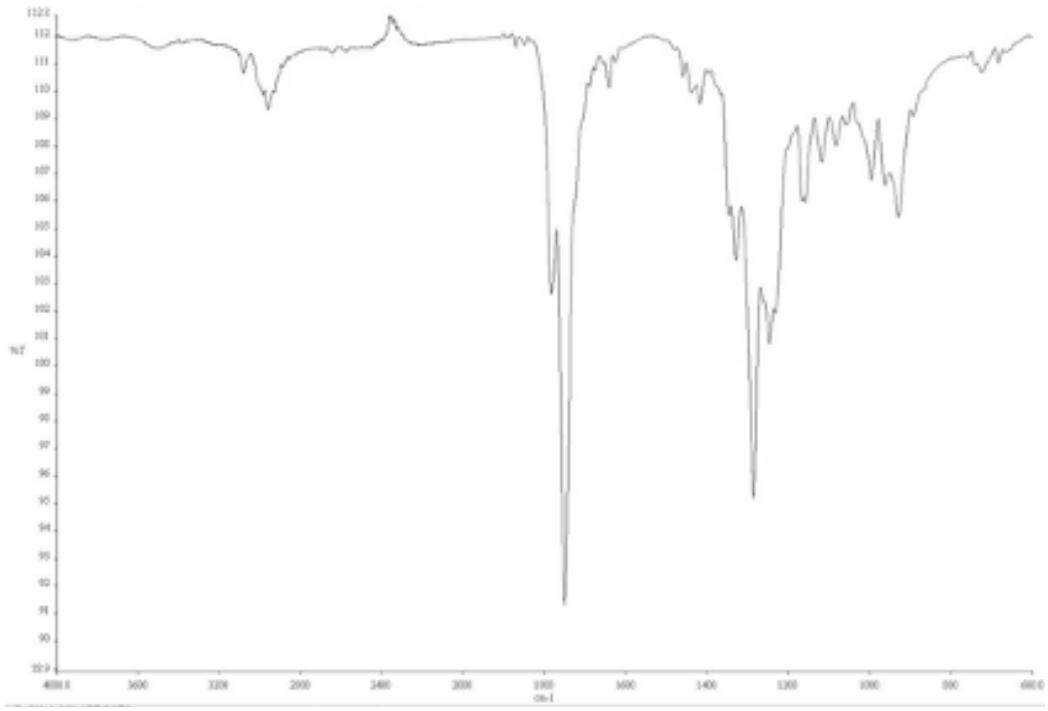

Figure A5.45 *Infrared spectrum (Thin Film, NaCl) of compound* ***168****.*

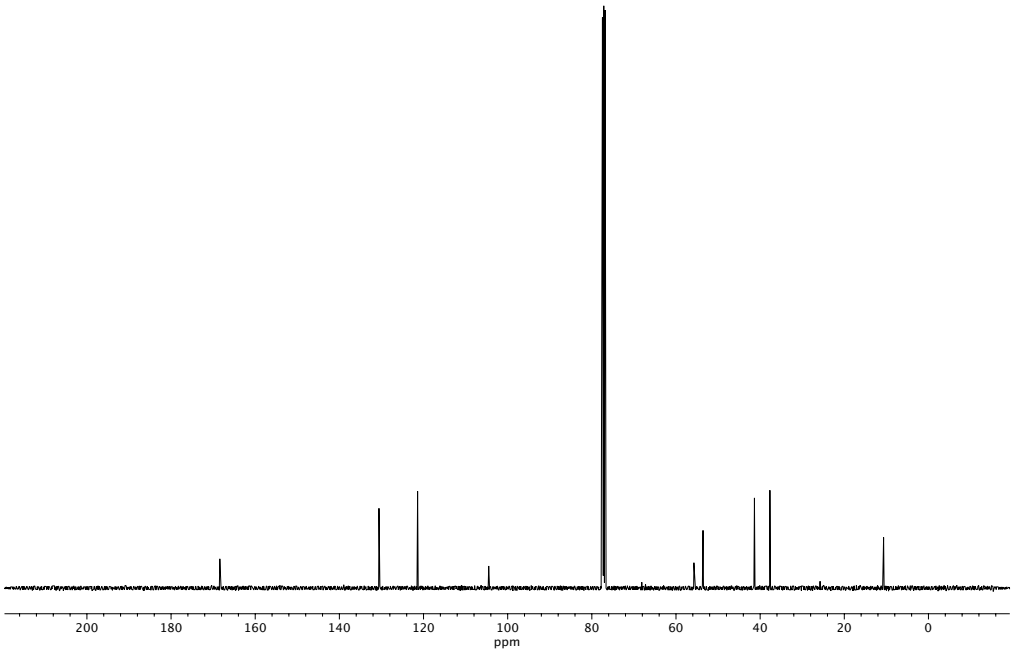

Figure A5.46 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***168****.*

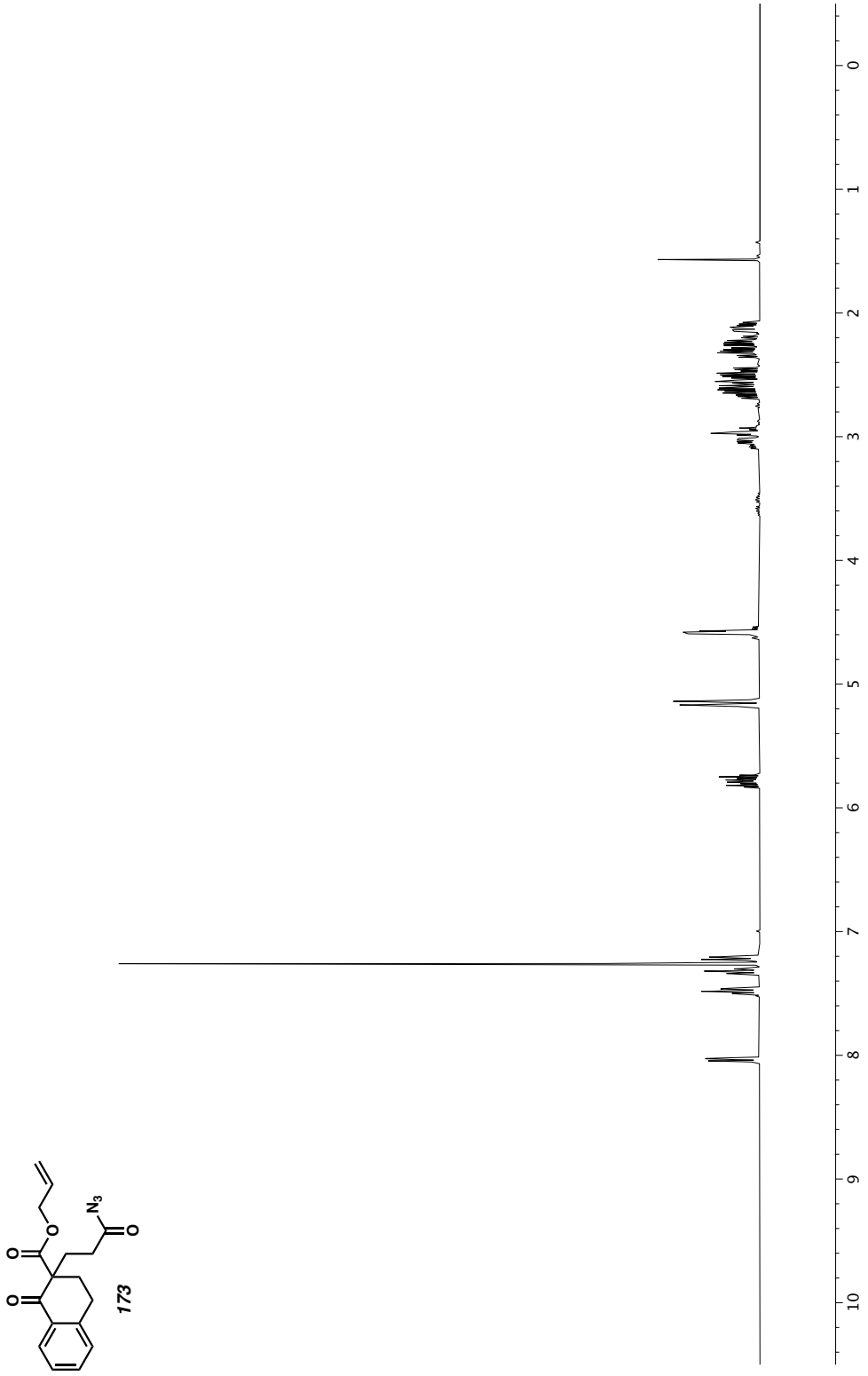

Figure A5.47 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***173****.*

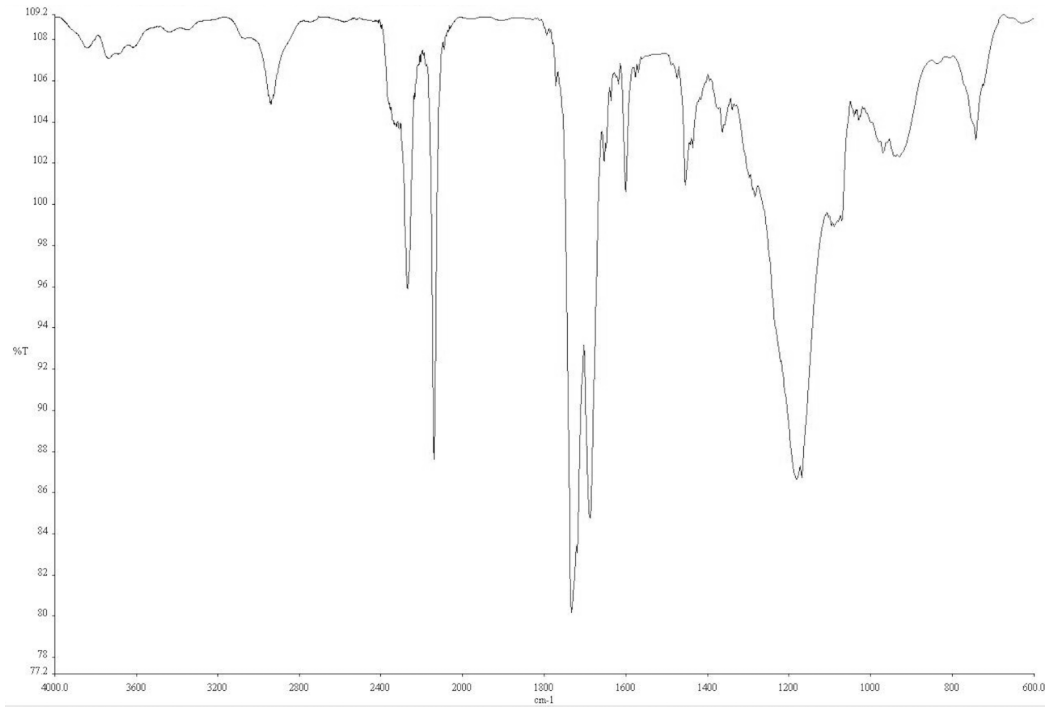

Figure A5.48 *Infrared spectrum (Thin Film, NaCl) of compound* ***173***.

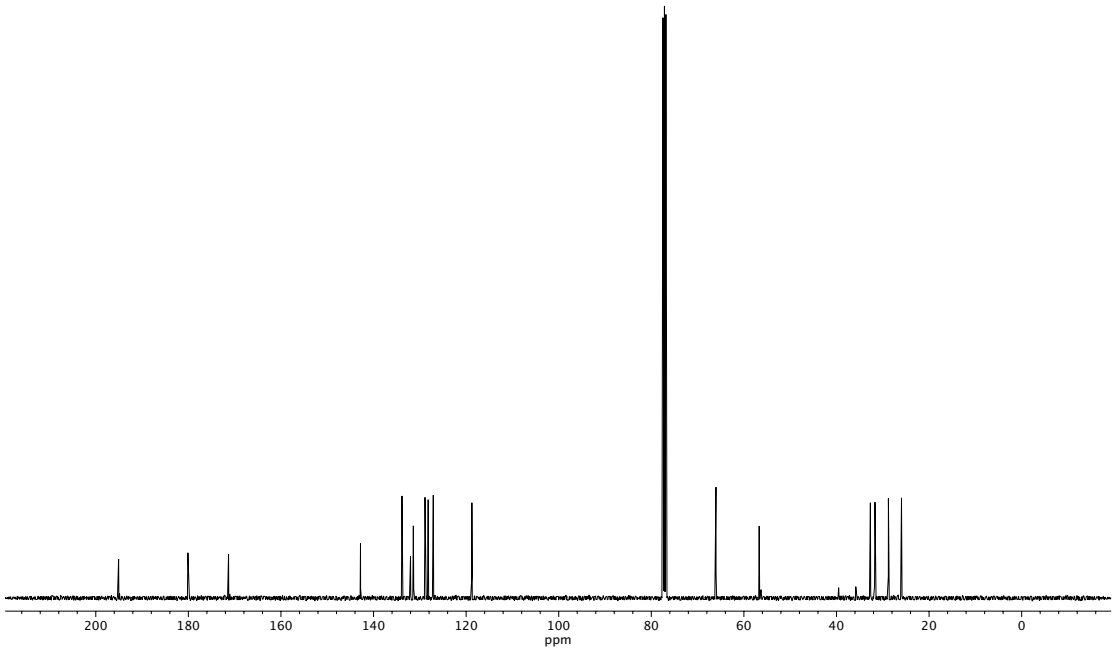

Figure A5.49 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***173***.

Figure A5.50 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***172****.*

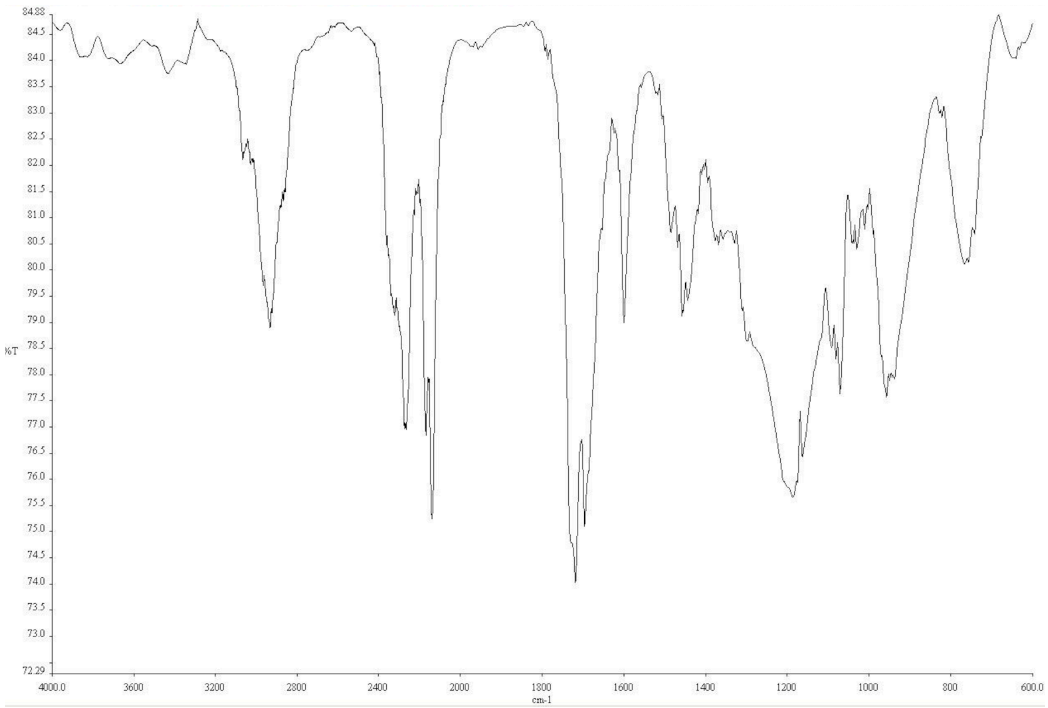

Figure A5.51 *Infrared spectrum (Thin Film, NaCl) of compound* ***172****.*

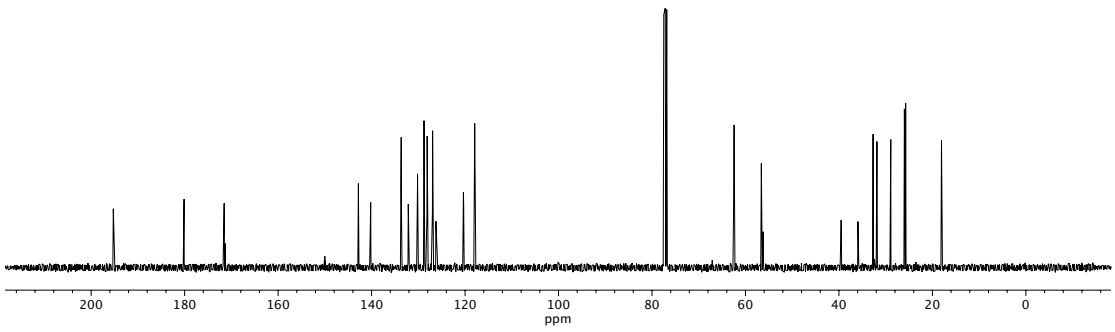

Figure A5.52 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***172****.*

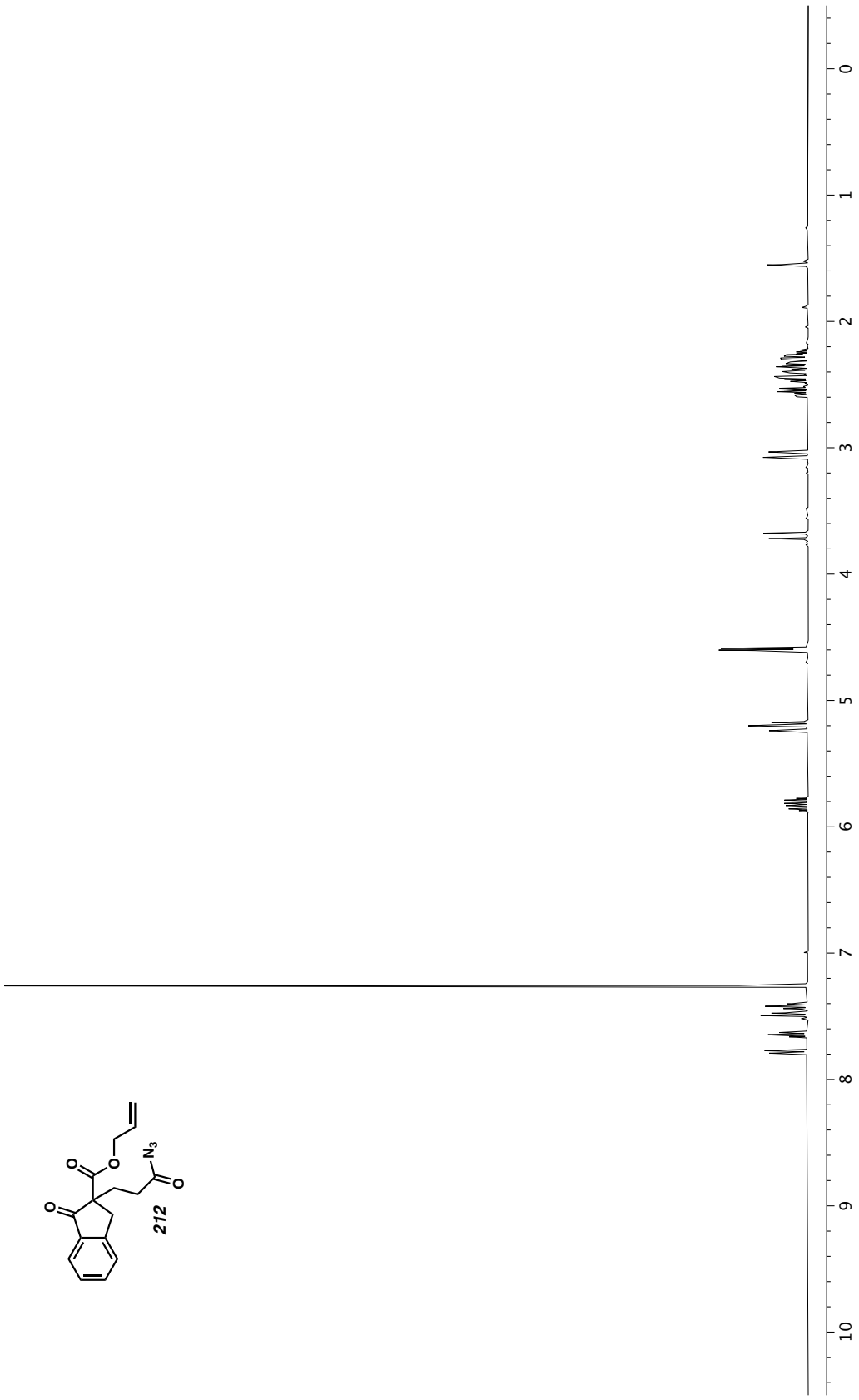

Figure A5.53 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***212****.*

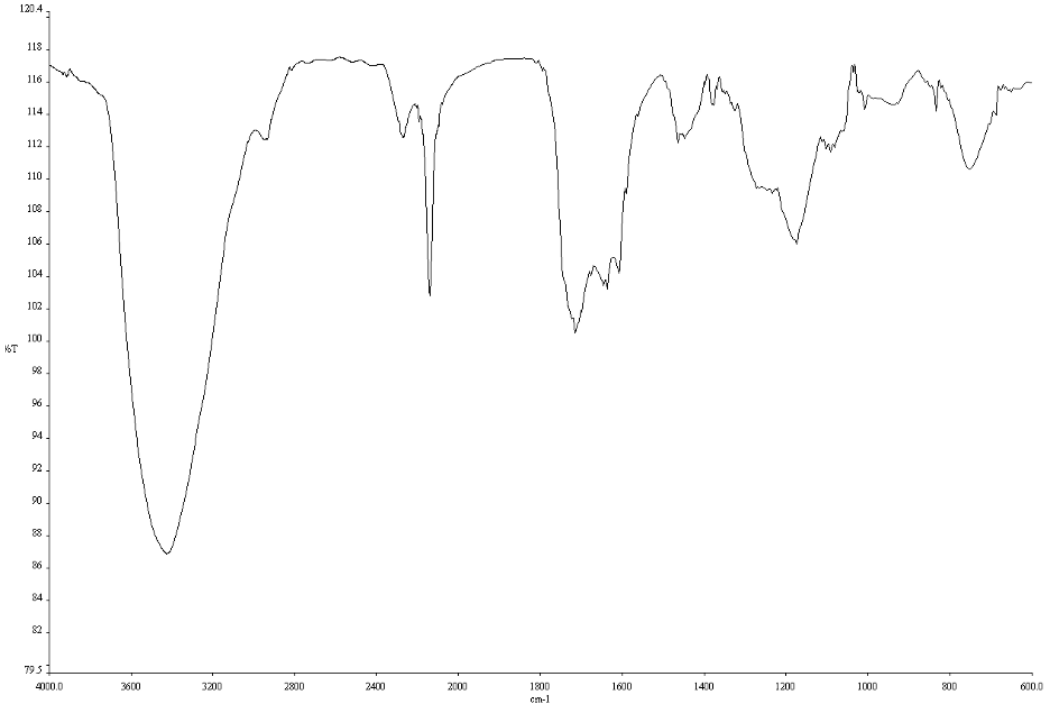

Figure A5.54 *Infrared spectrum (Thin Film, NaCl) of compound* ***212****.*

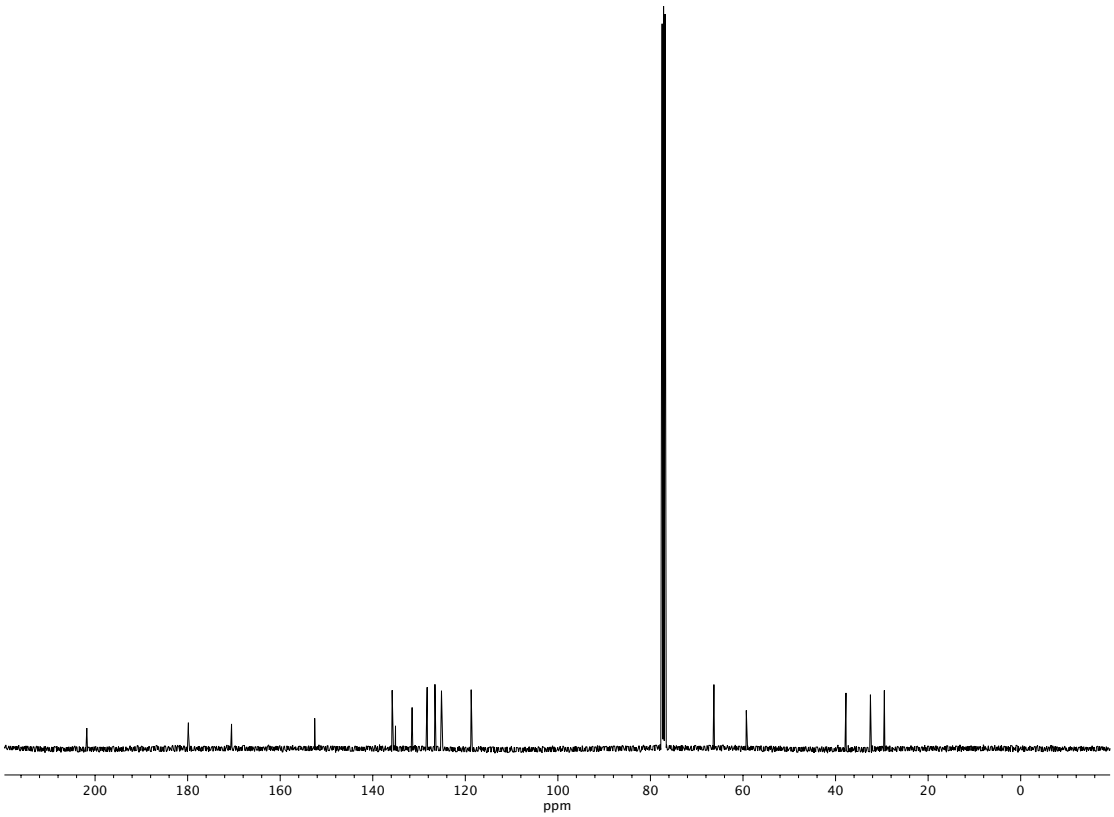

Figure A5.55 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***212****.*

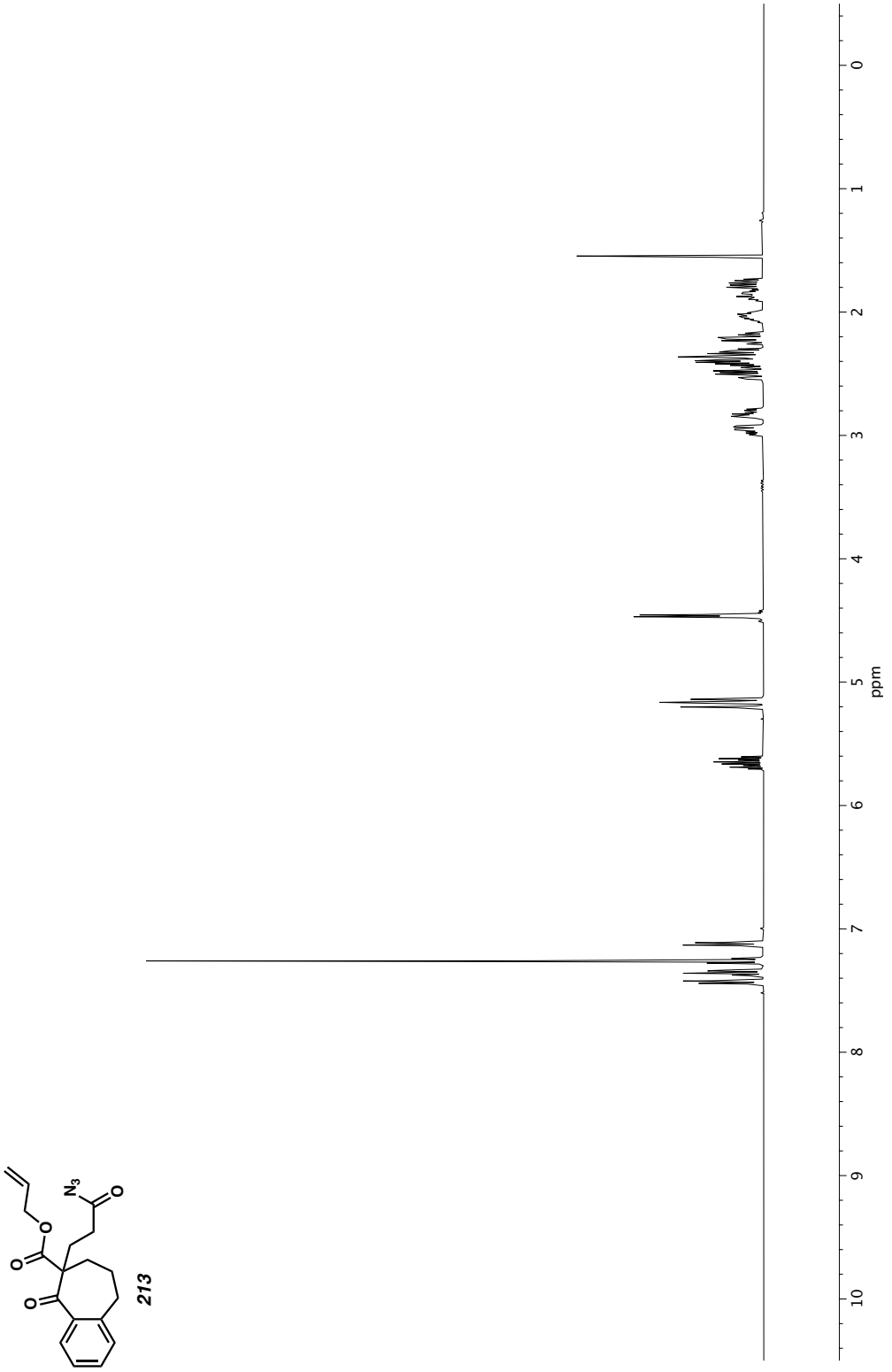

Figure A5.56 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***213***.

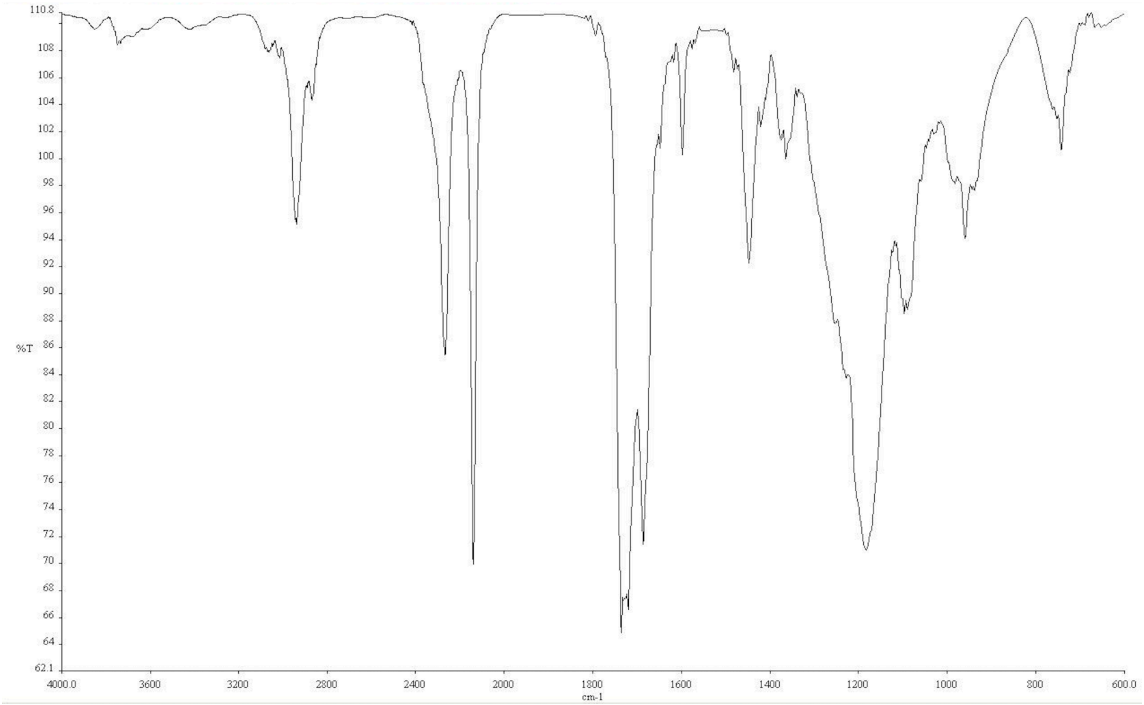

Figure A5.57 *Infrared spectrum (Thin Film, NaCl) of compound* ***213***.

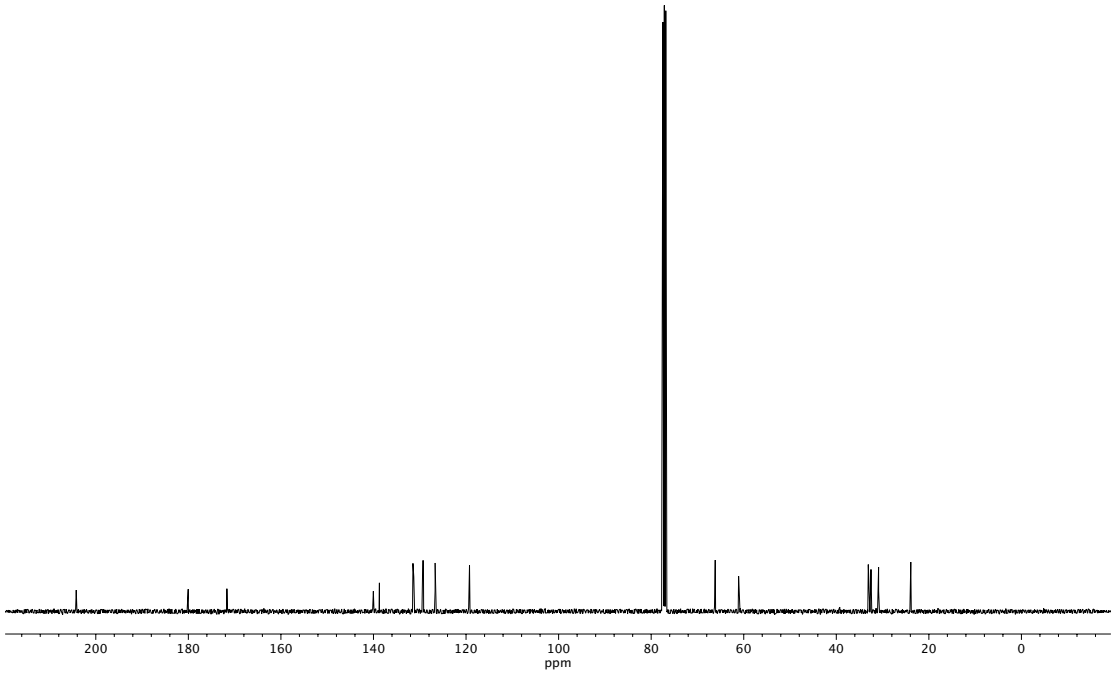

Figure A5.58 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***213***.

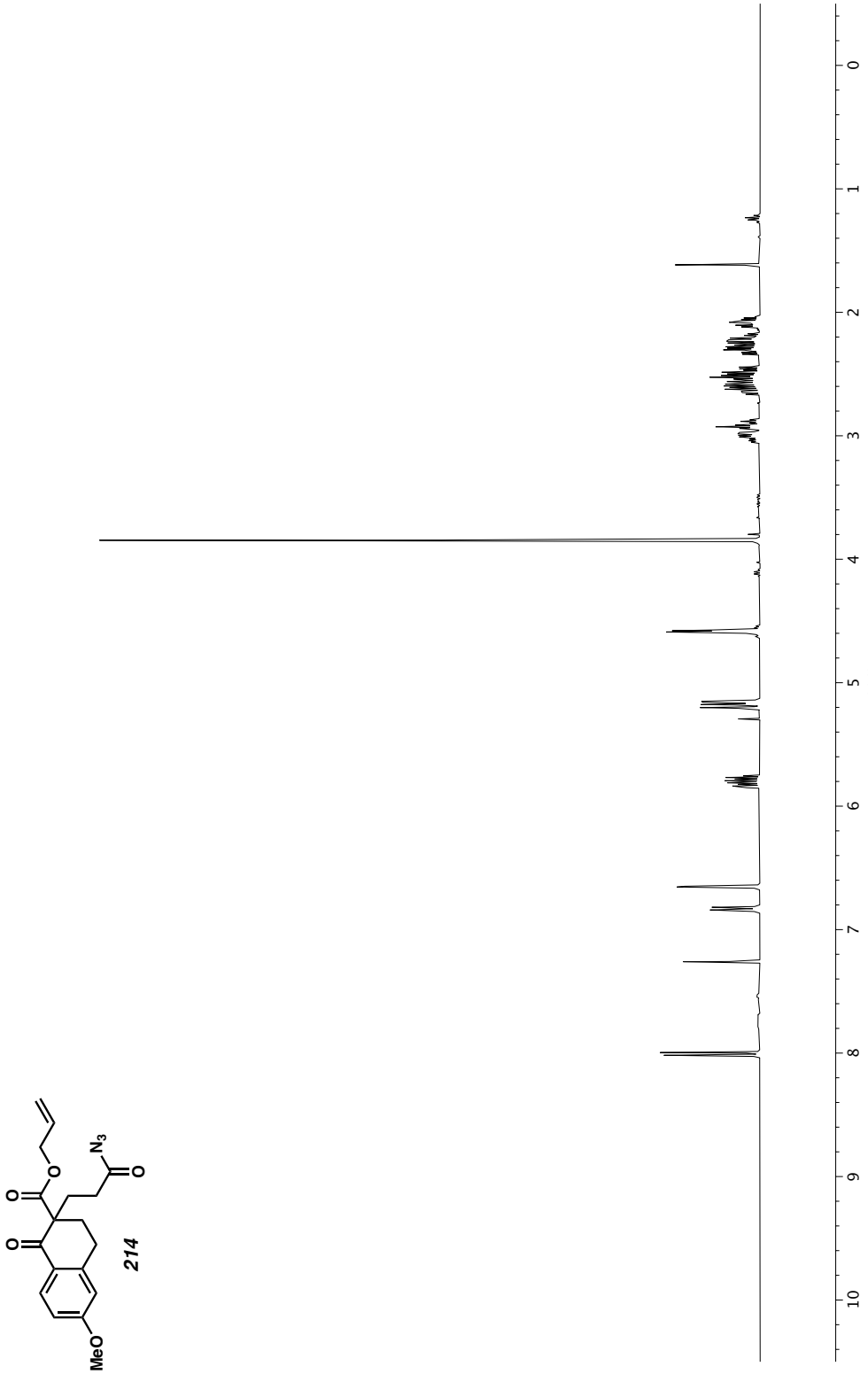

Figure A5.59 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***214****.*

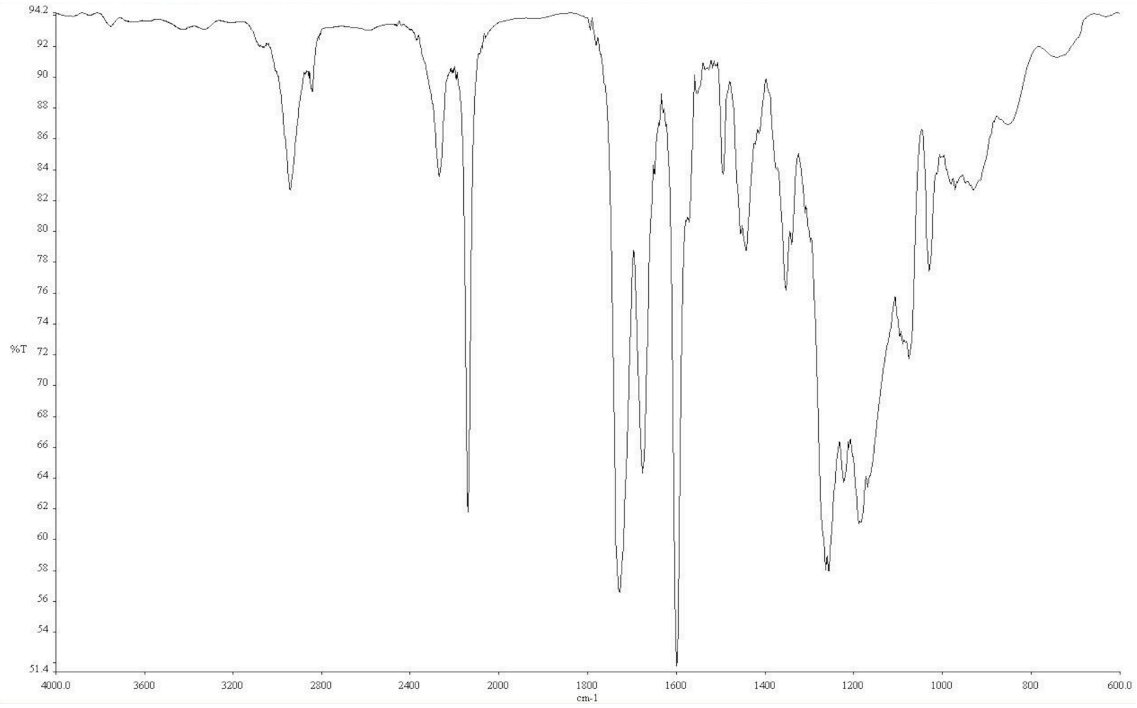

Figure A5.60 *Infrared spectrum (Thin Film, NaCl) of compound* ***214****.*

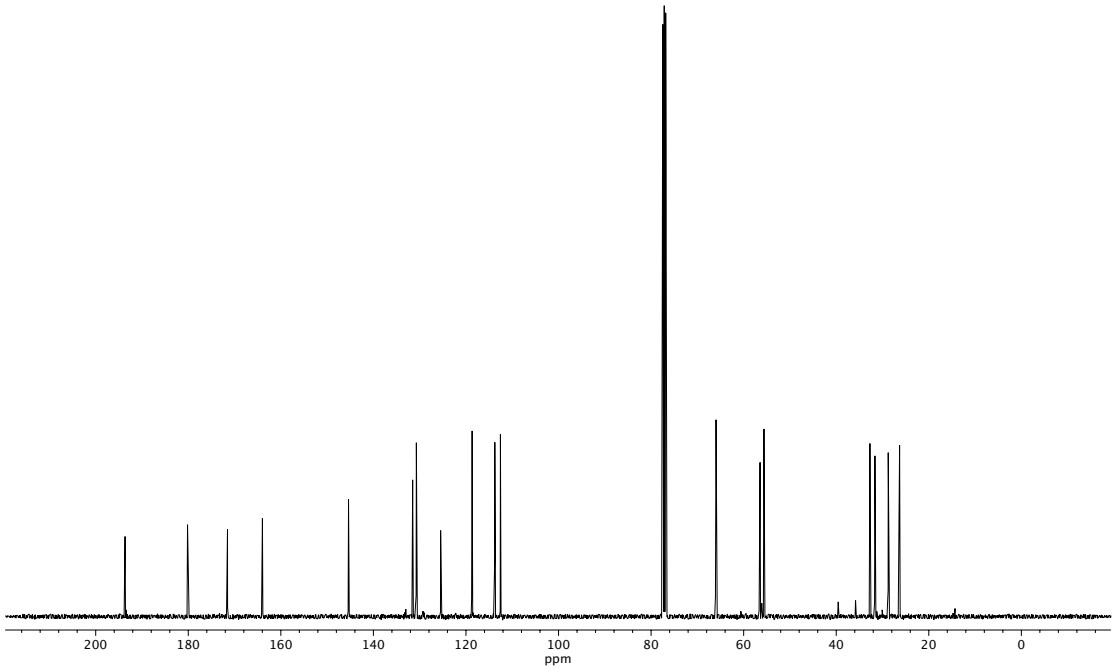

Figure A5.61 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***214****.*

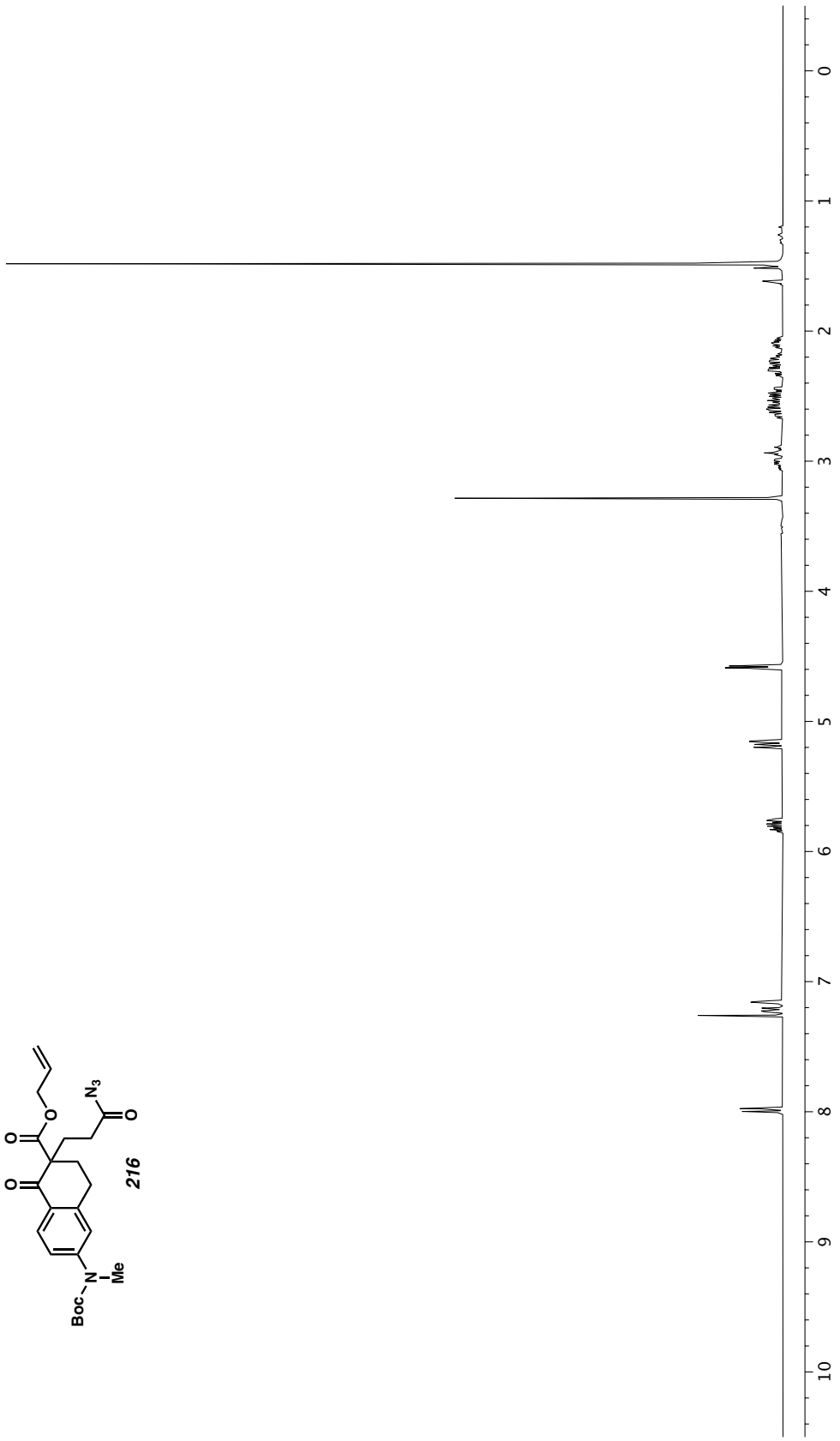

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Figure A5.62 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***216***.

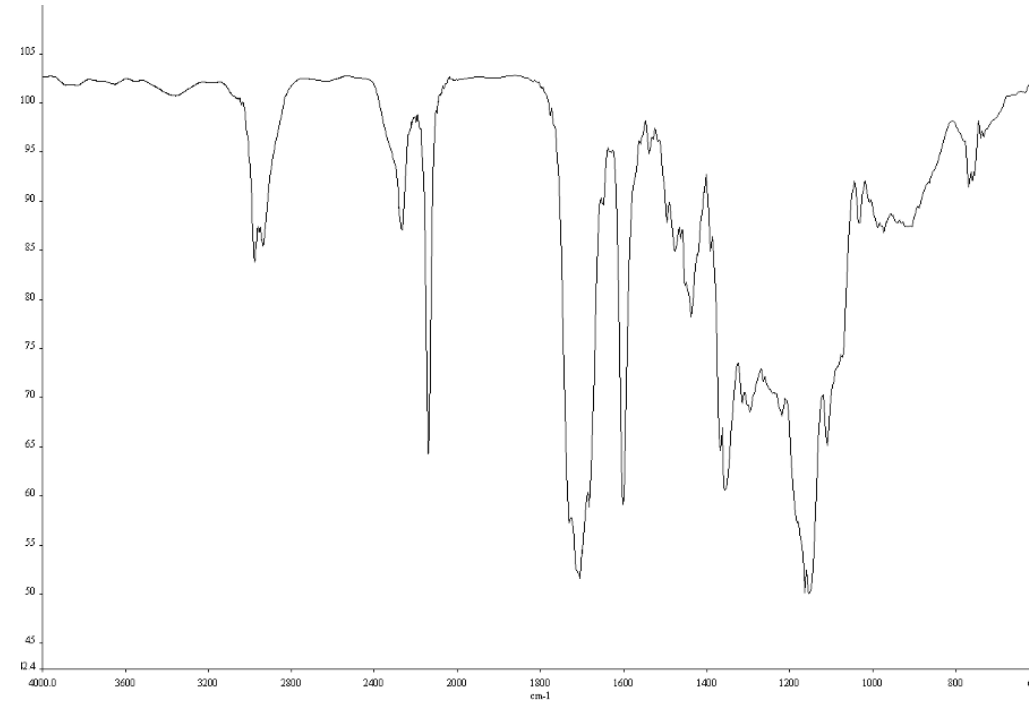

Figure A5.63 *Infrared spectrum (Thin Film, NaCl) of compound* ***216***.

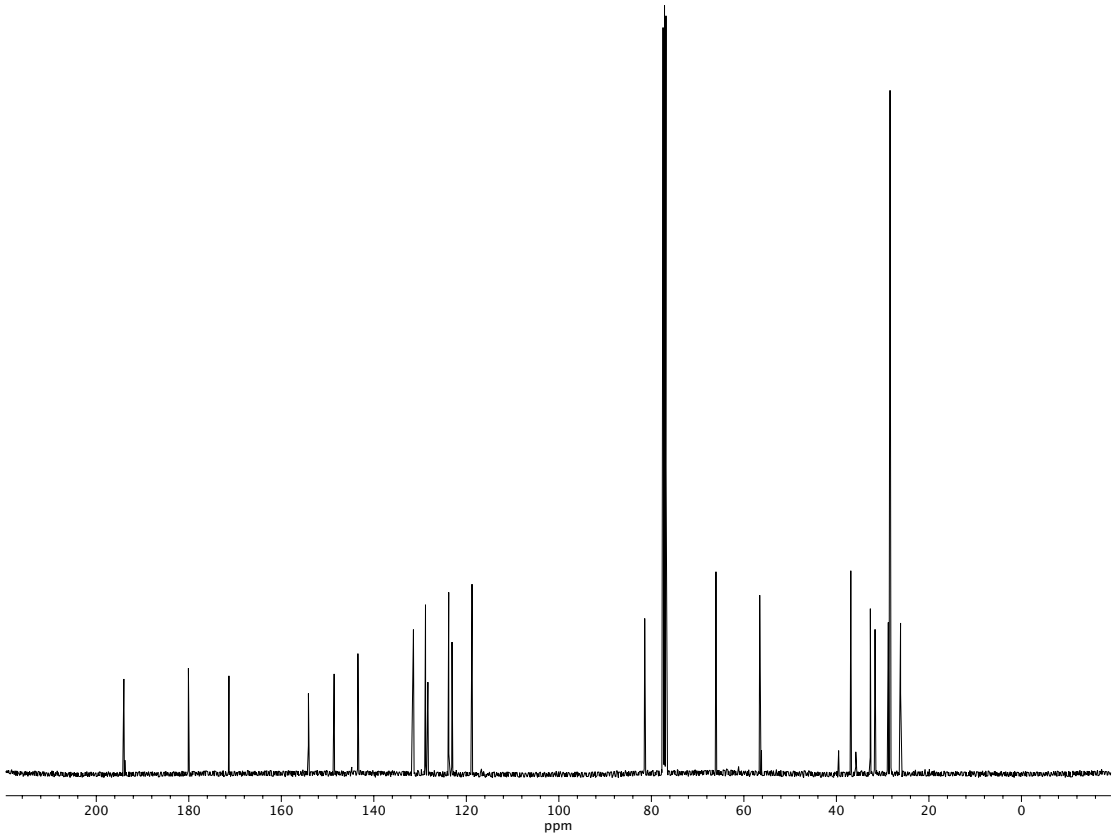

Figure A5.64 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***216***.

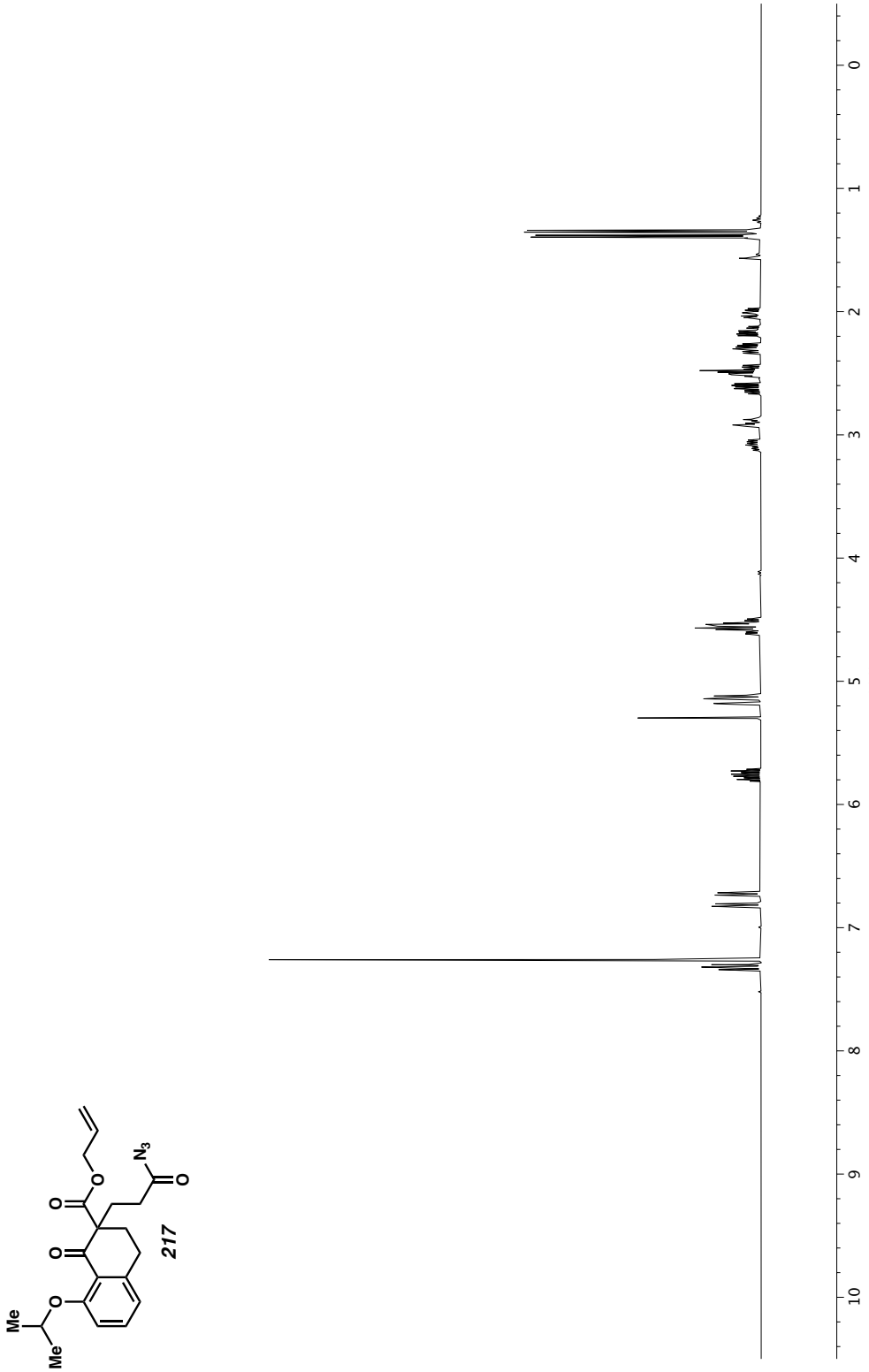

Figure A5.65 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***217****.*

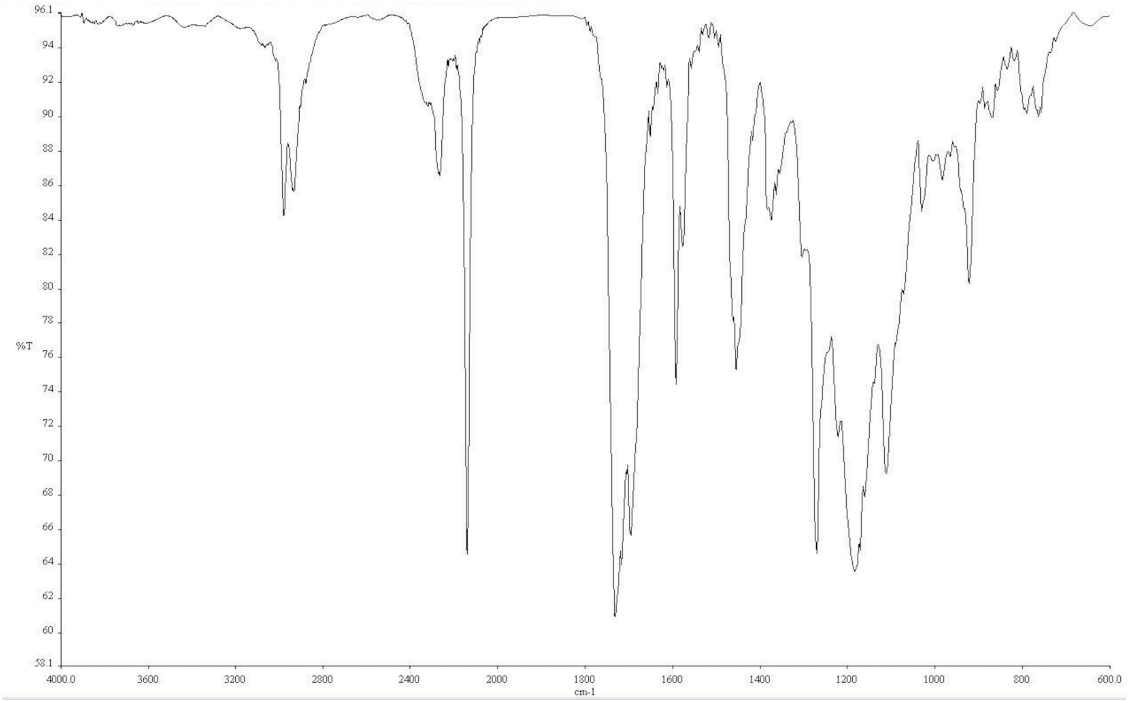

Figure A5.66 *Infrared spectrum (Thin Film, NaCl) of compound* ***217****.*

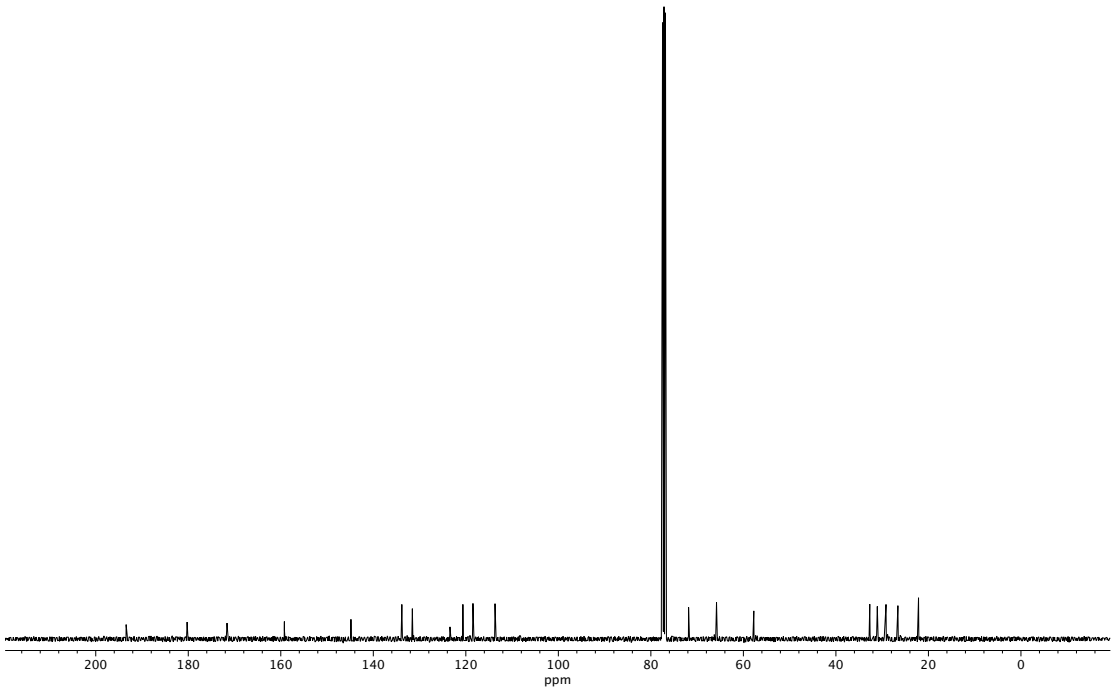

Figure A5.67 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***217****.*

Figure A5.68 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***218****.*

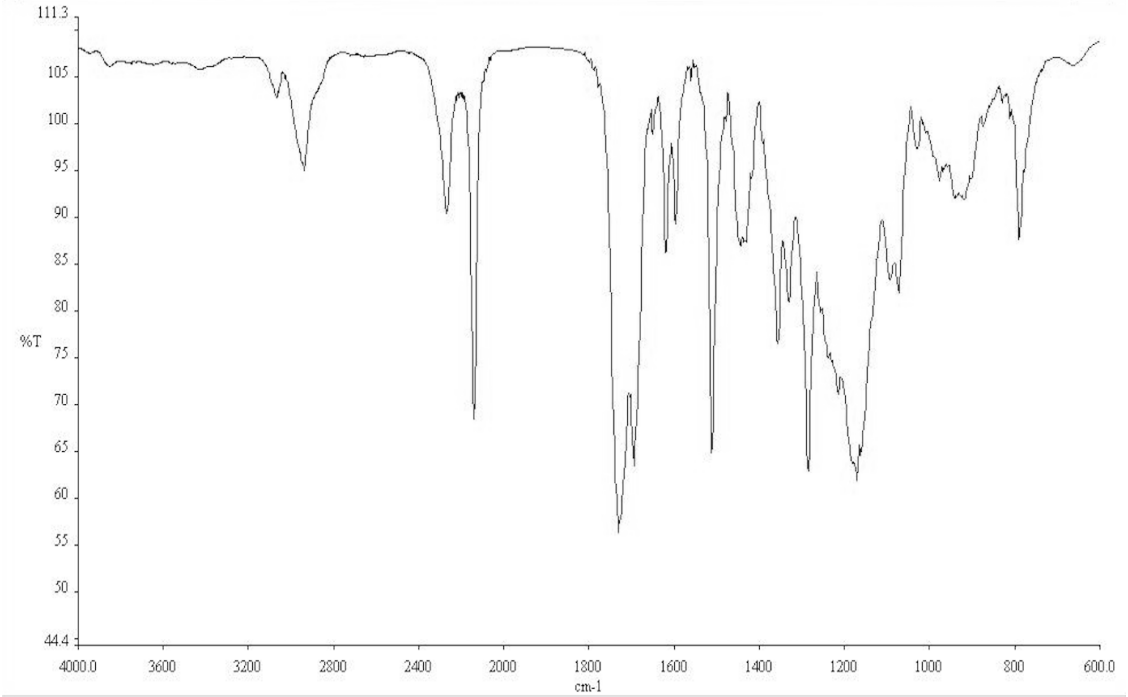

Figure A5.69 *Infrared spectrum (Thin Film, NaCl) of compound* ***218****.*

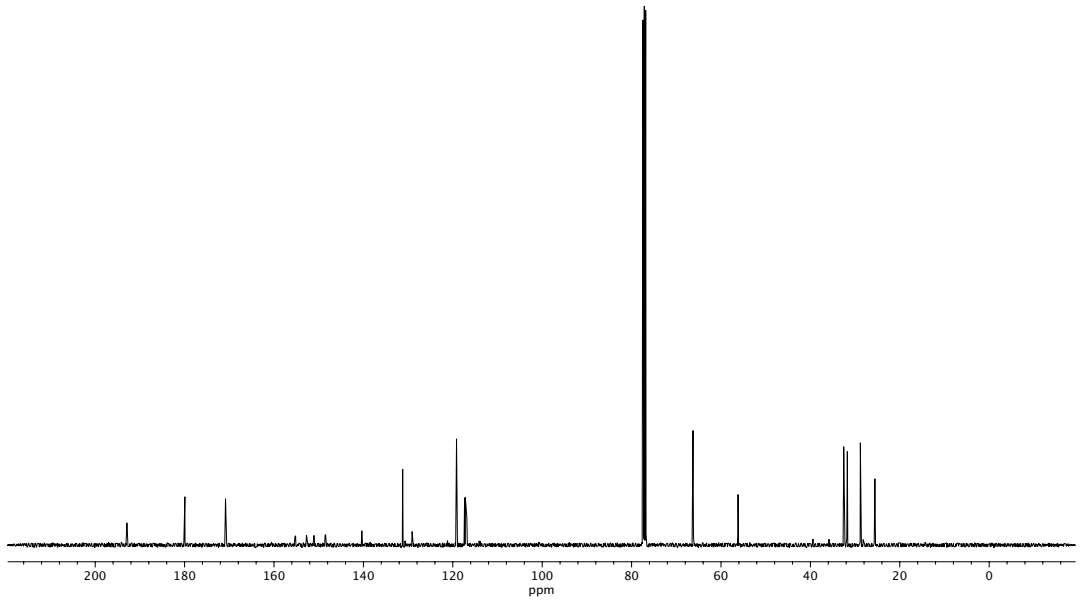

Figure A5.70 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***218****.*

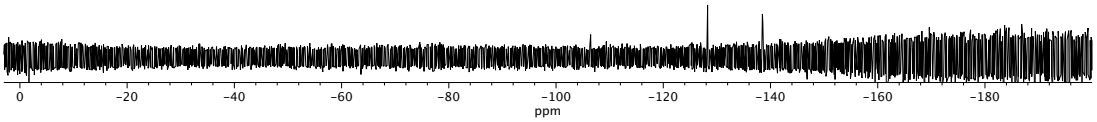

Figure A5.71 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***218***.

Figure A5.72 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***219***.

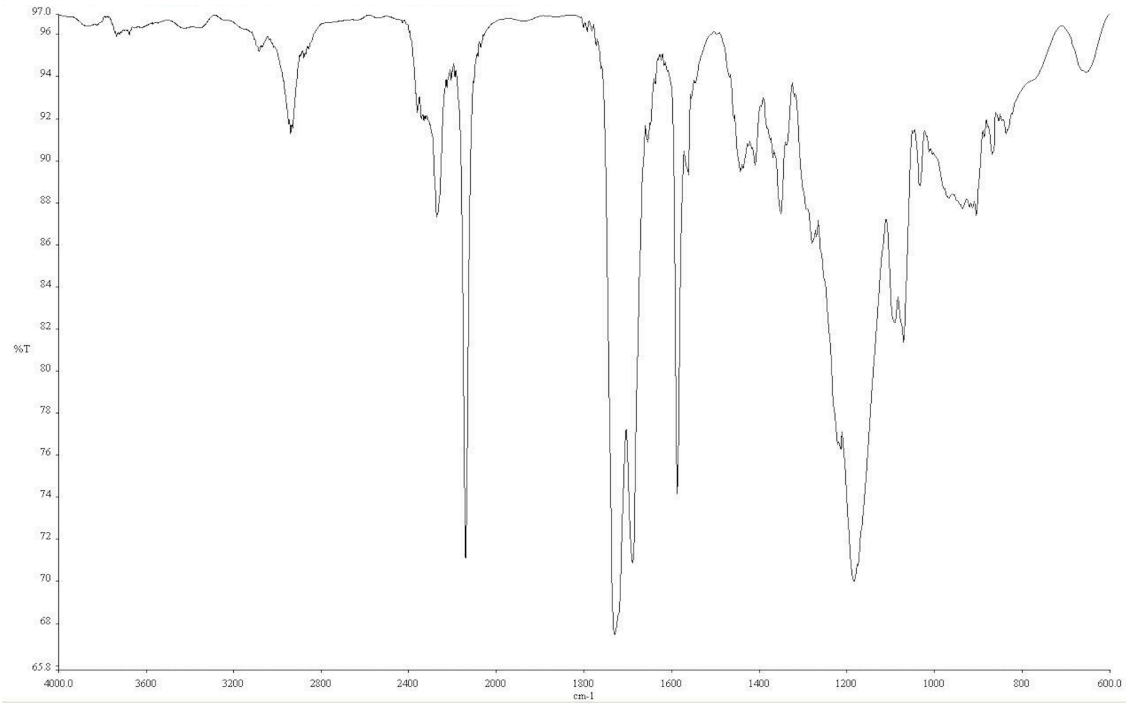

Figure A5.73 *Infrared spectrum (Thin Film, NaCl) of compound* ***219***.

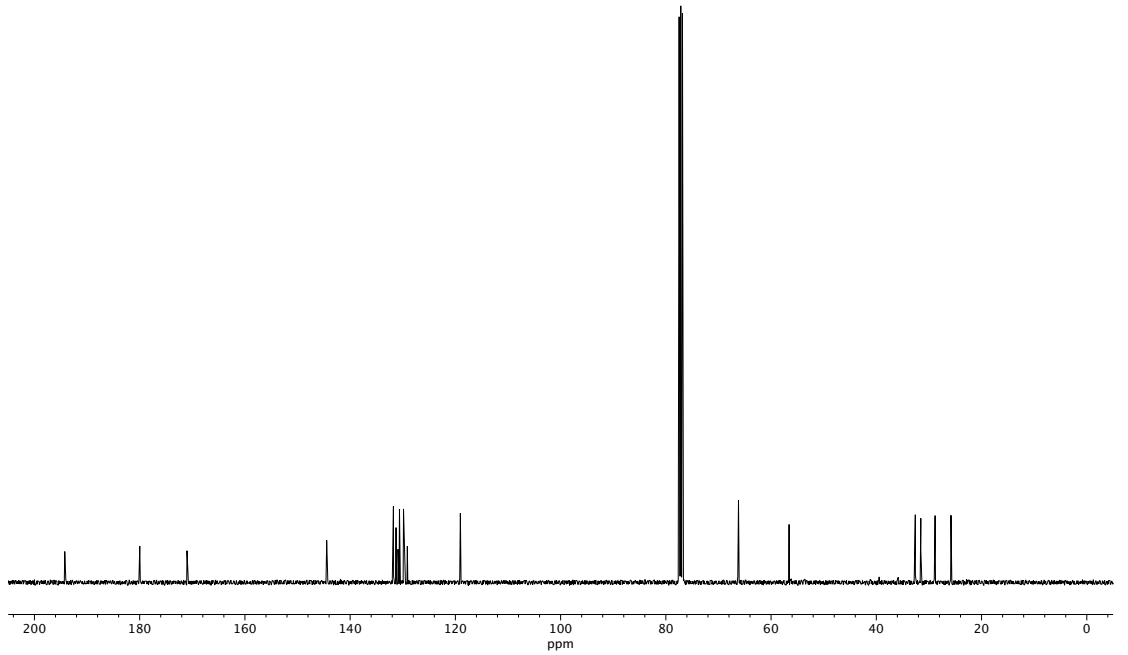

Figure A5.74 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***219***.

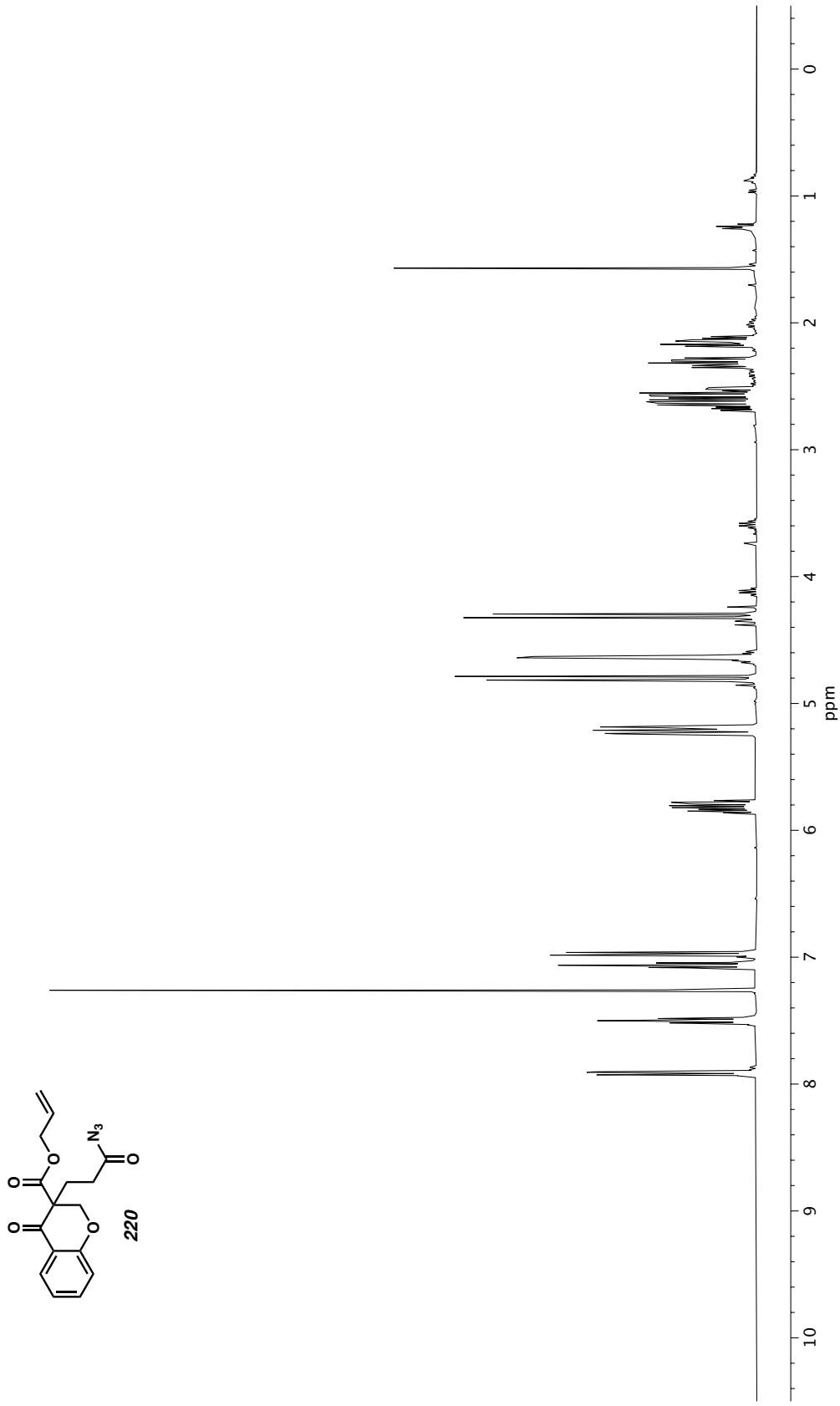

Figure A5.75 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***220***.

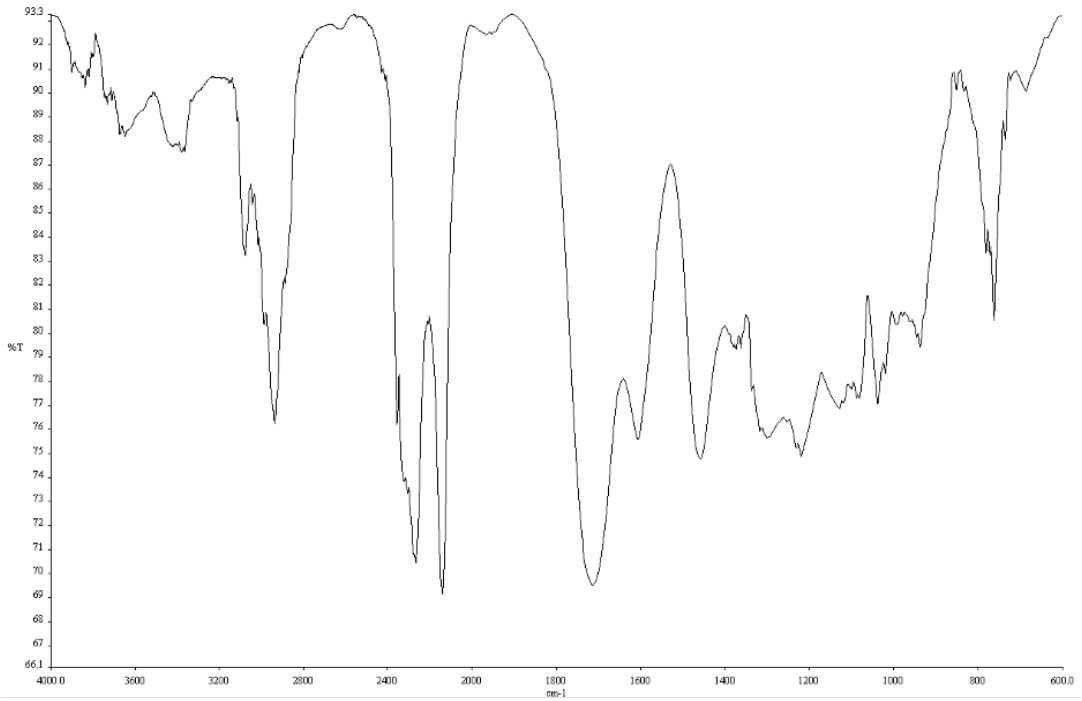

Figure A5.76 *Infrared spectrum (Thin Film, NaCl) of compound* ***220****.*

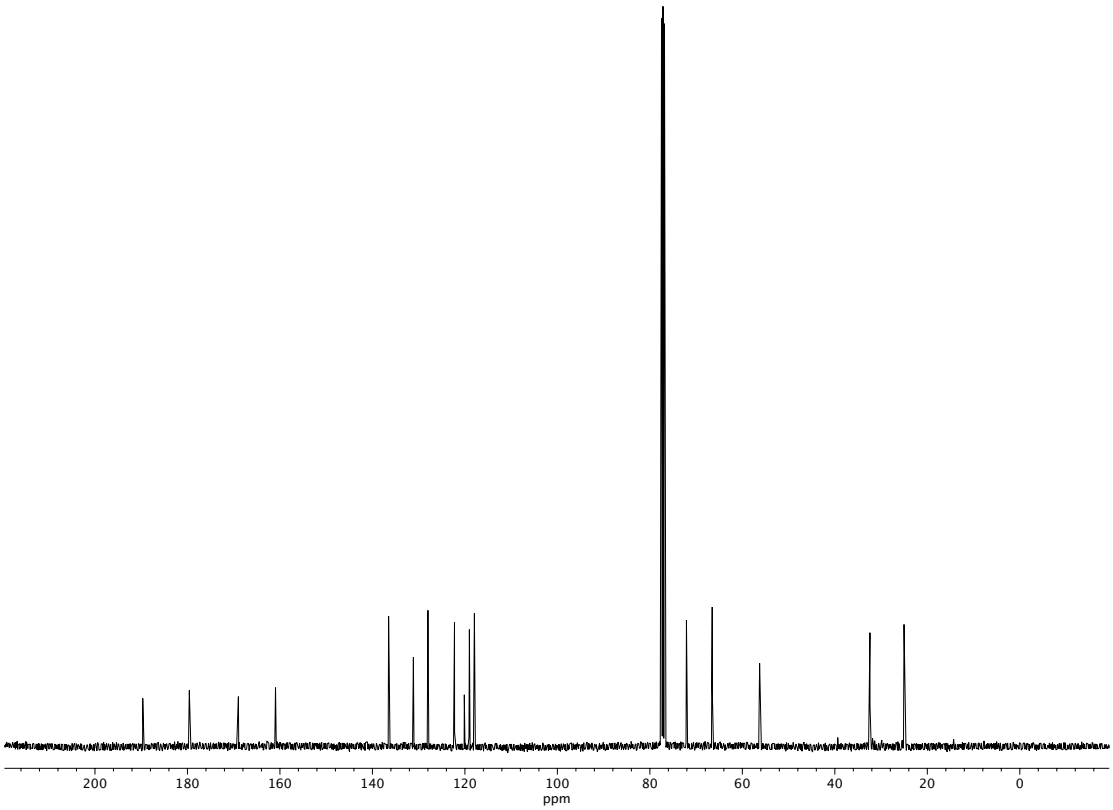

Figure A5.77 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***220****.*

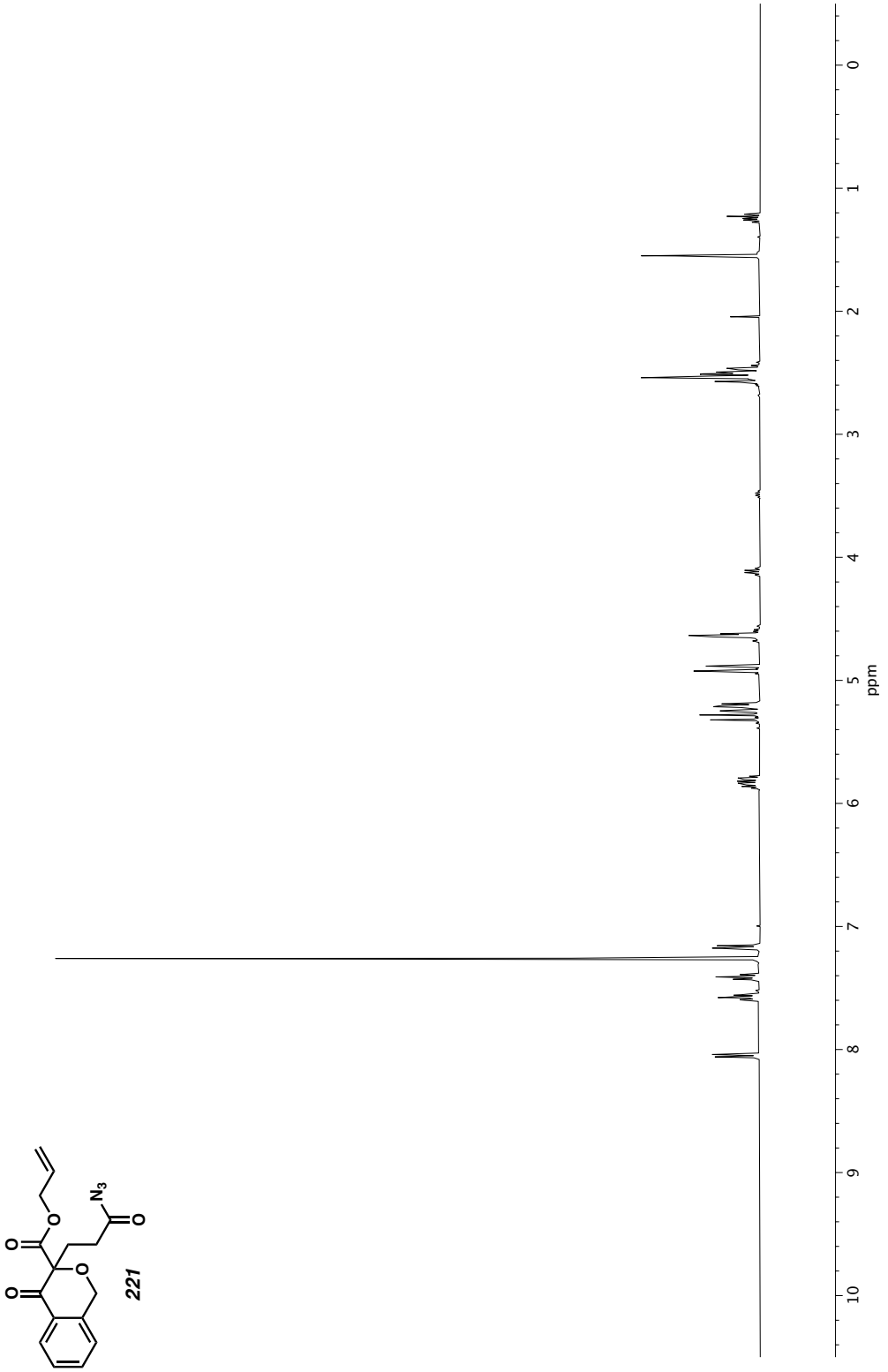

Figure A5.78 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***221****.*

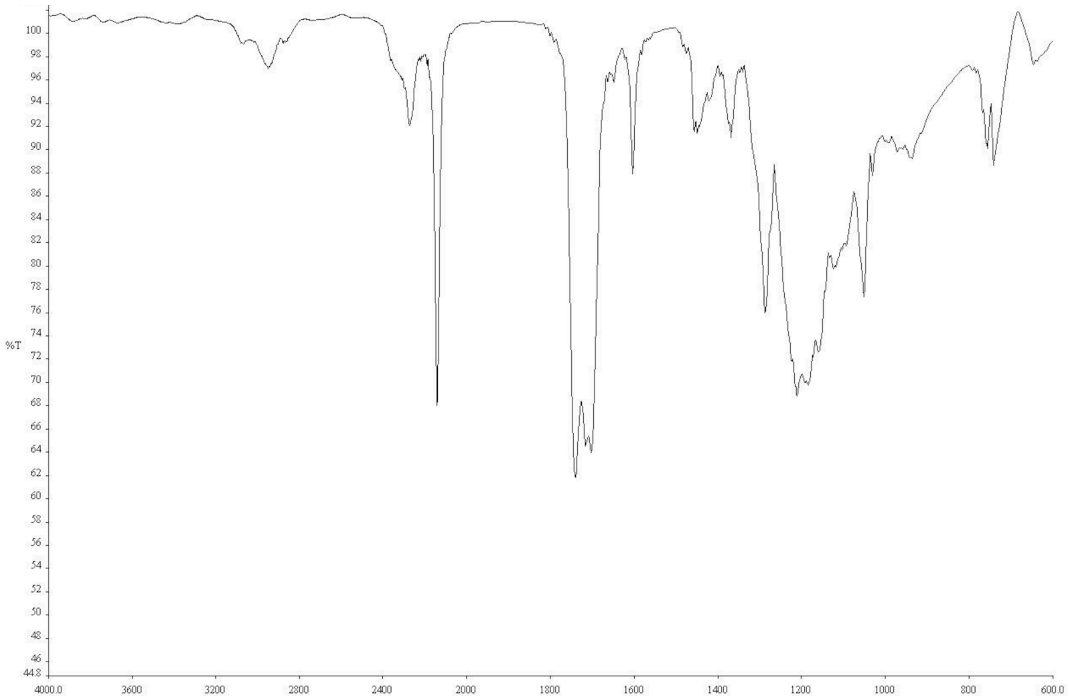

Figure A5.79 *Infrared spectrum (Thin Film, NaCl) of compound* ***221***.

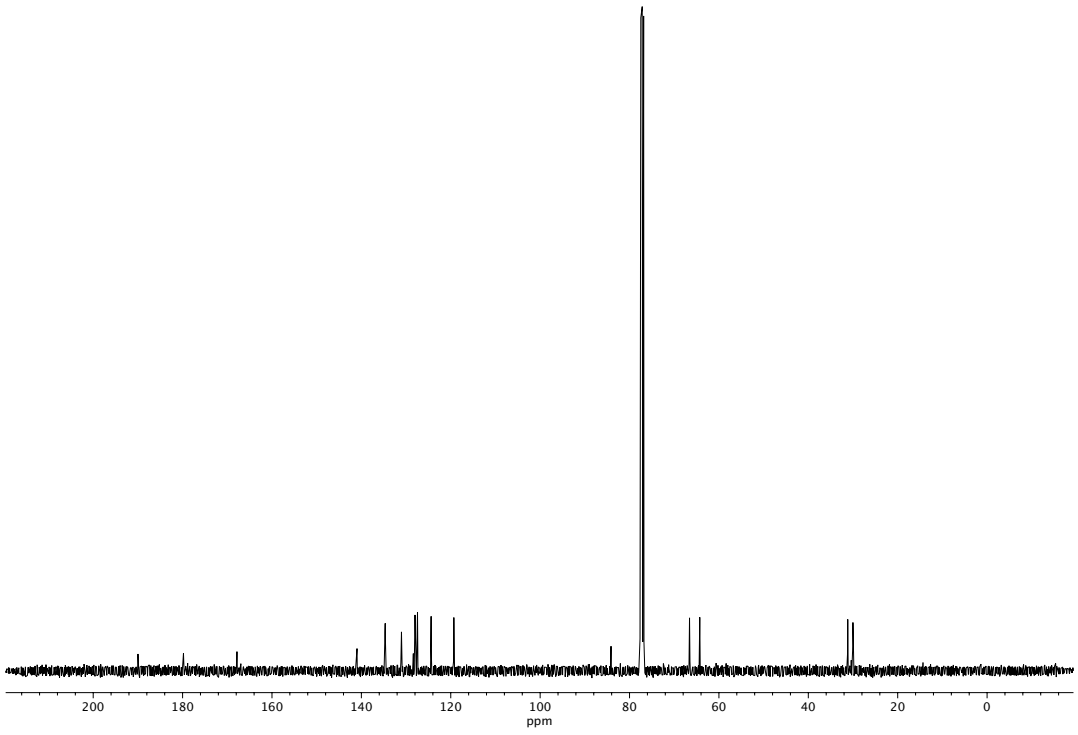

Figure A5.80 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***221***.

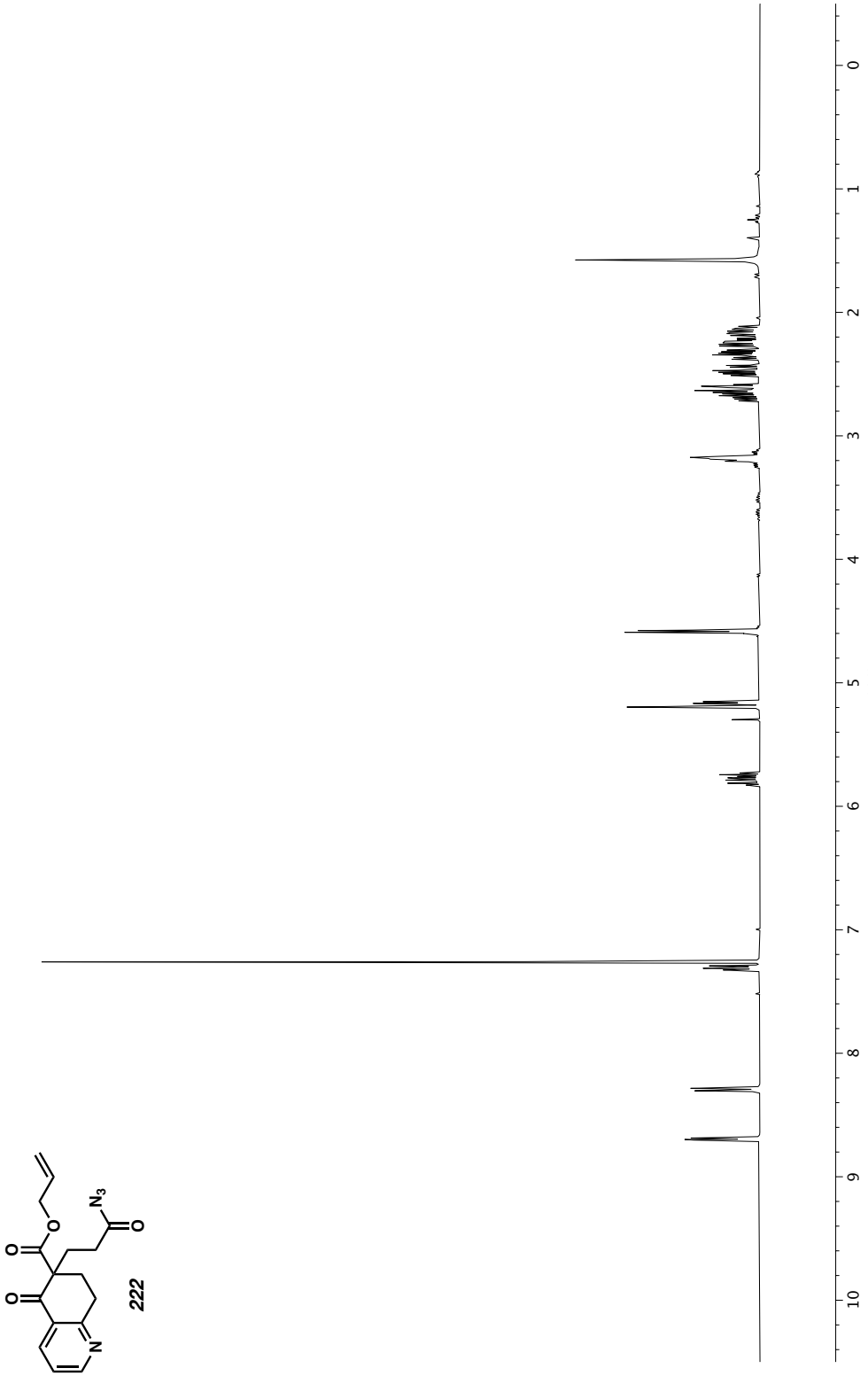

Figure A5.81 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***222***.

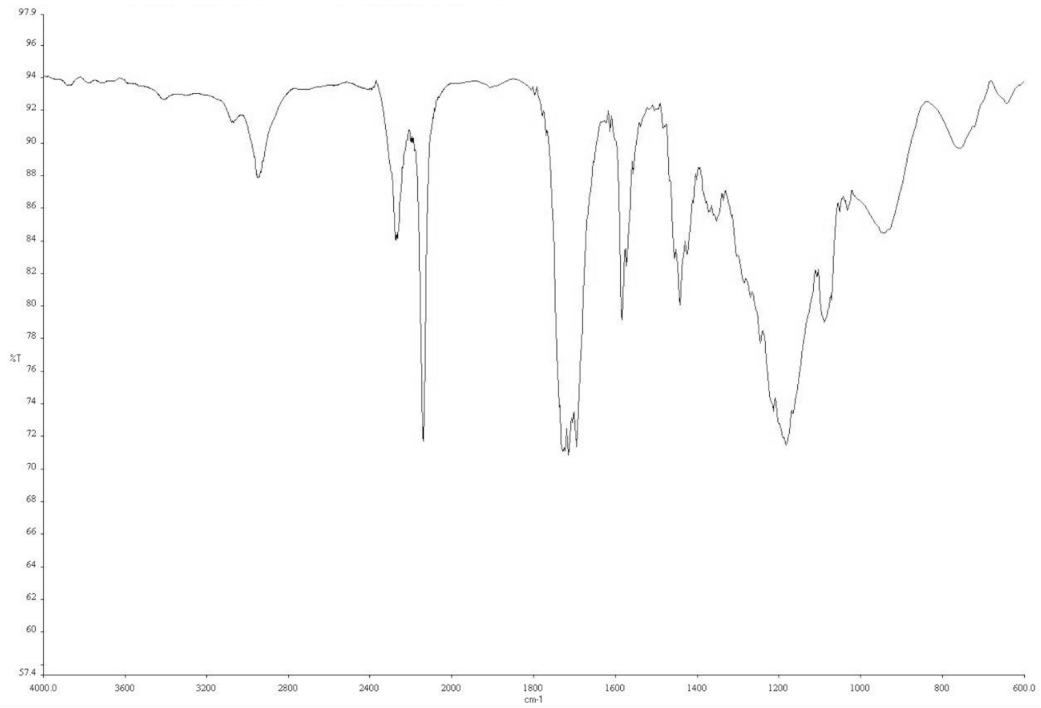

Figure A5.82 *Infrared spectrum (Thin Film, NaCl) of compound* ***222***.

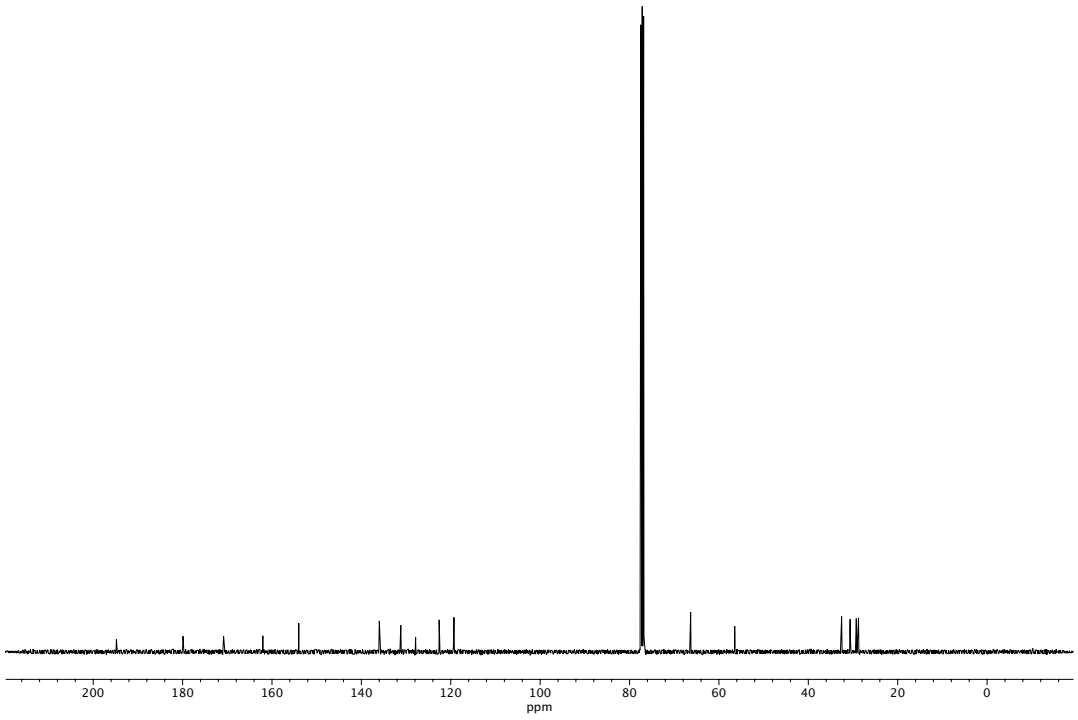

Figure A5.83 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***222***.

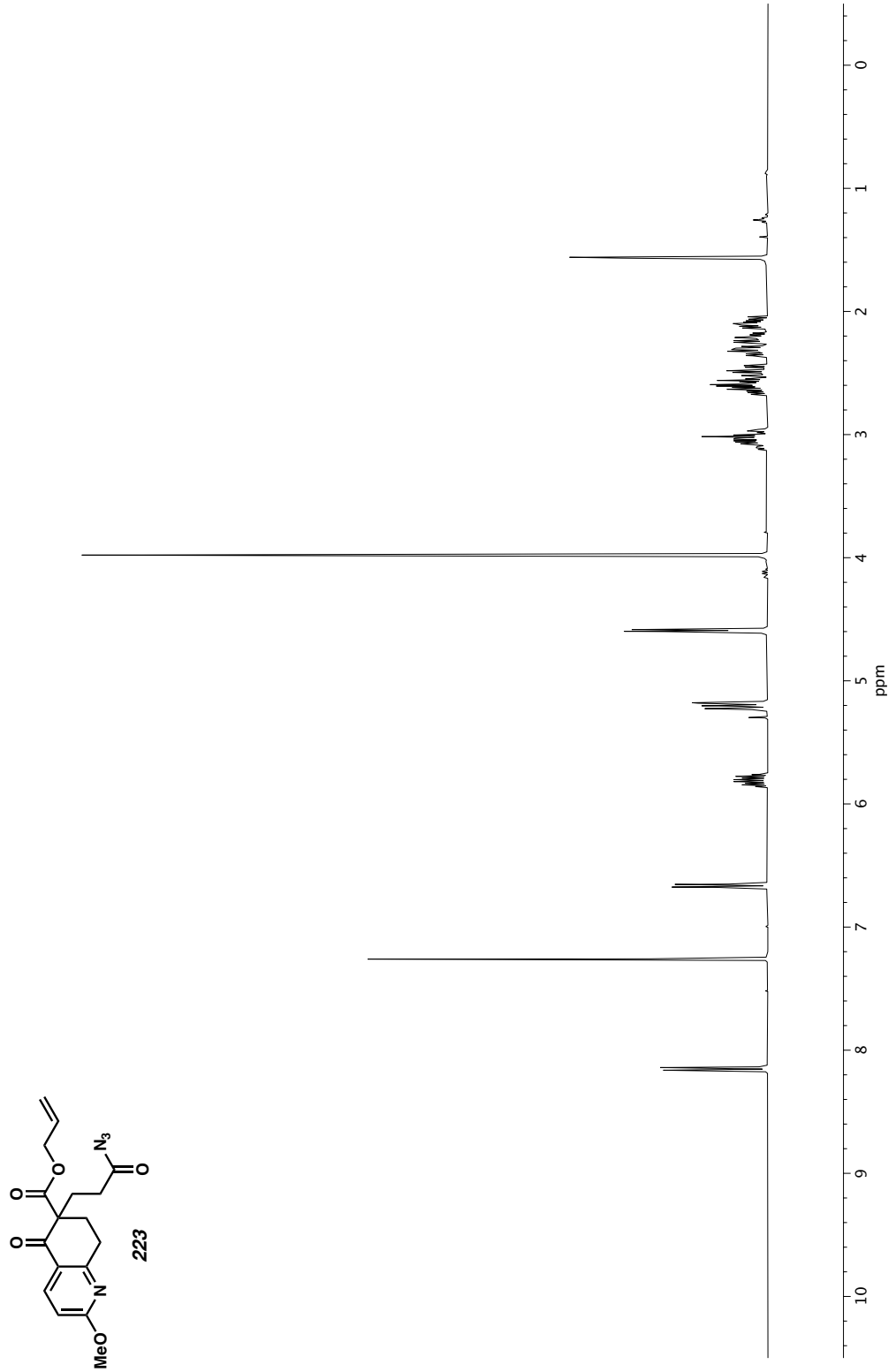

Figure A5.84 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***223****.*

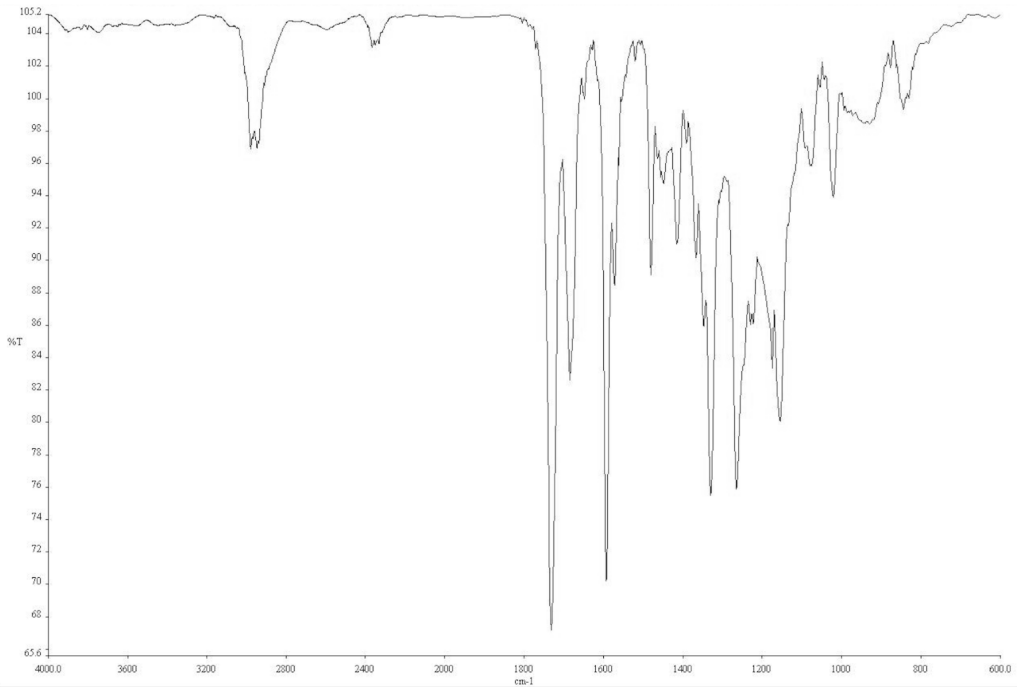

Figure A5.85 *Infrared spectrum (Thin Film, NaCl) of compound* ***223***.

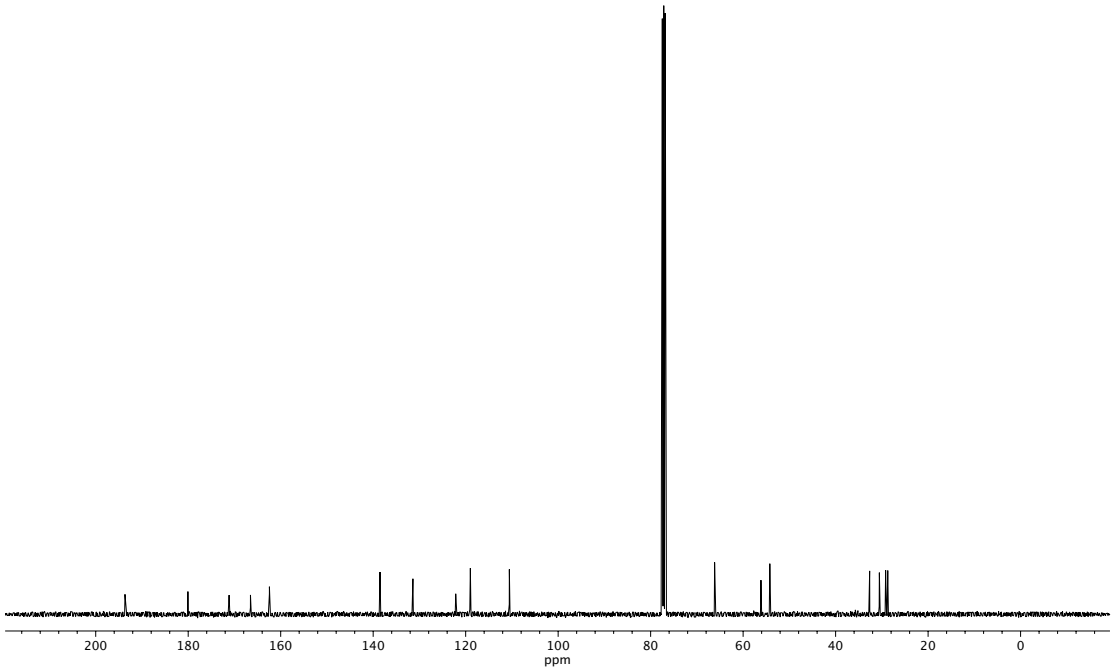

Figure A5.86 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***223***.

Figure A5.87 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***224****.*

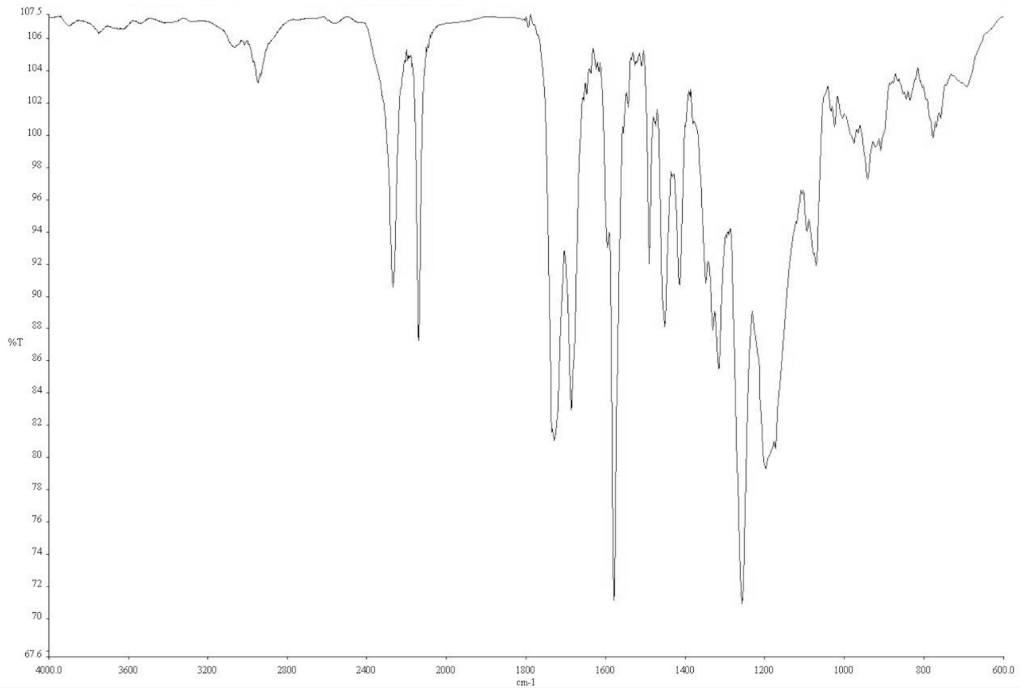

Figure A5.88 *Infrared spectrum (Thin Film, NaCl) of compound* ***224****.*

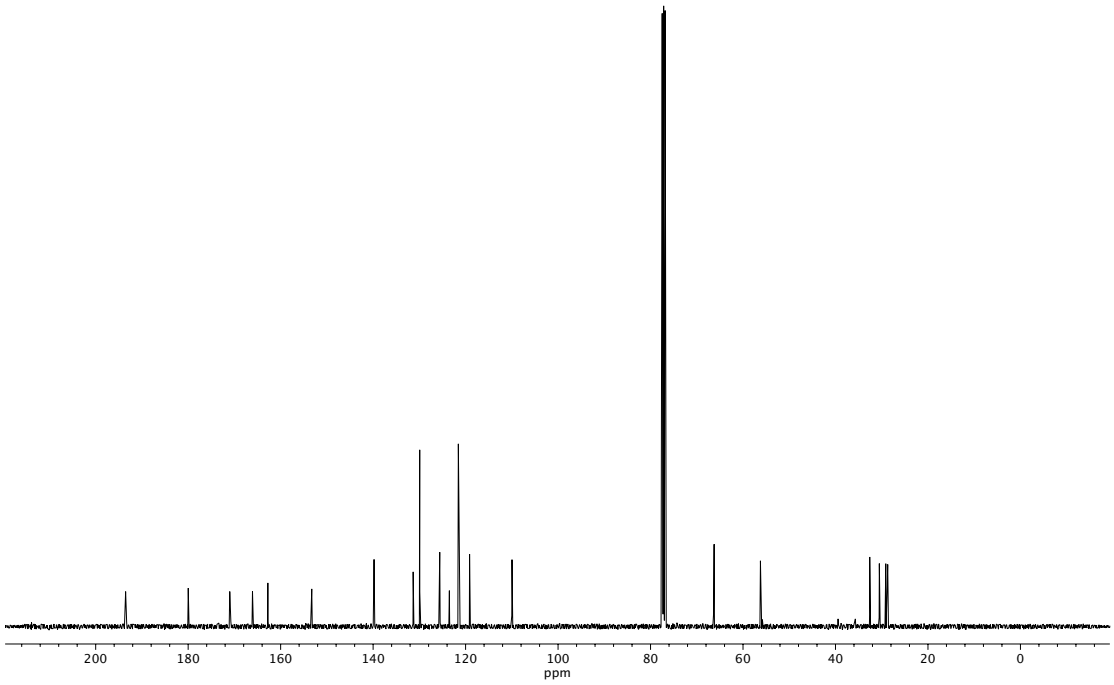

Figure A5.89 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***224****.*

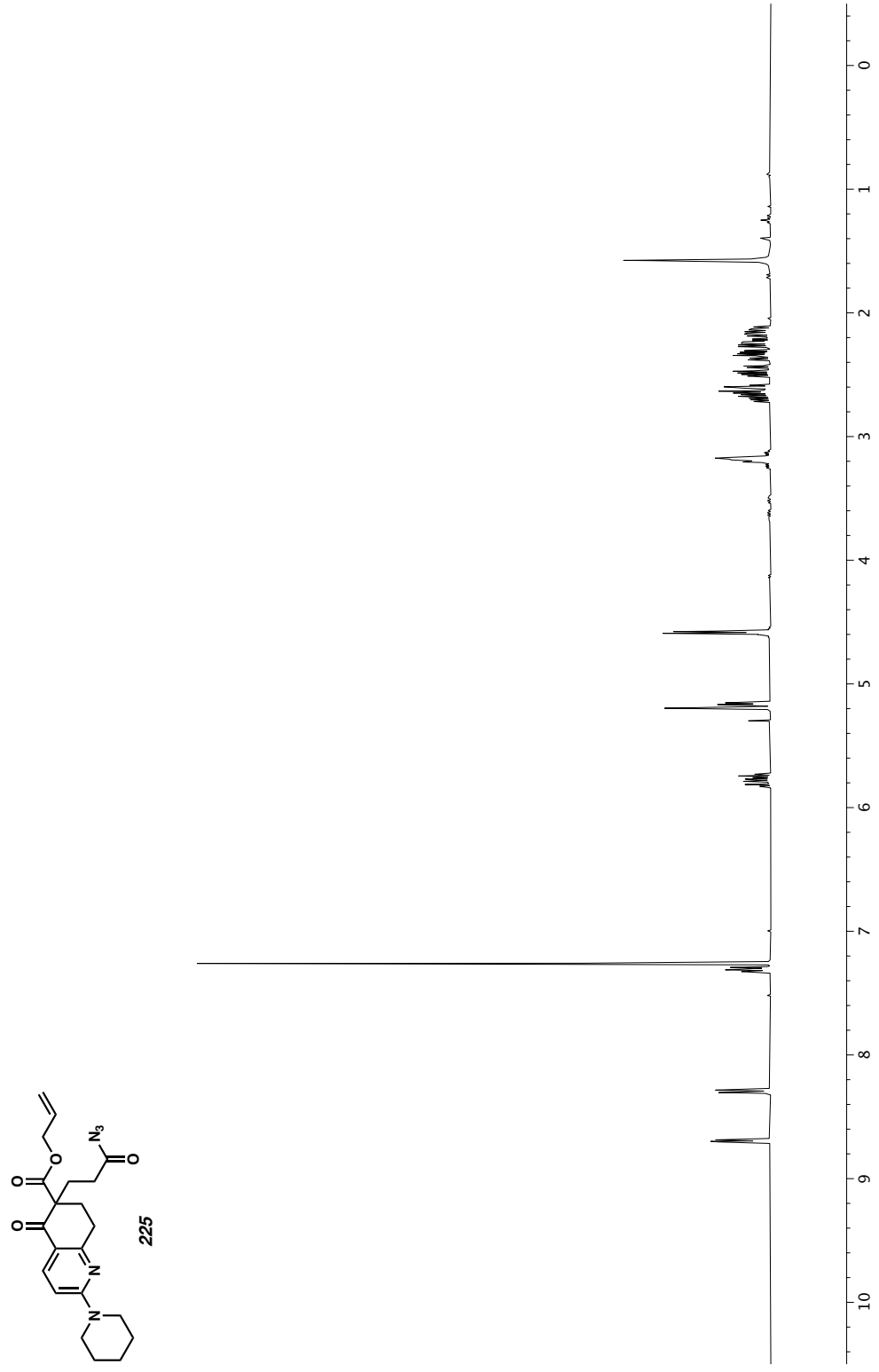

Figure A5.90 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***225****.*

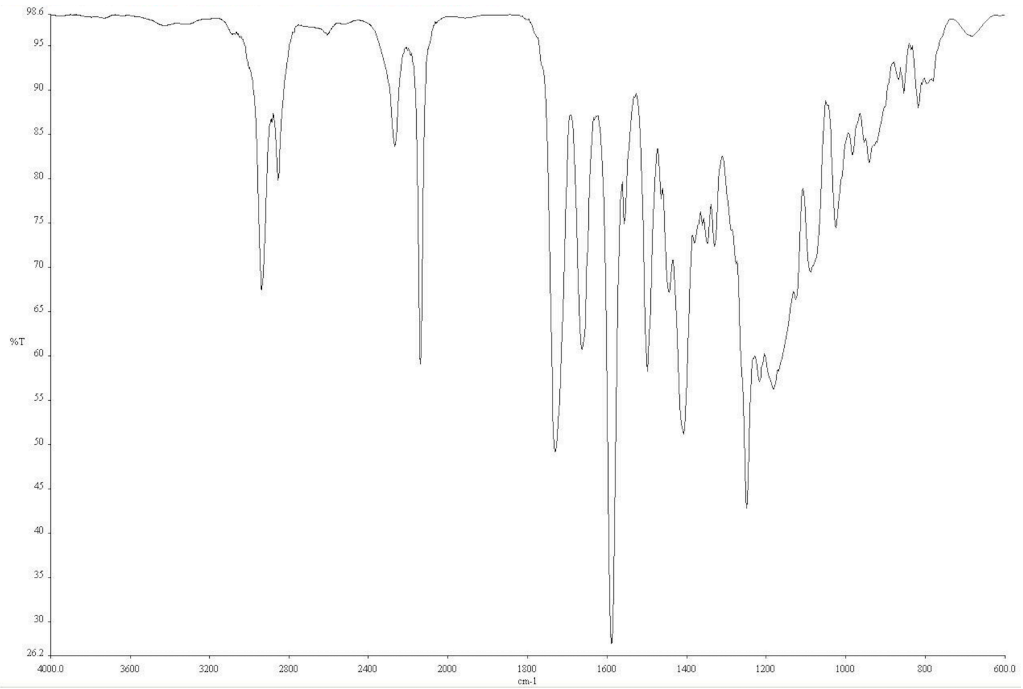

Figure A5.91 *Infrared spectrum (Thin Film, NaCl) of compound* ***225***.

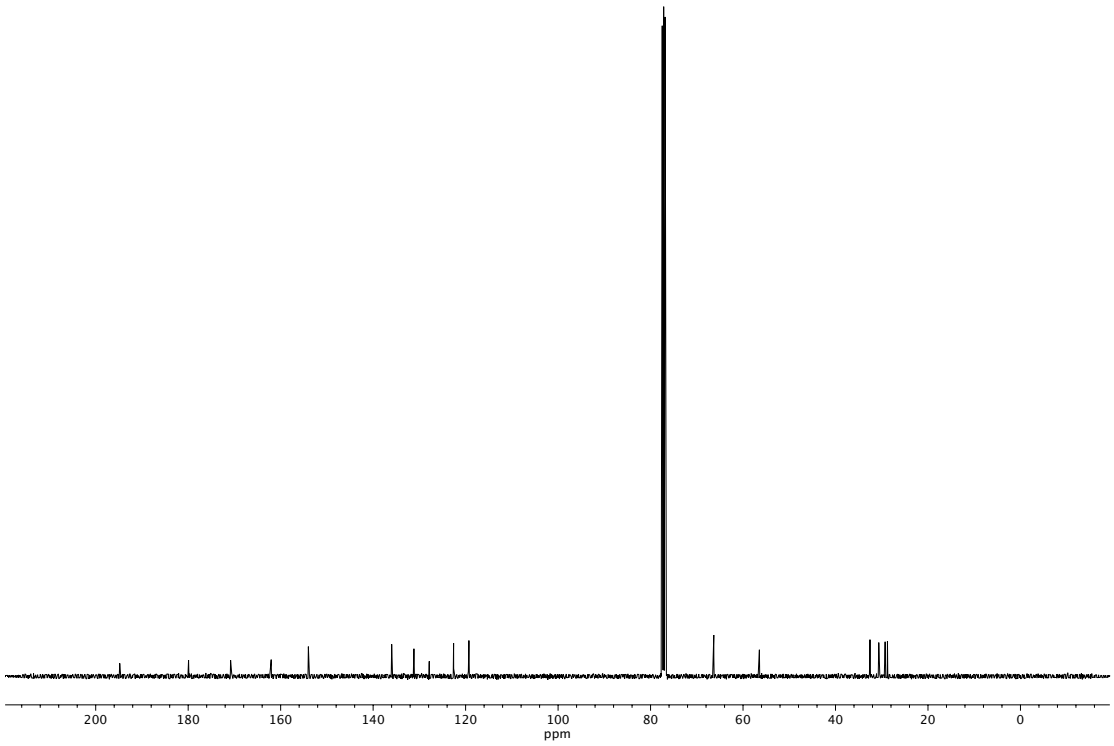

Figure A5.92 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***225***.

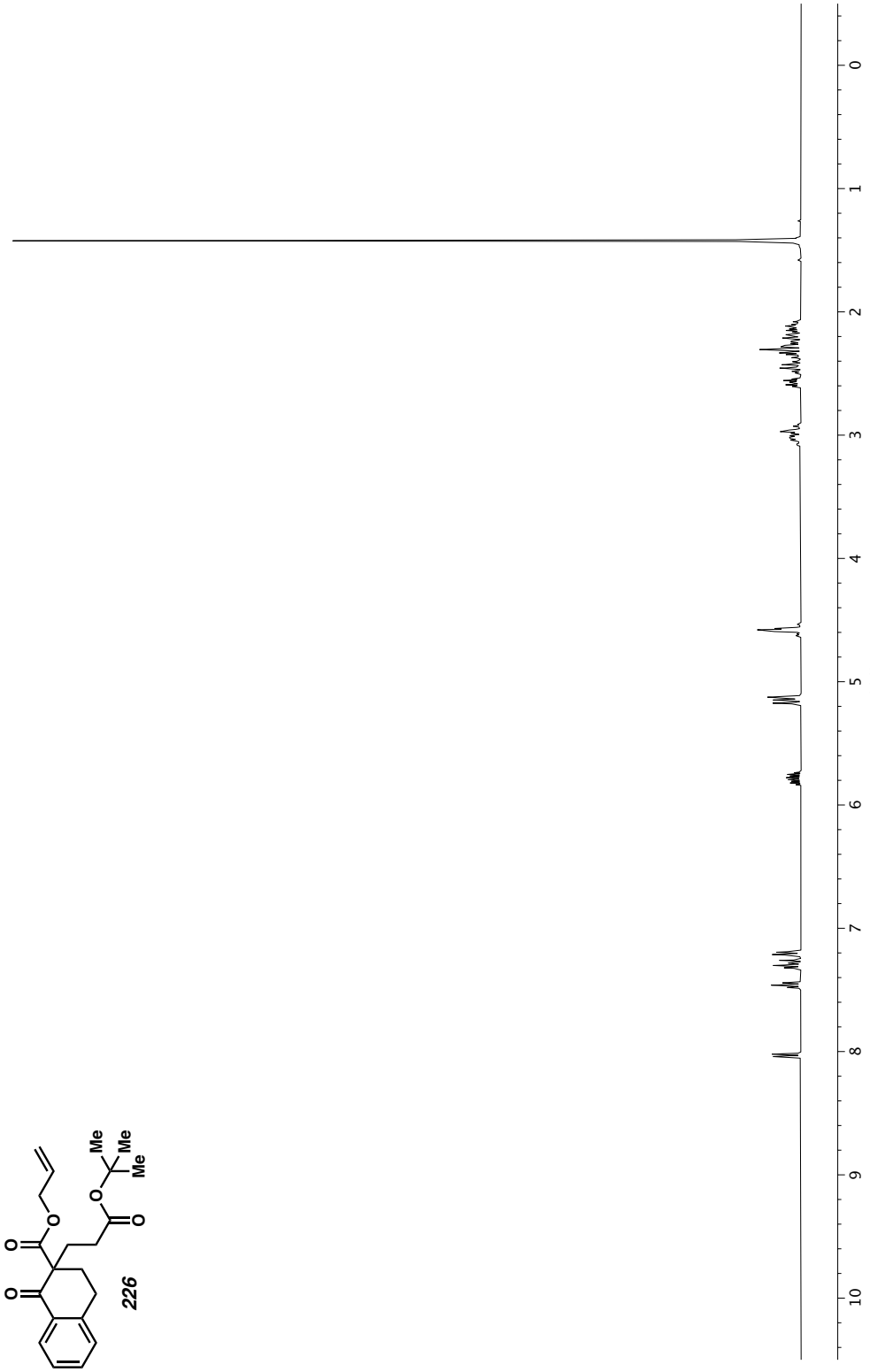

Figure A5.93 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***226***.

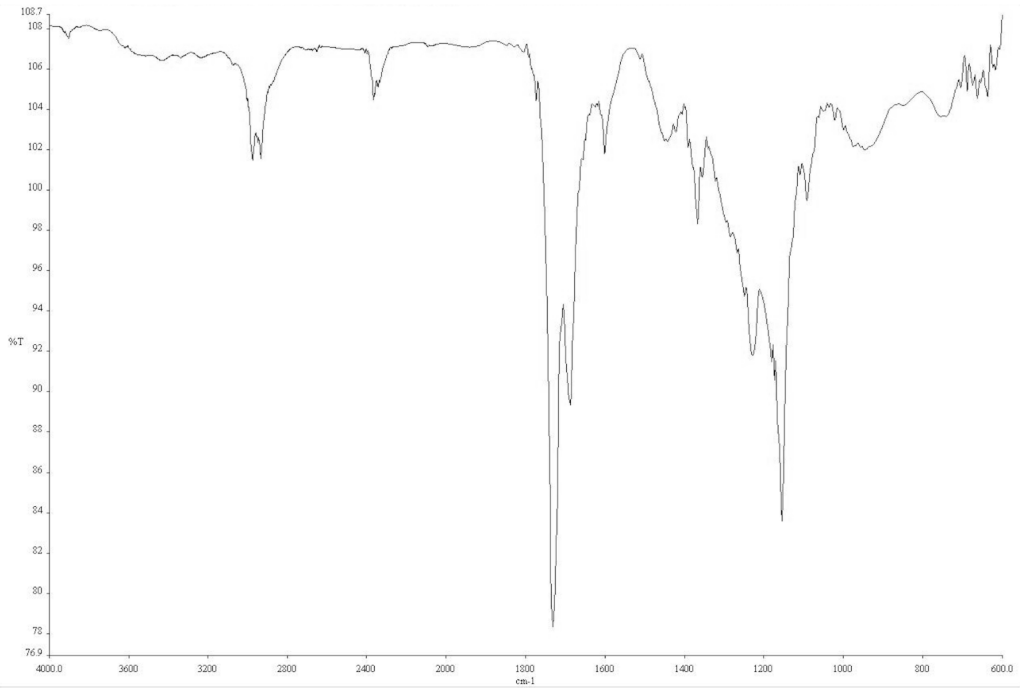

Figure A5.94 *Infrared spectrum (Thin Film, NaCl) of compound* ***226***.

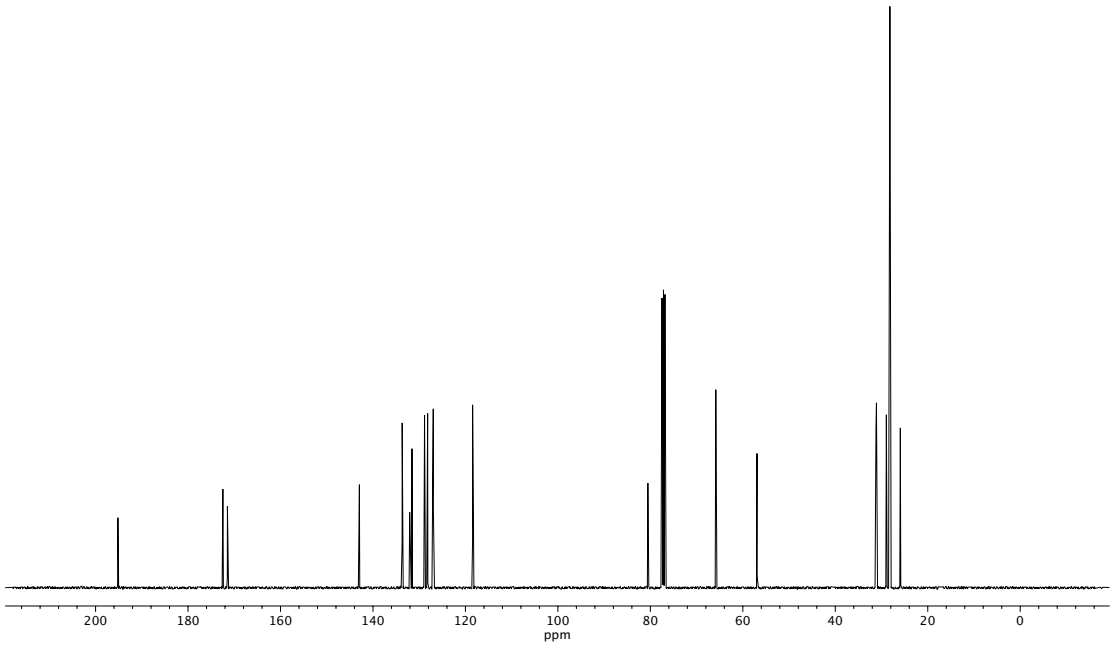

Figure A5.95 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***226***.

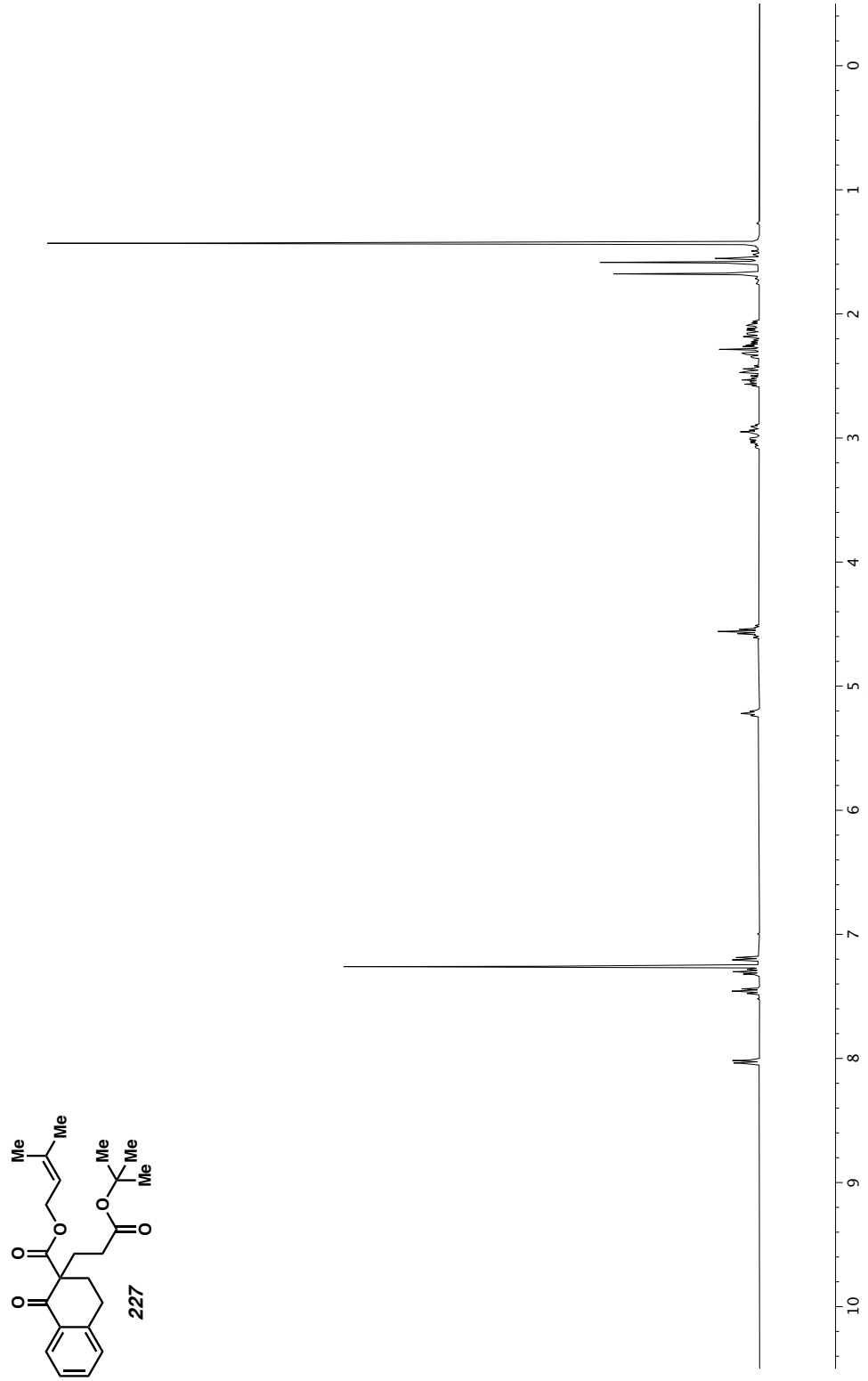

Figure A5.96 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***227****.*

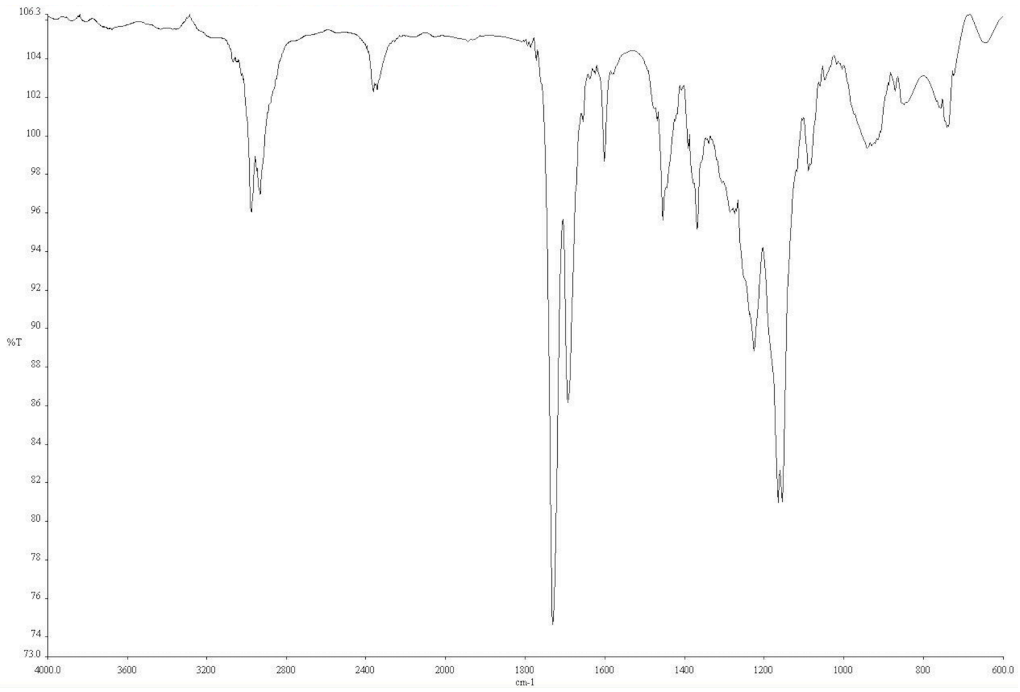

Figure A5.97 *Infrared spectrum (Thin Film, NaCl) of compound* ***227****.*

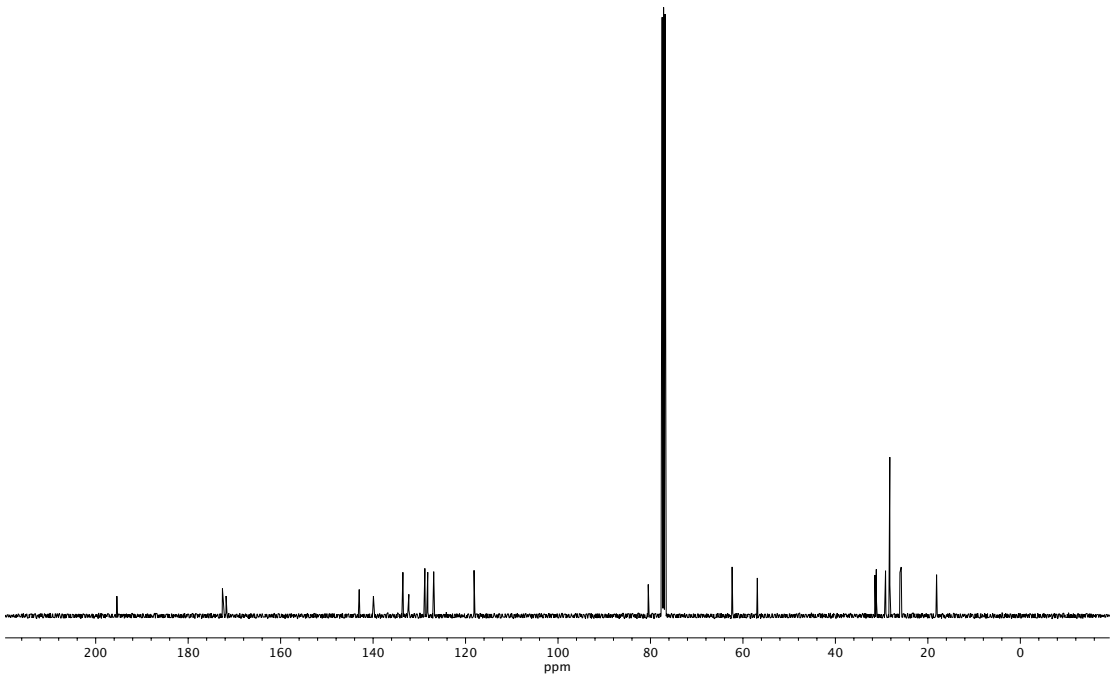

Figure A5.98 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***227****.*

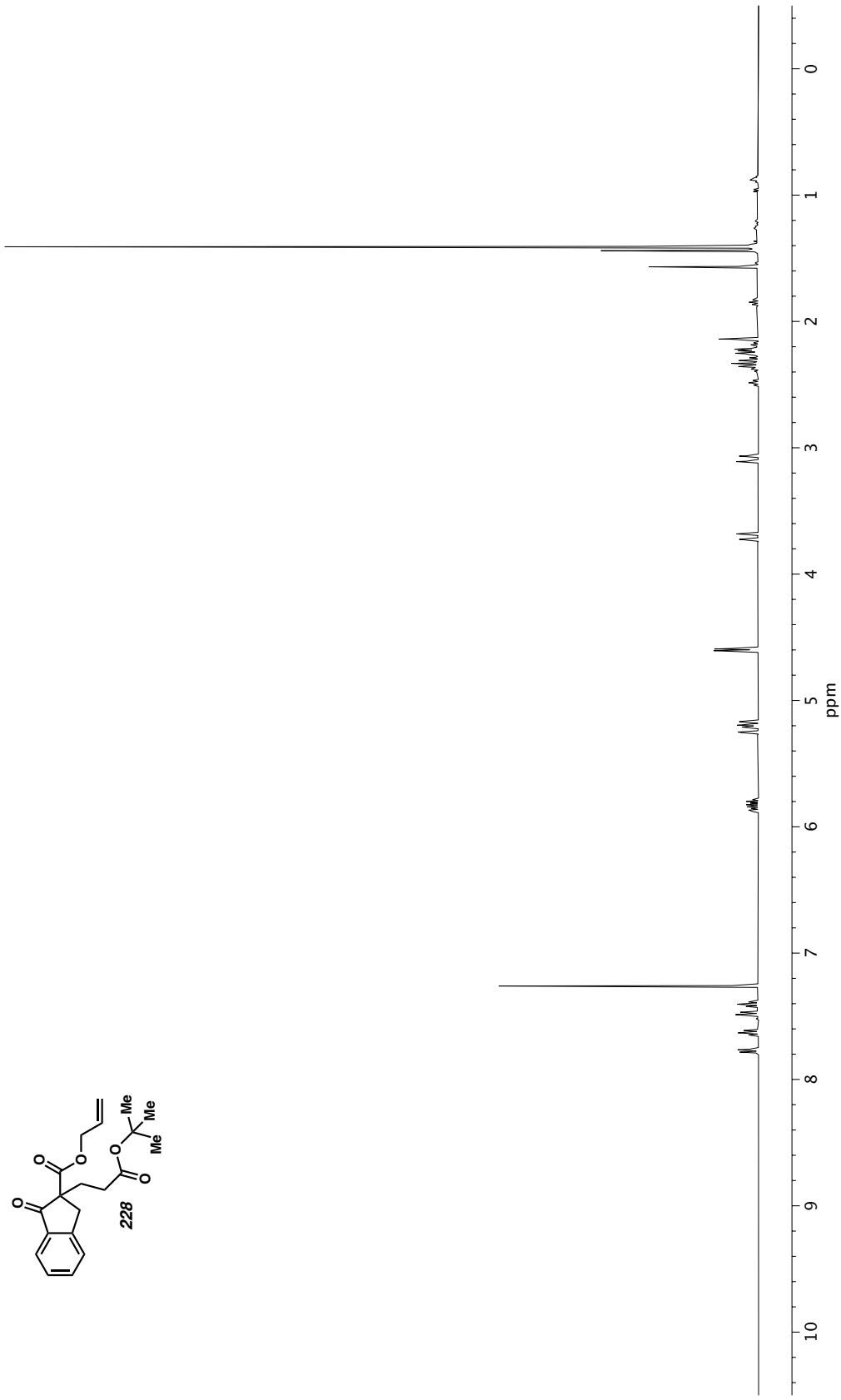

Figure A5.99 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***228****.*

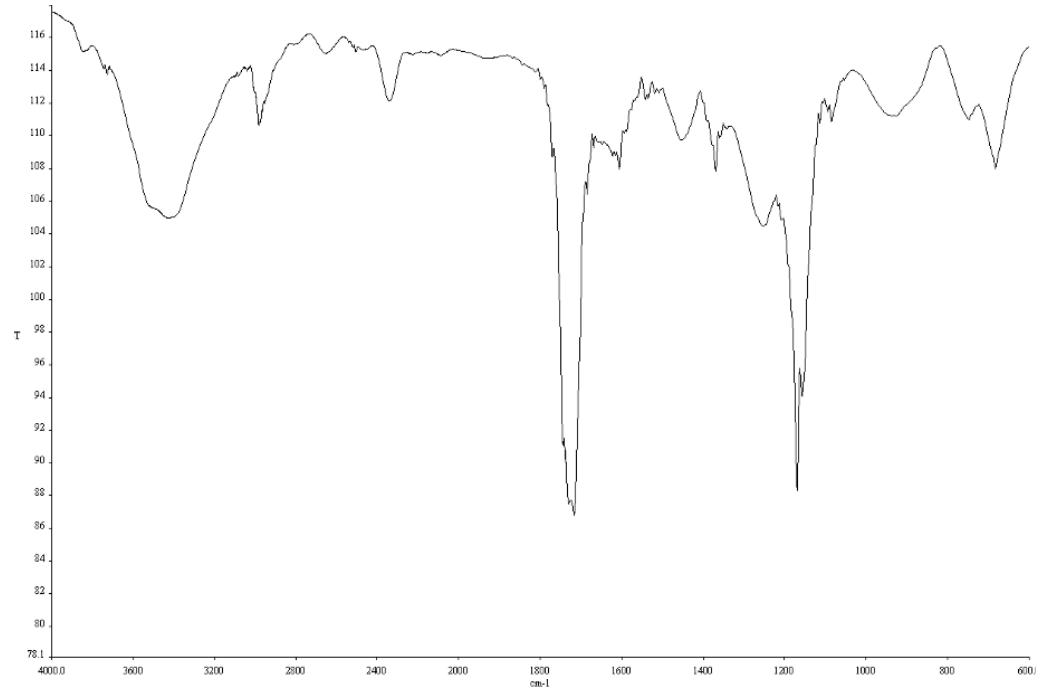

Figure A5.100 *Infrared spectrum (Thin Film, NaCl) of compound* ***228****.*

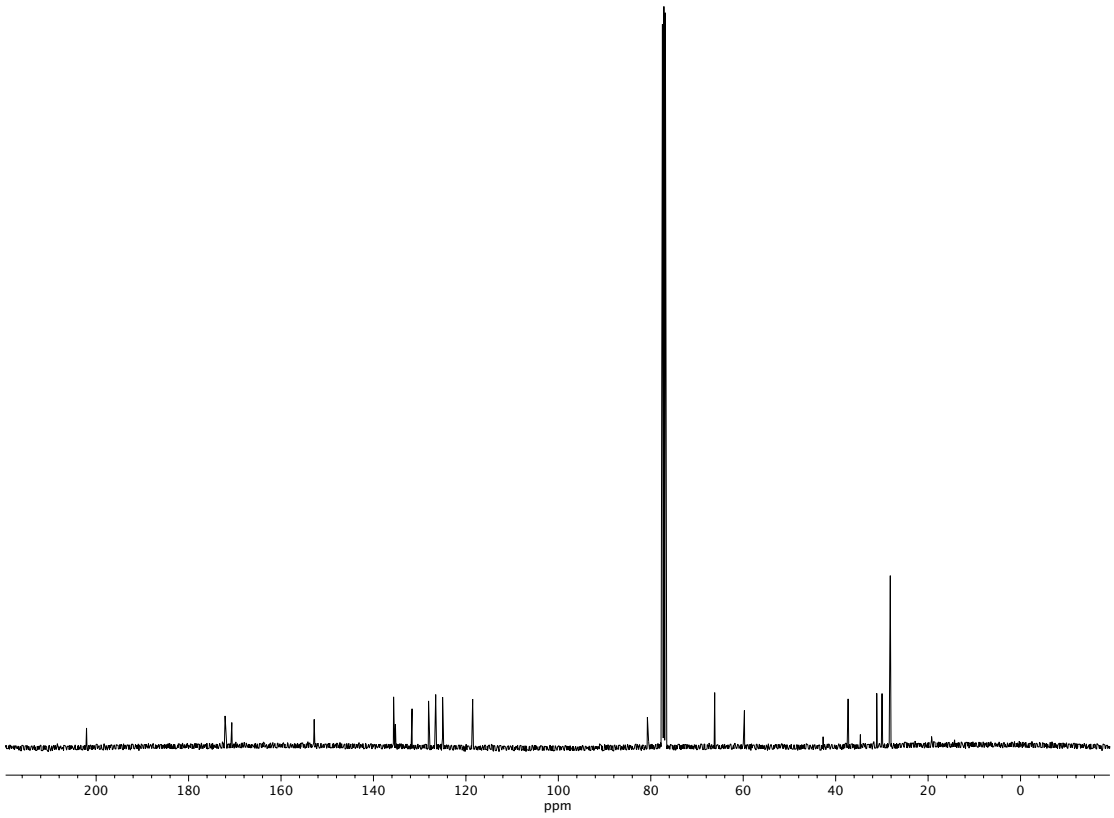

Figure A5.101 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***228****.*

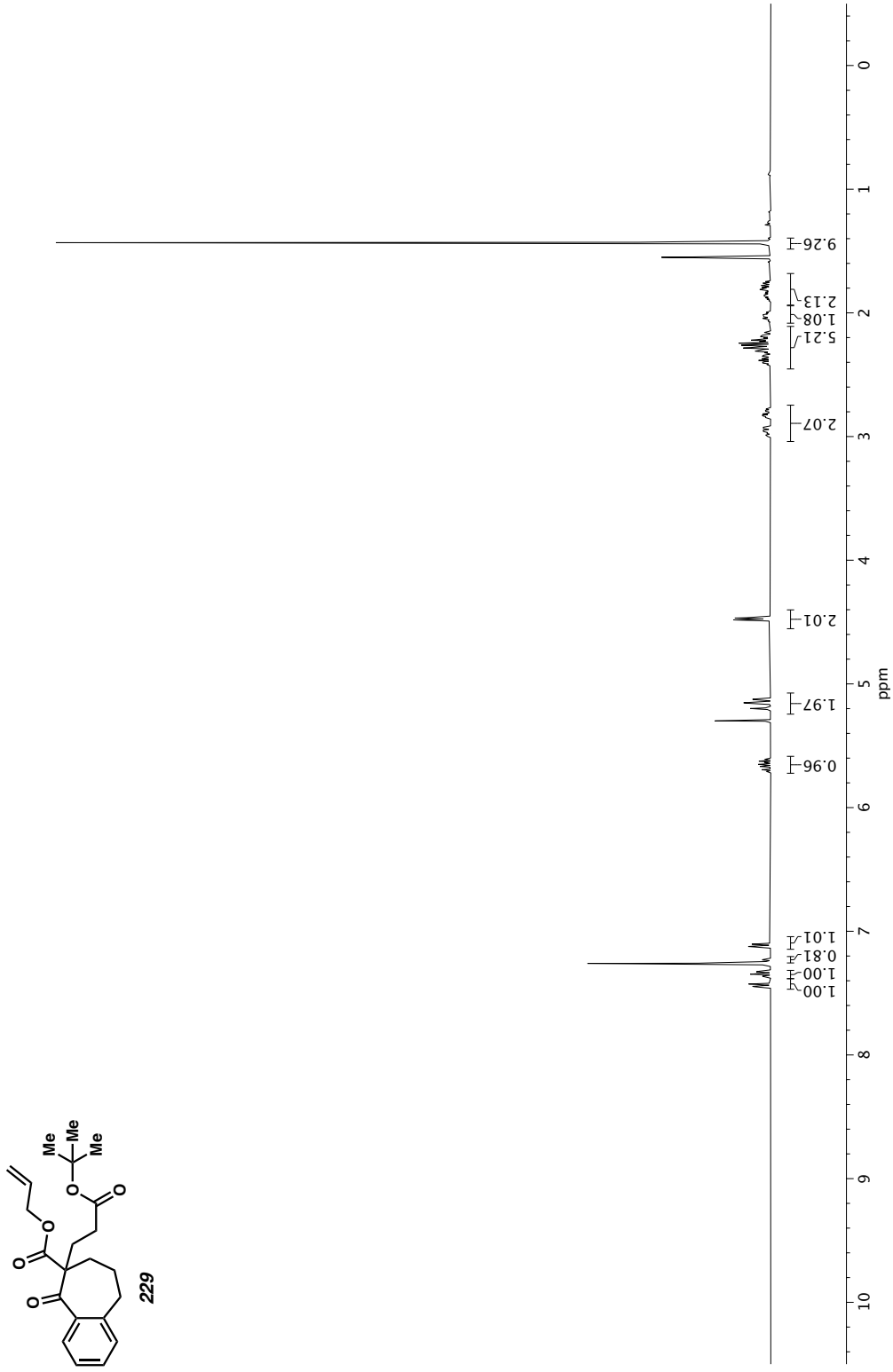

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Figure A5.102 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***229***.

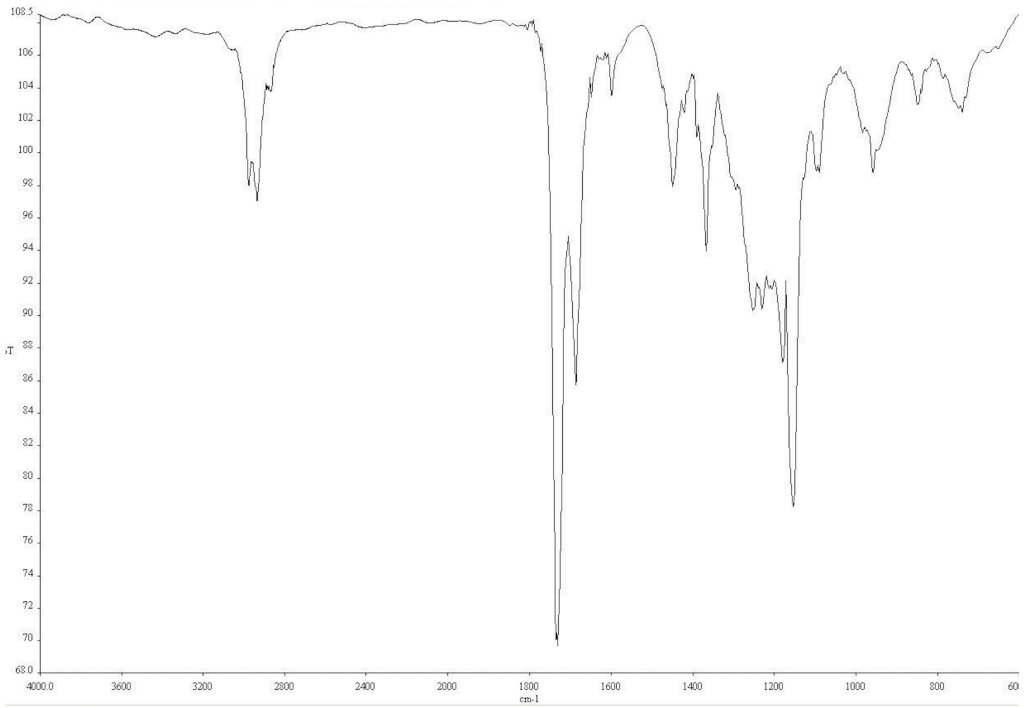

Figure A5.103 *Infrared spectrum (Thin Film, NaCl) of compound* ***229***.

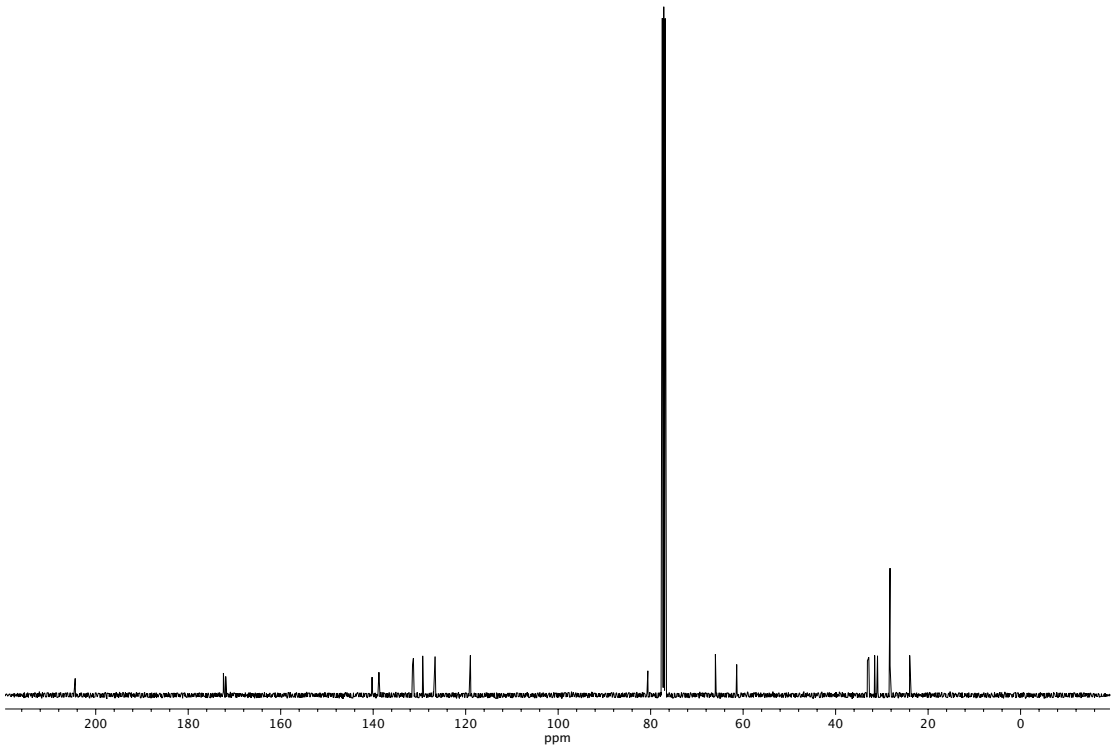

Figure A5.104 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***229***.

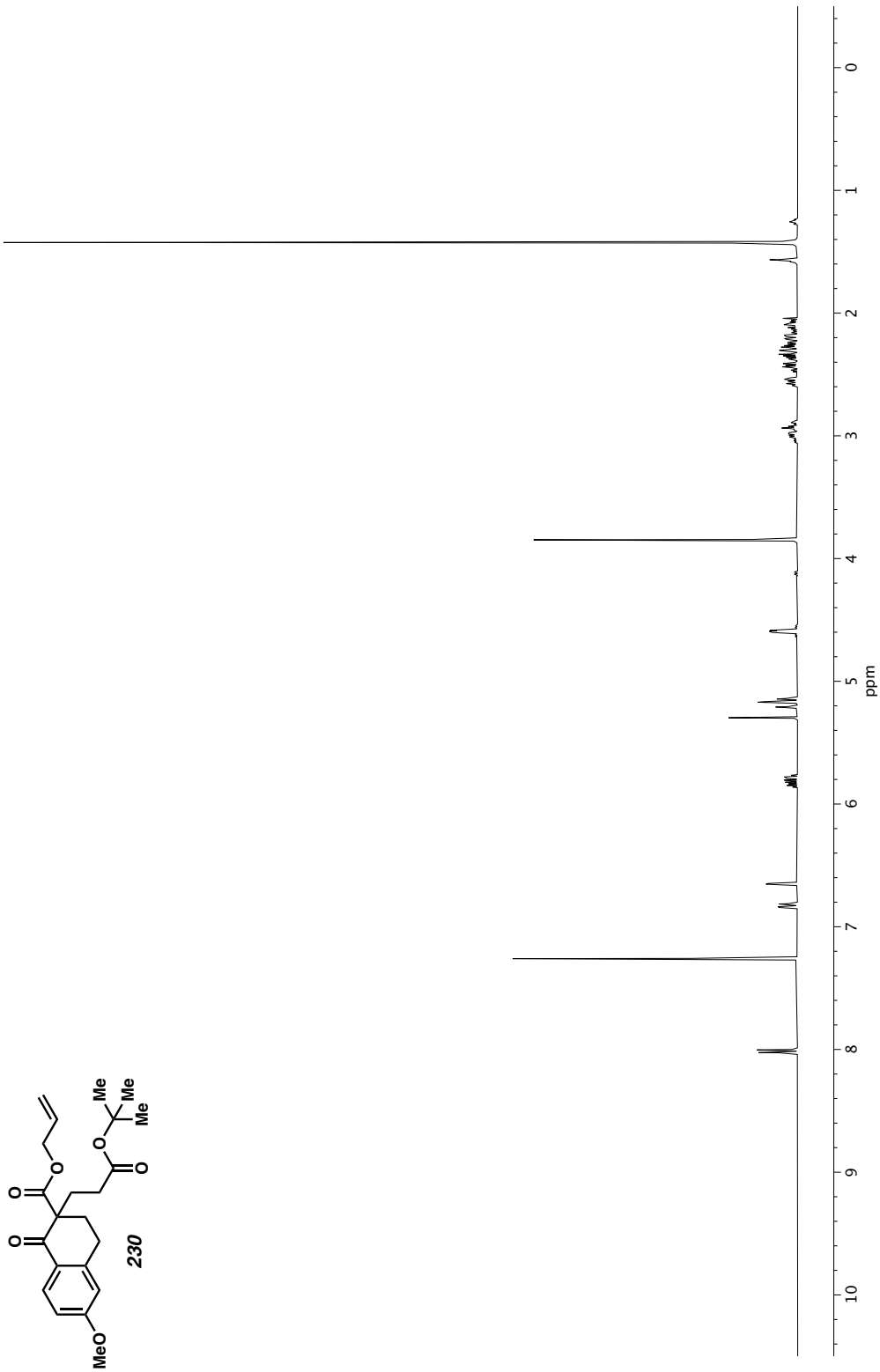

Figure A5.105 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***230***.

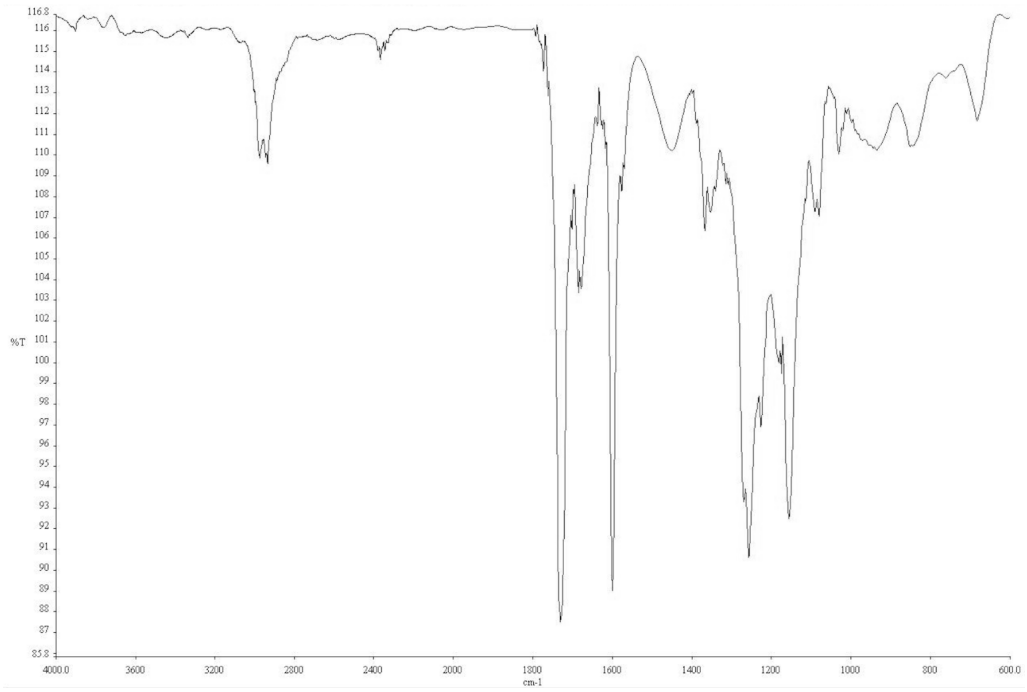

Figure A5.106 *Infrared spectrum (Thin Film, NaCl) of compound* ***230****.*

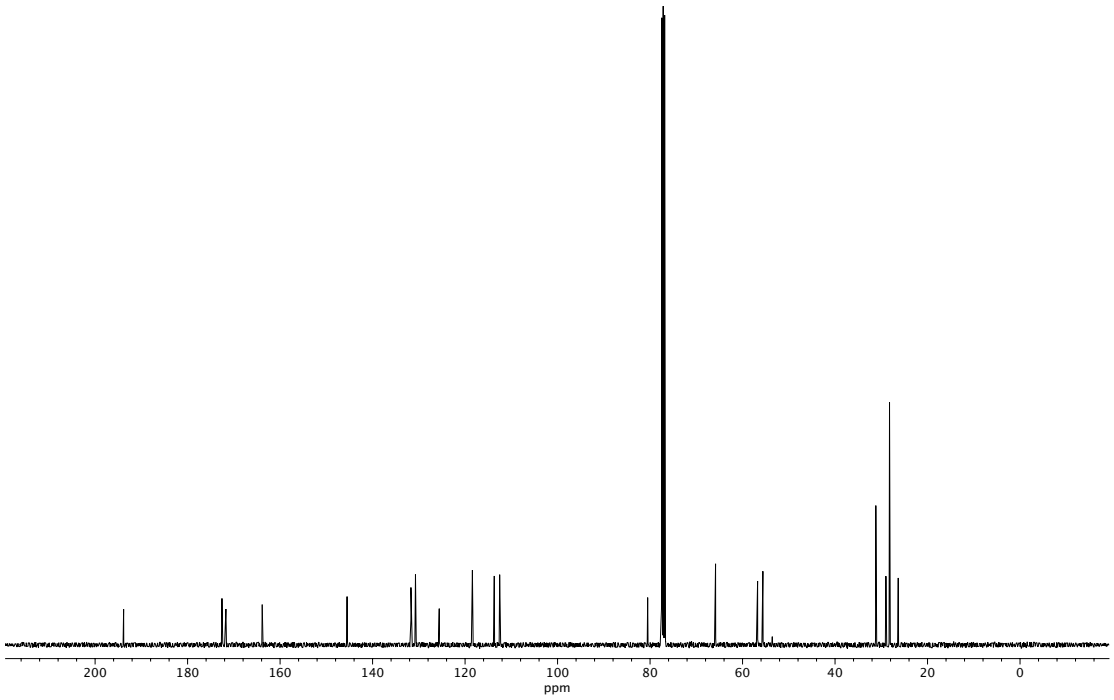

Figure A5.107 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***230****.*

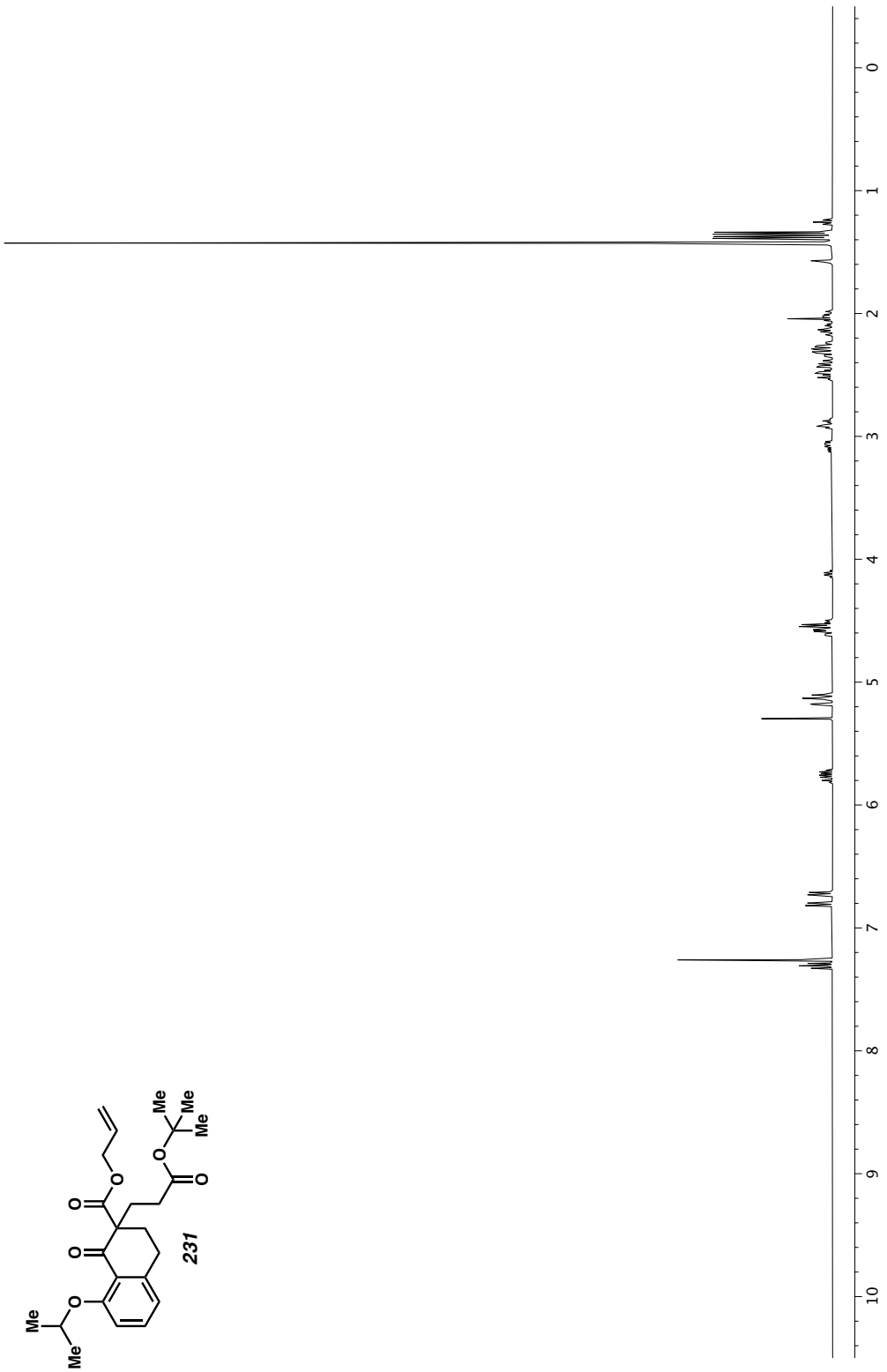

Figure A5.108 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***231****.*

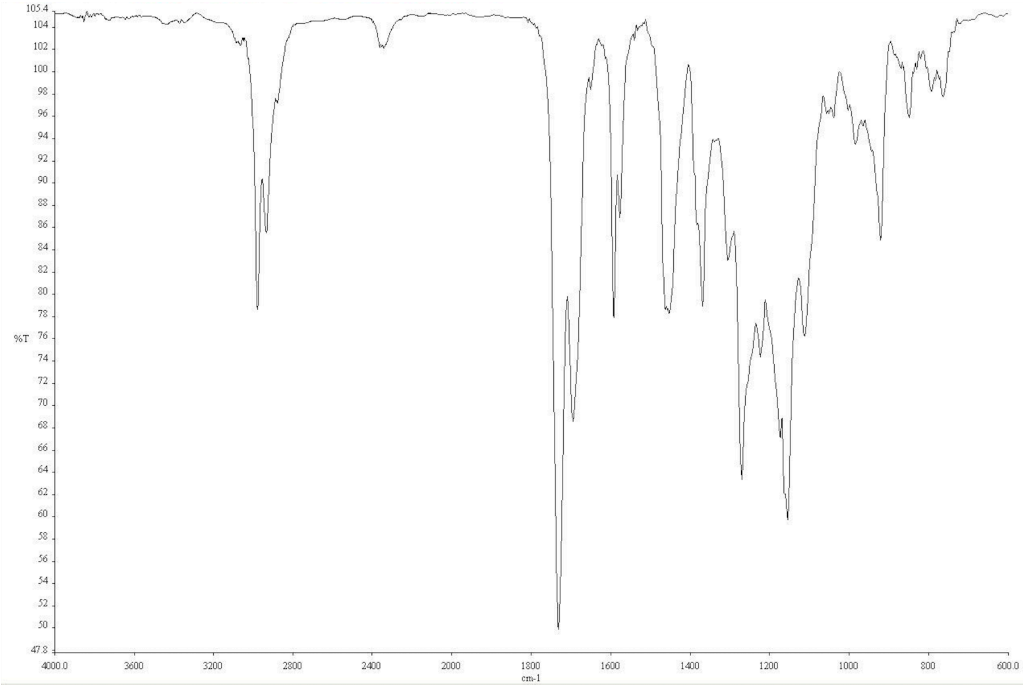

Figure A5.109 *Infrared spectrum (Thin Film, NaCl) of compound* ***231***.

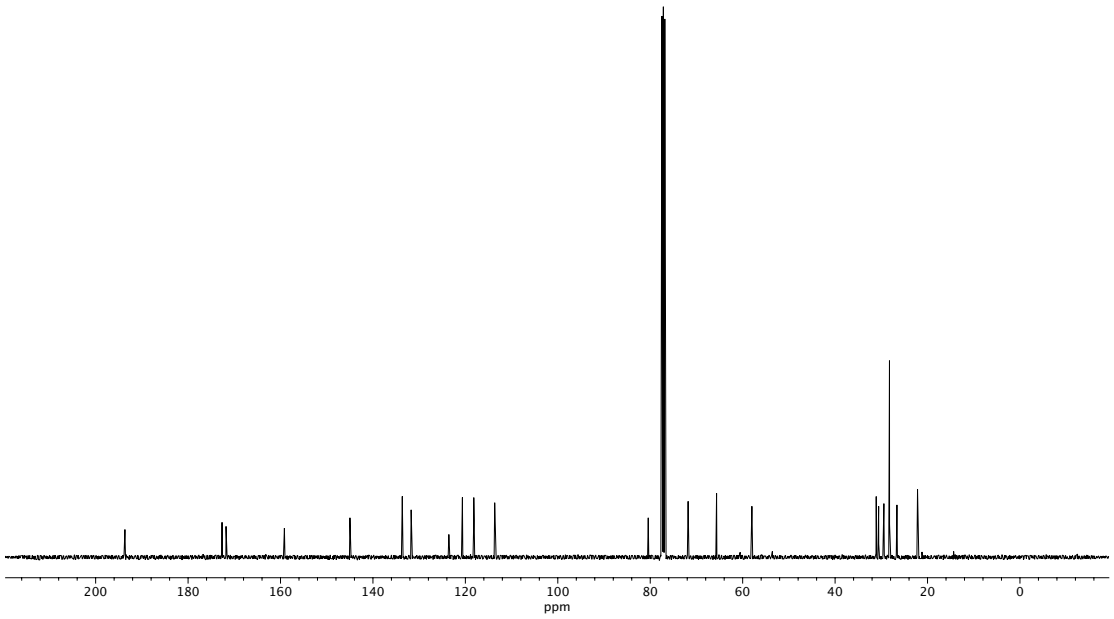

Figure A5.110 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***231***.

Figure A5.111 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***232***.

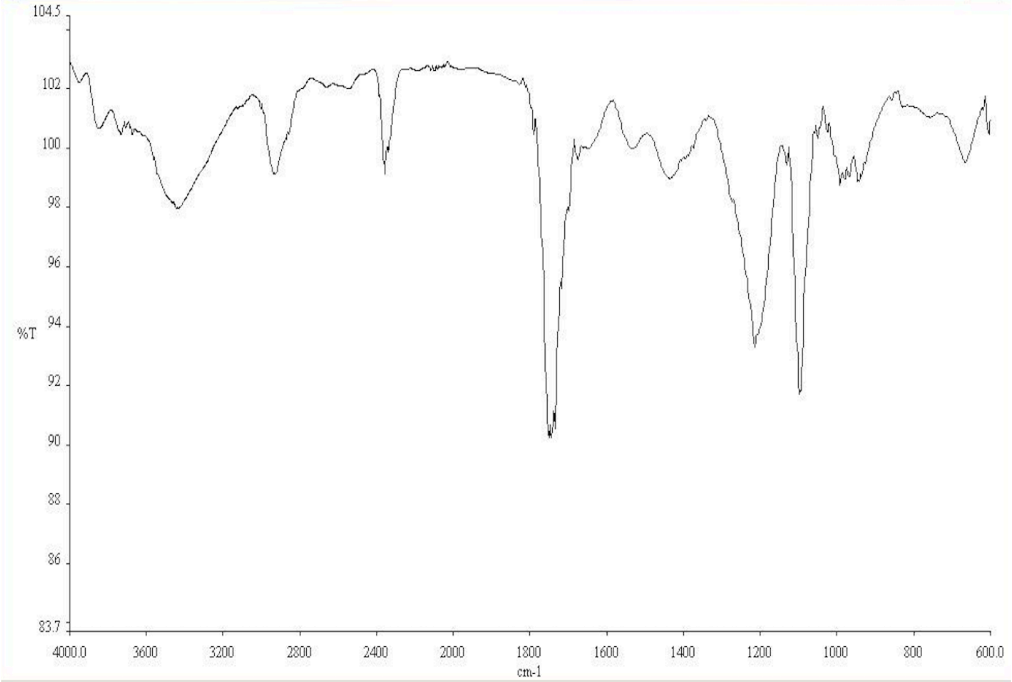

Figure A5.112 *Infrared spectrum (Thin Film, NaCl) of compound* ***232***.

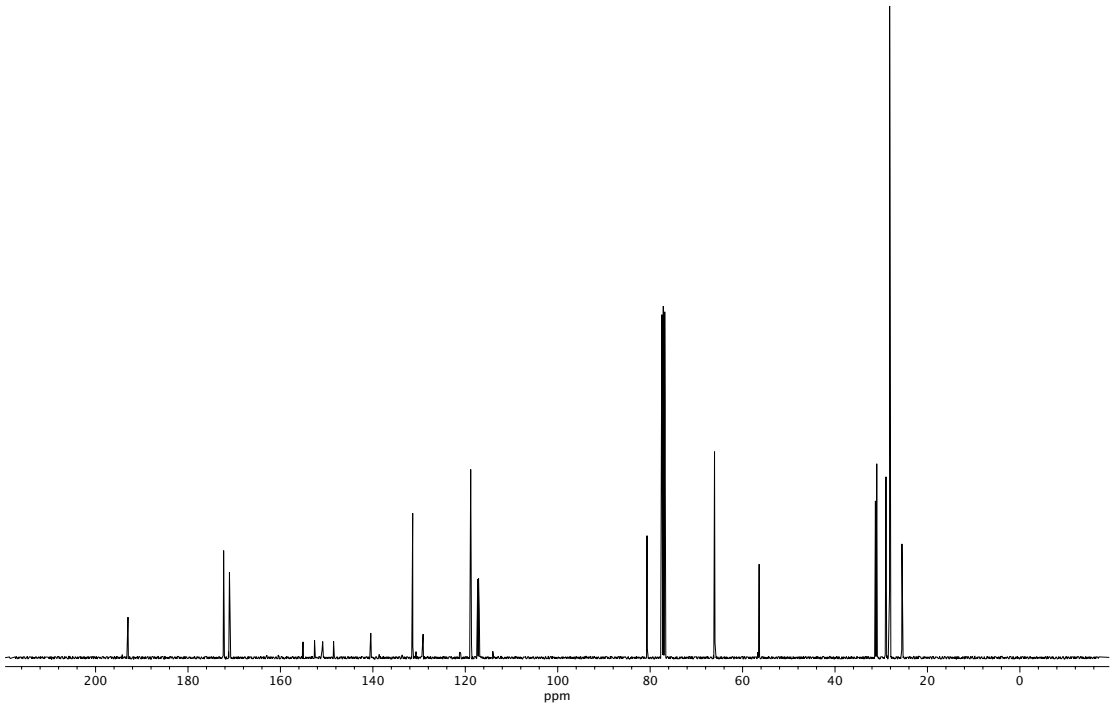

Figure A5.113 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***232***.

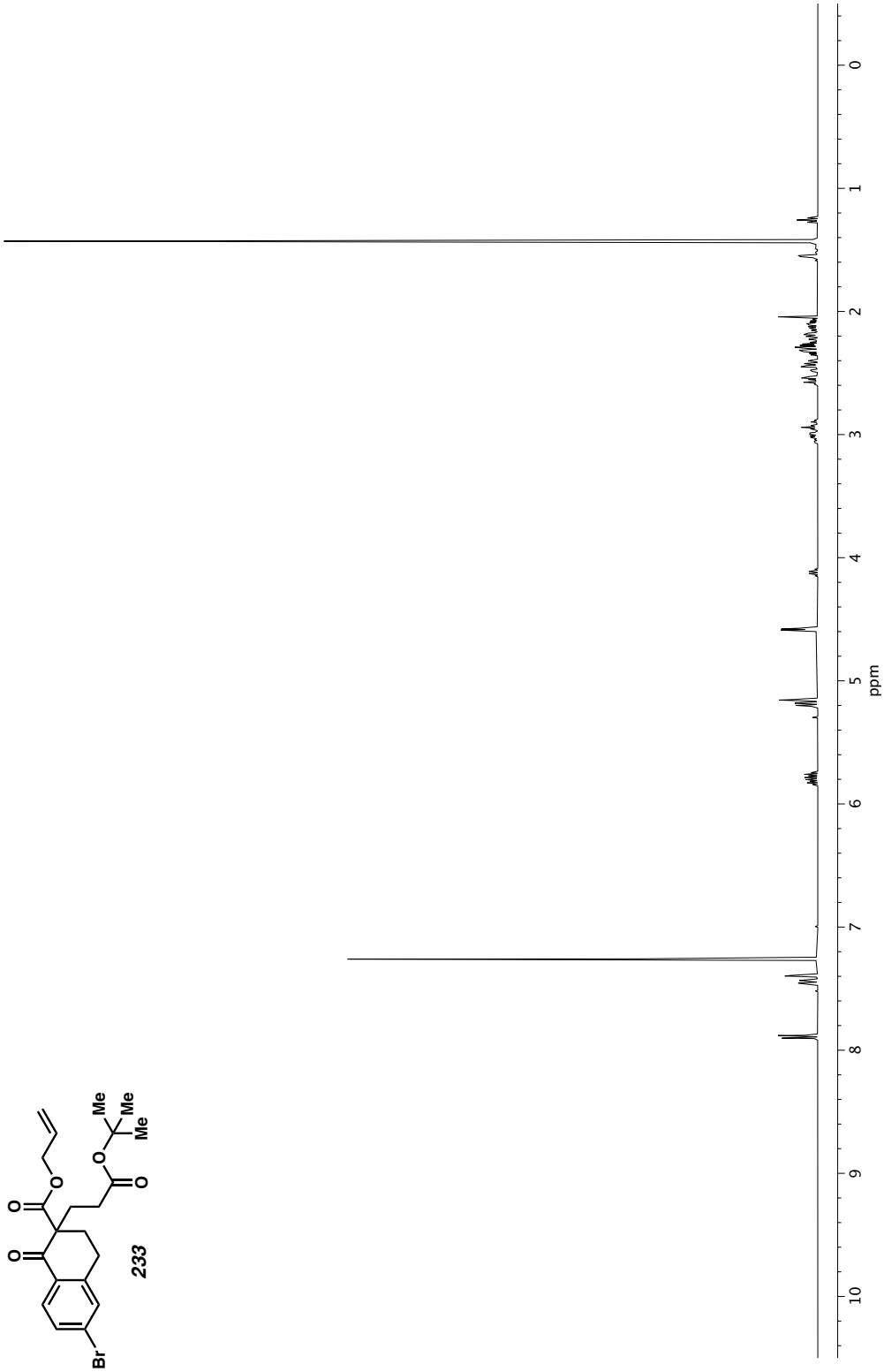

Figure A5.114 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***233***.

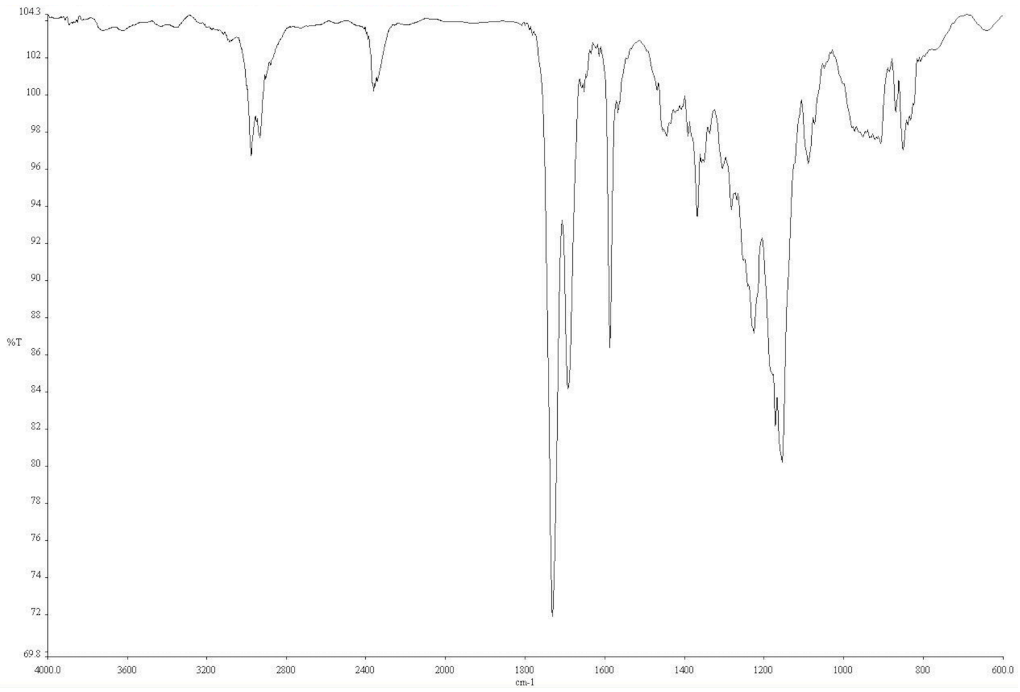

Figure A5.115 *Infrared spectrum (Thin Film, NaCl) of compound* ***233***.

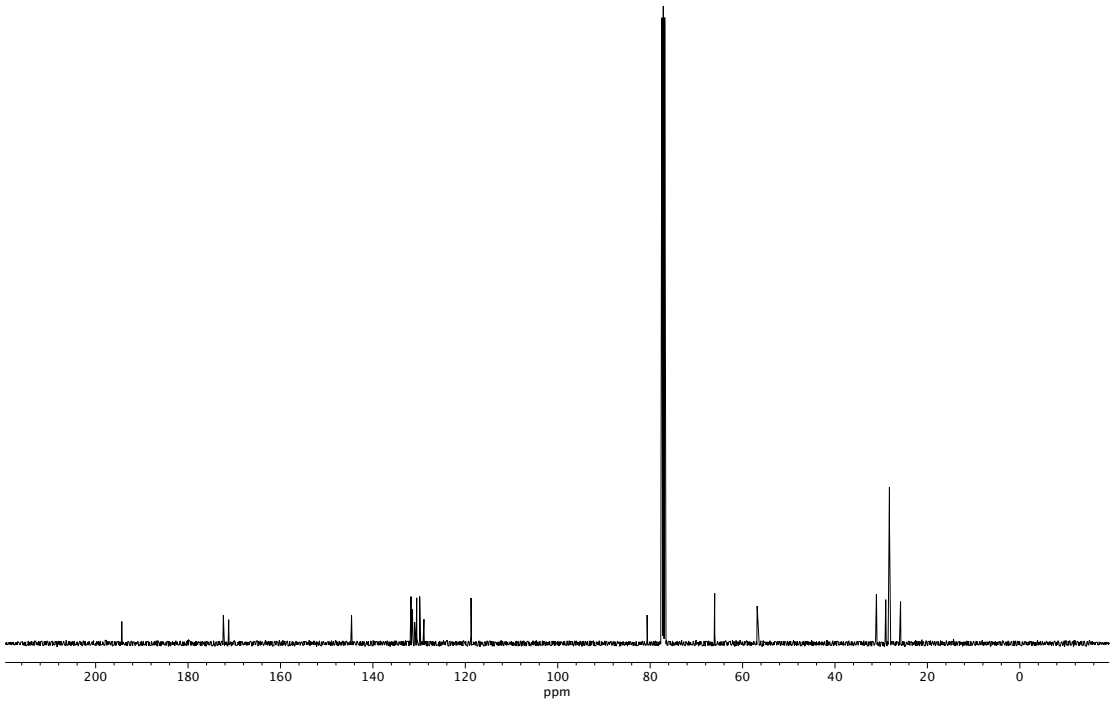

Figure A5.116 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***233***.

Figure A5.117 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***234****.*

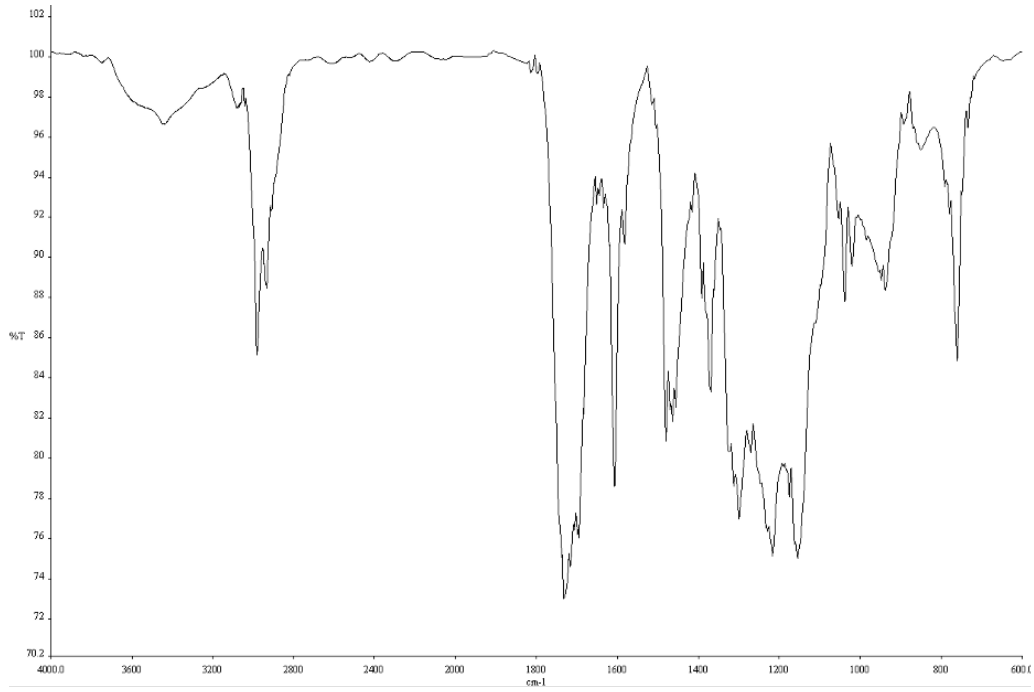

Figure A5.118 *Infrared spectrum (Thin Film, NaCl) of compound* ***234***.

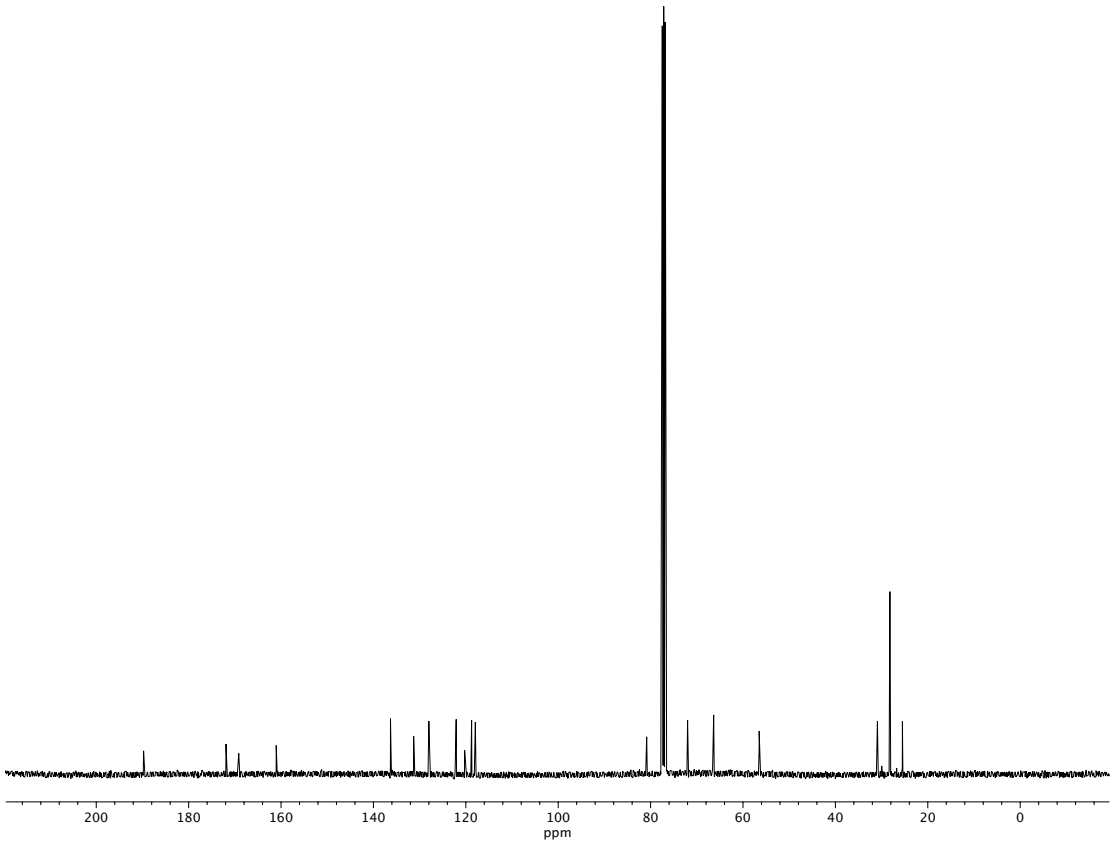

Figure A5.119 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***234***.

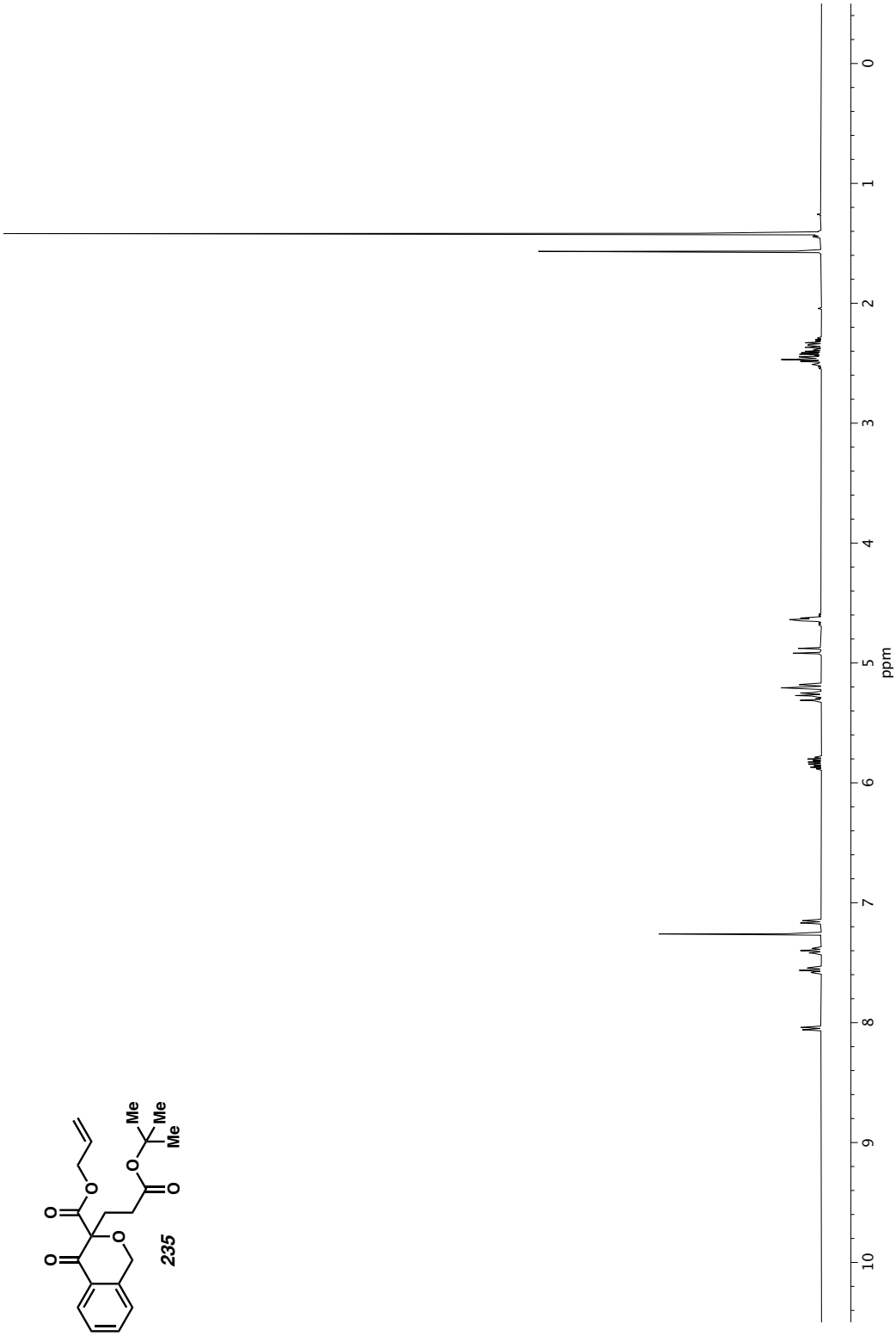

Figure A5.120 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***235****.*

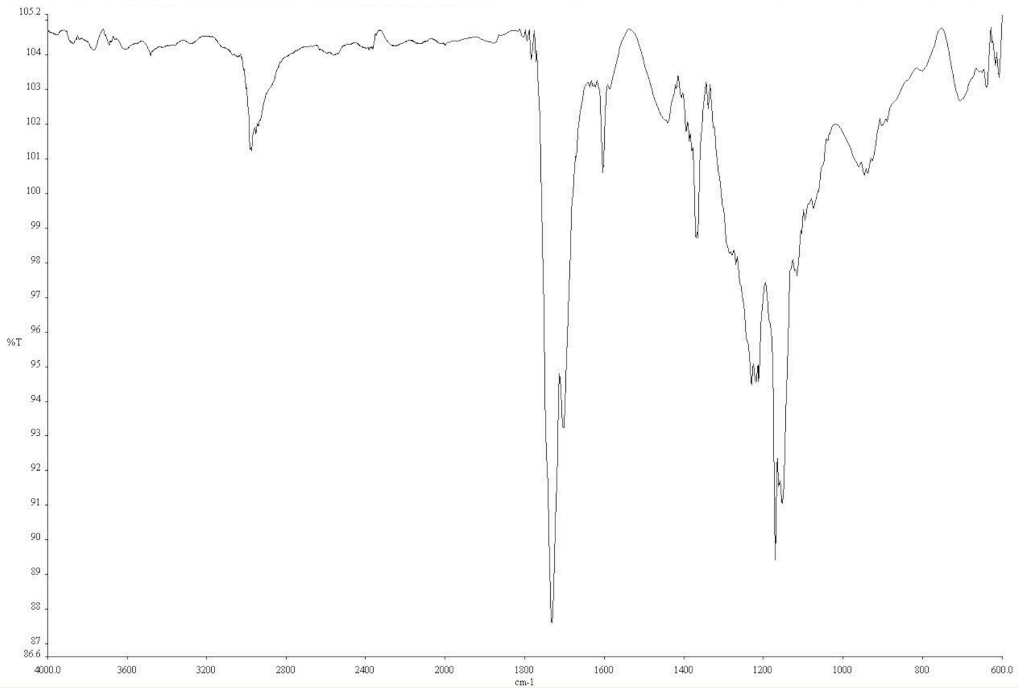

Figure A5.121 *Infrared spectrum (Thin Film, NaCl) of compound* ***235****.*

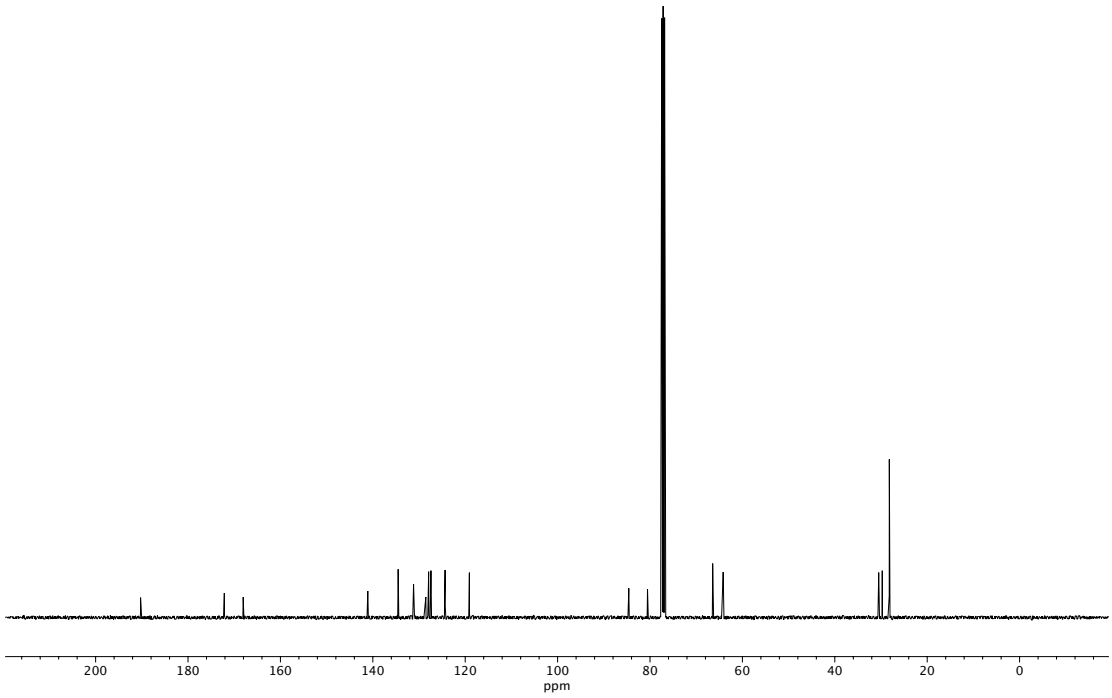

Figure A5.122 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***235****.*

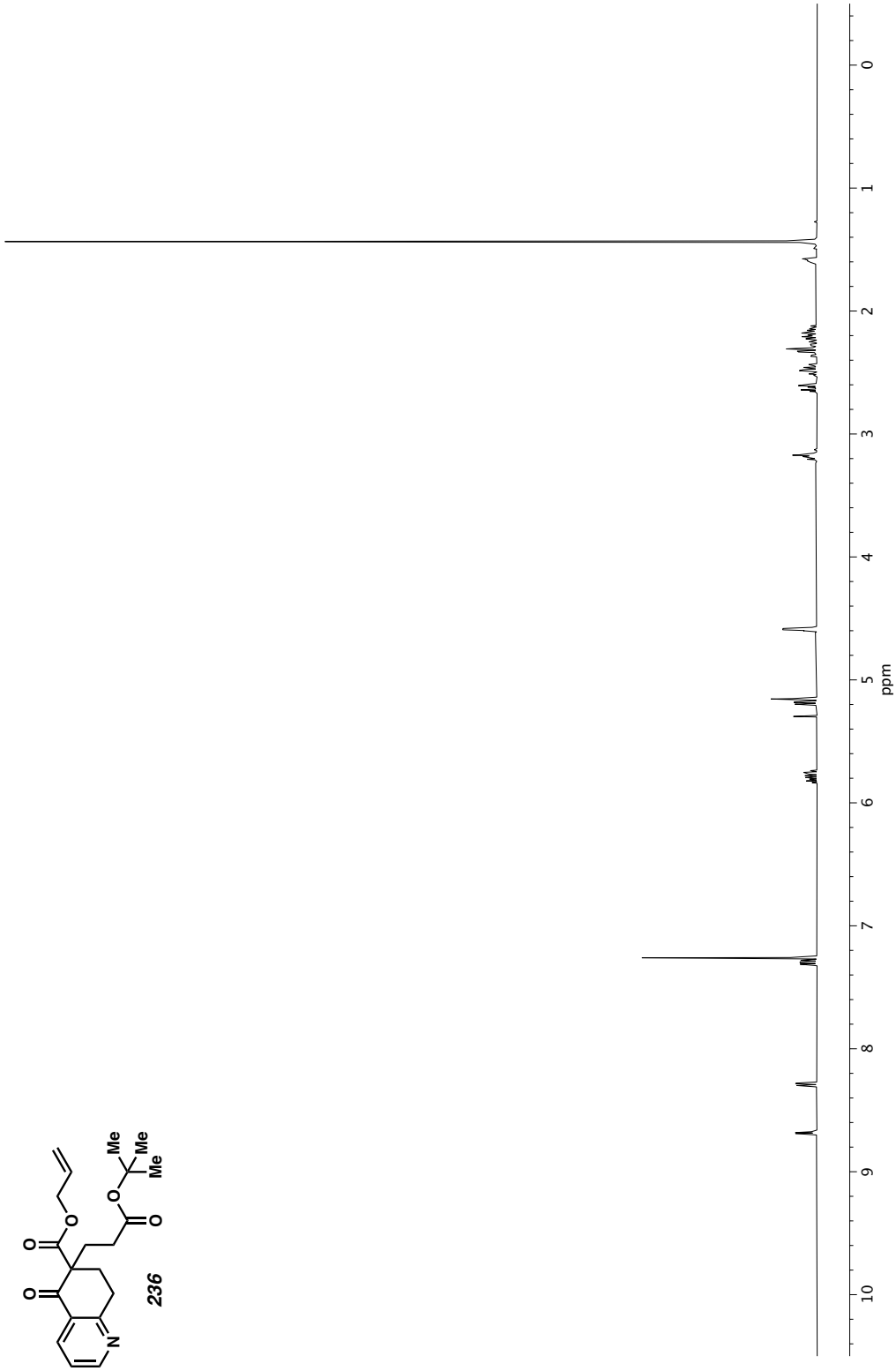

Figure A5.123 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***236****.*

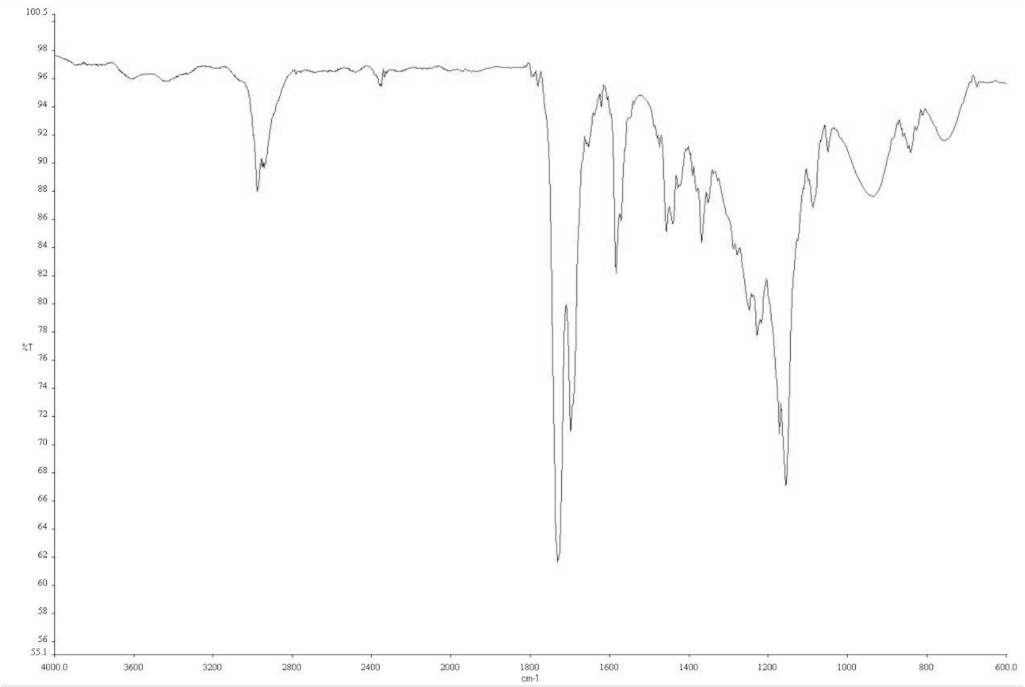

Figure A5.124 *Infrared spectrum (Thin Film, NaCl) of compound* ***236****.*

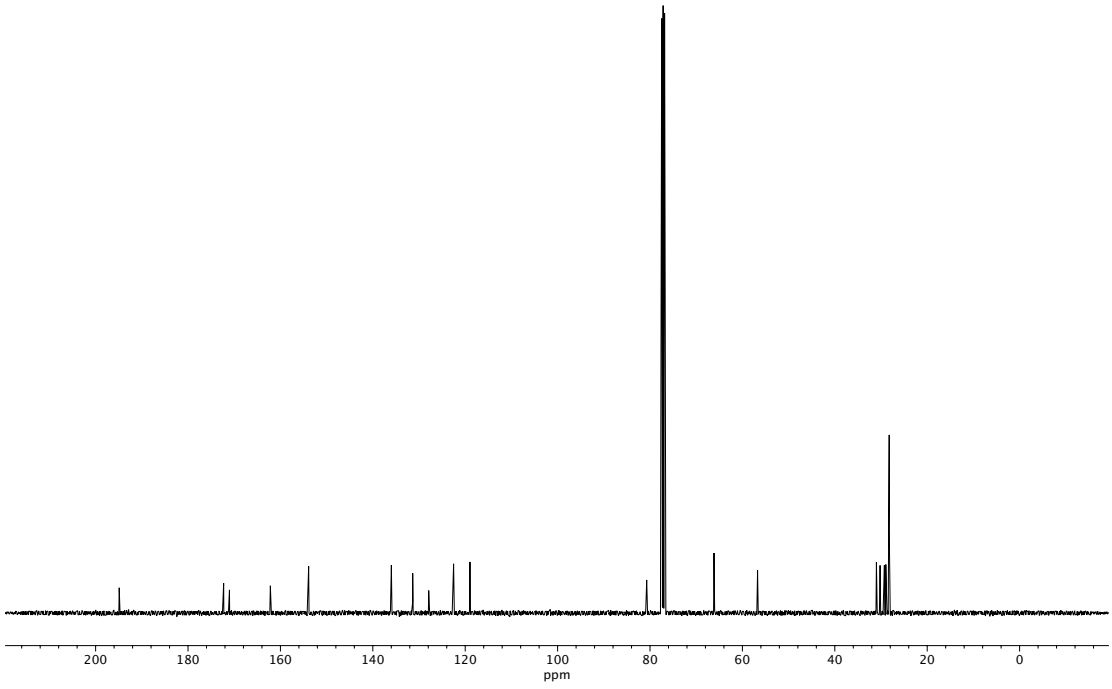

Figure A5.125 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***236****.*

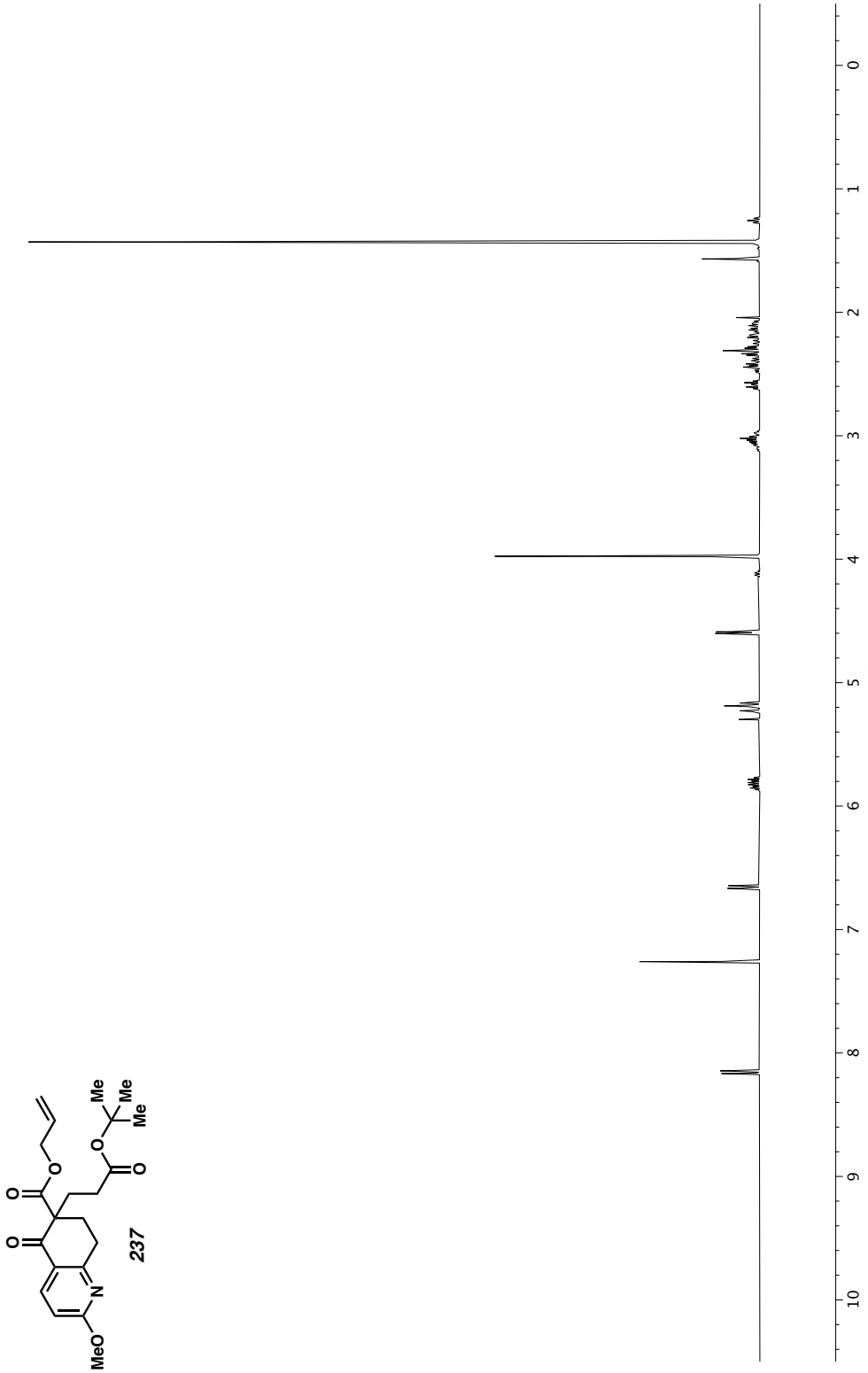

Figure A5.126 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***237****.*

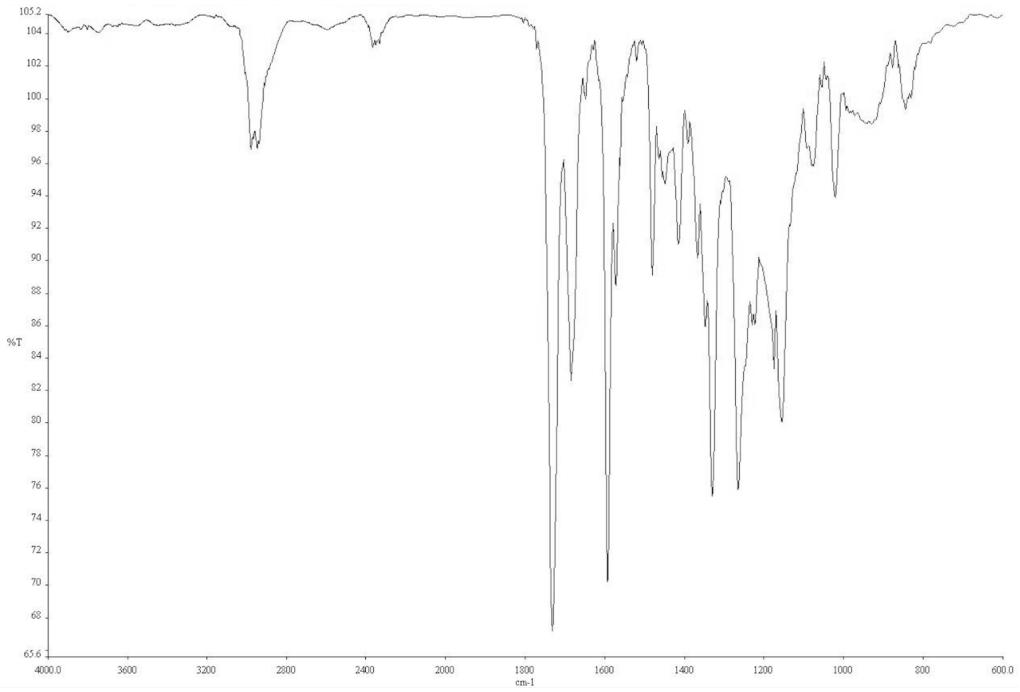

Figure A5.127 *Infrared spectrum (Thin Film, NaCl) of compound* ***237****.*

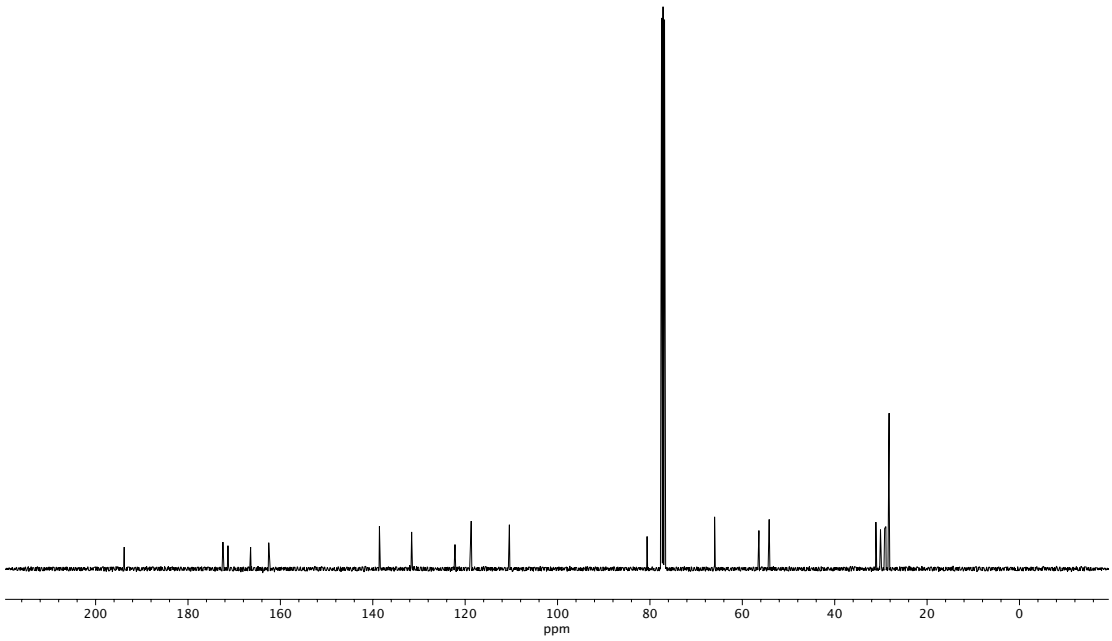

Figure A5.128 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***237****.*

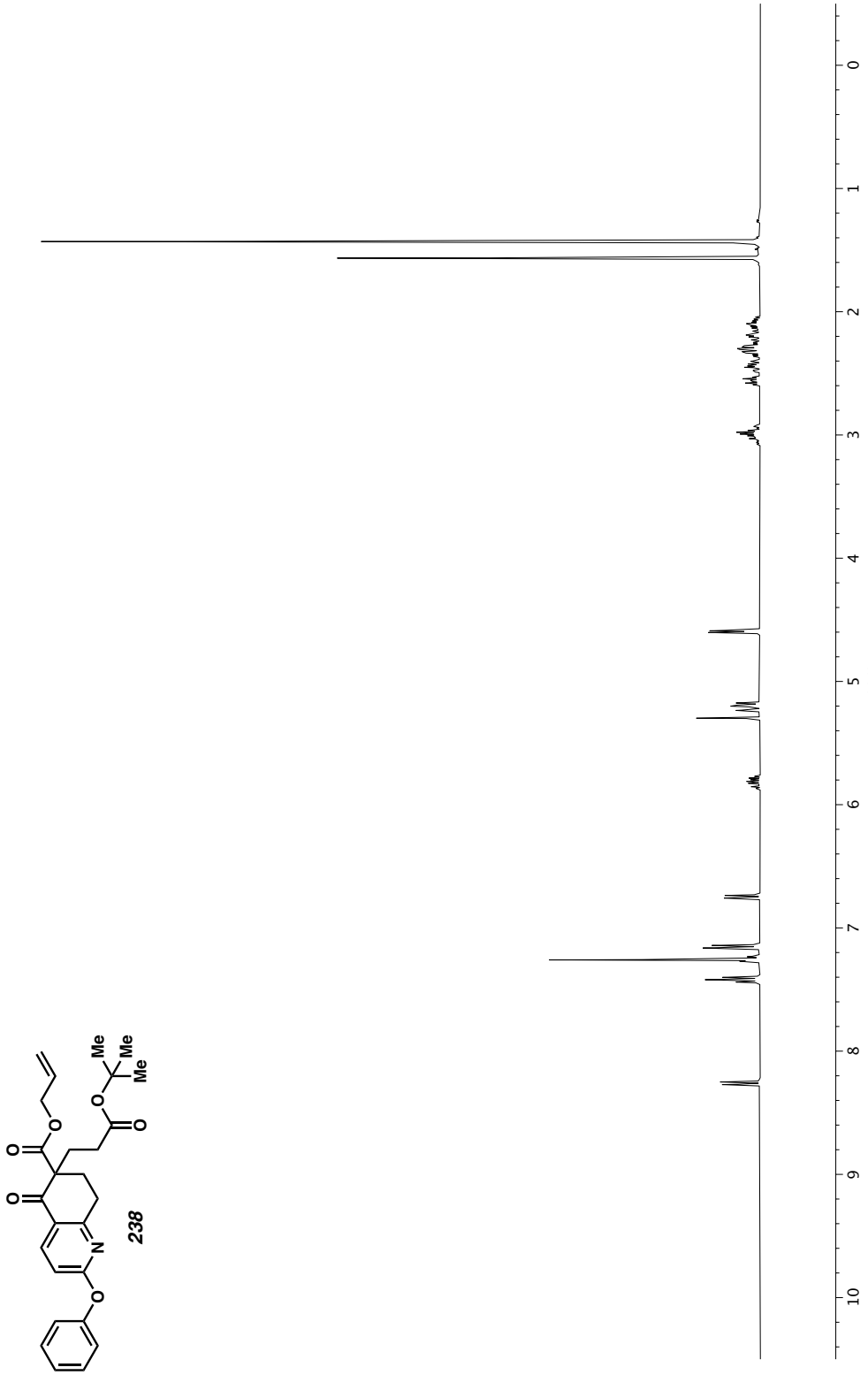

Figure A5.129 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***238****.*

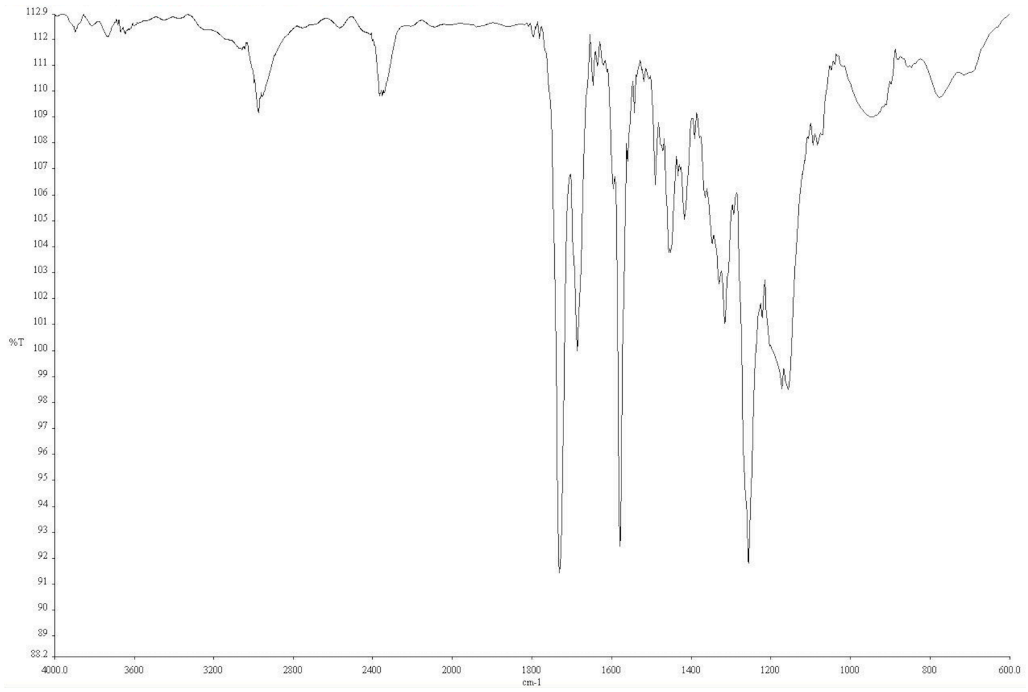

Figure A5.130 *Infrared spectrum (Thin Film, NaCl) of compound* ***238****.*

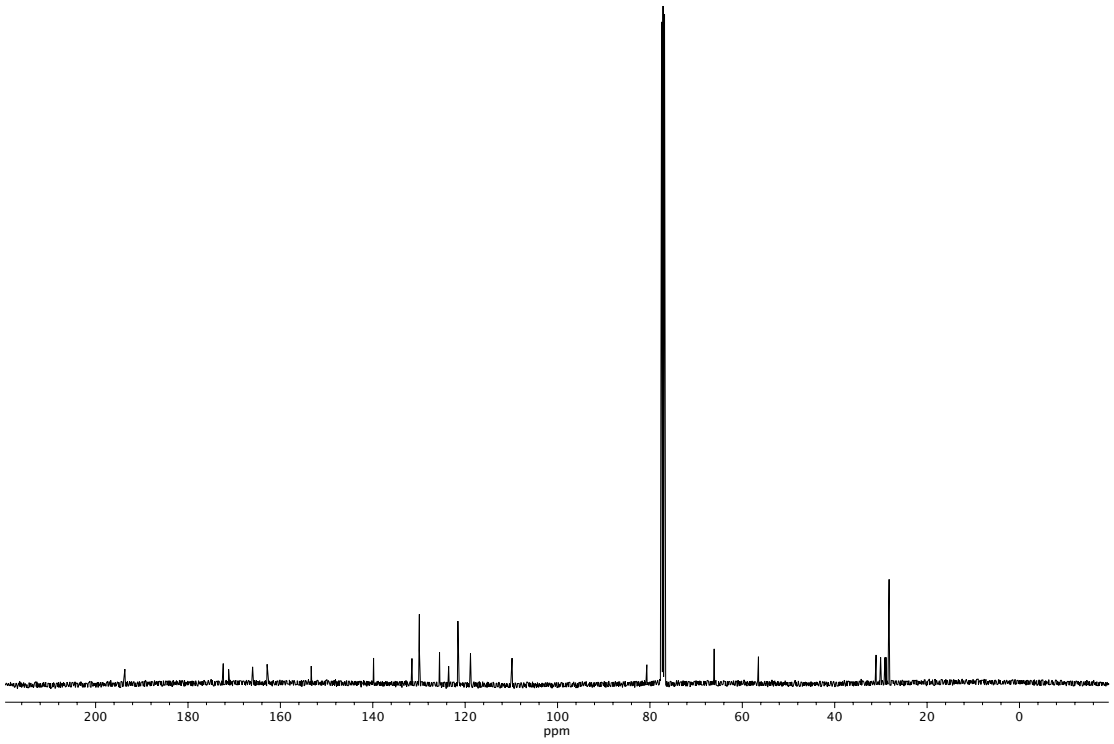

Figure A5.131 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***238****.*

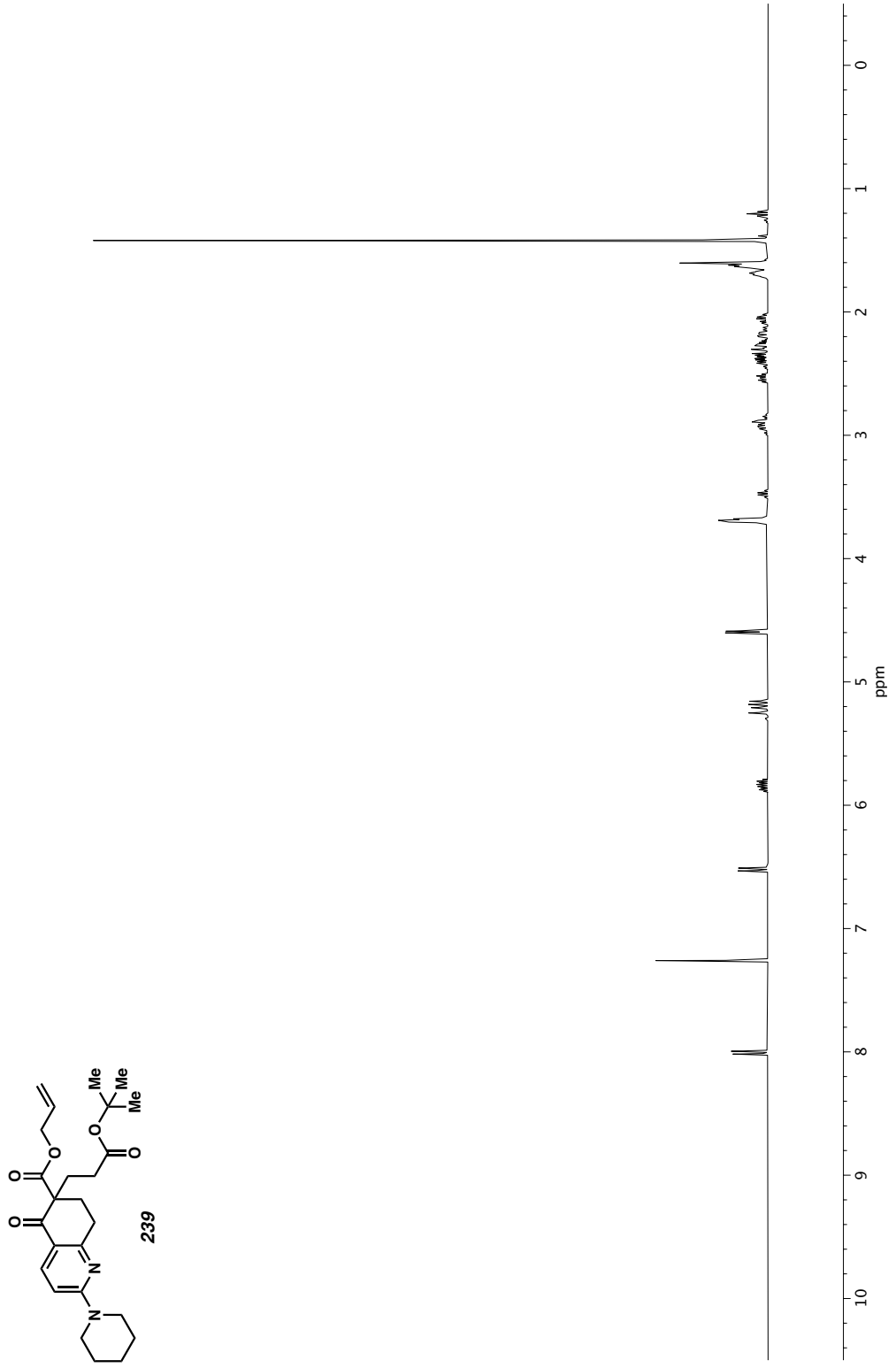

Figure A5.132 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***239***.

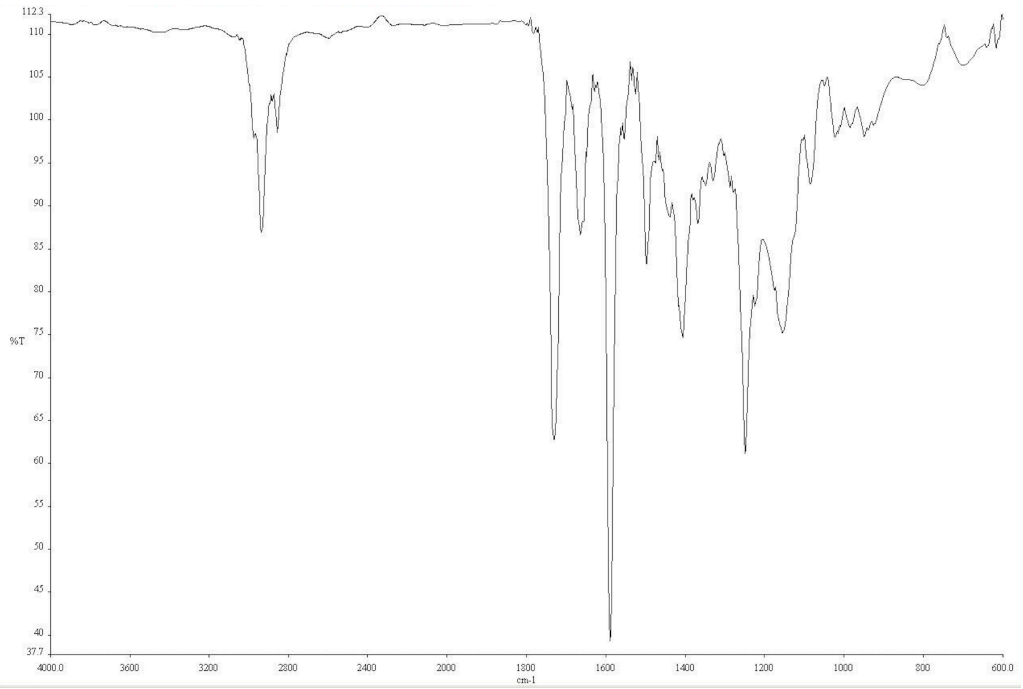

Figure A5.133 *Infrared spectrum (Thin Film, NaCl) of compound* ***239***.

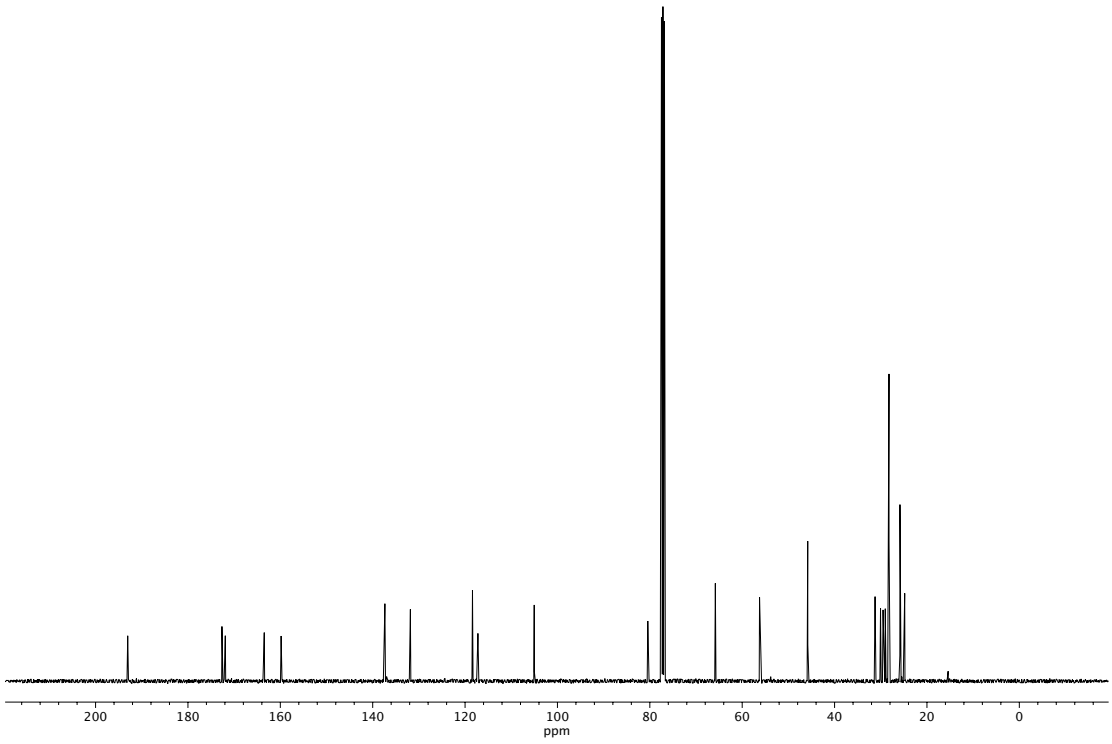

Figure A5.134 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***239***.

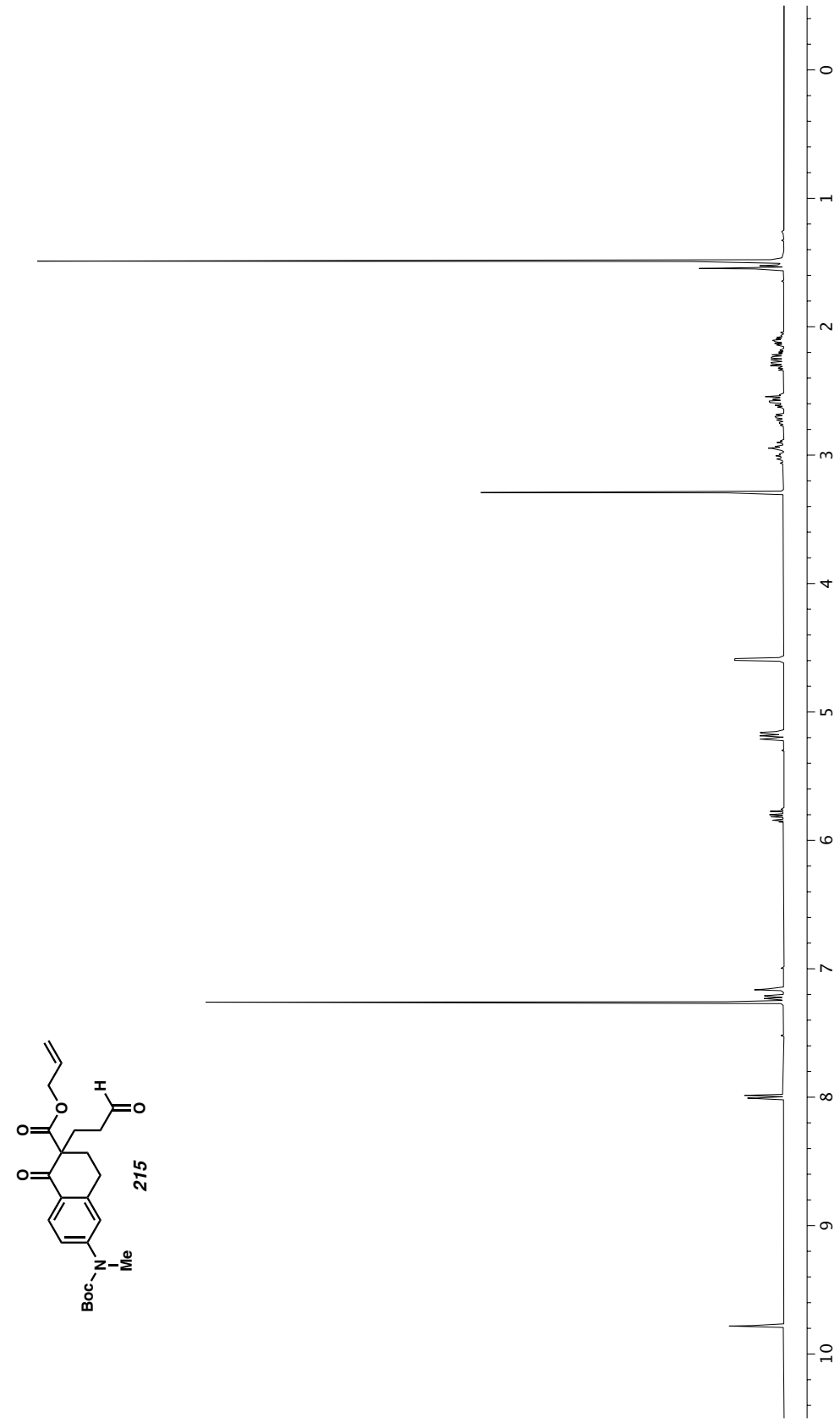

Figure A5.135 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***215***.

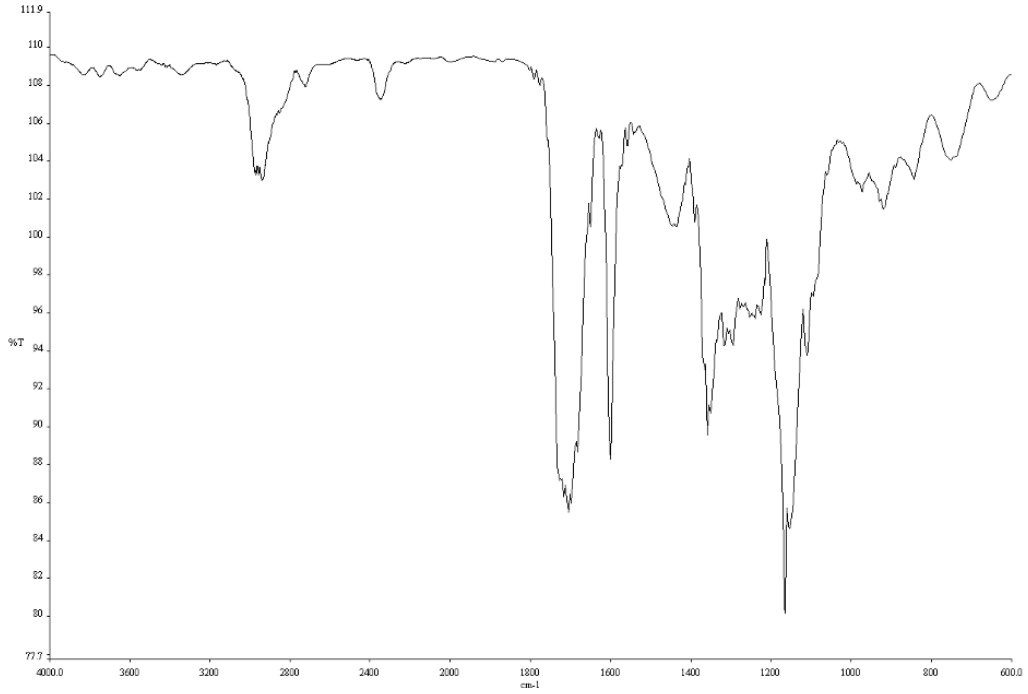

Figure A5.136 *Infrared spectrum (Thin Film, NaCl) of compound* ***215****.*

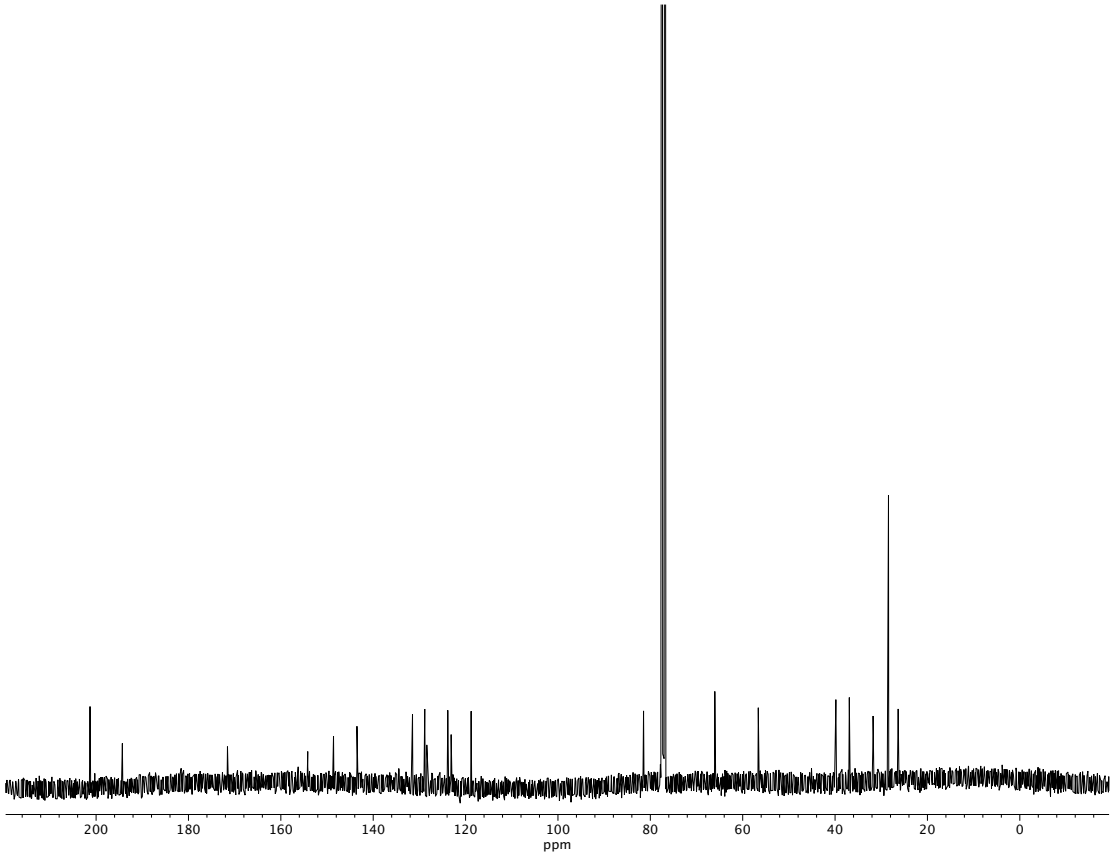

Figure A5.137 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***215****.*

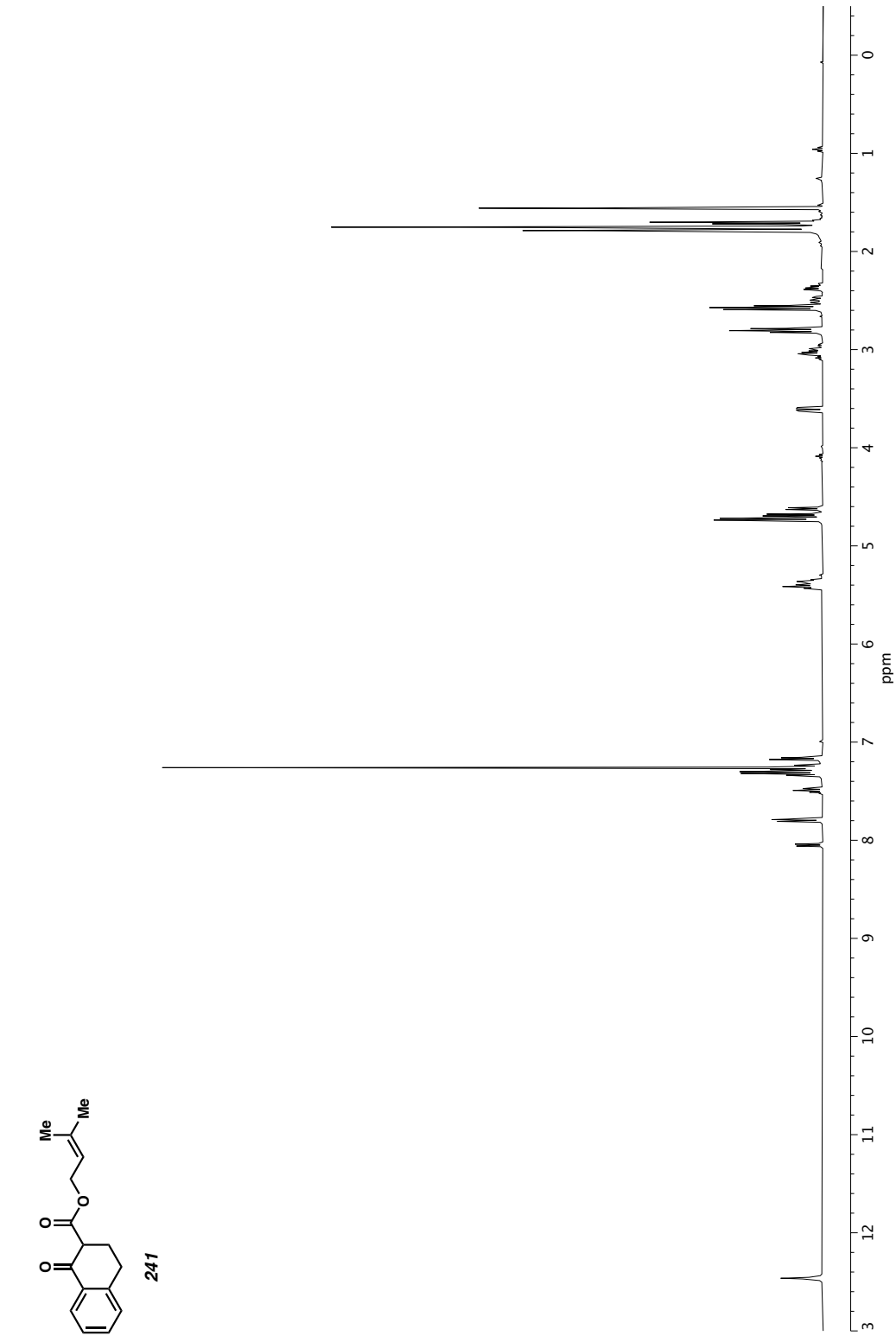

Figure A5.138 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***241****.*

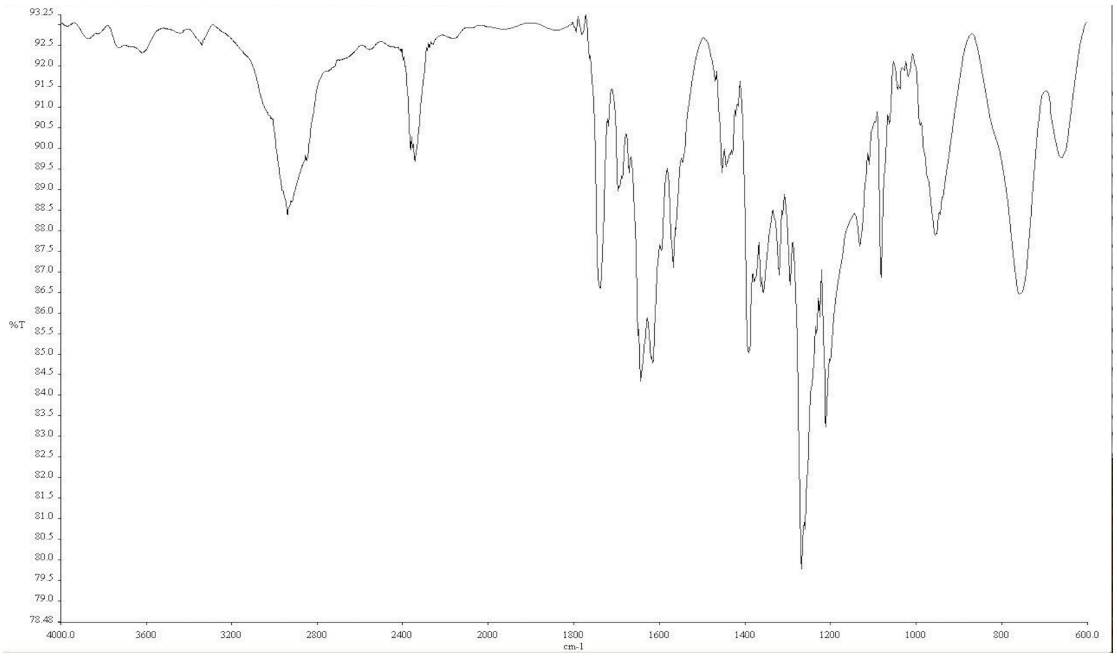

Figure A5.139 *Infrared spectrum (Thin Film, NaCl) of compound* ***241***.

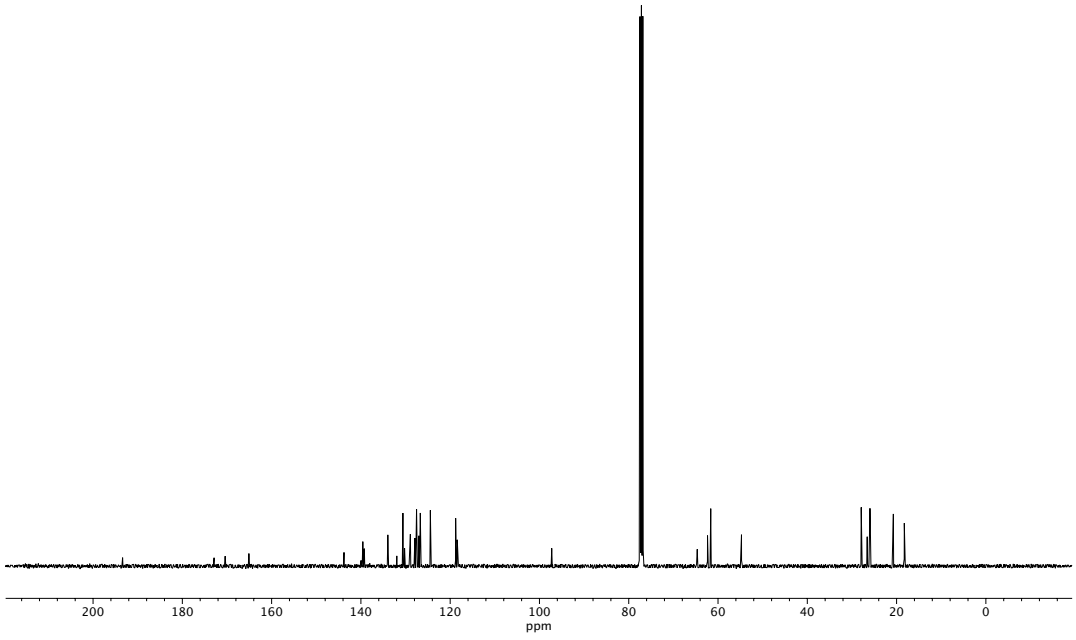

Figure A5.140 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***241***.

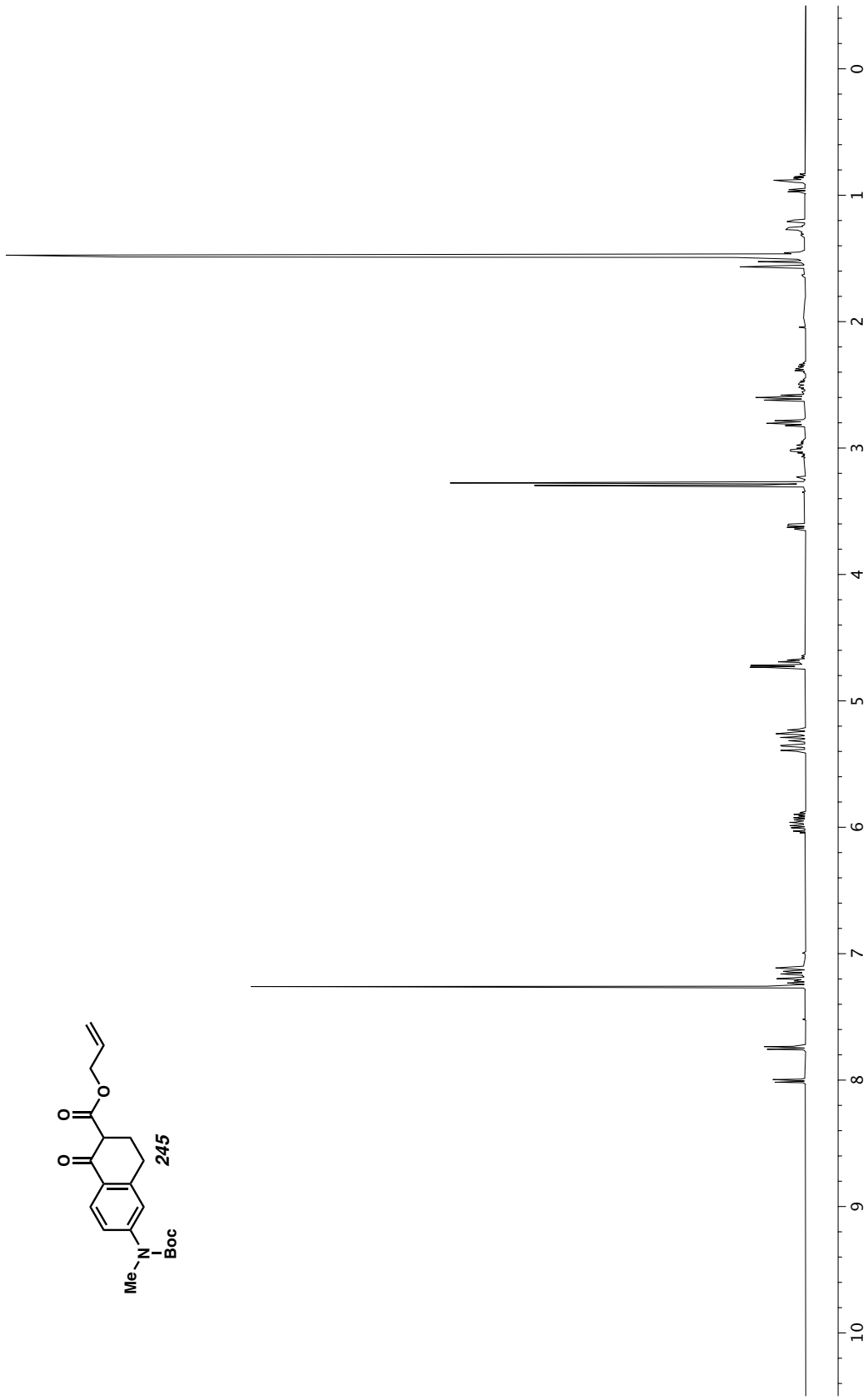

Figure A5.141 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***245****.*

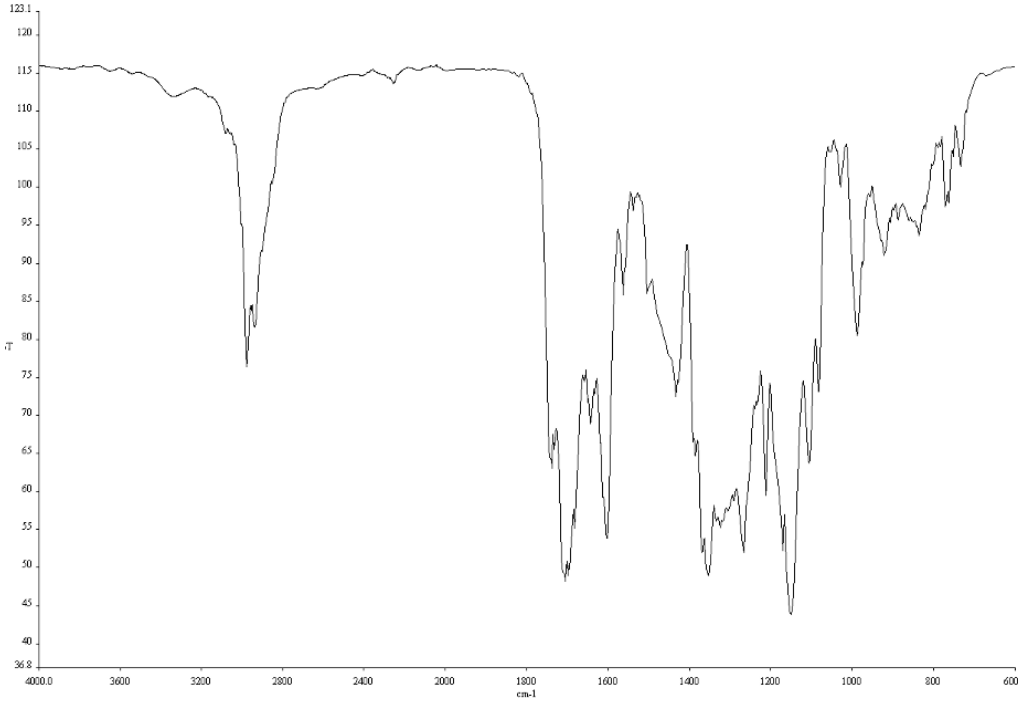

Figure A5.142 *Infrared spectrum (Thin Film, NaCl) of compound* ***245***.

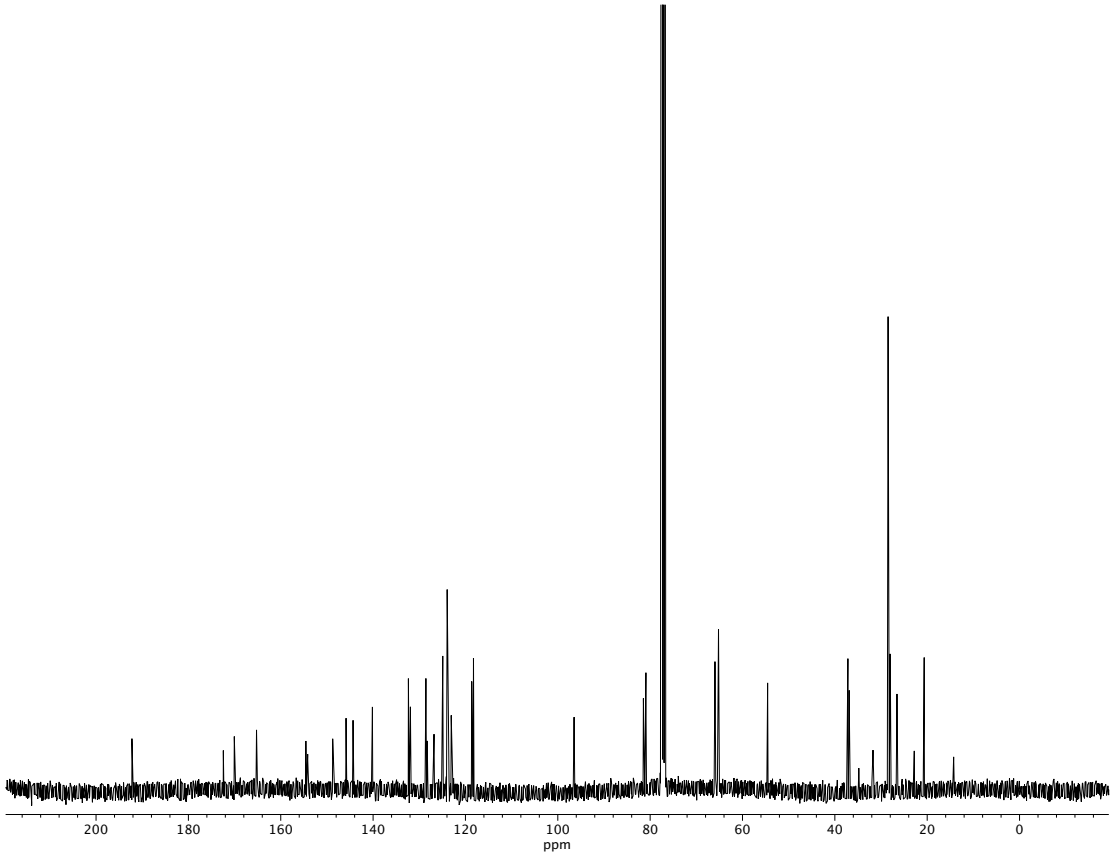

Figure A5.143 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***245***.

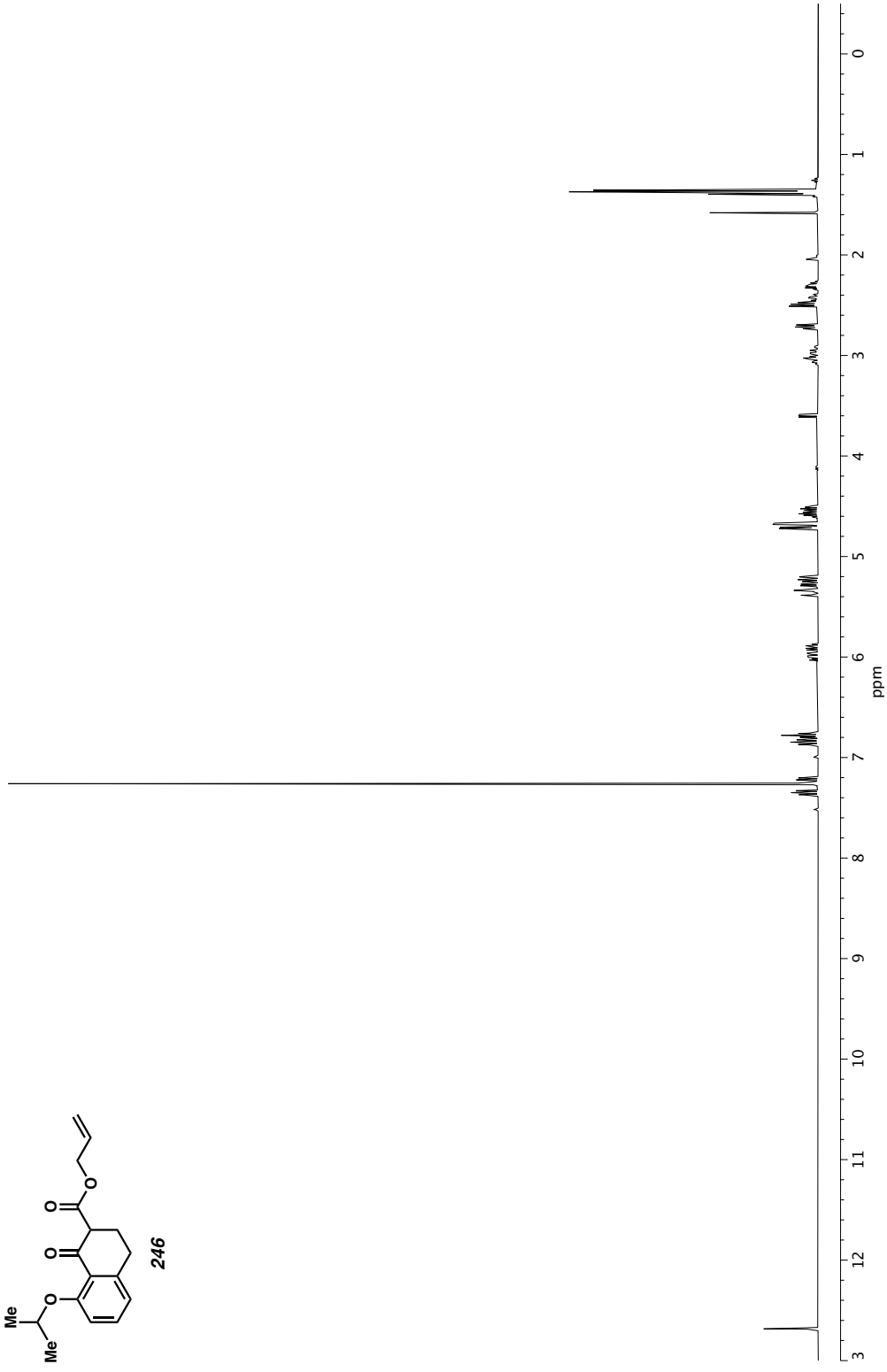

Figure A5.144 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***246****.*

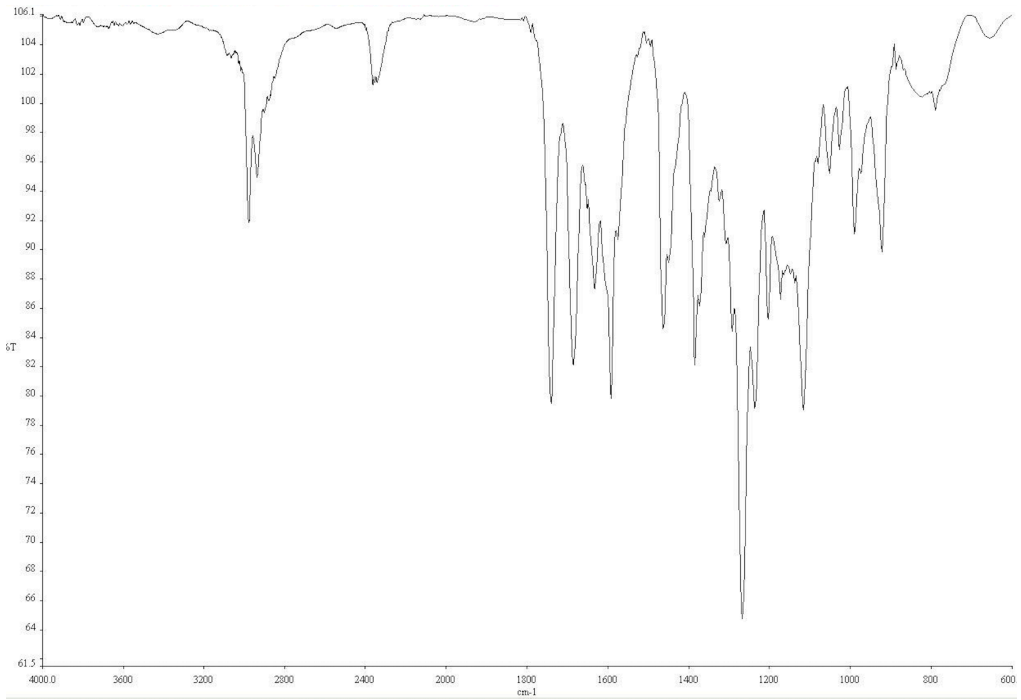

Figure A5.145 *Infrared spectrum (Thin Film, NaCl) of compound* ***246***.

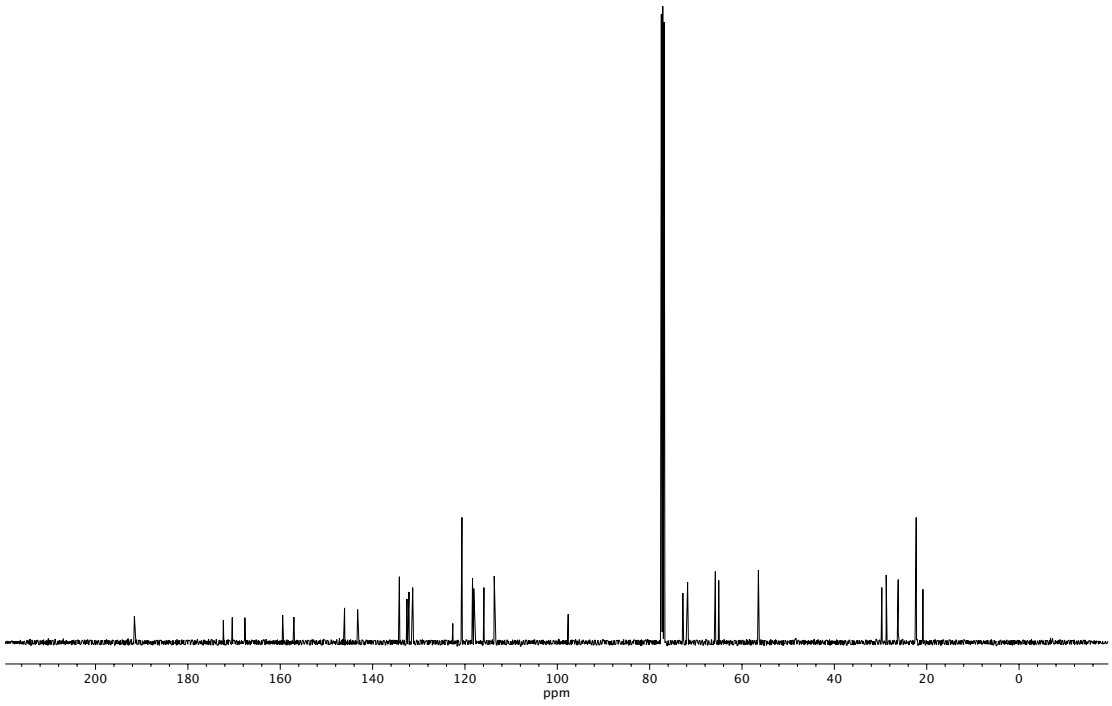

Figure A5.146 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***246***.

Figure A5.147 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***247****.*

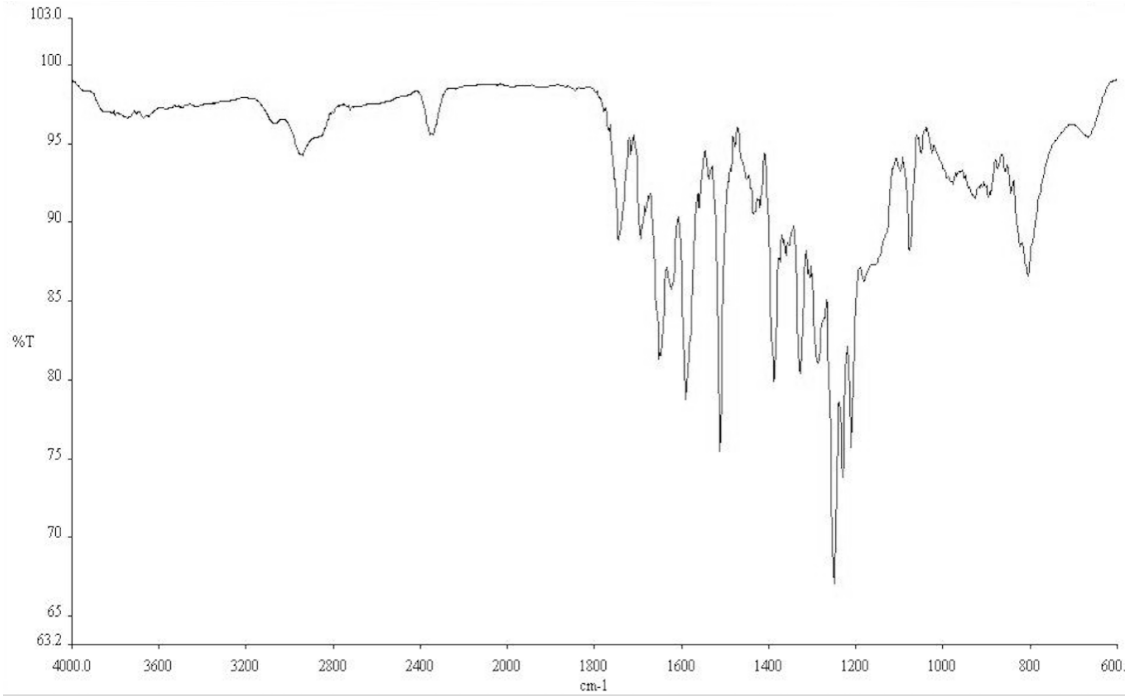

Figure A5.148 *Infrared spectrum (Thin Film, NaCl) of compound* ***247****.*

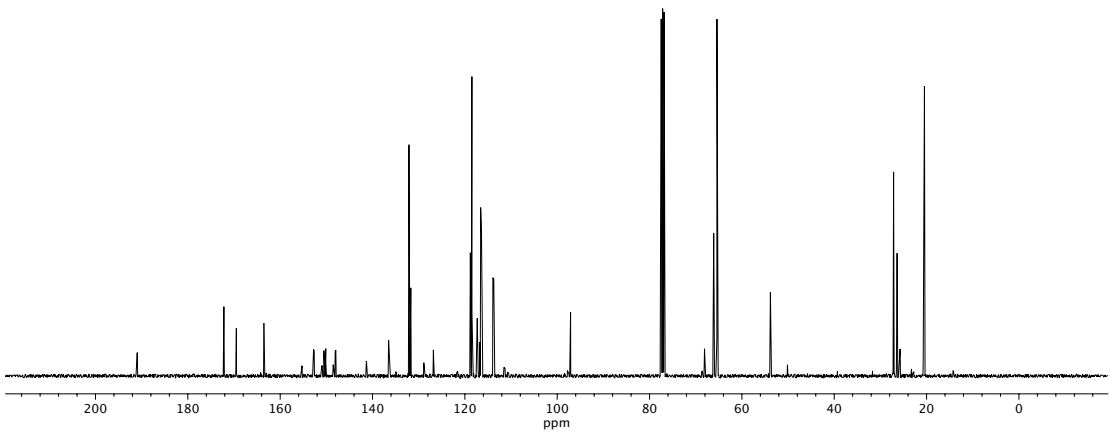

Figure A5.149 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***247****.*

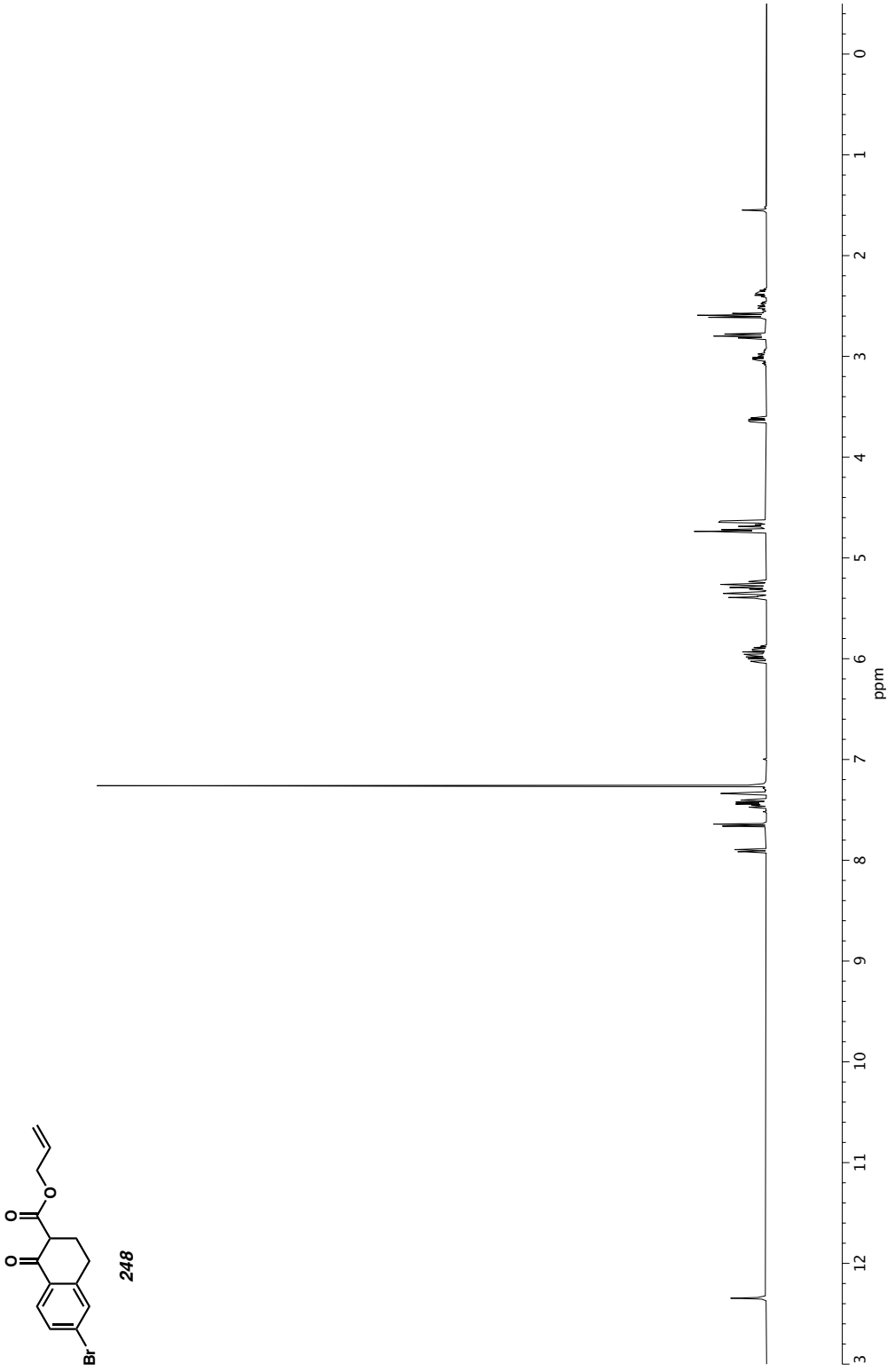

Figure A5.150 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***248****.*

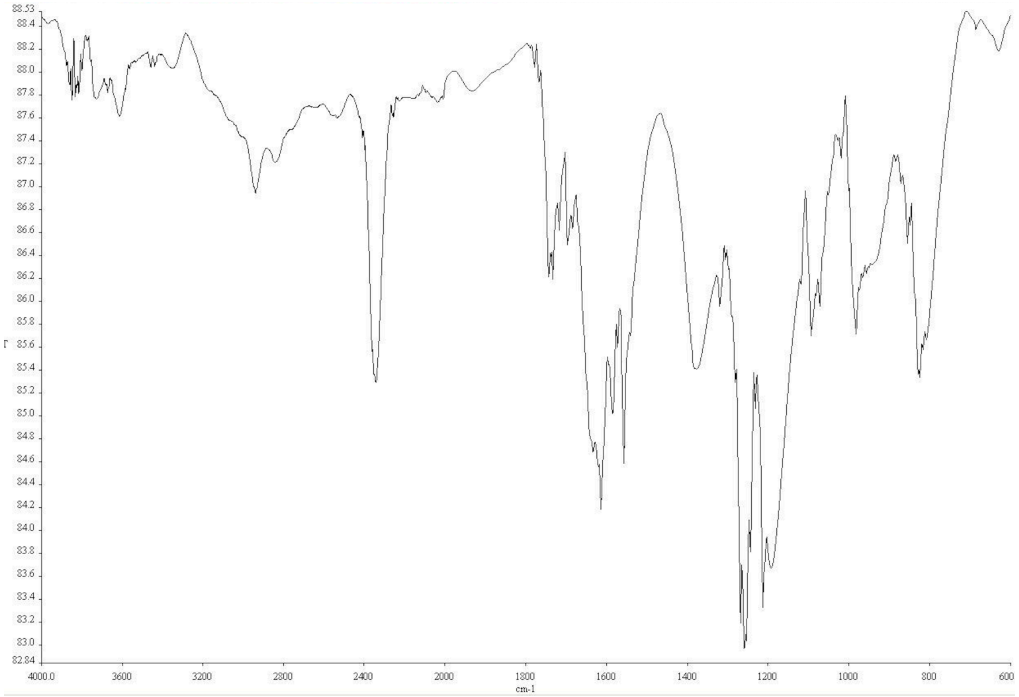

Figure A5.151 *Infrared spectrum (Thin Film, NaCl) of compound* ***248****.*

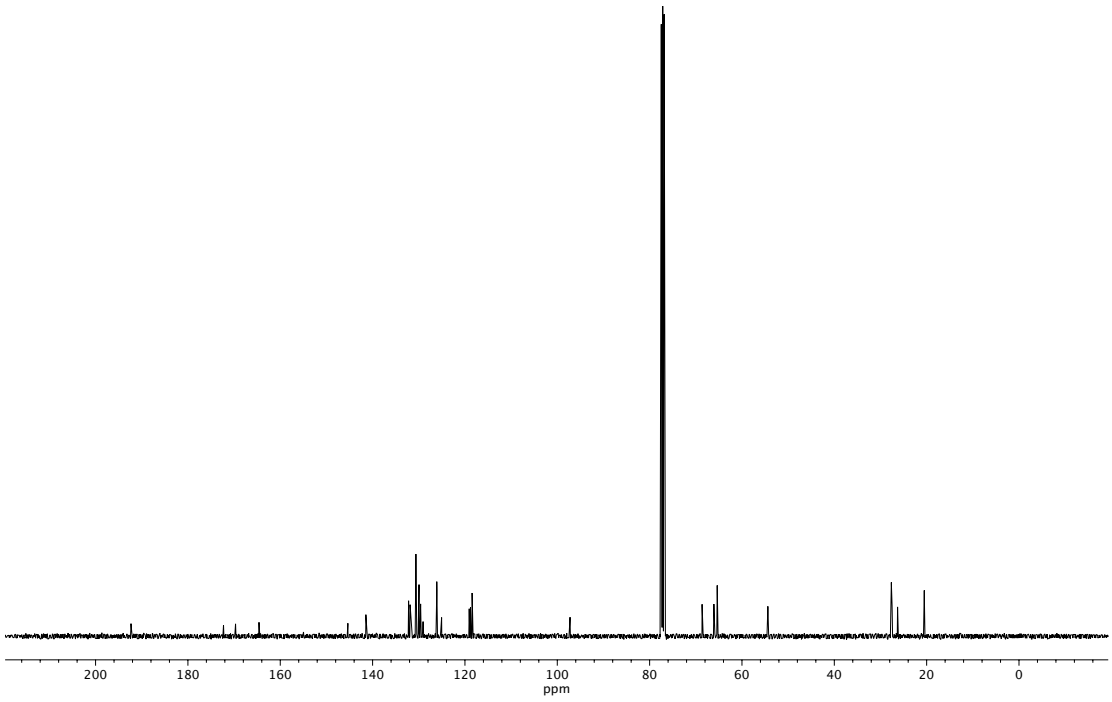

Figure A5.152 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***248****.*

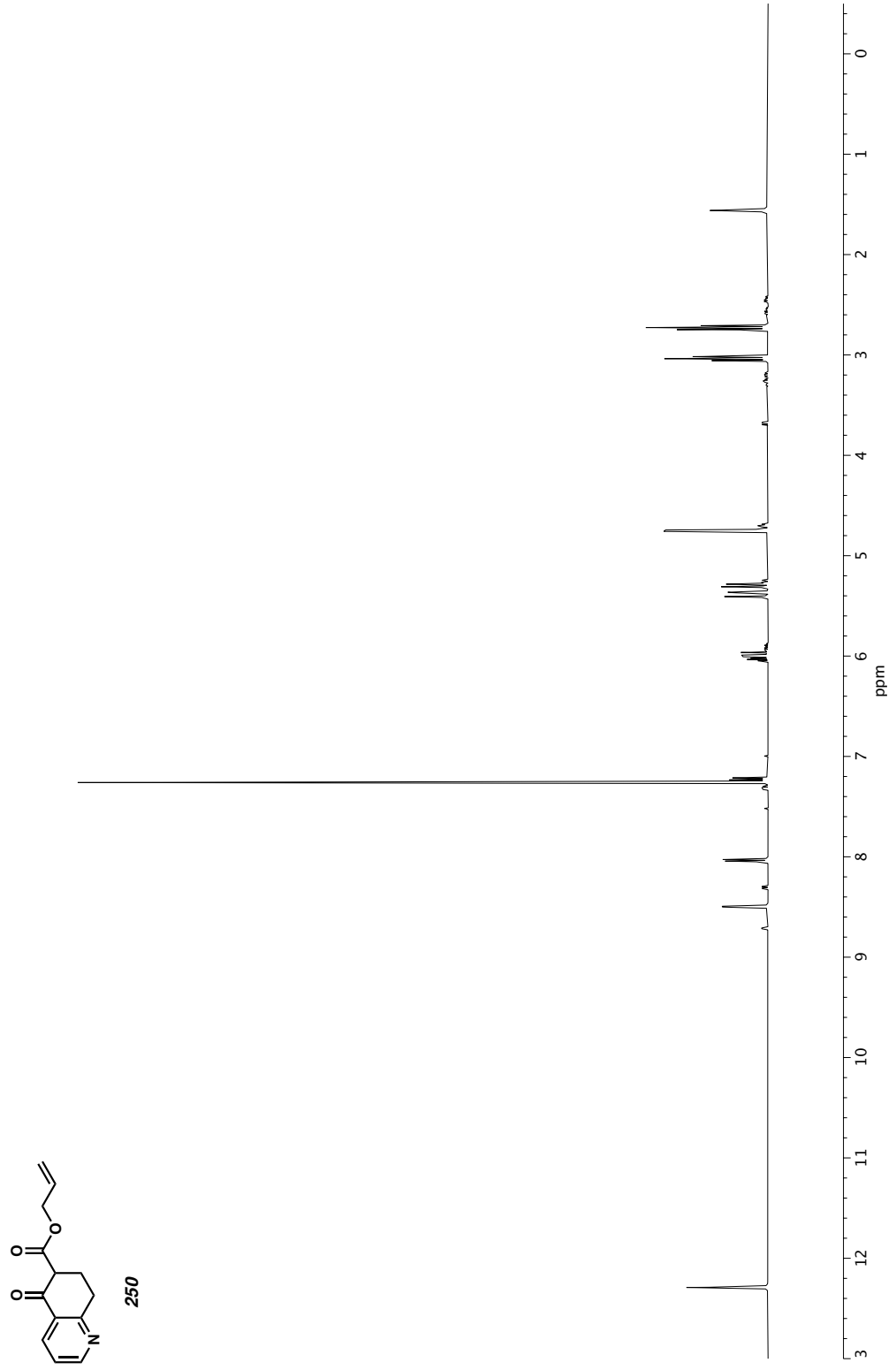

Figure A5.153 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***250***.

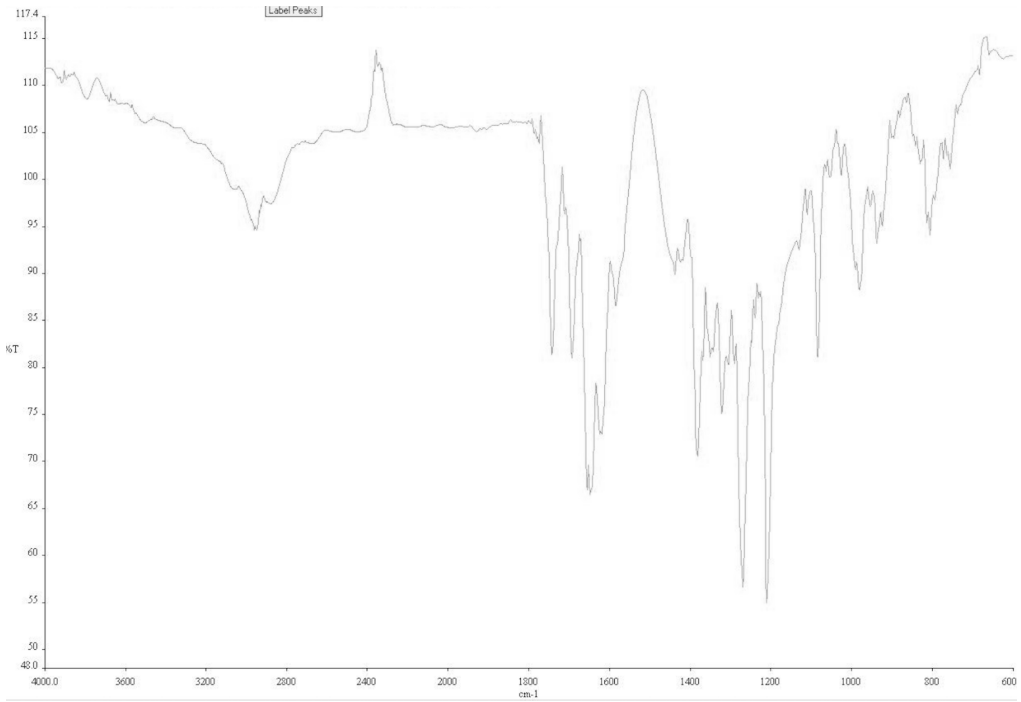

Figure A5.154 *Infrared spectrum (Thin Film, NaCl) of compound* ***250****.*

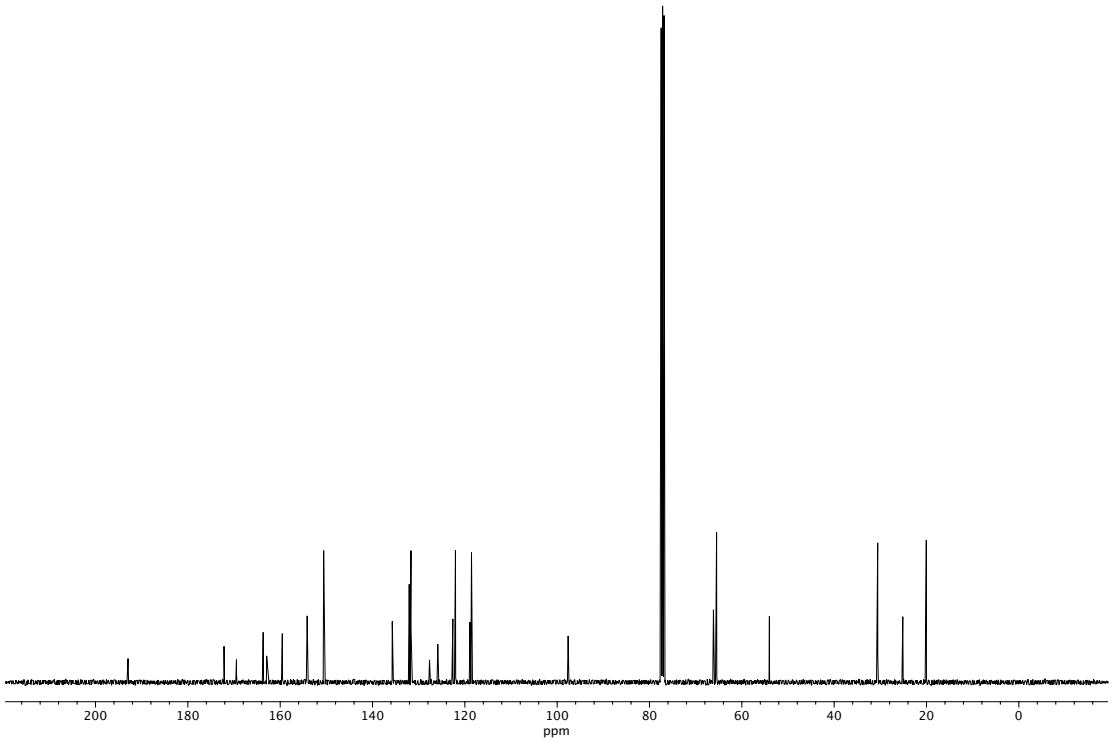

Figure A5.155 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***250****.*

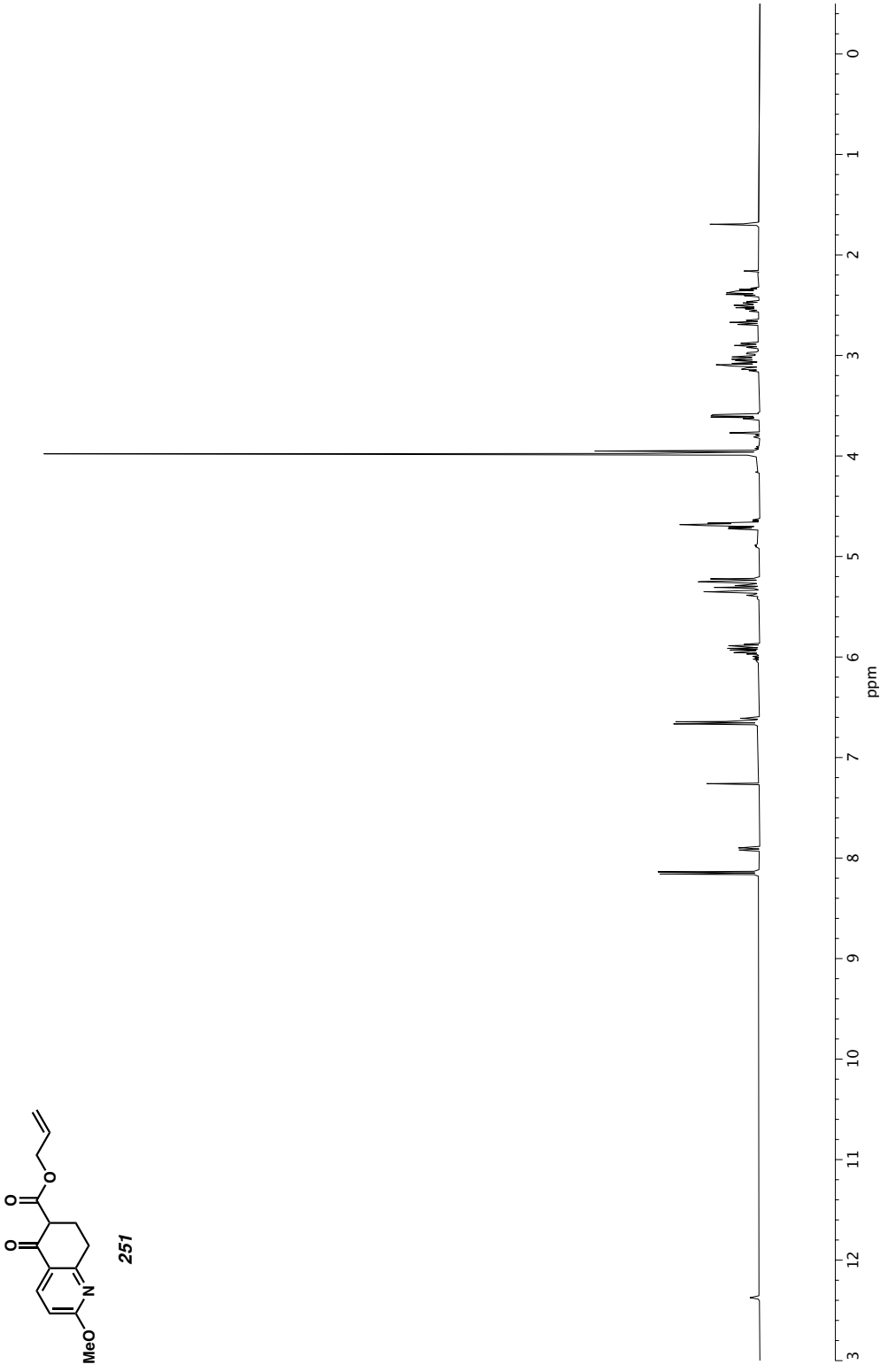

Figure A5.156 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***251****.*

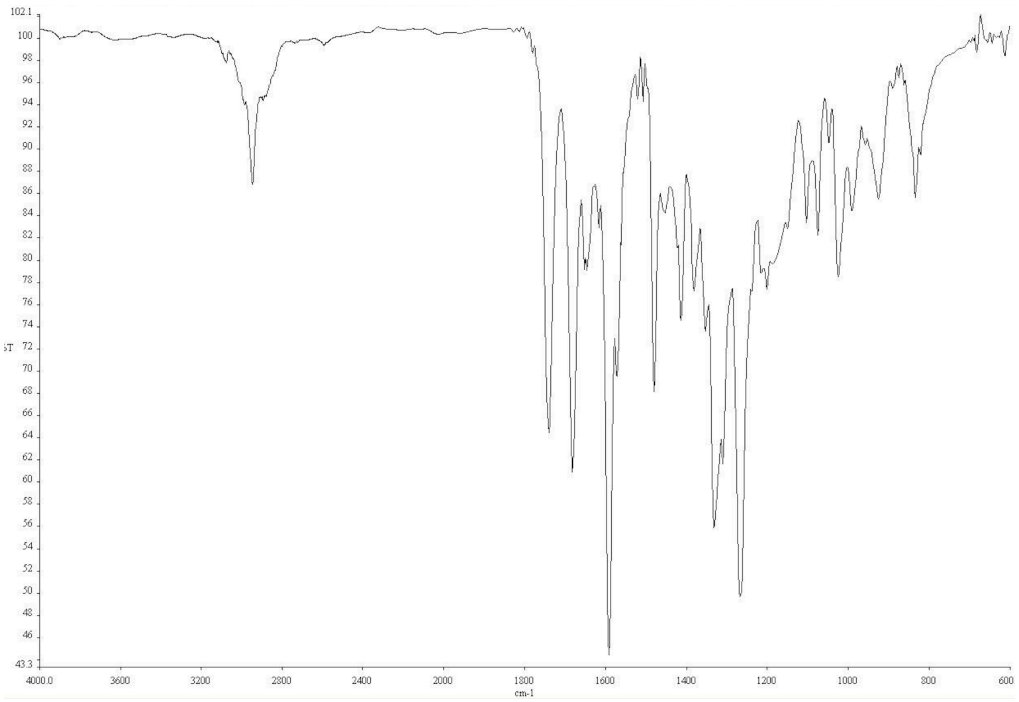

Figure A5.157 *Infrared spectrum (Thin Film, NaCl) of compound* ***251***.

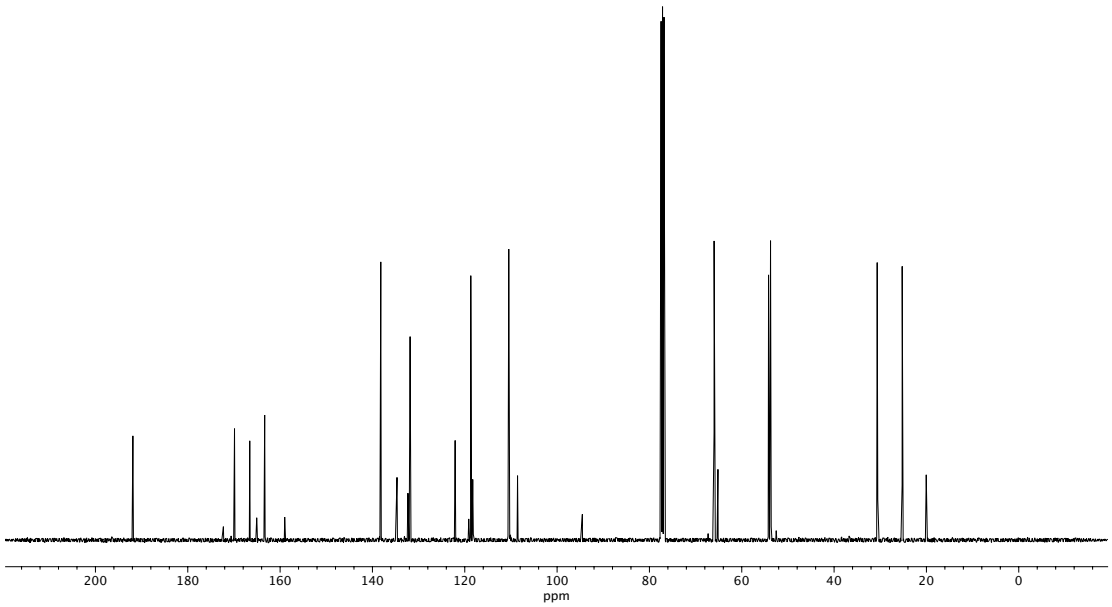

Figure A5.158 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***251***.

Figure A5.159 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***252***.

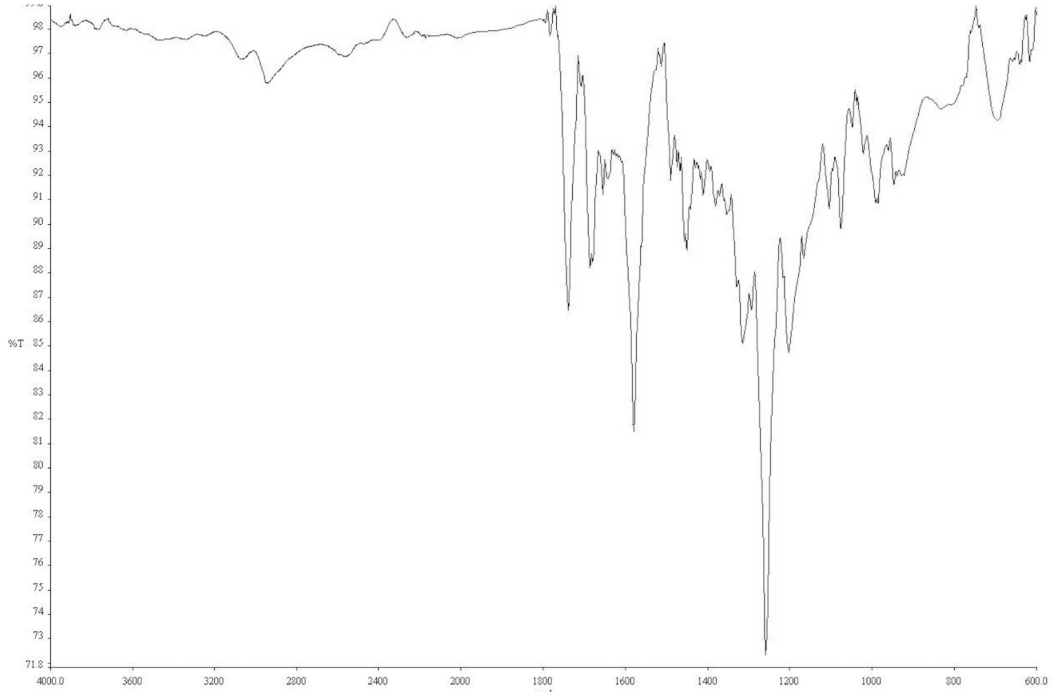

Figure A5.160 *Infrared spectrum (Thin Film, NaCl) of compound* ***252****.*

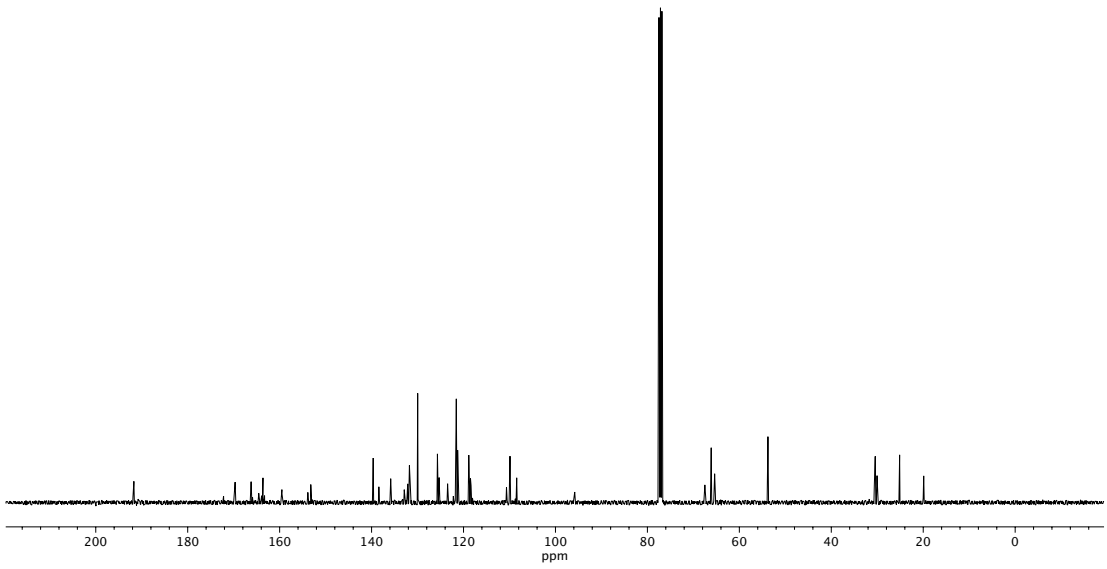

Figure A5.161 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***252****.*

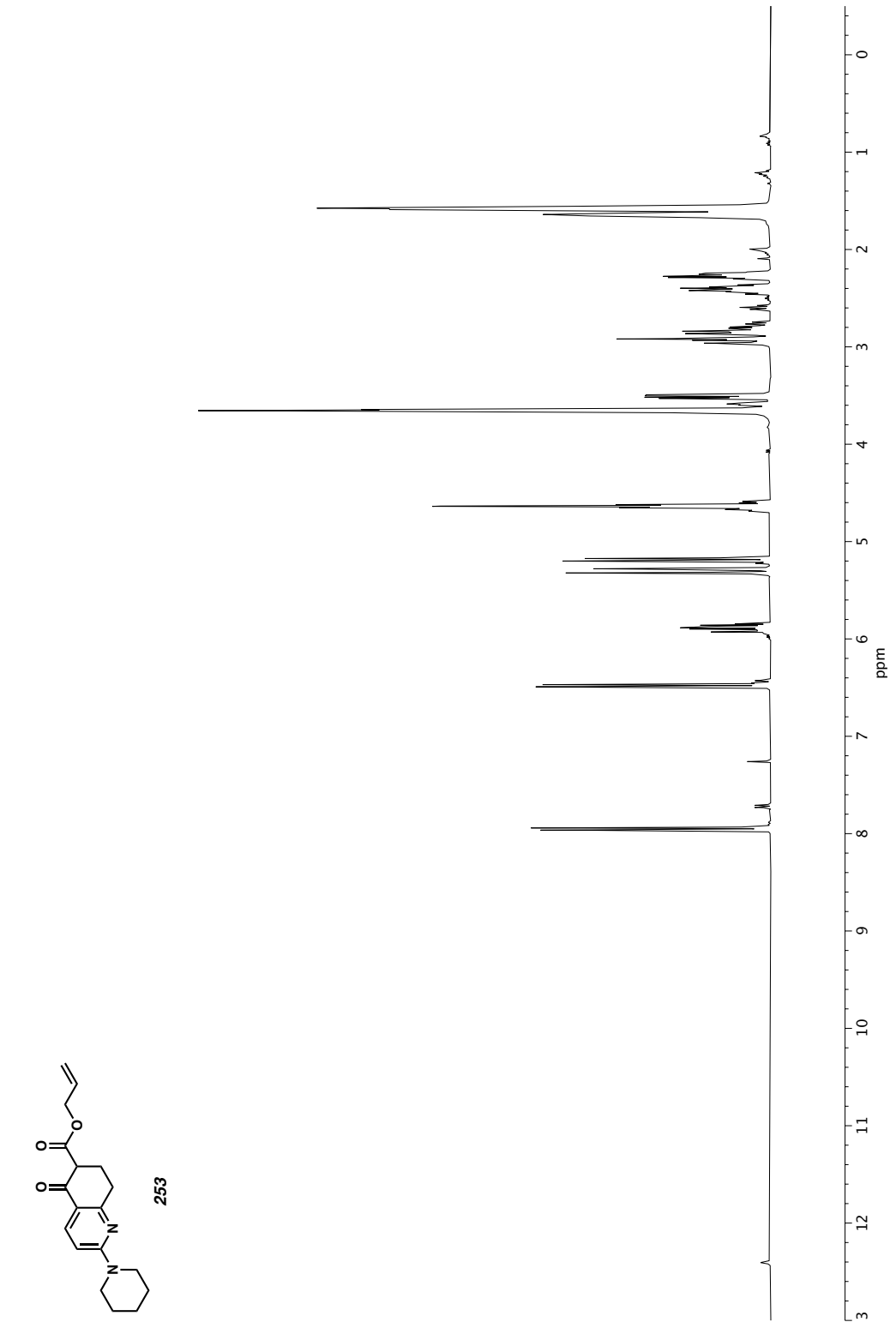

Figure A5.162 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***253***.

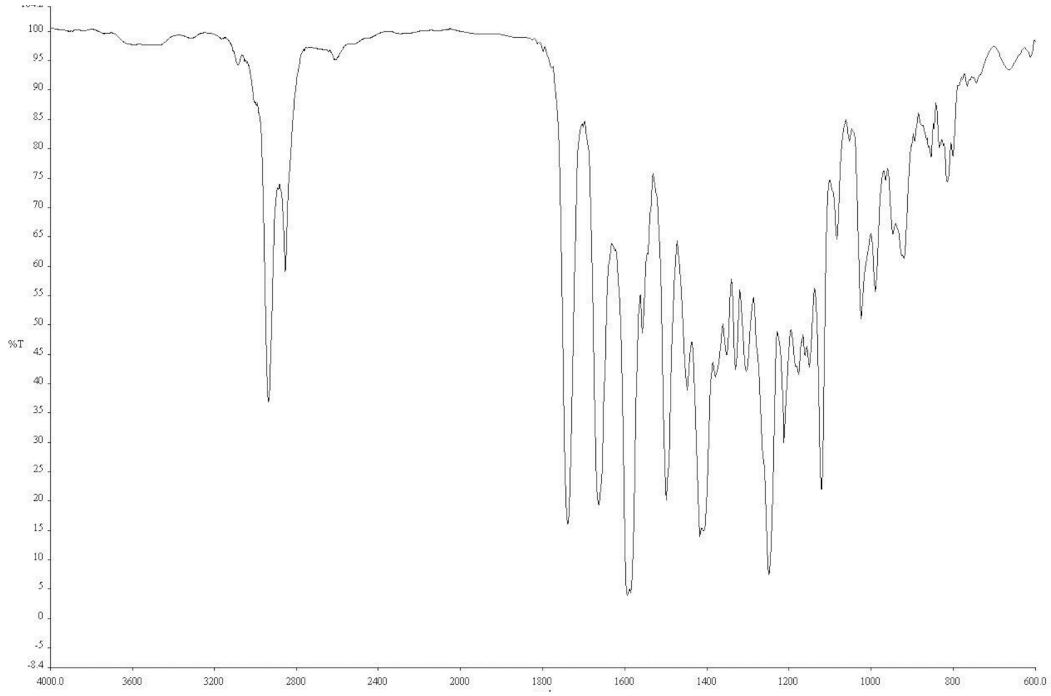

Figure A5.163 *Infrared spectrum (Thin Film, NaCl) of compound* ***253***.

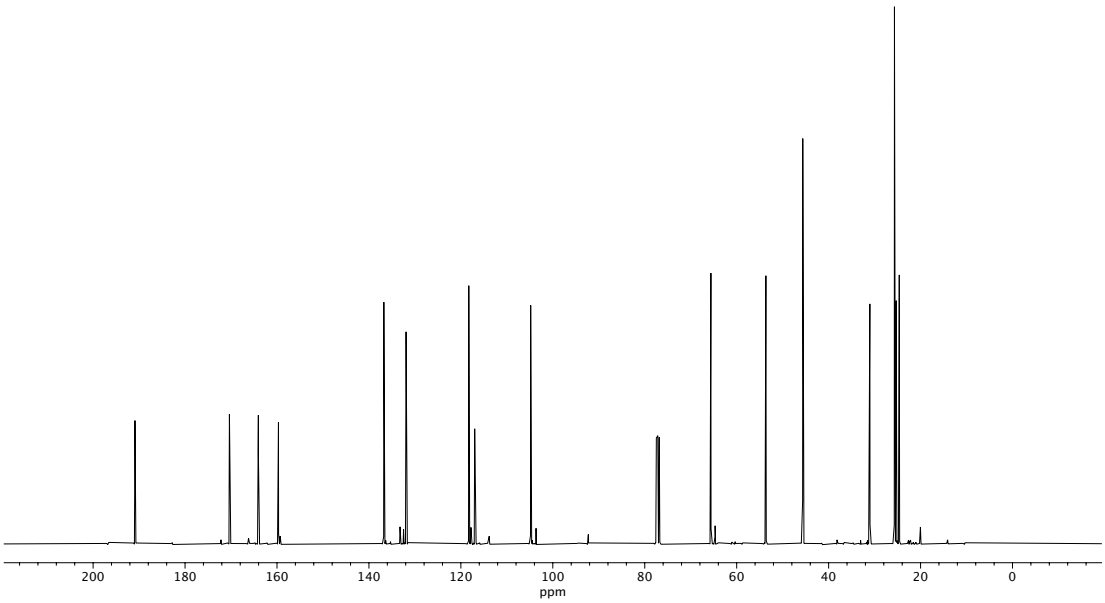

Figure A5.164 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***253***.

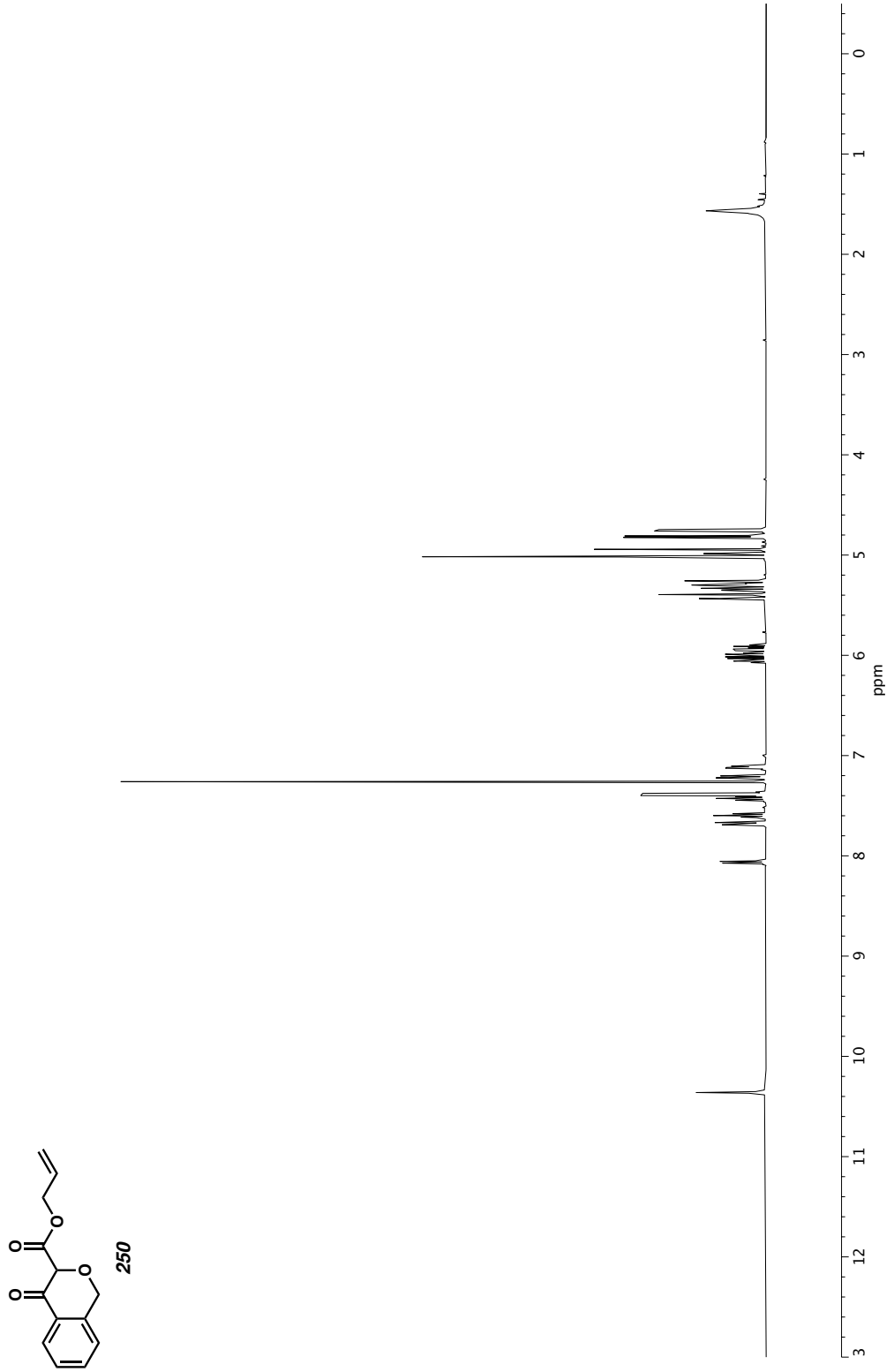

Figure A5.165 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***250****.*

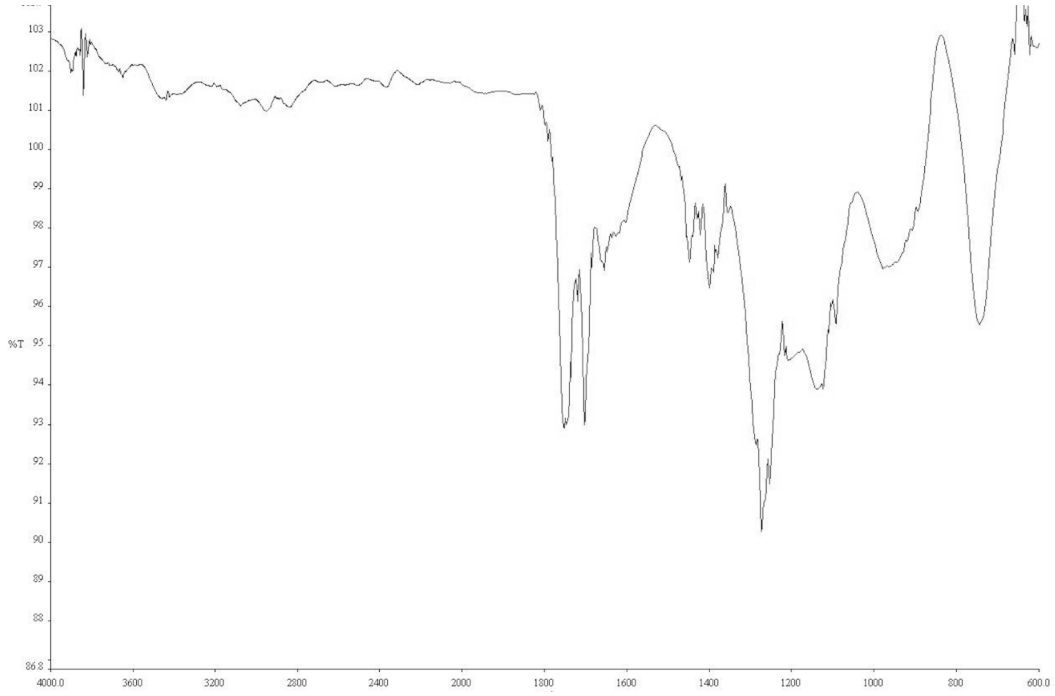

Figure A5.166 *Infrared spectrum (Thin Film, NaCl) of compound* ***250***.

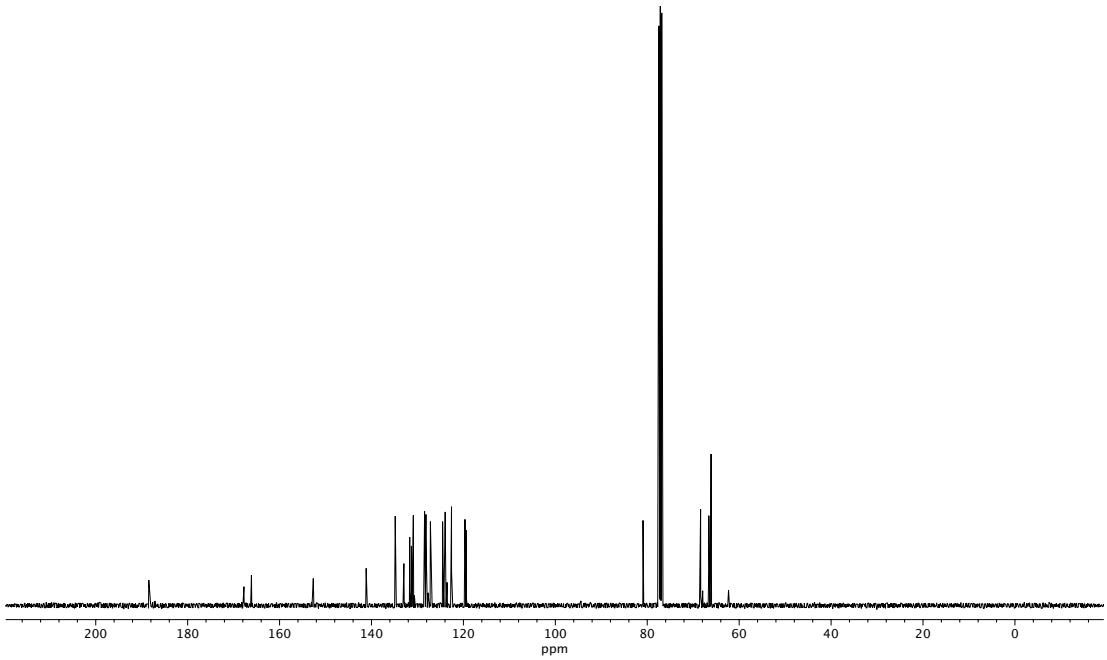

Figure A5.167 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***250***.

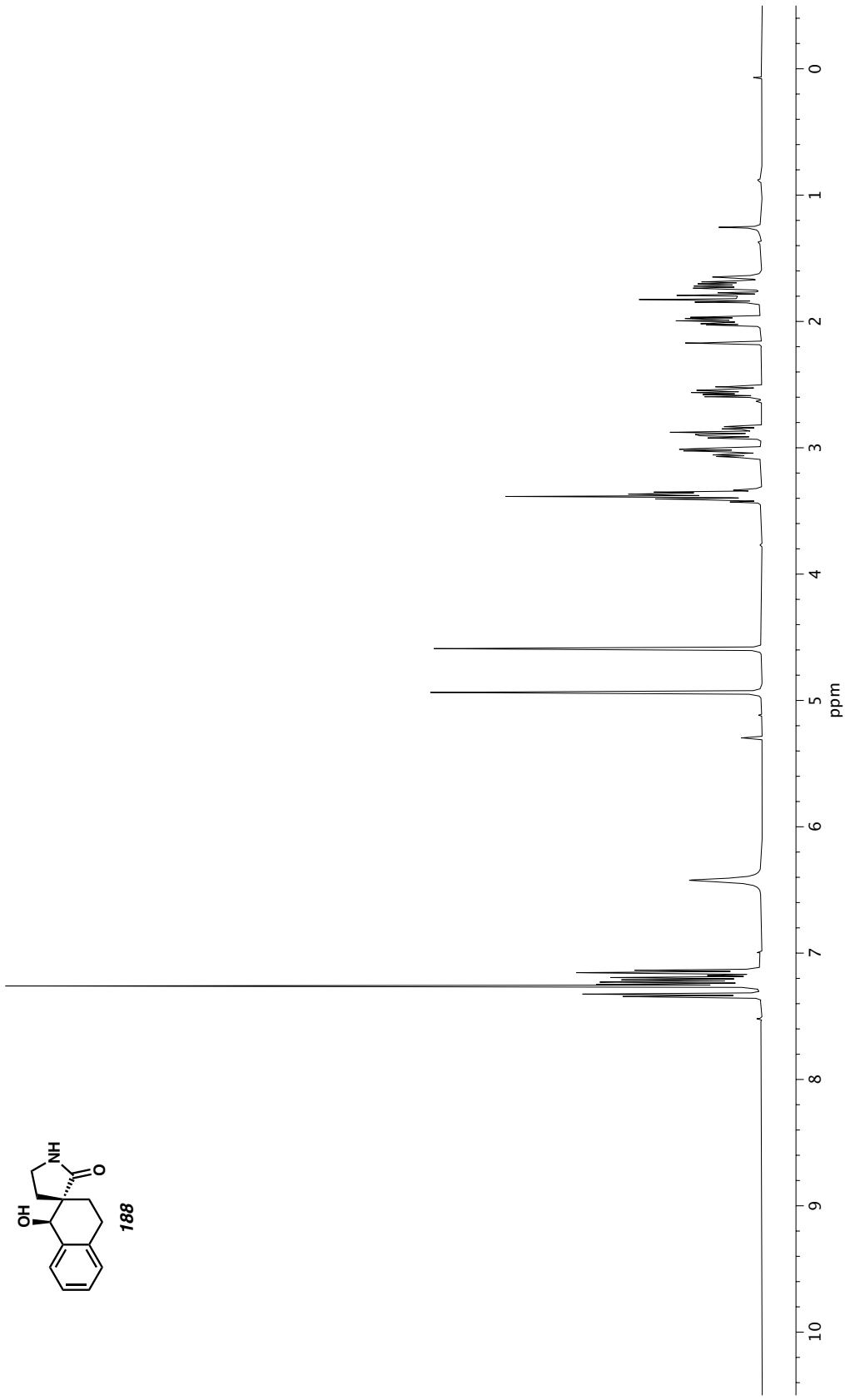

Figure A5.168 *^{1}H NMR (400 MHz, $CDCl_3$) of compound **188**.*

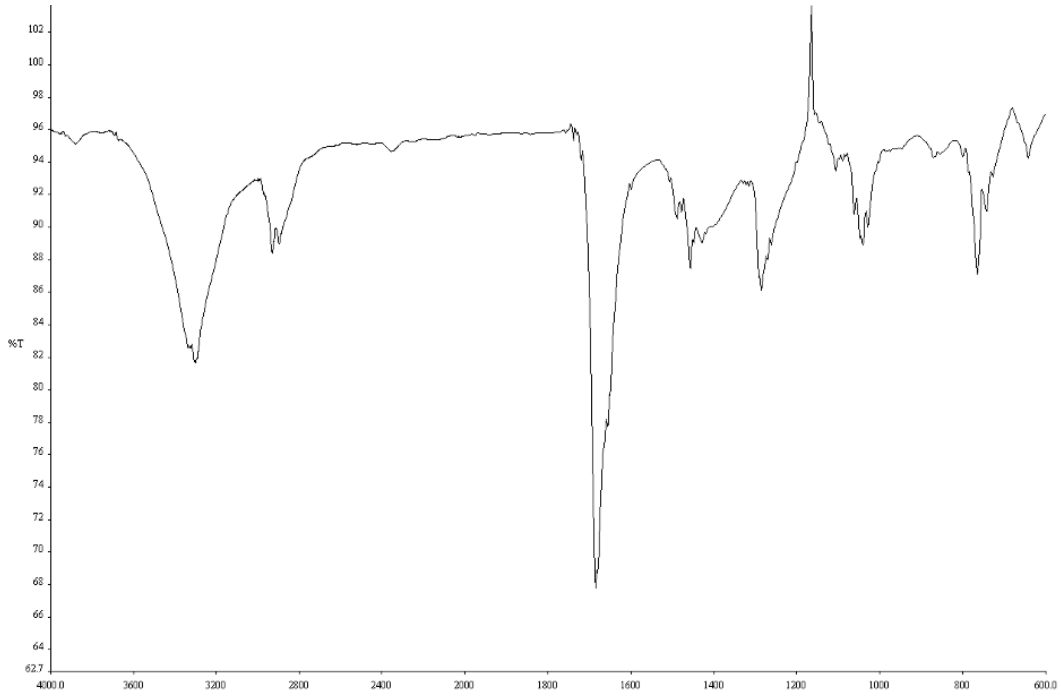

Figure A5.169 *Infrared spectrum (Thin Film, NaCl) of compound* ***188****.*

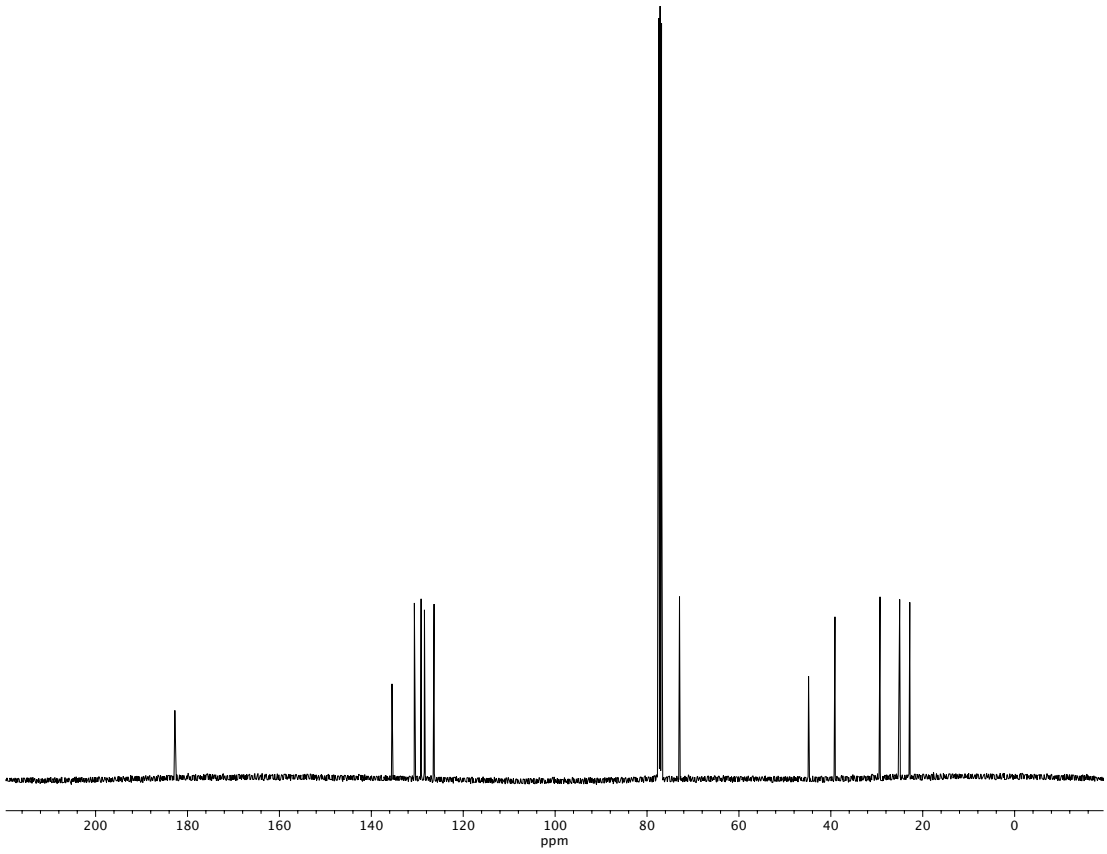

Figure A5.170 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***188****.*

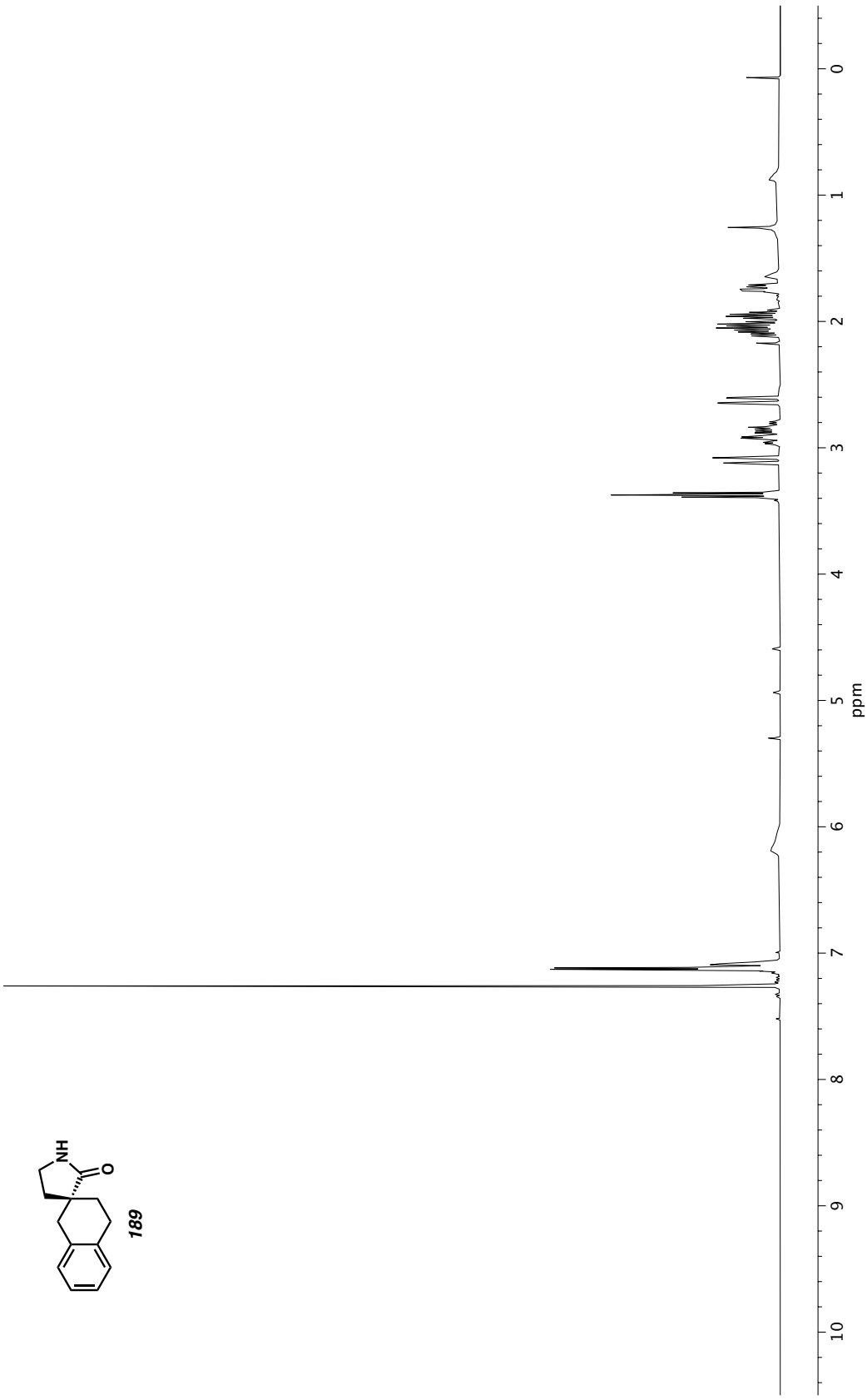

Figure A5.171 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***189***.

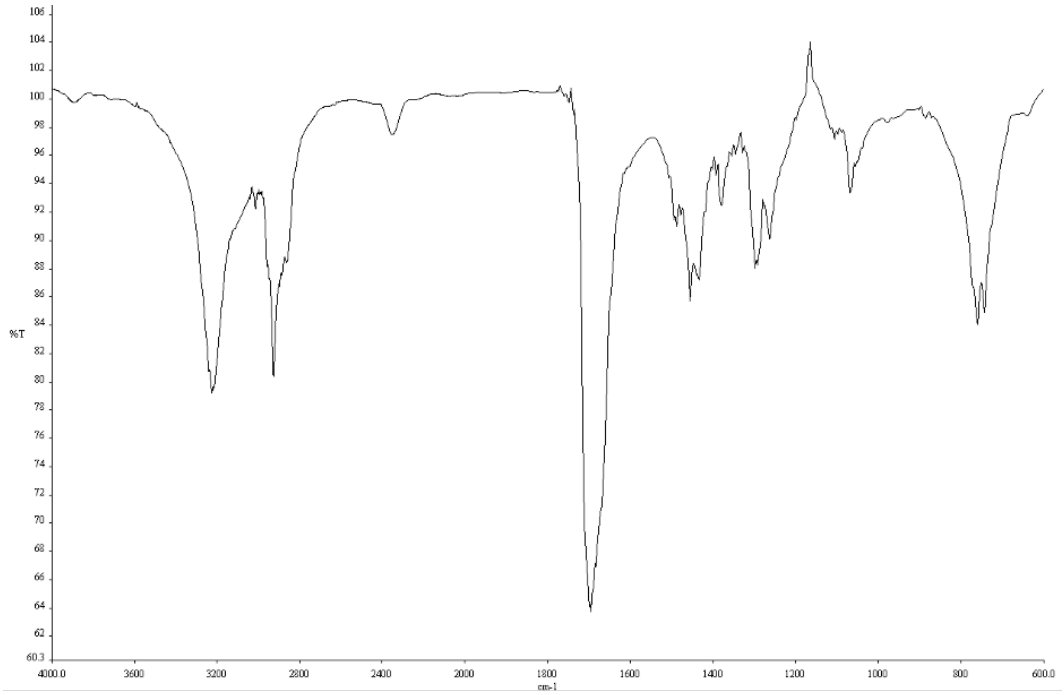

Figure A5.172 *Infrared spectrum (Thin Film, NaCl) of compound* ***189***.

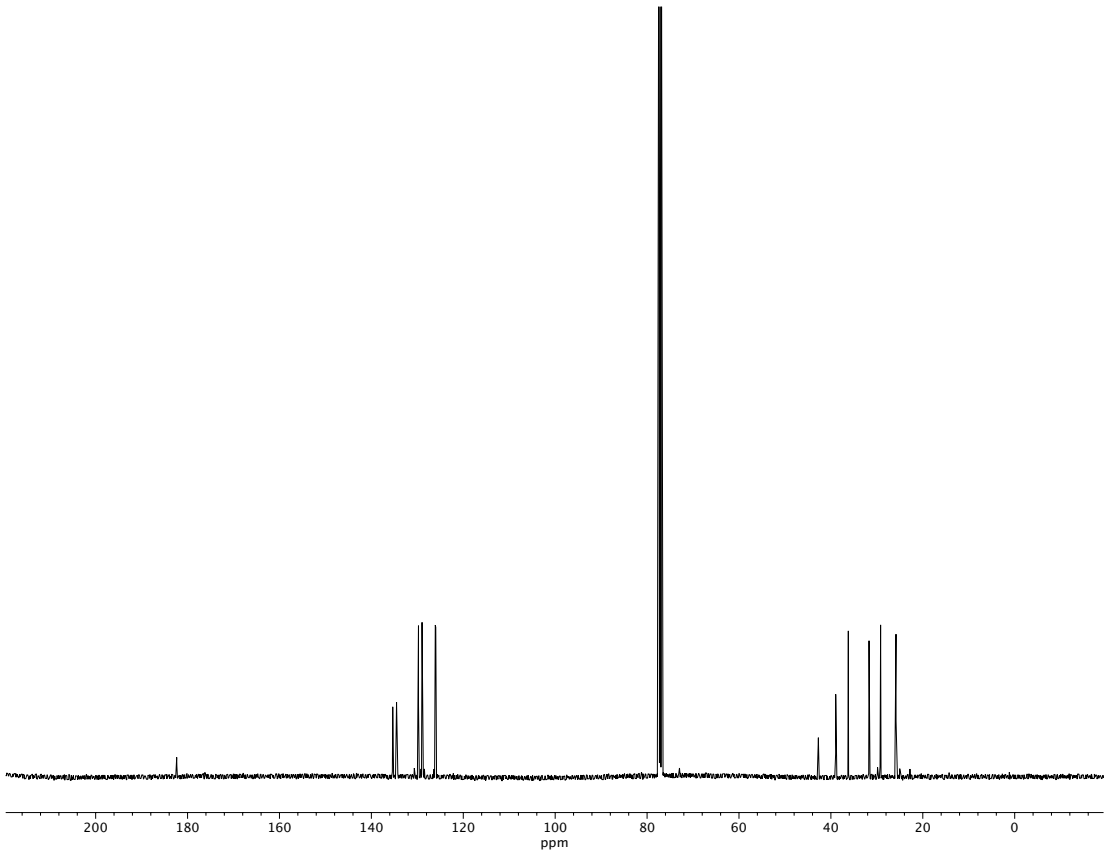

Figure A5.173 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***189***.

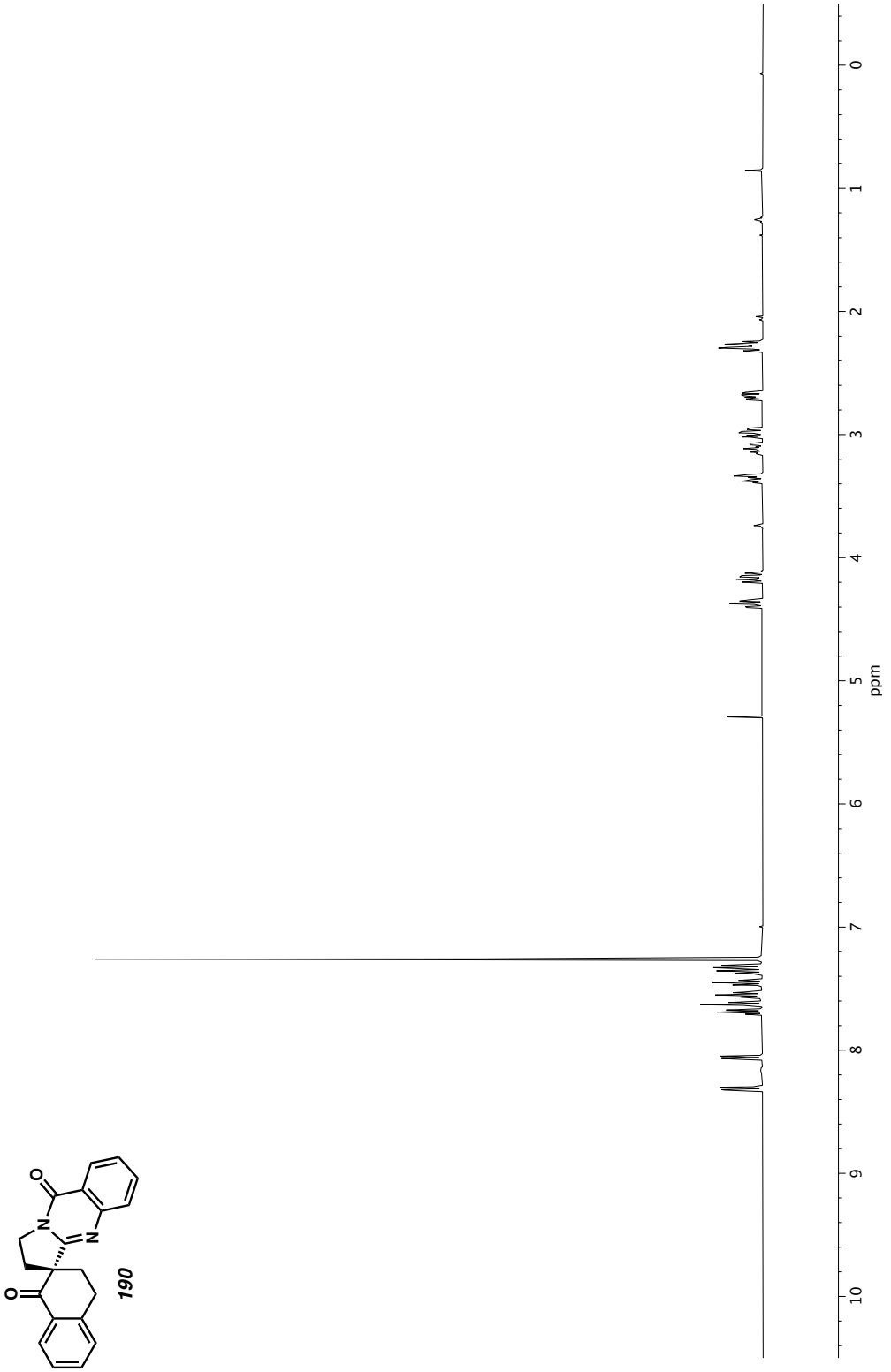

Figure A5.174 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***190***.

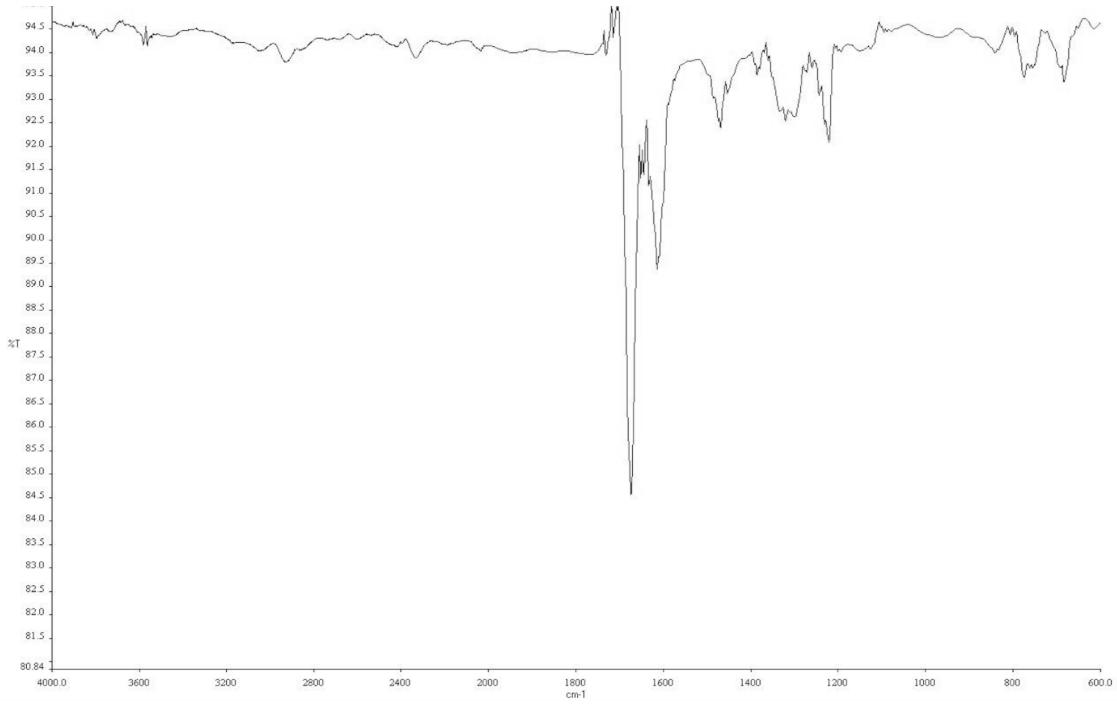

Figure A5.175 *Infrared spectrum (Thin Film, NaCl) of compound* ***190***.

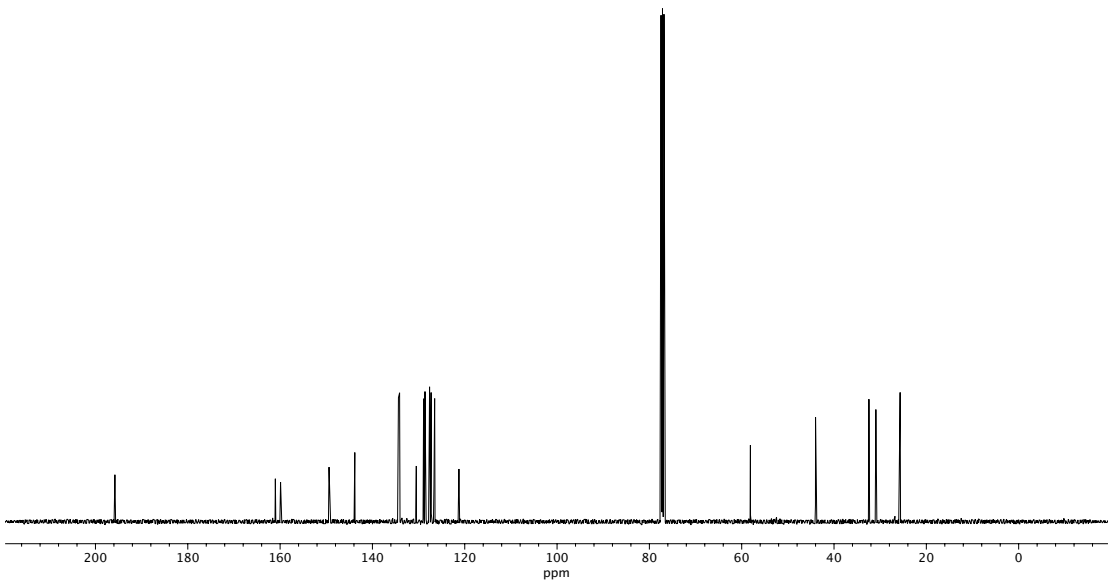

Figure A5.176 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***190***.

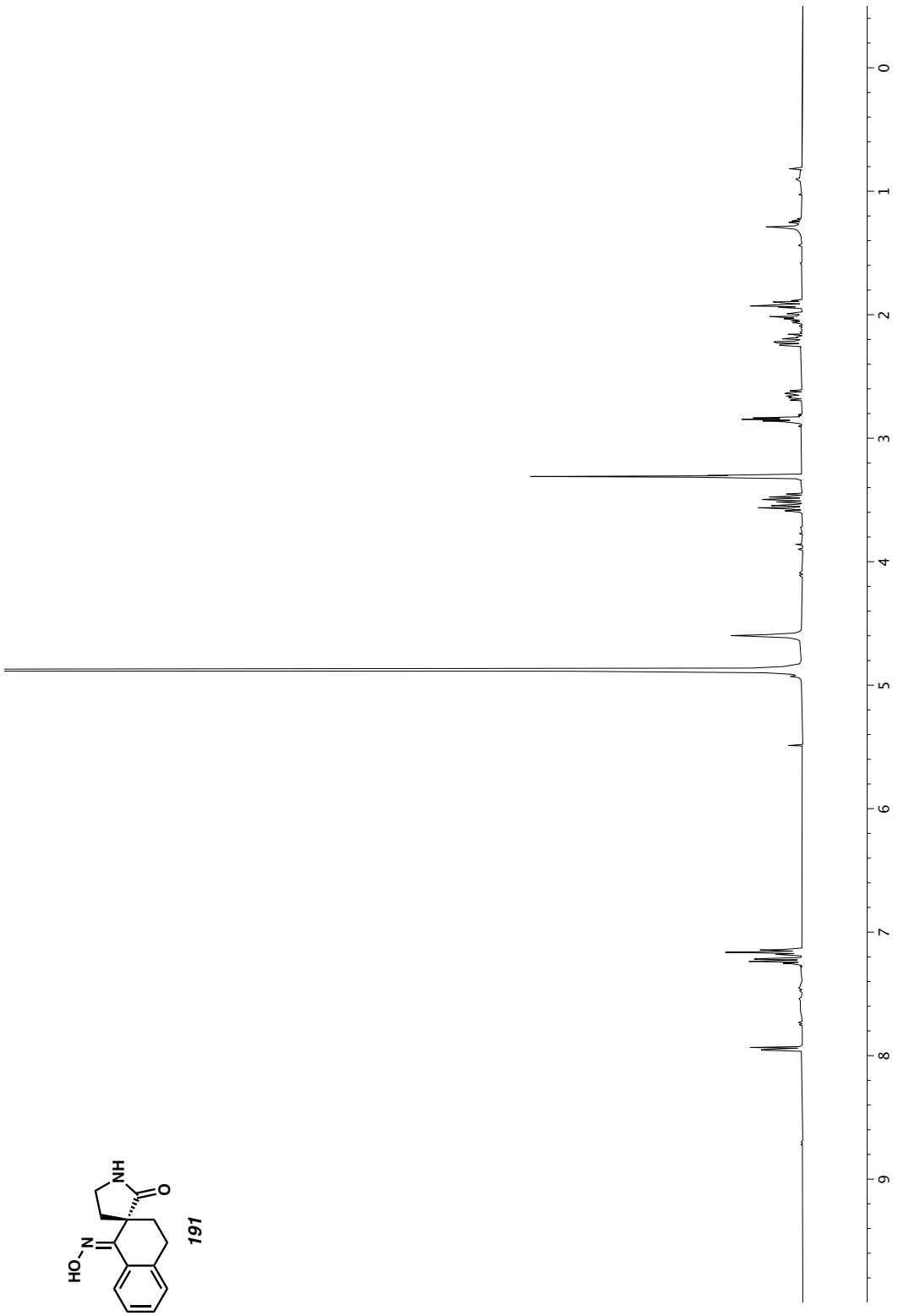

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Figure A5.177 *^1H NMR (400 MHz, CD_3OD) of compound* ***191****.*

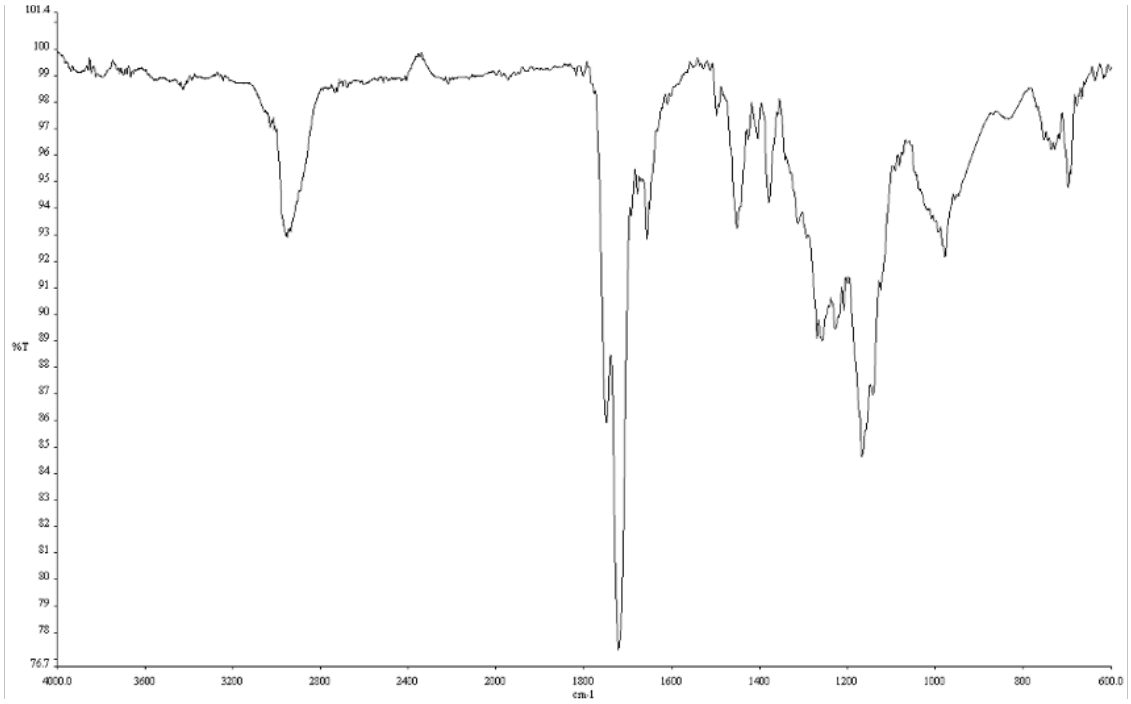


Figure A5.178 *Infrared spectrum (Thin Film, NaCl) of compound* ***191***.

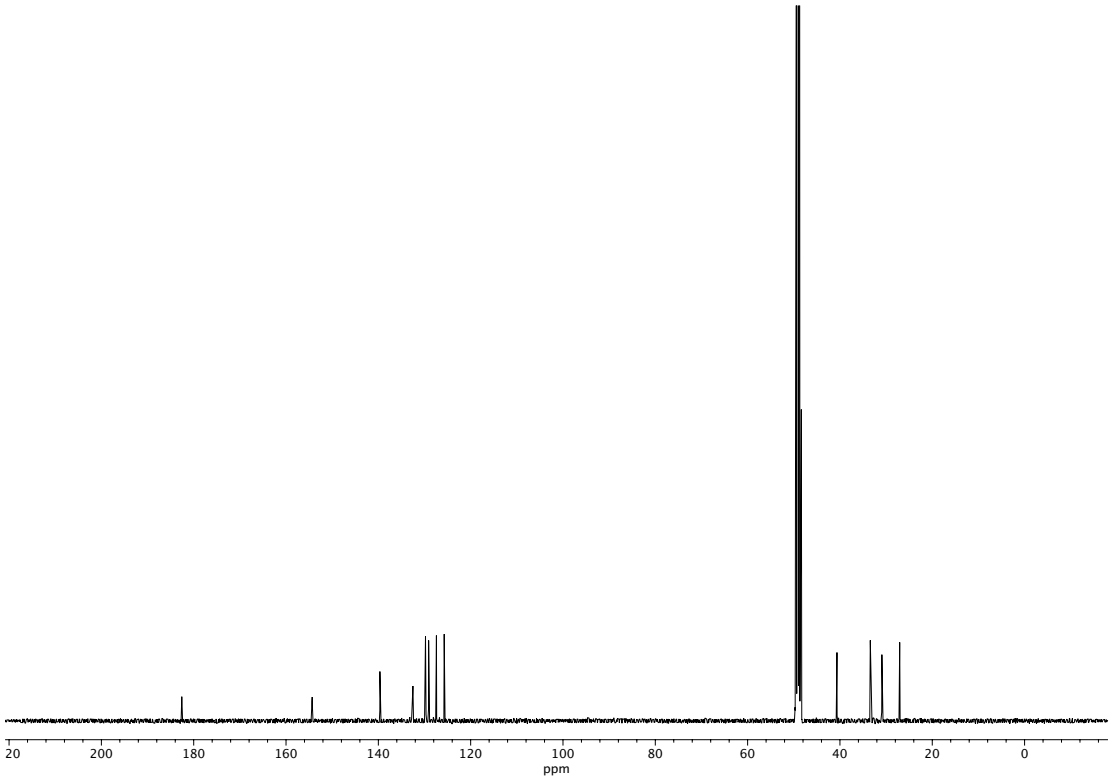


Figure A5.179 *^{13}C NMR (100 MHz, CD_3OD) of compound* ***191***.

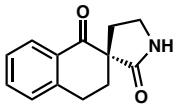
APPENDIX 6

X-Ray Crystallographic Reports Relevant to Chapter 2: An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates

A6.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A6.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF PRODUCT 167



167

Compound **167** was crystallized from a mixture of dichloromethane and pentane at 23 °C to provide crystals suitable for X-ray analysis.

Figure A6.1 *X-ray crystal structure of spirocycle* ***167****.*

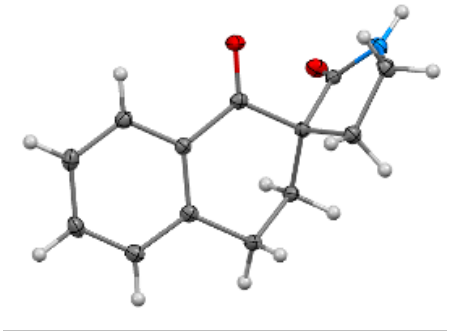


Table A6.1. *Crystal data and structure refinement for spirocycle* ***167****.*

Empirical formula	C13 H13 N O2	
Formula weight	215.24	
Temperature	101(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.9799(8) Å	a= 90°.
	b = 6.1366(5) Å	b= 105.205(7)°.
	c = 12.9790(12) Å	g = 90°.
Volume	536.47(9) Å3	
Z	2	
Density (calculated)	1.332 Mg/m3	
Absorption coefficient	0.730 mm-1	
F(000)	228	
Crystal size	0.200 x 0.200 x 0.100 mm3	
Theta range for data collection	3.529 to 74.548°.	
Index ranges	-8<=h<=8, -7<=k<=7, -15<=l<=16	
Reflections collected	11830	
Independent reflections	2157 [R(int) = 0.0460]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.6123	
Refinement method	Full-matrix least-squares on F2	

Data / restraints / parameters	2157 / 2 / 148
Goodness-of-fit on F2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0740
R indices (all data)	R1 = 0.0294, wR2 = 0.0744
Absolute structure parameter	-0.05(13)
Extinction coefficient	n/a
Largest diff. peak and hole	0.161 and -0.205 e.Å-3

Table A6.2 *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***167****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
N(1)	1891(2)	7872(2)	5903(1)	14(1)
C(1)	2707(2)	5936(3)	5824(1)	12(1)
O(1)	1974(2)	4411(2)	5235(1)	17(1)
C(2)	4792(2)	5877(3)	6599(1)	11(1)
C(3)	5210(2)	8322(3)	6870(1)	14(1)
C(4)	3131(2)	9317(3)	6693(1)	16(1)
C(5)	4621(2)	4699(3)	7611(1)	12(1)
O(2)	3133(2)	4913(2)	7929(1)	18(1)
C(6)	6324(2)	3348(3)	8200(1)	12(1)
C(7)	6133(3)	2167(3)	9098(1)	14(1)
C(8)	7667(3)	855(3)	9653(1)	17(1)
C(9)	9402(3)	700(3)	9313(1)	17(1)
C(10)	9604(2)	1876(3)	8432(1)	15(1)
C(11)	8077(2)	3216(3)	7865(1)	13(1)
C(12)	8296(2)	4492(3)	6908(1)	14(1)
C(13)	6290(2)	4788(3)	6095(1)	13(1)

Table A6.3 *Bond lengths [Å] and angles [°] for* ***167****.*

N(1)-C(1)	1.333(2)
N(1)-C(4)	1.457(2)
N(1)-H(1N)	0.886(18)
C(1)-O(1)	1.231(2)
C(1)-C(2)	1.537(2)
C(2)-C(13)	1.525(2)
C(2)-C(5)	1.532(2)
C(2)-C(3)	1.551(2)
C(3)-C(4)	1.535(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-O(2)	1.221(2)
C(5)-C(6)	1.486(2)
C(6)-C(11)	1.405(2)
C(6)-C(7)	1.408(2)
C(7)-C(8)	1.382(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.396(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.390(3)

C(9)-H(9)	0.9500
C(10)-C(11)	1.394(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.509(2)
C(12)-C(13)	1.527(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(1)-N(1)-C(4)	114.20(14)
C(1)-N(1)-H(1N)	123.6(16)
C(4)-N(1)-H(1N)	122.0(16)
O(1)-C(1)-N(1)	127.51(15)
O(1)-C(1)-C(2)	123.79(15)
N(1)-C(1)-C(2)	108.71(14)
C(13)-C(2)-C(5)	112.16(14)
C(13)-C(2)-C(1)	111.58(13)
C(5)-C(2)-C(1)	107.40(12)
C(13)-C(2)-C(3)	114.31(13)
C(5)-C(2)-C(3)	108.32(13)
C(1)-C(2)-C(3)	102.44(13)
C(4)-C(3)-C(2)	103.69(13)
C(4)-C(3)-H(3A)	111.0

C(2)-C(3)-H(3A)	111.0
C(4)-C(3)-H(3B)	111.0
C(2)-C(3)-H(3B)	111.0
H(3A)-C(3)-H(3B)	109.0
N(1)-C(4)-C(3)	103.11(13)
N(1)-C(4)-H(4A)	111.1
C(3)-C(4)-H(4A)	111.1
N(1)-C(4)-H(4B)	111.1
C(3)-C(4)-H(4B)	111.1
H(4A)-C(4)-H(4B)	109.1
O(2)-C(5)-C(6)	121.53(14)
O(2)-C(5)-C(2)	120.25(14)
C(6)-C(5)-C(2)	118.21(13)
C(11)-C(6)-C(7)	120.39(15)
C(11)-C(6)-C(5)	121.15(14)
C(7)-C(6)-C(5)	118.45(14)
C(8)-C(7)-C(6)	120.23(15)
C(8)-C(7)-H(7)	119.9
C(6)-C(7)-H(7)	119.9
C(7)-C(8)-C(9)	119.46(16)
C(7)-C(8)-H(8)	120.3
C(9)-C(8)-H(8)	120.3
C(10)-C(9)-C(8)	120.54(16)

C(10)-C(9)-H(9)	119.7
C(8)-C(9)-H(9)	119.7
C(9)-C(10)-C(11)	120.83(15)
C(9)-C(10)-H(10)	119.6
C(11)-C(10)-H(10)	119.6
C(10)-C(11)-C(6)	118.54(15)
C(10)-C(11)-C(12)	120.84(14)
C(6)-C(11)-C(12)	120.62(14)
C(11)-C(12)-C(13)	110.96(13)
C(11)-C(12)-H(12A)	109.4
C(13)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12B)	109.4
C(13)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108.0
C(2)-C(13)-C(12)	111.33(13)
C(2)-C(13)-H(13A)	109.4
C(12)-C(13)-H(13A)	109.4
C(2)-C(13)-H(13B)	109.4
C(12)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0

Symmetry transformations used to generate equivalent atoms:

Table A6.4 *Anisotropic displacement parameters ($Å^2$ x 10^3) for* ***167****. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.*

	U11	U22	U33	U23	U13	U12
N(1)	11(1)	14(1)	17(1)	2(1)	2(1)	3(1)
C(1)	10(1)	14(1)	12(1)	1(1)	4(1)	-1(1)
O(1)	13(1)	17(1)	19(1)	-4(1)	1(1)	-2(1)
C(2)	10(1)	11(1)	12(1)	0(1)	1(1)	0(1)
C(3)	13(1)	12(1)	17(1)	-1(1)	2(1)	-1(1)
C(4)	17(1)	12(1)	19(1)	-2(1)	3(1)	2(1)
C(5)	11(1)	12(1)	13(1)	-2(1)	2(1)	-2(1)
O(2)	14(1)	24(1)	20(1)	6(1)	8(1)	4(1)
C(6)	12(1)	11(1)	13(1)	-1(1)	2(1)	-1(1)
C(7)	15(1)	14(1)	16(1)	1(1)	5(1)	-1(1)
C(8)	20(1)	14(1)	15(1)	3(1)	2(1)	-2(1)
C(9)	16(1)	13(1)	19(1)	1(1)	-1(1)	2(1)
C(10)	13(1)	14(1)	18(1)	-2(1)	3(1)	1(1)
C(11)	12(1)	12(1)	13(1)	-2(1)	2(1)	-2(1)
C(12)	11(1)	17(1)	16(1)	3(1)	5(1)	1(1)
C(13)	11(1)	14(1)	13(1)	0(1)	3(1)	1(1)

Table A6.5 *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for* ***167****.*

	x	y	z	U(eq)
H(1N)	660(30)	8230(40)	5550(16)	17
H(3A)	5996	8511	7619	17
H(3B)	5935	8996	6390	17
H(4A)	2705	9325	7362	20
H(4B)	3093	10826	6417	20
H(7)	4946	2272	9322	17
H(8)	7543	64	10262	20
H(9)	10452	-216	9687	20
H(10)	10797	1765	8214	18
H(12A)	9214	3715	6568	17
H(12B)	8876	5939	7143	17
H(13A)	6464	5690	5494	15
H(13B)	5775	3347	5807	15

Table A6.6 *Torsion angles [°] for* ***167****.*

C(4)-N(1)-C(1)-O(1)	178.91(16)
C(4)-N(1)-C(1)-C(2)	-1.57(19)
O(1)-C(1)-C(2)-C(13)	41.0(2)
N(1)-C(1)-C(2)-C(13)	-138.59(14)
O(1)-C(1)-C(2)-C(5)	-82.34(19)
N(1)-C(1)-C(2)-C(5)	98.11(16)
O(1)-C(1)-C(2)-C(3)	163.67(15)
N(1)-C(1)-C(2)-C(3)	-15.87(17)
C(13)-C(2)-C(3)-C(4)	146.75(14)
C(5)-C(2)-C(3)-C(4)	-87.42(14)
C(1)-C(2)-C(3)-C(4)	25.89(16)
C(1)-N(1)-C(4)-C(3)	18.53(19)
C(2)-C(3)-C(4)-N(1)	-26.88(16)
C(13)-C(2)-C(5)-O(2)	-157.93(15)
C(1)-C(2)-C(5)-O(2)	-35.0(2)
C(3)-C(2)-C(5)-O(2)	74.98(18)
C(13)-C(2)-C(5)-C(6)	23.5(2)
C(1)-C(2)-C(5)-C(6)	146.42(15)
C(3)-C(2)-C(5)-C(6)	-103.61(16)
O(2)-C(5)-C(6)-C(11)	-176.14(16)
C(2)-C(5)-C(6)-C(11)	2.4(2)
O(2)-C(5)-C(6)-C(7)	4.9(2)

C(2)-C(5)-C(6)-C(7)	-176.55(15)
C(11)-C(6)-C(7)-C(8)	-0.4(2)
C(5)-C(6)-C(7)-C(8)	178.63(15)
C(6)-C(7)-C(8)-C(9)	-0.4(3)
C(7)-C(8)-C(9)-C(10)	0.9(3)
C(8)-C(9)-C(10)-C(11)	-0.6(3)
C(9)-C(10)-C(11)-C(6)	-0.2(2)
C(9)-C(10)-C(11)-C(12)	-179.98(16)
C(7)-C(6)-C(11)-C(10)	0.7(2)
C(5)-C(6)-C(11)-C(10)	-178.30(15)
C(7)-C(6)-C(11)-C(12)	-179.55(15)
C(5)-C(6)-C(11)-C(12)	1.5(2)
C(10)-C(11)-C(12)-C(13)	149.00(15)
C(6)-C(11)-C(12)-C(13)	-30.8(2)
C(5)-C(2)-C(13)-C(12)	-52.74(18)
C(1)-C(2)-C(13)-C(12)	-173.29(14)
C(3)-C(2)-C(13)-C(12)	71.06(18)
C(11)-C(12)-C(13)-C(2)	56.21(19)

Symmetry transformations used to generate equivalent atoms:

Table A6.7 *Hydrogen bonds for* ***167*** *[Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.886(18)	1.994(19)	2.8742(18)	173(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+1

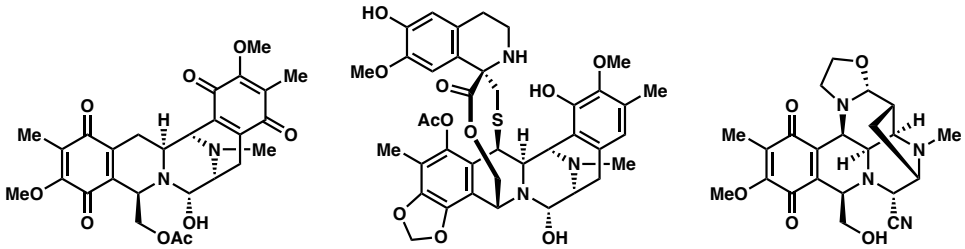
APPENDIX 7

Revised Route Toward the bis-THIQ Natural Products and Synthesis of Non-Natural Analogs[†]

A7.1 INTRODUCTION

Tetrahydroisoquinoline (THIQ) natural products, including the saframycin, ecteinascidin and naphthyridinomycin families, demonstrate remarkable and diverse biological activities, most notably as antitumor antibiotics (Figure A7.1).[1,2]

Figure A7.1 *THIQ natural products.*



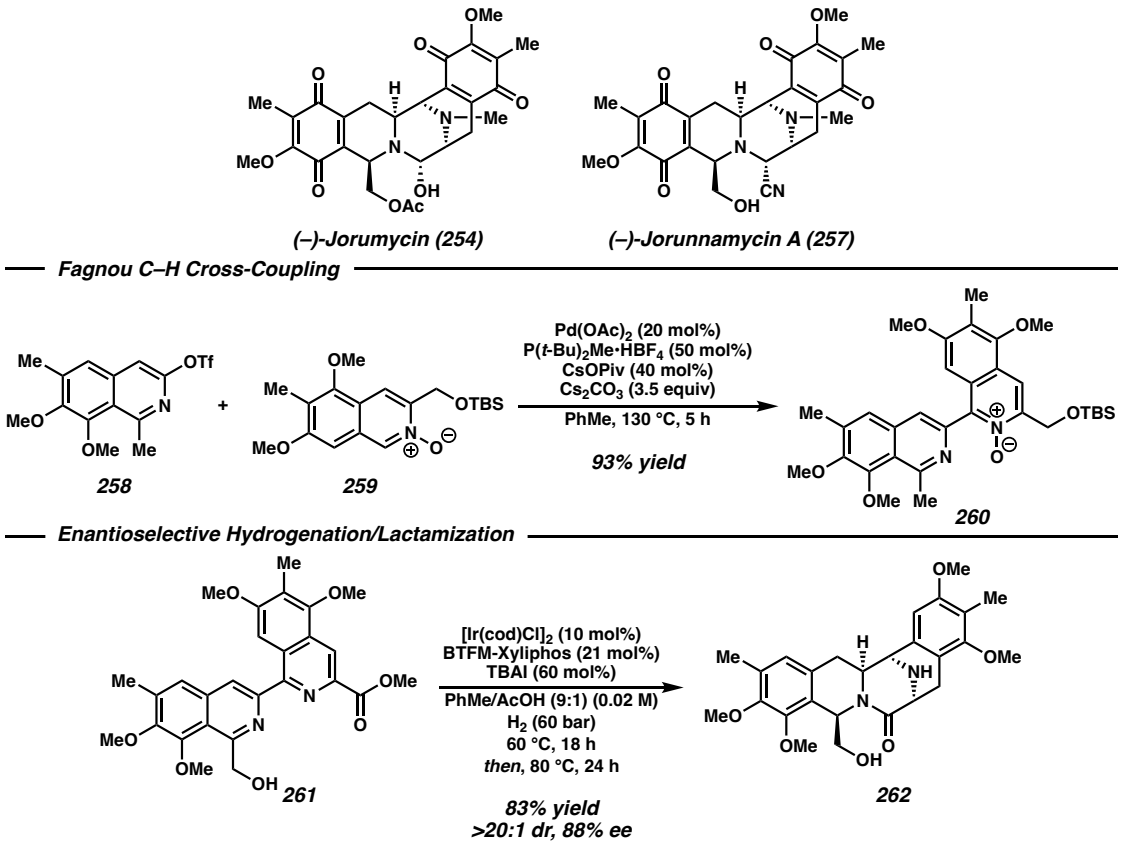
Essential to the biological activities of these natural products is a latent iminium ion—either a hemiaminal, as in (–)-jorumycin or ecteinascidin 743 (Et-743), or an amino nitrile

[†] This research was performed as an extension of the chemistry developed by Dr. Eric Welin, Dr. Gerit Pototschnig, and Dr. Aurapat Ngamnithiporn in collaboration with Rakel Ang and has not been published.

moiety as in (+)-cyanocycline A—which functions as a potent alkylating agent *in vivo*, covalently modifying DNA which ultimately leads to cell death.[3] The promise of these natural products as antitumor agents has already been demonstrated in the case of Et-743, a tris-THIQ natural product used in the treatment of advanced soft-tissue sarcoma (SCS) and ovarian cancer.[3,4]

In 2019, our group completed the convergent total syntheses of (–)-jorumycin and (–)-jorunnamycin A.[5] Key to the synthetic strategy of these complex natural products is a highly enabling C–H cross coupling of the two isoquinoline fragments. Following a series of redox manipulations, we utilized a novel Ir-catalyzed asymmetric hydrogenation to forge all requisite stereochemistry and cyclize the central ring (Figure A7.2).[6]

Figure A7.2 *Key synthetic steps toward (–)-jorumycin and (–)-jorunnamycin A.*

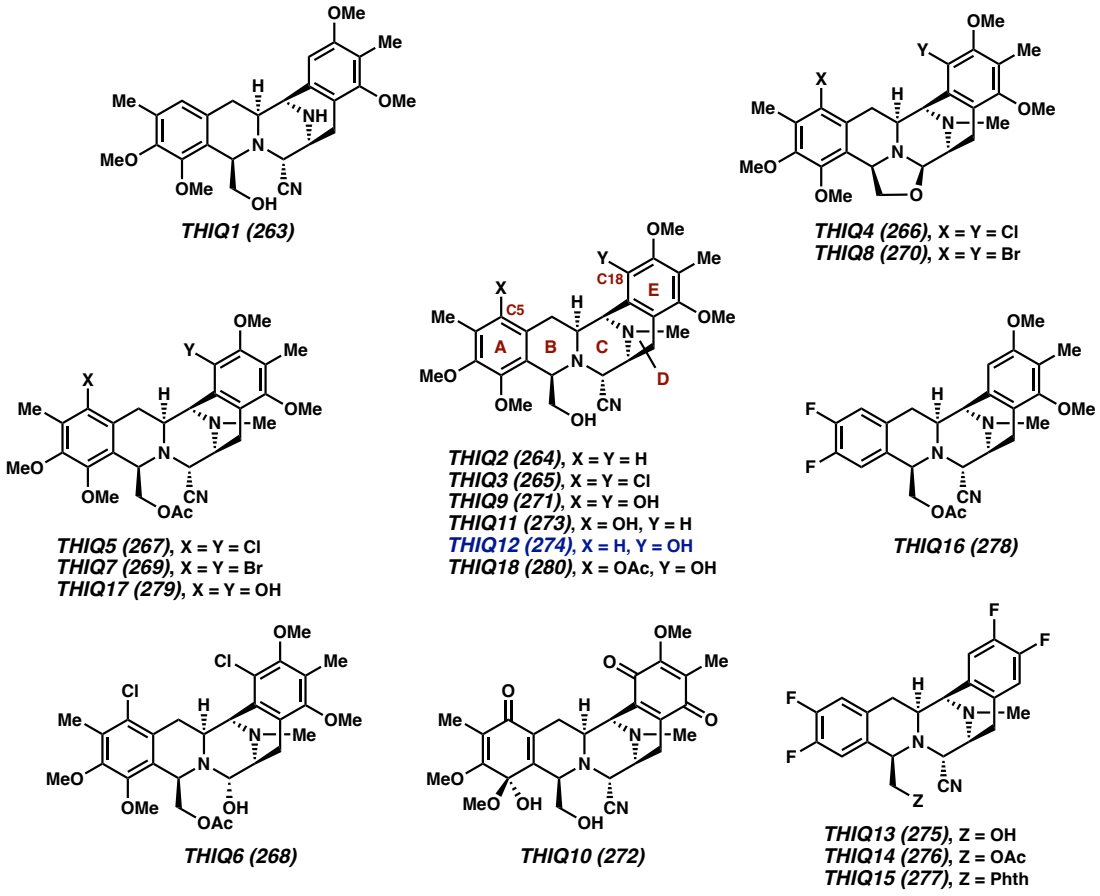


Importantly, this non-biomimetic strategy enables access to derivatives with substantial structural and electronic variation. Although structurally simplified bis-THIQ analogs have been developed by other groups, synthetic efforts have largely focused on alteration of groups appendant to the hydroxymethyl group due to the synthetic constraints of synthesizing electronically differentiated THIQ rings, and electron-deficient analogs have yet to be explored.[7]

A7.2 NON-NATURAL ANALOGS

A7.2.1 SAR of Non-Natural Analogs

Figure A7.3 *Non-natural analogs of (–)-jorumycin and (–)-jorunnamycin A.*



In addition to the completed synthesis of (–)-jorumycin and (–)-jorunnamycin A, our group synthesized a set of 18 non-natural analogs, varying both the substitution and oxidation of the outer aromatic rings as well as exploring alteration to the hydroxymethyl appended to the B ring (Figure A7.3).

Table A7.1 *Assay data for selected analogs of* ***THIQ1*** *(**263**) through* ***THIQ18*** *(**280**).*

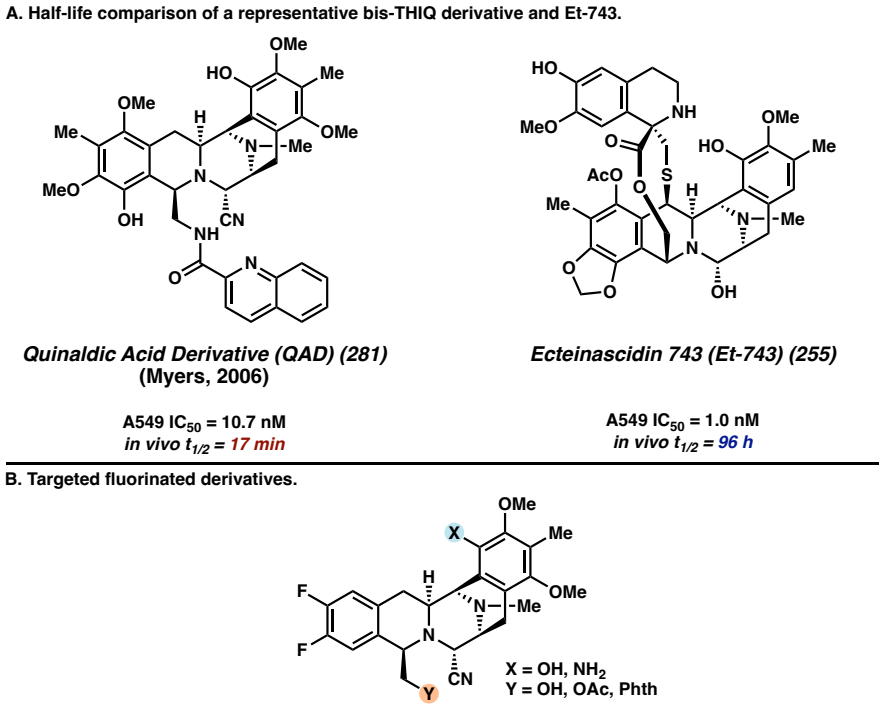
	EC_{50} (uM)		
analog	A427	H810	H1437
THIQ1	38	34	>42
THIQ2	21	11	24
THIQ3	15	18	26
THIQ5	34	>42	>42
THIQ6	42	>42	>42
THIQ7	37	>42	>42
THIQ9	0.71	0.68	3.0
THIQ11	6.3	9.6	21
THIQ12	0.60	0.59	1.5
THIQ13	19	18	15
THIQ14	8.3	5.0	19
THIQ15	6.8	6.3	33
THIQ16	21	16	37
THIQ17	0.07	0.063	0.2
THIQ18	0.32	0.28	1.3

In subsequent biological studies against three cancer cell lines, **THIQ12** (**274**)—an amino nitrile derivative with oxidation deleted at C5 of the A ring—was found to be one of the most potent analogs developed by our group, displaying broad-spectrum activity exceeding **THIQ9** (**271**) bearing both C5 and C18 oxidation (Table A7.1).[5] Moreover, both **THIQ17** (**279**) and **THIQ18** (**280**) possess remarkable potency, with **THIQ17** (**279**) demonstrating sub-micromolar potency against all cell lines tested.

Other groups, most notably Corey and Myers, have also prepared non-natural bis-THIQ derivatives, and our observations are in alignment with the structure-activity relationships (SAR) that their studies established.[7a,b] Their studies suggest that the presence of a hydrogen-bond donor at C18 on the E ring improves biological potency, and

modification of the hydroxymethyl has also been correlated with improved potency.[7a,b] Computational studies examining the pre-covalent interactions of Et-743 suggest that the hydroxyl at C18 participates in critical H-bonding interactions within the DNA minor groove, enhancing their binding affinity prior to covalent alkylation.[8]

Figure A7.4 *Comparison of metabolic stability and targeted fluorinated analogs.*



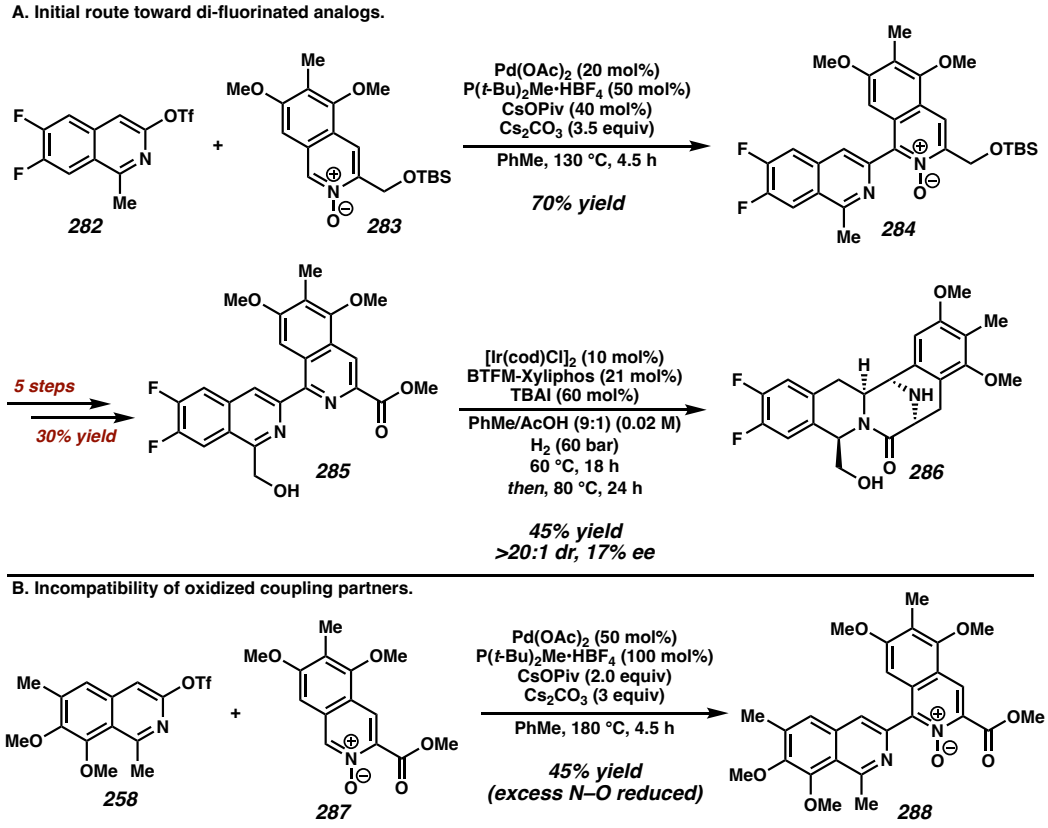
Although typically displaying similar potency, bis-THIQ natural products tend to have shorter half-lives than the larger tris-THIQs, like Et-743 (Figure A7.4a). Because the installation of electron-withdrawing groups is a commonly employed strategy to improve a drug molecule's metabolic stability, we postulate the exploration of simpler, electron-deficient analogs may reveal a promising direction for future antitumor drug development. With these precedents in mind, we are now targeting fluorinated compounds bearing a hydrogen-bond donor at C18 with the aim of exploring whether these derivatives might have improved metabolic stability while maintaining or improving their overall potency (Figure A7.4b). Although the biological activity of fluorinated derivatives **THIQ13** (**275**)–

THIQ16 (**278**) is quite modest, we are optimistic that further oxidation of the E ring may restore potency.

A7.2.1 Development of a Revised Synthetic Route

As we set out to synthesize these fluorinated derivatives, we began our studies following roughly the same route as had been utilized for the synthesis of (–)-jorumycin and (–)-jorunnamycin A, adapting as needed (Scheme A7.1a).[9]

Scheme A7.1 *Initial attempts toward fluorinated analogs.*

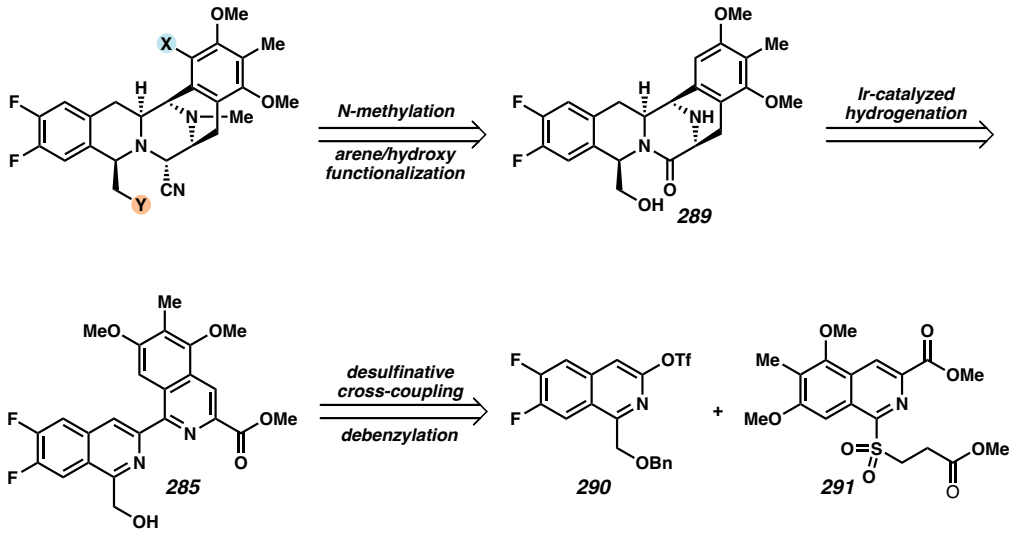


Although the key C-H cross-coupling could be performed in satisfactory yield, the enantioselectivity of the Ir-catalyzed hydrogenation was much poorer, yielding **286** in 45% yield and 17% ee, albeit maintaining an excellent >20:1 dr. We hypothesize that the lower enantioselectivity is due to the poorer chelation of the electron-deficient western isoquinoline, and future studies aim to identify ligands that may be able to better effect this

hydrogenation with improved enantioselectivity. Critically, as adapted for these compounds, the series of redox manipulations utilized to transform **284** to **285** had to be carried out over five steps, losing roughly 70% of the material in the middle of the synthetic sequence.

The initial decision to couple two isoquinoline fragments in the incorrect oxidation state was not an oversight. During the development of the original synthetic route toward these natural products, the isoquinoline oxide **287** was found to be incompatible with the C-H cross-coupling (Scheme A7.1b).[10] To overcome this limitation, we searched the literature for an alternative coupling strategy that might be amenable to more heavily decorated coupling partners, and we were drawn to reports of the desulfinative cross-couplings developed by the Willis group (Scheme A7.2).[11] We envisioned that we may be able to utilize this type of coupling to design a more efficient sequence. To explore this strategy, we first needed to devise new synthetic routes toward the oxidized coupling partners **290** and **291**.

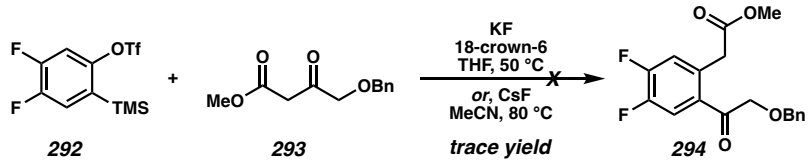
Scheme A7.2 *Retrosynthetic analysis.*



A7.2.1 Synthesis of di-Fluorinated Isoquinoline Triflate

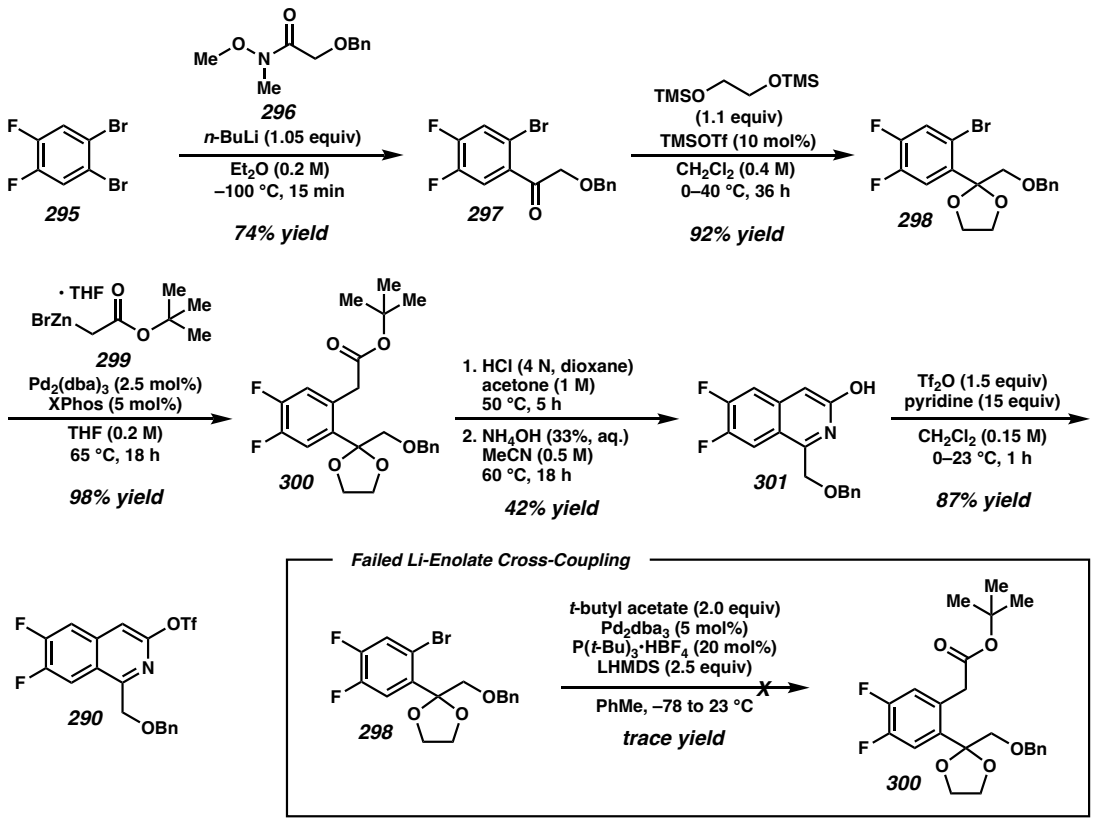
To synthesize the isoquinoline triflate **290**, we first attempted to utilize the aryne annulation strategy developed by our group (Scheme A7.3).[5,12,13]

Scheme A7.3 *Failed aryne annulation.*



Unfortunately, under a variety of conditions, we only observed trace product formation, instead obtaining an intractable mixture of constitutional isomers and oligomers. Owing to the symmetry of our targeted arene, we instead decided to pursue a desymmetrizing strategy (Scheme A7.4).

Scheme A7.4 *Desymmetrizing strategy toward isoquinoline* ***290****.*



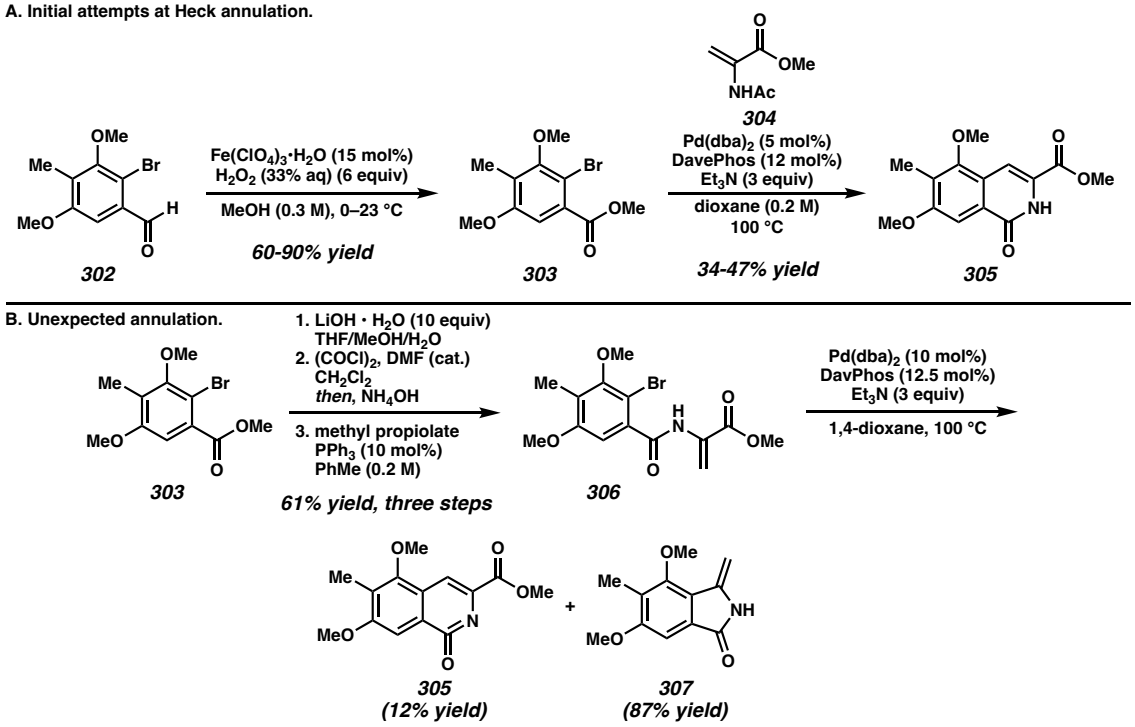
Treatment of dibrominated arene **295** with *n*-BuLi in Et_2O at –100 °C enabled lithium halogen exchange while minimizing formation of an undesired aryne;[14] nucleophilic addition with Weinreb amide **296** delivered ketone **297** in good yield.[15] Noyori ketalization at slightly elevated temperatures proceeded smoothly; all other attempts to generate the desired ketal failed to deliver meaningful yields of **298**, possibly due to the stability of the hemiketal. While a Pd-catalyzed cross-coupling with a lithium enolate only afforded complex mixtures of byproducts, a Negishi reaction with Zn-enolate **299** delivered **300** in near quantitative yield.[16] Exhaustive acid-mediated cleavage of the *t*-butyl ester and ketal and subsequent cyclization with ammonium hydroxide delivered 3-hydroxy isoquinoline **301** in good yield.[5] Triflation completes the synthesis of coupling partner **290**.

A7.2.2 Synthesis of Isoquinoline Sulfone

To synthesize the nucleophilic coupling partner, we first envisioned utilizing a Heck annulation with ester **303** and enamide **304** to generate isoquinolinone **305** that could later be elaborated to the sulfone (Scheme A7.5a).[17] Oxidation of aldehyde **302** with $Fe(ClO_4)_3 \bullet H_2O$ and hydrogen peroxide in the presence of methanol yielded ester **303** in variable, but generally good, yields.[5,18] After surveying a wide array of conditions to effect the desired annulation, we identified DavePhos as the optimal ligand; however, the reaction failed to deliver product exceeding 50% yield, and significant Pd black was formed throughout the reaction, indicating catalyst instability. In addition to the desired isoquinolinone **305**, we noticed an uncyclized Heck byproduct as the main mass balance. To address this issue, we developed an alternative strategy starting from enamide **306**, which we then subjected to our previously developed Heck conditions (Scheme A7.5b).

Surprisingly, this transformation delivered high yields of isoindolinone **307**, presumambly via a decarboxylative annulation. To the best of our knowledge, this specific transformation has not been explicitly studied, and this undesired reaction may serve as inspiration for a future methods project.

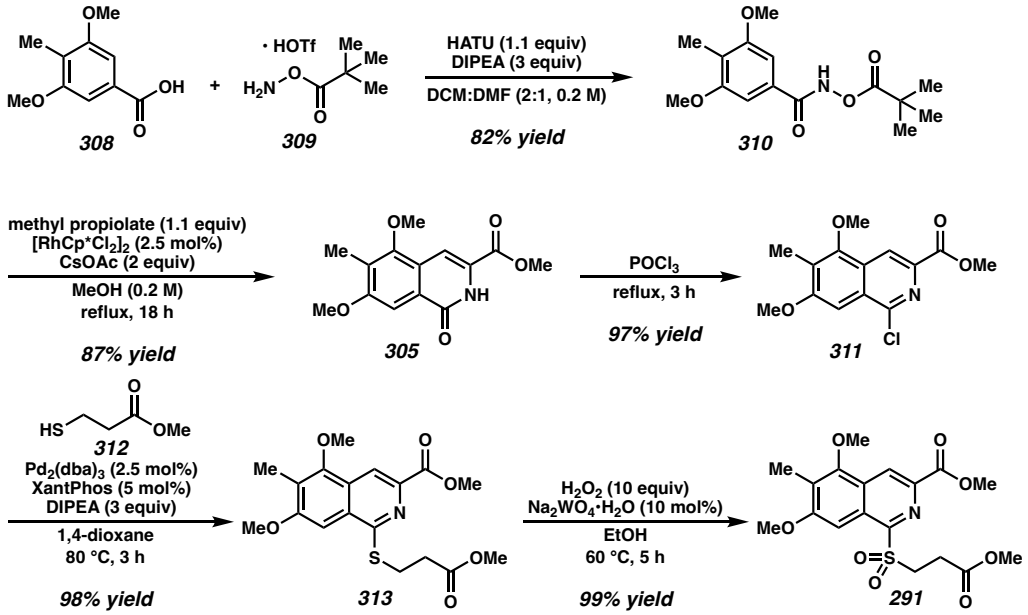
Scheme A7.5 *Heck annulation strategy to access isoquinolinone **305**.*



Due to the difficult oxidative addition of the electron-rich aryl bromide, we devised an alternative strategy utilizing C-H insertion chemistry (Scheme A7.6). Starting from known carboxylic acid **308**, amide coupling with hydroxylamine derivative **309** delivers hydroxamate **310**, which can undergo a subsequent Rh-catalyzed annulation with methyl propiolate to deliver isoquinolinone **305** in good yield.[19] Dehydrative chlorination with $POCl_3$ proceeded smoothly, and the sulfone could be installed over two steps utilizing a sequential Buchwald cross-coupling followed by oxidation of the thioether to the sulfone.[11c] We settled with this two-step approach rather than direct installation of the

sulfone utilizing CuI and SMOPS from a related isoquinoline bromide, which delivered **291** in inferior yields.[11c]

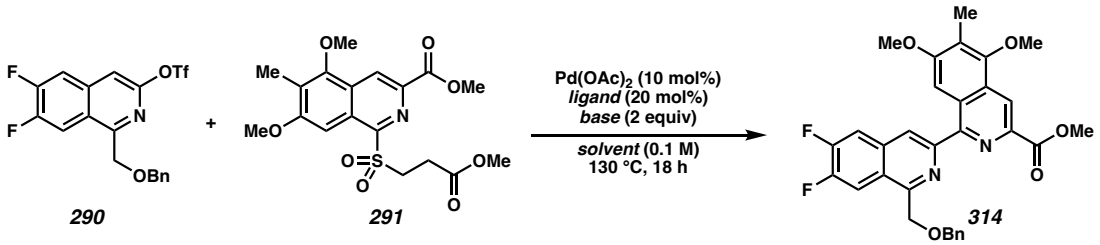
Scheme A7.6 *Optimized route toward sulfone* ***291***.



A7.3 SYNTHESIS OF FLUORINATED ANALOGS

A7.3.1 Optimization of Desulfinative Cross-Coupling

Table A7.2 *Optimization of desulfinative cross-coupling.*



entry	ligand	base	solvent	NMR Yield (%)
1	cataCXium A	K_2CO_3	*m*-xylene	40
2	cataCXium A	Cs_2CO_3	*m*-xylene	0
3	cataCXium A	K_2CO_3	DMF	38
4	P(*t*-Bu)$_3$·HBF$_4$	K_2CO_3	*m*-xylene	5
5	PCy$_3$·HBF$_4$	K_2CO_3	*m*-xylene	10
6	P(*t*-Bu)$_2$Me·HBF$_4$	K_2CO_3	*m*-xylene	81
7[a]	P(*t*-Bu)$_2$Me·HBF$_4$	K_2CO_3	*m*-xylene	92 (88[b])

With both coupling partners in hand, we began optimizing the desulfinative cross-coupling (Table A7.2). Excitingly, using the exact conditions from Willis, we were able to obtain a 40% yield of our desired product.[11c] We found that the use of K_2CO_3 was essential, as a reaction with Cs_2CO_3 failed to product any product. After surveying an array of electron-rich phosphine ligands, we were pleased to find that the use of P(*t*-Bu)$_2$Me•HBF$_4$ delivered our desired product in an excellent 81% yield. Increasing the temperature of the reaction to 140 °C improved the yield to an optimized 88% isolated yield. Gratifyingly, this yield was found to be generally reproducible in up to 2 mmol scale.

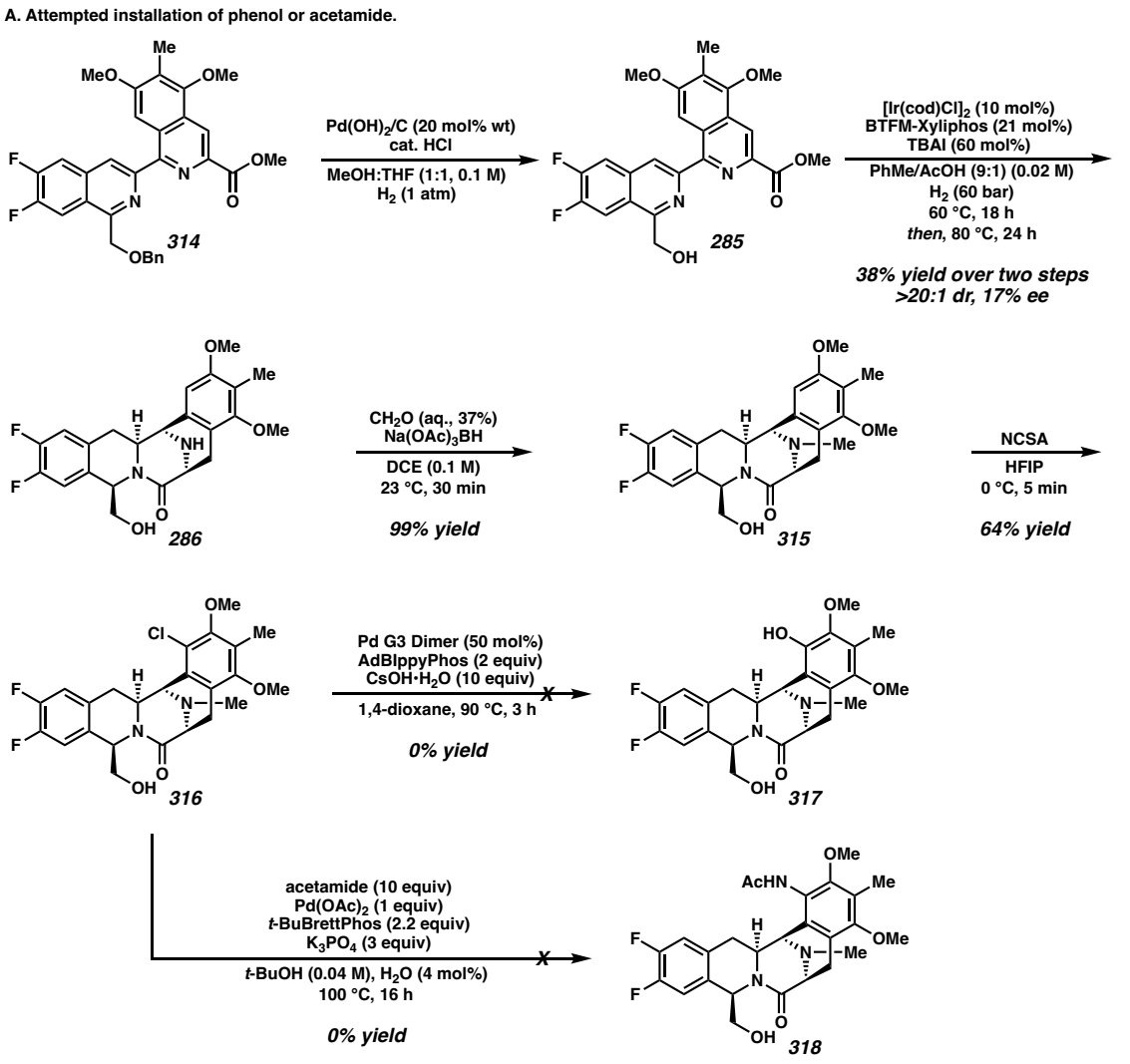
A7.3.2 Endgame Synthesis of Fluorinated Derivatives

Having validated our new strategy, we carried forward with the synthesis of the fluorinated derivatives (Scheme A7.7). The benzyl ether could be efficiently cleaved with Pearlman's catalyst under an atmosphere of H_2, and intermediate **285** was directly subjected to the Ir-catalyzed enantioselective hydrogenation, delivering intermediate **286** in 38% yield over two steps. Methylation via reductive amination proceeded smoothly, and similar to the endgame utilized in our synthesis of (–)-jorumycin and (–)-jorunnamycin A, we could chlorinate the E ring using *N*-chlorosaccharin.[5] Unfortunately, we failed to advance this material to the phenolic aniline derivatives using Buchwald chemistry, although we were able to advance the chlorinated intermediates onward to THIQ19 (**319**) and THIQ20 (**320**).[5]

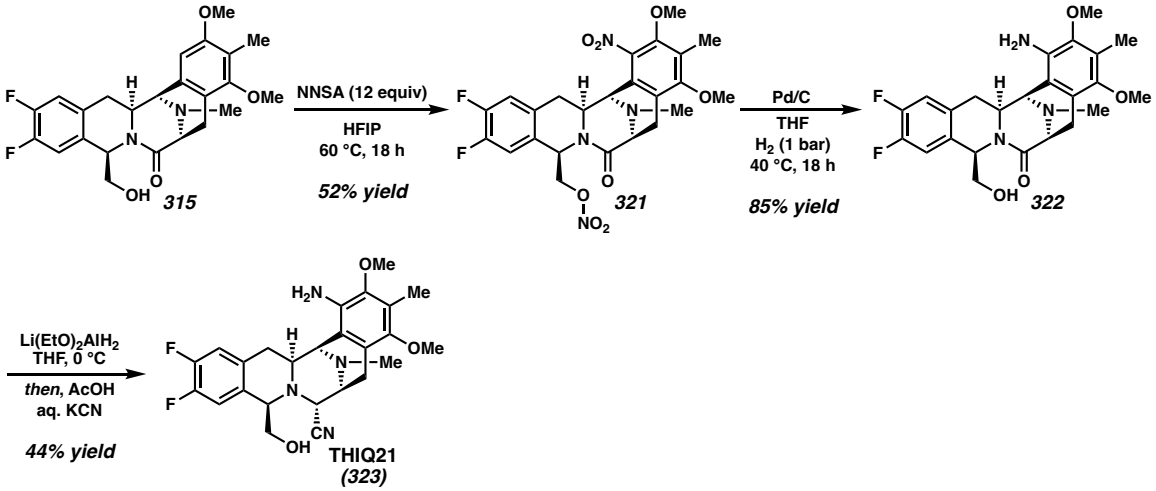
Owing to the efficiency of the chlorination reaction, we decided to utilize *N*-nitrosaccharin to nitrate the E ring, which occurred with concomitant formation of a nitrate ester (Scheme A7.8).[20] Hydrogenolysis with Pd/C reduced both the nitro group and cleaved

the nitrate ester, delivering aniline **322**. Finally, we were able to advance this material onward to derivative **323** following the same previously utilized protocol.

Scheme A7.7 *Endgame toward chlorinated difluorinated analogs* ***THIQ19*** *and* ***THIQ20****.*



Scheme A7.8 *Endgame toward aminated difluorinated analog* ***THIQ21***.



A7.5 BIOLOGICAL ACTIVITY OF FLUORINATED DERIVATIVES

Although we are still awaiting the assay results for **THIQ21**, we were able to assess the biological activity of fluorinated derivatives **THIQ19** and **THIQ20** against three cancer cell lines (Table A7.3).

Table A7.3 *Biological activity of fluorinated derivatives.*

	EC_{50} (uM)		
analog	A427	H810	H1437
THIQ13	19	18	15
THIQ14	8.3	5.0	19
THIQ15	6.8	6.3	33
THIQ16	21	16	37
THIQ19	9.7	7.4	17
THIQ20	5.4	4.6	10

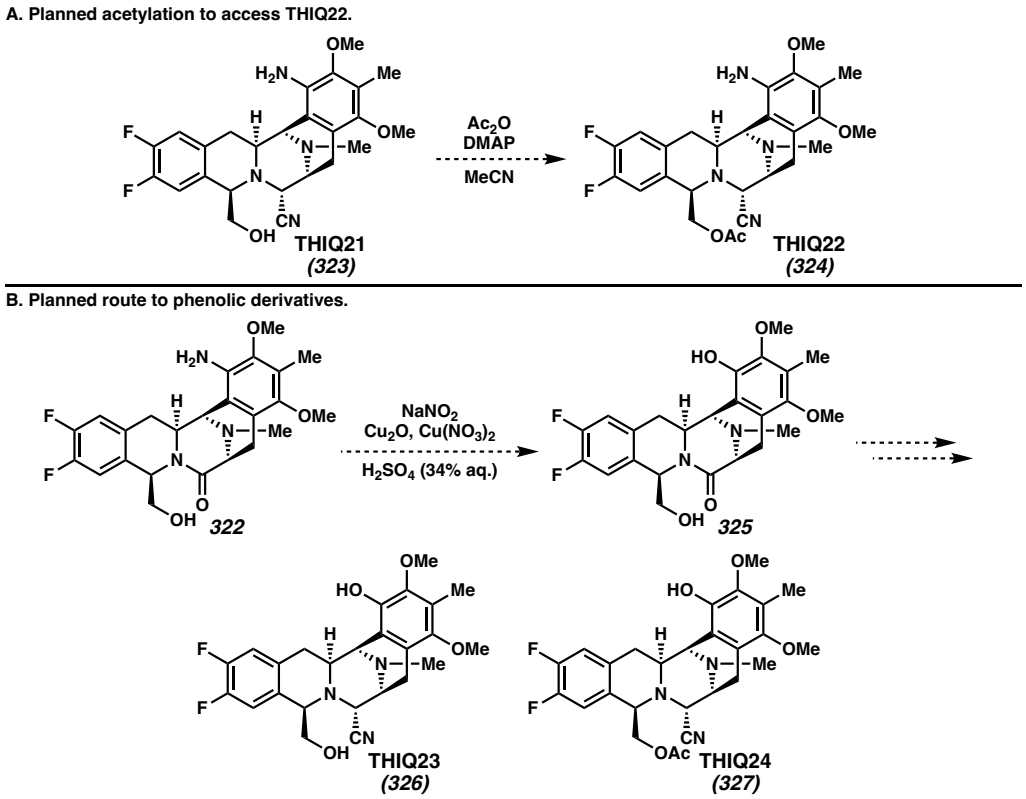
We had anticipated that the chlorinated derivatives would not be as potent as analogs **THIQ17** and **THIQ18** due to the lack of a hydrogen bond donor on the A and E ring. Excitingly, however, we do see an improvement in potency as compared to the other fluorinated derivatives. Comparing **THIQ20** against **THIQ16**, differing only in chlorination at C18, we observe about a three- to four-fold improvement in activity across

all evaluated cell lines, suggesting that regardless of the presence of a hydrogen bond-donor, substitution of C18 is beneficial for activity.

A7.5 CONCLUSIONS AND FUTURE DIRECTIONS

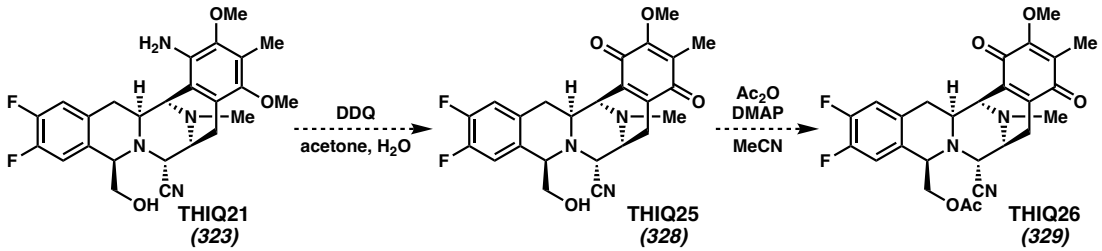
In conclusion, we have presented a modified route toward the bis-THIQ natural product scaffold. Maintaining the same core strategy as the route previously developed in our group, we have redesigned the route to utilize a Pd-catalyzed desulfinative coupling, minimizing redox manipulations and maximizing the convergency of the overall sequence. While we have successfully utilized this strategy to synthesize **THIQ19**, **THIQ20**, and **THIQ21**, in the immediate future, we intend to synthesize acetylated derivative **THIQ22** (Scheme A7.9).

Scheme A7.9 *Planned derivatization of* ***THIQ21***.



Additionally, we plan to explore whether the aniline of intermediate **322** can be converted to a phenol via the formation of a diazonium compound. Moreover, we envision treatment of **THIQ22** (**324**) with an oxidant, like DDQ, in the presence of water could deliver quinones **THIQ25** (**328**) and **THIQ26** (**329**) (Scheme A7.10).[5]

Scheme A7.9 *Planned synthesis of quinone derivatives.*



Ultimately, we intend to evaluate these compounds for both potency and metabolic stability to determine if fluorination is a viable strategy for improving the druglikeness of the smaller bis-THIQ compounds.

A7.6 EXPERIMENTAL SECTION

A7.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[35] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400

MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64.[36] Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a ThermoScientific Nicolet iS50 FT-IR spectrometer, or a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$).

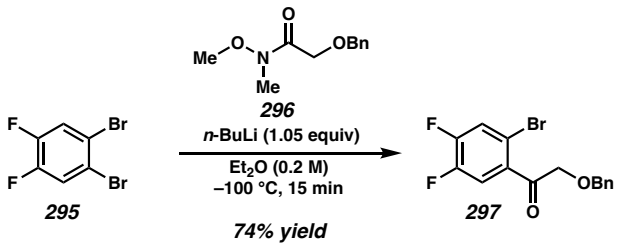
A7.6.1.1 Preparation of Known Compounds

Reagents were purchased from commercial sources and used as received unless otherwise stated. 6,7-difluoro-1-methylisoquinolin-3-yl trifluoromethanesulfonate (**282**),[9] 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,7-dimethoxy-6-methylisoquinoline 2-oxide (**283**),[5] 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate.(**292**),[12b] methyl 4-(benzyloxy)-3-oxobutanoate (**293**),[13] 2-(benzyloxy)-N-methoxy-N-methylacetamide (**296**),[15] (2-(tert-butoxy)-2-oxoethyl)zinc(II) bromide THF adduct (**299**),[16b] and 2-bromo-

3,5-dimethoxy-4-methylbenzaldehyde (**302**)[5] were prepared according to literature procedures. Although known carboxylic acid **308** is commercially available, it was typically accessed via a Pinnick oxidation of the corresponding aldehyde, which can be prepared following a literature procedure.[5]

A7.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

A7.6.2.1 Synthesis of di-Fluorinated Isoquinoline Triflate (290)



2-(benzyloxy)-1-(2-bromo-4,5-difluorophenyl)ethan-1-one (297)

To a flame-dried 250 mL round bottom flask was added aryl bromide **295** (4.08 g, 15 mmol) and Et_2O (140 mL). The flask was purged with N_2 for 3 minutes and cooled to –100 °C. Then, *n*-BuLi (2.5 M in hexanes, 6 mL, 1 equiv) was added dropwise. After 1 minute, Weinreb amide **296** (3.14 g, 15 mmol, 1 equiv) in Et_2O (7 mL) was added in a thin stream, washing with Et_2O (3 mL). After 30 minutes, the reaction was quenched with HCl (50 mL, 1 N) after removal of the cold bath, stirred for 10 minutes, and then transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted twice with Et_2O. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ketone **297** (3.81 g, 11.2 mmol, 74% yield).

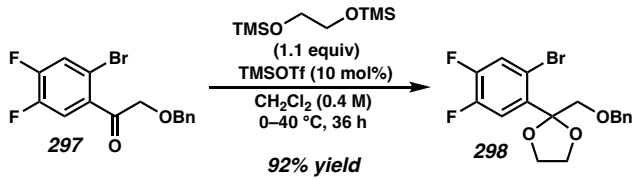
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 9.4, 6.9 Hz, 1H), 7.41 – 7.28 (m, 6H), 4.64 (s, 2H), 4.57 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.59, 151.77 (dd, *J* = 206.1, 13.0 Hz), 149.23 (dd, *J* = 200.0, 13.1 Hz), 136.85, 135.41 (t, *J* = 4.3 Hz), 128.68, 128.30, 128.19, 123.03 (d, *J* = 20.2 Hz), 118.70 (d, *J* = 19.6 Hz), 113.95 (dd, *J* = 7.5, 4.1 Hz), 74.28, 73.71.

^{19}F NMR (282 MHz, $CDCl_3$): δ -130.00, -136.85

IR (neat film, NaCl): 3059, 1717, 1598, 1531, 1493, 1384, 1293, 1167, 1125, 1030, 883, 777 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{15}H_{11}BrF_2O_2$ $[M]^{+\bullet}$: 339.9905, found 339.9904.



To an oven-dried microwave vial was added ketone **297** (500 mg, 1.47 mmol) in CH_2Cl_2 (4 mL, 0.4 M). The solution was purged with N_2 for 3 minutes, and then 1,2-bis(trimethylsiloxy)ethane (0.40 mL, 1.61 mmol, 1.1 equiv) was added. The reaction was cooled to 0 °C, and TMSOTf (0.03 mL, 0.147 mmol, 10 mol%) was added dropwise. The cooling bath was removed, and the reaction was heated to 40 °C for 18 h, or until starting material was consumed by TLC. The reaction was cooled, quenched with saturated aqueous $NaHCO_3$, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ketal **298** (519.3 mg, 1.35 mmol, 92% yield).

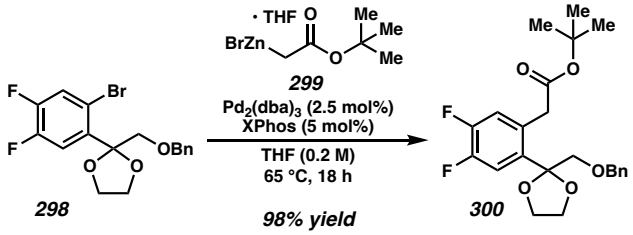
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 11.6, 8.5 Hz, 1H), 7.40 (dd, *J* = 9.6, 7.3 Hz, 1H), 7.34 – 7.20 (m, 5H), 4.60 (s, 2H), 4.20 – 4.08 (m, 2H), 3.91 (s, 2H), 3.90 – 3.86 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.78 (dd, *J* = 253.9, 13.5 Hz), 149.21 (dd, *J* = 249.2, 12.0 Hz), 138.04, 136.12 (dd, *J* = 4.0, 4.0 Hz), 128.44, 127.74, 127.71, 123.60 (d, *J* = 19.9 Hz), 118.55 (d, *J* = 19.9 Hz), 114.30 (dd, *J* = 7.1, 3.8 Hz), 108.58, 73.87, 71.66, 65.40.

^{19}F NMR (282 MHz, $CDCl_3$): δ -135.76 (d, *J* = 21.5 Hz), -138.53 (d, *J* = 21.5 Hz).

IR (neat film, NaCl): 3059, 2891, 1604, 1491, 1453, 1383, 1287, 1212, 1167, 1105, 1031, 951, 893, 796, 741 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{17}H_{15}BrF_2O_2$ $[M]^{+\bullet}$: 384.0167, found 384.0164.



To a flame-dried two-neck round bottom flask equipped with a reflux condenser was added $Pd_2(dba)_3$ (81 mg, 0.089 mmol, 2.5 mol%), XPhos (85 mg, 0.178 mmol, 5 mol%) and freshly prepared solid **299** (1.77 g, 5.32 mmol, 1.5 equiv).[16b] The flask was backfilled three times with N_2, and a solution of ketal **298** (1.37 g, 3.56 mmol) in THF (15 mL) was added, rinsing with THF (3 mL). The reaction was heated to 65 °C and continued overnight. Upon completion, the reaction was cooled, quenched with saturated aqueous NH_4Cl, and transferred to a separatory funnel. The aqueous layer was extracted three times with ethyl acetate, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel

chromatography (0–20% EtOAc/hexanes) to yield ester **300** (1.46 g, 3.47 mmol, 98% yield).

Note: although enolate **299** was typically isolated as a solid for this reaction following a literature procedure, solutions of **299** have also been utilized for this transformation to satisfactory yield.

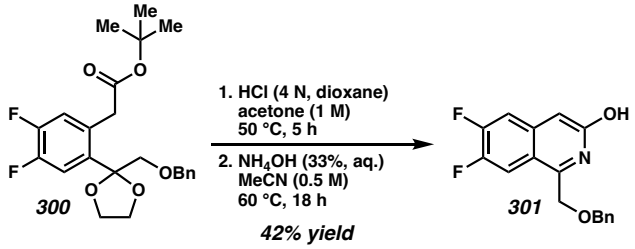
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 11.8, 8.4 Hz, 1H), 7.35 – 7.16 (m, 5H), 6.99 (dd, *J* = 11.1, 7.7 Hz, 1H), 4.58 (s, 2H), 4.12 – 4.00 (m, 2H), 3.88 – 3.76 (m, 2H), 3.70 (s, 2H), 3.64 (s, 2H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.94, 149.74 (dd, *J* = 248.8, 12.7 Hz), 148.95 (dd, *J* = 247.2, 12.4 Hz), 137.89, 135.59, 130.04 (dd, *J* = 6.0, 3.9 Hz), 128.35, 127.63, 127.51, 120.84 (d, *J* = 17.3 Hz), 116.93 (d, *J* = 18.8 Hz), 80.76, 73.80, 65.18, 39.81, 28.12.

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.80 (d, *J* = 22.1 Hz), -140.23 (d, *J* = 22.1 Hz).

IR (neat film, NaCl): 2978, 1731, 1606, 1510, 1453, 1366, 1306, 1147 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{23}H_{26}F_2O_5$ $[M]^{+\bullet}$: 420.1743, found 420.1743.



To a round bottom flask equipped with a reflux condenser was added ester **300** (3.49 mg, 8.3 mmol), acetone (10 mL) and HCl (4N in dioxane, 21 mL, 83 mmol, 10 equiv). The mixture was heated to 50 °C for 5 h, or until an aliquot by ^{1}H NMR indicated full cleavage of both the *t*-butyl ester and ketal. The crude mixture was concentrated under reduced pressure and transferred to a Schlenk flask with MeCN (17 mL). NH_4OH (33 mL, 33% aq.) was added, and the flask was sealed and heated to 60 °C overnight, at which point

it was cooled, concentrated, partitioned between ethyl acetate and sat. aqueous NH_4Cl, and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–5% MeOH/CH_2Cl_2) to yield 3-hydroxy isoquinoline **301** (1.05 g, 3.5 mmol, 42% yield).

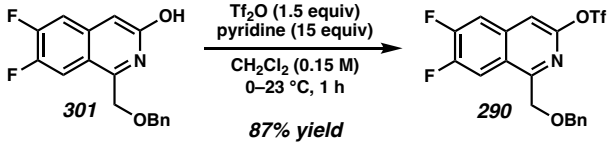
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 11.2, 8.0 Hz, 1H), 7.42 – 7.31 (m, 6H), 6.93 (s, 1H), 5.00 (s, 2H), 4.68 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.99 (d, *J* = 2.1 Hz), 154.03 (dd, *J* = 259.0, 16.9 Hz), 148.52 (dd, *J* = 251.0, 16.6 Hz), 139.75 (d, *J* = 9.2 Hz), 137.23, 128.68, 128.27, 118.21 (d, *J* = 6.9 Hz), 113.93 – 111.88 (m), 111.39 (d, *J* = 17.3 Hz), 104.12 – 103.50 (m), 73.41, 69.76, 65.36.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.00 (d, *J* = 19.5 Hz), -136.68 (d, *J* = 20.0 Hz).

IR (neat film, NaCl): 2863, 1573, 1515, 1331 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{17}H_{13}F_2NO_2$ $[M]^{+\bullet}$: 301.0909, found 301.0900.



To a flame-dried round bottom flask was added 3-hydroxy isoquinoline **301** (424 mg, 1.41 mmol), CH_2Cl_2 (10 mL) and pyridine (1.7 mL, 21 mmol, 15 equiv). The mixture was sparged with N_2 for three minutes and then cooled to 0 °C. Tf_2O (0.35 mL, 2.1 mmol, 2 equiv) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for 1 h, or until starting material was consumed by TLC. The crude mixture was quenched with saturated aq. $NaHCO_3$ and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield isoquinoline triflate **290** (531 mg, 1.23 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (ddd, *J* = 10.8, 7.8, 0.9 Hz, 1H), 7.64 (dd, *J* = 9.9, 7.5 Hz, 1H), 7.48 (s, 1H), 7.41 – 7.29 (m, 5H), 5.02 (s, 2H), 4.61 (s, 2H).

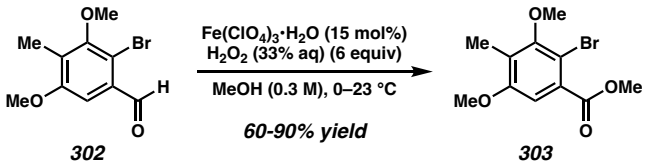
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.85 (dd, *J* = 6.2, 1.6 Hz), 153.98 (dd, *J* = 260.7, 16.3 Hz), 151.37 (d, *J* = 3.2 Hz), 150.88 (dd, *J* = 256.1, 15.7 Hz), 137.18, 128.68, 128.33, 128.28, 124.65 (d, *J* = 6.2 Hz), 120.45, 117.27, 113.61 (d, *J* = 3.2 Hz), 113.52 – 113.38 (m), 110.56 (dd, *J* = 5.4, 2.1 Hz), 73.20, 72.14.

^{19}F NMR (282 MHz, $CDCl_3$): δ -72.81, -126.37 (dd, *J* = 20.3, 3.2 Hz), -130.00 (dd, *J* = 20.2, 2.7 Hz).

IR (neat film, NaCl): 3065, 2864, 1606, 1572, 1518, 1452, 1422, 1384, 1222, 1132, 1089, 964, 889, 831, 744 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{12}F_5NSO_4$ $[M]^{+\bullet}$: 433.0367, found 433.0350.

A7.6.2.2 Synthesis of Isoquinoline Sulfone (291)



To a round bottom flask was added aldehyde **302** (300 mg, 1.16 mmol), $Fe(ClO_4)_3$•H_2O (62 mg, 0.174 mmol, 15 mol%) and methanol (4 mL). The mixture was cooled to 0 °C. H_2O_2 (0.91 mL, 11.6 mmol, 10 equiv) was added dropwise via syringe pump over 4 h. Upon the complete addition of H_2O_2, the reaction was allowed to warm to room temperature and stirred overnight. The crude mixture was concentrated behind a blast shield, then quenched with aq. $Na_2S_2O_3$ and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and

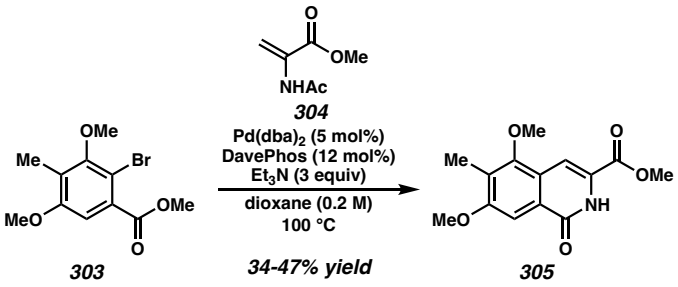
concentrated. The crude solid was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ester **303** (303 mg, 1.05 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 157.5, 156.5, 130.9, 125.7, 108.5, 108.4, 60.5, 55.9, 52.5, 10.1.

IR (neat film, NaCl): 2999, 2949, 2846, 1783, 1565, 1445, 1388 1329, 1377, 1329, 1242, 1122, 1035, 1007 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{11}H_{13}BrO_4$ $[M]^{+\bullet}$: 287.9992, found 287.9980.



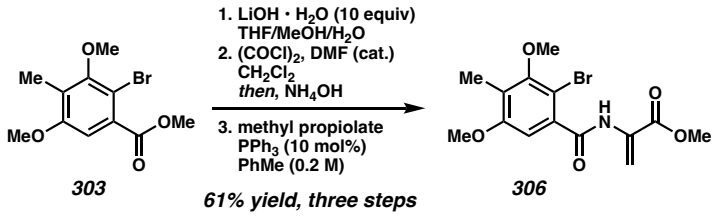
To a flame-dried vial was added $Pd(dba)_2$ (2.9 mg), DavePhos (4.7 mg) and dioxane (0.5 mL). The Pd stock solution was stirred for 20 minutes, then 0.25 mL of the stock solution was added to a separate vial containing ester **303** (14.5 mg, 0.05 mmol), enamide **304** (10.7 mg, 0.075 mmol, 1.5 equiv), and triethylamine (20 uL, 0.15 mmol, 3 equiv). The reaction vial was sealed and heated to 100 °C for 18 h, at which point the reaction was diluted with water and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/CH_2Cl_2) to yield isoquinolinone **305** (4.7 g, 0.017 mmol, 34% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 161.4, 160.4, 156.0, 128.1, 126.6, 125.3, 124.4, 106.7, 103.0, 62.3, 56.3, 53.2, 9.9.

IR (neat film, NaCl): 2930, 1725, 1640, 1260 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{15}NO_5$ $[M]^{+\bullet}$: 277.0945, found 277.0933.



To a round bottom flask was added ester **303** (230 mg, 0.8 mmol) and LiOH•H_2O (336 mg, 8.0 mmol, 10 equiv) in THF/MeOH/H_2O (3:1:1, 0.1 M overall). The reaction was stirred at room temperature for 18 h, then concentrated. The crude mixture was acidified with HCl (1 N), then extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

To the crude acid in CH_2Cl_2 (3 mL, 0.27 M) and 1 drop of DMF at 0 °C was added oxalyl chloride (0.1 mL, 1.2 mmol, 1.5 equiv) dropwise. After 2 h, the crude acid chloride was added dropwise to a flask containing NH_4OH (33% aq, 3 mL) at 0 °C. After stirring for an hour, the reaction was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield 215 mg of the benzamide intermediate. This intermediate was used without further purification.

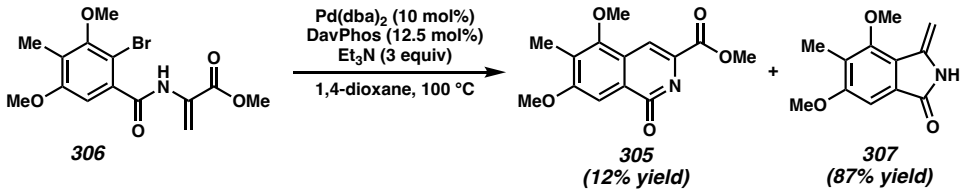
To a vial containing crude benzamide intermediate (110 mg, 0.4 mmol) was added triphenylphosphine (21 mg, 0.08 mmol, 20 mol%), PhMe (4 mL) and methyl propionate (43 uL, 0.48 mmol, 1.2 equiv). The mixture was sparged with N_2 for three minutes and heated to reflux for one hour, at which point the reaction had reached completion by TLC. The reaction was cooled, concentrated, and purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield enamide **306** (87 mg, 0.24 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 6.01 (d, J = 1.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 164.5, 158.1, 156.2, 135.7, 131.0, 124.6, 109.7, 107.4, 105.9, 60.7, 56.0, 53.2, 10.0.

IR (neat film, NaCl): 3361, 2942, 1726, 1678, 1564, 1519, 1440, 1379, 1338, 1200, 1121, 905 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{16}BrNO_5$ $[M]^{+\bullet}$: 357.0206, found 357.0199.



To a flame-dried vial was added $Pd(dba)_2$ (2.9 mg), DavePhos (4.9 mg) and dioxane (0.5 mL). The Pd stock solution was stirred for 20 minutes, then 0.25 mL of the stock solution was added to a separate vial containing enamide **306** (18 mg, 0.05 mmol) and triethylamine (20 uL, 0.15 mmol, 3 equiv) in dioxane (0.25 mL). The reaction vial was sealed and heated to 100 °C for 18 h, at which point the reaction was cooled, filtered through Celite with CH_2Cl_2 and concentrated. The reaction was purified with preparatory TLC, eluting with 50% ethyl acetate/hexanes, to isoquinolinone **305** (1.6 g, 0.006 mmol, 12% yield) and isoindolinone **307** (9.5 mg, 0.044 mmol, 87% yield).

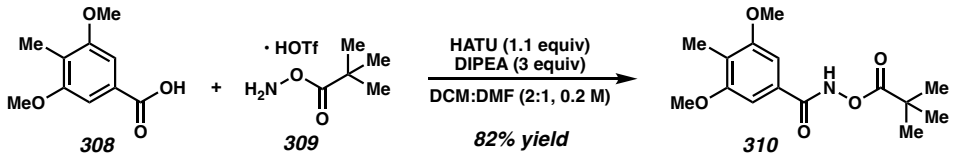
Spectral data for **307**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.12 (s, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.99 (d, *J* = 1.2 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 160.5, 154.8, 138.3, 130.2, 125.8, 121.6, 100.5, 93.5, 60.2, 56.3, 9.5.

IR (neat film, NaCl): 3180, 1706, 1643, 1613, 1477, 1359, 1167, 1123, 1005 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{12}H_{13}NO_3$ $[M]^{+\bullet}$: 219.0890, found 219.0885.



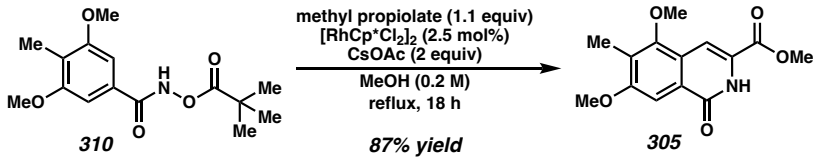
To a round bottom flask was added carboxylic acid **308** (1.76 g, 9.0 mmol), CH_2Cl_2 (30 mL), DMF (15 mL), hydroxylamine **309** (3.61 g, 13.5 mmol, 1.5 equiv), HATU (3.76 g, 9.9 mmol, 1.1 equiv), and DIPEA (4.7 mL, 27 mmol, 3 equiv). The mixture was stirred at 23 °c for 3 h, or until complete consumption of starting material by TLC. The crude mixture was diluted with water and extracted three times with ethyl acetate. The combined organics were washed three times with saturated aq. LiCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield hydroxamate **301** (2.17 g, 7.35 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H), 6.94 (s, 2H), 3.83 (s, 6H), 2.09 (s, 3H), 1.36 (s, 9H).

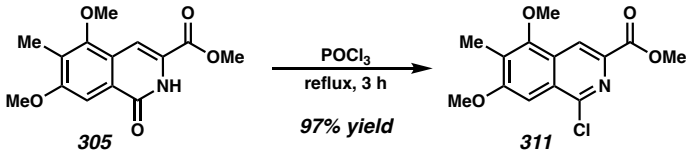
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5, 167.3, 158.4, 128.9, 120.2, 102.7, 56.0, 38.6, 27.2, 8.7.

IR (neat film, NaCl): 3187, 2976, 1780, 1662, 1587, 1465, 1411, 1324, 1242, 1141, 1083, 845 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{15}H_{21}NO_5$ $[M]^{+\bullet}$: 295.1414, found 295.1429.



To a round bottom flask equipped with a reflux condenser was added hydroxamate **310** (1.97 g, 6.67 mmol), methanol (33 mL), CsOAc (2.56 g, 13.3 mmol, 2 equiv), $[RhCp^*Cl_2]_2$ (103 mg, 0.167 mmol, 2.5 mol%), and the alkyne (0.65 mL, 7.34 mmol, 1.1 equiv). The reaction was heated to 65 °C for 18 h, then cooled, filtered through Celite with acetone, and concentrated. The crude mixture was purified with silica gel chromatography (0–15% EtOAc/CH_2Cl_2) to yield isoquinolinone **305** (1.615 g, 5.82 mmol, 87% yield). See above preparation for characterization of **305**.



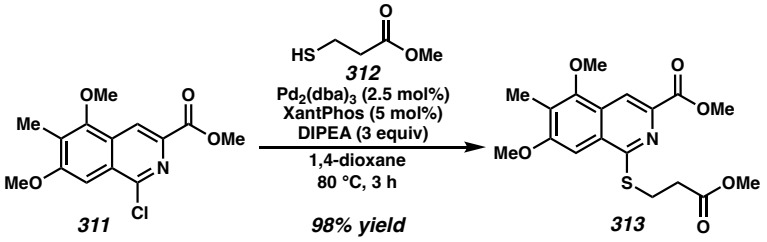
To a round bottom flask was added isoquinolinone **305** (4.15 g, 15 mmol) and $POCl_3$ (30 mL, 0.5 M). The reaction was heated to 90 °C for 4 h, then cooled, carefully poured over $NaHCO_3$ and ice, then transferred to a separatory funnel with ethyl acetate. The crude mixture was extracted three times with ethyl acetate, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline chloride **311** (4.31 g, 14.6 mmol, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 0.9 Hz, 1H), 7.39 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.94 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 161.1, 155.4, 138.4, 128.6, 128.1, 126.8, 118.8, 99.8, 62.5, 56.3, 53.0, 10.1.

IR (neat film, NaCl): 2945, 2369, 2340, 1715, 1407, 1233 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{14}ClNO_4$ $[M]^{+\bullet}$: 295.0606, found 295.0618.



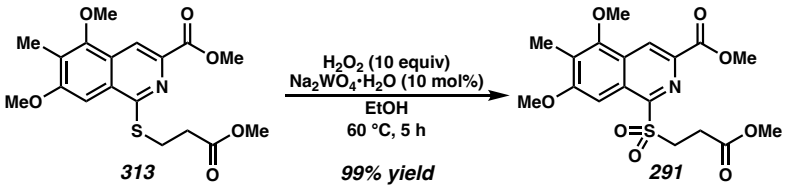
To a flame-dried two-neck round bottom flask equipped with a reflux condenser was added isoquinoline chloride **311** (296 mg, 1 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 5 mol%), and XantPhos (58 mg, 0.10 mmol, 10 mol%). The flask was backfilled with N_2 three times, then dioxane (5 mL) and DIPEA (0.52 mL, 3 mmol, 3 equiv) were added, followed by thiol **312** (0.13 mL, 1.2 mmol, 1.2 equiv). The reaction was heated to 80 °C for 3 h, or until starting material was consumed by TLC. The crude mixture was cooled to room temperature, diluted with water, and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline **313** (373 g, 0.98 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.13 (s, 1H), 3.98 (s, 4H), 3.97 (s, 3H), 3.89 (s, 3H), 3.71 (s, 4H), 3.68 (t, J = 6.8 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 166.6, 160.0, 157.1, 155.4, 138.8, 128.3, 125.4, 125.3, 115.4, 98.1, 62.3, 56.1, 52.5, 51.9, 34.2, 25.3, 9.9.

IR (neat film, NaCl): 2953, 1731, 1618, 1435, 1299, 1231, 1132, 997, 896 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{21}NSO_6$ $[M]^{+\bullet}$: 379.1084, found 379.1094.



To a round bottom flask was thioether **313** (529 mg, 1.39 mmol), ethanol (10 mL) and $Na_2WO_4•H_2O$ (46 mg, 0.14 mmol, 10 mol%). H_2O_2 (33% aq, 1.22 mL, 13.9 mmol, 10 equiv) was added slowly, and the reaction was heated to reflux. After 3 h, the reaction was cooled to room temperature and concentrated behind a blast shield. The crude mixture was partitioned between water and ethyl acetate and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline sulfone **291** (563 mg, 1.37 mmol, 99% yield).

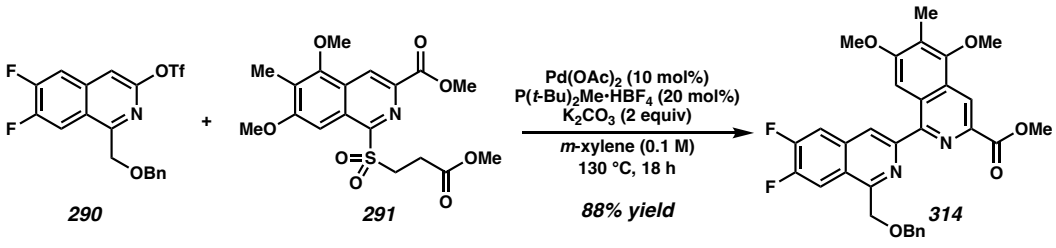
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, *J* = 0.9 Hz, 1H), 7.99 (s, 1H), 4.14 (dd, *J* = 8.0, 7.2 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 3.93 (d, *J* = 0.7 Hz, 3H), 3.76 (s, 3H), 3.18 (dd, *J* = 8.1, 7.0 Hz, 2H), 2.38 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 165.2, 161.8, 155.4, 153.8, 136.9, 128.9, 127.5, 125.0, 122.3, 98.2, 62.6, 56.5, 52.9, 52.4, 48.4, 28.6, 10.2.

IR (neat film, NaCl): 2951, 1737, 1613, 1435, 1306, 1235, 1135, 992, 897 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{21}NSO_8$ $[M]^{+\bullet}$: 411.0982, found 411.0990.

A7.6.2.3 Synthesis of Non-Natural Analogs



To a flame-dried two neck round bottom flask equipped with a reflux condenser was added freshly powdered K_2CO_3 (612 mg, 4.43 mmol, 2 equiv), sulfone **291** (1.094 g, 2.66 mmol, 1.5 equiv), $Pd(OAc)_2$ (50 mg, 0.222 mmol, 10 mol%), and $P(t\text{-Bu})_2Me{\bullet}HBF_4$ (110 mg, 0.443 mmol, 20 mol%). The flask was backfilled with N_2 three times, and isoquinoline triflate **290** (960 mg, 2.22 mmol, 1 equiv) in *m*-xylene (20 mL) was added, rinsing with 2 mL. The reaction was heated to 140 °C overnight, or until complete by TLC. The crude mixture was filtered through Celite with CH_2Cl_2 and acetone (1:1, x mL) and concentrated. The crude solid was purified with silica gel chromatography (15% EtOAc/hexanes + 3% Et_3N) to yield bis-isoquinoline **314** (981 mg, 1.80 mmol, 81% yield). Note: on 0.1 mmol scale, 88% yield could be reliably obtained.

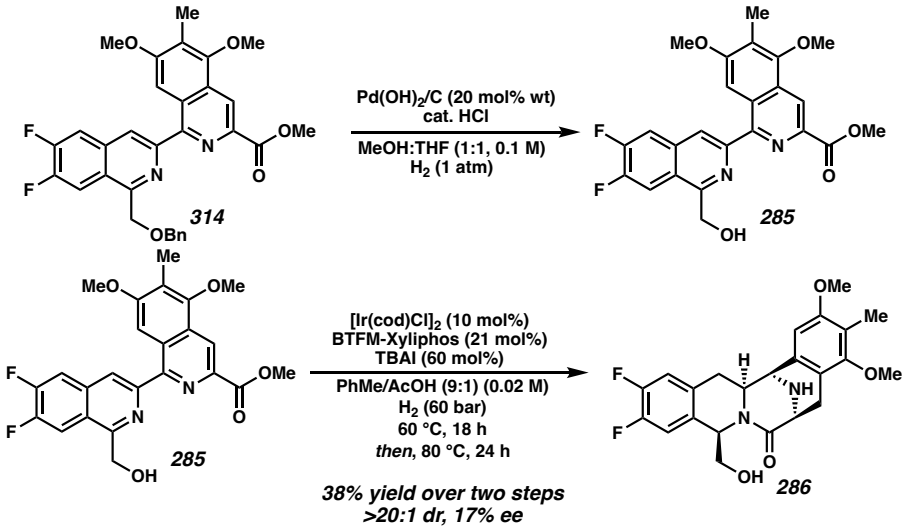
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 1.0 Hz, 1H), 8.48 (d, *J* = 0.9 Hz, 1H), 8.19 (ddd, *J* = 11.1, 7.9, 0.9 Hz, 1H), 8.06 (s, 1H), 7.73 (dd, *J* = 10.3, 7.7 Hz, 1H), 7.40 – 7.27 (m, 5H), 5.17 (s, 2H), 4.65 (s, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 3.80 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.74, 160.26, 154.95, 153.24 (dd, *J* = 230.4, 15.9 Hz), 151.65 (d, *J* = 2.8 Hz), 150.70 (dd, *J* = 227.3, 15.7 Hz), 138.97, 137.52, 135.53 (d, *J* = 8.4 Hz), 128.68, 128.49, 128.16, 125.37, 124.21 – 124.03 (m), 122.47 (dd, *J* = 5.1, 2.2 Hz), 119.07, 114.11 (d, *J* = 17.2 Hz), 112.74 (d, *J* = 18.4 Hz), 101.41, 73.37, 73.23, 65.76 – 51.57 (m), 9.93.

^{19}F NMR (282 MHz, $CDCl_3$): δ -129.26 (ddd, *J* = 18.7, 10.3, 7.8 Hz), -131.28 (ddd, *J* = 20.0, 11.1, 7.7 Hz).

IR (neat film, NaCl): 2951, 2361, 1716, 1619, 1577, 1512, 1451, 1398, 1311, 1230, 1100, 1071, 996, 901 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{31}H_{26}F_2N_2O_5$ $[M]^{+\bullet}$: 544.1804, found 544.1804.



To a round bottom flask containing bis-isoquinoline **314** (240 mg, 0.44 mmol, 1 equiv) dissolved in MeOH and THF (14 mL, 1:1) and HCl (1 drop) was added $Pd(OH)_2/C$ (24 mg, 20% wt). The backfilled with H_2 five times and then allowed to continue for 5 h, or until ~95% complete by LC/MS. The mixture was then filtered through Celite, washing with acetone, and concentrated. The crude solid was then dissolved in 4:1 $CHCl_3$:IPA and washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude solid was used without further purification.

A flame-dried round bottom flask with crude alcohol **285** (180 mg, 0.386 mmol, 1 equiv) was placed into a Parr bomb and brought into a nitrogen-filled glovebox, with the exception of the pressure gauge. To the flask of **285** was added TBAI (88 mg, 0.238 mmol, 0.6 equiv), PhMe (3 mL) and AcOH (1 mL). In as separatre vial, a solution of SL-J008-2 (BTFM-xyliphos) (89.0 mg, 0.098 mmol, 0.24 equiv) and $[Ir(cod)Cl]_2$ (27 mg, 0.04 mmol, 0.10 equiv) in PhMe (5 mL) was prepared and allowed to stand for 10 minutes, then transferred to the reaction flask, rinsing with PhMe (2 mL). After sealing the flask with a rubber septum that was pierced with three 16-gauge (purple) needles, each bent at a 90º angle, the flask was placed inside the bomb, and the top was covered tightly with plastic

wrap secured by a rubber band, and the bomb was then removed from the glovebox. The pressure gauge was quickly screwed into place and tightened. The bomb was charged to 5-10 bar H_2 and slowly released three times, then charged to 60 bar H_2 and heated to 60 °C. After 18 h, the reaction was heated to 80 °C and continued for an additional 36 h, at which point it was cooled, opened to air, and basified to pH > 7 with saturated aq. K_2CO_3. The biphasic mixture was transferred to a separatory funnel, and the aqueous was extracted five times with ethyl acetate. The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified using reverse-phase (C18) chromatography (30 g RediSep Rf Gold column, 0.4% AcOH in H_2O/MeCN, 10–40% MeCN over 10 minutes, then 95% MeCN for 8 minutes) to afford bis-THIQ **286** (72.4 mg, 0.168 mmol, 38% over two steps, 17% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (ddd, J = 10.9, 7.6, 3.3 Hz, 2H), 6.33 (s, 1H), 5.31 (t, J = 5.5 Hz, 1H), 4.13 (d, J = 3.3 Hz, 1H), 4.10 (d, J = 5.6 Hz, 1H), 3.95 (dt, J = 12.5, 2.9 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.29 (d, J = 5.5 Hz, 2H), 3.13 (dd, J = 17.4, 1.5 Hz, 1H), 3.02 (dd, J = 17.4, 6.4 Hz, 1H), 2.80 (dd, J = 14.7, 2.6 Hz, 1H), 2.73 – 2.54 (m, 3H, overlapped with OH and NH), 2.14 (s, 3H)

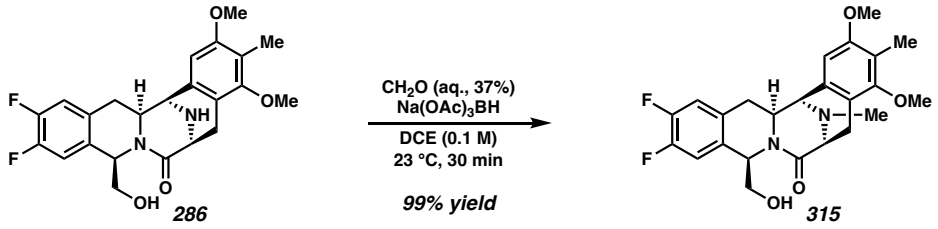
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 157.8, 156.8, 149.6 (dd, J = 243.6, 7.3 Hz), 149.5 (dd, J = 246.3, 11.2 Hz), 132.1 (dd, J = 6.1, 3.9 Hz), 130.6, 130.70 – 130.48 (m), 120.1, 119.7, 117.1 (d, J = 17.8 Hz), 116.6 (d, J = 17.4 Hz), 106.1, 68.2, 61.0, 60.5, 57.5, 56.0, 54.9, 54.3, 33.0, 30.0, 9.3

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.67 – -139.26 (m), -139.30 – -139.75 (m)

IR (neat film, NaCl): 3288, 2941, 1634, 1513, 1455, 1407, 1371, 1335, 1310, 1296, 1274, 1214, 1125, 1061, 753 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{23}H_{24}F_2N_2O_4$ $[M]^{+\bullet}$: 430.1699, found 430.1709.

SFC: 10% IPA/hexanes, 1.0 mL/min, Chiralcel OD-H column, $\lambda = 220$ nm, t_R (min): major = 6.73, minor = 7.77.



To bis-THIQ **286** (724 mg, 0.168 mmol, 1 equiv) in DCE (3.5 mL) was added formaldehyde (37% aq., 23 uL, 0.311 mmol, 1.85 equiv). After stirring for 10 minutes, $Na(OAc)_3BH$ (178 mg, 0.841 mmol, 5 equiv). After 30 minutes, the reaction was complete by LC/MS. Citric acid monohydrate (265 mg, 1.26 mmol, 7.5 equiv) was added, along with H_2O (3 mL), and the biphasic mixture was stirred for 10 minutes. The pH was then adjusted to pH > 7 with sat. aq. K_2CO_3. The layers were separated, and then the aqueous was extracted twice with ethyl acetate. The combined organics were dried over anhydrous Na_2CO_3, filtered, and dried under reduced pressure to deliver methylated bis-THIQ **315** (73.6 mg, 0.166 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 – 6.96 (m, 2H), 6.32 (s, 1H), 5.24 (t, *J* = 5.7 Hz, 1H), 4.06 – 3.90 (m, 1H), 3.82 (s, 3H), 3.78 – 3.72 (m, 2H), 3.66 (s, 3H), 3.39 – 3.27 (m, 1H), 3.10 (dd, *J* = 17.8, 6.5 Hz, 1H), 2.87 (d, *J* = 17.7 Hz, 1H), 2.72 (dd, *J* = 14.7, 2.6 Hz, 1H), 2.57 (t, *J* = 13.7 Hz, 1H), 2.44 (s, 3H), 2.12 (s, 3H).

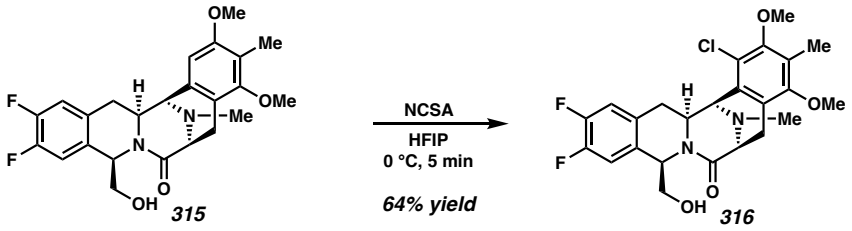
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 157.3, 156.8, 149.4 (dd, *J* = 245.0, 9.1 Hz), 149.2 (dd, *J* = 246.2, 11.6 Hz), 132.2 (dd, *J* = 6.0, 3.7 Hz), 130.6 (d, *J* = 2.1 Hz), 128.4, 119.8, 118.7, 117.1 (d, *J* = 17.9 Hz), 116.4 (d, *J* = 17.4 Hz), 106.8, 67.5, 61.1, 60.3, 60.0, 57.8, 57.2, 55.8, 40.0, 32.8, 23.7, 9.1.

Note: ^{13}C spectra contaminated with aliphatic grease.

^{19}F NMR (282 MHz, $CDCl_3$): δ 139.37 (dt, *J* = 19.0, 8.4 Hz), -139.76 – -139.94 (m).

IR (neat film, NaCl): 2940, 1643, 1513, 1443, 1271, 1168, 1123, 910, 731, 679 cm^{-1}.

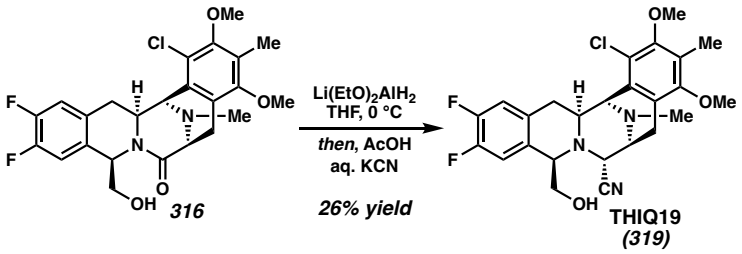
HRMS (FD+): m/z calc'd for $C_{24}H_{27}F_2N_2O_4$ $[M+H]^+$: 445.1933, found 445.1940.



To a solution of **315** (14.7 mg, 0.034 mmol, 1 equiv) in HFIP (1.5 mL, 0.02 M) at 0 °C was added *N*-chlorosaccharin (7.7 mg, 0.035 mmol, 1.05 equiv), after which the cloudy white mixture turned yellow and became homogeneous. After complete addition, the LC/MS showed complete consumption of **315**, so the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$. The resulting mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 and water, creating a triphasic system with HFIP on bottom, CH_2Cl_2 in the middle, and the aqueous phase on top. The bottom two phases were collected. The aqueous phase was basified with saturated aqueous K_2CO_3 solution and extracted with CH_2Cl_2. The organic phases were combined, concentrated, and azeotropically dried twice with benzene. The crude solid was purified with preparatory TLC (5% MeOH/CH_2Cl_2) to afford chlorinated bis-THIQ **316** (10.3 mg, 0.021 mmol, 64% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 10.3, 7.6 Hz, 2H), 5.40 (t, *J* = 5.9 Hz, 1H), 4.44 (dd, *J* = 3.7, 1.2 Hz, 1H), 4.09 (ddd, *J* = 12.8, 3.7, 2.6 Hz, 1H), 3.81 (s, 3H), 3.77 (dt, *J* = 6.9, 1.2 Hz, 1H), 3.71 (s, 3H), 3.48 – 3.19 (m, 3H), 3.12 (dd, *J* = 18.2, 6.8 Hz, 1H), 2.97 (dd, *J* = 18.2, 1.2 Hz, 1H), 2.43 (s, 3H), 2.39 (t, *J* = 13.9 Hz, 1H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.86, 156.21, 153.80, 152.27 – 148.21 (m), 149.38 (dd, *J* = 246.7, 11.7 Hz), 132.42 – 132.26 (m), 130.03 – 129.85 (m), 128.48, 127.69, 126.39, 124.49, 123.69, 116.87 (dd, *J* = 19.6, 17.7 Hz), 68.65, 60.52, 60.37, 59.39, 59.05, 57.59, 56.81, 40.28, 31.70, 24.52, 10.11.



In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 0.5 mL, 0.5 mmol) was cooled to 0 ºC. A solution of ethyl acetate (57 µL, 0.58 mmol) in 0.5 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. Chlorinated bis-THIQ **316** (10.3 mg, 0.0215 mmol, 1 equiv) was dissolved in THF (1 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 0.7 mL, 0.32 mmol, 15 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 30 min, the LC/MS showed complete consumption of **316**, so the reaction was quenched with acetic acid (26 µL, 0.45 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 27 µL, 0.13 mmol, 6 equiv) was added, followed by Celite and anhydrous Na_2SO_4 (roughly 250 mg each). The solution was diluted with 3 mL THF and stirred at 50 °C overnight. Upon full consumption of iminium by LC/MS, additional Celite and K_2CO_3 (1 g) were added, and the suspension was filtered through Celite, rinsing with EtOAc. The filtrate was transferred to a round bottom flask and concentrated, and the crude product was purified with reverse phase C18 chromatography (0.4% AcOH in H_2O/MeCN, 40–90% MeCN over 9 minutes, then 100%

MeCN for 1 min, t_R = 8.5 min) to afford amino nitrile **THIQ19** (**319**) (2.7 mg, 0.0055 mmol, 26% yield).

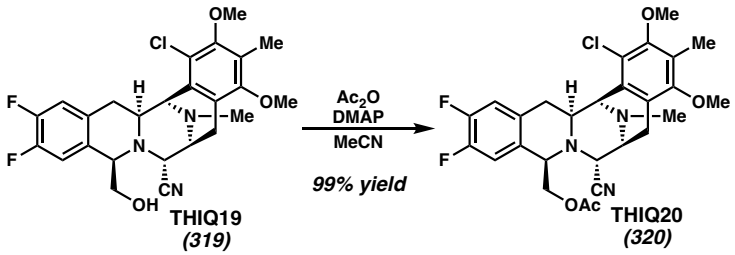
$[\alpha]_D^{25}$ = 0.193 (*c* = 0.1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 – 6.83 (m, 2H), 4.34 (dd, *J* = 3.0, 1.2 Hz, 1H), 4.08 (d, *J* = 2.6 Hz, 1H), 3.83 (m, *J* = 4.4 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.62 (dt, *J* = 11.1, 4.0 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.31 – 3.20 (m, 1H), 3.08 (dd, *J* = 18.6, 7.9 Hz, 1H), 2.99 (dd, *J* = 15.5, 2.7 Hz, 1H), 2.53 (d, *J* = 18.6 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.22 – 2.09 (m, 1H), 1.70 (dd, *J* = 8.4, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.89, 153.44, 131.70, 129.76 (d, *J* = 4.4 Hz), 128.77, 125.60, 125.02, 124.22, 117.56, 116.76 (d, *J* = 17.0 Hz), 115.71 (d, *J* = 17.6 Hz), 67.00, 62.50, 60.70, 60.53, 60.04, 59.17, 57.00, 54.97, 41.93, 31.36, 21.87, 10.08.

Note: ^{13}C signal intensity low; peaks missing.

HRMS (FD+): m/z calc'd for $C_{25}H_{27}ClF_2N_3O_3$ $[M+H]^+$: 490.1704, found 490.1712.



In a 1-dram vial, **THIQ19** (1.6 mg, 0.003 mmol, 1 equiv) and DMAP (0.001 mg, 0.01 mmol, equiv) were dissolved in acetonitrile (150 μL, 0.02 M) and acetic anhydride (1 μL, 0.01 μmol, 3 equiv) was added neat. After 30 minutes, LC/MS showed complete consumption of **THIQ19**. The reaction was concentrated, and the crude material was purified using reverse-phase (C18) preparative HPLC (0.4% acetic acid in water/MeCN, 5.0 mL/min, monitor wavelength = 260 nm, 60–90% MeCN over 6 min, ramp to 95 over

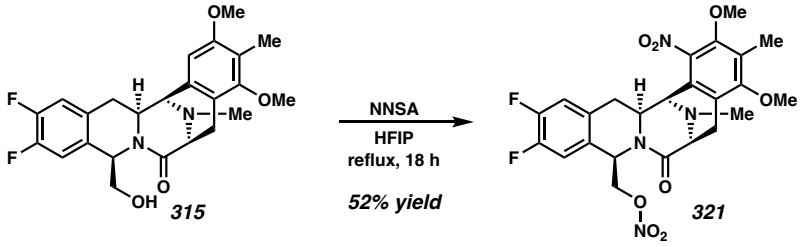
0.5 min, hold at 95% for 1.5 min) to afford acylated bis-THIQ analog **THIQ20** as a colorless solid (1.6 mg, 0.003 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (ddd, *J* = 13.3, 10.5, 7.7 Hz, 2H), 4.28 (dd, *J* = 3.1, 1.2 Hz, 1H), 4.06 (d, *J* = 2.6 Hz, 1H), 4.03 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.89 (t, *J* = 5.1 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.65 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.43 – 3.33 (m, 2H), 3.08 – 2.97 (m, 2H), 2.52 (d, *J* = 18.5 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.20 – 2.08 (m, 1H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.42, 154.78, 153.09, 128.65, 125.72, 125.18, 123.86, 117.79, 116.46 (dd, *J* = 69.3, 17.6 Hz), 68.27, 61.05, 60.51 (d, *J* = 4.0 Hz), 59.80, 59.18, 57.30, 54.99, 41.90, 31.53, 21.60, 20.67, 10.07.

Note: ^{13}C signal intensity low; peaks missing.

HRMS (ESI+): m/z calc'd for $C_{27}H_{29}ClF_2N_3O_4$ $[M+H]^+$: 532.1809, found 532.1811.



A vial containing bis-THIQ **315** (73.6 mg, 0.166 mmol, 1 equiv) and *N*-nitrosaccharin (453 mg, 1.99 mmol, 12 equiv) was backfilled with argon three times. HFIP (1.1 mL) was added, and the reaction was heated to 60 °C for 18 h, or until full conversion to nitroester **321** by LC/MS. The reaction was quenched with sat. aq. $NaHCO_3$, extracted three times with ethyl acetate, and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified with silica gel chromatography (0–20% ethyl acetate/CH_2Cl_2 + 1% Et_3N) to afford nitroester **321** (45.9 mg, 0.086 mmol, 52% yield).

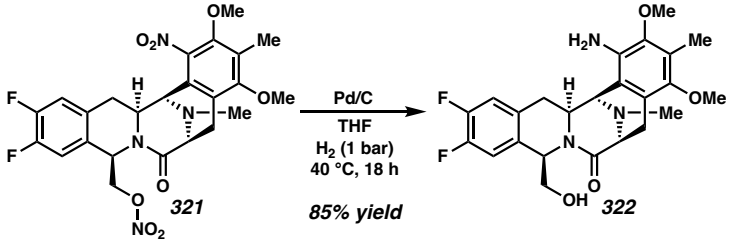
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 10.2, 7.6 Hz, 1H), 6.97 (dd, *J* = 10.1, 7.4 Hz, 1H), 5.48 (t, *J* = 3.6 Hz, 1H), 5.01 (dd, *J* = 11.9, 3.9 Hz, 1H), 4.33 (dd, *J* = 3.5, 1.2 Hz, 1H), 3.99 (ddd, *J* = 11.8, 7.6, 3.9 Hz, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.14 (dd, *J* = 18.4, 7.0 Hz, 1H), 2.86 (dd, *J* = 18.4, 1.1 Hz, 1H), 2.65 – 2.46 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.23, 159.23, 150.76, 149.91 (dd, *J* = 250.4, 12.3 Hz), 149.66 (dd, *J* = 248.8, 12.9 Hz), 142.96, 132.44 (dd, *J* = 6.4, 3.9 Hz), 128.14 (dd, *J* = 5.8, 3.9 Hz), 126.98, 124.19, 122.18, 117.50 (d, *J* = 17.7 Hz), 116.18 (d, *J* = 18.1 Hz), 74.01, 62.80, 60.32, 58.89, 58.68, 55.88, 52.75 (d, *J* = 1.5 Hz), 39.85, 31.23, 23.04, 10.16.

^{19}F NMR (282 MHz, $CDCl_3$): δ -139.02 – -140.35 (m), -140.78 – -142.25 (m).

IR (neat film, NaCl): 2944, 2357, 1649, 1520, 1446, 1363, 1275, 1106, 1003, 859, 731, 680 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{24}H_{25}F_2N_4O_8$ $[M+H]^+$: 535.1635, found 535.1562.



To a vial of nitroester **321** (21.6 mg, 0.04 mmol, 1 equiv) in THF (0.75 mL, 0.05 M) with conc. HCl (1 drop) was added Pd/C (5% wt, 20 mg). The vial was sealed, bubbled through with H_2 for three minutes, and heated to 40 °C under 1 atm H_2. After 18 h, the reaction was complete by LC/MS. The reaction was cooled, and the crude solution was passed through a short bed of Celite, eluting with methanol. The solution was concentrated under reduced pressure and purified via preparatory TLC (3% MeOH/CH_2Cl_2 + 1% Et_3N) to deliver **322** (15.7 mg, 0.034 mmol, 85% yield).

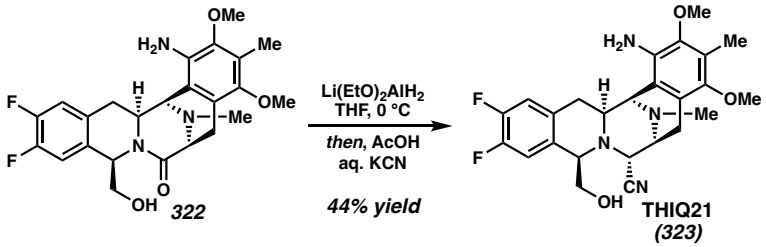
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 – 6.91 (m, 2H), 5.36 – 5.29 (m, 1H), 4.06 (dt, *J* = 12.8, 3.0 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.77 – 3.68 (m, 4H), 3.64 (m, 4H), 3.38 – 3.24 (m, 2H), 3.16 – 2.76 (m, 4H), 2.53 (dd, *J* = 15.1, 12.6 Hz, 1H), 2.46 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.83, 149.50 (dd, *J* = 245.2, 9.3 Hz), 149.28, 149.27 (dd, *J* = 246.3, 11.6 Hz), 145.23, 134.46, 132.50 (dd, *J* = 6.2, 3.7 Hz), 130.30 (dd, *J* = 6.0, 3.7 Hz), 124.00, 122.18, 116.78 (dd, *J* = 17.6, 10.9 Hz), 115.15, 70.68, 68.13 (d, *J* = 3.3 Hz), 60.41, 59.74, 59.61, 58.70, 56.74 (d, *J* = 49.6 Hz), 45.93, 40.56, 32.07, 24.77 (d, *J* = 2.8 Hz), 9.59.

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.13 – -139.56 (m), -139.82 (m).

IR (neat film, NaCl): 2925, 2857, 1748, 1633, 1453, 1168, 680 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{24}H_{28}F_2N_3O_4$ $[M+H]^+$: 460.2042, found 460.2043.



In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 1.0 mL, 0.5 mmol) was cooled to 0 ºC. A solution of ethyl acetate (115 µL, 1.18 mmol) in 1.0 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. Aminated bis-THIQ **322** (15.7 mg, 0.034 mmol, 1 equiv) was dissolved in THF (1.7 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 1.1 mL, 0.52 mmol, 15 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 30 min, the LC/MS showed complete consumption of **322**, so the reaction was quenched with acetic acid (41 µL, 0.727 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 43 µL, 0.21 mmol, 6 equiv) was added,

followed by Celite and anhydrous Na_2SO_4 (roughly 250 mg each). The solution was diluted with 2 mL THF and allowed to warm to 23 °C and continued overnight.

After 18 h, some residual iminium remained by LC/MS. Additional Na_2SO_4 (roughly 200 mg) was added, and the reaction was heated to 50 °C. After two hours, only trace iminium remained by LC/MS. Solid K_2CO_3 was added to the suspension, and the mixture was filtered through Celite, rinsing with EtOAc. The filtrate was concentrated under reduced pressure, and the crude product was purified with reverse phase C18 chromatography (0.4% AcOH in H_2O/MeCN, 45–70% MeCN over 5 minutes, then 95% MeCN for 3 min, t_R = 4.91 min) to afford amino nitrile **THIQ21** (**323**) (7.1 mg, 0.015 mmol, 44% yield).

^{1}H NMR (400 MHz, C_6D_6): δ 6.33 (dd, *J* = 10.7, 7.8 Hz, 1H), 6.26 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.46 (s, 3H), 3.40 – 3.34 (m, 1H), 3.33 – 3.30 (m, 1H), 3.25 (s, 3H), 3.22 (m, 1H), 3.13 (m, 1H), 3.04 (dd, *J* = 11.0, 4.1 Hz, 1H), 2.79 (dd, *J* = 11.1, 4.2 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.12 (s, 3H), 2.10 – 2.03 (m, 2H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 149.5 (d, *J* = 216.6 Hz), 149.4 (d, *J* = 249.1 Hz), 148.4, 144.8, 135.0, 132.0 (m), 130.9 (dd, *J* = 5.6, 3.5 Hz), 123.4, 123.1, 117.6, 116.5 (d, *J* = 16.9 Hz), 116.0 (d, *J* = 17.5 Hz), 115.7, 67.0, 62.4, 60.4, 59.7, 58.9, 57.7, 57.1, 55.1, 41.7, 31.5, 21.9, 9.6.

^{19}F NMR (282 MHz, C_6D_6): δ -140.26 – -140.51 (m), -140.70 (m).

IR (neat film, NaCl): 3464, 2927, 1615, 1517, 1464, 1320, 1100, 1055, 880, 679 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{25}H_{29}F_2N_4O_3$ $[M+H]^+$: 471.2202, found 471.2221.

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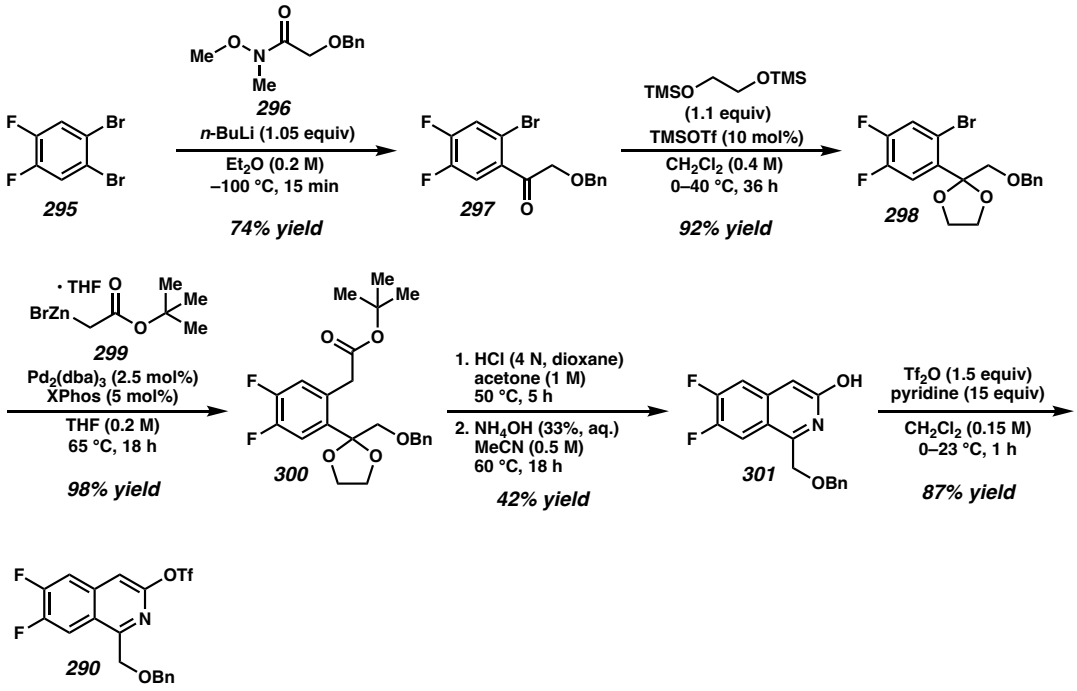
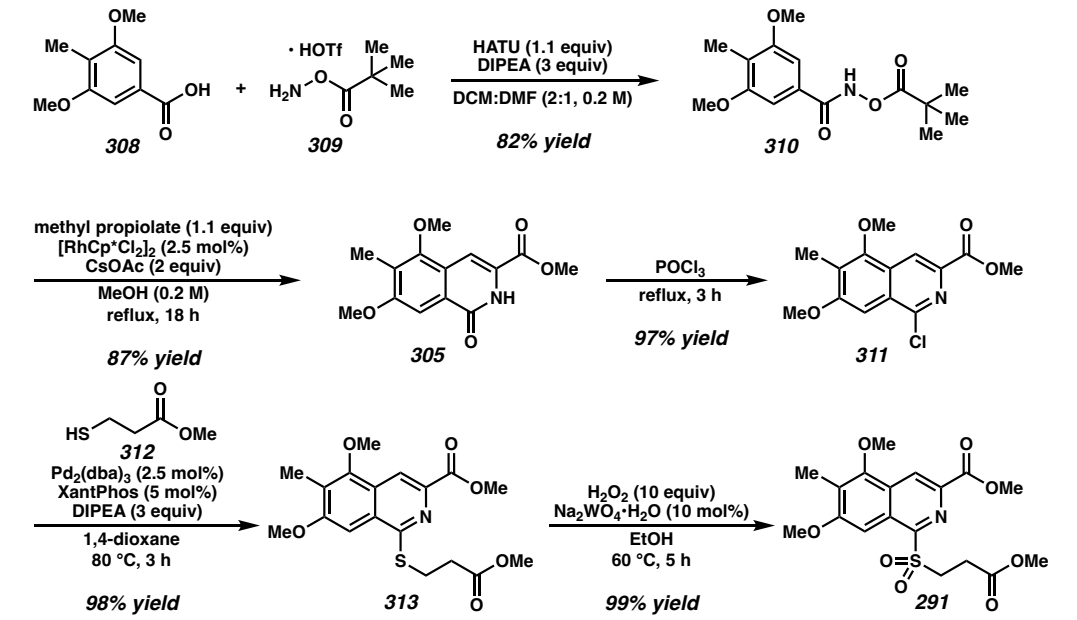
APPENDIX 8

Synthetic Summary of Appendix 7: Revised Route Toward the bis-THIQ Natural Products and Synthesis of Non-Natural Analogs

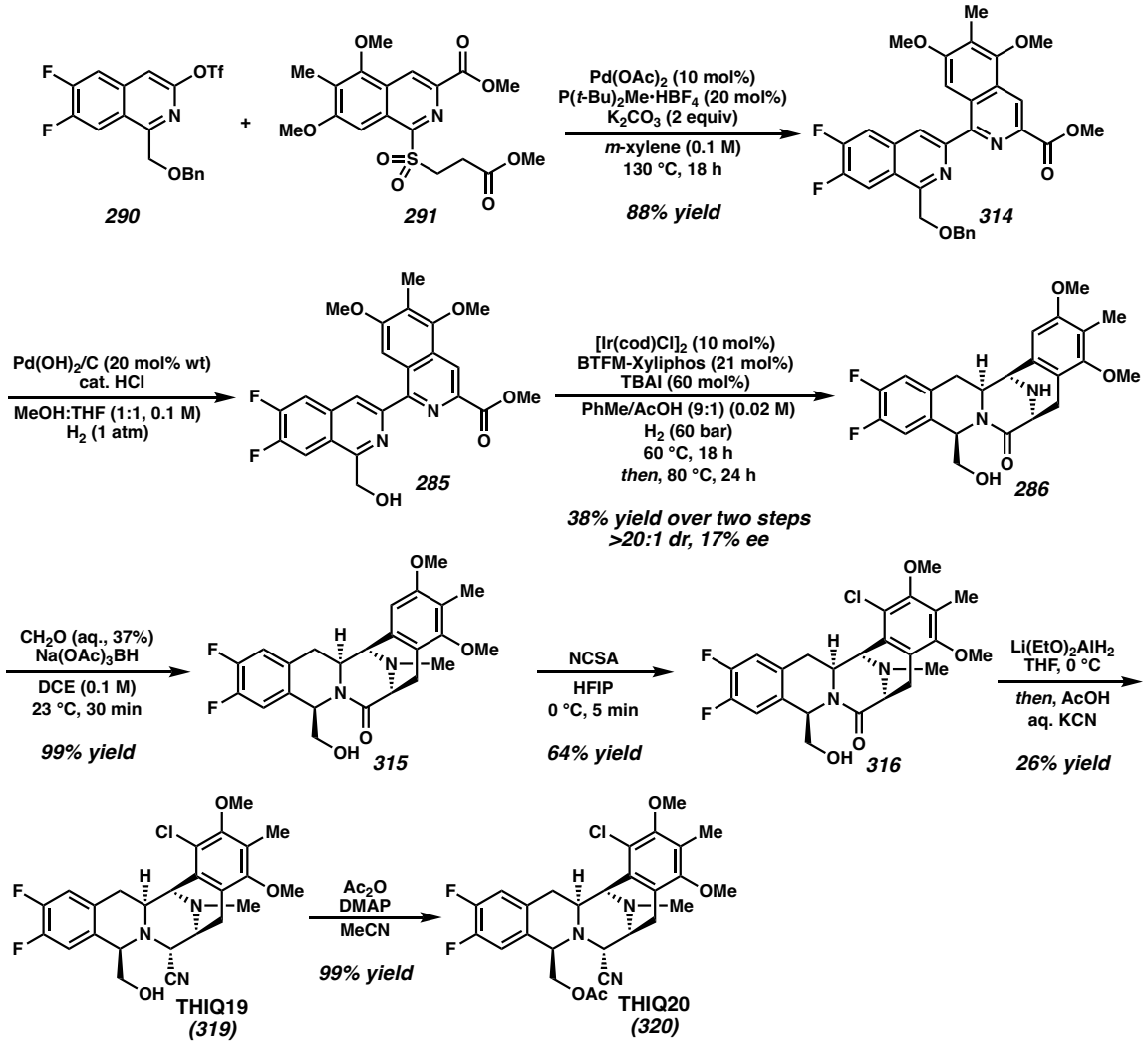
Scheme A8.1 *Synthesis of isoquinoline triflate* ***290***.



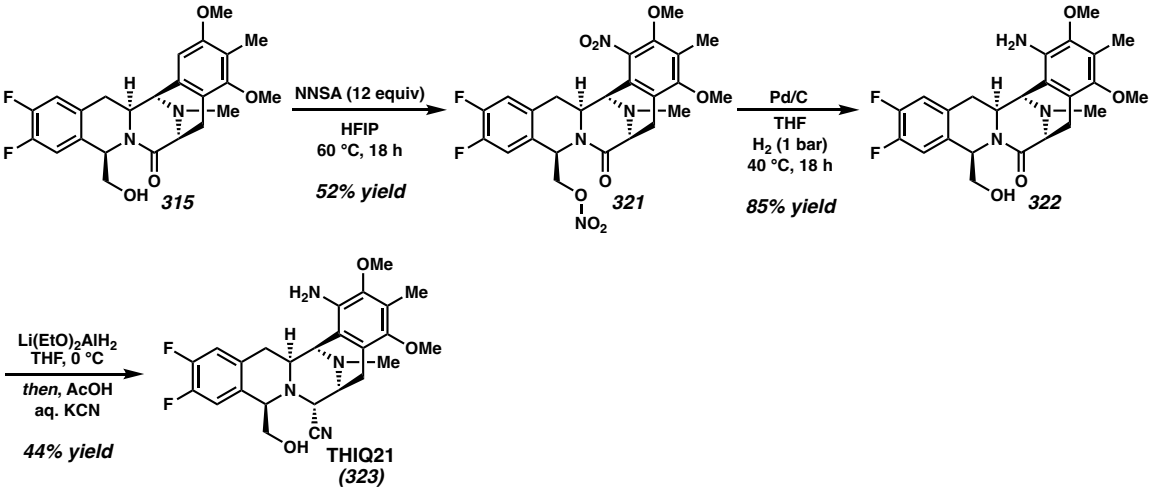
Scheme A8.2 *Synthesis of isoquinoline sulfone* ***291***.



Scheme A8.3 *Synthesis of analogs* ***THIQ19*** *(****319****) and* ***THIQ20*** *(****320****).*



Scheme A8.4 *Synthesis of* ***THIQ21*** *(****323****).*



APPENDIX 9

Spectra Relevant to Appendix 7: Revised Route Toward the bis-THIQ Natural Products and Synthesis of Non-Natural Analogs

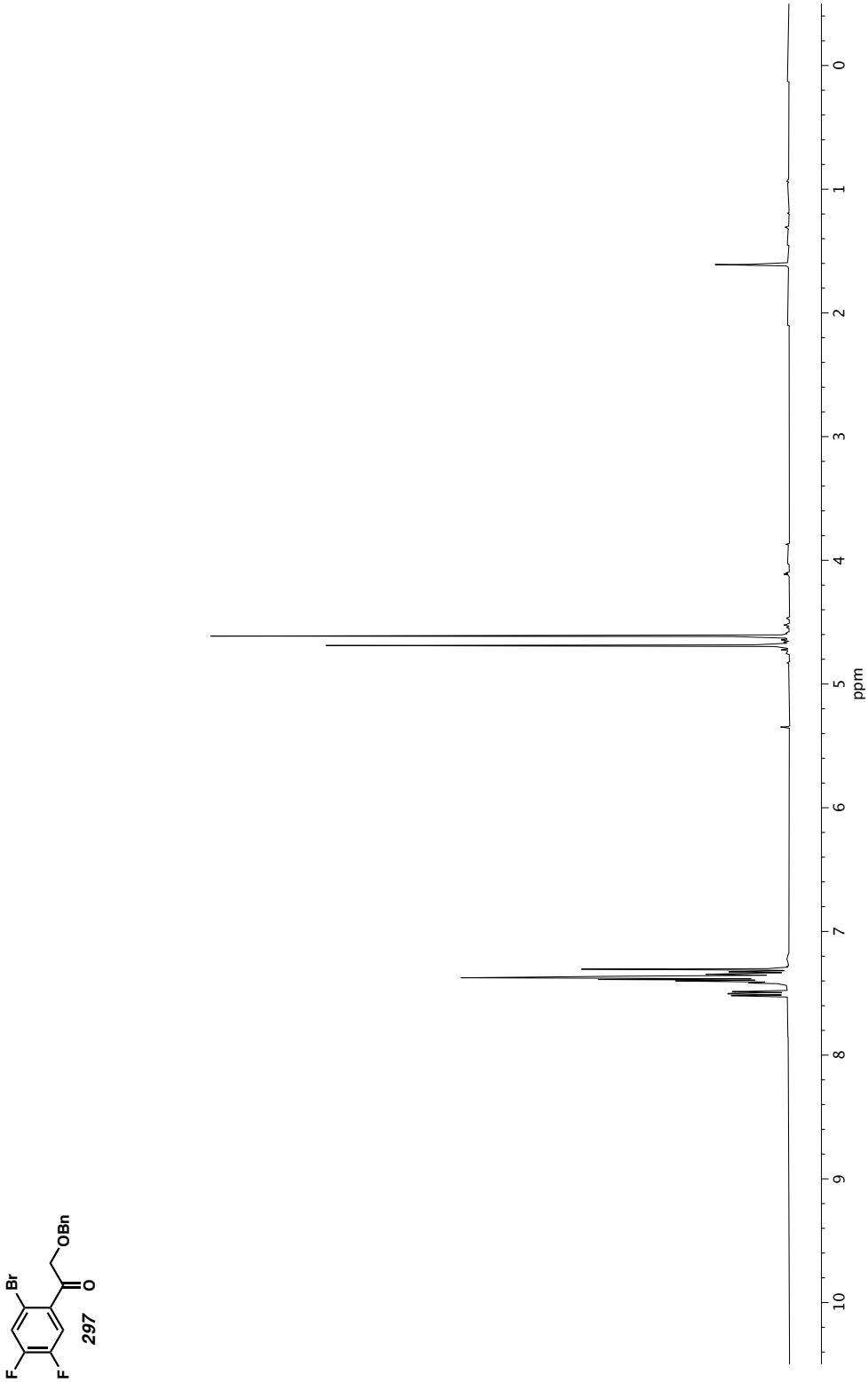


Figure A9.1 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***297****.*

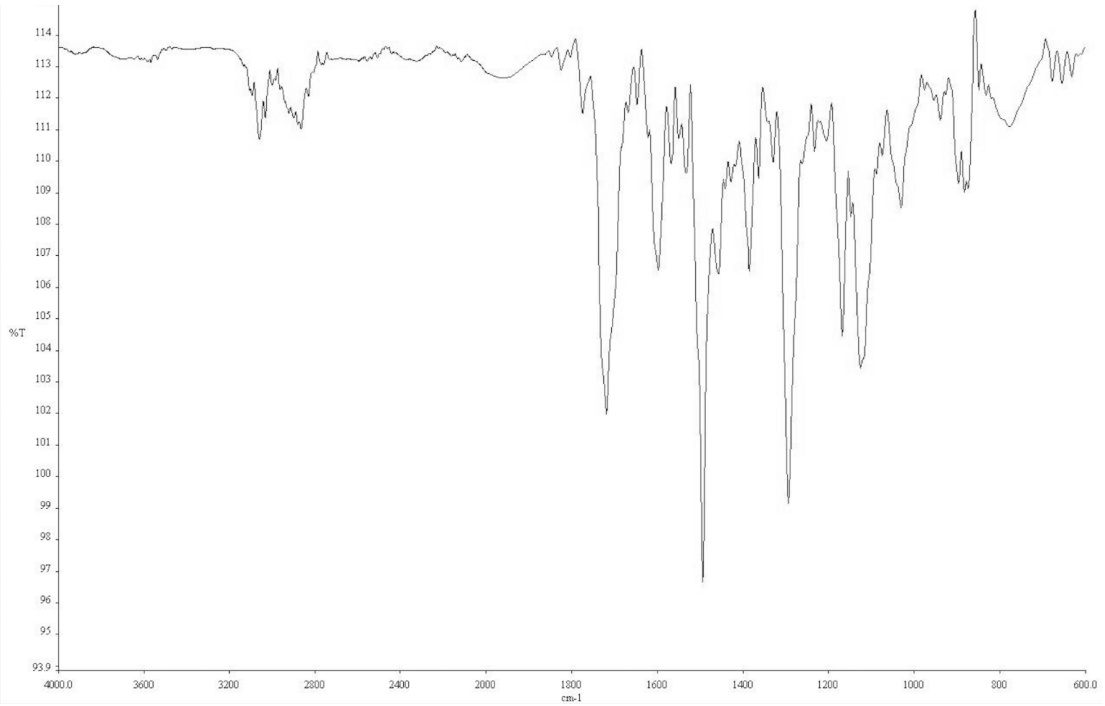


Figure A9.2 *Infrared spectrum (Thin Film, NaCl) of compound* ***297****.*

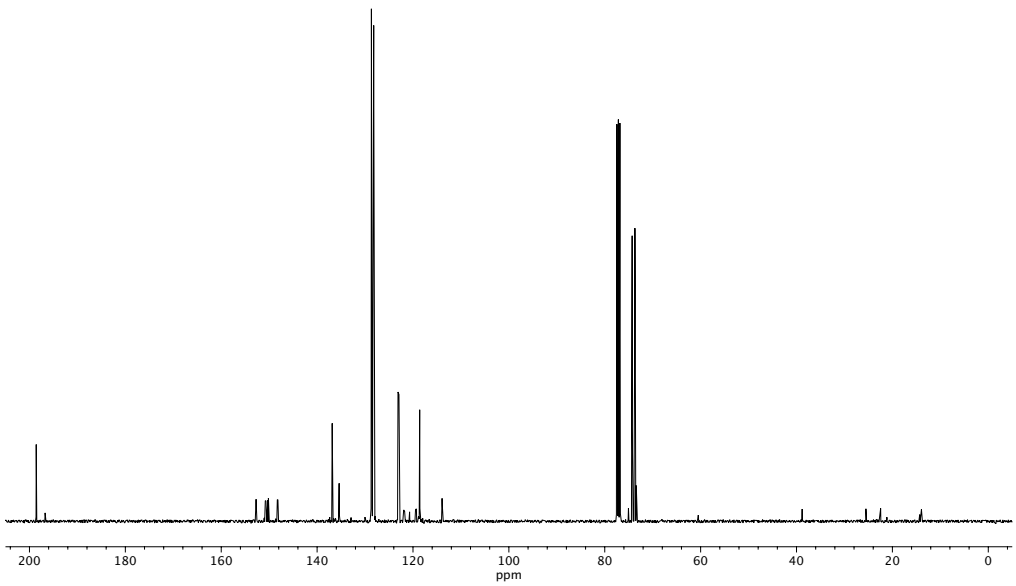


Figure A9.3 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***297****.*

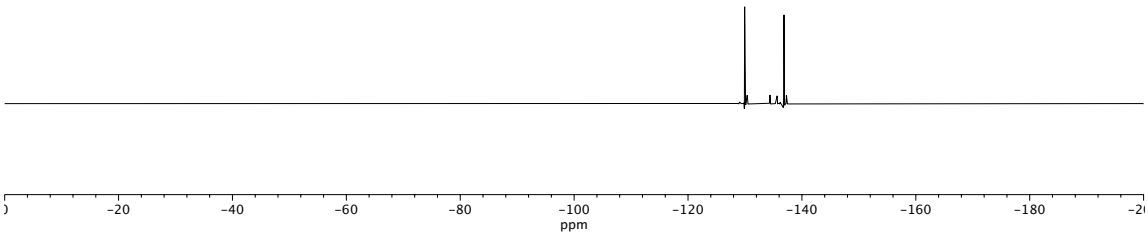


Figure A9.4 *^{19}F NMR (282 MHz, $CDCl_3$) of compound **297**.*

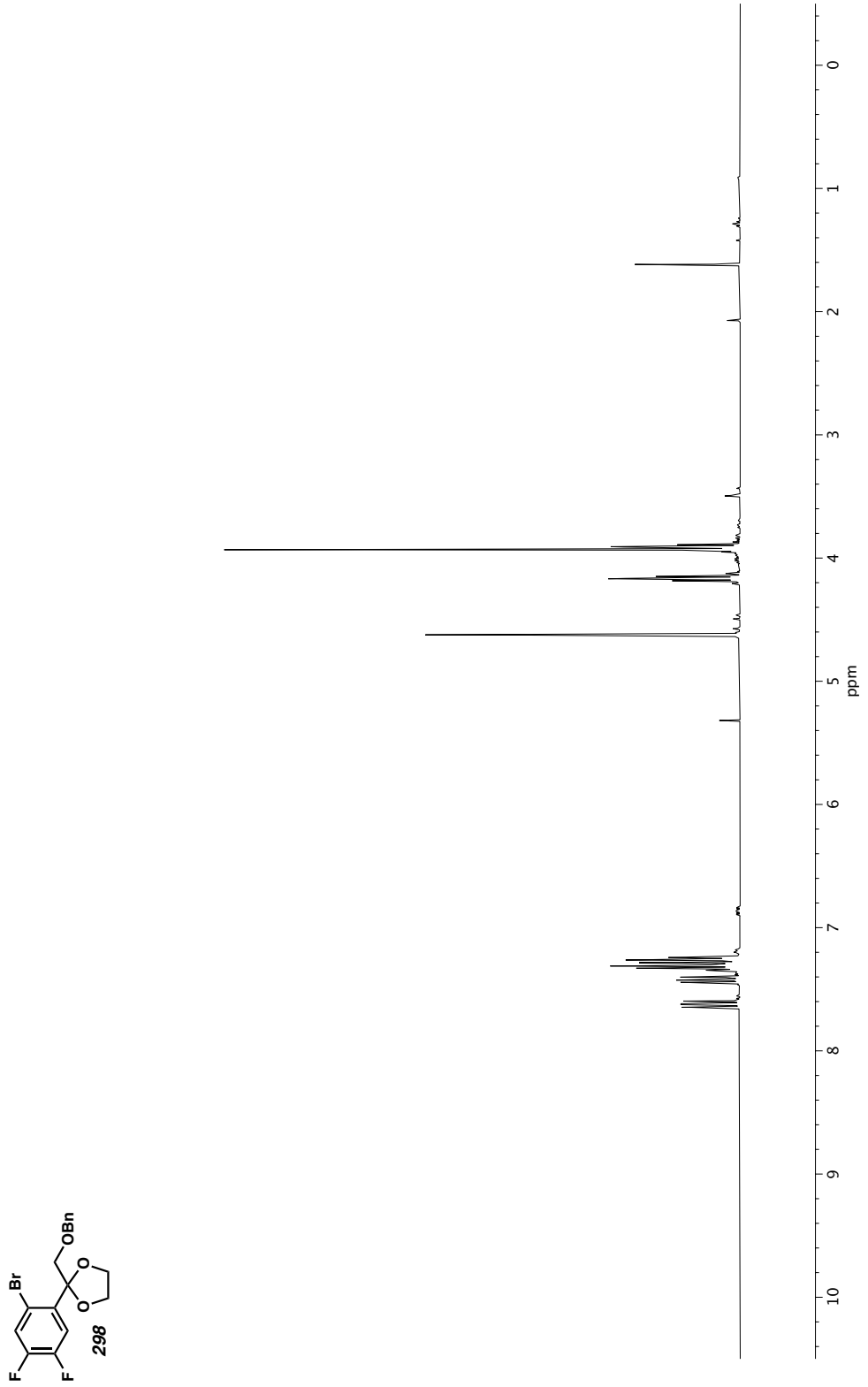


Figure A9.5 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***298****.*

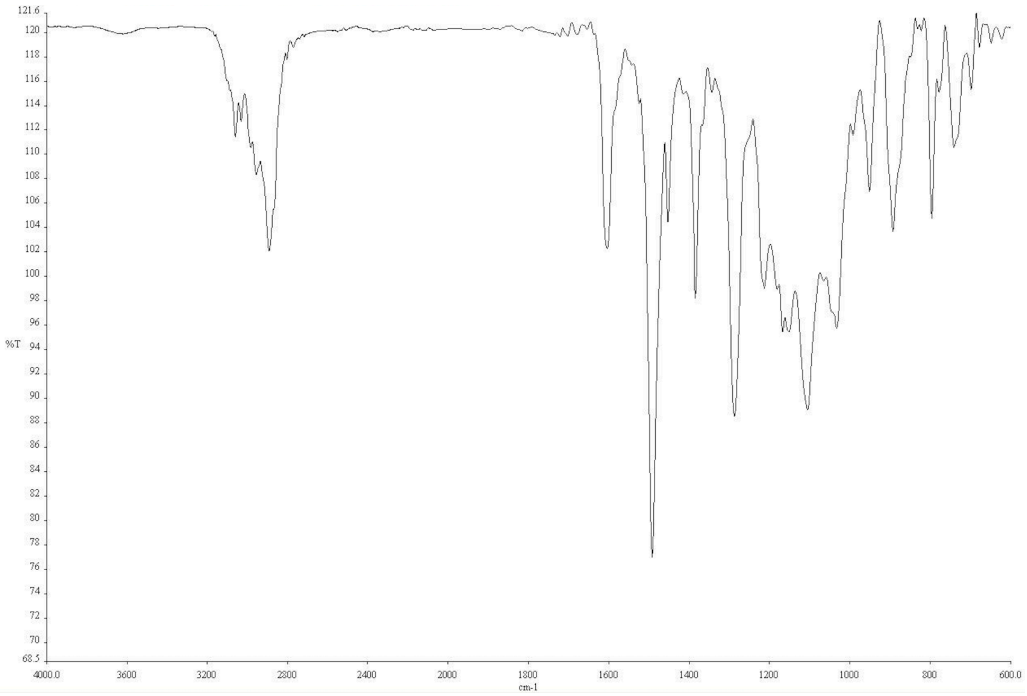


Figure A9.6 *Infrared spectrum (Thin Film, NaCl) of compound* ***298***.

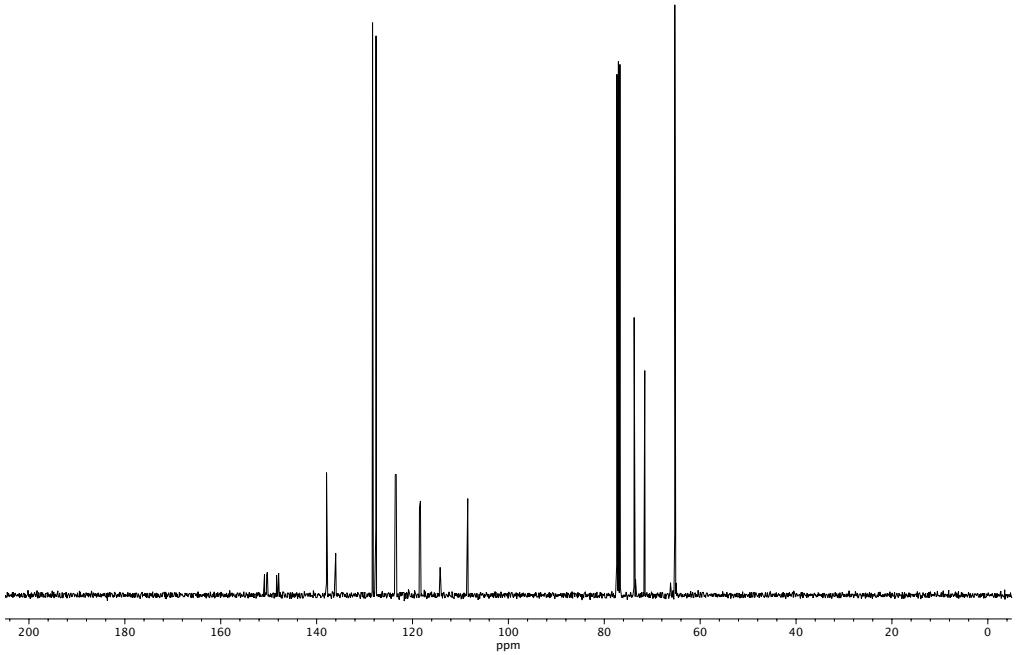


Figure A9.7 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***298***.

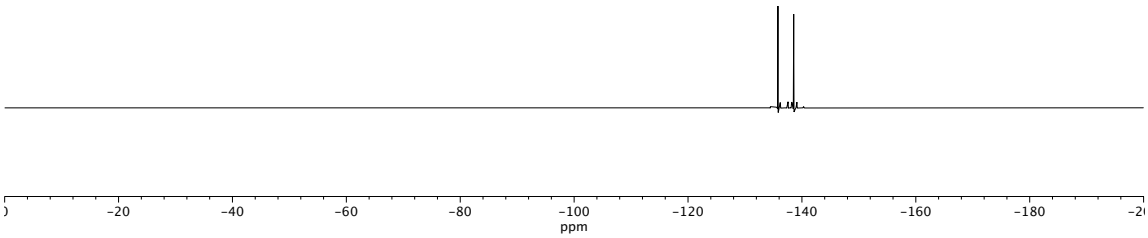


Figure A9.8 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***298****.*

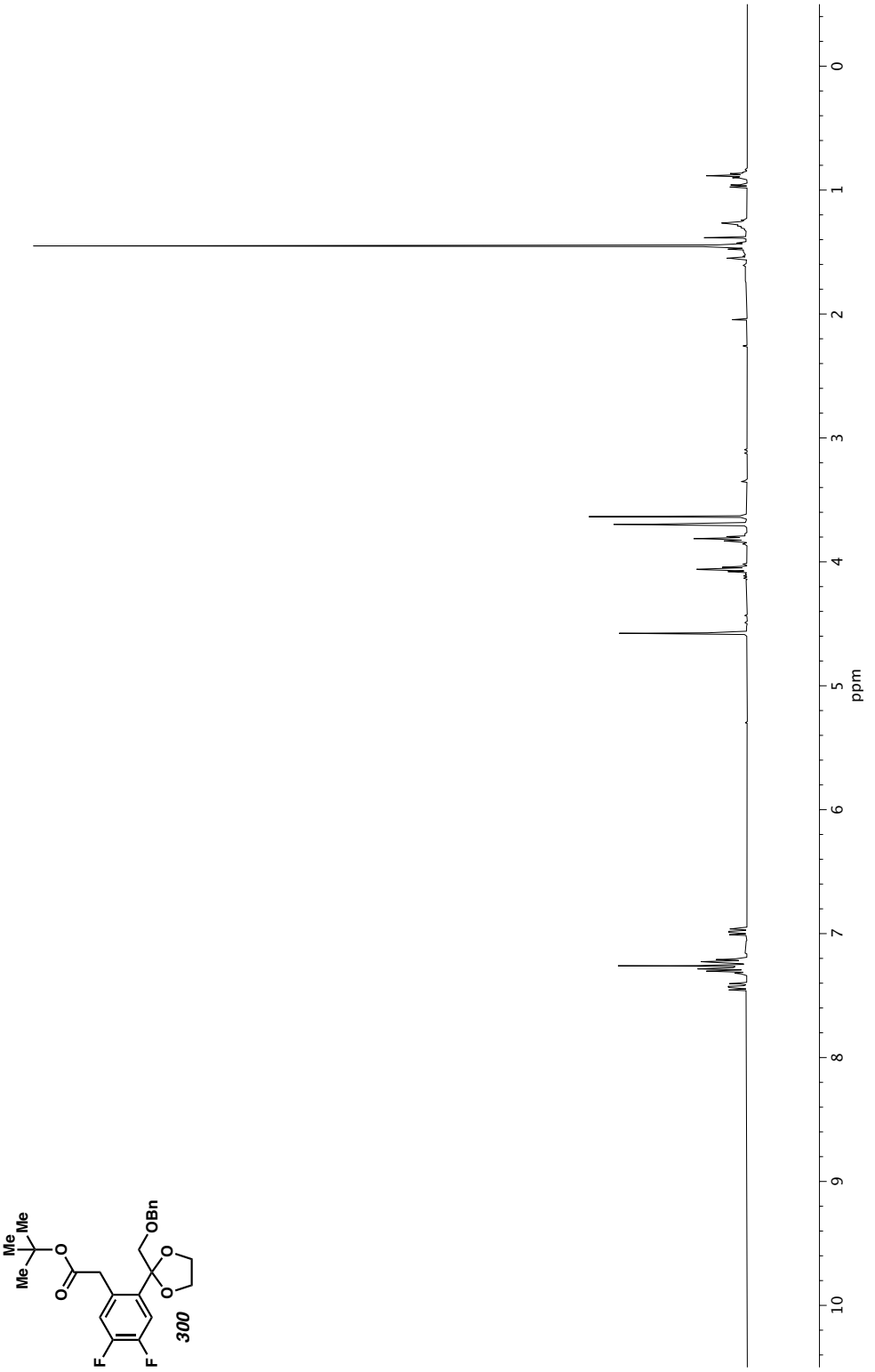


Figure A9.9 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***300****.*

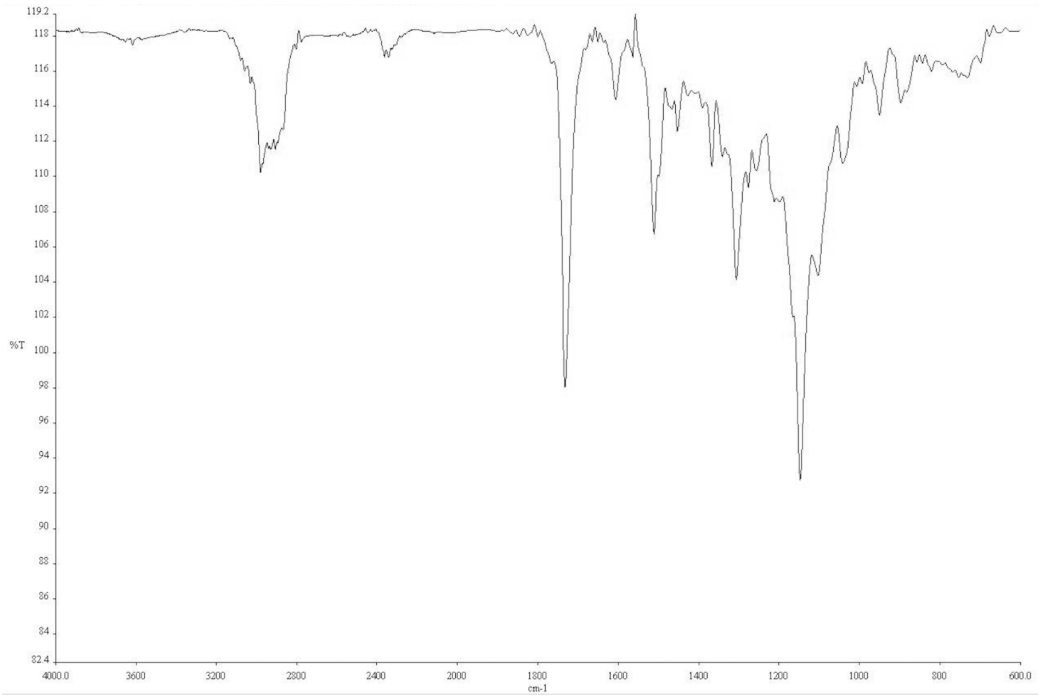


Figure A9.10 *Infrared spectrum (Thin Film, NaCl) of compound* ***300****.*

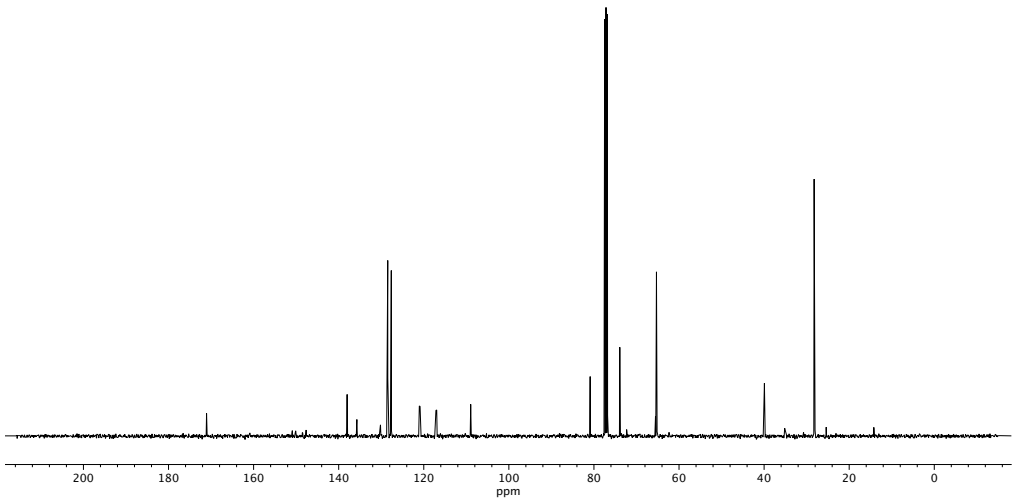


Figure A9.11 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***300****.*

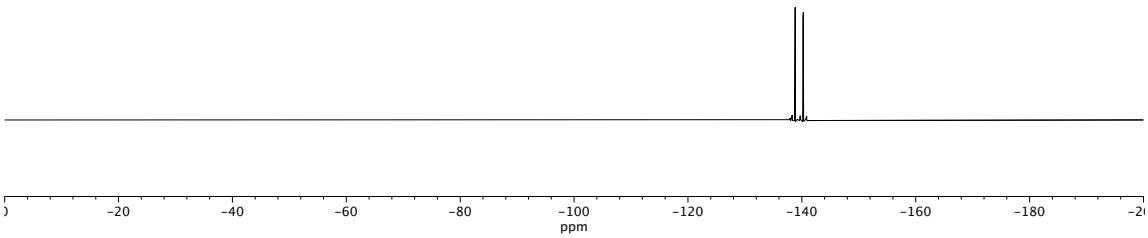


Figure A9.12 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***300***.

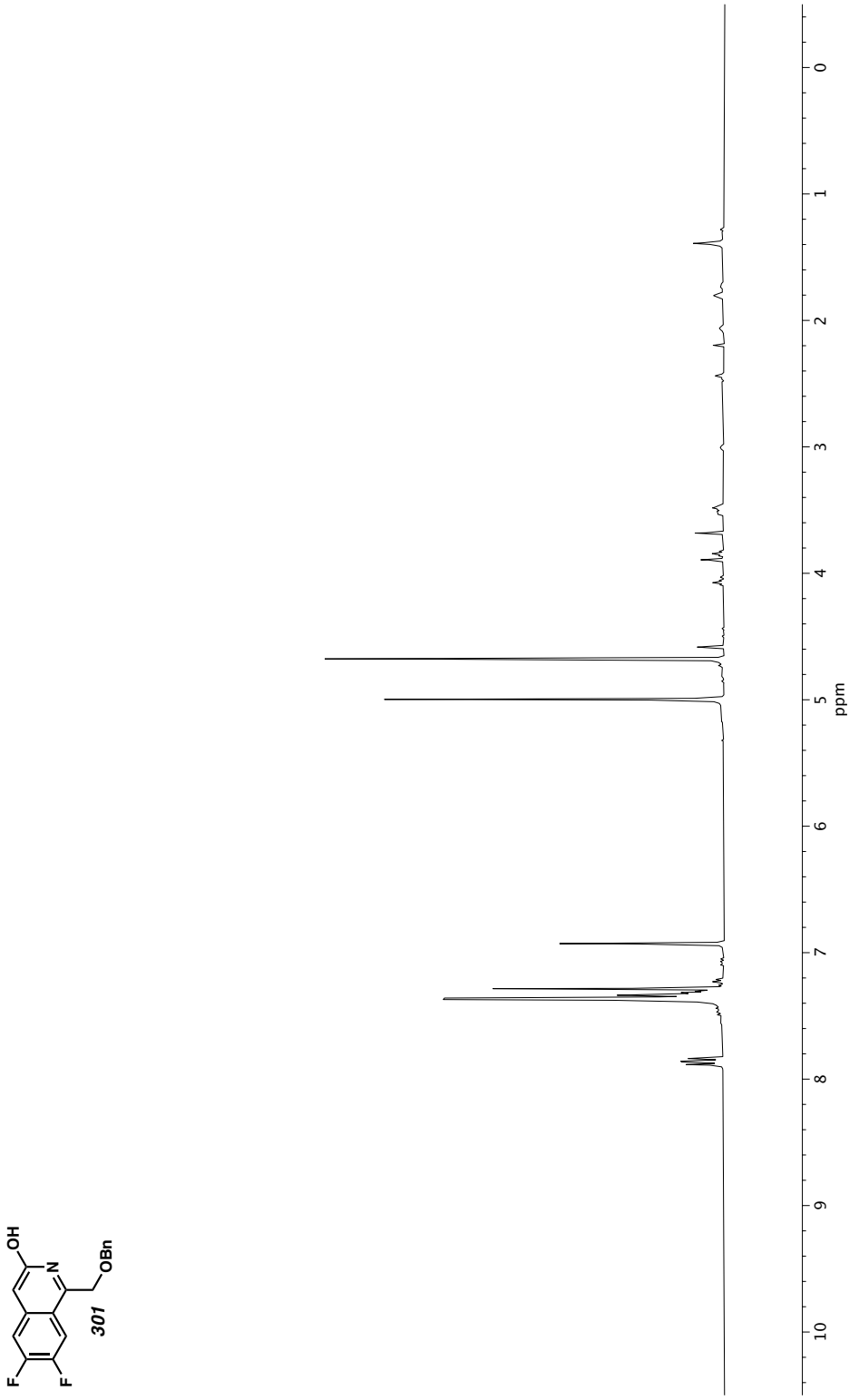


Figure A9.13 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***301****.*

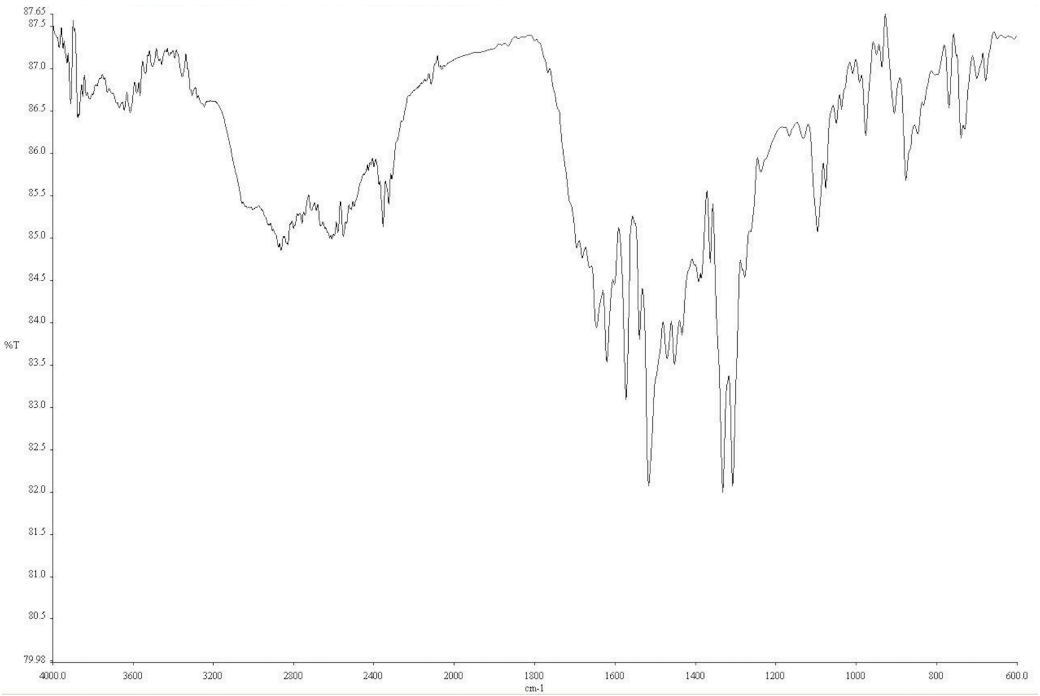


Figure A9.14 *Infrared spectrum (Thin Film, NaCl) of compound* ***301***.

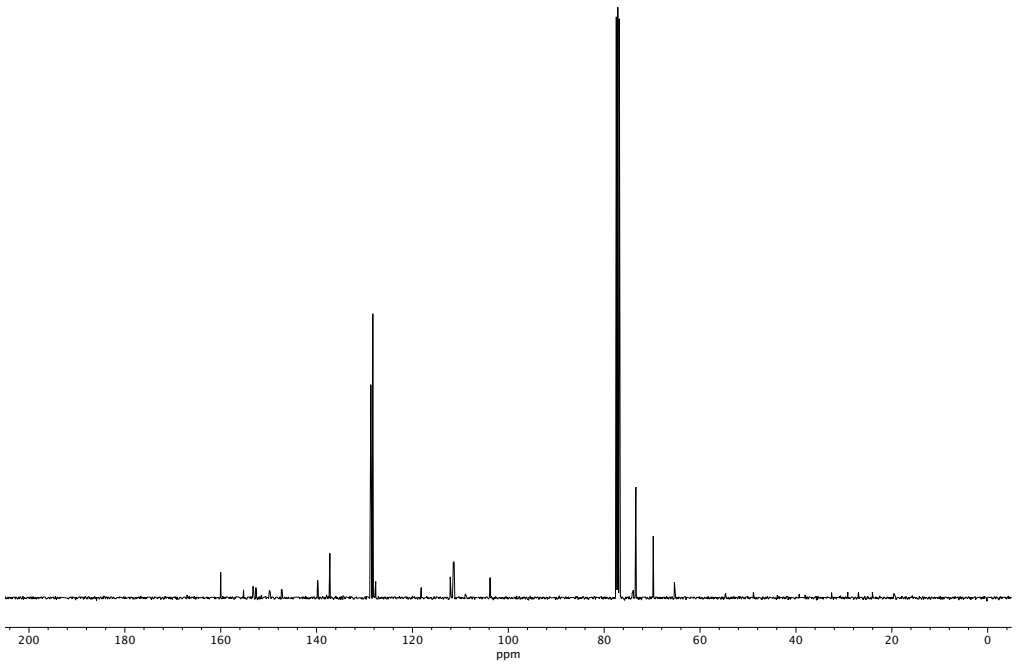


Figure A9.15 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***301***.

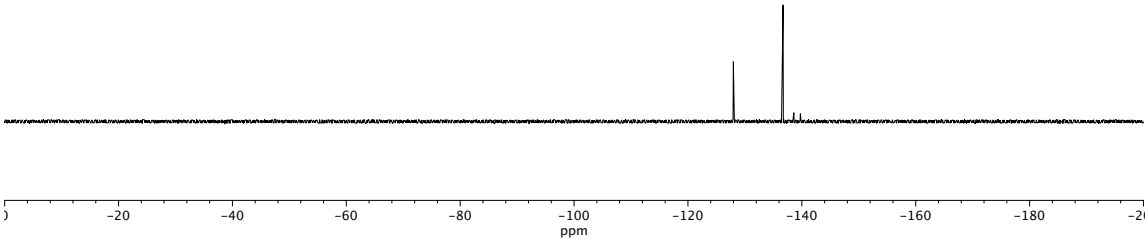


Figure A9.16 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***301***.

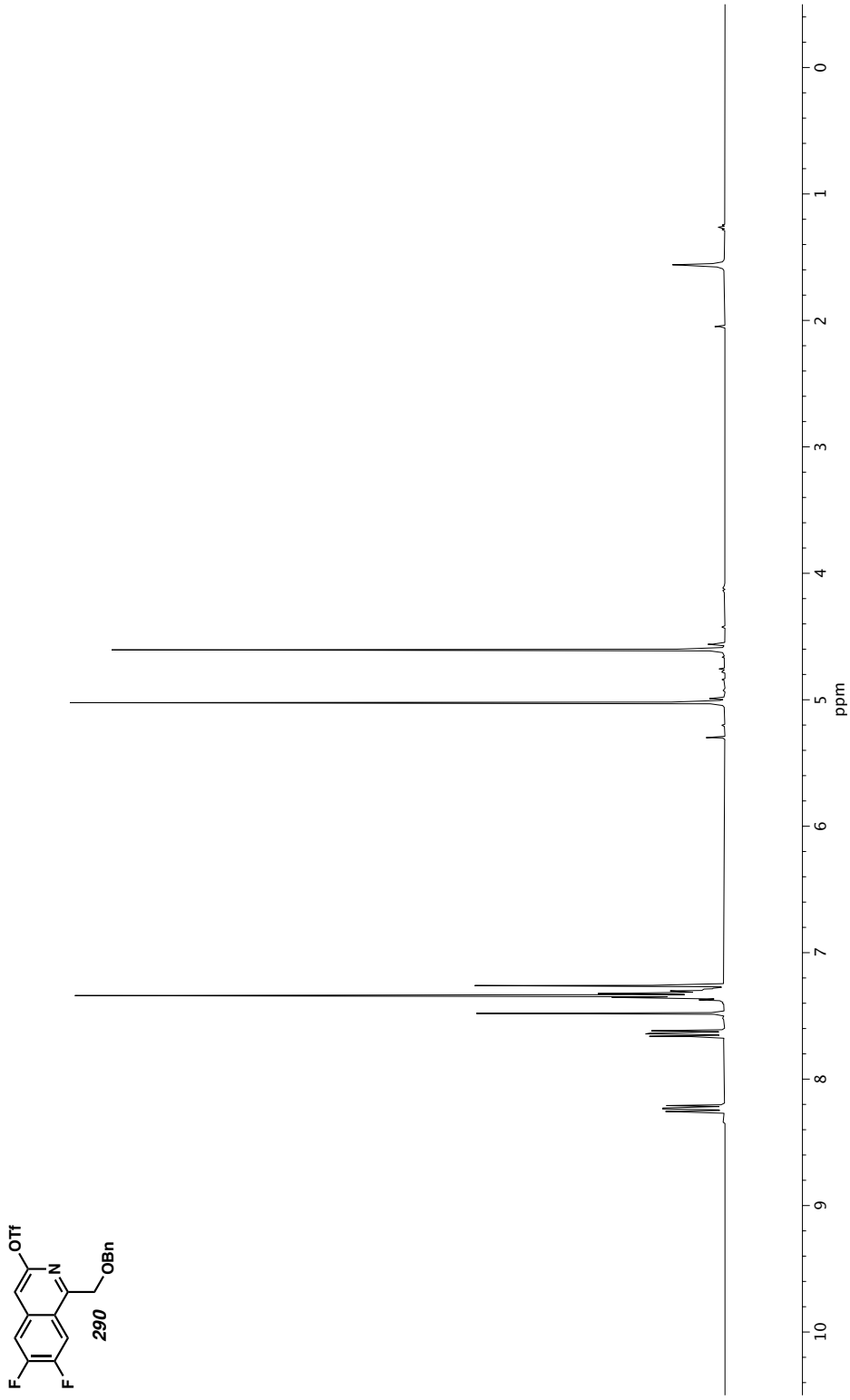


Figure A9.17 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***290****.*

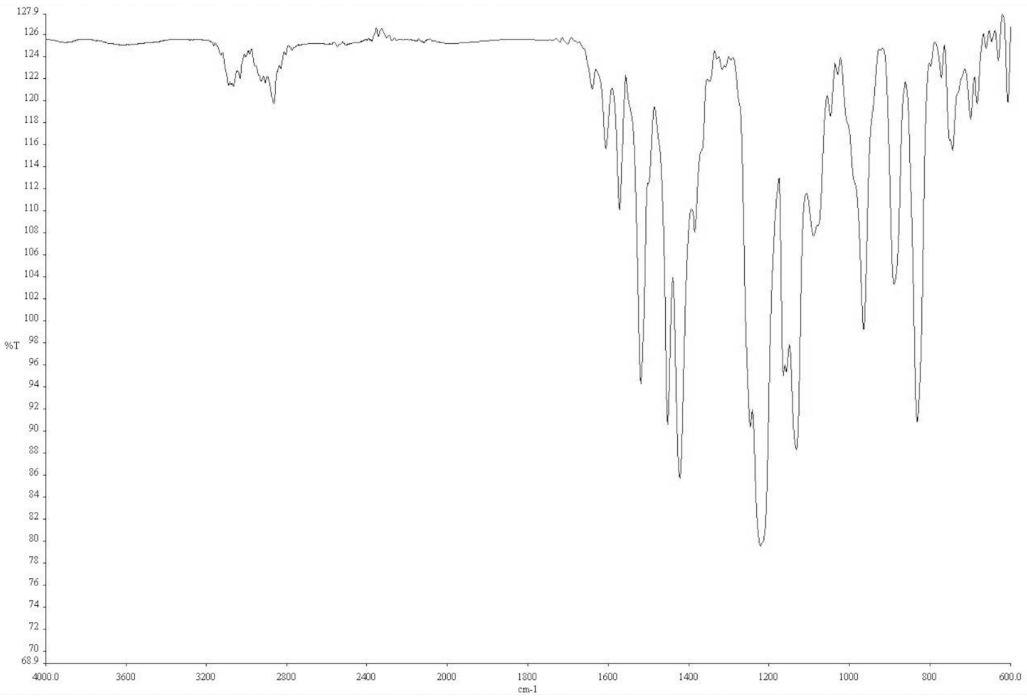


Figure A9.18 *Infrared spectrum (Thin Film, NaCl) of compound* ***290****.*

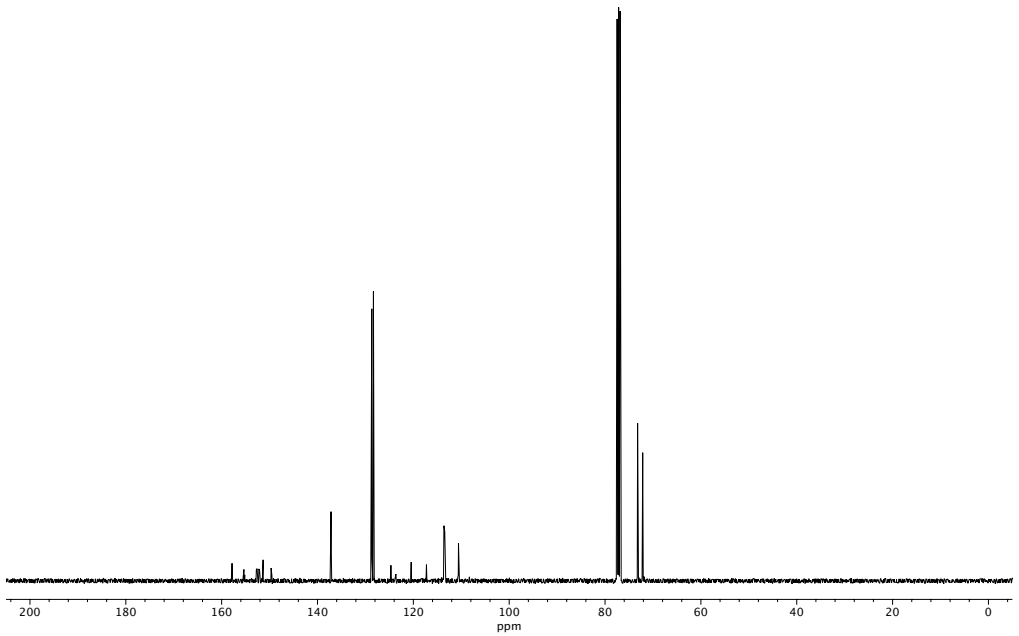


Figure A9.19 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***290****.*

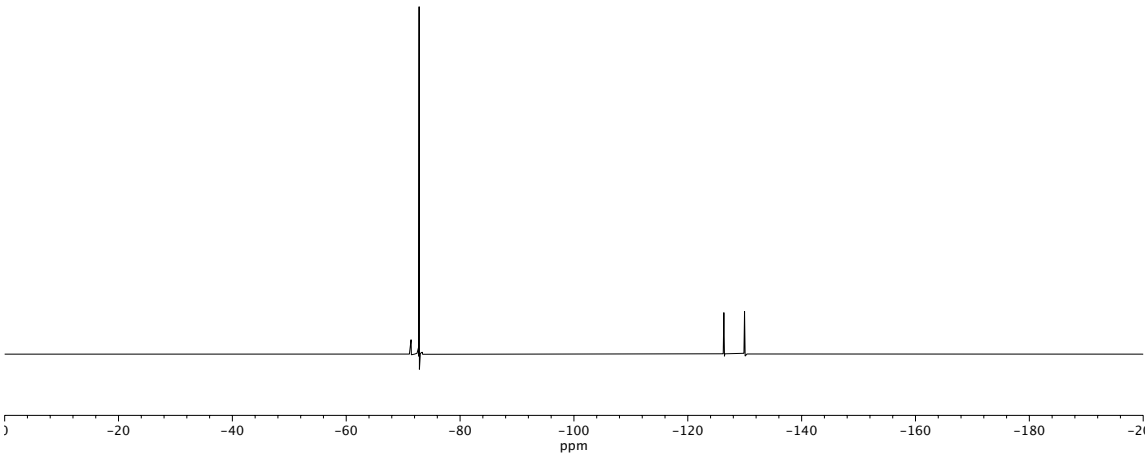


Figure A9.20 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***290***.

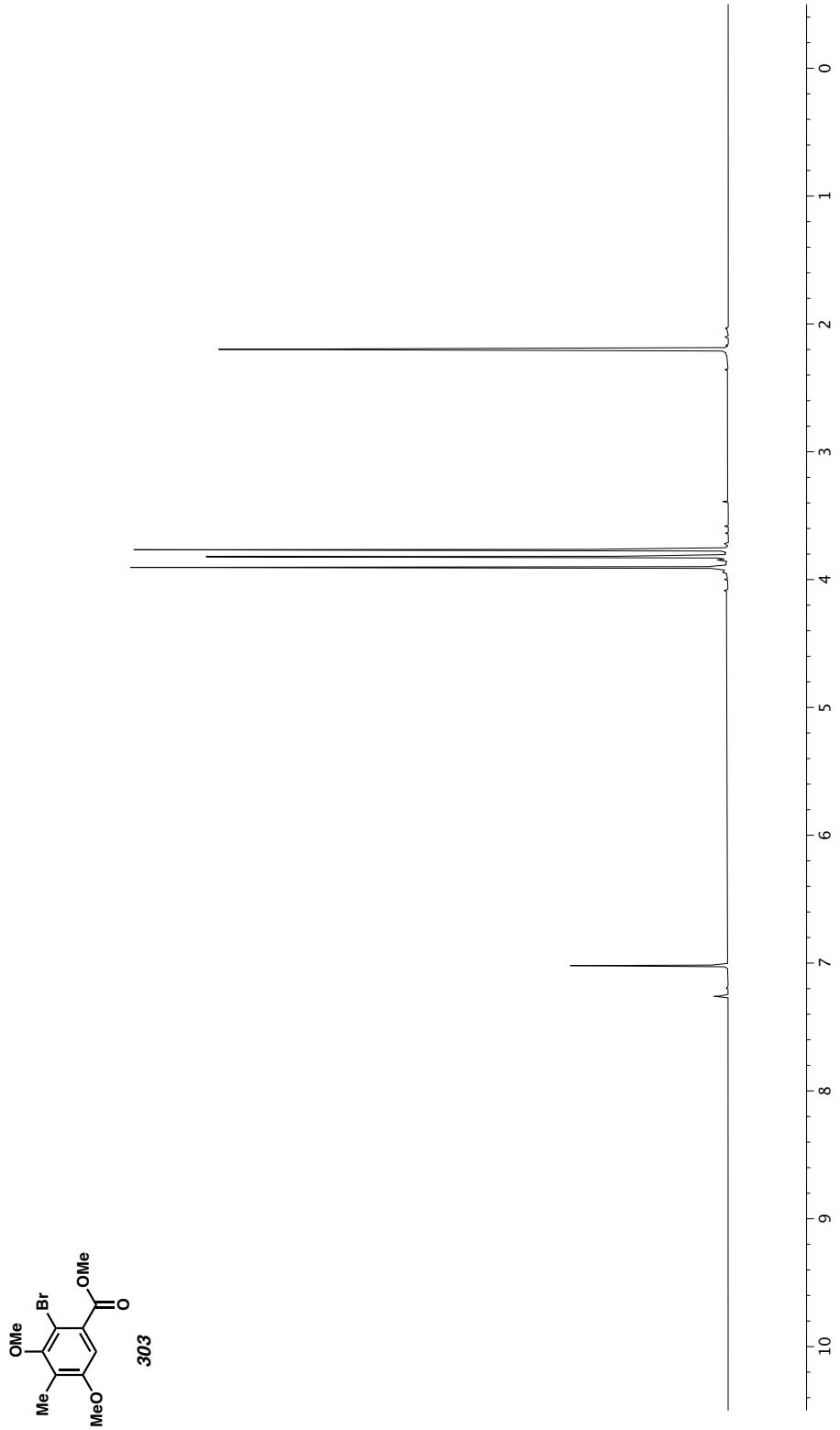


Figure A9.21 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***303***.

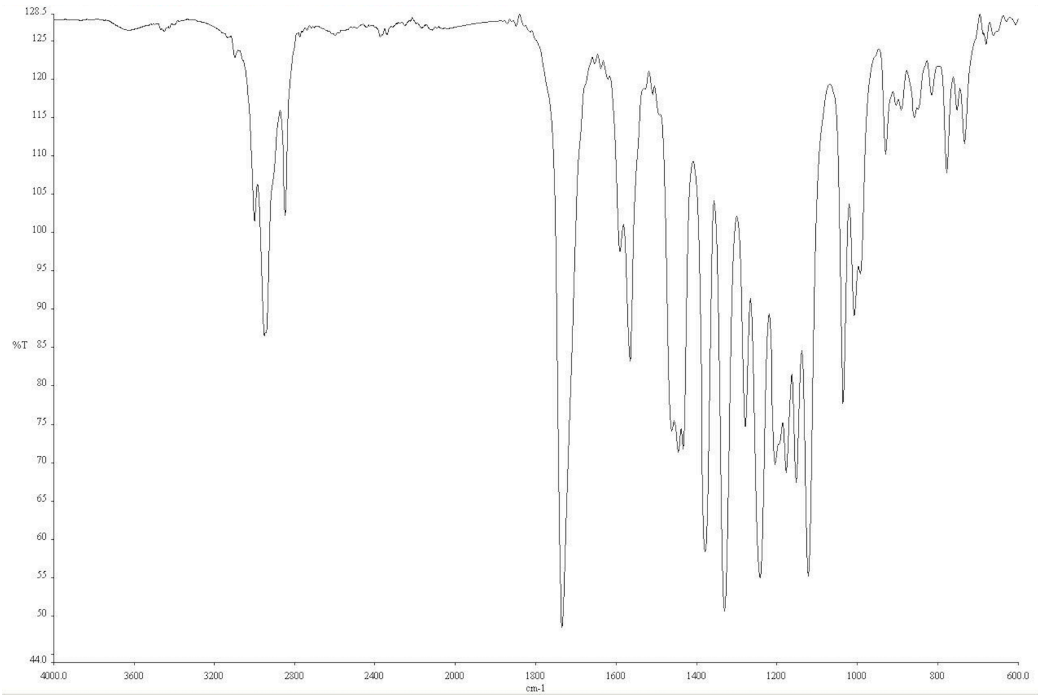


Figure A9.22 *Infrared spectrum (Thin Film, NaCl) of compound* ***303***.

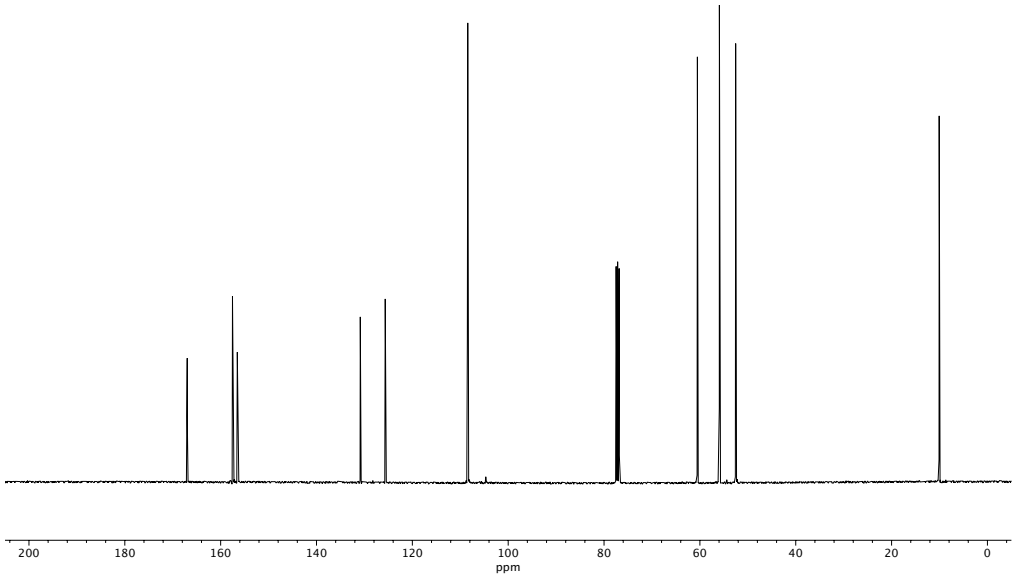


Figure A9.23 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***303***.

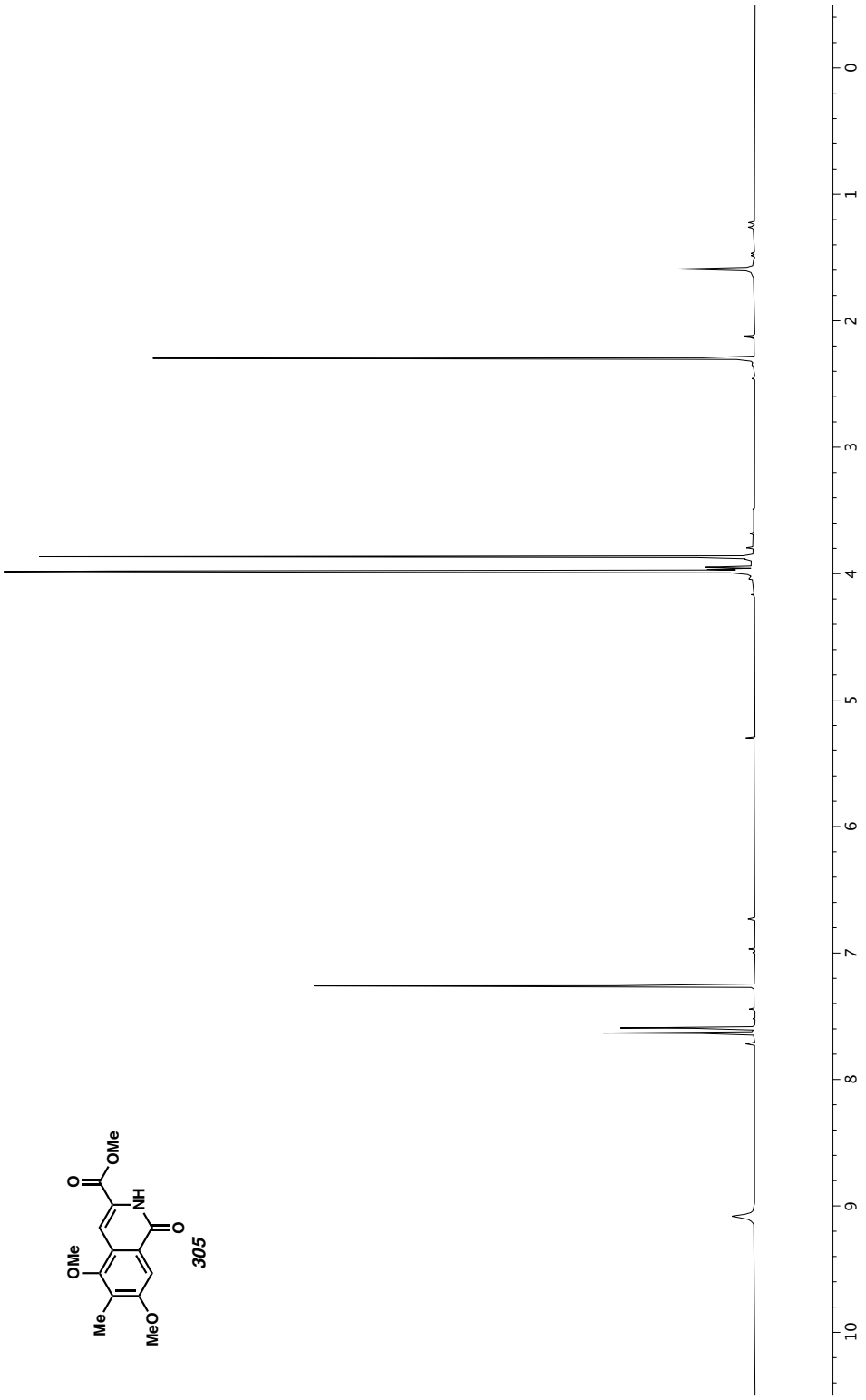


Figure A9.24 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***305****.*

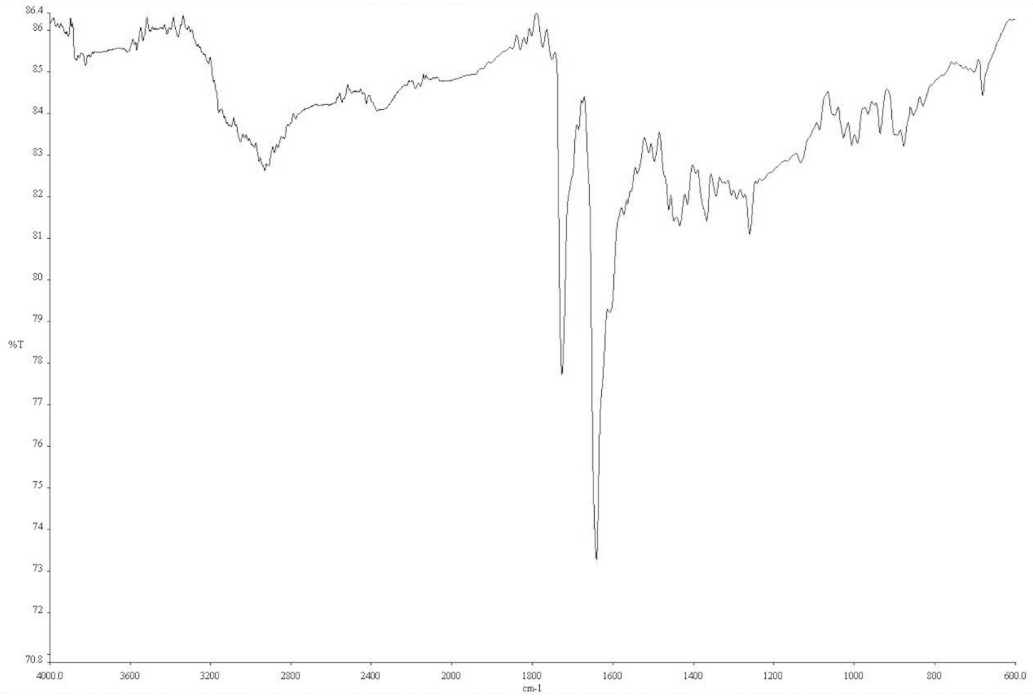


Figure A9.25 *Infrared spectrum (Thin Film, NaCl) of compound* ***305***.

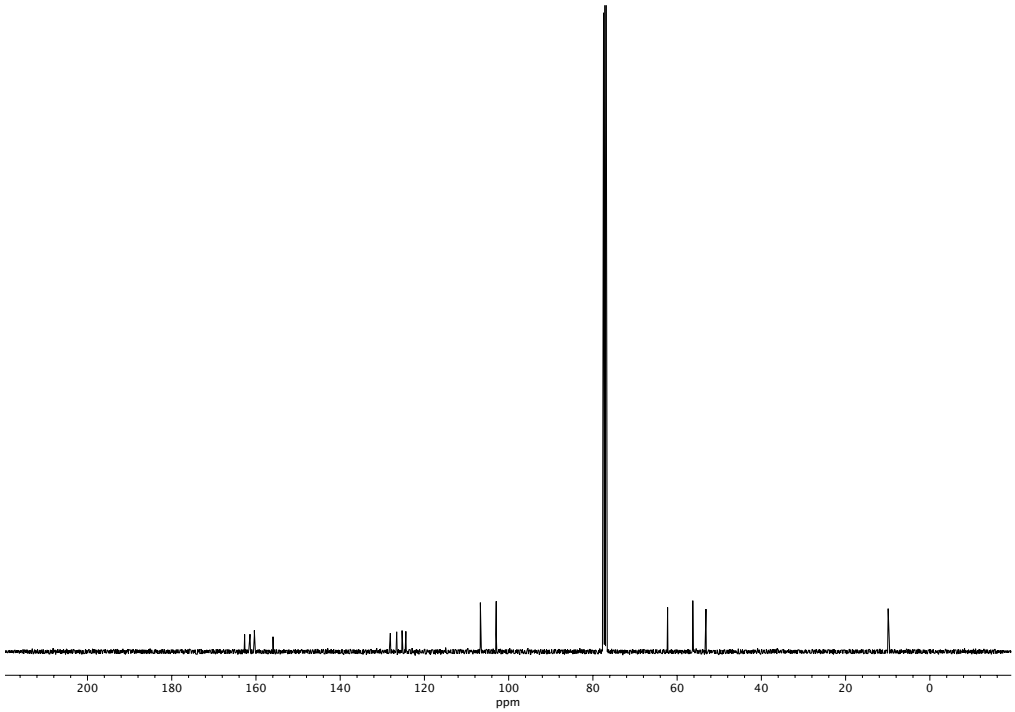


Figure A9.26 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***305***.

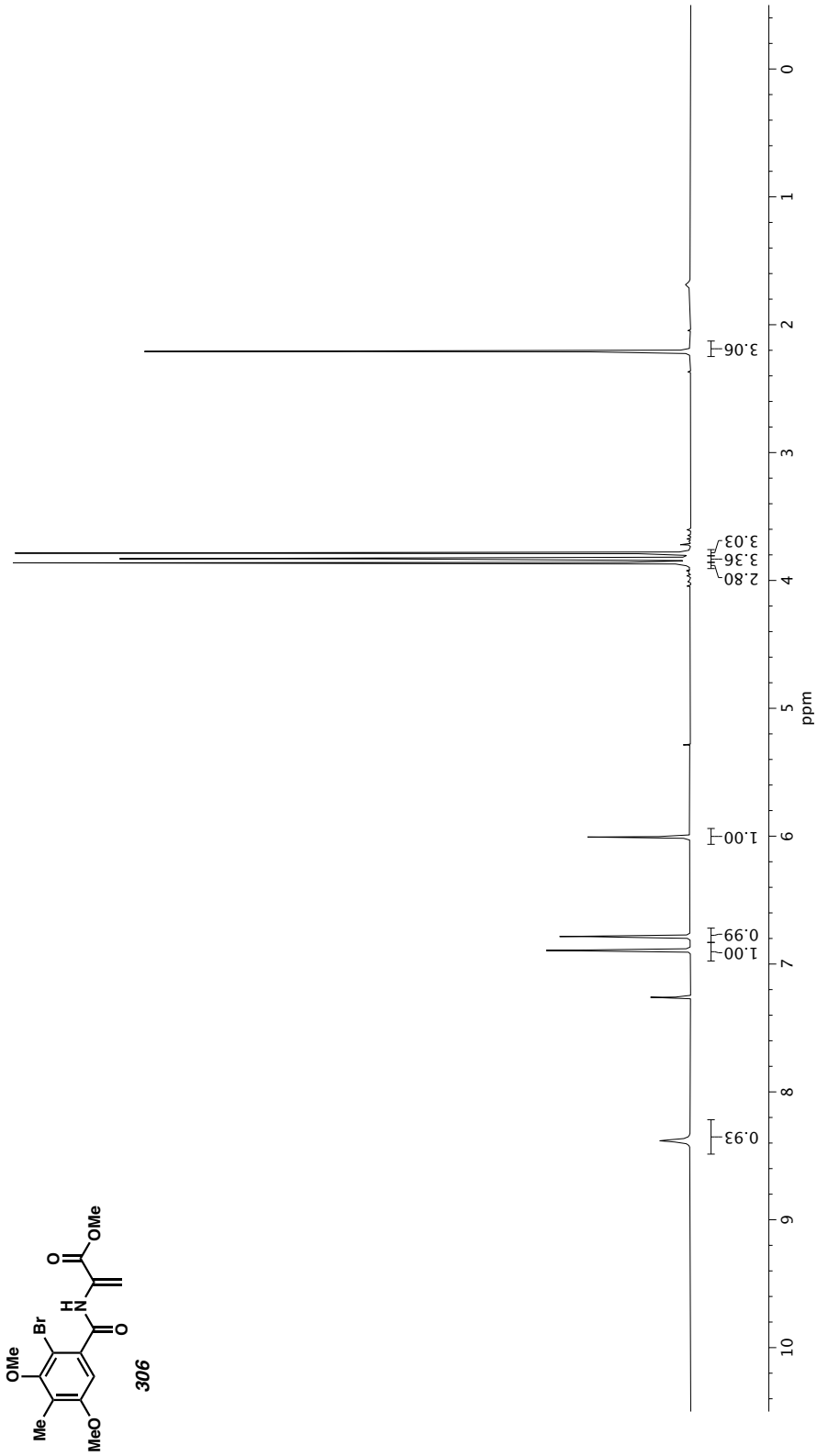


Figure A9.27 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***306****.*

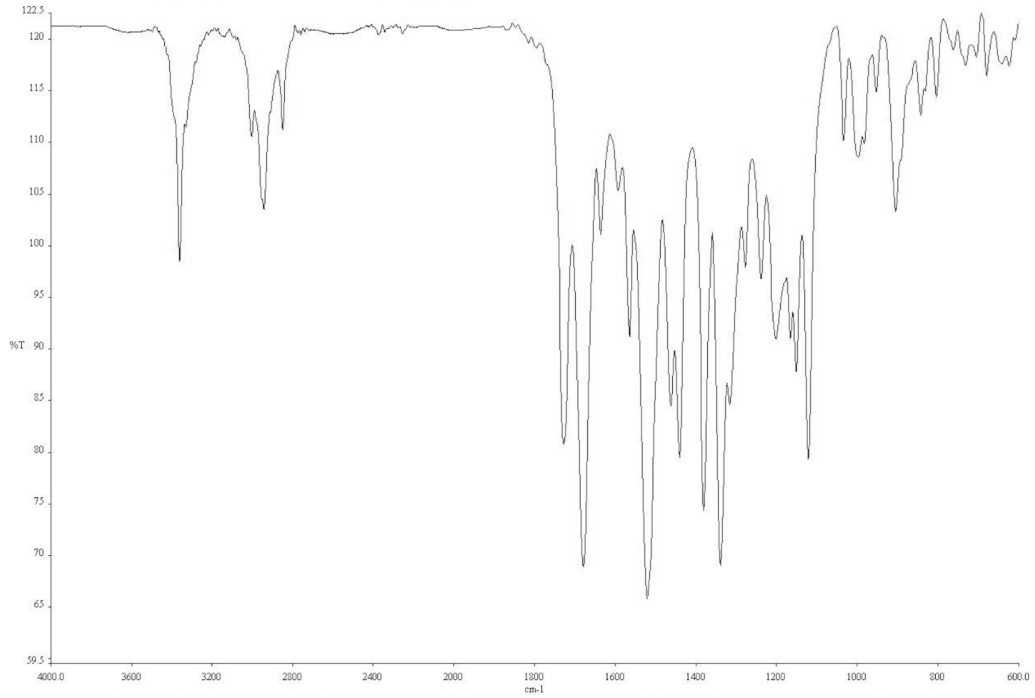


Figure A9.28 *Infrared spectrum (Thin Film, NaCl) of compound* ***306***.

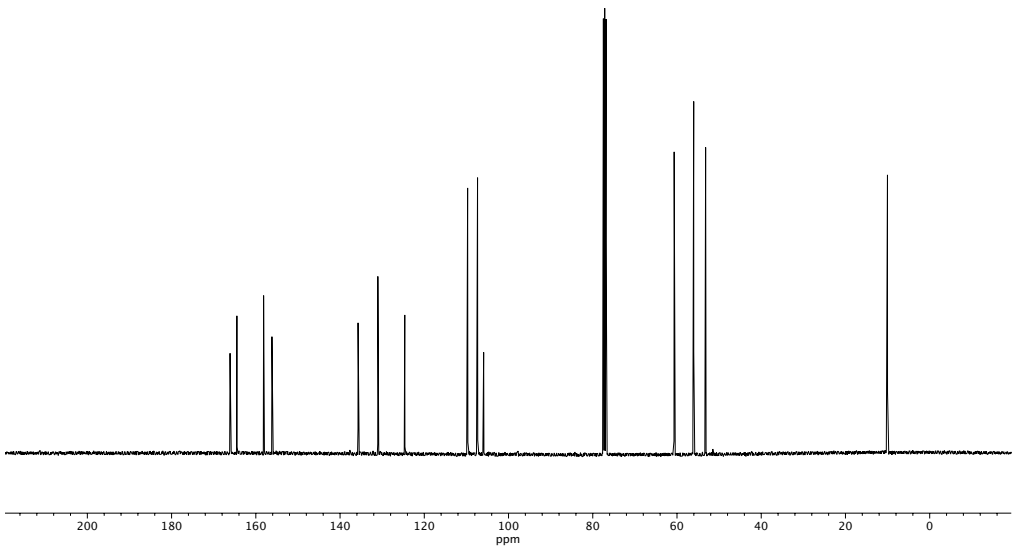


Figure A9.29 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***306***.

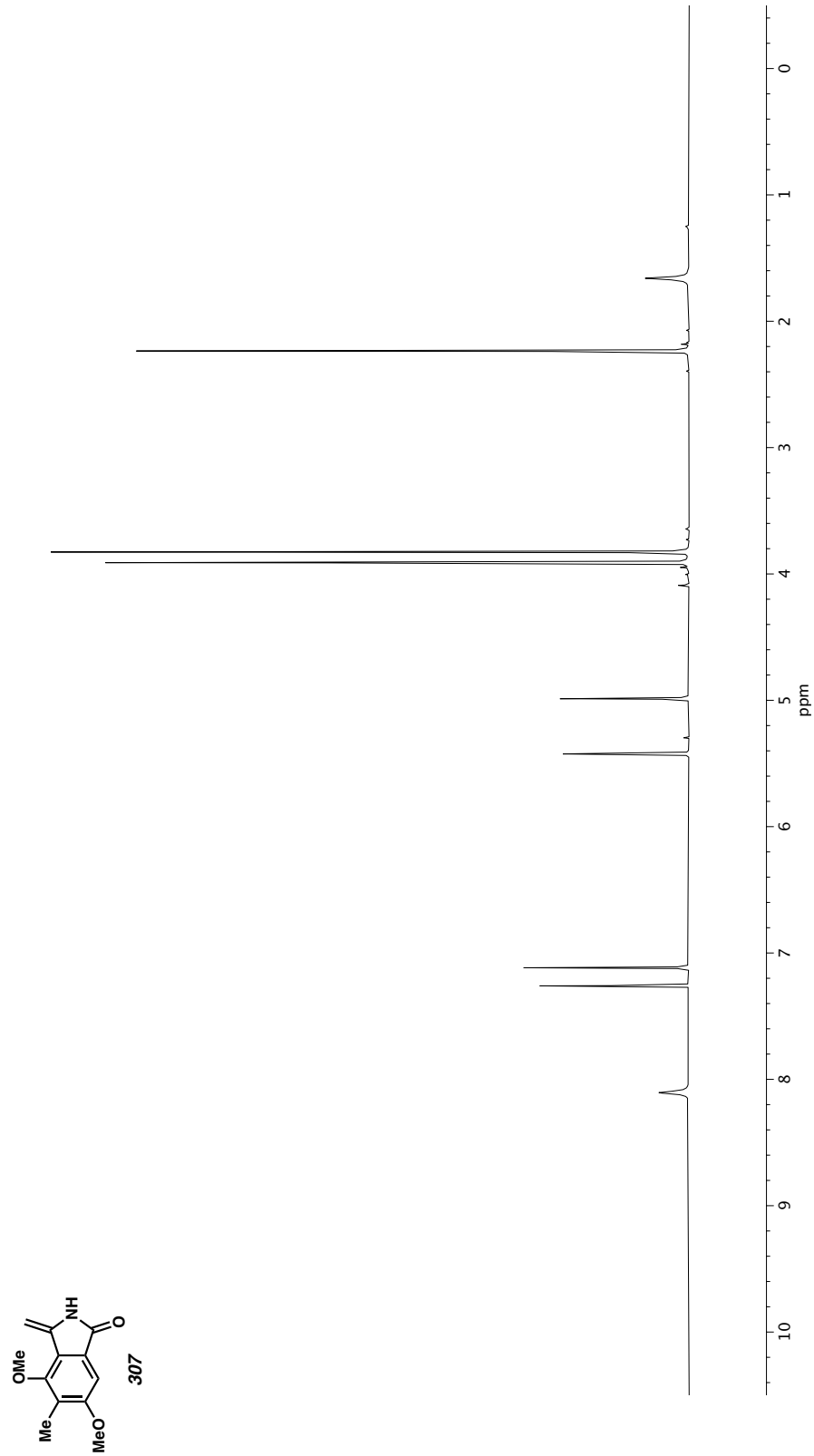


Figure A9.30 *^1H NMR (400 MHz, $CDCl_3$) of compound **307**.*

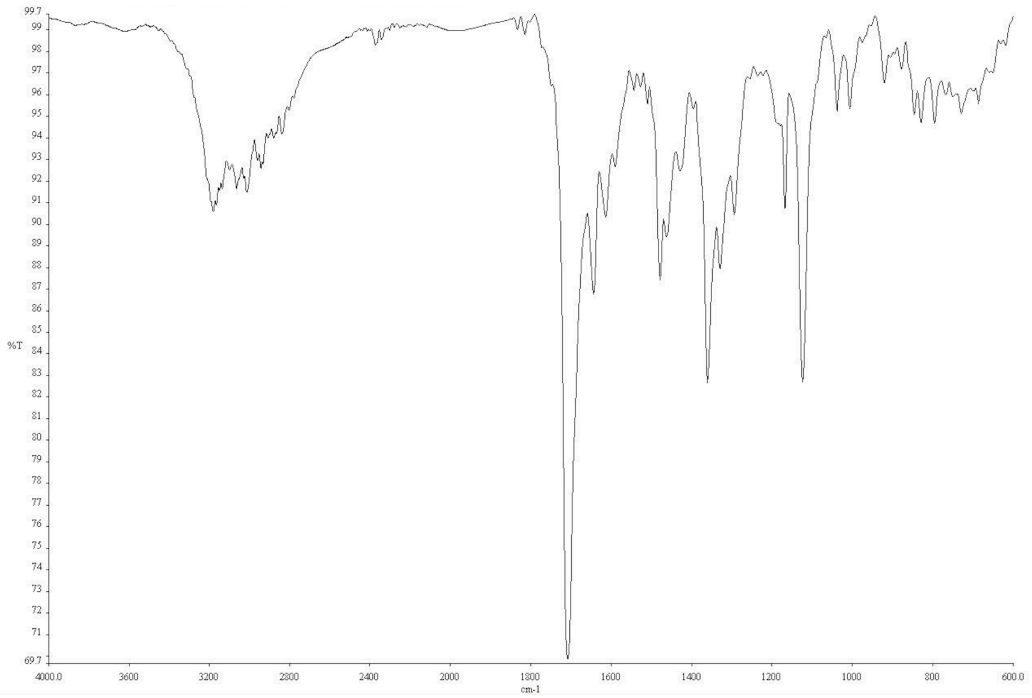


Figure A9.31 *Infrared spectrum (Thin Film, NaCl) of compound* ***307****.*

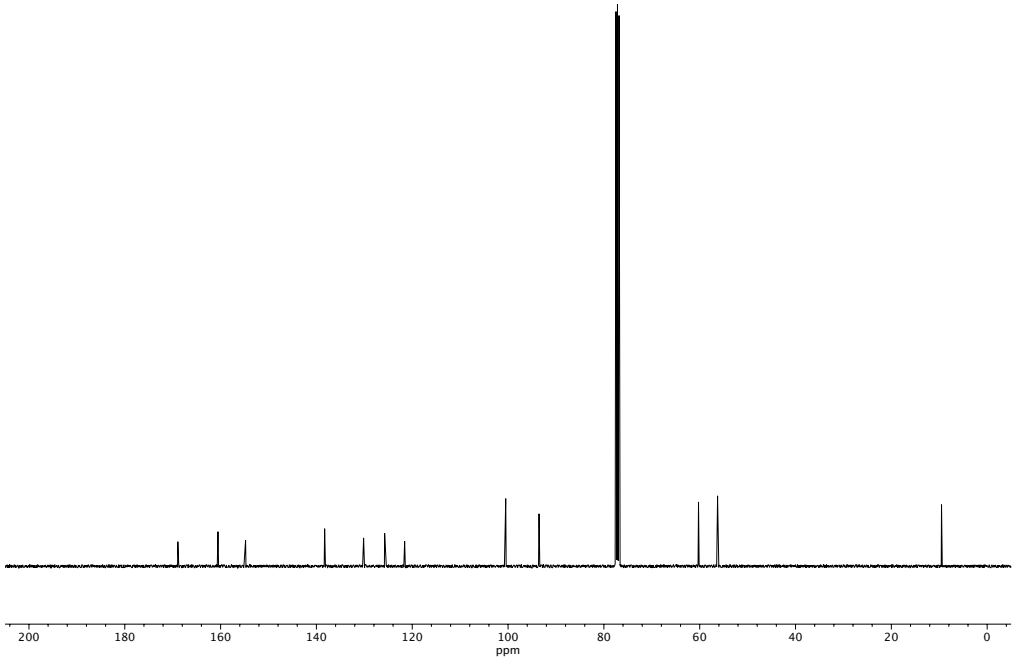


Figure A9.32 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***307****.*

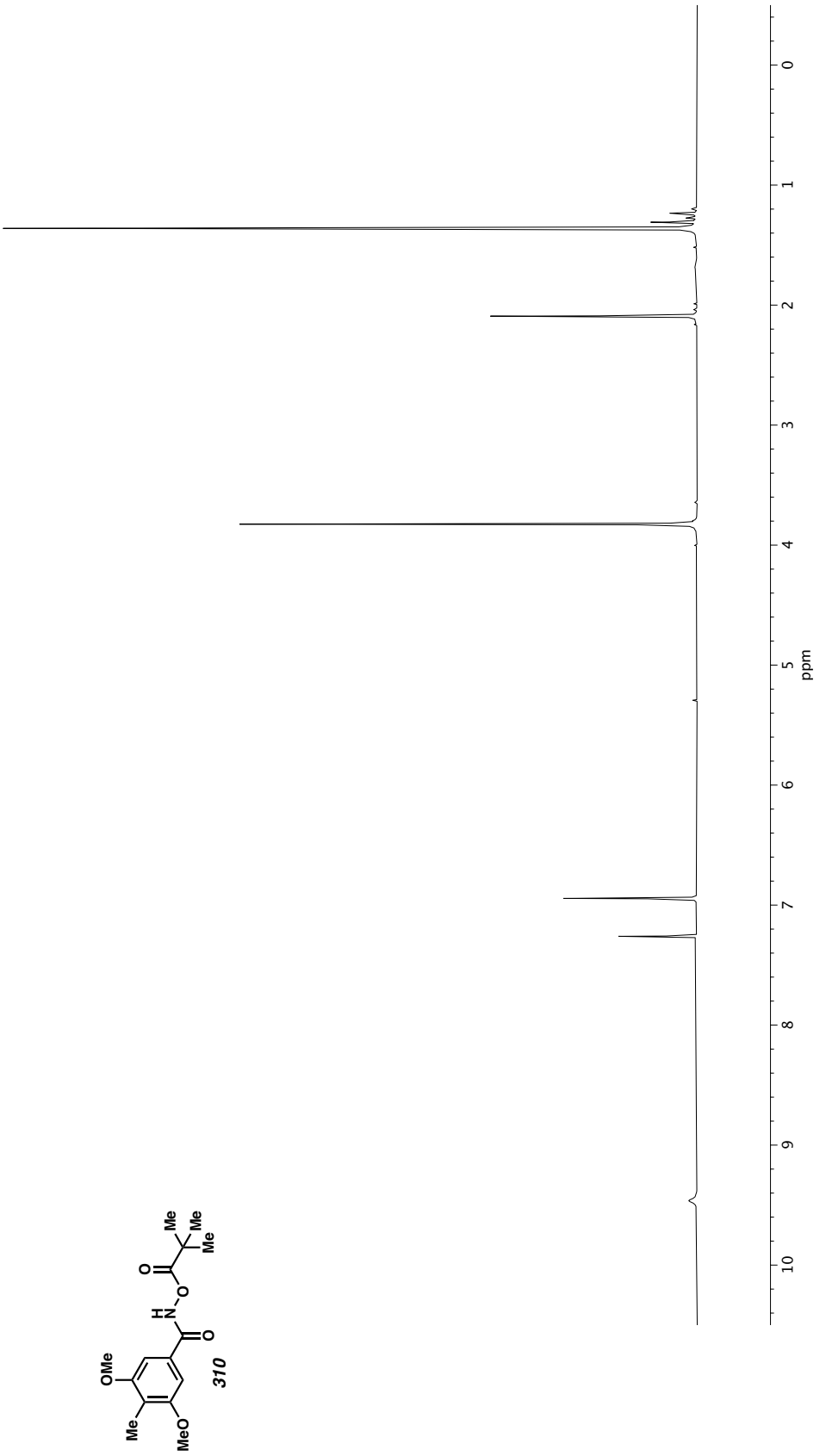


Figure A9.33 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***310***.

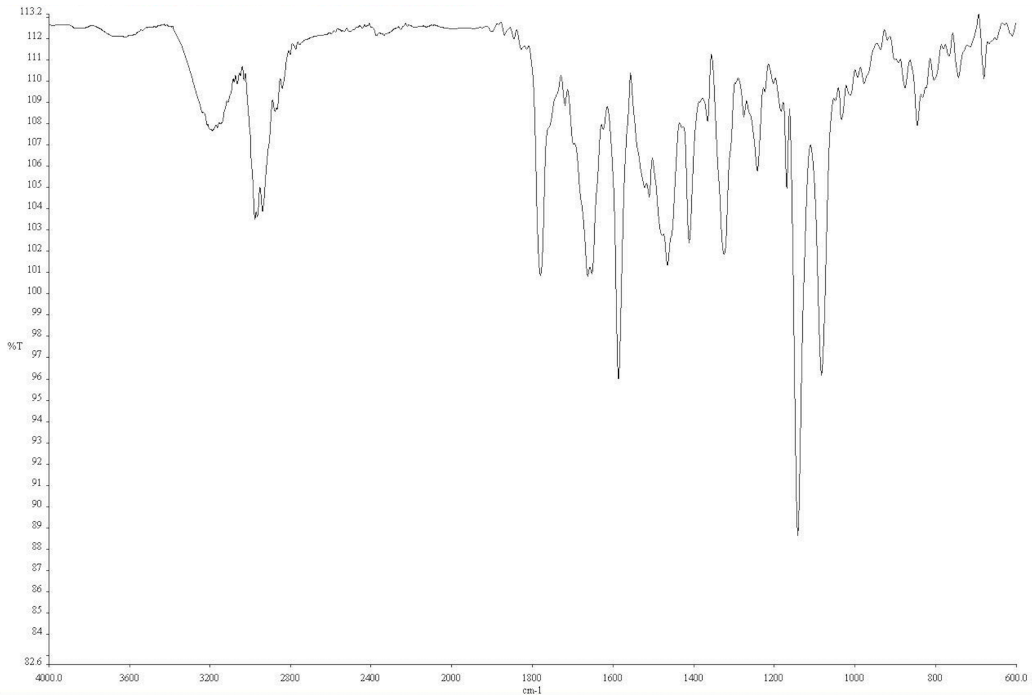


Figure A9.34 *Infrared spectrum (Thin Film, NaCl) of compound* ***310***.

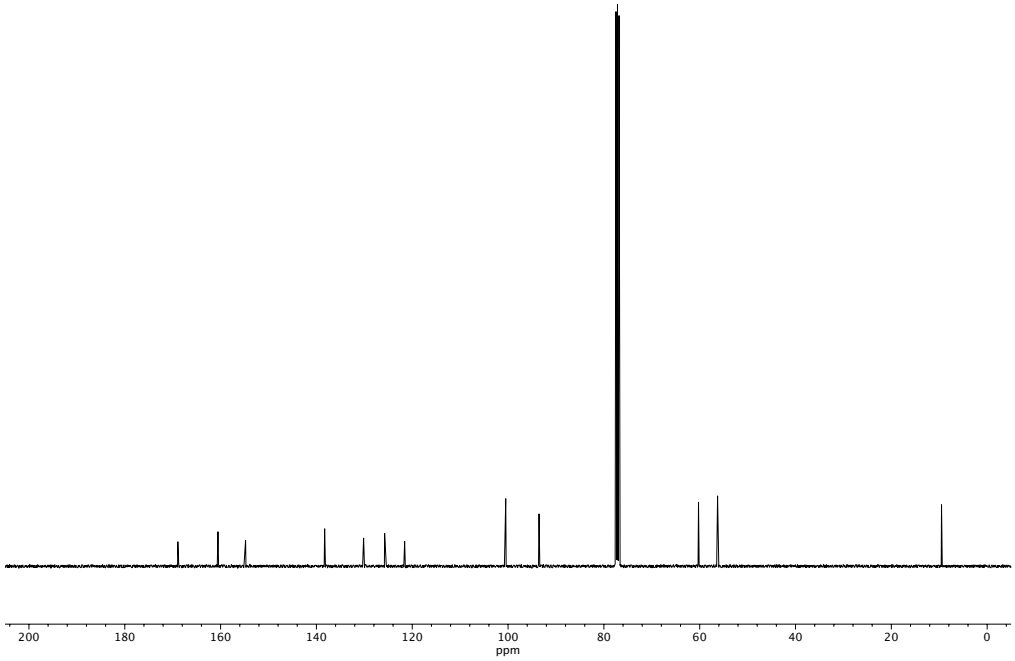


Figure A9.35 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***310***.

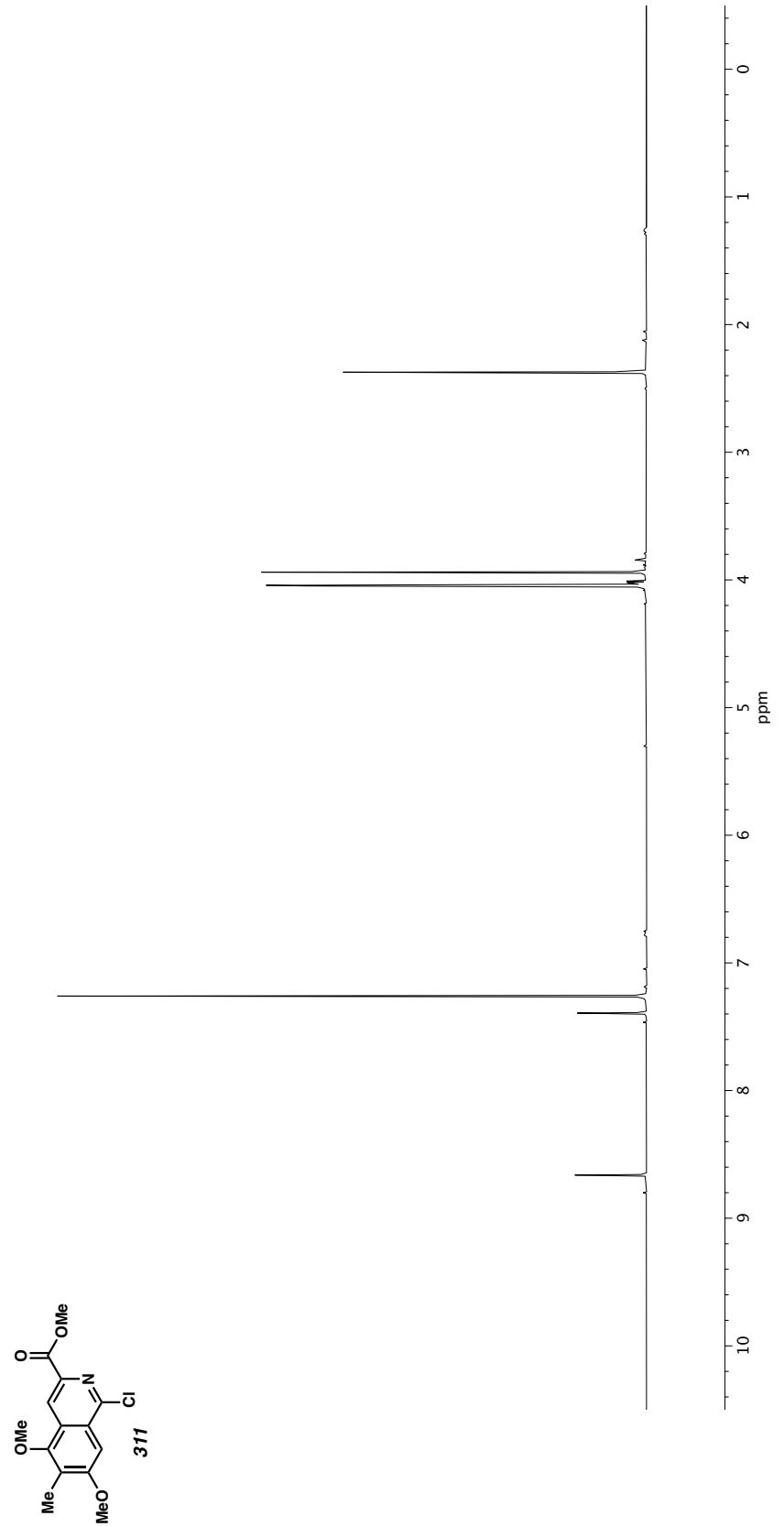


Figure A9.36 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***311***.

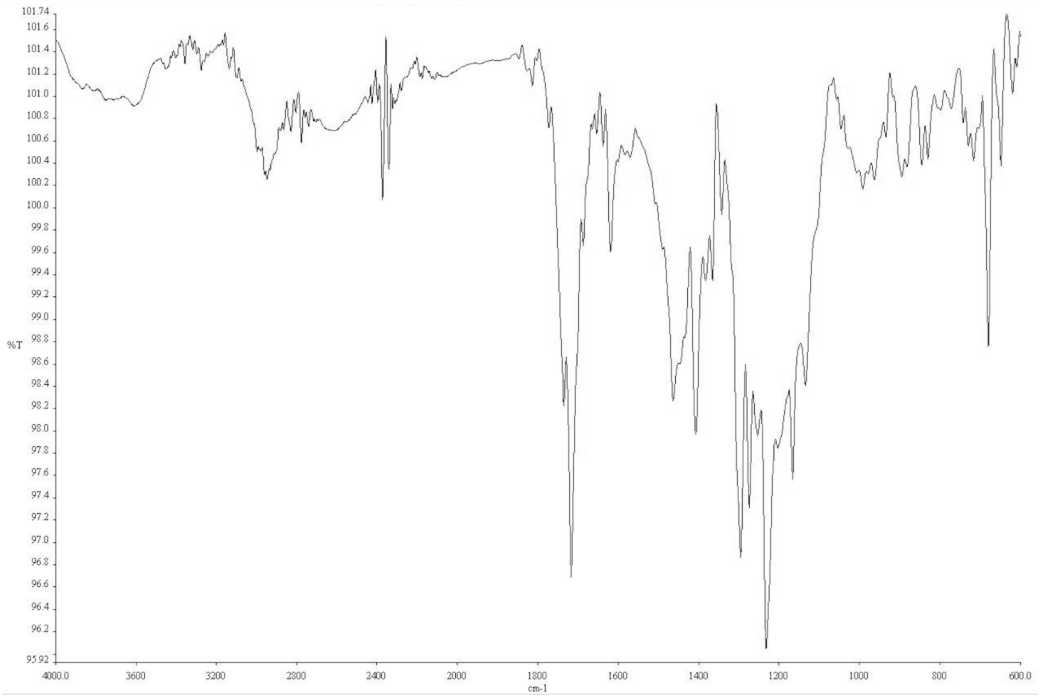


Figure A9.37 *Infrared spectrum (Thin Film, NaCl) of compound* ***311***.

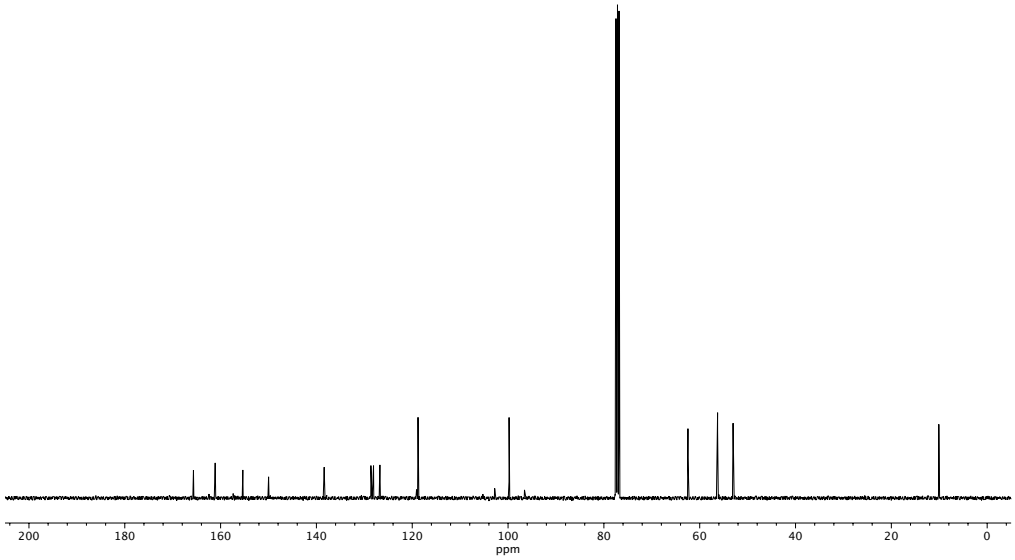


Figure A9.38 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***311***.

Figure A9.39 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***313****.*

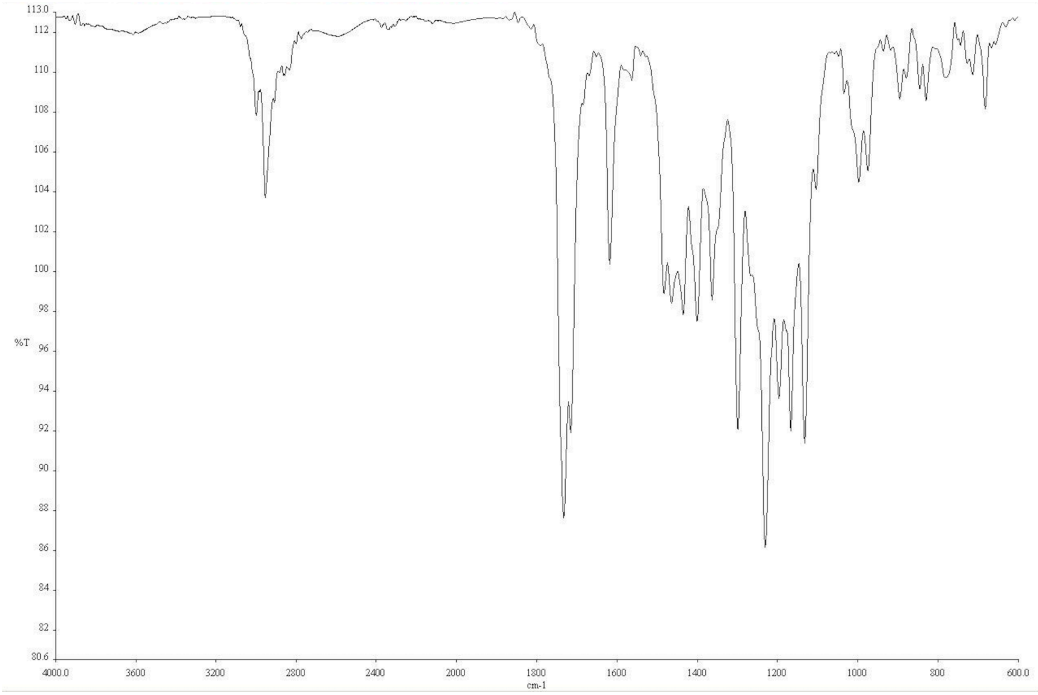


Figure A9.40 *Infrared spectrum (Thin Film, NaCl) of compound* ***313***.

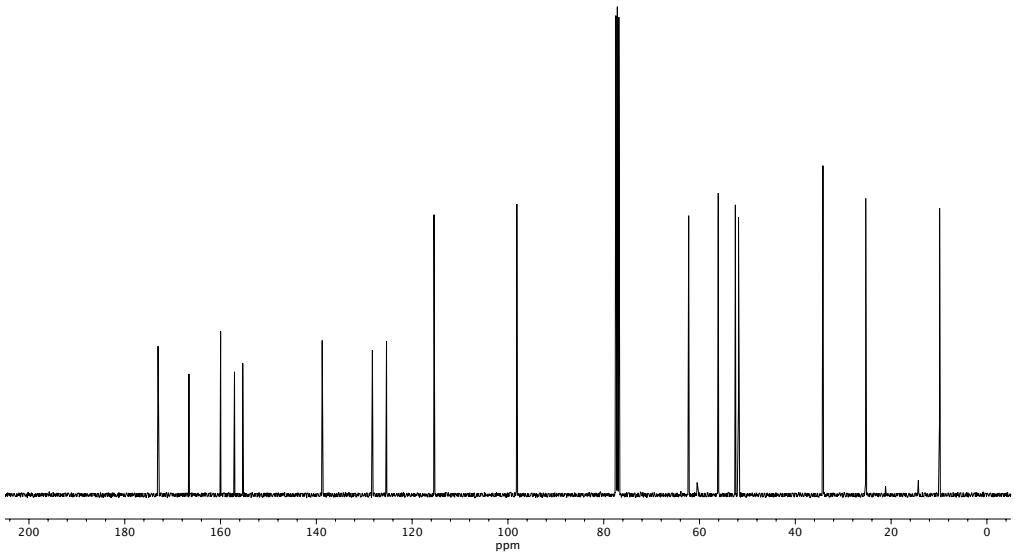


Figure A9.41 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***313***.

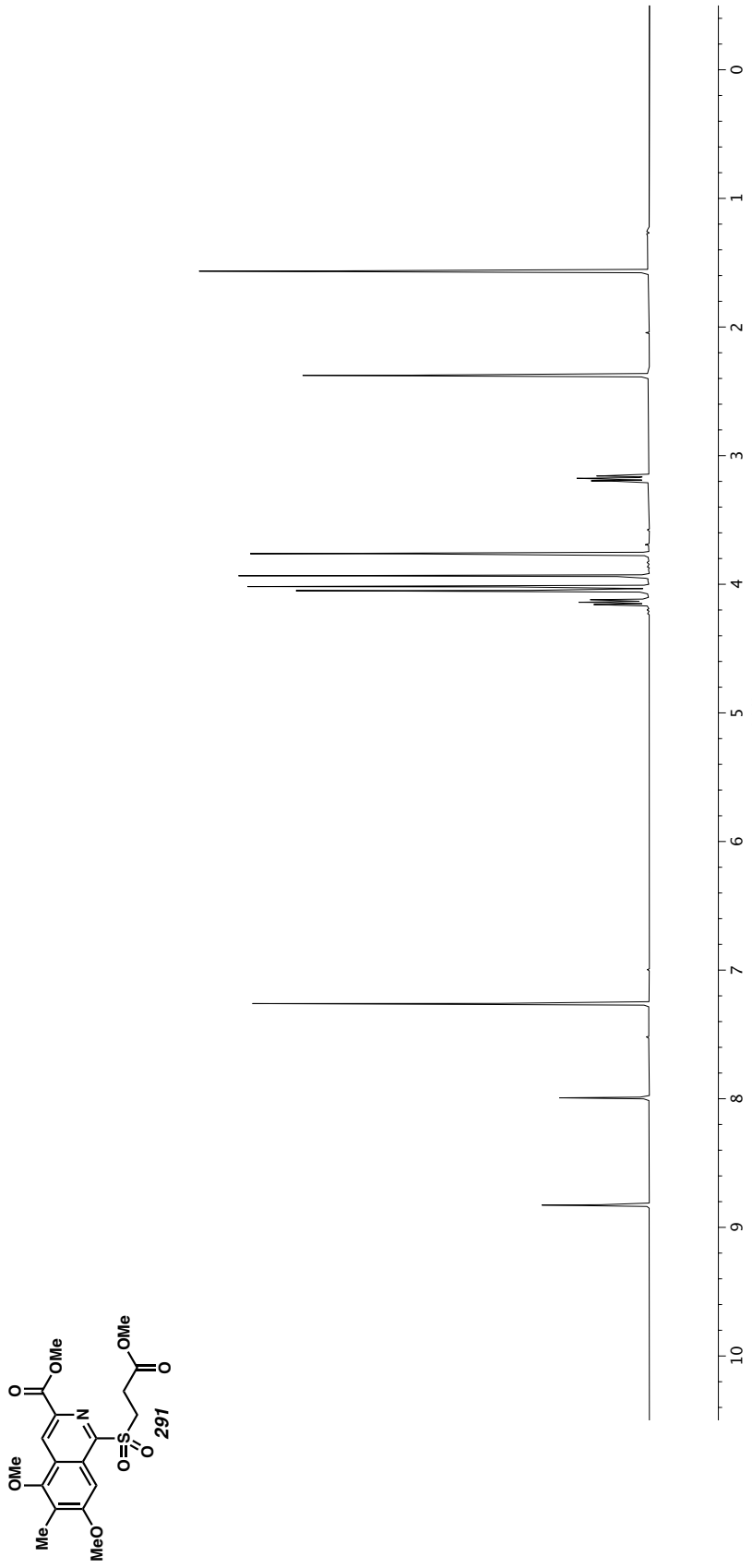


Figure A9.42 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***291****.*

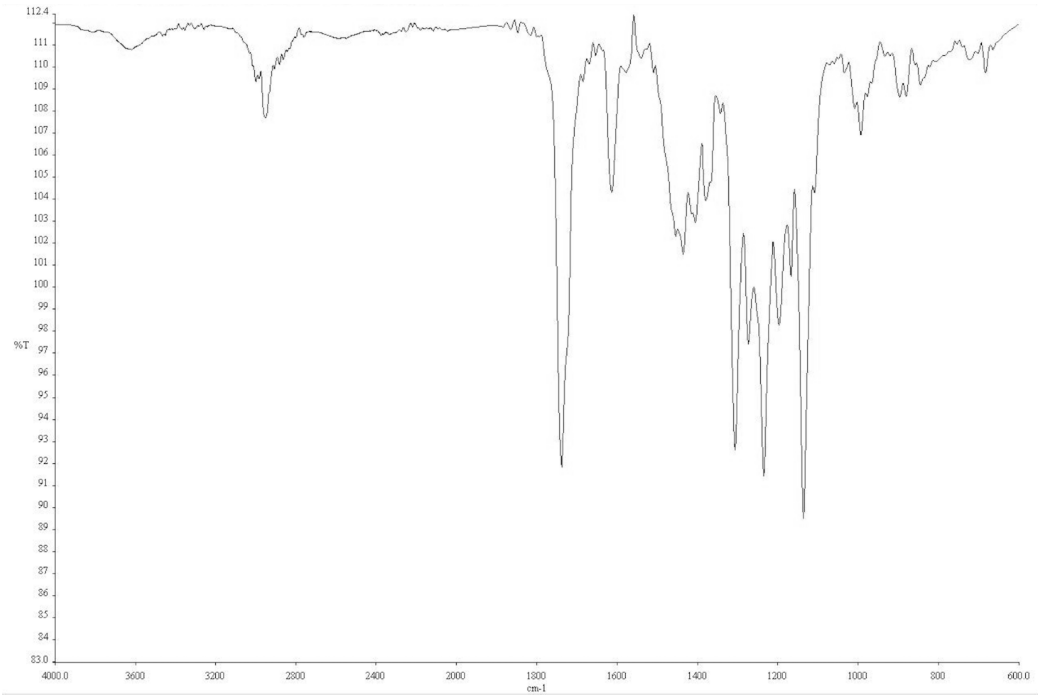


Figure A9.43 *Infrared spectrum (Thin Film, NaCl) of compound* ***291***.

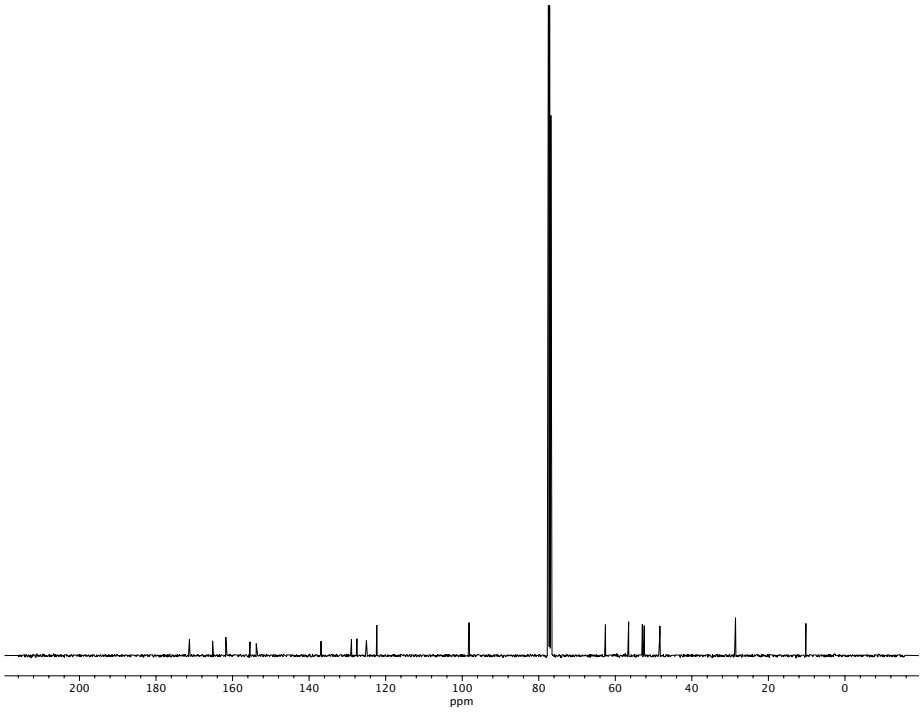


Figure A9.44 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***291***.

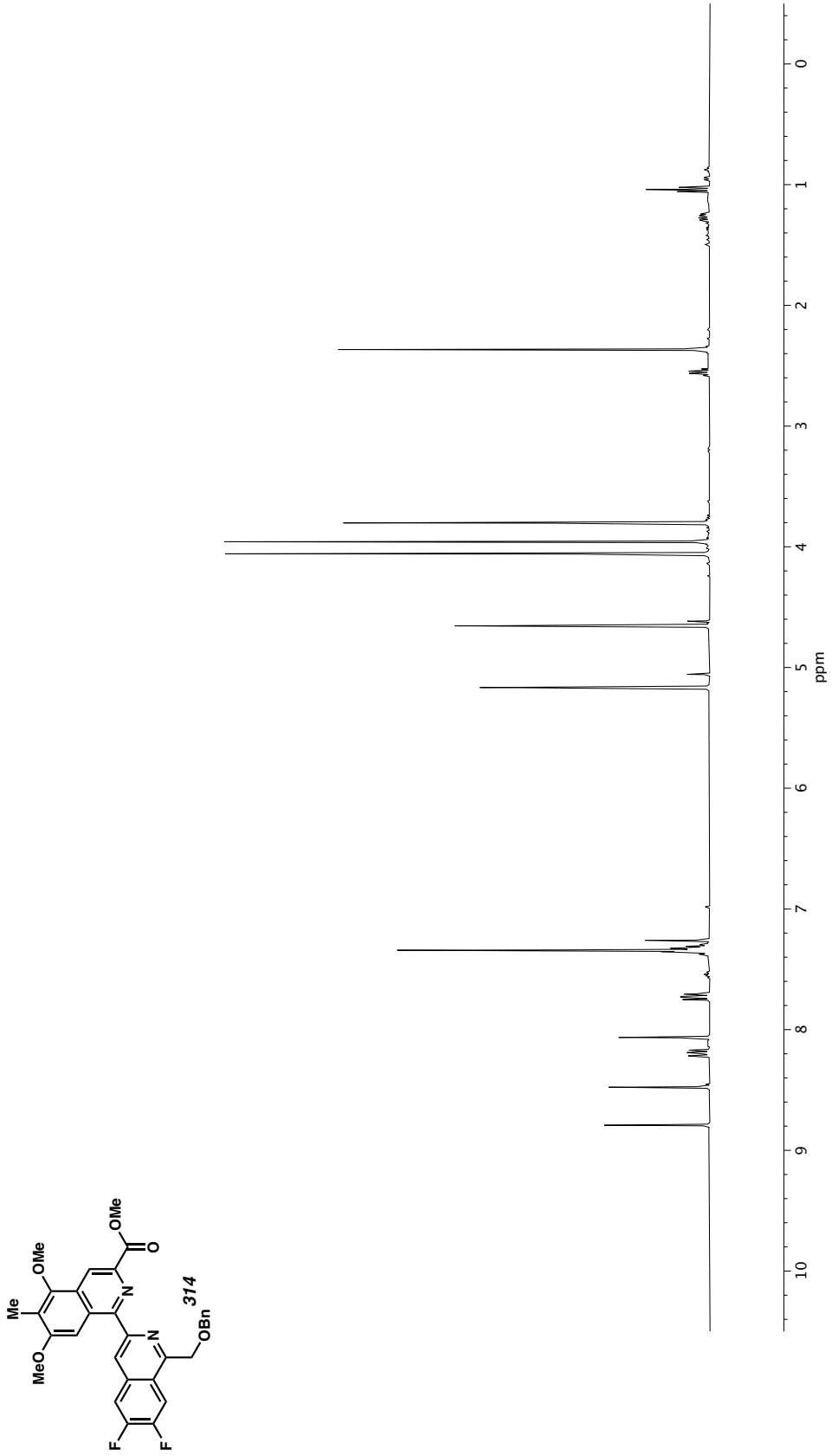


Figure A9.45 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***314****.*

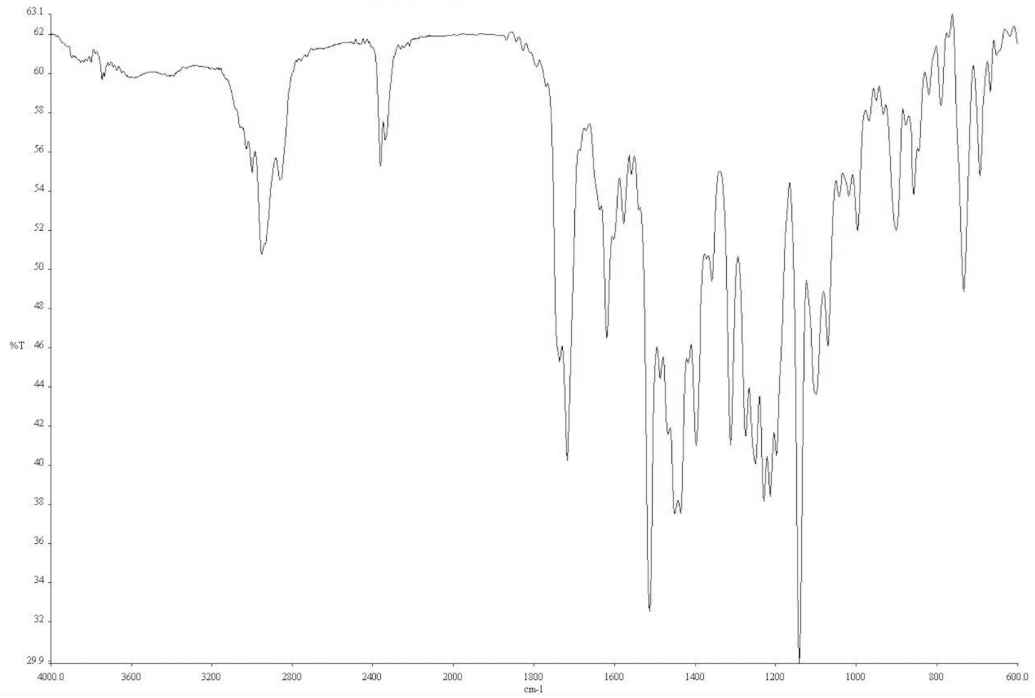


Figure A9.46 *Infrared spectrum (Thin Film, NaCl) of compound* ***314****.*

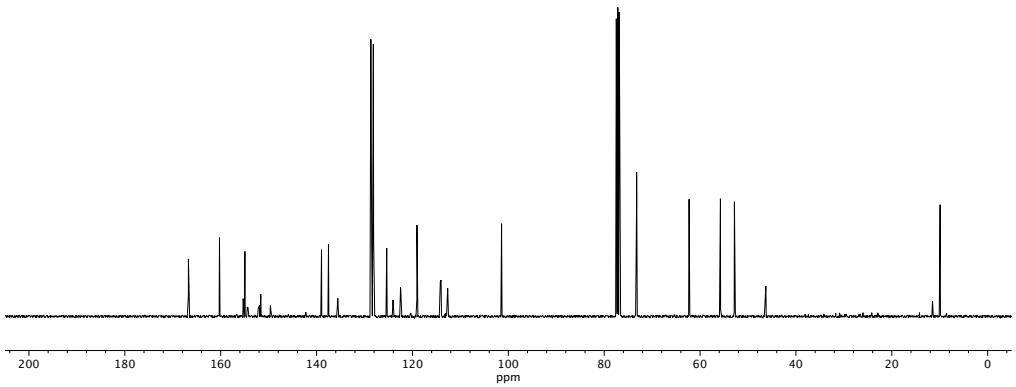


Figure A9.47 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***314****.*

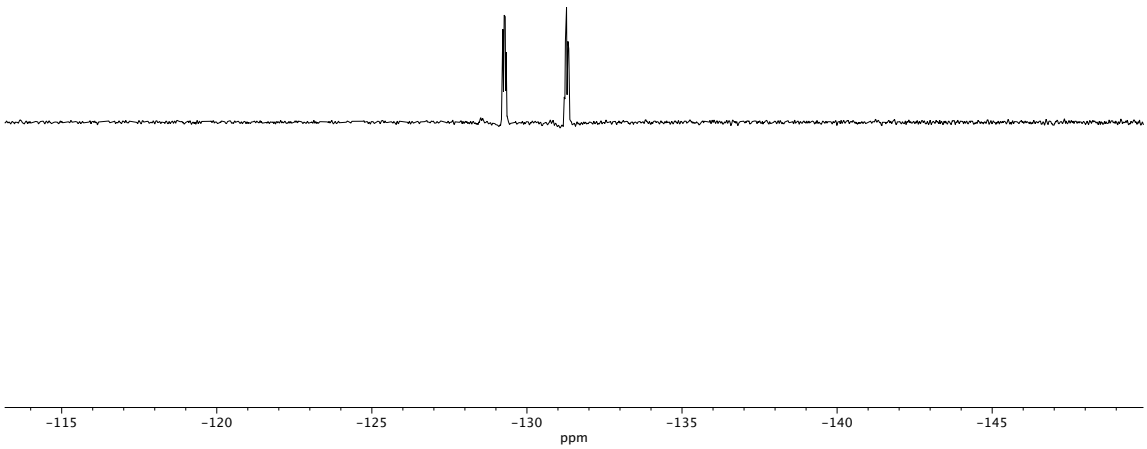


Figure A9.48 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***314***.

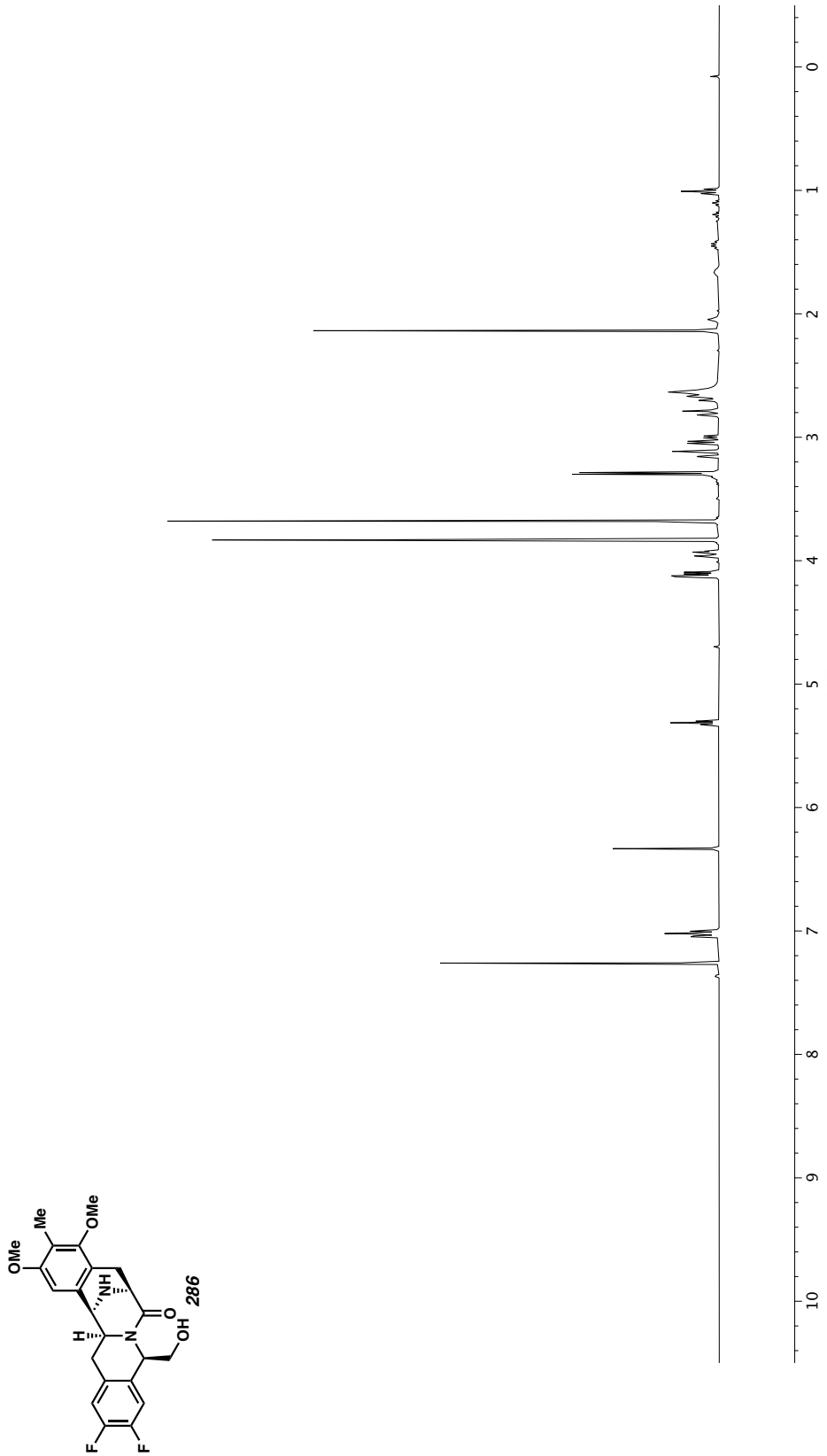


Figure A9.49 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***286***.

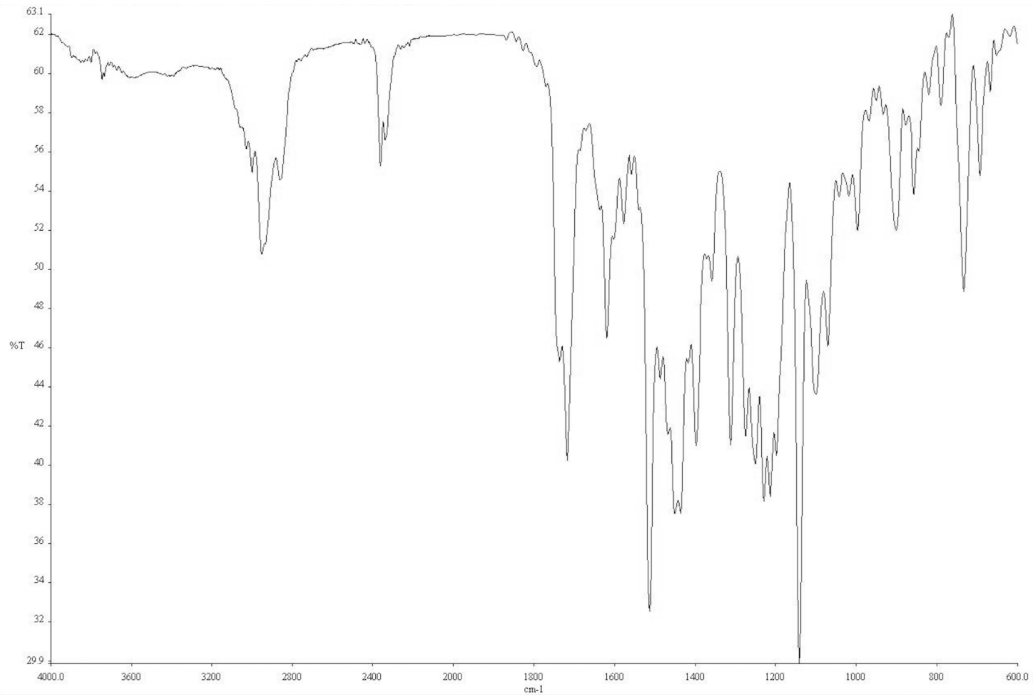


Figure A9.50 *Infrared spectrum (Thin Film, NaCl) of compound* ***286***.

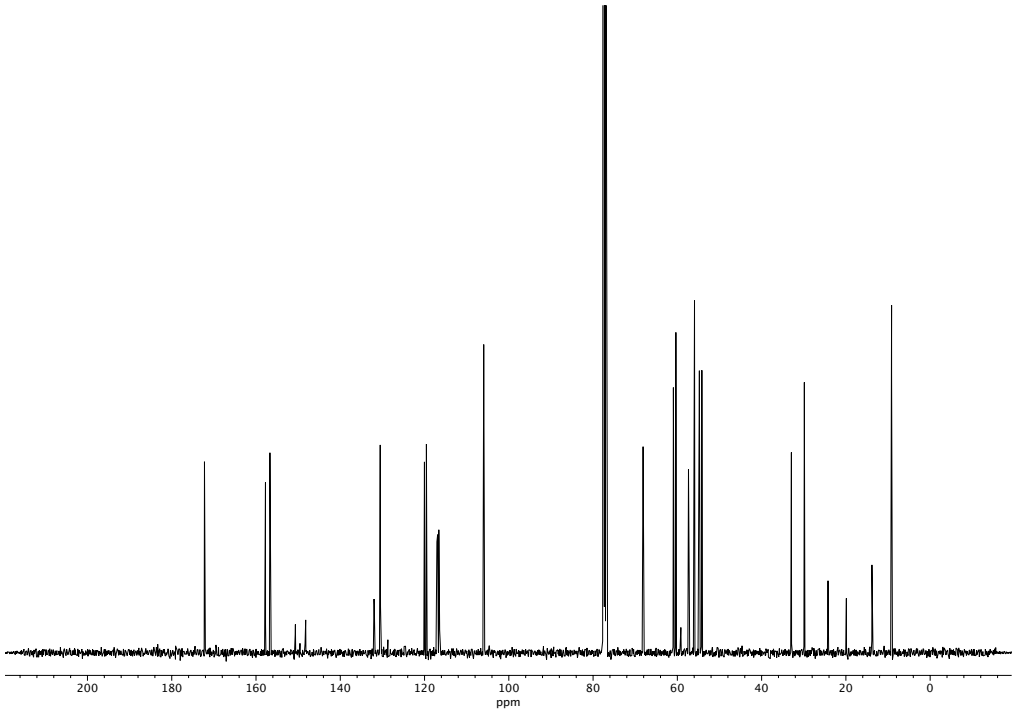


Figure A9.51 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***286***.

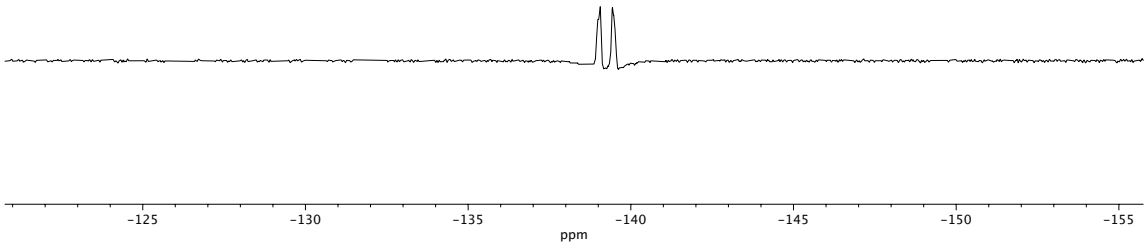


Figure A9.52 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***286***.

Figure A9.53 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***315****.*

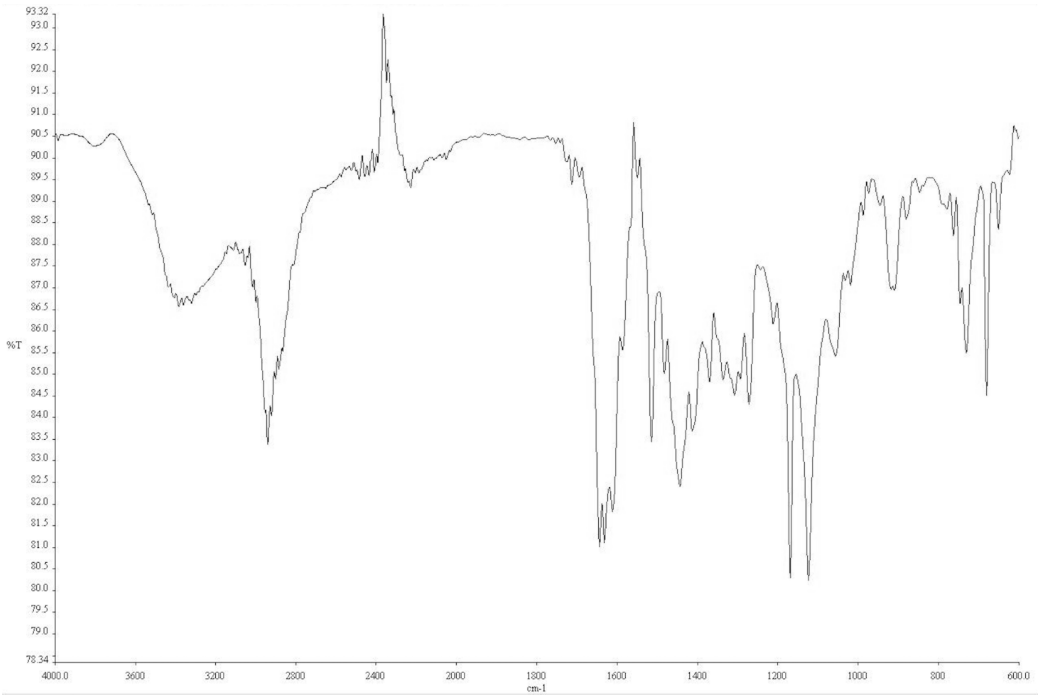


Figure A9.54 *Infrared spectrum (Thin Film, NaCl) of compound* ***315****.*

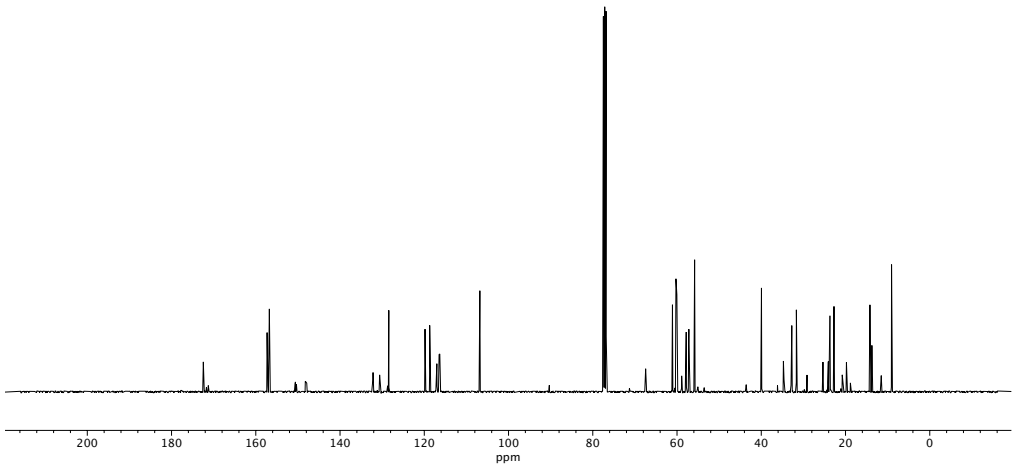


Figure A9.55 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***315****.*

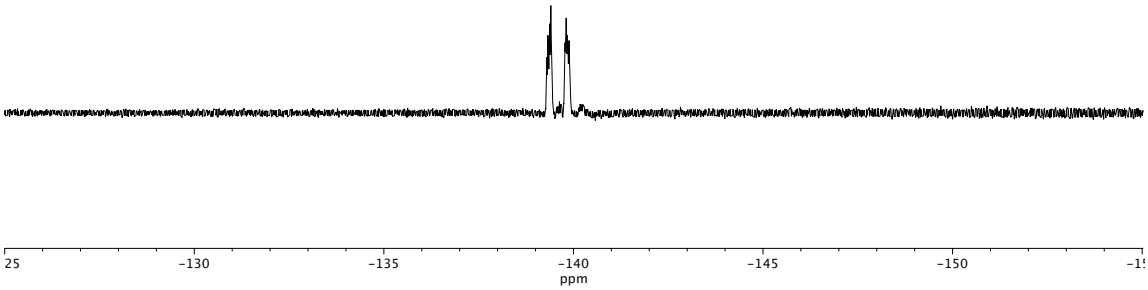


Figure A9.56 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***315***.

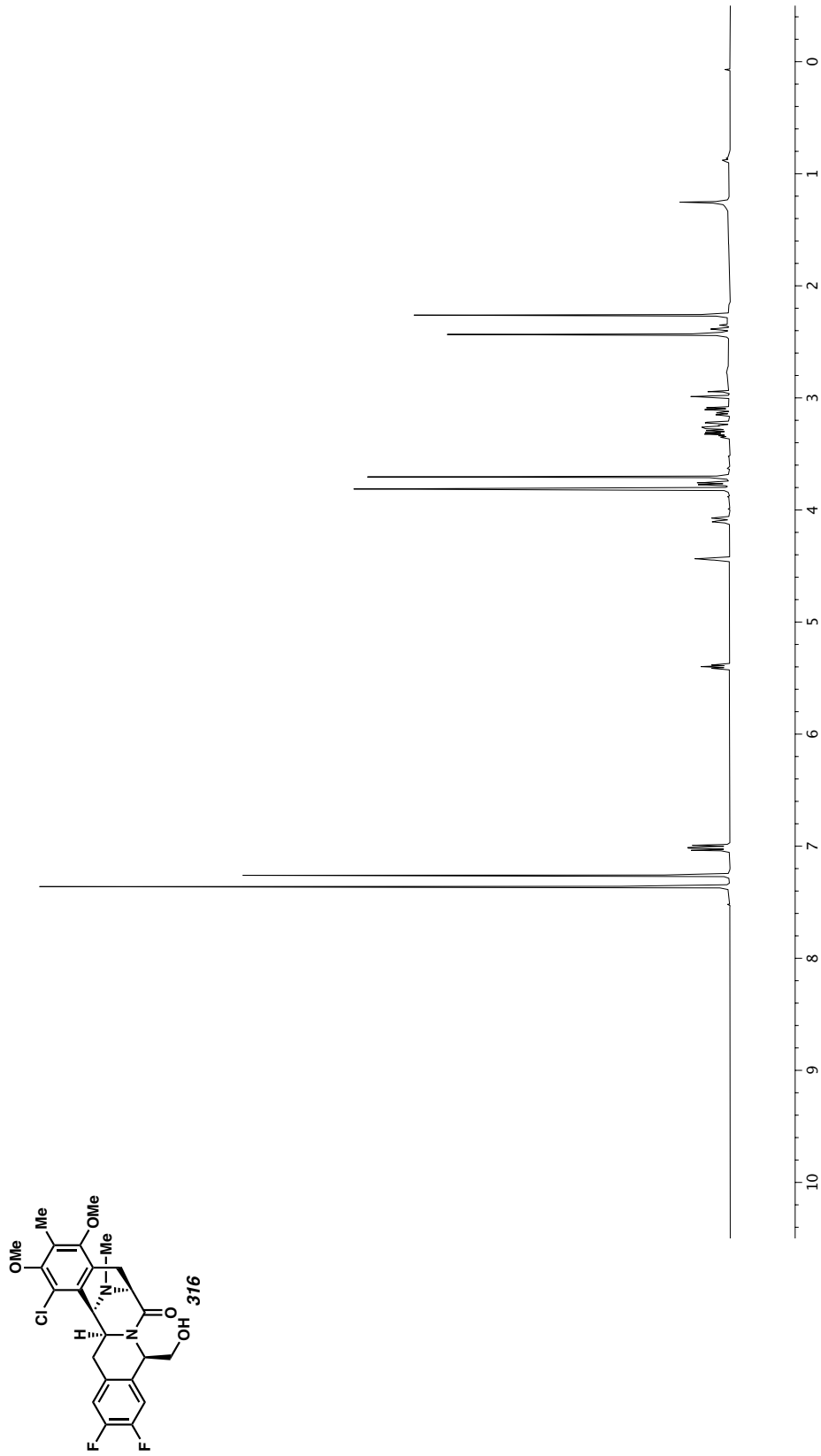


Figure A9.57 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***316****.*

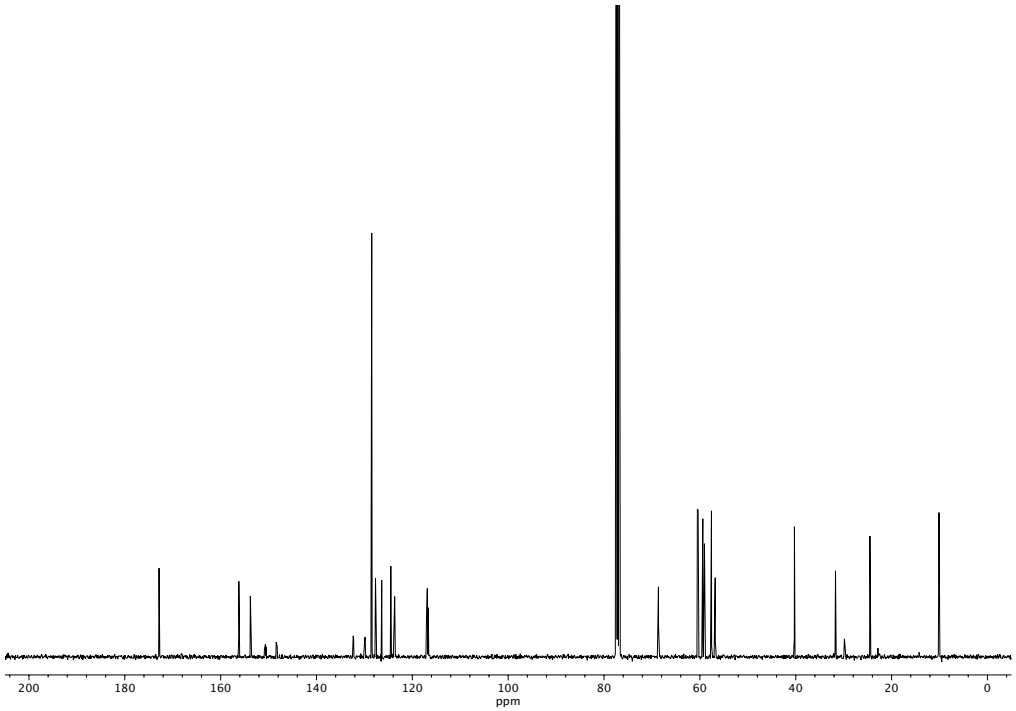


Figure A9.58 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***316***.

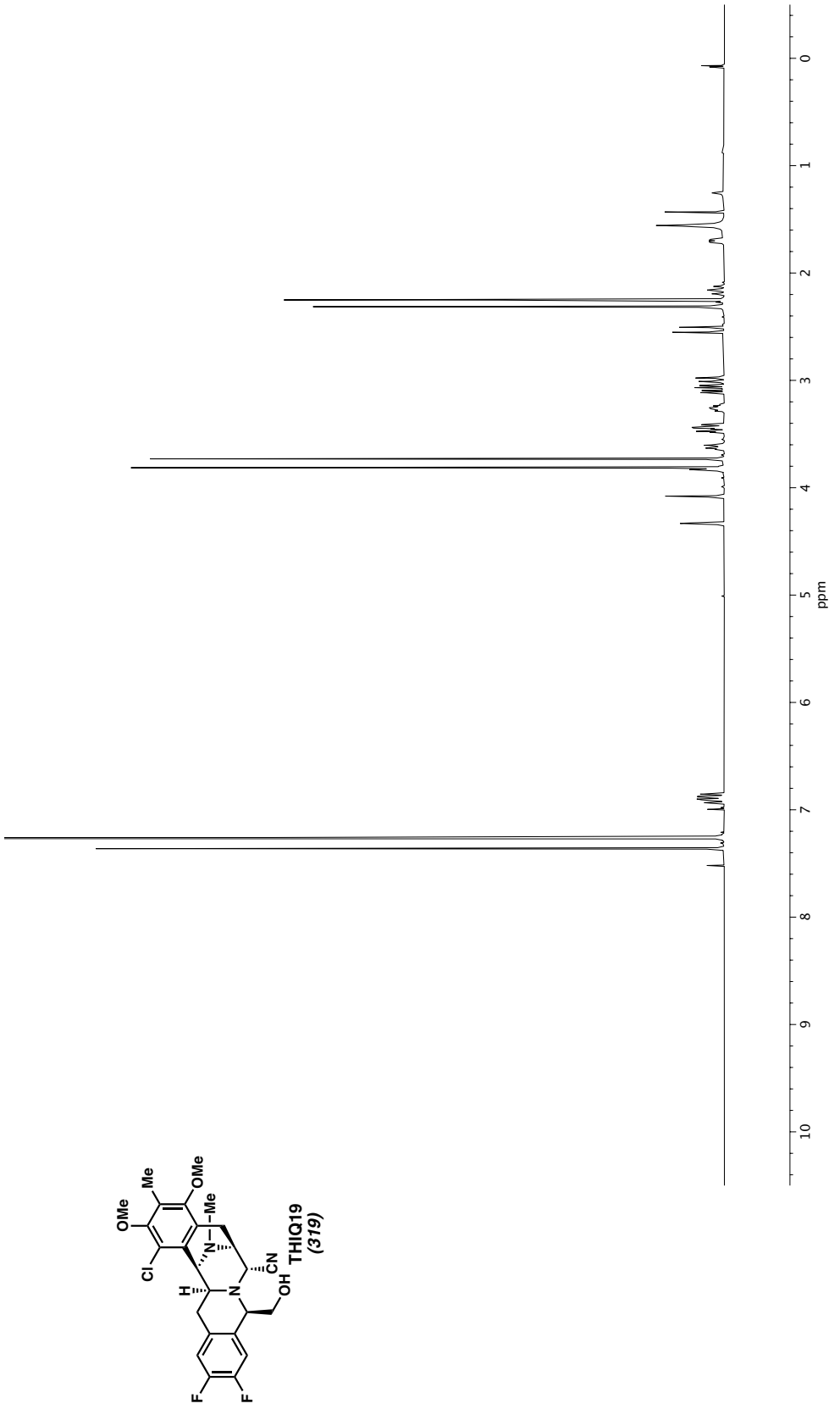


Figure A9.59 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***319 (THIO19)***.

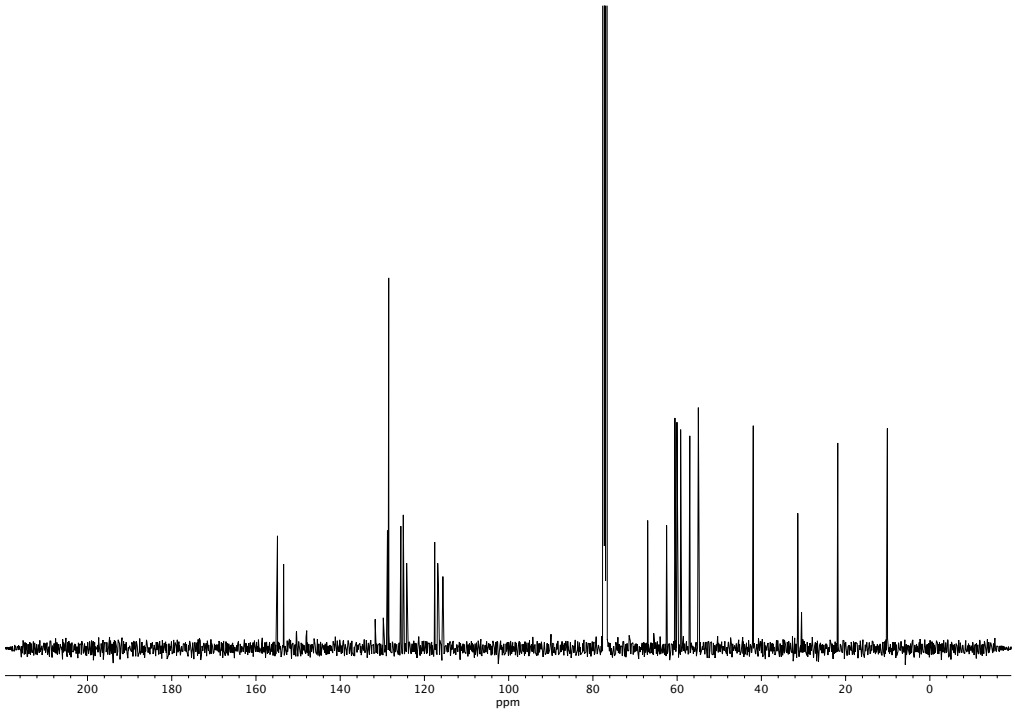


Figure A9.60 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***319 (THIQ19)***.

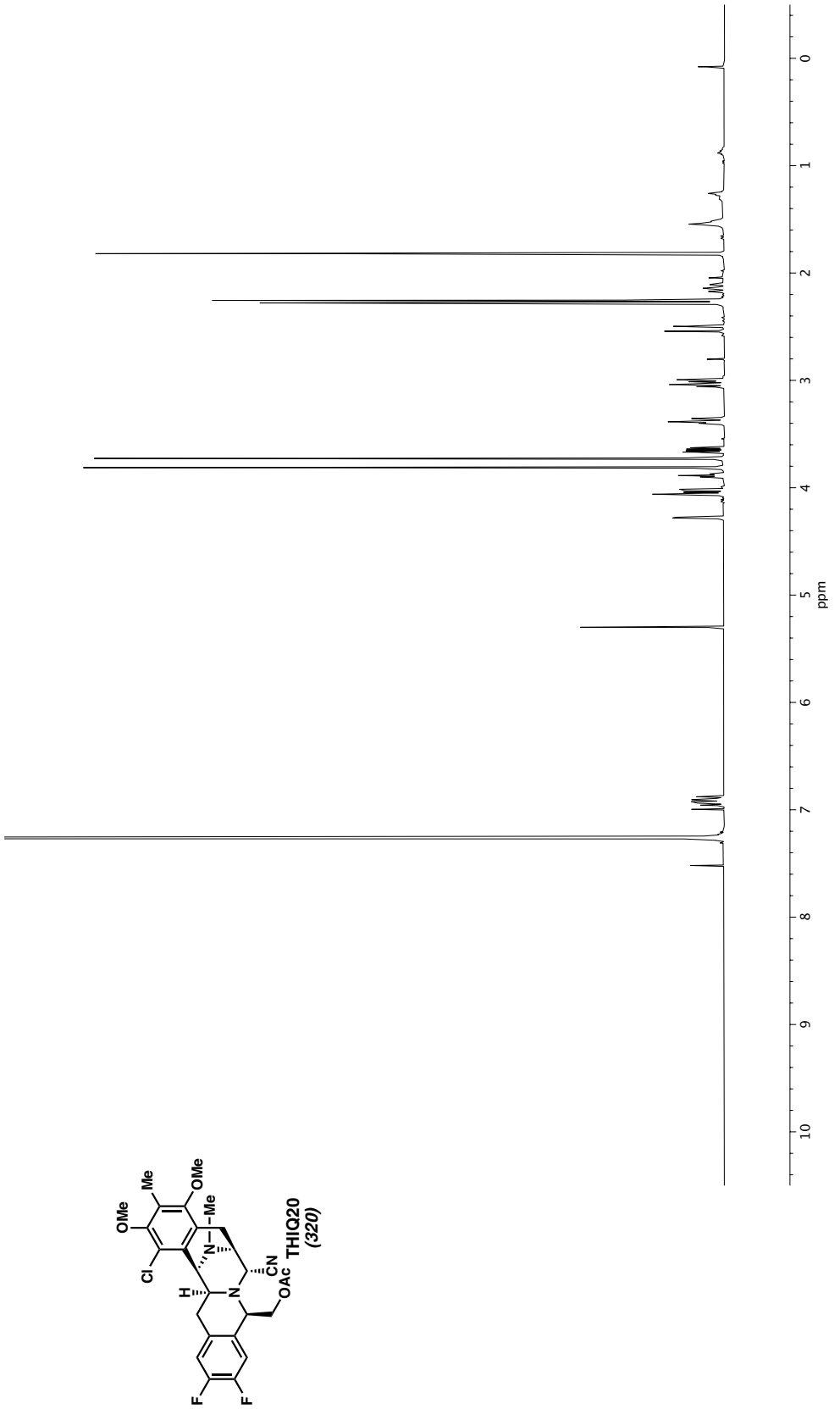


Figure A9.61 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***320 (THIO20)***.

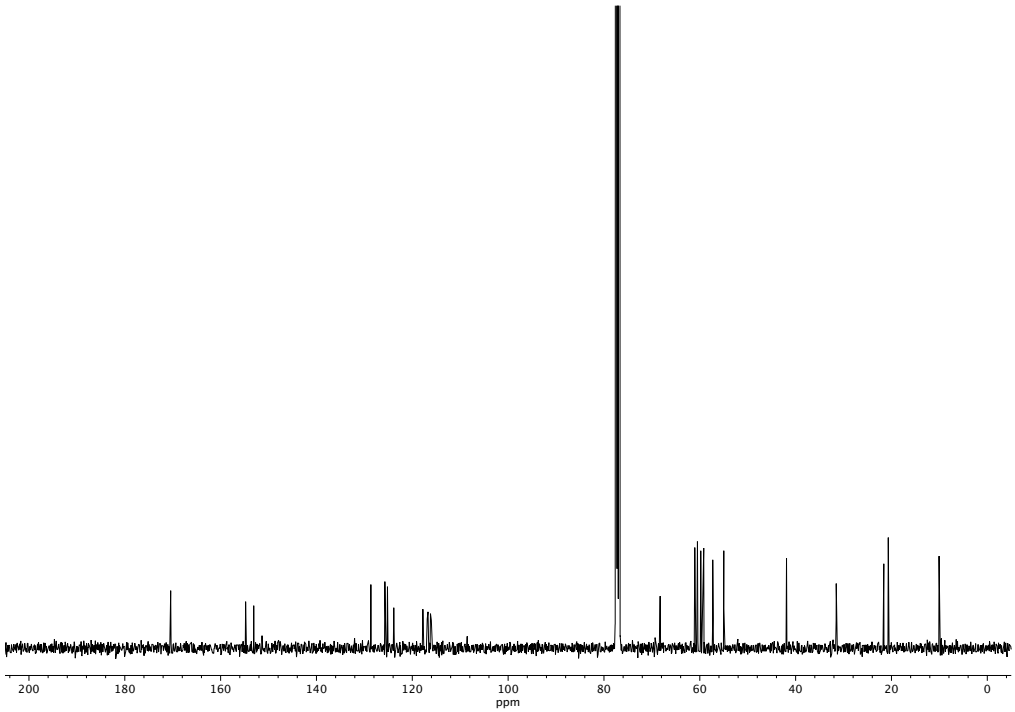


Figure A9.62 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***320 (THIQ20)***.

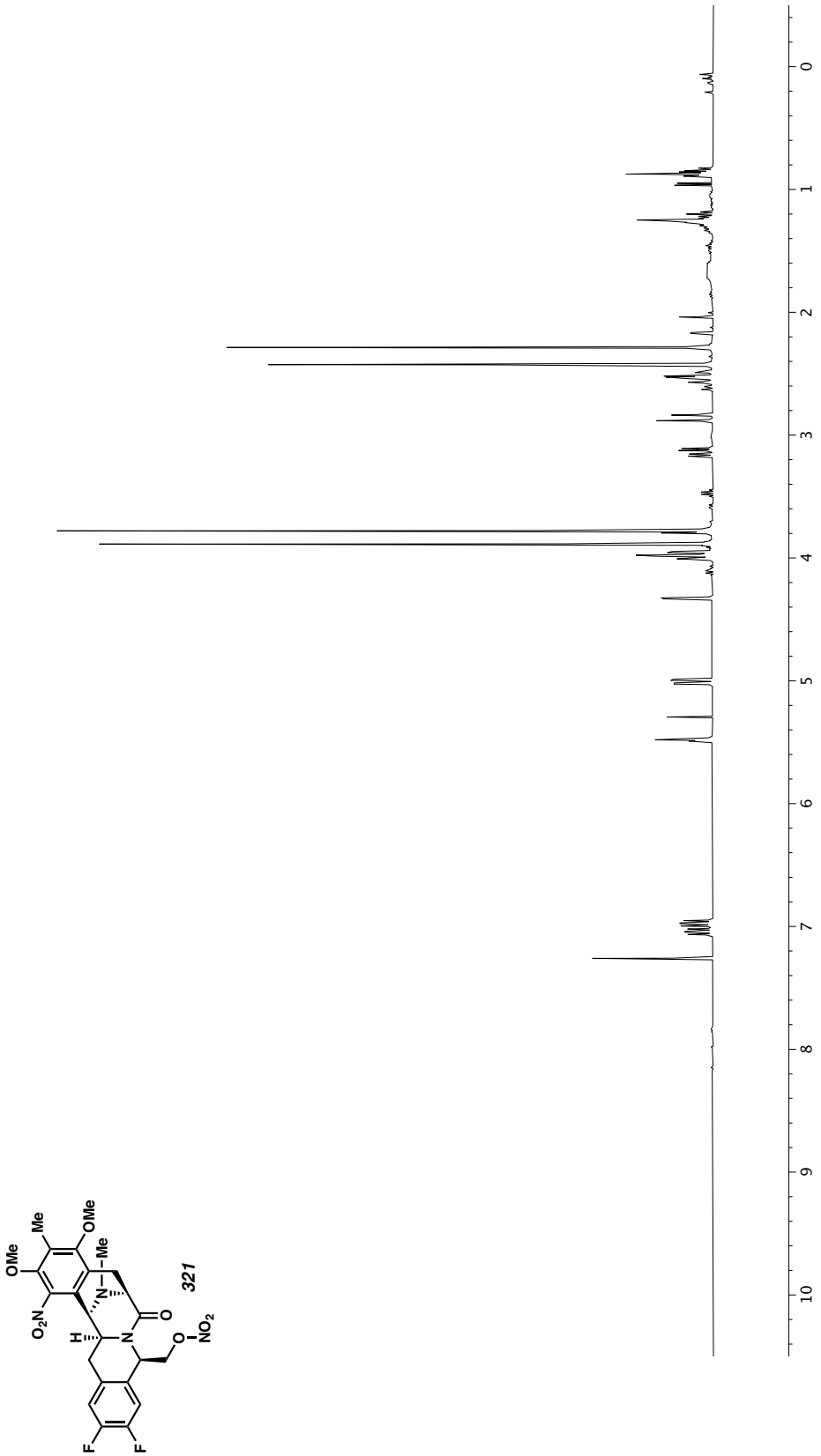


Figure A9.63 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***321***.

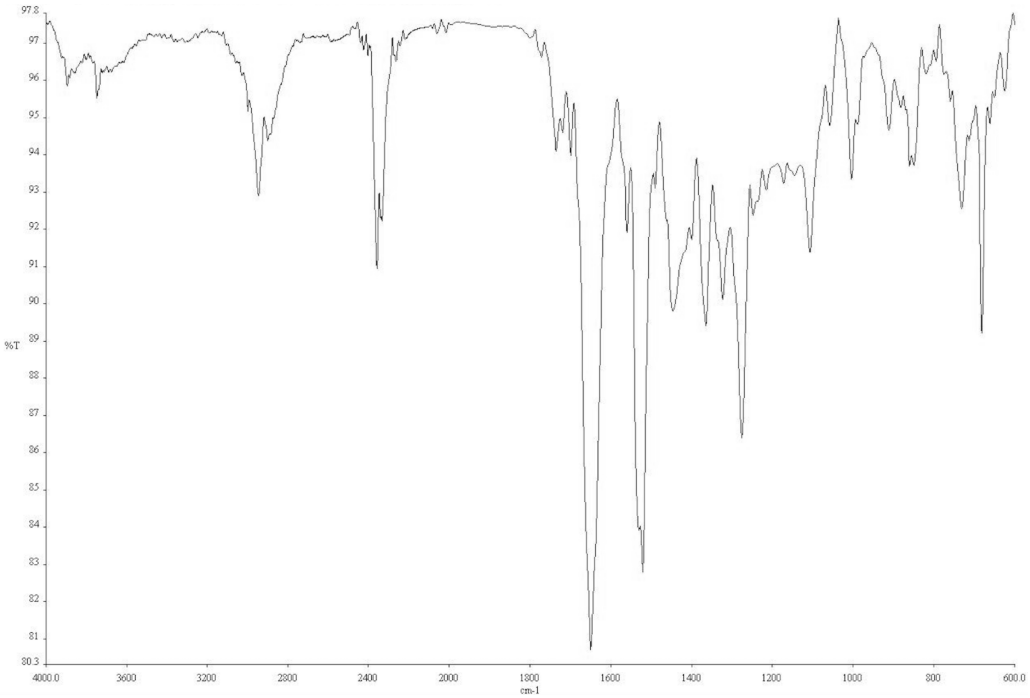


Figure A9.64 *Infrared spectrum (Thin Film, NaCl) of compound* ***321***.

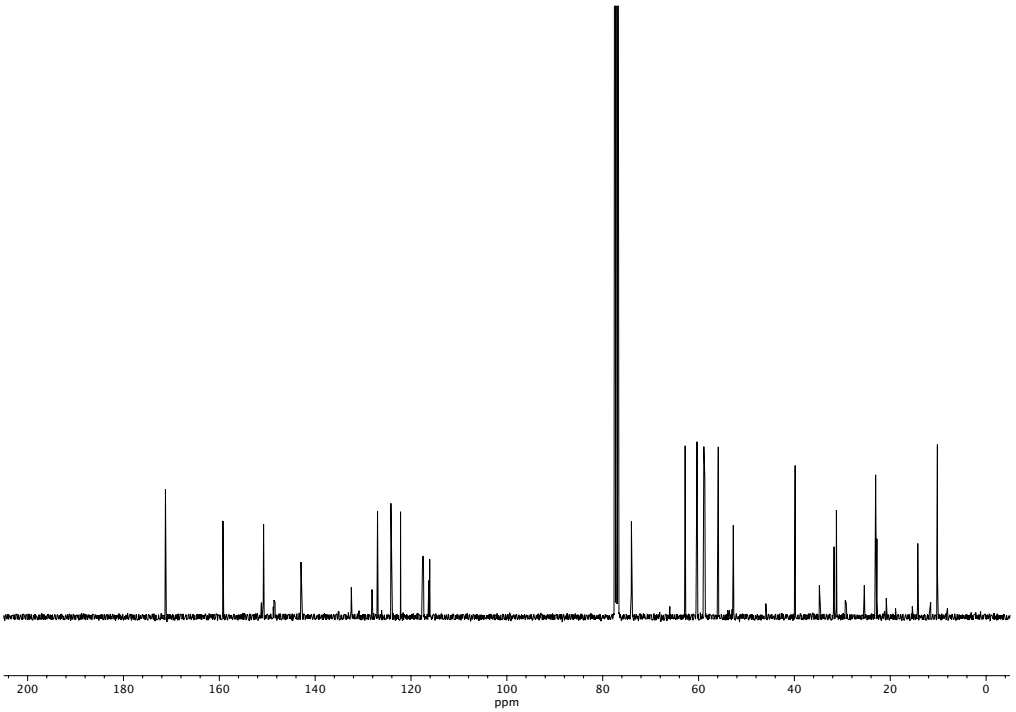


Figure A9.65 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***321***.

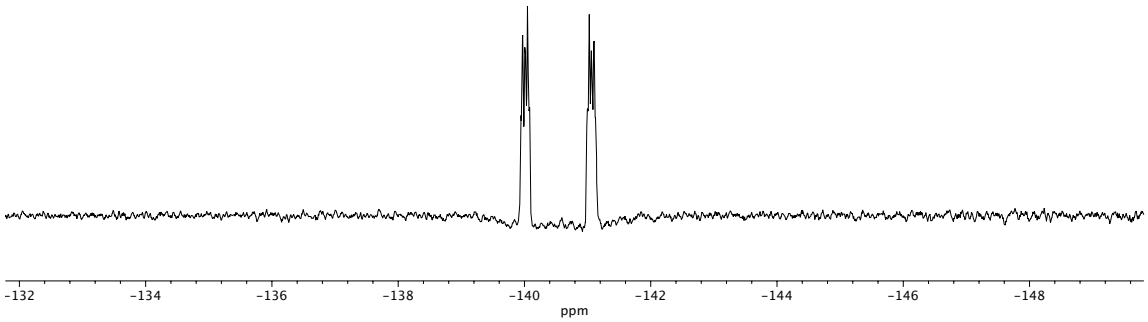


Figure A9.66 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***321***.

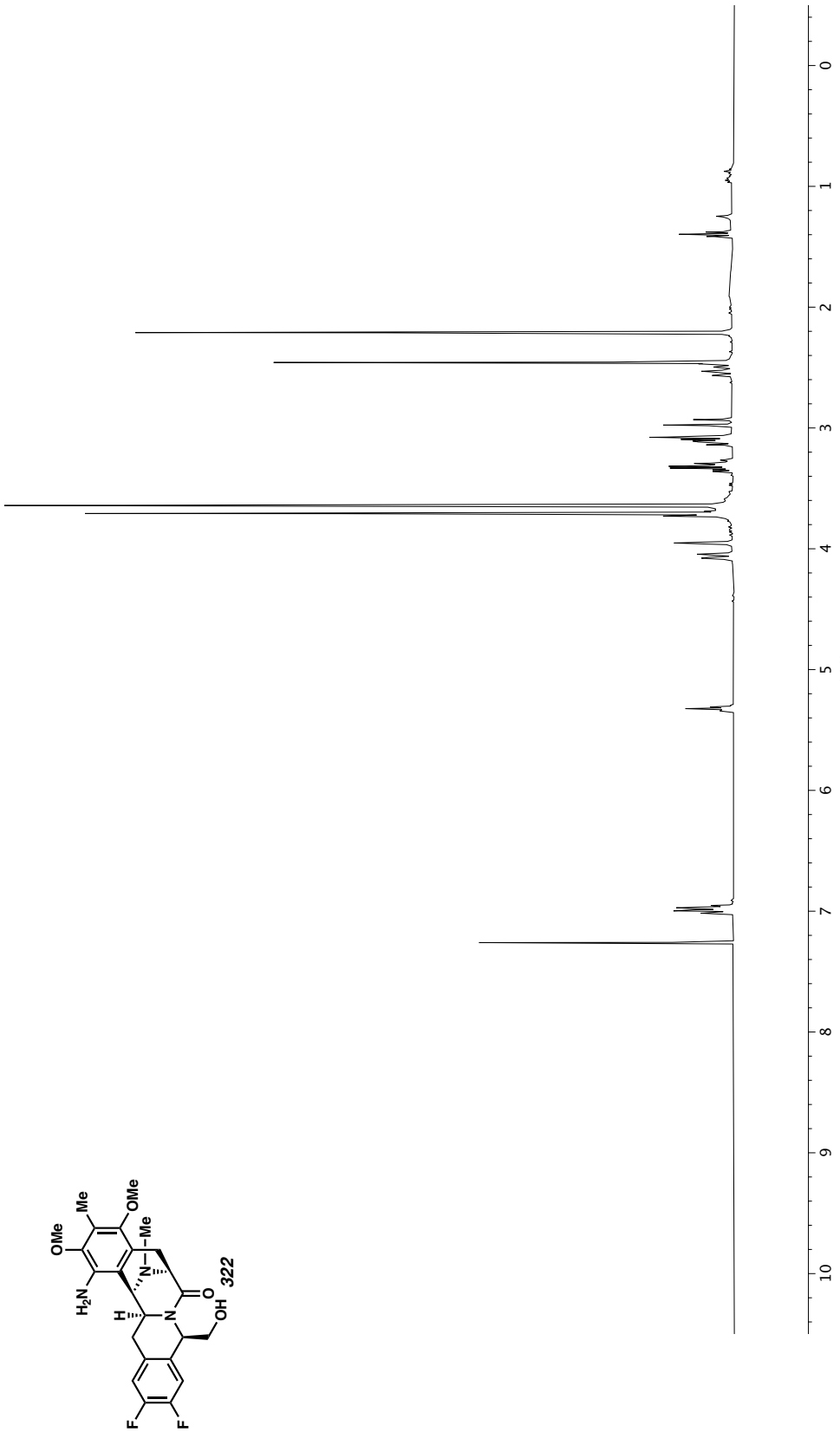


Figure A9.67 *^1H NMR (400 MHz, $CDCl_3$) of compound* ***322***.

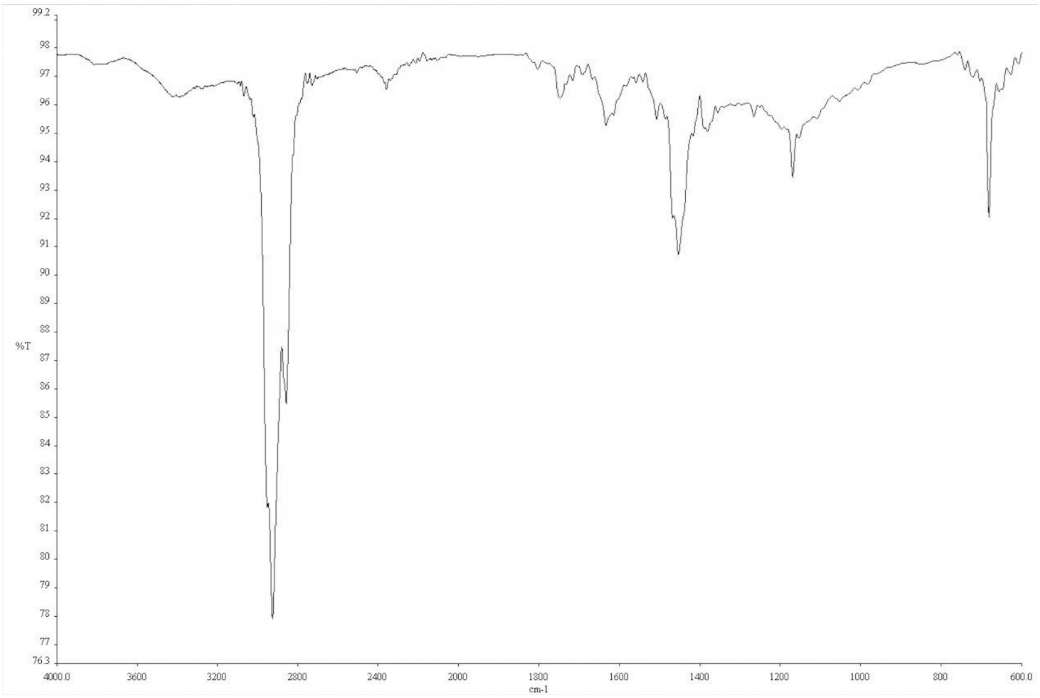


Figure A9.68 *Infrared spectrum (Thin Film, NaCl) of compound* ***322****.*

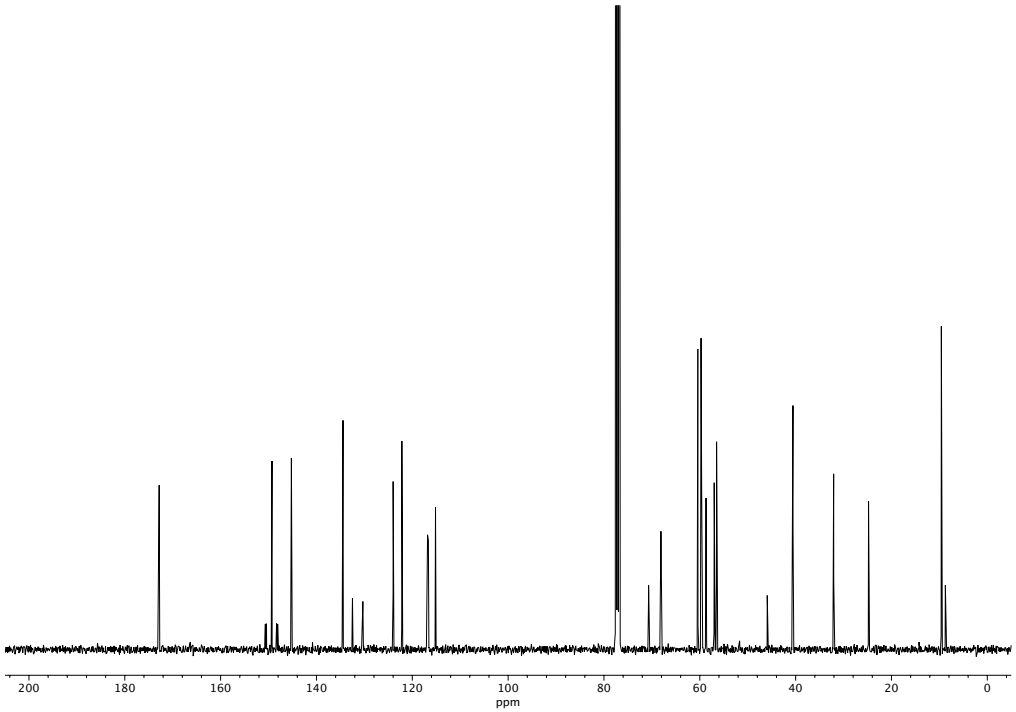


Figure A9.69 *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***322****.*

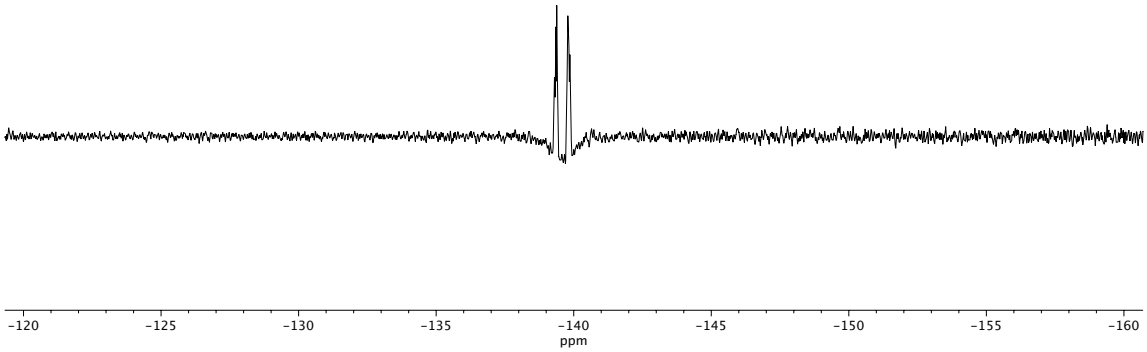


Figure A9.70 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***322***.

Figure A9.71 *^1H NMR (400 MHz, C_6D_6) of compound* ***323*** *(**THIQ21**).*

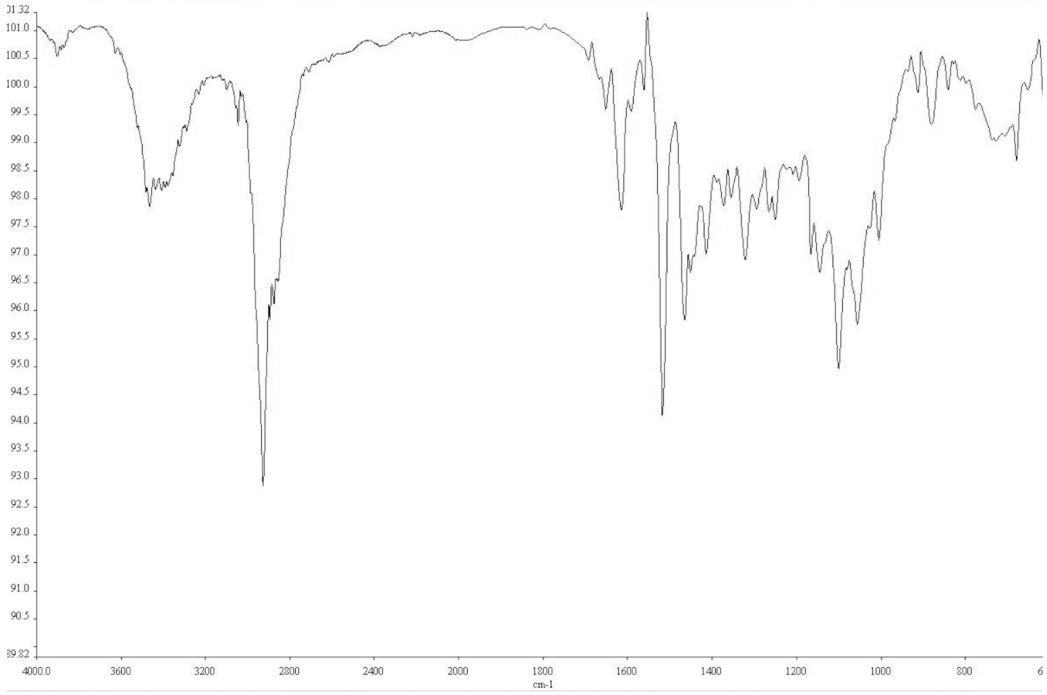


Figure A9.72 *Infrared spectrum (Thin Film, NaCl) of compound* ***323*** *(**THIQ21**).*

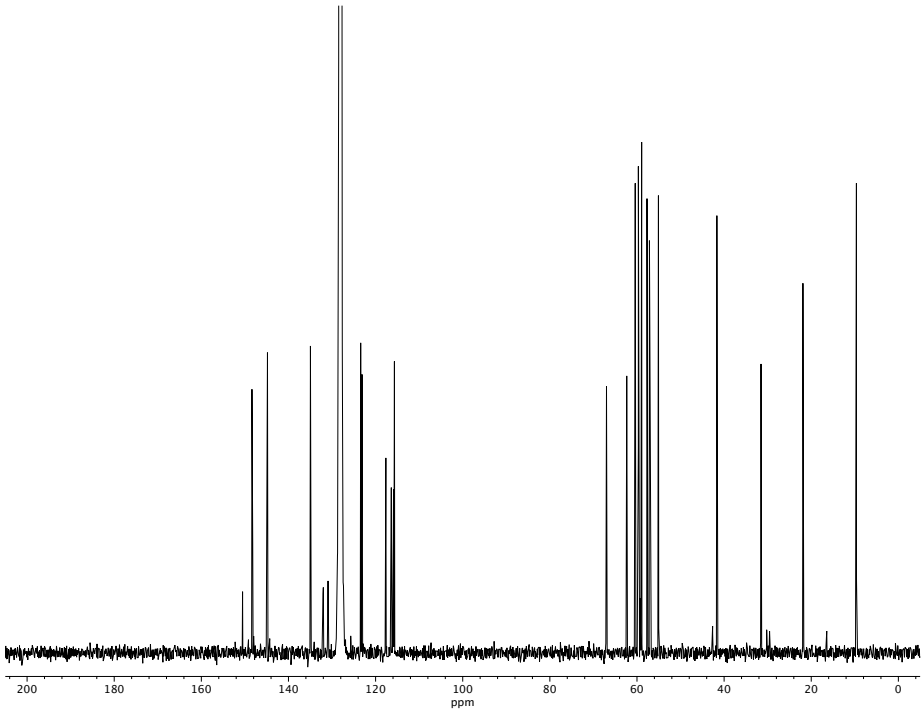


Figure A9.73 *^{13}C NMR (100 MHz, C_6D_6) of compound* ***323*** *(**THIQ21**).*

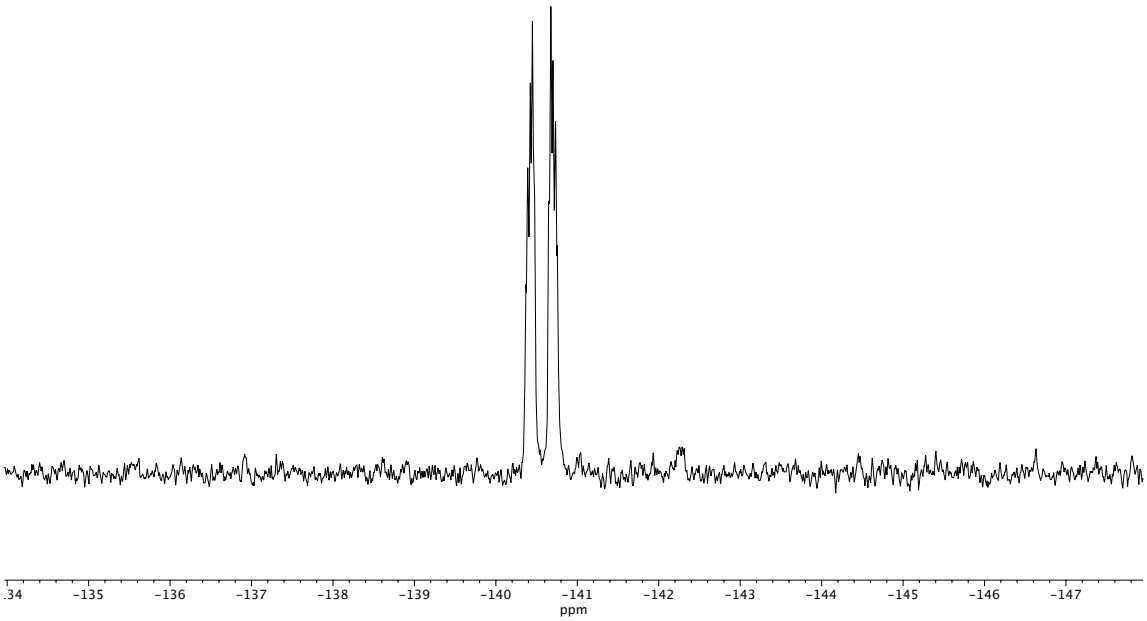


Figure A9.74 *^{19}F NMR (282 MHz, C_6D_6) of compound **323** (**THIQ21**).*

APPENDIX 10

Notebook Cross-Reference for New Compounds

Table A10.1 *Notebook cross-reference for Chapter 1.*

Compound	Notebook Ref.
90	TDL-I-289
91	TDL-II-088
92	KRS-II-253
93	VNN-I-151
94	JB-II-239
95	JB-IV-189-01
96	JB-IV-189-02
98	SED-5-033
99	KNF-7-103
101	TDL-II-090
102	VNN-II-275
103	VNN-II-065
104	JB-IV-105-01
105	VNN-II-067
106	VNN-II-095
107	VNN-II-131
108	VNN-II-119
110	JB-VII-087
111	JB-VII-153
21	KRS-II-139
30	JB-XIII-077
31	JB-V-213-03
32	JB-V-257-03
33	JB-VI-253-03
34	JB-VI-253-02
35	JB-V-223-01
36	JB-V-233-02
37	JB-VI-239
38	JB-V-233-03
39	JB-V-257-01
40	JB-V-253-04
41	JB-V-233-03
42	JB-VI-107-01
43	JB-V_229-01
27	VNN-I-059
65	VNN-II-143

Compound	Notebook Ref.
66	JB-VI-119-01
67	JB-VI-119-02
68	JB-VI-041-04
69	VNN-II-103a
70	JB-XII-235
71	JB-VI-025-05
72	VNN-II-143a
46	KRS-II-169
47	KRS-II-215-A
48	KRS-II-291
49	KRS-II-225-A
50	KRS-II-167-A
51	KRS-II-147-A
52	KRS-II-167-B
53	JB-V-289-02
54	KRS-II-225-B
55	KRS-II-229
56	JB-V-301-02
57	JB-V-301-03
58	VNN-II-123
59	VNN-II-085
60	JB-V-301-01
61	VNN-II-087
62	VNN-II-121
63	VNN-II-135
64	VNN-II-127
74	VNN-II-157a
75	VNN-II-157b
76	VNN-II-113
77	JB-VI-037-02
80	JB-VI-041-02
78	JB-VI-037-01
81	VNN-II-139b
79	VNN-II-137
82	JB-VI-025-01
83	VNN-II-163

84	VNN-II-165b
85	JB-VI-165
89	JB-VII-089
24	JB-V-175
22	KRS-III-157

Table A10.2 *Notebook cross-reference for Chapter 2.*

Compound	Notebook Ref.
127	FAM-II-169
155	JB-VIII-101-01
156	JB-VIII-067-02
157	JB-VIII-067-03
158	FAM-IV-181
159	FAM-IV-183
161	MC-VI-297
160	MC-VI-203-01
162	MC-VI-203-03
130	FAM-IV-227
133	JB-VIII-101-01
134	JB-VIII-101-02
135	JB-VIII-101-03
136	FAM-IV-185-1
137	FAM-IV-185-2
138	MC-VI-221-02
139	MC-VI-221-01
140	MC-VI-231-01
141	FAM-IV-075-1
143	JB-XI-155-01
145	FAM-II-255
146	MC-VI-095
147	FAM-IV-231
148	MC-VI-265
149	JB-VIII-237
150	JB-VIII-281
151	FAM-IV-233
152	MC-VI-041
163	FAM-IV-041
165	FAM-IV-051
167	FAM-IV-065
144	FAM-II-245

Table A10.3 *Notebook cross-reference for Chapter 3.*

Compound	Notebook Ref.
167	JB-X-237
176	JB-XI-061
177	JB-XI-163-01
178	JB-XI-111-01
179	KNF-7-273
180	JB-XIII-101
181	RA-I-077
182	JB-XIII-103
183	KNF-7-103
184	JB-XIII-0101
185	RA-I-023
186	JB-XII-257
187	JB-XIII-067
188	JB-XIII-015-02
173	JB-IX-151
172	JB-VIII-055-02
212	KNF-6-121
213	JB-XI-197
214	JB-XII-109
216	KNF-7-271
217	JB-XIII-077
218	RA-I-065
219	JB-XIII-089
220	KNF-7-099
221	JB-XII-303
222	RA-I-017
223	JB-XII-251
224	JB-XIII-025
225	JB-XII-299
226	JB-VIII-261
227	JB-XIII-107
228	KNF-6-105
229	JB-XI-145
230	JB-XII-029
231	JB-XIII-057
232	RA-I-061

Compound	Notebook Ref.
233	JB-XIII-085
234	KNF-7-073
235	JB-XII-279
236	RA-I-011
237	JB-XII-235
238	JB-XII-293
239	JB-XII-281
215	KNF-7-261
241	JB-XIII-097
245	KNF-7-211-B
246	JB-XIII-049
247	RA-I-059
248	JB-XIII-063
250	RA_I-009
251	JB-XII-223
252	JB-XII-273
253	JB-XII-275
250	JB-XII-265
189	KNF-7-287
190	KNF-7-223
191	JB-XIII-173
192	JB-XIII-079

Table A10.4 *Notebook cross-reference for Appendix 7.*

Compound	Notebook Ref.
297	JB-XIII-191
298	JB-XII-127
300	JB-XIII-115
301	JB-XIII-205
290	JB-XIII-147
303	JB-XI-227
306	JB-XI-255
307	JB-XI-265
305	JB-XIII-089
310	JB-XII-045
311	JB-XIII-213
313	JB-XIII-113
291	JB-XIII-119
314	JB-XIII-241
286	JB-XIII-253
315	JB-IV-027
316	JB-IV-029
320	JB-IV-071
321	JB-IV-075
322	JB-XIII-259
323	JB-XIII-263

ABOUT THE AUTHOR

Jay Park Barbor was born on September 27th, 1993 to John and Gretchen Barbor. He and his older brother, Peter, were born and raised in Indiana, Pennsylvania. After graduating from Indiana Area Senior High School in 2011, Jay attended Smith College in Northampton, Massachusetts. Initially unsure of a major, he had always had a special fondness for chemistry and quickly decided that this would be the focus of his studies. While at Smith, he was lucky to work in the lab of Professor Kevin Shea, studying the use of the Nicholas reaction to form medium-sized cycloalkynes.

After earning his B.A. in 2015, he moved on to work as a medicinal chemist at Microbiotix in Worcester, Massachusetts. While there, he refined his passion for chemical research and was encouraged to pursue a doctoral degree. After spending four years as an industrial researcher, he moved to Pasadena, California with his partner, Jessie Ricker, and cat, Maeby, to study under the guidance of Professor Brian Stoltz at Caltech.

In the Stoltz group, Jay has largely focused on the development of new Ni- and Pd-catalyzed cross-couplings. While at Caltech, he has added a new member to his family, Tuna, who came in off the streets shortly before his candidacy. Following the completion of his doctoral studies, he will be moving back to Massachusetts to start work as a medicinal chemist at Merck.