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A Green Halogenation of Pyrazoles using NaX/ Oxone[®] and the Total Synthesis of the Natural Product Withasomnine

Matthew R. Jensen
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**A Green Halogenation of Pyrazoles using
NaX/Oxone® and the Total Synthesis of the Natural
Product Withasomnine**

By

Matthew R. Jensen

A Thesis Submitted
in Partial Fulfillment of
the Requirements of CH 491/492

Department of Chemistry and Biochemistry
Elizabethtown College
May 5, 2016

Elizabethtown College
Department of Chemistry & Biochemistry

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“A Green Halogenation of Pyrazoles using NaX/Oxone® and the Total Synthesis of the Natural Product Withasomnine”

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Abstract

The research presented here demonstrates a halogenation reaction for pyrazoles from the generation of electrophilic halogens through a reaction between halide anions and Oxone®. Halogenation occurs at the 4-position, which is the most nucleophilic atom of the heterocycle. The sodium halide salt and Oxone serve as the halogen source in an electrophilic aromatic substitution. Oxone is a water-soluble, relatively innocuous reagent produced by DuPont that makes this reaction environmentally friendly. The reaction functions with good yields on a wide scope of substrates, works best without a co-solvent, is performed at room temperature, and requires short reaction times. These factors, along with its operational simplicity and ease of purification make this reaction highly valuable.

To demonstrate the utility of the reaction, a concise synthesis of the natural product withasomnine was undertaken. Withasomnine is a compound isolated from the flower *withania somnifera* and is a popular target for total syntheses involving pyrazoles. Our synthesis is completed in five steps from pyrazole. A halogenation and subsequent Suzuki-Miyaura cross-coupling reaction couples a phenyl ring to the 4-position. Alkylation at position 1 using 3-bromopropanol followed by formation of the xanthate ester enables a radical-initiated cyclization that forms the fused ring connecting to the 5-position of pyrazole. Reaction sequence and conditions were explored and optimized and are presented here.

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First and foremost, I would like to acknowledge all of the staff and faculty of the Elizabethtown College Department of Chemistry and Biochemistry for all of the teaching, training, and support provided throughout my time as an undergraduate. Specifically, I would like to thank Dr. James A. MacKay for his support and guidance throughout this project, and consistently challenging and inspiring me. Additionally, I cannot express enough gratitude to Dr. Thomas E. Hagan, my academic advisor, for consistently believing in me and encouraging me to challenge myself as a student. I would like to thank and recognize past and present members of the MacKay Group including: Kathryn L. Olsen for providing the expansive base of this study, Christopher A. Ryan for sharing the lab with me for my first summer and showing me the ropes, and Sam H. Brooks and Holly A. Sofka for contributing through group meetings and sharing laughs through the summer and semester. Without everyone's tireless support over these four years, I doubt submitting this Honors in the Discipline thesis would even be within my consideration.

On a more personal note, I would like to thank my parents, Kathy M. and Michael R. Jensen, for keeping their expectations high and always believing I could accomplish what I set out to do. Additionally I cannot help but extend my gratitude to Mrs. Sarah Stocking, for making me fall in love with chemistry at Steinert and encouraging me to pursue it at Elizabethtown, the University of Delaware, and beyond.

Table of Contents

Abstract	i
Acknowledgements	ii
List of Tables	iv
List of Figures	v
List of Reaction Schemes.....	vi
Introduction.....	1
Results and Discussion	25
Experimental	50
References.....	60

List of Tables

Table 1: Co-solvent studies evaluated by conversion with ^1H NMR.	25
Table 2: Co-solvent studies evaluated by percent yield, performed by K. Olsen. ¹⁷	26
Table 3: Substrate scope of the electrophilic halogenation of pyrazoles using NaX and Oxone.....	28
Table 4: Effects of catalyst loading on Suzuki-Miyaura cross-coupling of phenylboronic acid on 4-bromopyrazole.	38

List of Figures

Figure 1: The structure of pyrazole, numbered ring positions with π -electron densities of atoms and π -bond orders between atoms. ¹¹	5
Figure 2: Examples of pyrazoles in medicine.....	6
Figure 3: The structures of Tebufenpyrad, Fipronil and a Strobilurin derivative.....	7
Figure 4: The structure of withasomnine and related natural product analogs.....	9
Figure 5: The catalytic cycle of the Suzuki-Miyaura cross coupling.	20
Figure 6: The CataCXium® A and A- ^{ta} Phos ligands.	21
Figure 7: General retrosynthetic strategy of the total synthesis of withasomnine from pyrazole.	30
Figure 8: The first retrosynthetic pathway attempted for the total synthesis of withasomnine from pyrazole.	31
Figure 9: The second retrosynthetic pathway proposed for the synthesis of withasomnine.....	33
Figure 10: The third and working retrosynthetic pathway for the total synthesis of withasomnine.....	36
Figure 11: Retrosynthetic strategy for the remaining reactions of synthetic path 3.	40
Figure 12: Proposed mechanism for the 5- <i>exo</i> -trig radical-initiated cyclization of 37 to 1	43

List of Reaction Schemes

Scheme 1: Regioselective oxazole cyclization as proposed by Pérez et al. ¹	2
Scheme 2: A green iodination for pyrazole using iodine and hydrogen peroxide.	3
Scheme 3: A halogenation reaction using <i>N</i> -halosuccinimide.....	3
Scheme 4: Pyrazole halogenation promoted by microwave irradiation.....	4
Scheme 5: Synthesis of withasomnine from 3-hydroxymethyl-4-phenylpyrazole (2). ...	11
Scheme 6: Synthesis of withasomnine from indole, expressed in two paths.	13
Scheme 7: Synthesis of withasomnine from 4-phenyl-3-pyrazolepropionic acid.....	14
Scheme 8: Total synthesis of withasomnine described by Kulinkovich et al. ²⁵	16
Scheme 9: Synthesis of withasomnine from ethyl 4-chlorobutanoate described by Potáček et al. ²¹	17
Scheme 10: Synthesis of withasomnine from 4-bromopyrazole.....	18
Scheme 11: A radical initiated cyclization demonstrated by Allin et al. ²³	22
Scheme 12: Several examples of xanthates being used as radical precursors in organic synthesis, in methods published by Zard et al. ³⁴⁻³⁷	23
Scheme 13: Reaction model used for co-solvent experiments.....	25
Scheme 14: Substituent placement in substrate scope experiments.....	27
Scheme 15: Progress on the first attempt at the synthesis of withasomnine.....	32
Scheme 16: Progress on the second route to withasomnine synthesis.	33
Scheme 17: Reaction scheme and conditions for the Suzuki coupling of the xanthate ester product, in the presence of aqueous basic conditions.	34

Scheme 18: Reaction conditions for the Suzuki coupling of the xanthate ester in dry conditions with triphenylphosphine as the catalyst ligand.	34
Scheme 19: Reaction conditions for the Suzuki coupling of the xanthate ester in dry conditions with triphenylphosphine as the catalyst ligand, and the organic base HMDS.....	35
Scheme 20: Suzuki-Miyaura cross-coupling with phenylboronic acid on 4-bromopyrazole.	37
Scheme 21: A crude three-step sequence to form the xanthate ester from 4-bromopyrazole.	41
Scheme 22: Radical cyclization of the xanthate ester using AIBN, SnBu ₃ H, in benzene to form withasomnine in <14% yield.	43
Scheme 23: Attempted radical cyclization using ACCN, SnBu ₃ H, in toluene to form withasomnine, resulting in degradation of starting material.	44
Scheme 24: Attempted radical cyclization using benzoyl peroxide in benzene to form withasomnine, resulting in formation of biphenyl.....	45

Table of Appendices

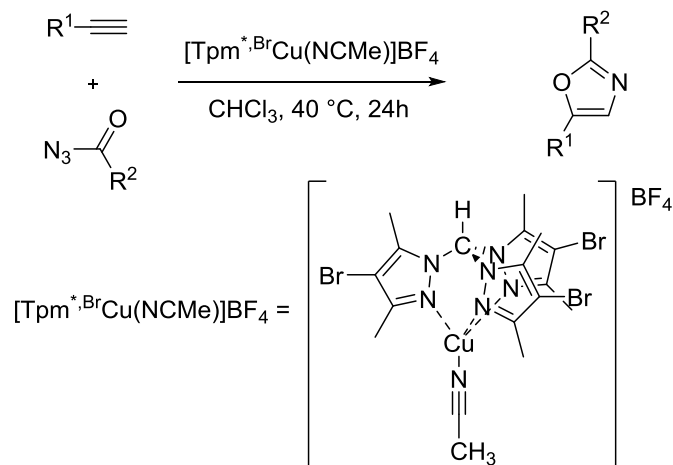
Appendix 1: ^1H NMR Spectrum of 33a	65
Appendix 2: ^1H NMR Spectrum of 33b	66
Appendix 3: ^1H NMR Spectrum of 34a	67
Appendix 4: ^1H NMR Spectrum of 34b	68
Appendix 5: ^1H NMR Spectrum of 35a	69
Appendix 6: ^1H NMR Spectrum of 35b	70
Appendix 7: ^1H NMR Spectrum of 36	71
Appendix 8: ^1H NMR Spectrum of 32	72
Appendix 9: ^1H NMR Spectrum of 24	73
Appendix 10: ^1H NMR Spectrum of 40	74
Appendix 11: ^1H NMR Spectrum of 38	75
Appendix 12: ^1H NMR Spectrum of 3,5-dimethyl-4-phenylpyrazole.....	76
Appendix 13: ^1H NMR Spectrum of 44	77
Appendix 14: ^1H NMR Spectrum of 37	78
Appendix 15: ^1H NMR Spectrum of 1	79
Appendix 16: ^{13}C NMR Spectrum of 33a	80
Appendix 17: ^{13}C NMR Spectrum of 33b	81
Appendix 18: ^{13}C NMR Spectrum of 34a	82
Appendix 19: ^{13}C NMR Spectrum of 34b	83
Appendix 20: ^{13}C NMR Spectrum of 35a	84
Appendix 21: ^{13}C NMR Spectrum of 35b	85

Appendix 22: ^{13}C NMR Spectrum of 36	86
Appendix 23: ^{13}C NMR Spectrum of 40	87
Appendix 24: ^{13}C NMR Spectrum of 38	88
Appendix 25: ^{13}C NMR Spectrum of 37	89
Appendix 26: IR Spectrum of 33a	90
Appendix 27: IR Spectrum of 33b	91
Appendix 28: IR Spectrum of 34a	92
Appendix 29: IR Spectrum of 34b	93
Appendix 30: IR Spectrum of 35a	94
Appendix 31: IR Spectrum of 35b	95
Appendix 32: IR Spectrum of 36	96
Appendix 33: IR Spectrum of 40	97
Appendix 34: IR Spectrum of 38	98
Appendix 35: IR Spectrum of 37	99

INTRODUCTION

Project Conception

Dapoxyl sulfonic acid (DSA) is a fluorescent molecule that can be efficiently incorporated into a polymeric matrix. A project initiated by the Kneas research group sought to use DSA as a fluorescent probe in a hydrogel-based humidity sensor that swells in response to absorbed water molecules. An effective synthesis of DSA, desirable due to its high cost and opportunities for derivatization, required a cyclization reaction to form an oxazole in order to bring the two components of DSA together. Pérez et al. developed a regioselective oxazole cyclization mediated by a copper catalyst and Scheme 1 shows the catalyst used that contains a tridentate brominated pyrazole ligand.¹⁻² 4-Bromo-3,5-dimethylpyrazole is commercially available, but the corresponding chloropyrazole was not. Given the need for halogenated pyrazoles, a search in the chemical literature revealed several different methods of 4-halogenation, some with green characteristics.³⁻⁷ Herein, these methods will be reviewed for their approaches to pyrazole 4-halogenation and respective advantages and disadvantages, in the context of green chemistry.

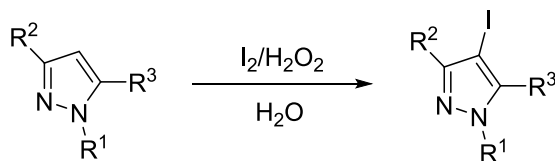


Scheme 1: Regioselective oxazole cyclization as proposed by Pérez et al.¹

The United States Environmental Protection Agency (US EPA) outlines twelve principles of “Green Chemistry,” which advocates for sustainable principles. Among the 12 principles of green chemistry are preventing waste, designing non-hazardous syntheses, using safe solvents, increasing energy efficiency, and avoiding derivatives.⁸ Pike Research, a market intelligence firm, estimated in 2011 that the chemical industry would save approximately \$65.5 billion by 2020 through green chemistry initiatives.⁹

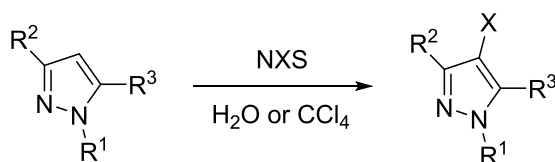
Scheme 2 shows a method for iodination proposed by Kim et al.³ The researchers report extensive substrate scope in an aqueous solution, and limited innocuous byproducts (water), simplifying purification. The reaction can be run at room temperature in several hours to completion if the substrate is electron rich. However, this method has only been applied to iodination, and although there was preference for monoiodination at

the 4-position, the paper indicates that there may be problems with multiply-iodinated byproducts.³



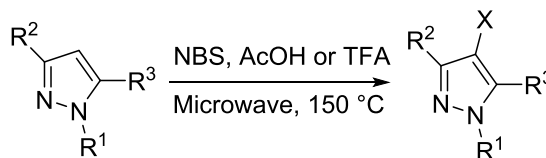
Scheme 2: A green iodination for pyrazole using iodine and hydrogen peroxide.

Zhao et al. have demonstrated a reaction that halogenates pyrazoles using *N*-chlorosuccinimide and *N*-bromosuccinimide to form the respective chloropyrazoles and bromopyrazoles, as shown in Scheme 3.⁴ Most of the reactions can be completed in a few hours, performed at room temperature, and completed effectively with water as a solvent.⁴ However, the reaction is undesirable due to the dependence of some reactions on using CCl_4 as a solvent, which is generally expensive and toxic. If a project's goals include reducing costs, environmental impact, and the overall amount of toxic substances in the lab, this method may not be ideal.



Scheme 3: A halogenation reaction using *N*-halosuccinimide.

One particular pyrazole transformation (Scheme 4) demonstrated by Li et al. is extremely versatile at completion times of approximately ten minutes, using a combination of *N*-bromosuccinimide, an acidic solvent (CH₃COOH, 5% HNO₃ in CH₃COOH, or trifluoroacetic acid), and microwave irradiation.¹⁰ The reaction yields exceed 67%, where the lowest-yielding pyrazoles are highly electron-poor. The electron-poor substituents include esters and halogenated phenyl rings.¹⁰ Whereas many other methods have shown very low yields for these types of compounds, this method has proven practical with unfavorable substrates, such as those that are electron-poor. The only downsides to this method are the need for a highly acidic solvent, and the necessity of using a microwave which is not highly energy efficient.



Scheme 4: Pyrazole halogenation promoted by microwave irradiation.

In summary, multiple green methods for pyrazole halogenation are known, and some have advantages that surpass the limitations of typical electrophilic aromatic substitution reactions. However, few meet the desirable criteria of inexpensive reagents and operational simplicity. The methods exhibit some adherence to the US EPA's principles of green chemistry but are limited somewhat by their use of potentially hazardous solvent systems.⁸ A method for the halogenation of pyrazoles that has wide

substrate scope, avoids toxic and expensive solvents, and can be performed at room temperature to afford high rates of conversion was still desired.

Pyrazoles and their Importance

Pyrazoles are a well-studied class of aromatic heterocycles that are relatively rare in natural products, yet have been extensively developed in pharmaceutical applications and agrochemicals. Pyrazoles are structural isomers to imidazoles, differing in the placement of N atoms in the 5-membered ring. Pyrazoles and imidazoles are often considered analogous in reactivity, and many comparisons are drawn between the two.¹¹ Pyrazole is considered a “ π -excessive” heterocycle, suggesting it is relatively electron-rich, making for a good aromatic nucleophile. In Figure 1, the pyrazole ring positions are labeled – position 1 holds the acidic proton of the heterocycle, while position 4 is the most nucleophilic carbon atom of the ring, which is supported by experimentation with electrophiles as well as electronic structure computations using methods focused on the linear combination of atomic orbital/molecular orbital basis functions.¹¹

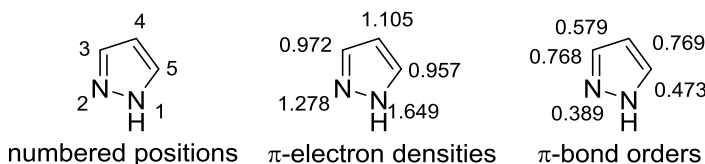


Figure 1: The structure of pyrazole, numbered ring positions with π -electron densities of atoms and π -bond orders between atoms.¹¹

Pyrazole's interesting properties as a highly nucleophilic, relatively polar heterocycle lend to its applications in various pharmaceutical avenues. Anti-inflammatory, antimicrobial, and even anticancer applications have been developed for pyrazole derivatives.¹²⁻¹⁴ Celecoxib, commercially known as Celebrex, is an anti-inflammatory and analgesic cyclooxygenase-2 inhibitor, typically prescribed for rheumatoid arthritis and osteoarthritis.¹² Pyrazofurin is a C-nucleoside antibiotic, and functions as a competitive inhibitor to proteins involved in transcription and translation in bacteria.¹⁴ Some pyrazole-based metal complexes are being explored for applications in cancer treatment; $\text{PtCl}_2(\text{pzH})_2$ is a platinum complex with similar antitumor activity to cisplatin.¹² The structures of these compounds are shown in Figure 2.

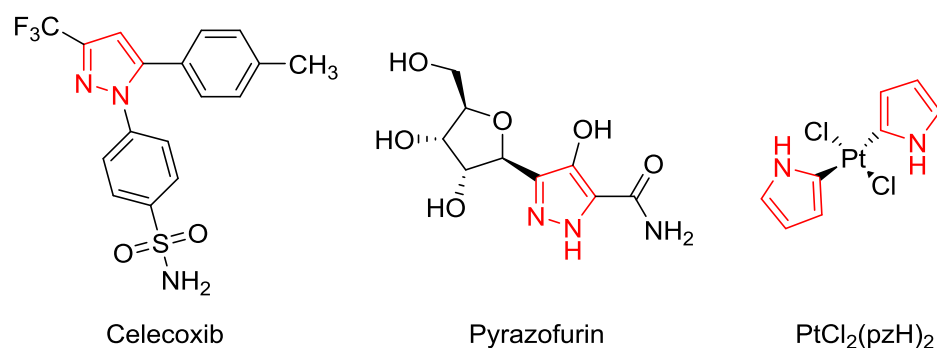


Figure 2: Examples of pyrazoles in medicine.

In addition to medicinal applications, pyrazoles have been incorporated in the structures of agrochemicals. One example is the acaricide (referring to insecticides designed to kill members of subclass *Acari*) Tebufenpyrad, commonly used to suppress populations of the two-spotted spider mite *Tetranychus urticae*. The adaptation of *T.*

urticae to Tebufenpyrad and other acaricides has prompted extensive derivatization.¹⁵ Fipronil is another pyrazole that is used as a seed coating formulation. The insecticide protects corn and sunflower from wireworms and other soil insects, but it has been hypothesized that uptake into the phloem of sunflower could be causing harm to pollinating bees. A recent study by Raveton et al. suggested that radiolabeled Fipronil may be taken up by transfer from roots into the phloem of sunflower.¹⁶ Strobilurins constitute a class of antifungal chemicals by inhibition of Complex III in the electron transport chain, stopping electron transfer from ubiquinol and cutting aerobic respiration. Although Strobilurins are not commonly derivatized with pyrazole, a 2006 paper by Li et al. demonstrates some of these derivatives and their antifungal activities. Tebufenpyrad, Fipronil, and one such Strobilurin derivative with a broad spectrum of fungal growth inhibition⁵ are shown in Figure 3.

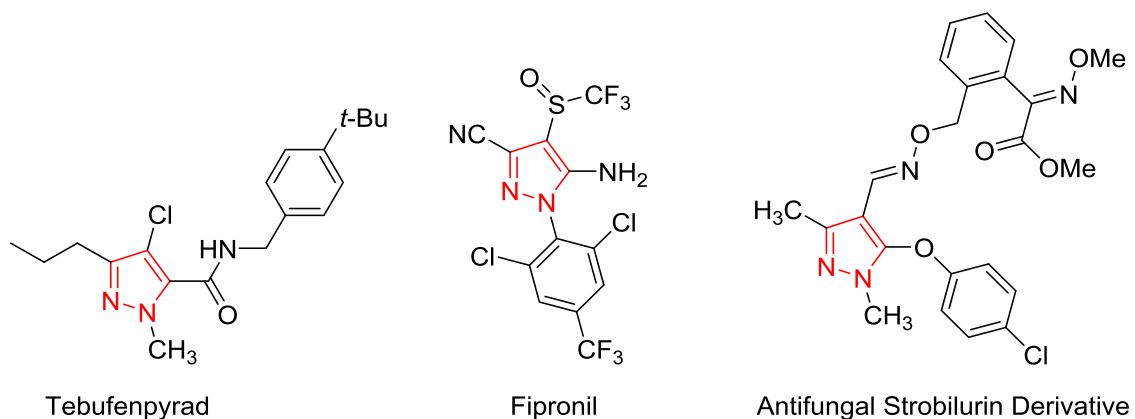


Figure 3: The structures of Tebufenpyrad, Fipronil and a Strobilurin derivative.

Pyrazoles in the MacKay Group

A recent discovery in our lab demonstrated a method to halogenate pyrazoles at the 4-position. While this work is not the first instance of pyrazole halogenation, it is unique because it uses Oxone® (a triple salt, $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) and a sodium halide salt, which are entirely water soluble, to result in the transformation. This reaction is complete in several hours, operates at room temperature, and has tolerance to functionality including allyl groups and aromatic systems. Oxone is used in stoichiometric quantities to produce electrophilic halogens *in situ* from halide anions by oxidation. Katie Olsen set up the basic methodology for this reaction, including the bulk of substrate scope, solvent experimentation, and characterization of novel products.¹⁷

The very recent applications of pyrazoles in pharmaceuticals and agrochemicals bring the importance of the heterocycle moiety into perspective. A total synthesis would then showcase the importance of a pyrazole halogenation, and demonstrate the recently-developed method in the context of a natural product synthesis. Pyrazole-containing natural products are relatively limited in number due to the rarity of N-N bond-forming reactions in biosynthetic pathways. To further limit the available options, the number of 4-substituted pyrazoles that could be synthesized using a bromopyrazole intermediate is an even smaller quantity. One option that would facilitate such a proof of concept is withasomnine.

Withasomnine (structure and derivatives in Figure 4) is a compound extracted from the flower *Withania somnifera* and is traditionally used in holistic Ayurvedic

medicine.¹⁸ Withasomnine has been clinically demonstrated to be an analgesic as well as a circulatory and central nervous system depressant.¹⁹ Withasomnine is a relatively popular target for total synthesis due to its structural simplicity and its presence as one of the very few pyrazole-containing natural products. The product was isolated by Schröter et al. in 1966, and first synthesized by Morimoto et al. in 1968.^{13, 19-28}

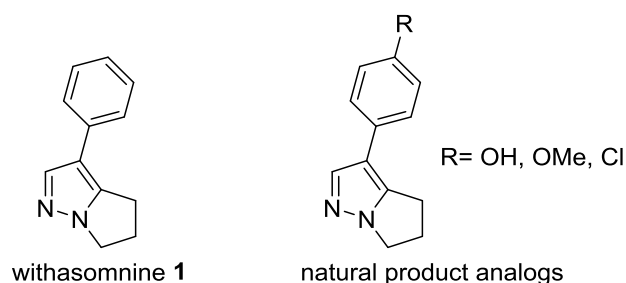


Figure 4: The structure of withasomnine and related natural product analogs.

With a novel method of pyrazole halogenation, the research question was centered around the possibility of synthesizing withasomnine from pyrazole, by employing a synthetic route specific to pyrazole chemistry. It was hypothesized that a concise synthesis could be sufficiently modular to be applied to the synthesis of biologically relevant and useful analogues. Additionally, if the reaction could be applied to a functionalized substrate in the middle of a synthesis, it may show the reaction's versatility.

Different synthetic methods have been developed for pyrazoles in recent years.¹³ Choosing to start from pyrazole narrows the field of available transformations to those that are specific to pyrazole, demonstrating the applications of these methods. Most

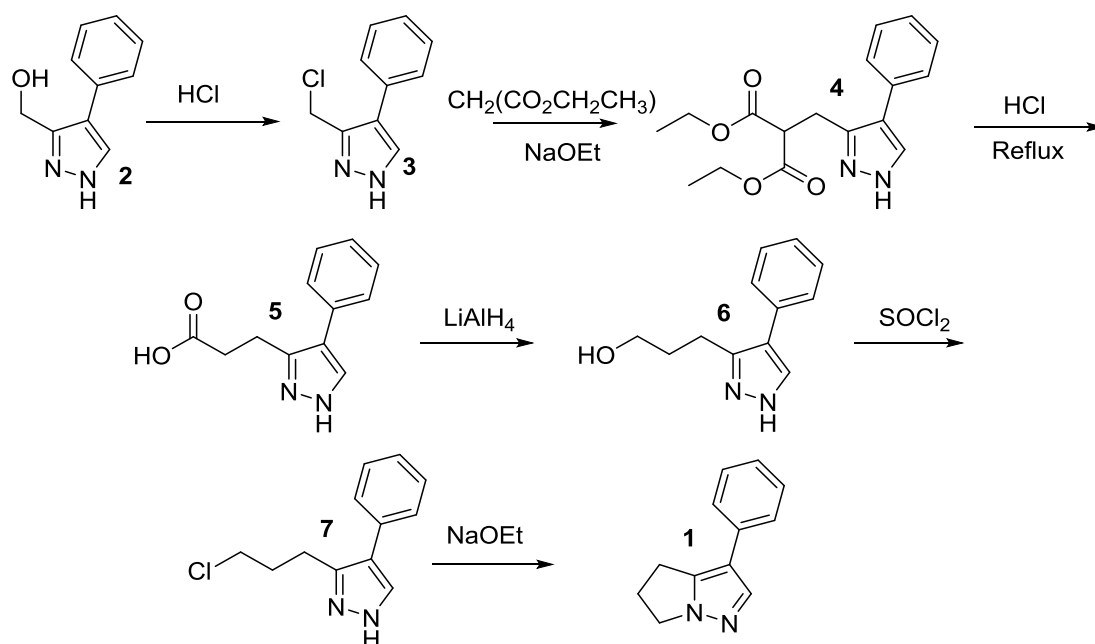
syntheses of withasomnine are concise, so in order to keep up to those standards, this approach will attempt to use no more than five transformations to produce withasomnine. A concise synthesis should be feasible by utilizing the halogenation described previously to lead into a Suzuki-Miyaura Coupling reaction, in addition to alkylating the pyrazole at position 1, and then using a radical precursor xanthate ester to generate a radical, which will cyclize onto the 5-position of the ring in an intramolecular reaction.

Previous Syntheses of Withasomnine

After withasomnine was first isolated from *withania somnifera* by Schroter et al. in 1966,¹⁸ numerous syntheses were later published. The first complete synthesis was reported by Akira Morimoto in 1968, which covered three methods to produce withasomnine from 4-phenyl-3-hydroxymethylpyrazole (Scheme 5), indole (Scheme 6), and 4-phenyl-3-pyrazolepropionic acid (Scheme 7).

Morimoto's first reported synthesis from 4-phenyl-3-hydroxymethylpyrazole (commercially available), shown in Scheme 5, follows a strategy of lengthening the existing alkyl chain by a malonic ester synthesis to **4**, acidic hydrolysis and decarboxylation to **5** to limit the alkyl chain length to three carbon atoms, and to later cyclize the fused 5-member ring. The resultant carboxylic acid is reduced to an alcohol (**6**), the alcohol is exchanged for a chloro- substituent to form **7**, and the ring closure is completed using a strong base to give withasomnine, **1**.²⁰ This synthesis was completed in six steps, and the approach here appears to be the most simplistic, consisting of S_N2

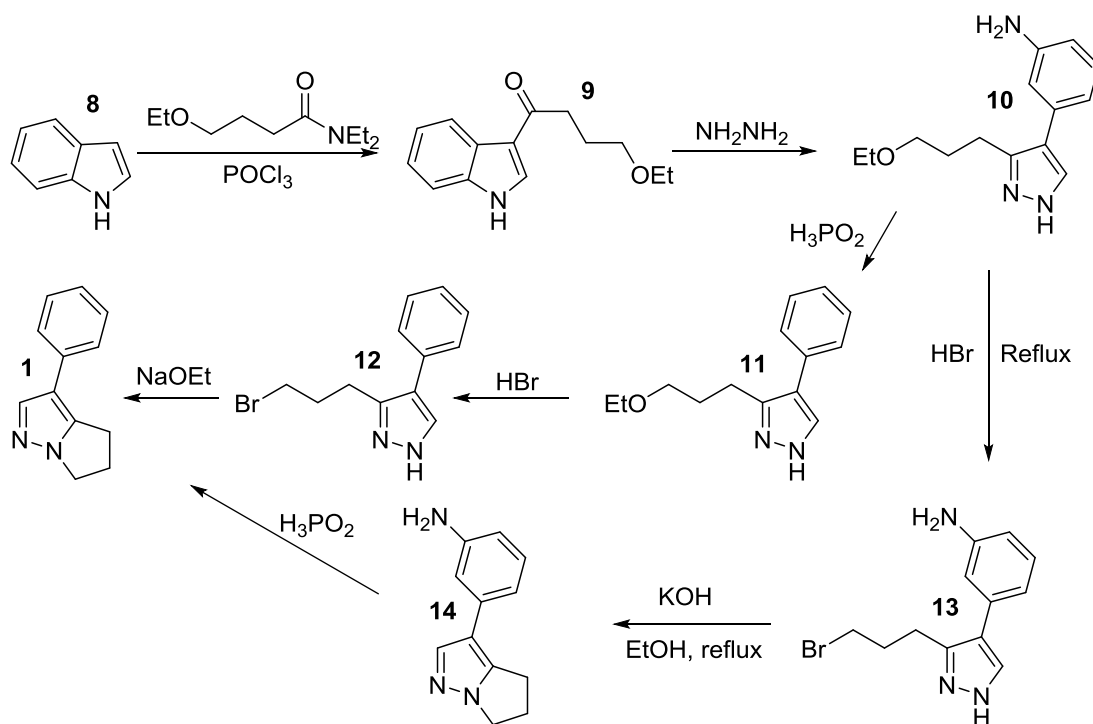
reactions and decarboxylation. From a green chemistry perspective, this synthesis is limited because it is six steps, and it uses harsh reagents like LiAlH_4 and SOCl_2 . Thionyl chloride generates toxic SO_2 as a byproduct. In both cases, the reagents are used in stoichiometric amounts. Currently, lithium is an element becoming increasingly rare, as demand for use in batteries increases around the globe. The principles of green chemistry include using renewable feedstocks, so lithium use as a reagent should be avoided where possible.



Scheme 5: Synthesis of withasomnine from 3-hydroxymethyl-4-phenylpyrazole (2).

Morimoto's second synthesis (Scheme 6) begins with indole, and acylation is effected via a Vilsmeier-Haack reaction to form **9**. A selective transformation attributed to a publication by Alberti et al. in 1957 that describes the use of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ to convert

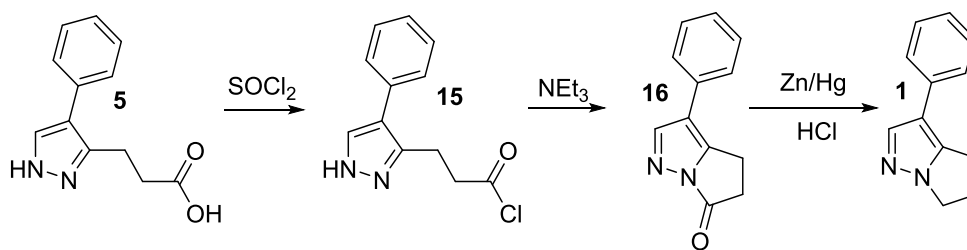
3-acylindoles to 4-(2'-aminophenyl)-pyrazoles is used to form **10**.²⁹ In one path, the amine group is removed by reductive deamination to **11**, the ether is exchanged for a bromo substituent in **12**, and base-catalyzed ring closure completes the synthesis. In the other path, the ether is exchanged first to form **13**, basic reflux closes the ring to **14**, and reductive deamination completes the sequence.²⁰ This synthesis is five steps, and is more efficient because it begins from a common heterocycle and uses the Vilsmeier-Haack reaction and ring transformation as central steps. This pathway is a slight improvement over Morimoto's first synthesis in terms of green chemistry by reducing steps, but it uses very hazardous reagents. POCl₃ is toxic and used stoichiometrically in the Vilsmeier-Haack reaction, hydrazine is highly toxic and reactive, and remaining steps use highly acidic or basic conditions for group removal and cyclization.



Scheme 6: Synthesis of withasomnine from indole, expressed in two paths.

The final synthesis (Scheme 7) outlines a second path from one of the intermediates (**5**) of the first synthesis. In this case, the formation of an acyl chloride (**15**) using thionyl chloride is performed first, followed by a lactam formation to effect ring closure using trimethylamine. Following ring closure, a Clemmensen reduction reduces **16** to form withasomnine as a minor product. Using the first synthesis to generate the starting material, this pathway consists of six steps and is marginally more complicated than the first synthesis. Formation of the acyl chloride and cyclization using triethylamine could be performed in one pot, which may simplify performing the synthesis, but the Clemmensen reduction appears to be a limiting factor in this path's total efficiency.

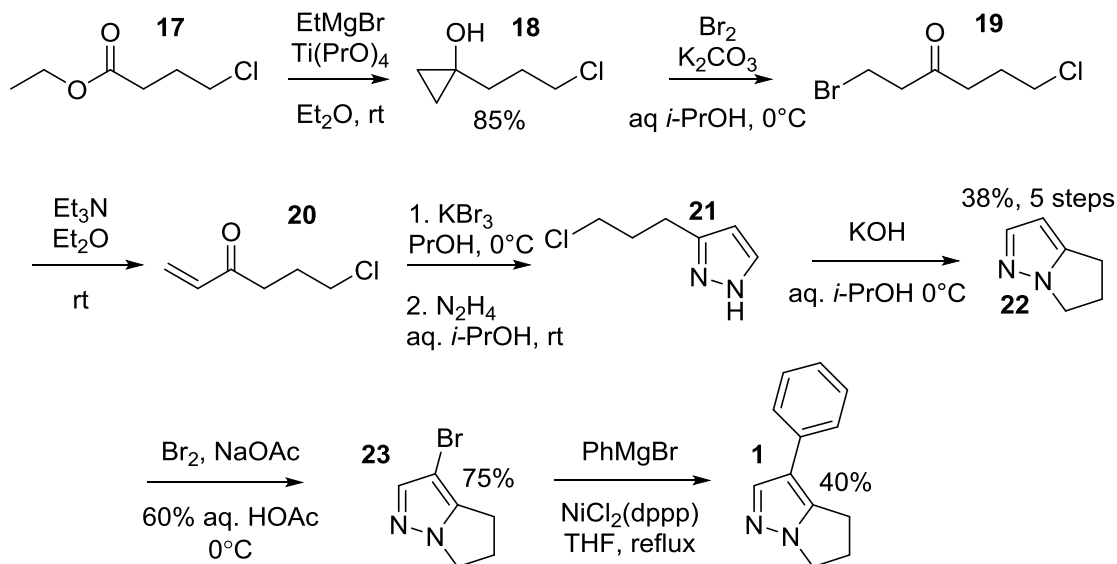
Morimoto's third pathway is one step longer than the first synthesis, and uses SOCl_2 and a Zn/Hg amalgam. As mentioned before, chlorination by SOCl_2 generates SO_2 which is toxic, and mercury is well-known to be toxic. Additionally, amalgam preparation is a hazardous process involving the dropwise addition of mercury to a heated metal. Mercury is not consumed by the reaction, so it must also be disposed of appropriately.



Scheme 7: Synthesis of withasomnine from 4-phenyl-3-pyrazolepropionic acid.

A notable follow-up to Morimoto's syntheses of withasomnine is detailed in a publication by Kulinkovich et al. in 1996 (Scheme 8). Kulinkovich's strategy consisted of building an α,β -unsaturated ketone from ethyl 4-chlorobutanoate (**17**). Similar to Morimoto's synthesis of withasomnine from indole,²⁰ this synthesis used hydrazine to construct the pyrazole ring with the chloroalkane chain pre-installed in **21**. Cyclization of the fused ring proceeds by a simple $\text{S}_{\text{N}}2$ reaction to form **22**. Interestingly, Kulinkovich uses molecular bromine to halogenate the pyrazole, similar to the method proposed here – the presence of weak base serves to scavenge the acidic HBr formed. A Grignard reagent is coupled to the halopyrazole in a nickel-catalyzed reaction.²⁵ Although this synthesis is complicated by how many steps it takes in preparing the α,β -unsaturated ketone **20**, it

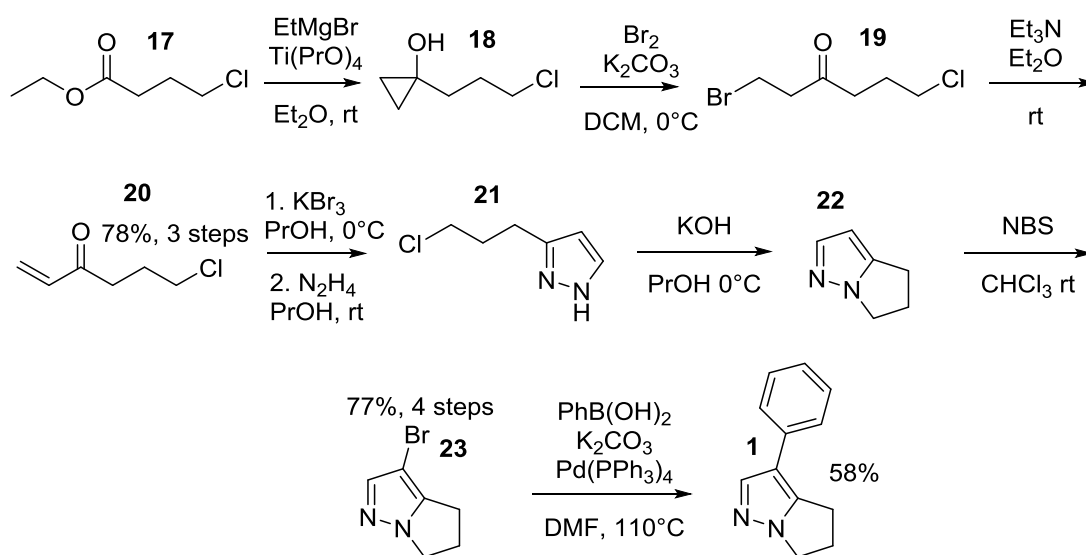
approaches pyrazole construction in a manner that avoids most complications with its reactivity. The bromination method to form **23** described here simply shows that pyrazole can be halogenated by the presence of an electrophilic molecular halogen species. Additionally, the Grignard-like coupling reaction is used to couple pyrazole to the phenyl ring.^{20, 25} The approach in Kulinkovich's strategy represents common methods for substituted pyrazole synthesis, which use hydrazine and a 1,3-dipole (in this case, the α,β -unsaturated ketone).¹³ This synthesis is limited in terms of green chemistry because it is relatively long and uses multiple hazardous reagents. The pathway includes highly reactive Grignard reagents, toxic molecular bromine, and highly toxic and reactive hydrazine all as stoichiometric reagents. C-C bond coupling is achieved in the final step using a harsh reagent, rather than a selective catalyst. Atom economy in the synthesis is poor, as very few of the reagents are incorporated into the structure of the final product.



Scheme 8: Total synthesis of withasomnine described by Kulinkovich et al.²⁵

Potáček et al. also reported a total synthesis (Scheme 9) for withasomnine that constructs the pyrazole using the Kulinkovich strategy, but with improvements on yield (35% total synthetic yield from 10%). This synthesis proceeds from **17**. A series of preparative steps allows ring construction of the pyrazole, alkylated at position 3 (**21**). Ring closure is completed in basic conditions, bromination is performed with *N*-bromosuccinimide (NBS, using a method similar to that of Zhao et al.) to form **23**, and the resultant protected pyrazole is coupled to the phenyl ring by a Suzuki-Miyaura cross-coupling.²¹ The work presented by Potáček is an improvement on the Kulinkovich strategy due to its use of an NBS bromination and a Suzuki coupling. However, the ring construction strategy still limits the method in terms of the number of steps. By performing a Suzuki coupling on an unprotected pyrazole, the phenyl ring can be

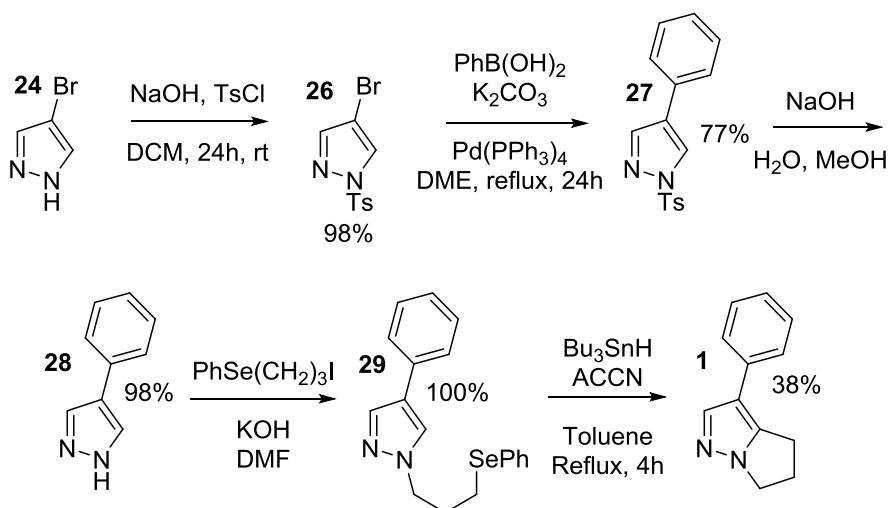
installed before the fused ring is made, making the synthesis more straightforward, and reducing the number of steps. Potáček's synthesis is an improvement over Kulinkovich's synthesis in terms of green chemistry as well. The pathway eliminates one instance of using a Grignard reagent in place of a stable and innocuous boronic acid, eliminates one instance where molecular bromine is used for NBS, and has a significant increase in synthetic yield which makes the pathway efficient. However, it still uses a Grignard reagent, molecular bromine, and hydrazine in stoichiometric amounts, and is the same number of steps as the Kulinkovich synthesis. Due to the stepwise strategy of the synthesis, atom economy remains poor.



Scheme 9: Synthesis of withasomnine from ethyl 4-chlorobutanoate described by Potáček et al.²¹

A method presented by Allin et al. in 2002 describes a more concise total synthesis using more modern synthetic advancements. The method, shown in Scheme 10,

begins with 4-bromopyrazole (**24**). The synthesis proceeds by protection with tosyl chloride to form **25**, and subsequent Suzuki-Miyaura coupling to **27**. Deprotection removes the tosyl group at position 1, allowing alkylation with a phenylselenide radical precursor to form **29**. A radical-initiated cyclization closes the ring to form withasomnine.²³ Allin's synthesis is the most green of the pathways reviewed: it is five steps, high-yielding, and avoids toxic reagents for the most part. However, the pathway uses the toxic radical initiator SnBu_3H and uses a 1-protected pyrazole for its Suzuki coupling, which is wasteful in terms of atom economy and forming derivatives.²³ Despite these issues, the Allin synthesis stands as using the most innocuous reagents of the literature pathways, with the fewest steps and highest atom economy.



Scheme 10: Synthesis of withasomnine from 4-bromopyrazole.

The previously explored syntheses take different approaches to the synthesis of withasomnine, include starting from substituted pyrazoles, construction of a 1,3-dipole to

synthesize a substituted pyrazole, and beginning from a halogenated pyrazole. The synthetic strategy presented in the current work takes advantage of several transformations that have been extensively developed in the recent past. The synthetic strategy hinges around two major transformations to install the distinct features of withasomnine: a palladium-catalyzed cross-coupling to attach a phenyl ring, and a radical cyclization to install a fused ring. Our strategy follows the logic of the Allin synthesis, but seeks to improve it in terms of atom economy by avoiding protection steps that create unnecessary waste, and utilizing an innocuous radical initiator. Herein, the methodologies behind the Suzuki coupling and radical-initiated cyclization are reviewed, with the intent of atom economy improvement and the avoidance of toxic reagents.

The Suzuki-Miyaura Cross-Coupling

Akira Suzuki won the Nobel Prize in Chemistry in 2010 along with Richard F. Heck and Ei-ichi Negishi for their combined contributions in palladium-catalyzed cross couplings. Suzuki developed carbon-carbon bond forming reactions using halides and organoboron coupling partners, and the method rapidly found applications in organic synthesis and the development of pharmaceuticals.³⁰ Through mechanistic analysis, it was determined that the catalytic cycle proceeds through an oxidative addition of the carbon-halide bond across Pd(0). Transmetalation results in exchange of the halide for the organoboron species, expelling the boronate and halide together. Finally, reductive elimination releases the newly coupled species and returns the neutral palladium catalyst.

Suzuki couplings have been applied to many different types of halopyrazoles, but there is limited precedent for unprotected $-NH$ pyrazoles.¹³ The catalytic cycle, when concerning phenylboronic acid and halopyrazole, is shown in Figure 5.

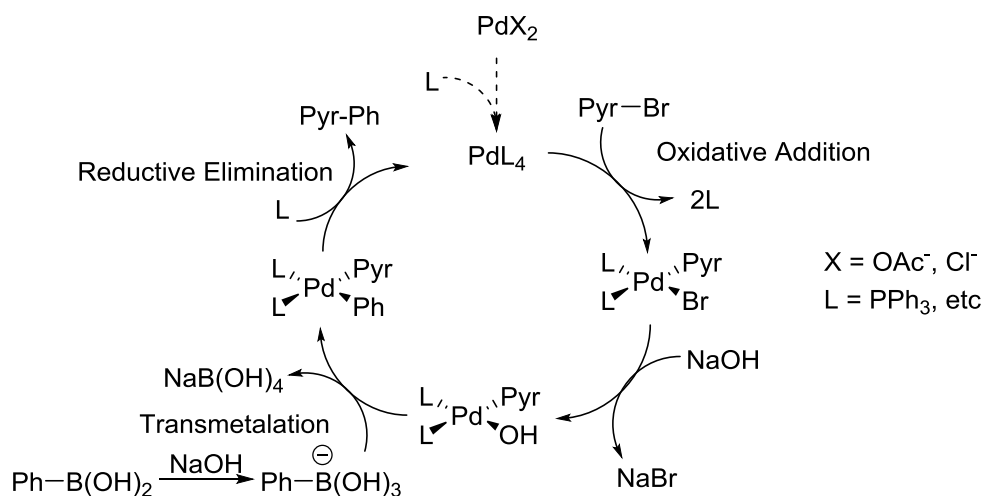


Figure 5: The catalytic cycle of the Suzuki-Miyaura cross coupling.

Considering that oxidative addition is the first step, and often treated as the step that is rate-limiting in the catalytic cycle, the success of the reaction is most likely dependent on electronic effects from the ligands coordinated to the palladium center. Success of the reaction is limited by the attraction of deprotonated pyrazole to palladium. This hypothesis is confirmed in a publication by Buchwald et al. The inhibitory effect of several unprotected N -rich heterocycles is explored, and experiments show that 4-substituted pyrazoles administered as an additive tend to be highly inhibiting. This inhibition is caused by a dimerization that essentially suspends the catalyst, making it ineffective.³¹ If the pyrazole is too nucleophilic relative to the metal center, the

unprotected lone pair on nitrogen will complex to palladium, causing dimerization in which pyrazole acts as a bridging ligand between two palladium atoms. Therefore, the addition of highly electron-donating ligands will be necessary to prevent this competing interaction.

Beller et al. discovered new catalyst systems for deactivated aryl chlorides with arylboronic acids,³² and their work has impacted a recent publication, by Tan et al. exploring favorable conditions to cross-coupling reactions for unprotected haloimidazoles. In addition to imidazoles, pyrazoles were explored. A ligand screen showed that favorable conditions for these compounds required highly electron-rich phosphines. Indeed, the most successful ligands were A-^{ta}Phos and CataCXium® A.³³ The structures of these compounds, lending to their high electron-donating character, are shown in Figure 6.

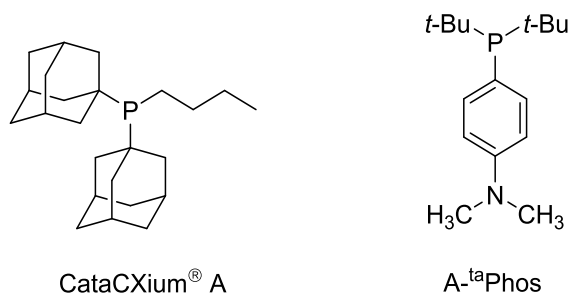


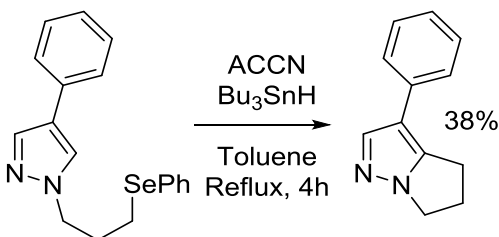
Figure 6: The CataCXium® A and A-^{ta}Phos ligands.

With the understanding from the mechanistic investigation by Buchwald et al.³¹ and the success of this ligand as demonstrated by Tan et al.³³, it can be hypothesized that the bulky and electron-rich ligand serves a twofold purpose – it allows the palladium

center to outperform pyrazole as a nucleophile, preventing complexation, and it creates steric hindrance that would make the inhibitory dimer less likely.

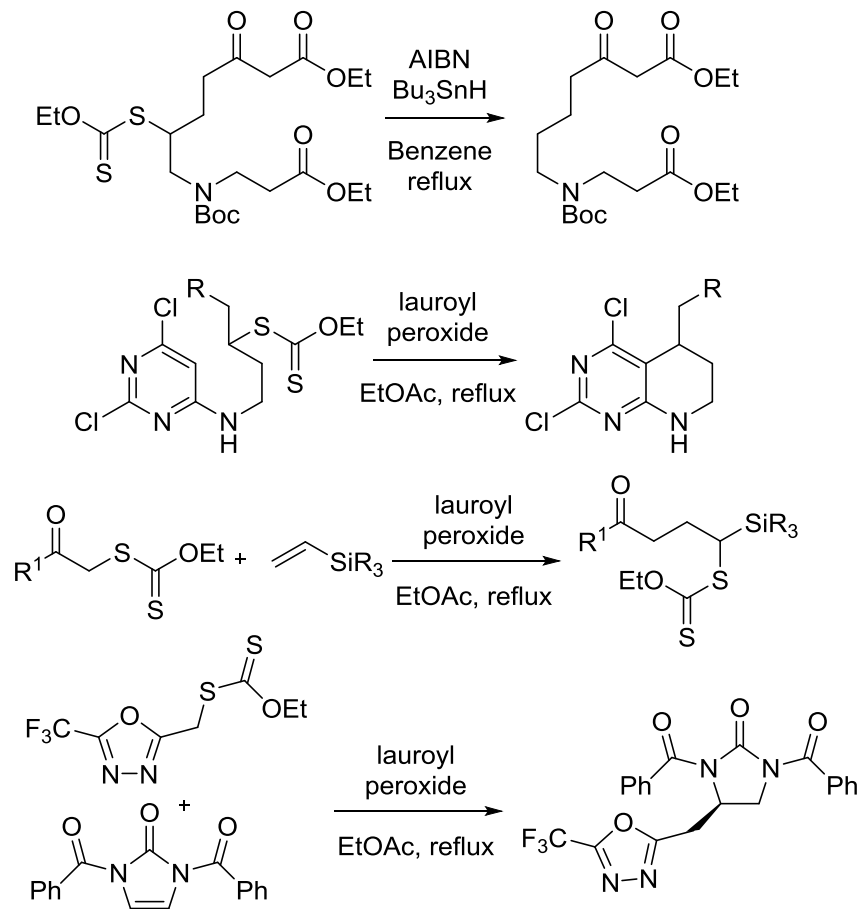
The Radical-Initiated 5-*exo* trig Cyclization

The radical cyclization proposed in our work has precedent in the synthesis of withasomnine published by Allin et al. That synthesis used 1,1'-Azobis(cyclohexanecarbonitrile), or ACCN, as a radical initiator, in order to cause hydrogen abstraction of HSnBu_3 .²³ Conditions for this transformation are shown in Scheme 11.



Scheme 11: A radical initiated cyclization demonstrated by Allin et al.²³

Following hydrogen abstraction, tributyltin radical would interact with the phenylselenide group at the end of the alkyl chain, generating a primary radical. Another common radical precursor in organic synthesis is the xanthate ester, which is likewise fragmented by interacting with the tributyltin radical. Publications in recent years by Zard et al. (Scheme 12) have shown various radical transformations using xanthate precursors with a variety of radical initiators.³⁴⁻³⁷



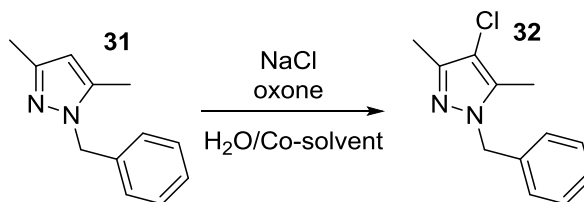
Scheme 12: Several examples of xanthates being used as radical precursors in organic synthesis, in methods published by Zard et al.³⁴⁻³⁷

Thus, the use of a xanthate as an alkyl radical precursor is advantageous due to the flexibility of appropriate radical initiators and solvent systems. This flexibility in initiators presents an opportunity to use greener alternatives than toxic SnBu_3H , and the xanthate group is an improvement on atom economy due to its relatively small size compared to the phenylselenide group.

In the next section, a new method for the halogenation of pyrazoles will be explored. The new method is an intended improvement upon current methods in adherence to the principles of green chemistry by using benign solvent systems, innocuous reagents, and avoiding energy input entirely. This method will generate electrophilic halogens *in situ* in order to make the handling of these carcinogenic species negligible. Explored factors include the impact of co-solvent on reaction conversion, and the scope of substrates for which the method is effective. With this method established, a new total synthesis of the natural product withasomnine is explored. This approach uses the least number of steps feasible in a straightforward total synthesis, enlisting the methods that have just been reviewed.

RESULTS AND DISCUSSION

Solvent Studies and Reaction Tolerance



Scheme 13: Reaction model used for co-solvent experiments.

Solvent experiments were performed in order to determine if a co-solvent was appropriate for this reaction, and which co-solvent would work best. For this study, a substrate was used that would be relatively nonpolar as to make any aqueous reactions heterogeneous. In experiments where no co-solvent was used, a distinct layer of 1-benzyl-3,5-dimethylpyrazole was visible that only dissolved with vigorous mixing.

Table 1: Co-solvent studies evaluated by conversion with ¹H NMR.

Entry	Co-solvent	Time (h)	Conversion (%)
1	None	24	100
2	None	1	80
3	CH ₃ CN	24	77
4	EtOAc	24	55

Solvent studies performed with **31** showed that the reaction was most effective without a co-solvent. In all reactions, the same total volume was used. Where co-solvent

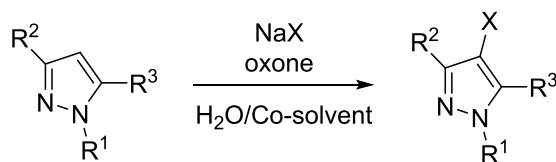
was involved, the water and co-solvent were present in a 7:3 volumetric ratio. The use of water as a reaction medium allows for the partial dissolution of oxone, but the substrate remains in a separate phase. Regardless of the use of co-solvent, the reaction should occur at the interface of these two layers. By diluting the interface with an organic solvent and limiting the total amount of water to dissolve Oxone, the reaction concentration can be considered to be diluted. Therefore, it seems reasonable to expect that omitting nonpolar solvent would increase yield. This result contrasted from the original hypothesis which suggested that a nonpolar co-solvent could mediate the heterogeneous reaction. Interestingly, however, the polar co-solvent appears only to limit reaction efficacy. This finding disagrees with previous work, which was focused on determining reaction efficacy based on yield, rather than conversion.

Table 2: Co-solvent studies evaluated by percent yield, performed by K. Olsen.¹⁷

Entry	Co-solvent	Time (h)	Yield (%)	Conversion (%)
1	None	1	N/A	65
2	CH ₃ CN	2.5	62	81
3	Acetone	24	52	83
4	THF	24	45	70
5	CH ₂ Cl ₂	24	18	48
6	Toluene	24	24	42
7	EtOAc	24	70	75

The studies described in Table 1 contrast with that of Table 2, which were performed by K. Olsen '14. Originally, Olsen evaluated the effectiveness of the co-

solvent based on product yield.¹⁷ In an effort to control reaction variables, the recent experiments were all conducted over 24 h, were carried out in the same type of flask using oven-dried glassware, and were carried out on the same scale. Furthermore, the data were reported using percent conversion by ¹H NMR as a basis of comparison to remove the effect of product loss or any other source of variation in purification. Olsen's work suggested that EtOAc was the more effective solvent, and water was considered because it had limited yield. The recent experiments demonstrated that water was more effective, even on a limited amount of time. However, the nonpolar solvents were not explored, as NMR conversions between the two studies generally agreed, given some variability, and Olsen's work did not suggest that the co-solvents dichloromethane, toluene, or tetrahydrofuran would be highly effective.¹⁷



Scheme 14: Substituent placement in substrate scope experiments.

Table 3: Substrate scope of the electrophilic halogenation of pyrazoles using NaX and Oxone.

Entry	X	R ¹	R ²	R ³	Co-solvent	Yield (%)	Conversion (%)
33a	Cl	-CH ₂ CH ₃	-CH ₃	-CH ₃	None	50	100
33b	Br	-CH ₂ CH ₃	-CH ₃	-CH ₃	None	11	95
34a	Cl	-CH ₂ CH=CH ₂	-CH ₃	-CH ₃	None	36	78
34b	Br	-CH ₂ CH=CH ₂	-CH ₃	-CH ₃	None	17	51
35a	Cl	-H	-H	-Ph	EtOAc	71	90
35b	Br	-H	-H	-Ph	EtOAc	73	85
36	Br	-H	-H	-CH ₂ Ph	None	86	100
32	Cl	-CH ₃	-CH ₃	-CH ₂ Ph	None	57	100
24	Br	-H	-H	-H	None	80	100

Alkyl substituted substrates generally had high rates of conversion (**33a**, **33b**, **32**, **36**). The high conversion may be attributed to the substituents increasing the overall electron density of the ring, which facilitates the electrophilic aromatic substitution reaction. However, yield among the ethylpyrazoles is low, most likely due to volatility preventing purification. Product isolation using column chromatography requires concentrating the product *in vacuo* to remove solvents. The phenylpyrazoles (Entries **35a** and **36b**) are apparently significantly less volatile than the ethylpyrazoles, improving yield but having similar product conversion. One of the more problematic classes of substrates were the allyl pyrazoles (Entries **34a** and **34b**) which should be limited in conversion due to the competitive reactivity between position 4 of the pyrazole and the

alkene. Low conversions among these reactions confirm this hypothesis, and secondary products were difficult to remove from the product mixture, which further lowered yield. Competition between aromatic substitution and alkenyl substitution is a limitation of the substrate, as would be expected.

Substrates with aromatic substitution (Entries **35a**, **35b**, **36**, **32**) regardless of conjugation did not show byproducts that were a result of competition, and yields were generally high, in the range of 57% and above. This could be attributed to a phenyl ring having more aromatic character than a pyrazole, resulting in a higher activation energy to halogenate. When the phenyl ring is conjugated with the pyrazole ring (Entries **36**, **32**), there is also no type of distribution of nucleophilicity into the conjugated ring, as suggested by the high conversions of these substrates into the product.

It should be worthwhile to more thoroughly examine and repeat some of the substrate experiments in order to get a more thorough perspective of substrate scope, and exactly what compounds are tolerable to what degree. Modifications may include improving workup or eliminating co-solvent when it was originally included, in order to improve yield. Additionally, it may be important to isolate variables like reaction time in order to compare effectiveness on a level field.

Total Synthesis of Withasomnine

The main goal of the synthesis was to demonstrate the use of a pyrazole halogenation in a total synthesis. The specific goal of the total synthesis of withasomnine was to couple a phenyl ring to position 4 of pyrazole and to attach a 5-member fused ring connected at positions 1 and 5. Attaching the phenyl group may be effected by the NaX/Oxone method (X= Br) followed by Suzuki-Miyaura cross-coupling of phenylboronic acid (W= B(OH)₂). Attaching the fused ring system would be completed by alkylation (Y= Cl, Z= OH), formation of a xanthate ester radical precursor (Z= OCSSCH₃), and radical-initiated 5-*exo*-trig cyclization.

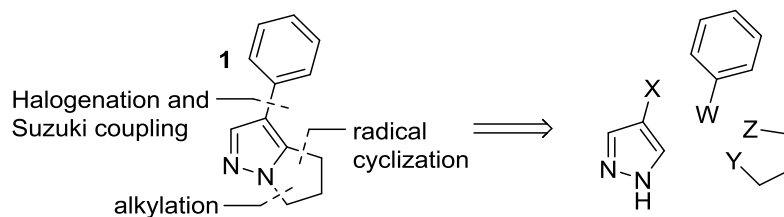


Figure 7: General retrosynthetic strategy of the total synthesis of withasomnine from pyrazole.

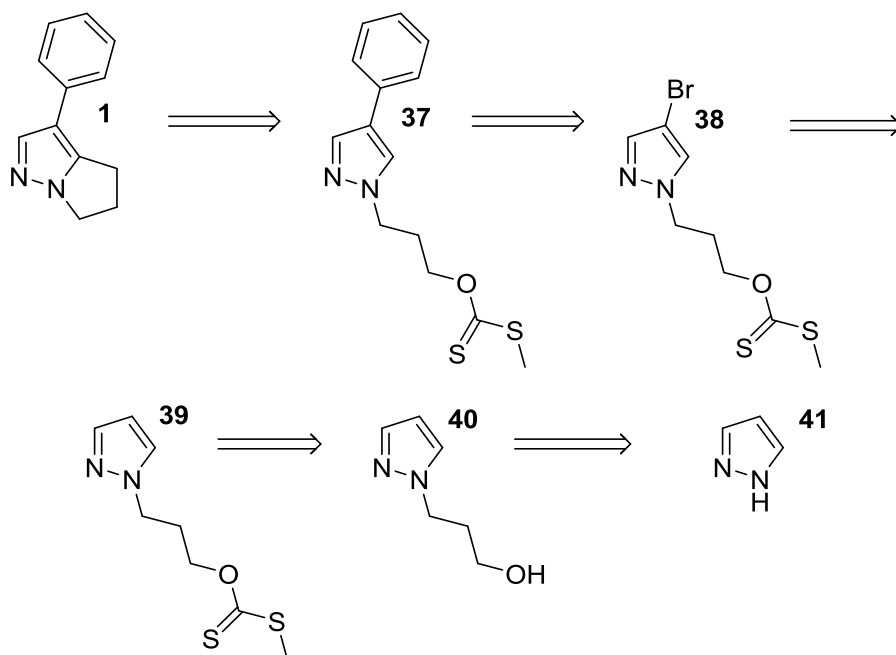
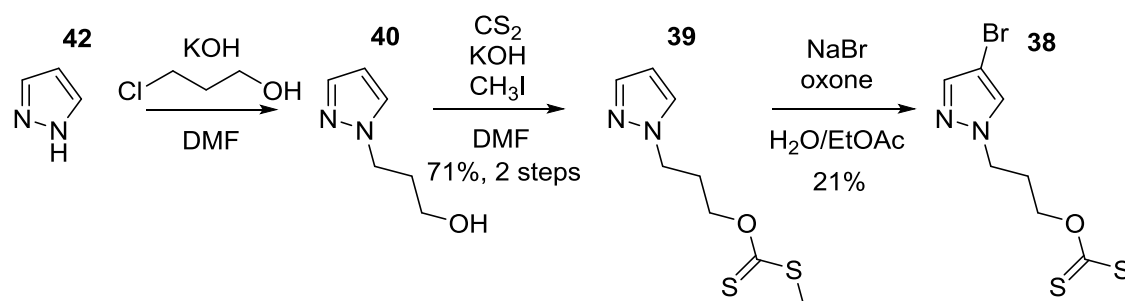


Figure 8: The first retrosynthetic pathway attempted for the total synthesis of withasomnine from pyrazole.

The initial plan was to set up the reaction sequence such that alkylation and xanthate formation would precede the bromination and Suzuki steps, therefore showing the utility of the bromination reaction. After brominating, the Suzuki reaction would install the phenyl ring, with the added benefit of using the alkyl chain as a pseudo protecting group to prevent N-coordination of the pyrazole to the Pd catalyst. The radical cyclization would benefit from the resulting conjugated phenyl ring in stabilizing the radical intermediate, improving yield.

This approach, presented in

Scheme 15 was eventually abandoned because of low yields in the halogenation reaction (21%), possibly due to competition from the xanthate ester acting as nucleophile. Additionally, xanthates are understood to be particularly sensitive to acidic aqueous conditions, in which the presented halogenation method operates. Either effect may have contributed to the low yield of the desired product 38. This complication, which was not anticipated, prevented using the bromination reaction on a functionalized substrate. While this was a simple change in terms of reaction sequence, it was a significant setback in terms of the original hypothesis of this study, which proposed that the bromination could be showcased as an intermediate step in the synthesis of withasomnine. Regardless of the setback, this problem helped refine the synthesis into a more successful and efficient pathway.



Scheme 15: Progress on the first attempt at the synthesis of withasomnine.

In light of the unexpected problems with halogenation in the presence of a xanthate ester, the second approach to withasomnine was planned such that halogenation would precede functionalization. The remaining transformations: alkylation and xanthate

ester formation to **38**, Suzuki-Miyaura coupling to **37**, and radical cyclization, to **1** would follow.

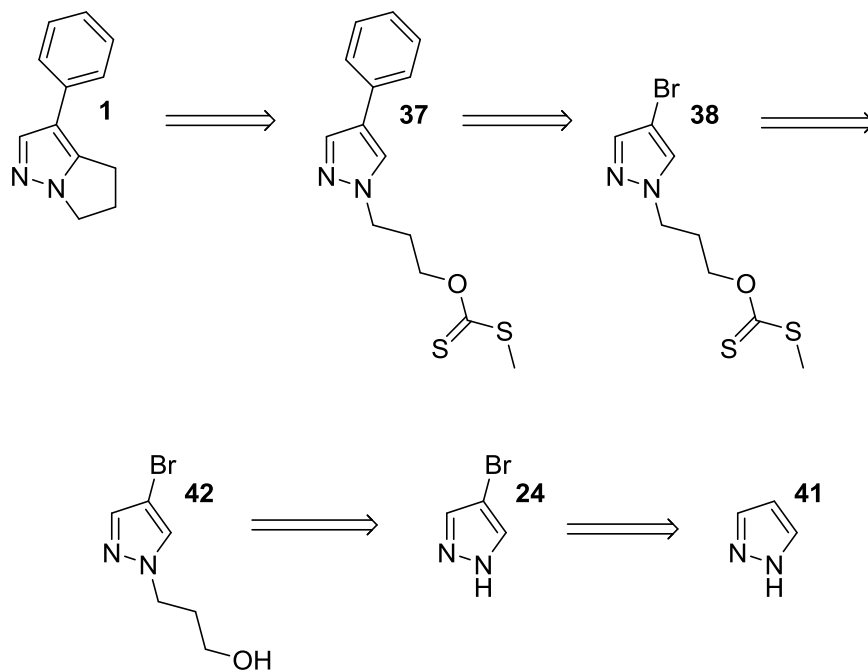
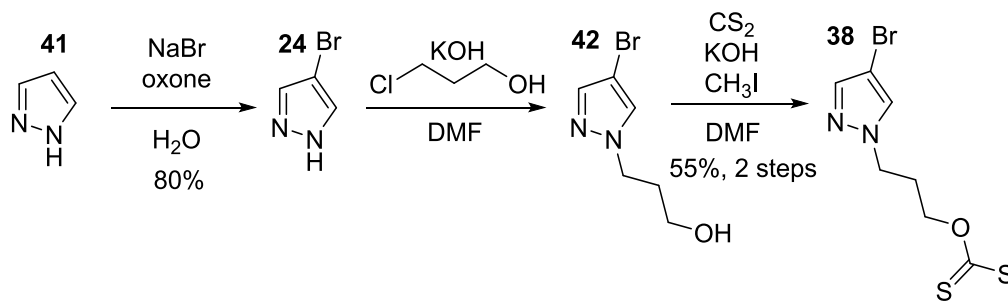


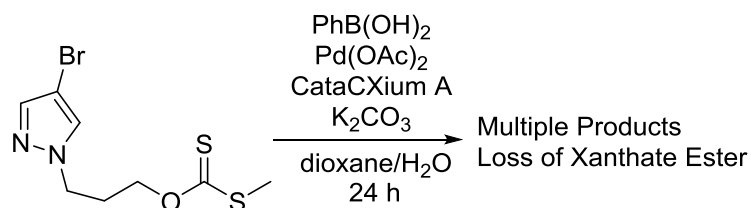
Figure 9: The second retrosynthetic pathway proposed for the synthesis of withasomnine.

Formation of xanthate ester **38** was successful on the halogenated pyrazole **24** in 55% yield (Scheme 16). The product **42** was not isolated due to it degrading on silica.



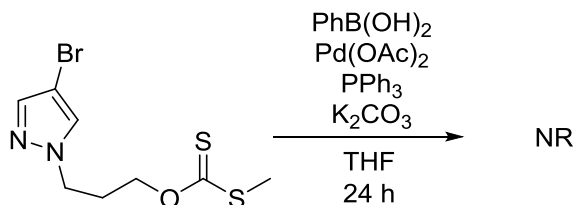
Scheme 16: Progress on the second route to withasomnine synthesis.

Pursuit of the coupling was complicated and unprecedented in the literature. The first attempt at this transformation used a catalyst system that was similar to what was shown in the introduction (Beller et al.)³² for an unprotected NH pyrazole (Scheme 17).



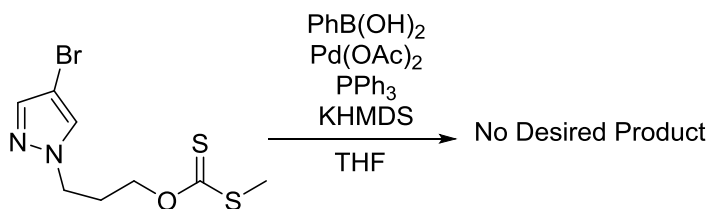
Scheme 17: Reaction scheme and conditions for the Suzuki coupling of the xanthate ester product, in the presence of aqueous basic conditions.

The basic aqueous conditions of this reaction appeared to cause a hydrolysis of the xanthate ester, resulting in a mix of products, which did not appear to contain the desired product as evidenced by ¹H NMR. The next attempt (Scheme 18) would eliminate water from the process, to keep the xanthate ester group intact.



Scheme 18: Reaction conditions for the Suzuki coupling of the xanthate ester in dry conditions with triphenylphosphine as the catalyst ligand.

The attempt (Scheme 19) also did not appear to form the product, presumably due to the insolubility of the base, resulting in the omission from the catalytic cycle. Here, triphenylphosphine was used as ligand, instead of CataCXium A, because previously reported catalyst systems for the protected coupling typically included the cheaper and simpler triphenylphosphine ligand.²² Although this was a multi-variable change in steps forward, the steric bulk of the alkyl chain xanthate group made it seem as though the bulky adamantyl groups would not be needed from the perspective of steric hindrance.



Scheme 19: Reaction conditions for the Suzuki coupling of the xanthate ester in dry conditions with triphenylphosphine as the catalyst ligand, and the organic base HMDS.

The problems with aqueous bases were avoided by using potassium hexamethyldisilazide (Scheme 28), which was soluble in THF. However, this reaction did

not appear to produce the desired product. The reaction returned primarily starting material and byproducts, which were not identified due to time constraints. This confirmed that an aqueous base is required for the Suzuki catalytic mechanism.

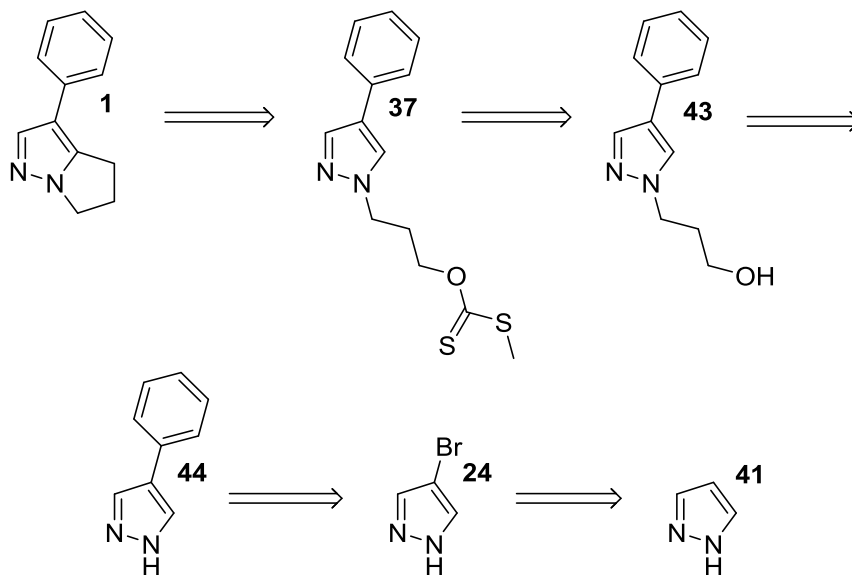
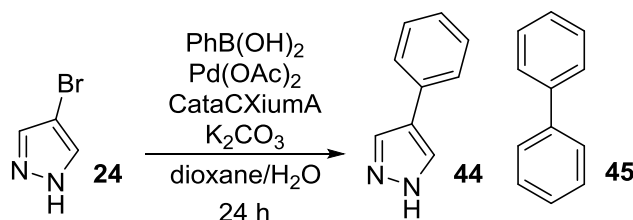


Figure 10: The third and working retrosynthetic pathway for the total synthesis of withasomnine.

The previous routes demonstrated two major obstacles. First, the xanthate ester was not highly compatible with the halogenation method presented in this work. Second, the xanthate ester was sensitive to aqueous basic conditions, which were necessary for the Suzuki coupling. The final route attempted for withasomnine synthesis was planned in the order of halogenation, coupling, alkylation, xanthate ester formation, and cyclization. The intent here is to avoid the complications of the xanthate ester such that the step following xanthate ester formation would be the cyclization itself. Having the xanthate and alkyl chain installed pre-Suzuki was disadvantageous - alkylation increases electron

density which is unfavorable to the Suzuki catalytic cycle's oxidative addition step, the xanthate ester could complex to palladium, and the aqueous basic conditions could lead to xanthate hydrolysis. The original strategy of using the conjugated phenyl ring to stabilize a radical cyclization could be preserved, because installation of the phenyl ring would still precede the cyclization. The difficulty in this approach appeared to be performing the Suzuki coupling on an unprotected pyrazole. The catalyst system determined by Beller et al. and developed by Tan et al.³³ described the necessary transformation in the presence of the unprotected halopyrazole.

The halogenation reaction was effective at producing **24** in 80% yield. Effecting C-C bond formation in the following step was a formidable task. Suzuki-Miyaura cross-coupling of unprotected haloimidazoles and halopyrazoles is a problematic reaction, and most syntheses (including Allin et al., who uses a similar synthetic strategy²³) use an *N*-protection in order to use simpler catalyst systems.^{26, 33, 38-42} A method by Tan et al.³³ overcomes the problems of unprotected azole couplings identified by Buchwald et al.³¹ and prevents the need of a protecting group at position 1 of the pyrazole, making a significant improvement in terms of atom economy over the Allin synthesis.²³



Scheme 20: Suzuki-Miyaura cross-coupling with phenylboronic acid on 4-bromopyrazole.

The coupling of **24** with phenylboronic acid was designed based on an identical transformation performed by Tan et al.³³ However, there were some discrepancies between what was presented in the body of the paper concerning catalyst loading, and the actual catalyst loading reported in the experimental section. This caused some difficulty in reproducing the results of Tan's work. With some modifications, increased catalyst load was able to drive the reaction forward to the formation of **44**. In all attempts, a byproduct, biphenyl (**45**), was identified by its GC-MS molecular ion and distinct fragmentation pattern from the electron-ionization ion source.

Table 4: Effects of catalyst loading on Suzuki-Miyaura cross-coupling of phenylboronic acid on 4-bromopyrazole.

Entry	Pd(OAc) ₂ (mol %)	CataCXium® A (mol%)	PhB(OH) ₂ (equiv.)	Products	Yield (%)	Time (h)
1 ^a	3.75	0.9	1.25	24, 45	N/A	24
2 ^a	2.5	6	1.25	24, 45	N/A	24
3 ^a	10	20	1.25	24, 44, 45	N/A	24
4 ^b	10	20	1.25	44, 45	12	24
5 ^b	5	10	1.25	24, 42, 45	51	72
6 ^b	2.5	5	1.25	24, 44, 45	42	24
7 ^a	2.5	5	1.75	24, 44, 45	N/A	24

^aProducts worked up by filtration through celite. ^bProducts worked up by aqueous extraction.

Entry 1 represents the results of multiple attempts to form the desired product **44** explicitly using the experimental details from Tan et al.³³ No desired product was formed,

but starting material was retrieved along with biphenyl, the homo-coupling byproduct. In Entry 2, the catalyst loading was varied to increase the amount of ligand relative to metal, and likewise returned no product. Catalyst loading was increased drastically in Entry 3 which yielded **44**, but the product was not isolated. To improve likelihood of isolating product, reaction scale was increased threefold in entry 4. The reaction pressure vessel size was the same, which increased pressure and diminished the amount of **24** present such that it was not detected by GC-MS. Another difference between entries 3 and 4 was that aqueous extraction was used in entry 4 instead of filtration through celite, assisting in identification of the product by tlc. In entries 5 and 6, catalyst loading was decreased by half in each step to reduce the use of an expensive ligand. Entries 5 and 6 produced the product in high conversion, however in 6 there was a considerable amount of **24** remaining as detected by GC-MS. In Entry 7, it was expected that an increased amount of the boronic acid reactant would result in complete consumption of **24**. However, only an increase in **45** was indicated by the results, suggesting the importance of the catalyst to the coupling conversion rate.

Entry 5 would be used as a model for further experiments; increasing reaction scale allowed isolation of the product in 51% yield, the highest thus far for the reaction. This catalyst loading would be used for the synthesis because it returned high

conversions without using a large amount of ligand. Yield appeared to be limited due to product volatility, as Entry 4 appeared to go to 100% conversion but had a low yield.

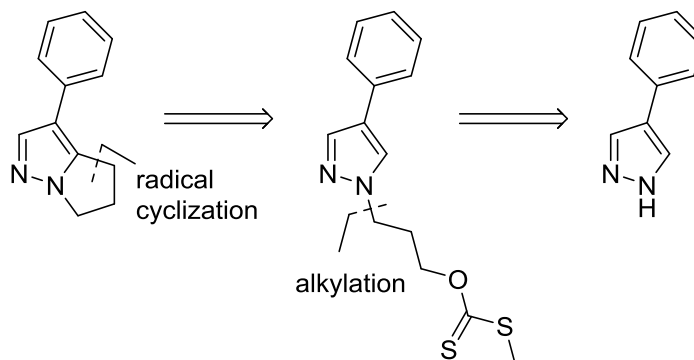
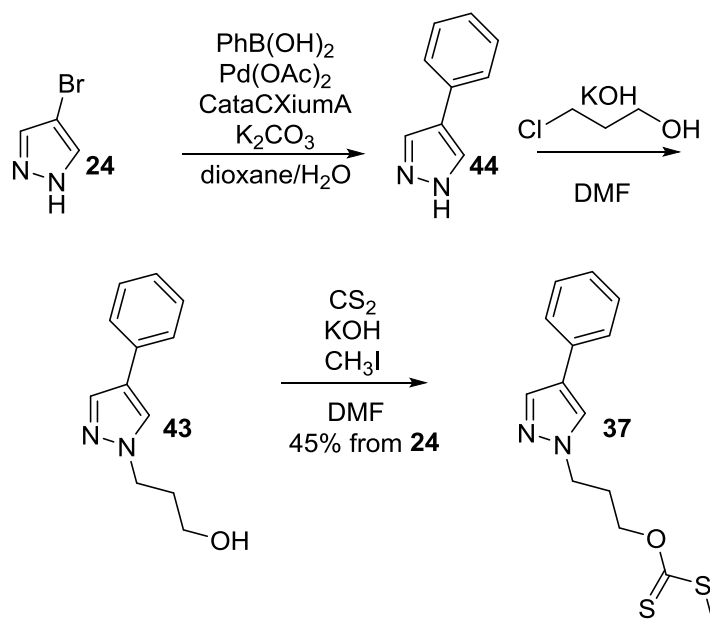


Figure 11: Retrosynthetic strategy for the remaining reactions of synthetic path 3.

With one challenging transformation completed, the goal of the remainder of the work of this total synthesis was to prepare the alkyl radical precursor, and initiate a cyclization to form the fused ring system. Considering that 4-phenylpyrazole is volatile, and the byproduct biphenyl should be inert under the alkylation and xanthate formation conditions, the crude product was submitted without purification directly to the alkylation reaction, avoiding loss by evaporation of **44**. Scheme 21 outlines the results of this synthesis.

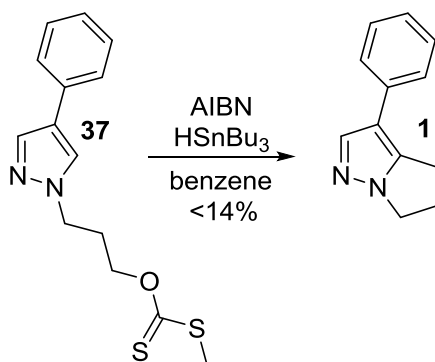


Scheme 21: A crude three-step sequence to form the xanthate ester from 4-bromopyrazole.

This crude multi-step sequence proved to be effective with an excess of reagents (8 equivalents KOH, 4 equivalents 3-chloro-1-propanol, 4 equivalents carbon disulfide, 10 equivalents methyl iodide) and the resulting xanthate ester was not volatile. The only complications with this strategy were that the high mass of crude product mixture contained relatively small amounts of desired product, so flash columns had to be disproportionately large in order to handle the sample loading. While this strategy limited waste by preventing the loss of the product to evaporation, it did not limit any waste in the amount of solvent required for purification, and excess use of stoichiometric reagents. The crude synthesis was only a minor step forward for green chemistry in this total synthesis. The Suzuki coupling is a relatively green reaction due to its use of catalysis,

and phenylboronic acid as a stable and innocuous reagent. The alkylation and xanthate esterification reactions are less green. The alkylation uses 3-chloro-1-propanol which is reasonably toxic, and the xanthate esterification uses carbon disulfide and methyl iodide, which are both toxic. The xanthate esterification is therefore a limitation in carrying out this synthesis. Supercritical fluid extraction would purify **44** with limited product loss, allowing for the pure product to be submitted to the reaction, reducing the need for excess reagents. Safe removal methods for carbon disulfide may clean up reaction waste and make it easier to use a smaller column, limiting solvent waste. These methods were not explored due to time constraints.

With the pure xanthate **37**, the first attempt at radical cyclization was made. The radical cyclization was designed to use 1,1-azobisisobutyronitrile with tributyltin hydride in benzene, which are common conditions for radical transformations and well documented for xanthate radical reactions.³⁴⁻³⁷ Yield was minimal, but the natural product identified at the start of this project was finally made. Formation of the product on the first attempt was encouraging, because precedent in the literature reports low yields for this type of cyclization. The success of this reaction laid the groundwork for improvements to make the reaction have higher conversion rates and potentially use more green reagents. Flash chromatography was complicated by the presence of streaking tributyltin hydride, so preparatory TLC was used to isolate the product with minor impurities. The next attempt at this transformation sought to raise the total energy of the reaction by using a less volatile solvent than benzene, in order to facilitate the 5-*exo*-trig cyclization rate limiting step.



Scheme 22: Radical cyclization of the xanthate ester using AIBN, SnBu_3H , in benzene to form withasomnine in <14% yield.

The proposed mechanism for this transformation involves using tributyltin hydride as a radical initiator to cause the xanthate ester to fragment off and leave behind a primary radical. The radical, which is highly reactive, should cyclize with the nearby carbon atom at the 5-position. Fragmentation is highly unfavorable because it generates a primary radical, but cyclization is also highly unfavorable because it breaks the pyrazole's aromaticity.

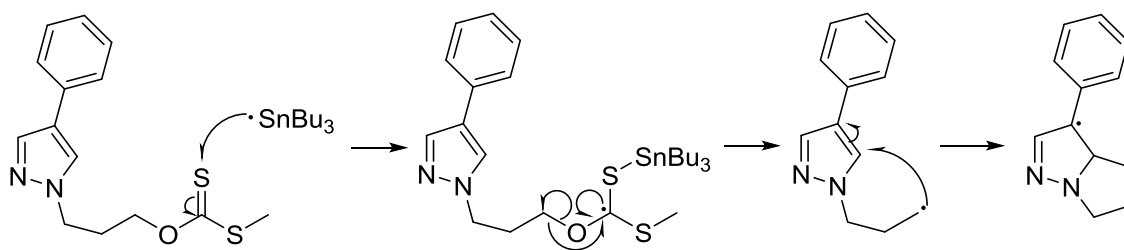
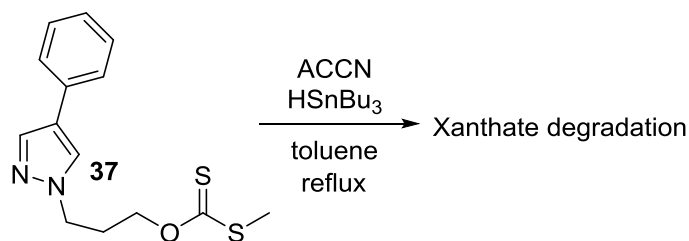


Figure 12: Proposed mechanism for the 5-*exo*-trig radical-initiated cyclization of **37** to **1**.

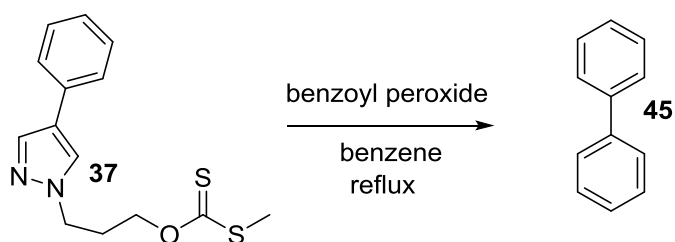
Regardless of which of these steps is rate-determining, both formation of a primary radical and dearomatization of pyrazole are very high energy interactions. Therefore, it was hypothesized that performing the reaction at a higher temperature would effect the 5-exo-trig cyclization in higher conversion, or assist in initiating the fragment that leads to the cyclization.

The reaction in toluene at reflux temperature with the more heat stable 1,1-azobiscyclohexanecarbonitrile (ACCN) as a radical initiator was also performed (Scheme 23). The reaction appeared to result in degradation of the xanthate ester, and no formation of product. It is likely that the xanthate ester degraded while **37** was in toluene at reflux temperature, before the radical initiator mixture is slowly added to the reaction. This proposal is corroborated by laboratory observations in which xanthates left on the bench for long periods of time tended to show more degradation than those stored. The following attempt explored using a peroxide in place of the toxic ACCN/ HSnBu_3 combination, following precedent of Zard et al.^{34, 36-37}



Scheme 23: Attempted radical cyclization using ACCN, SnBu_3H , in toluene to form withasomnine, resulting in degradation of starting material.

Use of a peroxide should generate radicals similar to AIBN or ACCN, but be stable enough on its own to interact with the xanthate and fragment the radical. Benzoyl peroxide was chosen as an initiator for its stability and reduced atom economy as well as the fact that it was relatively inexpensive. The resulting byproduct should be benzoic acid, which should be easily removable. However, when this was attempted with benzoyl peroxide as the initiator (Scheme 24), **45** formed possibly as a result of phenyl radical fragmentation driven by loss of carbon dioxide. The reaction only returned this product and starting material.



Scheme 24: Attempted radical cyclization using benzoyl peroxide in benzene to form withasomnine, resulting in formation of biphenyl.

With raising temperature of the reaction in an effort to increase the reaction's energy as an ineffective method of increasing yield, it was unclear as to how conversion could be improved. It was also unclear as to how this reaction could be made into a green staple of the synthesis by using peroxide initiators in place of toxic SnBu_3H . Further attempts to improve yield could be directed toward understanding the limits of the xanthate ester in terms of heat stability. Increased energy to drive the cyclization is still a reasonable hypothesis, so it may be possible to find a "sweet spot" that forms the product

reasonably quickly without degrading the starting material to a considerable degree. Such an experiment could consist of attempting the reaction at 10°C increments up from the reflux temperature of benzene. Attempts at finding a green radical initiator could be an exploration of different peroxides. Coupling of benzoyl peroxide to **45** could be a unique problem to benzoyl peroxide, not the initiator itself. Zard et al. used lauroyl peroxide, which may benefit in radical stabilization from the lengthy lauryl chain.^{34, 36-37}

CONCLUSIONS

The halogenation of pyrazoles by the *in situ* formation of electrophilic halogens is an effective tool as a part of a synthetic arsenal. This work has demonstrated that the formation of halogens through this method can be easily applied to pyrazole halogenation.

Higher yields were apparently limited in some cases by product volatility. Using an efficient purification method like supercritical fluid extraction may allow users of this method to overcome the challenge of volatility relatively easily, and depending on the mobile phase, it may be a more green way of purifying than standard flash chromatography. Additionally, the acidic nature of oxone has shown, through this synthesis, to be a limiting factor in terms of the sensitivity of functional groups to this reaction's conditions. For substrates with acid-sensitive functional groups, this reaction may not be appropriate due to the possibility of degradation.

However, what this method lacks in functional group tolerance, it makes up in its operational simplicity and overall green chemistry – byproducts are water soluble salts, there is no energy input in the reaction, and potentially harmful solvents or reagents are not necessary for the reaction. This method has the potential to be useful in total synthesis where minimal environmental impact is desired. As demonstrated in the synthesis of withasomnine, halogenated pyrazoles can be used to effect Suzuki chemistry or otherwise functionalize the 4-position of the pyrazole ring. The common nature of pyrazoles in

pharmaceuticals and agrochemicals convey the point that such syntheses may be common in applications very close to human health.

The total synthesis of withasomnine has been completed. The challenging transformation of a bromopyrazole to a phenylpyrazole has been overcome, which was a significant hurdle in the completion of this synthesis. Likewise, alkylation and xanthate ester formation proved to be relatively effective, and may only need some improvements in yield to make a robust synthesis. Radical cyclization, the single most limiting factor of the overall synthetic yield, has been successfully performed.

All steps of the synthesis need to be improved in method in order to afford higher yields. Most of this work needs to be done in improving the overall yield of the cyclization, so further experiments will be aimed at determining what steps of the proposed radical mechanism are rate-limiting in order to effect the highest possible conversion of the xanthate radical precursor to withasomnine.

The most pertinent experiments should be directed at determining the byproducts of the cyclization and quantifying them in order to better understand which step is rate-limiting. High quantities of byproduct from fragmentation should indicate that fragmentation is occurring, and should go to show that fragmentation is not the rate-limiting step. High quantities of 4-phenyl-1-propylpyrazole should indicate that the cyclization is rate-limiting. Minor quantities of either may suggest that the fragmentation is rate-limiting, and it is possible that adjustments could be made.

To improve yield, other radical precursors could be explored, such as the phenylselenide group. Experiments designed to improve yield will most likely also include finding a temperature that does not cause rapid xanthate ester degradation but promotes radical fragmentation and dearomatization. This should increase reaction energy to more favorably form the product, while ideally avoiding degradation of the starting material. This aspect of the synthesis is one of the least green parts due to its use of toxic SnBu_3H as a radical initiator, but this problem can be potentially circumvented by using a peroxide initiator. Much of the recent work by Zard et al.³⁵ used lauroyl peroxide as radical initiator in place of AIBN or ACCN with tributyltin hydride. These methods would be greener reactions, and would be a good strategy to pursue in the event that fragmentation is indeed the issue. In order to improve this aspect of the synthesis, different peroxides should be explored, with a range of stabilities that will ideally be able to interact with and fragment the xanthate radical.

EXPERIMENTAL

Unless otherwise specified, solvents were used as purchased from the manufacturer. Hexanes for flash chromatography was distilled over CaH₂ and Ethyl Acetate (EtOAc) for flash chromatography was distilled. 1,4-Dioxane was distilled from sodium and benzophenone. Dimethylformamide (DMF) was stored under nitrogen. All reactions were monitored by tlc using Merck F₂₅₄ Analytical Chromatography TLC silica 60 plates and visualized by UV light, iodine, or KMnO₄ stain. Flash chromatography was run using Selectra HI surface area silica (40-63 μm) according to the method described by Still.⁴³ NMR spectra were collected using a 400 MHz Varian-MR spectrometer. GC-MS chromatograms and mass spectra obtained using HP 6890 Plus GC with FID and 5973 MSD on an open column, with samples injected by syringe as 3 μL, with 2 μL pockets of air on either side. General settings for GC as follows: 200°C inlet temp, 200°C detector temp, 1.0 mL/min flow rate.

General Procedure for Pyrazole Halogenation. To a flask, pyrazole substrate (3 mmol), deionized water (3 mL), and co-solvent (1.5 mL) were added and stirred together. If the reaction did not involve co-solvent, no additional water was added. Sodium halide (6 mmol) was added followed by Oxone (1.5 mmol). The flask was capped and stirred constantly. On completion, the reaction mixture was quenched using portion-wise addition of solid sodium metabisulfite until starch-iodide paper tested negative. The remaining salts were dissolved by adding more deionized water (1-3 mL). The product was extracted using 1:1 hexanes/ether (3 x 5 mL). The organic extract was dried with

magnesium sulfate, then filtered and concentrated on rotary evaporator. Crude products were purified using silica gel column chromatography.

4-Chloro-1-ethyl-3,5-dimethylpyrazole. (33a) Purified by flash chromatography (1.5 x 14.5 cm), 1:1 hexanes/Et₂O eluent collecting 22 x 4 mL fractions. Eluted in fractions 8-10; analytical tlc, 1:1 hexanes/Et₂O, R_f= 0.30. 50% yield as a yellow oil. IR (neat, cm⁻¹) 2981.1, C-H; 1557, C=C; 1385.6, -CH₃; 400 MHz NMR (CDCl₃, ppm) δ 3.97 (2H, q, J= 7.1 Hz) 2.17 (3H, s) 2.15 (3H, s) 1.32 (3H, t, J= 7.4 Hz). ¹³C NMR (100.53 MHz, CDCl₃, ppm) δ 143.95, 134.40, 107.27, 44.59, 15.31, 11.22, 9.13.

4-Bromo-1-ethyl-3,5-dimethylpyrazole. (33b) Purified by flash chromatography (1.5 x 14.9 cm), 1:1 hexanes/Et₂O eluent collecting 30 x 4 mL fractions. Eluted in fractions 7-12; analytical tlc, 1:1 hexanes/Et₂O, R_f= 0.25. 11% yield as a yellow oil. IR (neat, cm⁻¹) 2980.0, C-H; 1547.3, C=C; 1383.0, -CH₃; 400 MHz NMR (CDCl₃, ppm) δ 4.02 (2H, q, J= 7.1 Hz) 2.21 (3H, s) 2.19 (3H, s) 1.34 (3H, t, J= 7.3 Hz). ¹³C NMR (100.53 MHz, CDCl₃, ppm) δ 145.58, 136.28, 93.74, 44.79, 15.38, 12.21, 10.12.

4-Chloro-1-allyl-3,5-dimethylpyrazole. (34a) Purified by flash chromatography (2 x 14.7 cm), 4:1 hexanes/EtOAc eluent collecting 60 x 5 mL fractions. Eluted in fractions 15-26; analytical tlc, 4:1 hexanes/EtOAc, R_f= 0.24. 36% yield as a yellow oil. IR (neat, cm⁻¹) 1557.7, C=C; 1385.4, -CH₃; 400 MHz NMR (CDCl₃, ppm) δ 5.89 (1H, dddd, J= 17.2, 10.5, 5.5, 5.5 Hz) 5.18 (1H, dddd, J= 10.5, 1.6, 1.6, 1.6 Hz) 4.99 (1H, dddd, J= 17.2, 1.6, 1.6, 1.6 Hz) 4.60 (2H, ddd, J= 5.5, 1.6, 1.6 Hz) 2.19 (3H, s) 2.17 (3H, s). ¹³C

NMR (100.53 MHz, CDCl₃, ppm) δ 146.03, 137.29, 132.61, 117.42, 94.22, 52.62, 12.24, 10.17.

4-Bromo-1-allyl-3,5-dimethylpyrazole. (34b) Purified by flash chromatography (2 x 14.9 cm), 2:1 hexanes/EtOAc eluent collecting 32 x 5 mL fractions. Eluted in fractions 10-15; analytical tlc, 2:1 hexanes/EtOAc, R_f= 0.35. 17% yield as a yellow oil. IR (neat, cm⁻¹) 1548.9, C=C; 1384, -CH₃; 400 MHz NMR (CDCl₃, ppm) δ 5.89 (1H, dddd, J= 17.0, 10.7, 5.5, 5.5 Hz) 5.18 (1H, dddd, J= 10.8, 1.6, 1.6, 1.6 Hz) 4.99 (1H, dddd, 17.0, 1.5, 1.5, 1.5 Hz) 4.62 (2H, ddd, J= 5.2, 1.6, 1.6 Hz) 2.20 (3H, s) 2.19 (3H, s). ¹³C NMR (100.53 MHz, CDCl₃, ppm) δ 146.02, 137.26, 132.61, 117.40, 94.20, 52.60, 12.23, 10.15.

4-Chloro-5-phenylpyrazole. (35a) Purified by flash chromatography (3 x 15.5 cm), 3:1 hexanes/EtOAc eluent collecting 40 x 10 mL fractions. Eluted in fractions 15-28; analytical tlc, 3:1 hexanes/EtOAc, R_f= 0.21. 71% yield. IR (neat, cm⁻¹) 3127.6, N-H ar; 3073.8, C-H ar; 1442.0, C-C; 1097.1, C-Cl. 400 MHz NMR (CDCl₃, ppm) δ 10-12 (1H, br s) 7.78 (2H, d, J= 7.6 Hz) 7.57 (1H, s) 7.4-7.5 (3H, m). ¹³C NMR (100.53 MHz, CDCl₃, ppm) δ 142.8 (br), 134.5 (br), 129.3, 128.81, 128.77, 127.2, 108.1.

4-Bromo-5-phenylpyrazole. (35b) Purified by flash chromatography (3 x 15.0 cm), 3:1 hexanes/EtOAc eluent collecting 50 x 10 mL fractions. Eluted in fractions 22-41; analytical tlc, 3:1 hexanes/EtOAc, R_f= 0.22. 73% yield. mp= 114.0-117.5 °C. IR (neat, cm⁻¹) 3108.7, N-H; 3066.7, C-H; 1436.4, C-C; 1099.1, C-Br. 400 MHz NMR (CDCl₃, ppm) δ 7.77 (2H, d, J= 8.1 Hz) 7.60 (1H, s) 7.3-7.5 (3H, m) 10-12 (1H, br s) ¹³C NMR (100.53 MHz, CDCl₃, ppm) δ 144.4 (br), 136.9 (br), 129.6, 128.9, 128.7, 127.6, 92.3.

1-Benzyl-4-Bromopyrazole. (36) Purified by flash chromatography (1.5 x 15.0 cm), 2:1 hexanes/EtOAc eluent collecting 19 x 10 mL fractions Eluted in fractions 2-5; analytical tlc, 2:1 hexanes/EtOAc, Rf= 0.37. 84% yield. IR (neat, cm^{-1}) 1496.63, C-C; 713.08, C-H. 400 MHz NMR (CDCl_3 , ppm) δ 5.28 (2H, s) 7.2-7.5 (7H, m) ^{13}C NMR (100.53 MHz, CDCl_3 , ppm) δ 140.09 (br), 135.66, 129.58 (br), 128.95, 128.41, 127.88, 56.68.

4-Chloro-1-benzyl-3,5-dimethylpyrazole. (32) Purified by flash chromatography (1.5 x 15 cm), 4:1 hexanes/EtOAc eluent collecting 40 x 5 mL fractions. Eluted in fractions 4-8; analytical tlc. 4:1 hexanes/EtOAc, Rf= 0.35. 57% yield as a yellow oil. 400 MHz NMR (CDCl_3 , ppm) δ 7.2-7.3 (3H, m) 7.06 (2H, d, J= 7.6 Hz) 5.19 (2H, s) 2.22 (3H, s) 2.11, (3H, s) ^{13}C NMR (100.53 MHz, CDCl_3 , ppm) δ 144.532, 136.593, 135.493, 128.753, 127.699, 126.659, 108.103, 53.787, 11.347, 4.435.

4-Bromopyrazole. (24) Recrystallized from hexanes. 80% yield as white crystalline solid, hydrate. m.p. 89.1-92.4 °C. 400 MHz NMR (CDCl_3 , ppm) δ 7.69 (2H, s) 7.18-7.40 (3H, br s).

Procedure for Suzuki-Miyaura Coupling for 1H-pyrazoles. In the glove box under N_2 atmosphere, CataCXium® A (0.06 mmol) was measured out into a conical vial fitted with a septum along with a triangular stir bar. Outside the box, 4-bromopyrazole (0.60 mmol) and phenylboronic acid (0.75 mmol) were added to a glass pressure tube with a stir bar and flushed with N_2 for 20 minutes. Into a conical vial with a triangular stir bar, $\text{Pd}(\text{OAc})_2$ (0.060 mmol) was added and flushed with N_2 for 20 minutes. The contents of the ligand vial were transferred to the $\text{Pd}(\text{OAc})_2$ vial by cannulation with distilled

dioxane (2 x 0.75 mL) and the contents were stirred together. The contents of the vial containing the mixed catalyst were transferred to the pressure tube by cannulation (2 x 1.5 mL). A solution of 1.2 M K₂CO₃ (1.5 mL, 1.8 mmol) in H₂O was degassed for 30 minutes by purging with N₂ and added by syringe to the vial containing the reactants and catalyst. The septum on the pressure tube was quickly exchanged for a teflon cap, sealed, and the tube was immersed in a 115 °C oil bath with constant stirring for 24 hours. The pressure tube was removed from heat and allowed to return to r.t. The product was filtered through a small pad of celite with 30 mL EtOAc, remaining water was separated and extracted with 3 x 5 mL EtOAc. Extract was dried over MgSO₄, filtered, and concentrated down by rotary evaporator. The dried extract was used to determine completion using GC-MS.

1H-3,5-dimethyl-4-phenylpyrazole. Obtained using 3.75% Pd(OAc)₂ and 0.9% CataCXium A. Workup performed by filtering through celite with 25 mL EtOAc. Purified using flash chromatography in 1:2 hexanes/EtOAc, collecting 32 x 5 mL fractions. Eluted in fractions 14-31; analytical tlc, 1:2 hexanes/EtOAc, R_f= 0.26. 35% yield, white crystalline solid as hydrate. GC-MS (150°C): 11.356 min, m/z= 144 (M⁺), 117, 90. 400 MHz NMR (CDCl₃, ppm) δ 7.42 (2H, t, J= 7.4 Hz) 7.24-7.34 (3H, m) 5.14-5.40 (3H, br s) 2.34 (6H, s).

1H-4-phenylpyrazole. (44) Purified using flash chromatography in 3:5 hexanes/EtOAc, collecting 35 x 5 mL fractions. Eluted in fractions 9-20; analytical tlc, 3:5 hexanes/EtOAc, R_f= 0.33. 51% yield, white crystalline solid as hydrate. 400 MHz NMR

(CDCl₃, ppm) δ 7.62 (2H, d, J= 7.9 Hz) 7.35 (2H, t, J= 7.9 Hz) 7.19 (1H, t, J= 7.9 Hz) 2.93-4.34 (3H, br s).

Procedure for Alkylation and Xanthate Esterification of Pyrazole and 4-

Bromopyrazole. To an oven-dried flask fitted to a cold-water condenser, pyrazole (3.62 mmol) and powdered KOH (4.63 mmol, 0.2616 g) were added. The apparatus was flushed with N₂ for 15 minutes and dry DMF (43 mL) was added by syringe. The flask was immersed in an oil bath at 50 °C and the solution was constantly stirred. After 10 minutes, 3-chloro-1-propanol (4.63 mmol, 0.334 mL) was added by syringe. After starting materials were not visible by tlc, the flask was removed from heat and cooled to room temperature. Carbon disulfide was added by syringe (7.42 mmol, 0.438 mL). To the flask, powdered KOH was added by quickly breaking the seal on the condenser (7.26 mmol, 0.4075g). To the flask, CH₃I was added by syringe (7.24 mmol, 0.451 mL) and the mixture was allowed to react at r.t. until the intermediate product no longer visible by tlc. The salts were dissolved using 10 mL deionized H₂O. The product was extracted in 3 x 50 mL EtOAc and 3 x 30 mL DCM. The combined organic layers were washed with 3 x 150 mL H₂O. The organic layer was dried over MgSO₄, filtered, and concentrated on a rotary evaporator.

***O*-(3-(1*H*-pyrazol-1-yl)propyl) *S*-methyl carbonodithioate. (40)** Purified using flash chromatography (3 x 14.9 cm), 2:1 hexanes/EtOAc, collecting 40 x 15 mL fractions. Eluted in fractions 10-19; analytical tlc, 2:1 hexanes/EtOAc, R_f= 0.31. 71% yield as a yellow oil. 400 MHz NMR (CDCl₃, ppm) δ 7.50 (1H, d, J= 1.6 Hz) 7.36 (1H, d, J= 2.4

Hz) 6.22 (1H, t, J= 2.2 Hz) 4.54 (2H, t, J= 6.1 Hz) 4.25 (2H, t, J= 6.9 Hz) 2.55 (3H, s) 2.35 (2H, ddd, J= 12.8, 6.4, 6.4 Hz) ¹³C NMR (100.53 Hz, CDCl₃, ppm) δ 215.82, 139.69, 129.41, 105.48, 70.43, 48.51, 29.13, 19.13.

***O*-(3-(4-bromo-1H-pyrazol-1-yl)propyl) S-methyl carbonodithioate. (38)** Purified using flash chromatography (3 x 15.0 cm), 4:1 Hexanes/EtOAc, collecting 40 x 20 mL fractions. Eluted in fractions 6-14; analytical tlc, 4:1 hexanes/EtOAc, R_f= 0.39. 55% yield as a yellow oil. IR (neat, cm⁻¹) 1208.73, C-O-C; 1057.51, C=S. 400 MHz NMR (CDCl₃, ppm) δ 7.48 (1H, s) 7.42 (1H, s) 4.59 (2H, t, J= 6.1 Hz) 4.24 (2H, t, J= 6.8) 2.57 (2H, s) 2.36 (3H, p, J= 6.13 Hz).

Procedure for Suzuki-Miyaura Coupling, Alkylation, and Xanthate Esterification of 4-bromopyrazole. In the glove box under N₂ atmosphere, CataCXium® A (0.158 mmol, 0.0567 g) was measured out into a conical vial fitted with a septum along with a triangular stir bar. Outside the box, 4-bromopyrazole (1.58 mmol, 0.2464 g) and phenylboronic acid (1.97 mmol, 0.2408 g) were added to a glass pressure bomb with a stir bar and flushed with N₂ for 6 hours, then dissolved in 3.05 mL distilled dioxane. Into a conical vial with a triangular stir bar, Pd(OAc)₂ (0.078 mmol, 0.0175 g) was added and flushed with N₂ for 30 minutes. The contents of the ligand vial were transferred to the Pd(OAc)₂ vial by cannulation with distilled dioxane (2 x 1.5 mL) and stirred together. The contents of the vial containing the mixed catalyst were transferred to the pressure tube by cannulation (2 x 3.0 mL). A solution of 1.2 M K₂CO₃ (3.95 mL, 7.1 mmol) in H₂O was degassed for 30 minutes by purging with N₂ and added by syringe to the vial

containing the reactants and catalyst. The septum on the pressure tube was quickly exchanged for a teflon cap, sealed, and the tube was immersed in a 115 °C oil bath with constant stirring for 24 hours. The pressure tube was removed from heat and allowed to return to r.t. The product was filtered through a small pad of celite with 30 mL EtOAc, remaining water was separated and extracted with 3 x 5 mL EtOAc. The organic layers were combined and dried over MgSO₄, filtered, and concentrated down by rotary evaporator. To an oven-dried flask fitted to a cold-water condenser, the crude extract and powdered KOH (2.05 mmol, 0.1150 g) were added. The apparatus was flushed with N₂ for 15 minutes and dry DMF (18.8 mL) was added by syringe. The flask was immersed in an oil bath at 50 °C and the solution was constantly stirred. After 10 minutes, 3-chloro-1-propanol (2.08 mmol, 0.150 mL) was added by syringe. After 4 days, monitoring by tlc and GC-MS indicated the presence of starting materials, so powdered KOH (1.57 mmol, 0.0885 g) and 3-chloro-1-propanol (1.58 mmol, 0.114 mL) were added. After 5 days, monitoring by tlc and GC-MS indicated the presence of starting materials, so powdered KOH (1.62 mmol, 0.0908 g) and 3-chloro-1-propanol (1.58 mmol, 0.114 mL) were added. After starting materials were not visible by tlc or GC-MS, the flask was removed from heat and cooled to room temperature. Carbon disulfide was added by syringe (6.77 mmol, 0.409 mL). To the flask, powdered KOH was added by quickly breaking the seal on the condenser (6.88 mmol, 0.3861 g). To the flask, CH₃I was added by syringe (13.5 mmol, 0.824 mL) and allowed to react at r.t. After 4 days following the addition of the last reagent, the intermediate product was no longer visible by tlc. The salts were dissolved using 10 mL deionized H₂O. The product was extracted in 3 x 30 mL EtOAc

and 3 x 30 mL DCM. The combined organic layers were washed with 5 x 100 mL H₂O. The organic layer was dried over MgSO₄, filtered, and concentrated on rotary evaporator.

***O*-(3-(4-phenyl-1H-pyrazol-1-yl)propyl) S-methyl carbonodithioate. (37).** Purified using flash chromatography (3 x 15.0 cm), 2:1 Hexanes/EtOAc, collecting 36 x 15 mL fractions. Eluted in fractions 11-13; analytical tlc, 2:1 hexanes/EtOAc, R_f= 0.32. 45% yield from 4-bromopyrazole as a yellow oil. IR (neat, cm⁻¹) 1212.36, C-O-C; 1058.66, C=S. 400 MHz NMR (CDCl₃, ppm) 400 MHz NMR (CDCl₃, ppm) δ 7.80 (1H, s) 7.64 (1H, s) 7.47 (2H, d, J= 7.5 Hz) 7.36 (2H, t, J= 7.5 Hz) 7.23 (2H, t, J= 7.5 Hz) 4.63 (2H, t, J= 5.8 Hz) 4.30 (2H, t, J= 6.8 Hz) 2.57 (3H, s) 2.42 (2H, p, J= 6.3 Hz).

Procedure for Radical-initiated Cyclization. To an oven-dried flask, 0.13 mmol of *O*-(3-(4-phenyl-1H-pyrazol-1-yl)propyl) S-methyl carbonodithioate (**37**) was added, and the flask was fitted with a condenser. After purging with N₂, the pyrazole was dissolved in degassed benzene (150 mL) and the flask was immersed in a constant-temperature oil bath at 80°C. To a separate flask, AIBN was added (0.17 mmol) and dissolved in degassed benzene (30 mL). After dissolution, SnBu₃H was added to this flask by syringe and the solution was mixed together. The solution containing AIBN and SnBu₃H was added manually over the course of four hours by syringe to the heated solution containing the pyrazole at a rate of 1.2 mL/10 min. The mixture was kept on heat overnight. The next day, benzene was removed by rotary evaporator, and the product was isolated by flash chromatography in 4:1 hexanes/EtOAc, then withasomnine (**1**) was separated from other contaminants by preparatory TLC in 2:1 benzene/EtOAc, analytical tlc, R_f= 0.23.

14% yield as a white solid. GC-MS (150°C/5 min, 200°C): 15.117 min, m/z= 184 (M+), 129, 77 (Ph). 400 MHz NMR (CDCl₃, ppm) δ 7.45 (2H, d, J= 8.3 Hz) 7.37 (2H, t, J= 8.3 Hz) 7.20 (1H, t, J= 8.3 Hz) 4.22 (2H, t, J= 8.1 Hz) 3.12 (2H, t, J= 8.1 Hz) 2.71 (2H, p, J= 8.1).

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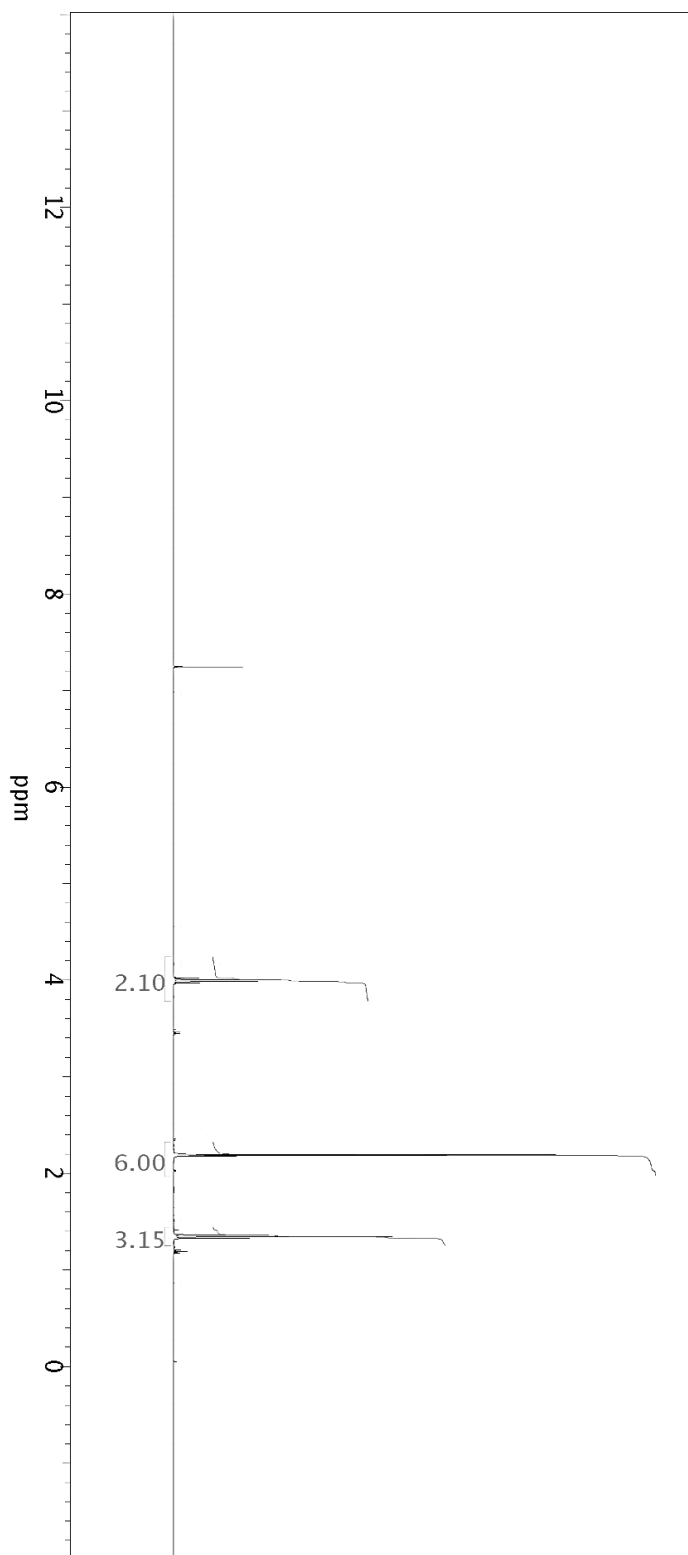
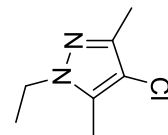
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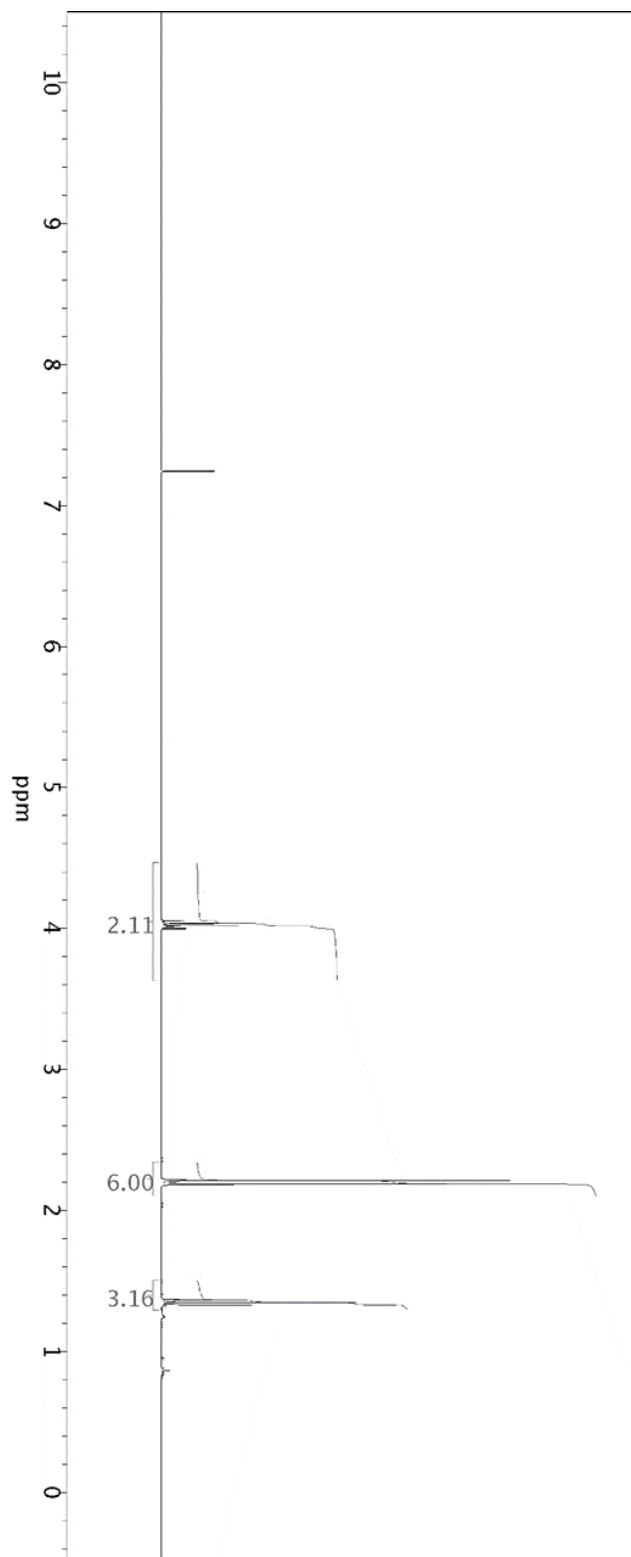
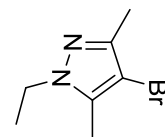
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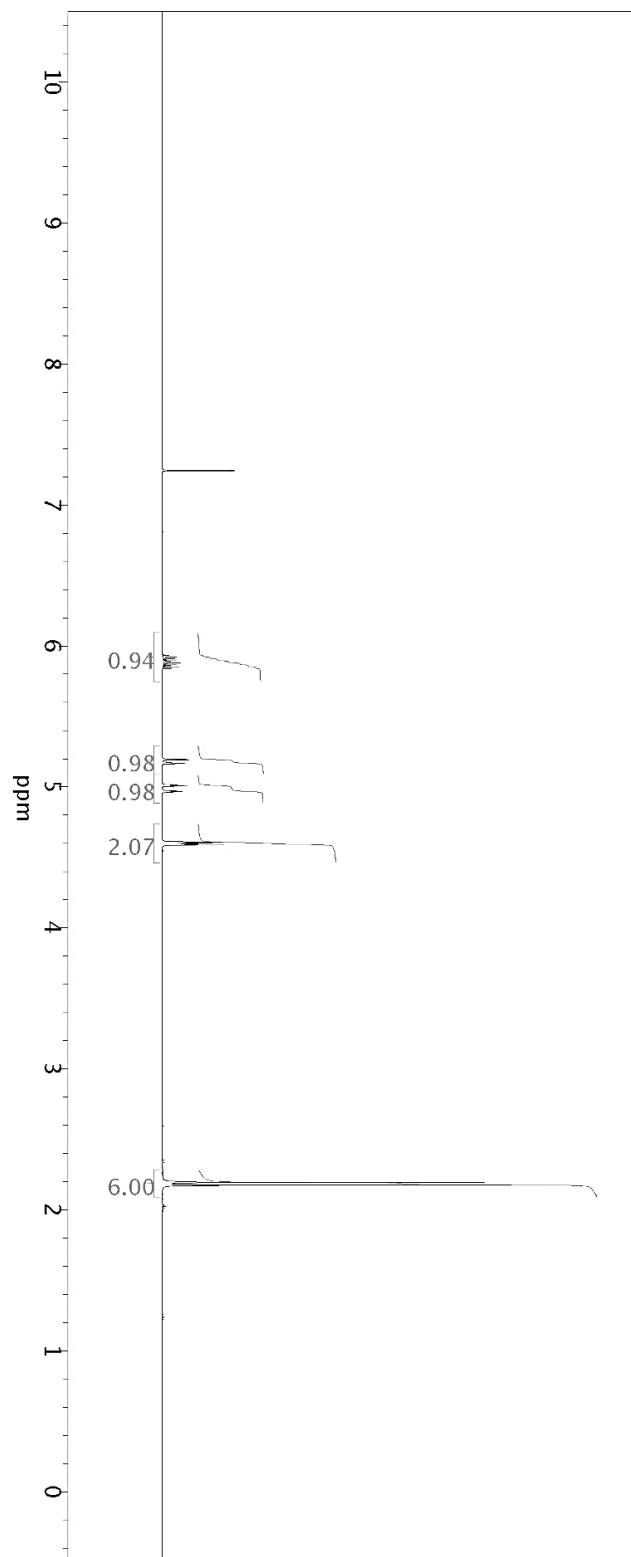
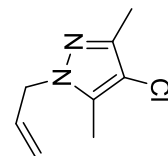
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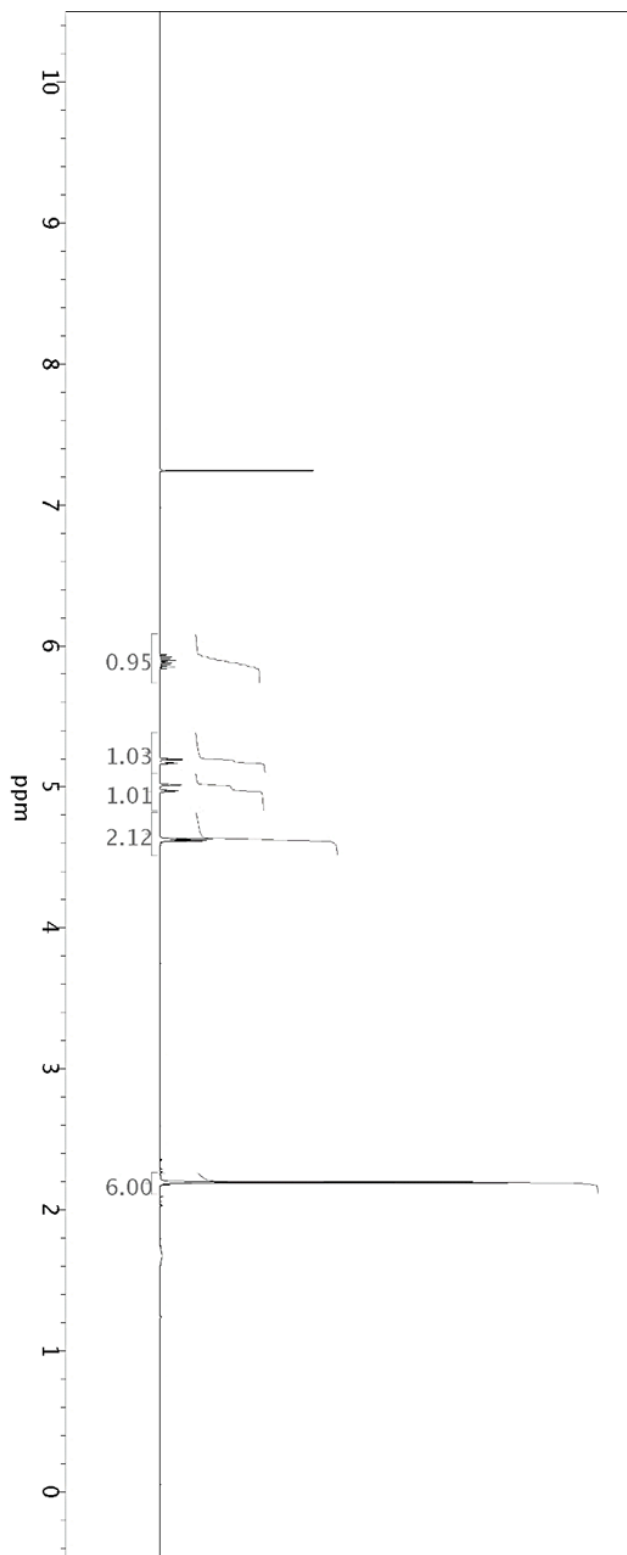
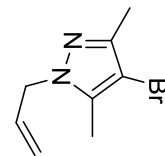
Appendix 1: ¹H NMR Spectrum of **33a**.



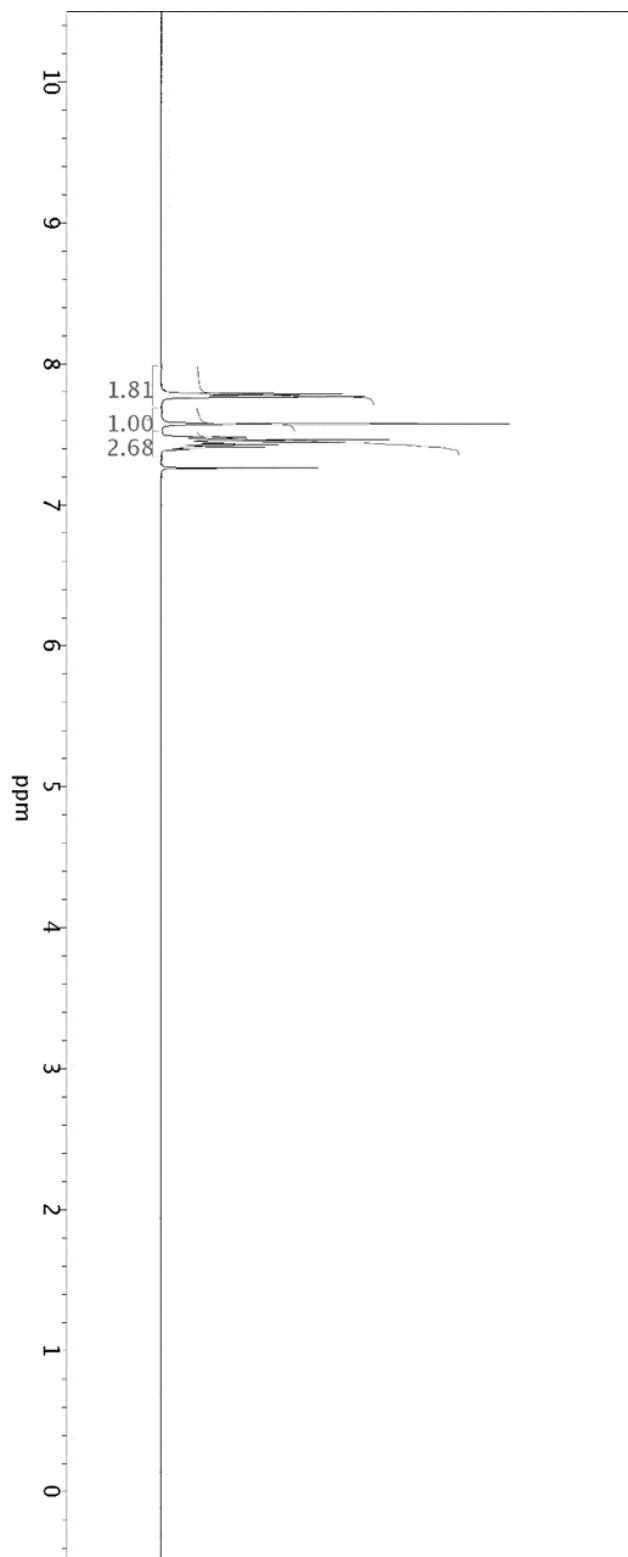
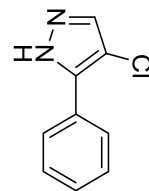
Appendix 2: ^1H NMR Spectrum of **33b**.



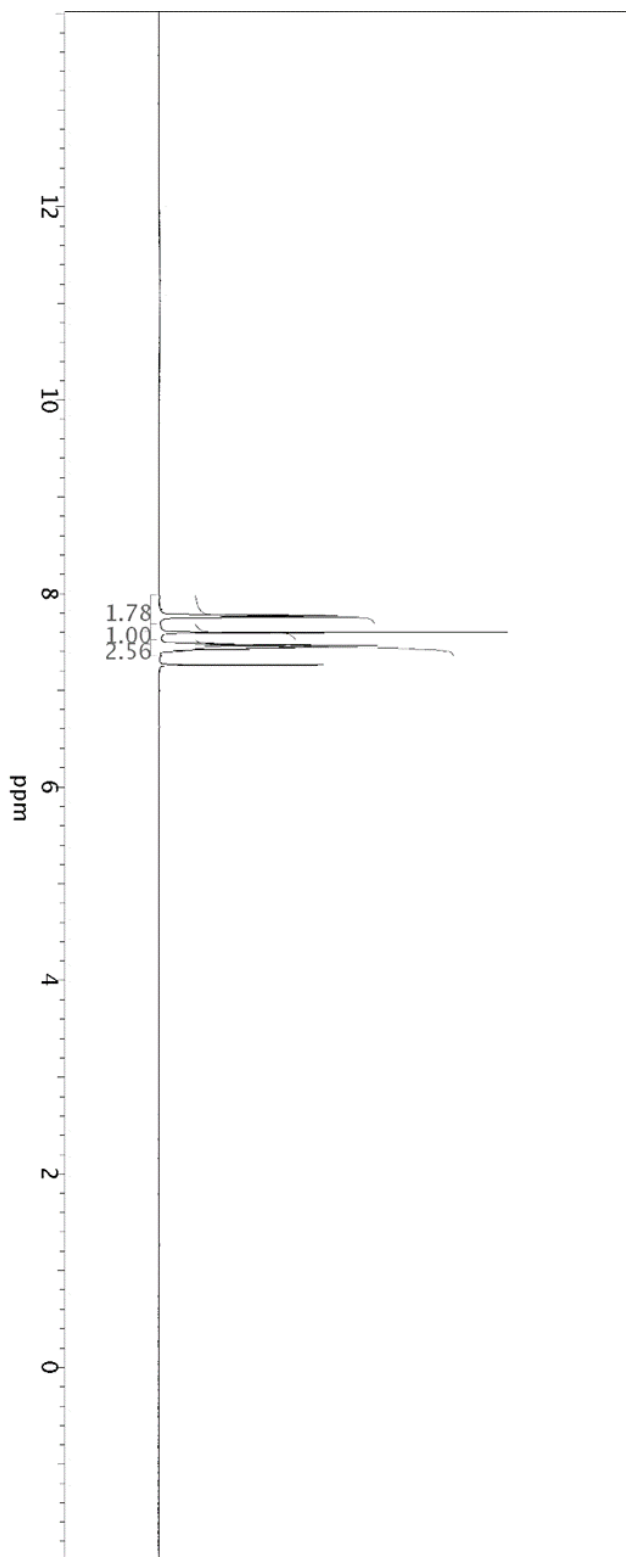
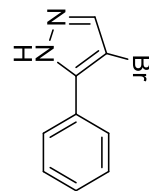
Appendix 3: ^1H NMR Spectrum of **34a**.



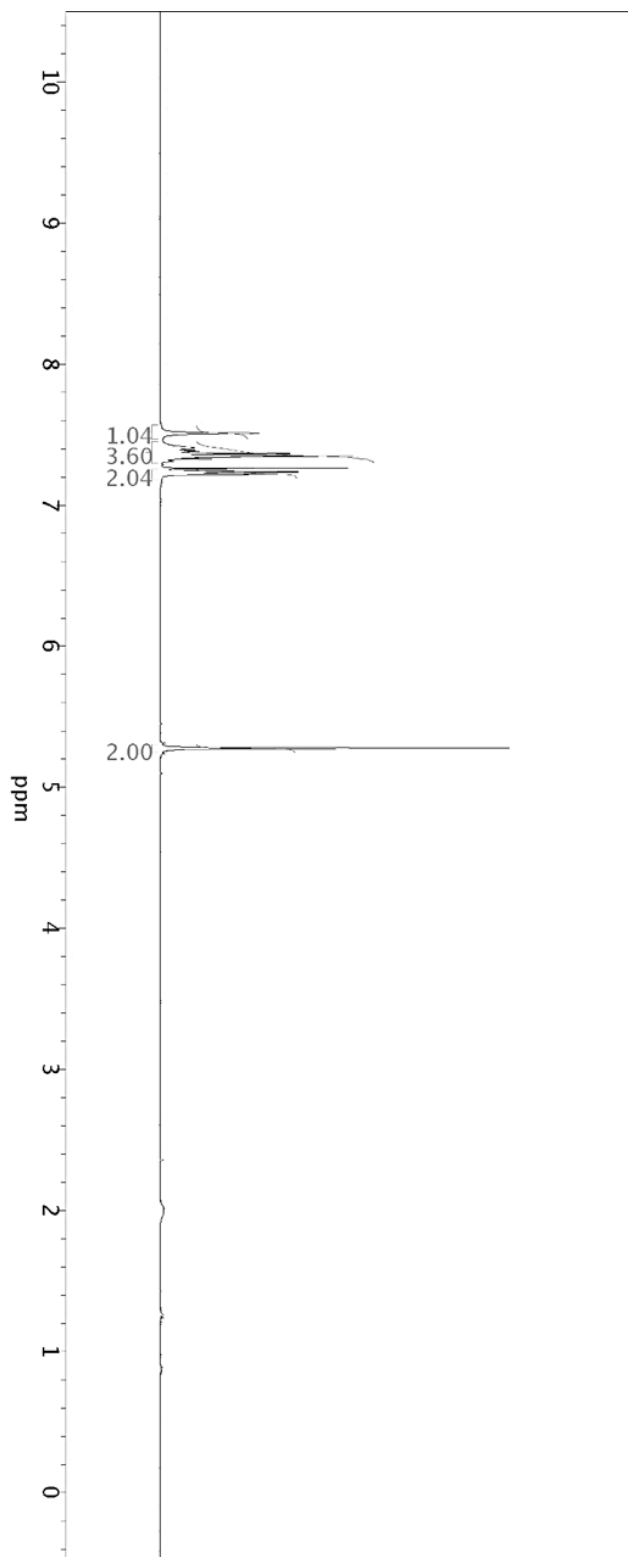
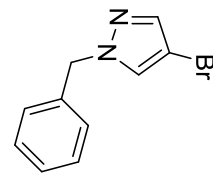
Appendix 4: ¹H NMR Spectrum of **34b**.



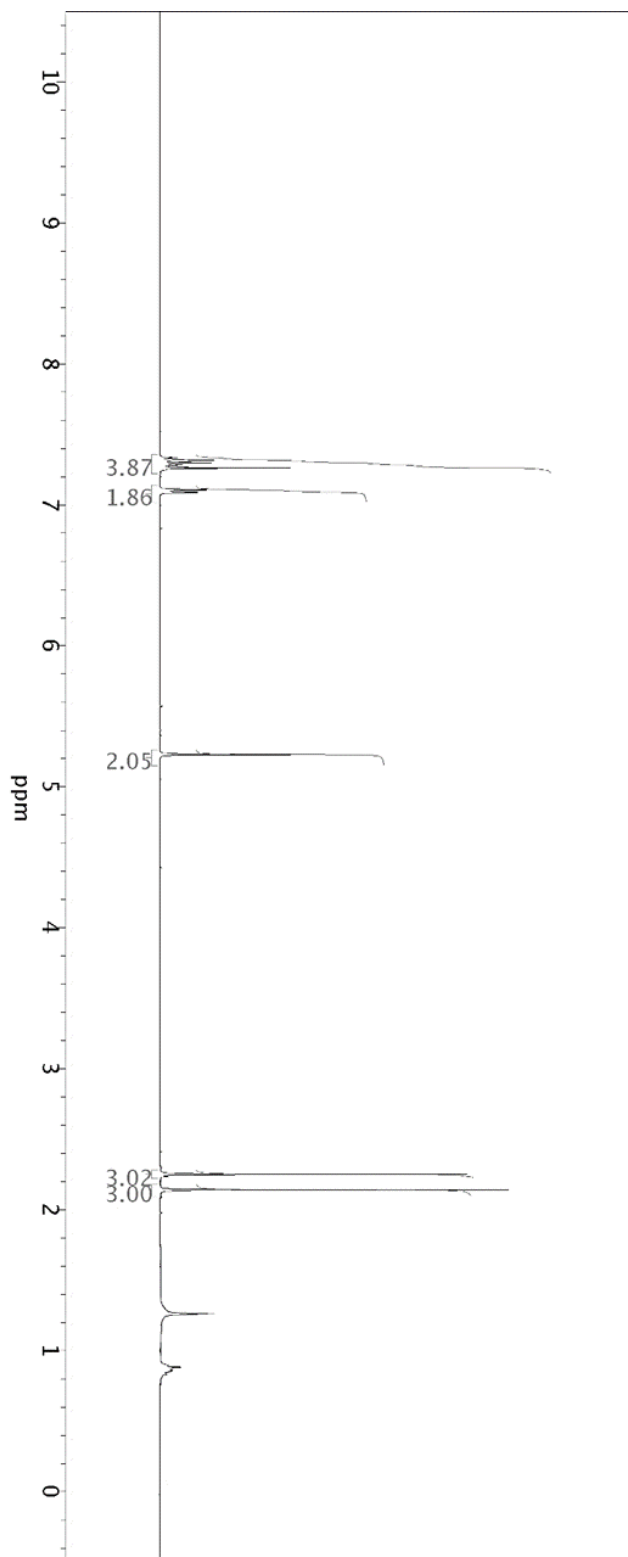
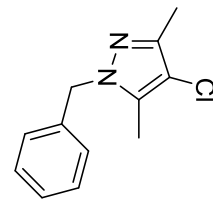
Appendix 5: ^1H NMR Spectrum of 35a.



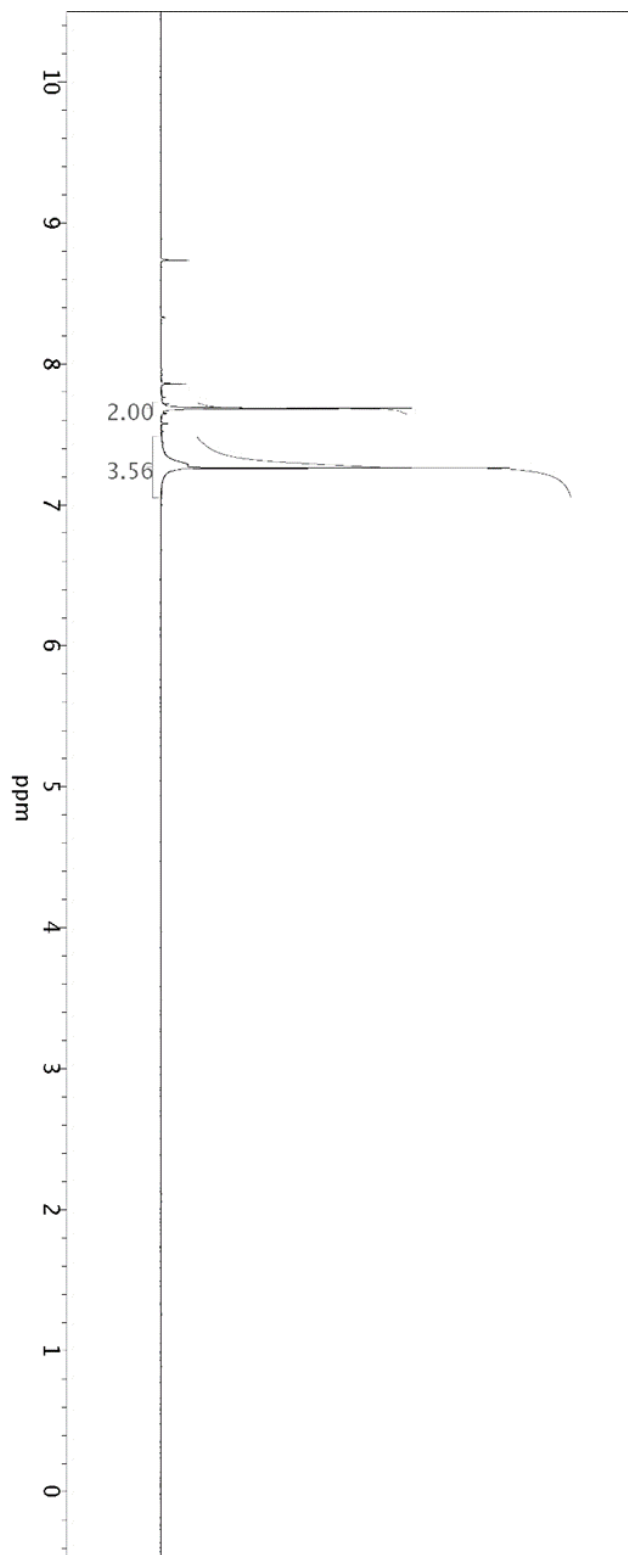
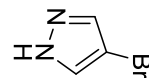
Appendix 6: ¹H NMR Spectrum of **35b**.



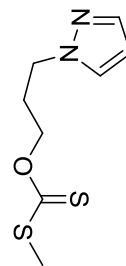
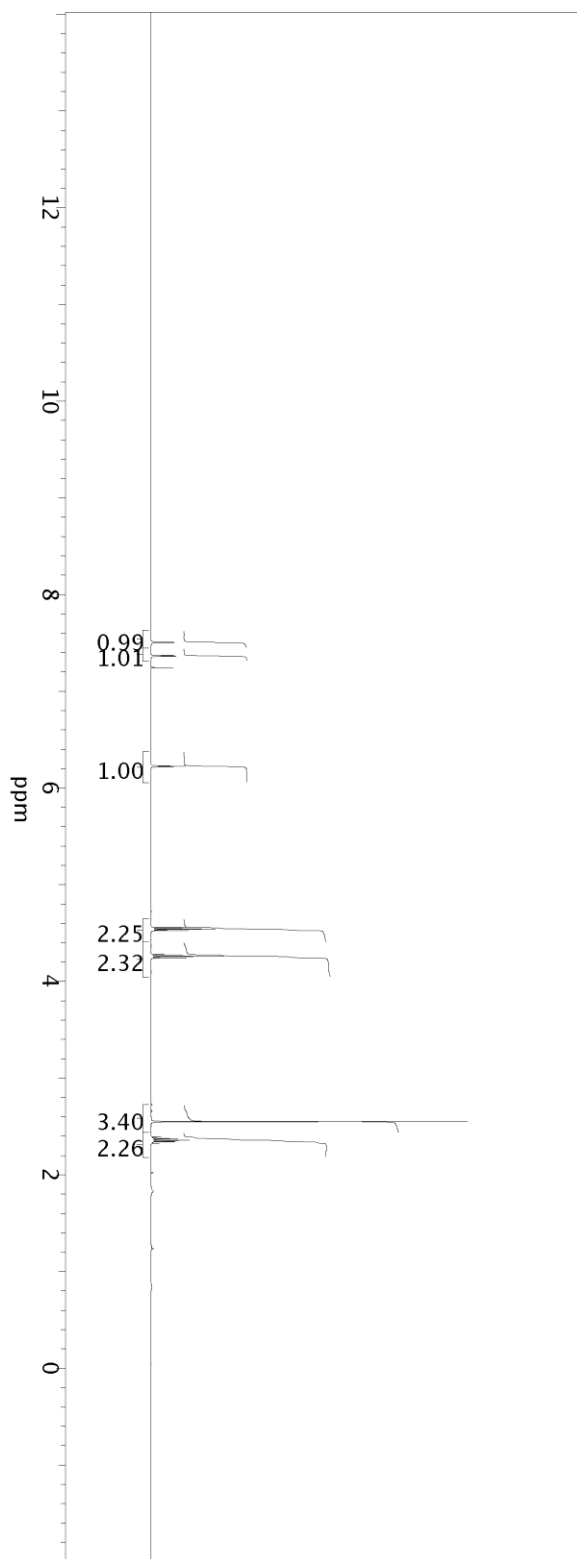
Appendix 7: ^1H NMR Spectrum of 36.



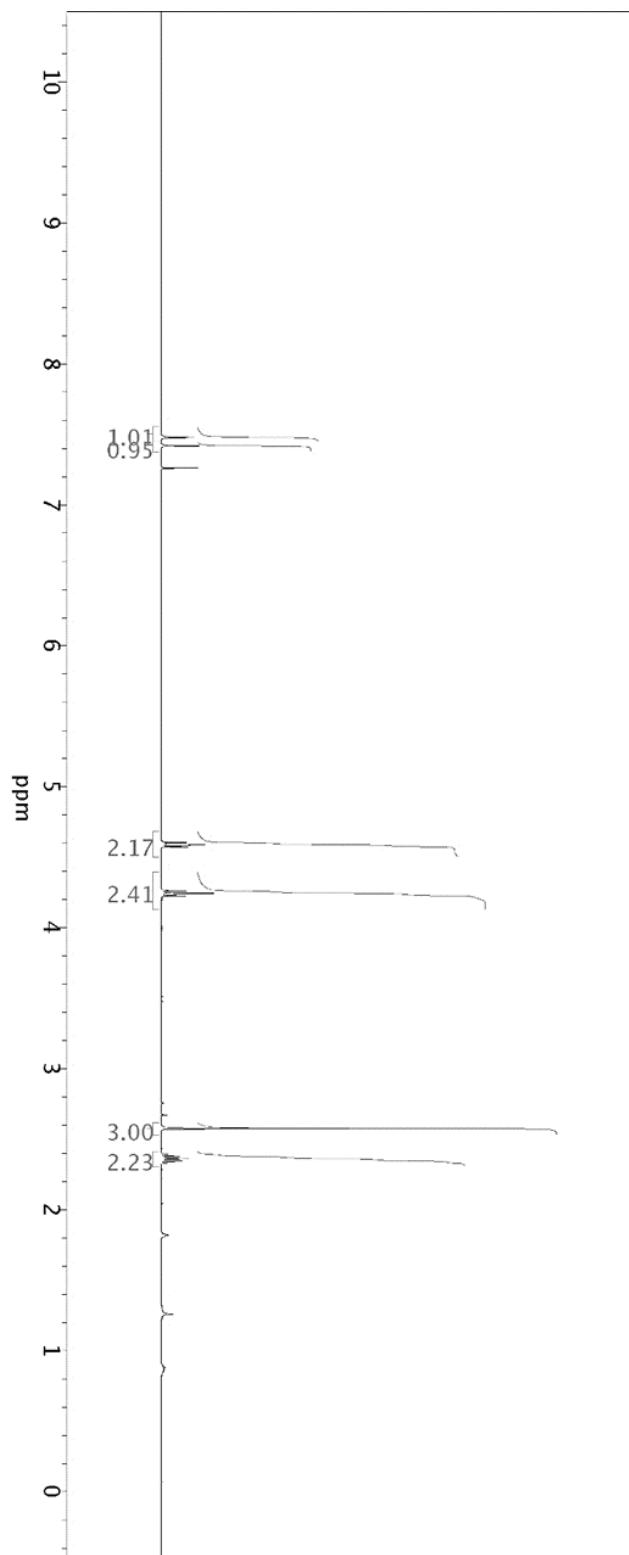
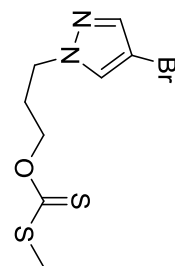
Appendix 8: ¹H NMR Spectrum of **32**.



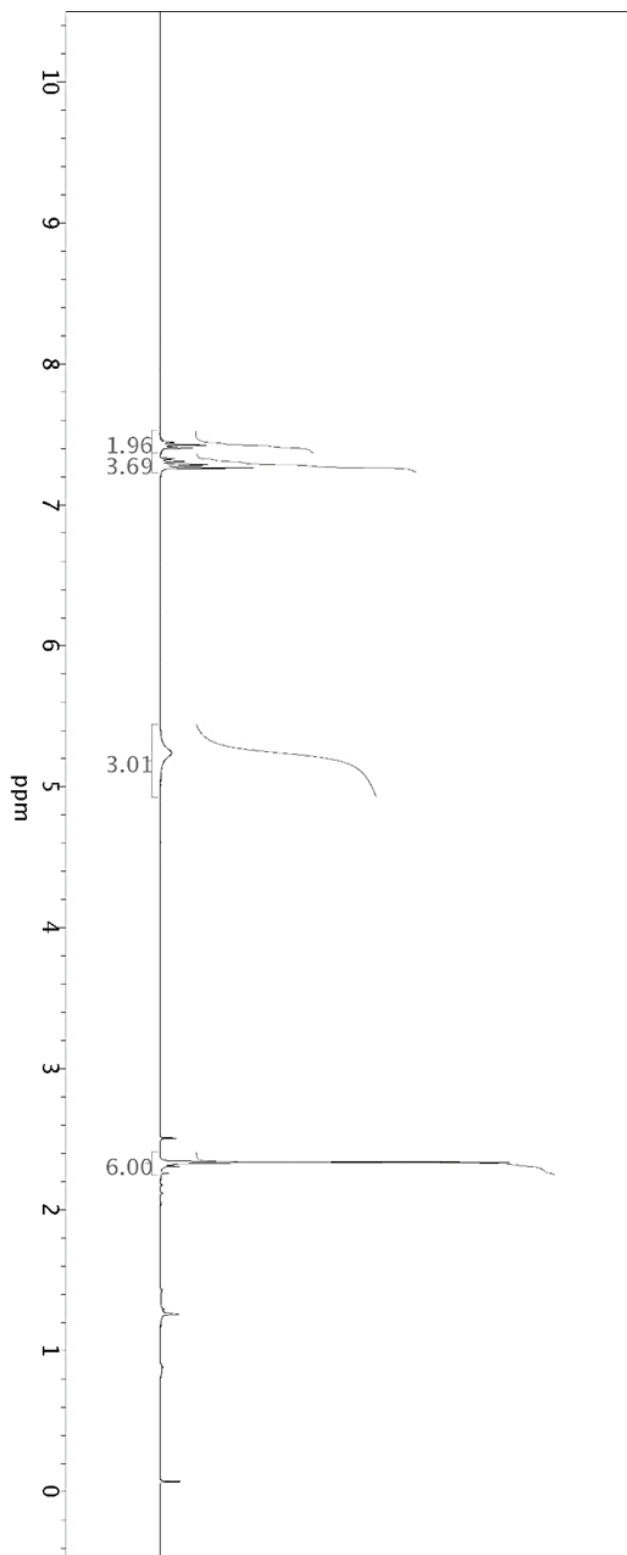
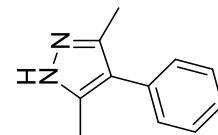
Appendix 9: ^1H NMR Spectrum of **24**.



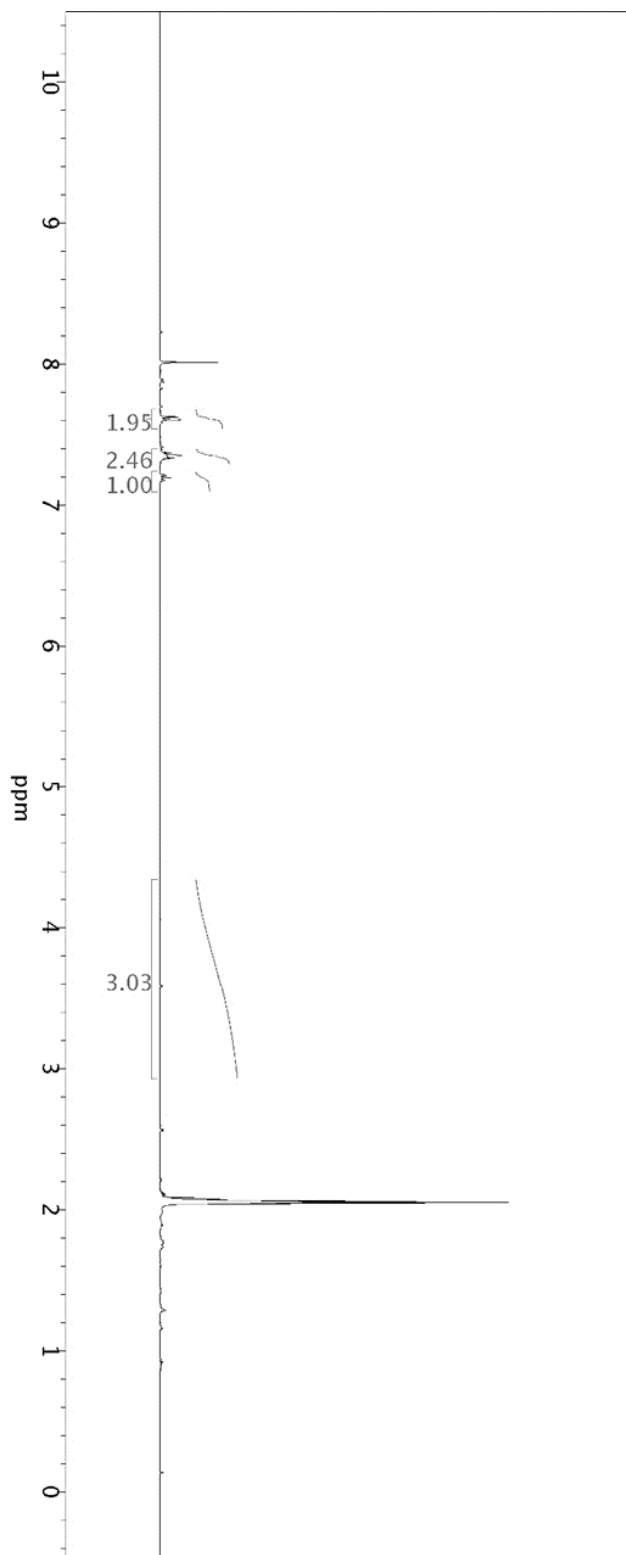
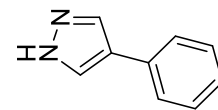
Appendix 10: ¹H NMR Spectrum of **40**.



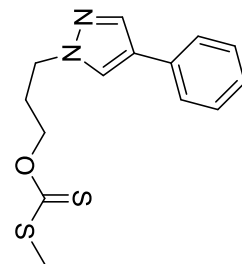
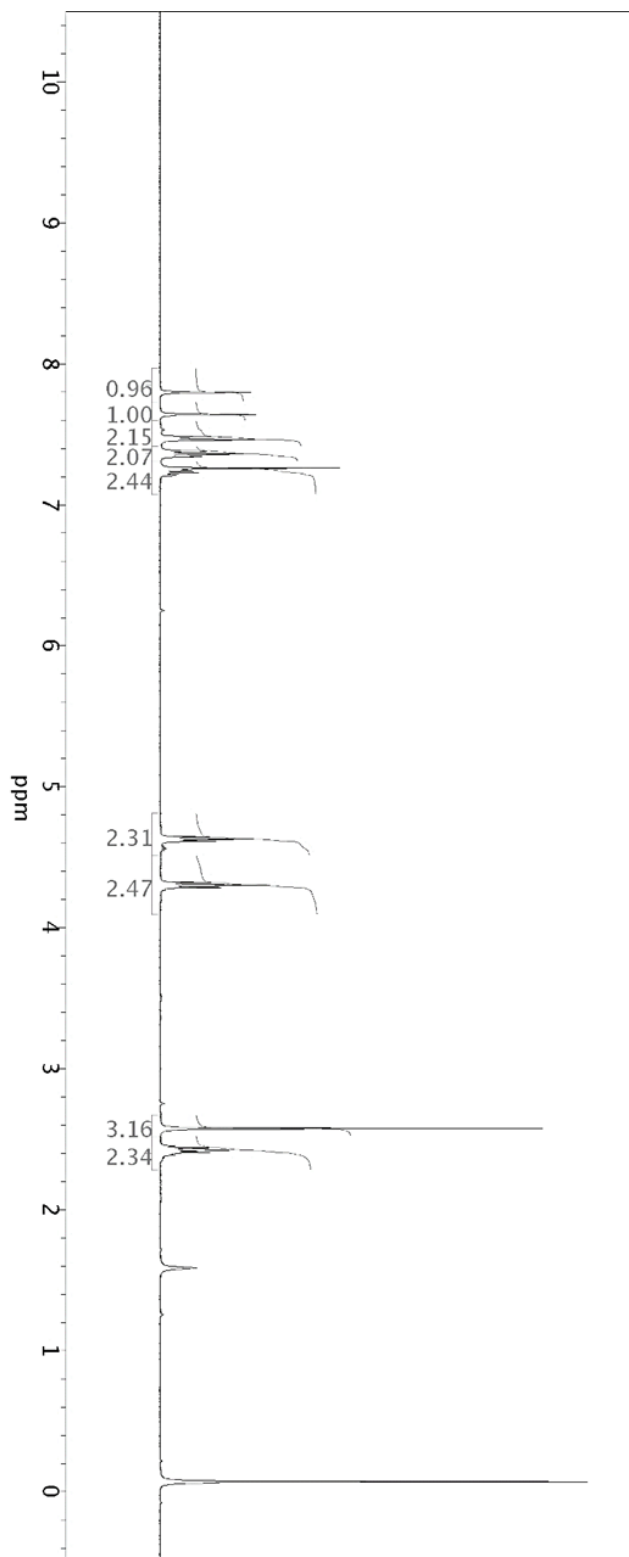
Appendix 11: ^1H NMR Spectrum of **38**.



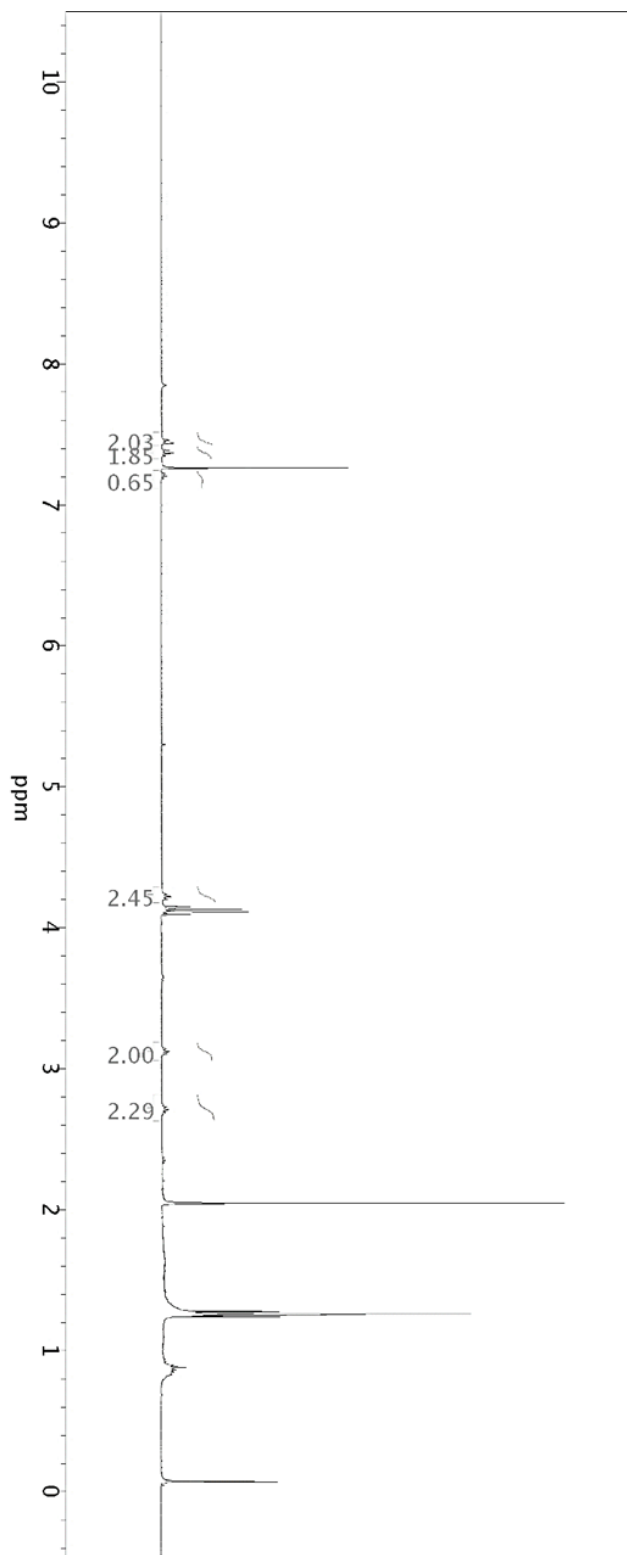
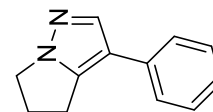
Appendix 12: ¹H NMR Spectrum of 3,5-dimethyl-4-phenylpyrazole.



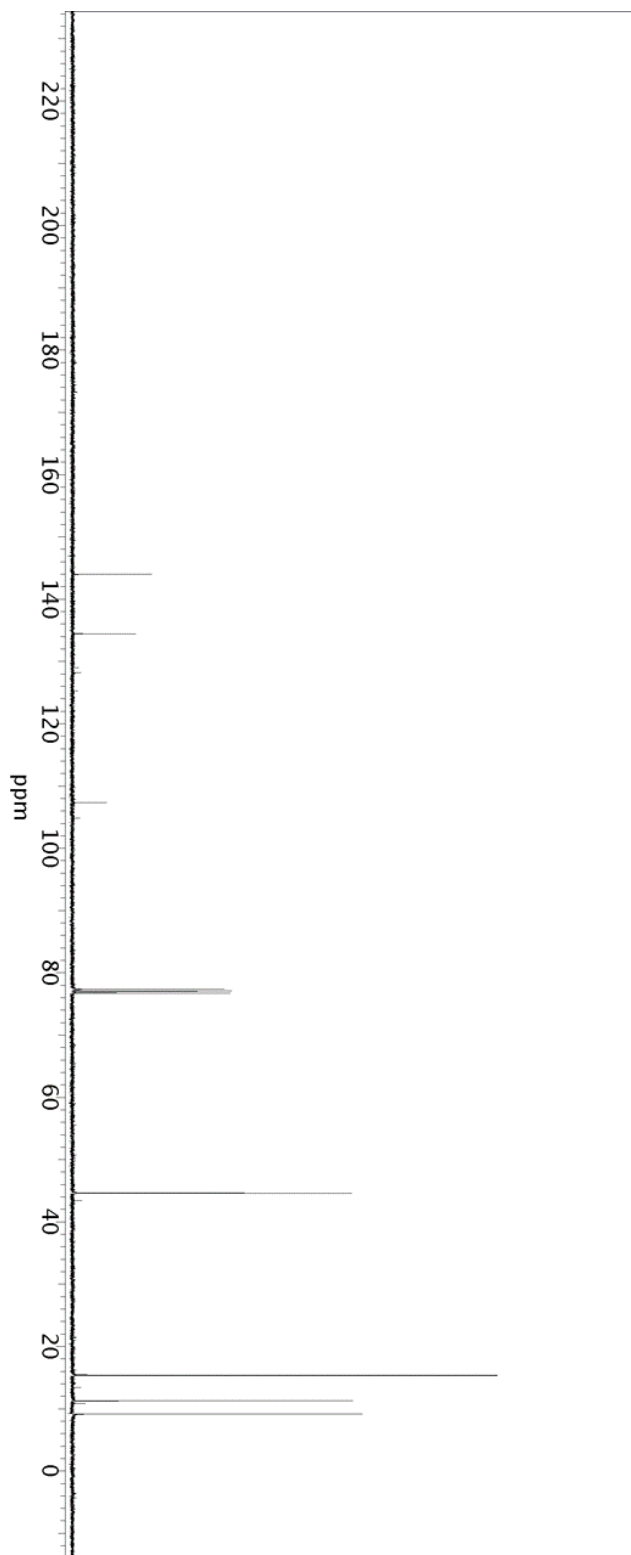
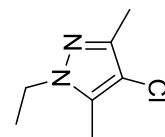
Appendix 13: ^1H NMR Spectrum of 44.



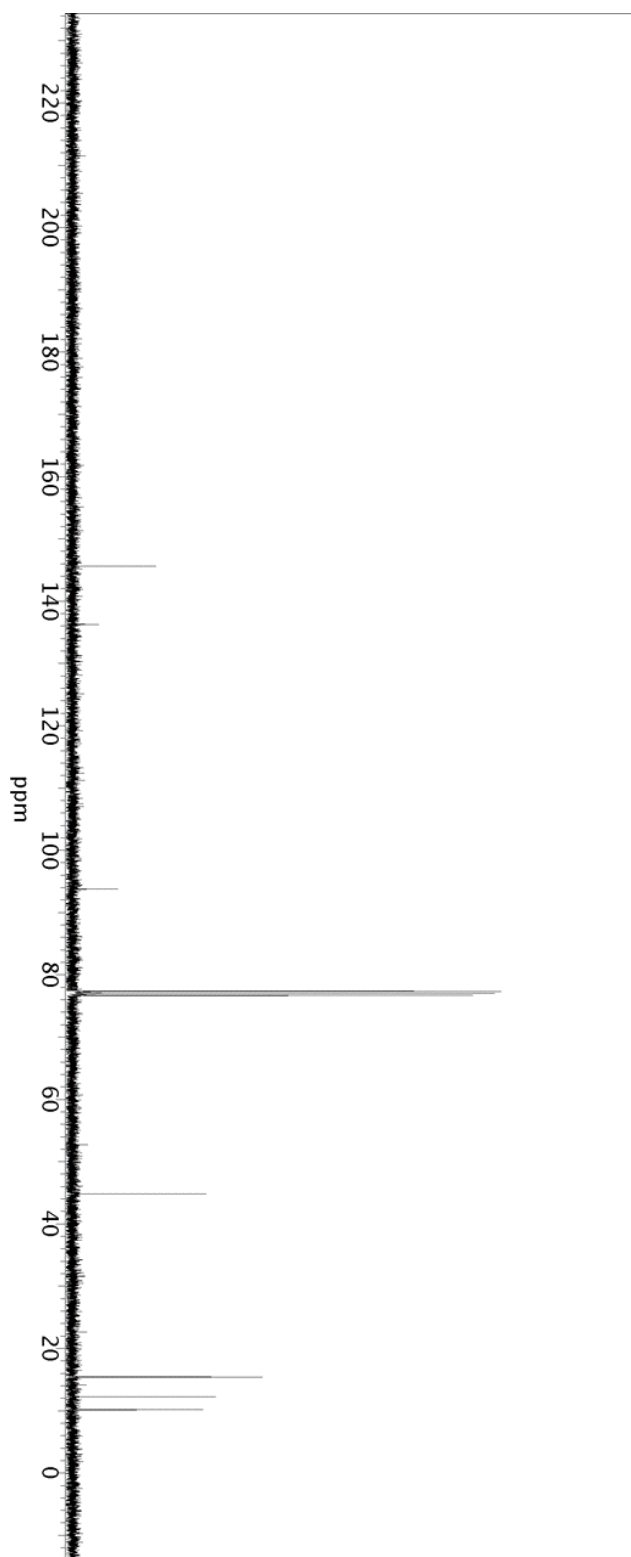
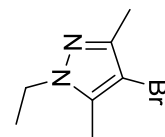
Appendix 14: ¹H NMR Spectrum of **37**.



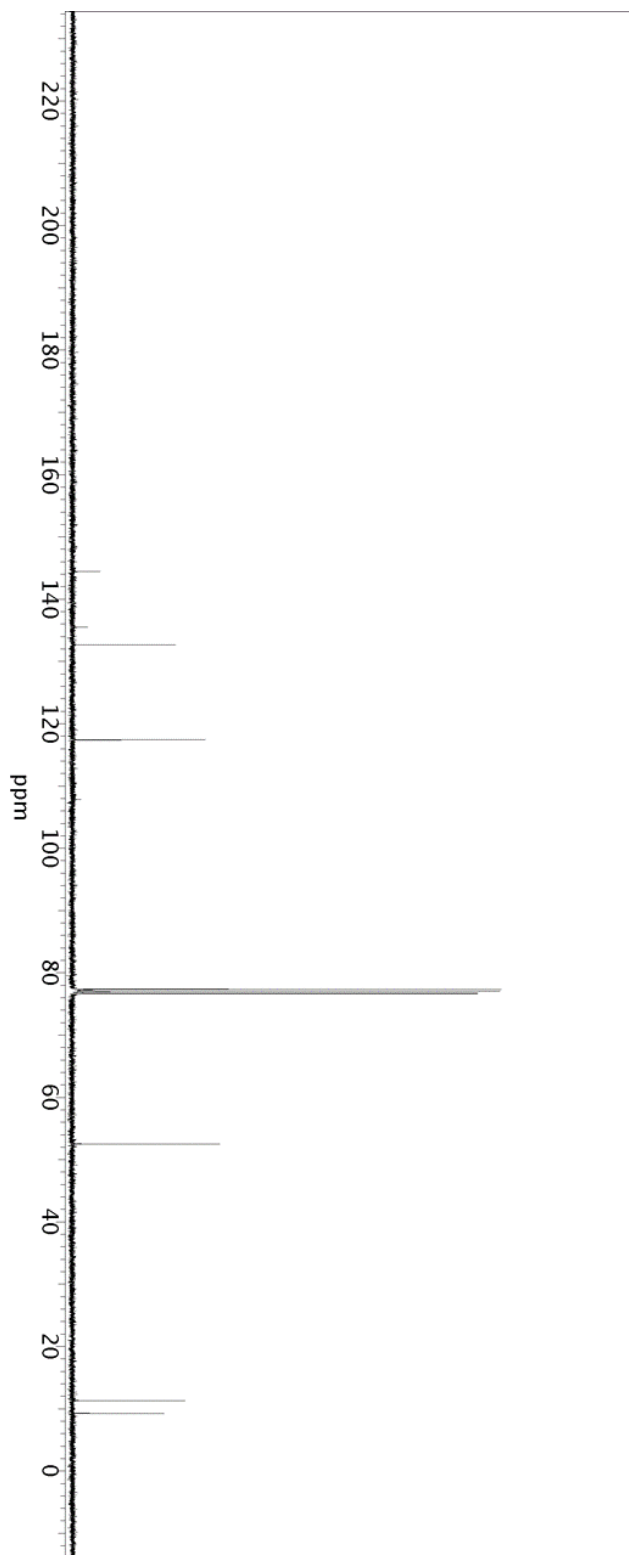
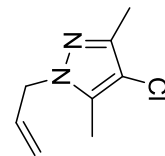
Appendix 15: ^1H NMR Spectrum of **1**.



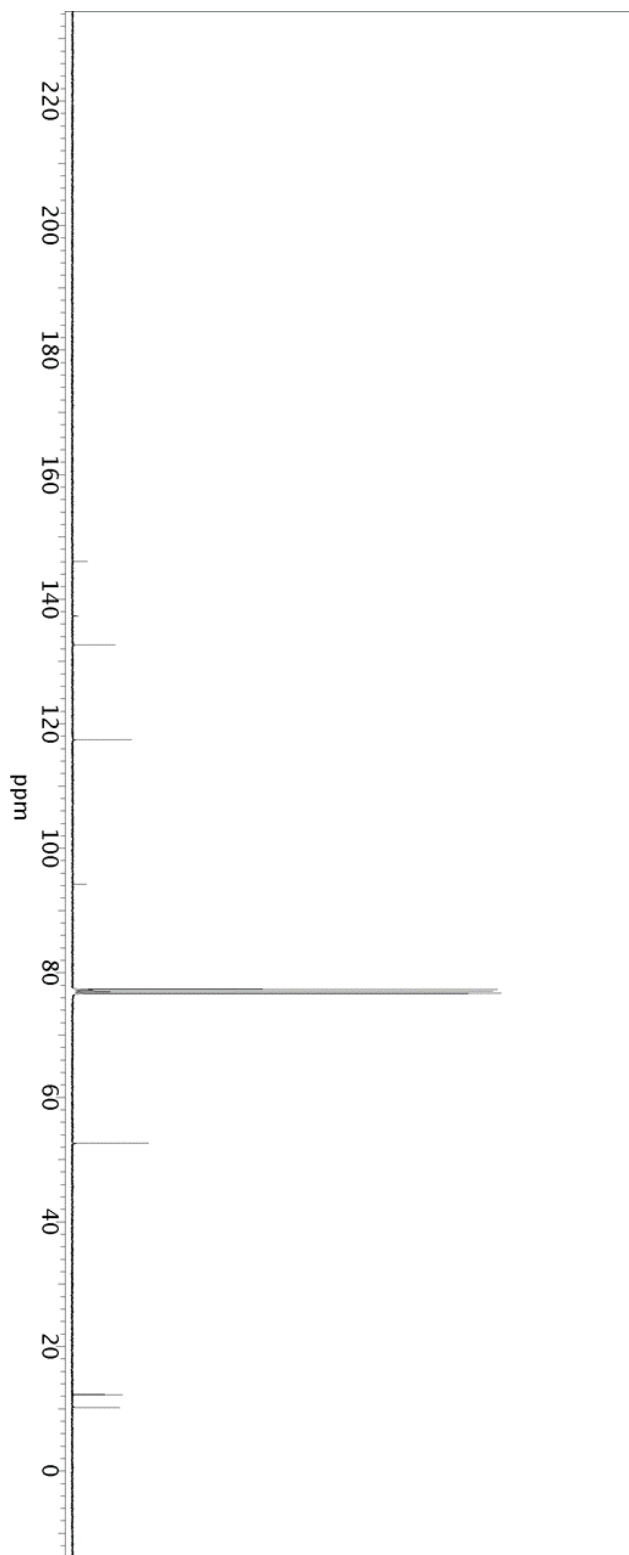
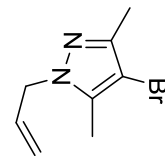
Appendix 16: ^{13}C NMR Spectrum of 33a.



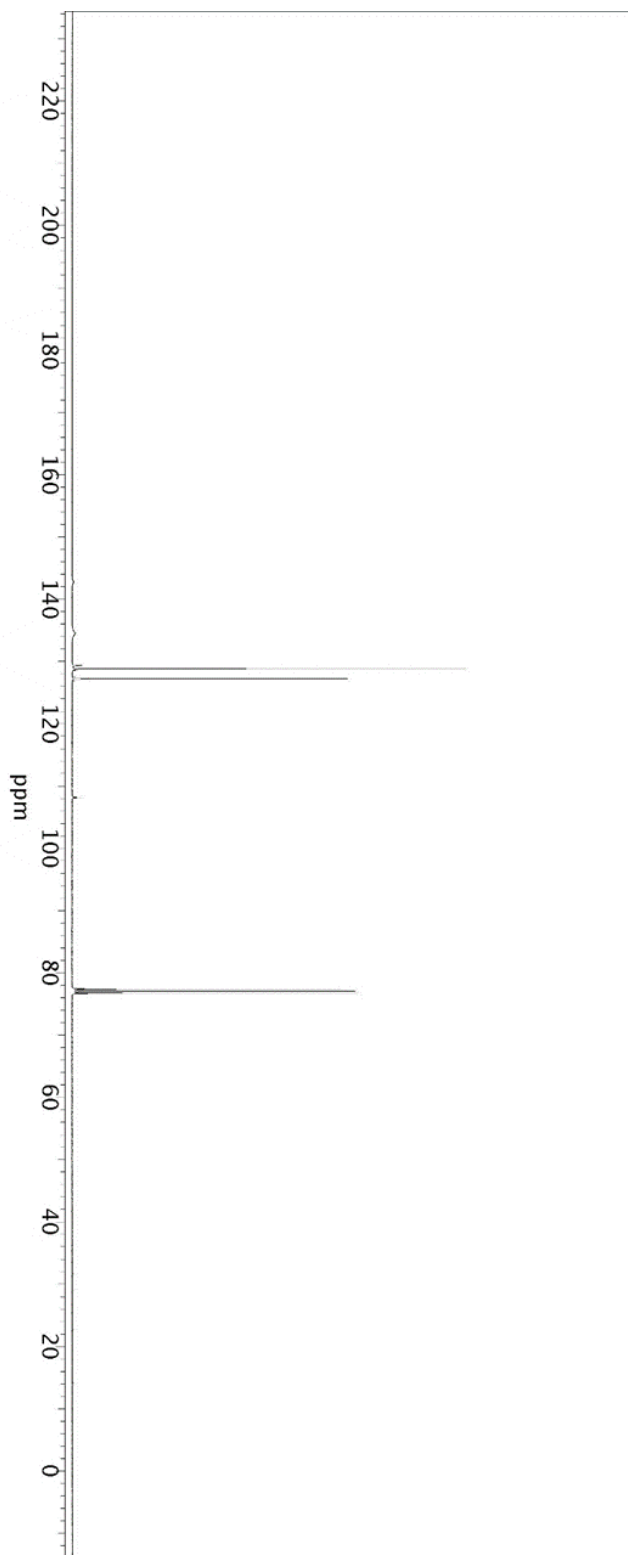
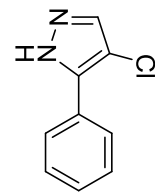
Appendix 17: ^{13}C NMR Spectrum of **33b**.



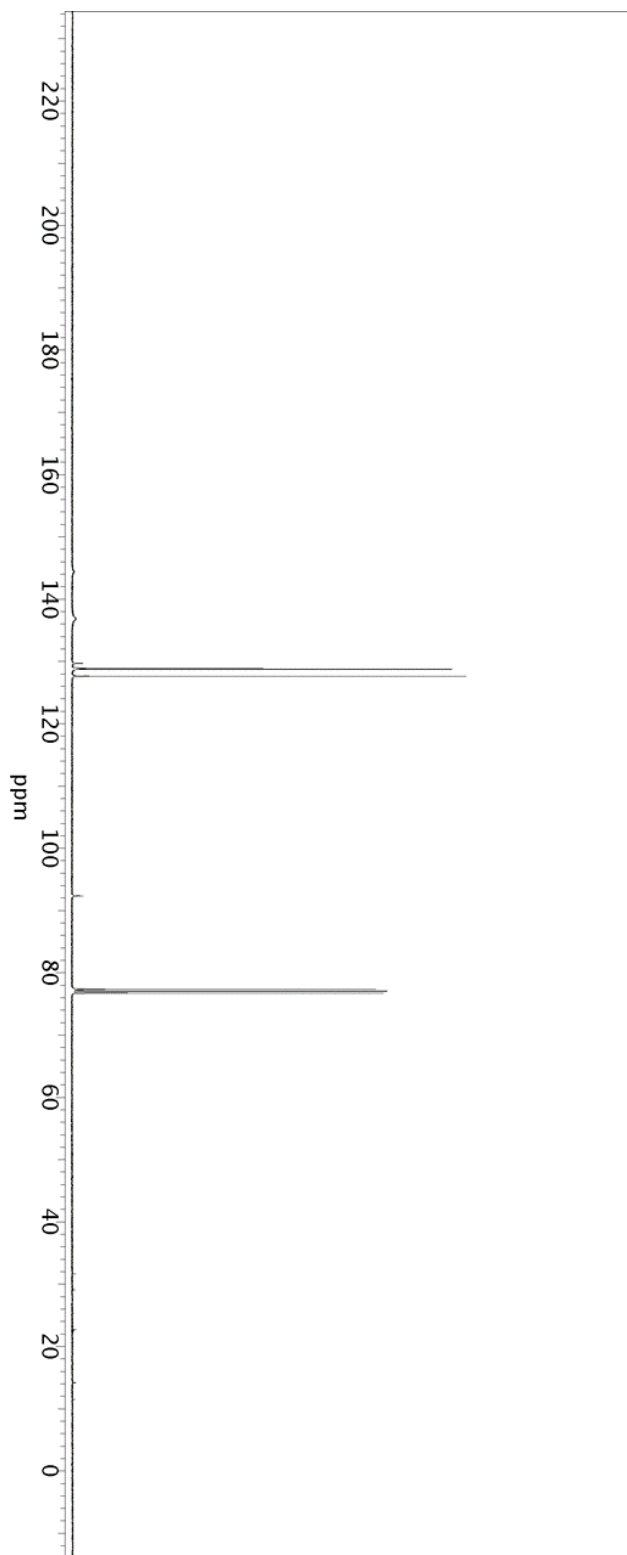
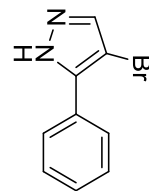
Appendix 18: ^{13}C NMR Spectrum of **34a**.



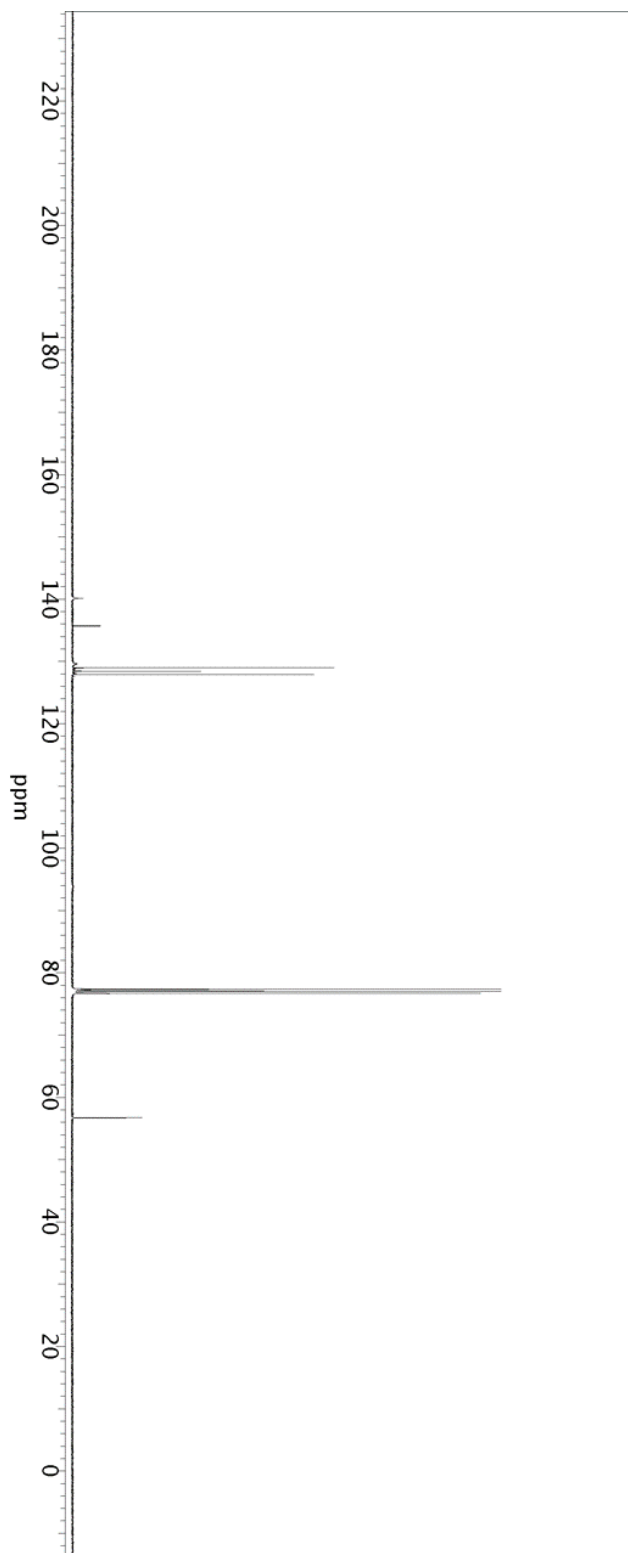
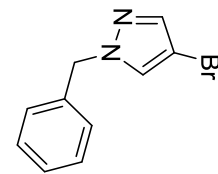
Appendix 19: ^{13}C NMR Spectrum of **34b**.



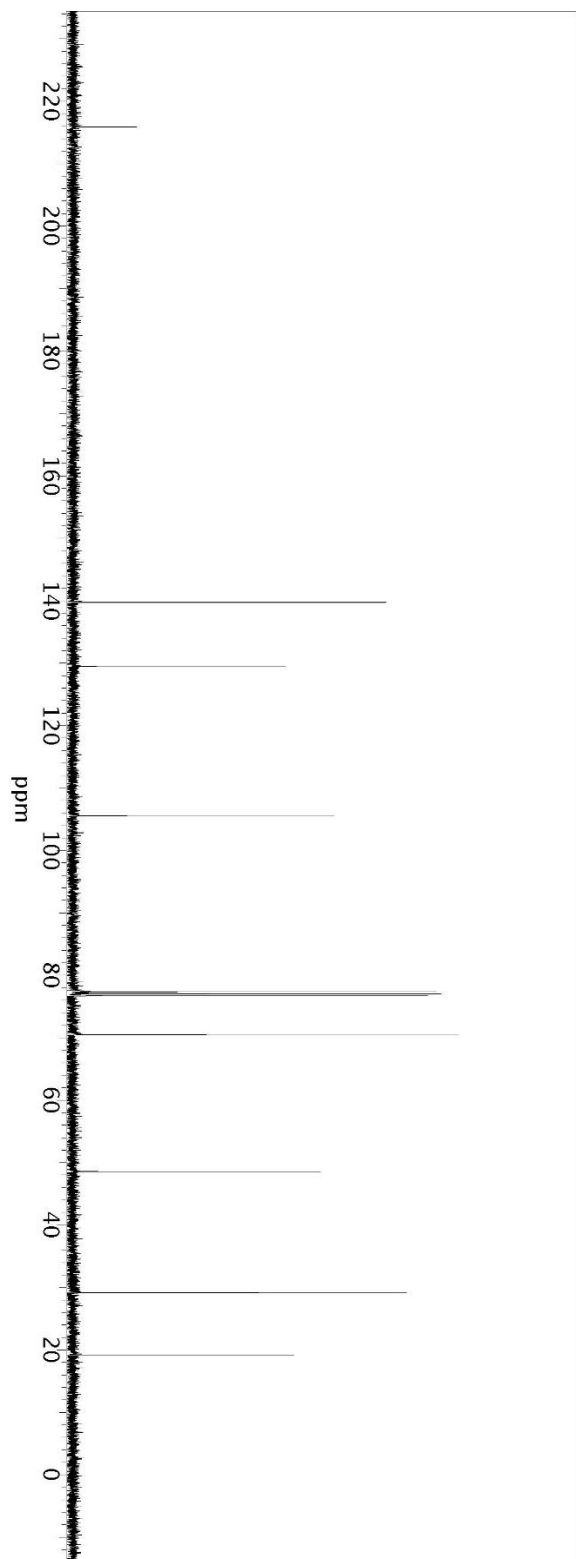
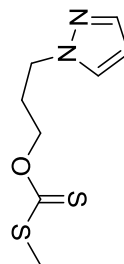
Appendix 20: ^{13}C NMR Spectrum of **35a**.



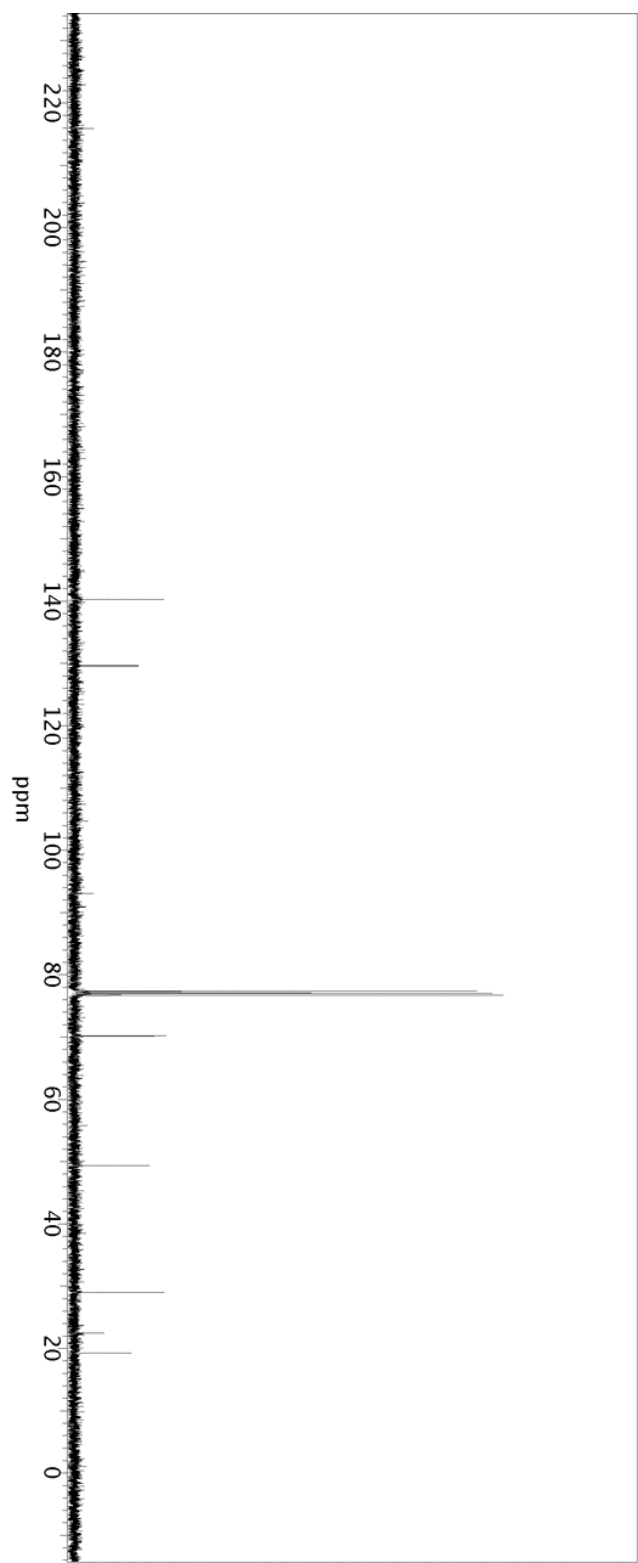
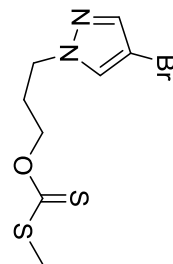
Appendix 21: ^{13}C NMR Spectrum of **35b**.



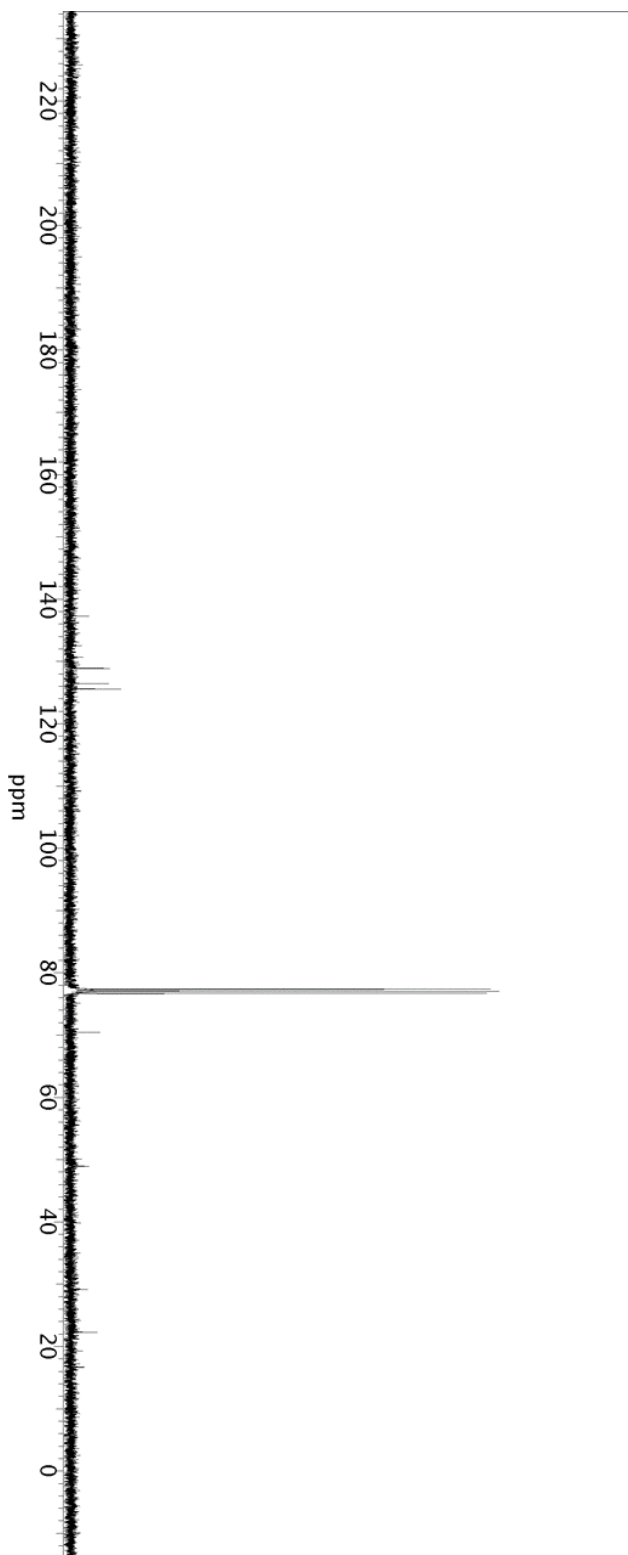
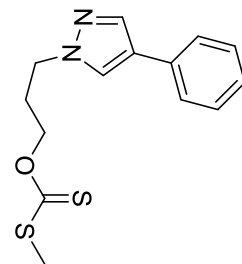
Appendix 22: ^{13}C NMR Spectrum of **36**.



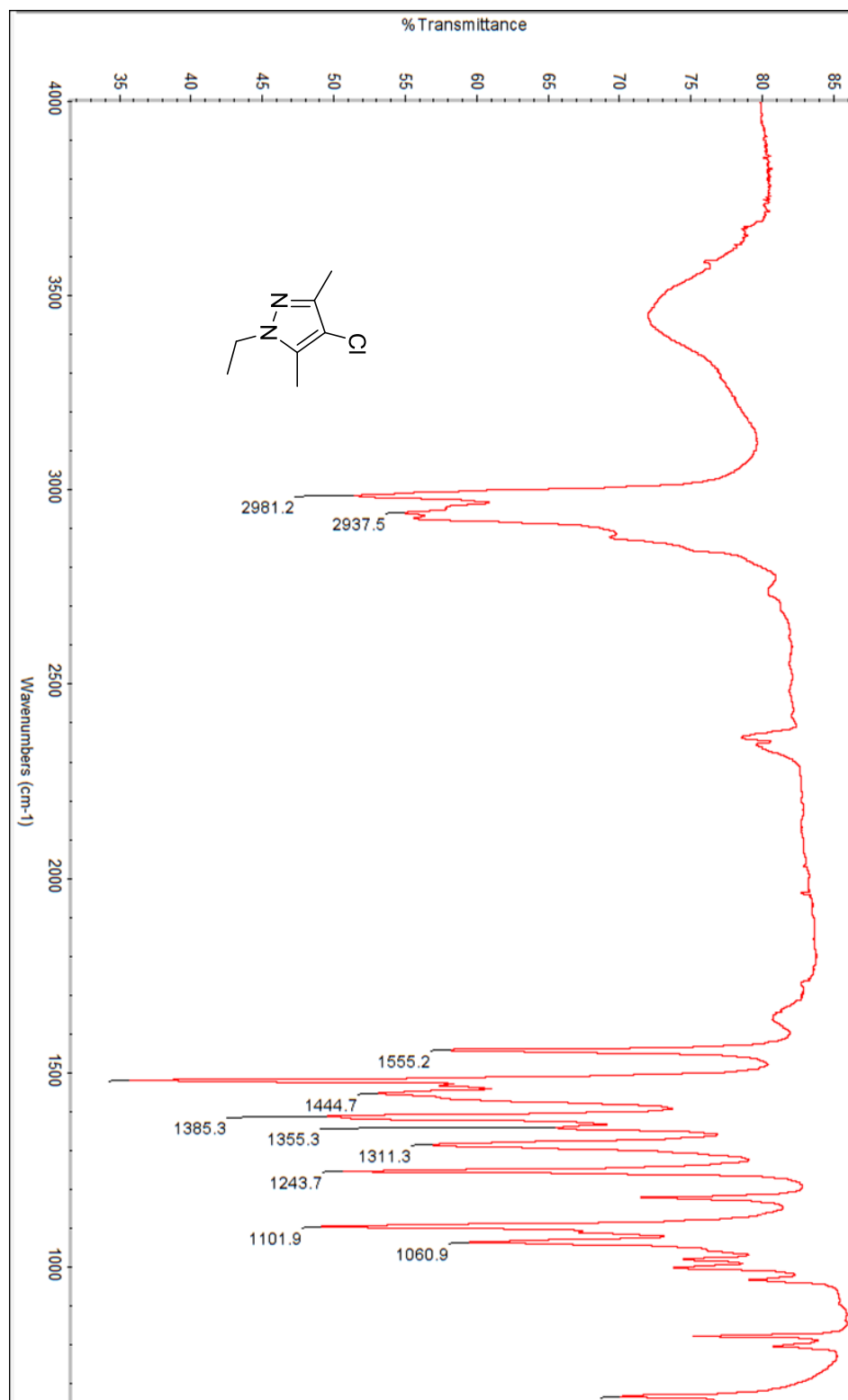
Appendix 23: ^{13}C NMR Spectrum of **40**.



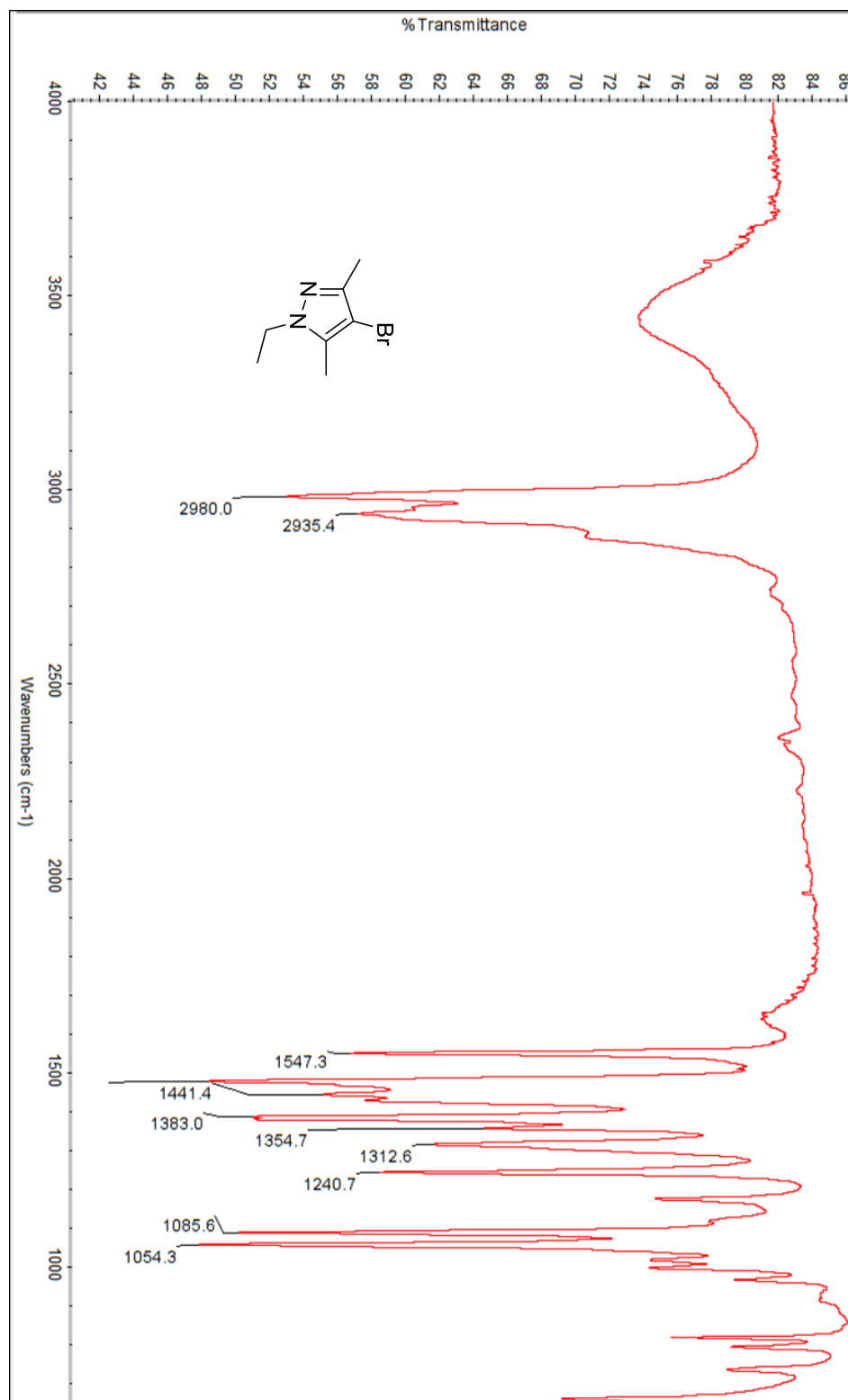
Appendix 24: ^{13}C NMR Spectrum of 38.



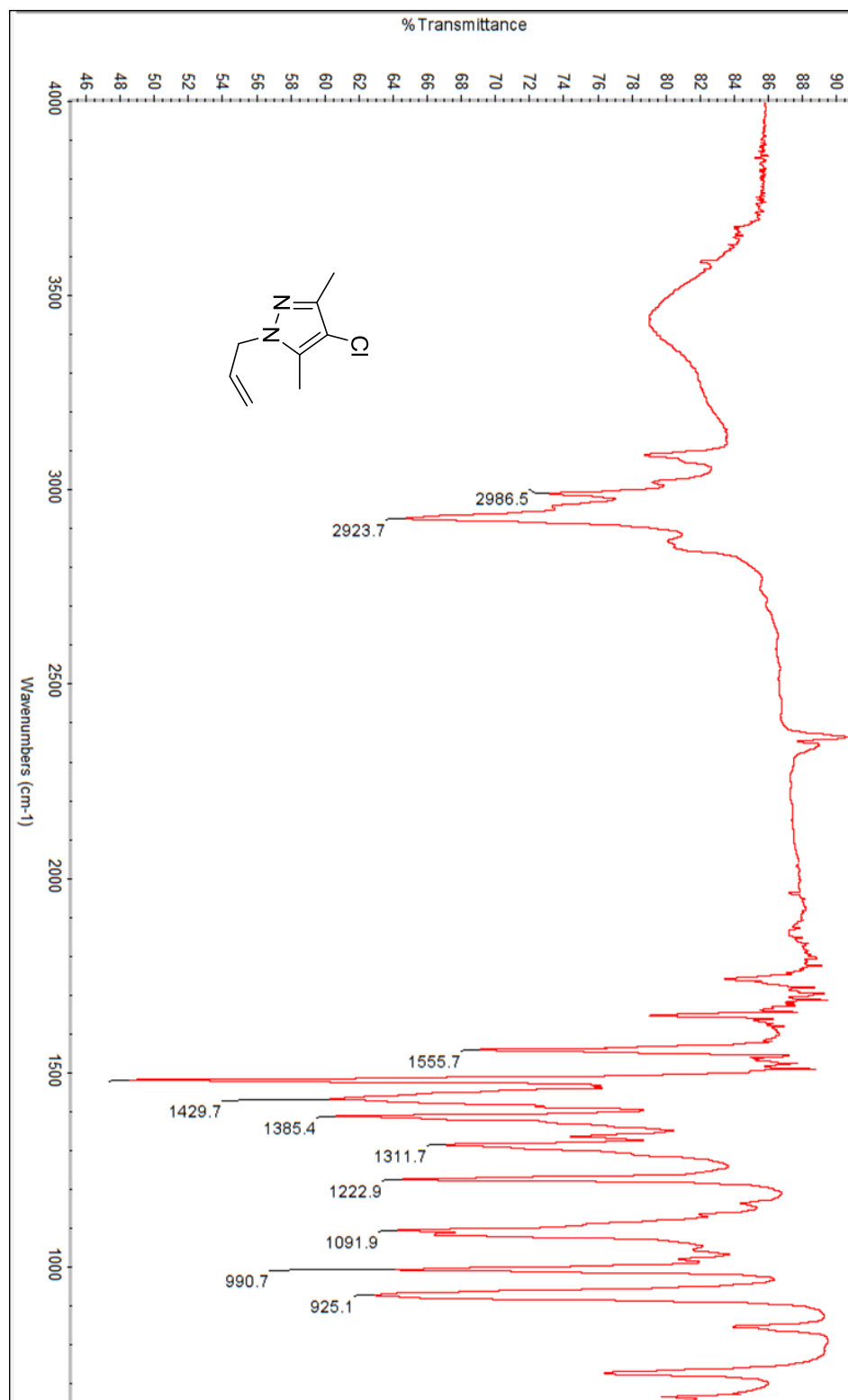
Appendix 25: ^{13}C NMR Spectrum of 37.



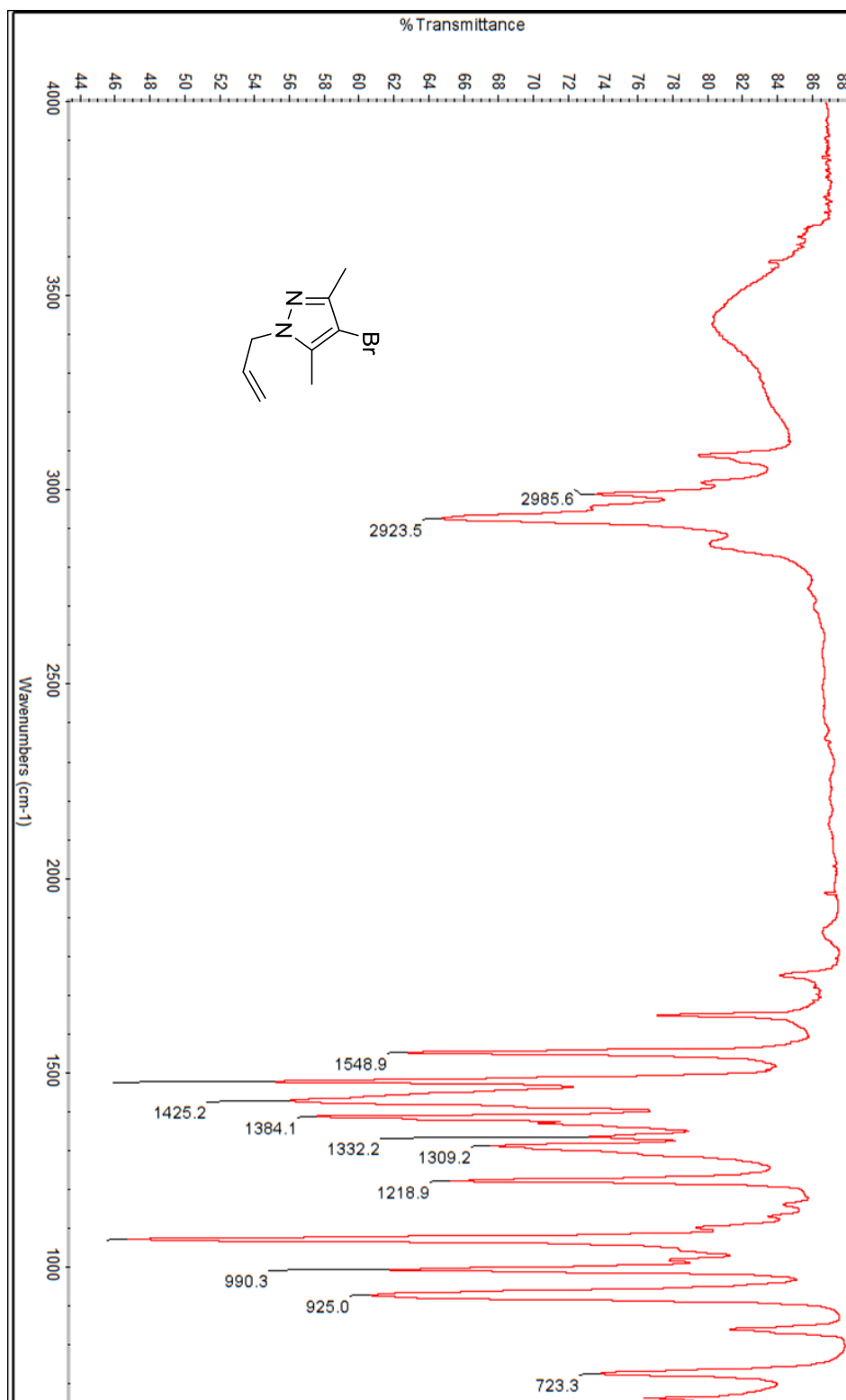
Appendix 26: IR Spectrum of 33a.



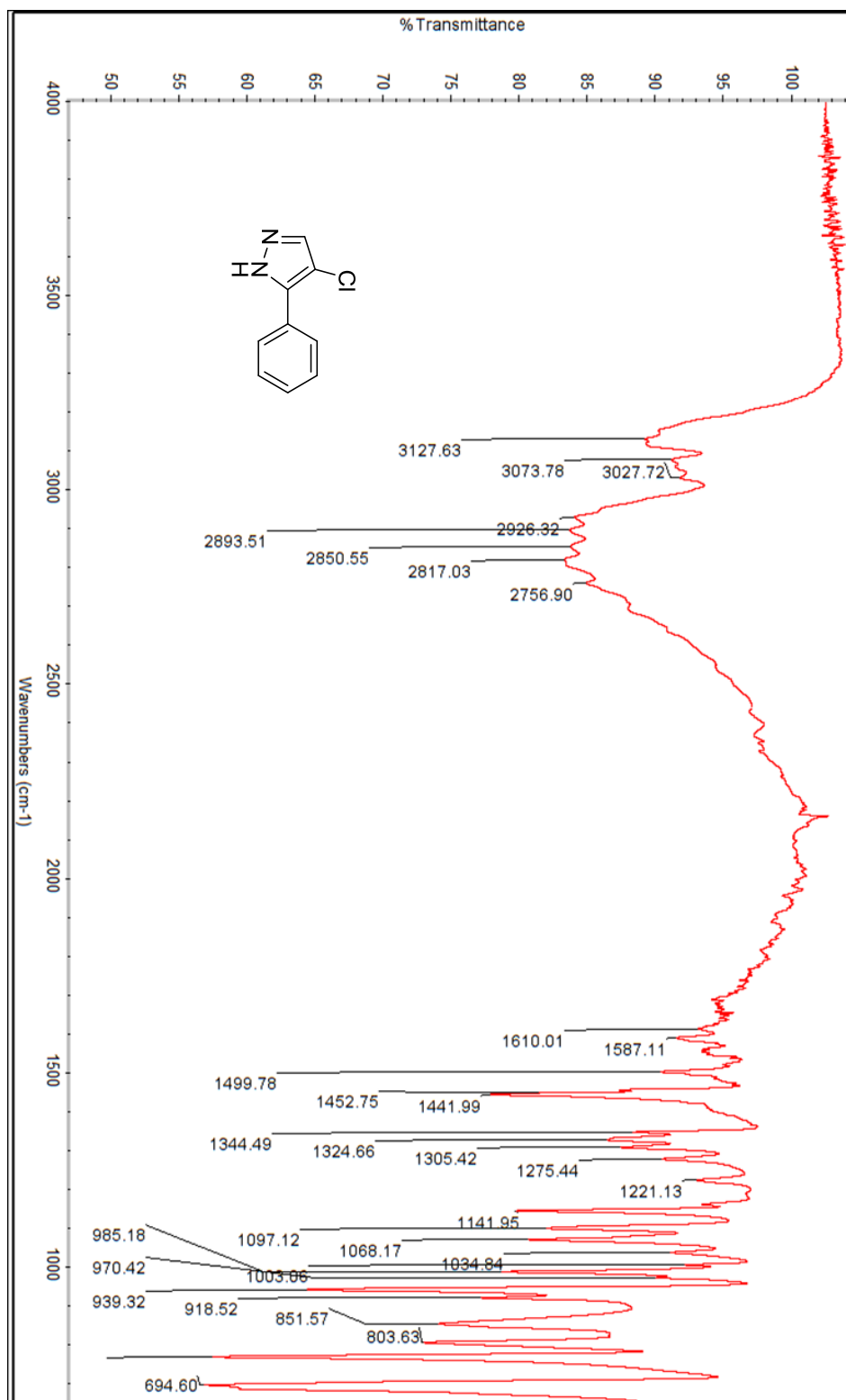
Appendix 27: IR Spectrum of 33b.



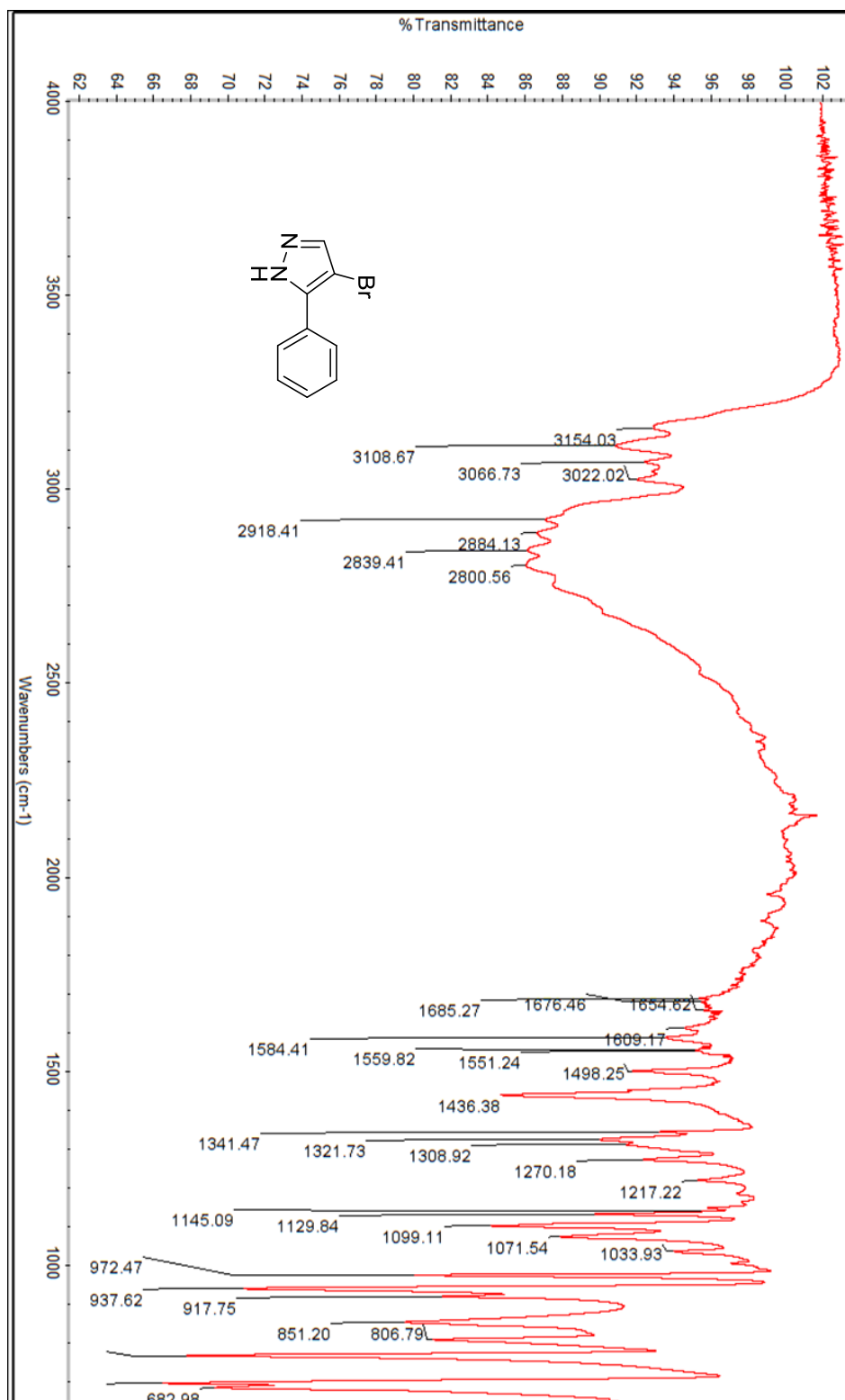
Appendix 28: IR Spectrum of 34a.



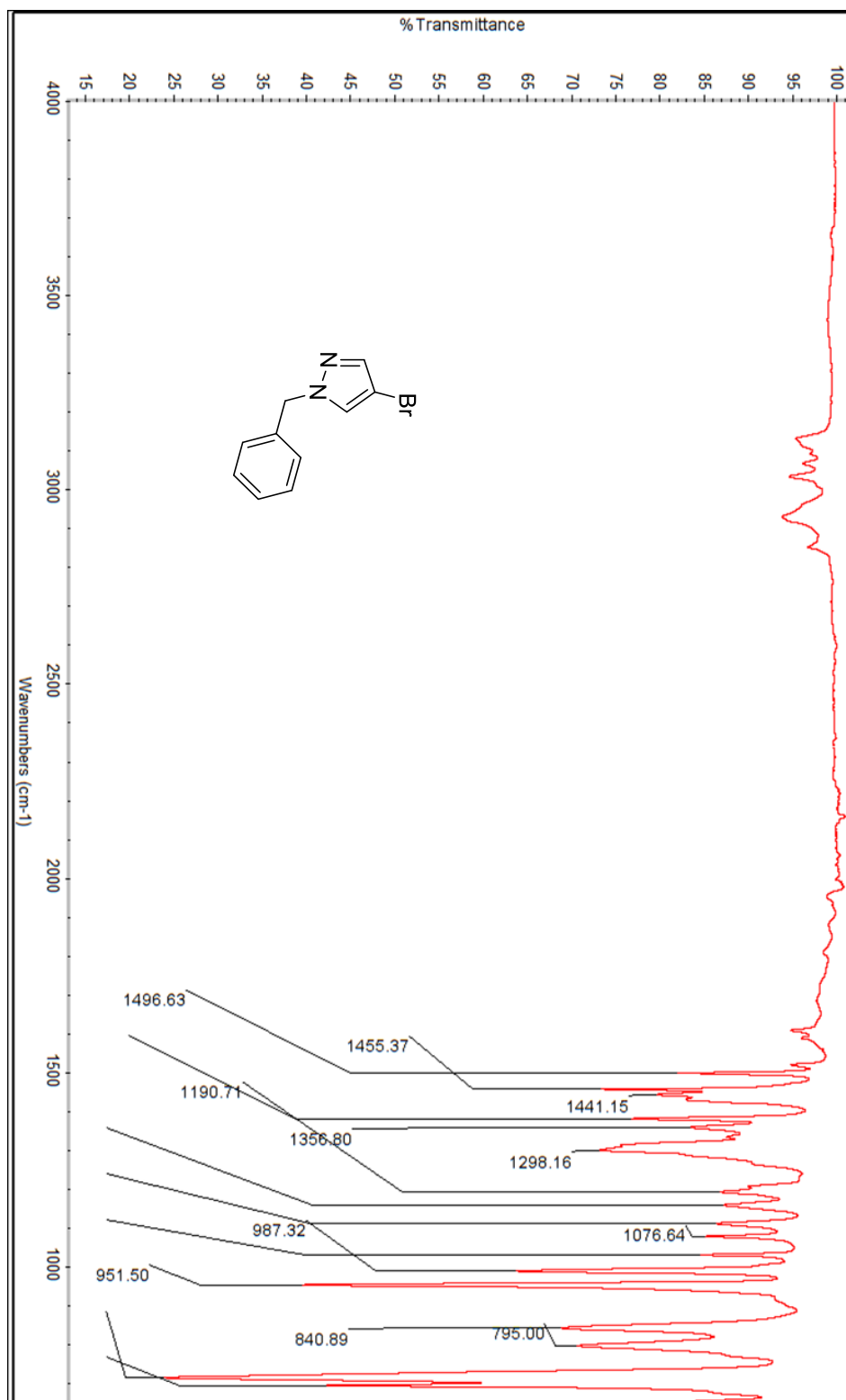
Appendix 29: IR Spectrum of 34b.



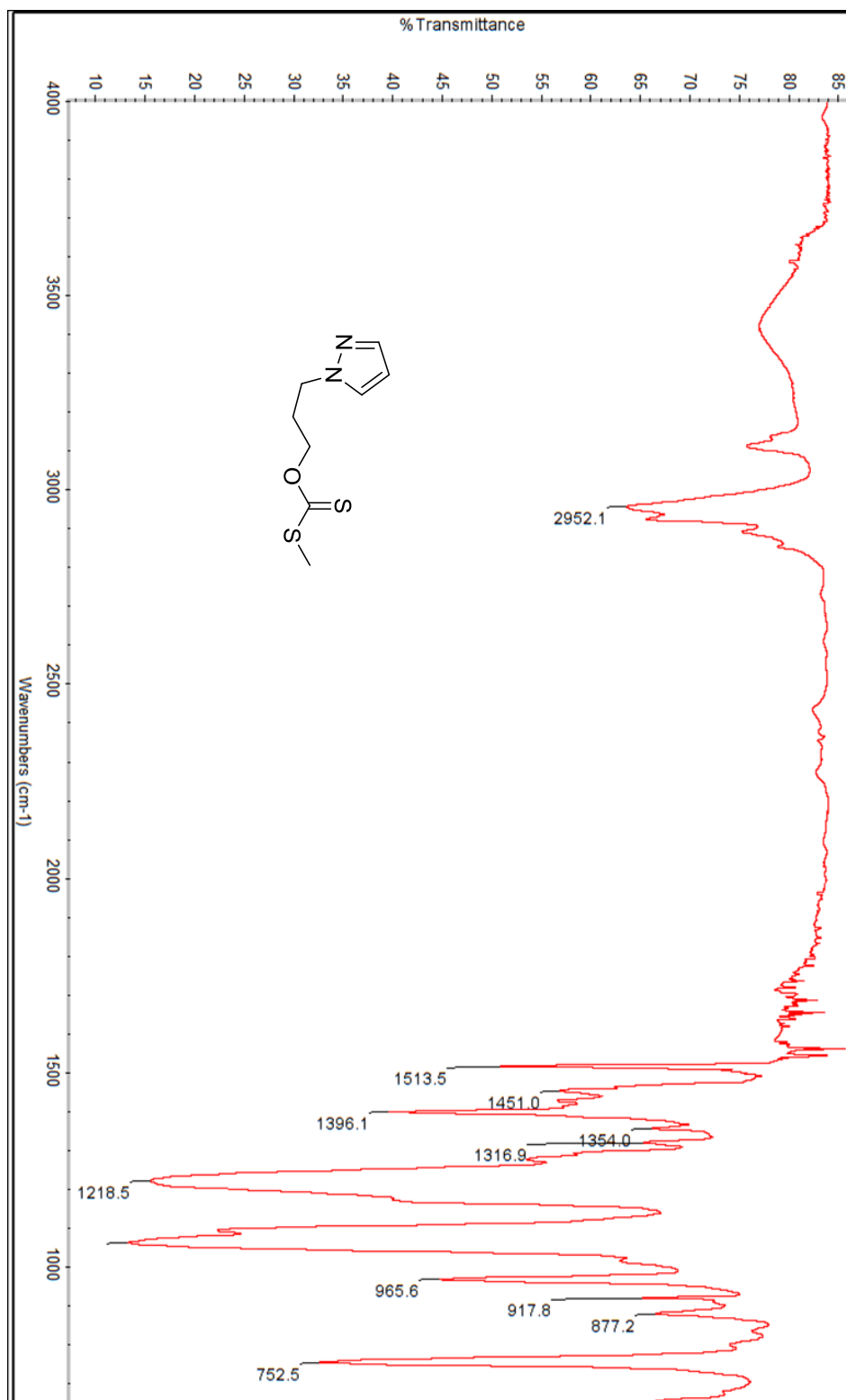
Appendix 30: IR Spectrum of 35a.



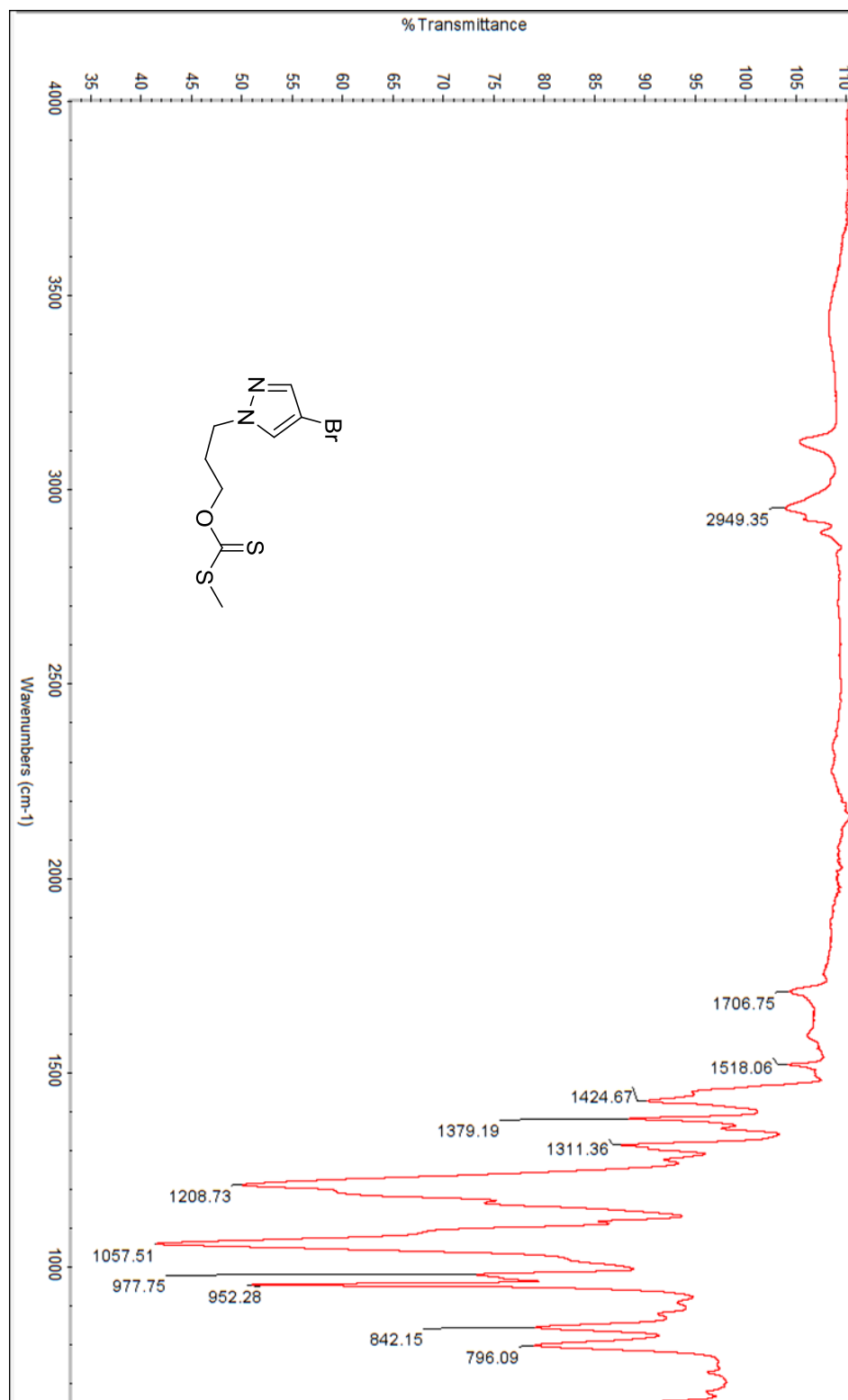
Appendix 31: IR Spectrum of 35b.



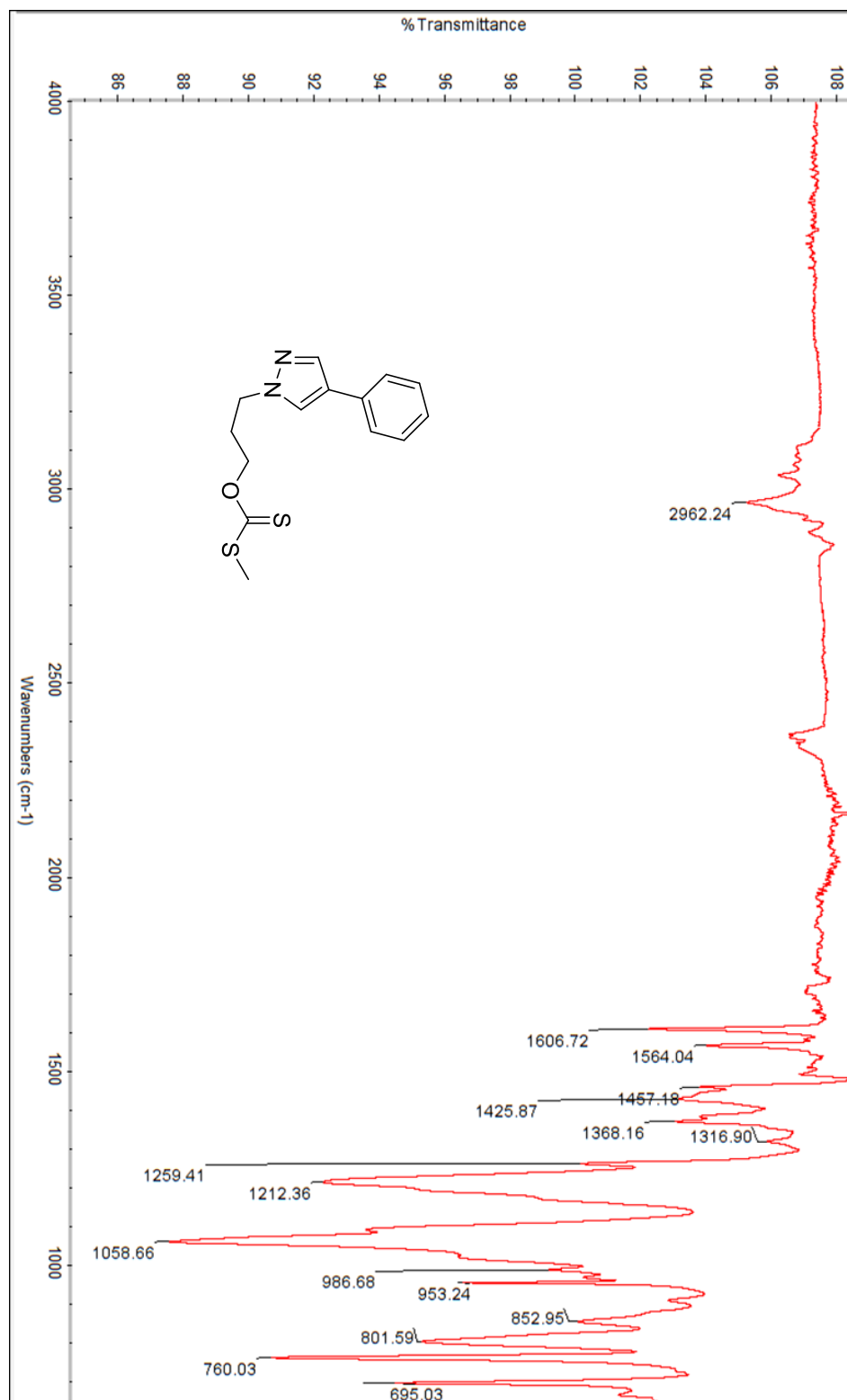
Appendix 32: IR Spectrum of 36.



Appendix 33: IR Spectrum of 40.



Appendix 34: IR Spectrum of **38**.



Appendix 35: IR Spectrum of 37.