REACTIVE AZOLYL INTERMEDIATES:

GENERATION VIA PHOTOCATALYSIS AND SYNTHETIC

UTILITY

By

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Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
December 2017

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ACKNOWLEDGEMENTS

“For My Family”

Acknowledgements reflect the views of the author and are not endorsed by committee members or Oklahoma State University.

ACKNOWLEDGEMENTS

I would like to express my appreciation to my PhD advisor, Dr. Jimmie D. Weaver. Throughout my time here, he has constantly pushed me toward scientific excellence and given me a considerable amount of freedom for the exploration in my research. I know that Weaver's approach to scientific problems will guide me throughout my career.

I would also to thank my thesis committee, which includes Dr. Rahaim Ronald, Dr. Richard Bunce, Dr. Jeffery L. White and Dr. Wouter Hoff. These individuals have played an important role in my professional growth at OSU, and I appreciate their guidance.

I would also like to thank research funding sources which includes NSF, OSU-startup funds, and also to the chemistry department for providing TA support in the first two and half years of my graduate studies.

These acknowledgements are not complete without mentioning my siblings, Harsh and Navpreet. Thank you for always standing by my side; I adore both of you. Finally, to my research lab colleagues Kamaljeet, Kip, Sonal, Jon, Manjula, Winston, Sameera, Dr. Mohammad O. B. Khaled, and Dr. Anuradha Singh. It was a great pleasure working with you and sharing your ideas, help, and humor.

Lastly, I could not have made it throughout my time in graduate school without my husband and biggest supporter, Kamaljeet Singh. He has always encouraged me to aim higher.

I would to like to thank and dedicate this thesis to my parents, Amarjeet Singh and Nirmala and my parent in laws, Gurbachan Singh and Balbir Kaur, for supporting me and helping me to realize my potential. I appreciate all of the time that they have been there for me and their support has made an enormous impact on my lif

Name: AMANDEEP ARORA

Date of Degree: DECEMBER, 2017

Title of Study:

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Major Field: CHEMISTRY

Abstract:

We have conducted a systematic study of photocatalyst-mediated electron transfer from amines to 2-haloazoles with a particular interest in the nature, reactivity, and utility of the intermediates that can be generated. Electron transfer converts these stable molecules into reactive intermediates, whose behavior often depends entirely on the identity of the halogen that undergoes substitution. The result is both diverse chemistry and an alternative way of thinking about the chemical reactivity of these motifs. The divergent pathway is illustrated by 2-bromoazoles as well as 2-diazonium benzothiazole, which yield azolyl radicals that can be added to π-bonds. In contrast, 2-chloroazole substrates give an entirely different reaction profile, and we believe that bond formation takes place with a radical anion, rather than a radical. Under the appropriate reaction conditions, the transient reactive intermediates can be coupled with various partners to provide rapid access to new chemical methods such as alkylation, arylation and alkenylation as well as iterative synthesis of azoles and other arenes. Furthermore, since the reaction is mediated by electron transfer, minimal prefunctionalization of the coupling partners is needed, making this strategy attractive for synthesis.

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INTRODUCTION

1.1 Historical background

Substituted azoles and other heteroarenes are important structural motifs in a number of natural products,[1] and pharmaceuticals,[2] as well as functional organic molecules[3] (Figure 1). Substituted imidazole, oxazole, thiazole, and other heteroarene derivatives have exhibited a wide range of bioactivities, including anti-tumor activity,[4] ROCK-II inhibition,[5] anti-depressant,[6] anti-inflammatory,[7] anti-psychotic,[8] and anti-fungal,[9] as well as anti-bacterial.[10] Not only in medicinal chemistry are they an indispensable motif, but poly-arylated azoles, and other heteroarenes can also be found in a number of organic electronic devices.[11] Because of their importance, development of cost-effective, and step-economic methodologies that allow the rapid exploration of azolyl and heteroaryl chemical space is always in demand. As such, a great deal of attention has been given to the synthesis of these heterocycles development *via* cyclodehydration,[12] or *de novo* synthesis (Scheme 1). While these methods are often ideal for delivering the desired heterocycles with minimum waste (i.e. water), they often suffer from the requirement of particular functional groups at strategic locations, which often requires a lengthy synthetic process to deliver the desired product. For example, in Scheme 1, if we want to install a different group at any other positions such as C-4 and C-5 on the azole ring **1e** (Scheme 1),[13] we would have to begin the synthetic sequence again, using the appropriately substituted starting material for every substrate. Furthermore, the appropriately substituted starting material may not be available, or may not react well, which poses a further limitation to the synthesis of azole derivatives *via de novo* synthesis. Thus, in a situation where studying the structure activity relationships (SAR) is the objective, these strategies often leave chemists wanting, since they require the synthesis of coorectly derivatized piece which can then be utilized to build the core heterocycle for every substrate.

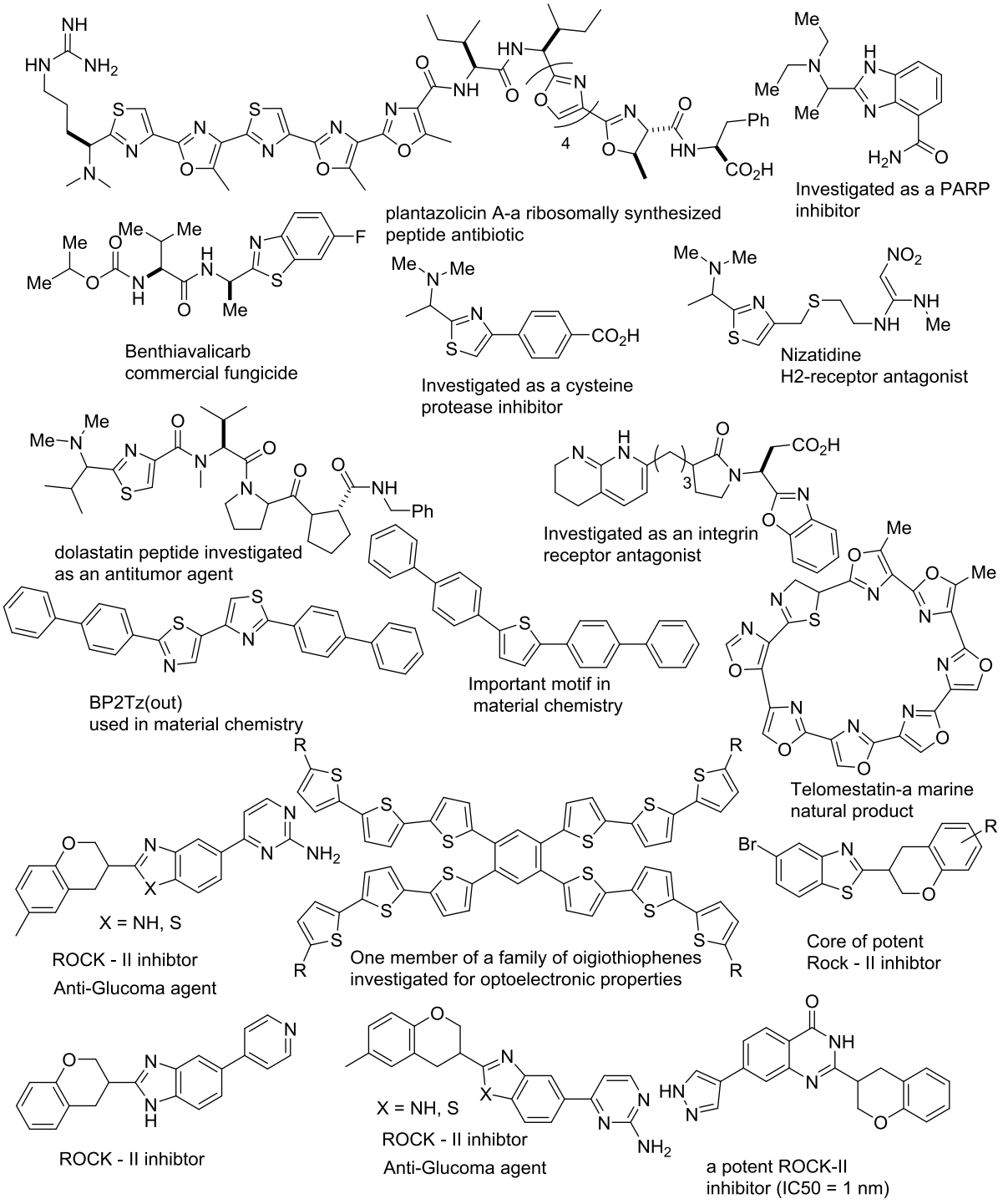
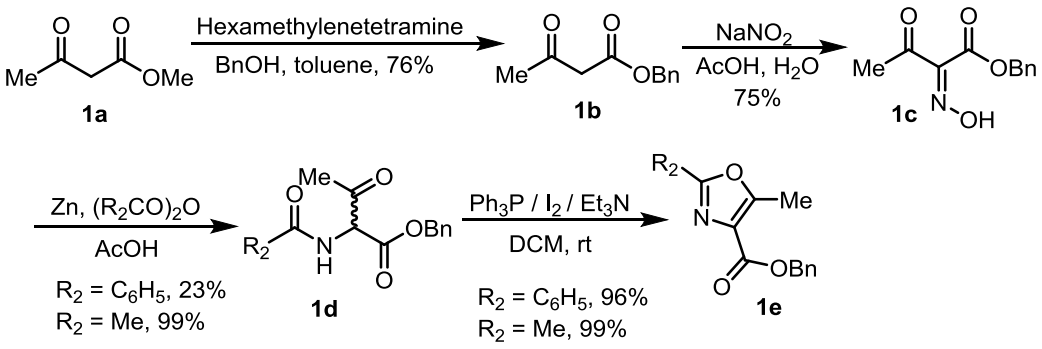


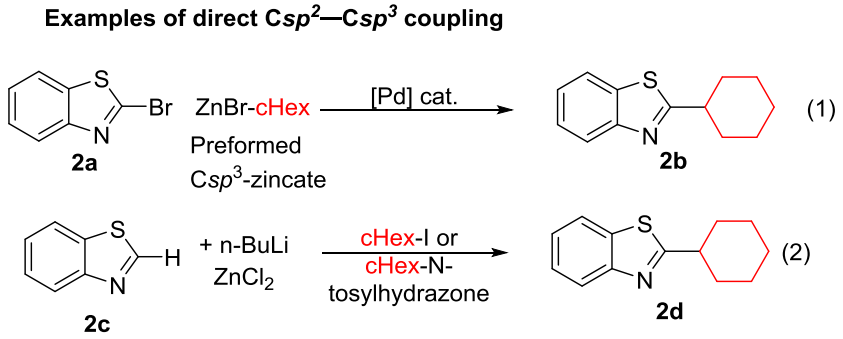
Figure 1. Important biological active and optoelectronically substituted azoles and heteroarenes.

In some cases, it can be difficult, if not impossible, to synthesize the desired substrate. Moreover, in this particular case (Scheme 1), triphenylphosphine oxide (TPP=O) is formed as a byproduct in the cyclization step, which is considerably less green than water.



Scheme 1. A typical synthesis of an oxazole *via* a cyclodehydration strategy.

In addition to the aforementioned strategies, transition metal catalyzed cross-couplings[14,15,16] reactions have also received much attention, with respect to azole . In this context, Pd-mediated cross-couplings[17] have also been extensively developed (Scheme 2, eq 1). Other methods include lithiation[18] either by C–H deprotonation or lithium-halogen exchange (eq 2). In both cases, reactivity patterns and limitations are well established. One drawback to these methods are the need for preformed organometallics, which are often basic, and sometimes difficult to store and handle. In addition, often transition metal mediated reactions are limited by the ability of the heterocycles to coordinate the catalyst. Nonetheless, these methods are attractive because they allow the rapid cross coupling of an azole.



Scheme 2. Selected examples of direct cross-coupling reactions to synthesize substituted azoles.

Assuming that the azole core is desired, a more convenient approach to SAR of the azole or heteroarene motifs, than *de novo* synthesis, would be a direct fucntionalization of the azole or heteroarene with the desired substituents. This would not only reduce the number of steps required to prepare azole libraries, but might also provide a greater number of potential analogs, and serve as a more general synthetic strategy. We envisioned an approach in which photoredox catalysis enabled single electron transfer to azole or heteroarene halides, which would result in the formation of reactive azolyl or heteroaryl intermediates. We further postulated that these reactive intermediates could be exploited for the elaboration of the cores of azoles and heteroarenes.

The bulk of this research dealt with the systematic investigation of the reactive azolyl or heteroaryl intermediate generated *via* photoredox catalyzed single electron transfer from tertiary amines to azolyl- or heteroarylhalides. We found that the precise nature, and behavior, of the azolyl intermediate, which forms after electron transfer, depends completely on the type of halogen that undergoes substitution. Said differently, we have found that the identity of the halogen attached at the 2-position is the key factor in determining the chemistry of the reactive intermediate. Under visible light photocatalytic conditions, we propose that 2-chloroazoles result in the generation of chloro azolyl radical anions upon single electron transfer (SET), and that this is the primary intermediate. Furthermore, we showed that the reactive chloro azolyl radical anion intermediate can be utilized in the C–H functionalization of tertiary aliphatic amines to synthesize α-azole carbinamines (Chapter 2).[19] In sharp contrast to this, 2-bromoazoles, as well as 2-diazonium azoles, and other heteroaryl bromides, result in formation of relatively long-lived azolyl or heteroaryl radical intermediates upon SET, rather than radical anions. This is evidenced largely by the entirely different reaction profiles that this intermediate displays. Utilizing the radical intermediate generated from 2-bromoazoles, we demonstrated reductive alkylation (Chapter 3),[20] alkenylation (Chapter 4), and arylation via C–H functionalization of the arene[21] (Chapter 5) were all possible. Furthermore, we showed that they can also be utilized for the direct C–H arylation of electron deficient heterocycles starting

with 2-aminoarenes converting them *in situ* to the 2-diazonium arenes (chapter 6), and with clever planning that this reactivity can also be used for the iterative synthesis of oligoarenes (chapter 7).

1.2 Radical anion fragmentation

The diverse outcomes of these reactions can be understood to be a result of visible light photoredox catalysis mediated SET process in which an electron is added to the LUMO of the azole or heteroarene, which is typically π* in character. As the electron undergoes intersystem crossing from a π-radical to a σ-radical, a differential rate of fragmentation is observed between substrates (Figure 2A).[22] However, if the π-type radical anion is planar in nature, monomolecular fragmentation is symmetry forbidden, since the orbitals are orthogonal. Thus, for fragmentation to occur, the radical anion needs to distort away from planarity. The C–X bond distortion from planarity, ultimately creates orbital overlap, and allows intramolecular electron transfer to the C–X σ*-orbital.

Despite the importance of distortion from planarity to fragmentation, the energy barrier for the intramolecular electron transfer correlates to the intersection of the π* and σ*orbitals. Substitution of the aromatic motif can affect the rate of fragmentation in a couple of ways. Stabilization of the aryl radical anion *via* substitution with electronegative substituents results in a decrease in the energy of the π* energy level (Figure 2, Part B). This occurs in heteroaromatics which are more stabilized than benzenes. On the other hand, with increasing difficulty in the reduction step of the substrate, i.e. an increase to the blue line, results in a reduced energy barrier to intramolecular electron transfer, and faster extrusion of the attached halogen atom is expected. Provided that the initial electron transfer to the LUMO from the photocatalyst is exergonic, this leads to overall faster fragmentation.

The rate of fragmentation also corresponds to the size of halogen atom attached to it, though it is not the cause. As the size of the halogen atom increases, the energy of the σ*-orbital decreases, and the barrier for intramolecular electron transfer decreases (Figure 2B). Thus, in order to get a long-lived radical anion, electronegative substituents should be attached to the arene core, or an electronegative heteroatom

should be present in the aryl radical anion core, as either of these would result in the energy of π*-orbital (LUMO) being decreased, and a smaller halogen with a greater σ*-orbital energy should be used as this will increase the crossing barrier. In this case, the πRA becomes a viable intermediate for bimolecular reaction.[23]

Based on our work, we believe that for 2-chloroazoles, a long-lived πRA (radical anion) intermediate is formed. In the case of 2-bromoazoles, and 2-diazonium arenes, the πRA intermediates is short-lived, and rapidly undergoes intramolecular transfer and extrusion of the halogen (or pseudo halogen), to give rise to a long-lived σ-radical. In the case of the diazoniums, it is also conceivable that the energy of the σ* orbital drops so low, that we could enter the Marcus inverted region, and actually observe slower kinetics. However, in practice, we have not observed this. It may be that the initial electron transfer from the photocatalyst to the substrate goes directly into the σ*orbital, and not into the π*orbital.

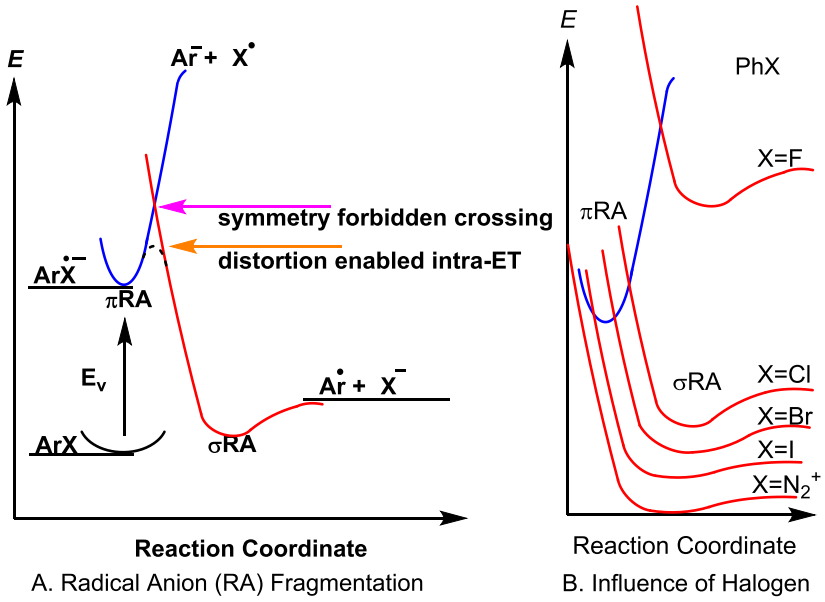


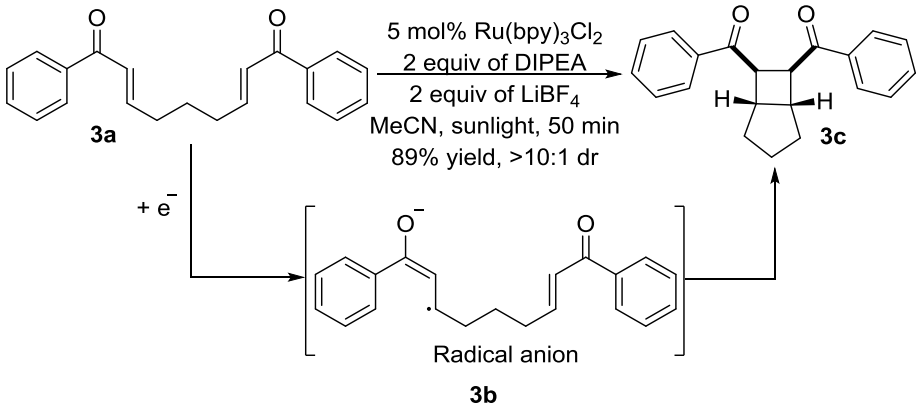
Figure 2. Radical anion fragmentation.

1.3 Synthesis of radical ion intermediate

Visible light photoredox catalysis is not only useful in terms of providing environmentally friendly and relatively benign conditions to access a variety of reactive radical intermediates, but it also provides an additional, albeit less obvious, advantage when compared to other methods. Namely, it generates transient, and reactive, intermediates in low concentrations, often resulting in better reaction outcomes. By contrast, traditionally used hazardous radical initiators such as AIBN along with stoichiometric amount of Bu_3SnH[24] , typically result in stoichiometric formation of radical intermediates in the reaction.[25] The relatively high concentration of reactive intermediates often has a deleterious effect on the overall reaction in terms of both yield and scope. The visible light irradiation used in these reactions also provides an advantage over more traditional high-energy UV-light. Since most organic molecules do not absorb photons in the range of visible light, they are impervious to unintended photochemistry. However, this situation necessitates the need for a photocatalyst. In our work, the photocatalysts were typically used in less than, or equal to, 1 mol% of the substrate in the reaction. This serves to maintain catalytic concentrations of reactive intermediates. A common reaction profile of visible light photoredox catalysis involves a photoinduced single electron transfer from a relatively poor electron donor, such as an amine, to a relatively poor electron acceptor such as a C–halogen bond. This, of course, is an oversimplification of the process, and speaks only to the ultimate location of the electrons, and not to the order of events. Ultimately, the electron transfer relies on photochemical energy to facilitate an otherwise endergonic electron transfer. The results of SET is to generate reactive radical anion intermediates, whose behavior is often dramatically different when compared to their ground states.[26] The unique reactivity of these unstable intermediates can potentially be utilized for making C−C bonds that might be difficult to achieve through established protocols.[27] In this context, recent efforts from the labs of Yoon,[26,27b] Macmillan,[28] Stephenson[27c,27e] and others[29] have demonstrated the utility of photoredox catalysis in forming C−C *via* radical reactions.

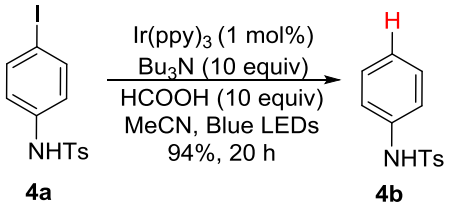
In 2008, Yoon demonstrated that a radical anion intermediate **3b** (Scheme 3) could be generated using a $Ru(bpy)_3Cl_2$ photocatalyst mediated by visible light. He further utilized this reactive intermediate

in the intramolecular synthesis of the mesodiastereomer of cyclobutane-containing bicyclic dione **3c** *via* the [2+2] cycloaddition of aryl enones **3a**.[30] This early example elegantly demonstrated the remarkable ability of the addition of an electron to alter the normal reactivity of substrates.



Scheme 3. [2+2] enone cycloaddition reaction.

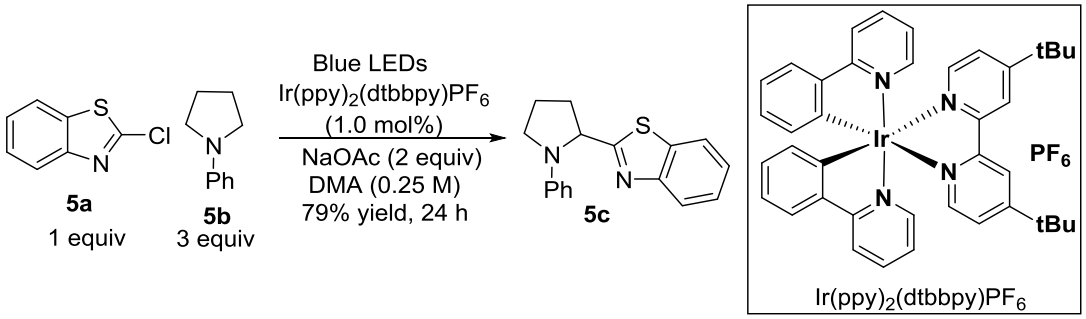
In 2012, Stephenson and co-workers demonstrated that a combination of *fac*-Ir(ppy)$_3$, photoredox catalyst and an amine and in the presence of visible light could hydrodeiodination of unactivated aryl iodides **4b** (Scheme 4).[31] Importantly, we learned several things from this example. First, the amine in the reaction was acting as an efficient quencher for the photoexcited states of the photocatalyst, which resulted in the formation of the reduced catalyst, and a potent single electron reductant, capable of adding electrons to the LUMO of iodoarenes.[32] Second, it was also shown that the amine or formate ion or amine/formic acid combination could serve as an effective H-atom donor.



Scheme 4. Stephenson's photocatalytic dehalogenation reactions.

As a part of a study of a diverse set of electron acceptors, but mostly dicyano benzenes, Macmillan and co-worker[33] (Scheme 5) demonstrated that 2–chlorobenzothiazole **5a** could be substituted using visible

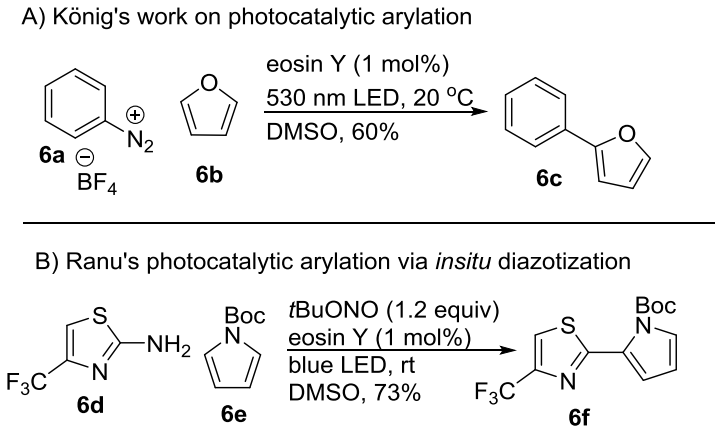
light photoredox catalysis, which facilitated a C−C bond formation with 1-phenylpyrrolidine **5b**. The authors proposed a general mechanism for all electron acceptors in which halogen (or cyanide) fragmentation led to an aryl σ-radical, though little evidence was provided, and it is not clear if a single mechanism would even be expected to hold across the diverse substrate scope. Nonetheless, it did suggest that chloroazoles were capable of inserting into an amine C–H bond, though it appears to have been limited in scope to aryl amines.



Scheme 5. Macmillan's work on photocatalytic heteroaryl carbinamine synthesis.

SET to an aryl diazonium is another way to generate a σ-radical intermediate which takes place with the loss of N_2 gas. In this context, Konig[34] has utilized pre-formed aryl diazonium salts **6a** (Scheme 6A) in a photocatalyzed aromatic substitution reaction.[29] Notably, diazonium salts are easy to reduce, resulting in better selectivity and functional group tolerance.[35]

However, in general, diazonium salts are high energy materials that can decompose violently either by heating or by mechanical force (shock-sensitive), specifically, and they are potentially hazardous on a large scale.[36] In response to this issue, Ranu demonstrated that *in situ* aniline nitrosation (Scheme 6B),[37] could result in diazonium formation, and could be utilized to generate an aryl radical utilizing a photoredox catalyst, and subsequent addition to electron rich arene-Hs.



Scheme 6. A) Konig's work on photocatalytic arylation B) Ranu's photocatalytic arylation via *in situ* diazotization.

1.4 Photoredox catalysts

The development of methods that could convert visible light energy into electrochemical potential has been an important, and active, area of investigation for nearly 40 years.[38] Driven primarily by a fundamental interest in accessing alternative energy sources (e.g., photovoltaics), a great deal of research has been devoted to the photochemistry of transition metal complexes[38] and organic dyes.[29] In addition to serving as photocatalysts within chemical synthesis, these metal complexes have wide applications within the field of inorganic and materials chemistry. For example, Ru(II) metal complexes are used as following. a) an important structural motif in dye sensitized solar cells,[39] b) as an initiator in atom transfer radical polymerization (ATRP),[40] and c) in photodynamic therapy.[41] These photoredox catalysts are generally bench stable, and poor single electron oxidants and reductants in their ground states.

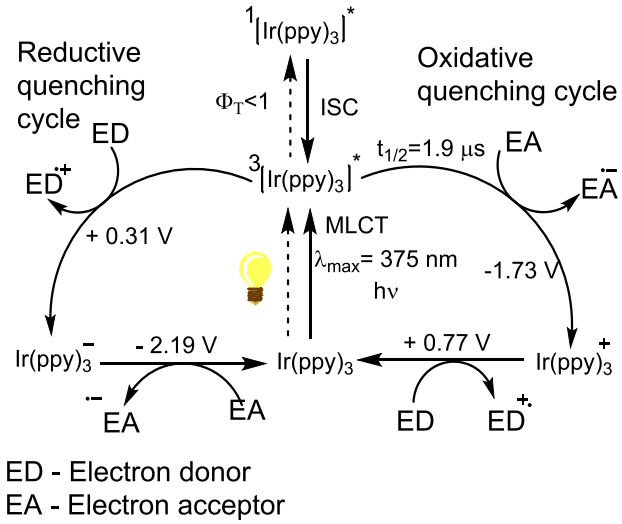
1.5 Photochemistry of the photoredox catalysts

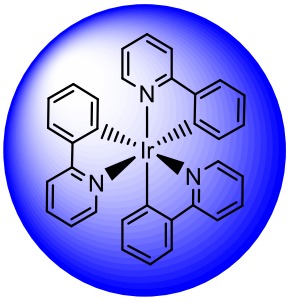
The transition metal complex that has been utilized the most in this work is *fac*-tris[2-phenylpyridinato-C_2, N]iridium(III), ($Ir(ppy)_3$), along with a few other Ir-complexes. This photocatalyst shows an absorption band that extends into the visible region from 320 to 480 nm, which originates from both allowed, and spin-forbidden, metal to ligand charge transfer (MLCT) transitions, with λ_{max} centered at

375 nm.[42] Upon absorption of a photon in the visible region (Figure 3A), an electron in the metal t_{2g} orbital gets excited to a ligand centered LUMO or the π*-orbital. This process is known as MLCT (metal to ligand charge transfer). The resulting species behaves in a unique fashion in which the metal center is simultaneously oxidized and the ligand is reduced. The MLCT singlet excited state will rapidly convert itself to more stable triplet state *via* intersystem crossing (ISC). The triplet state is generally the longest-lived photo-excited state, and stems from the fact that its decay to singlet state is spin forbidden.[43] The excited state of Ir(III) metal complexes are adequately long lived ($\tau_{1/2}$ for $Ir(ppy)_3^{3+}$ is 1.9 μs)[38] for bimolecular interactions to occur.[28] From the excited state, it can either be quenched (oxidatively or reductively),[33a] or alternatively by an energy transfer pathway.[44] To quantify this phenomenan, we refer to the standard reduction potential, which is described as an electrochemical half reaction written in the direction from oxidized to reduced species. For example, for the reaction, $Ir^{3+*} + e^- \rightarrow Ir^{2+}$, the reduction potential for *fac*-$Ir(ppy)_3$ is $E_{1/2}^{(III)*/(II)} = 0.31$ V *vs* SCE.[33a]

In the reductive quenching pathway, *fac*-$Ir(ppy)_3^*$ ($E_{1/2}^{(III)*/(II)} = 0.31$ V vs SCE[33a]) functions as an oxidant, accepting an electron from an electron donor (ED), such as triethylamine ($E_{1/2}^{red} = +0.79$ V vs SCE)[45] to give the reduced species Ir(II). This Ir(II) intermediate is one of the strongest single electron reductants known, with a reduction potential for ground state of $E_{1/2}^{(III)/(II)} = -2.19$ V vs SCE.[33a] Consequently, the Ir(II) may donate an electron to even a very weak electron acceptor (EA) to afford the ground-state Ir(III) (Figure 3A), and initiate the chemistry on the substrate. It is important to mention here, that under ideal reaction conditions, electron transfer from an amine to the excited triplet state of an Ir(III) catalyst is an endergonic process.[46] These redox potentials are likely to change with the change in experimental conditions and often deviates away from the calculated electrochemical experiments, which are performed in the absence of any additional stabilizing interactions. In such a scenario, an endergonic electron transfer could happen, but becomes less probable.[47]

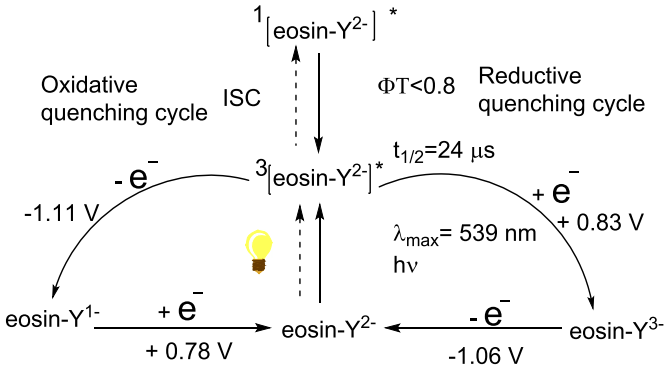
A) Summary of photoredox properties of *fac*-Ir(ppy)$_3$

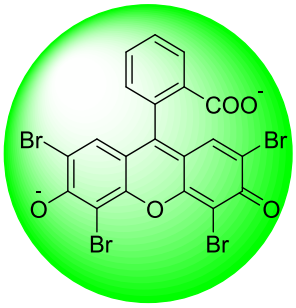




Ir(ppy)$_3$, *fac*-tris[2-phenylpyridinato-C2,N]iridium(III) is commercially available
mol. weight = 654.15 g/mol

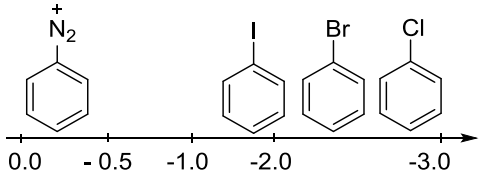
B) Summary of photoredox properties of EosinY $^{2-}$





eosin. Na_2, 2',4',5',7'-Tetrabromofluorescein disodium salt is commercial available
mol. weight = 691.9 g/mol

C) Reduction potenial of diazonium vs aryl haiides



Reduction potenial vs SCE

Figure 3. A) Summary of photoredox properties of *fac*-Ir(ppy)$_3$ B) Summary of photoredox properties of EosinY $^{2-}$ C) Reduction potential of diazonium vs aryl halide.

Alternatively, oxidative quenching of *fac*-Ir(ppy)$_3^{3+}$* ($E_{1/2}^{(IV)/(III)*}$ = -1.73 V vs SCE)[48] takes place readily, which results in the reduction of the electron acceptor (EA). Examples of oxidative quenchers are aryl-iodides ($E_{1/2}^{red}$ = – 1.67 V vs SCE).[31] The products of this single electron-transfer event are the radical anion of the EA and the oxidized form of the photocatalyst, Ir(ppy)$_3^{4+}$. This species is a strong oxidant ($E_{1/2}^{(IV)/(III)}$ is 0.77 V vs SCE),[48] which may accept an electron from even a very weak ED, to give the radical cation of ED, and return the catalyst to the Ir(III) ground-state species, completing the photocatalytic cycle.

Eosin-Y^{2-} is another photocatalyst which has been utilized in this work. It absorbs photons within the visible spectrum, and shows a characteristic absorption peak at 539 nm.[35] Upon excitation, the photoexcited state undergoes rapid intersystem crossing to the lowest energy triplet state, which has a lifetime of 24 μs.[35] As expected, the excited state of Eosin-Y^{2-} becomes both more reducing and more oxidizing when compared to its ground state, and is capable of single electron transfer.[35] The measured ground state and the estimated excited state oxidation and reduction potentials are given in (Figure 3B).[28, 49]

fac-Ir(ppy)$_3^{3+}$ ($E_{1/2}^{(IV)/(III)*}$ = -1.73 V vs SCE)[48] is a stronger reductant than Eosin-Y^{2-} (E_{red} for the exicted state=-1.11 V SCE)[34] in the excited state, and one can use this knowledge to predict reaction outcomes. For example, considering the reduction potentials of aryl diazoniums and aryl halides (Cl, Br and I) as shown in (Figure 3C).[50] Comparatively, aryl diazoniums are more easily reduced when compared to aryl halides. Therefore, a reductant such as Eosin-Y ($E_{1/2}^{II*/I}$=-1.11 V SCE)[29] can easily reduce the aryl diazonium species to generate an aryl radical. Thus, given that Eosin-Y^{2-} is cheaper than *fac*-Ir(ppy)$_3$ and can provide the necessary redox potentials for some of our reactions, we also utilized this catalyst at times.

1.6 References

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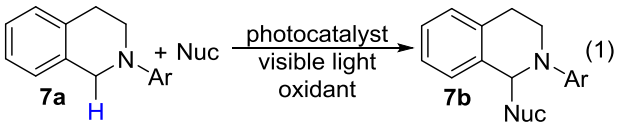
CHAPTER II

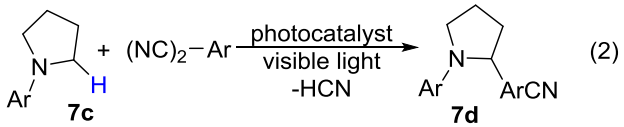
VISIBLE LIGHT MEDIATED CROSS-COUPLING OF AZOLYL CHLORIDES AND TERTIARY ALIPHATIC AMINES

With the aim of developing direct coupling methods, we investigated the synthesis of α-azole-carbinamines *via* a visible light enabled SET process. α-Azole-carbinamines are important subclass of natural products,[1] drugs,[2] and pesticides,[3] which consists of an azole attached to carbon bearing an *N*-atom of an aliphatic amine (Figure 1, Chapter 1). Recently, a number of photoredox methods have demonstrated α-amino C–H functionalization of both isoquinoline[4] (Scheme 7, eq 1) and aniline derivatives[5, 6] (Scheme 7, eq 2).

A) C-H functionalizations of isoquinoline



B) C-H functionalizations of Aniline derivatives



Scheme 7. Other strategies for photoredox mediated C–H functionalization of anilines.

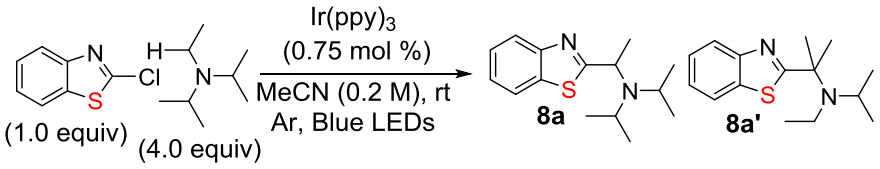
However, these methods are relatively limited since they require an *N*-aryl group such as is found within isoquinoline or other aniline derivatives. While methods have now provided access to isoquinolinyl- and anilinyl-carbinamine derivatives, along with the frequent use of simple aliphatic amines in photoredox catalysis, it was surprising to find that the C–H functionalization of simpler and far more abundant aliphatic amine had been developed.[5, 6b].

Thus, we decided to investigate whether simple aliphatic amines and heteroaryl chlorides could be cross coupled *via* photoredox catalysis. Herein, we report the use of tertiary aliphatic amines as coupling partners in the photocatalytic cross-coupling of 2-chloro-benzimidazoles, -benzoxazoles, -benzothiazoles, and -thiazoles and related derivatives.

2.1 Optimization of conditions

We began our study with 2-chloro benzothiazole, diisopropylethylamine (DIPEA, or Hünig's base) and *fac*-tris[2-phenylpyridinato-C2,N]iridium(III) *fac*-Ir(ppy)$_3$ as the photocatalyst (Scheme 8, entry 1). Initial solvent screening (entry 2) revealed that dichloromethane, toluene, tetrahydrofuran, and nitromethane gave trace conversion at best, while several polar solvents (entry 3) facilitated the reaction, with acetonitrile being optimal and giving smooth conversion using only 0.75 mol% catalyst. In all cases the major product was the coupled product **8a** arising from coupling with the carbon of the methylene rather than the methine carbon **8a'**.[7] The photocatalyst was a necessary component of the reaction and furthermore popular Ru(bpy)$_3$Cl$_2$ did not facilitate the reaction (entry 4). While initial results indicated (entry 5) that rigorous exclusion of air was not essential, we found this to be more of the exception than the rule. While most reactions still worked in air, some amines gave substantial byproducts under arerobic conditions. Therefore, we opted to run all of the substrates under an atmosphere of argon. In an effort to improve the reaction conditions, we sought to minimize the amount of amine needed. We envisioned that at least one equivalent was simply serving as a base and might be replaced with a convenient alternative. Indeed, we found that while the reaction would stall without the extra equivalents of amine (entry 6), simply replacing the extra equivalents with pyridine, imidazole, or carbonates worked well (entries 7-10). DBU (entry 11) on the other hand, gave decreased conversion and increased amounts of side products. Again, in an attempt to simplify the reaction procedure, we looked at the effect of water (entry 12). We were pleased to find water had little effect on the reaction, implying that rigorous drying of reagents and solvents were not necessary for a successful reaction. Finally, we investigated temperature as a control element. We found that the rate of reaction was dependent on temperature up to a point (entries 13-15), above which the conversion dropped

severely and was accompanied by a change in the color of the reaction solution (it turned black, entry 15). However, the regioisomeric ratio (rr) proved to be relatively insensitive to temperature, thus allowing temperature to be used as a handle for sluggish reactions. Thus, we ultimately settled on running the reaction under argon, at 45 °C, with 1.2 equivalents of amine and 2.0 equivalents of imidazole.



Entry	Modification of Experimental Conditions	GC/MS conversion[a]	GC/MS **8a**/**8a'**[a]
1	None, 13 h	67%	9:1
2	DCM, CH_3NO_2, Tol or THF	<6%	nd[b]
3	DMF, DMSO, or DMA	29-44%	nd[b]
4	No Photocatalyst or $Ru(bpy)_3Cl_2$	0%	nd[b]
5	MeCN exposed to air	57%	9:1
6	1.2 eq amine at 24 h	21%	9:1
7	2.0 eq Pyridine and 1.2 eq amine	63%	9:1
8	2.0 eq Imidazole and 1.2 eq amine	68%	13:1
9	2.0 eq Cs_2CO_3 and 1.2 eq amine	69%	9:1
10	2.0 eq K_2CO_3 and 1.2 eq amine	59%	9:1
11	2.0 eq DBU and 1.2 eq amine	32%	9:1
12	up to 15% vol:vol H_2O	65%	9:1
13	reaction run at 27 °C, 7 h	46%	9:1
14	reaction run at 45 °C, 7 h	62%	12:1
15	reaction run at 65 °C, 7 h	22%	8:1

[a]conversion were determined by GC/MS

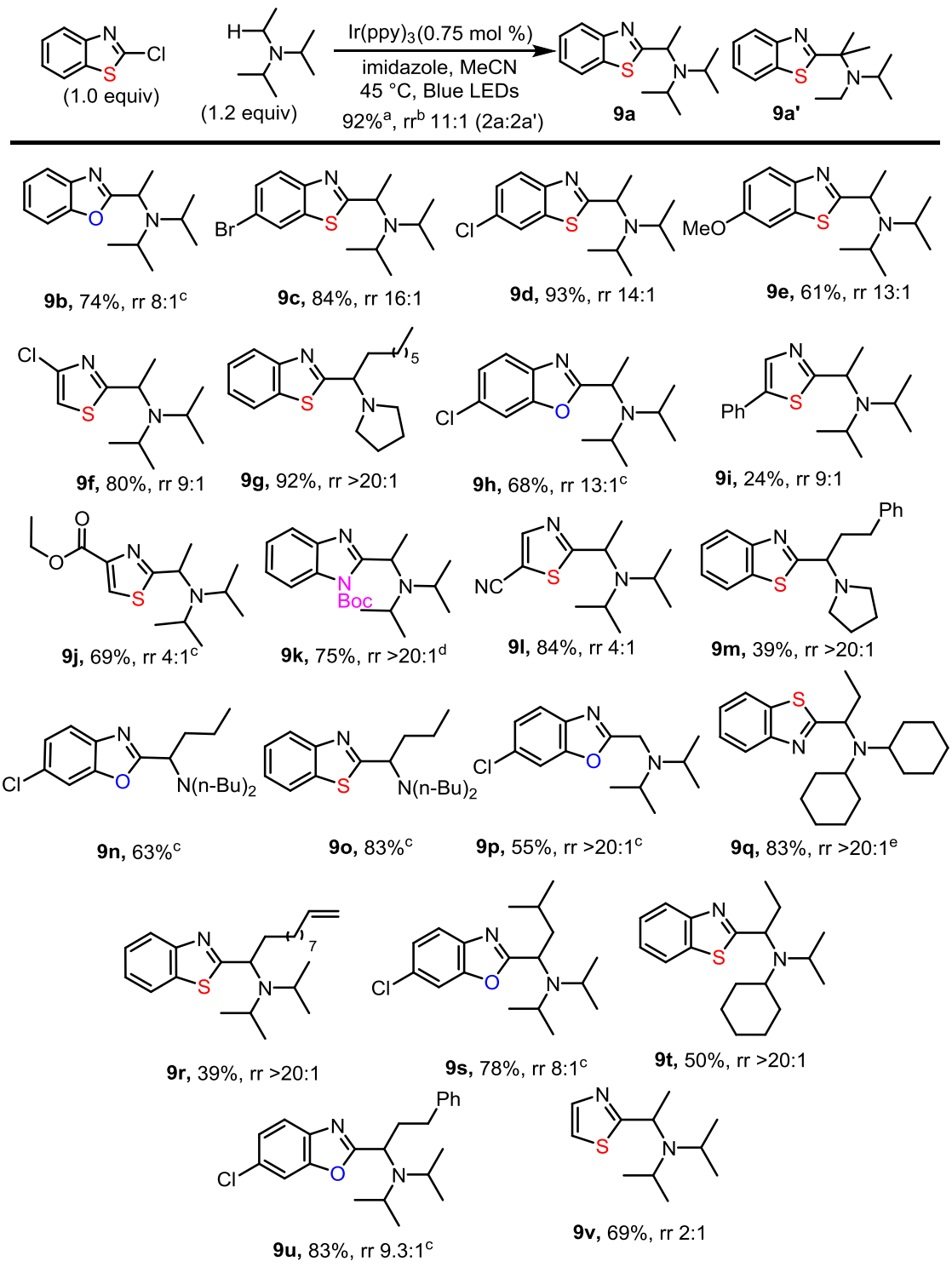
Scheme 8. Identification of the optimal conditions.

2.2- Scope of α-azole-carbinamine

With ideal conditions in hand, we next attempted to explore the scope (Scheme 9). Gratifyingly, we saw that the reaction worked well for benzothiazole **9a** (92%, rr 11:1) and a number of substituted benzothiazole substrates including those substituted with a bromide **9b**, and a chloride **9c**, which provideed the opportunity for further elaboration of the products *via* more traditional cross-coupling methodologies. The fact that neither 6-Br nor 6-Cl substituted substrates reacted suggested that the reaction is highly chemo- and regioselective for the 2-Cl position. Survival of the aryl bromide under these conditions was somewhat surprising considering that reduction of electron deficient aryl bromides has been observed under similar conditions.[7c] The reaction also works well for more electron rich benzothiazole **9e** (61%, 13:1 rr), albeit dilution was found to be necessary to achieve reasonable reaction rates. Importantly, exploration of other related heterocycles revealed that the method was not limited to benzothiazole but could be applied to benzoxazoles **9b**, **9h**, **9n**, **9p**, **9s**, and **9u**, boc-protected benzimidazole **9k** as well as simple thiazole derivatives **9f**, **9i**, **9j**, **9l**, and **9v**. In all the heterocycles studied, similar regioselectivity was observed where coupling of the less hindered C–H of the amine dominated. Gratifyingly, the reaction proved tolerant of a number of functional groups, including cyano **9l**, ester **9j**, halogens **9c**, **9d**, **9f**, **9h**, **9n**, **9p**, **9s**, and **9u**, and methyl ethers **9e** as well as terminal olefins **9r**. Finally, Boc groups **9k** survived albeit loss of the Boc group was initially problematic, but was easily circumvented by replacing the imidazole with Cs_2CO_3.

The C–H regioselectivity appears to be sensitive, in part, to substitution of the heteroaryl chloride. Comparison of benzothiazole **9a** to functionalized benzothiazoles **9c**, **9d**, and **9e** suggested that substitution at the 6-position resulted in increased selectivity. On the other hand, simplification of benzothiazole **9a** to simple thiazole **9v** resulted in diminished selectivity (11:1 vs. 2:1). Additional substitution of the thiazole, however cause the selectivity to return to more desirable levels. Substitution with an ester or a cyano group increases the regioselectivity from 2:1 to 4:1, **9v** *vs* **9j** and **9l** while substitution with a chloride or phenyl ring resulted in even more dramatic increases from 2:1 to 9:1, **9v** *vs* **9f** and **9i**. However, coupling of phenyl substituted thiazole **9i** proved to be sluggish, giving incomplete conversion and an isolated yield of only

24%. The reaction also worked well with less hindered linear amines such as tributylamine **9n** and **9o**. However, an increase in the amount of the amine was used to prevent a second arylation of the product which occurred as the reaction neared completion. Pyrrolidinyl amines also proved to be competent coupling partners **9g**, and **9m**. We observed excellent selectivity (> 20:1 rr) for the acyclic methylene over the cyclic pair of methylenes. This selectivity is particularly interesting since the vast majority of examples of *N*-oxidation[8] initiated functionalizations, as well as photochemical,[9] couplings of alkyl pyrolidines in the literature are highly selective for the endocyclic position. This finding suggests a different controlling element in this coupling reaction when compared to these processes which otherwise seem related. The reaction also works well using amines with 3 different alkyl groups **9t** and highlights the advantage of this coupling method which provides facile access to a product that would be difficult to access *via* other methods. Finally, while substrate **9p** derived from a methyl-amine offers less complexity than other substrates, it shows that the reaction also works with simpler amines giving the product as a single regioisomer.



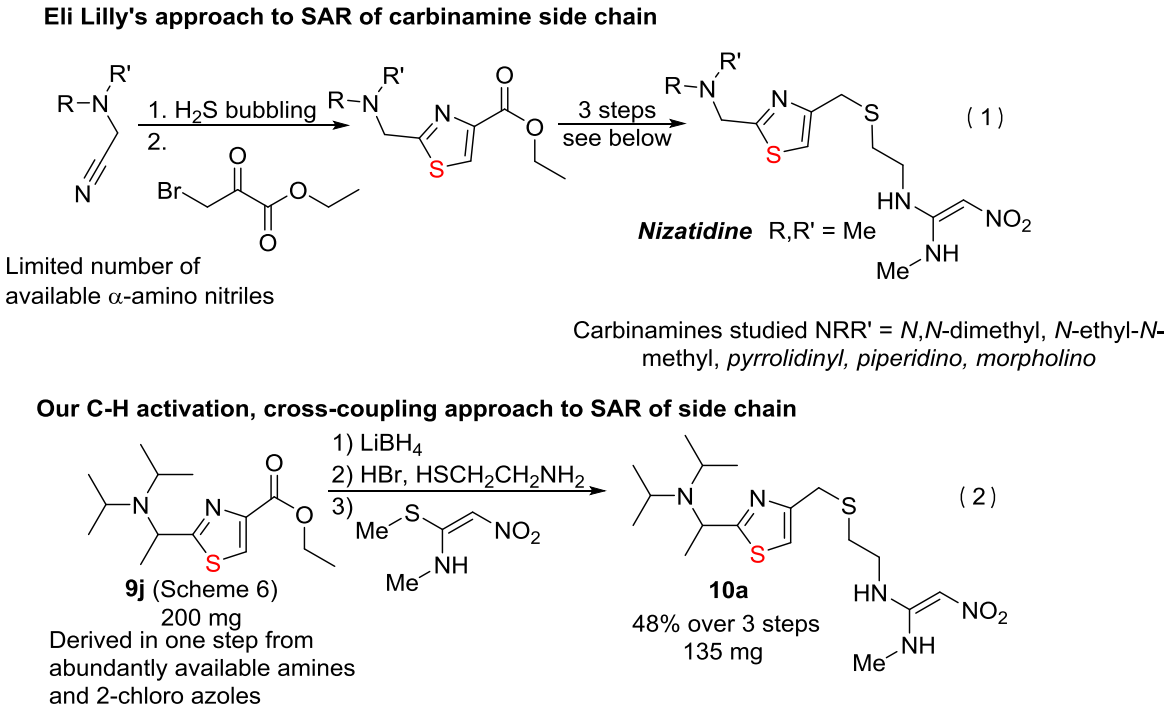
[a]Yields are of isolated products after chromatography. [b]Regioisomeric ratios were determined on crude material via ^{1}H NMR. [c]Imidazole was replaced with 4.0 equiv (total) of amine. [d]Cs_2CO_3 was used instead of imidazole. [e]No other possible regioisomer was detected by ^{1}H NMR.

Scheme 9. Scope of the α-azole-carbinamine.

2.3 Application (synthesis of nizatidine)

We suspected that our method would be ideal for rapidly performing the SAR of heterocycles substituted with an aliphatic carbinamine. Take for instance the drug Nizatidine, which is an H-2 histamine agonist developed by Eli Lilly[10] and sold under the trade names Taxzad and Axid. It was one of the most widely used drugs for a number of years in combating health issues related to the overproduction of stomach acid. In the development of this drug, SAR of the carbinamine was determined by variation of the amine in the acetonitrile component during initial step of the reaction sequence (Scheme 10, eq 1). With regards to the carbinamine side group, Eli Lilly only looked at 5 variations of the nitrogen substituent, and no substitution of the carbinamine methylene unit was explored.[50] Given the minimal SAR performed on the carbinamine component, we thought this would be an ideal opportunity to demonstrate how we could use our method to rapidly make a Nizatidine analog **10a**. Beginning with commercially available 2-chlorothiazole-4-carboxylate, we coupled Hünig's base to afford **9j** (from Scheme 9).

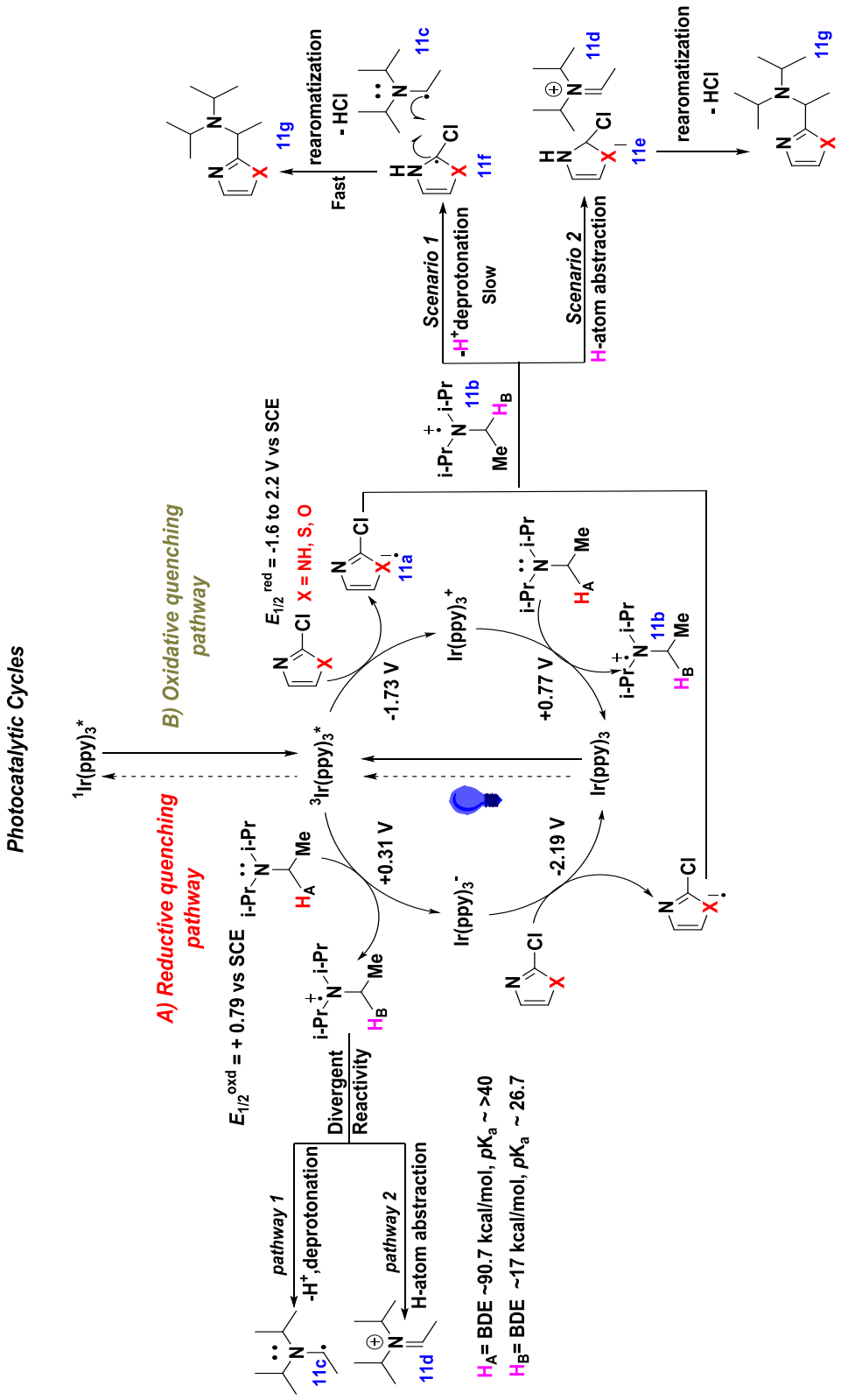
Taking 200 mg of **9j** forward (Scheme 10, eq 2), we followed the procedure of Eli Lilly.[11] First, we subjected our coupled product to a telescoped synthesis beginning with reduction of the ester with $LiBH_4$, followed by HBr mediated thiol substitution and finally coupling with the active pharmacophore, to afford 135 mg, 48% yield of the desired analog **10a** as a single regioisomer[12] with only one purification after the final step. Thus, we were able to readily access a previously unknown analog of Nizatidine differing at the carbinamine side chain from commercially available components in fewer steps and with greater structural diversity than previously investigated.



Scheme 10. Application-Synthesis of Nizatidine analog.

2.4. Possible mechanism

Based on observations and results, it is not clear that we have a true understanding of all aspects of the mechanism and intermediates involved in this reaction, however, many things about this reaction are understood. Later, after further discussion of other works, a holistic description is provided. To begin, the amine must be oxidized at some point during the reaction (Scheme 11). Based on redox potentials, oxidation by Ir(IV) to give Ir(III) ($E_{1/2}$ for $Ir^{(IV)/(III)}$ = +0.77)[13] to give the amine radical cation species[14] could be occurring. Use of the Ir(IV/III) redox, would necessitate an oxidative quenching mechanism (Scheme 11). However, others[15] have shown that reductive quenching of the excited state catalyst is also possible with aliphatic amines i.e. $Ir^{*(III)/(II)}$ ($E_{1/2}$ = +0.31vs SCE)[13] despite the difference in redox potentials, Et_3N (E_{red} = +0.79 vs SCE)[16] versus $E_{1/2}$ $Ir^{(III)*/(II)}$ = +0.31 V vs SCE.[5]

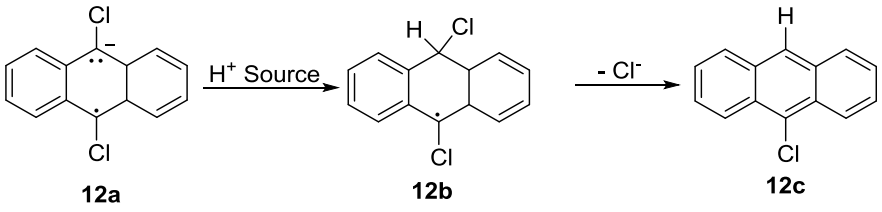


Scheme 11. Possible reductive and oxidative quenching mechanism.

Regardless of whether the amine radical cation is formed *via* direct reductive quenching of the excited state catalyst, or formed indirectly *via* reduction of the Ir(IV) species, one of the following scenarios involving the amine radical cation must take place; 1) generation of electrophilic iminium species *via* C_α-H abstraction **11d** (Scheme 11, pathway 2), or 2) synthesis of α-amino radical ($E_{1/2}$ = –1.05 V vs SCE)[17] *via* C_α-H deprotonation **11c** (pathway 1). Further convoluting the mechanism, is that an α-amino radical formed by pathway 1 could be further oxidized to give an iminium species, making it difficult to distinguish between the mechanisms.

Based on Stephenson's work, we proposed the formation of an α-amino radical intermediate, as the reaction works equally well in, the presence or absence of air (Scheme 8, entry 5). We believe that the α-amino radical **11c** formed in the reaction is a short lived specie and it is rapidly consumed in the formation of a C–C bond. Upon oxidation of the *N*-atom, the pK_a of the C_α–H of the amine radical cation is significantly weakened, and correspondingly acidified. For Et_3N, Stephenson has estimated this pK_a to be 26.7.[18] However, in order for deprotonation to occur, a base must be present. The tertiary amine substrates are significantly more basic in MeCN than DMSO, such that the pK_a for Et_3NH^+ is 18.8.[19] While these are rough estimates, the 8-9 order of magnitude difference suggests that, at best, only a small amount of deprotonation of an amine radical cation by a tertiary amine would occur at any given time.

On the other hand, another potential base present in the reaction is the heteroaryl radical anion. Prior to electron transfer, the pK_a of the protonated heterocycle (2-chloro thiazolium) is 13.7 in MeCN **14b** (Scheme 14),[20] which also suggests that it would not be capable of deprotonation. However, upon electron addition it is conceivable that the radical anion serves as the base **14c**.[21] In this context, in 2009, Saltiel demonstrated that radical anion of 9, 10-dichloroanthracene **12a** could undergo protonation **12b** followed by the loss of chloride loss to result monochloroanthracene **12c**.[21]



Scheme 12. Saltiel's mechanistic investigation of induced photodechlorination of 9, 10-dichloroanthracene.

The pK_a of the protonated radical anion can be estimated. It is expected to be in the range of 28.7 to 33.7 which is expected to be sufficiently basic to deprotonate the amine radical cation, which would result in a neutral azolyl chloride radical **14d**.[22] pK_a values for both radical cations and radical anions could be calculated by using the formula given in Scheme 13.[14, 23] The electrode potentials could be easily calculated by using a potentiometer.

$$\text{BDE for } HA^{\bullet+} = 1.37\ pK_{HA} + 23.1\ E_{oxd}\ [\bar{A}] + 73.3$$

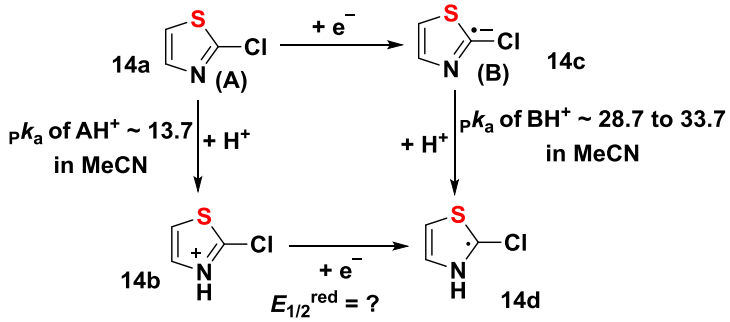
$$pK_a\ HA^{\bullet+} = pK_{HA} + 16.8\ [E_{ox}(\bar{A}) + E_{ox}(HA)]$$

$$\text{BDE for } HA^{\bullet-} = 1.37\ pK_{HA} + 23.1\ E_{red}\ [HA] + 73.3$$

$$pK_a = \frac{\text{BDE} - 37.6}{1.36} - \frac{E_{1/2}}{0.0592}$$

Scheme 13. Formulas for calculating pK_a values for radical cation and radical anion.

Thus, it seems most feasible that the azolyl radical anion is responsible for deprotonation of the amine radical cation. This is an underexploited reaction pathway, ripe for further development.



Scheme 14. Estimated pk_a value for 2-chlorothiazole and its radical anion.

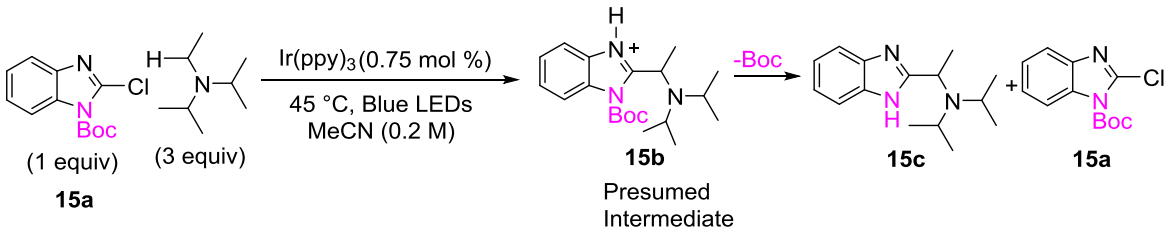
Importantly, in sluggish reactions small amounts of *N*, *N*-diisopropylacetamide (presumably arising from *i*Pr_2NEt) were observed by GC-MS, however, no attempts were made to quantify the amount produced in these reactions. An argument for the formation of the α-amino radical[24] is supported by the presence of the acetamide, because the radical would be expected to react rapidly with advantageous O_2. Dimerized amine, arising from homocoupling of the α-amino radical, would also support the formation of the radical,[4a] however, was not observed by GC-MS. Furthermore, amide formation was most prevalent when the amine substrate bore an alcohol group. It is not unreasonable to think that the amide could also arise from attack of the alcohol on the iminium carbon, followed by subsequent oxidation of the hemiaminal ether to give the amide, through hydrolysis after exposure to wet solvent.

Further evidence against the formation of a long lived α-amino radical, was the observed good regioselectivity for the sterically less crowded amine C–H. It should be noted that this is contrathermodynamic, which presumably would be important for a C–H abstraction process. Further evidence supporting the idea of participation by the heteroaryl radical anion in the deprotonation of an amine radical cation, is that the sterically larger azoles resulted in better regioselectivity. Thus, while the evidence is not overwhelming, the reactions seems most consistent with a C–C bond formation proceeds through deprotonation of the amine radical cation (Scheme 11, Scenario 1) by the azolyl radical anion **11a** to simultaneously form an azolyl **11f** and α-amino radical **11c**, which may rapidly recombine and rearomatize by extruding HCl.

Concerning the possible oxidative quenching of the excited photocatalyst, it is worth noting that O_2 (E_{red} = -1.48 in MeCN[25]) and structurally related 2-heteroaryl benzazoles typically fall within E_{red} = -1.65 to -2.2 (for 2-chlorobenzothiazole $E_{1/2}^{red}$ = -1.98 V vs SCE).[26] The relevant photocatalyst potential for $Ir^{*(III/IV)}$ is $E_{1/2}^{red}$ = -1.73 V vs SCE, suggesting that either the heterocycle or oxygen could potentially undergo electron transfer (albeit an equilibrium would likely be established) from the photoexcited catalyst. Unfortunately, our quenching studies showed that the substrate absorbs light at the emission wavelength of the photocatalyst in MeCN (512 nM). Changing the solvent to DCM allowed us to excite the photocatalyst

and observe its emission without interference. A linear response to increases in substrate concentration was observed, possibly due to oxidative quenching. However, the reaction did not work in DCM, creating doubt as to whether the photocatalyst is oxidatively quenched. Furthermore, if reductive quenching by the amine is taking place, then the Ir(II) ($E_{1/2}$ = -2.19 V vs SCE)[13] species would be sufficiently reducing to transfer an electron to the chloroazole.

If the radical anion of the 2-chloroazole is formed, it could undergo C–Cl bond fragmentation. Chloroarenes with reduction potentials more negative than ~1.6 V are unstable and undergo fragmentation to form an aryl radical and a chloride ion.[27] If the heteroaryl radical, for which little information is known, is nucleophilic in nature then attack on an iminium would be a likely manner of C–C bond formation. In contrast to this, and perhaps more interesting, (Scheme 11, scenario 2) would involve the radical anion **11a** associating with the amine radical cation **11b** and then abstracting a hydrogen atom from the C_α–H of the amine radical cation **11b**. The result would be to form a carbanion **11e** and iminium **11d** in close proximity, facilitating C–C bond formation followed by loss of HCl to rearomatize the heterocycle. Giving some support for this idea, a chelated protonated species may play an important role in protecting the product α-azole carbinamine from over oxidation. For example, when Boc-protected benzimidazole (Scheme 15) is run without a carbonate base present, loss of the Boc group is observed on the product **15c** but not the starting heterocycle **15a**, which presumably occurs *via* protonation of the benzimidazole imine nitrogen **15b** after reaction which would facilitate the loss of the Boc group but also prevent over oxidation. Also, noteworthy is the selectivity of the C–H functionalization. The reaction is selective for both the thermodynamically stronger CH_2 as well as the exocyclic CH_2, which is suggestive of an irreversible kinetically controlled deprotonation (or C–H abstraction) similar to that seen by Schreiber.[28]



Scheme 15. Photocatalytic reaction of *N*-Boc imidazole with DIPEA.

Furthermore, we must recognize that it is possible to have more than one quenching pathway as the Stern-Volmer plot provides the rate of quenching of the photoexcited catalyst in the absence of the other suspect reagents and does not tell you if unproductive quenching is occurring.

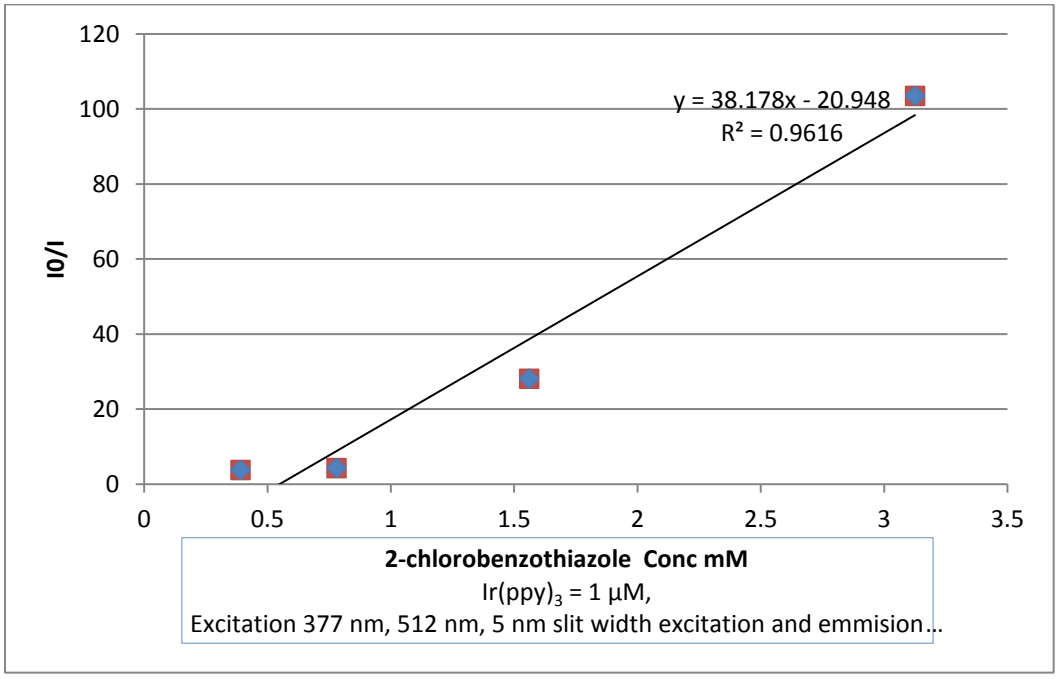


Figure 4. Stern volmer plot.

Based on our observations, we can say that most likely it is oxidative quenching by the 2-chloroazole, followed by oxidation of the amine, then proton transfer from the amine radical cation to the radical anion. This results in transient generation of two radicals, which rapidly recombine and eliminate HCl to form α-azolecarbinamine.

2.5. Conclusions

In summary, we have been able to highlight the enabling nature of this reaction as well as the conceptual advance it represents. The reaction setup is simple and utilizes commercially available reagents. It has proven to be functional group tolerant and chemoselective. This work highlights the ability of photoredox catalysis to mediate C–C bond formation with simple tertiary aliphatic amines.

2.6 Acknowledgement

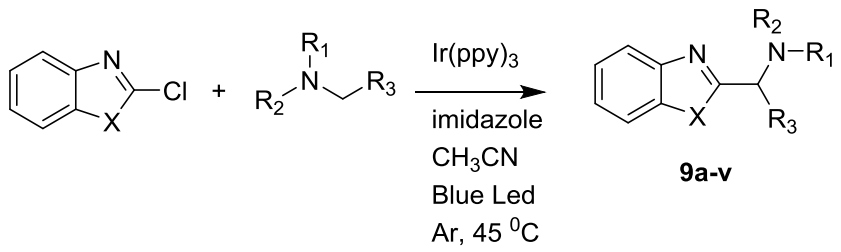
I am thankful to Dr. Mohammad Bani Khaled for determining the pK_a value for the 2–chlorothiazole.

2.7 Experiments

All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI, Oakwood) and used without further purification unless otherwise noted. Acetonitrile (CH_3CN) was dried using a molecular sieves. Ethyl 2-chlorothiazole-4-carboxylate was purchased from Aldrich and synthesized according to the literature procedure.[29] Amines were synthesized according to literature procedure[30] except tributylamine, *N*, *N*-diisopropylethylamine, *N*, *N*-diisopropylmethylamine which were commericial. Photocatalyst *tris*(2-phenylpyridinato-C^2, *N*)iridium(III)($Ir(ppy)_3$), 99%(purity), ($Ir(ppy)_3$) was obtained from Sigma Aldrich and other photocatalyst ruthenium-*tris(*2,2′-bipyridyl) dichloride $Ru(bpy)_3Cl_2$ was synthesized according to literature procedure.[31] Reactions were monitored by thin layer chromatography (TLC), obtained from Sorbent Technology ISCO Silica XHL TLC Plates, w/UV254, glass backed, 250 um, 20 x 20 cm, and were visualized with ultraviolet light, potassium permanganate stain and GC-MS (QP 2010S, Shimadzu equipped with auto sampler).

Photocatalytic reactions were set up in a light bath which is described below. Strips of blue LEDs (18 LEDs/ft) were purchased from Solid Apollo and were wrapped around on the walls of a glass crystallization dish, secured with masking tape and then wrapped with aluminum foil. A lid which rested on the top was fashioned from cardboard with holes that were made such that reaction tubes (12 × 75 mm cultural borosilicate tube) were held firmly in the cardboard lid. Water was added to the bath such that the tubes were submerged in the water which was maintained at 45 ^oC with the aid of a sand bath connected to a thermostat. Flash chromatography was carried out with Merck 60 Å, mesh 230-400 silica gel. NMR spectra were obtained on a Varian 400 spectrometer unless noted. ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^1H, ^{13}C). IR spectra were recorded on a Varian 800 FT-IR. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Mass spectra (HRMS) analysis was performed on LTQ-OrbitrapXL by Thermo Scientific Ltd.

General procedure A for the photocatalytic arylation of alipahatic amines with heteroaromatic chlorides



A 12 x 75 mm borosilicate test tube fitted with a rubber septum was charged with *tris*(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.007 equiv, X mL of a 1.33 mM stock solution of catalyst in CH_3CN where X was used to make 0.19 M solution of the hetroaromatic chloride. Hetroaromatic chloride (1 equiv), amine (1.2 equiv) and imidazole (2 equiv) were added and the reaction was degassed *via* Ar bubbling for 5-10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged in a the water bath which was maintained at 45 ^oC. The reaction was monitored by TLC and GC-MS. After the complete consumption of aryl chloride, the CH_3CN was removed *via* rotovap and the residue was treated with sat. aq $NaHCO_3$ (2 mL) and extracted with EtOAc (5 x 1 mL). The organic portions were combined and dried with anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified by normal phase chromatography. Normal phase chromatography was performed with a Teledyne ISCO automated chromatography system using hexane:EtOAc gradients over 40-90 column volumes(cv) using flow rates from 18 mL/min to 35 mL/min on a Redisep column of 4 g, 12 g, or 24 g with product detection at 254 and 288 nm.

General procedure B photocatalytic arylation of alipahatic amines with heteroaromatic chlorides (no imidazole).

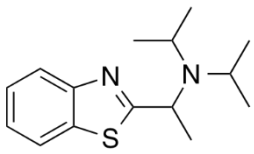
A 12 x 75 mm borosilicate test tube fitted with a rubber septum, was charged with *tris*(2-phenyl pyridinato-C^2, *N*) Iridium(III) (0.007 equiv, X mL of a 1.33 mM stock solution of catalyst in CH_3CN where X was used to make 0.19M solution of the hetroaromatic chloride. Hetroaromatic chloride (1 equiv) and amine (4

equiv) were added and the reaction was degassed *via* Ar bubling for 5-10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube submerged under the water bath which was maintained at 45 °C. The reaction was monitored, worked up, and isolated as in general procedure **A**.

General procedure C photocatalytic arylation of alipahatic amines with heteroaromatic chlorides (Cs_2CO_3 instead of imidazole)

A 12 x 75 mm borosilicate test tube fitted with a rubber septum, was charged with *tris*(2-phenyl pyridinato-C^2, *N*) Iridium(III) (0.007 equiv, X mL of a 1.33 mM stock solution of catalyst in CH_3CN where X was used to make 0.19M solution of the hetroaromatic chloride. Hetroaromatic chloride (1 equiv), amine (1.2 equiv) and cesium carbonate (Cs_2CO_3) (2 equiv), and a small stirbar were added and the reaction was degassed *via* Ar bubling for 5-10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube submerged in a water bath which was maintained at 45 °C and the reaction was vigourously stirred. The reaction was monitored, worked up, and isolated as in general procedure **A**.

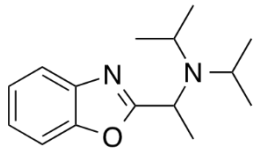
Synthesis of 9a (*N*-(1-(benzo[*d*]thiazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **A** was followed using 2-chlorobenzothizole (0.06 mL, 0.47 mmol), N, N-diisopropylethylamine (0.98 mL, 0.56 mmol), imidazole (64 mg, 0.94 mmol) and 2.47 mL of stoc solution of $Ir(ppy)_3$ in CH_3CN was used to afford **9a** in 92% yield (114 mg, 0.43 mmol), rr 11:1 (based on crude ^1H NMR) as pale yellow oil. It was purified by automated flash chromatography using hexane:EtOAc in 1% AcOH (0% for 5 cv, slowly ramped to 20% EtOAc for 5-30 cv then ramped to 100% EtOAc for 30- 44 cv, then held at 100% EtOAc for 44-60 cv), on a 4 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 4.29 (q, *J* = 6.8 Hz, 1H), 3.15 (hept, *J* = 6.6 Hz, 2H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 6H), 1.08 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CdCl_3$) δ 183.93,

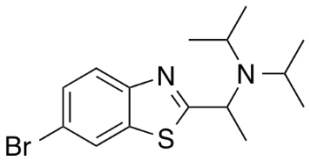
154.50, 136.60, 125.50, 124.47, 122.64, 121.72, 53.38, 46.40, 23.65, 22.32, 18.90. FT-IR (neat) cm^{-1} 3022, 2964, 1659, 1462. 1389. Calculated HRMS [ESI] for $C_{15}H_{22}N_2S$ $[M+H]^+$ is 263.1582 observed 263.1568.

Synthesis of 9b (*N*-(1-(benzo[*d*]oxazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **B** was followed using 2-chlorobenzoxazole (46 mg, 0.30 mmol), N, N-diisoproylethylamine (0.2 mL, 1.2 mmol), and 1.5 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9b** in 74% yield (55 mg, 0.22 mmol) rr 8:1(based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc 0% for 2.5 cv, slowly ramped to 10% EtOAc for 2.5-49 cv, then ramped to 100% EtOAc for 49-51 cv, then held at 100% EtOAc for 51-65 cv, on a 4 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 - 7.62 (m, 1H), 7.53 - 7.42 (m, 1H), 7.35 - 7.21 (m, 2H), 4.37 (q, *J* = 7.0 Hz, 1H), 3.28 (hept, *J* = 6.6 Hz, 2H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 6H), 0.97 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.25, 150.82, 141.47, 124.69, 124.09, 119.92, 110.63, 47.82, 45.64, 23.32, 22.66, 19.20. FT-IR (neat) cm^{-1} 3110, 2963, 1526, 1454, 1390. Calculated HRMS [ESI] for $C_{15}H_{22}N_2O$ $[M+K]^+$ is 285.1369 observed 285.2109.

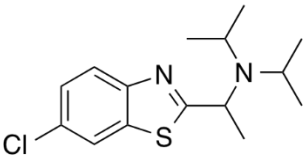
Synthesis of 9c (*N*-(1-(6-bromobenzo[*d*]thiazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **A** was followed using 2-chloro-6-bromo-benzothizole (37 mg, 0.15 mmol), N, N-diisopropylethylamine (0.03 mL , 0.18 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN and imidazole (20 mg, 0.30 mmol) to afford **9c** in 84% yield (43 mg, 0.13 mmol) rr 16:1 (based on crude ^1H NMR) as colorless solid, mp-84-87 ^oC. It was purified by automated flash chromatography using hexane:EtOAc (0% for 2.5 cv, slowly ramped to 10% EtOAc for 2.5-7 cv then ramped to 100% EtOAc for 7- 32 cv, then held at 100% EtOAc for 32- 40 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.93 (d, *J* = 2.0 Hz, 1H), 7.74 (s, 1H), 7.48 (d, *J* = 6.7 Hz, 1H), 4.31 (q, *J* = 6.8 Hz, 1H), 3.18 (hept, *J* = 6.6 Hz, 2H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.14 (dd, *J* = 8.7, 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ184.81, 153.43, 138.42, 128.92, 124.32,

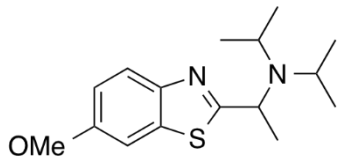
123.82, 117.97, 53.40, 46.47, 23.64, 22.27, 18.74. FT-IR (neat) cm^{-1} 2958, 2930, 1587, 1439, 1384. HRMS [ESI] calcd. $C_{15}H_{21}N_2SBr$ $[M+H]^+$ 341.0687 observed 341.0672.

Synthesis of 9d (*N*-(1-(6-chlorobenzo[*d*]thiazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **A** was followed using 2,6-dichlorobenzothizole (31 mg, 0.15 mmol), *N*, *N*-diisopropylethylamine (0.03 mL, 0.18 mmol), imidazole (20 mg, 0.30 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in $CH_3CN$to afford **9d** in 93% yield (41 mg, 0.14 mmol) rr 14:1 (based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0-5 % for 38 cv, slowly ramped to 100 % EtOAc for 38- 52 cv, then held at 100% EtOAc for 52- 68 cv), on a 4 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 1H), 7.77 (s, 1H), 7.36 - 7.33 (m, 1H), 4.32 (q, *J* = 6.7 Hz, 1H), 3.18 (hept, *J* = 6.5 Hz, 2H), 1.68 (d, *J* = 6.8 Hz, 3H) 1.14 (dd, *J* = 8.7, 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.67, 153.09, 137.90, 130.28, 126.22, 123.42, 121.38, 53.40, 46.46, 23.63, 22.26, 18.75. FT-IR (neat) cm^{-1}3025, 2966, 1614, 1462, 1365. HRMS [ESI]calcd. $C_{15}H_{21}N_2SCl$ $[M+H]^+$ 297.1192 observed 297.1192.

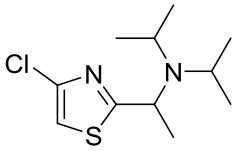
Synthesis of 9e (*N*-isopropyl-*N*-(1-(6-methoxybenzo[*d*]thiazol-2-yl) ethyl)propan-2-amine)



The general procedure **A** was followed using 2-chloro-6-methoxybenzothizole (30 mg, 0.15 mmol*)*, N, N-diisopropylethylamine (0.03 mL, 0.18 mmol), imidazole (20 mg, 0.30 mmol) and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN and more 0.38 mL of CH_3CN to afford **9e** in 61 % yield (27 mg, 0.09 mmol) rr 13:1 (based on crude ^1H NMR) as an colorless solid, mp- 74-76 ^oC. It was purified by automated flash chromatography using hexane:EtOAc (0-10% for 17 cv, slowly ramped to 100% EtOAc for 17-19 cv, then held at 100% EtOAc for19-22 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 1H), 7.24 (s, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 4.31 (q, *J* = 5.7, 4.6 Hz, 1H), 3.84 (s, 3H), 3.20 (hept, *J* = 13.2, 7.3, 6.6 Hz, 2H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.16 (dd, *J* = 10.7 Hz, *J* = 6.5 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.24, 157.21, 148.96, 137.84, 123.11, 114.56, 104.45, 55.96, 53.22, 46.34, 23.65, 22.34,

18.87. FT-IR (neat) cm^{-1} 3112, 2956, 1605, 1519, 1469, 1364. HRMS [ESI] calcd. $C_{16}H_{24}N_2SO$ $[M+H]^+$ 293.1688 observed 293.1668.

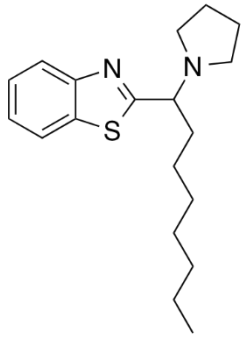
Synthesis of 9f (*N*-(1-(5-chlorothiazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **A** was followed using 2, 4-dichlorothizole (23 mg, 0.15 mmol), N, N-diisoproylethylamine (0.03 mL, 0.18 mmol), imidazole (20 mg, 0.3 mmol), and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9f** in 68% yield (25 mg, 0.10 mmol) rr 9:1 (based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc in 1% AcOH (0% for 2.5 cv, slowly ramped to 20% EtOAc for 2.5-30 cv then ramped to 100% EtOAc for 30-31 cv, then held at 100% EtOAc 31- 40 cv, on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 6.95 (s, 1H), 4.18 (q, *J* = 6.9 Hz, 1H), 3.15 (hept, *J* = 6.6 Hz, 2H), 1.59 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.60, 137.51, 114.37, 52.99, 46.19, 23.63, 22.13, 18.67. FT-IR (neat) cm^{-1} 2963, 2929, 1612, 1485, 1385. HRMS [ESI] calcd. $C_{11}H_{19}N_2SCl$ $[M+H]^+$ 247.1036 observed 247.1017.

Synthesis of 9g (2-(1-(pyrrolidin-1-yl) octyl)benzo[*d*]thiazole)

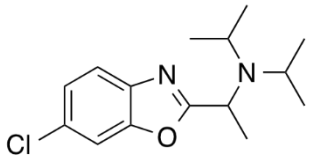
The general procedure **A** was followed using 2-chlorobenzothizole (0.01 mL, 0.08 mmol), octyl pyrrolidine



(17 mg, 0.09 mmol), imidazole (10 mg, 0.15 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ to afford **9g** in 92% yield (23 mg, 0.07 mmol) rr 20:1(based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0-0% for 5 cv, slowly ramped to 10% EtOAc for 5-48 cv then ramped to 100% EtOAc for 48-60 cv, then held at 100% EtOAc for 60-70 cv), on a 4 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.44 - 7.41 (m, 1H), 7.35 - 7.31 (m, 1H), 3.98 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.35 (t, *J* = 9.1 Hz, 1H), 2.77 - 2.69 (m, 1H), 2.43 - 2.32 (m, 4H), 1.93 - 1.83 (m, 4H), 1.47-1.49 (m, 2H), 1.22(m, 8 H), 0.83(t, *J*=6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.82, 153.85, 135.23, 125.67, 124.49, 122.55, 121.87, 66.95, 55.52, 53.75,

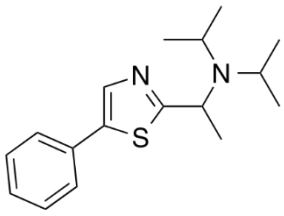
34.06, 31.85, 29.53, 29.28, 29.01, 27.31, 23.67, 22.65, 14.18. FT-Ir (neat) cm^{-1} 3020, 2925, 2854, 1524, 1485, 1308. HRMS [ESI] calcd. $C_{15}H_{20}N_2S$ $[M+H]^+$ 269.1264 observed 269.0372.

Synthesis of 9h (*N*-(1-(6-chlorobenzo[*d*]oxazol-2-yl) ethyl)-*N*-isopropylpropan-2-amine)



The general procedure **A** was followed using 2,6-dichlorobenzooxazole (56 mg, 0.30 mmol) *N, N*-diisopropylethylamine (0.2 mL, 1.2 mmol) and, 1.5 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9h** in 68% yield (57 mg, 0.20 mmol) rr 13:1(based on crude ^1H NMR) as colorless oil. It was purified by automated flash chromatography using hexane:EtOAc (0-10% for 13 cv, slowly ramped to 100% EtOAc for 13-16 cv, then held at 100% EtOAc for 16-25 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.29 - 7.21 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 1H), 3.25 (hept, *J* = 6.6 Hz, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.01, 151.03, 140.24, 130.31, 124.80, 120.41, 111.33, 47.81, 45.64, 23.26, 22.67, 19.06. FT-IR(neat) cm^{-1} 2966, 1614, 1462, 1365. HRMS [ESI] calcd. $C_{15}H_{21}ClN_2O$ $[M+H]^+$ 281.1421 observed 281.1349

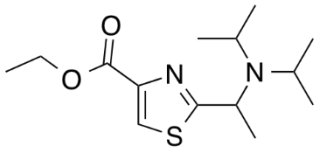
Synthesis of 9i (*N*-Isopropyl-*N*-(1-(5-phenylthiazol-2-yl) ethyl) propan-2-amine)



The general procedure **A** was followed using 2-chloro-5-phenyl thizole (24 mg, 0.13 mmol), *N, N*-diisopropylethylamine (0.03 mL, 0.18 mmol), imidazole (20 mg, 0.30 mmol) and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9i** in 24% yield (10.5 mg, 0.035 mmol) rr 9:1(based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 2.5 cv, slowly ramped to 20% EtOAc for 2.5-16 cv then ramped to 100% EtOAc for 16-18 cv, then held at 100% EtOAc for18-29 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.88 (d, *J* = 7.1 Hz, 1H), 7.41 - 7.25 (m, 5H), 4.29 (q, *J* = 6.8 Hz, 1H), 3.20 (hept, *J* = 6.6 Hz, 2H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 6H). 1.12 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.23, 155.29, 135.40, 128.82, 127.78,

126.30, 113.59, 52.93, 46.12, 23.66, 22.31, 19.16. FT-IR(neat) cm^{-1} 3025, 2961, 1505, 1385. HRMS [ESI] calcd. $C_{19}H_{30}N_2S$ $[M+H]^+$ 289.1739 observed 289.1719.

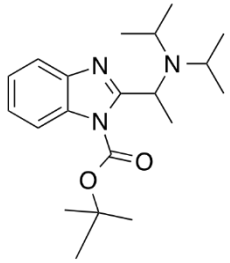
Synthesis of 9j ethyl 2-(1-(diisopropylamino) ethyl)thiazole-4-carboxylate



The general procedure **B** was followed using ethyl 2-chlorothiazole-4-carboxylate (29 mg, 0.15 mmol), *N*, *N*-diisopropylethylamine (0.1 mL, 0.6 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9j** in 69% yield (30 mg, 0.105mmol) rr 4:1 (based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc in 1% AcOH (0% for 4 cv, slowly ramped to 45% for 4-35 cv then ramped to 100% EtOAc for 35-40 cv, then held at 100% EtOAc for 40-50 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 8.04 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 6.9 Hz, 1H), 3.16 (hept, *J* = 6.5 Hz, 2H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.10 (dd, *J* = 6.6, 1.6 Hz, 12H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 183.76, 162.04, 147.63, 128.61, 61.39, 52.96, 46.24, 23.59, 22.14, 18.96, 14.58. FT-IR (neat) cm^{-1} 2956, 1715, 1485, 1367, 1202. HRMS [ESI] calcd. $C_{14}H_{24}N_2O_2$ $[M+H]^+$ 285.1637 observed 285.1618.

Synthesis of 9k (*tert*-butyl 2-(1-(diisopropylamino) ethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate)

The general procedure **C** was followed using *N*-boc-2-chlorobenzimidazole (38 mg, 0.15 mmol), *N*, *N*-

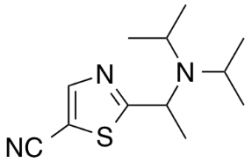


diisopropylethylamine (0.03 mL, 0.18 mmol), Cs_2CO_3 (98 mg, 0.3 mmole), 0.75 mL stock solution of $Ir(ppy)_3$ was used to afford **9k** in 75% yield (38 mg, 0.109 mmol) rr 20:1 (based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0-25% for 48 cv, slowly ramped to 100% EtOAc for 48-60 cv, then held at 100% EtOAc for 60 - 75 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.81 – 7.77 (m, 1H), 7.70 – 7.67 (m, 1H), 7.29 – 7.25 (m, 2H), 5.23 (q, *J* = 6.9 Hz, 1H), 3.48 (hept, *J* = 6.5 Hz, 2H), 1.70 (s, 9H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CdCl_3$) δ 161.01, 149.42, 142.45, 133.02, 124.16, 123.92, 119.93,

114.62, 85.27, 47.73, 45.44, 28.38, 23.43, 22.91, 19.37. FT-IR (neat) cm^{-1} 2957, 2928, 2871, 1729, 1603, 1462, 1365. HRMS [ESI] calcd. $C_{20}H_{31}N_3O_2$ $[M+H]^+$ 346.2495and observed 346.2480.

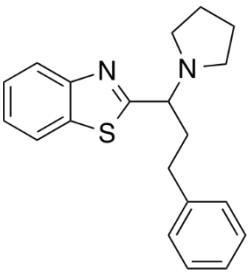
Synthesis of 9l (2-(1-(diisopropylamino) ethyl) thiazole-5-carbonitrile)

The general procedure **A** was followed using 2-chloro-5-cyano thiazole (44 mg, 0.3 mmol), *N*, *N*-



diisopropylethylamine (0.06 mL, 0.36 mmol), imidazole (40 mg, 0.60 mmol) and 1.5 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9l** in 84% yield (61 mg, 0.25 mmol) rr 4:1 (based on crude ^1H NMR) as solid, mp-92-94 ^oC. It was purified by automated flash chromatography using hexane:EtOAc (0-100% for 16 cv, then held at 100% EtOAc for 16- 20 cv), on 24 g column silica. ^1H NMR (400 MHz, $CdCl_3$) δ 8.10 (s, 1H), 4.23 (q, *J* = 6.9 Hz, 1H), 3.16 (hept, *J* = 6.6 Hz, 2H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.12 (dd, *J* = 6.6, 4.1 Hz,12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.15, 152.58, 113.09, 106.77, 53.47, 46.53, 23.64, 21.97, 18.36. FT-IR(neat) cm^{-1} 2969, 2945, 2218, 1614, 1504, 1386. HRMS [ESI] calcd. $C_{12}H_{19}N_3S$ $[M+H]^+$ 238.1378 observed 238.1364.

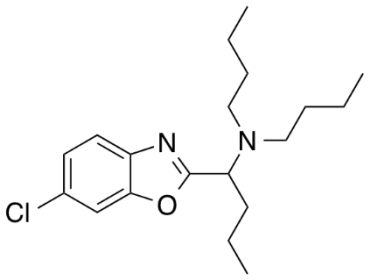
Synthesis of 9m (2-(3-phenyl-1-(pyrrolidin-1-yl) propyl) benzo[*d*]thiazole)



The general procedure **A** was followed using 2-chlorobenzothizole (0.04 mL, 0.3 mmol), 1-(3-phenylpropyl)pyrrolidine (68 mg, 0.36 mmol), imidazole (40 mg, 0.6 mmol), 1.5 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9m** in 39% yield (38 mg, 0.12 mmol) rr 20:1 (based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 2.5 cv, slowly ramped to 20% EtOAc for 2.5-25 cv then ramped to 100% EtOAc for 25-26 cv, then held at 100% EtOAc for 26-37 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.44 - 7.41 (m, 1H), 7.35 - 7.31 (m, 1H), 7.24 - 7.20 (m, 2H), 7.15 - 7.12 (m, 3H), 3.98 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.35 (t, *J* = 9.1 Hz, 1H), 2.87 - 2.69 (m, 3H), 2.60 - 2.45 (m, 2H), 2.43 - 2.31 (m, 2H), 2.02 - 1.89 (m, 2H), 1.89 - 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.82, 154.07, 142.62, 135.39, 128.53, 128.48, 125.89, 125.85, 124.71, 122.75, 122.02, 67.13, 55.35, 53.98, 34.32, 33.87, 31.04, 23.95. FT-

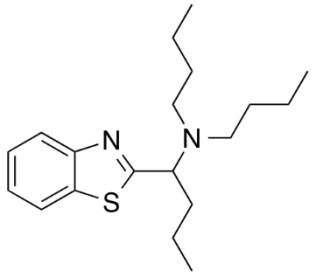
IR(neat) cm^{-1} 2940, 2802, 1608, 1519, 1312. HRMS [ESI] calcd. $C_{20}H_{22}N_2S$ $[M+H]^+$ 323.1582 observed 323.1573.

Synthesis of 9n (*N*, *N*-dibutyl-1-(6-chlorobenzo[*d*]oxazol-2-yl) butan-1-amine)



The General procedure **B** was followed using 2,6-dichlorobenzoxazole (25 mg, 0.13 mmol), tributylamine (0.13 mL, 0.53mmol), and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9n** in 63% yield (28 mg, 0.081 mmol) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 5 cv, slowly ramped to 10% EtOAc for 5- 40 cv then ramped to 100% EtOAc for 40-72 cv, on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.30 - 7.25 (m, 1H), 3.99 (t, *J* = 7.5 Hz, 1H), 2.62 (dt, *J* = 13.0, 7.6 Hz, 2H), 2.34 - 2.24 (m, 2H), 2.01 - 1.82 (m, 2H), 1.44 - 1.34 (m, 6H), 1.32 - 1.24 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ168.10, 150.90, 139.79, 130.46, 124.94, 120.58, 111.43, 58.59, 50.94, 33.11, 31.18, 20.62, 19.95, 14.28, 14.12. FT-IR(neat) cm^{-1} 2957, 2930, 2871, 1607, 1462, 1378. HRMS [ESI] calcd. $C_{19}H_{29}N_2OCl$ $[M+H]^+$ 359.1866 observed 359.2052.

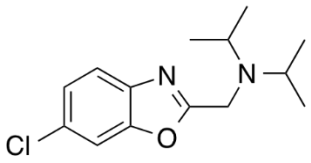
Synthesis of 9o (1-(benzo[*d*]thiazol-2-yl)-*N*, *N*-dibutylbutan-1-amine)



The general procedure **B** was followed using 2-chlorobenzothizole (25 mg, 0.14 mmol), tributylamine (0.17 mL, 0.56 mmol) 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford, to afford **9o** in 83% yield (37 mg, 0.12 mmol), as pale yellow color oily liquid. It was purified by automated flash chromatography using hexane:EtOAc (0% for 5 cv, slowly ramped to 10% EtOAc for 5-28 cv then ramped to 100% EtOAc for 28-48cv, then held at 100% EtOAc for 48- 60 cv), on a 4 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.09 (t, *J* = 6.9 Hz, 1H), 2.64 - 2.57 (m, 2H), 2.50 - 2.42 (m, 2H), 2.07 - 1.96 (m, 1H), 1.95 - 1.83 (m, 1H), 1.57 - 1.40 (m, 5H), 1.31 (dt, *J* = 14.7, 7.4 Hz, 5H), 0.96

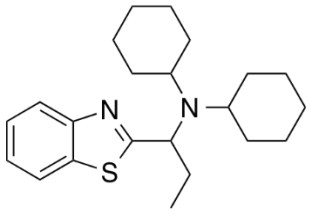
(t, J = 7.7 Hz, 3H), 0.88 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.66, 153.46, 135.68, 125.67, 124.73, 122.97, 121.70, 63.41, 50.82, 33.72, 31.19, 20.81, 20.74, 14.42, 14.34. FT-IR (neat) cm^{-1} 3025, 2956, 2930, 2871, 1461, 1377. HRMS [ESI] calcd. $C_{19}H_{30}N_2S$ $[M+H]^+$ 319.2208 observed 319.2288.

Synthesis of 9p (*N*-((6-chlorobenzo[*d*]oxazol-2-yl) methyl)-*N*-isopropylpropan-2-amine)



The general procedure **B** was followed using 2,6-dichlorobenzoxazole (28 mg, 0.15 mmol), *N*, *N*-diisopropylmethylamine (0.1 mL, 0.6 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9p** in 55% yield (22 mg, 0.08 mmol) rr 20:1(based on crude 1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 6 cv, slowly ramped to 20% EtOAc for 6-52 cv then ramped to 100% EtOAc for 52-80 cv, then held at 100% EtOAc for 80-93cv), on a 4 g silica column. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.56 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 3.89 (s, 2H), 3.14 (hept, J = 6.5 Hz, 2H), 1.07 (d, J = 6.5 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.34, 151.27, 140.26, 130.41, 124.90, 120.44, 111.50, 50.12, 43.54, 25.57, 20.81. FT-IR (neat) cm^{-1} 2962, 1452, 1262. HRMS [ESI] calcd. $C_{14}H_{19}N_2OCl$ $[M+H]^+$ 289.1084 observed 289.3285

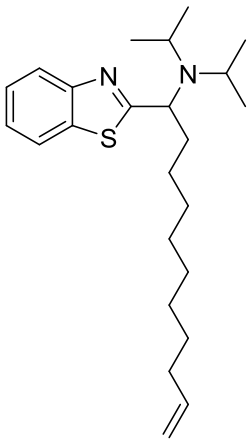
Synthesis of 9q (*N*-(1-(benzo[*d*]thiazol-2-yl) propyl)-*N*-cyclohexylcyclohexanamine)



The general procedure **A** was followed using 2-chlorobenzothizole (0.02 mL, 0.15 mmol), *N*-cyclohexyl-*N*-propylcyclohexanamine (40 mg, 0.18 mmol), imidazole (20 mg, 0.3 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9q** in 83% yield (44 mg, 0.12 mmol) rr 20:1(based on crude ^{1}H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 5 cv, slowly ramped to 10 % EtOAc for 5-52 cv then ramped to 100% EtOAc for 52 - 60 cv, then held at 100% EtOAc for 62-68 cv), on a 4 g silica column. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.94 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 4.10 (dd, J = 8.6, 4.8 Hz, 1H), 2.75 (tt, J = 11.5, 3.2 Hz, 2H), 2.29 – 2.17 (m, 1H), 1.91 – 1.81 (m, 1H), 1.81 – 1.62 (m, 8H), 1.59 –

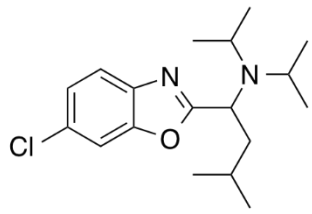
1.52 (m, 2H), 1.42 – 1.28 (m, 4H), 1.27 – 1.16 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H), 1.08 – 1.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ180.00, 153.64, 135.95, 125.48, 124.57, 122.83, 121.64, 60.81, 55.79, 34.51, 34.29, 28.07, 26.96, 26.82, 26.13, 12.75. FT-IR(neat) cm^{-1} 3110, 2925, 1612, 1518, 1450, 1390. HRMS [ESI] calcd. $C_{22}H_{32}N_2S$ $[M+H]^+$ 357.2364 observed 357.2349.

Synthesis of 9r (1-(benzo[*d*]thiazol-2-yl)-*N*, *N*-diisopropylpent-4-en-1-amine)



The general procedure **A** was followed using 2-chlorobenzothizole (0.02 mL, 0.15 mmol), *N*, *N*-diisopropyl-10-undecenalamine (46 mg, 0.18 mmol), imidazole (20 mg, 0.3 mmol), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9r** in 39% yield (22 mg, 0.05 mmol) rr 20:1 (based on crude ^{1}H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc in 1% AcOH (0-5 % for 18 cv, slowly ramped to 100 % EtOAc for 18-27 cv, then held at 100% EtOAc for 27-30 cv), on a 12g silica column. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.0, 1.2 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.33 - 7.27 (m, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.8 Hz, 1H), 5.04 - 4.87 (m, 2H), 4.16 (dd, *J* = 8.7, 4.6 Hz, 1H), 3.30 (hept, *J* = 7.0 Hz, 2H), 2.25 - 2.14 (m, 1H), 2.05 - 1.96 (m, 2H), 1.81 (ddt, *J* = 13.1, 10.2, 4.8 Hz, 1H), 1.42 - 1.20 (m, 12H), 1.10 (d, *J* = 6.5 Hz, 6H) 1.05 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.98, 153.70, 139.47, 135.92, 125.48, 124.58, 122.88, 121.62, 114.28, 58.11, 46.16, 34.51, 34.03, 30.16, 29.74, 29.67, 29.34, 29.15, 28.04, 23.44, 22.98. FT-IR (neat) cm^{-1} 3124, 2926, 2854, 1384, 1241. HRMS [ESI] calcd. $C_{18}H_{26}N_2S$ $[M+K]^+$ 341.1454 observed 341.1560.

Synthesis of 9s (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N*, *N*-diisopropyl-3-methylbutan-1-amine)

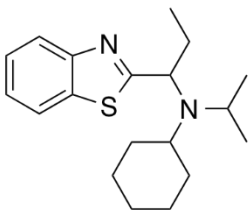


The General procedure **B** was followed using 2,6-dichlorobenzothizole (25 mg, 0.13 mmol), *N*, *N*-diisopropyl-3-methylbutan-1-amine (32 mg, 0.17 mmol), and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN afford **9s** in 78% yield (33 mg, 0.10 mmol), rr 8:1(based on crude ^{1}H NMR), as low melting

solid, mp- 47-49 °C. It was purified by automated flash chromatography using hexane:EtOAc (0% for 5 cv, slowly ramped to 10% EtOAc for 5-50 cv then ramped to 100% EtOAc for 50-60 cv, then held at 100% EtOAc for 60-72 cv), on a 4 g silica column. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.27 - 7.25 (m, 1H), 4.19 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.36 (hept, *J* = 6.6 Hz, 2H), 1.94 (dddd, *J* = 13.0, 8.3, 6.1, 1.6 Hz, 1H), 1.69 - 1.53 (m, 2H), 1.07 (d, *J* = 6.7 Hz, 6H), 0.92 (d, *J* = 6.5 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.30, 150.67, 140.21, 130.26, 124.84, 120.44, 111.28, 50.49, 45.55, 42.56, 24.92, 23.68, 23.26, 22.72, 22.16. FT-IR(neat) cm^{-1} 2960, 1607, 1557, 1462, 1386. HRMS [ESI] calcd. $C_{18}H_{27}N_2OCl$ $[M+H]^+$ 323.1890 observed 323.1832.

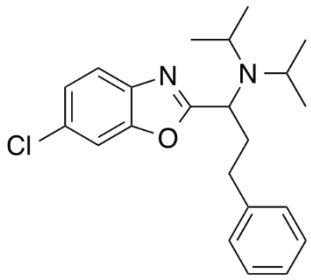
Note- **9s** has another regio- isomer in the spectra, labeled as dark filled circle

<u>Synthesis of 9t</u> (*N*-(1-(benzo[*d*]thiazol-2-yl) propyl)-*N*-isopropylcyclohexanamine)



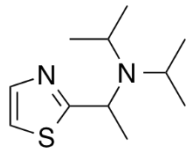
The general procedure **A** was followed using 2-chlorobenzothizole (20 ul mL, 0.15 mmol), *N*-isopropyl-*N*-propylcyclohexanamine (33 mg, 0.18 mmol), imidazole (20 mg, 0.3) mL), 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9t** in 50% yield (24 mg, .075 mmol) rr 20:1(based on crude ^{1}H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc in 1% AcOH (0% for 10 cv, slowly ramped to 20% EtOAc for 10-70 cv then ramped to 100% EtOAc for 70-79 cv, then held at 100% EtOAc for 79-90 cv), on a 4 g silica column. ^{1}H NMR (400 MHz, $CdCl_3$) 7.94 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.40 (t, *J* = 7.1 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.09 (dd, *J* = 8.7, 4.6 Hz, 1H), 3.29 (hept, *J* = 7.0 Hz, 1H), 2.75 (tt, *J* = 11.6, 3.3 Hz, 1H), 2.23 (ddt, *J* = 13.4, 8.9, 7.2 Hz, 2H), 1.90 - 1.82 (m, 1H), 1.76 - 1.55 (m, 6H), 1.40 - 1.28 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.00, 153.67, 135.95, 125.49, 124.59, 122.83, 121.63, 60.34, 55.07, 46.82, 34.30, 31.15, 27.79, 26.96, 26.83, 26.15, 23.48, 23.15, 12.76. FT-IR(neat) cm^{-1} 3025, 2927, 2852, 1612, 1438, 1385. HRMS [ESI] calcd. $C_{19}H_{328}N_2S$ $[M+H]^+$ 317.2051 observed 317.2036.

Synthesis of 9u (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N*, *N*-diisopropyl-3-phenylpropan-1-amine)



The general procedure **B** was followed using 2,6-dichlorobenzoxazole (25 mg, 0.13 mmol), *N*, *N*-diisopropyl-3-phenylpropan-1-amine (116 mg, 0.53 mmol), and 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN was used to afford to afford **9u** in 83% yield (40 mg, 0.10 mmol), rr 9.3:1 (based on crude ^1H NMR) as pale yellow oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 2.5 cv, slowly ramped to 10 % EtOAc for 2.5-27 cv then ramped to 100% EtOAc for 27-30 cv, then held at 100% EtOAc for 30-35 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.30 - 7.23 (m, 4H), 7.16 (dt, *J* = 6.5, 1.8 Hz, 2H), 4.14 (t, *J* = 7.5 Hz, 1H), 3.37 (hept, *J* = 6.6 Hz, 2H), 2.72 (ddd, *J* = 13.8, 9.9, 6.5 Hz, 1H), 2.64 - 2.58 (m, 1H), 2.41 - 2.32 (m, 1H), 2.12 (dtd, *J* = 13.6, 6.8, 3.1 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.76, 150.75, 141.99, 140.19, 130.41, 128.62, 128.57, 126.06, 124.95, 120.52, 111.34, 52.12, 45.61, 35.05, 33.30, 23.72, 22.10. FT-IR (neat) cm^{-1} 3022, 2961, 1678, 1513, 1384. HRMS [ESI] calcd. $C_{22}H_{27}N_2OCl$ $[M+H]^+$ 371.1890 observed 371.1873.

Synthesis of 9v (N-isopropyl-N-(1-(thiazol-2-yl) ethyl)propan-2-amine)

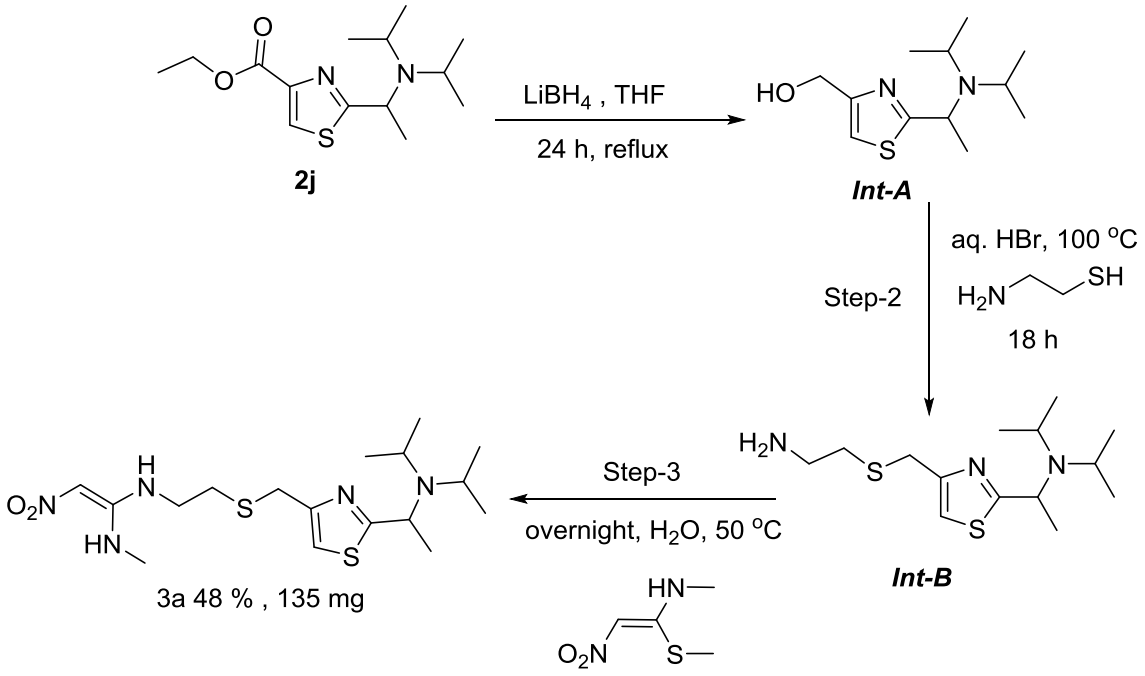


The general procedure **A** was followed using 2-chlorothizole (20 ul , 0.13 mmol), *N*, *N*-diisopropylethylamine (0.03 mL, 0.18 mmol), imidazole (20 mg, 0.18 mol) 0.75 mL of stock solution of $Ir(ppy)_3$ in CH_3CN to afford **9v** in 69% yield (22 mg, 0.081 mmol) rr 2:1(based on crude ^1H NMR) as an oil. It was purified by automated flash chromatography using hexane:EtOAc (0% for 3 cv, slowly ramped to 10 % EtOAc for 3-15 cv then ramped to 100% EtOAc for 15-27 cv, then held at 100% EtOAc for 27-32 cv), on a 12 g silica column. ^1H NMR (400 MHz, $CdCl_3$) δ 7.64 (d, *J* = 3.3 Hz, 1H), 7.18 (d, *J* = 3.3 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 1H), 3.16 (hept, *J* = 6.7, 6.3 Hz, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.42, 142.57,

119.69, 52.67, 46.08, 28.11, 22.31, 19.03. FT-IR (neat) cm^{-1} 3120, 2961, 2869, 1605, 1500, 1385. HRMS [ESI] calcd. $C_{11}H_{20}N_2S$ $[M+H]^+$ 213.1425 observed 213.1410.

Note – **9v** has the other regio-isomer present in the spectra, labeled as dark filled circle.

<u>10a Synthesis of nizatidine analog</u>-(Z)-*N*-2-(2-(((2-(1-(diisopropylamino)ethyl)thiazol-4-yl)methyl)thio)ethyl)-*N*1-methyl-1-nitroethene-1,2-diamine



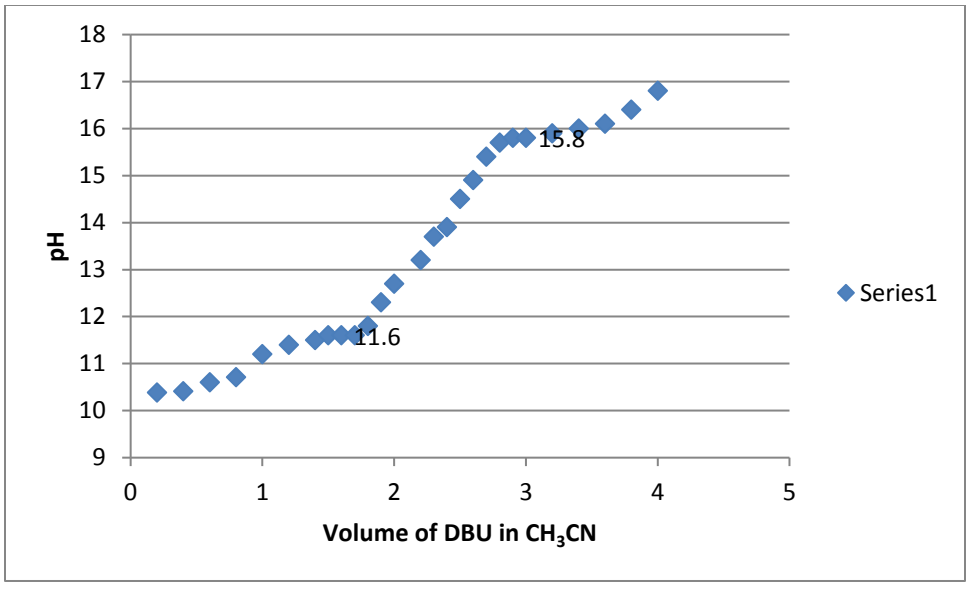
Follo wingliterature procedure[4-5], to a round bottom flask, 200 mg of **9j** (0.70 mmol) was added along with 30 mg lithium borohydride ($LiBH_4$) (1.4 mmol) in THF (10 mL) and was refluxed for 22 h. After cooling water (10 mL) was added and the mixture was extracted with EtOAc (4×5 mL). The combined organic portions were dried over anhydrous $MgSO_4$. It was filtered and concentrated to afford ***int-A*** with a crude yield of 90% (152 mg, 0.63 mmol).

In the second step, 152 mg of crude ***int-A***, 2-aminoethane-1-thiol (74 mg, 0.65 mmol) and aq HBr (0.9 mL) were added. The reaction mixture was heated at 100 °C for 18 h. After cooling, water (10 mL) and solid K_2CO_3 were added and the resulting solution was extracted with EtOAc (5×5 mL). The organic portions were combined and dried over $MgSO_4$ and concentrated over *via* rotovap to afford ***int- B*** in greater than quantitative yield by mass. In the final step, the crude material from the previous step and (*Z*)-N-methyl-1-(methylthio)-2-nitroethen-1-amine (114 mg, 0.768 mmol) were combined and water (3 mL) was added. The reaction mixture was heated at 50 °C overnight. After the complete conversion of reactant to product (monitored by TLC), the reaction mixture was quenched by adding saturated aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (5×5 mL) and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated *via* rotovap. The crude material was subjected to automated flash chromatography DCM/MeOH, (0% for 2.5 cv, slowly ramped to 25% MeOH for 2.5-75 cv then ramped to 50% MeOH for 75-92 cv, then held at 100% EtOAc f 98cv), on a 4 g silica column to obtain **10a,** 48% (135 mg, 0.336 mmol) over three steps, starting from the coupled product **9j**. ^{1}H NMR (400 MHz, $CdCl_3$) δ 6.93 (s, 1H), 6.51 (d, *J* = 1.1 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 2H), 3.29 (d, *J* = 7.2 Hz, 2H), 3.09 (hept, *J* = 12.8, 8.1, 6.2 Hz, 2H), 2.87 (s, 2H), 2.78 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.05 (dd, *J* = 6.6, 1.4 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.56, 156.89, 152.85, 116.69, 98.40, 52.80, 46.17, 41.56, 31.49, 31.05, 27.76, 23.60, 22.22, 19.10. FT-IR (neat) cm^{-1} 3257, 3010, 2961, 1613, 1571, 1382, 1362. HRMS [ESI] calcd. $C_{17}H_{31}N_5S_2O$ $[M+H]^+$ 402.1997 observed 402.1977.

Calculation of pK_a value of 2-chlorothiazole

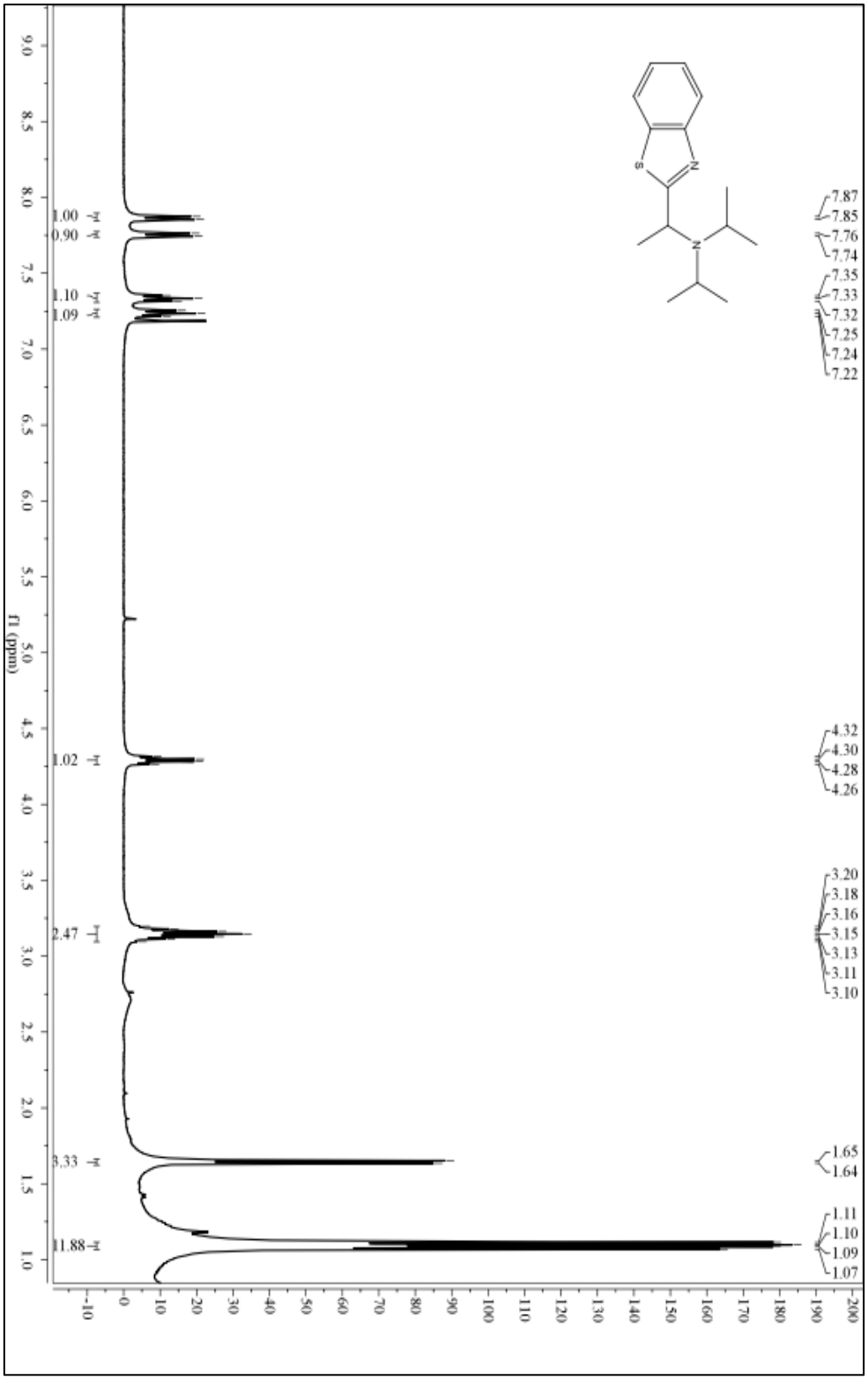
Apparatus - 50 mL Burette, Vernier Hanna Instruments HI98103 Checker pH Tester, 250 mL beakers (2), stir bar and stir plate, DI water, ring stand, burette clamp, clamp for pH Tester S-58 and the pH tester was calibrated using buffer solution (pH=10, 7).

Procedure - Fill the burette with 1 M DBU (1, 8-Diazabicyclo[5.4.0]undec-7-ene) in CH_3CN. Add (50 mg of 2-chlorothiazole in 10 mL of CH_3CN) into a 250 mL beaker. Titrate the solution by adding the DBU in MeCN solution as the titrant in 0.2–0.4 mL increments, and stir. Measure and record the pH of the solution in the beaker after 3-10 minutes of stirring. After each measurement, rinse the pH probe with DI water and MeCN and replace the probe into a pH 7.0 buffered solution. Keep recording the pH until the change between readings becomes very slight. At the equivalence point, the volume of base added is just enough to exactly neutralize all of the acid. A plot of the pH vs. the volume will reveal the equivalence point and allow the pKa to be determined. The measured pH is equal to pKa, at exactly one-half the volume of the equivalence point.[32]

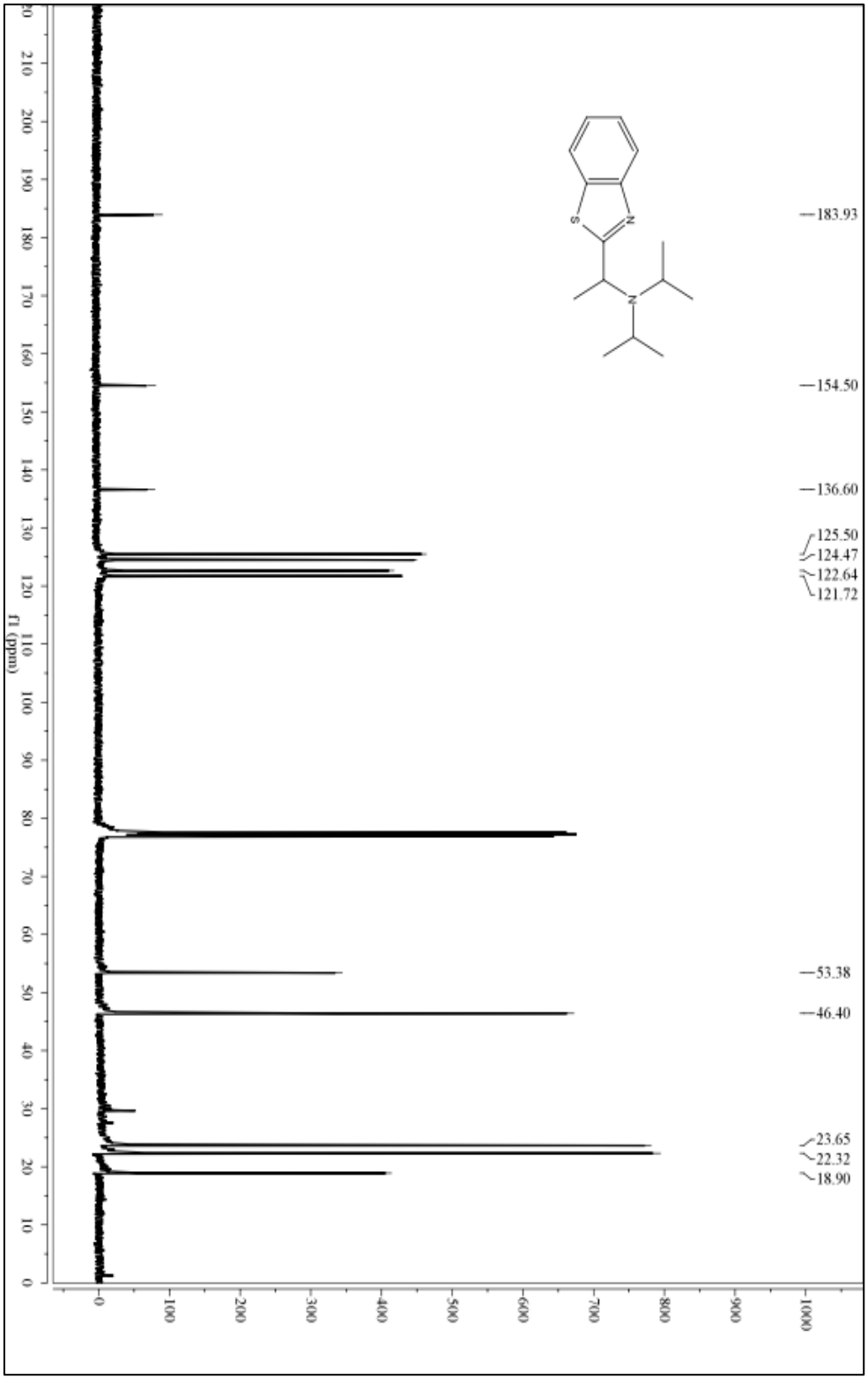


Titration curve for the titration of 50 mg of 2-chlorothiazole in CH_3CN with 1 M DBU in CH_3CN

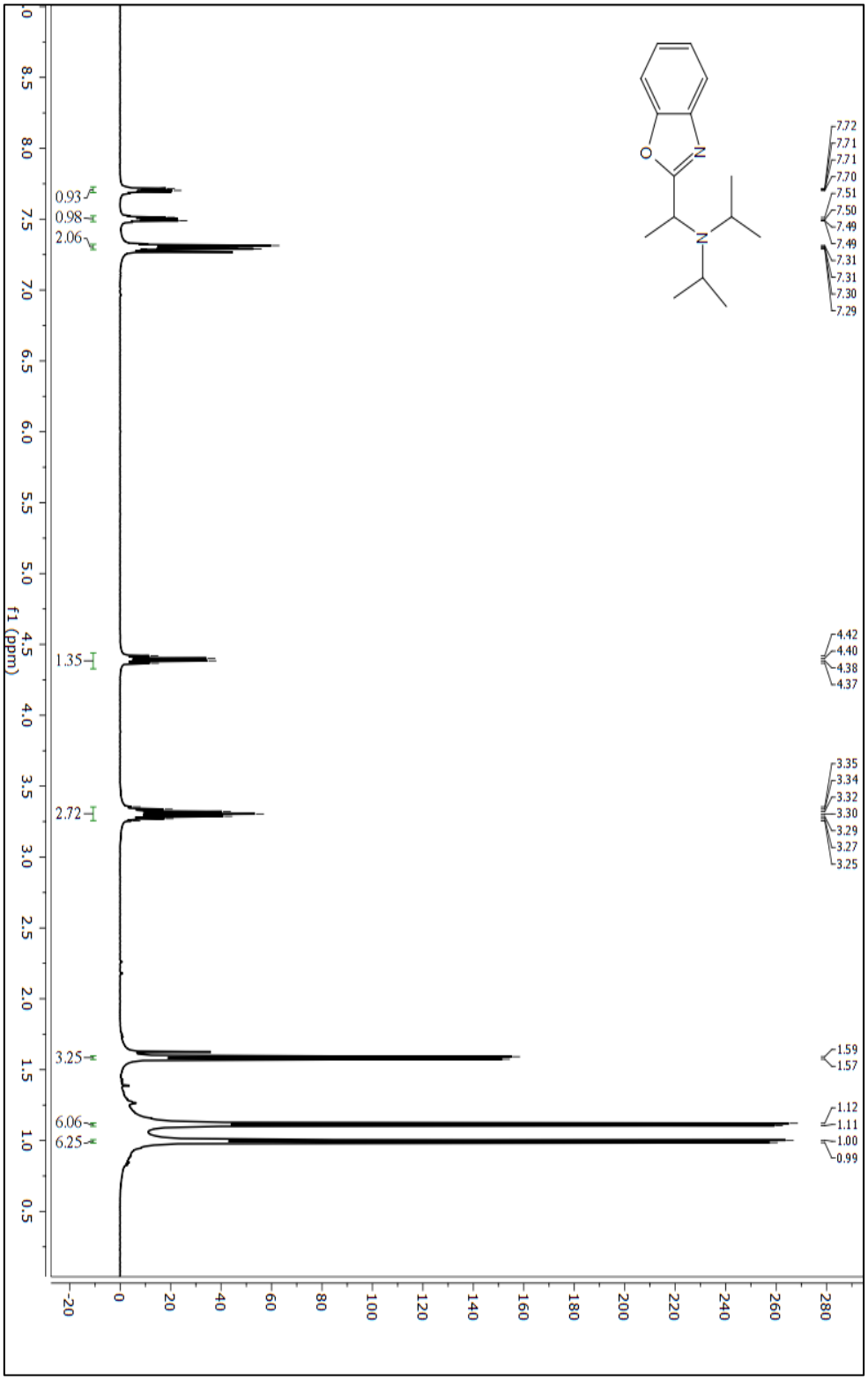
9a (*N*(benzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



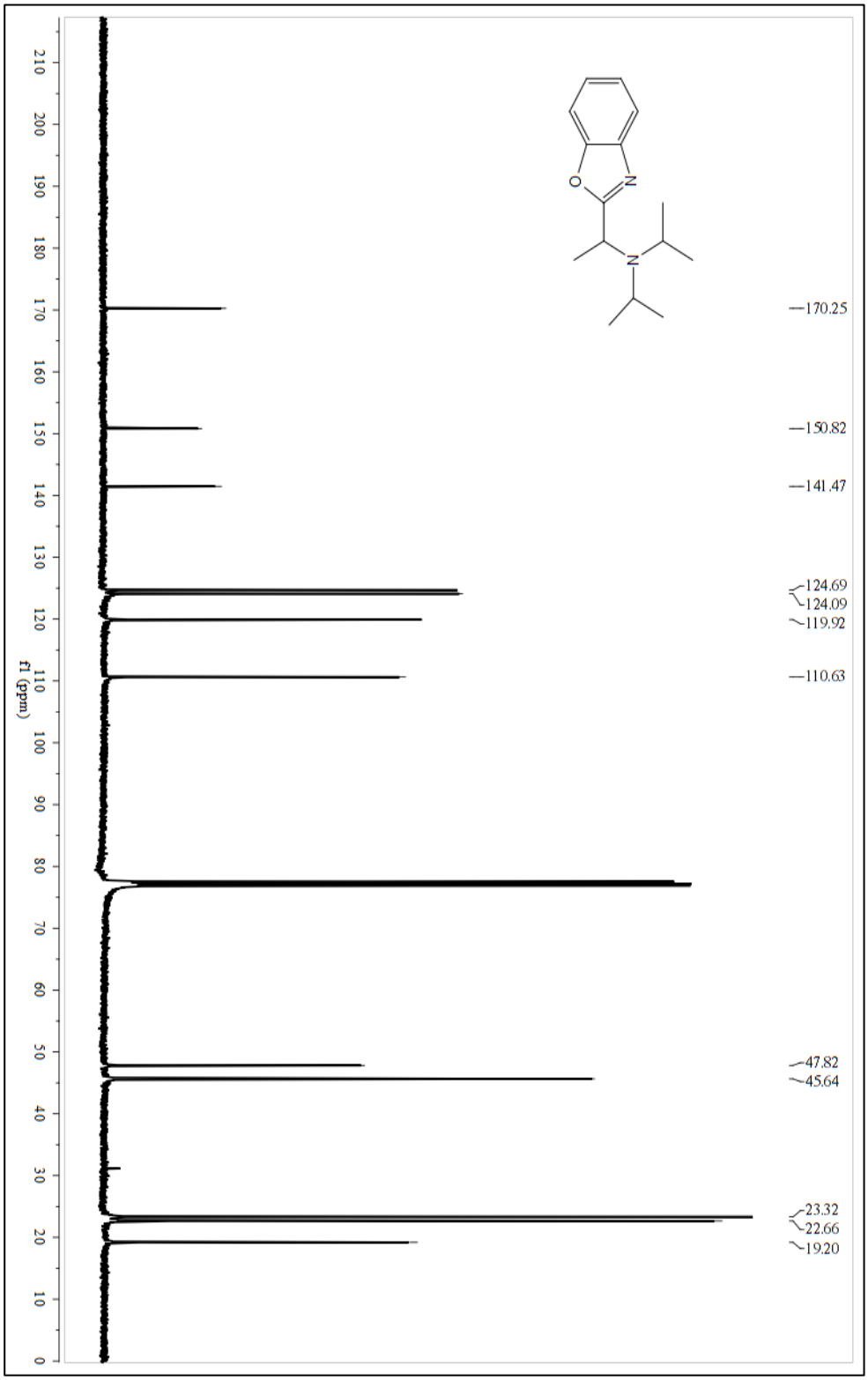
9a (*N*-(1-(benzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



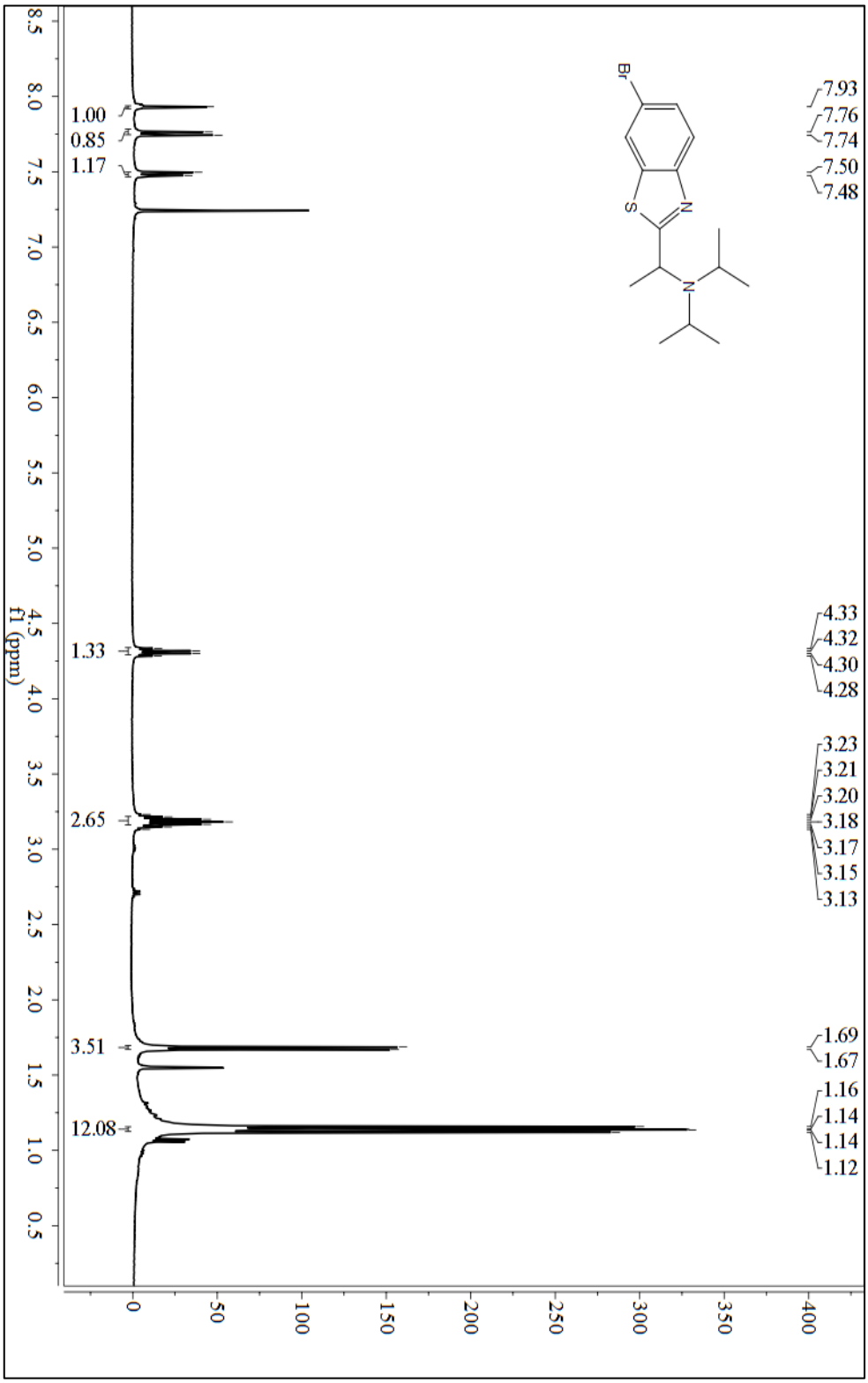
9b (1-(benzo[*d*]thiazol-2-yl)-*N, N*-dibutylbutan-1-amine



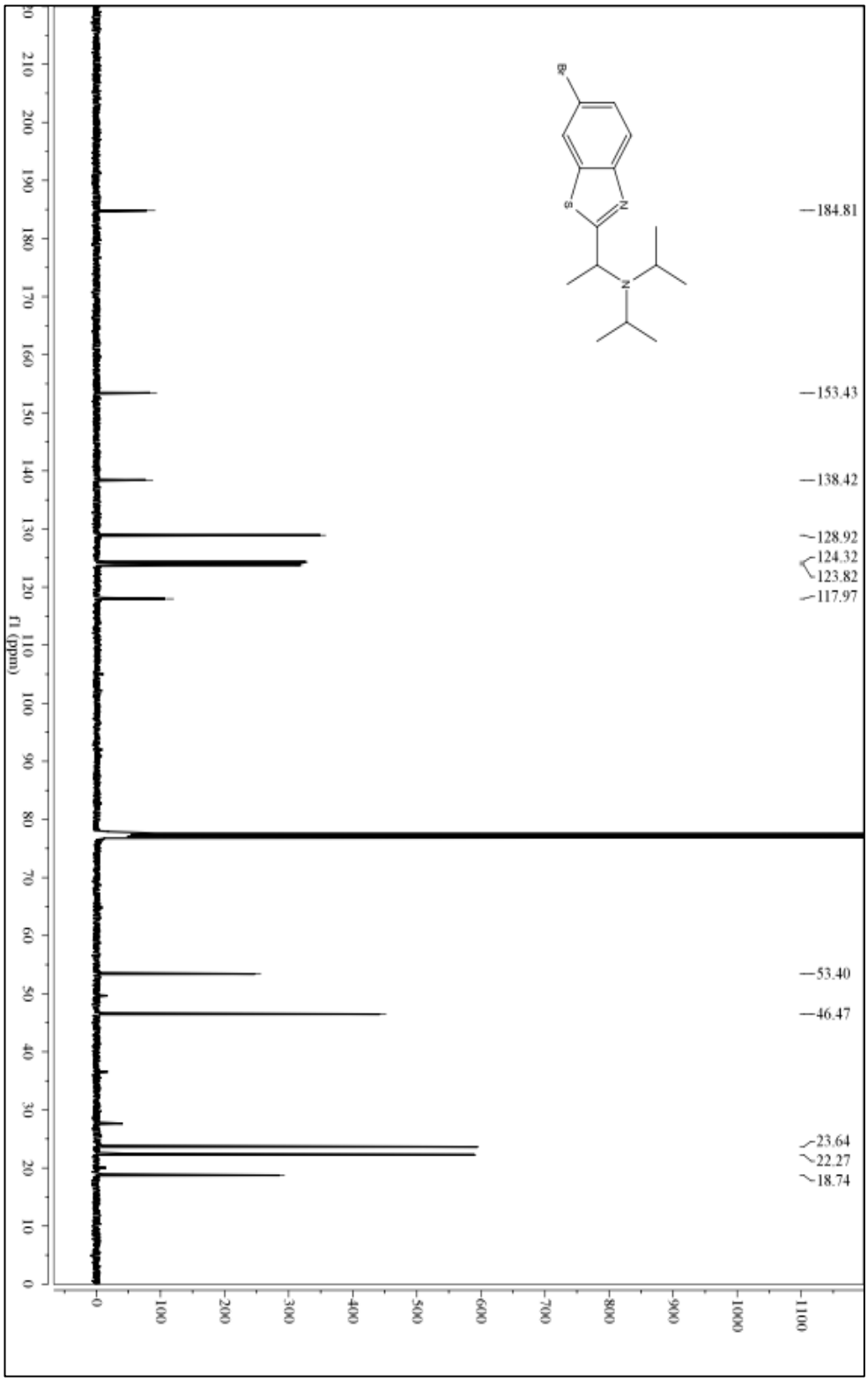
9b (1-(benzo[*d*]thiazol-2-yl)-*N, N*-dibutylbutan-1-amine)



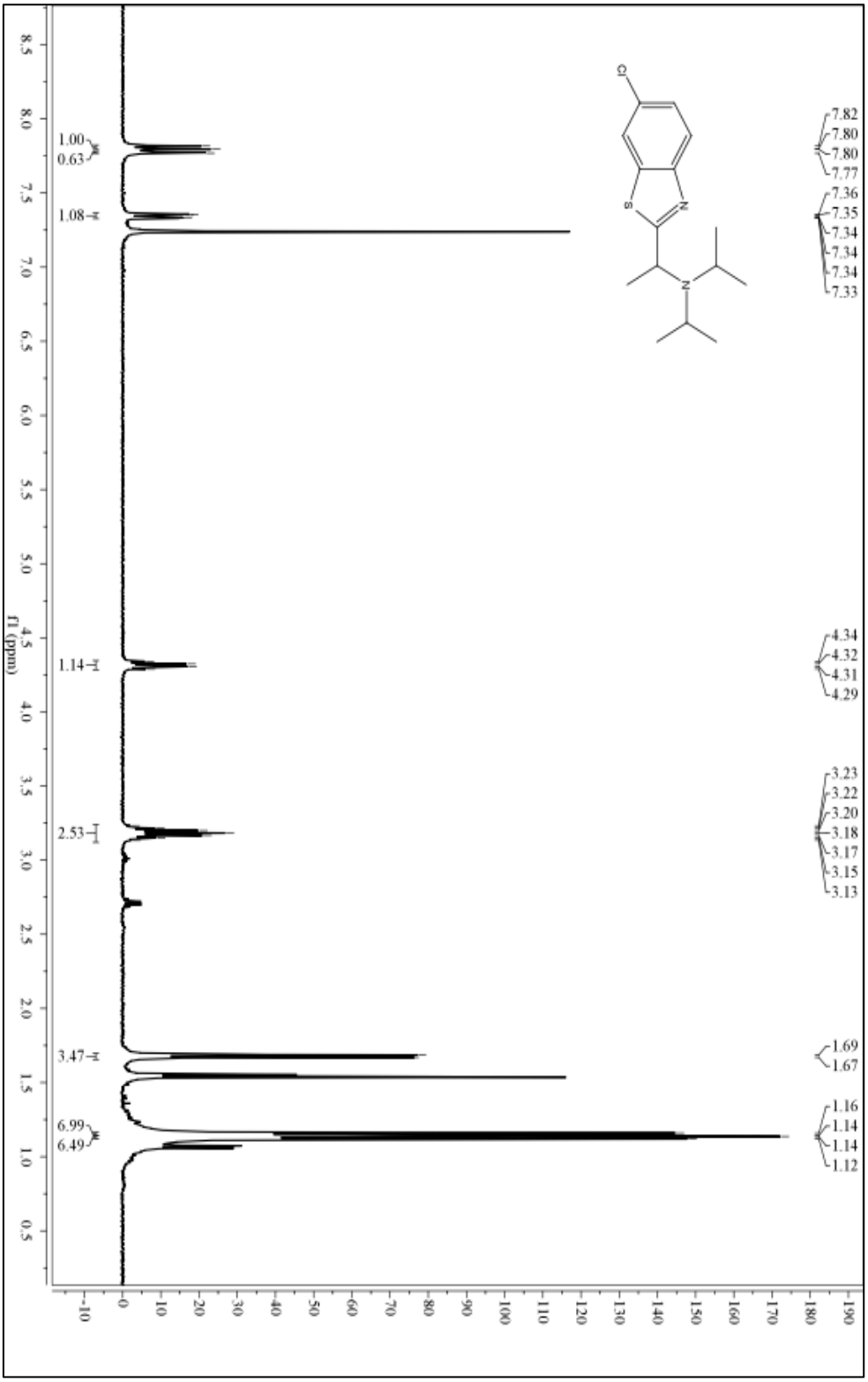
9c (*N*-(1-(6-bromobenzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



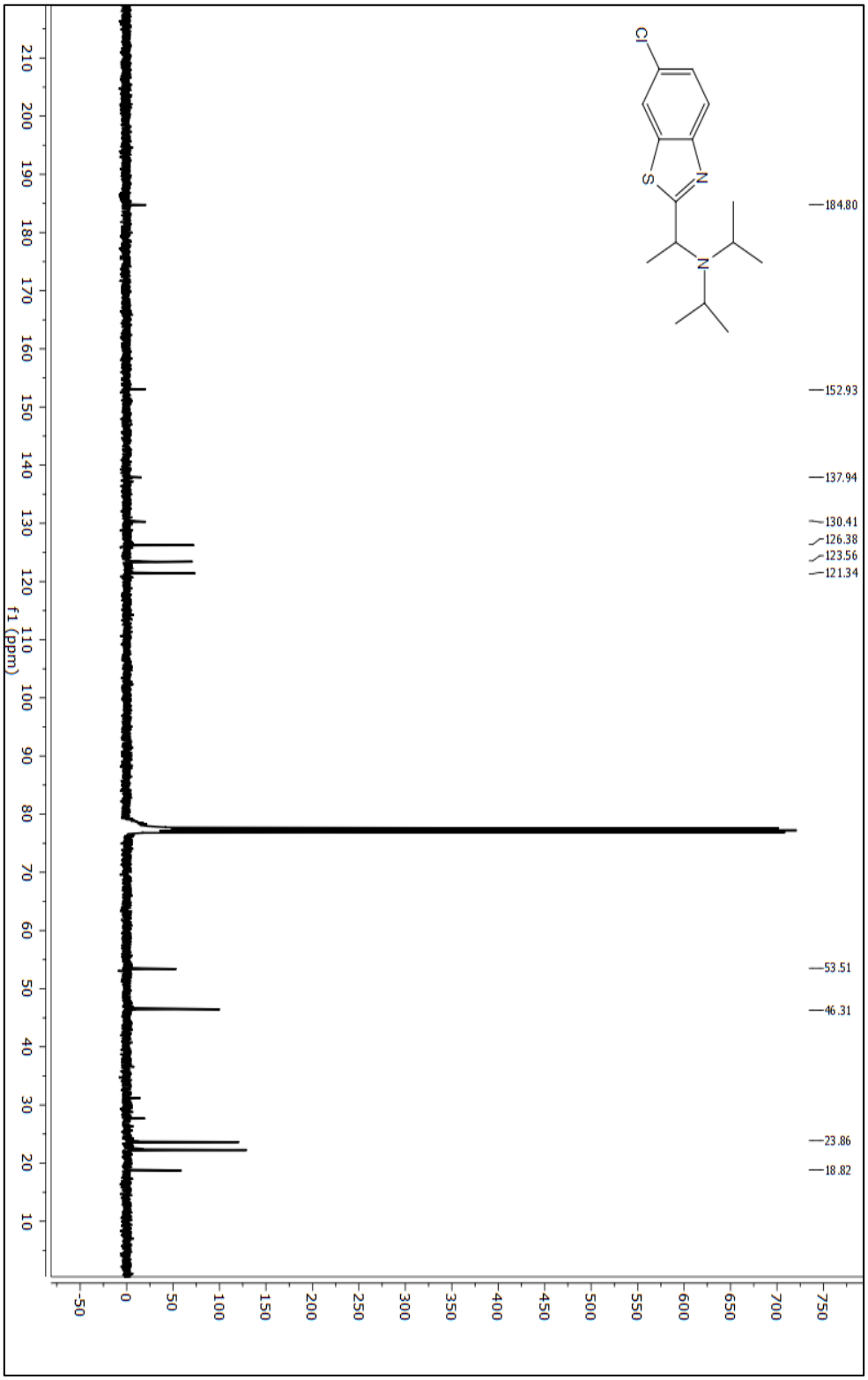
9c (*N*-(1-(6-bromobenzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



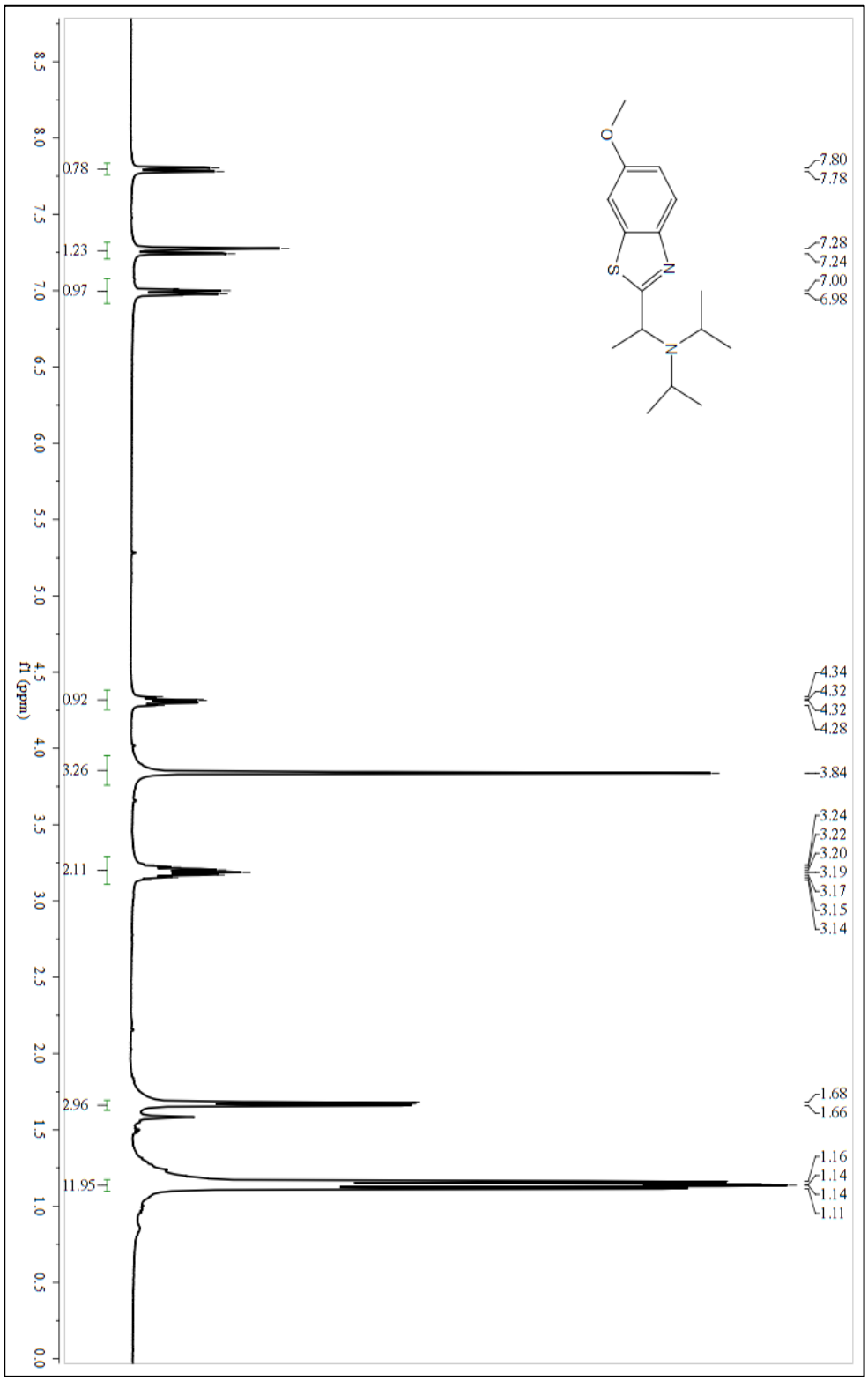
9d ***(N*-(1-(6-chlorobenzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine**



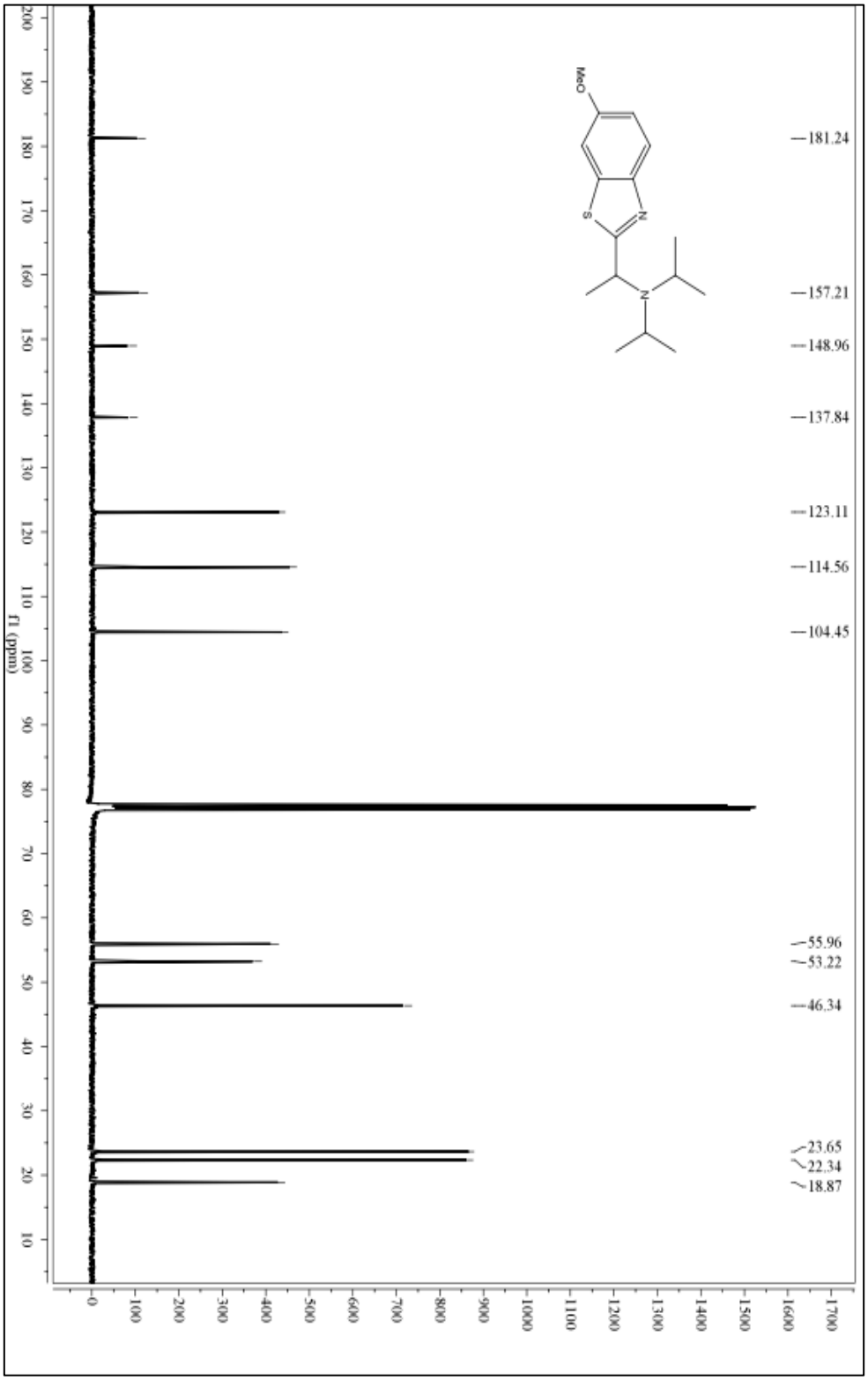
9d *(N*-(1-(6-chlorobenzo[*d*]thiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



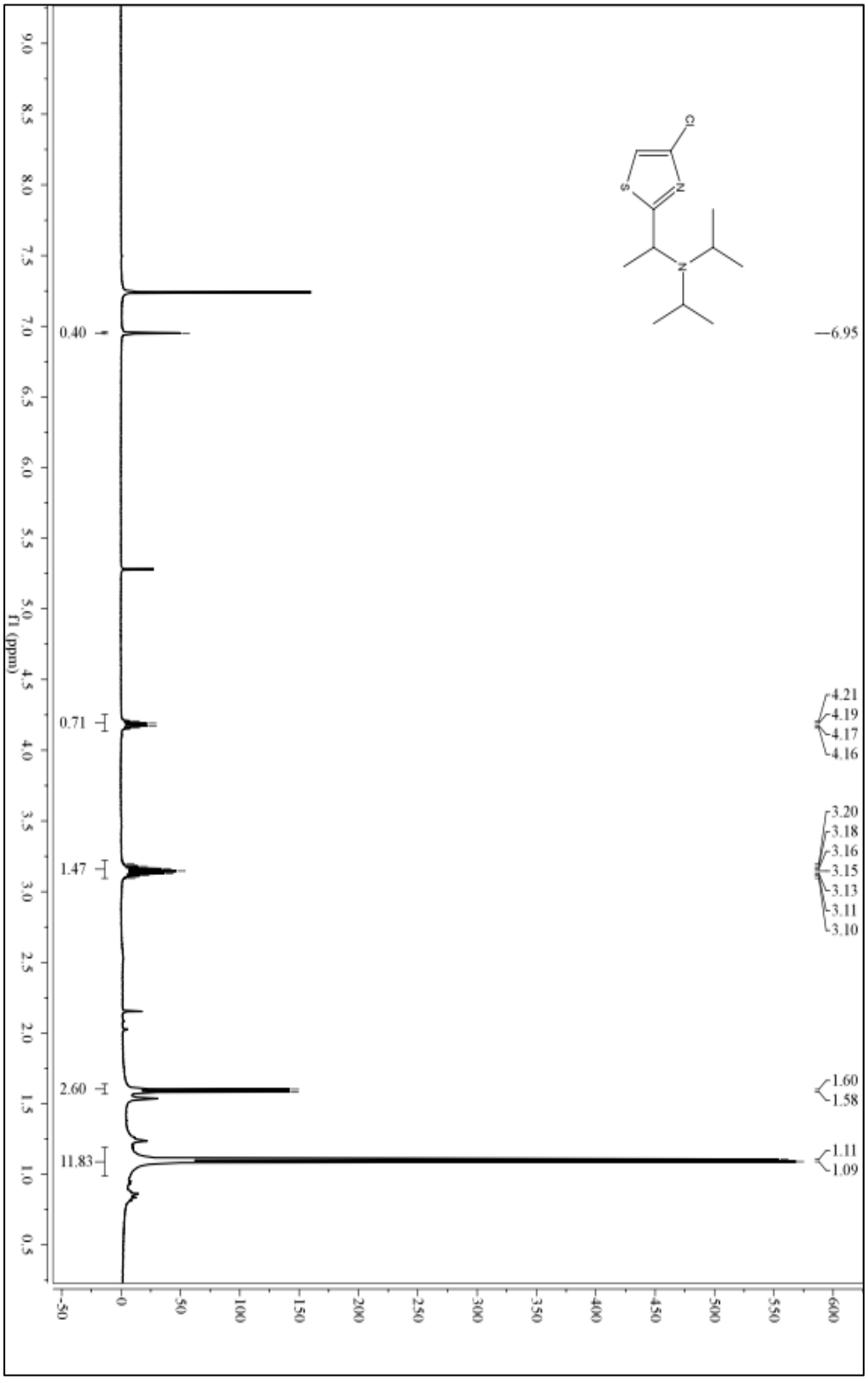
9e **(*N*-isopropyl-*N*-(1-(6-methoxybenzo[*d*]thiazol-2-yl)ethyl)propan-2-amine)**



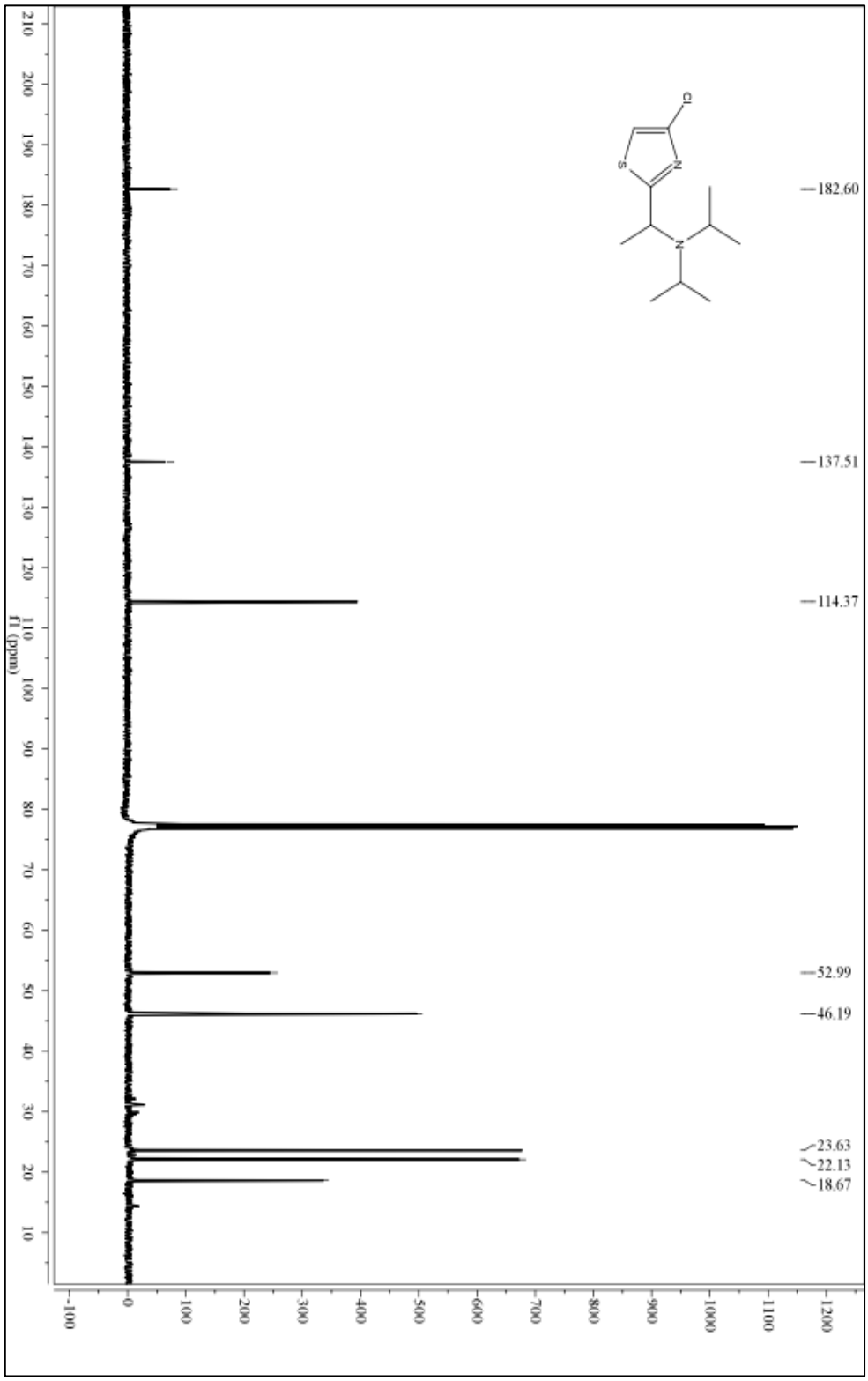
9e (*N*-isopropyl-*N*-(1-(6-methoxybenzo[*d*]thiazol-2-yl)ethyl)propan-2-amine



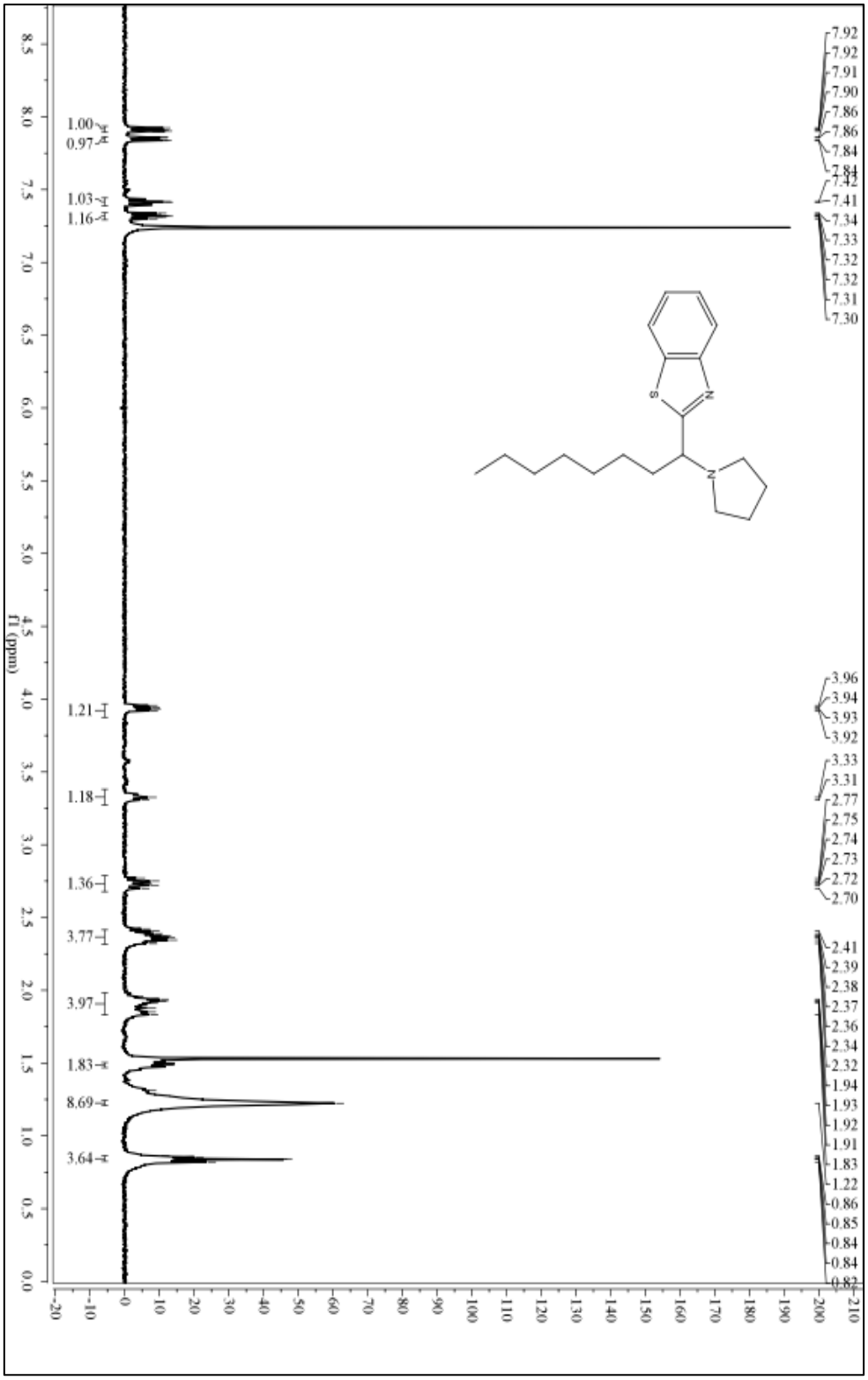
9f (*N*-(1-(5-chlorothiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



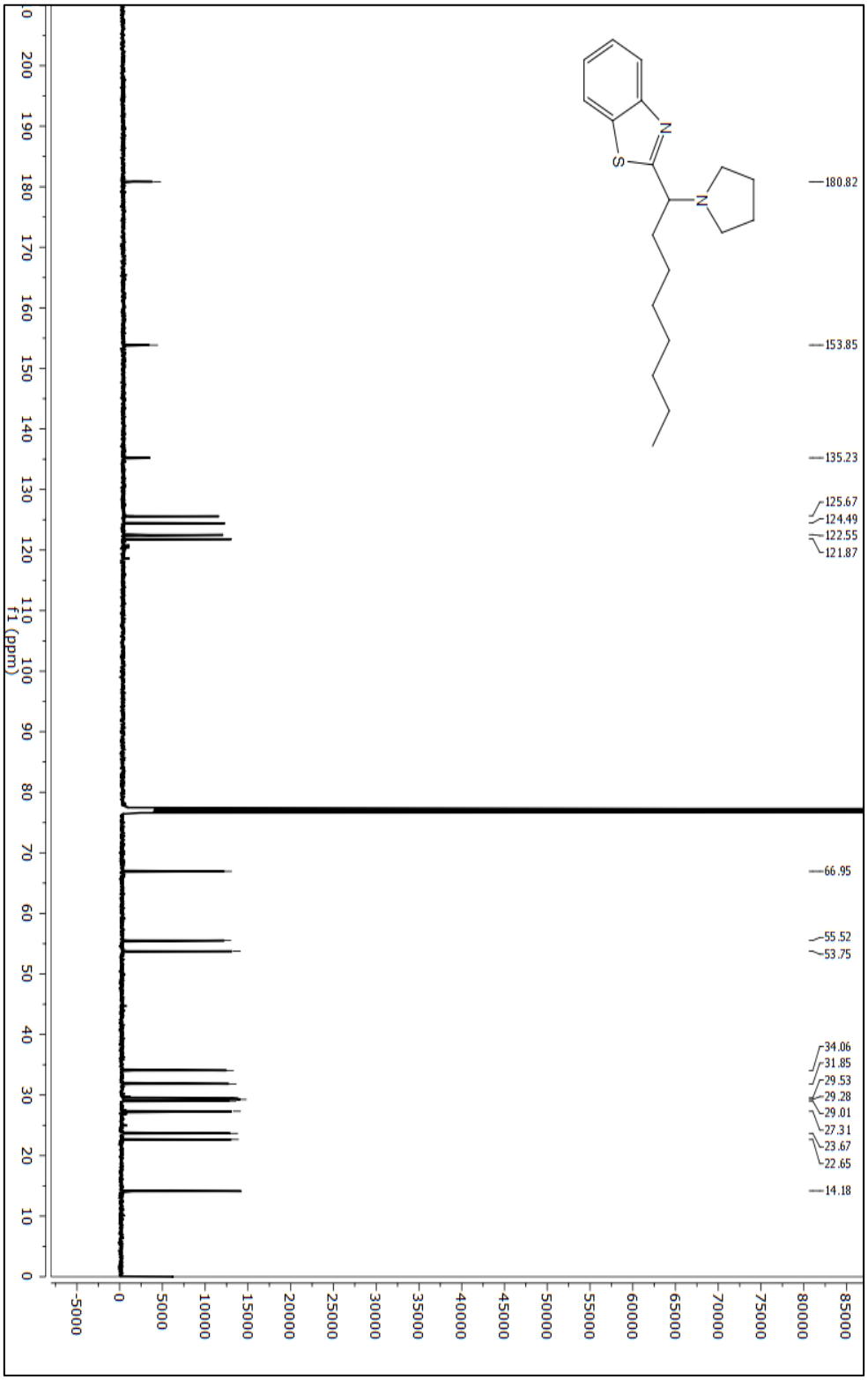
9f (*N*-(1-(5-chlorothiazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



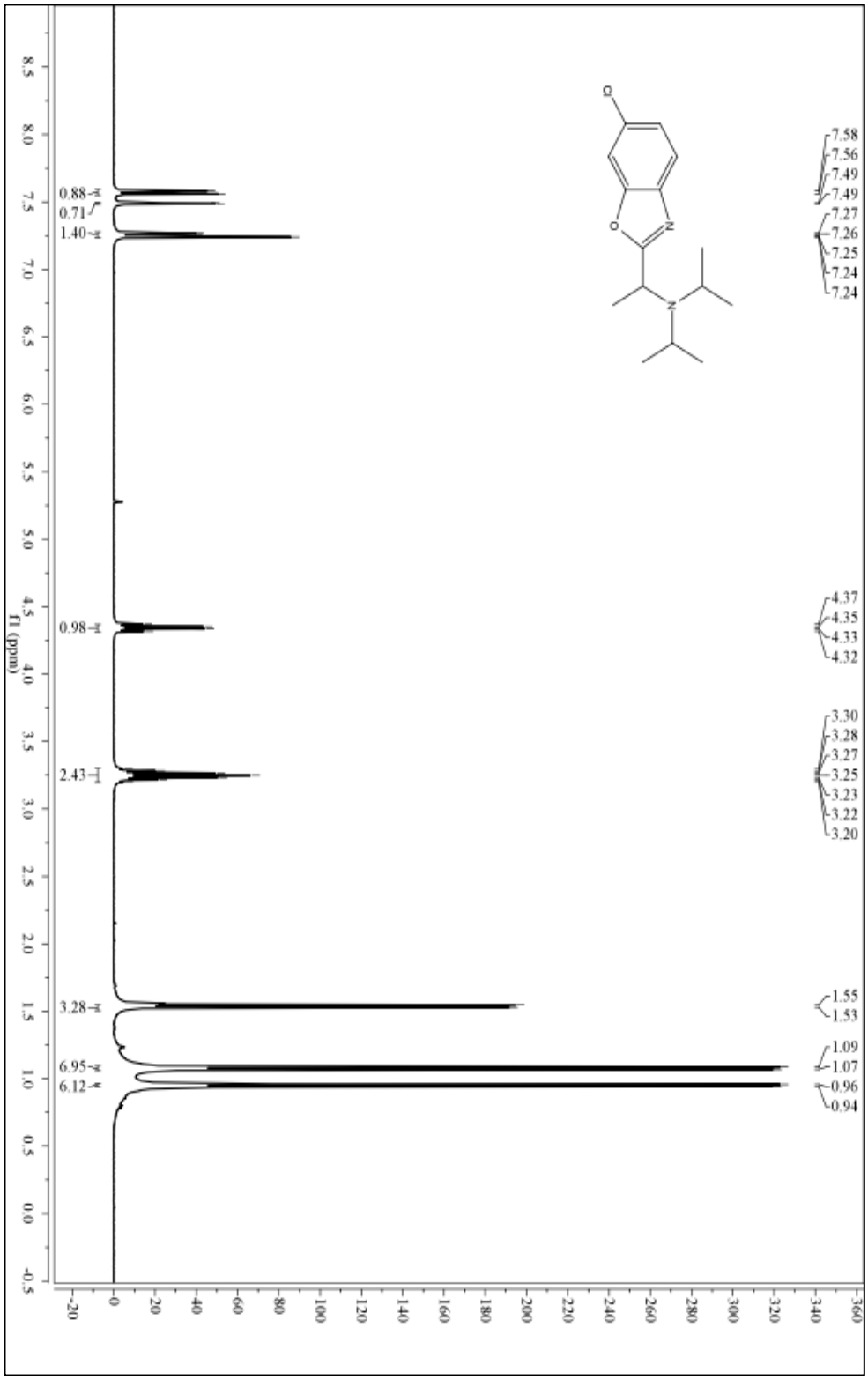
9g (2-(1-(pyrrolidin-1-yl)octyl)benzo[*d*]thiazole)



9g (2-(1-(pyrrolidin-1-yl)octyl)benzo[*d*]thiazole)



9h (*N*-(1-(6-chlorobenzo[*d*]oxazol-2-yl)ethyl)-*N*-isopropylpropan-2-amine)



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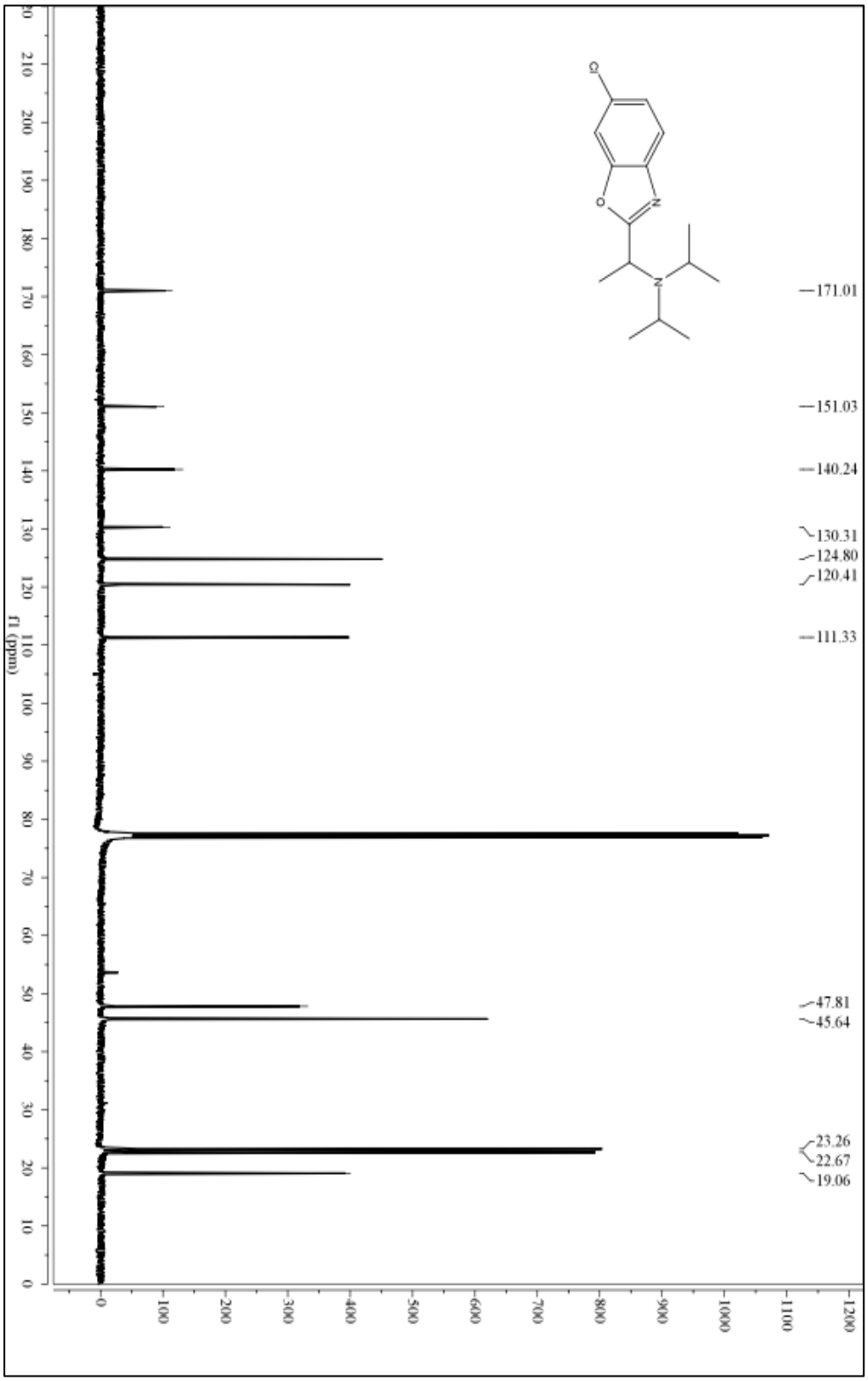
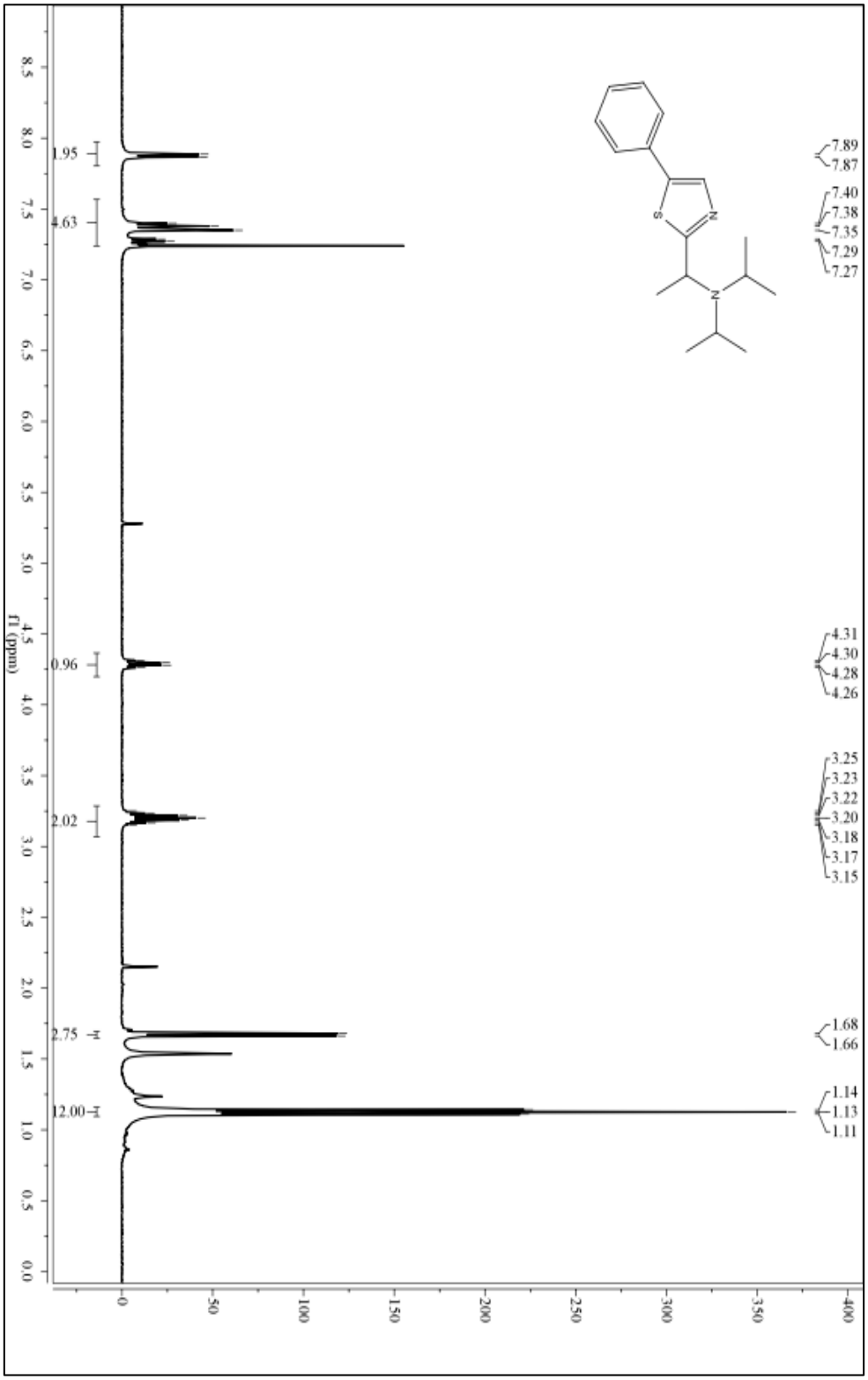
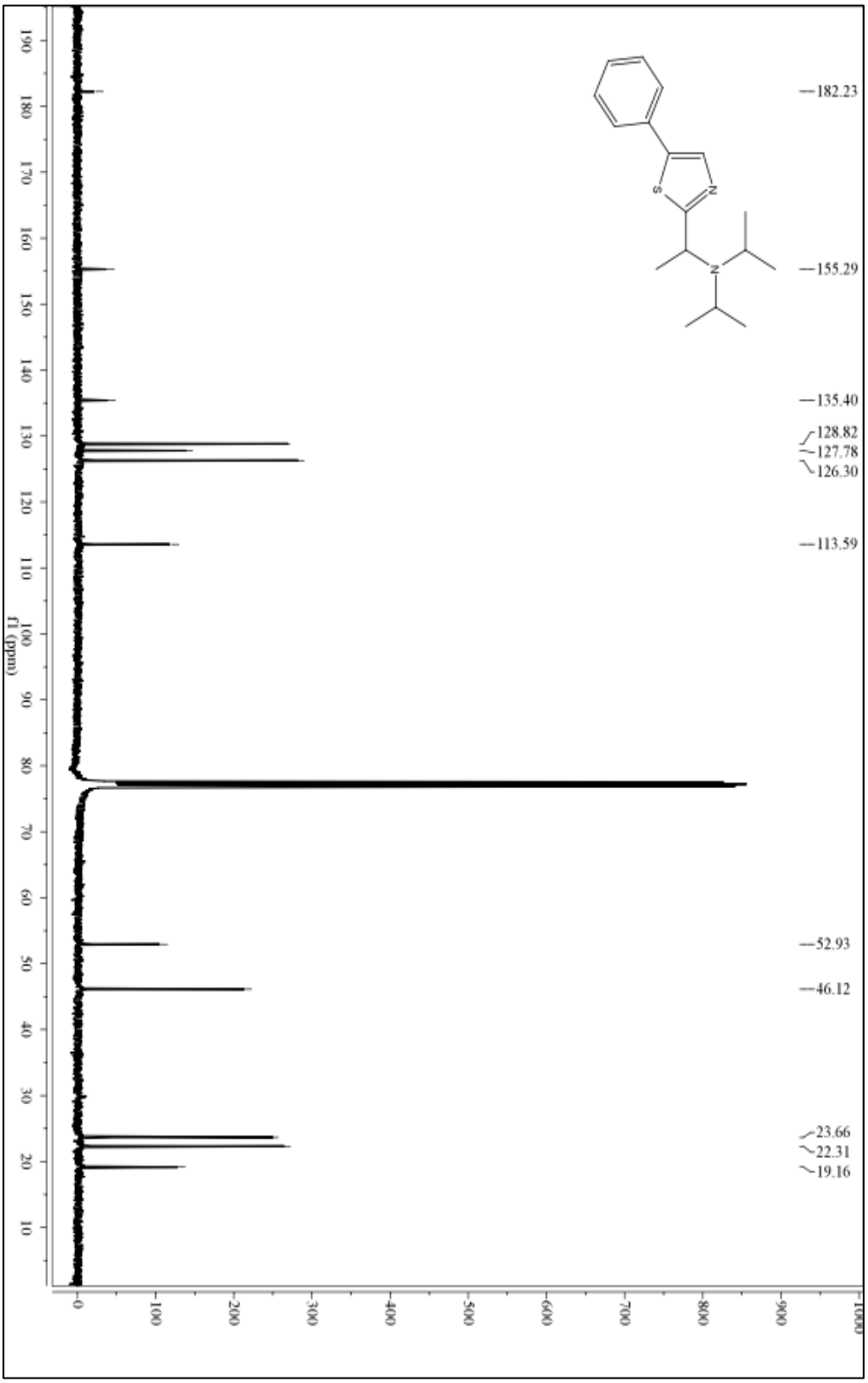


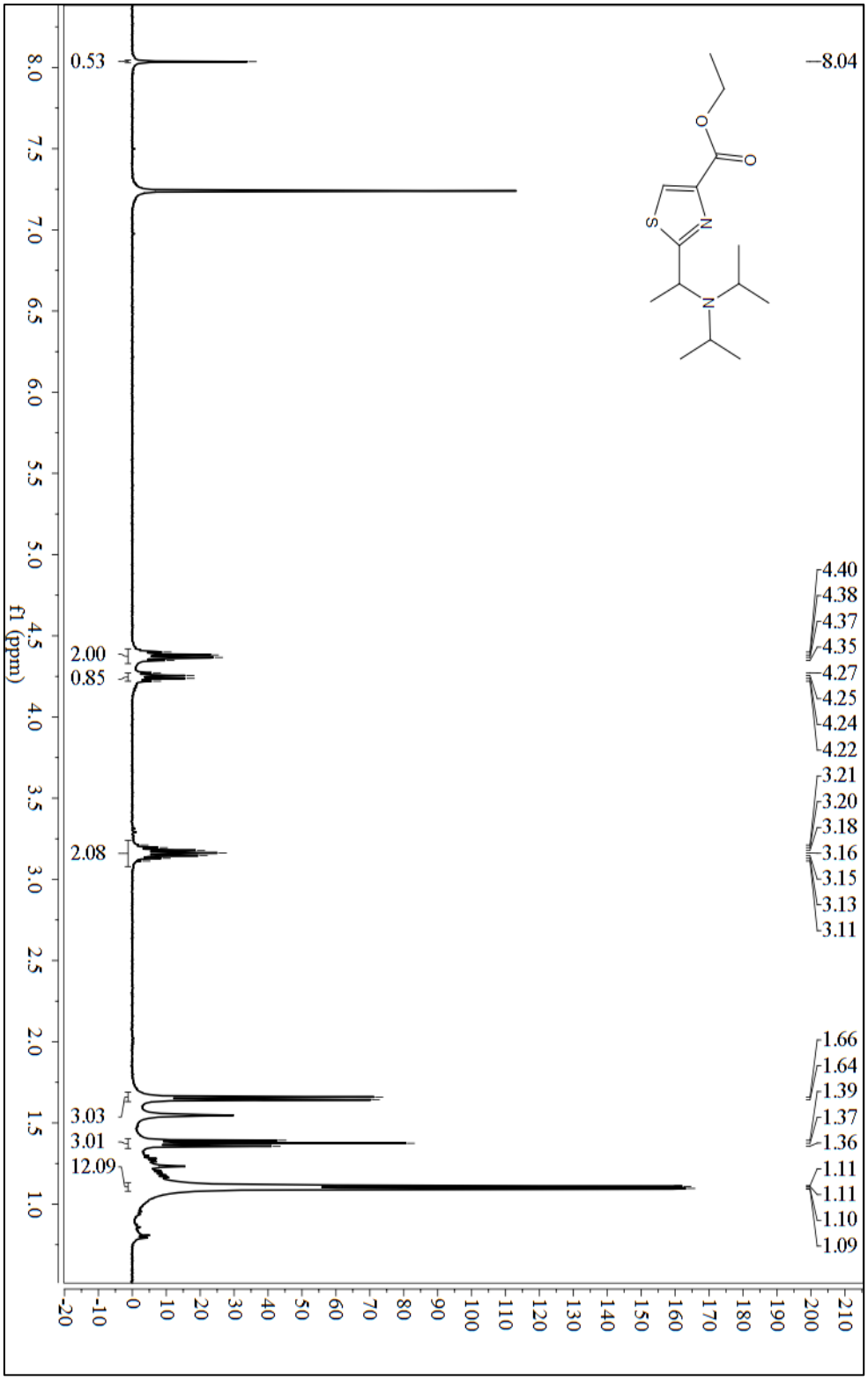
9i (*N*-isopropyl-*N*-(1-(5-phenylthiazol-2-yl) ethyl) propan-2-amine)



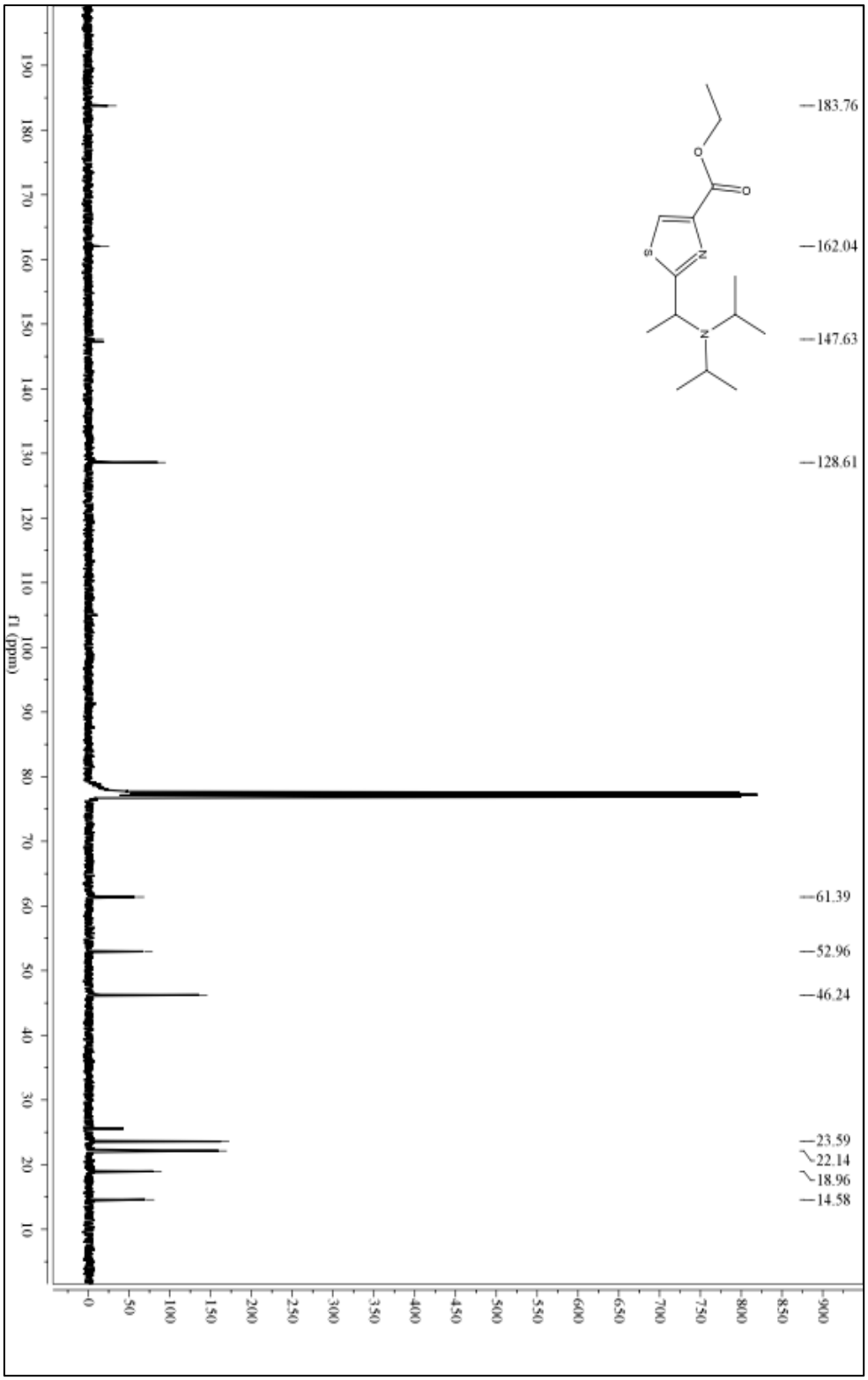
9i (*N*-isopropyl-*N*-(1-(5-phenylthiazol-2-yl) ethyl)propan-2-amine)



9j ethyl 2-(1-(diisopropylamino)ethyl)thiazole-4-carboxylate

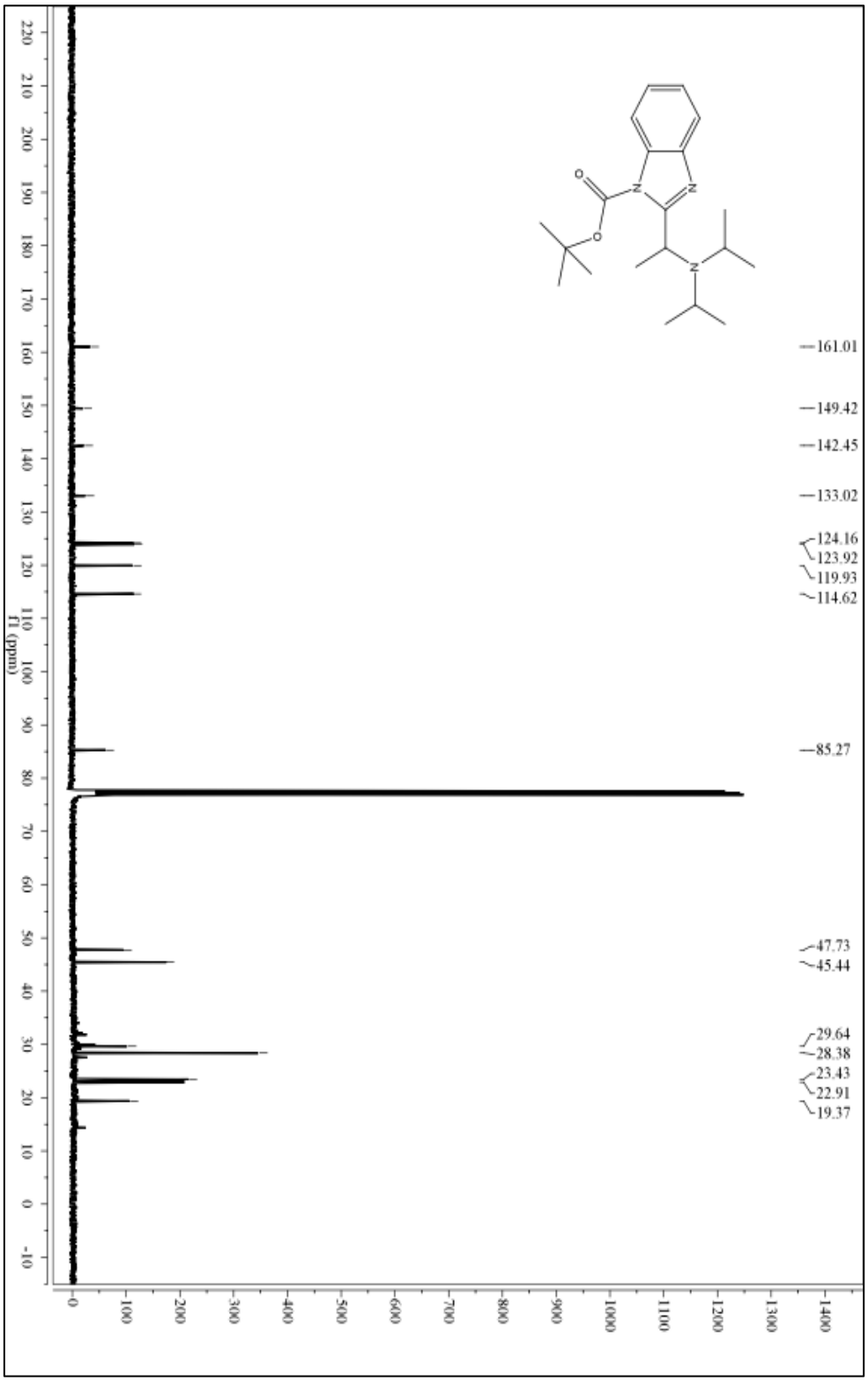


9j ethyl 2-(1-(diisopropylamino)ethyl)thiazole-4-carboxylate

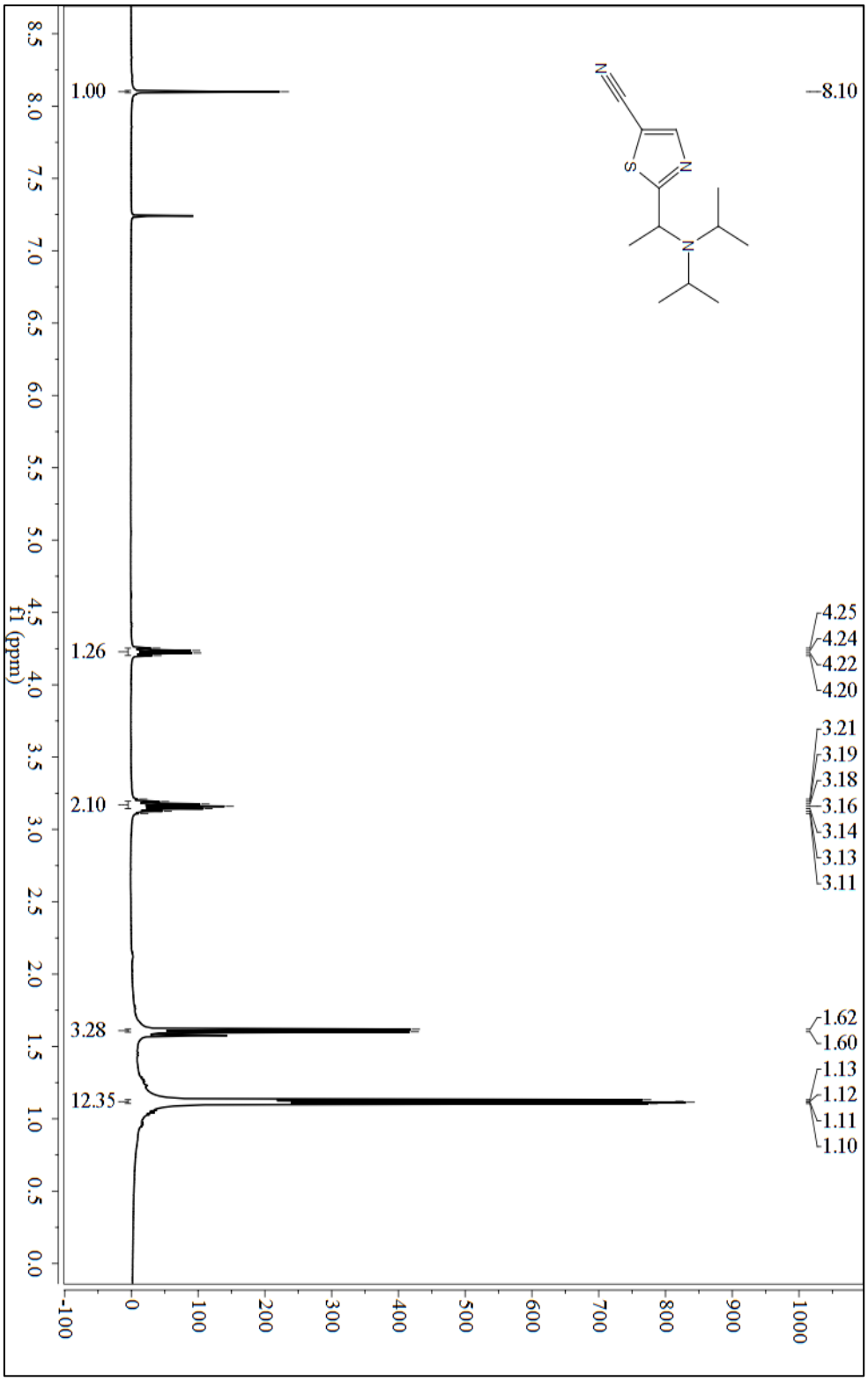


9k (*tert*-butyl 2-(1-(diisopropylamino) ethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate)

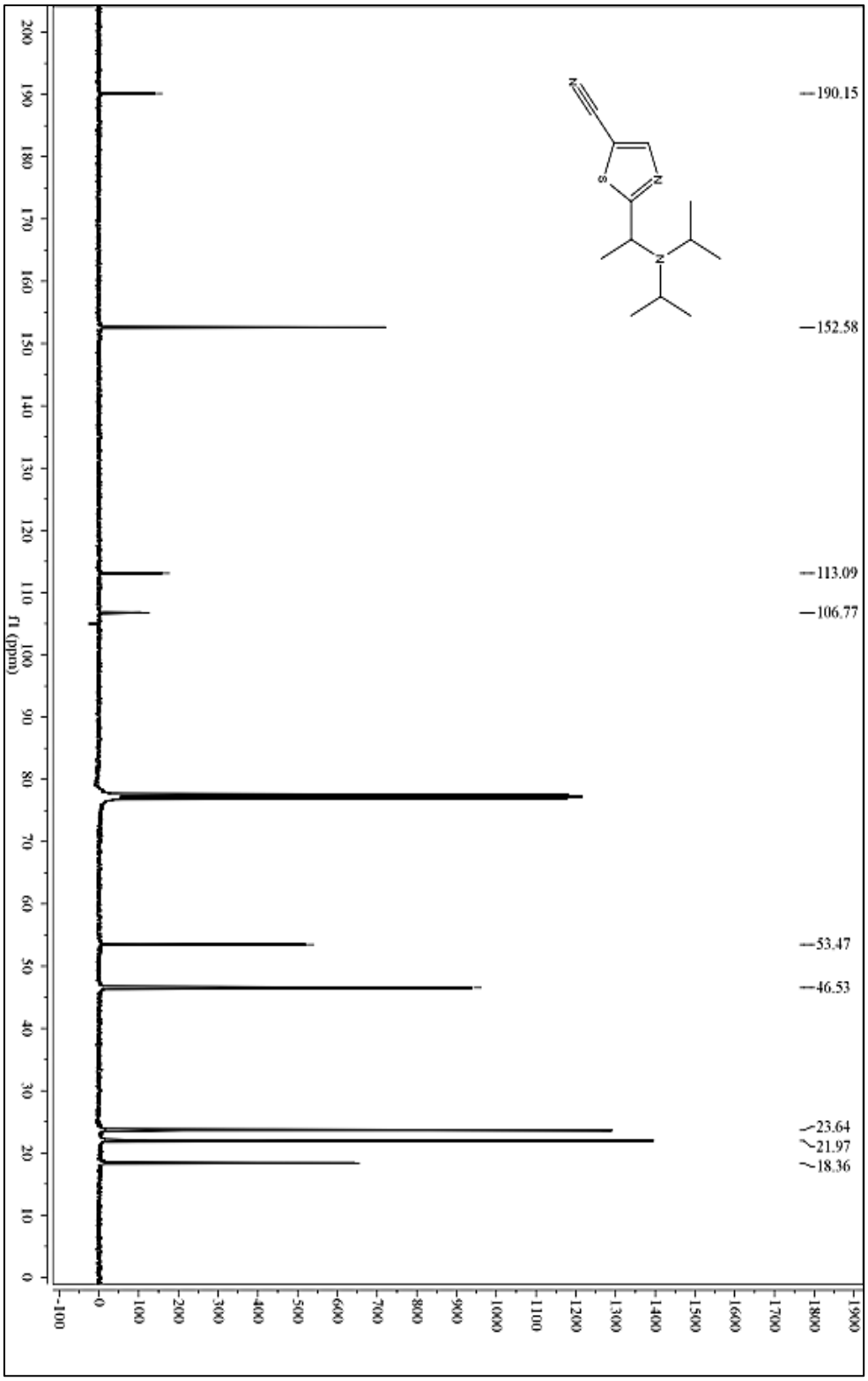
9k (*tert*-butyl 2-(1-(diisopropylamino)ethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate)



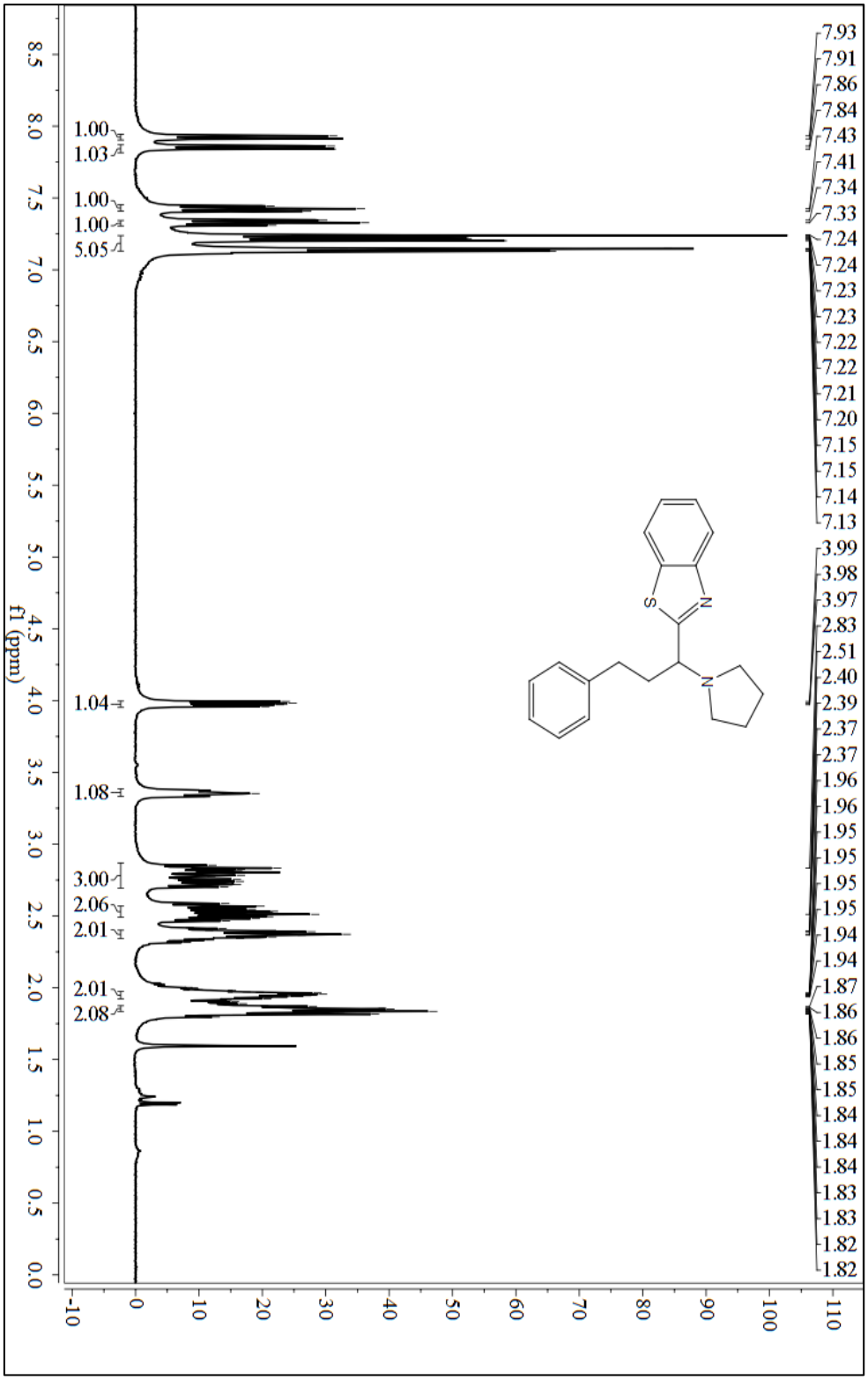
9l (2-(1-(diisopropylamino) ethyl) thiazole-5-carbonitrile)



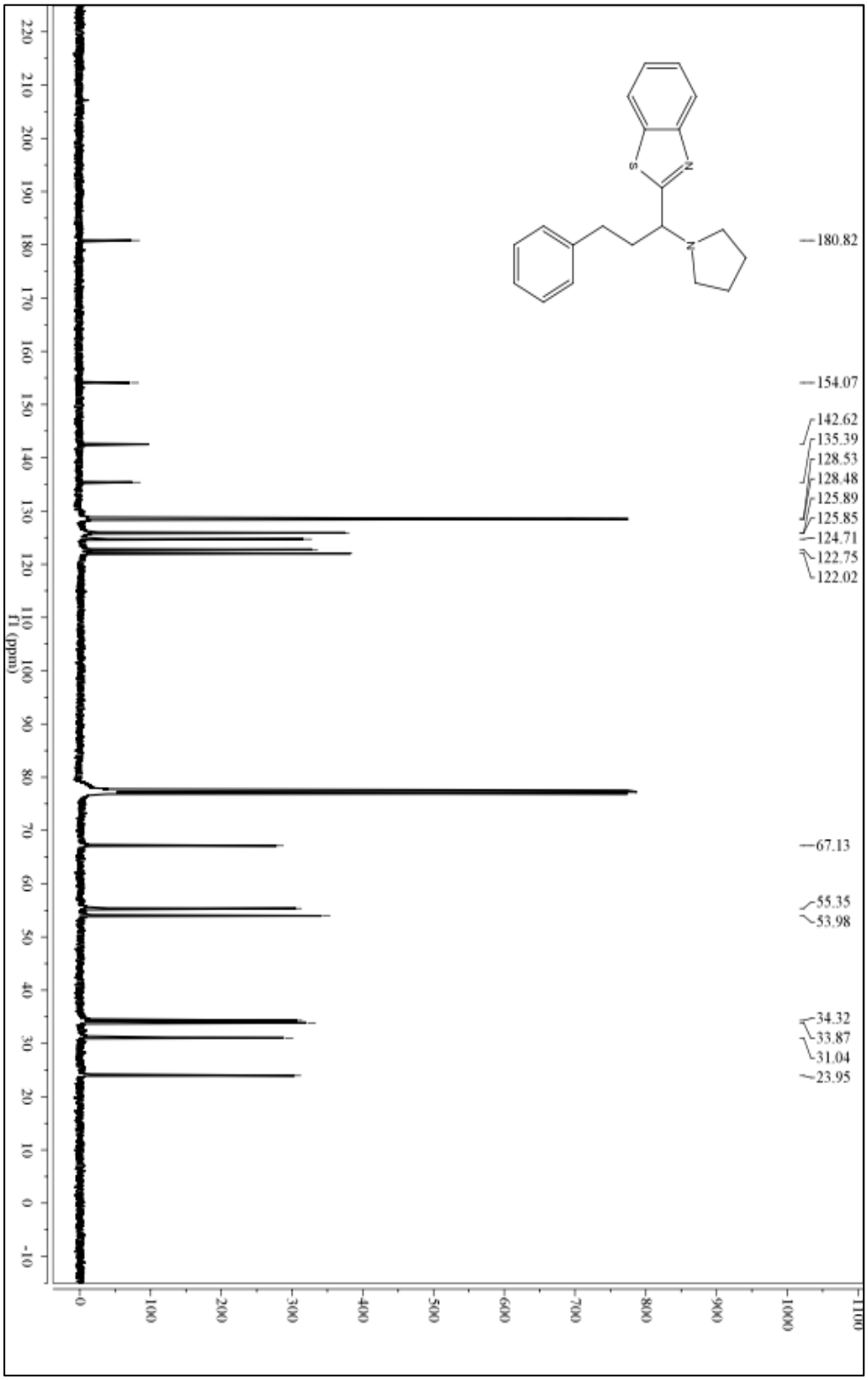
9l (2-(1-(diisopropylamino) ethyl) thiazole-5-carbonitrile)



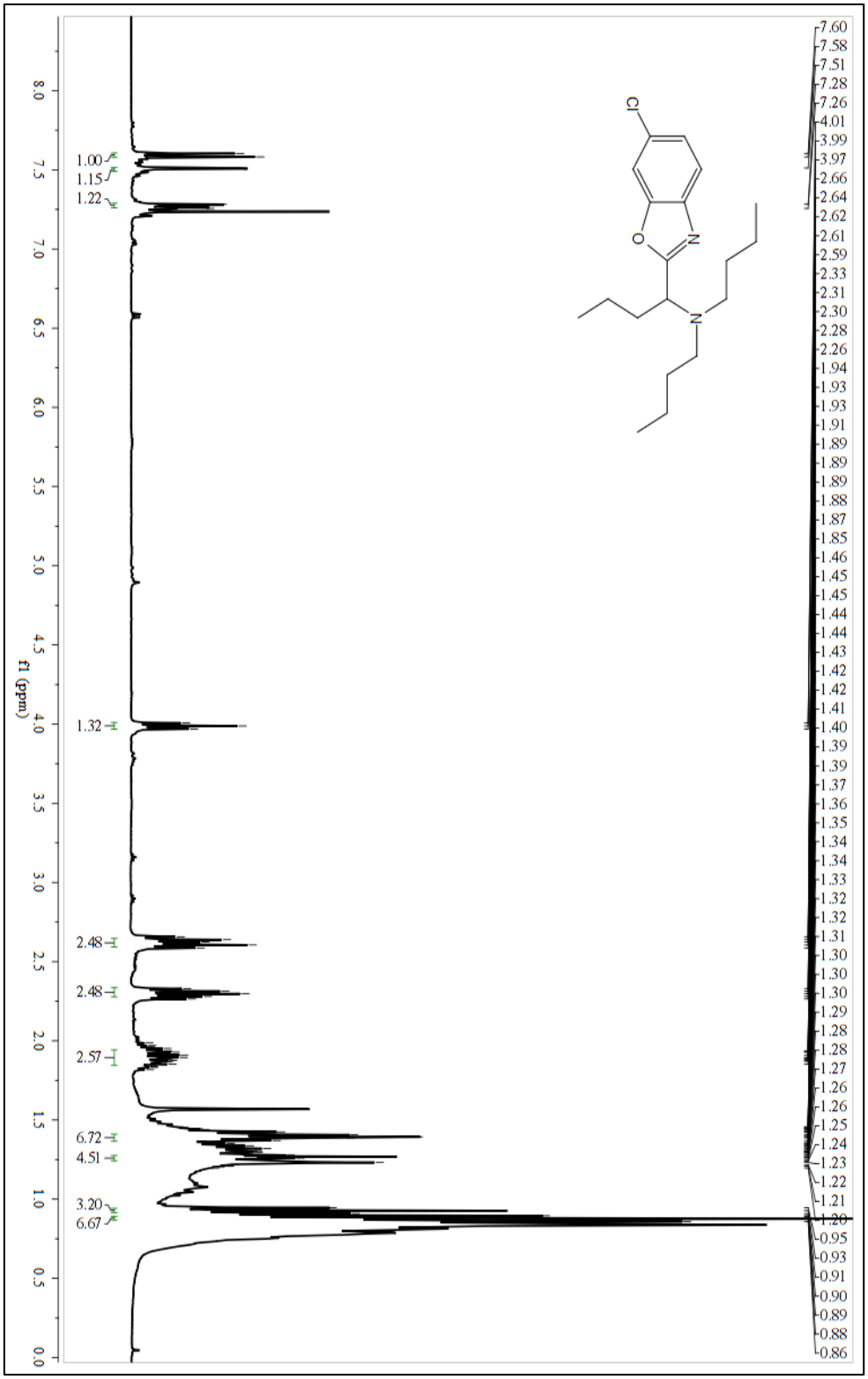
9m (2-(3-phenyl-1-(pyrrolidin-1-yl)propyl)benzo[*d*]thiazole



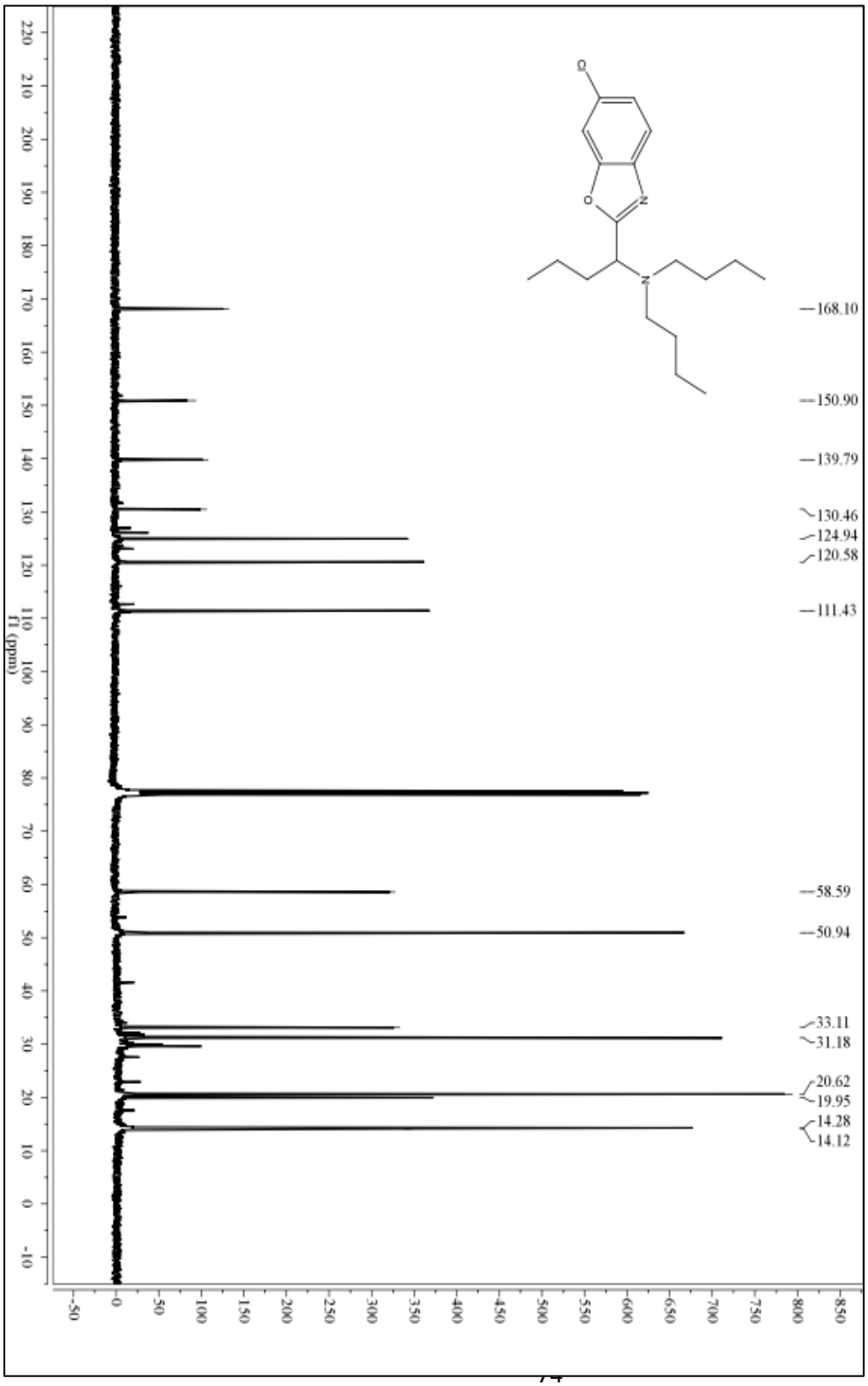
9m (2-(3-phenyl-1-(pyrrolidin-1-yl)propyl)benzo[*d*]thiazole



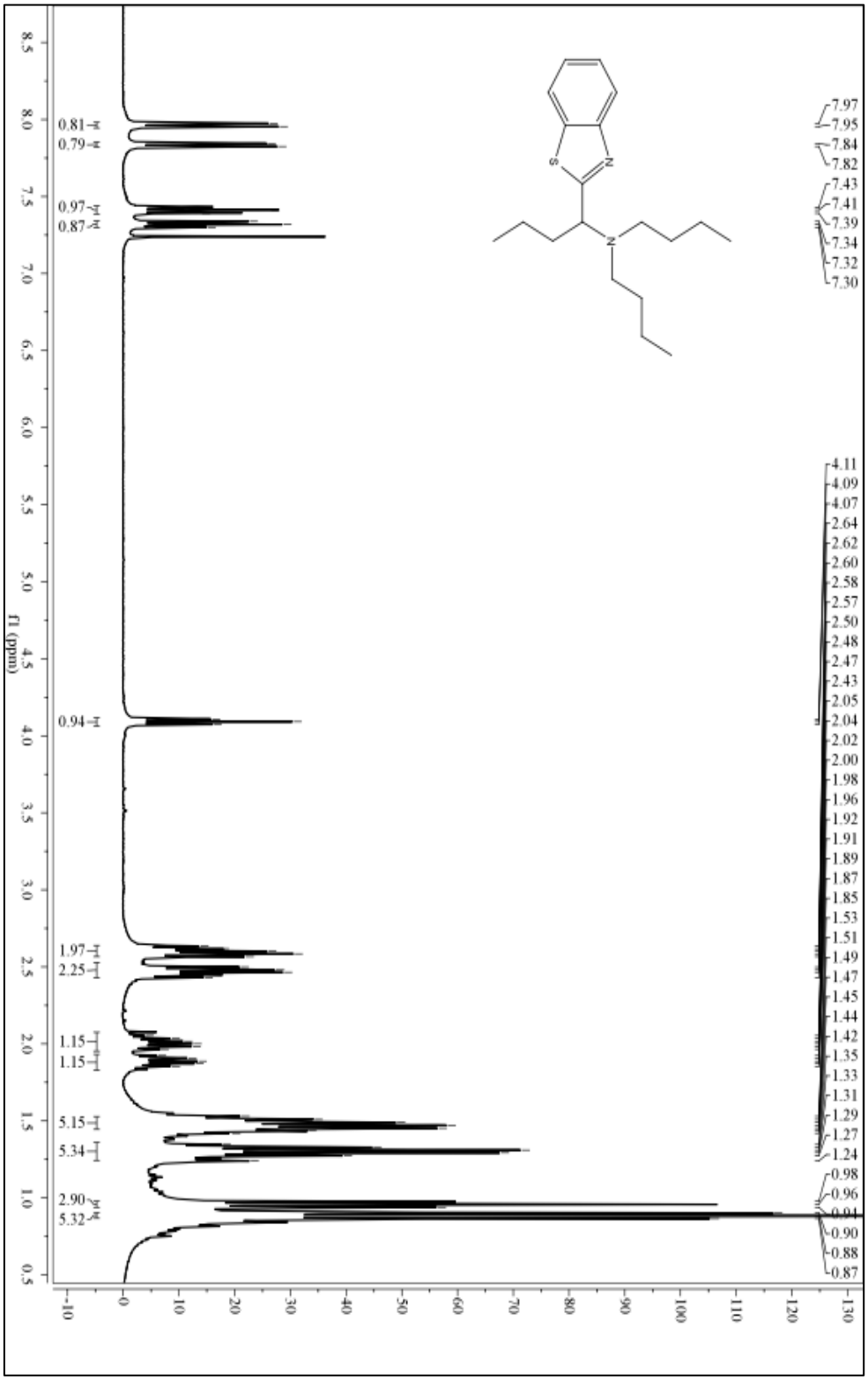
9n **(*N, N*-dibutyl-1-(6-chlorobenzo[*d*]oxazol-2-yl)butan-1-amine**



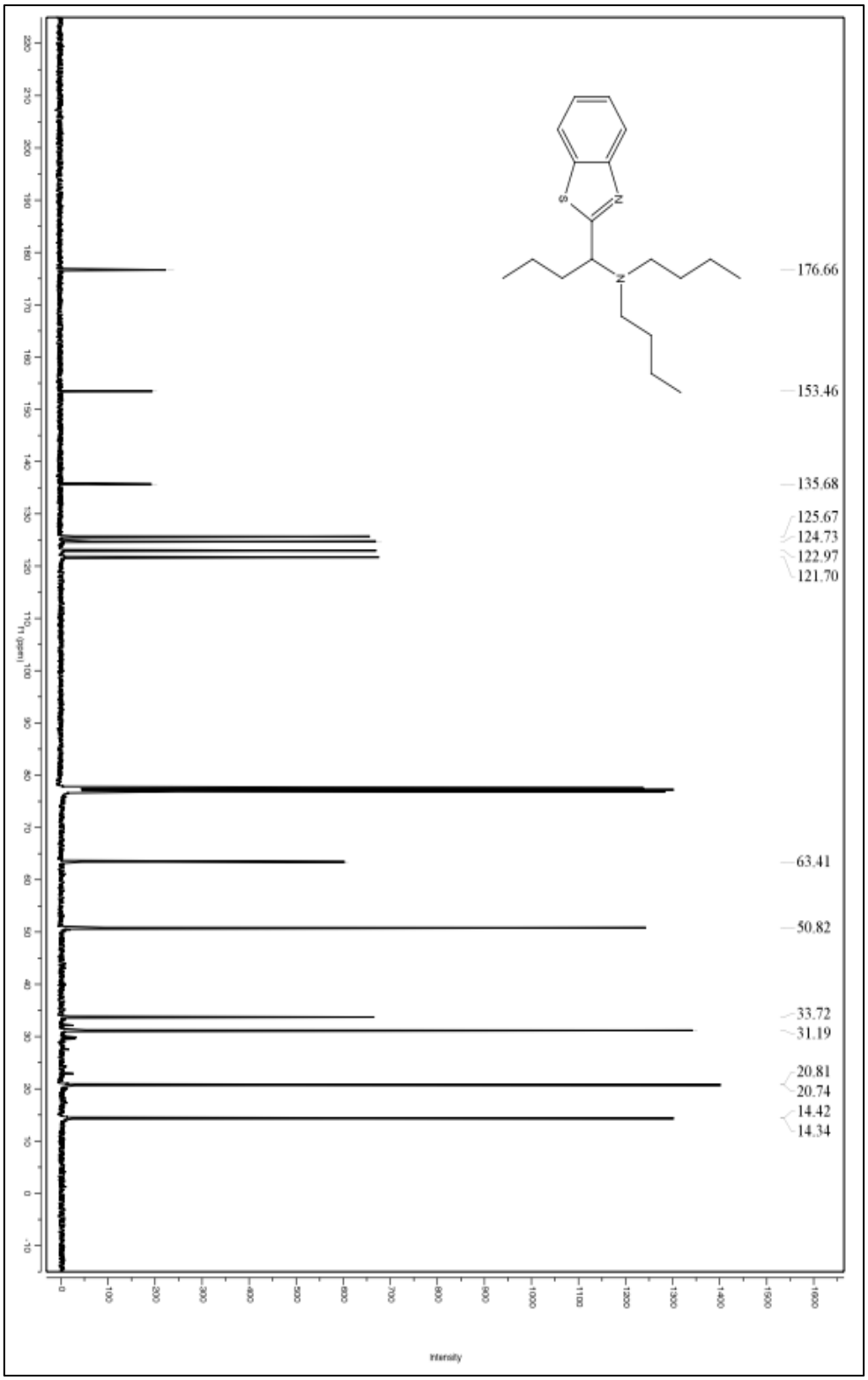
9n (*N, N*-dibutyl-1-(6-chlorobenzo[*d*]oxazol-2-yl)butan-1-amine



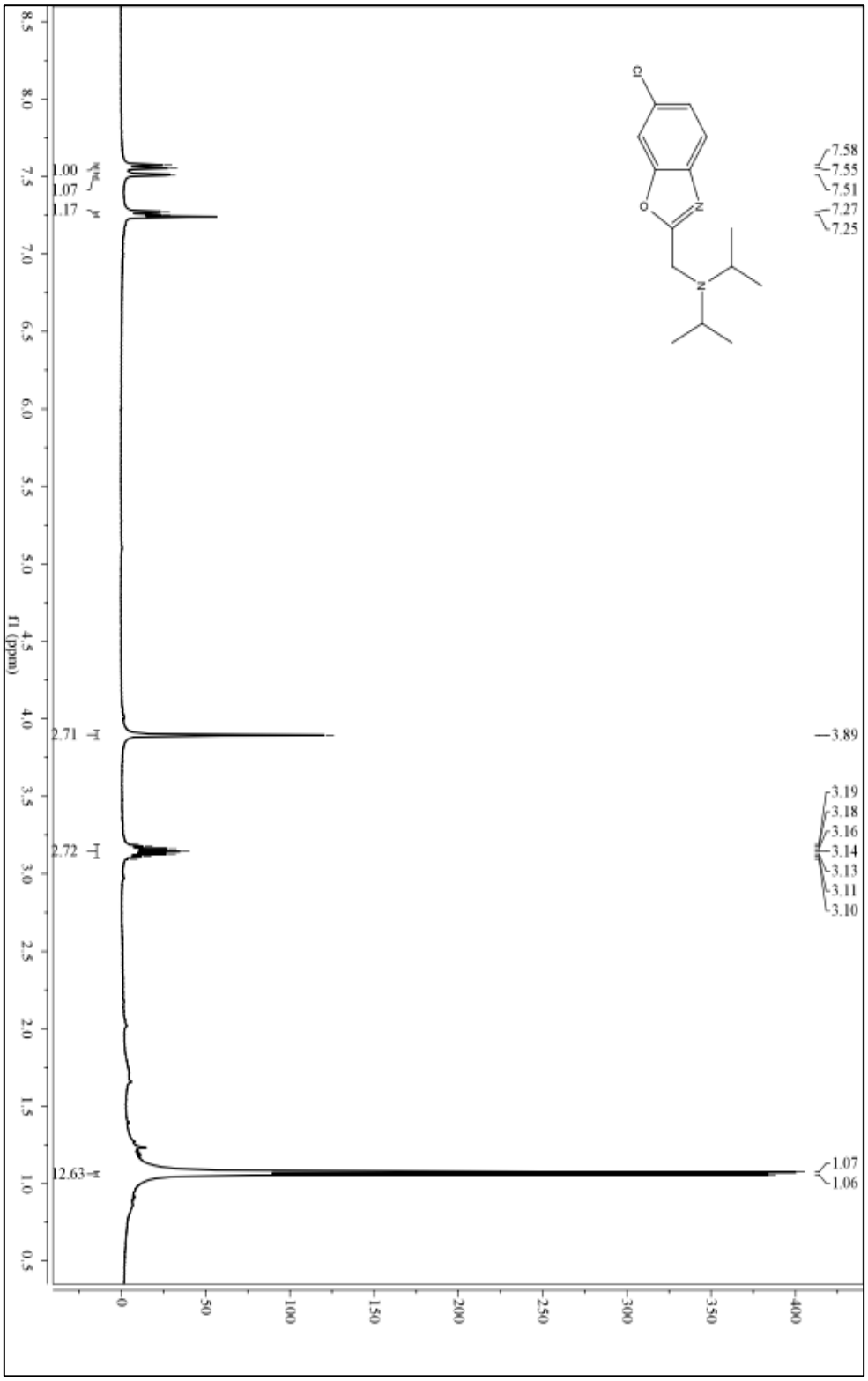
9o (1-(benzo[*d*]thiazol-2-yl)-*N, N*-dibutylbutan-1-amine)



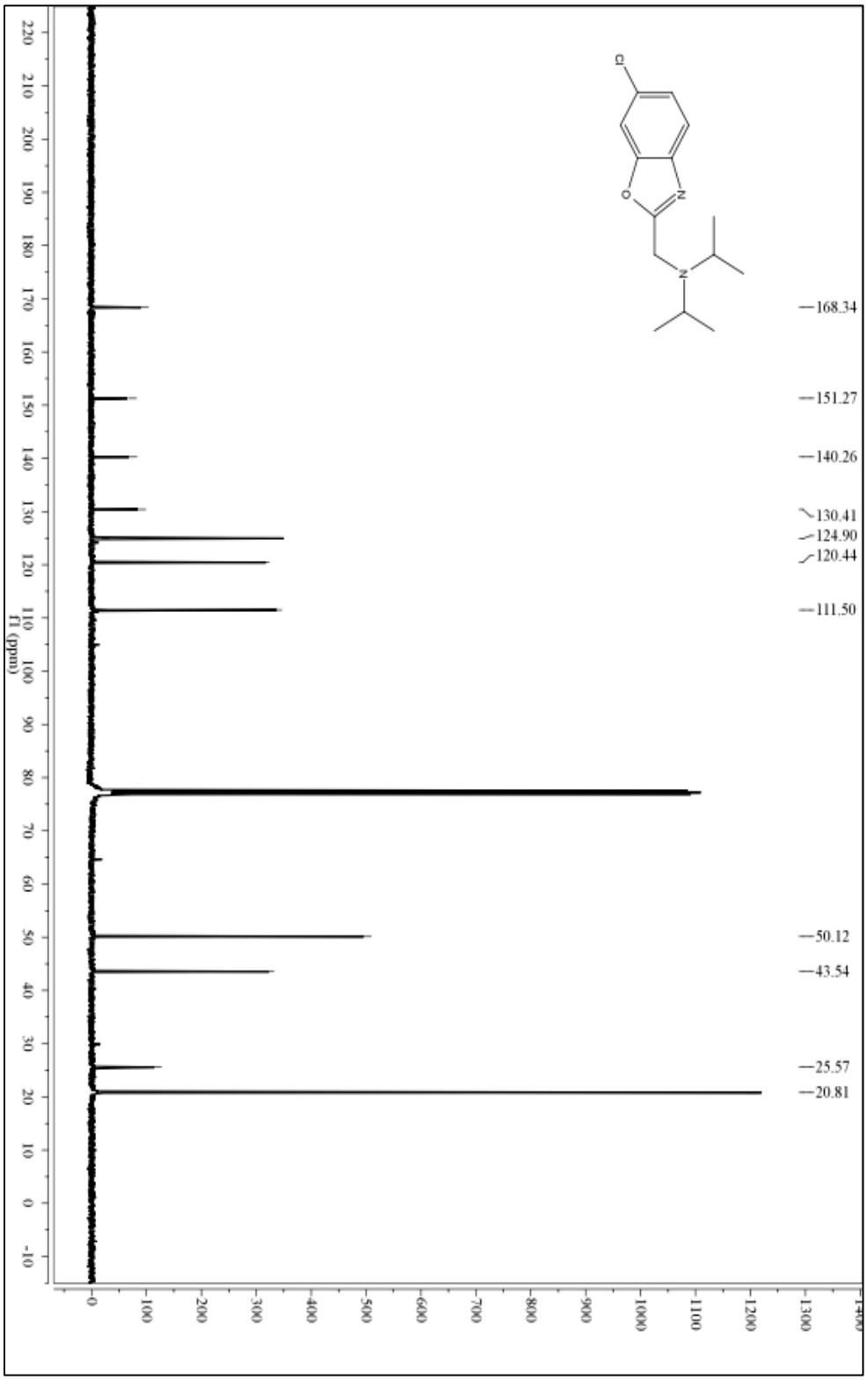
9o (1-(benzo[*d*]thiazol-2-yl)-*N, N*-dibutylbutan-1-amine)



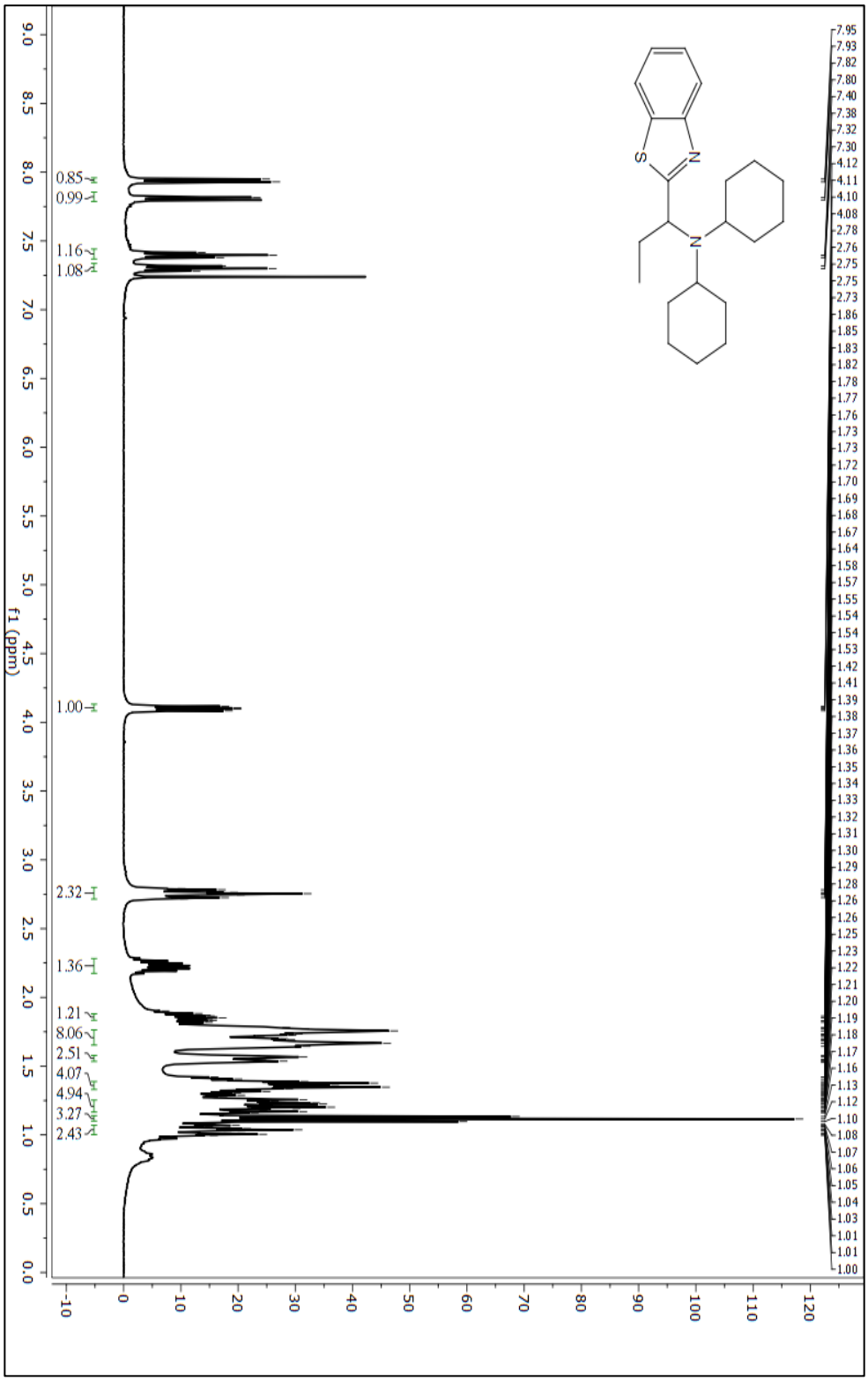
9p (*N*-((6-chlorobenzo[*d*]oxazol-2-yl)methyl)-*N*-isopropylpropan-2-amine)



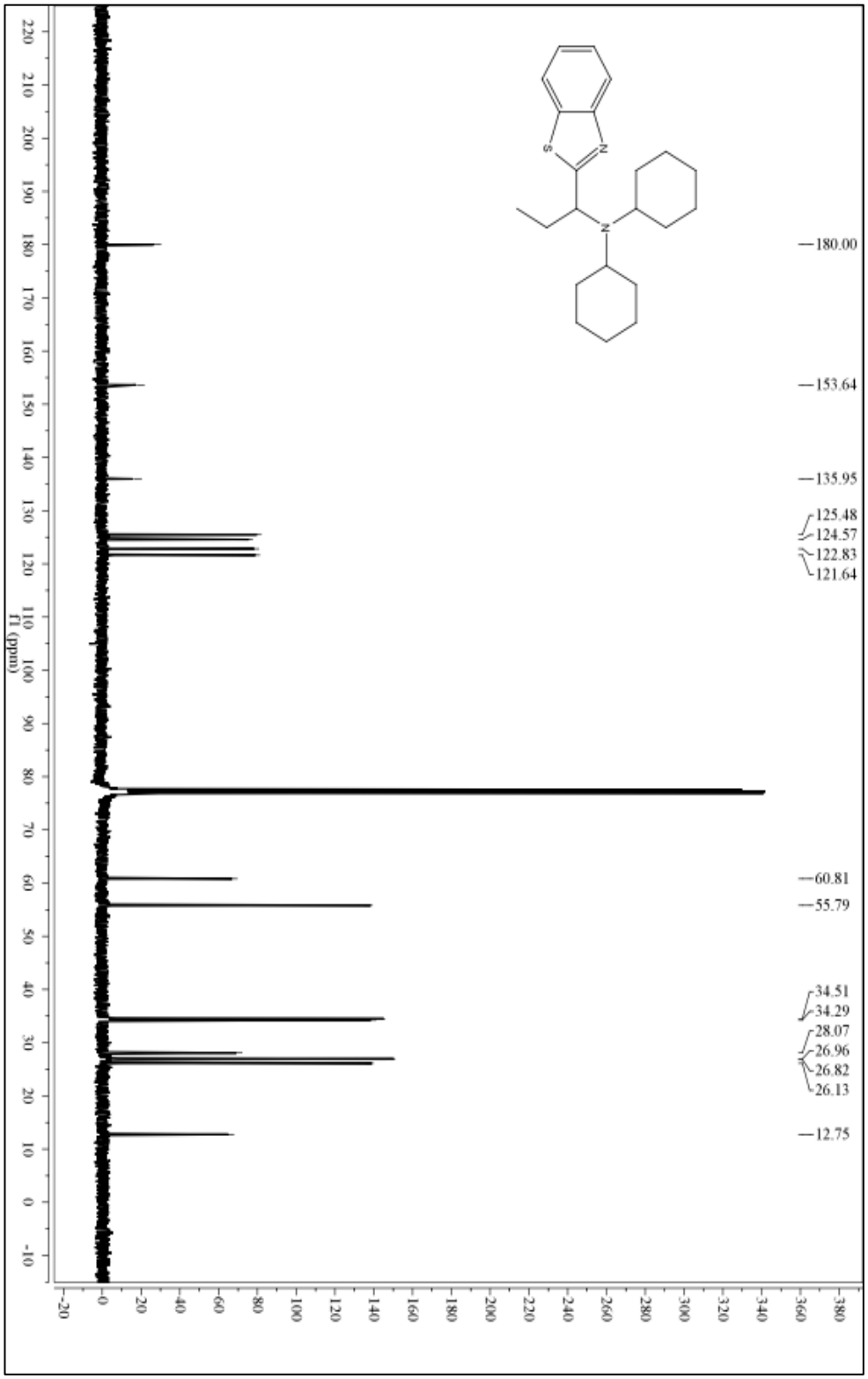
9p (*N*-((6-chlorobenzo[*d*]oxazol-2-yl)methyl)-*N*-isopropylpropan-2-amine)



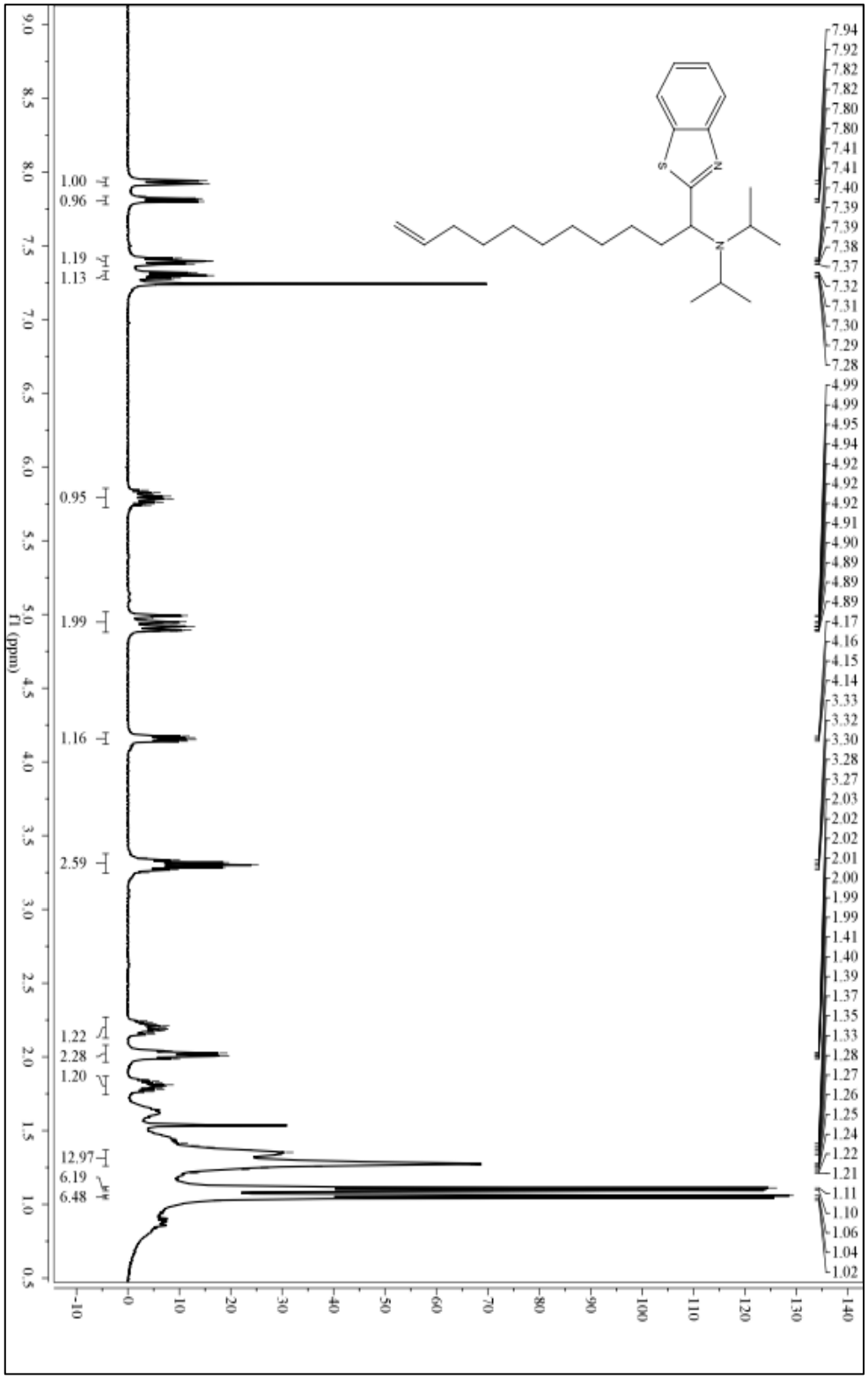
9q *(N*-(1-(benzo[*d*]thiazol-2-yl)propyl)-*N*-cyclohexylcyclohexanamine)



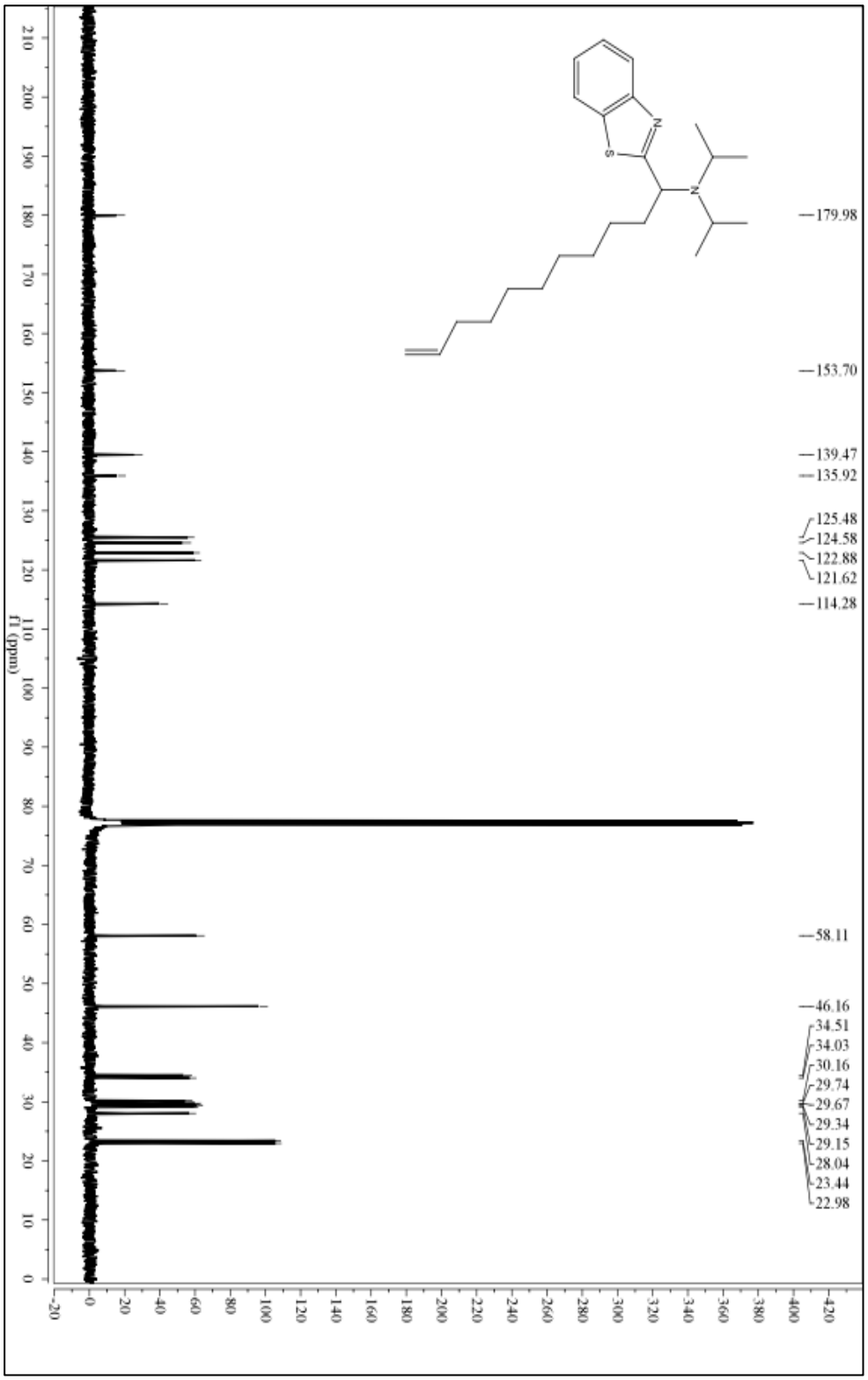
9q *(N*-(1-(benzo[*d*]thiazol-2-yl)propyl)-*N*-cyclohexylcyclohexanamine)



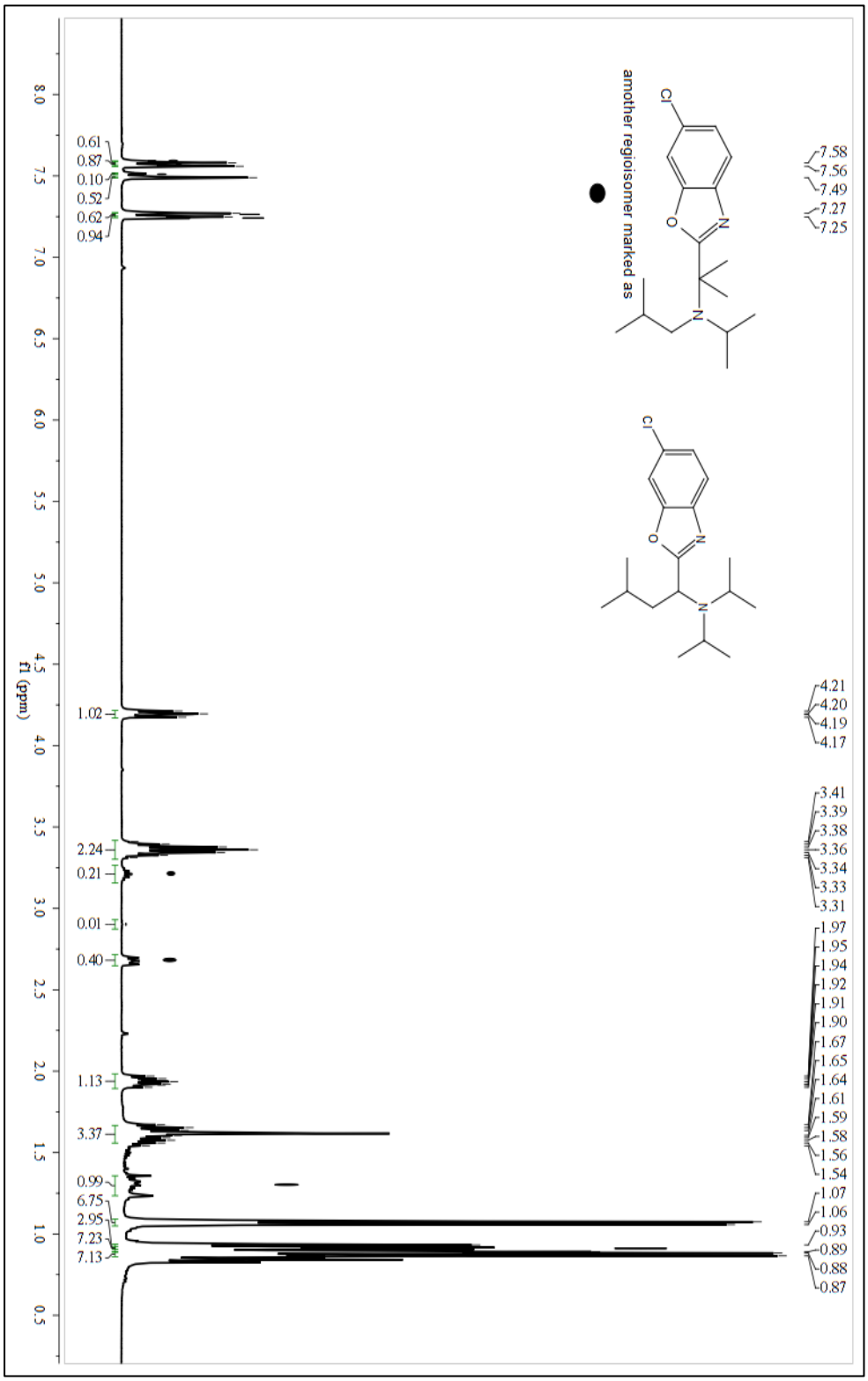
9r (1-(benzo[*d*]thiazol-2-yl)-*N, N*-diisopropylpent-4-en-1-amine)



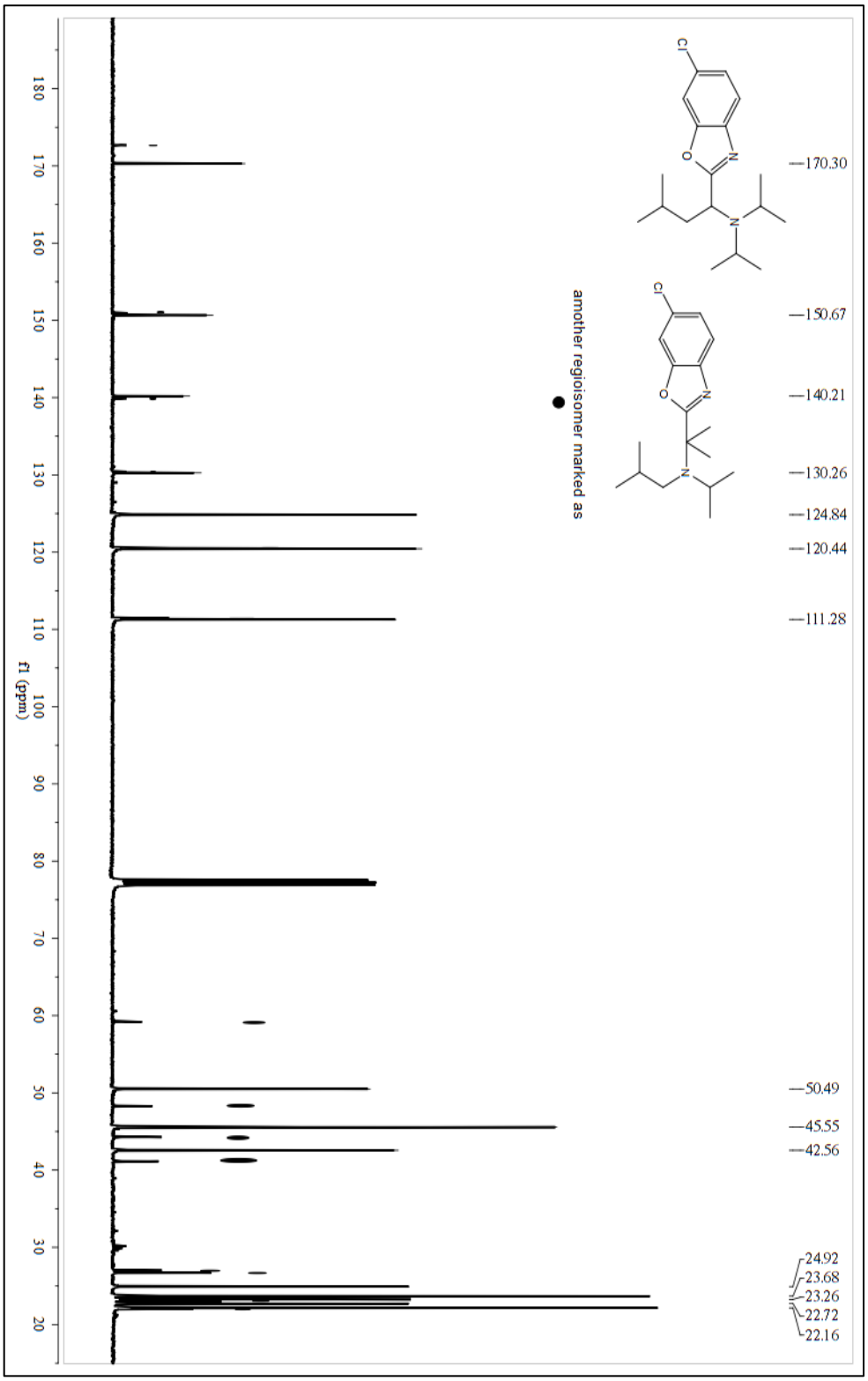
9r (1-(benzo[*d*]thiazol-2-yl)-*N, N*-diisopropylpent-4-en-1-amine)



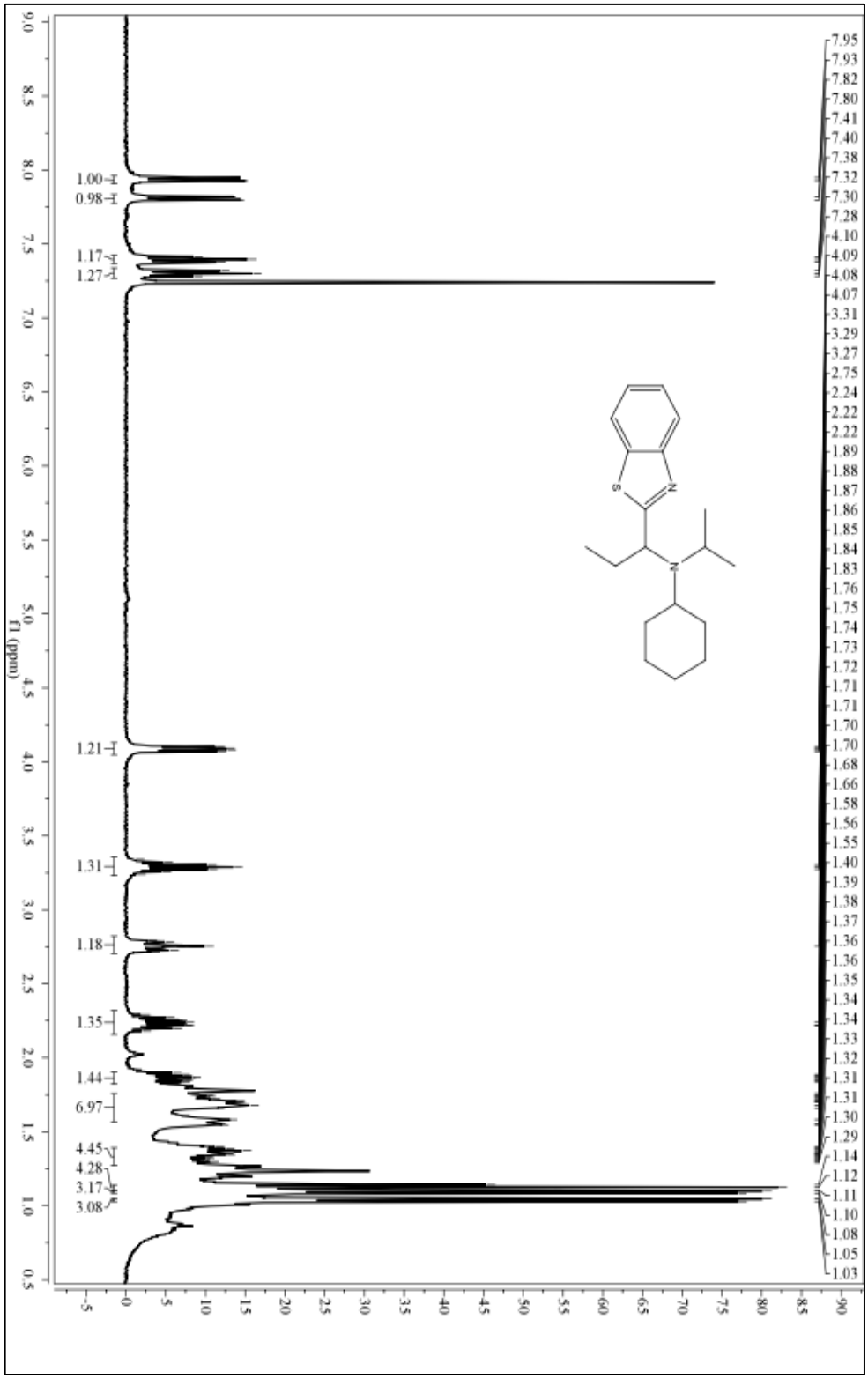
9s (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N, N*-diisopropyl-3-methylbutan-1-amine)



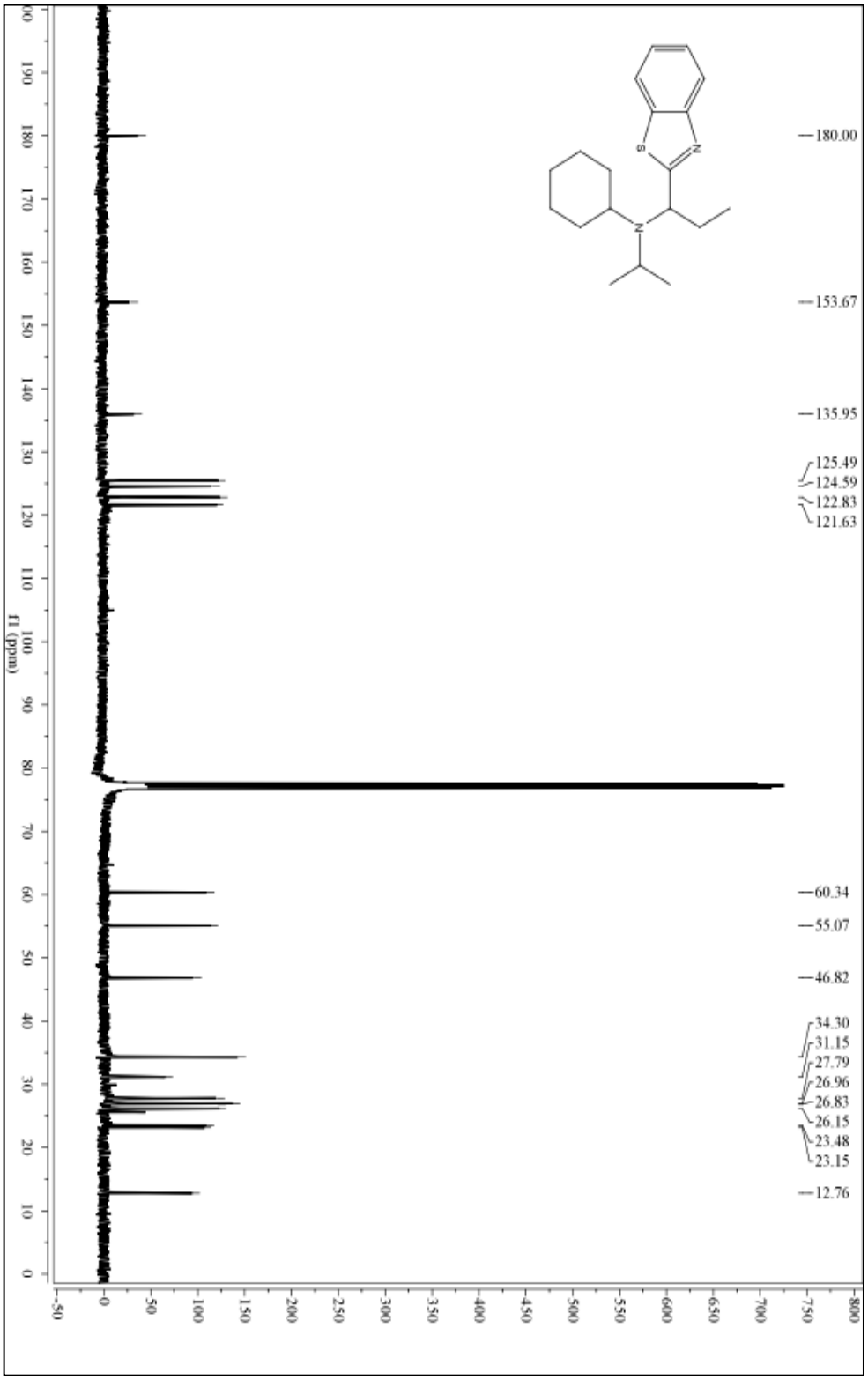
9s (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N, N*-diisopropyl-3-methylbutan-1-amine)



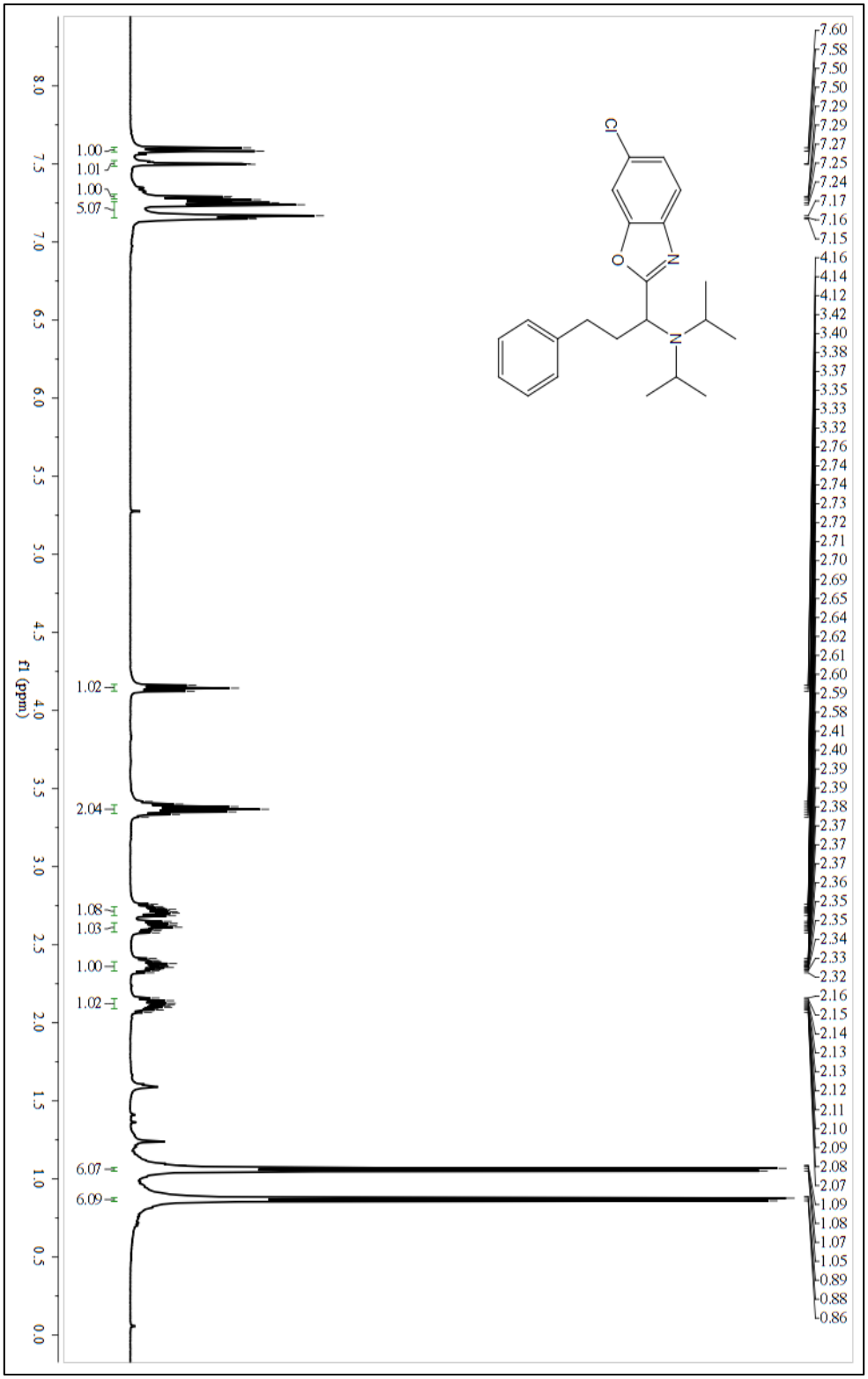
9t (*N*-(1-(benzo[*d*]thiazol-2-yl)propyl)-*N*-isopropylcyclohexanamine)



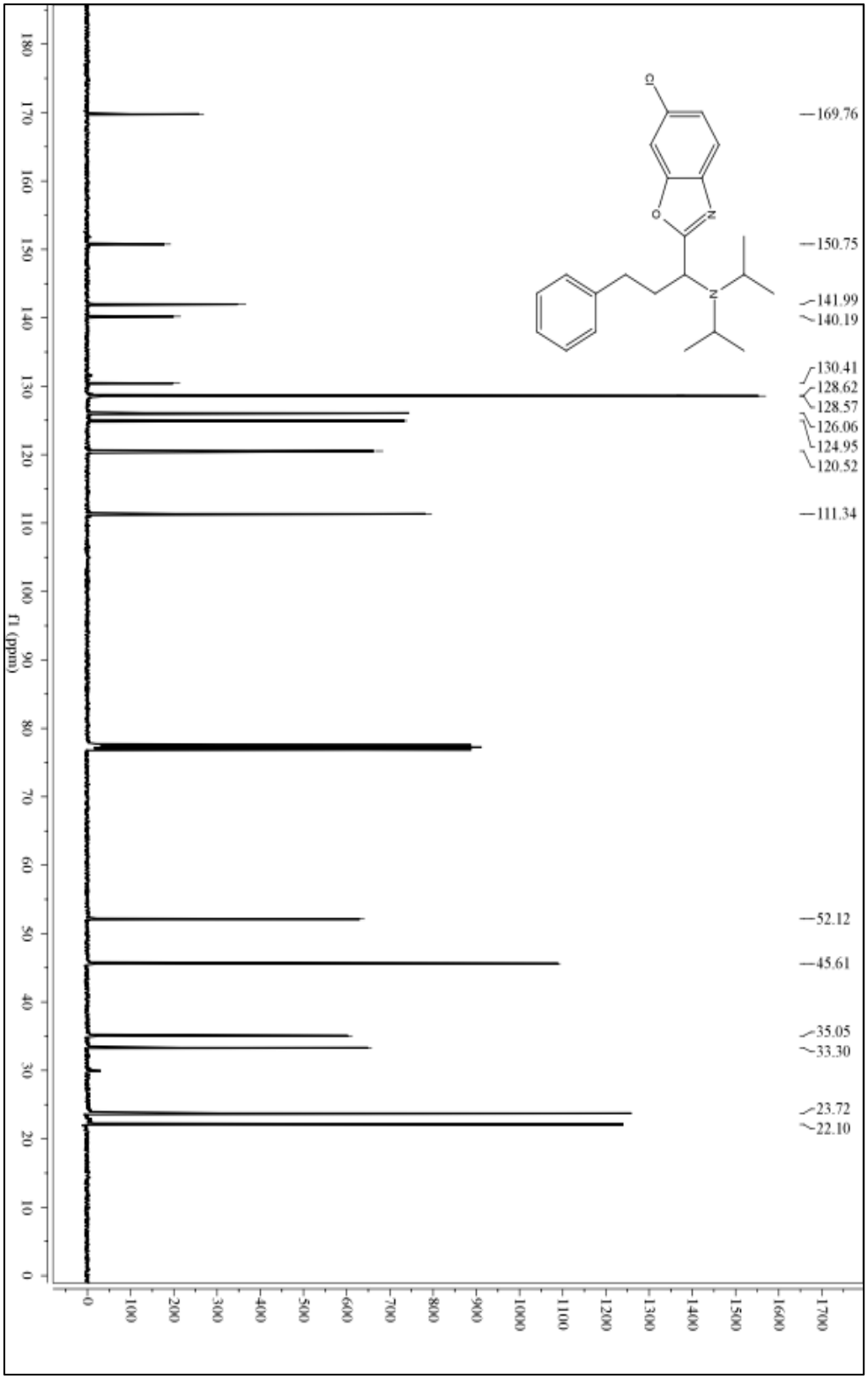
9t (*N*-(1-(benzo[*d*]thiazol-2-yl)propyl)-*N*-isopropylcyclohexanamine)



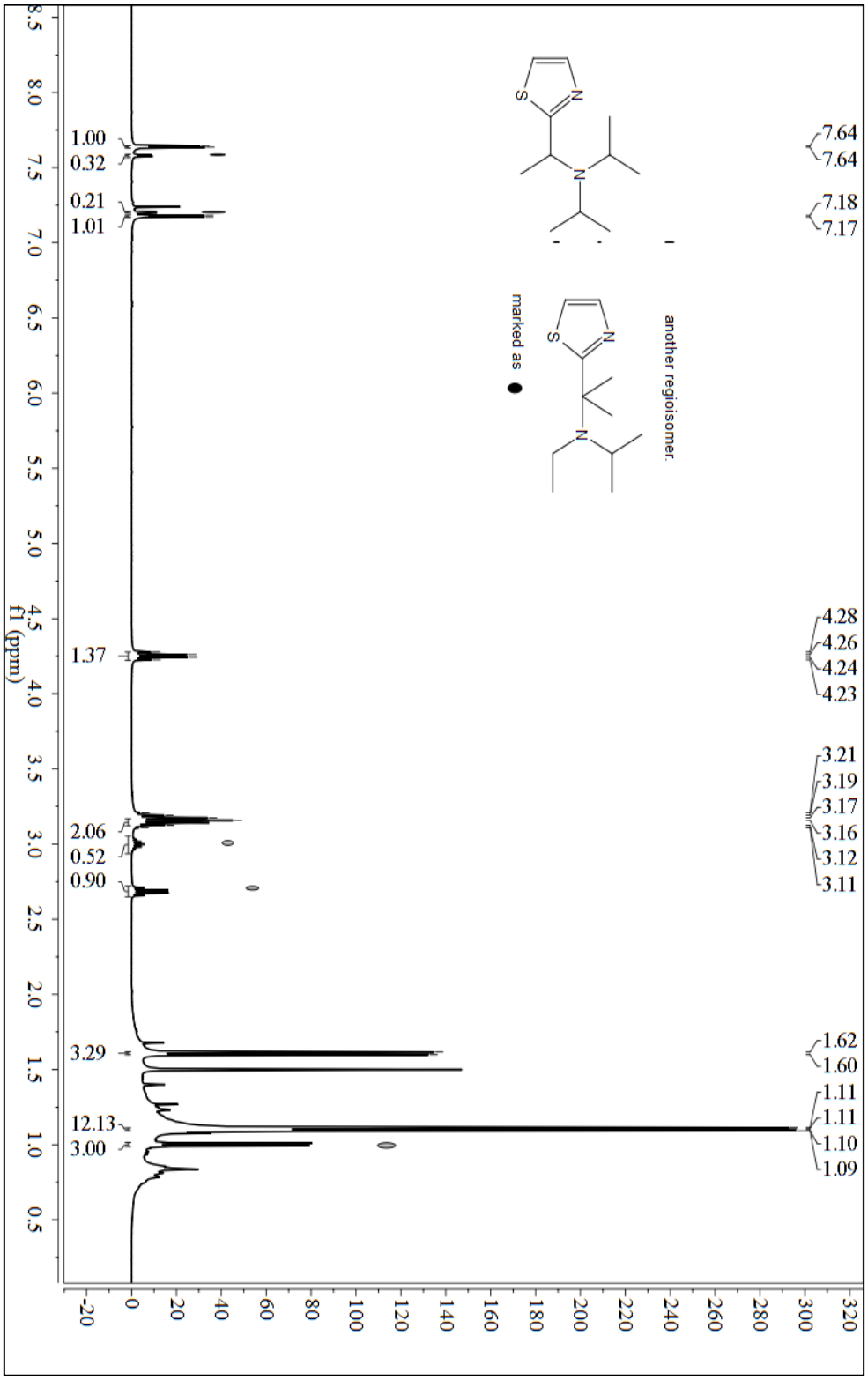
9u (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N, N*-diisopropyl-3-phenylpropan-1-amine



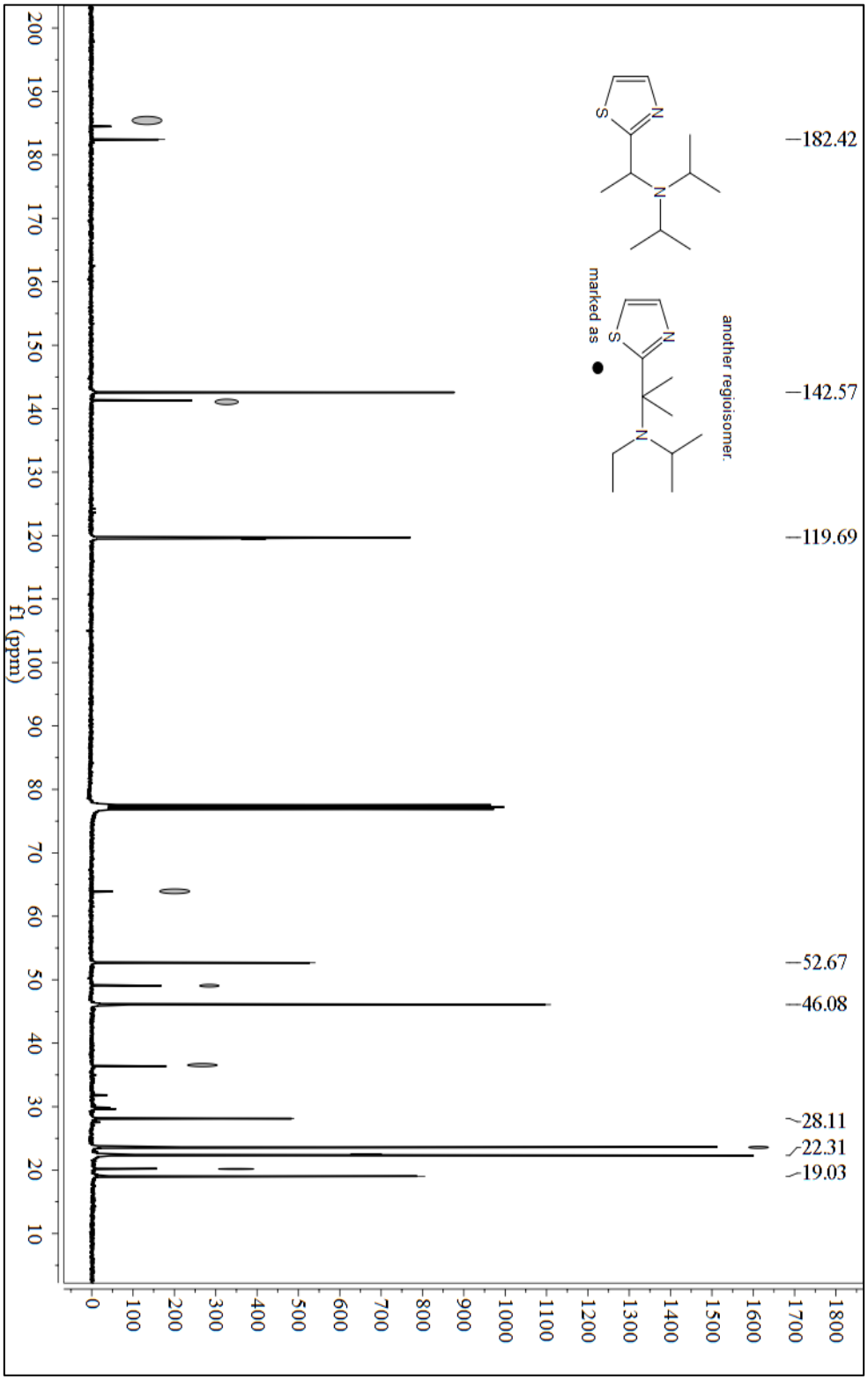
9u- (1-(6-chlorobenzo[*d*]oxazol-2-yl)-*N, N*-diisopropyl-3-phenylpropan-1-amine)



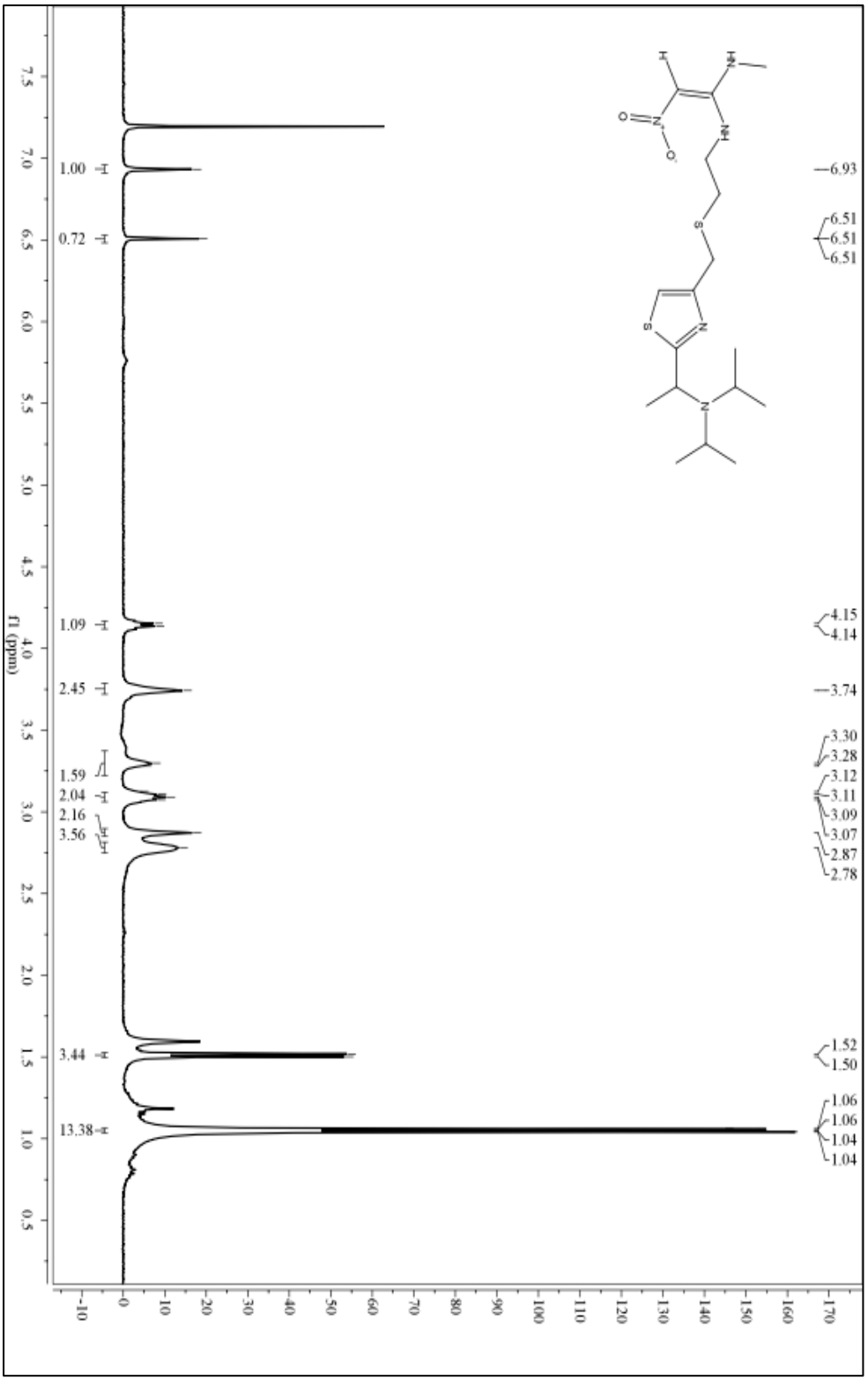
9v (N-isopropyl-N-(1-(thiazol-2-yl)ethyl)propan-2-amine)



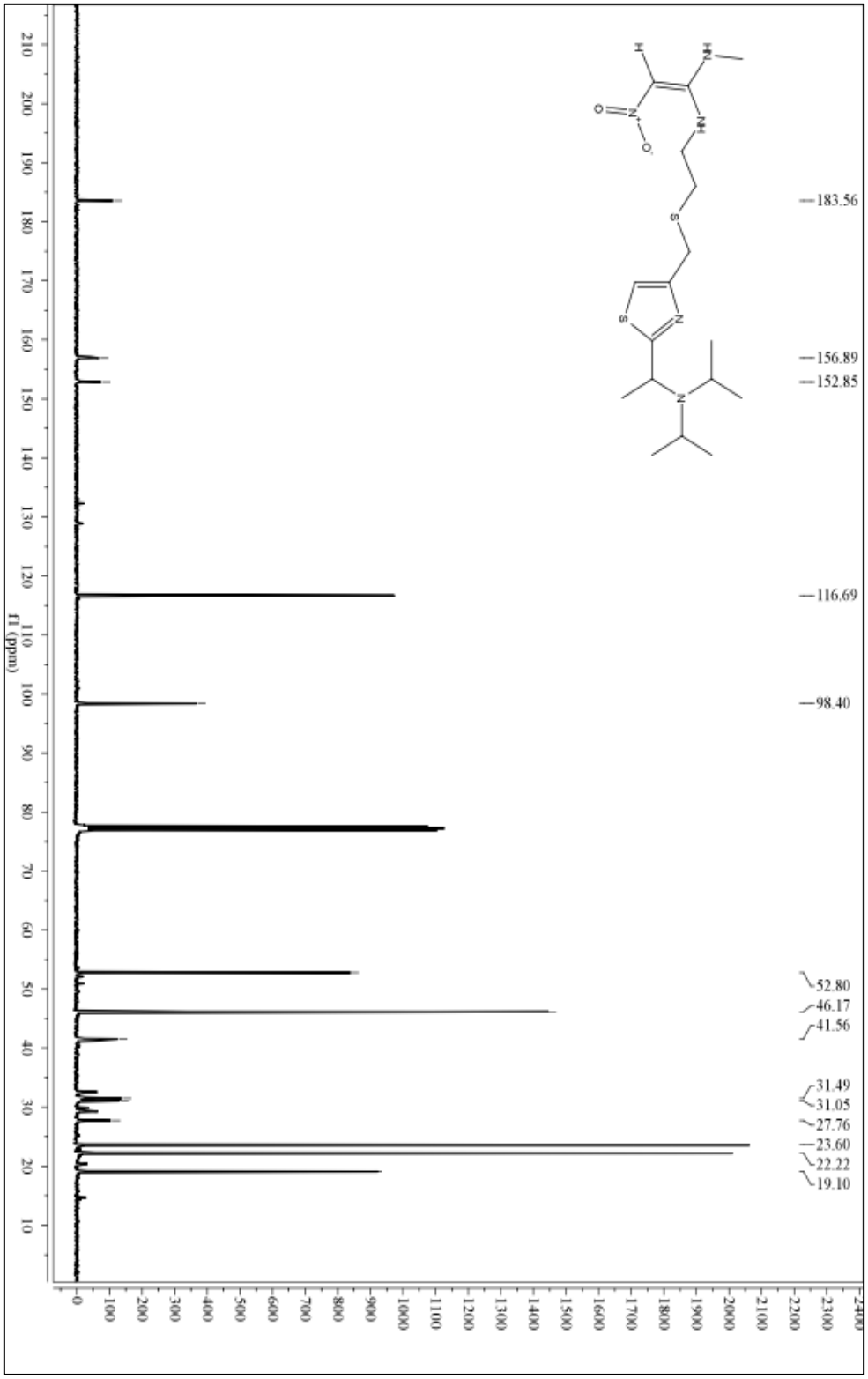
9v (N-isopropyl-N-(1-(thiazol-2-yl)ethyl)propan-2-amine)



10a) (Z)-N-2-(2-(((2-(1-(diisopropylamino)ethyl)thiazol-4-yl)methyl)thio)ethyl)-N1-methyl-1-nitroethene-1,2-diamine



10 a) (Z)-*N*-2-(2-(((2-(1-(diisopropylamino)ethyl)thiazol-4-yl)methyl)thio)ethyl)-*N*1-methyl-1-nitroethene-1,2-diamine



2.8 References

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CHAPTER III

REDUCTIVE ALKYLATION OF AZOLES AND HETEROARENES

3.1 Reductive alkylation of azole

Continuing our efforts to develop late-stage direct couplings that allow the rapid synthesis of substituted azole derivatives, we sought to develop methodology for direct alkylation of azole and heteroarene molecules. Alkylated azoles, specifically 2-alkyl azoles, have proven to be remarkable ROCK-II inhibitors.[1] Yet, the synthesis of this family of inhibitors is made *via* a cyclodehdration strategy, which requires the nontrivial synthesis of the corresponding carboxylic acids. A one-step alkylation strategy would allow a more rapid and direct synthesis of the relevant alkylated azoles. This would be especially true, if the alkylation could directly utilize alkenes which are abundant, stable, and functional group tolerant to incorporate alkyl groups to the azoles.

A strategy that has not been explored is the use of the photocatalytically generated 2-azolyl radical which we hoped would add to an alkene, and followed by hydrogen atom transfer to the incipient alkyl radical, amount to a formal Csp^2–Csp^3 cross-coupling.[2] Given the ubiquitous nature of alkenes, this proposed transformation would be advantageous compared to the traditional approach for alkylation of azoles in terms of synthetic steps, and the method by which radical addition is traditionally accomplished. Where some earlier work has shown that arylbromides can be converted to the aryl radical, this is most often accomplished through the use of Bu_3SnH (a toxic reagent)[3] or by SmI_2/HMPA.[4] Almost all synthetically useful examples of aryl radical addition to unactivated alkenes are intramolecular cyclizations, presumably, so that the C–C formation can outcompete fast hydrogen atom transfer (HAT).[5, 6] However,

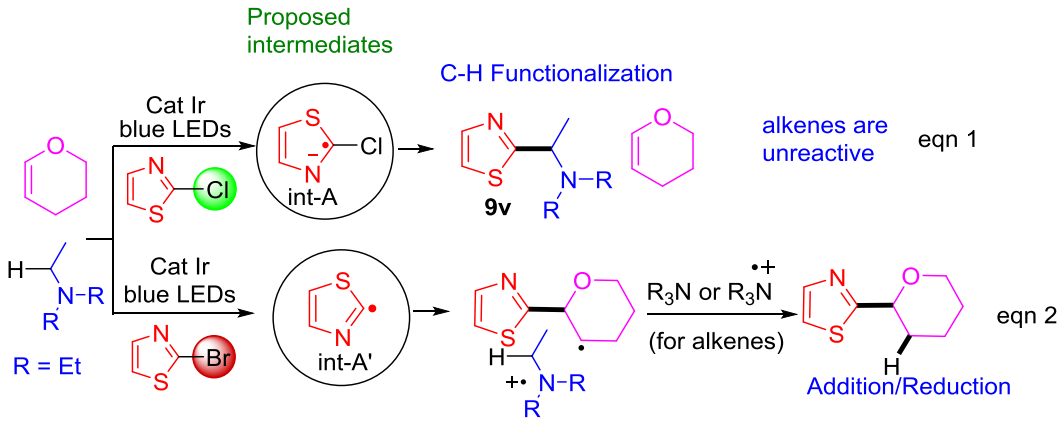
general methods that allow intermolecular reductive alkylation of aryl bromides have not been well developed.[78]

We speculated that a visible light photocatalyst could facilitate a photoinduced electron transfer (PET) to the 2-bromobenzothiazole which would generate a chemo- and regioselectively 2-azolyl radical[9] that could add to unactivated alkenes to build a new C–C bond. Importantly, utilization of a photocatalyst and an amine might prove to be sufficiently slow at reduction of the aryl radical so as to allow the intermolecular C–C bond formation take place, which is not generally possible when using stoichiometric radical generators such as $HSnBu_3$.

3.2 Orthogonal reactivity

In Chapter I, we demonstrated that 2-chloroazoles could be used to functionalize the α-C–H of tertiary aliphatic amines.[12] However, addition of the electron-rich alkene, dihydropyran to the reaction of 2-chlorothiazole (Scheme 16, 1 eq 1) yielded only the azole-carbinamine and reduction product (thiazole) as the major products.

In contrast, use of the 2-bromothiazole, instead of 2-chlorothiazole, resulted in a complete change in reactivity (Scheme 16, eq 2). In this case, the reductively coupled, *i.e.* alkylated, product was the major C–C product, along with hydrodebrominated thiazole. In fact, we did not observe any carbinamine product **9v** in the reaction. Recalling the discussion in Chapter 1 about the topic of radical anion fragmentation, it is expected that a given radical anion will fragment a bromide faster than the corresponding chloride. It is reasonable to think that the observed change in reactivity is due to a change in the nature of the reactive intermediates involved.[10] Specifically, we postulate that 2-chloroazoles undergo C–C formation *via* the radical anion, while 2-bromoazoles undergo C–C bond formation *via* the radical (post fragmentation).



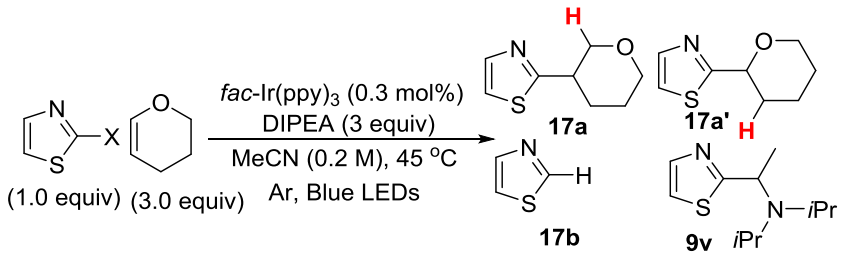
Scheme 16. Effect of leaving group.

3.3 Optimization of conditions

Having initial results in hand, we sought to optimize the reaction conditions (Scheme 17). First, we wanted to increase the relative amount of C–C bond forming product **17a** and **17a'** to reduction product **17b**. Exchanging the ethyl of DIPEA for an isobutyl group (entry 3) resulted in a significant increase in the desired product, albeit at the expense of reaction time (22 h *vs* 48 h). Furthermore, we observed that the product ratio was not constant throughout the course of the reaction (entry 4 *vs* 5), with relative increases of **17a** as the reaction progressed. We suspected that this might be a result of acidic species generated under the reaction conditions that could be reducing the amount of free amine in solution, which has been postulated to lead to HAT of aryl radicals,[11] or possibly accelerating the formation of the desired product *via* a proton-coupled-electron-transfer.[11-12]

Thus, we next explored acidic additives (see Experiment Section 3.10). We found a 1:1 mix of formic acid and tributylamine as the optimal additive.[13] We next explored the concentration of alkene. Consistent with a process in which there is a competition for HAT and alkylation of the azolyl radical, increased concentration of alkene led to more alkylated product **17a** + **17a'** entries 8-11. Further concentrating the reaction also led to a slight improvement in the product distribution. In an attempt to check the operational flexibility of the reaction, we added water, which resulted in only a slight decrease of the desired products. Finally, controls (entries 14 and 15) indicated that photocatalyst, light are necessary

components of the reaction. Using 0.3 mol% *fac*-tris-(2-phenylpyridine) ($Ir(ppy)_3$), a 1:1 mix of amine and formic acid (3 equiv), and 5 equivalents of alkenes, we began to explore the scope of the reaction.



Entry	X	Modifications	Conv.[a]	17a:17a':17b:9v	Time
1.	Cl		100%	0:0:31:69	23 h
2.	Br	None	100%	38:10:52:0	22 h
3.	Br	Used $(iPr)_2NiBu$ instead of DIPEA	100%	52:13:35:0	2 d
4.	Br	Used NBu_3 instead of DIPEA	24%	17:8:75:0	2 h
5.	Br	Used NBu_3 instead of DIPEA	69%	30:8:62:0	23 h
6.	Br	Used $(iPr)_2NiBu$ w/ HCO_2H (1:1)	100%	44:6:50:0	22 h
7.	Br	Used NBu_3 w/ HCO_2H (1:1)	100%	51:8:41:0	22 h
8.	Br	Same as Entry 7, but 1.2 equiv alkene	100%	17:3:80:0	22 h
9.	Br	Same as Entry 7, but 2.0 equiv alkene	100%	26:6:67:0	22 h
10.	Br	Same as Entry 7, but 3.0 equiv alkene	100%	39:9:52:0	22 h
11.	Br	Same as Entry 7, but 5.0 equiv alkene	100%	57:13:32:0	22 h
12.	Br	Same as Entry 11, at 0.25 M	100%	65:10:25:0	22 h
13.	Br	Same as Entry 12, with 20% v:v H_2O	100%	60:10:30:0	22 h
14.	Br	Same as Entry 12, no $Ir(ppy)_3$	0%		22 h
15.	Br	Same as Entry 12, no light	0%		22 h

[a] Conversion determined by ^1H NMR, [b] product ratios determined by GCMS.

Scheme 17. Investigation of optimal reaction conditions.

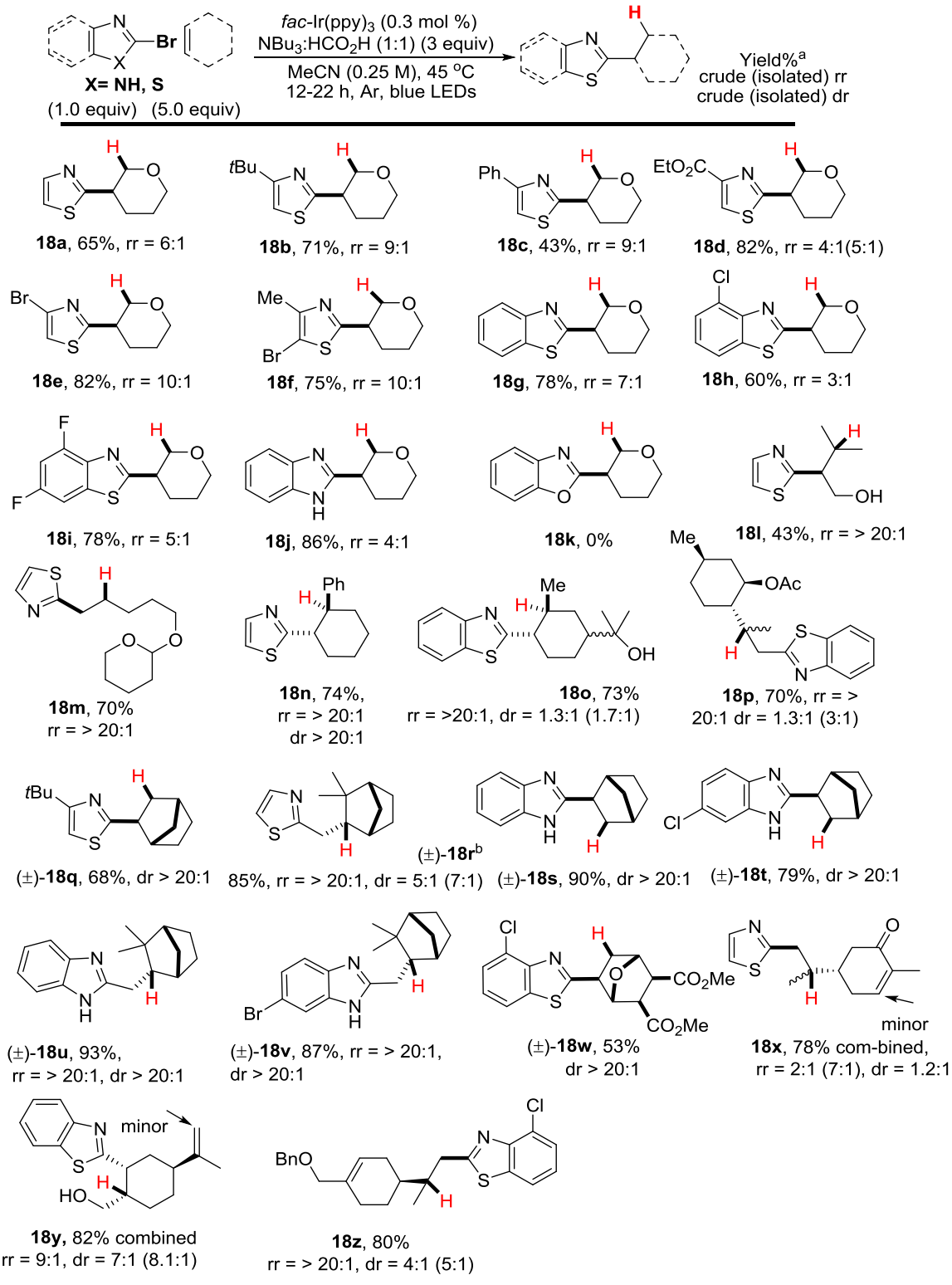
3.4 Scope of the reaction

Initially, we reacted a series of bromothiazoles with dihydropyran. We obtained a 65% yield in a 6:1 regioisomeric ratio (rr) for simple 2-bromothiazole **18a** (Scheme 18). In most cases, expansion of the thiazole motif increased the product selectivity **18a** *vs* **18b-18g**. Products **18e** and **18f** highlight an important feature of electron-addition induced fragmentation events which can be very selective, and in these cases display perfect chemoselectivity for the 2-bromo over the 4-bromo and 5-bromo positions. While the reaction works well for benzothiazole **18g**, the inclusion of 5-chloro or 5, 7-difluoro groups slightly reduces the regioselectivity **18h**, and **18i**. In contrast to thiazoles, we do not observe competitive reduction when S is exchanged for an NH, such as in 2-bromobenzimidazoles **18j**, and consequently, the

yields are higher. Under these conditions, 2-bromooxazole **18k** does not undergo reductive alkylation and this highlights the impact that the nature of the heterocycle has on the reaction. As a follow up, it will be interesting to see whether a 2-diazooxazole or 2-iodooxazole could undergo reductive alkylation with alkene. Next, we evaluated the nature of the alkene that could participate in the reductive alkylation. In general, we found the addition to be remarkably sensitive to the substitution pattern of the alkene. Specifically, the addition typically occurred at the less substituted carbon to provide the alkylated azoles in high regioselectivity.

This product is likely favored both kinetically and thermodynamically. Kinetically, the less substituted terminus is more accessible, and leads to the more substituted and stable radical. The reaction works for mono-substituted-**18m**, 1, 1-disubstuted **18p, 18r**, **18u**, **18v**, **18x** and **18z**, 1, 2-disubstituted **18e-18j**, **18q**, **18s**, **18t**, **18w**, trisubstituted **18l**, **18n**, **18o**, and alkenes within bridged-carbocylces **18q-18w**. A number of functional groups that likely would be sensitive to basic organometallics work well in this method, including free alcohols **18l**, **18o**, acetates **18p**, esters **18w**, and enones **18x**. Believing that we were forming an azolyl radical, we were pleased to see that weaker bonds, such as benzylic **18z**, allylic **18y**, **18z** as well as acetal C–Hs **18m** were well tolerated. Furthermore, we saw no addition to the phenyl rings **18n**, **18z**, suggesting a preference for π-electrons of alkenes over those of arenes.

Additionally, in more complex molecules containing multiple alkenes we observed synthetically useful selectivities **18x-18z**. Interestingly, comparison of perillyl alcohol derivatives **18y**, **18z** suggests that the presence of the free hydroxyl group can alter the inherent regioselectivity, which holds promise for further exploitation within more complex substrates.

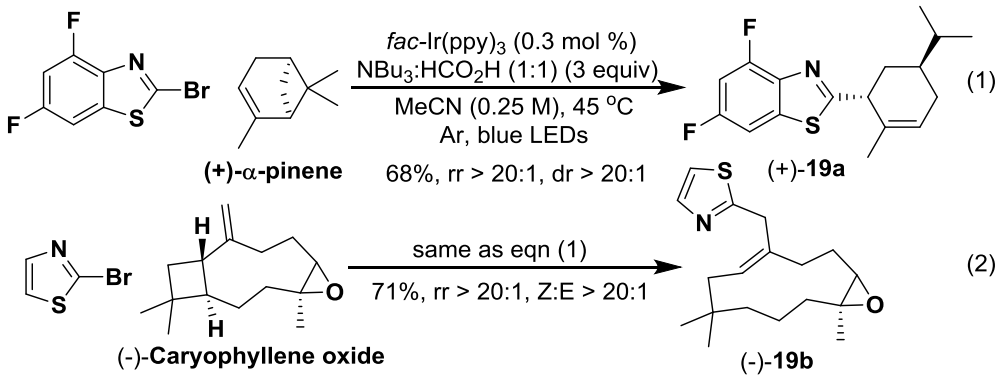


[a]Yields correspond to isolated product. Regioisomeric ratio (rr) and diastereomeric ratio (dr) were determined by ^{1}H NMR of the crude reaction mixture after workup and on the isolated material. [b]Isolated as an inseparable mixture (7:1) of product and oxidatively coupled product.

Scheme 18. Investigation of the scope of the reaction

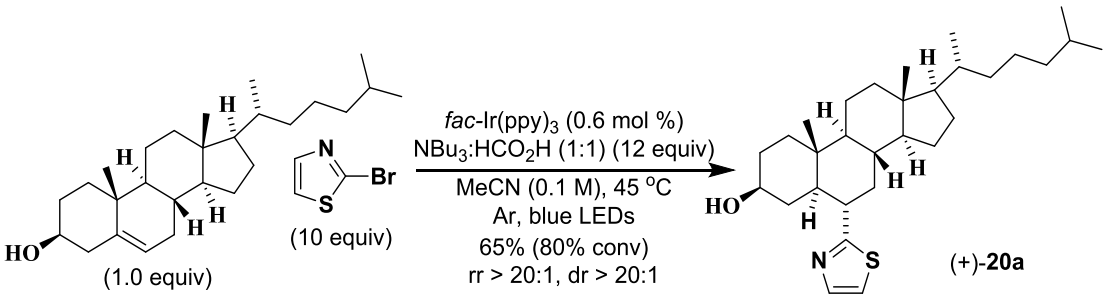
3.5 Azolylzation of natural products

We next applied these reaction conditions to terpenoids containing a vinylcyclobutane motif. A clean reductive ring opening occurred in good yields, with high regioselectivity and diastereoselectivity. Addition of difluorobenzothiazole to α-pinene provided a 68% yield of an enantio- and diastereomerically pure trisubstituted cyclohexene **19a** (Scheme 19, eq 1). The reaction of caryophyllene oxide afforded a single stereoisomeric product in good yield **19b** (Scheme 19, eq 2) with the epoxide functional group remaining unchanged. The selectivity of the ring opening event suggests that reductive azoylation of vinyl cyclobutanes may be a general and convenient method for the formal allylic substitution with concomitant ring enlargement.



Scheme 19. Ring opening of vinyl cyclobutanes.

The ability to easily and directly expand the carbon framework of alkenes situated within complex molecules presents exciting possibilities as a method for late stage functional group modification. Thus, we examined the azolylization of unprotected cholesterol which gave a single stereoisomeric product **20a** (Scheme 20). The use of an alkene to affect the highly selective installation of a heterocycle, compares favorably to currently popular efforts to develop similarly selective C–H functionalizations, which must contend with many C–H bonds in complex molecules.[14]



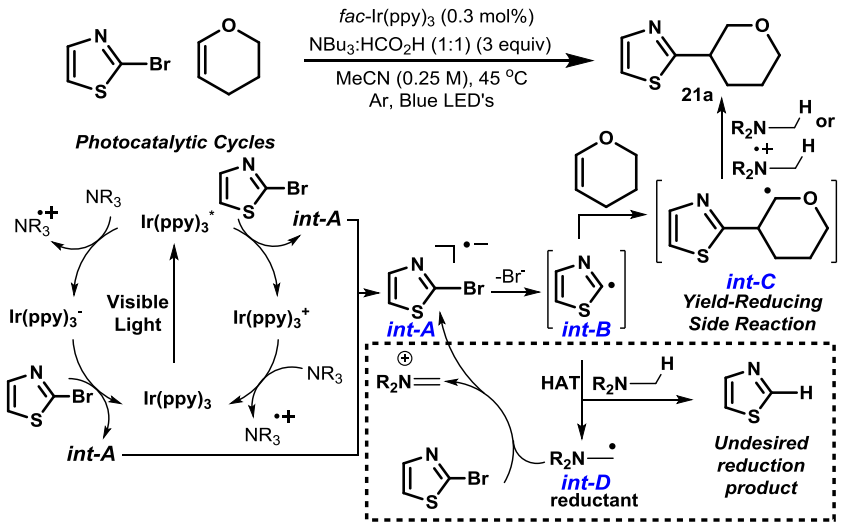
Scheme 20. Late stage thiazolylzation of cholesterol.

We recognized that in some scenarios the alkene would be more precious than the azole, and we wanted to address this type of situation. This required us to look at the underlying problematic reduction that necessitated the use of an excess of 2-bromothiazole. The amine is the stoichiometric reductant[15] and is essential to the reaction. We speculated that it could also be facilitating undesired reduction of the bromoazole, which then dictated that we use a substantial excess of alkene in an attempt to effectively capture the radical before it was reduced.

3.6 Discussion of possible mechanism

We hypothesized that problematic reduction might depend upon amine concentration in the reaction mixture.[13, 16] We began by considering the mechanism (Scheme 21). We posited that upon absorption of a photon in the visible region, the excited $Ir(ppy)_3^*$ is capable of being quenched either oxidatively by the bromoazole, or reductively by the amine and followed by electron transfer to the azole from the reduced Ir(II).[17] In either scenario, the ultimate outcome could be the formation of the radical anion (***int-A***). The radical anion is expected to undergo bromide extrusion to give an azolyl radical (***int-B***). The azolyl radical (***int-B***) then undergoes addition to the alkene with a significant preference for the less substituted terminus to give the more stable alkyl radical (***int-C***). The alkyl radical ultimately undergoes HAT to give the alkylated azole. It was envisioned that the undesired reduced azole arose from a parasitic propagation reaction. In this scenario, the azolyl radical (***int-B***) undergoes HAT from the neutral amine to give the reduced azole and an α-amino radical (***int-D***). Based on the work of Scaiano,[18] we believed that ***int-D*** may play an active role in the reaction. Specifically, we suspected that it may be transferring an

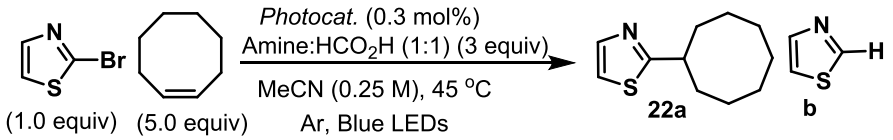
electron to the bromoazole to give an iminium and another radical anion, which would propagate the parasitic pathway.



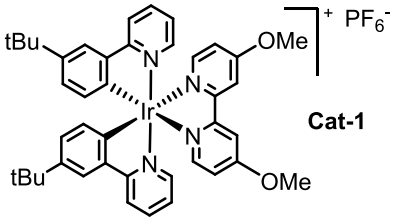
Scheme 21. Possible mechanism.

3.7 Avoiding parasitic HAT

We hypothesized that lowering the concentration of free amine could decrease the undesired reduction pathway, since the reduction was likely directly dependent on the amine concentration, whereas in other parts of the reaction, the rate may be less dependent on amine concentration. We tested this hypothesis using 2-bromothiazole which is particularly prone to reduction (Scheme 22). Our hypothesis was supported by the iterative addition of amine, which improved the product ratio (entry 2 *vs* 1) and supported our hypothesis. We speculated that we could take advantage of the low solubility of tertiary amines with long alkyl chains (in MeCN) to provide a convenient method for keeping a low concentration throughout the duration of a reaction. Thus, we evaluated the solubility of several amine derivatives and chose (*i*Pr)$_2$N-*n*-Oct, which was approximately half as soluble as NBu$_3$. We were pleased to find that the use of the less soluble amine did lead to an improved ratio of the desired product (entry 3 *vs* 1).



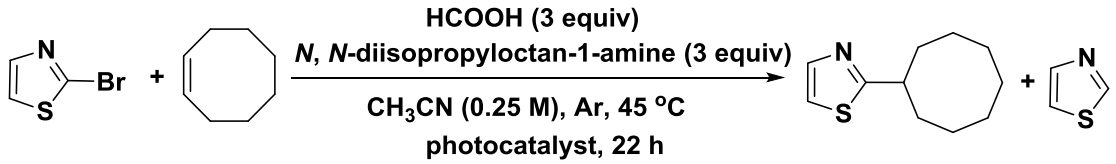
Entry	Cat	Amine	Conv.	20a/b
1.	$Ir(ppy)_3$	Bu_3N	100%	**25:75**
2.	$Ir(ppy)_3$	Bu_3N (iterative incremental addition)	100%	**52:48**
3.	$Ir(ppy)_3$	$(iPr)_2Nn$-Oct	84%	**36:64**
4.	Cat-1	Bu_3N	100%	**22:78**
5.	Cat-1	$(iPr)_2Nn$-Oct	48%	**44:56**

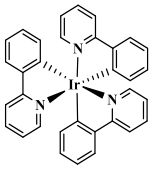
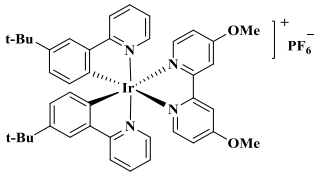


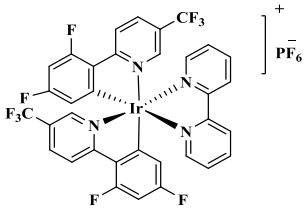
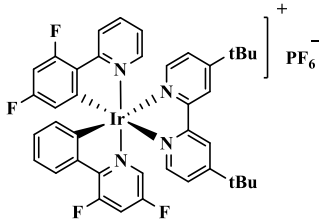
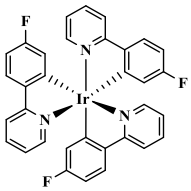
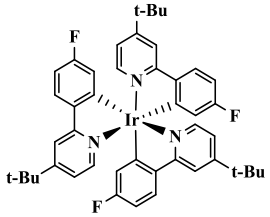
cat-1

Scheme 22. Amine dependent reduction pathway study.

We also recognized that decreasing the amine concentration might affect the rate of the photocatalytic reaction, especially if the reaction was proceeding through a reductive quenching pathway. Thus, we rescreened photocatalysts using the less soluble amine (Scheme 23).



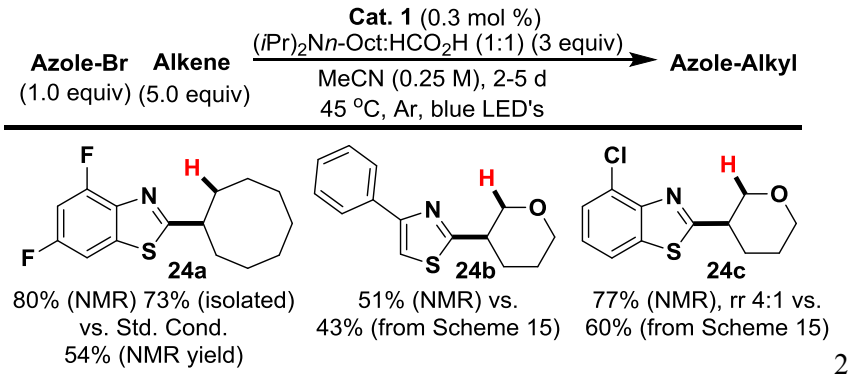
Entry	Catalyst	NMR conversion in 22 h	Reduction	Alkylated product
1	 $E_{1/2}^{oxd}$ 0.783 *vs* SCE $E_{1/2}^{red}$ -2.2 *vs* SCE	**84%**	**54%**	**30%**
2	**cat - 1** 	**48%**	**27%**	**21%**

3	$E_{1/2}^{oxd}$ 1.171 *vs* SCE $E_{1/2}^{red}$ -1.503 *vs* SCE 	43%	22%	21%
4	$E_{1/2}^{oxd}$ 1.226 *vs* SCE $E_{1/2}^{red}$ -1.234 *vs* SCE 	48%	26%	22%
5	$E_{1/2}^{oxd}$ 1.17 *vs* SCE $E_{1/2}^{red}$ -1.80 *vs* SCE 	25%	9%	16%
6	$E_{1/2}^{oxd}$ 1.004 *vs* SCE $E_{1/2}^{red}$ -2.13 *vs* SCE  $E_{1/2}^{oxd}$ 0.93 *vs* SCE $E_{1/2}^{red}$ -1.58 *vs* SCE	5%	5%	na

Scheme 23. Screening of photocatalysts using with less soluble amine.

We found that several more oxidizing photocatalysts resulted in increased alkylated product ratios, with **Cat. 1** providing the fastest reaction among these catalysts. The potenials of the above listed photocatalysts are adapted from the literature.[21] Given that in the photoexcited state, **Cat-1** is significantly

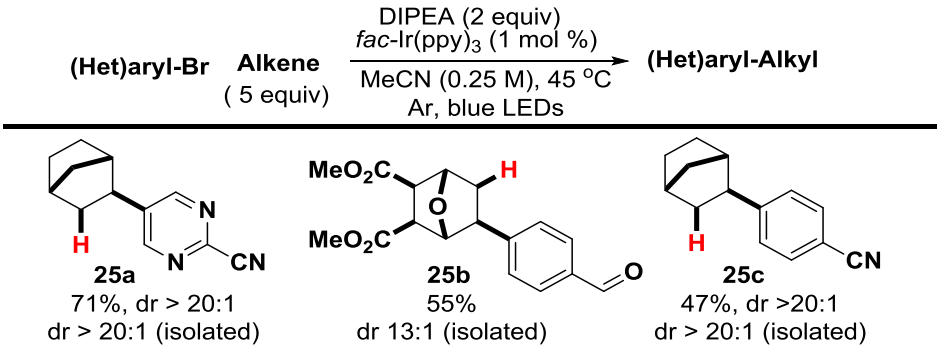
more oxidizing than $Ir(ppy)_3$, it would be expected to perform better if reductive quenching was operative. Using our modified conditions, we investigated more valuable 2-bromo-4, 6-difluorobenzothiazole as well as several of the poorer yielding substrates from (Scheme 18). In all cases we observed increases in yield (Scheme 24). We expect that these conditions will be more ideal in cases where the azole is more precious, and reaction time is not as important.



Scheme 24. Conditions for minimizing reduction.

3.8 A general strategy-reductive alkyation

We anticipated that this type of reactivity should be possible not only with bromo-azoles, but also with other reducible bromoarenes. In our initial attempt, we subjected electron deficient bromopyrimidnes, and benzenes to unoptimized conditions (Scheme 25). We found that all underwent reductive alkylation, allowing isolation of the alkylated pyrimidine **25a,** and benzenes **25b, 25c**. Importantly, these unoptimized results suggest that photocatalytic reductive alkylation may be a general strategy for Csp^2–Csp^3 cross-coupling. This maybe particularly useful for heteroaromatics and basic heterocycles, which are often challenging for traditional cross-coupling because of the ability of the product to coordinate the metal. Furthermore, these results warrant development of substrate specific conditions which will likely be different for any given class of arene, given the significant electronic differences between the aromatic motifs.



Scheme 25. Reductive alkylation of non-azole aromatics.

3.9 Summary

In conclusion, we have shown that photocatalysis has the ability to deliver Csp^2–Csp^3 cross-coupled products directly from 2-bromoazoles and unactivated alkenes. The ability to utilize alkenes directly as a surrogate for the corresponding alkyl group is a powerful synthetic strategy. In addition, the scope of the azole is general for thiazoles, benzothiazoles, and benzimidazoles. In many cases, the coupling occurs with excellent selectivity for the less substituted terminus of the alkene. The optional use of either alkene or azole as the limiting reagent is an attractive feature that should further enhance the utility. We have shown that this concept can be extended to other bromoarenes to generate both aryl and heteroaryl radicals in a controlled fashion, giving a sufficiently long-lived radical that is capable of undergoing intermolecular C–C bond formation.

3.10 General Experimental

All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI, and Oakwood) and used without further purification unless otherwise noted. 2-bromobenzo[*d*]thiazole, 2-bromo-4-chlorobenzo[*d*]thiazole, 2-bromo-4,6-difluorobenzo[*d*]thiazole, 2,5-dibromo-4-methylthiazole, ethyl 2-bromothiazole-4-carboxylate, 2,6-dibromo-1*H*-benzo[*d*]imidazole and 2-bromo-6-chloro-1*H*-benzo[*d*]imidazole which were synthesized according to literature procedures.[19] *N, N*-diisopropyloctan-1-amine was synthesized according to a literature procedure.[20] Photocatalyst fac-*tris*(2-phenyl pyridinato-C^2, *N*)iridium(III) ($Ir(ppy)_3$) and all other photocatalysts were synthesized according to the literature procedure.[21] Reactions were monitored by thin layer chromatography (TLC), (obtained from sorbent technology Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm) and were visualized with ultraviolet light, potassium permanganate stain, GC-MS (QP 2010S, Shimadzu equipped with auto sampler) and ^{1}H NMR.

Photocatalytic reactions were set up in a light bath as described below. Blue LEDs (in the form of strips 18 LEDs/ft) from Solid Apollo were wrapped around the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rest on the top was fashioned from cardboard and holes were made such that reaction tubes (5mm NMR tube) were held firmly in the cardboard lid, which was placed on the top of bath. Water was added to the bath such that the tubes were submerged in the water which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat.

Isolations were carried out using a Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and evaporative light scattering detection. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer and a 600 MHz Unity Inova spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^{1}H, ^{13}C). IR spectra were recorded on a Varian 800 FT-IR. Melting points were determined on a Stuart Digital (SMP10), Melting point-apparatus, 120 VAC. Mass spectra (HRMS)

analysis was performed on a LTQ-OrbitrapXL by Thermo Scientific Ltd. Quenching studies were performed on a Varian Carey Eclipse fluorescence spectrophotometer. Optical rotation was measured on an Autopol V polarimeter by Rudolph Research Analytical.

Emission Quenching Experiment

Emission intensities were recorded on Varian Carey Eclipse fluorescence spectrophotometer. All solutions of $Ir(ppy)_3$ in MeCN were excited at 370 nm and the emission intensities were observed at 520 nm. In this experiment, a 0.5 μM solution of $Ir(ppy)_3$ in MeCN was added to the appropriate amount of the quencher (Q) in a 1.0 cm quartz cuvette. After degassing each solution with a stream of argon for 15 minutes, the emission spectra were recorded.

Figure 1. $Ir(ppy)_3$ emission quenching by 2-bromothiazole (Q)

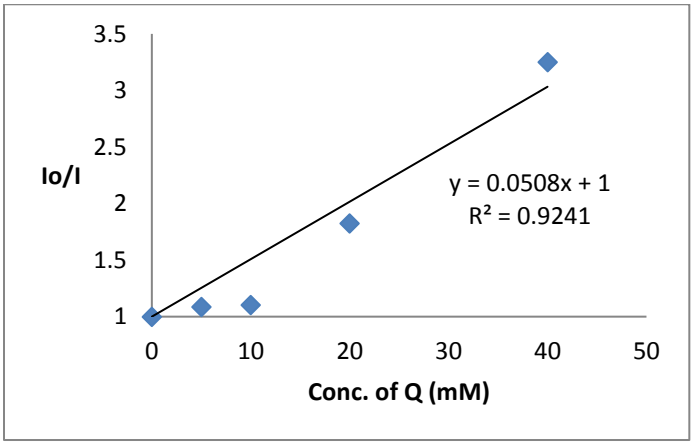


Figure 2. $Ir(ppy)_3$ emission quenching by dihydropyran (Q)

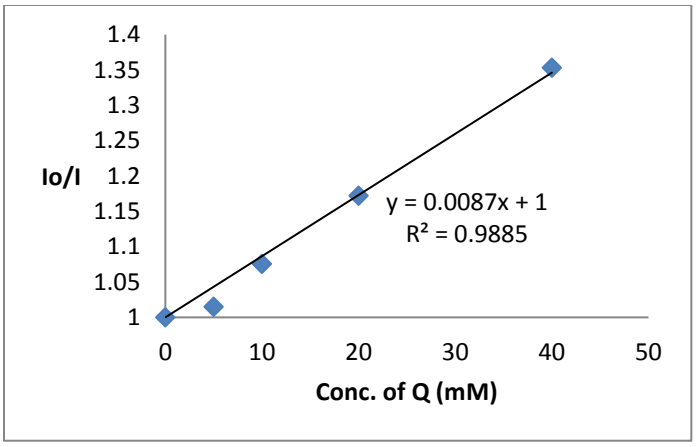


Figure 3. $Ir(ppy)_3$ emission quenching by tributylamine (Q)

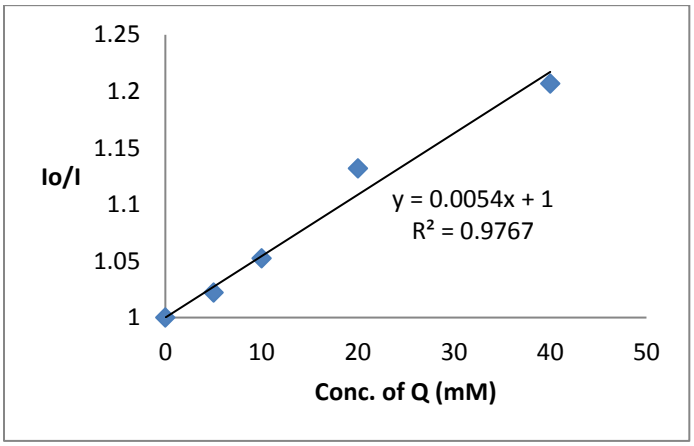


Figure 4. $Ir(ppy)_3$ emission quenching by tributylamine and formic acid (1:1) (Q)

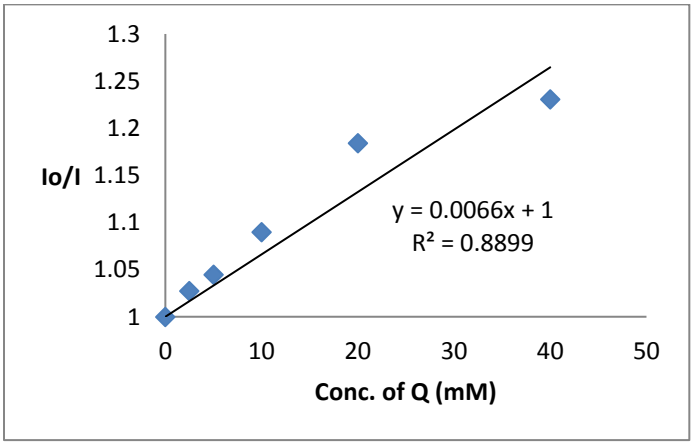


Figure 5. $Ir(ppy)_3$ emission quenching by 2-bromothiazole and formic acid (1:3) (Q)

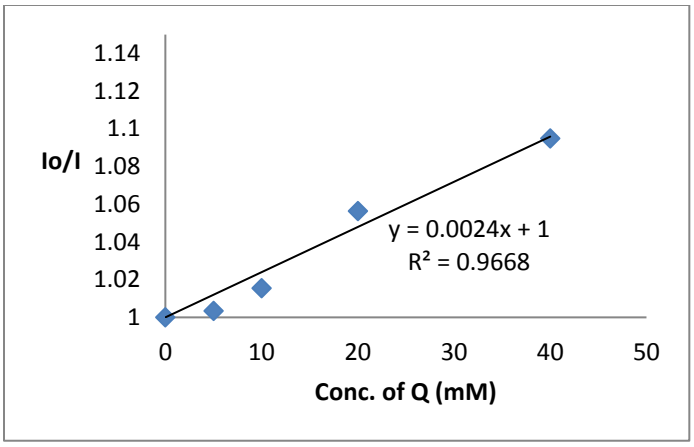
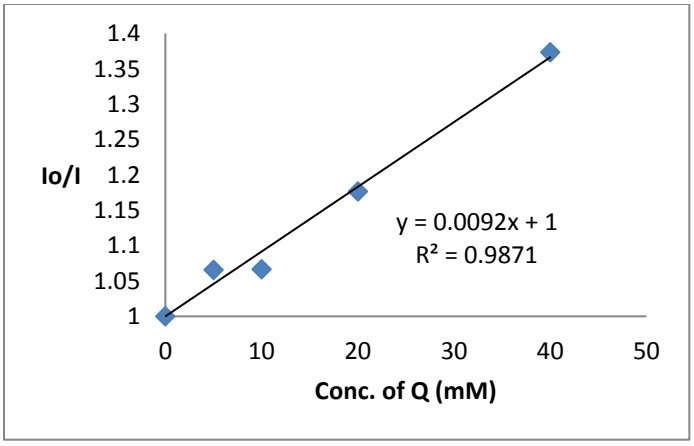


Figure 6. $Ir(ppy)_3$ emission quenching by 2-bromothiazole and tributylamine with formic acid (1:3:3) (Q)



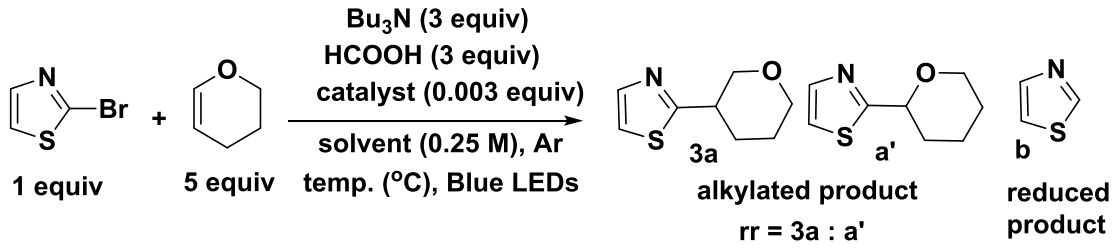
Conclusion

Quencher (Q)	Slope
2-Bromothiazole	0.0508
Dihydropyran	0.0087
Tributylamine	0.0054
Tributylamine and formic acid (1:1)	0.0066
2-Bromothiazole and formic acid (1:3)	0.0024
2-Bromothiazole and tributylamine with formic acid(1:3:3)	0.0092

Fluorescence quenching experiments suggest that as an individual component 2-bromothiazole provides the fastest quenching. The nonlinearity of the slope when bromoazole is used is interesting. However, the rate of quenching is significantly reduced when other reaction components are included with the

bromoazole and make interpretation of the quenching event uncertain given the relatively small differences in rates of quenching event and leave open the possibility of multiple types of quenching events occurring simultaneously.

Optimization of reaction conditions



Initial optimization studies

Solvent screening

Entry	Solvent	NMR Conversion	Reduction	Alkylated product (rr = 1a : 1a')
1	Dichloromethane	100%	37%	63% (5:1) + unidentified side product
2	DMA	100%	60%	40% (6:1)
3	DMF	100%	58%	42% (5:1)
4	DMSO	68%	23%	45% (4:1)
5	THF	50%	35%	15% (4:1)
6	Toluene	0%	na	na
7	MeOH	19%	7%	12% (3:1)
8	Nitromethane	0%	na	na
9	NMP	100%	72%	28% (7:1)
10	**CH_3CN**	**100%**	**30%**	**70% (6:1)**

rr = regioisomeric ratio

na = not applicable

CH_3CN was chosen as solvent for further optimization.

Effect of temperature

Entry	Temperature (°C)	NMR conversion	Reduction	Alkylated Product (rr = 1a : 1a')
1	30 °C	100%	51%	49% (4:1)
2	**45 °C**	**100%**	**34%**	**66% (6:1)**

3	60 °C	100%	40%	40% (5:1) + unidentified side product

45 °C was chosen as temperature for further optimization.

Effect of Concentration

Entry	Concentration	NMR conversion	Reduction	Alkylated product (rr = 1a : 1a')
1	0.10 M	100%	55%	45% (5:1)
2	0.15 M	100%	52%	48% (4:1)
3	0.20 M	100%	47%	53% (5:1)
4	**0.25 M**	**100%**	**38%**	**62% (5:1)**
5	0.30 M	100%	40%	60% (5:1)
6	0.35 M	100%	42%	58%(5:1)
7	0.40 M	100%	48%	52% (5:1)

0.25 M was chosen as concentration for the reaction

Effect of different acidic additives and amines

Entry	Acidic additives and amines	NMR Conversion	Reduction	Alkylated product (rr = 1a : 1a')
1	**Bu_3N + HCOOH (1:1)**	**100%**	**41%**	**59% (6:1)**
2	*N*, *N*-diisopropyl-2-methylpropan-1-amine + HCOOH (1:1)	100%	48%	52% (7:1)
3	Bu_3N + CH_3COOH (1:1)	56%	13%	43% (3:1)

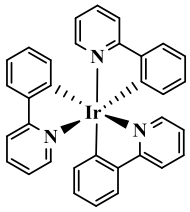
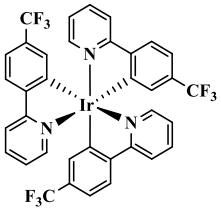
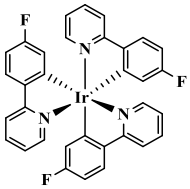
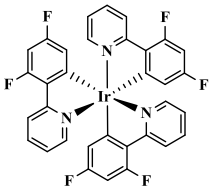
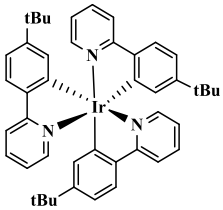
Note - Entry 3 reaction did not go to completion even at **extended** reaction times

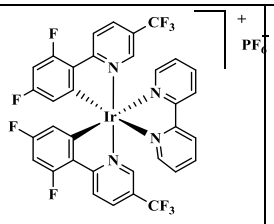
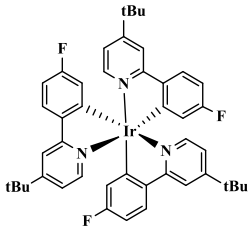
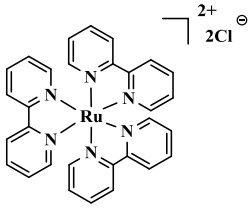
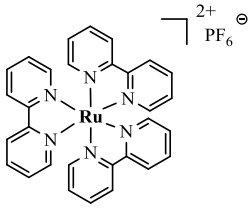
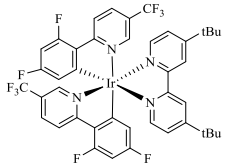
Bu_3N + HCOOH (1:1) was chosen as amine system for further reactions.

The addition of acetic or formic acid lead increased amounts of alkylated product (versus reduction). Furthermore, in the case of formic acid a significant rate enhancement is also observed. The cause of this difference is not yet clear. However, a few things are worth considering. Given that both benzimidazoles and benzathiazoles possess a basic nitrogen, it is reasonable to think that a hydrogen-bonding ammonium may be facilitating electron transfer to the bromoazole by lowering the LUMO of the heterocycle. Full proton and electron transfer would lead to a neutral radical with the bromine still attached to the heterocycle. This species may exist transiently or in equilibrium with several other conceivable intermediates. The net

effect of the acid is the enhancement the relative rate of C–C formation vs. C–H formation. One of the intermediates may be more prone to alkylation than it is reduction. However, currently this is mostly speculation and will be studied in more depth in the future.

Catalysts screening

Entry	Catalyst	NMR conversion	Reduction	Alkylated product (rr = 1a : 1a')
1		**100%**	**33%**	**67% (5:1)**
2		67%	32%	35% (4:1)
3		75%	38%	37% (5:1)
4		33%	17%	16% (4:1)
5		68%	37%	31% (4:1)

6		100%	42%	58% (4:1)
7		100%	47%	53% (4:1)
8		0%	na	na
9		18%	11%	7% (na)
10		100%	37%	63% (4:1)

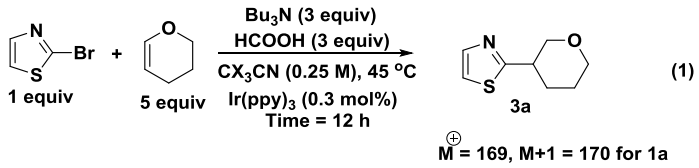
$Ir(ppy)_3$ was chosen as catalyst for the reaction

<u>Dueterium labeling study</u>

Our postulated mechanism assumed that the H-atom source was the amine and not the format. However, given that formate has been used as an H-atom source within related photocatalytic work,[22] we assessed the H-atom source by performing several photocatalytic reactions using deuterium labeled reagents. GC-MS

was used to determine the ratio of $M+1/M^+$ for each of reactions below *via* selected ion monitoring (SIM) mode. Increases in the M+1 peak are due to deuterium incorporation.

The first experiment evaluated the solvent as the source of H-atoms by changing the solvent from CH_3CN to CD_3CN in the reaction (eqn 1). Absorption intensity of each of the M^+ and M+1 of **1a** was determined by using SIM mode on GCMS.



(1)

X = H

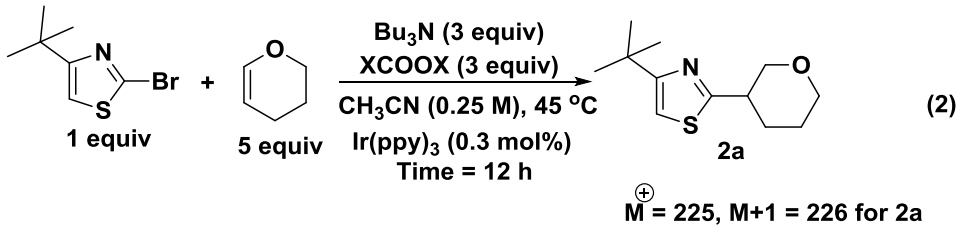
Entry	Selected ion	m/z	Abs. int.	$M+1/M^+$
1	M+1	170	410	
2	M^+	169	798	0.339 ($H_{solvent}$)

X = D

3	M+1	170	313	
4	M^+	169	589	0.347 ($D_{solvent}$)

The ratio of $D_{solvent}/ H_{solvent}$ = 2.3%. Thus, the solvent was playing only a minor role in providing H-atoms.

The second experiment demonstrates effect of changing HCOOH to DCOOD in the reaction (eqn 2). Absorption intensity of each of the M^+ and M+1 of **2a** is determined as described above.



(2)

X = H

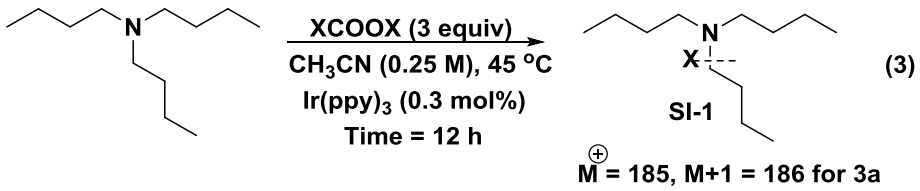
Entry	Selected ion	m/z	Abs. int.	$M+1/M^+$
1	M+1	226	5098	
2	M^+	225	23541	0.1780 (H_{acid})

X = D

3	M+1	226	4556	
4	M^+	225	20982	0.1784 (D_{acid})

The ratio of $D_{solvent}/ H_{solvent}$ = 0.2%. It appears that the role of the formic acid is not as a deuterium source, since very little was found to be incorporated. The formic acid is likely functioning as a Bronsted acid.

The third experiment demonstrates effect of changing HCOOH to DCOOD in the reaction (eqn 3). Absorption intensity of each of the M^+ and M+1 of **SI-1** is determined as described above.



(3)

X = H

Entry	Selected ion	m/z	Abs. int.	$M+1/M^+$
1	M+1	186	7554	
2	M^+	185	48136	0.1356 (H_{amine})

X = D

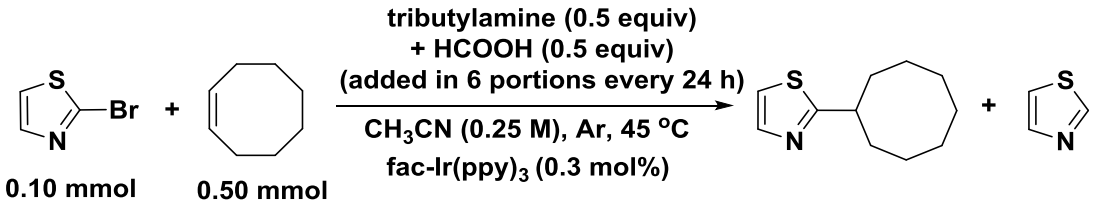
3	M+1	186	14118	
4	M^+	185	61589	0.1864 (D_{amine})

The ratio of $D_{solvent}/ H_{solvent}$ = 37.5%. It is an interesting observation that under these conditions (note, the absence of the bromoazole) significant H-atom scrambling occurs.

We conclude that the amine is infact serving as the primary reductant while the solvent serves to provide a small percentage of the H-atom. Additionally, in the absence of the substrate significant deuterium incorporation is seen in the amine.

Iterative addition of sub-stoichiometric amounts of amine

We speculated that the rate of the undesired reduction reaction might depend upon the concentration of the amine and we probed this by keeping the amine concentration artificially low *via* iterative addition of amine.



In this experiment, a 5 mm NMR tube capped with NMR septum (Ace glass, part no. 9096-25) was charged *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) (Ir(ppy)3) (0.4 mL [0.75 mM stock solution of catalyst in MeCN]). 2-bromothiazole (15 mg, 0.10 mmol) and cyclooctene (11.5 mg, 0.50 mmol) as well as tributylamine (9 mg, 0.05 mmol) and formic acid (2 mg, 0.05 mmol) were added in the beginning of reaction. A sealed glass capillary containing C_6D_6 was placed in NMR tube for locking purposes. Then the reaction tube was degassed *via* Ar bubbling for 10 min. and then the exit needle and Ar line were removed and reaction tube was sealed with parafilm. The NMR tube was placed in a light bath (as described above) and the lower portion of the tube was submerged under the water bath which was maintained at 45 ^oC. ^1H NMR was recorded after 24 h, followed by addition of 0.05 mmol of tributylamine and 0.05 mmol of formic acid. Then the reaction mixture was again degassed and placed in the light bath. After an additional 24 h, the ^1H NMR was once again recorded. This incremental addition of tributylamine and formic acid was repeated until a total of 0.3 mmol of tributylamine and formic acid were added to the reaction. The results have been tabulated, below.

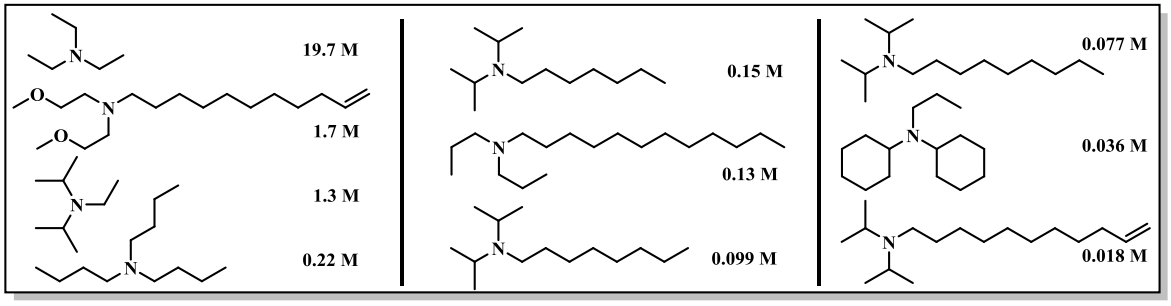
Entry	Total mmol of formic acid	Total mmol of tributylamine	NMR conversion	Reduction	Alkylated product
1	0.05	0.05	0%	na	na
2	1	1	0%	na	na

3	1.5	1.5	20%	9%	11%
4	2.0	2.0	36%	17%	19%
5	2.5	2.5	74%	32%	42%
6	3.0	3.0	100%	48%	52%
7	Single addition of HCOOH (3.0 mmol)	Single addition of Bu_3N (3.0 mmol)	100%	72%	28%

By comparison, when a single addition of tributylamine (3.0 equiv) and formic acid (3.0 equiv) is initially added, all at once , the reaction undergoes 100% conversion, out of which 72% is reduction and 28% is alkylated product (**3d-1**) in 12 h (reaction time) while incremental addition leads to a 48% reduction and 52% alkylated product. This experiment suggests that the rate of reduction of the azole has a greater amine concentration dependency than the alkylated product and encouraged further exploration of this question.

Alternatively, we could take advantage of the poor solubility of tertiary amine with long alkyl chains (in MeCN), which can provide a convenient method for keeping a low concentration over time. Thus we evaluated the solubility of various amines derivatives, which is given below.

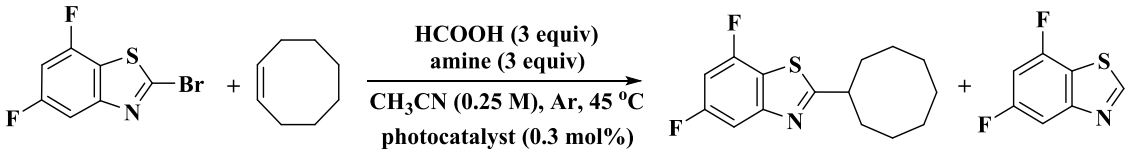
The Experimentally Determined Solubility of Several Amines at 23 ^{0}C



(*i*Pr)$_2$N*n*-Oct amine was chosen for second round of optimization.

Effect of change in equiv of alkene in (Conditions A) condition and modified conditions (Conditions B)

Using 2 sets of conditions, **conditions A**-tributylamine (3 equiv), HCOOH (3 equiv), *fac*-Ir(ppy)$_3$ (0.3 mol%) in 14 h and **conditions B**-*N*, *N*-diisopropyloctan-1-amine (3 equiv), HCOOH (3 equiv), cat-1 (0.3 mol%) in 5 days, we investigated the effect of changing the equivalents of alkene.

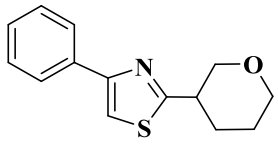


Entry	Reactions conditions	Equiv of Alkene	NMR conversion	Reduction	Alkylated product
1	**Cond. A**	1.2 equiv	100%	82%	18%
2	**Cond. B**	1.2 equiv	100%	56%	44%
3	**Cond. A**	2.4 equiv	100%	67%	33%
4	**Cond. B**	2.4 equiv	100%	32%	68%
5	**Cond. A**	5 equiv	100%	39%	61%
6	**Cond. B**	5 equiv	100%	20%	80%

Comparison of the two sets of conditions (**Conditions A** and **B)** at various alkene loadings, showed significant enhancements in the desired product formation by using the less soluble amine and more oxidizing catalyst (**Cat-1**) (**conditions B**), albeit at the expense of longer reaction time.

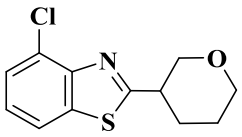
Improvement of percentage yield of substrate 3a and 8a with new modified conditions (Conditions B)

4-phenyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



The **Conditions B** were followed using 2-bromo-4-phenylthiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (42 mg, 0.50 mmol), *N*, *N*-diisopropyloctan-1-amine (64 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), 0.40 mL of stock solution of cat-1 in MeCN. After 3 days, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) was added as an internal standard and the yield of **3c** was calculated as 51% (based on ^{1}H NMR) with a rr 9:1 (based on crude ^{1}H NMR). **Note** – In comparison to **3c** (with **Conditions A**) the yield improved from 43% to 51%.

4-chloro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



The **Conditions B** were followed using 2-bromo-4-chlorobenzo[d]thiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (42 mg, 0.50 mmol), *N*, *N*-diisopropyloctan-1-amine (64 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of cat-1 in MeCN. After 4 days, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) was added as an internal standard and the yield of **3h** was calculated as 77% yield (based on ^{1}H NMR) and rr 4:1 (based on crude ^{1}H NMR). **Note** In comparison to **3h** (with **Conditions A**) the yield improved from 60% to 77% with slight improvement of rr 3:1 (with **Conditions A**) to rr 4:1.

Photocatalytic reductive coupling

General procedure E for the photocatalytic reductive alkylation of bromoazoles with alkenes **(limiting azole)**

A 5 mm NMR tube fitted with a NMR septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, X mL of 0.75 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.25 M with respect to the 2-bromoazoles), 2-bromoazoles (1 equiv), alkene (5 equiv), tributylamine (3 equiv) and formic acid (3 equiv) and the reaction mixture was degassed *via* Ar bubbling for 10 min and then the exit needle and Ar line were removed and reaction tube was sealed with parafilm. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 45 ^{o}C. The reaction was monitored by ^{1}H NMR

or GC-MS. After the complete consumption of aryl bromide, CH_3CN was removed *via* rotovap and the residue was treated with water (2 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified *via* normal phase chromatography.

General procedure F for the photocatalytic reductive alkylation of bromoazoles with alkenes **(limiting alkene)**

This procedure is identical to **general procedure E** except with following changes, where, 2-bromoazole (10 equiv), alkene (1 equiv), tributylamine (12 equiv) and formic acid (12 equiv) were used in MeCN (0.25 M with respect to 2-bromoazole).

General procedure G for the photocatalytic reductive alkylation of bromoazoles with alkenes **(Reduction minimizing conditions)**

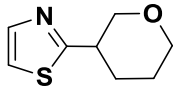
This procedure is identical to **general procedure E** except with following changes, where Iridium(+1)(4,4´-dimethoxy-2,2´bipyridine)bis[4-*tert*-butyl-2-(4-*tert*-butylpyridinal)phenyl]**(cat-1)** (0.003 equiv, X mL of 0.75 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.25 M with respect to the 2-bromoazoles) and 2-bromoazole (1 equiv), alkene (5 equiv), *N, N*-diisopropyloctan-1-amine (3 equiv) and formic acid (3 equiv) were used.

General procedure H for the photocatalytic reductive alkylation for heteroaromatic bromide with alkene

This procedure is identical to **general procedure E** except with following changes, where *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, X mL of 0.65 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.25 M with respect to heteroaromatic bromide), heteroaromatic bromide (1 equiv), alkene (5 equiv), *N*-ethyl-*N*-isopropylpropan-2-amine (DIPEA) (2 equiv) were used. The reaction was monitored by NMR or GCMS. After the complete consumption of heteroaromatic bromide, CH_3CN was removed *via* rotovap and the residue was treated with saturated

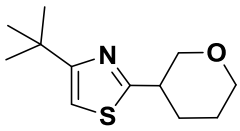
aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified *via* normal phase chromatography.

18a 2-(tetrahydro-2H-pyran-3-yl)thiazole



The **general procedure E** was followed using 2-bromothiazole (15 mg, 0.09 mmol), 3,4-dihydro-2H-pyran (38 mg, 0.46 mmol), tributylamine (51 mg, 0.27 mmol), formic acid (13 mg, 0.27 mmol) and 0.36 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18a** in 65% yield (10 mg, 0.059 mmol), rr 6:1 (based on crude ^1H NMR) as an oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 10% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 3.3 Hz, 1H), 7.23 (d, J = 3.3 Hz, 1H), 4.19 (ddd, J = 11.2, 4.1, 1.8 Hz, 1H), 3.96 (dt, J = 12.3, 3.4 Hz, 1H), 3.59 (dd, J = 11.2, 9.8 Hz, 1H), 3.56–3.46 (m, 1H), 3.38–3.27 (m, 1H), 2.30–2.21 (m, 1H), 1.96–1.83 (m, 1H), 1.83–1.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 142.2, 117.8, 72.1, 68.0, 40.6, 30.0, 25.1. FT-IR (neat) cm^{-1} 2933, 2848, 1434, 1085. HRMS [ESI] $C_8H_{11}NOS$ calcd. $[M+H]^+$ 170.0635 observed 170.0629.

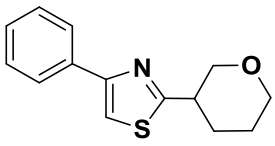
18b 4-(tert-butyl)-2-(tetrahydro-2H-pyran-3-yl)thiazole



The **general procedure E** was followed using 2-bromo-4-(tert-butyl)thiazole (25 mg, 0.11 mmol), 3,4-dihydro-2H-pyran (46 mg, 0.55 mmol), tributylamine (63 mg, 0.34 mmol), formic acid (16 mg, 0.34 mmol) and 0.45 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18b** in 71% yield (18 mg, 0.079 mmol), rr 9:1 (based on crude ^1H NMR) and isolated as rr 10:1 mixture as a yellow oil. After the completion of the reaction, 14 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 4 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 4.17 (ddd, J = 11.1, 4.0, 1.7 Hz, 1H), 3.94 (dt, J = 11.0, 3.8 Hz, 1H), 3.58–3.43 (m, 2H), 3.35–3.23 (m, 1H), 2.29–2.18

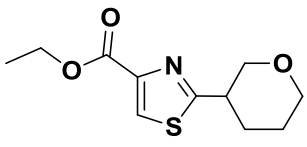
(m, 1H), 1.90–1.66 (m, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 166.2, 109.0, 72.4, 68.2, 41.1, 34.7, 30.3, 30.0, 25.4. FT-IR (neat) cm^{-1} 2957, 2866, 1513, 1150. HRMS [ESI] $C_{12}H_{19}NOS$ calcd. $[M+H]^+$ 226.1261 observed 226.1253. **Note** - The regioisomer is marked in all ^{1}H NMR and ^{13}C NMR spectra as ◯.

18c 4-phenyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



The **general procedure E** was followed using 2-bromo-4-phenylthiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (44 mg, 0.52 mmol), tributylamine (58 mg, 0.31 mmol), formic acid (14 mg, 0.31 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18c** in 43% yield (10 mg, 0.043 mmol), rr 9:1 (based on crude **^{1}**H NMR) as yellow oil. After the completion of the reaction, 13 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 3% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 1.4 Hz, 1H), 7.88 (t, J = 1.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.36 (s, 1H), 7.32 (t, J = 7.4 Hz, 1H), 4.25 (ddd, J = 11.2, 4.1, 1.7 Hz, 1H), 3.97 (dt, J = 11.1, 3.1 Hz, 1H), 3.65 (dd, J = 11.1, 9.8 Hz, 1H), 3.58–3.50 (m, 1H), 3.43–3.32 (m, 1H), 2.35–2.24 (m, 1H), 2.01–1.88 (m, 1H), 1.85–1.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.1, 134.6, 128.7, 128.0, 126.4, 111.8, 72.3, 68.2, 41.1, 30.2, 25.3. FT-IR (neat) cm^{-1} 2925, 2859, 1492, 1090. HRMS [ESI] $C_{14}H_{15}NOS$ calcd. $[M+H]^+$ 246.0948 observed 246.0935.

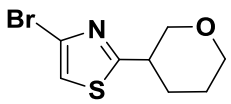
18d ethyl 2-(tetrahydro-2H-pyran-3-yl)thiazole-4-carboxylate



The **general procedure E** was followed using ethyl 2-bromothiazole-4-carboxylate (25 mg, 0.11 mmol), 3,4-dihydro-2H-pyran (44 mg, 0.53 mmol), tributylamine (58 mg, 0.32 mmol), formic acid (14 mg, 0.32 mmol), and 0.42 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18d** in 82% yield (22 mg, 0.090 mmol), rr 4:1(based on crude ^{1}H NMR) and isolated as mix of rr 5:1 as yellow oil. After the completion of the reaction, 14 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0%

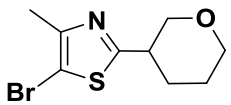
to 100%) with product eluting at 16% on a 12 g silica column. **Note** - Another regioisomer is marked as ○ in spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.16 (ddd, *J* = 11.5, 4.0, 1.7 Hz, 1H), 3.92 (dt, *J* = 11.4, 4.0 Hz, 1H), 3.63 (dd, *J* = 11.2, 9.0 Hz, 1H), 3.60–3.50 (m, 1H), 3.47–3.35 (m, 1H), 2.24 (m, 1H), 1.98–1.84 (m, 1H), 1.75 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 161.4, 146.9, 126.7, 71.9, 68.2, 61.5, 41.0, 30.0, 24.8, 14.4. FT-IR (neat) cm^{-1} 2933, 2851, 1735, 1722, 1100. HRMS [ESI] $C_{11}H_{15}NO_3S$ calcd. $[M+H]^+$ 242.0845 observed 242.0839.

18e 4-bromo-2-(tetrahydro-2H-pyran-3-yl)thiazole



The **general procedure E** was followed using 2,4-dibromothiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (44 mg, 0.52 mmol), tributylamine (57 mg, 0.31 mmol), formic acid (14 mg, 0.31 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18e** in 82% yield (19 mg, 0.082 mmol), rr 10:1 (based on crude ^{1}H NMR) as yellow oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 2% on a 4 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 1H), 4.14 (ddd, J = 11.2, 4.1, 1.7 Hz, 1H), 3.92 (dt, J = 11.3, 3.3 Hz, 1H), 3.59 (dd, J = 11.2, 9.4 Hz, 1H), 3.56–3.47 (m, 1H), 3.34–3.25 (m, 1H), 2.25–2.16 (m, 1H), 1.95–1.81 (m, 1H), 1.80–1.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 124.6, 115.9, 71.9, 68.1, 40.9, 29.8, 24.9. FT-IR (neat) cm^{-1} 2933, 2841, 1470, 1053, 670. HRMS [ESI] $C_8H_{10}BrNOS$ calcd. $[M+Na]^+$ 269.9559 observed 269.9551.

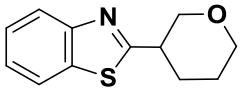
18f 5-bromo-4-methyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



The **general procedure E** was followed using 2,5-dibromo-4-methylthiazole (25 mg, 0.097 mmol), 3,4-dihydro-2H-pyran (41 mg, 0.49 mmol), tributylamine (54 mg, 0.29 mmol), formic acid (13 mg, 0.29 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18f** in 75% yield (19 mg, 0.073 mmol, including both isomers), rr 10:1 (based on crude ^{1}H NMR) as an oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash

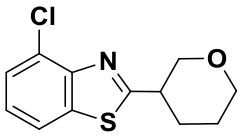
chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (dd, J = 11.8, 4.2 Hz, 1H), 3.91 (dt, J = 11.6, 3.9 Hz, 1H), 3.62–3.45 (m, 2H), 3.21 (td, J = 9.0, 4.4 Hz, 1H), 2.36 (s, 3H), 2.24–2.12 (m, 1H), 1.90–1.79 (m, 1H), 1.78–1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 151.0, 103.0, 71.9, 68.2, 41.3, 29.7, 25.0, 15.6. FT-IR (neat) cm^{-1} 2927, 2849, 1541, 1103, 695, HRMS [ESI] $C_9H_{12}BrNOS$ calcd. $[M+H]^+$ 261.9896 observed 261.9891.

18g 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



The **general procedure E** was followed using 2-benzobromothiazole (25 mg, 0.12 mmol), 3,4-dihydro-2H-pyran (49 mg, 0.58 mmol), tributylamine (65 mg, 0.35 mmol), formic acid (16 mg, 0.39 mmol), 0.48 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18g** in 78% yield (20 mg, 0.093 mmol), rr 7:1 (based on crude ^{1}H NMR) as yellow oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 11% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.46 (t. J = 8.1 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 4.30–4.22 (m, 1H), 4.02–3.94 (m, 1H), 3.72 (dd, J = 11.2, 9.7 Hz, 1H), 3.60–3.51 (m, 1H), 3.45–3.36 (m, 1H), 2.34-2.31 (m, 1H), 2.06–1.92 (m, 1H), 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 153.1, 134.5, 126.0, 124.9, 122.7, 121.6, 71.8, 68.2, 41.7, 30.0, 25.2. FT-IR (neat) cm^{-1} 2939, 2839, 1513, 1095. HRMS [ESI] $C_{12}H_{13}NOS$ calcd. $[M+H]^+$ 220.0791 observed 220.0787.

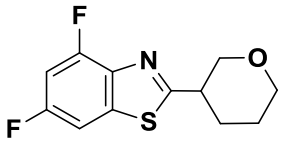
18h 4-chloro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



The **general procedure E** was followed using 2-bromo-4-chlorobenzo[d]thiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (42 mg, 0.51 mmol), tributylamine (56 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ of MeCN was used to afford **18h** in 60% yield (15 mg, 0.060 mmol), rr 3:1 (based on crude ^{1}H NMR) as an oil. After the completion of the reaction, 24 h, the substrate was purified *via* automated flash

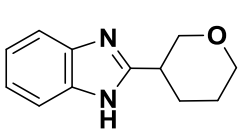
chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 13% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 4.25 (ddd, J = 11.5, 4.2, 1.8 Hz, 1H), 3.96 (dt, J = 11.1, 3.9 Hz, 1H), 3.72 (dd, J = 11.3, 9.3 Hz, 1H), 3.66–3.53 (m, 1H), 3.57–3.44 (m, 1H), 2.38–2.26 (m, 1H), 2.08–1.91 (m, 1H), 1.86–1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 150.0, 136.1, 127.6, 126.3, 125.4, 120.1, 71.8, 68.2, 41.8, 30.0, 25.0. FT-IR (neat) cm^{-1} 2941, 2842, 1524, 1117, 827. HRMS [ESI] $C_{12}H_{12}ClNOS$ calcd. $[M+H]^+$ 254.0401 observed 254.0394.

18i 4,6-difluoro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



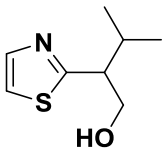
The **general procedure E** was followed using 2-bromo-4,6-difluorobenzo[d]thiazole (25 mg, 0.10 mmol), 3,4-dihydro-2H-pyran (42 mg, 0.50 mmol), tributylamine (55 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ of MeCN was used to afford **18i** in 78% yield (20 mg, 0.078 mmol), rr 5:1 (based on crude ^{1}H NMR) as an oil. After the completion of the reaction, 18 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 11% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 10.7 Hz, 1H), 4.23 (ddd, J = 11.7, 4.0, 1.8 Hz, 1H), 3.96 (dt, J = 11.5, 4.0 Hz, 1H), 3.77–3.70 (m, 1H), 3.63–3.53 (m, 1H), 3.48–3.37 (m, 1H), 2.35–2.24 (m, 1H), 2.06–1.94 (m, 1H), 1.84–1.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 160.4 (dd, J = 247.3, 10.4 Hz), 155.4 (dd, J = 259.0, 13.4 Hz), 139.2 (dd, J = 13.3, 2.6 Hz), 137.9 (dd, J = 12.7, 5.0 Hz), 104.1 (dd, J = 26.4, 4.7 Hz), 102.5 (dd, J = 28.3, 21.9 Hz). 72.0, 68.7, 42.1, 30.3, 25.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.0 (td, J = 8.4, 5.5 Hz), -117.7–118.2 (m). FT-IR (neat) cm^{-1} 2927, 2852, 1612, 1438, 1100. HRMS [ESI] calcd. $C_{12}H_{11}F_2NOS$ $[M+H]^+$ 256.0603 observed 256.0592

18j 2-(tetrahydro-2H-pyran-3-yl)-1H-benzo[d]imidazole



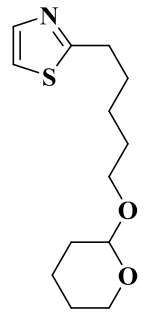
The **general procedure E** was followed using 2-bromo-1H-benzo[d]imidazole (25 mg, 0.13 mmol), 3,4-dihydro-2H-pyran (53 mg, 0.63 mmol), tributylamine (70 mg, 0.38 mmol), formic acid (17 mg, 0.38 mmol), and 0.50 mL of stock solution of $Ir(ppy)_3$ of MeCN was used to afford **18j** in 86% yield (22 mg, 0.108 mmol), rr 4:1 (based on crude ^1H NMR) as white solid. m.pt 235-238 ^oC. After the completion of the reaction, 24 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexane before running) (0% to 100%) with product eluting at 11% on a 24 g silica column. ^1H NMR (400 MHz, Methanol-d_4) δ 7.53–7.46 (m, 2H), 7.18 (dt, J = 6.1, 3.7 Hz, 2H), 4.12 (ddd, J = 11.6, 4.2, 1.8 Hz, 1H), 3.93 (dt, J = 11.3, 3.8 Hz, 1H), 3.69 (t, J = 10.6 Hz, 1H), 3.54 (dt, J = 11.4, 6.8 Hz, 1H), 3.34–3.27 (m, 1H), 3.17 (tt, J = 10.3, 4.1 Hz, 1H), 2.25–2.16 (m, 1H), 2.05–1.92 (m, 1H), 1.75 (dp, J = 7.7, 4.0 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.2, 122.0, 78.2, 77.9, 77.5, 76.8, 70.5, 67.8, 37.0, 28.0, 25.0. FT-IR (neat) cm^{-1} 2931, 2858, 1454, 1109. HRMS [ESI] calcd. $C_{12}H_{14}N_2O$ $[M+H]^+$ 203.1179 observed 203.1173

18l 3-methyl-2-(thiazol-2-yl)butan-1-ol



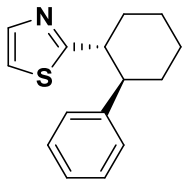
The **general procedure E** was followed using 2-bromothiazole (50 mg, 0.30 mmol) (E)-3-methylbut-1-en-1-ol (129 mg, 1.50 mmol), tributylamine (167 mg, 0.90 mmol), formic acid (41 mg, 0.90 mmol), and 1.2 mL of stock solution of $Ir(ppy)_3$ of MeCN was used to afford **18l** in 43% yield (22 mg, 0.13 mmol) rr >20:1 (based on crude ^1H NMR) as yellow oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered 1% Et_3N in hexanes before running) (0% to 100%) with product eluting at 26% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 3.3 Hz, 1H), 7.23 (d, J = 3.4 Hz, 1H), 4.05 (dt, J = 11.1, 6.7 Hz, 1H), 3.92 (ddd, J = 11.2, 5.5, 3.4 Hz, 1H), 3.26–3.16 (m, 1H), 2.96 (td, J = 7.0, 3.4 Hz, 1H), 2.23 (h, J = 6.9 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 142.1, 117.9, 63.2, 52.0, 30.4, 20.9, 20.2. FT-IR (neat) cm^{-1} 3342, 2962, 2872, 1512 HRMS [ESI] $C_8H_{13}NOS$ calcd. $[M+H]^+$ 172.0791 observed 172.0788.

18m 2-(5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)thiazole



The **general procedure E** was followed using 2-bromothiazole (25 mg, 0.15 mmol), 2-(pent-4-en-1-yloxy)tetrahydro-2H-pyran (130 mg, 0.76 mmol), tributylamine (85 mg, 0.46 mmol), formic acid (21 mg, 0.46 mmol), and 0.60 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18m** in 70% yield (27 mg, 0.11 mmol) rr>20:1 (based on crude ^{1}H NMR) as yellow oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexane before running) (0% to 100%) with product eluting at 4% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 3.3 Hz, 1H), 7.18 (d, *J* = 3.3 Hz, 1H), 4.56 (dd, *J* = 4.6, 2.6 Hz, 1H), 3.85 (ddd, *J* = 11.0, 7.5, 3.4 Hz, 1H), 3.74 (dt, *J* = 9.6, 6.7 Hz, 1H), 3.54–3.44 (m, 1H), 3.39 (dt, *J* = 9.6, 6.5 Hz, 1H), 3.04 (t, *J* = 7.8 Hz, 2H), 1.90–1.77 (m, 3H), 1.72–1.61 (m, 3H), 1.59–1.46 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 142.0, 118.0, 98.9, 67.3, 62.4, 33.2, 30.8, 29.9, 29.4, 25.8, 25.5, 19.7. FT-IR (neat) cm^{-1} 2938, 2865, 1507, 1032. HRMS [ESI] $C_{13}H_{21}NO_2S$ calcd. $[M+Na]^+$ 278.1185 observed 278.1183.

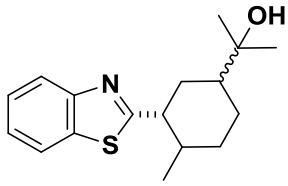
18n 2-(2-phenylcyclohexyl)thiazole



The **general procedure E** was followed using 2-bromothiazole (25 mg, 0.15 mmol), 2,3,4,5-tetrahydro-1,1'-biphenyl (120 mg, 0.76 mmol), tributylamine (85 mg, 0.46 mmol), formic acid (21 mg, 0.46 mmol) and 0.60 mL of stock solution of $Ir(ppy)_3$ in MeCN solution was used to afford **18n** in 74% yield (27 mg, 0.11 mmol), rr>20:1 (based on crude ^{1}H NMR), dr>20:1 (based on crude ^{1}H NMR) as colorless oil. After the completion of the reaction, 14 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 0.5% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 3.6 Hz, 1H), 7.40 (d, J = 3.5 Hz, 1H), 7.31 (d, J = 6.7 Hz, 1H), 7.28–7.21 (m, 1H), 7.19–7.12 (m, 3H), 3.97–3.86 (m, 1H), 3.31 (dt, J = 11.5, 4.1 Hz, 1H), 2.49–2.37 (m, 1H), 2.35–2.27 (m, 1H), 2.25–2.07 (m, 3H), 2.04–1.94 (m, 1H), 1.85–1.76 (m, 1H), 1.74–1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 144.1, 141.5, 128.0,

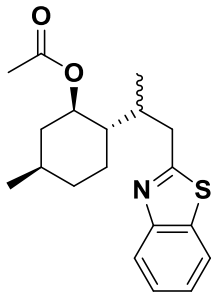
127.8, 126.0, 117.6, 46.4, 45.3, 31.3, 26.7, 25.9, 21.8. FT-IR (neat) cm^{-1} 2925, 2859, 1681, 1444. HRMS [ESI] $C_{15}H_{17}NS$ calcd. $[M+H]^+$ 244.1154 observed 244.1151.

18o 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



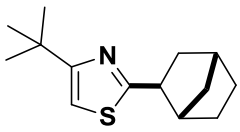
The **general procedure E** was followed using 2-benzobromothiazole (25 mg, 0.12 mmol), 2-(4-methylcyclohex-3-en-1-yl)propan-2-ol (90 mg, 0.58 mmol), tributylamine (65 mg, 0.35 mmol), formic acid (16 mg, 0.35 mmol) and 0.50 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18o** in 73% yield (25 mg, 0.087 mmol, including both diastereomers), rr >20:1 (based on crude ^1H NMR), dr 1.3:1 (based on crude ^1H NMR) and isolated as dr 1.7:1 as pale oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 10% (diastereomer **a**) and 11% (diastereomer **b**) on a 24 g silica column. Diastereomer **a**- ^1H NMR (400 MHz, $CDCl_3$), δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 3.66 (dq, *J* = 4.6, 2.3 Hz, 1H), 2.14 (dq, *J* = 13.3, 2.7 Hz, 1H), 2.06–1.95 (m, 2H), 1.89 (ddt, *J* = 10.6, 6.4, 3.7 Hz, 2H), 1.64 (td, *J* = 13.0, 5.2 Hz, 3H), 1.43 (d, *J* = 2.4 Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 0.92 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 152.9, 134.9, 125.7, 124.6, 122.8, 121.2, 72.7, 45.6, 42.9, 35.2, 32.6, 29.9, 27.2, 27.2, 27.0, 19.9. Diastereomer **b** - ^1H NMR (400 MHz, $CDCl_{3,}$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.44 (t, 1H), 7.34 (t, J = 8.1 Hz, 1H), 2.80 (td, J = 11.2, 3.4 Hz, 1H), 2.39–2.11 (m, 2H), 1.95 (ddt, J = 17.6, 11.8, 2.7 Hz, 2H), 1.88–1.73 (m, 2H), 1.53–1.43 (m, 3H), 1.19 (s, 6H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 153.0, 134.6, 125.8, 124.6, 122.6, 121.6, 72.6, 51.0, 48.8, 38.0, 35.8, 35.2, 27.2, 27.1, 26.9, 20.3. FT-IR (neat) cm^{-1} 3546, 2959, 2857, 1504. HRMS [ESI] $C_{17}H_{23}NOS$ calcd. $[M+H]^+$ 290.1573 observed 290.1569. **Note** - The diastereomer is marked in all ^1H NMR and ^{13}C NMR spectra.as ◯. The stereochemical assignment is based on detailed analysis of coupling constants.

18p (1R,2S,5R)-2-(1-(benzo[d]thiazol-2-yl)propan-2-yl)-5-methylcyclohexyl acetate



The **general procedure E** was followed using 2-benzobromothiazole (25 mg, 0.12 mmol), (1R,2S,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl acetate (110 mg, 0.58 mmol), tributylamine (65 mg, 0.35 mmol), formic acid (16 mg, 0.35 mmol), and 0.45 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18p** in 70% yield (28 mg, 0.084 mmol), rr >20:1 (based on crude ^{1}H NMR), dr 1.25:1 (based on crude ^{1}H NMR) and isolated as dr 3:1 mixture as yellow oil. After the completion of the reaction, 22 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 40 g silica column. ^{1}H NMR [mix of diastereomers] (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 4.83 (td, *J* = 10.9, 4.1 Hz, 1H), 3.20 (dd, *J* = 14.2, 3.7 Hz, 1H), 2.82 (dd, *J* = 14.0, 10.9 Hz, 1H), 2.44–2.21 (m, 2H), 2.14 (s, 3H), 1.77 (dd, *J* = 32.2, 14.6 Hz, 3H), 1.67–1.47 (m, 4H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 170.5, 153.0, 135.2, 125.6, 124.4, 122.4, 121.3, 73.4, 46.7, 40.7, 37.2, 34.5, 34.1, 31.2, 26.7, 25.5, 21.7, 16.9. FT-IR (neat) cm^{-1} 2922, 2841,1732, 1520. HRMS [ESI] calcd. $C_{19}H_{25}NO_2S$ $[M+H]^+$ 332.1679 observed 332.1673. **Note** - The diastereomer is marked in ^{1}H NMR and ^{13}C NMR spectra as ◯.

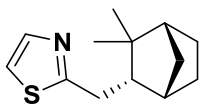
<u>18q</u> 2-((1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)-4-(tert-butyl)thiazole



The **general procedure E** was followed using 2-bromo-4-(tert-butyl)thiazole (25 mg, 0.11 mmol), norbornene (53 mg, 0.57 mmol), tributylamine (63 mg, 0.34 mmol), formic acid (16 mg, 0.34 mmol), and 0.45 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18q** in 68% yield (18 mg, 0.075 mmol), rr>20:1 (based on crude ^{1}H NMR), dr>20:1 (based on crude ^{1}H NMR) as colorless oil. After the completion of the reaction, 15 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 2% on a 24 g silica column. ^{1}H NMR (400 MHz,$CDCl_3$) δ 6.69 (s, 1H), 3.08 (dd, *J* = 8.6, 5.3 Hz, 1H), 2.46 (s, 1H), 2.36 (s, 1H), 2.01–1.90 (m, 1H), 1.86–1.74 (m, 1H), 1.69–1.50 (m, 5H), 1.40 (tt, *J* = 9.1, 2.8

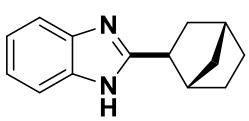
Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 164.1, 106.6, 44.5, 42.5, 37.1, 34.6, 34.2, 32.8, 28.1, 27.8, 26.9. FT-IR (neat) cm^{-1} 2928, 2851. HRMS [ESI] $C_{14}H_{21}NS$ calcd. $[M+H]^+$ 236.1467 observed 236.1460. Stereochemistry is assigned analogy to literature.[9]

18r 2-(((1S,4R)-3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)thiazole



The **general procedure F** was followed using 2-bromothiazole (288 mg, 1.8 mmol) camphene (24 mg , 0.18 mmol), tributylamine (400 mg, 2.2 mmol), formic acid (101 mg, 2.2 mmol), and 0.72 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18r** in 85% yield (34 mg, 0.15 mmol), rr>20:1 (based on crude ^{1}H NMR), 4:1 [(reduced:oxidized), based on crude ^{1}H NMR], dr 5:1 (based on crude ^{1}H NMR) and isolated as mixture of diastereomers with dr 7:1 and 7:1 (reduced : oxidized) mixture, as a pale oil. After the completion of the reaction, 20 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 8% on a 24 g silica column. ^{1}H NMR [mix of diastereomers and oxidized product] (400 MHz,$CDCl_3$) δ 7.65 (d, J = 3.3 Hz, 1H), 7.16 (d, J = 3.3 Hz, 1H), 3.08–2.92 (m, 2H), 2.07 (s, 1H), 2.01–1.91 (m, 1H), 1.78 (s, 1H), 1.63 (t, J = 9.8 Hz, 1H), 1.54–1.44 (m, 1H), 1.33–1.26 (m, 2H), 1.15 (dd, J = 13.2, 7.0 Hz, 2H), 1.00 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 142.0, 117.8, 51.1, 49.2, 41.2, 37.4, 36.9, 32.2, 30.8, 24.6, 21.6, 20.3. FT-IR (neat) cm^{-1} 2904, 2872, 1460. HRMS [ESI] $C_{13}H_{19}NS$ calcd. $[M+H]^+$ 222.1311 observed 222.1318. Diastereoselectivity is based on detailed analysis of coupling constants. **Note** – The diastereomer and oxidized product is marked in the ^{1}H NMR and ^{13}C NMR spectra as ◯ and ▢

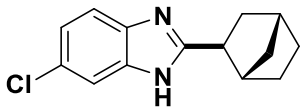
18s 2-(bicyclo[2.2.1]heptan-2-ylmethyl)-1H-benzo[d]imidazole



The **general procedure E** was followed using 2-bromo-1H-benzo[d]imidazole (25 mg, 0.13 mmol), norbornene (60 mg, 0.63 mmol), tributylamine (70 mg, 0.38 mmol), formic acid (17.3 mg, 0.38 mmol), and 0.50 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18s** in 90% yield (25 mg, 0.12 mmol), rr>20:1 (based on crude ^{1}H NMR), dr>20:1 (based on crude

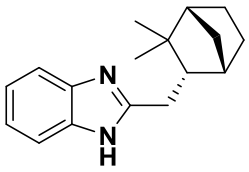
^{1}H NMR) as white solid, m.pt 242–245 ^{o}C. After the completion of the reaction, 24 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexane before running) (0% to 100%) with product eluting at 12% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.2, 3.0 Hz, 2H), 7.21 (dd, J = 5.8, 3.0 Hz, 2H), 2.99 (dd, J = 8.7, 5.2 Hz, 1H), 2.65–2.59 (m, 1H), 2.41 (s, 1H), 2.24–2.13 (s, 1H), 1.79 (ddd, J = 12.3, 9.2, 2.5 Hz, 1H), 1.69–1.54 (m, 3H), 1.42–1.27 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 137.9, 122.3, 114.6, 42.7, 41.9, 36.6, 36.3, 36.2, 29.7, 28.7. FT-IR (neat) cm^{-1} 2931, 2830, HRMS[ESI] calcd. $C_{14}H_{16}N_2$ $[M+H]^+$ 213.1387 observed 213.1379. Stereochemistry is assigned based on **18p**.

18t 2-(bicyclo[2.2.1]heptan-2-ylmethyl)-6-chloro-1H-benzo[d]imidazole



The **general procedure E** was followed using 2-bromo-6-chloro-1H-benzo[d]imidazole (25 mg, 0.11 mmol), norbornene (51 mg, 0.54 mmol), tributylamine (60 mg, 0.32 mmol), formic acid (15 mg, 0.32 mmol), and 0.45 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18t** in 79% yield (21 mg, 0.087 mmol), dr >20:1 (based on crude ^{1}H NMR) as white solid. m.pt. 223 - 225 ^{o}C. After the completion of the reaction, 24 h, thesubstrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexane before running) (0% to 100%) with product eluting at 12% on a 24 g silica column. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (s, 1H), 7.40 (d, J = 11.0 Hz, 1H), 7.12 (dd, J = 8.6, 2.0 Hz, 1H), 3.29 (p, J = 1.7 Hz, 1H), 2.94 (ddd, J = 8.8, 5.8, 2.9 Hz, 1H), 2.52 (dd, J = 4.0, 1.7 Hz, 1H), 2.37 (d, J = 4.2 Hz, 1H), 2.09–2.00 (m, 1H), 1.75 (ddd, J = 12.1, 9.1, 2.4 Hz, 1H), 1.69–1.60 (m, 1H), 1.60–1.54 (m, 1H), 1.46–1.38 (m, 1H), 1.34–1.21 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 162.0, 128.5, 123.4, 79.6, 79.6, 79.3, 78.9, 43.9, 43.1, 37.6, 37.2, 36.9, 30.7, 29.7. FT-IR (neat) cm^{-1} 2931, 2858, 780. HRMS [ESI] calcd. $C_{14}H_{15}ClN_2$ $[M+H]^+$ 247.0997 observed 247.0994. Stereochemistry is assigned based on **18s**.

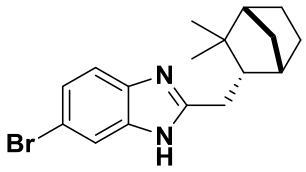
18u 2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole



The **general procedure E** was followed using 2-bromo-1H-benzo[d]imidazole (25 mg, 0.13 mmol), (+)-camphene (86 mg, 0.63 mmol), tributylamine (70 mg, 0.38 mmol), formic acid (17.3 mg, 0.38 mmol), and 0.52 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18u** in 93% yield (31 mg, 0.12 mmol), rr >20:1 (based on crude ^{1}H NMR), dr>20:1 (based on crude ^{1}H NMR) as white solid, m.pt 197–200 ^{o}C. After the completion of the reaction, 24 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexane before running) (0% to 100%) with product eluting at 17% on a 24 g silica column. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.47 (dd, *J*=5.9, 3.2 Hz, 1H), 7.16 (dd, *J*=6.0, 3.2 Hz, 1H), 3.30 (dt, *J*=3.0, 1.5 Hz, 0H), 2.94–2.77 (m, 1H), 2.09 (ddd, *J* = 10.2, 6.5, 3.6 Hz, 1H), 1.78 (s, 0H), 1.75–1.56 (m, 2H), 1.36–1.24 (m, 2H), 1.18 (d, *J*=9.6 Hz, 1H), 1.01 (s, 1H), 0.91 (s, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.5, 138.0, 121.7, 113.8, 49.5, 49.1, 41.4, 36.8, 36.4, 31.1, 25.8, 24.2, 20.6, 19.7. FT-IR (neat) cm^{-1} 3086, 2964, 1635, 1591. HRMS [ESI] calcd. $C_{17}H_{22}N_2$ $[M+H]^+$ 255.1856 observed 255.1849. Diastereoselectivity is based on detailed analysis of coupling constants.

18v 6-bromo-2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole

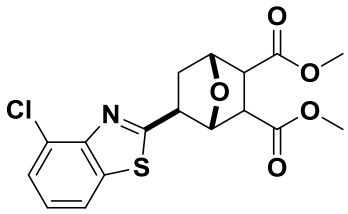
The **general procedure E** was followed using 2,6-dibromo-1H-benzo[d]imidazole (25 mg, 0.10 mmol),



(+)-camphene (61 mg, 0.45 mmol), tributylamine (50 mg, 0.27 mmol), formic acid (13 mg, 0.27 mmol), and 0.36 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18v** in 87% yield (29 mg, 0.087 mmol), rr>20:1 (based on crude ^{1}H NMR), dr>20:1 (based on crude ^{1}H NMR) as white solid. m.pt 200–203 ^{o}C. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 1% Et_3N in hexanes before running) (0% to 100%) with product eluting at 12% on a 4 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.5, 1.9 Hz, 1H), 2.90 (dd, J = 7.8, 4.9 Hz, 2H), 2.05 (dt, J = 10.6, 3.0 Hz, 2H), 1.74 (s, 1H), 1.52 (t, J = 9.6 Hz, 2H), 1.42 (t, J = 8.2 Hz, 1H), 1.29–1.19 (m, 2H), 1.13 (d, J = 9.7 Hz, 1H), 0.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 140.1, 137.4, 125.2, 117.6, 115.8, 115.1, 49.7, 48.8, 41.3, 37.2,

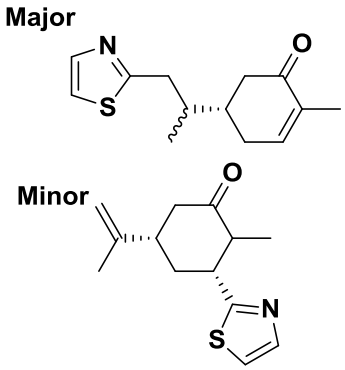
36.9, 31.9, 26.7, 24.6, 21.6, 20.2. FT-IR (neat) cm^{-1} 3021, 2954, 1625, 1596, 650. HRMS [ESI] calcd. $C_{17}H_{21}BrN_2$ $[M+H]^+$ 333.0962 observed 333.0961. Diastereoselectivity is based on detailed analysis of coupling constants.

18w dimethyl 5-(4-chlorobenzo[d]thiazol-2-yl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



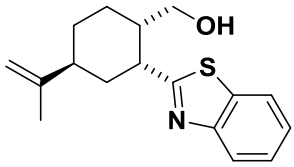
The **general procedure E** was followed using 2-bromo-4-chlorobenzo[d]thiazole (25 mg, 0.10 mmol), dimethyl 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (106 mg, 0.51 mmol), tributylamine (56 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18w** in 53% yield (19 mg, 0.053 mmol), rr >20:1 (based on crude ^1H NMR), dr>20:1 (based on crude ^1H NMR) as an oil. After the completion of the reaction, 14 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 17% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 5.12 (d, J = 5.4 Hz, 1H), 5.10 (s, 1H), 3.77 (dd, J = 8.8, 4.5 Hz, 1H), 3.70 (d, J = 8.7 Hz, 6H), 3.18 (q, J = 9.6 Hz, 2H), 2.29 (dd, J = 13.2, 8.8 Hz, 1H), 2.17 (dq, J = 15.0, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 170.9, 170.6, 149.2, 136.9, 127.5, 126.4, 125.6, 120.3, 83.3, 78.5, 52.4, 52.3, 51.8, 51.3, 47.8, 39.5. FT-IR (neat) cm^{-1} 2946, 1742, 1200, 1163. HRMS [ESI] calcd. $C_{17}H_{16}ClNO_5S$ $[M+H]^+$ 382.0510 observed 382.0506. Stereochemistry is assigned based on **18s**.

18x **Major** - (S)-2-methyl-5-(1-(thiazol-2-yl)propan-2-yl)cyclohex-2-en-1-one and **Minor** - (5R)-2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one (minor)



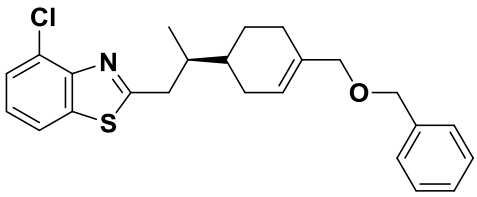
The **general procedure E** was followed using 2-bromothiazole (25 mg, 0.15 mmol), 2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one (110 mg, 0.76 mmol), tributylamine (85 mg, 0.46 mmol), formic acid (21 mg, 0.46 mmol), and 0.65 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18x** in 78% yield [28 mg (20 mg (major also contains small amount of minor) and 8 mg (minor, mix of diastereomers), 0.12 mmol], rr 2:1 (major : minor) (based on crude ^{1}H NMR), dr (major) 1.2:1 (based on crude ^{1}H NMR). After the completion of the reaction, 19 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with minor product eluting at 12% and major product eluting at 17% on a 24 g silica column. **Major isomer**-^{1}H NMR, [mix. of diastereomers and minor isomer] (400 MHz, $CDCl_3$) δ 7.67 (t, J = 3.0 Hz, 1H), 7.19 (t, J = 3.1 Hz, 1H), 6.73 (dq, J = 5.8, 1.7 Hz, 1H), 3.10 (ddd, J = 14.4, 9.2, 5.2 Hz, 1H), 2.86 (dt, J = 14.5, 8.3 Hz, 1H), 2.59–2.47 (m, 1H), 2.45–2.33 (m, 1H), 2.30–2.16 (m, 2H), 2.15–2.00 (m, 2H), 1.75 (dd, J = 2.6, 1.3 Hz, 3H), 0.94 (dd, J = 6.5, 2.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 199.7, 144.7, 144.6, 142.2, 142.2, 135.3, 135.3, 118.1, 118.1, 117.8, 113.5, 42.2, 40.5, 39.6, 39.4, 38.1, 37.9, 37.3, 37.2, 30.2, 28.0, 15.7, 15.6, 15.5, 15.5. **Note** - The diastereomer and regioisomer are marked as ● in spectra. **Minor Isomer** -^{1}H NMR, [mixture of diastereomers] (400 MHz, $CDCl_3$) δ 7.70 (d, J = 3.4 Hz, 1H), 7.18 (d, J = 3.3 Hz, 1H), 4.74 (d, J = 21.5 Hz, 2H), 3.91 (dt, J = 6.0, 4.0 Hz, 1H), 2.80–2.72 (m, 1H), 2.68 (ddd, J = 14.4, 4.1, 1.2 Hz, 1H), 2.51–2.42 (m, 1H), 2.37–2.27 (m, 1H), 2.18–2.11 (m, 2H), 1.70 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3, 169.6, 147.2, 142.8, 117.9, 110.2, 47.3, 45.5, 40.3, 35.8, 29.4, 22.7, 14.1. **Note** - The diastereomer is marked as ● in spectra. FT-IR (neat) cm^{-1} 2962, 1706, 1666, 1655. HRMS [ESI] calcd. $C_{13}H_{17}NOS$ $[M+H]^+$ 236.1104 observed 236.1102.

18y ((1S,2R,4S)-2-(benzo[d]thiazol-2-yl)-4-(prop-1-en-2-yl)cyclohexyl)methanol



The **general procedure E** was followed using 2-benzobromothiazole (25 mg, 0.12 mmol), (4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methanol (89 mg, 0.58 mmol), tributylamine (65 mg, 0.35 mmol), formic acid (16 mg, and 0.50 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **18y** in 82% yield (28 mg, 0.097 mmol), rr 9:1 (based on crude ^{1}H NMR), dr 7:1 (based on crude ^{1}H NMR) and isolated as dr 8.1:1 (mixture) as pale oil. After the completion of the reaction, 21 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 8% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 4.75 (s, 2H), 3.88 (s, 1H), 3.73–3.61 (m, 1H), 3.56–3.41 (m, 1H), 2.47 (t, J = 12.3 Hz, 1H), 2.29 (d, J = 14.0 Hz, 1H), 2.17–2.02 (m, 1H), 1.92 (d, J = 12.7 Hz, 1H), 1.83 (td, J = 13.5, 4.9 Hz, 1H), 1.76 (s, 3H), 1.61 (q, J = 14.1, 13.1 Hz, 2H), 1.45–1.30 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 152.0, 149.5, 134.5, 126.1, 125.0, 122.6, 121.4, 109.0, 65.2, 43.3, 41.9, 40.4, 36.5, 31.0, 24.6, 21.0. FT-IR (neat) 3435, 2985, 2854cm^{-1}. HRMS [ESI] $C_{17}H_{21}NOS$ calcd. $[M+H]^+$ 288.1417 observed 288.1414. Diastereoselectivity is based on detailed analysis of coupling constants.

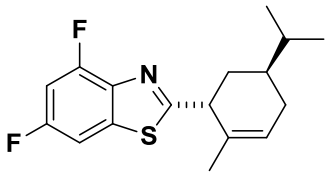
18z 2-(2-(4-((benzyloxy)methyl)cyclohex-3-en-1-yl)propyl)-4-chlorobenzo[d]thiazole



The **general procedure E** was followed using 2-bromo-4-chloro-1H-benzo[d]thiazole (25 mg, 0.10 mmol), (4-(prop-1-en-2-yl)cyclohex-1-en-yl)methoxy)methyl)benzene (120 mg, 0.51 mmol), tributylamine (56 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN solution was used to afford **18z** in 80% yield (33 mg, 0.08 mmol), rr >20:1 (based on crude ^{1}H NMR), dr 4:1 (based on crude ^{1}H NMR) and isolated dr 5:1 (mixture) as an oil. After the completion of the reaction, 17 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) [mix of diastereomers] δ 7.96 (d, J = 8.1 Hz, 1H), 7.86 (d,

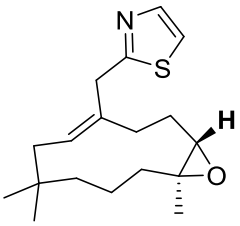
J = 7.9 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 4.75 (s, 2H), 3.88 (s, 1H), 3.73–3.61 (m, 1H), 3.56–3.41 (m, 1H), 2.47 (t, J = 12.3 Hz, 1H), 2.29 (d, J = 14.0 Hz, 1H), 2.17–2.02 (m, 1H), 1.92 (d, J = 12.7 Hz, 1H), 1.83 (td, J = 13.5, 4.9 Hz, 1H), 1.76 (s, 3H), 1.61 (q, J = 14.1, 13.1 Hz, 2H), 1.45–1.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 152.0, 149.5, 134.5, 126.1, 125.0, 122.6, 121.4, 109.0, 65.2, 43.3, 41.9, 40.4, 36.5, 31.0, 24.6, 21.0. FT-IR (neat) cm^{-1}. HRMS [ESI] $C_{24}H_{26}NClOS$ calcd. $[M+H]^+$ 412.1496 observed 412.1492. The diastereomer is marked as ● in spectra.

19a 4,6-difluoro-2-(5-isopropyl-2-methylcyclohex-2-en-1-yl)benzo[d]thiazole



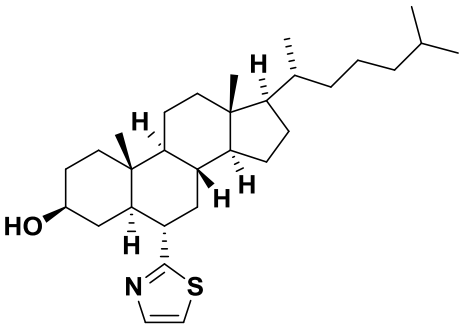
The **general procedure E** was followed using 2-bromo-4,6-difluorobenzo[d]thiazole (25 mg, 0.10 mmol), alpha-pinene (68 mg, 0.50 mmol), tributylamine (56 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **19a** in 68% yield (21 mg, 0.068 mmol), rr >20:1 (isolated) as yellow oil. After the completion of the reaction, 16 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 4% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 9.7 Hz, 1H), 5.76 (s, 1H), 3.89 (d, J = 6.1 Hz, 1H), 2.21 (d, J = 17.8 Hz, 2H), 2.08 (d, J = 13.1 Hz, 1H), 1.73 (s, 3H), 1.57 (s, 2H), 1.44 (dt, J = 12.7, 6.4 Hz, 1H), 0.84 (dd, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (d, J = 3.0 Hz), 159.6 (dd, J = 246.8, 10.4 Hz), 154.7 (dd, J = 258.7, 13.4 Hz),138.8 (dd, J = 13.2, 2.5 Hz), 138.1 (dd, J = 12.6, 5.1 Hz), 132.0, 126.6 103.3 (dd, J = 26.2, 4.7 Hz), 101.5 (dd, J = 28.3, 21.9 Hz).45.0, 34.7, 33.2, 31.9, 28.6, 22.4, 19.7, 19.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.6 (dd, *J* = 7.9 Hz), -117.8–-118.3 (m). FT-IR (neat) cm^{-1} 2956, 1617, 1585. HRMS [ESI] $C_{17}H_{19}F_2NS$ calcd $[M+H]^+$ 308.1279 observed 308.1278. $[\alpha]_D^{20}$ = +87.17 (c 0.016, $CHCl_3$).

19b 2-(((1S,11S,Z)-7,7,11-trimethyl-12-oxabicyclo[9.1.0]dodec-4-en-4-yl)methyl)thiazole



The **general procedure E** was followed using 2-bromothiazole (25 mg, 0.15 mmol) (-) caryophylleneoxide (170 mg, 0.76 mmol), tributylamine (85 mg, 0.46 mmol), formic acid (21 mg, 0.46 mmol), and 0.65 mL of stock solution of $Ir(ppy)_3$ in MeCN solution was used to afford **19b** in 71% yield (32 mg, 0.106 mmol) rr >20:1 (based on crude ^1H NMR), Z:E>20:1 as colorless oil. After the completion of the reaction, 19 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 14% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 3.3 Hz, 1H), 7.19 (d, J = 3.3 Hz, 1H), 5.49 (dd, J = 11.1, 2.6 Hz, 1H), 3.93 (d, J = 15.1 Hz, 1H), 3.52 (d, J = 15.2 Hz, 1H), 2.82 (dd, J = 11.1, 1.8 Hz, 1H), 2.50–2.38 (m, 1H), 2.36–2.21 (m, 2H), 2.18–1.97 (m, 2H), 1.83 (dt, J = 15.2, 2.7 Hz, 1H), 1.66–1.39 (m, 4H), 1.27 (s, 3H), 1.23 (d, J = 2.7 Hz, 1H), 1.12 (dd, J = 10.9, 7.2 Hz, 1H), 0.98 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 142.9, 134.8, 128.4, 119.2, 63.2, 63.1, 41.3, 38.9, 38.0, 35.5, 33.6, 33.5, 30.0, 28.7, 24.8, 19.0, 18.4. FT-IR (neat) cm^{-1} 2952, 1595, 850. HRMS [ESI] $C_{18}H_{27}NOS$ calcd $[M+H]^+$ 306.1886 observed 306.1877. $[\alpha]^D_{20}$ = -490.7 (c 0.013, $CHCl_3$). Stereochemistry is assigned based on NOE, HSQC and COSY.

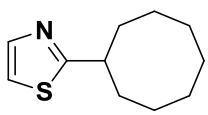
20a(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-6-(thiazol-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



The **general procedure F** was followed using 2-bromothiazole (110 mg, 0.65 mmol) cholesterol (25 mg, 0.064 mmol), tributylamine (140 mg, 0.77 mmol), formic acid (35 mg, 0.77 mmol), $Ir(ppy)_3$ (0.006 equiv, 0.64 mL of 0.6 mM stock solution of catalyst in MeCN, where 0.64 mL of MeCN is used to make 0.1 M with respect to cholesterol) was used to afford **20a** in 65% yield (19 mg, 0.042 mmol). After the completion of the reaction, 24 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 60% on a 12 g silica column as yellow oil. (**Note** – reaction went only up to 80% conversion with respect to cholesterol) rr

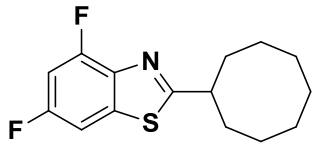
>20:1 (based on crude ^{1}H NMR) dr> 20:1 (based on crude ^{1}H NMR). ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.66 (d, J = 3.3 Hz, 1H), 7.17 (d, J = 3.3 Hz, 1H), 3.63 (tt, J = 11.0, 4.6 Hz, 1H), 3.26–3.19 (m, 1H), 2.34 (ddd, J = 13.8, 3.5, 1.8 Hz, 1H), 2.16–2.05 (m, 2H), 1.98 (ddt, J = 12.6, 5.2, 2.7 Hz, 2H), 1.89–1.82 (m, 1H), 1.82–1.75 (m, 1H), 1.72–1.62 (m, 3H), 1.57–1.47 (m, 3H), 1.45–1.37 (m, 2H), 1.34 (dd, J = 7.4, 4.0 Hz, 2H), 1.33–1.28 (m, 3H), 1.27–1.23 (m, 2H), 1.18–1.12 (m, 3H), 1.11–1.05 (m, 2H), 1.03–0.95 (m, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 2.8 Hz, 3H), 0.86 (d, J = 2.8 Hz, 3H), 0.71 (s, 3H), 0.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 141.5, 117.2, 71.9, 56.3, 56.1, 55.2, 47.6, 42.6, 42.5, 39.8, 39.4, 38.7, 37.9, 36.7, 36.0, 36.0, 35.7, 32.1, 31.3, 28.1, 27.8, 24.0, 23.7, 22.6, 22.4, 21.0, 18.5, 14.5, 12.1. FT-IR (neat) cm^{-1} 3465, 2933, 1680. HRMS [ESI] $C_{30}H_{49}NOS$ calcd $[M+H]^+$ 472.3607 observed 472.3608. $[\alpha]_D^{20}$ = + 5.54 (c 0.011, $CHCl_3$). Diastereoselectivity is based on detailed analysis of coupling constants.

22a 2-cyclooctylthiazole



The **general procedure E** was followed using 2-bromothiazole (25 mg, 0.15 mmol) cis-cyclooctene (84 mg, 0.75 mmol), tributylamine (85 mg, 0.46 mmol), formic acid (21 mg, 0.46 mmol), and 0.65 mL of stock solution of $Ir(ppy)_3$ in MeCN solution was used to afford **20a** in 23% yield (7 mg, 0.035 mmol) as yellow oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 7% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 3.3 Hz, 1H), 7.16 (d, J = 3.3 Hz, 1H), 3.37–3.22 (m, 1H), 2.16–2.03 (m, 2H), 1.96–1.84 (m, 2H), 1.83–1.70 (m, 2H), 1.66–1.57 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 141.8, 117.3, 42.7, 32.9, 27.1, 26.0, 25.3. FT-IR (neat) cm^{-1} 2872, 2920. HRMS [ESI] $C_{11}H_{17}NS$ calcd. $[M+H]^+$ 196.1154 observed 196.1150.

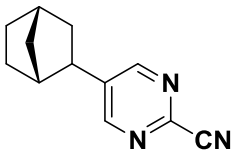
24a 2-cyclooctyl-4,6-difluorobenzo[d]thiazole



The **general procedure G** was followed using 2-bromo-4,6-difluorobenzo[d]thiazole (25 mg, 0.10 mmol), cyclooctene (55 mg, 0.50 mmol), *N*, *N*-diisopropyloctan-1-amine (55 mg, 0.30 mmol), formic acid (14 mg, 0.30 mmol), and 0.40 mL

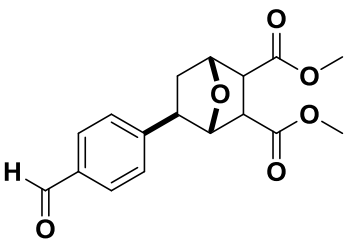
of stock solution of **cat-1** in MeCN was used to afford **24a** in 73% yield (20 mg, 0.073 mmol) as yellow oil. After the completion of the reaction, 48 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 3% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, J = 19.8, 7.9 Hz, 1H), 6.47 (qd, J = 10.4, 2.5 Hz, 1H), 4.11–3.88 (m, 1H), 2.64 (ddt, J = 85.9, 7.8, 3.3 Hz, 2H), 2.27–2.06 (m, 2H), 1.90–1.75 (m, 2H), 1.77–1.65 (m, 1H), 1.66–1.48 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (ddd, *J* = 241.0, 23.8, 10.7 Hz), 148.7 (dt, *J* = 244.1, 12.6 Hz), 133.8–127.8 (m), 104.7 (ddd, *J* = 26.3, 12.6, 3.5 Hz), 99.9 (ddd, *J* = 27.2, 22.6, 2.5 Hz), 94.1, 92.7, 48.7, 48.4, 31.6, 31.2, 28.7, 28.1, 24.9, 24.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.7 (dt, *J* = 30.0, 8.6 Hz), -128.6 (dd, *J* = 188.2, 10.2 Hz). FT-IR (neat) cm^{-1} 3025, 2927, 2852, 1612, 1438, 1385. HRMS [ESI] $C_{15}H_{17}F_2NS$ calcd $[M+NH_4]^+$ 299.1388 observed 299.1387.

25a 5-((1R,4S)-bicyclo[2.2.1]heptan-2-yl)pyrimidine-2-carbonitrile



The **general procedure H** was followed using 5-bromopyrimidine-2-carbonitrile (25 mg, 0.14 mmol), norbornene (64 mg, 0.68 mmol), *N*, *N*-diisopropylethylamine (21 mg, 0.30 mmol), and 0.56 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **25a** in 71% yield (21 mg, 0.10 mmol), dr > 20:1 (based on crude ^{1}H NMR) as an oil. After the completion of the reaction, 48 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 6% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 2H), 2.81 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.48 (t, *J* = 4.1 Hz, 1H), 2.43 (dd, *J* = 3.9, 1.6 Hz, 1H), 1.90 (ddd, *J* = 11.7, 8.9, 2.2 Hz, 1H), 1.75–1.57 (m, 3H), 1.48–1.38 (m, 2H), 1.37–1.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 143.0, 142.6, 115.8, 43.2, 37.0, 36.3, 30.3, 28.5. FT-IR (neat) cm^{-1} 1400, 2225, 2800, 2950.

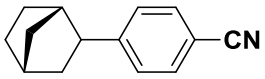
25b dimethyl (1R,4S,5R)-5-(4-formylphenyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



The **general procedure H** was followed using 4-bromobenzaldehyde (50 mg, 0.27 mmol), dimethyl (1R,4S)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (180 mg, 0.85 mmol), *N*, *N*-diisopropylethylamine (70 mg, 0.54 mmol), and 1.35 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **25b** in 55% yield (47 mg, 0.149 mmol), dr > 20:1 (based on crude ^1H NMR) as an oil. After the completion of the reaction, 72 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (column was buffered with 0.5% Et_3N in hexanes before running) (0% to 100%) with product eluting at 32% on a 4 g silica column.. ^1H NMR (400 MHz, Acetone-d_6) δ 10.00 (s, 1H), 7.91–7.79 (m, 2H), 7.57–7.47 (m, 2H), 4.99 (d, *J* = 5.3 Hz, 1H), 4.71 (s, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.36–3.24 (m, 3H), 2.32 (dd, *J* = 12.6, 8.9 Hz, 1H), 1.81 (dt, *J* = 12.6, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 368.9, 348.4, 348.2, 330.1, 312.5, 306.9, 305.3, 261.5, 255.8, 229.0, 228.6, 228.4, 224.7, 217.4. FT-IR (neat) cm^{-1} 2725, 2820, 1720, 1679, 1133.

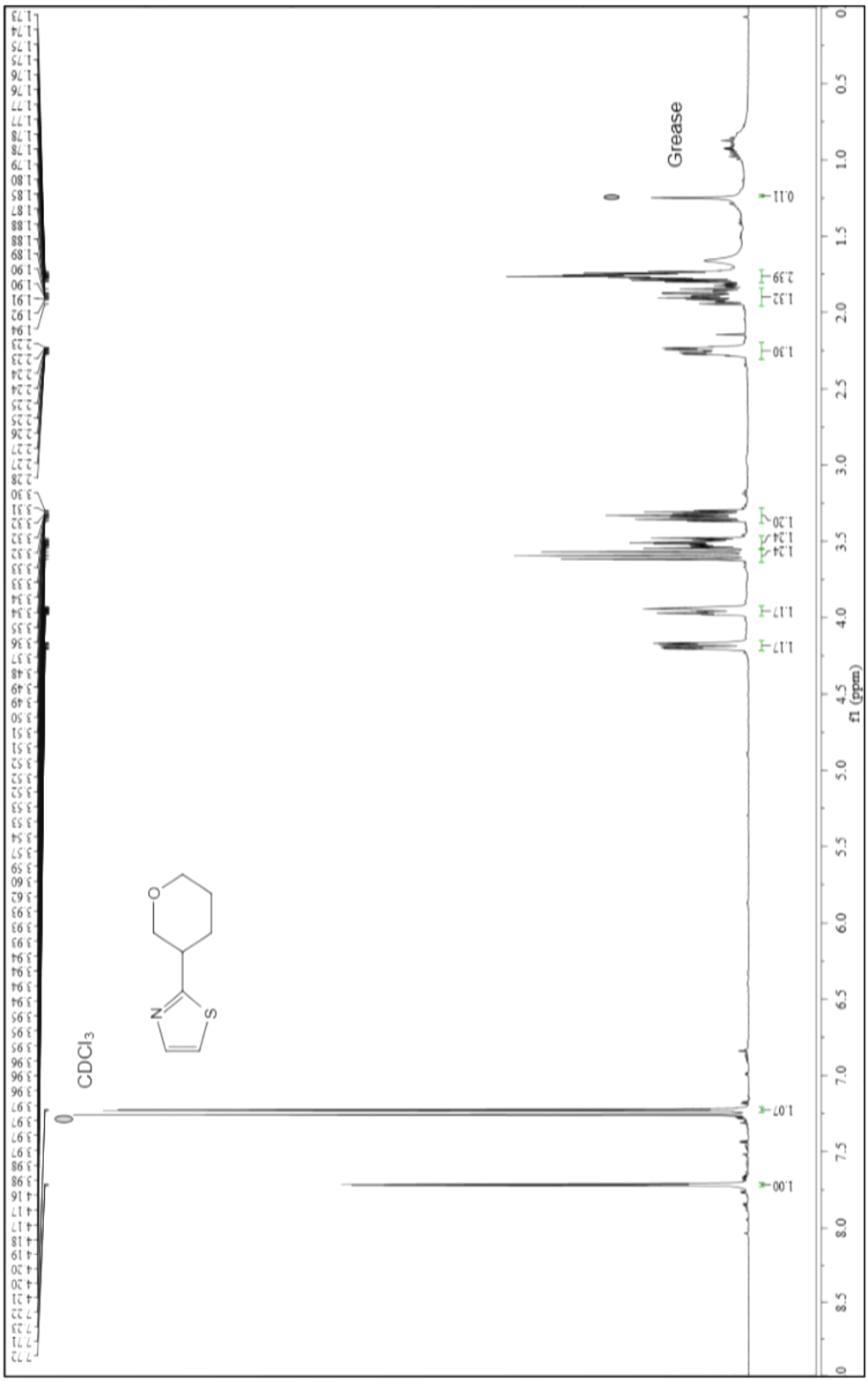
25c 4-((1S,4R)-bicyclo[2.2.1]heptan-2-yl)benzonitrile

The **general procedure H** was followed using 4-bromobenzonitrile (75 mg, 0.41 mmol), norbornene (193

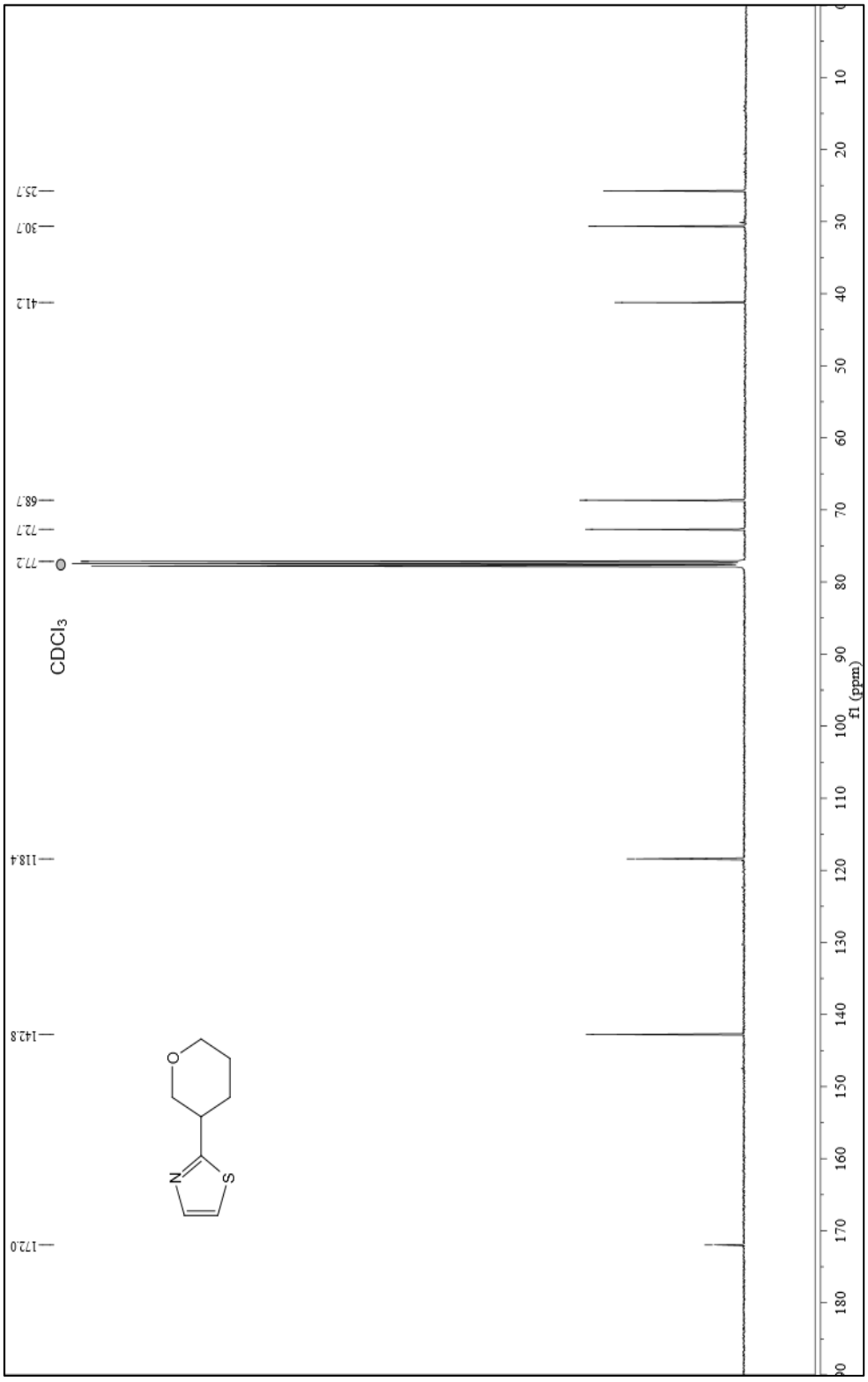


mg, 2.1 mmol)), *N*, *N*-diisopropylethylamine (106 mg, 0.82 mmol), and 1.7 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **25c** in 47% yield (38 mg, 0.19 mmol), dr>20:1 as an oil. After the completion of the reaction, 72 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 5% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 2.78 (t, J = 6.8 Hz, 1H), 2.38 (s, 2H), 1.82 (t, J = 10.8 Hz, 1H), 1.66–1.53 (m, 3H), 1.47 (d, J = 9.9 Hz, 1H), 1.37 (t, J = 9.0 Hz, 1H), 1.30 (d, J = 8.7 Hz, 1H), 1.23 (d, J = 10.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 132.2, 128.0, 119.4, 109.3, 47.7, 42.7, 39.3, 37.0, 36.3, 30.6, 28.9. FT-IR (neat) cm^{-1} 2949, 2874, 2226, 1608.

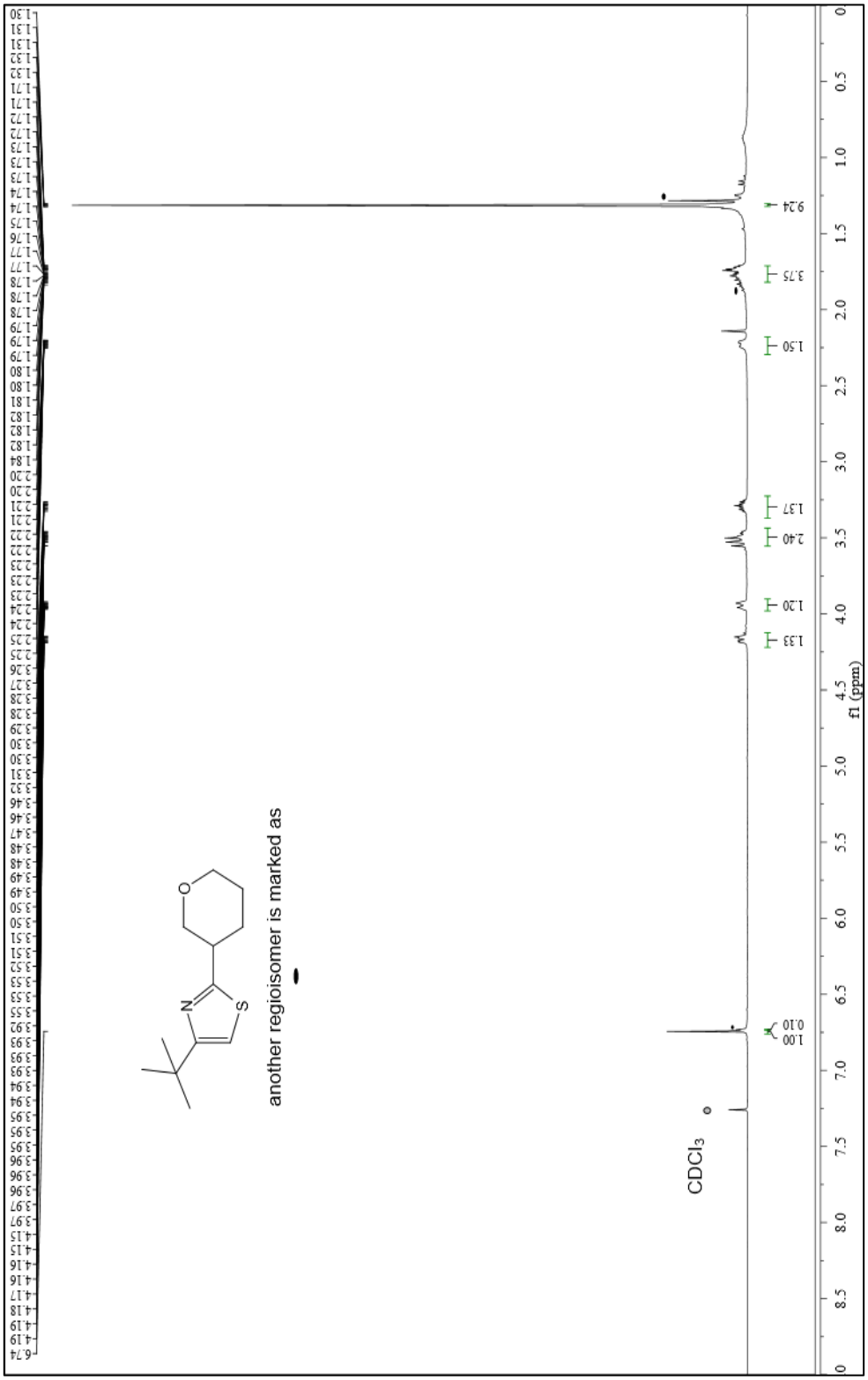
^{1}H NMR (400 MHz, $CDCl_3$) of **18a** - 2-(tetrahydro-2H-pyran-3-yl)thiazole



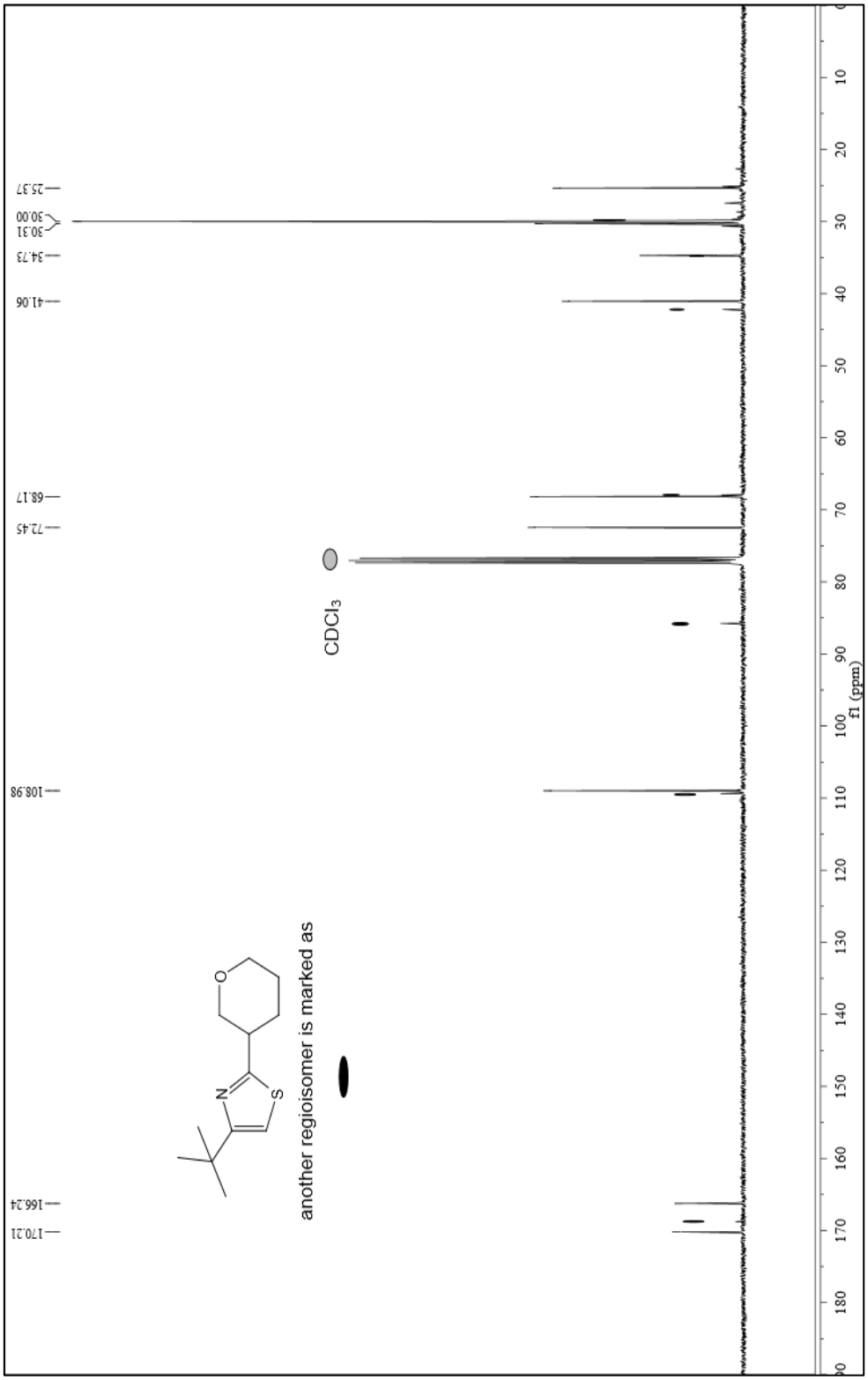
^{13}C NMR (101 MHz, $CDCl_3$) of **18a**-2-(tetrahydro-2H-pyran-3-yl)thiazole



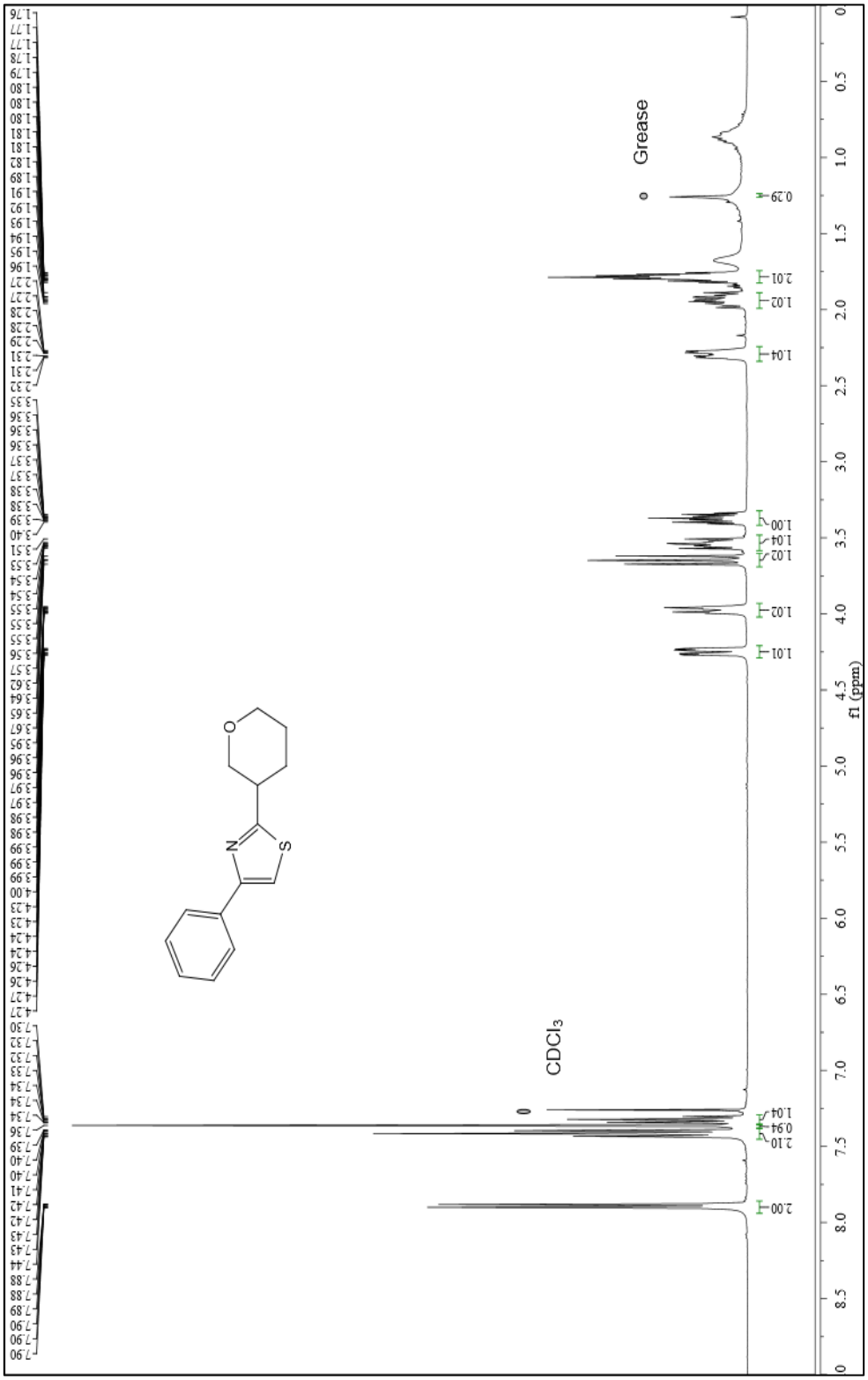
^{1}H NMR (400 MHz, $CDCl_3$) of **18b** 4-(tert-butyl)-2-(tetrahydro-2H-pyran-3-yl)thiazole



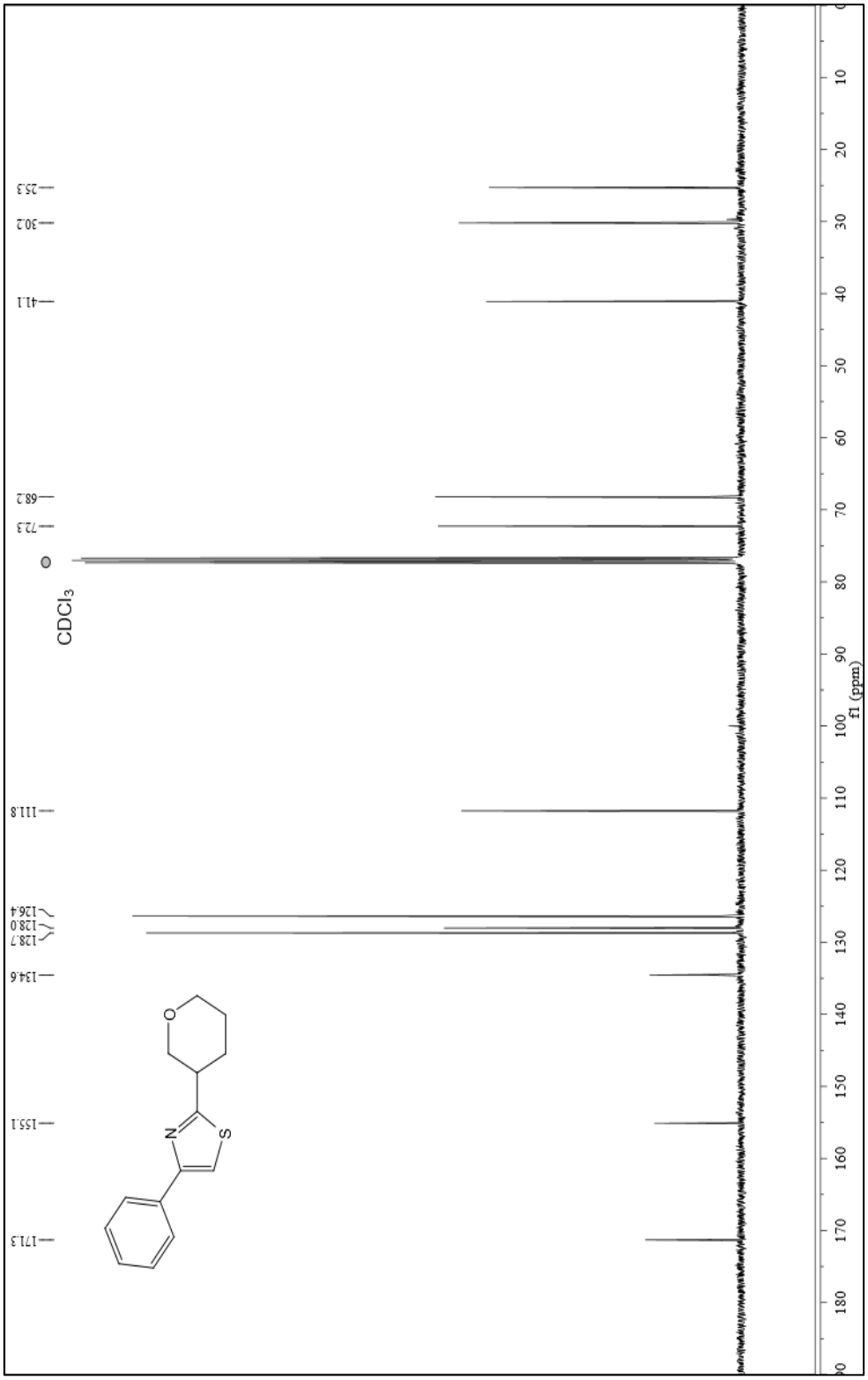
^{13}C NMR(101 MHz, $CDCl_3$) of **18b** 4-(tert-butyl)-2-(tetrahydro-2H-pyran-3-yl)thiazole



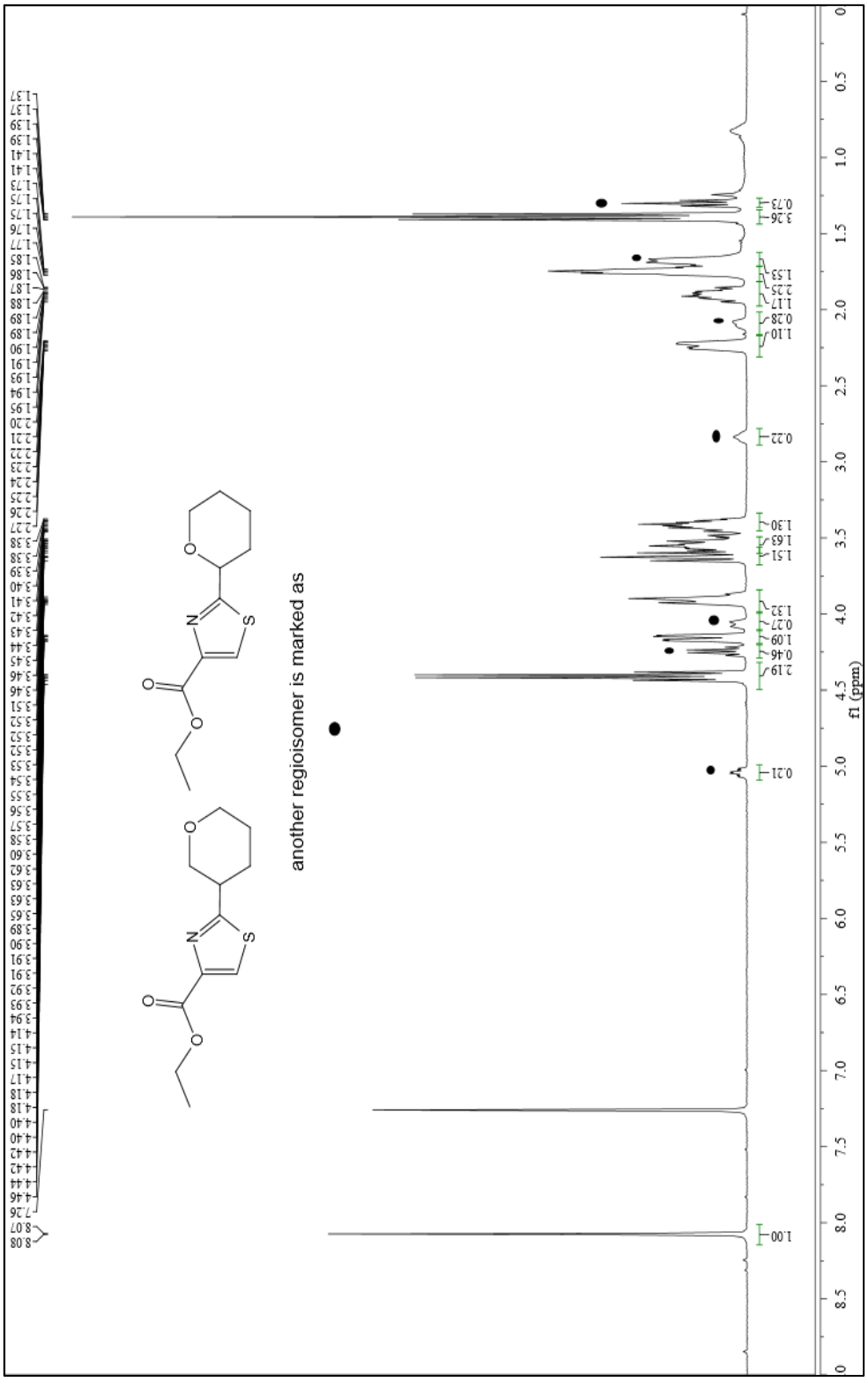
^{1}H NMR(400 MHz, $CDCl_3$) of **18c** 4-phenyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



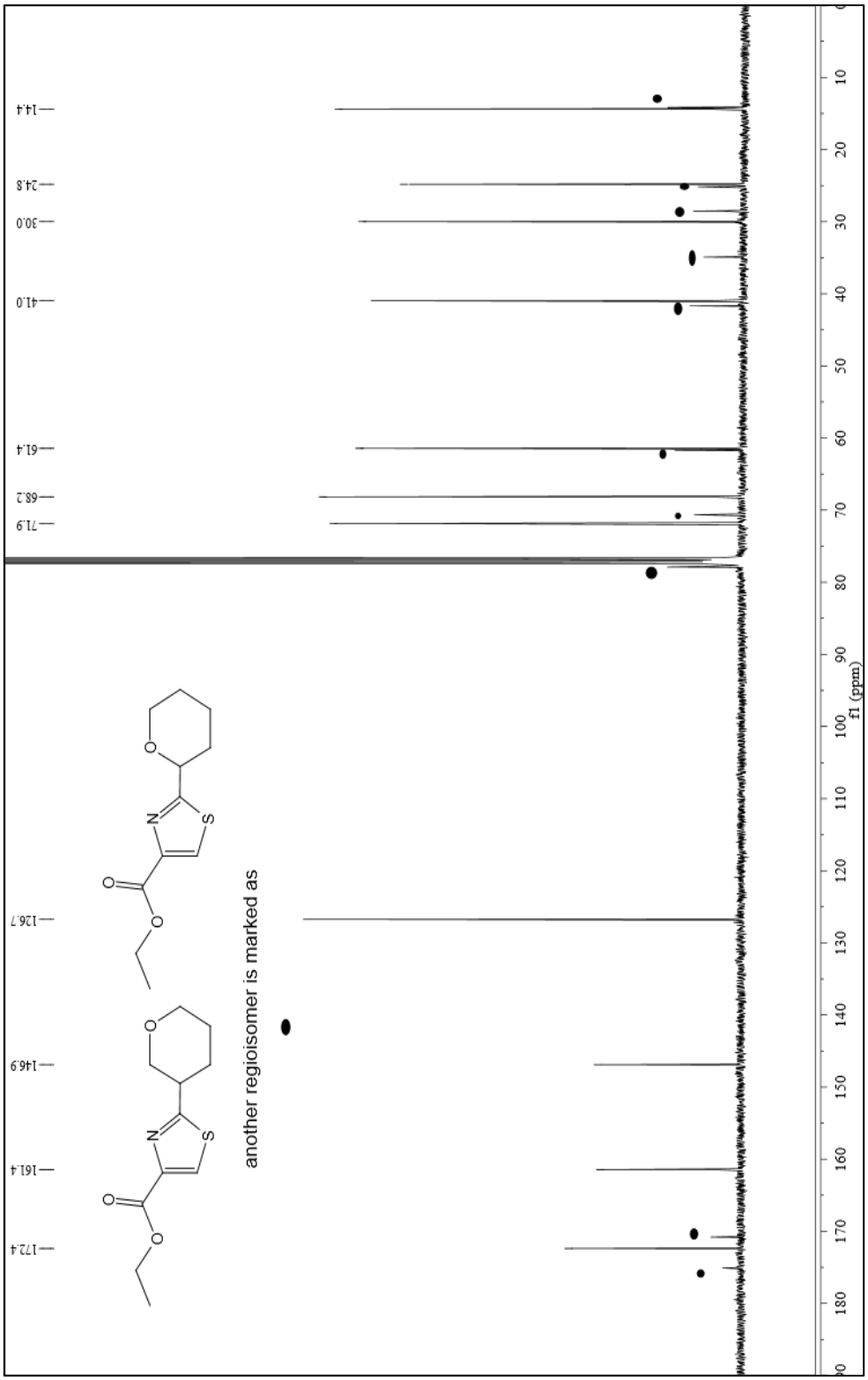
^{13}C NMR (101 MHz, $CDCl_3$) of **18c** 4-phenyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



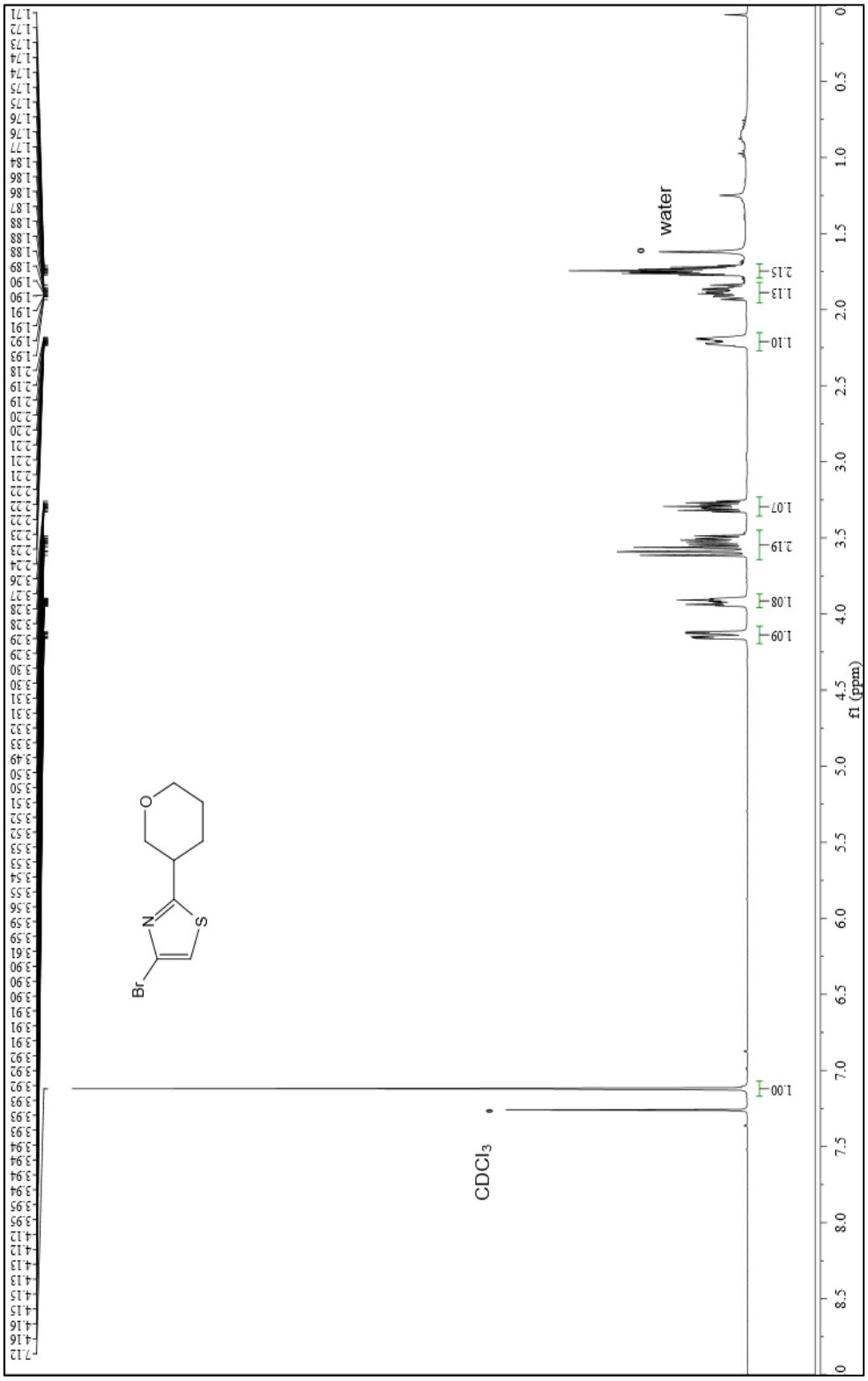
^{1}H NMR (400 MHz, $CDCl_3$) of **18d** ethyl 2-(tetrahydro-2H-pyran-3-yl)thiazole-4-carboxylate



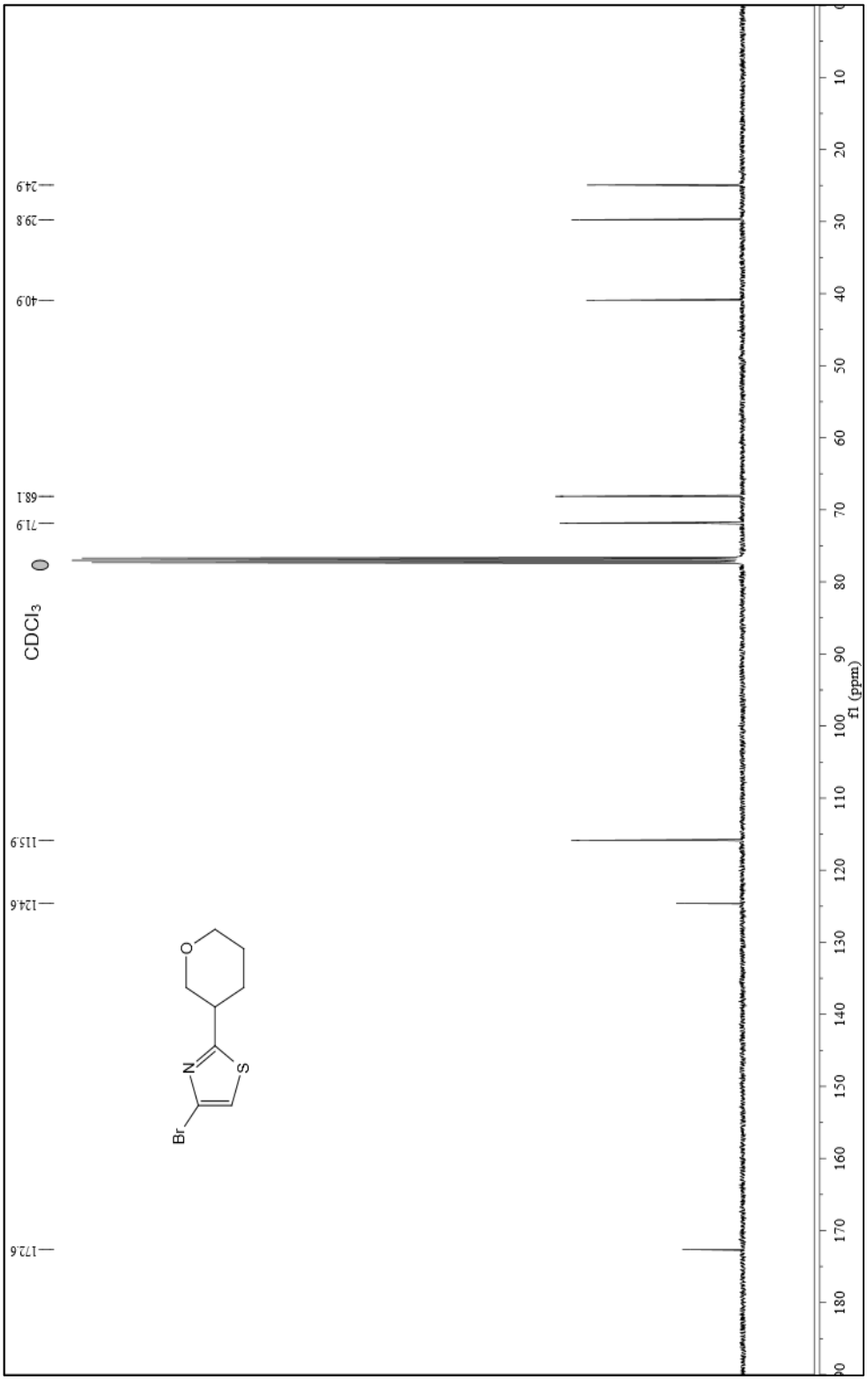
^{13}C NMR (101 MHz, $CDCl_3$) of **18d** ethyl 2-(tetrahydro-2H-pyran-3-yl)thiazole-4-carboxylate



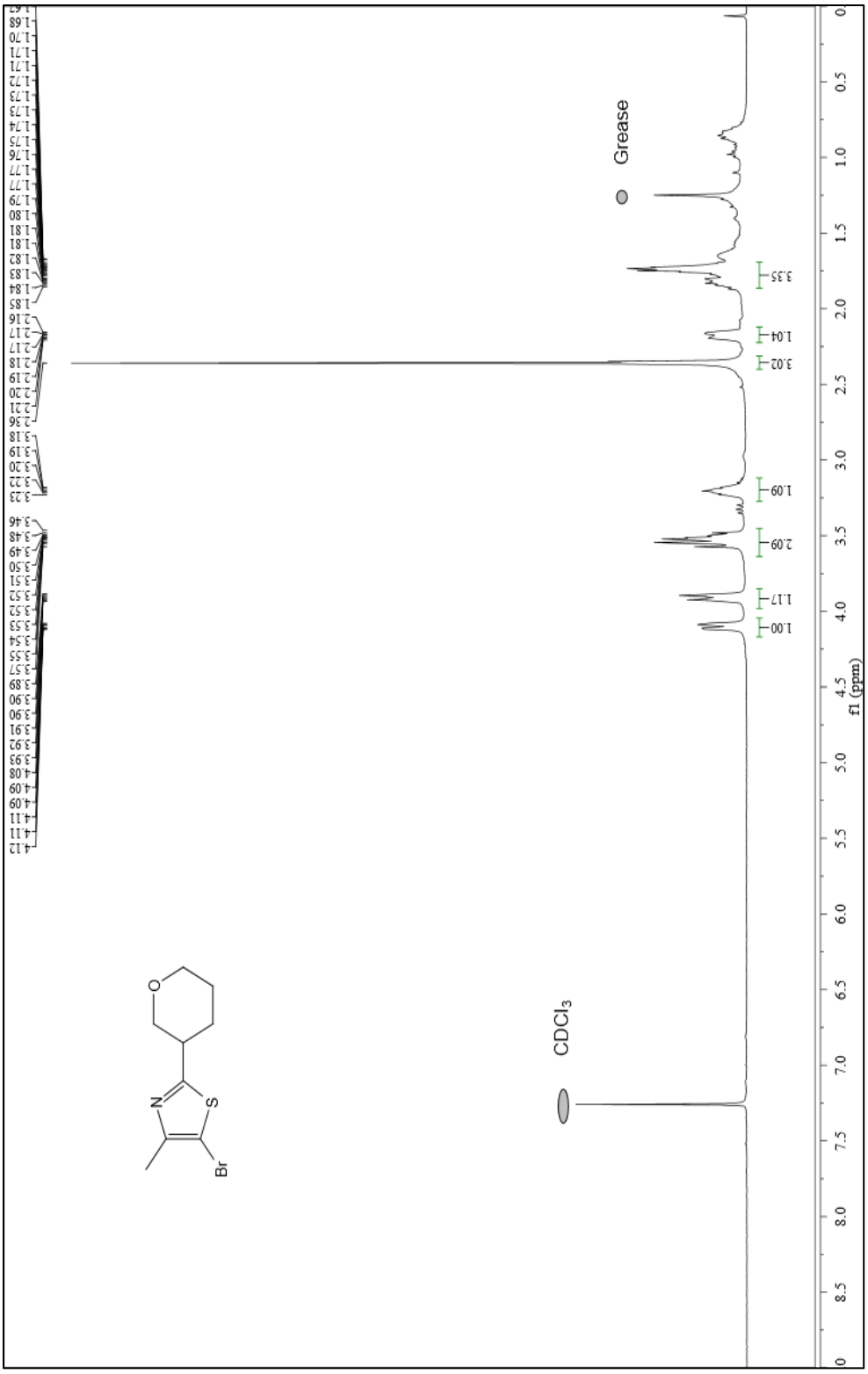
^{1}H NMR (400 MHz, $CDCl_3$) of **18e** 4-bromo-2-(tetrahydro-2H-pyran-3-yl)thiazole



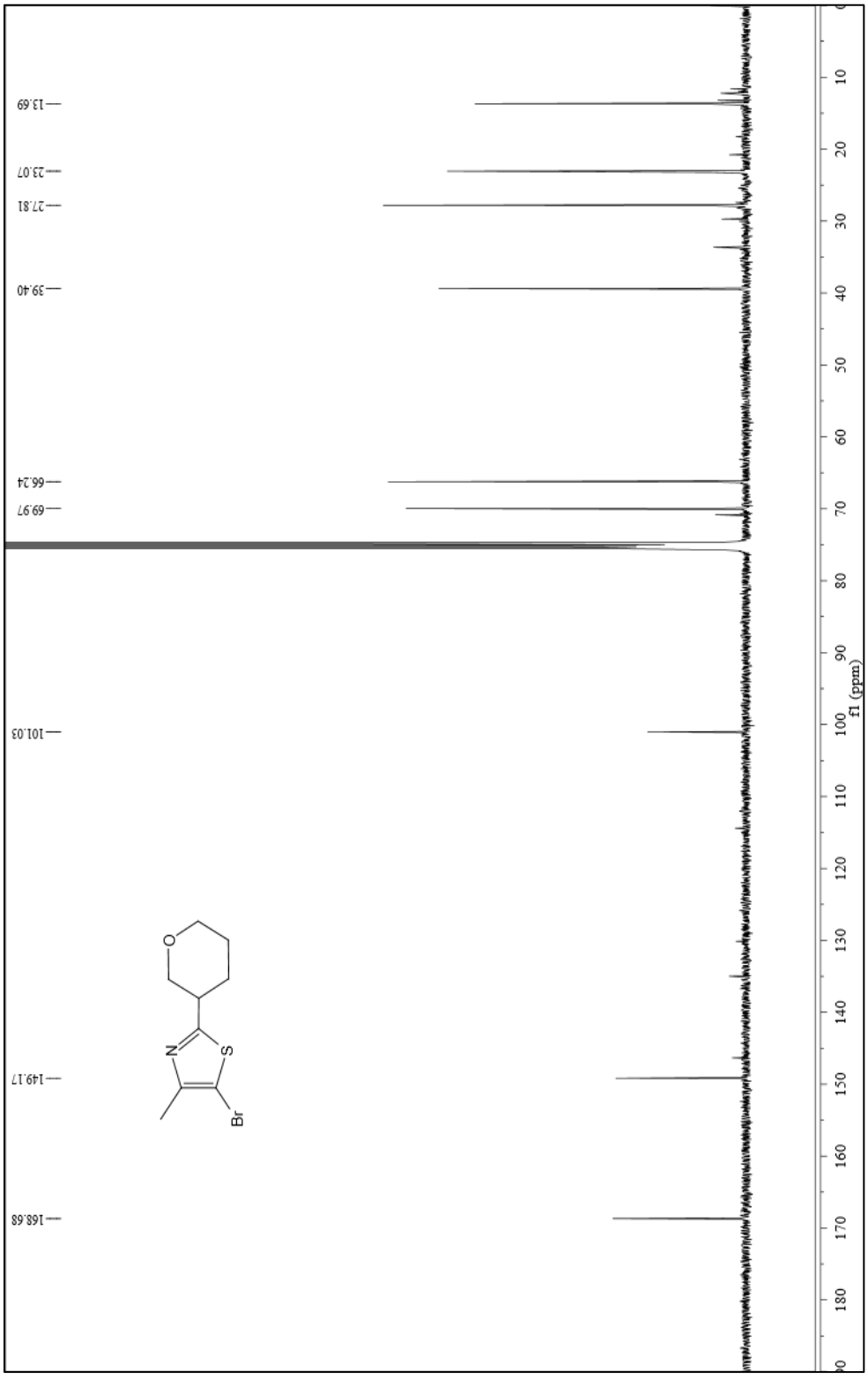
^{13}C NMR (101 MHz, $CDCl_3$) of **18e** 4-bromo-2-(tetrahydro-2H-pyran-3-yl)thiazole



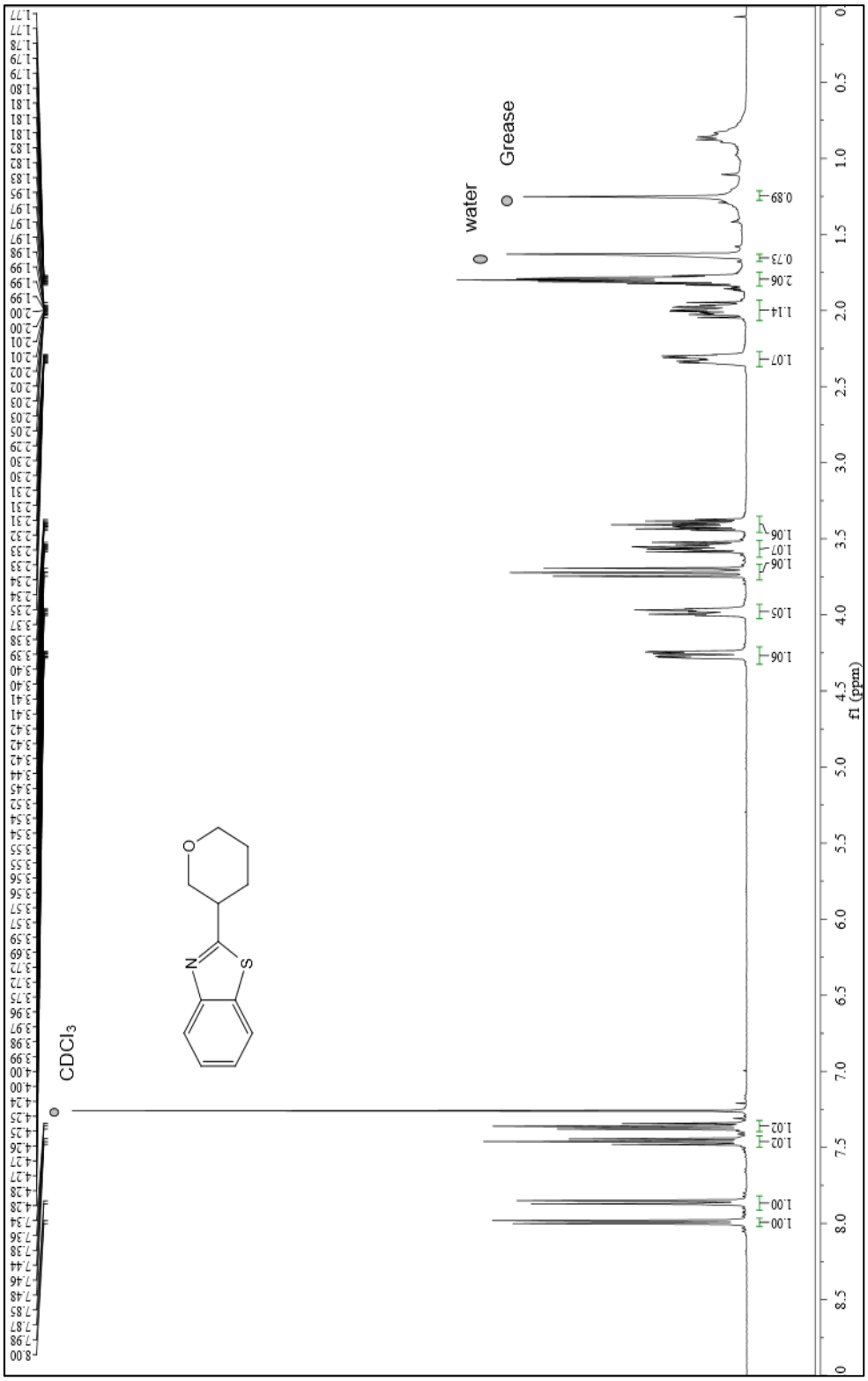
^{1}H NMR (400 MHz, $CDCl_3$) of **18f** 5-bromo-4-methyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



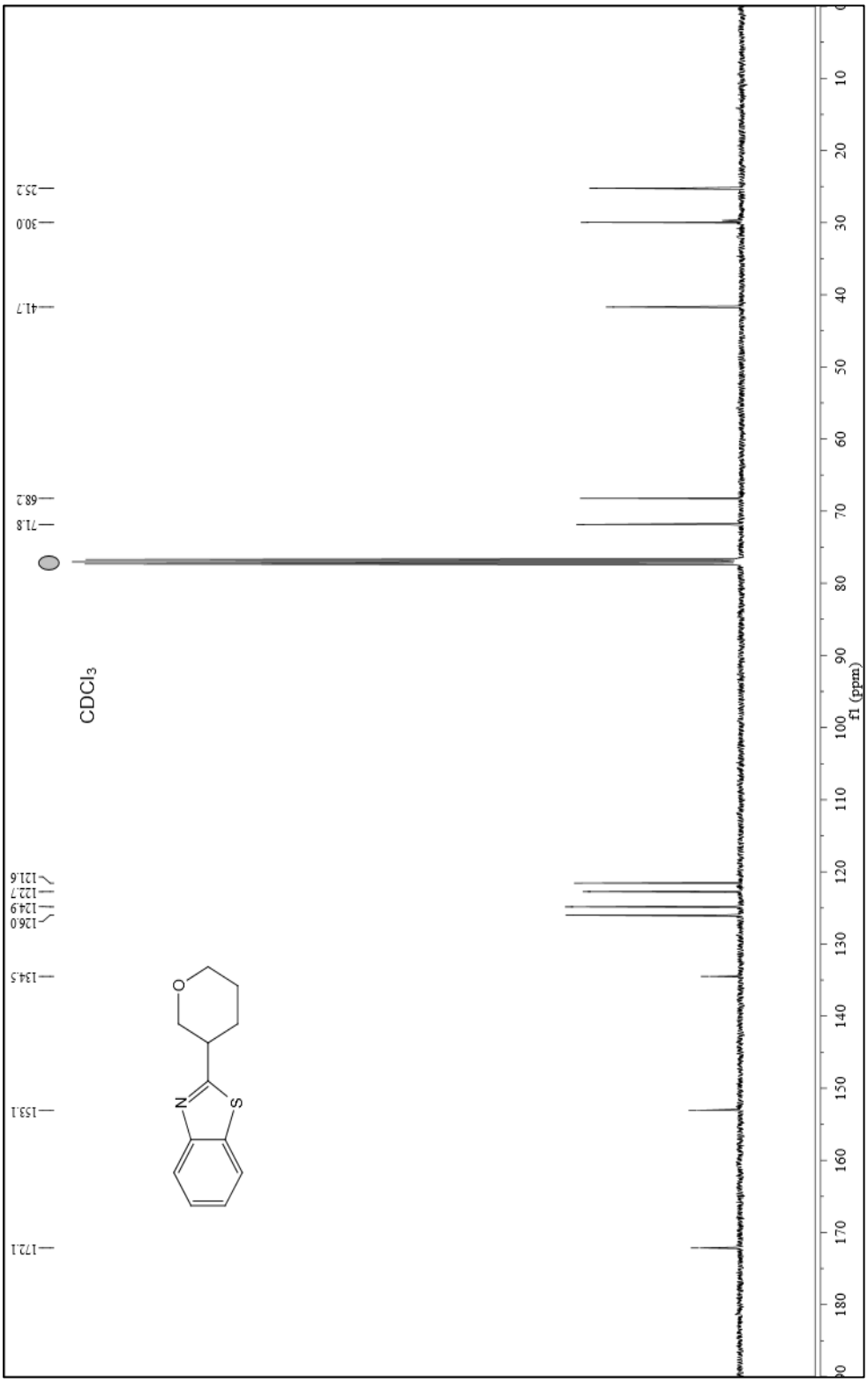
^{13}C NMR (101 MHz, $CDCl_3$) of **18f** 5-bromo-4-methyl-2-(tetrahydro-2H-pyran-3-yl)thiazole



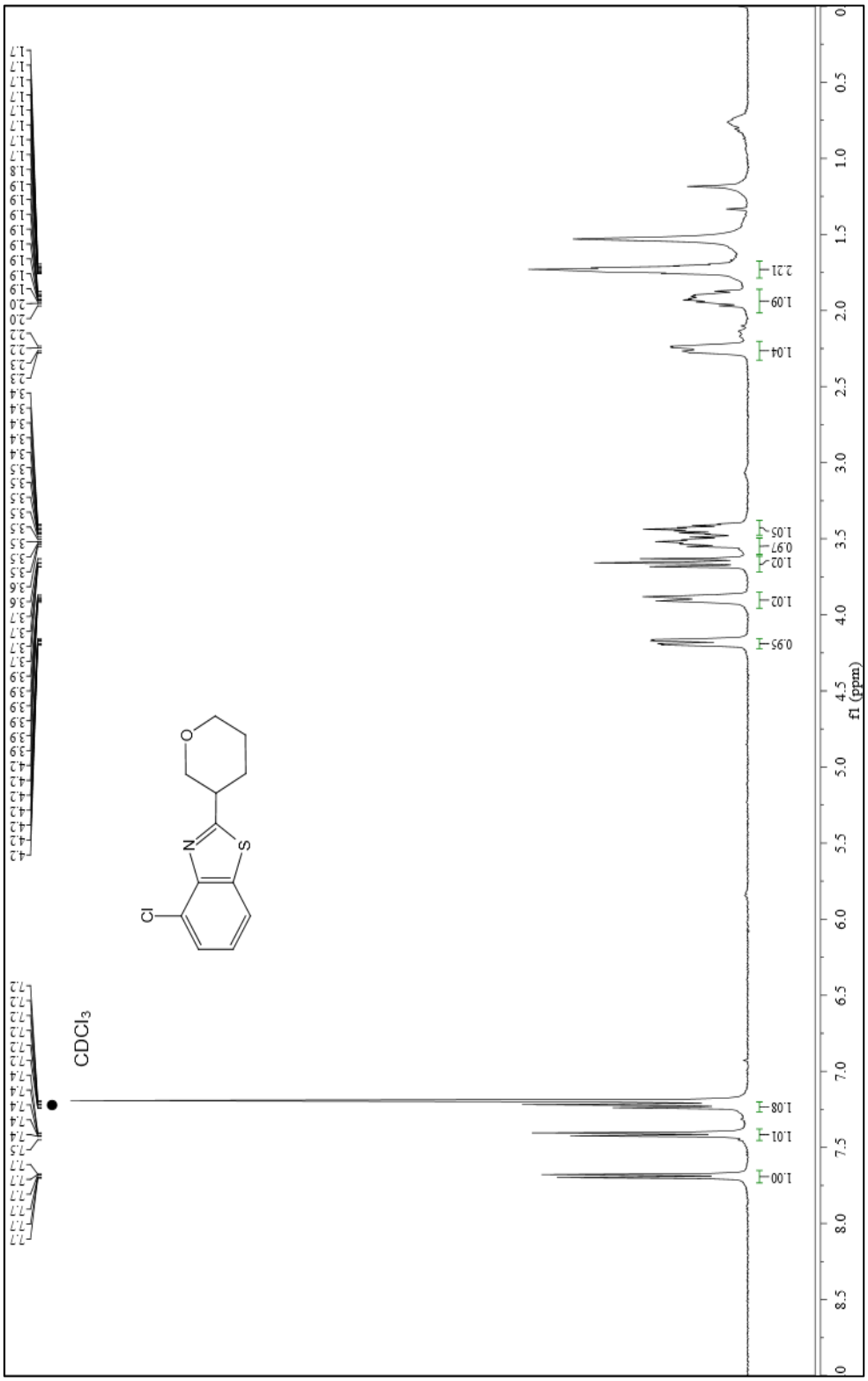
^{1}H NMR (400 MHz, $CDCl_3$) of **18g** 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



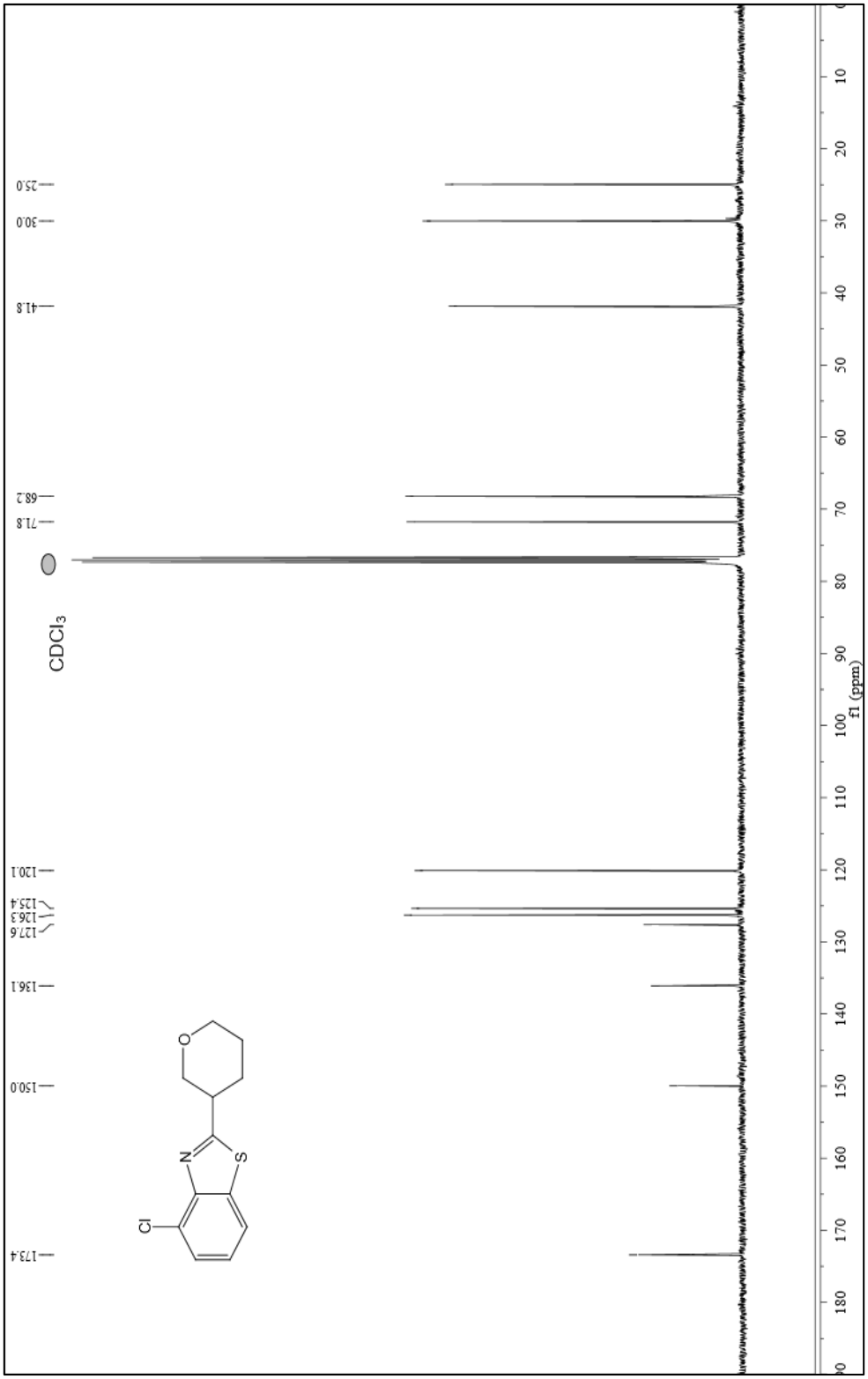
^{13}C NMR (101 MHz, $CDCl_3$) of **18g** 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



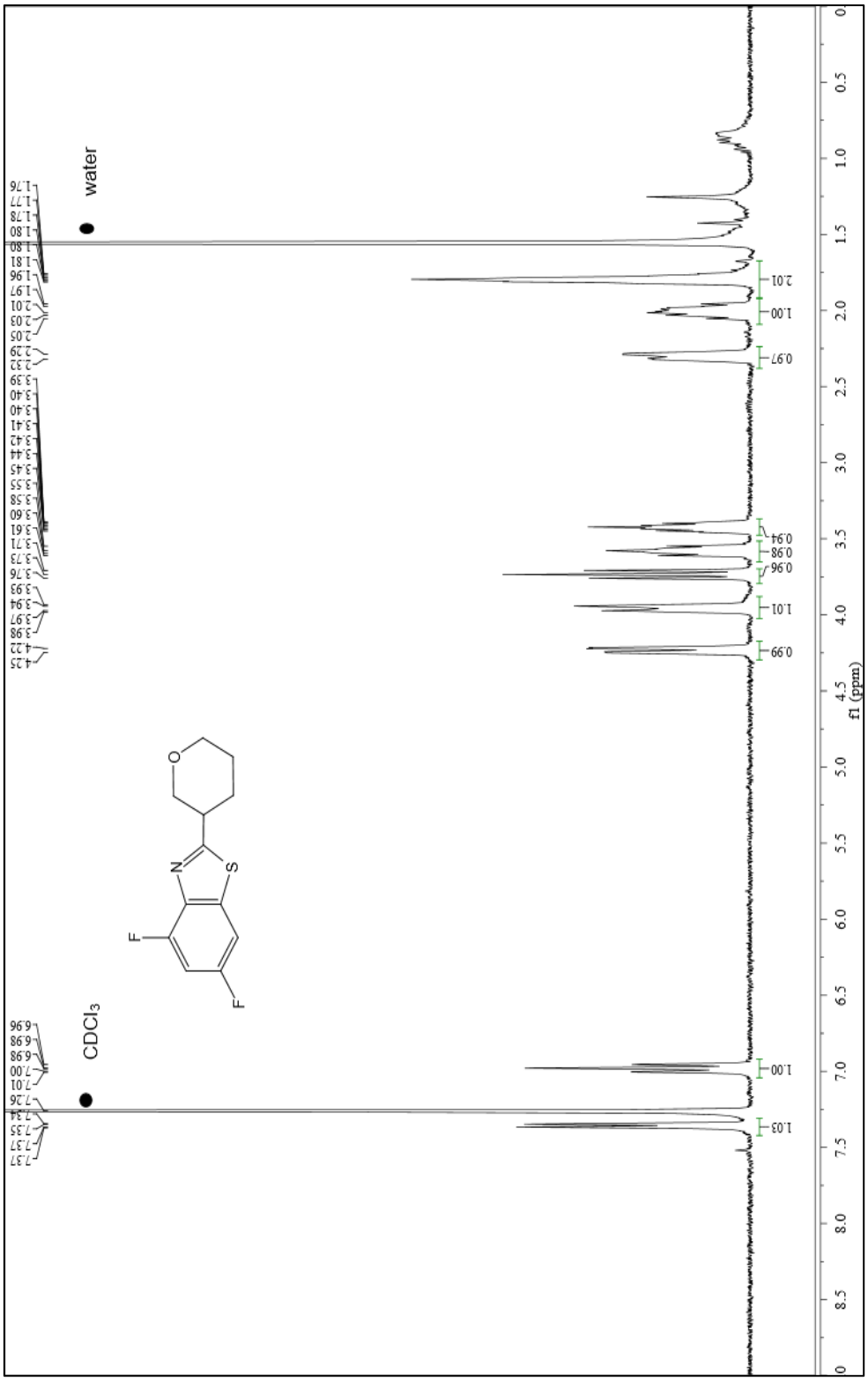
^{1}H NMR (400 MHz, $CDCl_3$) of **18h** 4-chloro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



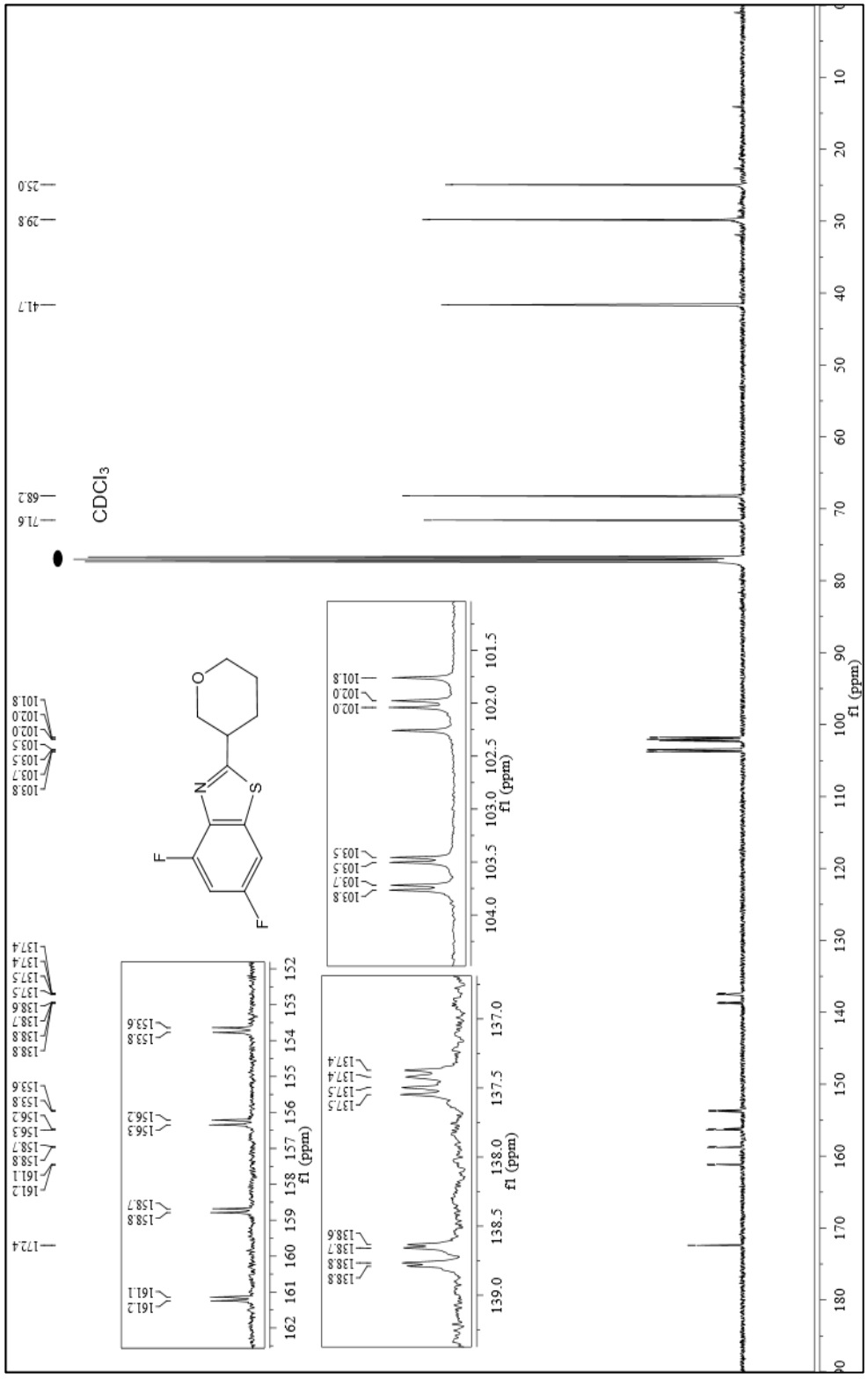
^{13}C NMR (101 MHz, $CDCl_3$) of **18h** 4-chloro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



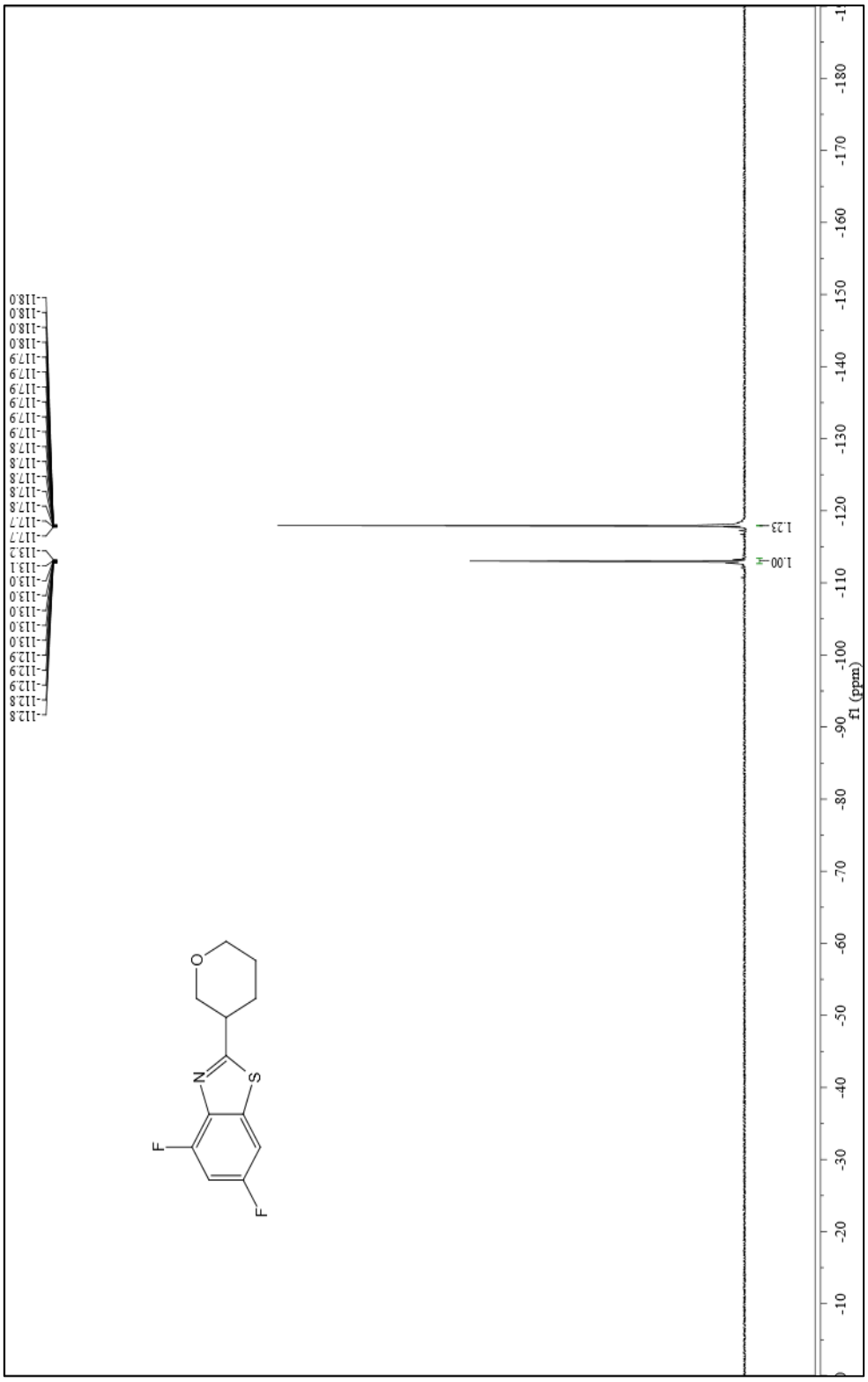
^{1}H NMR (400 MHz, $CDCl_3$) of **18i** 4,6-difluoro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



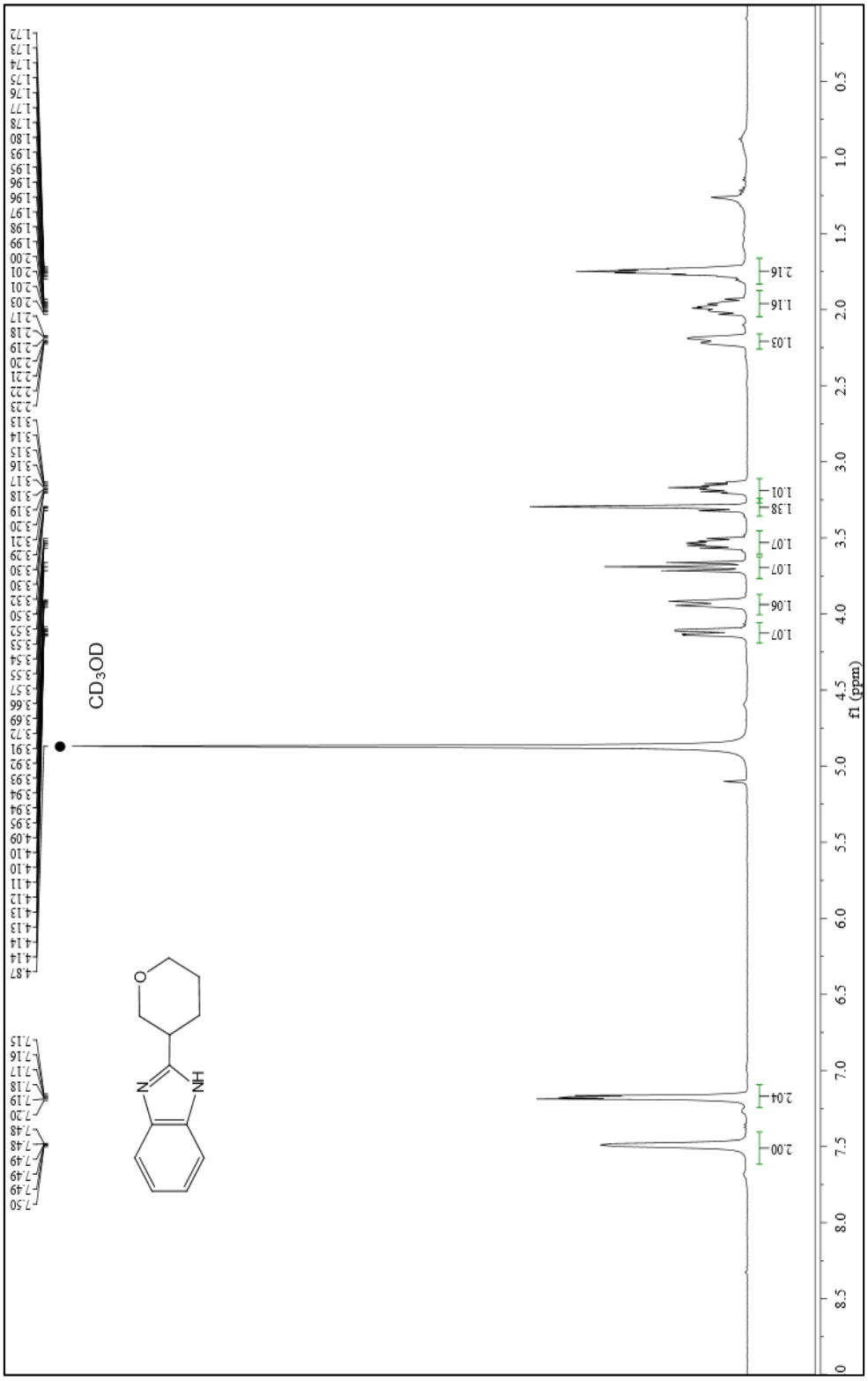
^{13}C NMR (101 MHz, $CDCl_3$) of **18i** 4,6-difluoro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



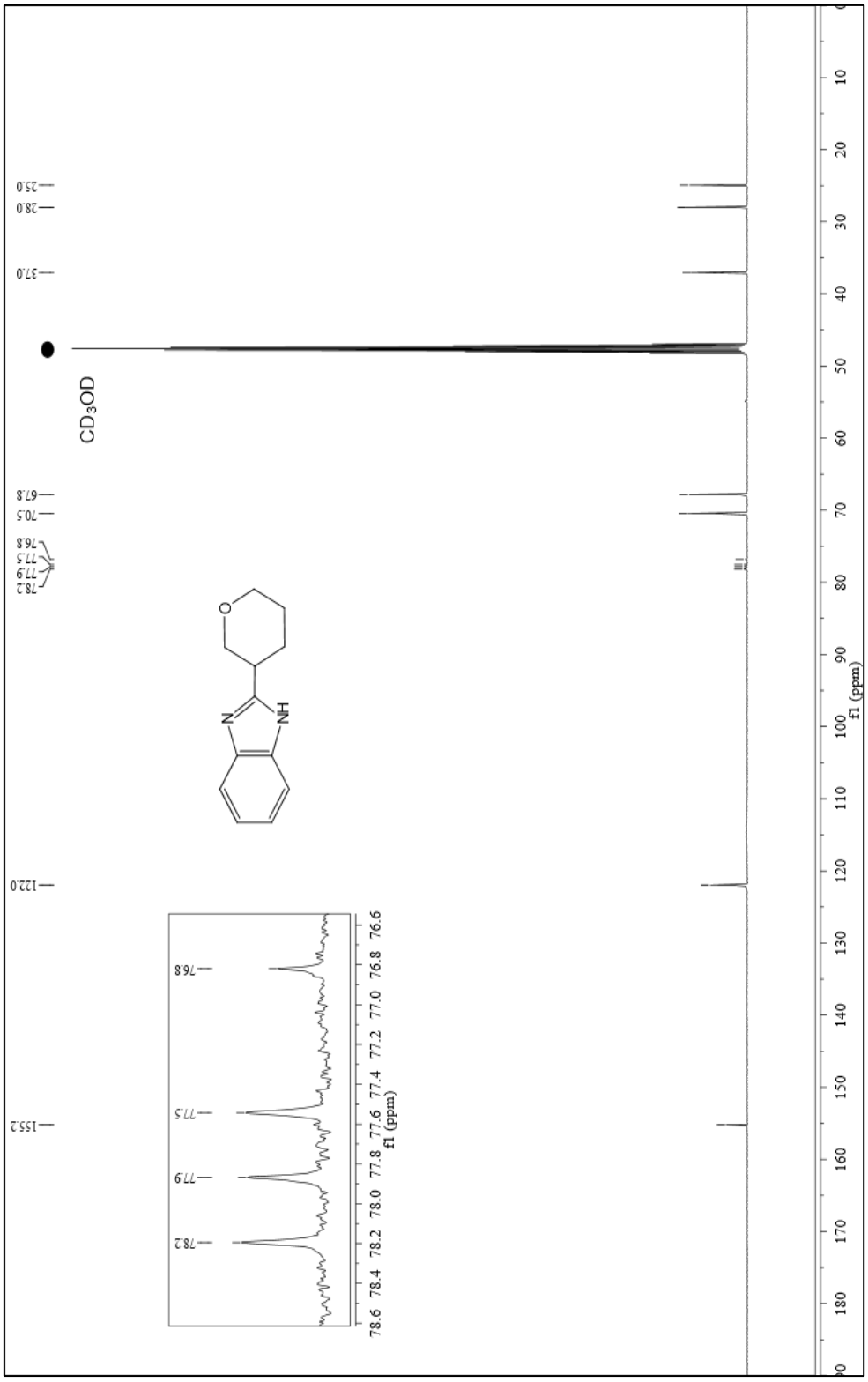
^{19}F NMR (376 MHz, $CDCl_3$) of **18i** 4,6-difluoro-2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



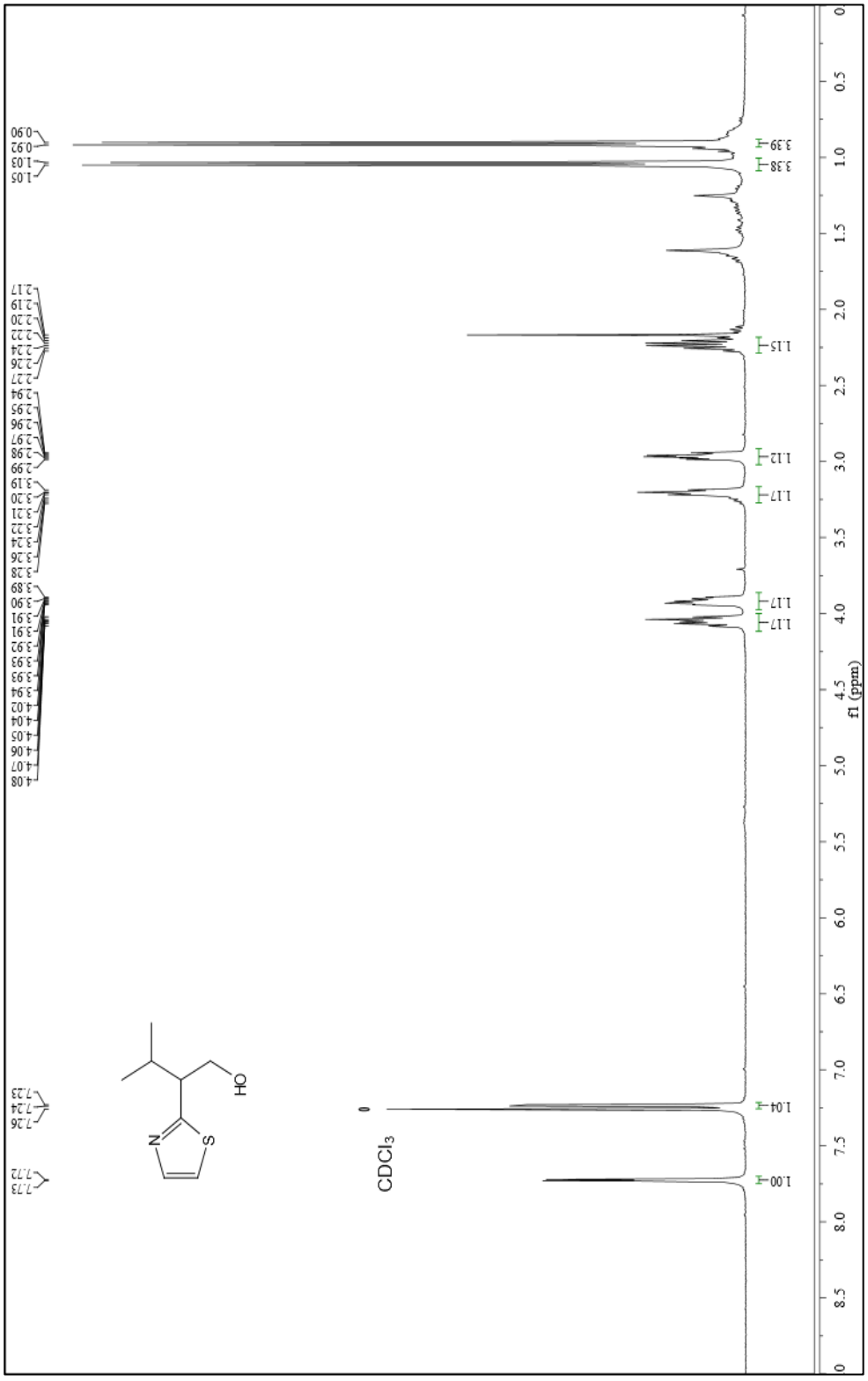
^{1}H NMR (400 MHz, CD_3OD) of **18j** 2-(tetrahydro-2H-pyran-3-yl)-1H-benzo[d]imidazole



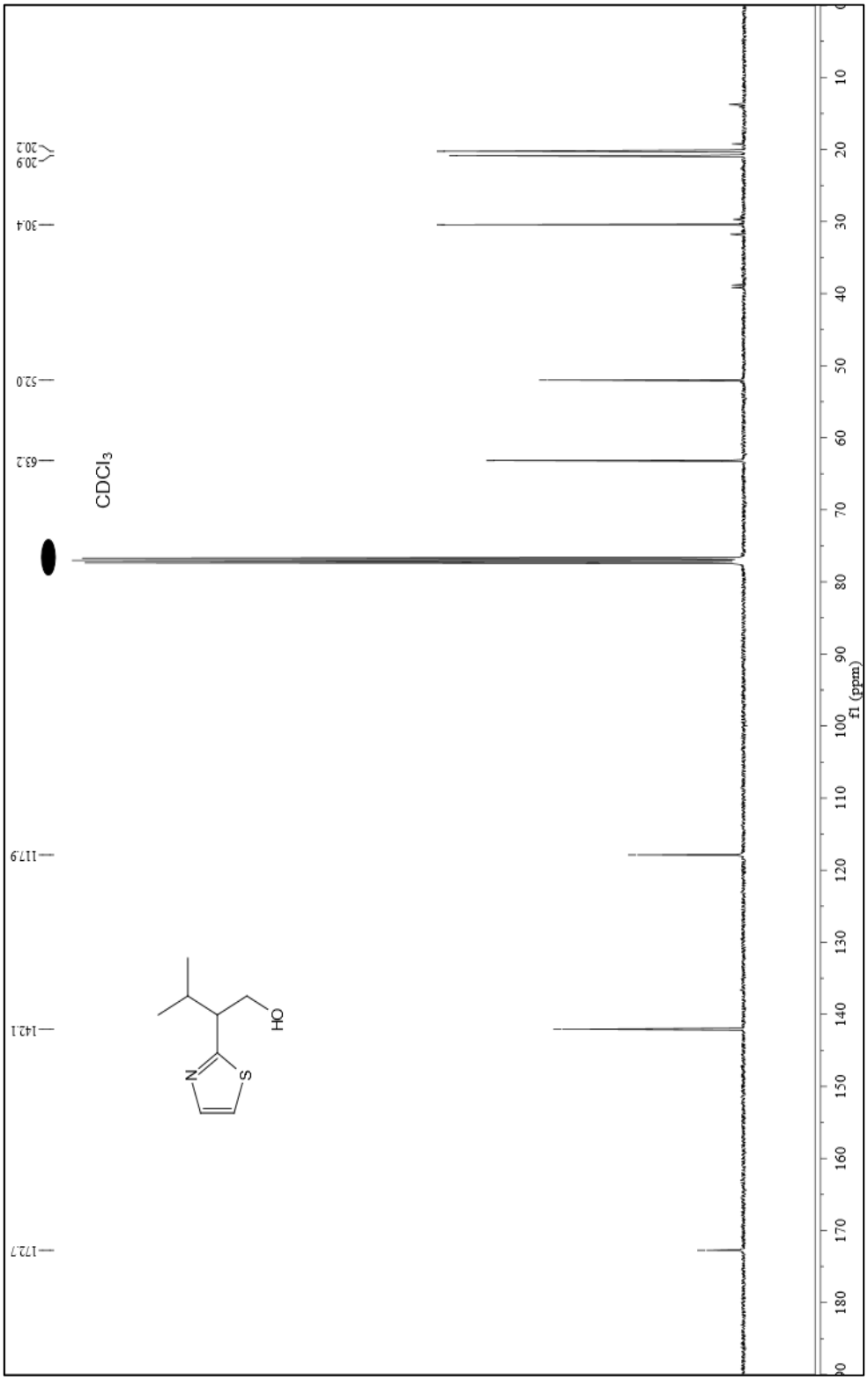
^{13}C NMR (101 MHz, CD_3OD) of **18j** 2-(tetrahydro-2H-pyran-3-yl)-1H-benzo[d]imidazole



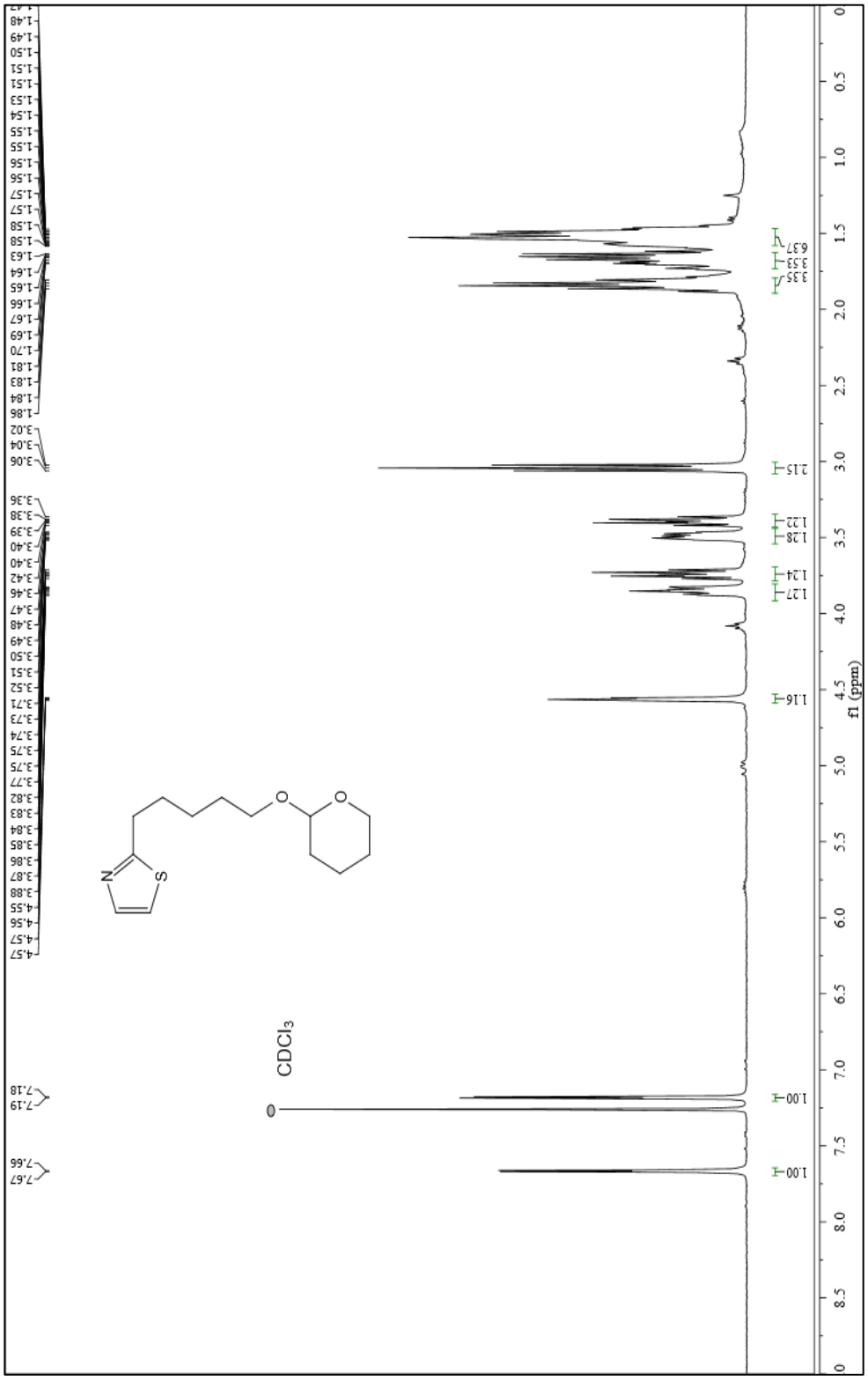
^{1}H NMR (400 MHz, $CDCl_3$) of **18l** 3-methyl-2-(thiazol-2-yl)butan-1-ol



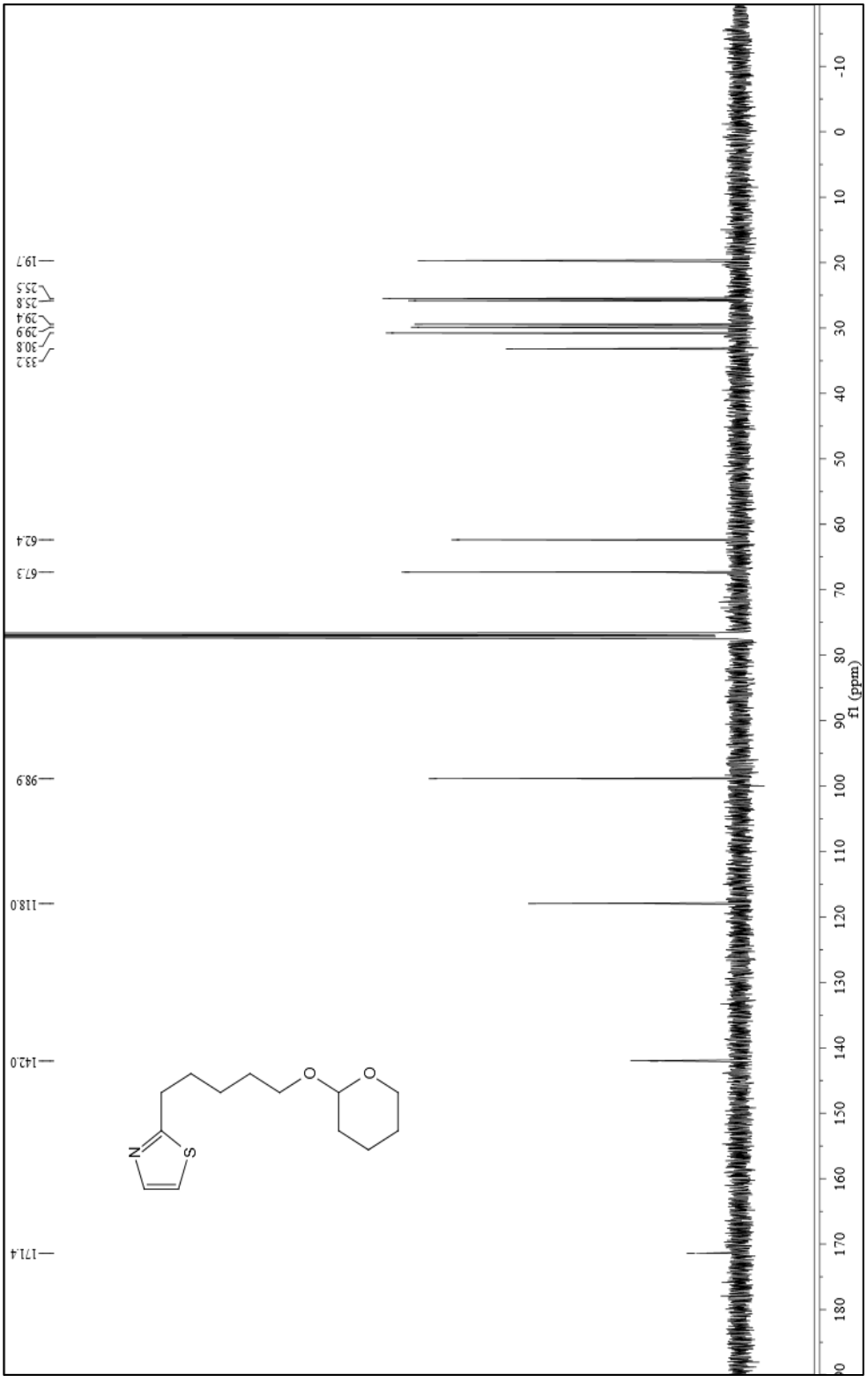
^{13}C NMR (101 MHz, $CDCl_3$) of **18l** 3-methyl-2-(thiazol-2-yl)butan-1-ol



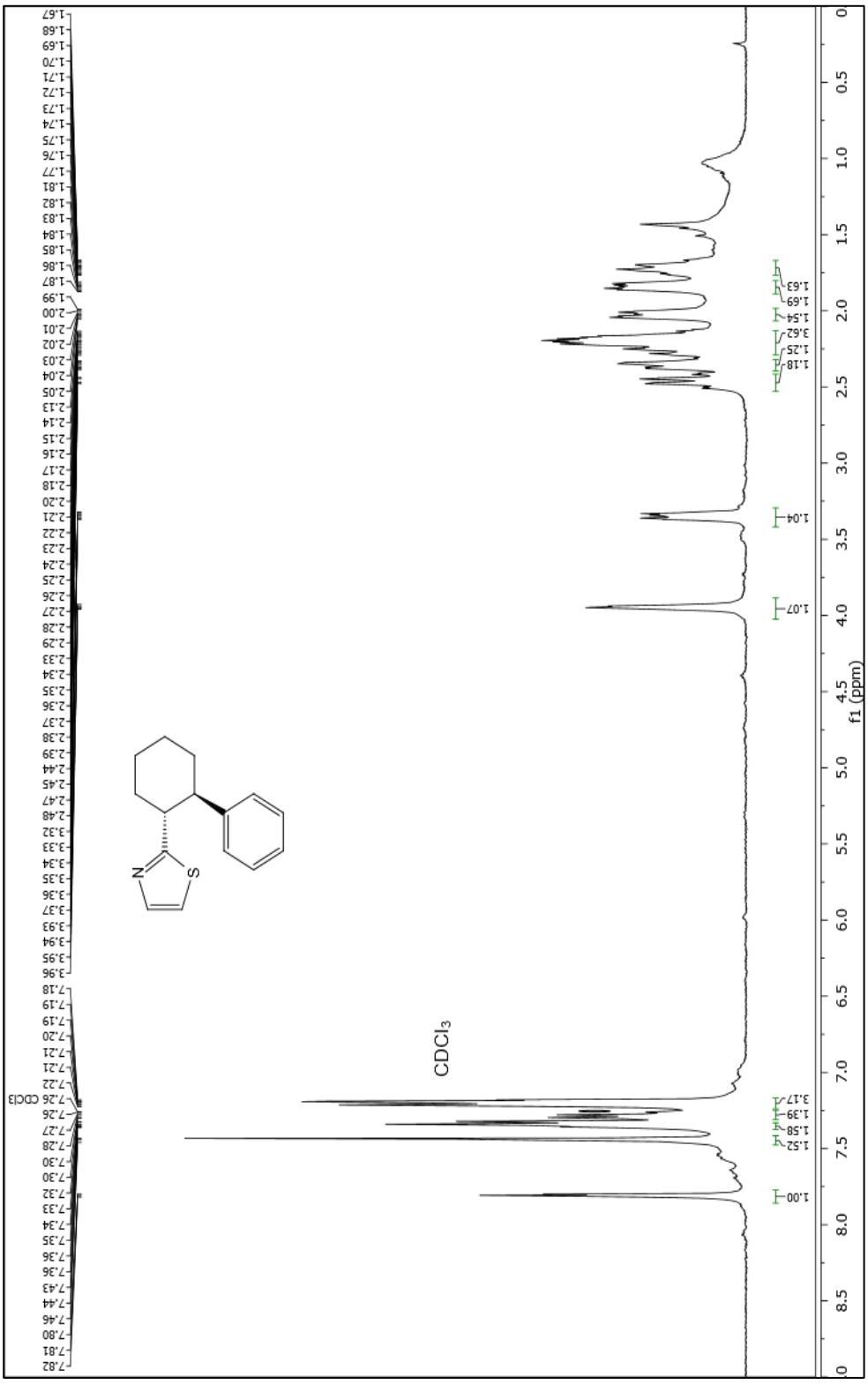
^{1}H NMR (400 MHz, $CDCl_3$) of **18m** 2-(5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)thiazole



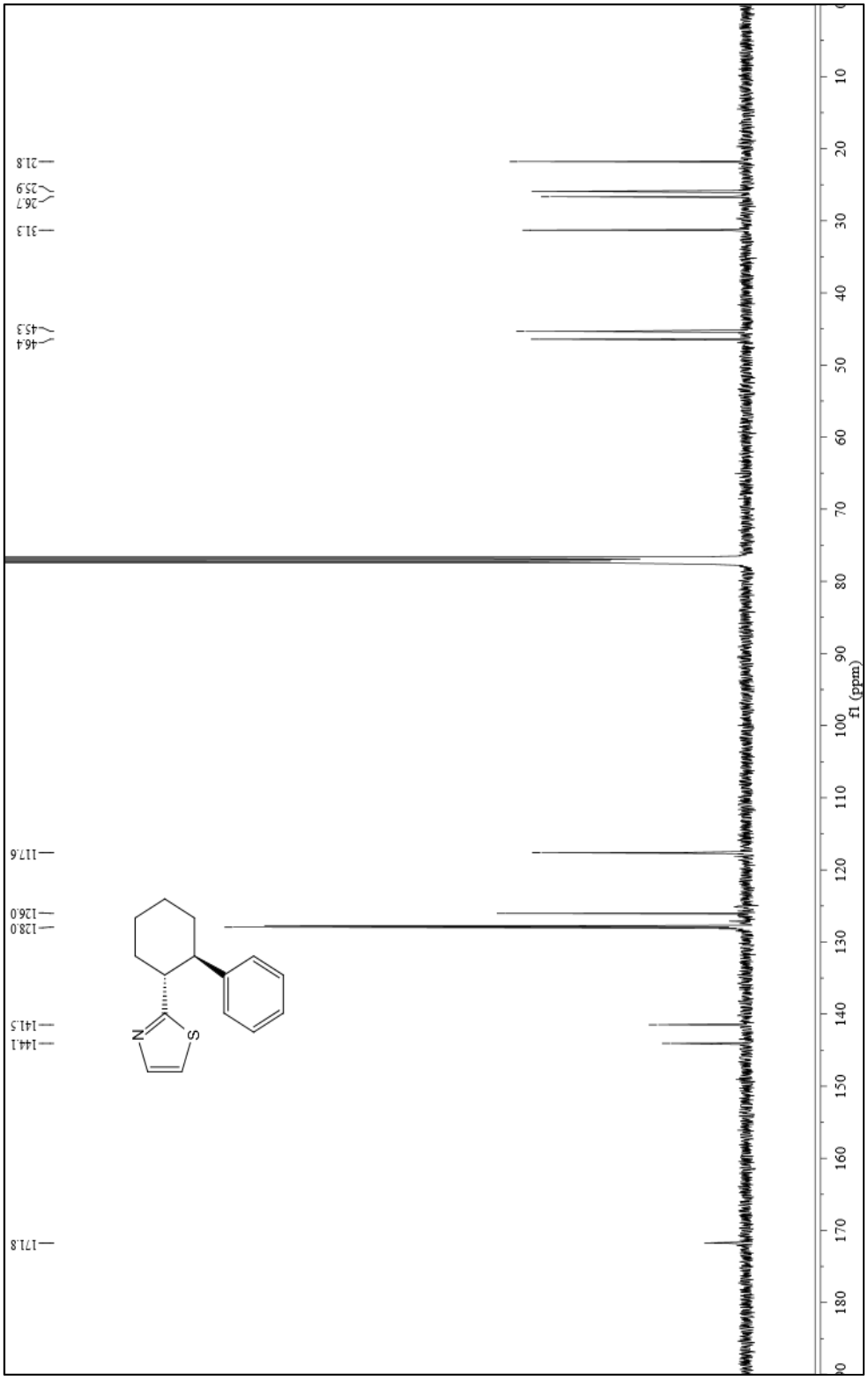
^{13}C NMR (101 MHz, $CDCl_3$) of **18m-** 2-(5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)thiazole



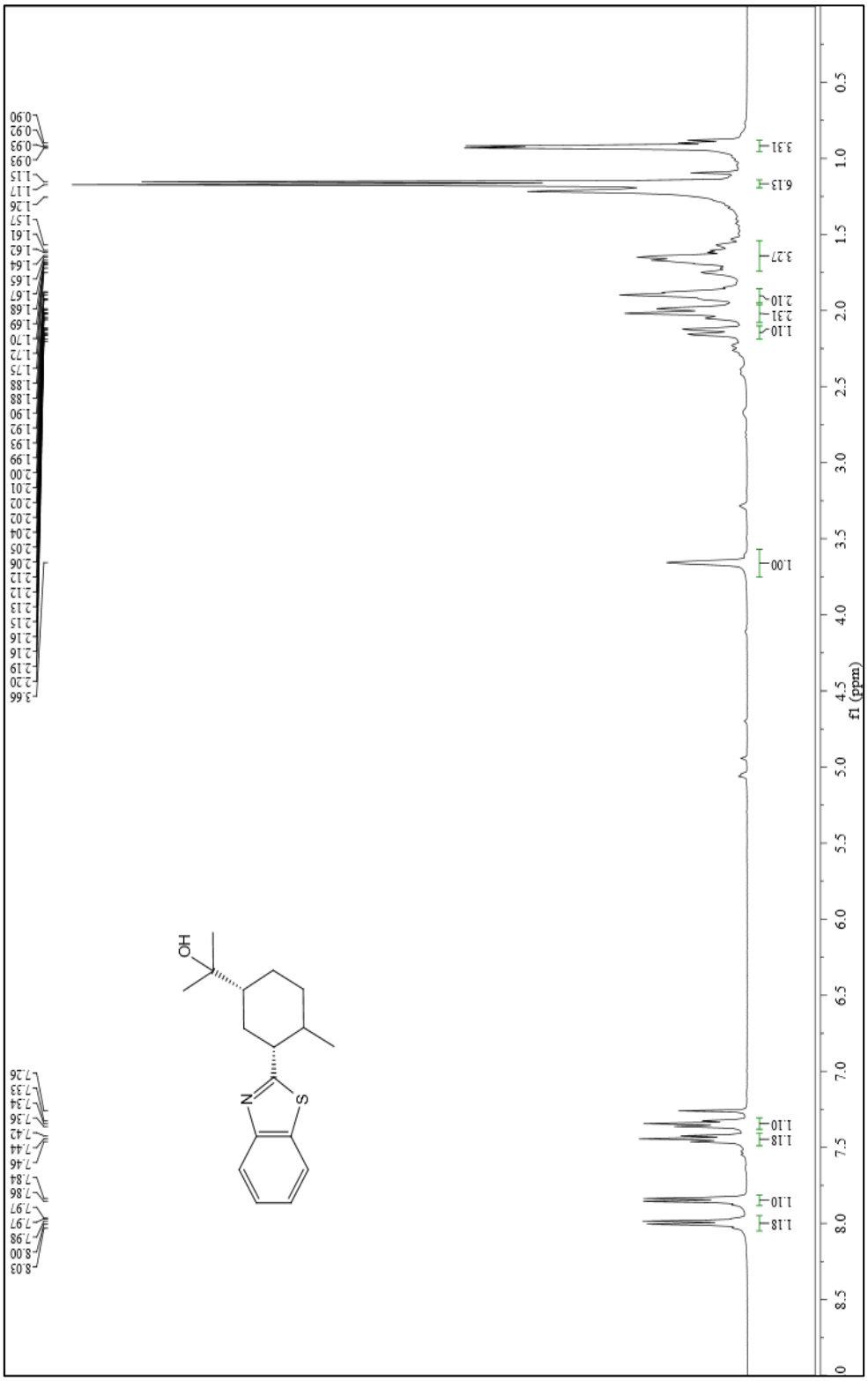
^{1}H NMR (400 MHz, $CDCl_3$) of **18n-** 2-(2-phenylcyclohexyl)thiazole



^{13}C NMR (101 MHz, $CDCl_3$) of **18n-** 2-(2-phenylcyclohexyl)thiazole

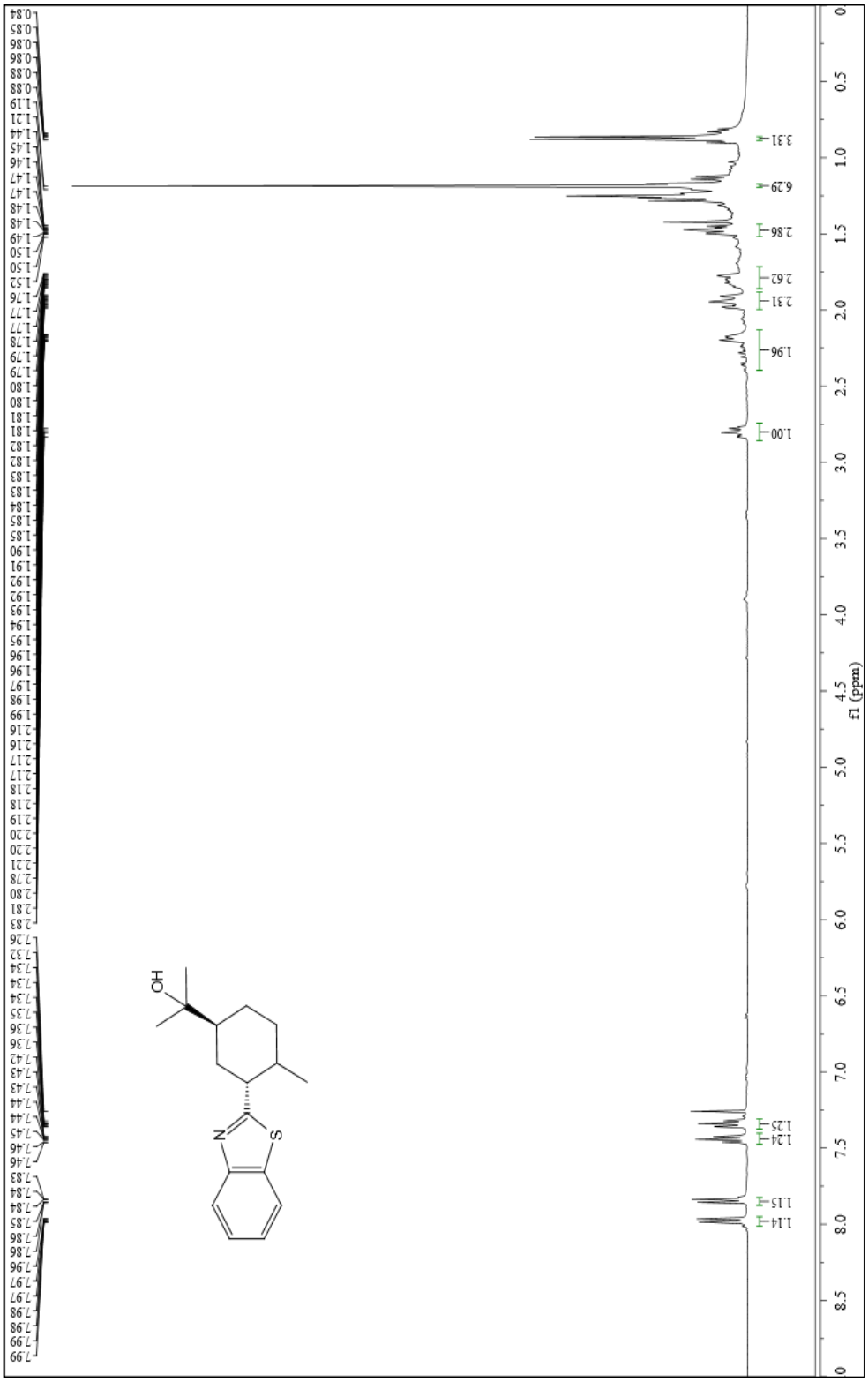


^{1}H NMR (400 MHz, $CDCl_3$) of **18o** (Diastereomer a) 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole

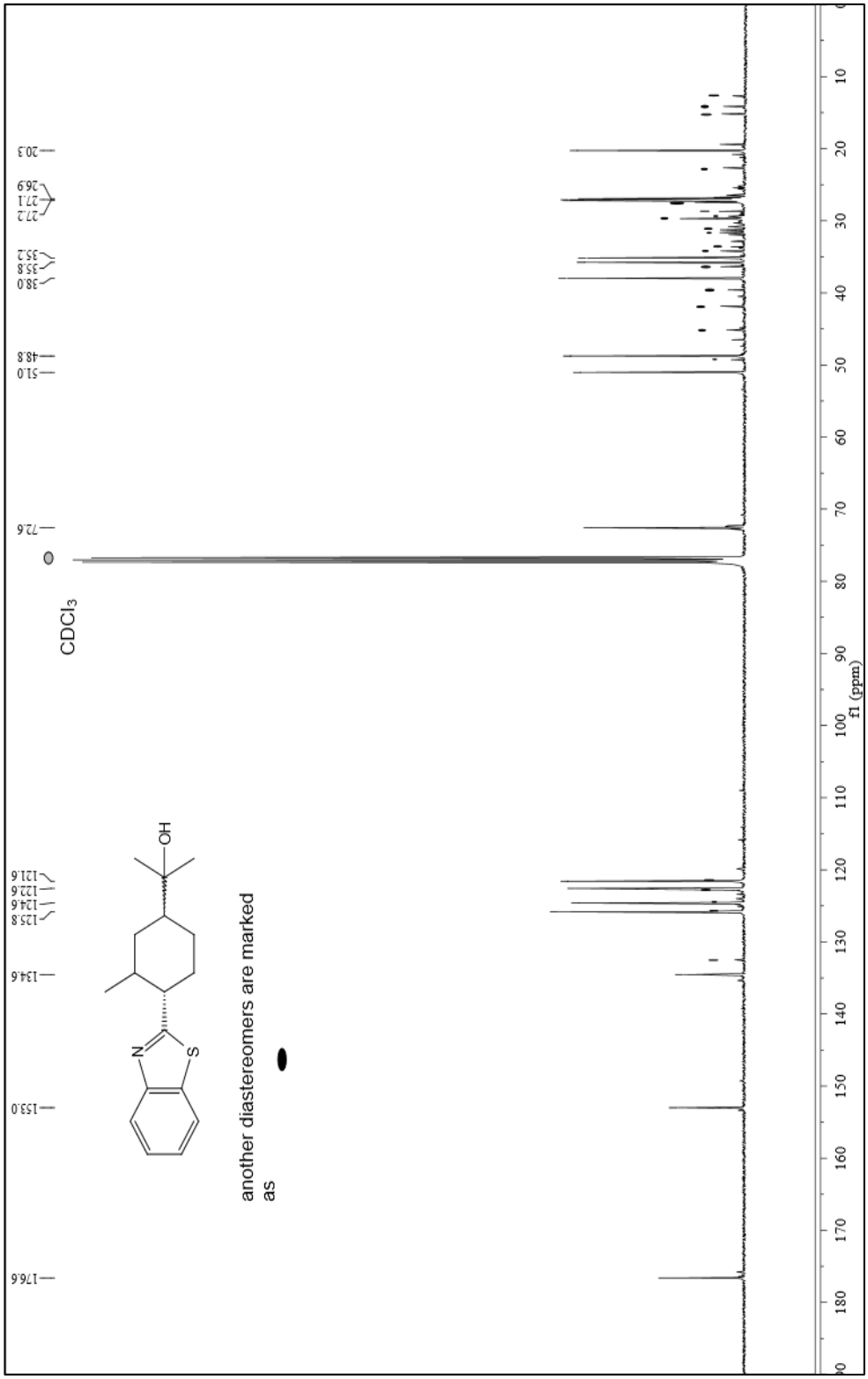


^{13}C NMR (101 MHz, $CDCl_3$) of **18o** (Diastereomer a) 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole

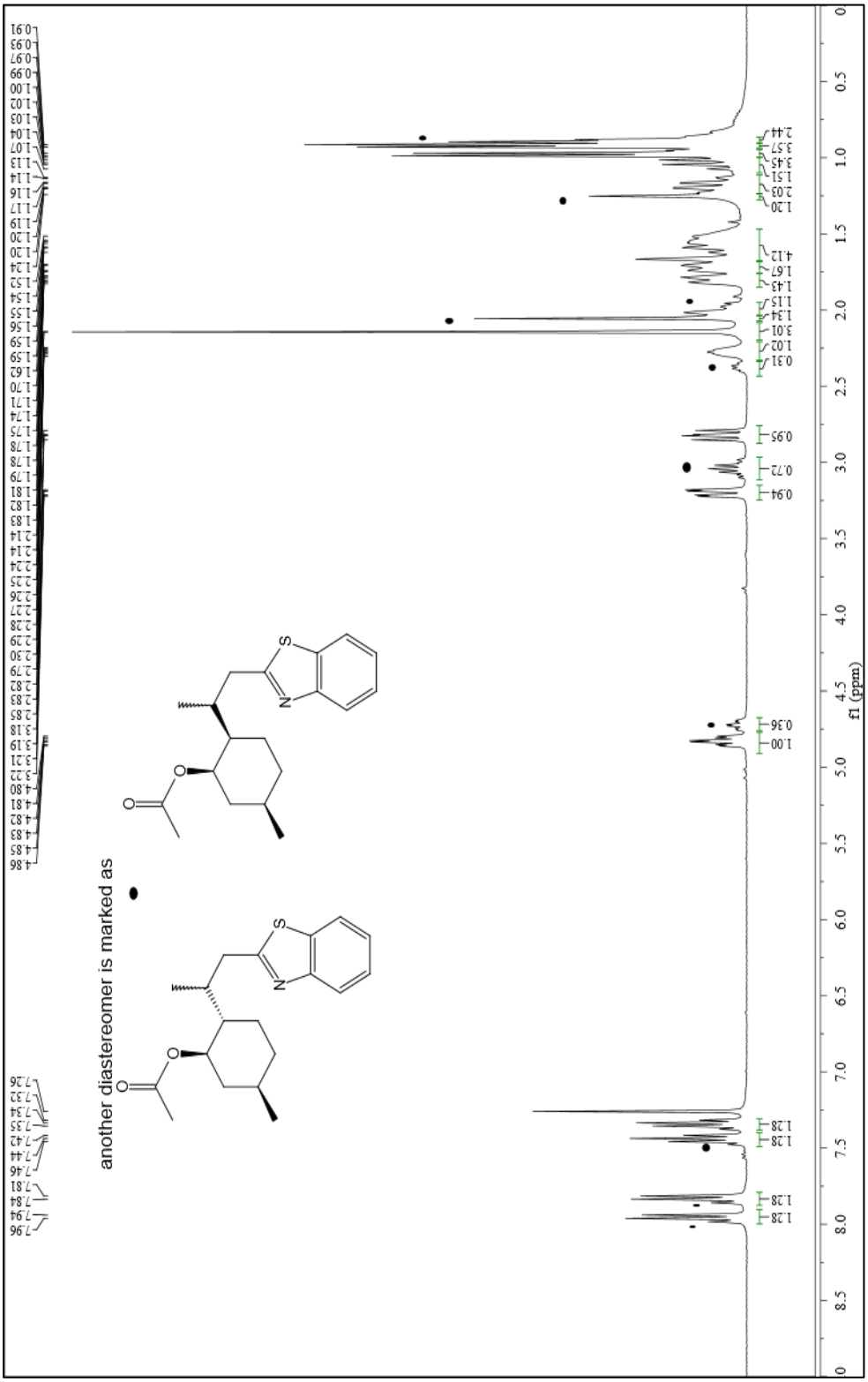
^{1}H NMR (400 MHz, $CDCl_3$) of **18o** (Diastereomer b) 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



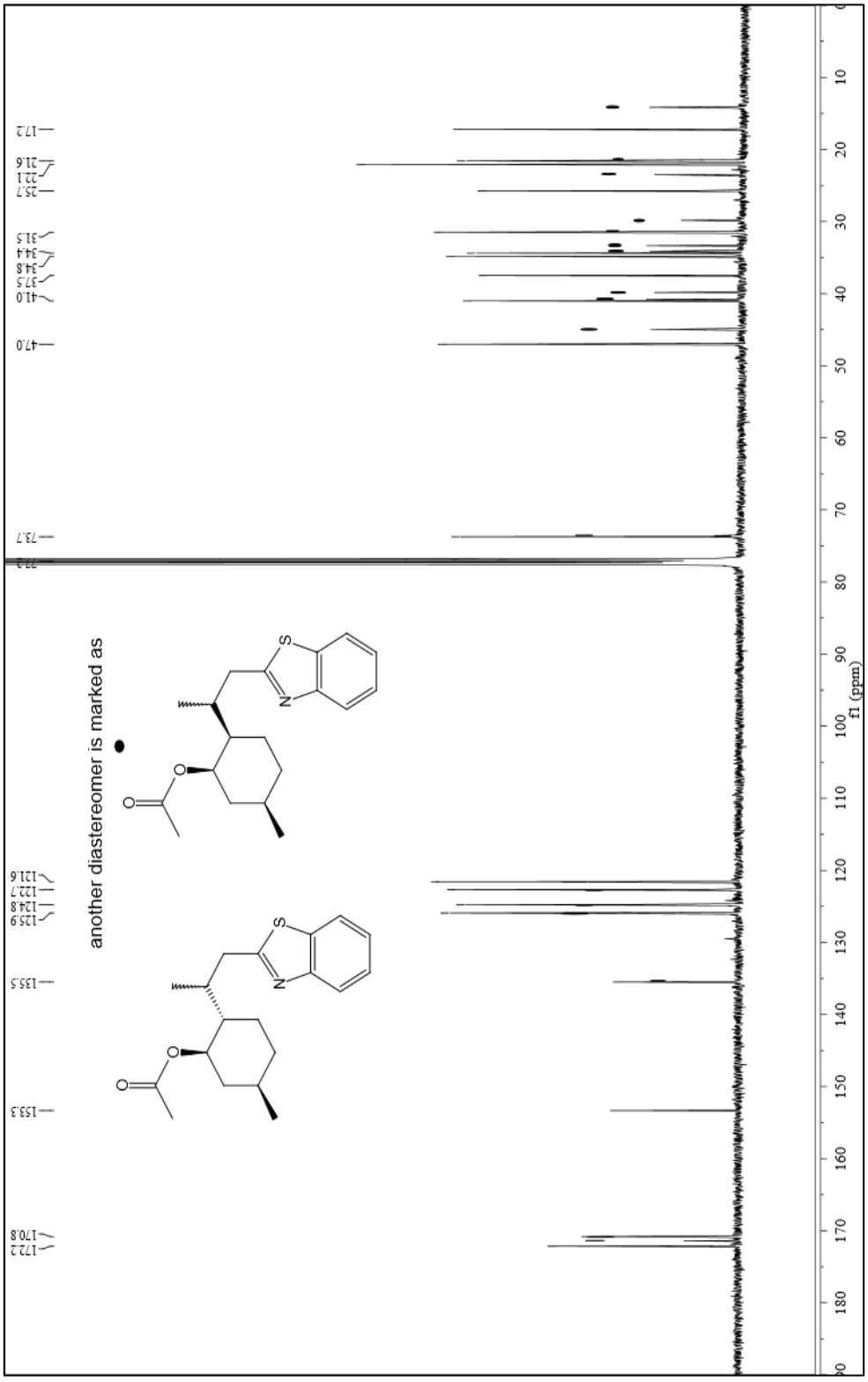
^{13}C NMR (101 MHz, $CDCl_3$) of **18o** (Diastereomer b) 2-(tetrahydro-2H-pyran-3-yl)benzo[d]thiazole



^{1}H NMR (400 MHz, $CDCl_3$) of **18p** (1R,2R,5R)-2-((R)-1-(benzo[d]thiazol-2-yl)propan-2-yl)-5-methylcyclohexyl acetate

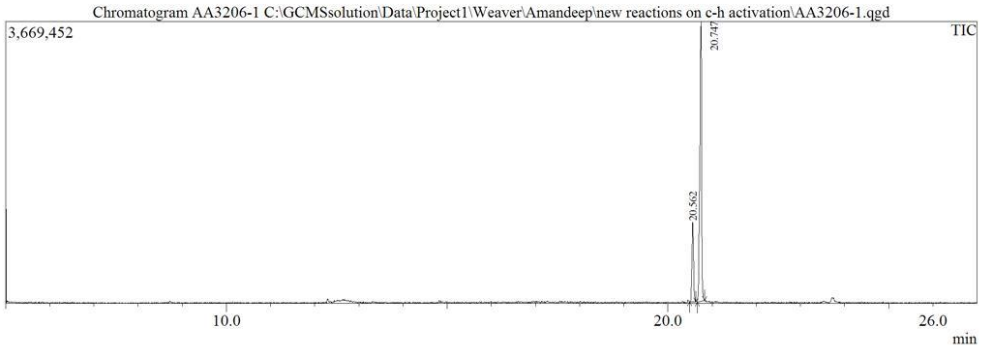


^{13}C NMR (101 MHz, $CDCl_3$) of **18p** (1R,2R,5R)-2-((R)-1-(benzo[d]thiazol-2-yl)propan-2-yl)-5-methylcyclohexyl acetate



GC of **18p** (1R,2R,5R)-2-((R)-1-(benzo[d]thiazol-2-yl)propan-2-yl)-5-methylcyclohexyl acetate

]



Peak Report TIC

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2	20.747	20.658	20.825	10584907	79.59	3639025	77.79	2.90	MI	
				13299692	100.00	4677967	100.00			

Spectrum

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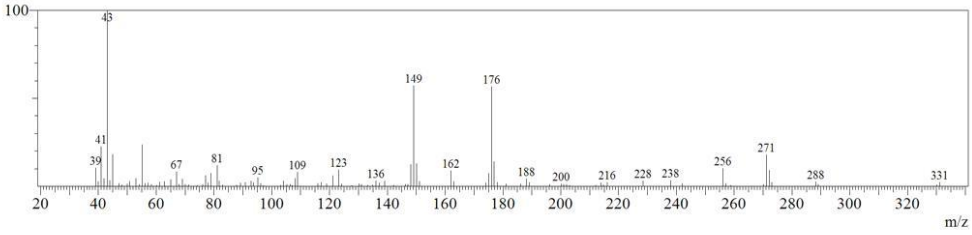
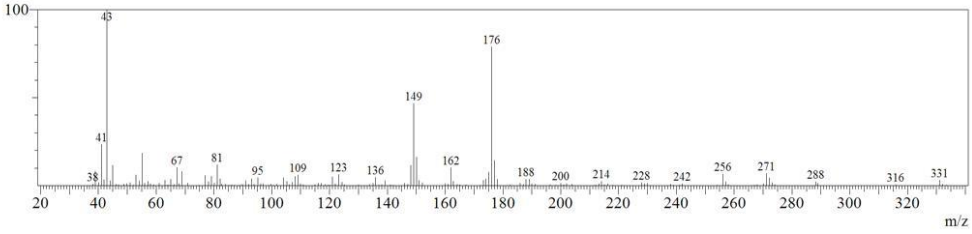
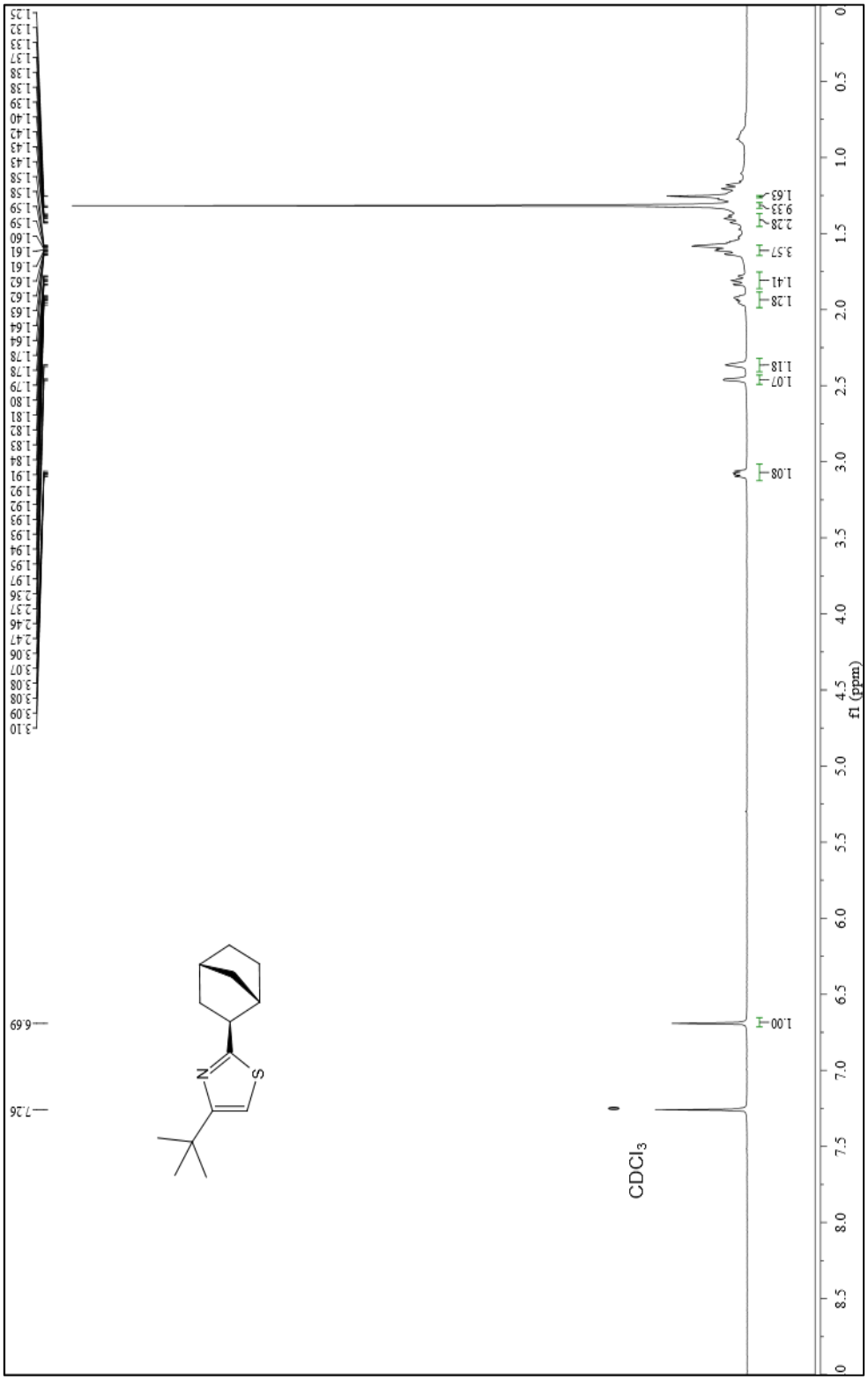
RawMode:Single 20.6(1868) BasePeak:43(179469)
BG Mode:None



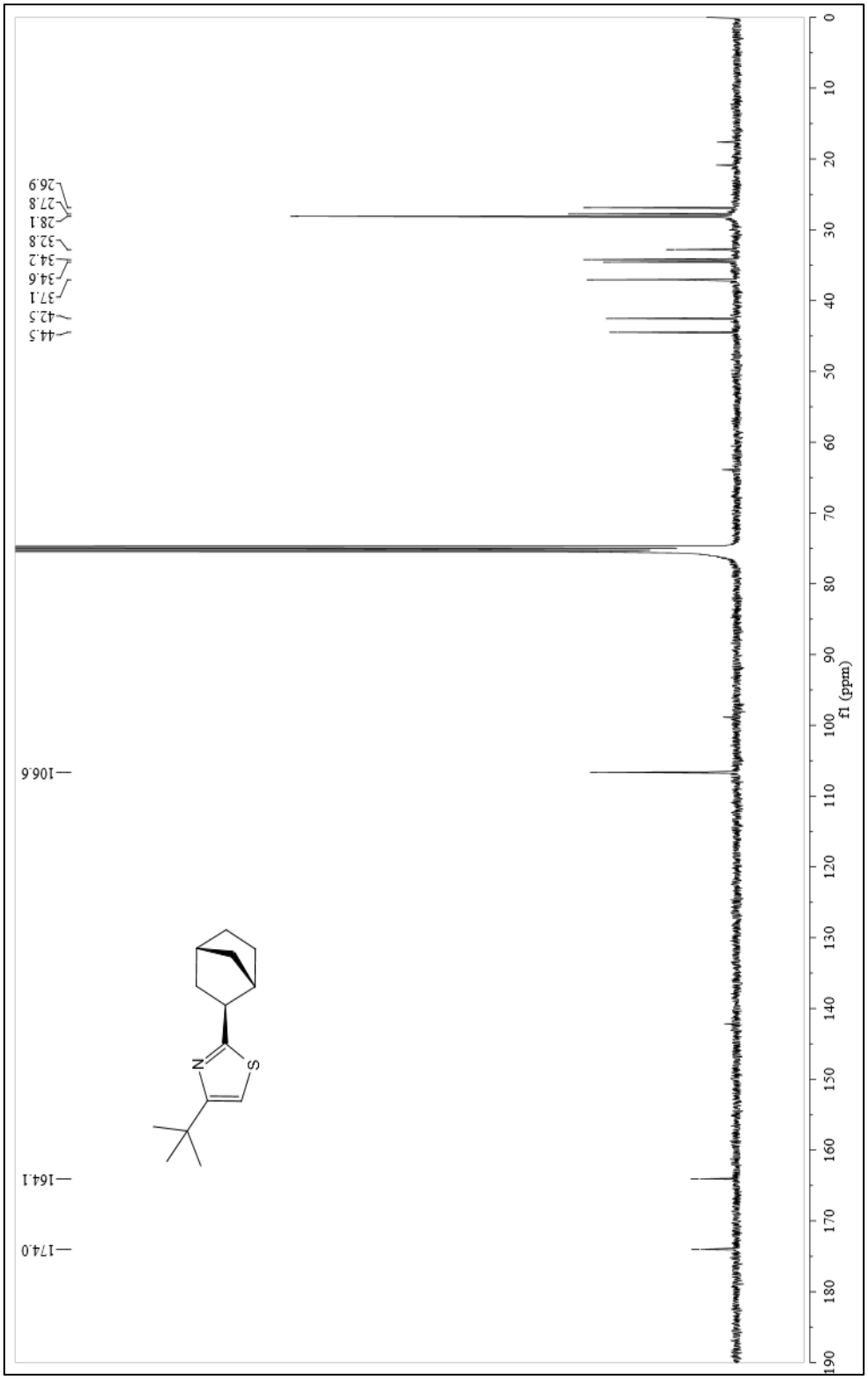
Line#:2 R.Time:20.7(Scan#:1888)
MassPeaks:149
RawMode:Single 20.7(1888) BasePeak:43(387940)
BG Mode:None



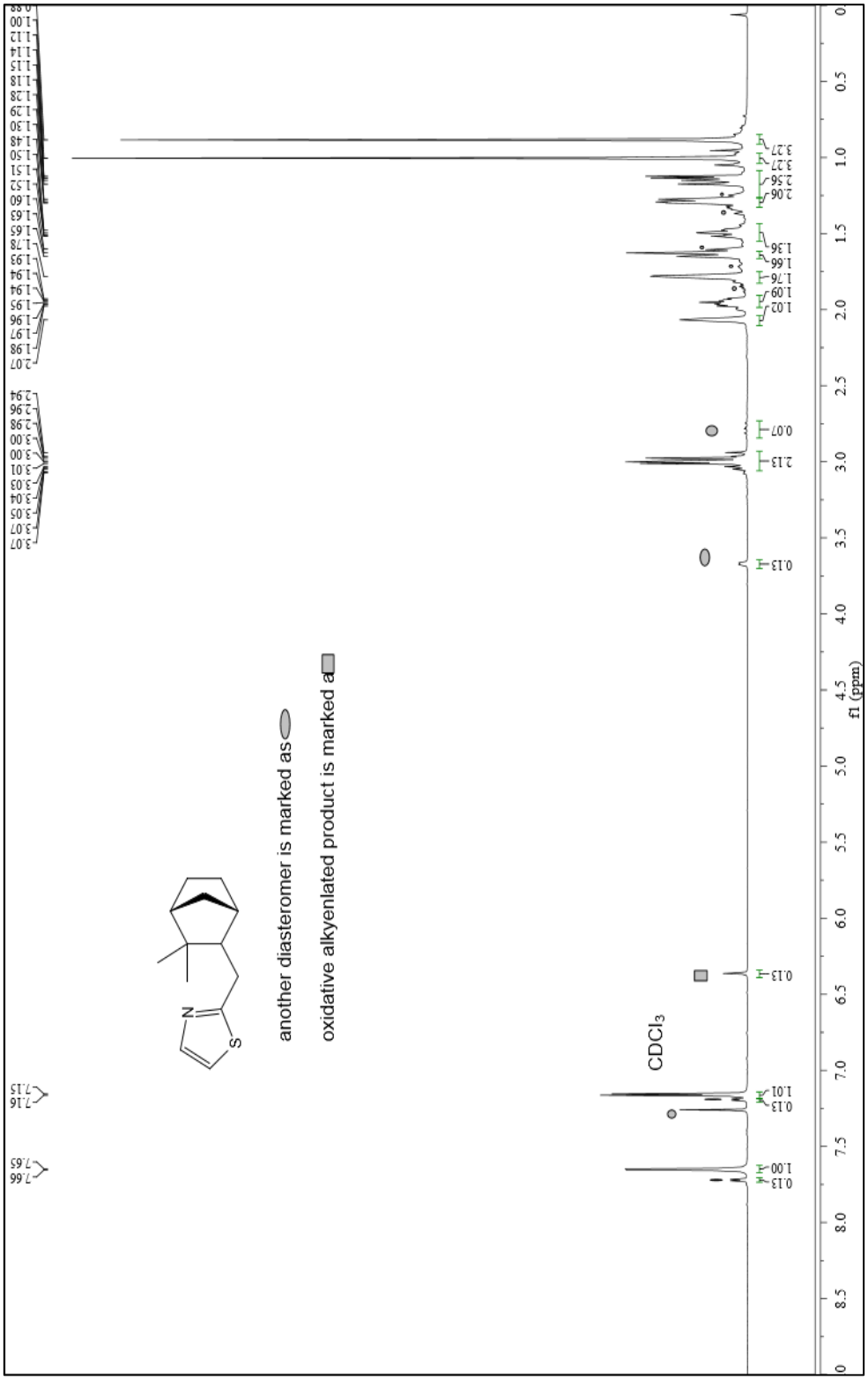
^{1}H NMR (400 MHz, $CDCl_3$) of **18q** 2-(bicyclo[2.2.1]heptan-2-yl)-4-(tert-butyl)thiazole



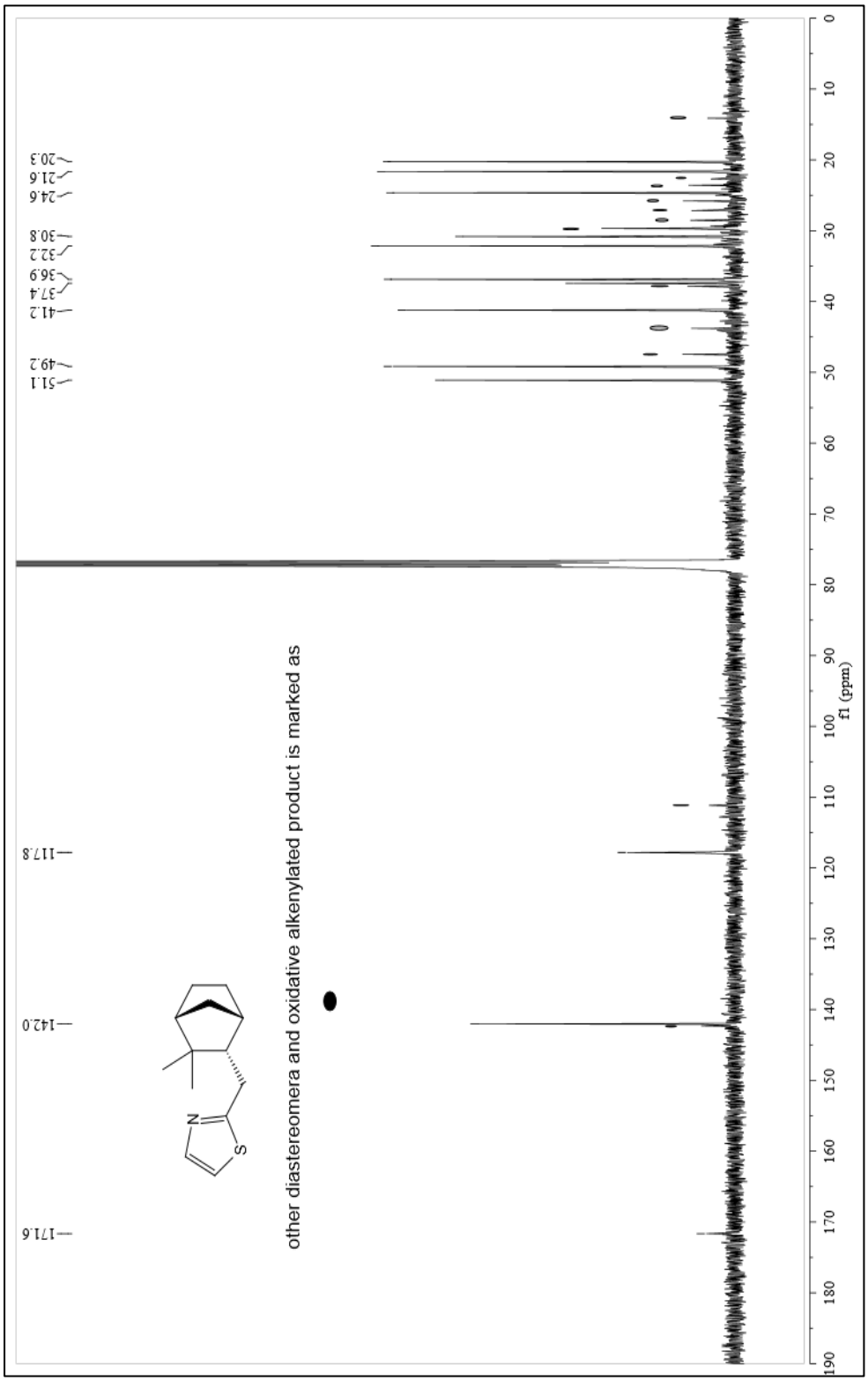
^{13}C NMR (101 MHz, $CDCl_3$) of **18q** 2-(bicyclo[2.2.1]heptan-2-yl)-4-(tert-butyl)thiazole



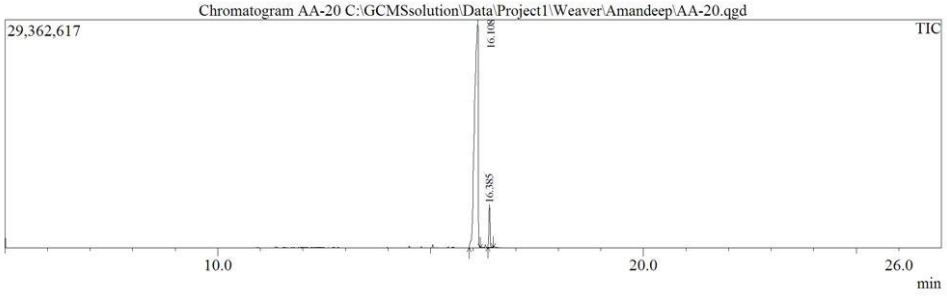
^{1}H NMR (400 MHz, $CDCl_3$) of **18r** 2-(((1S,4R)-3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)thiazole



^{13}C NMR (101 MHz, $CDCl_3$) of **18r** 2-(((1S,4R)-3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)thiazole



GC of **18r** 2-(((1S,4R)-3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)thiazole



Peak Report TIC

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2	16.385	16.342	16.467	10105309	5.50	5588343	16.01	1.80	MI	
				183573719	100.00	34910518	100.00			

Spectrum

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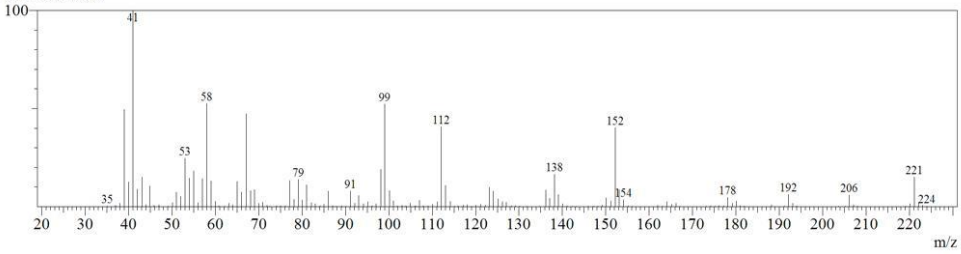
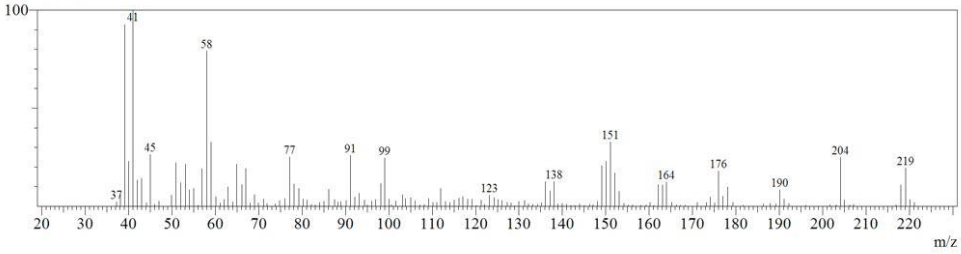
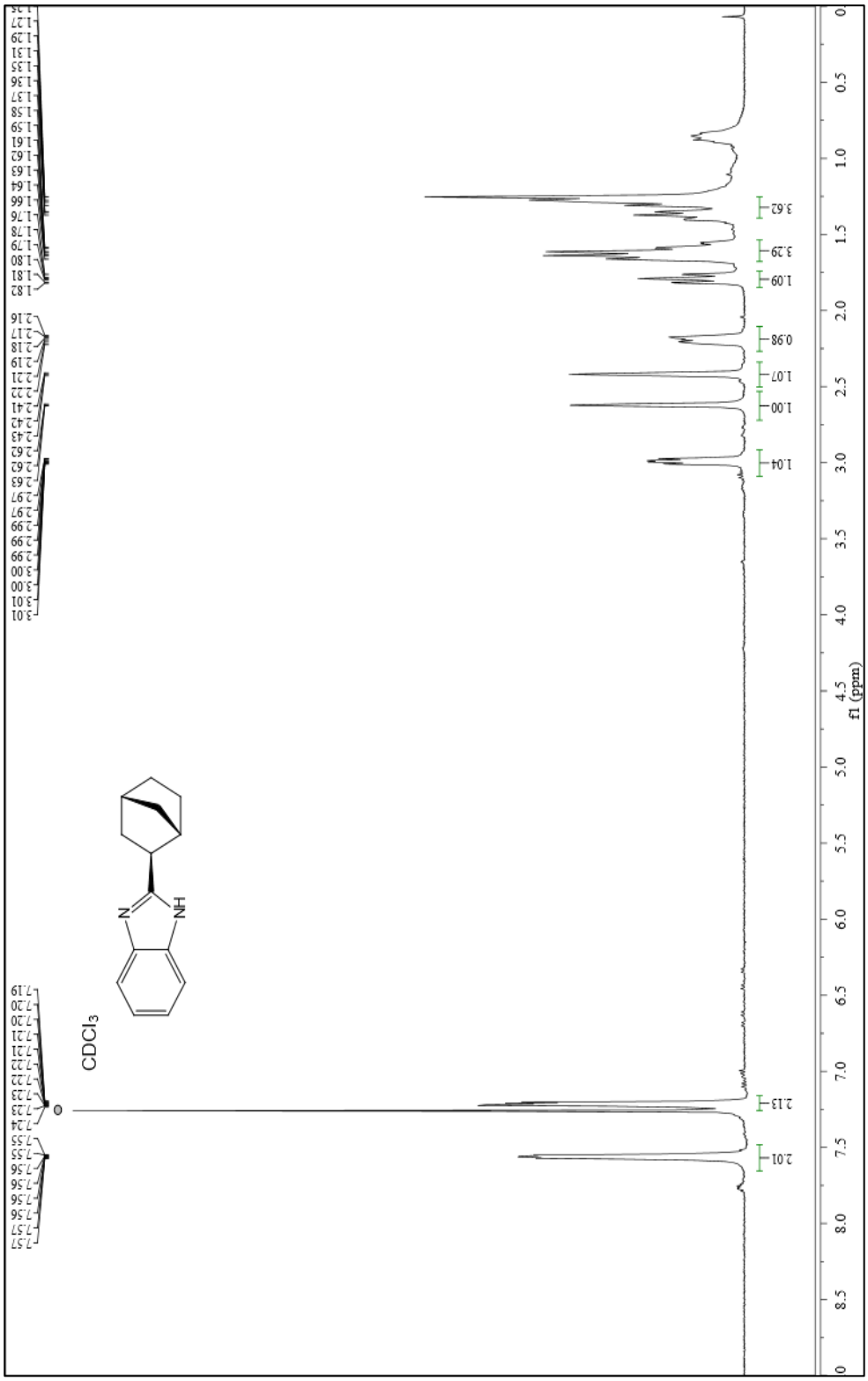
RawMode:Single 16.0(1324) BasePeak:41(1792897)
BG Mode:None



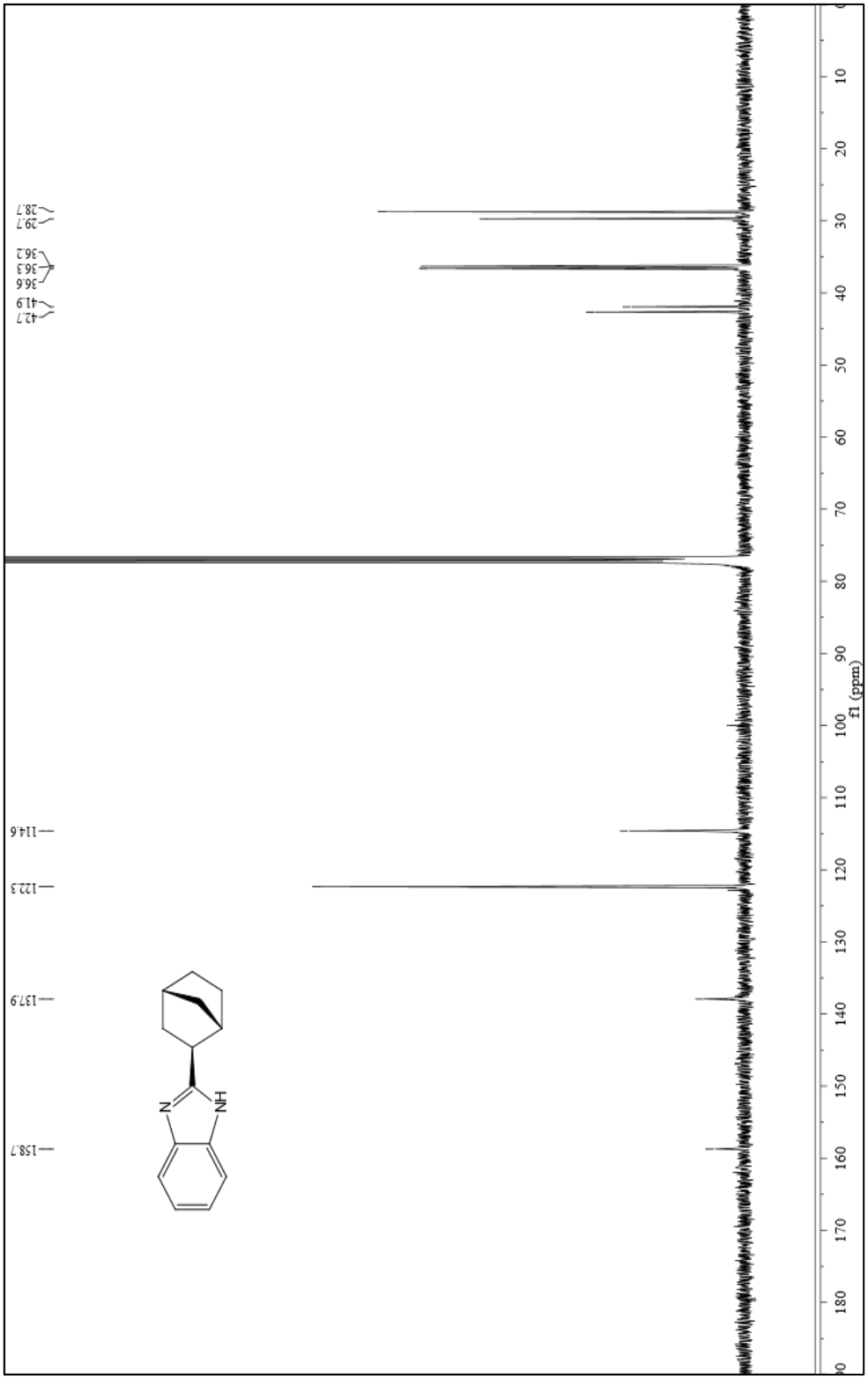
Line#:2 R.Time:16.4(Scan#:1366)
MassPeaks:157
RawMode:Single 16.4(1366) BasePeak:41(339510)
BG Mode:None



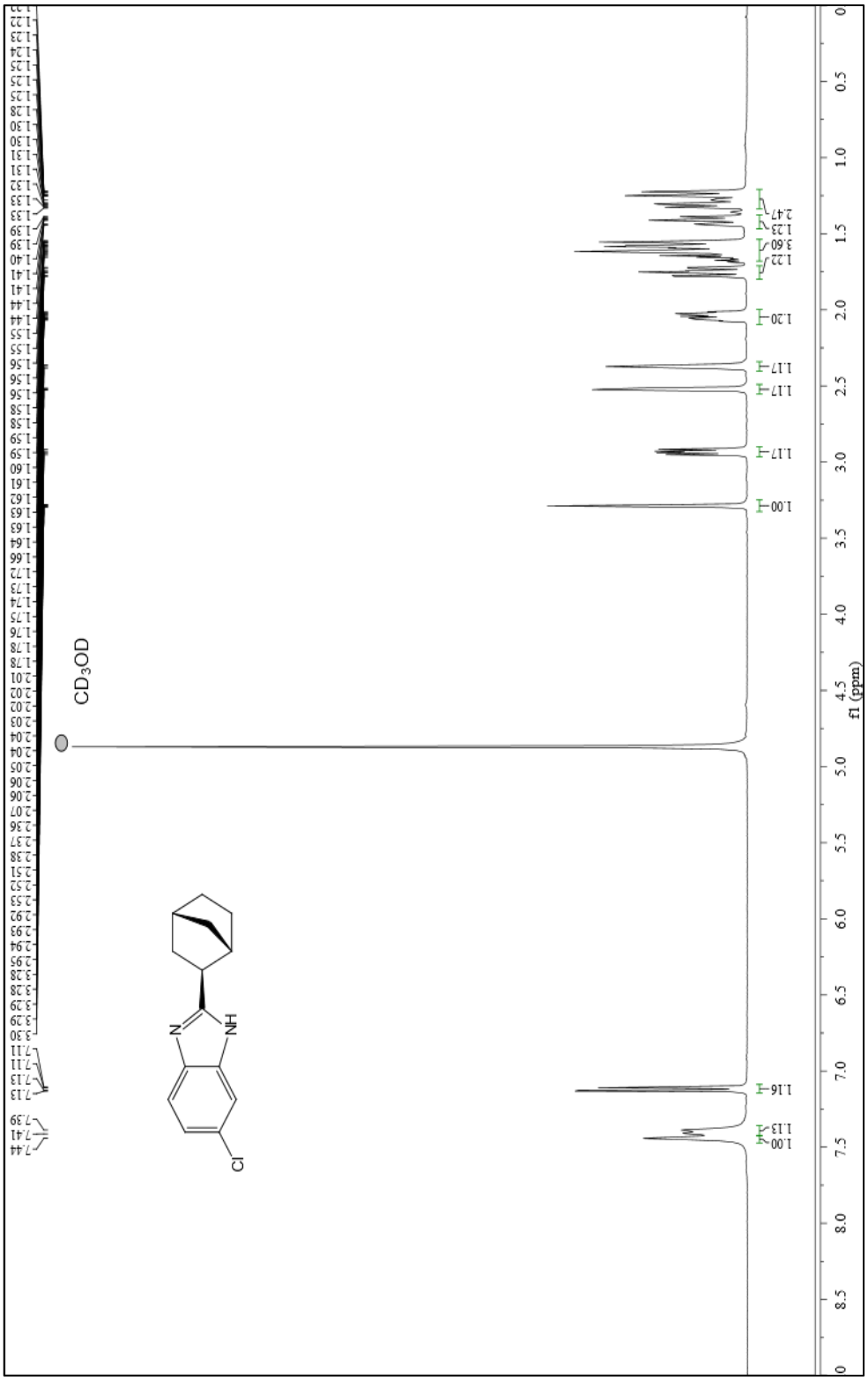
^{1}H NMR (400 MHz, $CDCl_3$) of **18s** 2-(bicyclo[2.2.1]heptan-2-ylmethyl)- 1H-benzo[d]imidazole



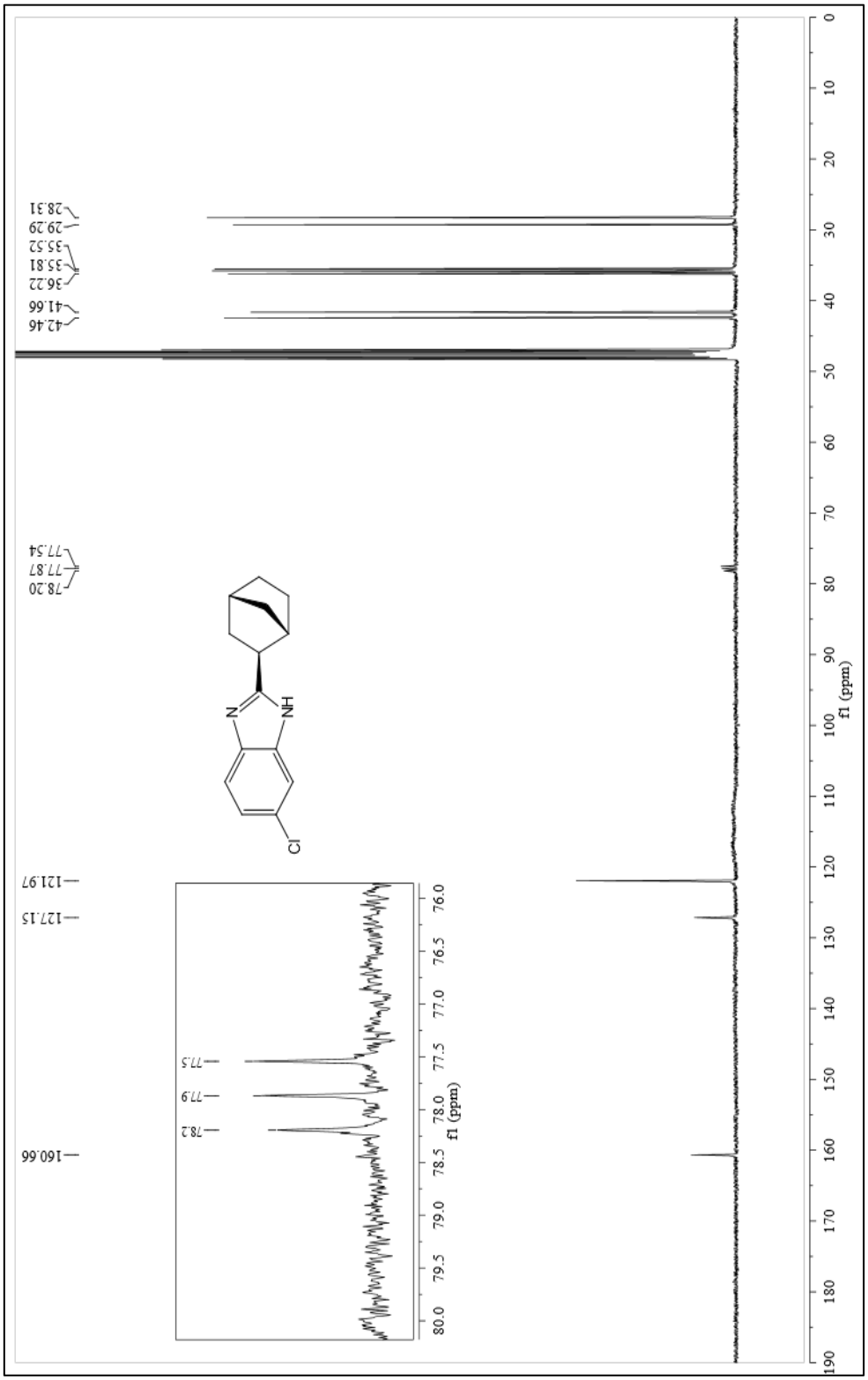
^{13}C NMR (101 MHz, $CDCl_3$) of **18s** 2-(bicyclo[2.2.1]heptan-2-ylmethyl)-1H-benzo[d]imidazole



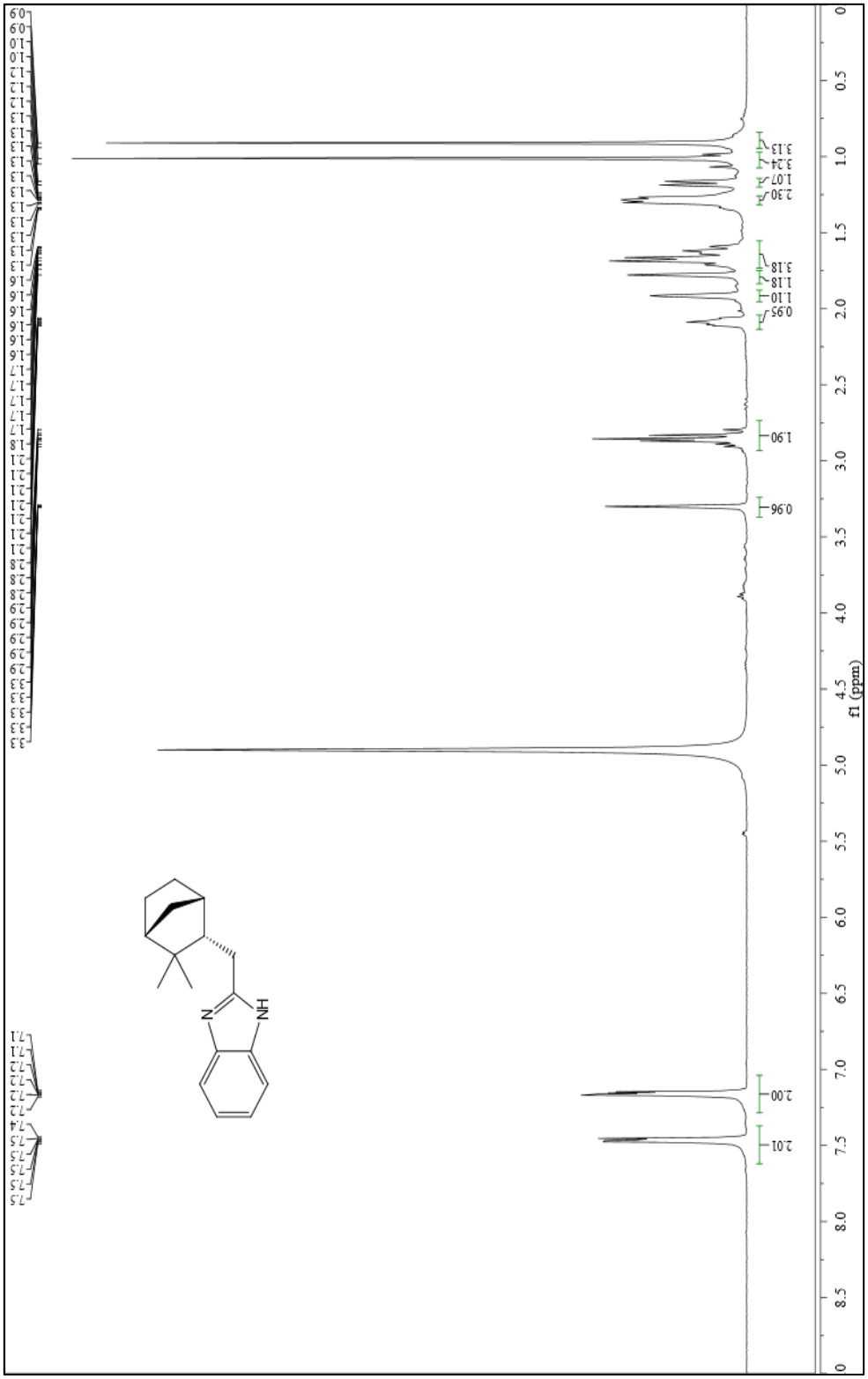
^{1}H NMR (400 MHz, CD_3OD) of **18t** 2-(bicyclo[2.2.1]heptan-2-ylmethyl)-6-chloro-1H-benzo[d]imidazole



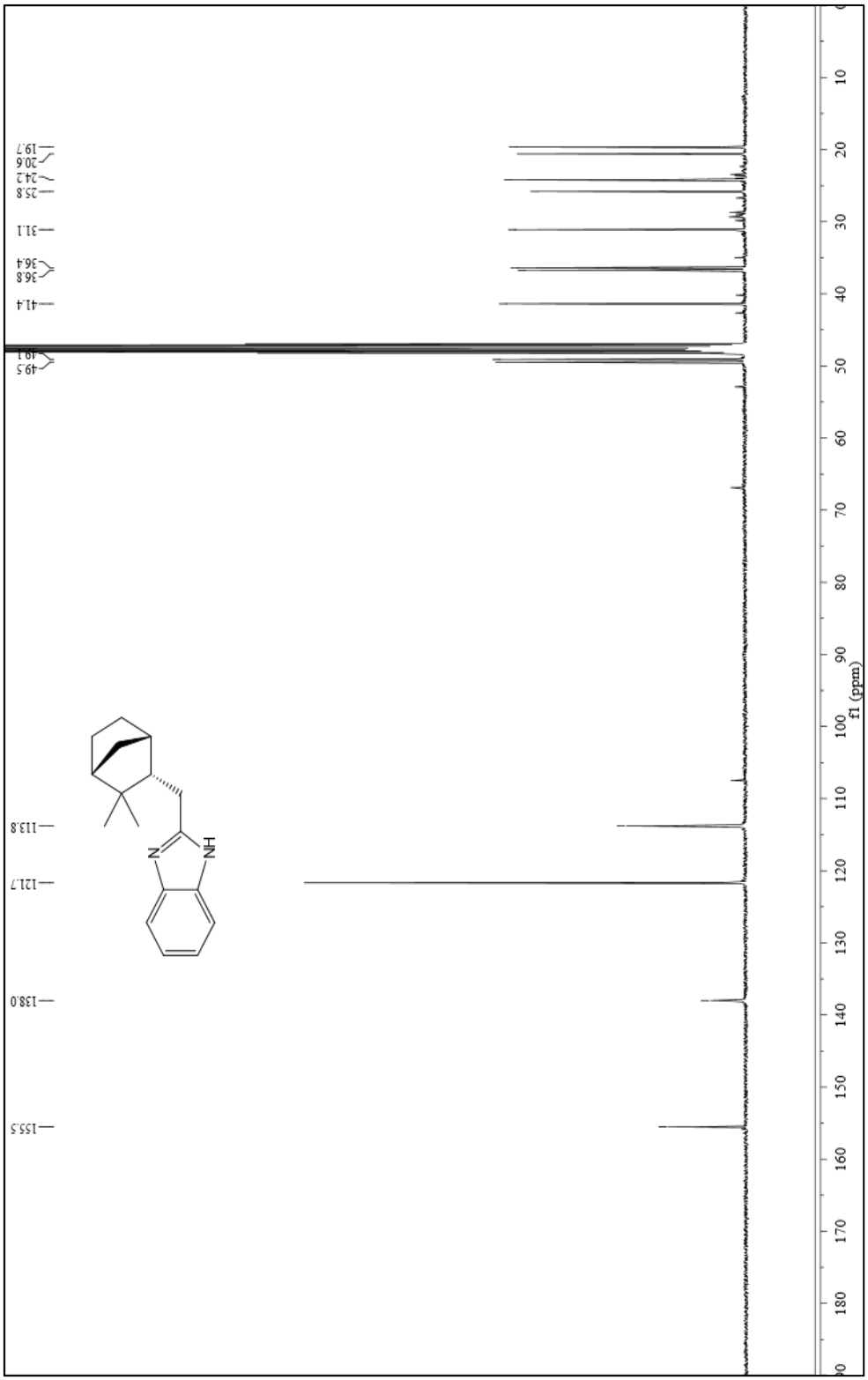
^{13}C NMR (101 MHz, CD_3OD) of **18t** 2-(bicyclo[2.2.1]heptan-2-ylmethyl)-6-chloro-1H-benzo[d]imidazole



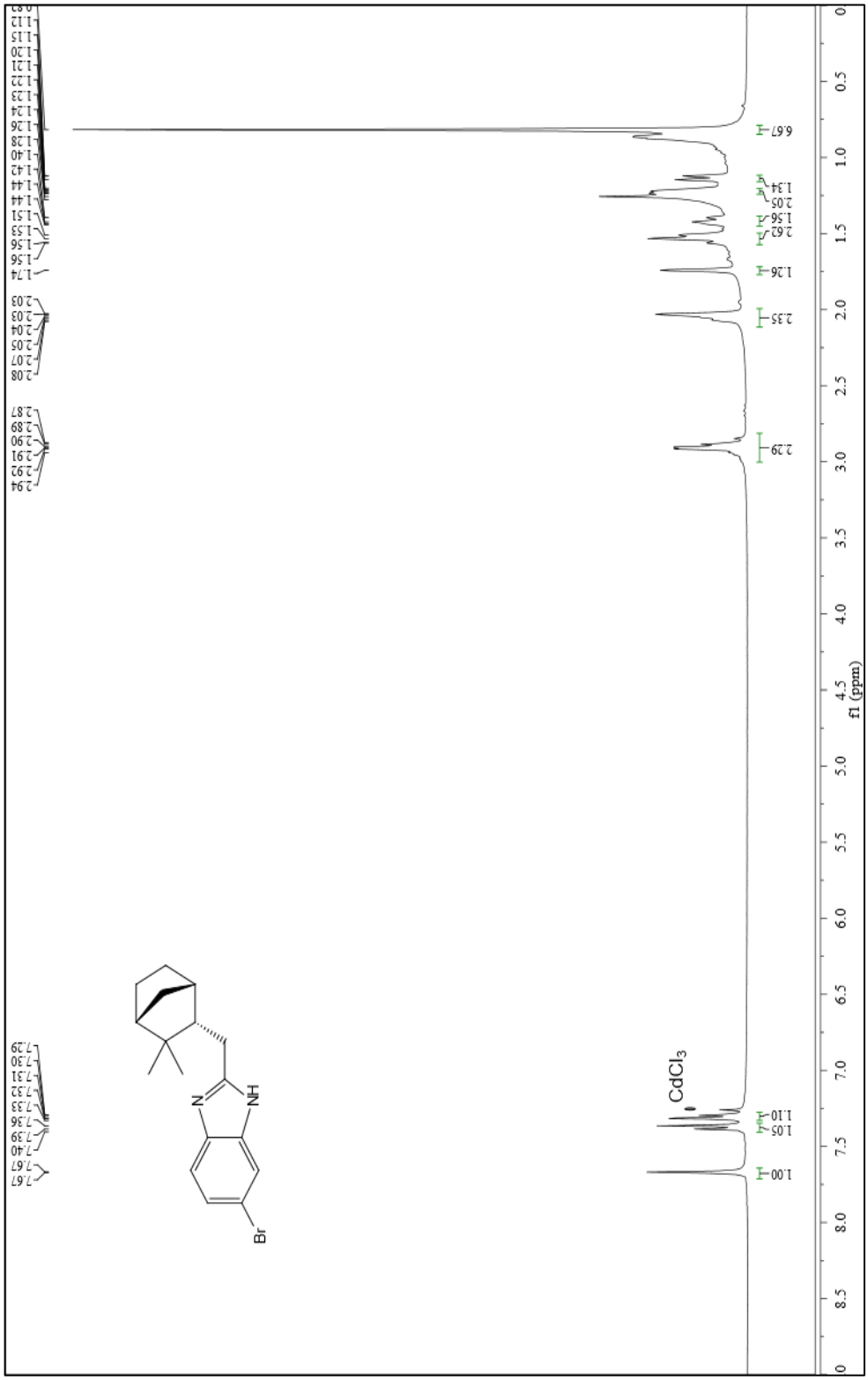
^{1}H NMR (400 MHz, CD_3OD) of **18u** 2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole



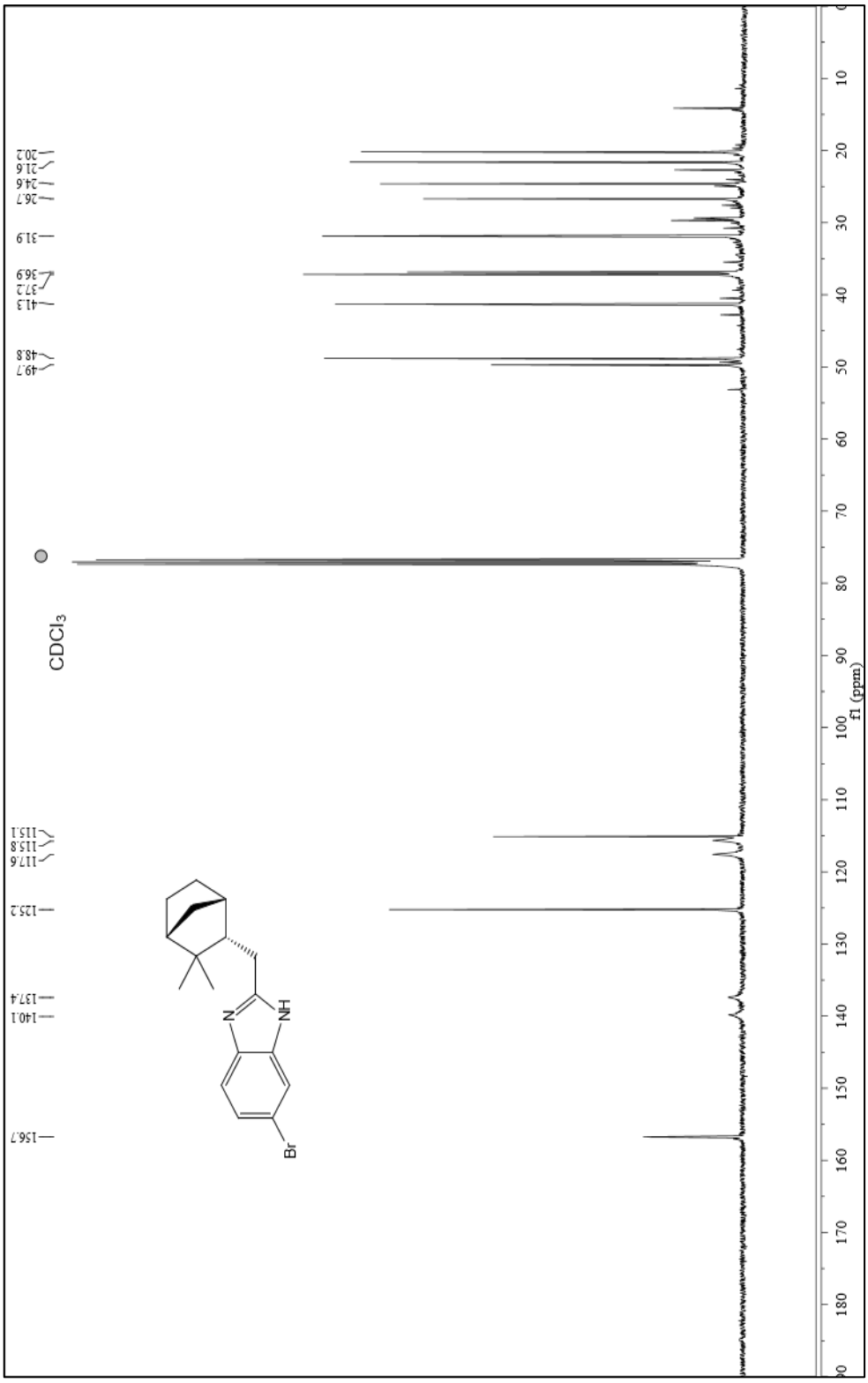
^{13}C NMR (101 MHz, CD_3OD) of **18u** 2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole



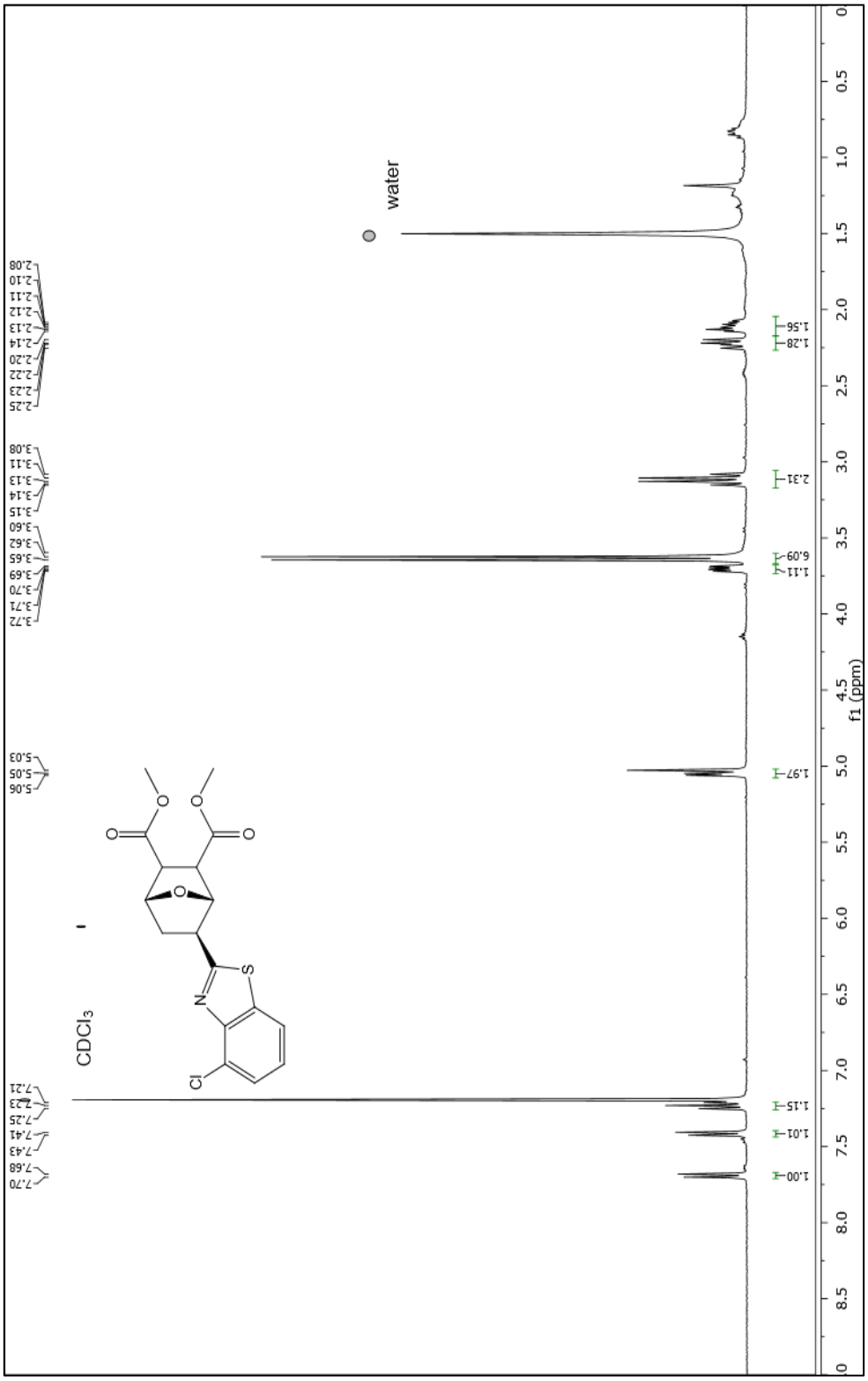
^{1}H NMR (400 MHz, $CDCl_3$) of **18v** 6-bromo-2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole



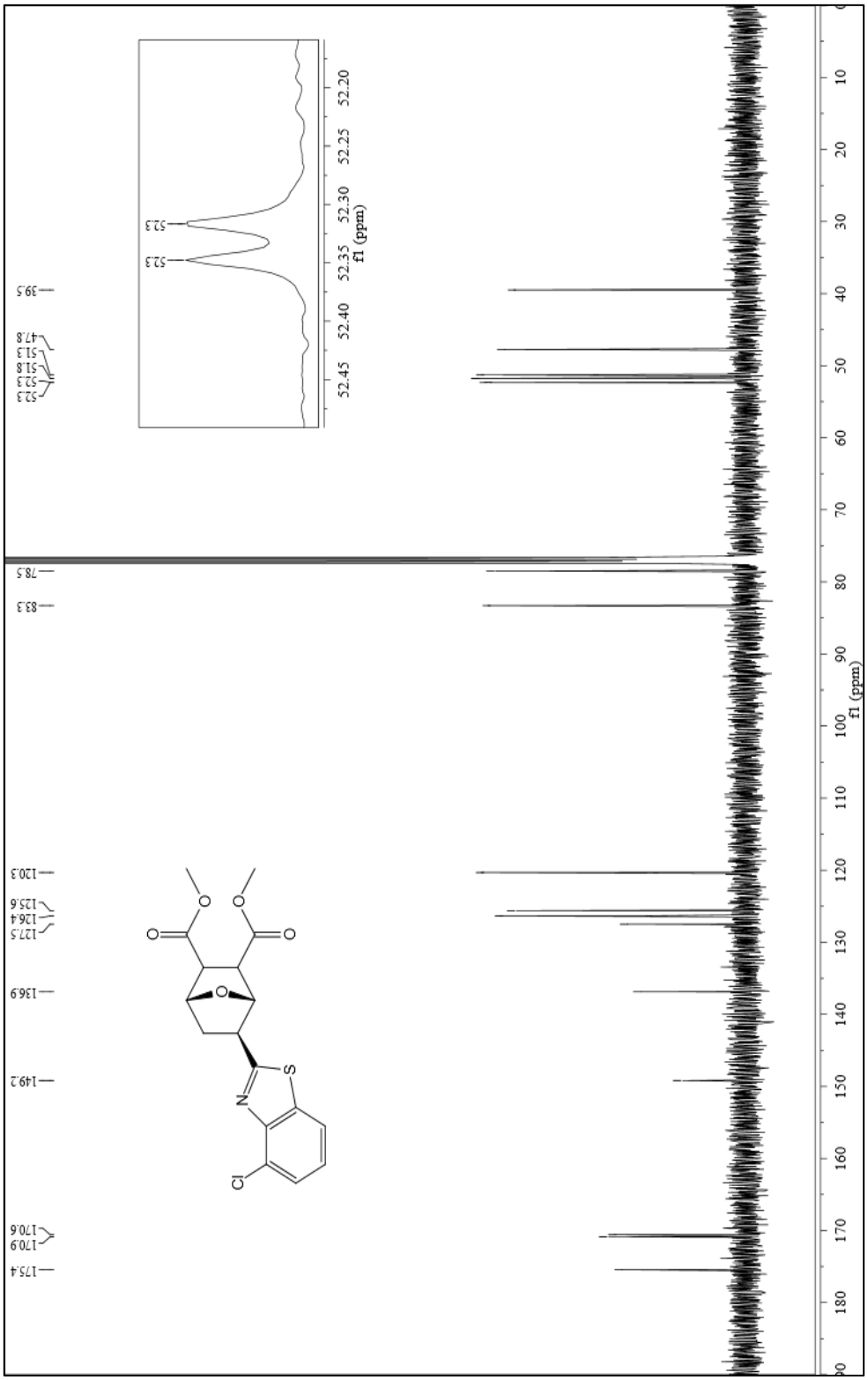
^{13}C NMR (101 MHz, $CDCl_3$) of **18v** 6-bromo-2-((3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-1H-benzo[d]imidazole



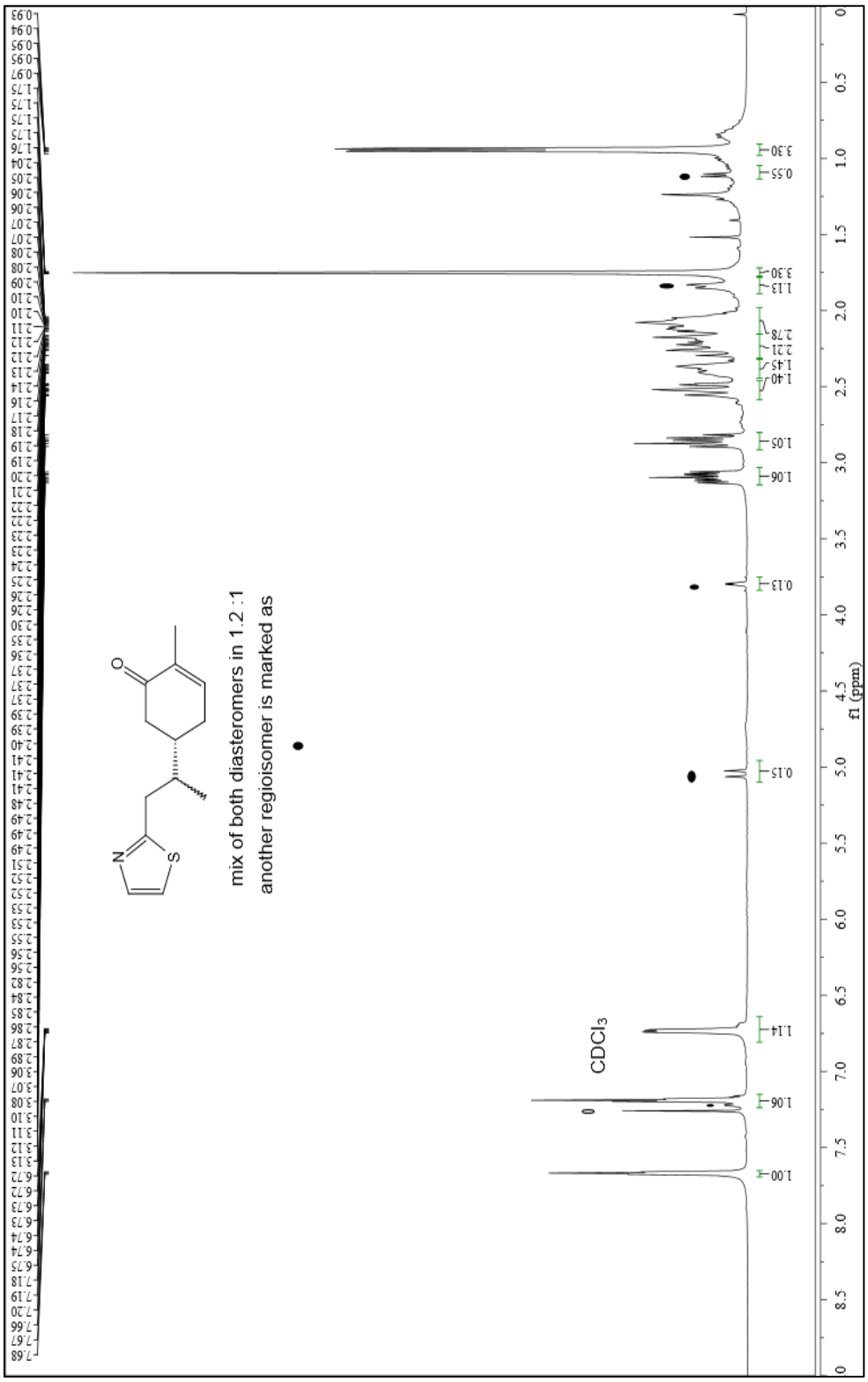
^{1}H NMR, (400 MHz, $CDCl_3$), of **18w** dimethyl 5-(4-chlorobenzo[d]thiazol-2-yl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



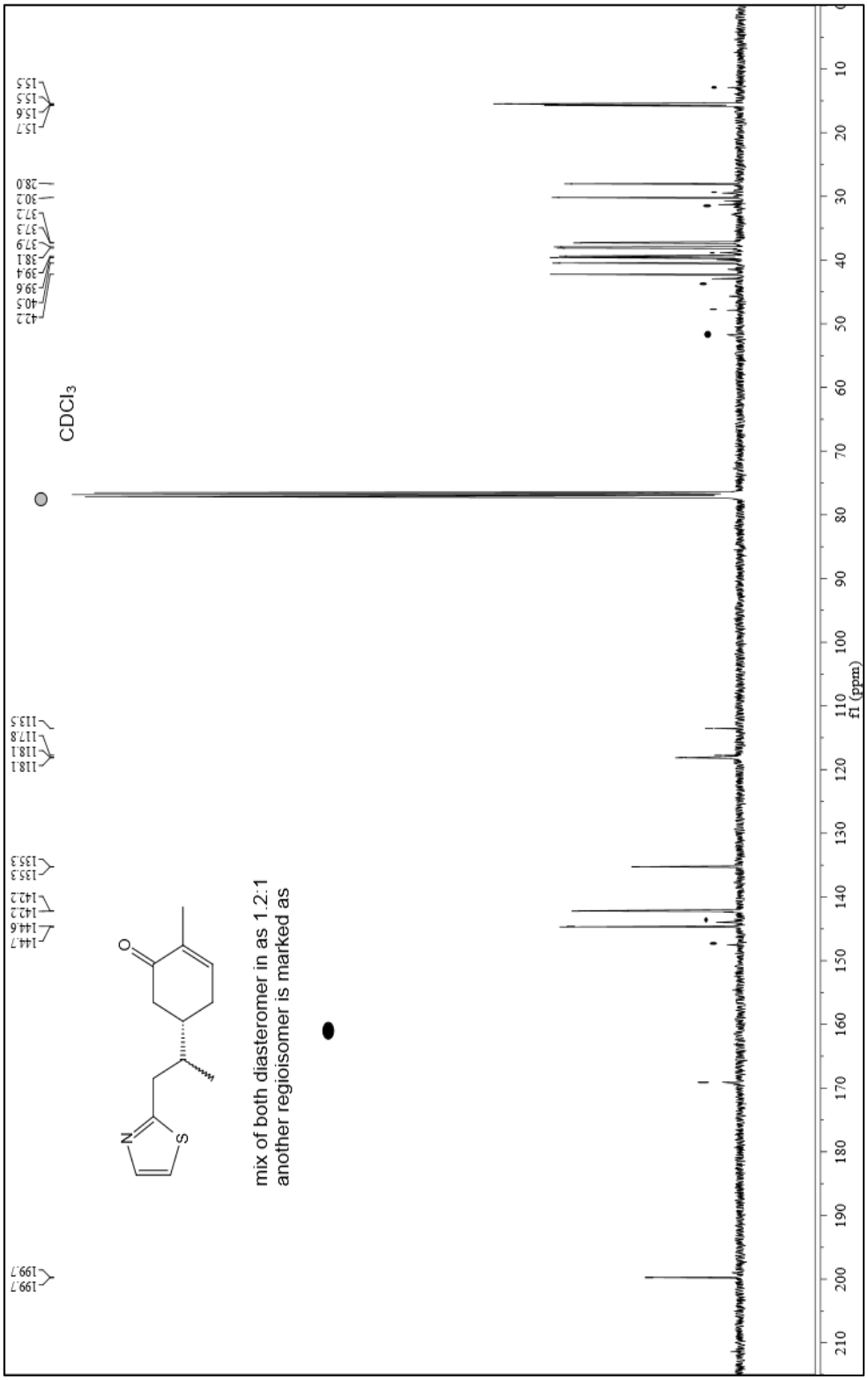
^{13}C NMR (101 MHz, $CDCl_3$) of **18w** dimethyl 5-(4-chlorobenzo[d]thiazol-2-yl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



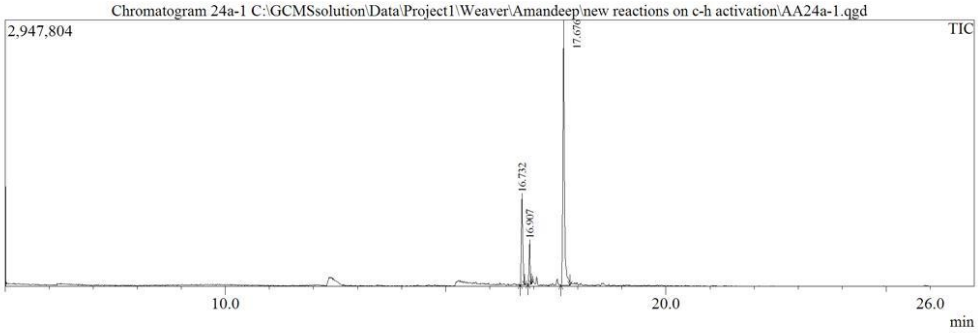
^{1}H NMR (400 MHz, $CDCl_3$) of **18x** (Major) 2-methyl-5-(1-(thiazol-2-yl)propan-2-yl)cyclohex-2-en-1-one and B) 2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



^{13}C NMR (101 MHz, $CDCl_3$) of **18x** (Major) 2-methyl-5-(1-(thiazol-2-yl)propan-2-yl)cyclohex-2-en-1-one and B) 2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



GC of **18x** (Major) 5R)-2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



Peak Report TIC

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2	16.907	16.867	16.950	786775	7.96	494055	11.13	1.59	MI	
3	17.676	17.617	17.825	6945002	70.26	2932388	66.05	2.36	MI	
				9884351	100.00	4439890	100.00			

Spectrum

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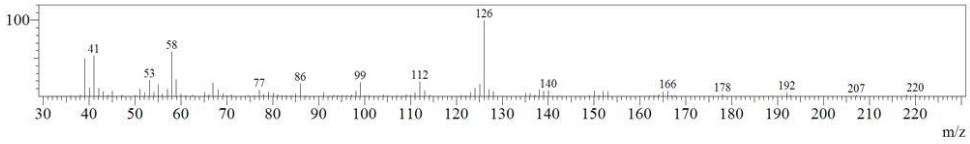
BG Mode:None



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MassPeaks:75
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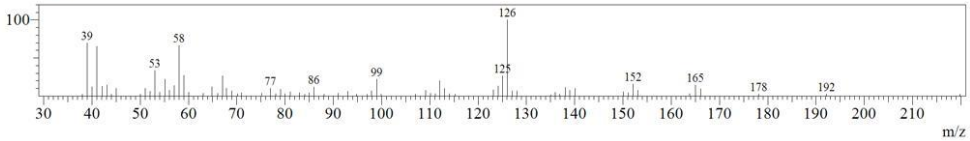
BG Mode:None



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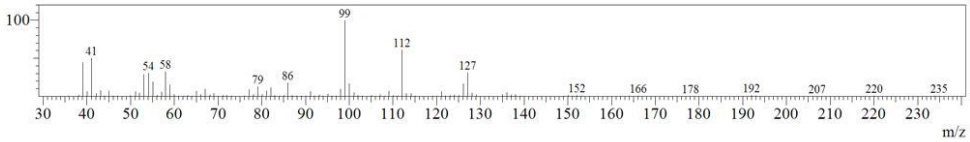
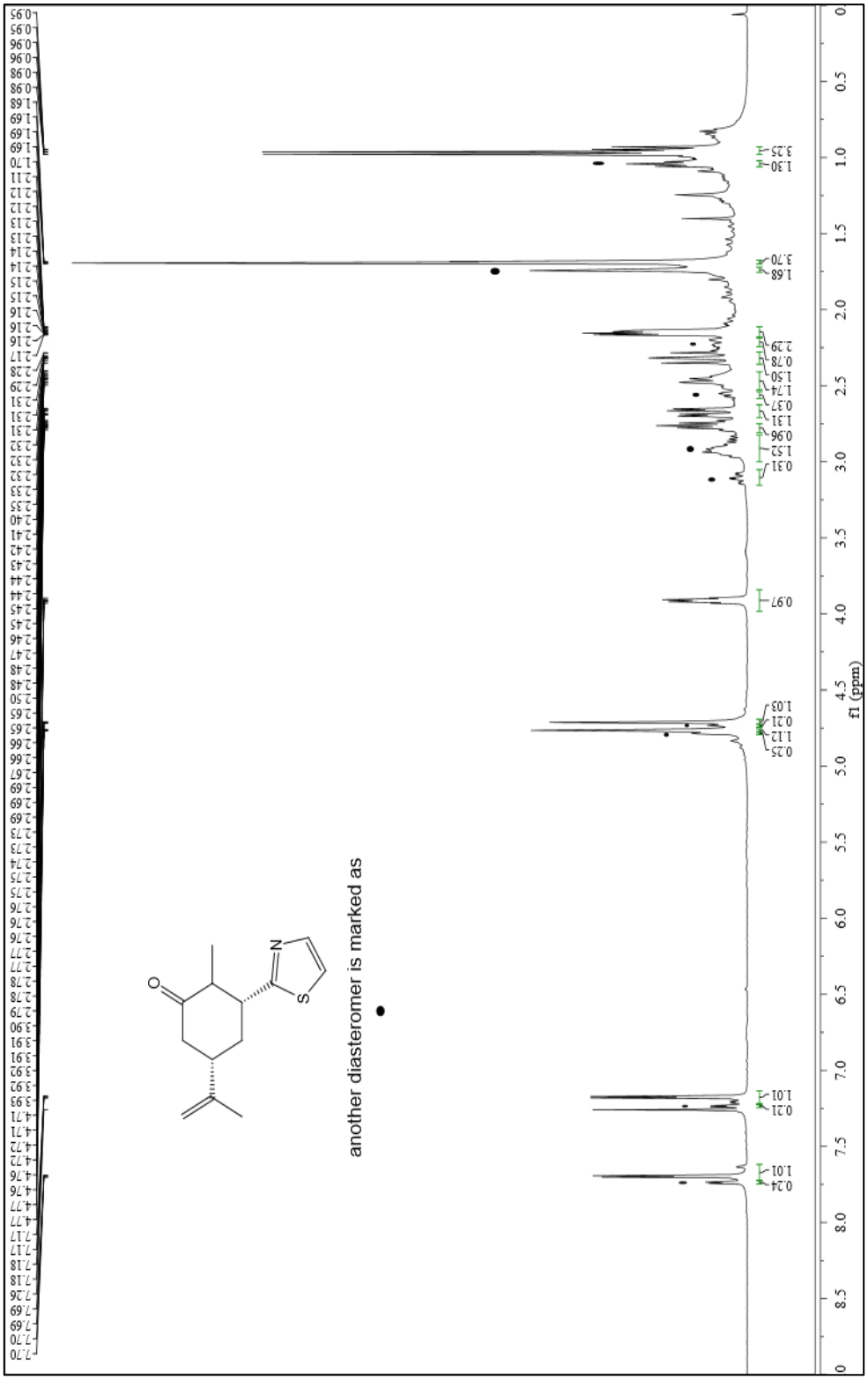
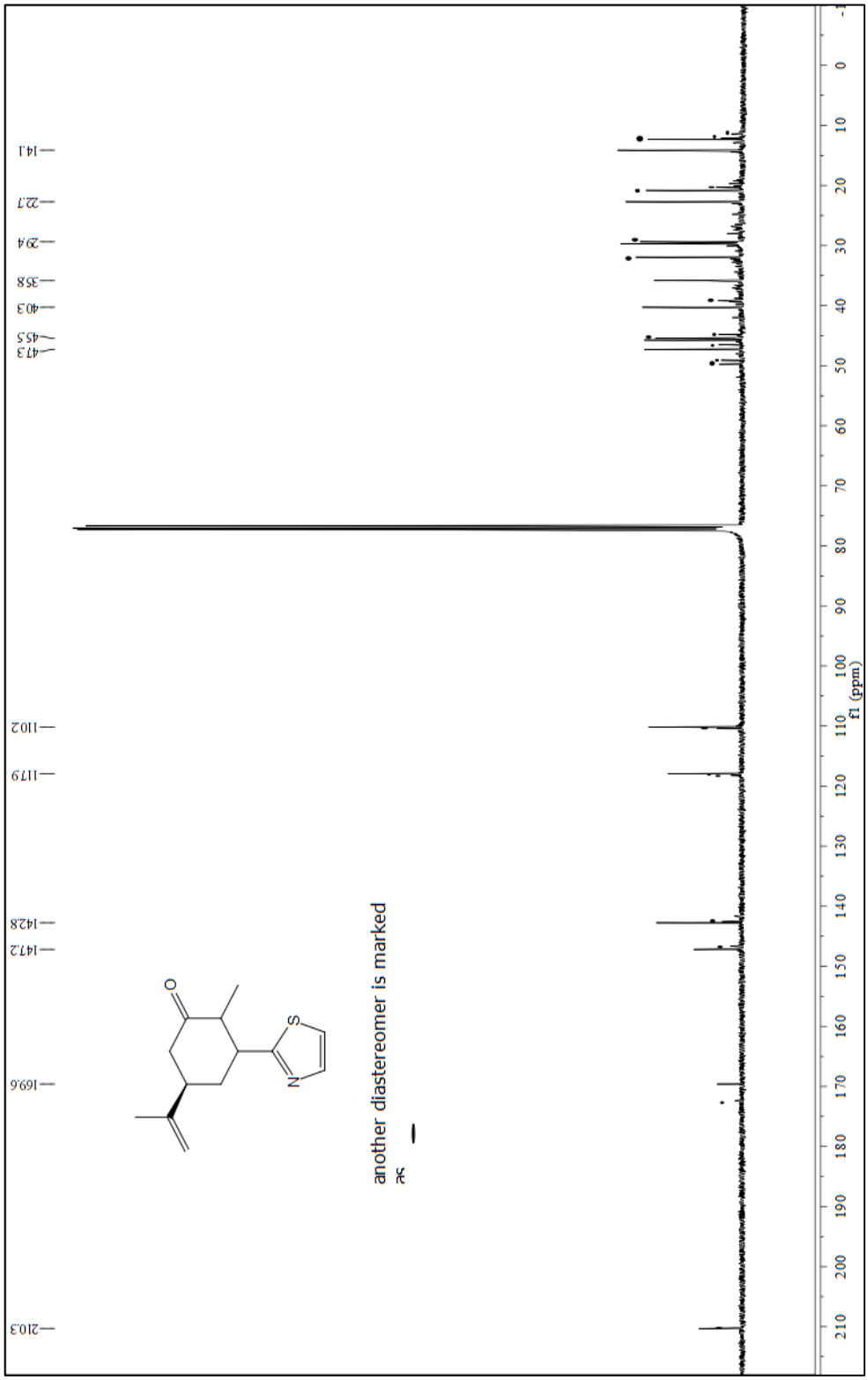
MassPeaks:107
RawMode:Single 17.7(1522) BasePeak:99(427613)
BG Mode:None



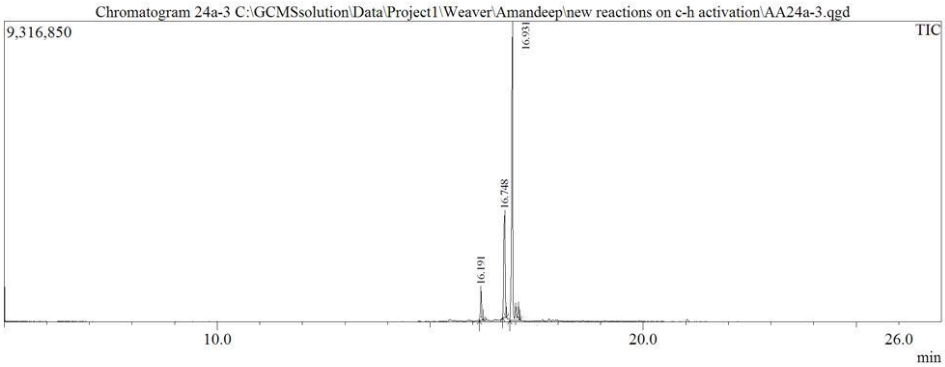
^{1}H NMR (400 MHz, $CDCl_3$) of **18x** (Minor) 5(R)-2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



^{13}C NMR (101 MHz, $CDCl_3$) of **18x** (Minor) 5(R)-2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



GC of **18x** (Minor) 5R)-2-methyl-5-(prop-1-en-2-yl)-3-(thiazol-2-yl)cyclohexan-1-one



Peak Report TIC

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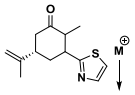
1	16.191	16.158	16.250	1710578	5.79	1063505	7.80	1.60	MI	
2	16.748	16.700	16.792	7865669	26.62	3315661	24.32	2.37	MI	
3	16.931	16.867	17.108	19970990	67.59	9257042	67.89	2.15	MI	
				29547237	100.00	13636208	100.00			

Diastereomer of minor regioisomer



Spectrum

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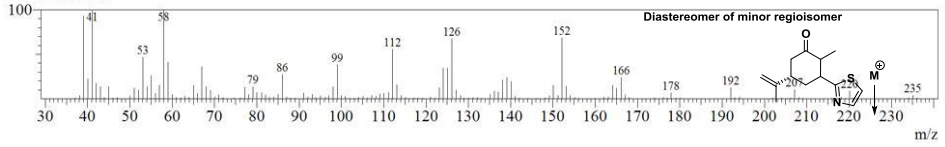
BG Mode:None



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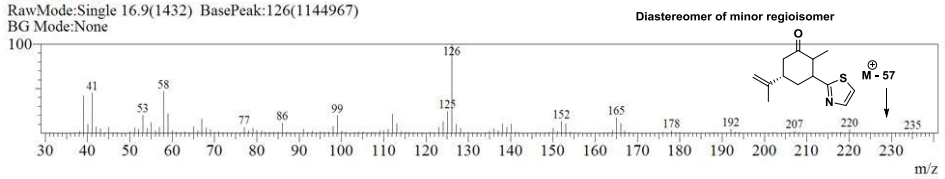
BG Mode:None



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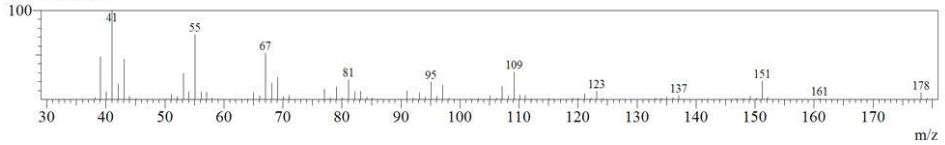
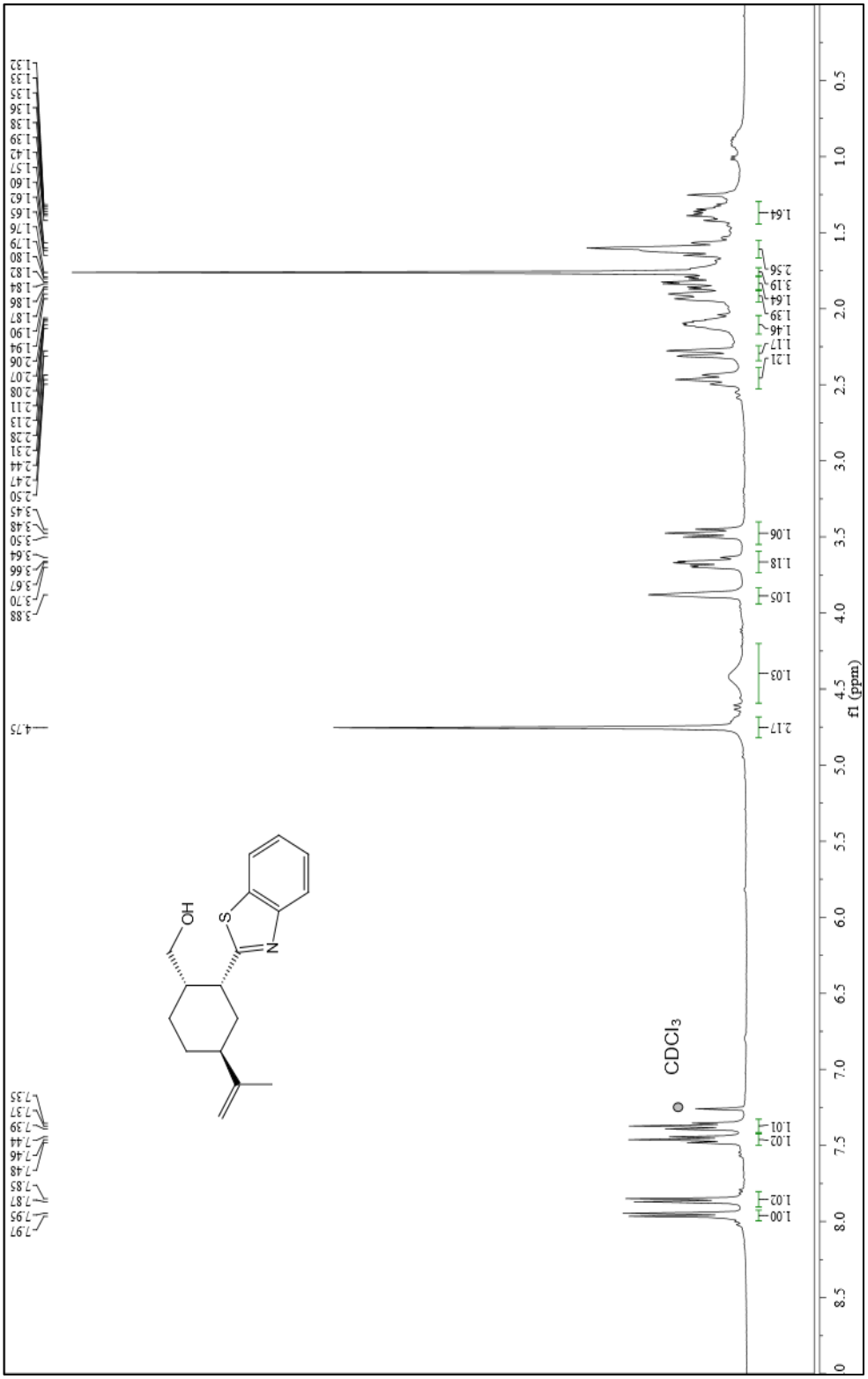
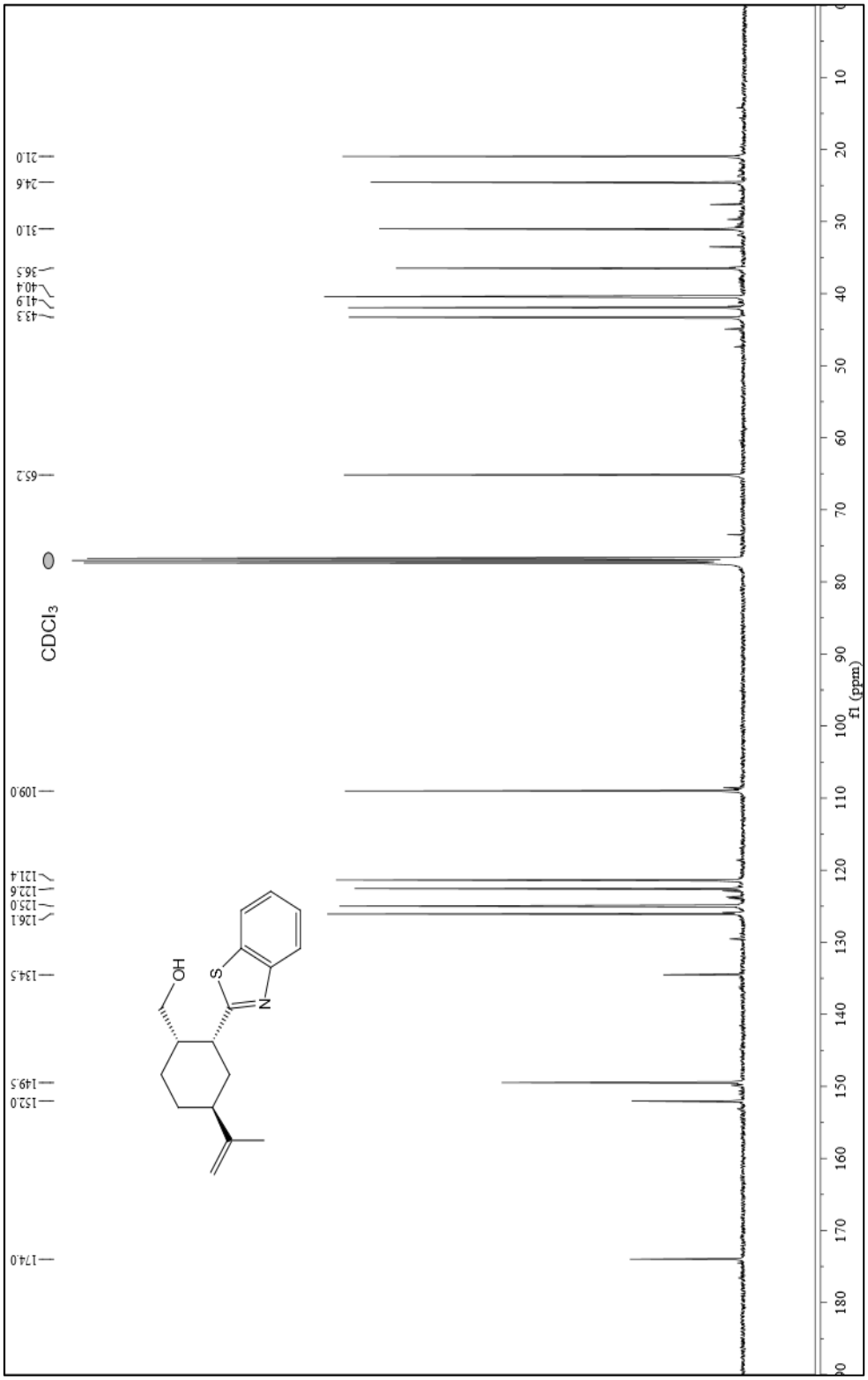
BG Mode:None



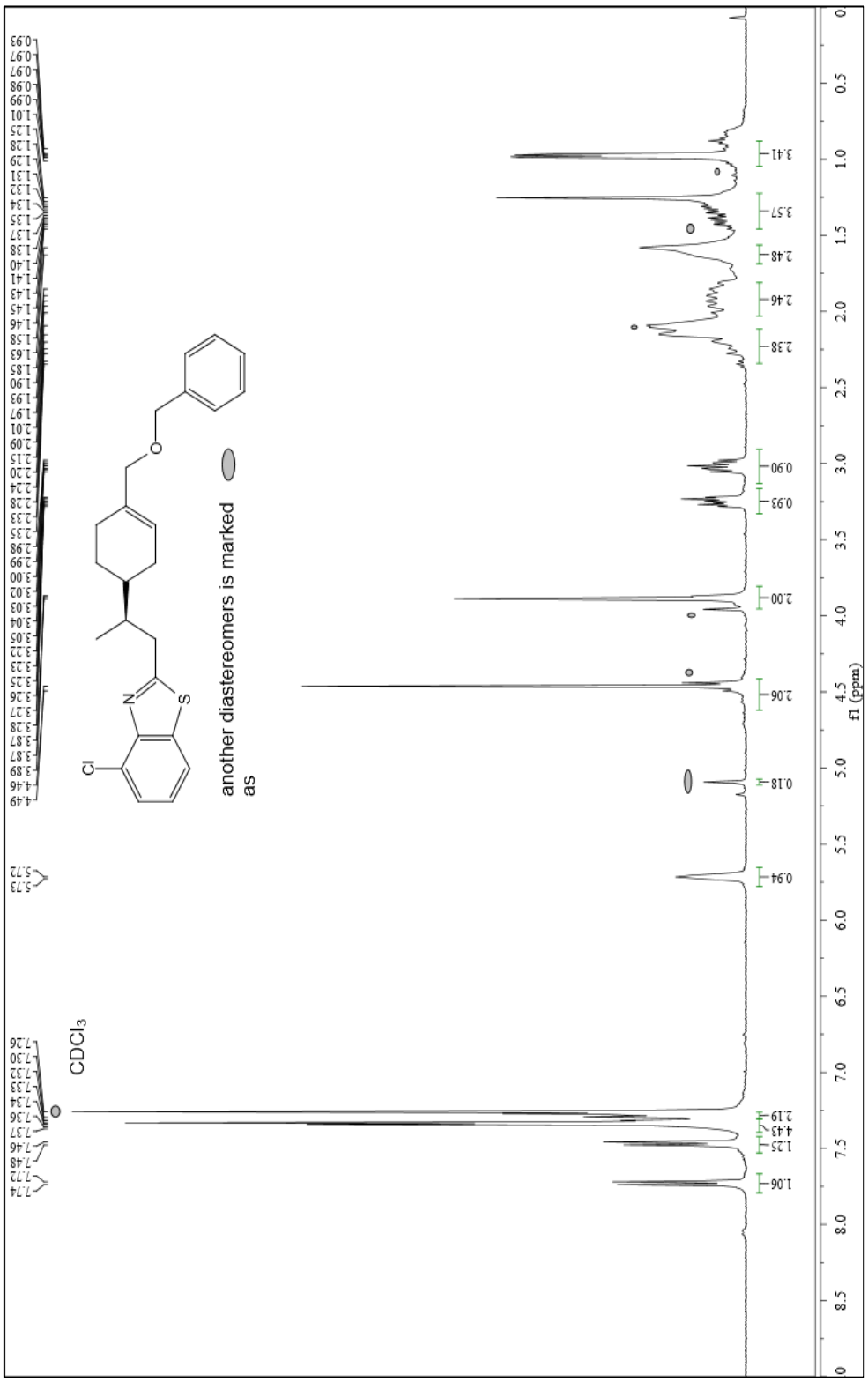
^{1}H NMR (400 MHz, $CDCl_3$) of **18y** (2-(benzo[d]thiazol-2-yl)-4-(prop-1-en-2-yl)cyclohexyl)methanol



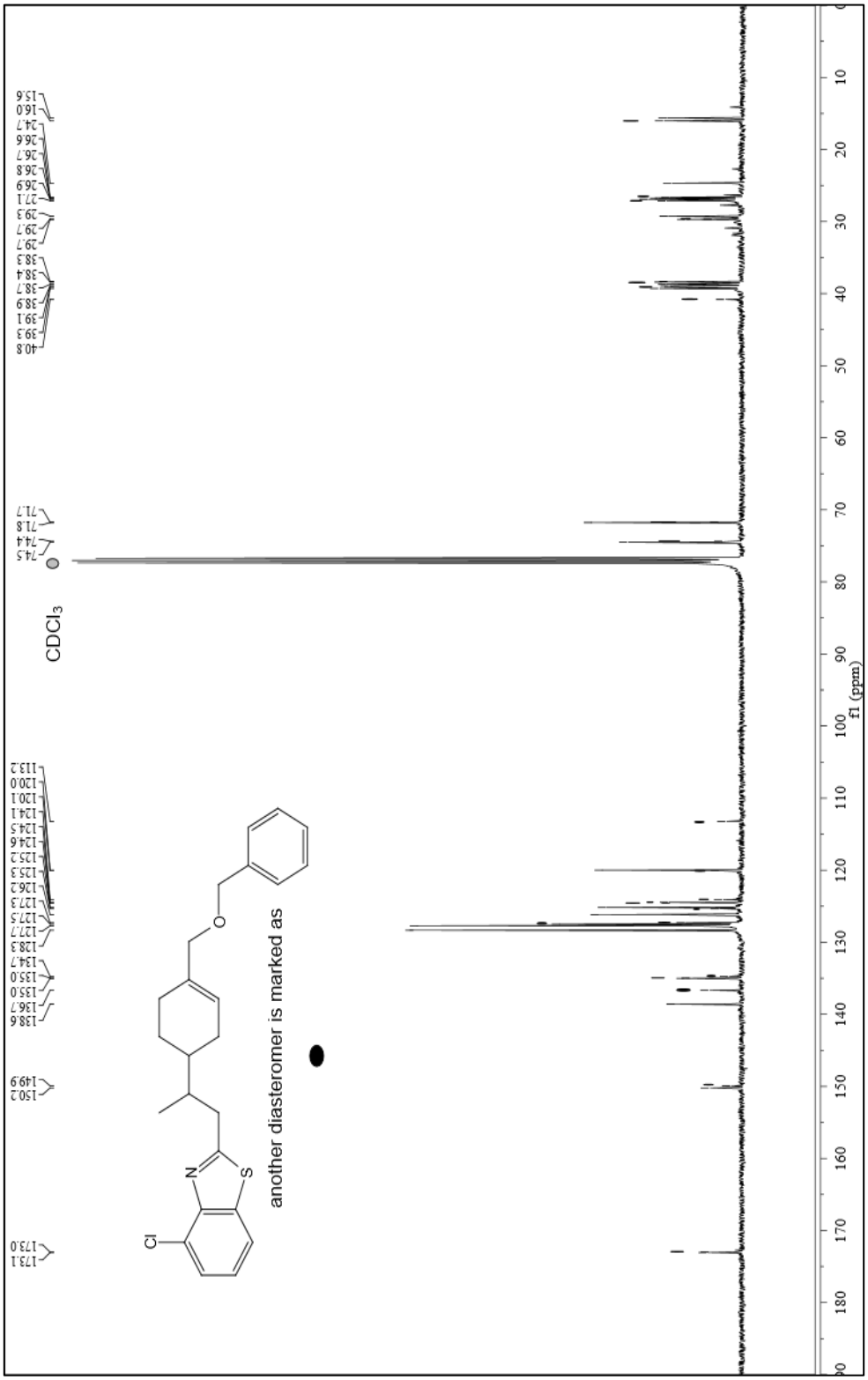
^{13}C NMR (101 MHz, $CDCl_3$) of **18y** (2-(benzo[d]thiazol-2-yl)-4-(prop-1-en-2-yl)cyclohexyl)methanol



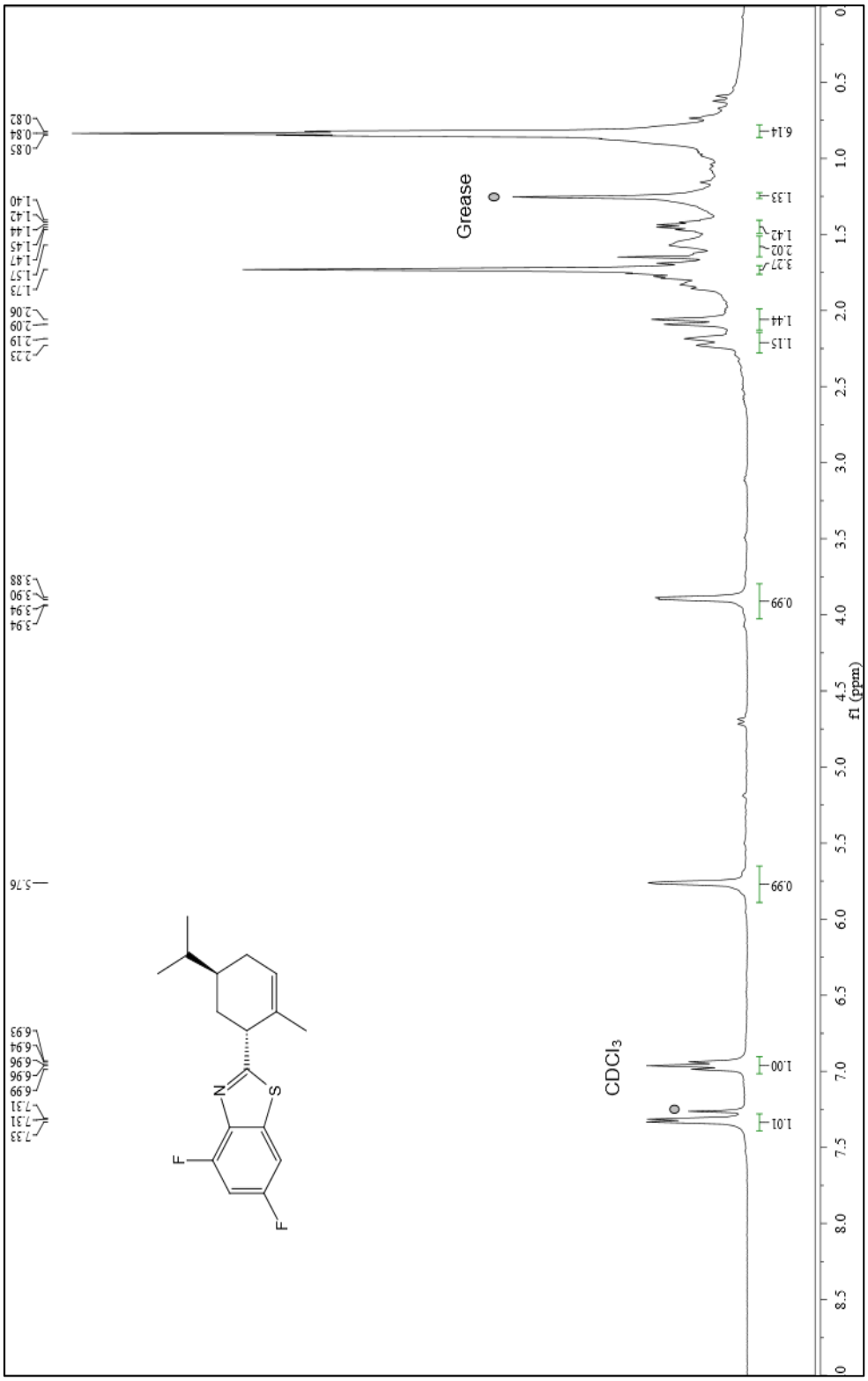
^{1}H NMR (400 MHz, $CDCl_3$) of **18z** 2-(2-(4-((benzyloxy)methyl)cyclohex-3-en-1-yl)propyl)-4-chlorobenzo[d]thiazole



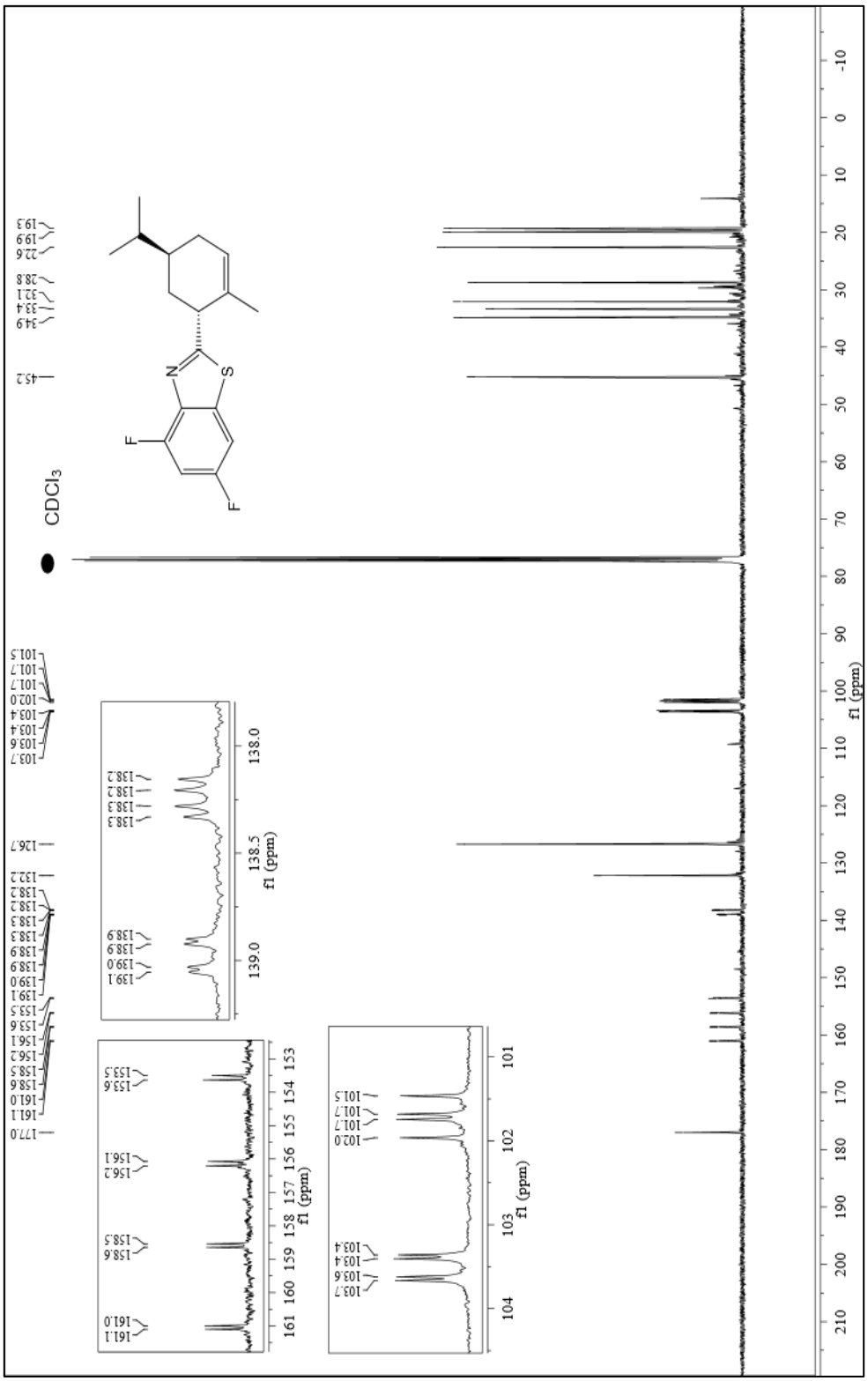
^{13}C NMR (101 MHz, $CDCl_3$) of **18z** 2-(2-(4-((benzyloxy)methyl)cyclohex-3-en-1-yl)propyl)-4-chlorobenzo[d]thiazole



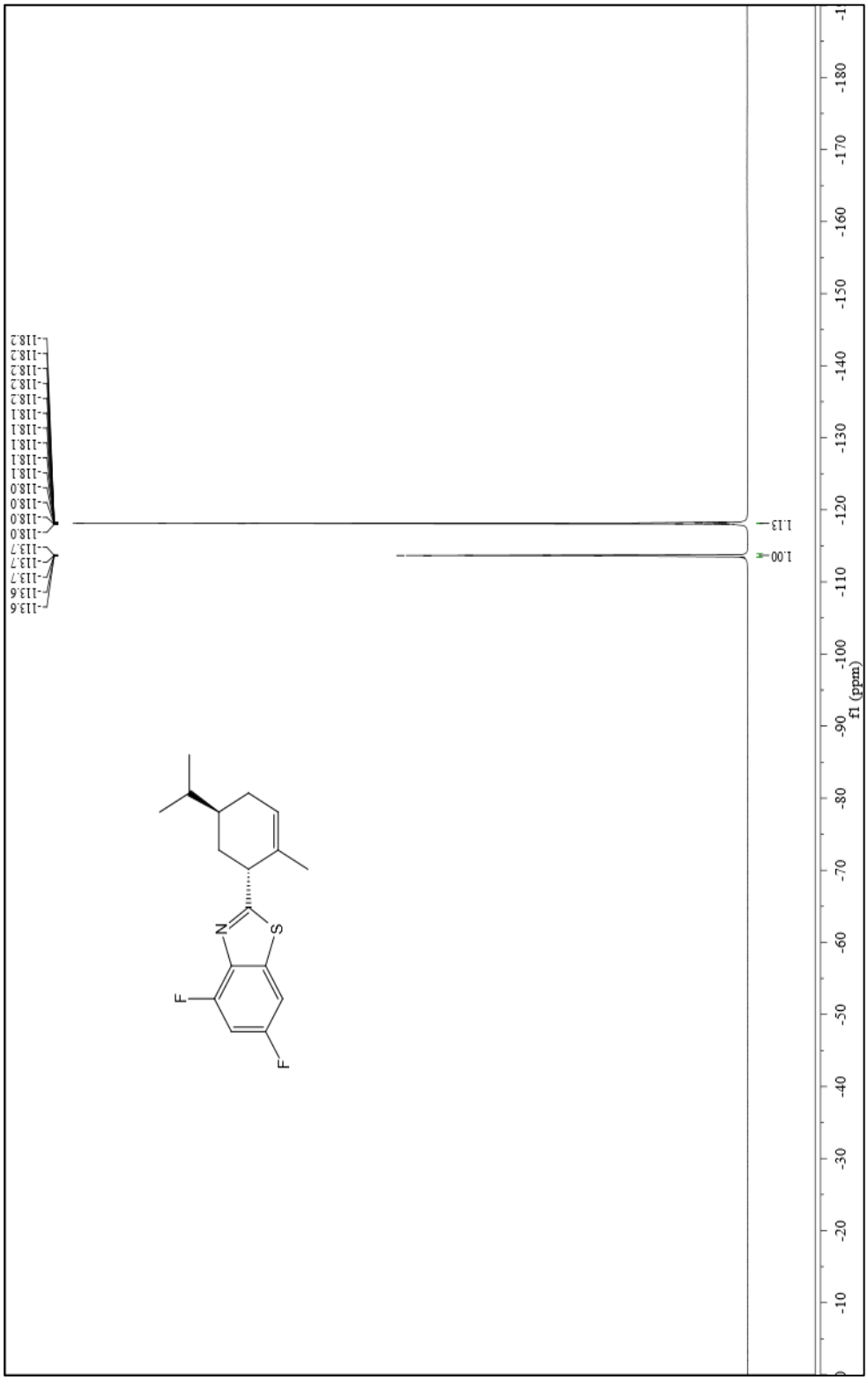
^{1}H NMR (400 MHz, $CDCl_3$) of **19a** 4,6-difluoro-2-(5-isopropyl-2-methylcyclohex-2-en-1-yl)benzo[d]thiazol



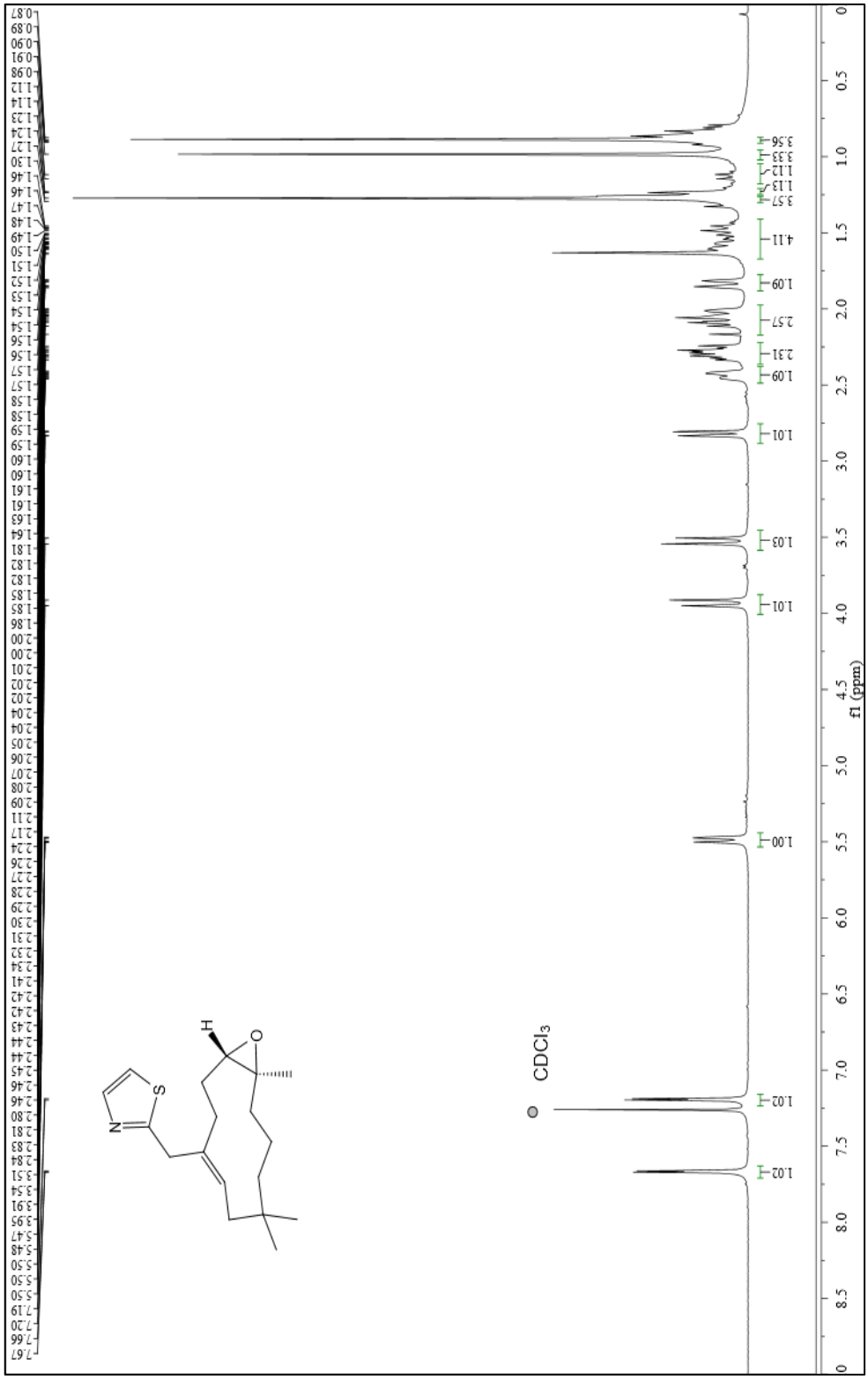
^{13}C NMR (101 MHz, $CDCl_3$) of **19a** 4,6-difluoro-2-(5-isopropyl-2-methylcyclohex-2-en-1-yl)benzo[d]thiazole



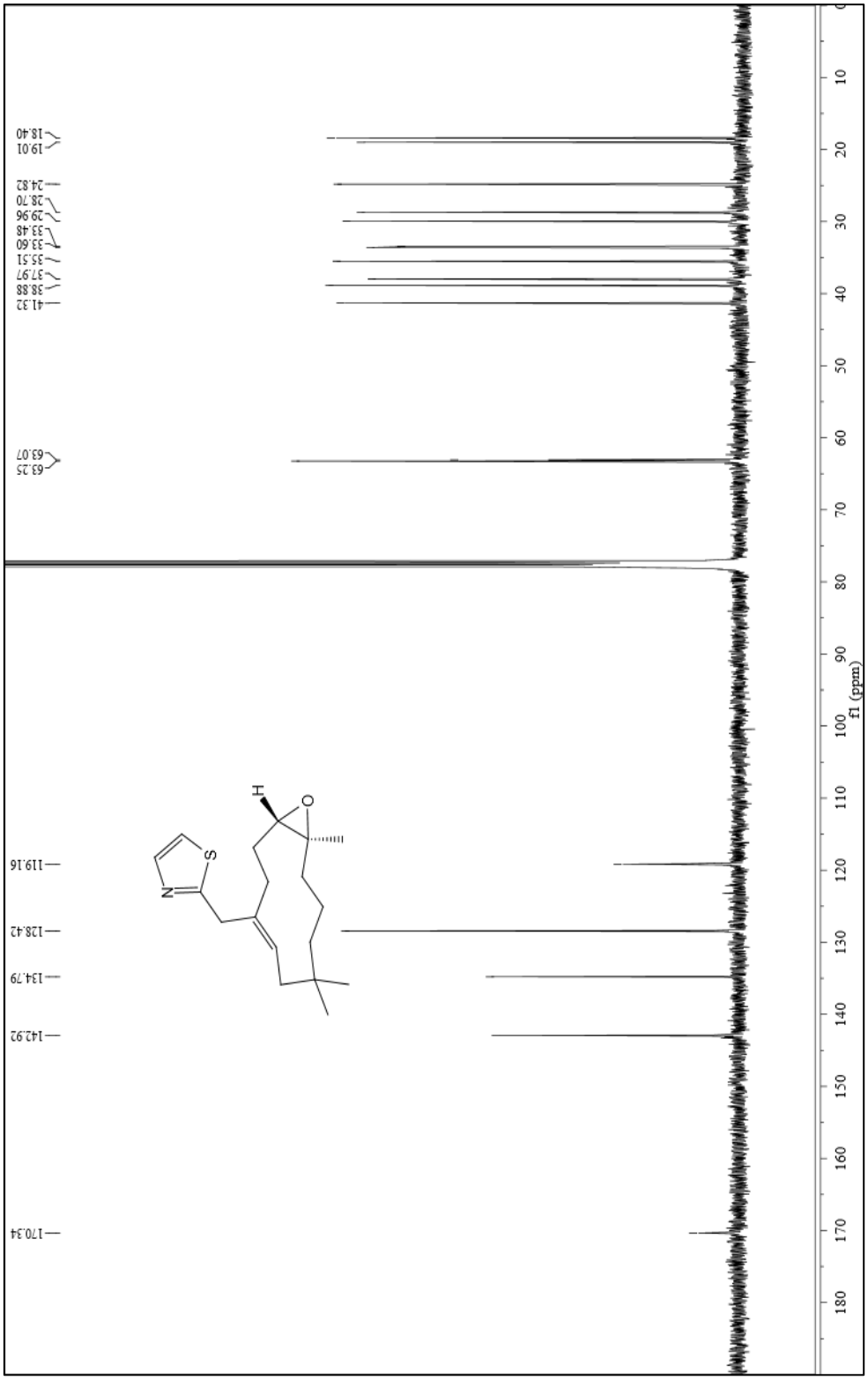
^{19}F NMR (376 MHz, $CDCl_3$) of **19a** 4,6-difluoro-2-(5-isopropyl-2-methylcyclohex-2-en-1-yl)benzo[d]thiazole



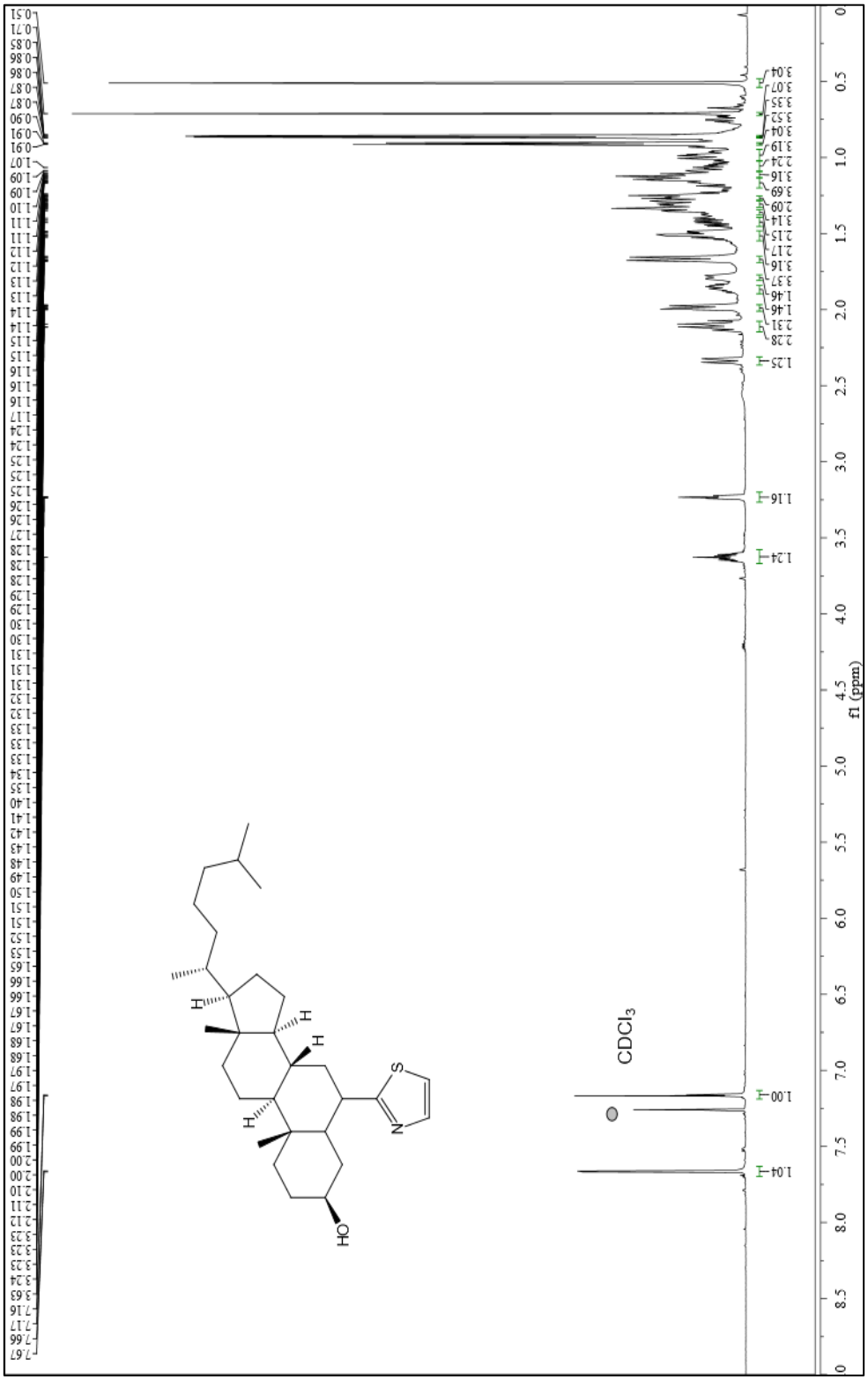
^{1}H NMR (400 MHz, $CDCl_3$) of **19b** 2-(((1S,11S,Z)-7,7,11-trimethyl-12-oxabicyclo[9.1.0]dodec-4-en-4-yl)methyl)thiazole



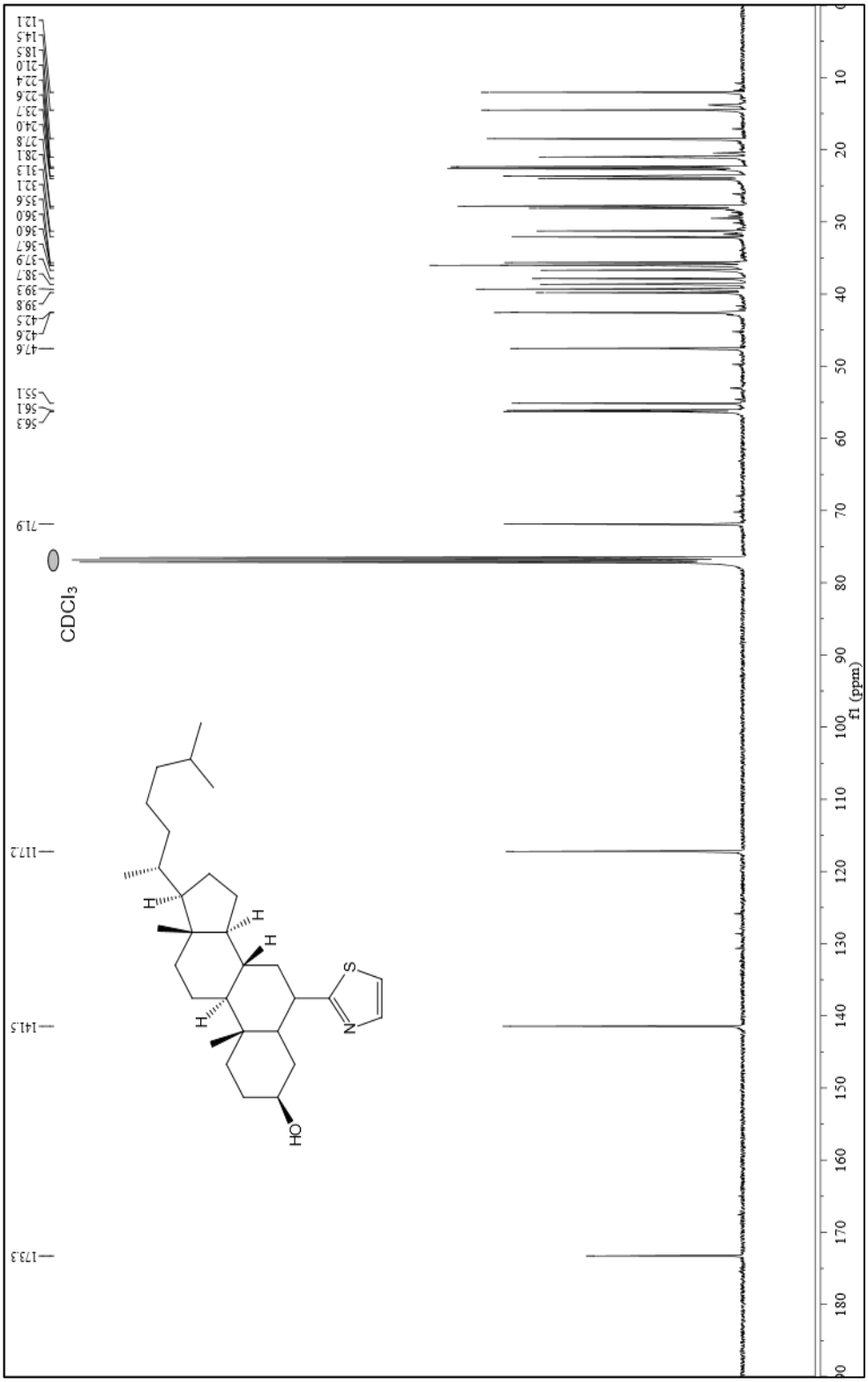
^{13}C NMR (101 MHz, $CDCl_3$) of **19b** 2-(((1S,11S,Z)-7,7,11-trimethyl-12-oxabicyclo[9.1.0]dodec-4-en-4-yl)methyl)thiazole



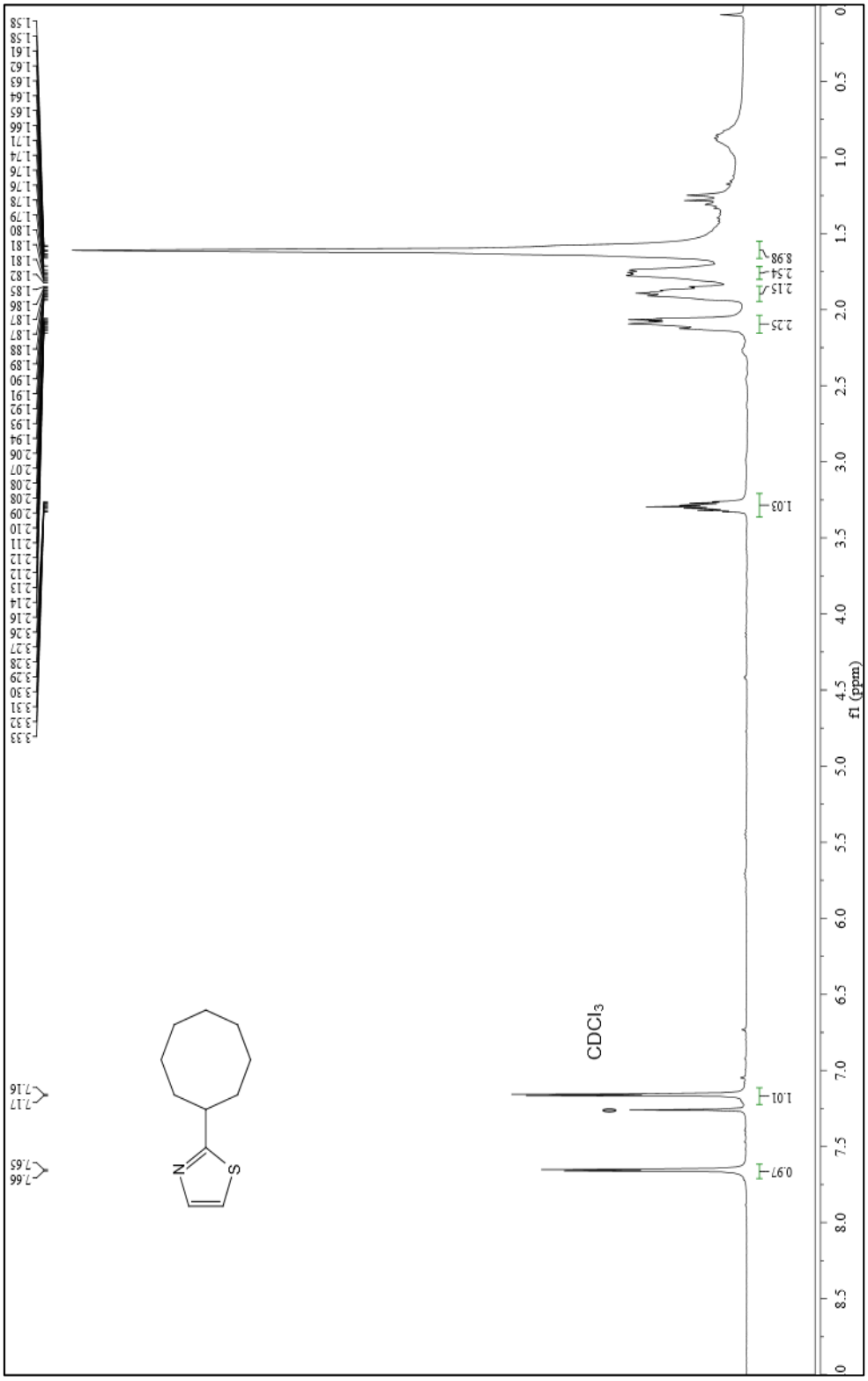
^{1}H NMR (599 MHz, $CDCl_3$) of **20a** (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-6-(thiazol-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



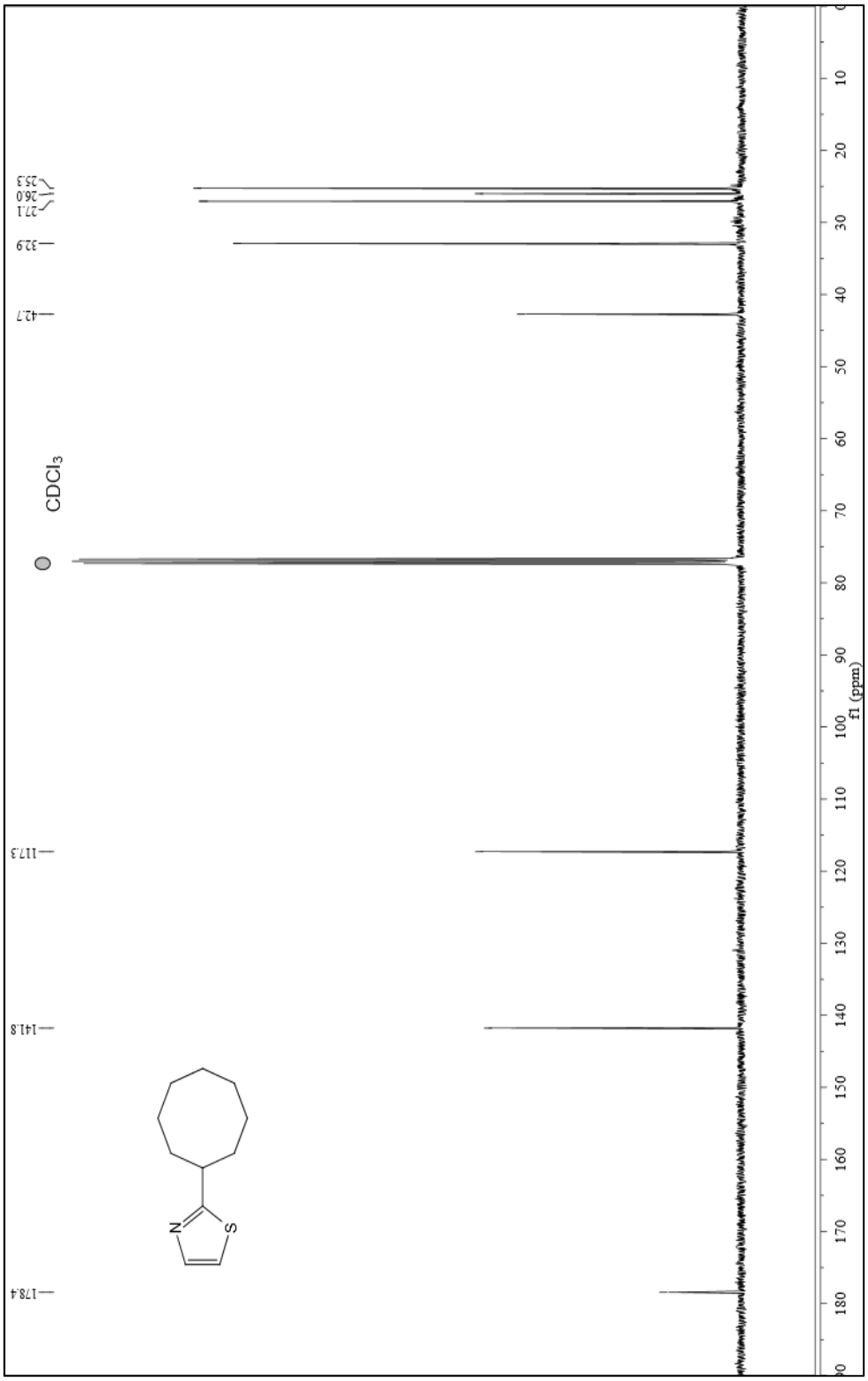
^{13} C NMR (101 MHz, $CDCl_3$) of **20a** (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-6-(thiazol-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



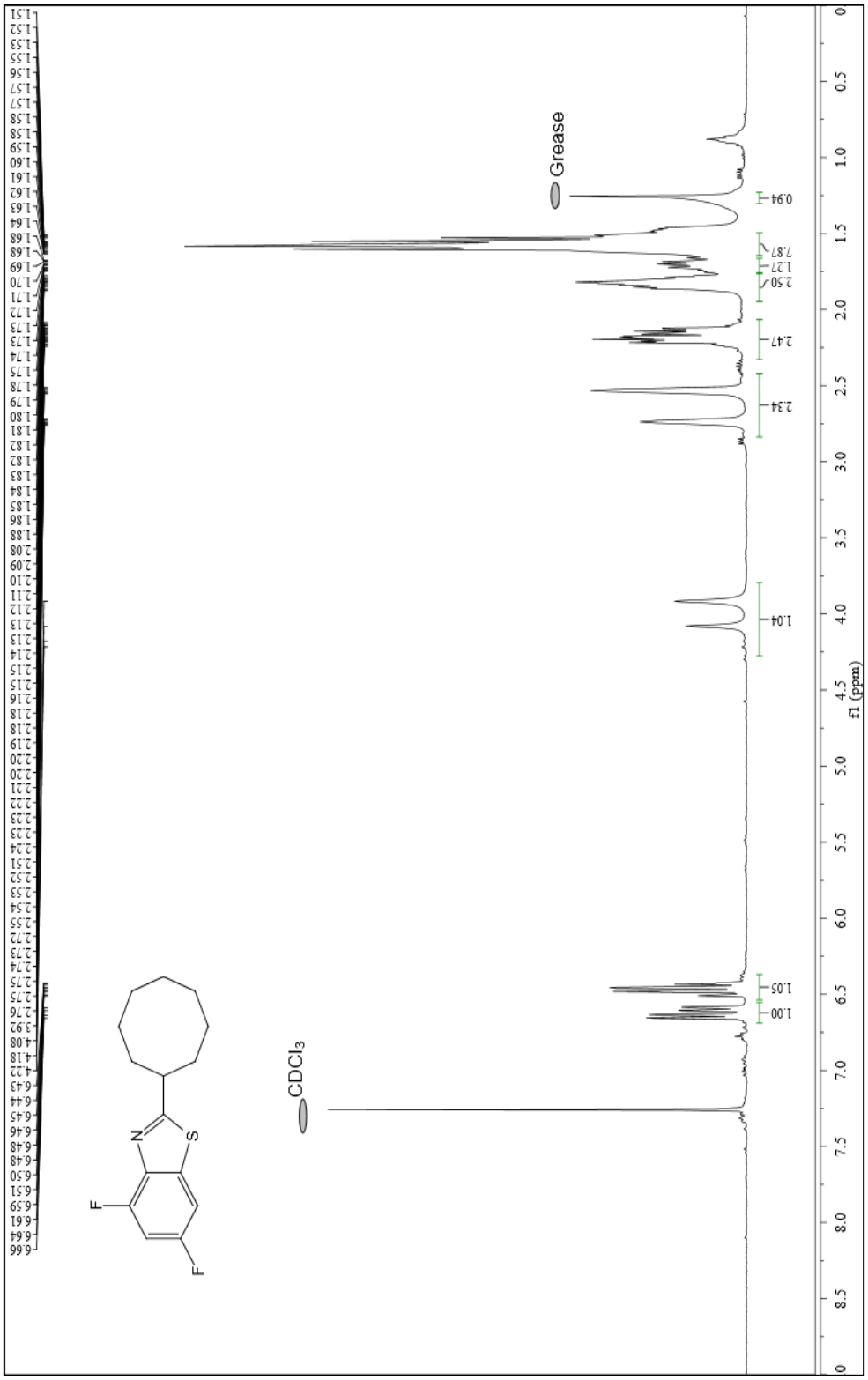
^{1}H NMR (400 MHz, $CDCl_3$) of **22a** 2-cyclooctylthiazole



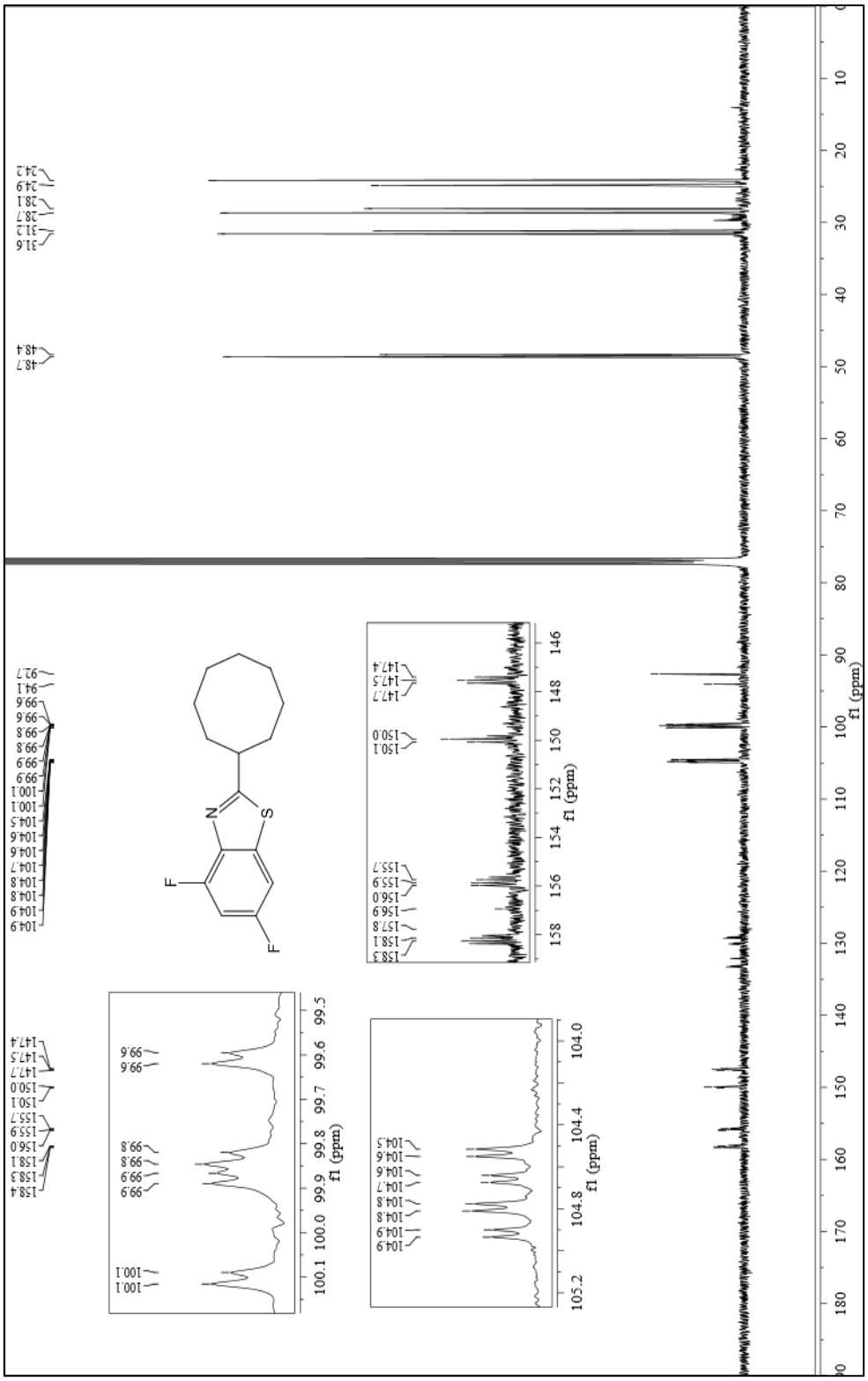
^{13}C NMR (101 MHz, $CDCl_3$) of **22a** 2-cyclooctylthiazole



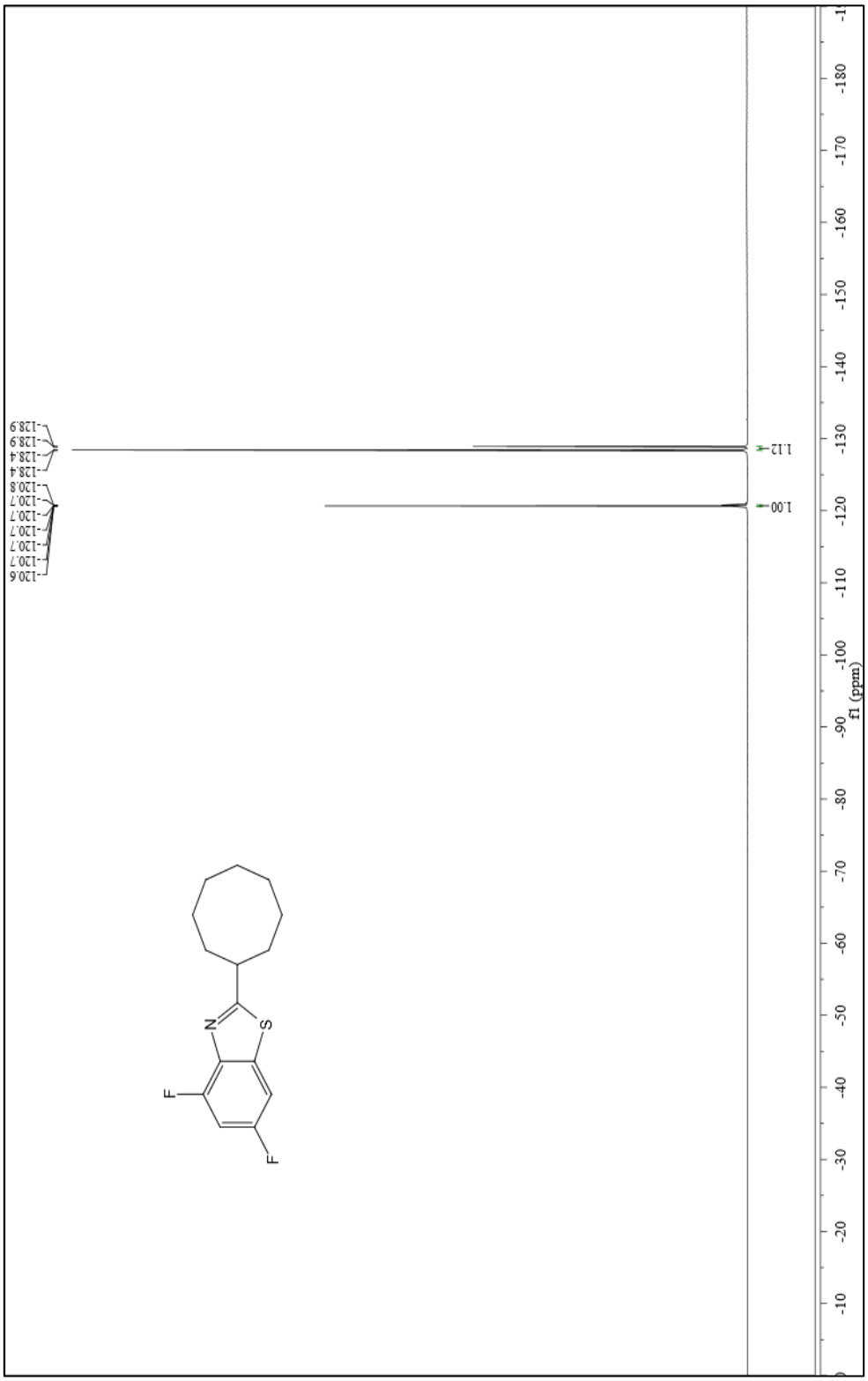
^{1}H NMR (400 MHz, $CDCl_3$) of **24a** 2-cyclooctyl-4,6-difluorobenzo[d]thiazole



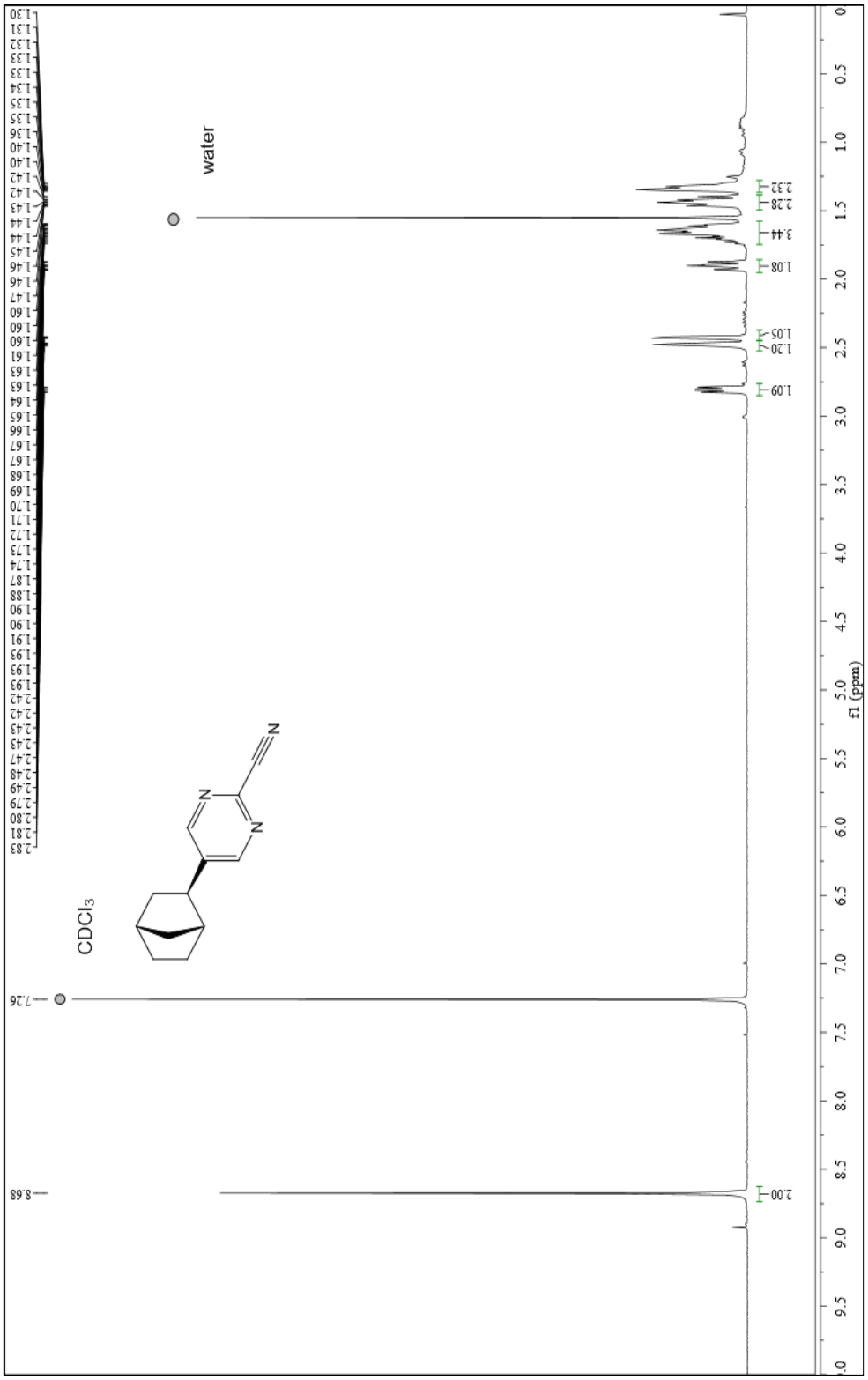
^{13}C NMR (101 MHz, $CDCl_3$) of **24a** -2-cyclooctyl-4,6-difluorobenzo[d]thiazole



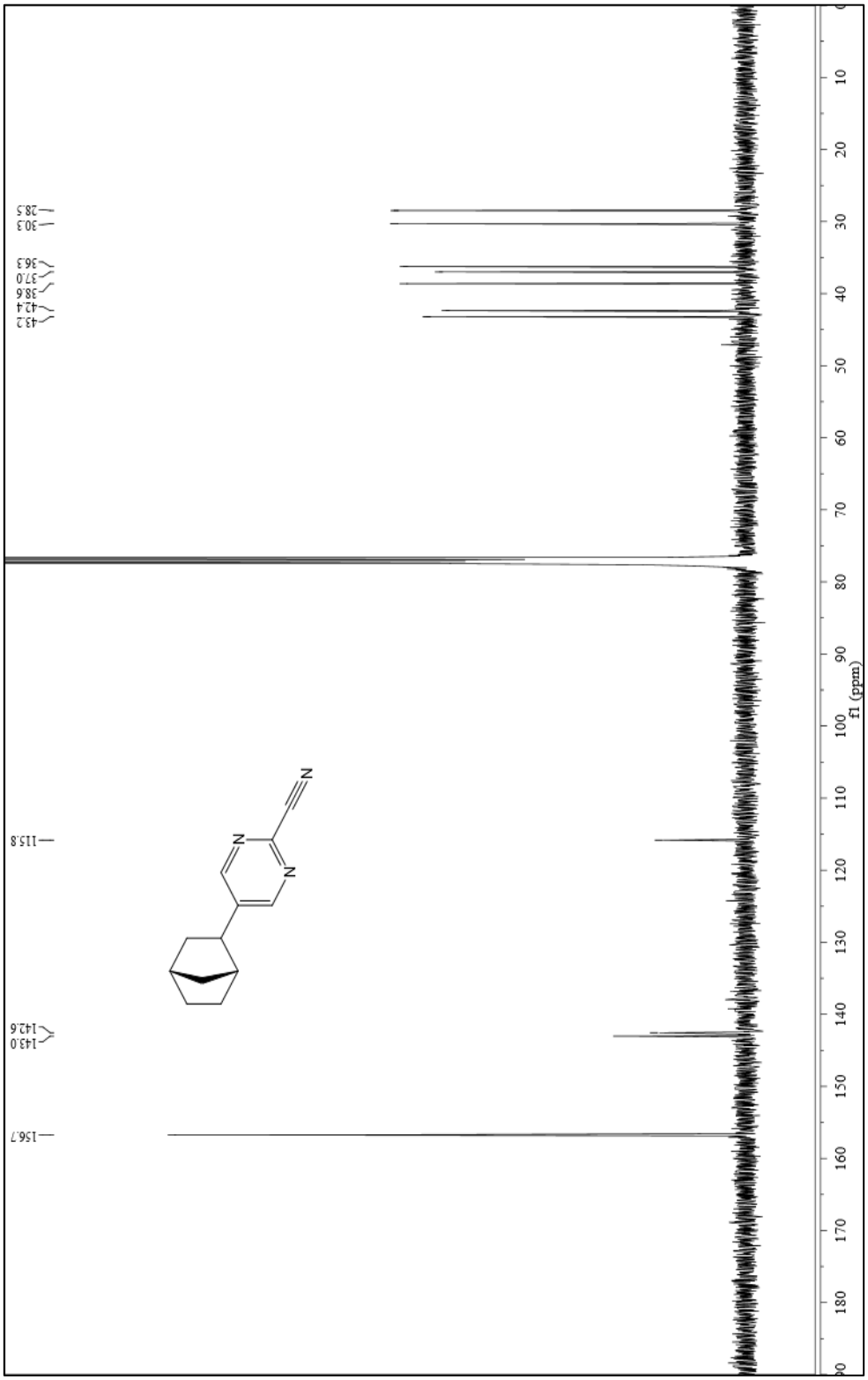
^{19} F NMR (376 MHz, $CDCl_3$) of **24a** 2-cyclooctyl-4,6-difluorobenzo[d]thiazole



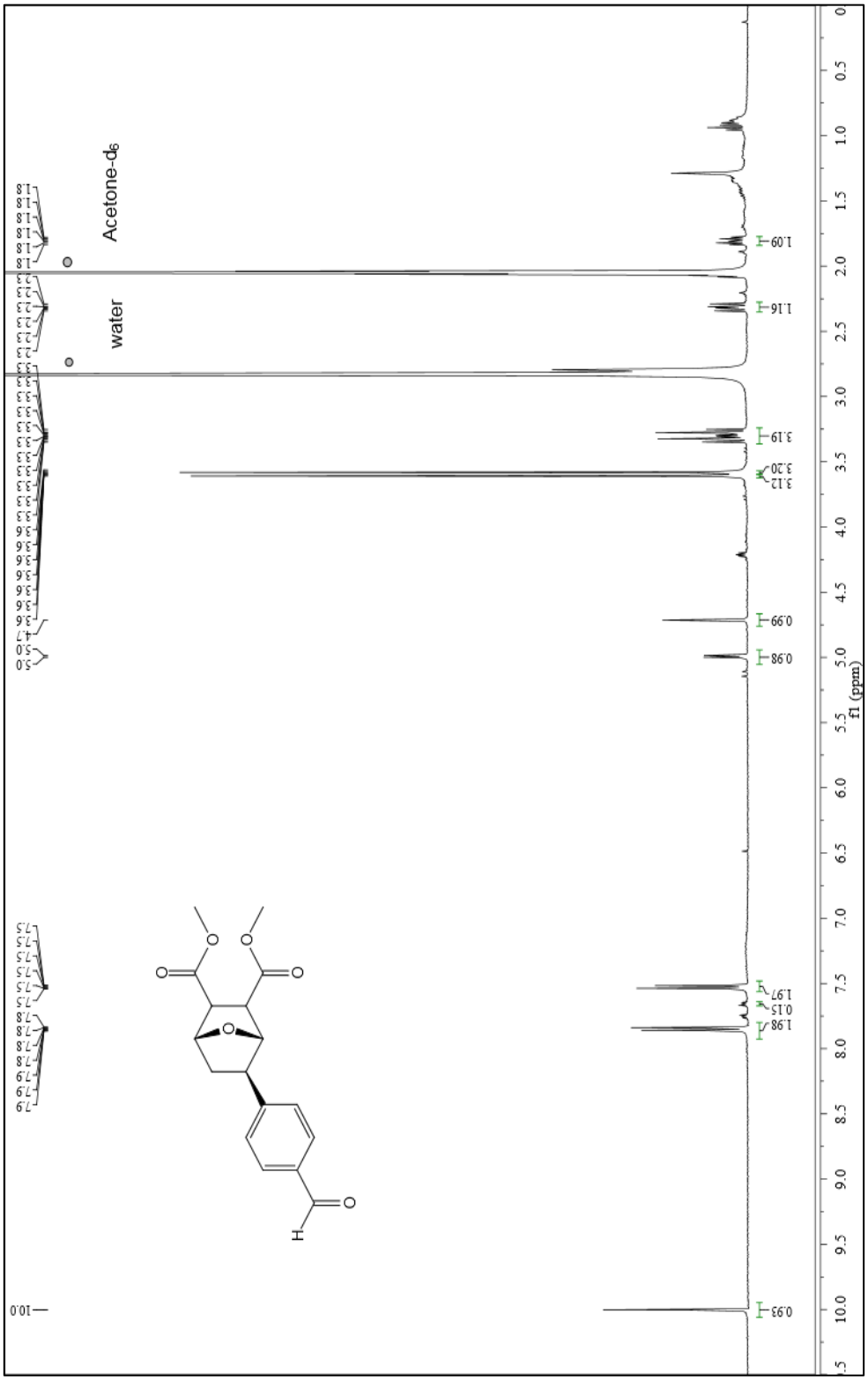
^{1}H NMR (400 MHz, $CDCl_3$) of **25a** 5-((1R,4S)-bicyclo[2.2.1]heptan-2-yl)pyrimidine-2-carbonitrile



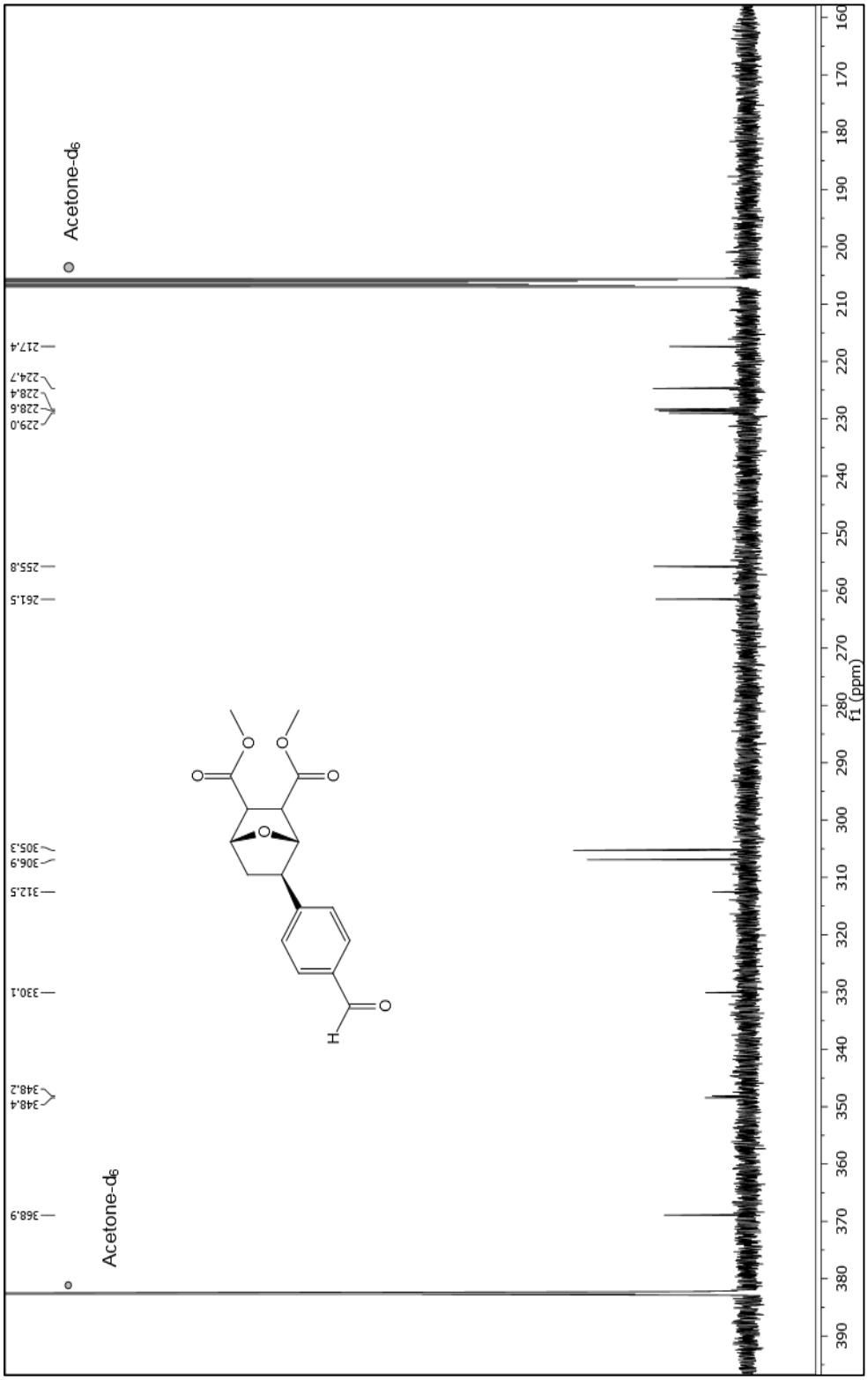
^{13}C NMR (101 MHz, $CDCl_3$) of **25a** 5-((1R,4S)-bicyclo[2.2.1]heptan-2-yl)pyrimidine-2-carbonitrile



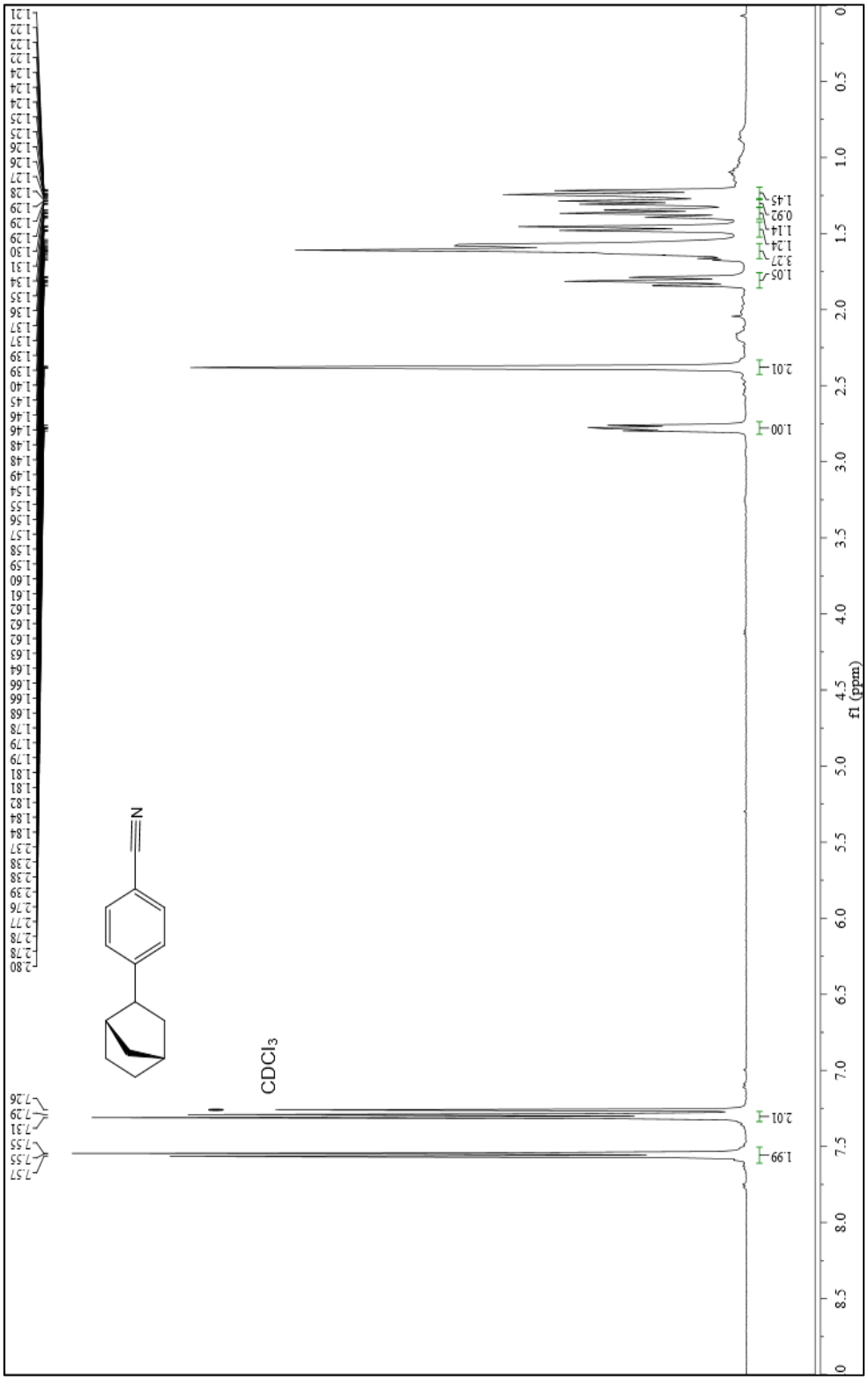
^{1}H NMR (400 MHz, CD_3OCD_3) of **25b** dimethyl (1R,4S,5R)-5-(4-formylphenyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



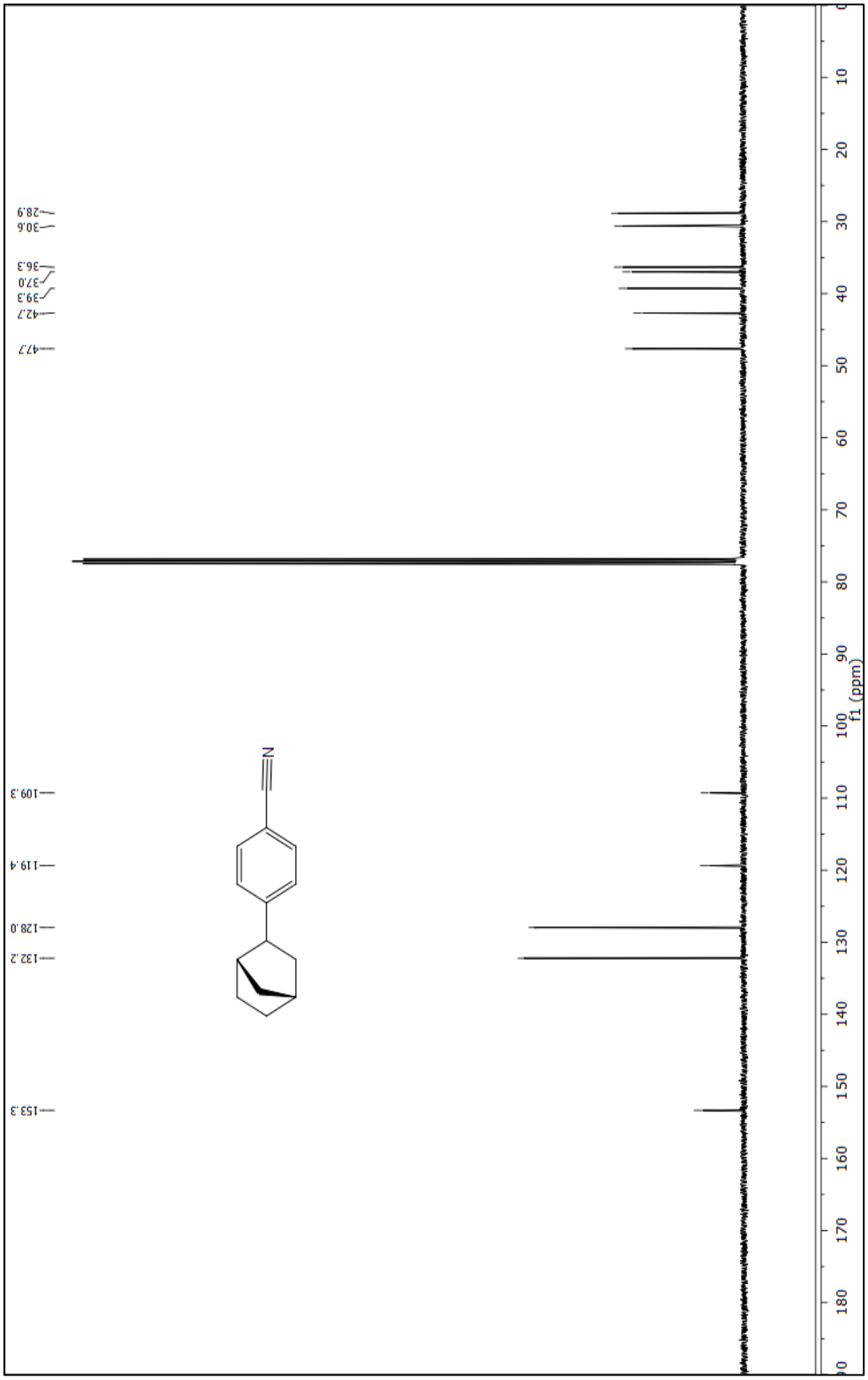
^{13}C NMR (400 MHz, CD_3OCD_3) of **25b** dimethyl (1R,4S,5R)-5-(4-formylphenyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate



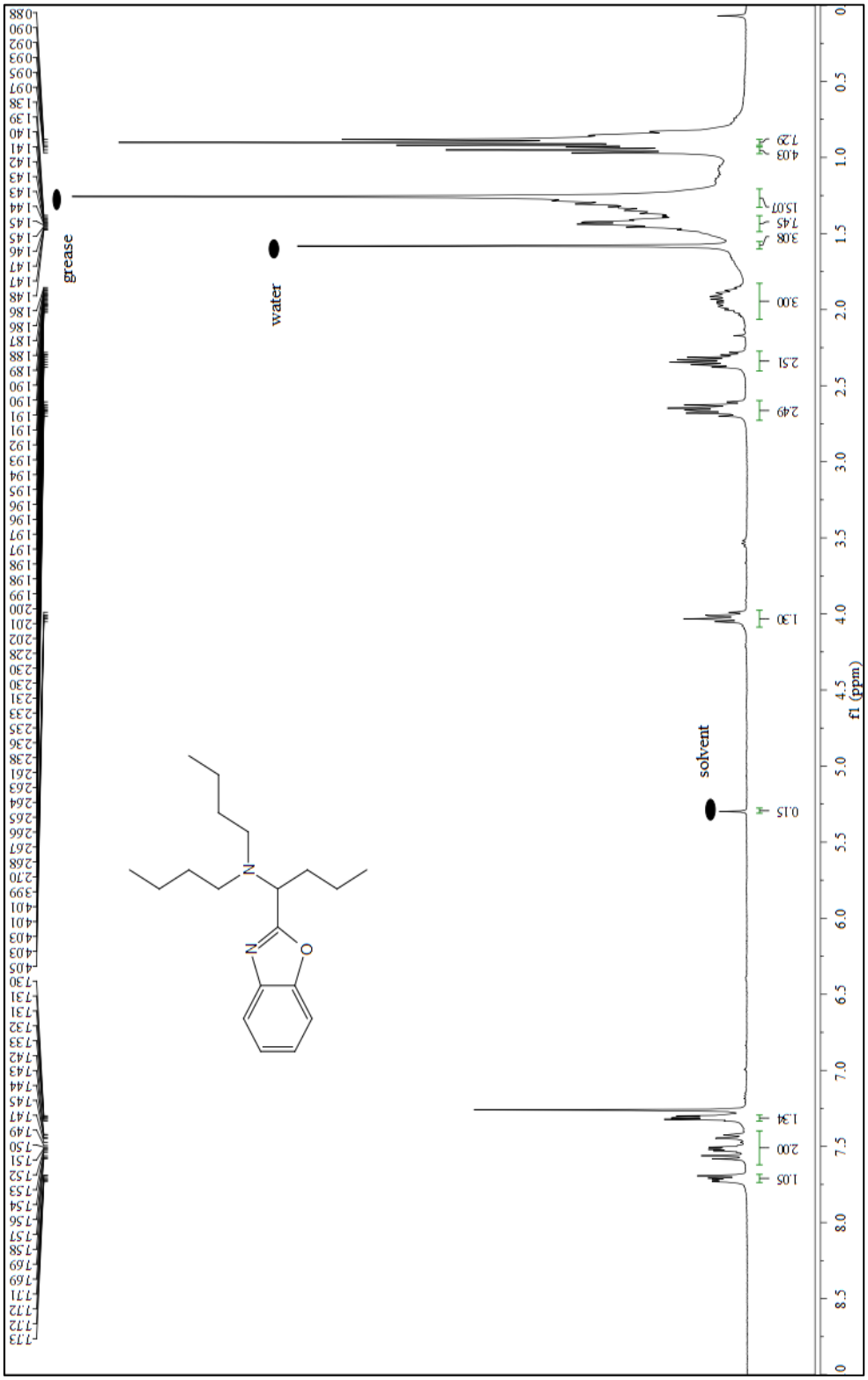
^{1}H NMR (400 MHz, $CDCl_3$) of **25c** 4-((1S,4R)-bicyclo[2.2.1]heptan-2-yl)benzonitrile



^{13}C NMR(101 MHz, $CDCl_3$) of **25c** 4-((1S,4R)-bicyclo[2.2.1]heptan-2-yl)benzonitrile



^{1}H NMR (400 MHz, $CDCl_3$) of **18k** 1-(benzo[d]oxazol-2-yl)-N, N-dibutylbutan-1-amine



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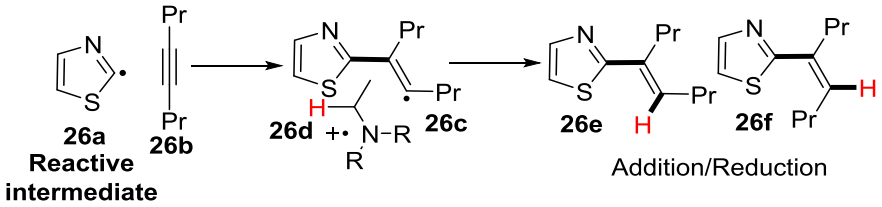
CHAPTER IV

REDUCTIVE ALKENYLATION AND ISOMERIZATION OF AZOLES

4.1 Introduction

Further, we turned our attention to the development of methodology that would allow for the alkenylation of azoles. By analogy to the alkylation of the azolyl radical, we hypothesized that if the azolyl radical **26a** (Scheme 26) intermediate added to an alkyne **26b** it would generate a vinyl radical intermediate **26c**. The vinyl radical would proceed to abstract a hydrogen atom from an amine or amine radical cation **26d**, leading to an alkenylated azole **26e** and **26f**. However, while hydrogen atom transfer (HAT) from both the amine and its radical cation were expected to be exothermic, at the outset we anticipated some challenges associated with this reaction sequence. Firstly, radical addition to alkynes is known to be generally slow.[1] This is particularly interesting, because addition reactions to alkynes are generally more exothermic than additions to alkenes. Recall, that the alkyne bond while strong in its entirety, 230 kcal/mol, the second π-bond is rather weak (67 kcal/mol after subtracting the BDE of C–C double bond. So the apparent departure from the commonly observed correlation between the thermodynamics and the kinetics of the reaction can be explained by two reasons. First, although there are more π-electrons associated with the triple bond (two π-bonds versus one), the sp-hybridized carbons exert a strong attraction for these π-electrons, consequently, electrons are bound more tightly to the functional group than the π-electrons of a double bond. Secondly, an alkenyl radical intermediate is less stable than the corresponding alkyl radical, which becomes apparent when looking at the C–H BDEs of t alkanes and alkenes.[2] The stability of radicals follows order for $sp^3 > sp^2 > sp$. Another issue that might arise because of the anticipated slow kinetics was that the product alkene might undergo further addition reaction.

Recall, we have just shown that alkene can engage in radical addition under very similar conditions.[3] In addition to these issues, regioselectivity and stereochemistry could be problematic. If the alkyne is unsymmetric, then the radical must discriminate between the two termini of the alkyne. Furthermore, it was expected that HAT to the incipient vinyl radical would dictate the alkene geometry, and this type of process is not known to be very selective hence, the product would be expected to form a mixture of both *E*- and *Z*-isomers. Thus, if methodology was to be synthetically useful, it would need to address all of these issues.



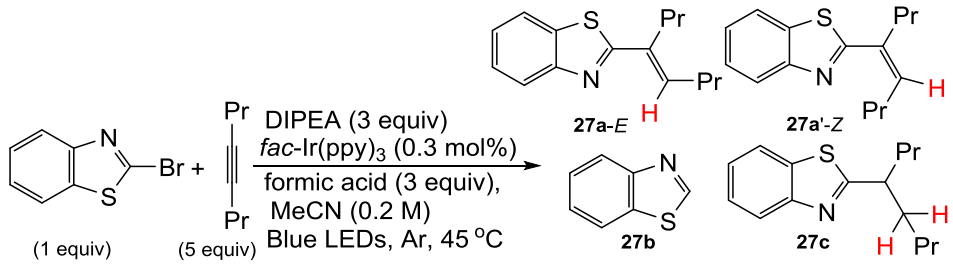
Challenges
- *Radical addition to alkyne is slow*
- *E-Z selectivity issue*
- *Regioselectivity issue*
- *Further reaction of alkene.*

Scheme 26. Hypothesized reductive alkenylation conditions.

4.2 Initial results and optimization of reaction conditions

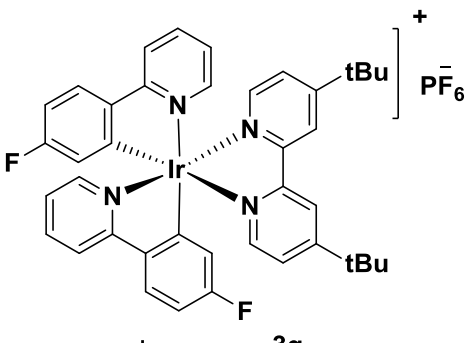
Keeping the aforementioned challenges in mind, we began our study with 2-bromobenzothiazole and 4-octyne using the conditions for reductive alkylation (Chapter. 3, Scheme 27, entry 1). We observed 30%, conversion to the alkenylated azole product **27a** and **27a'** as a 1:1.3 *Z*:*E* mixture, along with 70% conversion to the reduced benzothiazole **27b** in just 10 h reaction time. Assignments of both the *E* and *Z* isomers are based on literature values.[4] While the initial results left much to be desired in terms of increasing the yield and the olefin isomer selectivity, we were nonetheless pleased to not observe any alkylated azole product **27c** in the reaction mixture, which might have arisen from overaddition. Having preliminary results in hand, we set about to optimize of the reaction conditions to make the methodology more worthwhile. Our initial solvent screening included DMA, DCM, MeOH, THF, along with MeCN (Scheme 27, entries 1-5). In each of the solvents, we observed the desired product. However, MeCN

proved to be the best solvent, resulting in both higher conversion and a better product ratio. In the reductive alkylation reaction,[3a] we had found that the low solubility of certain amines could be used to increase the yields when competitive reduction of the azole was problematic. Consequently, we next performed a screen of low solubility amines.[5] We found that *N, N*-diisopropyloctan-1-amine,[6] which is more than 10x less soluble in MeCN (at 23 °C) than diisopropylethylamine (0.099 M vs 1.3 M) indeed gave an increased amount of the desired product (Scheme 27, entry 6 *vs* 1), albeit at the expense of reaction time. With increasing temperature, from 45 °C to 60 °C, higher conversion to the desired product was observed (entry 6 vs 7). However decrease in Z/E selectivity was also observed (from 1:1.8 to 1:1.3 *Z*/*E*) along with slight over addition of the alkenylated product, resulting in formation of the alkylated product **27c** at 60 °C. Furthermore, we explored the effect of changing the concentration of alkyne (entry 6, 8, 9). Consistent with a process in which there is a competition for reduction (HAT) and alkenylation of the azolyl radical, increased concentration of alkyne led to more alkenylated products **27a** +**27a'**. Further concentrating the reaction also led to a slight improvement (entry 10). Interestingly, changing to more oxidizing catalyst in the reaction conditions did not yield any alkenylated product **27a** and **27a'**. Instead, 65% conversion to alkylated product **27c** and 35% reduction of 2-bromobenzothiazole was observed (entry 11). Next, we evaluated the effect of air on the outcome of the reaction. In the presence of air, there is a decrease in overall conversion to the desired product along with formation of undetermined side products in the reaction (entry 12). Finally, control experiments revealed that light (entry 13), amine (entry 14), and catalyst (entry 15) are the necessary components for the desired reaction. Using 0.3 mol% *fac*-tris-(2-phenylpyridine) ($Ir(ppy)_3$), a 1:1 mix of amine and formic acid (3 equiv), and 5 equiv of alkynes, we began to explore the scope of the reaction.



Entry	Modification	GCMS Conversion **27a'+27a**(*Z*:*E*)[a]	**27b**	**27c**	**time, h**
1.	none	30 (13:17)	70%	0%	10[a]
2.	DMA instead of MeCN	15 (7:8)	85%	0%	10[a]
3.	CH_3OH instead of MeCN	11 (5:6)	89%	0%	10[a]
4.	DCM instead of MeCN	20 (10:11)	80%	0%	10[a]
5.	THF instead of MeCN	18 (8:10)	82%	0%	10[a]
6.	3 equiv *N*, *N*-diisopropyloctan-1-amine and 3 equiv of formic acid instead of Bu_3N, 5 equiv of Arene-H at 45 °C, 0.2 M	42 (15:27)	58%	0%	20[a]
7.	Entry 6 but at 60 °C	56 (25:31)	38%	6%	20[a]
8.	Entry 1 but 3.0 equiv of alkyne	25 (12:13)	75%	0%	9[a]
9.	Entry 1 but 10.0 equiv of alkyne	51 (21:30)	49%	0%	9[a]
10.	Entry 6 but at 0.4 M	66 (29:37)	34%	0%	20[a]
11.	Entry 7 but cat. 3g instead of $Ir(ppy)_3$	0	35%	65%	20[a]
12.	Entry 1 but in air	15 (5:10)	65%	0%	9[a,b]
13.	Entry 10, no light	0	0%	0%	19
14.	Entry 10, no amine	0	0%	0%	19
15.	Entry 10, without catalyst and in light	0	0%	0%	19

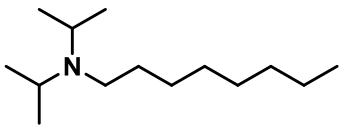
[a]Reaction reached completion.[b]20% unknown side product is formed



3g

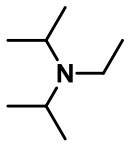
$E_{1/2}^{oxd}$ = 1.02
$E_{1/2}^{red}$ = -1.84
Ir^+/Ir^* = -1.035
Ir^-/Ir^* = 1.071

Solubility in MeCN at 23 °C



0.099 M

***N*,*N*-diisopropyloctan-1-amine**



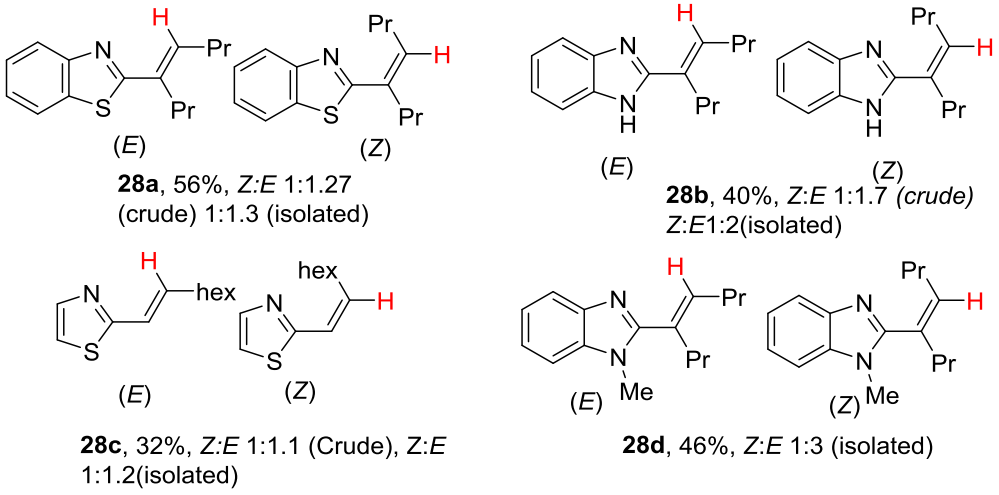
1.3 M

***N*-ethyl-*N*-isopropylpropan-2-amine**

Scheme 27. Optimization of alkenylated conditions.

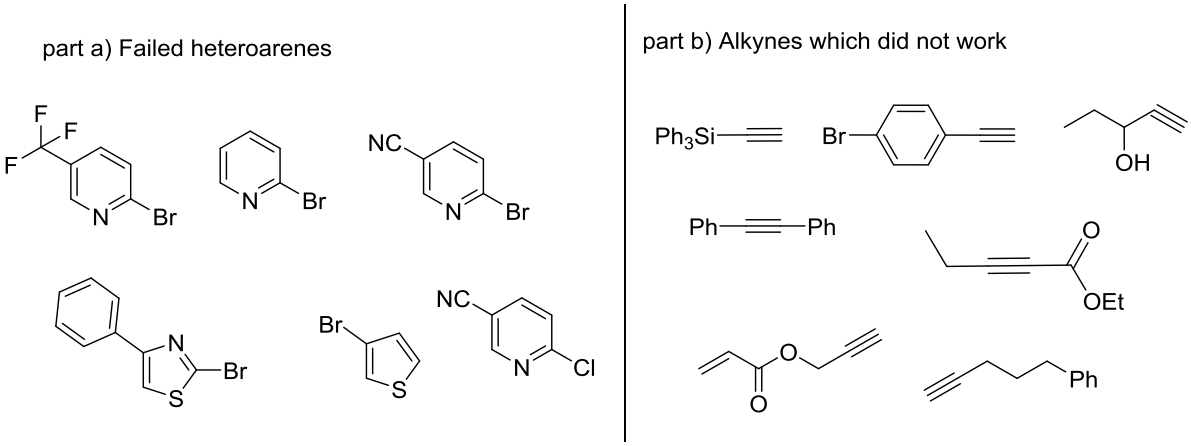
4.3 Initial scope of the reaction

With ideal conditions in hand, we obtained alkenylated azole **28a** in 56% yield with *Z*:*E*=1:1.3 (isolated). Bromo-thiazole **28c**, -benzimidazole **28b**, as well -*N*-methyl benzimidazole **28d** all worked well under the optimized reaction conditions.



Scheme 28. Initial scope of the reaction.

Other than azoles and simple aliphatic alkynes, other heteroarene and aromatic alkynes were also tested under the established protocols. Below is a list of substrates (Scheme 29) that did not yield the desired coupled product.



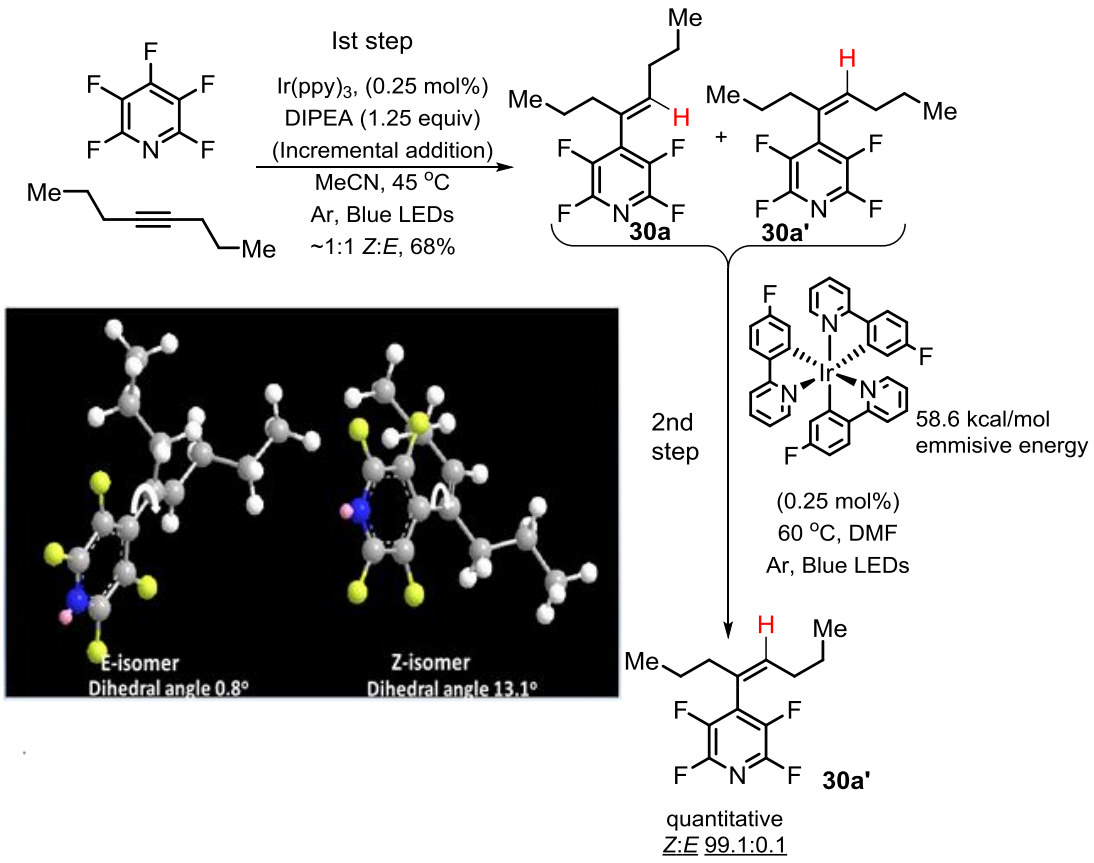
Scheme 29. List of failed heteroarenes and alkynes in the alkenylated conditions.

In all of the above cases, we reacted heteroarenes with 4-octyne (Scheme 29A) and we observed complete reduction of starting heteroarenes. In case of the failed alkynes (Scheme 29B), the reaction was carried out with 2-bromobenzothiazole under the optimaized conditions to give the complete reduction of 2-bromobenzothiazole, along with the formation of unidentified side products. The reasons for this are not clear, but may stem from the presence of other functional groups, such as alkenes and arenes. Currently, the scope of alkynes includes both internal and terminal alkynyl hydrocarbons devoid of other pi-systems.

4.4 *Z*/*E* selectivity

During the initial investigation of the scope of substrates (Scheme 28), alkenylated products were formed as a mixture of *E* and *Z* isomers. In order to increase the *Z*/*E* selectivity in the reaction conditions, we started investigating the role of the photocatalyst. In 2016, our group demonstrated the photocatalytic synthesis of alkenylated fluoroarenes *via* the formal hydroperfluoroarylation of alkynes from perfluoroarenes (Scheme 30).[7] First, they showed that that the C–F bond, of a multifluorinated arene, can be functionalized *via* photocatalytic electron transfer **30a** and **30a**', which resulted in fragmentation of the fluoride and formation of an aryl radical. The aryl radical would then add to the alkyne, in much the same fashion as we have proposed here. However, the initial formation of the vinyl substituent by HAT to the vinyl radical was often unselective. However, they showed that this same photocatalyst could engage in selective energy transfer, which led to the enrichment of the thermodynamically less favorable *Z*-isomer **30a'**. The primary factor that drives this selectivity is the increasing steric clash between *ortho*-arene fluorines and the alkene chain in the *Z*-isomer, which results in deconjugation of the alkene with the aryl pi-system, hindering extended conjugation. As a result, the excitation energy of the *Z*-isomer is believed to be significantly higher. One of the more remarkable findings was that the rate of isomerization changes as a function of choice of photocatalyst. More surprising was the observation of a strong correlation

between the rate and the steric volume of the photocatalyst. By exploiting this feature, they were able to access one isomer in excess, and achieve high *Z*:*E* ratios in the reaction.[8]

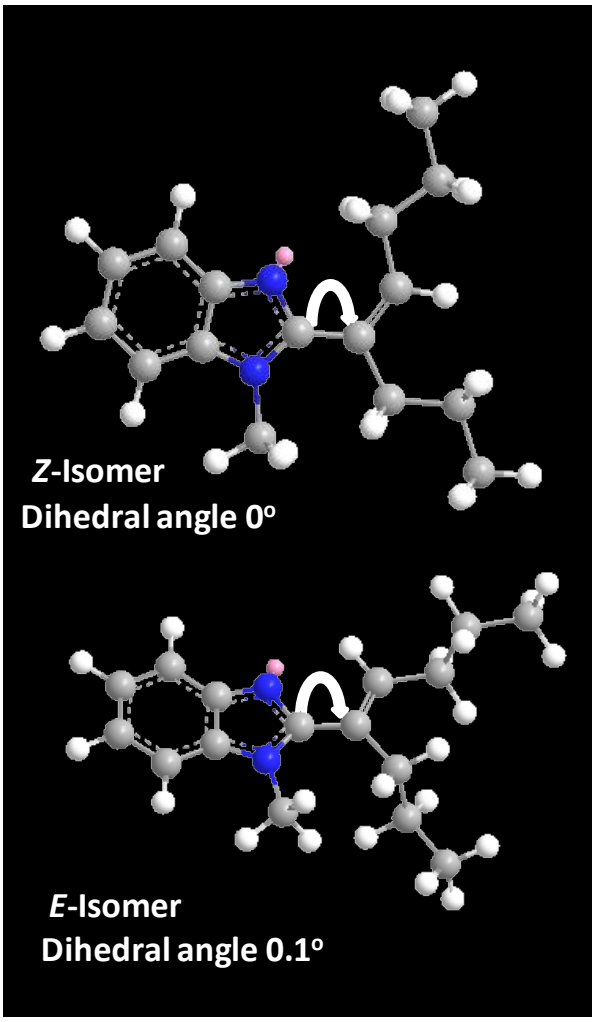


Scheme 30. Weaver's work on electron and energy transfer.

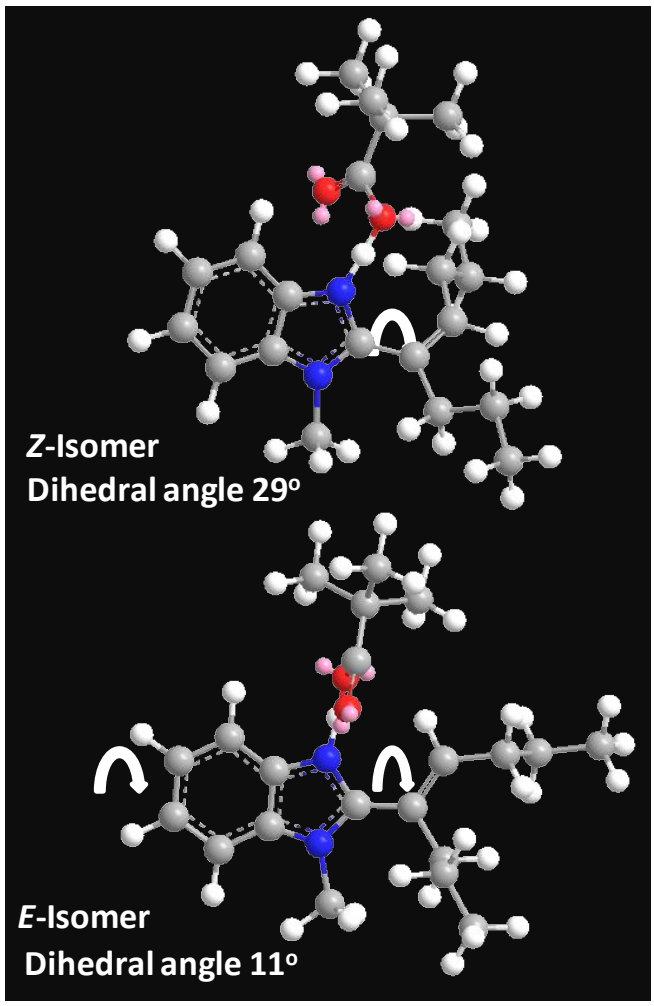
Realizing that the key to controlling the stereochemistry is the difference in the degree of conjugation of the two isomers, which is primarily driven by the sterics of the molecule, i.e. the large steric clash from the *ortho* fluorines and the allylic position of the Z-isomer, we sought to exploit this knowledge. We calculated the dihedral angle after minimizing the energy of both isomers using MM2 (Chem-3D software). Specifically, we evaluated both *E* and *Z* isomers of alkenylated *N*-methylbenzimidazole substrates **28d-*E*** and **28d-*Z*** (Scheme 31A). Not surprisingly, there was essentially no difference in dihedral angle for both *E* and *Z* isomers, which likely meant that both isomers would be nearly equally photoexcitable, and was likely the main reason for getting ~1:1 mixture of olefin isomers in the reaction.

However, we could not rule out that the HAT was completely unselective. The problem arises in that a 5-membered ring gives a more acute internal angle when compared to the 6-membered benzenes, and what is more, it often has only electrons pointing back at the olefin, rather than atoms, as is the case in the benzene system.

Thus, we hoped to take the advantage of the basic nature of imidazole (pK_a for N-H of benzimidazole is 16.4 in DMSO).[9] We hypothesized that if we could protonate the *N* atom of imidazole with a bulky and weak acid such as pivalic acid (pK_a = 14.0 in DMSO), there could be a steric clash between *N*-substituted pivalic acid and the alkene chain in the *E* or *Z*-isomer. This steric hindrance would cause the dihedral angle to increase, which in turn would increase the triplet state energy of the isomer. We anticipated that it would be important to not have too strong of an acid, which would easily transfer the proton and allow the ions to disassociate from one another. Instead, we hoped to use an acid that would form a hydrogen-bond which would hold the anion in close proximity. Thus, we calculated the dihedral angle for both isomers of *N*-methyl alkenylated imidazole **28d-*E*** and **28d-*Z*** in which they were hydrogen bonded to a pivalic acid unit, using Chem-3D software (Scheme 31B). We found that there is significant difference in the dihedral angles (18^o) of the isomers. We understand that the MM2 calculations we used are a very rough estimate, but are appropriate at this stage of project, and suggest that it may be possible to use a weak acid to manipulate the photostationary state.



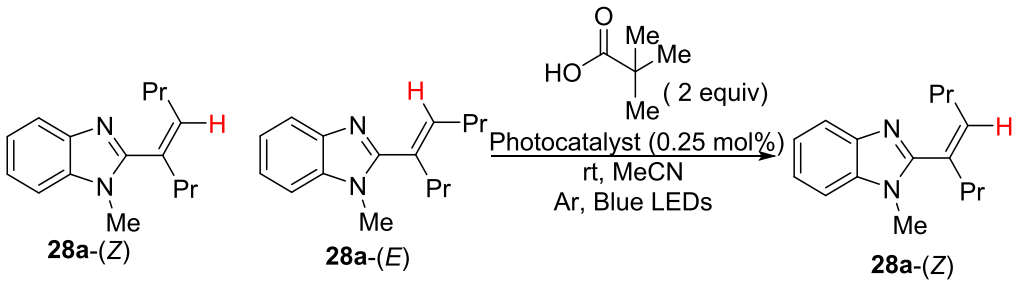
A) Dihedral angle was calculated using chem-3d software after energy minimzation of structure



B) Dihedral angle was calculated using chem-3d software after energy minimzation of structure with pivalic acid on it

Scheme 31. Dihedral angle calculation.

Next, we began our investigation with isolated alkenylated *N*-methyl benzimidazole, **28a'** and **28a**, as an isomeric mixture *Z*:*E*=1:3 (isolated). We screened various photocatalysts, solvents, and temperatures in an attempt to facilitate the isomerization (Scheme 32).

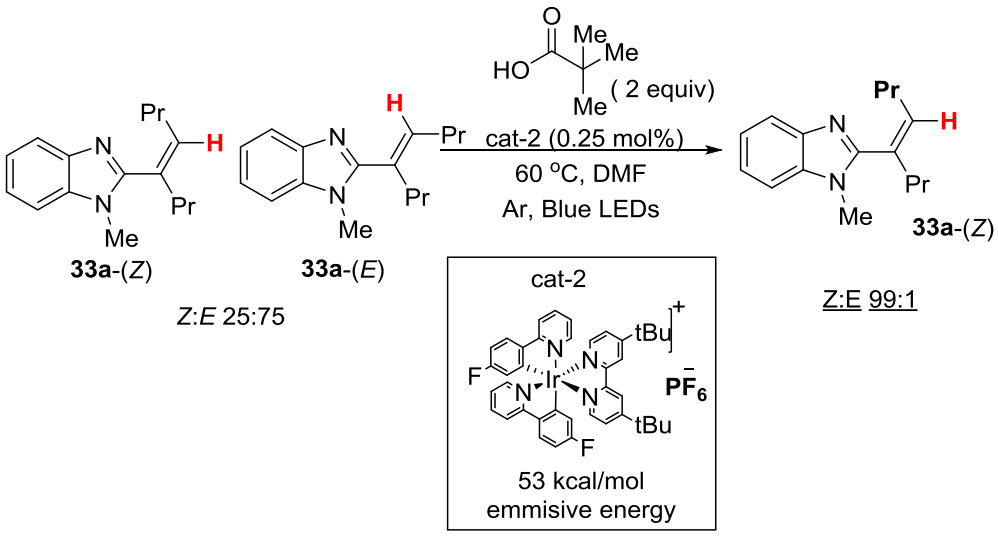


Entry	Photocatalyst (triplet energy, Kcal/mol)	Z:E ratio	Time, h
1	$Ir(ppy)_3$ without pivalic acid (55.2 Kcal/mol)	25:75	0 h
		31:69	3 h
		36:66	24 h
		40:60	2 d
2	$Ir(ppy)_3$ with Pivalic acid (2 equiv) (55.2 Kcal/mol)	25:75	0 h
		30:70	3 h
		35:65	24 h
		42:58	2 d
3	$Ir(Fppy)_3$ with Pivalic acid (2 equiv) (60.1 Kcal/mol)	25:75	0 h
		40:60	3 h
		48:52	24 h
		51:49	2 d
4	$Ir(Fppy)_2$tbubpy with Pivalic acid (2 equiv) (53.0 Kcal/mol) **Cat-2**	25:75	0 h
		35:65	3 h
		40:60	24 h
		60:40	2 d
5	$Ir(Fppy)_2$bpy with Pivalic acid (2 equiv) (51 kcal/mol)	25:75	0 h
		32:68	24 h
		43:53	48 h
6	$Ir(Fppy)_2$tbubpy with Pivalic acid (2 equiv) and DMF	25:75	0 h
		45:55	24 h
		92:8	48 h
7	$Ir(Fppy)_2$tbubpy with Pivalic acid (2 equiv) and MeOH	25:75	0 h
		48:52	24 h
		49:51	48 h
8	$Ir(Fppy)_2$tbubpy with Pivalic acid (2 equiv) and DMSO	25:75	0 h
		30:70	24 h
		32:68	48 h
9	$Ir(Fppy)_2$tbubpy with Pivalic acid (2 equiv) and DMF at 60 ^{0}C	25:75	0 h
		99:1	24 h
		99:1	48 h

Scheme 32. Optimization for isomerization conditions.

A screening of various photocatalysts (Scheme 32, entry 2 to 5 *vs* 1) ranging from 51.0 kcal/mol to 60.1 kcal/mol triplet energy, suggested that ideal photocatalysts had an emissive energy of 53 kcal/mol (entry 4), as the *Z*/*E* selectivity increased from 25:75 to 60:40 and it also suggests that bulky pivalic acid could play an important role. We also found that solvent has a significant impact on both the extent and

rate of isomerization. Changing from MeCN to DMF resulted in better *Z*/*E* selectivity (entry 5), whereas other solvents such as MeOH, and DMSO (entry 6 and 7) did not improve the *Z*/*E* ratio. Additionally, we found that increasing the temperature to 60 °C (entry 8), led to faster conversion (i.e.in 24 h rather than 48 h). We have not yet screened any weak bulky acids other than pivalic acid, and we anticipate that this will play a key role. However, utilizing pivalic acid (2 equiv) and cat-2 (0.3 mol %) in DMF (0.2 M), and at 60 °C (Scheme 33), we were able to start with a 1:3 *Z*/*E* isomeric mixture and drive the isomerization to give a 99:1 *Z*/*E* isomeric mixture, with no evidence of decomposition or any other products that would lead to a loss in yield.



Scheme 33. Initial reaction conditions of *Z*/*E* selectivity

4.5 Conclusion

This project is still ongoing and much work needs to be done. Thus far, the isomerization conditions are working only for *N*-substituted benzimidazole substrates. General conditions need to be developed for isomerization of alkenylated benzothiazole and alkenylated benzoxazole. It will also be worthwhile to screen other bulky acids with varying pK_a values, which could protonate the less basic heteroarenes along with photocatalysts with varying triplet energies and steric volume. Other future directions include expanding the scope for other heteroarenes and characterization of the final substrates.

4.6 Experimental

All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI, and Oakwood) and used without further purification unless otherwise noted. 2-Bromobenzo[*d*]thiazole, [10, 2, 3] Reactions were monitored by thin layer chromatography (TLC), obtained from Sorbent Technologies Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm) and were visualized with ultraviolet light, potassium permanganate stain, GC-MS (QP 2010S, Shimadzu equipped with auto sampler) and ^{1}H NMR.

Photocatalytic reactions were set up in a light bath as described below. Blue LEDs (in the form of strips 18 LEDs/ft, from Solid Apollo) were wrapped around the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rested on the top was fashioned from cardboard and holes were made such that reaction tubes (5 mm NMR tube) were held firmly in the cardboard lid which was placed on the top of bath. Water was added to the bath such that the tubes were submerged in the water which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat. Isolations were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and evaporative light scattering detection. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^{1}H, ^{13}C). Mass spectra (HRMS) analysis was performed on LTQ-OrbitrapXL by Thermo Scientific Ltd.

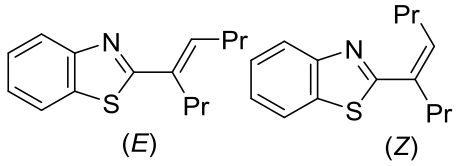
Photocatalytic reductive coupling

General procedure A for the photocatalytic reductive alkenylation of bromoazoles with alkynes **(limiting azole)**

A 5 mm NMR tube fitted with a NMR septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, X mL of 0.75 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.25 M with respect to the 2-bromoazoles), 2-bromoazoles (1 equiv), alkyne (5 equiv), *N, N*-diisopropyloctan-1-amine (3 equiv) and formic acid (3 equiv) and the reaction mixture was

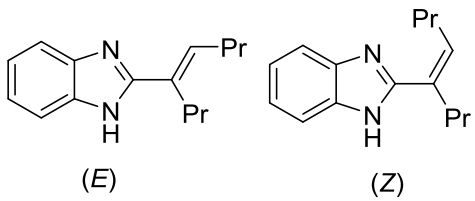
degassed *via* Ar bubbling for 10 min and then the exit needle and Ar line were removed and reaction tube was sealed with parafilm. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 45 °C. The reaction was monitored by ^{1}H NMR or GC-MS. After the complete consumption of aryl bromide, CH_3CN was removed *via* rotovap and the residue was treated with water (2 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified *via* normal phase chromatography.

28a (*E*)-2-(oct-4-en-4-yl)benzo[d]thiazole and (*Z*)-2-(oct-4-en-4-yl)benzo[d]thiazole



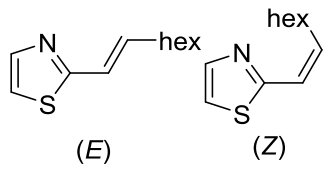
The **general procedure A** was followed using 2-bromobenzothiazole (50 mg, 0.23 mmol), 4-octyne (50 mg, 0.45 mmol), *N*, *N*-diisopropyloctan-1-amine (146 mg, 0.69 mmol), formic acid (32 mg, 0.69 mmol) and 0.57 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **28a** in 56% yield (32 mg, 0.13 mmol), E:Z 1.2:1 (based on crude ^{1}H NMR) and E:Z 1.3 :1 (isolated) as an oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 10% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2, 0.8, 0.8 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 5.88 (t, *J* = 7.5, 7.3 Hz, 1H), 2.57 (ddt, *J* = 8.7, 6.3, 1.1, 1.1 Hz, 2H), 2.44 (q, *J* = 7.5, 7.4, 7.4 Hz, 2H), 1.52 (m, 4H), 0.94 (td, *J* = 7.4, 7.4, 0.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.62, 153.21, 137.25, 135.94, 133.66, 125.86, 124.80, 123.11, 121.25, 40.15, 30.85, 23.00, 22.02, 14.02, 13.87. Z isomer is assigned in the spectra.[76]

28b (*E*)-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole and (*Z*)-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole



The **general procedure A** was followed using 2-bromobenzimidazole (50 mg, 0.25 mmol), 4-octyne (138 mg, 1.25 mmol), *N*, *N*-diisopropyloctan-1-amine (159 mg, 0.75 mmol), formic acid (34 mg, 0.75 mmol) and 0.62 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **28b** in 40% yield (22.8 mg, 0.1 mmol), E:Z 1.7:1 (based on crude ^{1}H NMR) and E:Z 2:1 (isolated) as an oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 20% on a 12 g silica column. E-isomer ^{1}H NMR (400 MHz, Acetone) δ 7.54 (d, 2H), 7.16 (dt, 2H), 5.84 (t, 1H), 2.54 (dq, 4H), 1.48 (qd, 4H), 0.91 (td, 6H). ^{13}C NMR (101 MHz, Acetone) δ 12.93, 13.21, 21.94, 22.75, 31.20, 38.45, 110.81, 119.00, 121.26, 122.07, 130.42, 134.58. Z-isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.38 (s, 1H), 7.21 (dt, *J* = 6.1, 3.6, 3.6 Hz, 2H), 6.38 (t, *J* = 7.4, 7.4 Hz, 1H), 2.66 (m, 1H), 2.29 (dq, *J* = 14.8, 7.4, 7.4, 7.4 Hz, 2H), 2.08 (d, *J* = 4.2 Hz, 2H), 1.55 (dt, *J* = 21.1, 7.4, 7.4 Hz, 4H), 0.97 (dt, *J* = 9.0, 7.4, 7.4 Hz, 6H).

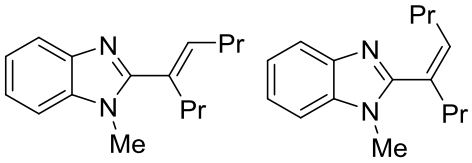
28c (*E*)-2-(oct-4-en-4-yl) thiazole and (*Z*)-2-(oct-4-en-4-yl)thiazole



The **general procedure A** was followed using 2-bromothiazole (50 mg, 0.30 mmol), 1-hexyne (123 mg, 1.5 mmol), *N*, *N*-diisopropyloctan-1-amine (192 mg, 0.90 mmol), formic acid (41 mg, 0.90 mmol) and 0.75 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **28c** in 32% yield (10.5 mg, 0.096 mmol, includes both isomers), E:Z 1.1 :1 (based on crude ^{1}H NMR) and E:Z 1.2:1(isolated) as an oil. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 15% on a 40 g silica column. Z-isomer-^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.3 Hz, 1H), 7.30 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.69 (dtd, *J* = 11.6, 1.9, 1.9, 0.7 Hz, 1H), 5.98 (dt, *J* = 11.7, 7.3, 7.3 Hz, 1H), 2.57 (qd, *J* = 7.4, 7.4, 7.3, 1.9 Hz, 2H), 1.53 (m, 2H), 1.42 (m, 2H), 0.94 (t, *J* = 7.3, 7.3 Hz, 3H). E-isomer-^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 3.3 Hz, 1H), 7.15 (d, *J* = 3.3 Hz,

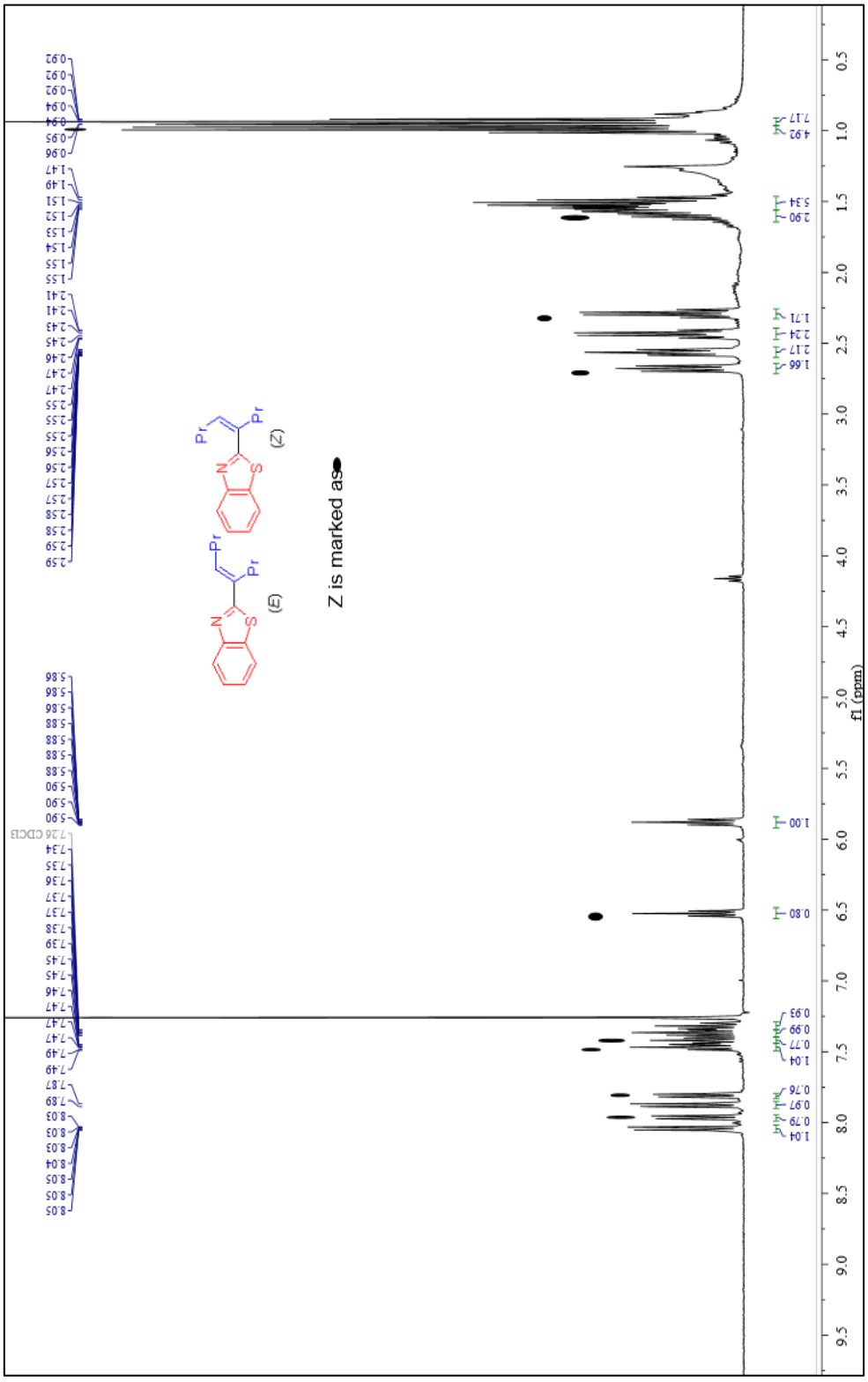
1H), 6.61 (m, 2H), 2.25 (td, *J* = 7.5, 7.3, 5.6 Hz, 2H), 1.48 (m, 2H), 1.38 (ddd, *J* = 9.9, 7.7, 6.0 Hz, 2H), 0.92 (t, *J* = 7.3, 7.3 Hz, 3H).

28d (*E*)-1-methyl-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole and (*Z*)-1-methyl-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole

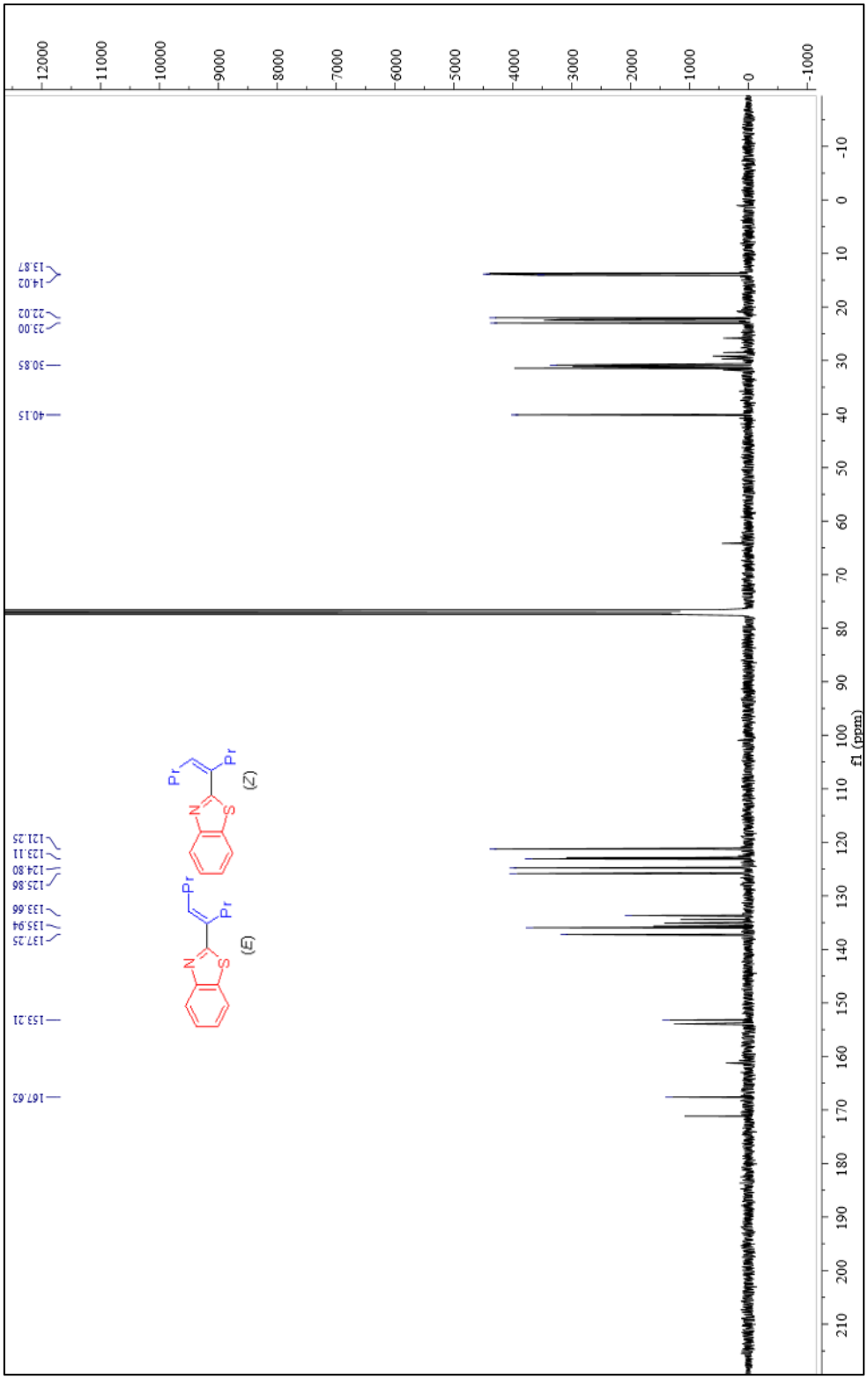


The **general procedure A** was followed using 2-bromo-N-methylimdazole (30 mg, 0.14 mmol), 4-octyne (79 mg, 0.71 mmol), *N*, *N*-diisopropyloctan-1-amine (59 mg, 0.28 mmol), formic acid (19 mg, 0.42 mmol) and 0.35 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **4a** in 46% yield (14.5 mg, 0.062 mmol), E:Z 3:1 (isolated) as a soild. After the completion of the reaction, 12 h, the substrate was purified *via* automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 1H), 7.31 (s, 1H), 7.28 (m, 2H), 5.78 (t, *J* = 7.4, 7.4 Hz, 1H), 3.77 (s, 3H), 2.64 (t, *J* = 7.7, 7.7 Hz, 2H), 2.30 (q, *J* = 7.4, 7.4, 7.4 Hz, 2H), 1.52 (m, 2H), 1.39 (q, *J* = 8.0, 8.0, 7.4 Hz, 3H), 1.00 (m, 3H), 0.89 (t, *J* = 7.1, 7.1 Hz, 2H). Assignments for both E and Z isomers are based on literature.

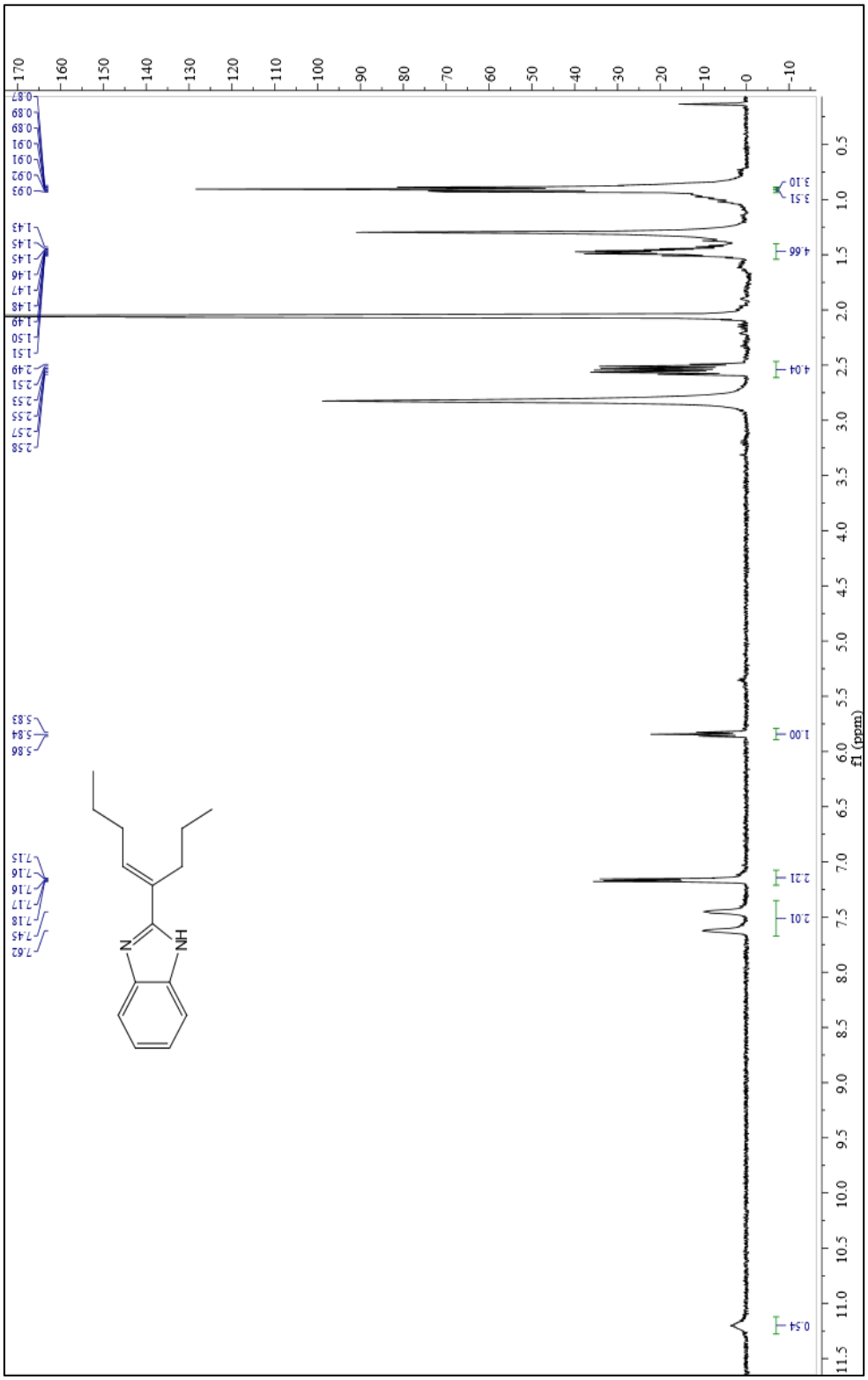
28a (*E*)-2-(oct-4-en-4-yl)benzo[d]thiazole and (*Z*)-2-(oct-4-en-4-yl)benzo[d]thiazole



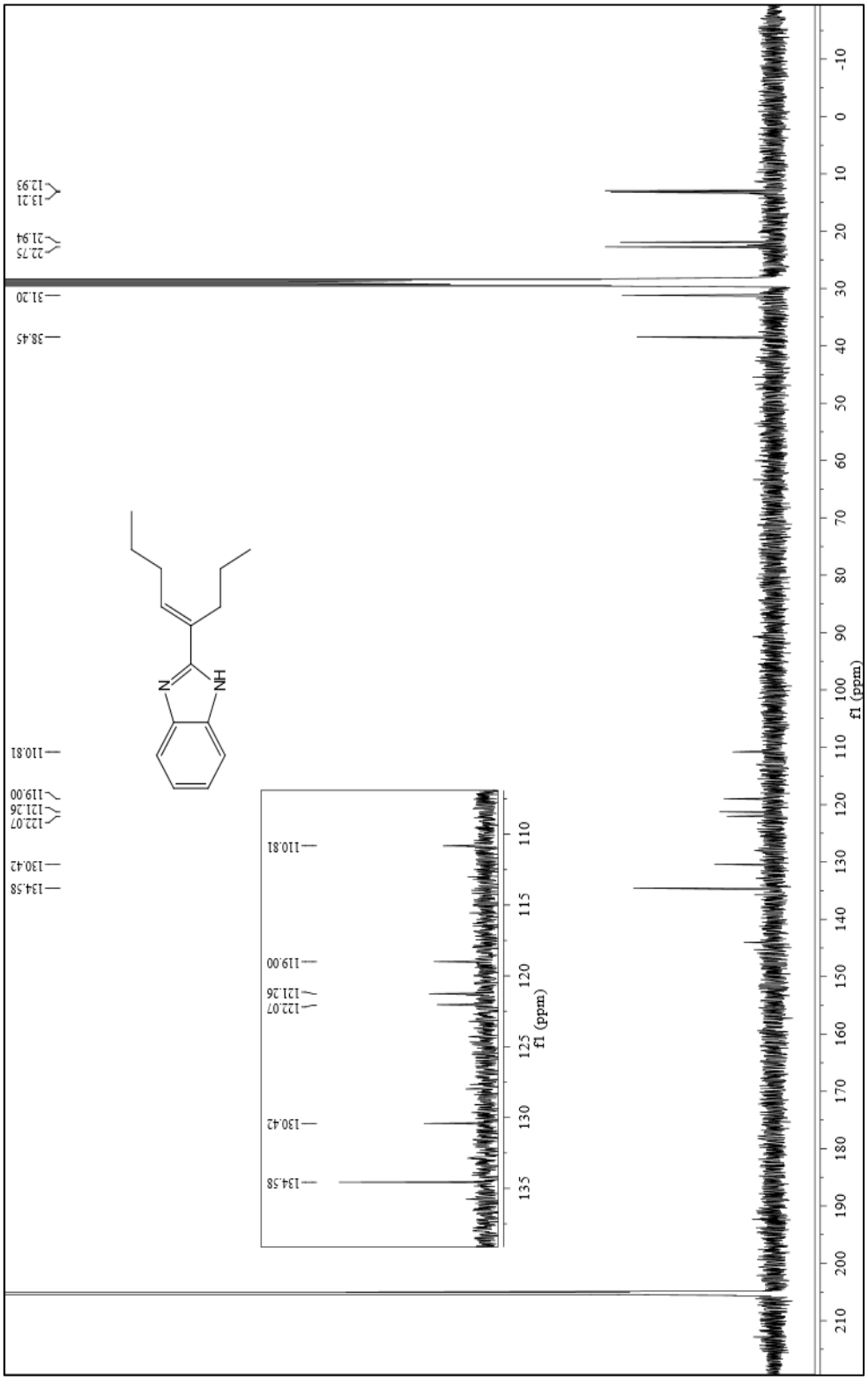
28a (*E*)-2-(oct-4-en-4-yl)benzo[d]thiazole and (*Z*)-2-(oct-4-en-4-yl)benzo[d]thiazole



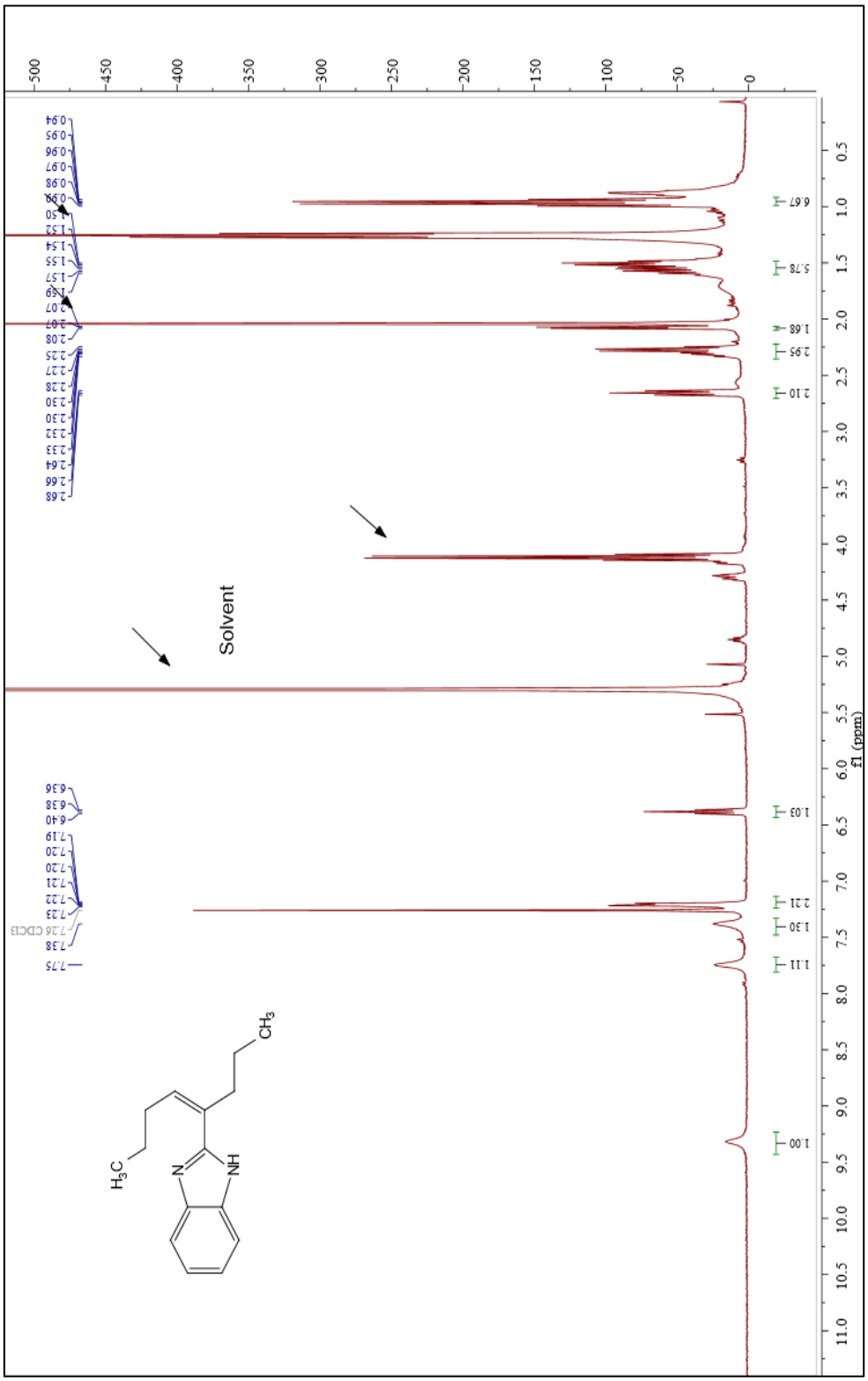
28b (*E*)-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole



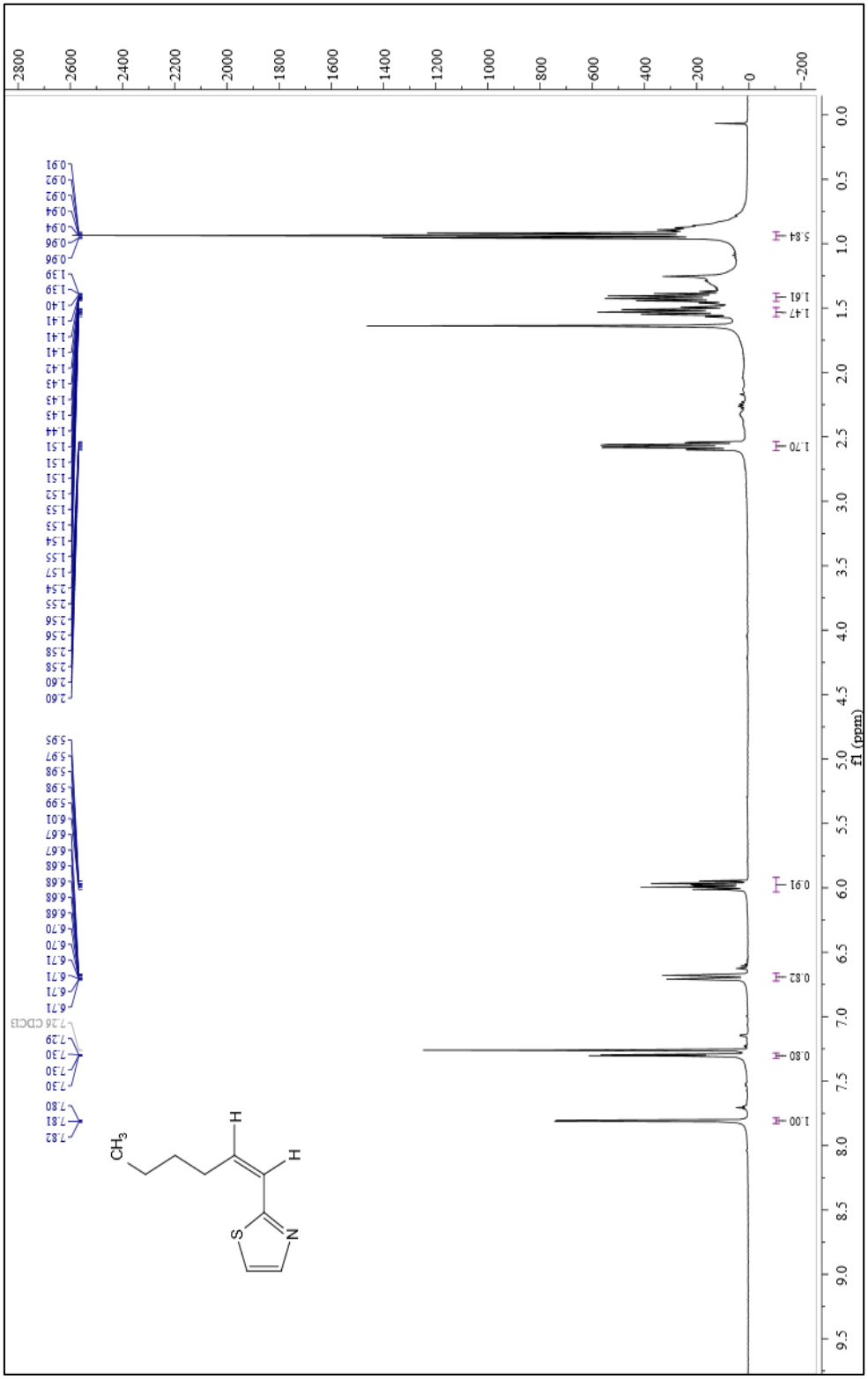
28b (*E*)-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole



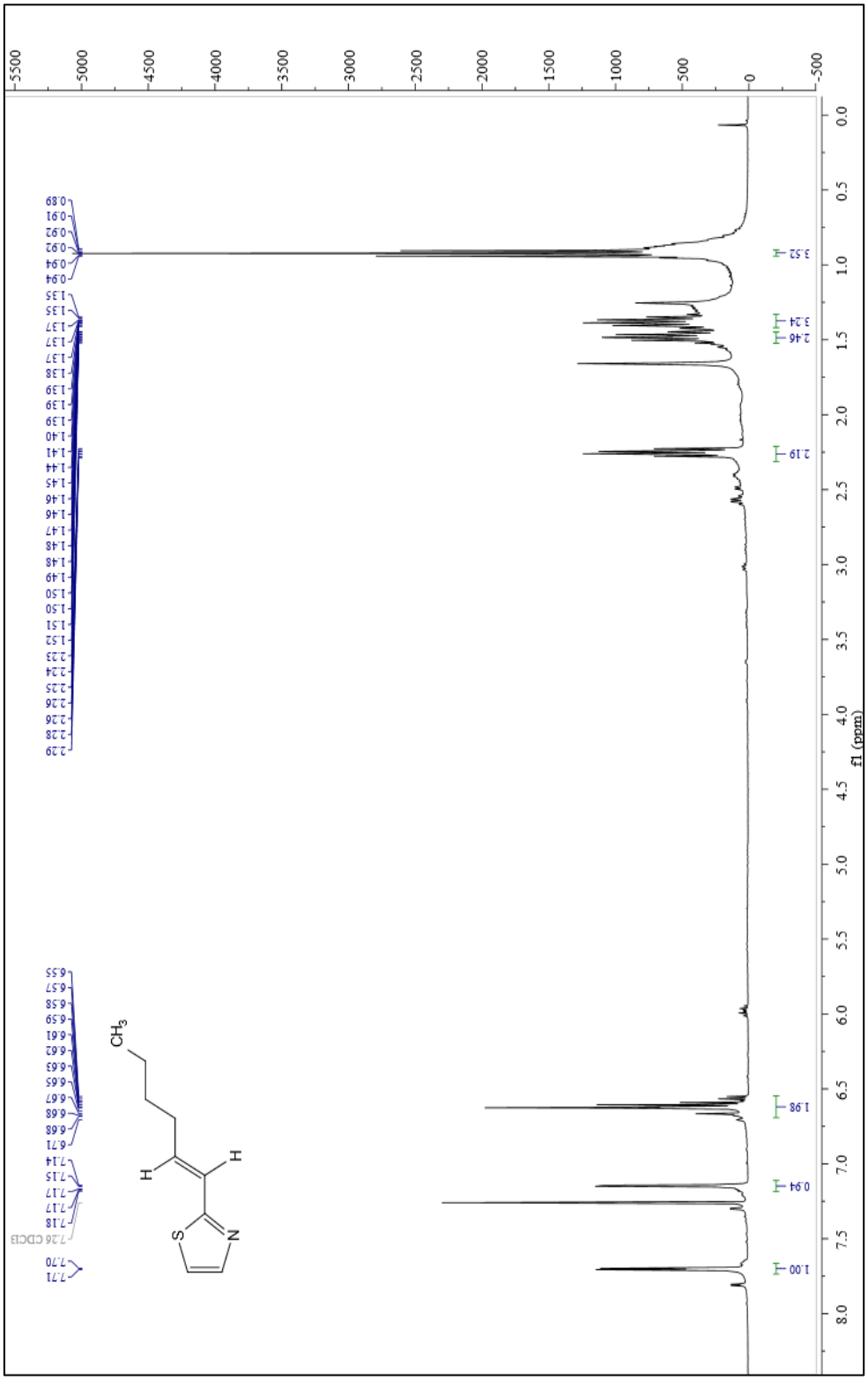
28b (*Z*)-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole



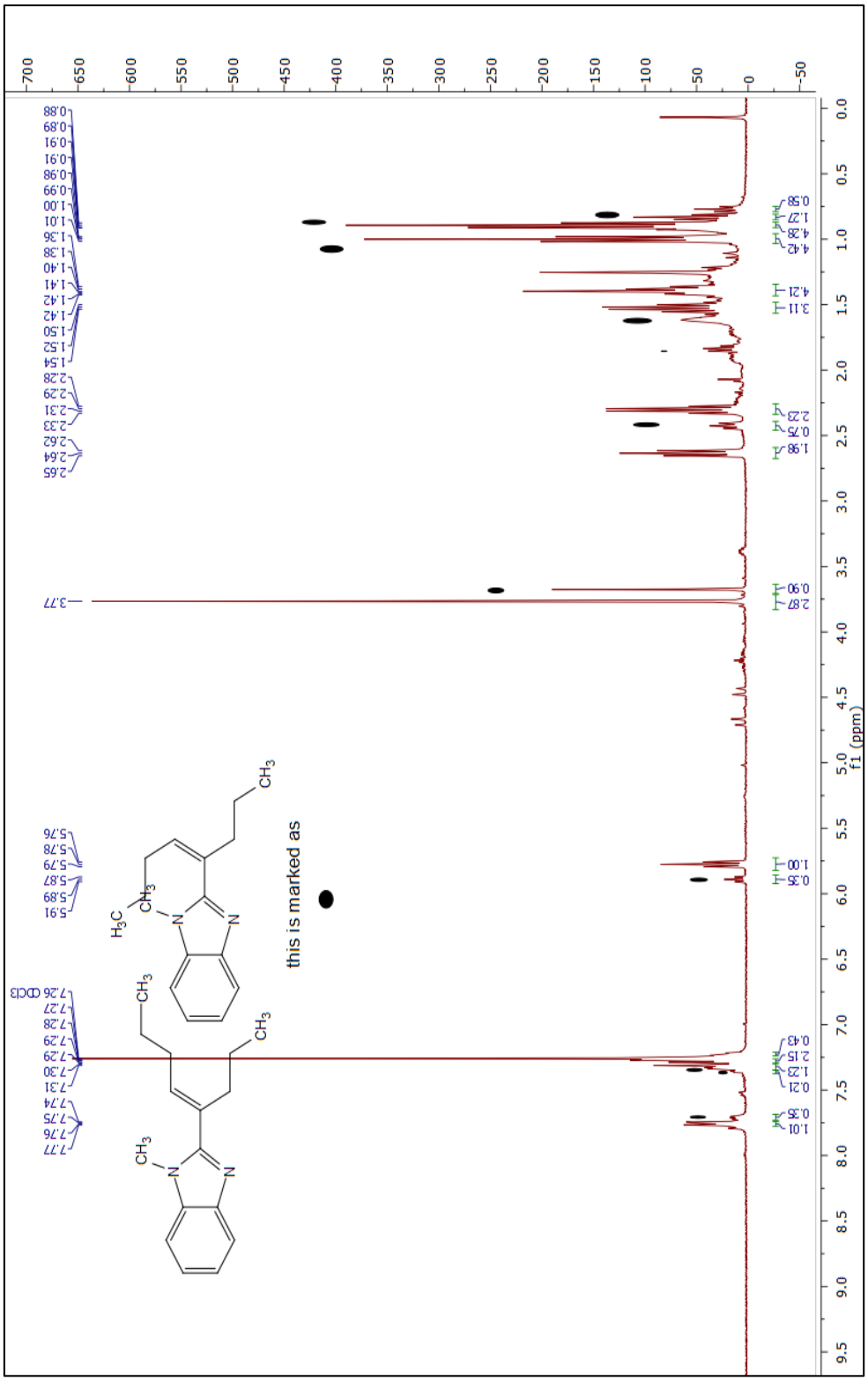
28c (*E*)-2-(oct-4-en-4-yl)thiazole



28c (*Z*)-2-(oct-4-en-4-yl)thiazole



28d (*E*)-1-methyl-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole and (*Z*)-1-methyl-2-(oct-4-en-4-yl)-1H-benzo[d]imidazole



4.7 References

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5. See Experimetal details.
6. The amine is conveniently synthesized in a single step via reductive amination of dicyclohexylamine with isobutyraldehyde.
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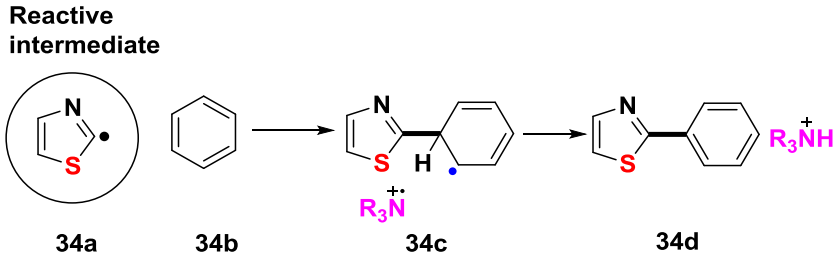
CHAPTER V

C–H ARYLATION OF AZOLES AND HETEROARENES

Further, we sought to capitalize on the ability to form a presumed azolyl radical (Scheme 34) by finding conditions that would allow the azolyl radical intermediate **34a** to undergo direct intermolecular addition to arenes **34b** followed by subsequent oxidation and rearomatization **34c**. The realization of this reaction is significant, in part, because it entails simultaneous reduction of the 2-bromoazole and oxidation of the arene-H. If possible, it would allow simple and direct access to an important motif from widely available starting materials.



- *Is subsequent oxidation and rearomatization of the radical possible?*

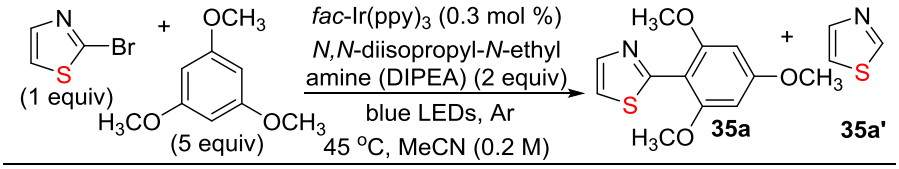
Scheme 34. Proposed C–H arylation strategy.

However, there is a challenge associated with this chemistry. The stoichiometric generation of reactive radicals via traditional methods such as hazardous radical initiators like AIBN along with stoichiometric use of Bu_3SnH at high temperture, often gives rise to undesired reaction pathways, such as reduction, unselective addition, and oligomerization, which can impose severe limitations on the scope of

intermolecular reactions.[1] In contrast, the photocatalytic generation of the reactive radical species can significantly reduce the amount of most of these side products[2]

5.1 Optimization of reaction conditions

We were pleased to see that when we started with similar conditions to those used in the photocatalytic alkylation of 2-bromoazoles (Chapter 2), with the exception that the alkene had been replaced with and arene, we observed the desired arylated azole **35a** (Scheme 35, entry 1) along with reduced starting azole **35a'.**



entry	modifications	**35a/35a'**[a]	time, h	conv[a]
1.	none	52:48	21	100%
2.	*N,N*-diphenyl-4-methoxyaniline instead of DIPEA	na	20	0%
3.[b]	(*c*Hex)$_2$N*i*Bu instead of DIPEA	68:32	20	100%
4.	(*c*Hex)$_2$N*i*Bu, at 15 °C	92:8	20	39%
5.	(*c*Hex)$_2$N*i*Bu, at 30 °C	84:16	20	100%
6.	(*c*Hex)$_2$N*i*Bu, at 60 °C	49:51	20	100%
7.	(*c*Hex)$_2$N*i*Bu, 30 °C, 3.0 equiv of arene-H	78:22	20	100%
8.	(*c*Hex)$_2$N*i*Bu, 30 °C, 1.2 equiv of arene-H	42:58	20	<45%[c]
9.	(*c*Hex)$_2$N*i*Bu, 30 °C, 3.0 equiv of arene-H, but at 0.05 M	94:6	20	100%
10.	**30 °C, 3.0 equiv of arene-H, 0.05 M, but 0.5 equiv (*c*Hex)$_2$N*i*Bu, 2 equiv K_2CO_3**	**95:5**	**20**	**100%**
11.	Entry 10, but Ir(*t*buppy)$_3$ instead of Ir(ppy)$_3$	86:14	20	<45%[c]
12.	Entry 10, but exposed to air	72:28	19	31%[d]
13.[e]	Entry 10, no light, no amine, or no Ir(ppy)$_3$	na	19	<2%

[a]Determined by ^{1}H NMR. [b]See supporting information for entire amine investigation. [c]Reaction did not proceed with extended time. [d]Conversion to an undesired product. [e]Three separate experiments.

Scheme 35. Optimization of reaction conditions.

Careful tracking of the electrons would suggest that it may be possible to use an oxidative quenching mechanism to initiate the chemistry, with the rearomatization process ultimately serving as the electron source.[3] The advantage would be the ability to avoid using a reductant that also serves as the H-atom source.[2a] Thus, eliminating the amine might allow us to avoid the undesired reduction pathway altogether.

Unfortunately, this was not a viable pathway because in the absence of amine, no reaction occurs, even though *fac*-Ir(ppy)$_3$ is very reducing from its excited state (-1.73 V vs. SCE)[4] (Scheme 35, entry 12).

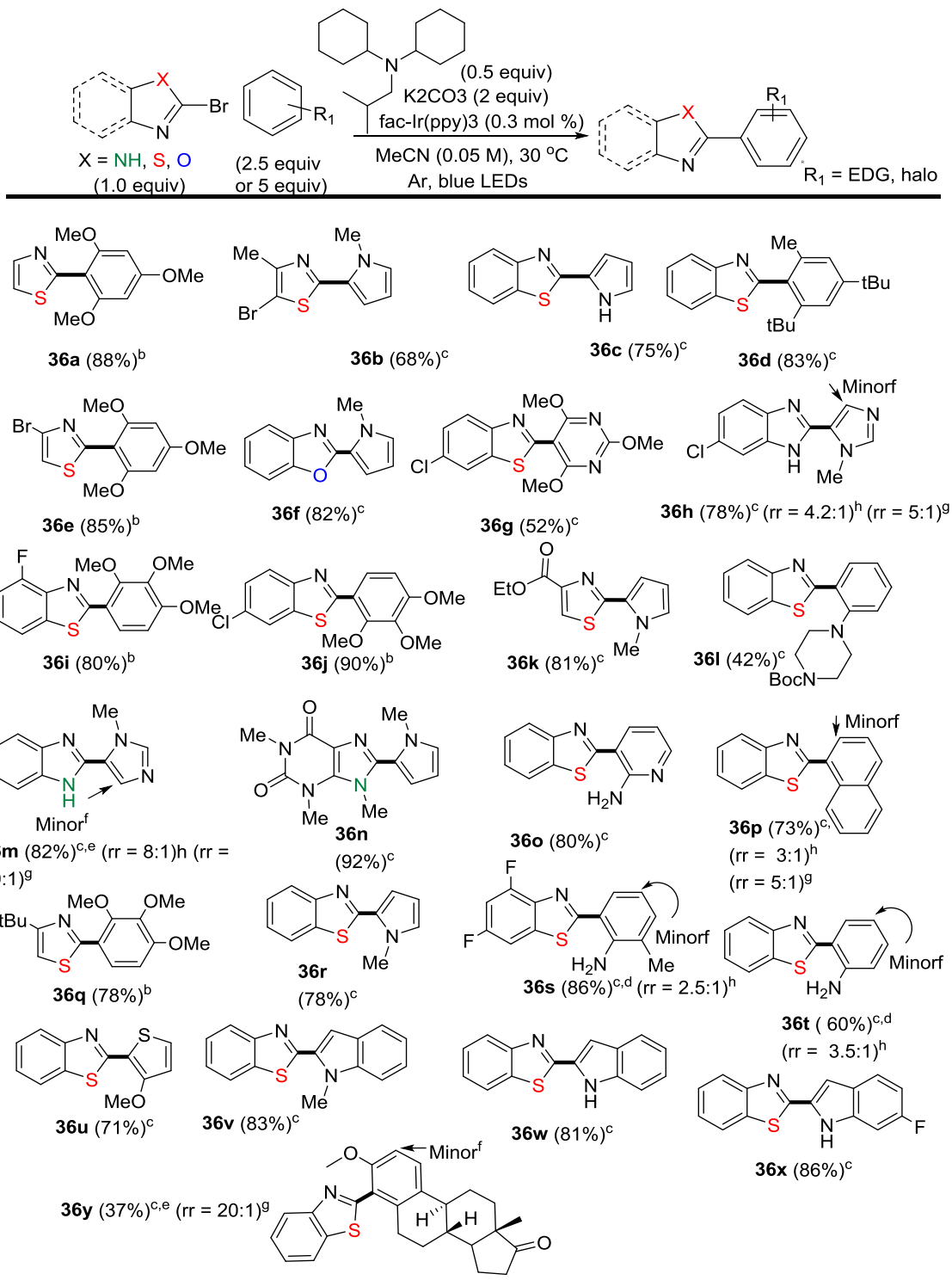
Along this line, Stephenson demonstrated that *N*, *N*-diphenyl-4-methoxyaniline, which is devoid of easily transferable hydrogen atoms, could serve as an electron donor to bromomalonates. In his case, addition of this amine helped avoid reduction of the bromides.[5] However, in the present case, no reaction occurred in the presence of this amine (Scheme 35, entry 2). Previously,[2a] we used the low solubility of certain amines to increase the yields in the related photocatalytic alkylation, and alkenylation reactions where competitive reduction of the azole was also problematic. Consequently, we performed a screen of low solubility amines.[6] We found that bulky *N*-cyclohexyl-*N*-isobutyl-*N*-cyclohexanamine,[7] which is far less soluble in MeCN at 23 ^{o}C than diisopropylethylamine, (0.01 M *vs* 1.3 M) gave an increased amount of the desired product (Scheme 35, entry 3 *vs* 1). We next evaluated the effect of temperature, and found that lowering the temperature led to an increase in ratio of desired product to HAT product (Scheme 35, entries 3-6), resulting **35a**:**35a**' 92:8 ratios, though at lower temperatures the reaction becomes sluggish. It is likely that both effects are due to a decreased amount of soluble amine at lower temperatures (0.00075 M at 15 ^{o}C vs 0.01 M at 23 ^{o}C). We next explored the effect of the concentration of arene (Scheme 35, entries 7 and 8). Dropping the arene loading from 5.0 to 3.0 equivalents resulted in only a slight decrease in product yield. However, further decrease to 1.2 equivalents led to both a decrease in the **35a**:**35a'** ratio, as well as incomplete conversion despite extended reaction times. Assessment of the overall concentration of the reaction revealed that 0.05 M was superior to 0.2 M (Scheme 33, entries 9 *vs* 7), giving **35a**:**35a'** in a 94:6 ratio. We believed the amine was playing two roles in the reaction. The first was to serve as a reductant, which served as a source of electrons that when injected into the LUMO of the bromoazole, were responsible for the C–Br fragmentation. The second was to sequester the HBr that was formed under the reaction conditions. However, we speculated that rearomatization may serve to propagate the reaction[8] and possibly regenerate the amine. To test this, we added a stoichiometric, non-redox active base, K_2CO_3, which would allow us to lower the amine loading to a substoichiometric amount (Scheme 33, entry 10 *vs*

9). Indeed, we found that using only 0.5 equiv of amine resulted in nearly identical **35a**:**35a'** ratio. Finally, control experiments confirmed the necessity of light, amine, and photocatalyst. Thus, using the optimal conditions (Scheme 33, entry 10), an isolated yield of 88% of arylated **35a** was obtained, and we began to explore the scope of this reaction (Scheme 36).

5.2 Scope of the reaction

The reaction worked remarkably well across all of the azoles investigated, thiazoles, benzothiazoles, benzoxazoles, and benzimidazoles, as well as purine derivatives. The selectivity of the reaction for the 2-bromo on the azole derivatives is absolute, allowing the presence of other bromine and chlorine substituents **36b**, **36e**, **36h**, and **36j** that could be used for further elaboration. Additionally, there was no evidence of the bromoazole (or its product) serving as the arene-H partner. In general, the azolyl radical appears electrophilic in nature.[9] The reaction worked well with electron rich benzene derivatives **36a**, **36e**, **36i**, **36j**, and **36q** and even sterically hindered benzenes **36d**. Commonly, pyrrolyl- and indolyl-azoles are made via cyclodehydration or isomerization of the pyrroles and indole precursors to form the azole heterocycle, rather than Suzuki-Miyaura cross-coupling, which is not possible because of the rapid protiodeborylation of 2-heteroatom boronic acids.[10] However, simple unmodified pyrroles coupled efficiently, requiring only 2.5 equivalents of the pyrrole or indole partner. The coupling worked well for *N*-substituted pyrroles and indoles **36b**, **36f**, **36k**, **36n**, and **36r** and should immediately simplify the synthesis of such motifs.[6] The transformation also worked equally well for *N*-unsubstituted pyrroles and indoles **36c**, **36x**, and **36y**, which typically undergo *N*-azolylation. Thus, these conditions provide an orthogonal type of reactivity from the same substrates.[11] 2-Azolyl thiophenes are typically synthesized via Pd-mediated coupling of 2-metallated thiophenes and 2-bromoazoles.[12] Using our protocol, 3-methoxythiophene is cleanly coupled to the bromoazole **36u** without prefunctionalization of the thiophene to deliver the azole-3-alkoxy thiophene motif, which has been frequently investigated because of its nonlinear optical response.[13]

The coupling of 2-aminopyridine took place smoothly, giving a single isomer **34o**. Normally, these same reagents under Pd-catalyzed conditions give rise to C–N coupling, but this is not observed, and again demonstrates the orthogonality of the reaction to currently used methods.[14] 2-bromo-6-chlorobenzothiazole underwent smooth coupling with trimethoxy pyrimidine **36g** to give the fully substituted pyrimidine.[15] *N*-Alkyl imidazoles **36h** and **36m** undergo smooth coupling with 2-bromoimidazoles, albeit at somewhat diminished rates compared to more electron rich arene-Hs. This type of bis(azole) has frequently been investigated because of the array of biological activity it displays, and its synthesis is usually accomplished via cyclodehydration or cross-coupling with an organometallic.[16] In contrast to acid-,[17] copper-,[18] or palladium-catalyzed[19] processes in which anilines undergo *N*-substitution with 2-bromoazoles, in the current protocol, both tertiary and primary anilines give the *ortho*-substituted products as the major to exclusive product **36l**, **36s**, and **36t** with the *para*-substituted aniline making up the mass balance. Addition of the radical to naphthalene affords mono α-azolylation as the major product with some β-addition product rr 3:1, **36p**. The generation of azolyl radical takes place under very mild conditions and appears to be quite compatible with all the functional groups that were tested. Furthermore, no arene-related by-products are observed, suggesting the method might be useful for late-stage azolylzation of pharmaceuticals, in which a major goal is to derivatize the molecule with minimal time and effort.

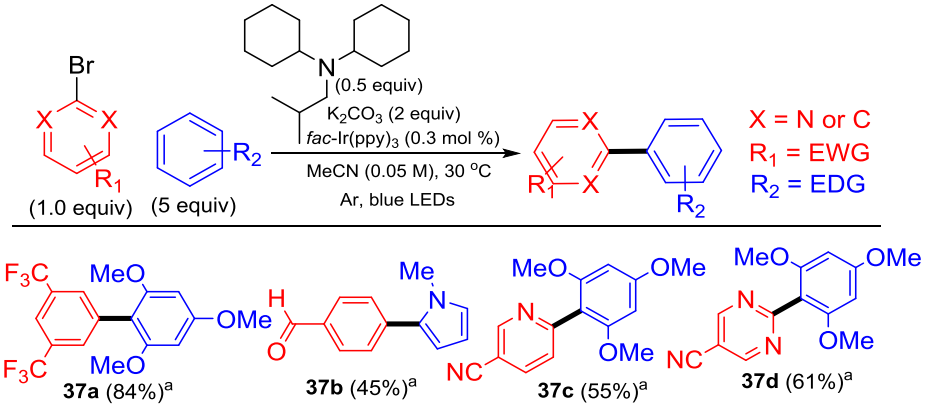


[a]Yields are of isolated products after chromatography. [b]5 equiv of Arene-H is used in the reaction. [c]2.5 equiv of Arene-H is used in the reaction. [d]Both isomers are separable on flash charomatography and yield includes mass of all isolated isomers. [e]Yield of shown isomer only. [f]Site of azolylation of minor regioisomer. Regioisomeric ratio (rr), [g]isolated rr, [h]crude rr is determined on crude material *via* ^{1}H NMR.

Scheme 36. Scope of the reaction.

To demonstrate this, we examined the photocatalytic azolylation reaction of commercially available methylestrone, in which derivatization of the carbonyl has already led to an FDA approved oral contraceptive (mestranol). Although the yield was modest due to low solubility of the substrate, we were able to isolate 37% of the desired product as a single regioisomer in which the C–H was benzothiazolylated at C_4, providing a functionalization strategy and suggesting that the photocatalytic C–H azolylation of arenes may be generally useful for late-stage functionalizations.

While we have been primarily focused on the functionalization of arenes with azoles, this process of electron transfer, radical anion fragmentation, addition, and rearomatization should extend beyond azoles. Thus, we subjected a few reducible (hetero)aryl bromides to the reaction conditions.[20] Modest to good yields could be obtained using the standard conditions without any further optimization (Scheme 37). Given the substantial differences between azoles and these electronically diverse arenes, these results are encouraging, and optimization would likely lead to improved yields.



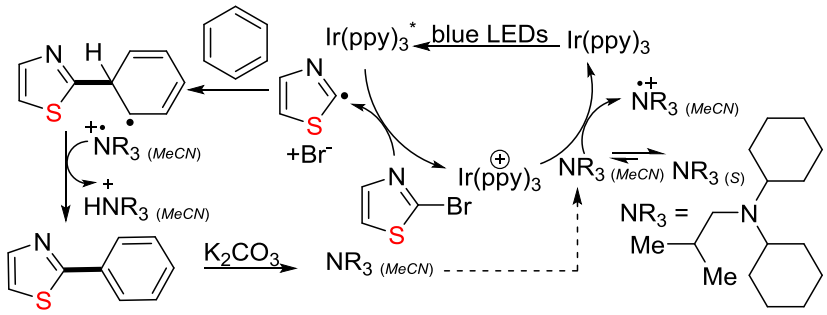
[a]Yields are of isolated products after chromatography

Scheme 37. Reaction of other hetero(aryl) bromide.

5.3 Possible working mechanism

Our working mechanism is outlined below (Scheme 38). Initially, absorption of a photon by the photocatalyst results in a long-lived excited state catalyst, $Ir(ppy)_3^*$.[21] Plausible arguments can be made for both oxidative and reductive quenching, but ultimately both result in electron transfer to the bromoazole, which is ultimately responsible for the formation of the reactive intermediate. Electron transfer to the 2-

bromoazole which after fragmentation of the C–Br bond, gives an azolyl radical.[22] In light of our earlier work with 2-chloroazoles[2b] and the distinct behavior of these intermediates (Scheme 16, eq 1 *vs* eq 2) we believe that a radical anion of the bromoazole is likely formed, but is short-lived and rapidly gives rise to the azolyl radical by unimolecular fragmentation of the C–Br bond.[23] The azolyl radical undergoes addition to the arene with regioselectivity that depends primarily upon the electronics of the arene–H substrate. Because the azolyl radical is generated under slightly basic conditions, as opposed to the strongly acidic conditions typical of the Minisci reaction, both the polarity of the heterocycles and the traditional Minisci-regioselectivities appear to be inverted.[24] Addition of the azolyl radical to the arene gives rise to a cyclohexadienyl radical. In the final step, the dienyl radical must undergo rearomatization. There are several possible pathways through which this may be accomplished. It may occur through 1) electron transfer to the amine radical cation along with deprotonation of the resulting cyclohexadienyl cation, 2) propagation,[8] i.e., transfer of the electron to another bromoazole along with deprotonation of the cyclohexadienyl cation, 3) transfer of the electron to an excited state catalyst along with deprotonation of a cyclohexadienyl cation or 4) deprotonation to generate a cyclohexadienyl radical anion stabilized by the presence of the conjugated azole, which would rearomatize upon loss of an electron to one of the aforementioned potential oxidants. It is reasonable to assume that the dominant rearomatization mechanism is dependent upon the exact nature of the arene-H. It is important to note that the key azolyl radical can undergo undesired hydrogen atom abstraction from either the amine, or the amine radical cation.[2a] Consequently, keeping the concentration of the amine low appears vital to avoiding reduction of the bromoazole.[25] Previously, the use of sparingly soluble amines proved effective at decreasing undesired reduction in the photocatalytic reductive alkylation.[2a] Again, we see that an amine that exhibits low solubility maintains a low concentration throughout the reaction. This allows electron transfer to occur at sufficient rates to facilitate the overall process while surpressing hydrogen atom transfer (HAT) and reduction of the bromoazole. Given that only substoichiometric amounts of amine are needed, it is possible that the amine is being regenerated under the reaction conditions, but this feature could also be a result of a propagation reaction in which the amine is only needed for initiation step.



Scheme 38. Mechanistic hypothesis.

5.4 Summary

Given the ability of the reaction to engage such a wide range of ubiquitous arenes and heteroarenes, the operational simplicity of the reaction, and the interest in such products, we expect that this reaction can immediately help those trying to explore the chemical space about a (hetero)arene-azole core. The developement of this C–H functionalization reaction is a consequence of the exploration of the azolyl intermediate and prompts further exploration of important motifs such as the azole, which could lead to significant advances in our technical ability to synthesize other priveledged scaffolds.

5.5 Experiments

All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI, and Oakwood) and used without further purification unless otherwise noted. 2-bromobenzo[*d*]thiazole, 2-bromo-4-chlorobenzo[*d*]thiazole, 2-bromo-4,6-difluorobenzo[*d*]thiazole, 2,5-dibromo-4-methylthiazole, ethyl 2-bromothiazole-4-carboxylate, 2,6-dibromo-1H-benzo[*d*]imidazole and 2-bromo-6-chloro-1H-benzo[*d*]imidazole which were synthesized according to literature procedures.[2a] *N*, *N*-diisopropyloctan-1-amine, *N*, *N*-diisopropyl-2-methylpropan-1-amine and *N*-cyclohexyl-*N*-isobutylcyclohexanamine were synthesized according to a literature procedure.[26]

Photocatalysts $Ir(ppy)_3$ *fac*-tris(2-phenyl pyridinato-C 2 , N)iridium(III), $Ir(tbppy)_3$ *fac*-tris[2-(4- tert-butylphenyl)pyridinato-C 2, N)]iridium(III), $Ir(CF_3ppy)_3$ *fac*-tris[2-(4- trifluoromethylphenyl)pyridinato-C 2, N)]iridium(III), $Ir(Fppy)_3$, *fac*-tris[2-(4- fluorophenyl)pyridinato-C 2, N)]]iridium(III), $Ir(dFppy)_3$ fac-tris(2-(4,6- difluorophenyl)pyridinato- C 2, N)iridium(III), $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ [4,4'-Bis(tertbutyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate were synthesized according to literature procedures.[27] Reactions were monitored by thin layer chromatography (TLC), Sorbent Technologies Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm) and were visualized with ultraviolet light, potassium permanganate stain, GC-MS (QP 2010S, Shimadzu equipped with auto sampler) and ^1H NMR.

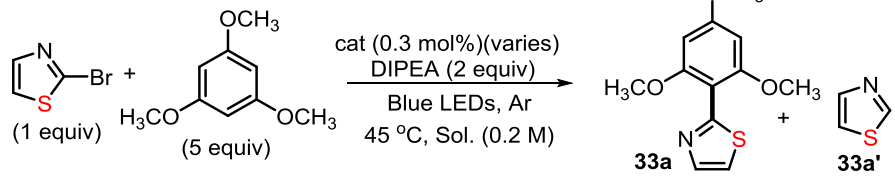
Isolations were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and by ELSD (evaporative light scattering detection). NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer and 400 MHz Unity Inova spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^1H, ^{13}C). IR spectra were recorded on Varian 800 FT-IR. Melting points were determined on Stuart Digital (SMP10), Melting point-apparatus, 120 VAC. Mass spectra (HRMS) analysis was performed on LTQ OrbitrapXL by Thermo Scientific ltd.

Reaction setup:

Photocatalytic reactions were set up in a light bath as described below. Blue LEDs, in the form of strips 18 LEDs/ft from Solid Apollo, were wrapped around the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rest on the top was fashioned from cardboard and holes were made such that reaction tubes (12×75 mm borosilicate tube) were held firmly in the cardboard lid which was placed on the top of bath. Water was added to the bath such that the lower half of the tubes were submerged in the water which was maintained at 30 °C with the aid of a sand bath connected to a thermostat.

Optimization of reaction conditions

Solvent Screening: In order to see the effect of solvent on the reaction several solvents were screened. MeCN was chosen as the optimal solvent for the reaction.

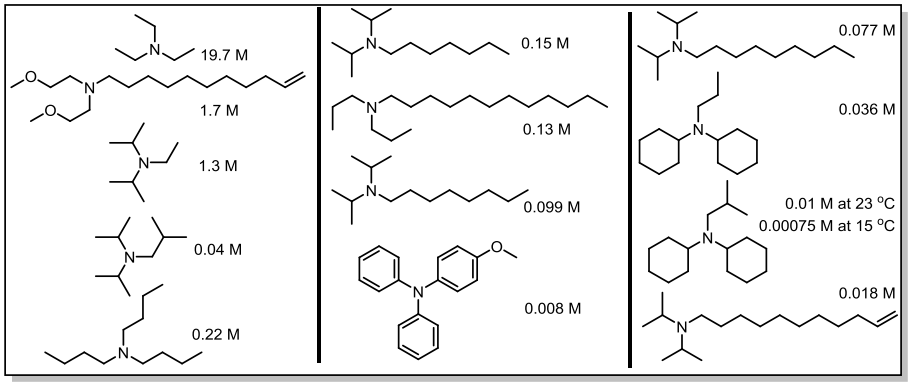


Entry	Solvent	Conversion	product ratio (**33a:33a'**)[a]	time(h)
1	MeCN	100%	49:51%	20
2	CH_3CH_2CN	100%	44:56%	20
3	DMA	79%	79:21%	20
4	DMSO	74%	29:71%	20
5	THF, Toulene or DCM	no conv.	No conv.	20

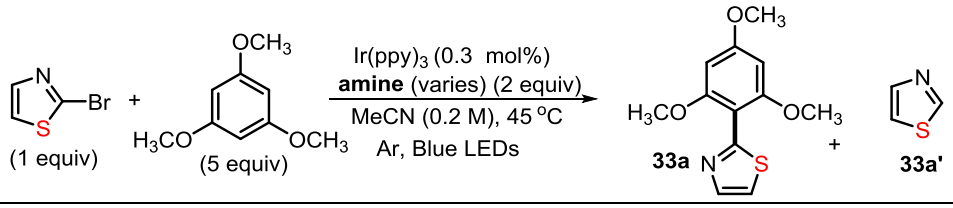
[a]Determined by ^{1}H NMR.

Evaluation of low solubility of amine in reaction mixture: Tertiary amines with large aliphatic groups are often of low solubility in MeCN. This can be used as a convenient method for maintaining a low concentration throughout the duration of the reaction. Thus, we evaluated the solubility of various amines derivatives (below).

Solubility in MeCN at 23 °C



The expectation was that maintaining a low concentration of amine would give an increased product ratio of arylation to reduction. Selected amines were chosen from the previous table and screened in the azoylation of trimethoxybenzene. *N*-cyclohexyl-*N*-isobutylcyclohexanamine was chosen as the optimal amine for the reaction.



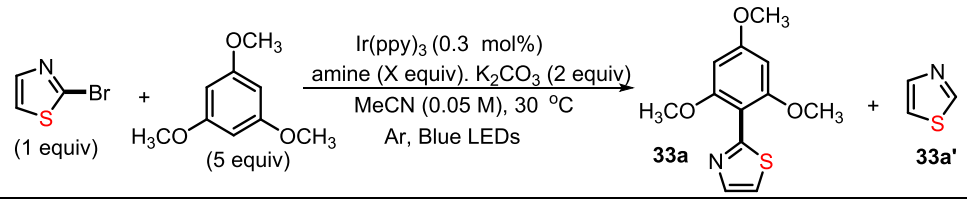
Entry	Amine	Solubilty of amine in MeCN at 23 °C	conversion	product ratio(**33a:33a'**)%[a]	time(h)
1	*N-ethyl*-N-isopropylpropan-2-amine(std)	1.3 M	100%	50:50%	20
2	*N,N*-diisopropyl-2-methylpropan-1-amine	0.04 M	53%	75:25%	20
3	*N*-cyclohexyl-*N*-isobutylcyclohexanamine	0.01 M	100%	68:32%	20
4	4-methoxy-*N,N*-diphenylaniline	0.008 M	0%	no conv.	20
5	*N,N*-diisopropyloctan-1-amine	0.099 M	100%	64:36%	20[b]
6	tributyl amine+formic acid (1:1)	0.22 M	100%	37:63%	20

[a] Determined by ^{1}H NMR. [b] 13% conversion to undesired products.

Evaluation of catalytic amounts of more soluble amine in the reaction

From the data above, it is clear that keeping a low concentration of amine in the reaction throughout the reaction resulted better product ratio (**33a**:**33a'**). However, if the amine is being regenerated (see below) it might be possible to use a catalytic amount of a more soluble amine to achieve similar results. To probe

this question, catalytic amounts of *N*-ethyl-*N*-isopropylpropan-2-amine (DIPEA) which is completely soluble under the conditions was used in the reaction instead of the less soluble amine. The results are below.



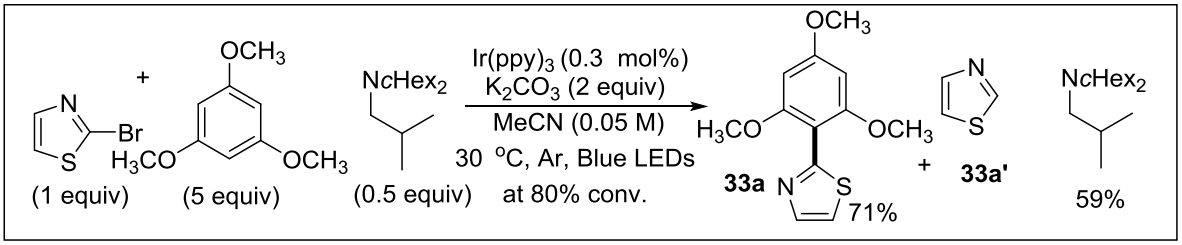
Entry	Amine	amount of amine in the reaction	Solubilty of amine in MeCN at 23 °C	conversion	Product ratio(**33a:33a'**)[a]	time (h)
1	*N-ethyl-N-isopropyl* propan-2-amine	5 mol%	1.3 M	6%	6:0	18
2	*N-ethyl-N-isopropyl* propan-2-amine	30 mol%	1.3 M	16%	14:2	18
3	*N*-cyclohexyl-*N*-isobutyl cyclohexanamine (Std.)	50 mol%	0.01 M	100%	93:7	18

[a] Determined by ^{1}H NMR.

As expected the use of a catalytic amount of DIPEA in the reaction (5 mol% and 30 mol%) gave improved product ratios (**33a**:**33a'**) when compared to its use at superstoichiometric amounts (vide supra) but simultaneously led to a significant retardation of the rate of the reaction. In a side by side reaction the use of *N*-cyclohexyl-*N*-isobutyl cyclohexanamine gave both a better ratio and a significantly faster rate of reaction.

Recovery of amine after the reaction.

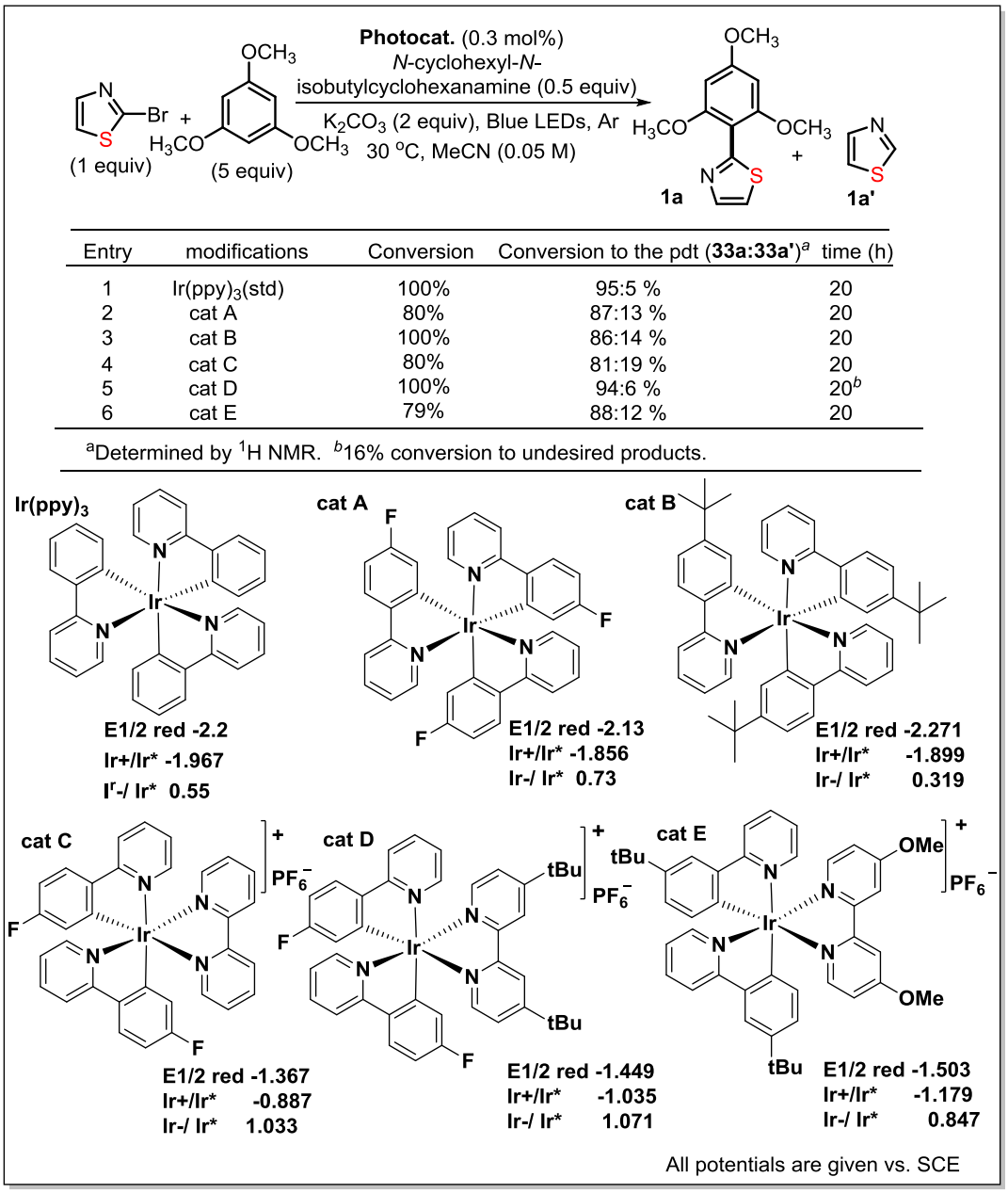
To probe the question of recyclability of the amine by attempting to recover the amine at the end of the reaction. At high conversion, using normal reaction conditions an NMR yield was obtained for the amine (59%). The result suggests that the amine could undergo regeneration, however, there is at least some consumption of the amine. If the reaction proceeds through a propagation reaction, it could be that the amine is consumed every time it transfers an electron. Thus, at this point it is not clear whether the amine is truly recyclable.



A 12×75 mm borosilicate tube fitted with a rubber septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, X mL of 0.15 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.05 M with respect to the 2-bromoazoles), 2-bromoazoles (25mg, 1 equiv), arene-H (128 mg, 5 equiv), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (18 mg, 0.5 equiv) and K_2CO_3 (41 mg, 2 equiv) and the reaction mixture was degassed via Ar bubbling for 10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 30 °C. The reaction was monitored by ^{1}H NMR. After the 80% consumption of aryl bromide, CH_3CN was removed via rotovap and the residue was treated with *sat.* NaOH solution (5 mL) and extracted with CH_2Cl_2 (3 ×10 mL). The organic portions were combined and dried over anhydrous $MgSO_4$. After 16 h of the reaction at 80% conversion, an internal standard 1,2,3-trimethoxybenzene (2.5 mg, 0.2 equiv) was added and the yield of *N*-cyclohexyl-*N*-isobutyl cyclohexanamine was calculated as 59% (based on ^{1}H NMR).

Catalysts Screening

As a part of our optimization, we screened several photocatalysts in the azoylation of trimethoxybenzene and are shown below. Although **cat. B**, **cat. D** and $Ir(ppy)_3$ all reached full conversion, **cat. D** gave 16 % conversion to an undesired product. **Cat. B** resulted in a slightly lower product ratio compared to $Ir(ppy)_3$. Other catalysts resulted in lower conversions. So $Ir(ppy)_3$ was chosen as the optimal catalyst for the reaction.

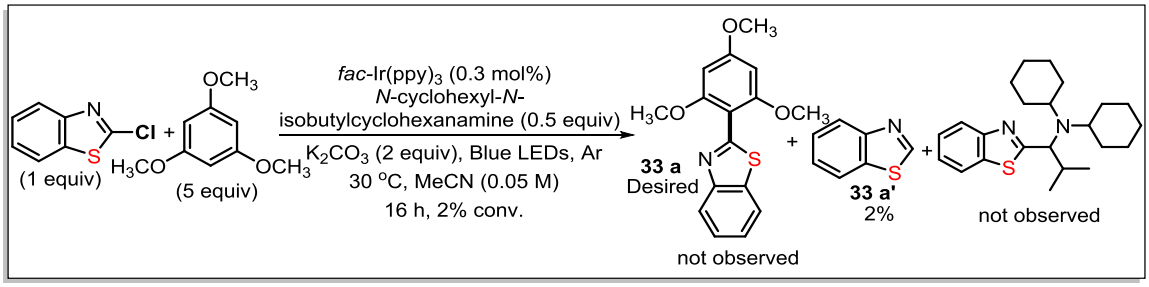


Entry	modifications	Conversion	Conversion to the pdt (**33a:33a'**)[a]	time (h)
1	$Ir(ppy)_3$(std)	100%	95:5 %	20
2	cat A	80%	87:13 %	20
3	cat B	100%	86:14 %	20
4	cat C	80%	81:19 %	20
5	cat D	100%	94:6 %	20[b]
6	cat E	79%	88:12 %	20

[a]Determined by ^{1}H NMR. [b]16% conversion to undesired products.

Control Experiment

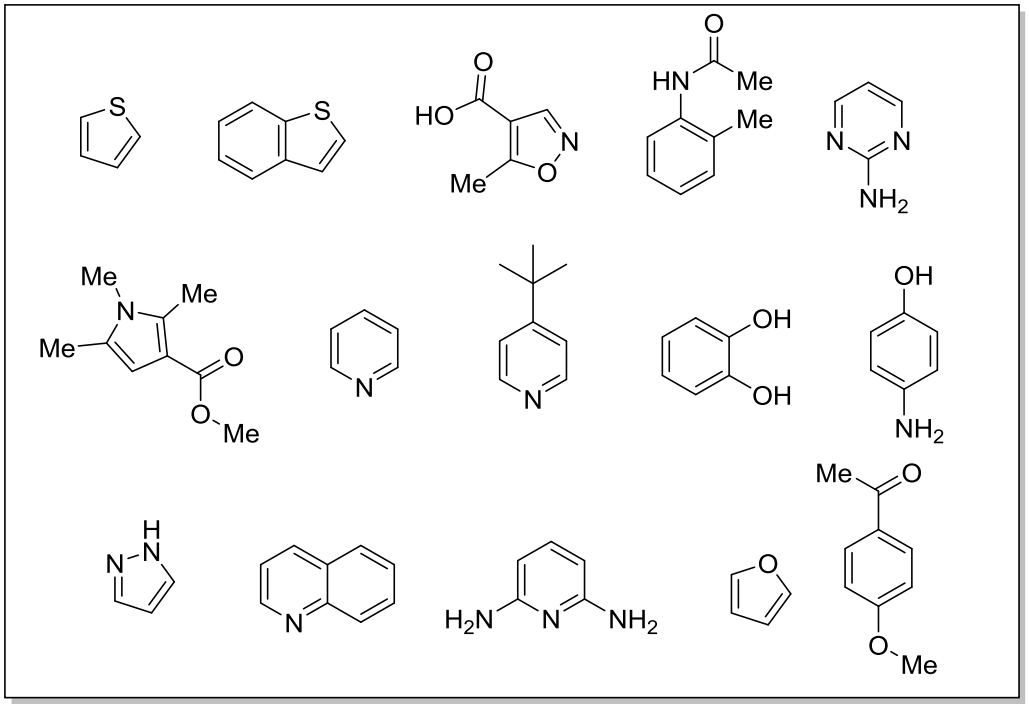
In order to see effect of leaving group i.e. 2–Cl vs 2–Br in the reaction, an attempted coupling was performed with 2-chlorobenzothiazole and 1, 3, 5-trimethoxybenzene under optimized conditions for arylation.



A 12×75 mm borosilicate tube fitted with a rubber septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, 6 mL of 0.15 mM stock solution of catalyst in MeCN, where 3 mL of MeCN is used to make 0.05 M with respect to the 2-chloroazoles), 2-chloroazoles (25 mg, 1 equiv), arene-H (126 mg, 5 equiv), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (18 mg, 0.5 equiv) and K_2CO_3 (41 mg, 2 equiv) and the reaction mixture was degassed via Ar bubbling for 10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 30 °C. The reaction was monitored by TLC and GC-MS. After 24 h of the reaction, there is only 2% **1a'** (reduced starting azole) and 98% starting 2-chloroazole is observed via GCMS. However, as compared to **1a** (Table 1 in the manuscript), where using Br as leaving group on 2-X-azole under similar conditions results 95% conversion of desired arylated azole (GCMS). This may indicate the importance of the concentration of amine in the photocatalytic coupling of the 2-chloroazoles with the amines.

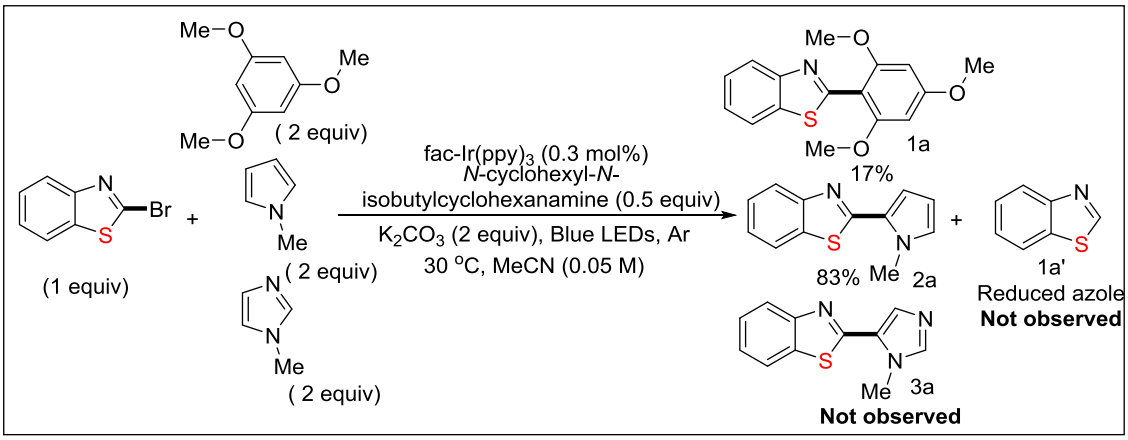
Substrates that did not work in our reaction conditions

While most arenes and heteroarenes we have attempted have worked under the standard conditions, below is a list of substrates that did not work under these reaction conditions with 2-bromobenzothiazole in the first attempt.



Competition Experiment

This experiment is designed to probe the electrophilic nature of azolyl radical in the reaction. Details of the experiment are given below.



A 12×75 mm borosilicate tube fitted with a rubber septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, 6 mL of 0.15 mM stock solution of catalyst in MeCN, where 2.4 mL of MeCN is used to make 0.05 M with respect to the 2-chloroazoles), 2-bromoazoles (25 mg, 1 equiv), 1,3,5-trimethoxybenzene (40 mg, 2 equiv), *N*-methyl pyrrole (19 mg, 2 equiv), *N*-methylimidazole (19 mg, 2 equiv), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (18 mg, 0.5 equiv) and K_2CO_3 (41 mg, 2 equiv) and the reaction mixture was degassed via Ar bubbling for 10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 30 °C. The reaction was monitored by GC-MS. After 24 h of the reaction, there is 17% of **1a** and 83% of **2a** and 0% of **3a** and 0% of **1a'** (reduced starting azole) of starting 2-bromoazole is observed via GCMS. As expected, more nucleophilic arene-H worked better than less nucleophilic arene-H in the reaction.

Photocatalytic arylation

General procedure A for the photocatalytic arylation of bromoazoles with Arene

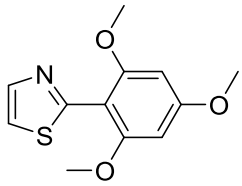
A 12×75 mm borosilicate tube fitted with a rubber septum was charged with *fac*-tris(2-phenyl pyridinato-C^2, *N*) Iridium(III) ($Ir(ppy)_3$) (0.003 equiv, X mL of 0.15 mM stock solution of catalyst in MeCN, where X mL of MeCN is used to make 0.05 M with respect to the 2-bromoazoles), 2-bromoazoles (1 equiv), arene (2.5 equiv), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (0.5 equiv) and K_2CO_3 (2 equiv) and the reaction

mixture was degassed via Ar bubbling for 10 min and then left under positive Ar pressure by removing the exit needle. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 30 °C. The reaction was monitored by TLC and GC-MS. After the complete consumption of aryl bromide, CH_3CN was removed via rotovap and the residue was treated with *sat.* $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified via normal phase chromatography.

General procedure B for the photocatalytic arylation of bromoazoles with Arene

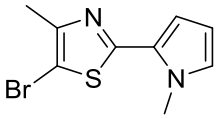
This procedure is identical to **general procedure A** except that 5 equivalents (instead of 2.5) of arene-H are utilized in the reaction.

36a) 2-(2,4,6-trimethoxyphenyl)thiazole



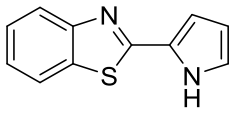
The **general procedure B** was followed using 2-bromothiazole (25 mg, 0.15 mmol), 1,3,5-trimethoxybenzene (128 mg, 0.76 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (18 mg, 0.08 mmol) and K_2CO_3 (41 mg, 0.30 mmol) and 3 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36a** in 88% yield (33 mg, 0.132 mmol) as a white solid. mp -120-123 °C. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 100% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 3.2 Hz, 1H), 6.17 (s, 2H), 3.82 (s, 3H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 160.8, 159.6, 142.1, 119.8, 104.9, 90.8, 56.0, 55.4. FT-IR (neat) cm^{-1} 1117, 1606, 2922. Calculated HRMS [ESI] for $C_{12}H_{14}NO_3S^+$ $(M+H)^+$ is 252.0689 observed 252.0678.

36b) 5-bromo-4-methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole



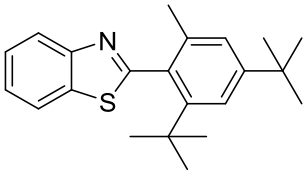
The **general procedure A** was followed using 2,5-dibromo-4-methylthiazole (25 mg, 0.10 mmol), 1-methyl-1H-pyrrole (20 mg, 0.25 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (12 mg, 0.05 mmol) and K_2CO_3 (27 mg, 0.2 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36b** in 68% yield (17.5 mg, 0.068 mmol), rr 20:1 as an oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column.$^{-1}$H NMR (400 MHz, $CDCl_3$) δ 6.72 (t, *J* = 2.2 Hz, 1H), 6.56 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.13 (dd, *J* = 3.9, 2.6 Hz, 1H), 3.96 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 151.6, 126.7, 126.2, 112.5, 108.4, 101.5, 36.5, 15.8. FT-IR (neat) cm-^{1} 603, 1520, 2923. Calculated HRMS[ESI] for $C_9H_{10}BrN_2S^+(M+H)^+$ is 256.9743 observed 256.9730. The structure matched the literature assignment[6] and additionally is consistent with the 1D-NOE.

36c) 2-(1H-pyrrol-2-yl)benzo[d]thiazole



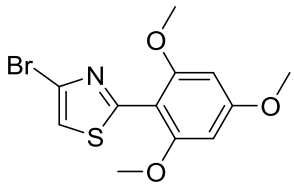
The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (50 mg, 0.23 mmol), 1H-pyrrole (38.5 mg, 0.60 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (27 mg, 0.12 mmol) and K_2CO_3 (63 mg, 0.46 mmol) and 4.8 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36c** in 75% yield (34.5 mg, 0.173 mmol), rr 20:1 as a white solid. mp-151-154 ^{o}C. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 40% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.92 – 7.87 (m, 1H), 7.84 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 6.97 (td, *J* = 2.7, 1.4 Hz, 1H), 6.86 (ddd, *J* = 3.9, 2.5, 1.4 Hz, 1H), 6.33 (dt, *J* = 3.6, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 153.5, 134.0, 126.4, 126.2, 124.5, 122.0, 121.9, 121.5, 112.4, 110.7. FT-IR (neat) cm^{-1} 1311, 1557, 2853, 3122. Calculated HRMS[ESI] for $C_{11}H_9N_2S^+(M+H)^+$ is 201.0481 observed 201.0473.

36d) 2-(2,4-di-tert-butyl-6-methylphenyl)benzo[d]thiazole



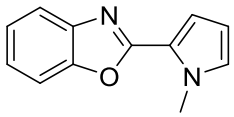
The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), 1,3-di-tert-butyl-5-methylbenzene (63 mg, 0.31 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36d** in 83% yield (33.7 mg, 0.10 mmol), rr 20:1 as a white solid. mp-130-133 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 5% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.93 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.52 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 7.49 – 7.48 (m, 1H), 7.43 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.15 (dd, *J* = 1.9, 0.8 Hz, 1H), 2.05 (s, 3H), 1.35 (s, 9H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 152.6, 151.8, 148.8, 137.8, 136.3, 129.3, 125.7, 125.0, 124.8, 123.3, 121.8, 121.2, 37.0, 34.6, 32.5, 31.1, 20.8. FT-IR (neat) cm^{-1} 956, 1237, 1455, 2922, 2954. Calculated HRMS[ESI] for is $C_{22}H_{28}NS^+(M+H)^+$ 338.1937 observed 338.1923.

36e) 4-bromo-2-(2,4,6-trimethoxyphenyl)thiazole



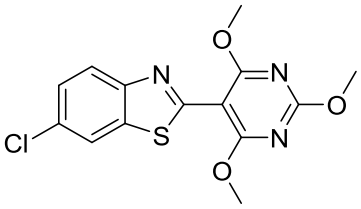
The **general procedure B** was followed using 2,4-dibromothiazole (100 mg, 0.41 mmol), 1,3,5-trimethoxybenzene (344 mg, 2.1 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (48 mg, 0.2 mmol) and K_2CO_3 (113 mg, 0.8 mmol) and 8.2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36e** in 85% yield (115 mg, 0.35 mmol), rr 20:1 as a colorless solid. mp-170-171 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.17 (s, 2H), 3.85 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 161.9, 159.7, 124.2, 117.7, 104.1, 90.7, 56.0, 55.4. FT-IR (neat) cm^{-1} 582, 822, 1127, 2943. Calculated HRMS[ESI] for $C_{12}H_{13}BrNO_3S^+(M+H)^+$ is 329.9794 observed 329.9783.

36f) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]oxazole



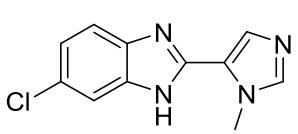
The **general procedure A** was followed using 2-bromobenzo[d]oxazole (60 mg, 0.30 mmol), 1-methyl-1H-pyrrole (60 mg, 0.75 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (35 mg, 0.15 mmol) and K_2CO_3 (83 mg, 0.60 mmol) and 6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36f** in 82% yield (48.7 mg, 0.245 mmol), rr 20:1 as a colorless solid. mp-85-87 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 3% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 1H), 7.51 (dd, *J* = 6.4, 2.6 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.09 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.25 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 149.6, 142.3, 128.5, 124.2 (m, 2 CH), 120.7, 119.3, 115.1, 110.1, 108.8, 37.0. FT-IR (neat) cm^{-1} 1577, 1074. Calculated HRMS[ESI] for $C_{12}H_{11}N_2O^+(M+H)^+$ is 199.0866 observed 199.0857. Structure is assigned based on **33b**.

36g) 6-chloro-2-(2,4,6-trimethoxypyrimidin-5-yl)benzo[d]thiazole



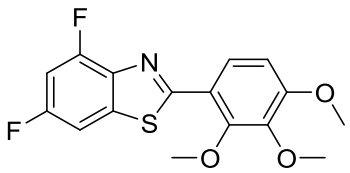
The **general procedure A** was followed using 2-bromo-6-chlorobenzo[d]thiazole (25 mg, 0.10 mmol), 2,4,6-trimethoxypyrimidine (44 mg, 0.25 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (12 mg, 0.05 mmol) and K_2CO_3 (28 mg, 0.2 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36g** in 52% yield (17.5 mg, 0.052 mmol), rr 20:1 as a white solid. mp-157-160 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 20% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 2.1 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.09 (s, 6H), 4.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 164.2, 159.6, 151.4, 136.8, 130.7, 126.6, 123.9, 120.5, 93.5, 55.1, 55.1. FT-IR (neat) cm^{-1} 795, 1226, 1555, 2944. Calculated HRMS[ESI] for $C_{14}H_{13}ClN_3O_3S^+(M+H)^+$ is 338.0361 observed 338.0350.

36h) 6-chloro-2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



The **general procedure A** was followed using 2-bromo-6-chloro-1H-benzo[d]imidazole (100 mg, 0.43 mmol), 1-methyl-1H-imidazole (88 mg, 1.1 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (51 mg, 0.21 mmol) and K_2CO_3 (118 mg, 0.86 mmol) and 8.6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36h** in 79% yield (78.8 mg, 0.34 mmol), rr 5:1(based on isolation) and rr 4.8:1(based on crude ^{1}H NMR) as a white solid. mp-200-202 ^{o}C. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 60% on a 40 g silica column. The column was buffered with 1% Et_3N in hexane before running. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.32 (s, 1H), 7.27 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.19 – 7.13 (m, 1H), 4.17 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 144.7 (2C), 137.7 (2C), 128.3(2C), 124.9, 123.2 (2C), 123.1, 34.3. FT-IR (neat) cm^{-1} 817, 972, 2474, 3345. Calculated HRMS[ESI] for is $C_{11}H_{10}ClN_4^+(M+H)^+$ 233.0589 observed 233.0581. The structure is matched the literature assignment[7] additionally is consistent with the 1D-NOE .

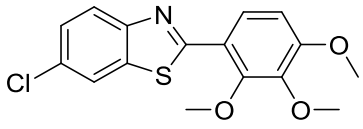
36i) 4,6-difluoro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



The **general procedure B** was followed using 2-bromo-4,6-difluorobenzo[d]thiazole (25 mg, 0.10 mmol), 1,2,3-trimethoxybenzene (84 mg, 0.5 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (12 mg, 0.05 mmol) and K_2CO_3 (27 mg, 0.2 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36i** in 80% yield (27 mg, 0.08 mmol), rr 20:1 as a white solid. mp -175-176 ^{o}C The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 10% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 1H), 7.39 (ddd, *J* = 7.8, 2.3, 1.1 Hz, 1H), 6.97 (ddd, *J* = 10.4, 9.3, 2.4 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.08 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.67 (td, *J* = 8.3, 4.9 Hz), -119.08 (dd, *J* = 10.4, 5.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 3.1 Hz), 159.5 (dd, *J* = 246.6, 10.1 Hz), 156.1, 156.3–153.3(m),152.1, 141.8, 138.6 (dd, *J* = 12.4, 4.9 Hz), 137.9 (d, *J* = 12.9 Hz), 123.9, 119.3, 107.7, 103.0 (dd,

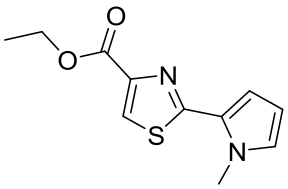
J = 26.0, 4.6 Hz), 101.6 (dd, J = 28.4, 22.0 Hz), 60.8, 60.7, 56.0. FT-IR (neat) cm^{-1} 1098, 1296, 1616, 2923. Calculated HRMS[ESI] for $C_{16}H_{14}F_2NO_3S^+$ $(M+H)^+$ is 338.0657 is observed 338.0645.

36j) 6-chloro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



The **general procedure B** was followed using 2-bromo-6-chlorobenzo[d]thiazole (25 mg, 0.10 mmol), 1,2,3-trimethoxybenzene (84 mg, 0.5 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (12 mg, 0.05 mmol) and K_2CO_3 (27 mg, 0.2 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36j** in 90% yield (30 mg, 0.09 mmol), rr 20:1 as white solid. mp-125-127 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 15% on a 24 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.42 (dd, J = 8.7, 2.1 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 4.08 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 156.0, 152.4, 150.9, 142.1, 137.0, 130.2, 126.7, 124.0, 123.3, 120.8, 119.7, 107.9, 61.0, 60.9, 56.2. FT-IR (neat) cm^{-1} 799, 1295, 1479, 2938. Calculated HRMS[ESI] for $C_{16}H_{15}ClNO_3S^+$ $(M+H)^+$ is 336.0456 observed 336.0444.

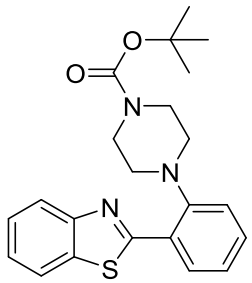
36k) Ethyl 2-(1-methyl-1H-pyrrol-2-yl)thiazole-4-carboxylate



The **general procedure A** was followed using ethyl 2-bromothiazole-4-carboxylate (25 mg, 0.10 mmol), 1-methyl-1H-pyrrole (22 mg, 0.27 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (12 mg, 0.05 mmol) and K_2CO_3 (27 mg, 0.20 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36k** in 81% yield (19 mg, 0.081 mmol), rr 20:1 as an oil. mp-72-73 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 6.78 – 6.73 (m, 1H), 6.68 (dd, J = 3.9, 1.8 Hz, 1H), 6.15 (dd, J = 3.9, 2.6 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.06 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C

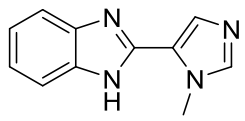
NMR (101 MHz, $CDCl_3$) δ 161.5(2C), 147.3, 127.2, 126.0, 125.0, 113.4, 108.5, 61.3, 36.7, 14.4. FT-IR (neat) cm^{-1} 1074, 1580, 1750, 3284. Calculated HRMS[ESI] for $C_{11}H_{13}N_2O_2S^+$ $(M+H)^+$ is 237.0692 observed 237.0682. Structure is assigned based on **33b**.

36l) tert-butyl 4-(2-(benzo[d]thiazol-2-yl)phenyl)piperazine-1-carboxylate



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), *tert*-butyl 4-phenylpiperazine-1-carboxylate (79 mg, 0.30 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36l** in 42% yield (20 mg, 0.05 mmol), rr 20:1 as an semi soild. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 9 % on a 24 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.35 (m, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.47 (dtd, *J* = 11.7, 7.4, 1.5 Hz, 2H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 3.73 (d, *J* = 9.8 Hz, 4H), 3.03 – 2.92 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 155.0, 152.1, 151.3, 136.2, 131.3, 130.4, 129.5, 125.9, 125.3, 125.1, 122.9, 121.5, 121.5, 79.9, 53.1, 53.1, 28.5. FT-IR (neat) cm^{-1} 759, 1418, 1693, 2926. Calculated HRMS[ESI] for $C_{22}H_{26}N_3O_2S^+$ $(M+H)^+$ is 396.1740 observed 396.1723.

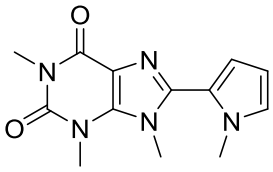
36m) 2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



The **general procedure A** was followed using 2-bromo-1H-benzo[d]imidazole (75 mg, 0.38 mmol), 1-methyl-1H-imidazole (78 mg, 0.95 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (45 mg, 0.20 mmol) and K_2CO_3 (104 mg, 0.76 mmol) and 7.6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36m** in 82% yield (61.6 mg, 0.31 mmol), rr 20:1(isolated) and rr 8:1 (based on crude ^1H NMR) as a buff color solid. mp-196-198 °C. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 12 g silica column. The column was buffered with 1% Et_3N in hexane before

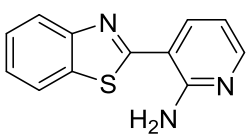
running. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 – 7.57 (m, 2H), 7.32 (s, 1H), 7.33 – 7.26 (m, 2H), 7.19 – 7.13 (m, 1H), 4.16 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 143.4 (2C), 138.1, 128.1, 124.6, 122.8 (2C), 34.2. FT-IR (neat) cm^{-1} 972, 2070, 2474. Calculated HRMS[ESI] for $C_{11}H_{11}N_4^+$ $(M+H)^+$ is 199.0978 observed 199.0969. Structure is assigned based on **36h.**

36n) 1,3,9-trimethyl-8-(1-methyl-1H-pyrrol-2-yl)-3,9-dihydro-1H-purine-2,6-dione

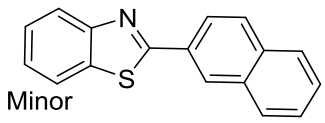


The **general procedure A** was followed using 8-bromo-1,3,9-trimethyl-3,9-dihydro-1H-purine-2,6-dione (100 mg, 0.36 mmol), 1-methyl-1H-pyrrole (73 mg, 0.90 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (43 mg, 0.18 mmol) and K_2CO_3 (99 mg, 0.72 mmol) and 7.2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36n** in 92% yield (90 mg, 0.33 mmol), rr 20:1 as a white solid. mp-184-186 °C. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 40% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 – 6.80 (m, 1H), 6.54 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.25 (ddd, *J* = 3.9, 2.8, 0.8 Hz, 1H), 4.06 (s, 3H), 3.91 (s, 3H), 3.60 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 151.7, 148.1, 145.5, 127.0, 120.0, 113.6, 108.3, 107.4, 36.3, 33.8, 29.7, 27.9. FT-IR (neat) cm^{-1} 1083, 1537, 1672, 2851, 3510. Calculated HRMS[ESI] for $C_{13}H_{16}N_5O_2^+$ $(M+H)^+$ is 274.1299 observed 274.1285. Structure is assigned based on **36b.**

36o) 3-(benzo[d]thiazol-2-yl)pyridin-2-amine

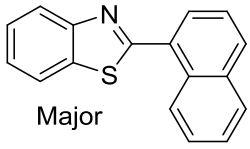


The **general procedure A** was followed using 2-bromobenzo[d]thiazole (25 mg, 0.12 mmol), pyridin-2-amine (28 mg, 0.30 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36o** in 80% yield (22 mg, 0.096 mmol), rr 20:1 as a white solid. mp-177-180 °C. The substrate was purified via automated flash chromatography



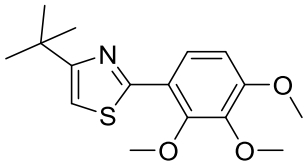
using EtOAc in hexanes (0% to 100%) with product eluting at 10% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.08 (br s, 2H), 6.65 (dd, *J* = 7.7, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 156.2, 153.4, 150.9, 138.1, 133.3, 126.4, 125.4, 122.8, 121.3, 112.9, 110.8. FT-IR (neat) cm^{-1} 756, 1437, 1620, 3128. Calculated HRMS[ESI] for $C_{12}H_{10}N_3S^+(M+H)^+$ is 228.0590 observed 228.0579.

36p) 2-(naphthalen-1-yl)benzo[d]thiazole



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), naphthalene (40 mg, 0.31 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36p** in 73% yield (22.7 mg, 0.087 mmol), rr 5:1(based on isolation) and rr 3:1(based on crude ^{1}H NMR) as an oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with both isomers eluting at 3% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 – 8.92 (m, 1H), 8.22 – 8.18 (m, 1H), 8.02 – 7.97 (m, 2H), 7.94 (dt, *J* = 7.8, 1.4 Hz, 2H), 7.63 (ddd, *J* = 8.5, 6.8, 1.6 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.57 – 7.54 (m, 1H), 7.46 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 154.2, 135.5, 134.0, 131.1, 130.9, 130.7, 129.4, 128.4, 127.6, 126.5, 126.3, 125.9, 125.3, 125.0, 123.6, 121.4. Minor isomer is designated in spectra. FT-IR (neat) cm^{-1} 1400, 2854, 2928. Calculated HRMS[ESI] for is $C_{17}H_{15}N_2S^+$ $(M+NH_4)^+$ 279.0950 observed 279.0971. The structure matched the literature assignment.[8]

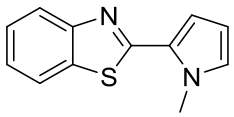
36q) 4-(*tert*-butyl)-2-(2,3,4-trimethoxyphenyl)thiazole



The **general procedure B** was followed using 2-bromo-4-(*tert*-butyl)thiazole (50 mg, 0.23 mmol), 1,2,3-trimethoxybenzene (201 mg, 1.2 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (27 mg, 0.12 mmol) and K_2CO_3 (63 mg, 0.46 mmol) and 4.6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36q** in 78% yield (55 mg, 0.18 mmol), rr 20:1 as a semi solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 9% on a 12 g silica column.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 1H), 6.82 (s, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 160.9, 154.5, 151.4, 142.2, 123.0, 121.0, 110.5, 107.8, 60.9, 60.5, 56.1, 34.7, 30.2. FT-IR (neat) cm^{-1} 1096, 1467, 1595, 2958. Calculated HRMS[ESI] for $C_{16}H_{22}NO_3S^+(M+H)^+$ is 308.1315 observed 308.1302

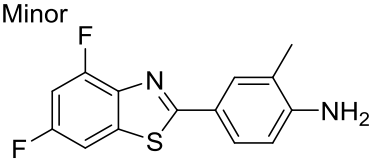
36r) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole



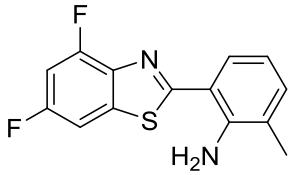
The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (50 mg, 0.23 mmol), 1-methyl-1H-pyrrole (47 mg, 0.60 mmol), N-cyclohexyl-N-isobutylcyclohexanamine (28 mg, 0.11 mmol) and K_2CO_3 (64 mg, 0.46 mmol) and 4.6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36r** in 78% yield (39 mg, 0.18 mmol), rr 20:1 as an oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 2% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.43 (td, J = 8.2, 7.8, 1.2 Hz, 1H), 7.31 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 6.82 (h, J = 1.6 Hz, 2H), 6.21 (dd, J = 3.8, 2.7 Hz, 1H), 4.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 154.3, 133.9, 128.0, 126.5, 125.9, 124.5, 122.4, 121.1, 114.8, 108.7, 37.2. FT-IR (neat) cm^{-1} 1227, 1552, 1437. Calculated HRMS[ESI] for $C_{12}H_{11}N_2S^+(M+H)^+$ is 215.0637 observed 215.0629. Structure is assigned based on **36b**

36s)-2-(4,6-difluorobenzo[d]thiazol-2-yl)-6-methylaniline(major) **36sb)** 4-(4,6-difluorobenzo[d]thiazol-2-yl)-2-methylaniline(minor)

Minor



Major

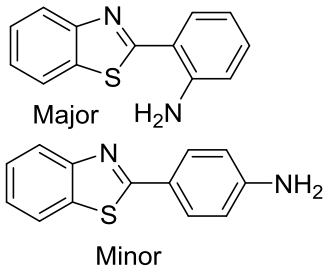


The **general procedure A** was followed using 2-bromo-4,6-difluorobenzo[d]thiazole (75 mg, 0.30 mmol), o-toluidine (80 mg, 0.75 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (35 mg, 0.15 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and 6 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36s and 36sb** in 86% yield, (72 mg, 0.26 mmol that includes both 54 mg (*ortho*) major and and 18 mg (*para*) minor) rr= 2.5:1 (based on crude ^{1}H NMR), as *ortho* isomer as yellow solid and *para* isomer as colorless semisolid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with ortho isomer eluting at 3% and *para* isomer eluting at 10% on a 12 g silica column. (**Major *ortho* isomer)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.35 (ddd, *J* = 7.8, 2.4, 1.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.96 (ddd, *J* = 10.1, 9.3, 2.4 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.47 (brs, 2H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 159.9 (dd, *J* = 247.1, 10.3 Hz), 154.7 (dd, *J* = 258.8, 13.3 Hz), 145.3, 139.20 (dd, *J* = 13.3, 2.5 Hz), 136.18 (dd, *J* = 12.8, 4.8 Hz) 132.8, 128.4, 123.4, 116.4, 114.0, 103.3 (dd, *J* = 26.5, 4.6 Hz), 102.0 (dd, *J* = 28.2, 21.8 Hz), 17.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.10 – -113.40 (m), -118.43 (dd, *J* = 10.2, 5.3 Hz). FT-IR (neat) cm^{-1} 725, 1619, 2851, 3383, 3475. mp-186-188 ^{o}C.

(Minor *para* isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.73 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.33 (ddd, *J* = 7.8, 2.4, 1.2 Hz, 1H), 6.95 (ddd, *J* = 10.3, 9.3, 2.4 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 3.98 (brs, 2H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 159.6 (dd, *J* = 246.4, 10.4 Hz), 154.8 (dd, *J* = 258.0, 13.3 Hz), 147.9, 140.1 – 139.7 (m), 137.3 (dd, *J* = 12.7, 5.3 Hz), 129.9, 127.2, 123.2, 122.2, 114.5, 103.6 (dd, *J* = 26.5, 4.6 Hz), 101.9 (dd, *J* = 28.2, 22.0 Hz), 17.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -

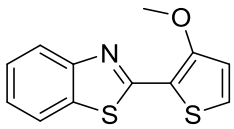
114.0 (ddd, *J* = 9.2, 7.7, 4.9 Hz), -118.6 (dd, *J* = 10.3, 4.9 Hz). FT-IR (neat) cm^{-1} 838, 1285. 1577, 3382. Calculated HRMS[ESI] for $C_{14}H_{11}F_2N_2S^+(M+H)^+$ is 277.0606 observed 277.0594.

36t) 2-(benzo[d]thiazol-2-yl)aniline (major) and 4-(benzo[d]thiazol-2-yl)aniline (minor)



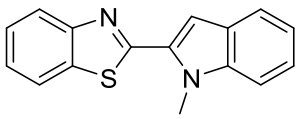
The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), Aniline (29 mg, 0.31 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36t** in 60% yield (16.3 mg, 0.072 mmol, that includes both *ortho* isomer (13.5 mg) and *para* isomer (2.8 mg)), and rr 3.5:1(based on crude ^1H NMR) as a yellow solid of *ortho* isomer and *para* isomer as a buff color solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with *ortho* isomer eluting at 8% and *para* isomer eluting at 14% on a 12 g silica column. **Major** isomer (*ortho*)-^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.46 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 7.36 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.23 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.75 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 6.40 (brs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 153.7, 146.7, 133.3, 131.6, 130.3, 126.0, 124.9, 122.4, 121.2, 116.9, 116.8, 115.3**.** FT-IR (neat) cm^{-1} 726, 1610, 3284. mp-99-100 °C. **Minor** isomer (*para*)- ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.99 (brs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 154.3, 149.2, 134.6, 129.2, 126.1, 124.4, 124.0, 122.5, 121.4, 114.8. FT-IR (neat) cm^{-1} 826, 1604, 3190, 3457. Calculated HRMS[ESI] for $C_{13}H_{11}N_2S^+$ $(M+H)^+$ is 227.0637 observed 227.0628. mp-160-162 °C

36u) 2-(3-methoxythiophen-2-yl)benzo[d]thiazole



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), 3-methoxythiophene (36 mg, 0.31 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36u** in 71% yield (21 mg, 0.085 mmol), rr 20:1 as a yellow solid. mp-135-137 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 7% on a 4 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.41 (d, J = 5.5 Hz, 1H), 7.32 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 6.95 (d, J = 5.5 Hz, 1H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 158.0, 152.4, 134.9, 128.1, 126.0, 124.2, 122.2, 121.2, 116.0, 115.5, 59.0. FT-IR (neat) cm^{-1} 728, 1070, 1550, 2926. Calculated HRMS[ESI] for $C_{12}H_{10}NOS_2^+$ $(M+H)^+$ is 248.0198 observed 248.0188. The structure matched the literature assignment[9] and additionally is consistent with the 1D-NOE.

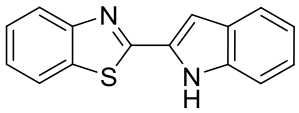
36v) 2-(1-methyl-1H-indol-2-yl)benzo[d]thiazole



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (50 mg, 0.24 mmol), 1-methyl-1H-indole (79 mg, 0.6 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (28 mg, 0.12 mmol) and K_2CO_3 (66 mg, 0.48 mmol) and 4.8 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36v** in 83% yield (52 mg, 0.2 mmol), rr 20:1 as a white solid. mp-140-143 ^oC. The substrate was purified via automated flash chromatography using CH_2Cl_2 in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.02 (m, 1H), 7.92 – 7.87 (m, 1H), 7.68 (dt, J = 8.0, 0.9 Hz, 1H), 7.50 (ddd, J = 8.2, 7.3, 1.3 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.39 (ddd, J = 8.2, 7.3, 1.2 Hz, 1H), 7.34 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.20 – 7.13 (m, 2H), 4.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 154.2, 139.7, 134.4, 132.2, 127.2, 126.2, 125.3, 124.1, 123.2, 121.5, 121.3, 120.5, 110.1, 107.2, 32.2. FT-IR (neat) cm^{-1} 1579, 1626.

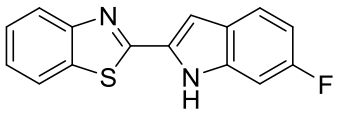
Calculated HRMS[ESI] for ($C_{16}H_{13}N_2S^+$(M+H)$^+$ is 265.0794 is observed 265.0784. The structure matched the literature assignment[10] and additionally is consistent with the 1D-NOE .

36w) 2-(1H-indol-2-yl)benzo[d]thiazole



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (100 mg, 0.46 mmol), indole (135 mg, 1.0 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (54.5 mg, 0.23 mmol) and K_2CO_3 (127 mg, 0.92 mmol) and 9.2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36w** in 81% yield (93 mg, 0.37 mmol), rr 20:1 as a white solid. mp-143-145 °C. The substrate was purified via automated flash chromatography using CH_2Cl_2 in hexanes (0% to 100%) with product eluting at 10% on a 40 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (brs, 1H), 7.91 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.60 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.20 (t, *J* = 1.3 Hz, 1H), 7.13 – 7.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 153.4, 137.0, 134.6, 131.3, 128.4, 126.5, 125.3, 124.7, 122.7, 121.7, 121.6, 120.8, 111.6, 105.6. FT-IR (neat) cm^{-1} 891, 1142, 1443, 2920, 3382. Calculated HRMS[ESI] for $C_{15}H_{11}N_2S^+$ (M+H)$^+$ is 251.0637 observed 251.0629. The structure matched the literature assignment[10] and additionally is consistent with the 1D-NOE .

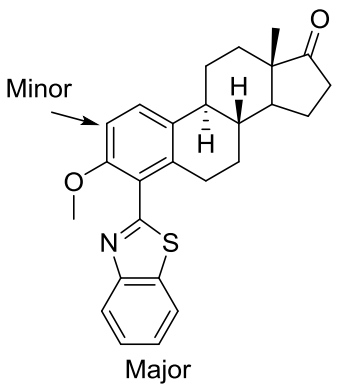
36x) 2-(6-fluoro-1H-indol-2-yl)benzo[d]thiazole



The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (150 mg, 0.70 mmol), 6-fluoro-1H-indole (237 mg, 1.75 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (83 mg, 0.35 mmol) and K_2CO_3 (193 mg, 1.4 mmol) and 14 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36x** in 86% yield (161.3 mg, 0.60 mmol), rr 20:1 as a colorless solid. mp-183-186 °C. The substrate was purified via automated flash chromatography using CH_2Cl_2 in hexanes (0% to 100%) with product eluting at 16% on a 80 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$ in one drop of D_2O) δ 7.97 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.88 (t, *J* = 6.6 Hz, 1H), 7.59 (dd, *J* = 8.8, 5.2

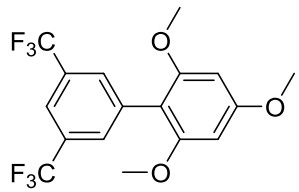
Hz, 1H), 7.53 – 7.45 (m, 1H), 7.43 – 7.35 (m, 1H), 7.12 (d, *J* = 5.1 Hz, 1H), 7.08 (dd, *J* = 9.5, 2.3 Hz, 1H), 6.92 (td, *J* = 9.1, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 160.0 (d, *J* = 5.8 Hz), 153.2, 137.2 (d, *J* = 12.8 Hz), 134.5, 131.9, 126.6, 125.4, 125.0, 122.7, 122.6, 121.7, 110.0 (d, *J* = 25.1 Hz), 105.7, 97.8 (d, *J* = 26.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.70 (td, *J* = 9.5, 5.3 Hz). FT-IR (neat) cm^{-1} 1014, 1241, 1549, 3266. Calculated HRMS[ESI] for $C_{15}H_{10}FN_2S^+$ $(M+H)^+$ is 269.0543 observed 269.0529. Structure is assigned based on **34w**.

36y) (8R,9S,13S)-2-(benzo[d]thiazol-2-yl)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one



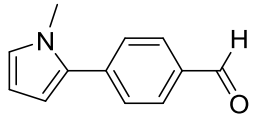
The **general procedure A** was followed using 2-bromo-benzo[d]thiazole (25 mg, 0.12 mmol), Mestrone (80 mg, 0.30 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (14 mg, 0.06 mmol) and K_2CO_3 (33 mg, 0.24 mmol) and 2.4 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **36y** in 37% yield (20 mg, 0.045 mmol, rr (isolated)20:1 and rr(crude) 6:1. mp-198-201 ^{o}C **Note-** yield corrosponds to isolated isomer. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 20%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.55-7.47 (m, 1H), 7.41 (t, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 1H), 3.75 (s, 3H), 2.81 – 2.68 (m, 2H), 2.55 – 2.40 (m, 2H), 2.31 (q, *J* = 10.7, 7.6 Hz, 1H), 2.13 (q, *J* = 9.7, 9.1 Hz, 1H), 1.99 (td, *J* = 10.6, 9.0, 4.8 Hz, 1H), 1.90 (ddd, *J* = 15.4, 7.9, 4.0 Hz, 1H), 1.62 (d, *J* = 12.3 Hz, 3H), 1.59 – 1.49 (m, 3H), 1.37 (d, *J* = 13.2 Hz, 1H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 156.0, 153.4, 137.6, 136.6, 132.7, 128.0, 125.7, 125.0, 123.4, 122.2, 121.5, 108.7, 55.9, 50.3, 47.9, 44.2, 37.7, 36.6, 35.9, 27.5, 26.2, 26.2, 21.5, 13.8

37a) 2,4,6-trimethoxy-3',5'-bis(trifluoromethyl)-1,1'-biphenyl



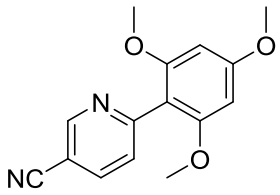
The **general procedure B** was followed using 1-bromo-3,5-bis(trifluoromethyl)benzene (25 mg, 0.09 mmol), 1,3,5-trimethoxybenzene (71 mg, 0.42 mmol), N-cyclohexyl-N-isobutylcyclohexanamine (10 mg, 0.04 mmol) and K_2CO_3 (23 mg, 0.17 mmol) and 1.7 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **37a** in 84% yield (29 mg, 0.076 mmol), rr 20:1 as a white solid. mp-110-112 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 8% on a 24 g silica column. ^1H NMR(400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.76 (s, 1H), 6.23 (s, 2H), 3.88 (s, 3H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 158.1, 136.2, 131.7, 130.5 (q, *J* = 32.8 Hz), 125.1(q, *J* = 1080), 120.0(h, *J* = 3.9 Hz), 109.2, 90.8, 55.8, 55.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.67. FT-IR (neat) cm^{-1} 1117, 1279, 1413, 2922. Calculated HRMS[ESI] for $C_{17}H_{15}F_6O_3^+$ $(M+H)^+$is 381.0920 is observed 381.1152.

37b) 4-(1-methyl-1H-pyrrol-2-yl)benzaldehyde



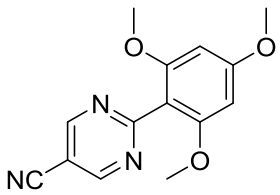
The **general procedure B** was followed using 4-bromobenzaldehyde (75 mg, 0.4 mmol), 1-methyl-1H-pyrrole (164 mg, 2.02 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (47 mg, 0.2 mmol) and K_2CO_3 (110 mg, 0.8 mmol) and 8 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **37b** in 45% yield (33 mg, 0.18 mmol), rr 20:1 as an orange semisolid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 9% on a 40 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.9 (d, *J* = 8.6 Hz, 2H), 7.6 (d, *J* = 8.2 Hz, 2H), 6.8 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.4 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.2 (dd, *J* = 3.7, 2.7 Hz, 1H), 3.7 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 139.3, 134.2, 133.2, 130.0, 128.2, 125.8, 110.8, 108.6, 35.6. FT-IR (neat) cm^{-1} 1166, 1598, 1691. Calculated HRMS[ESI] for $C_{12}H_{11}NNaO^+$ $(M+Na)^+$ is 208.0733 observed 208.0653. Structure is assigned based on **37b**.

37c) 6-(2,4,6-trimethoxyphenyl)nicotinonitrile



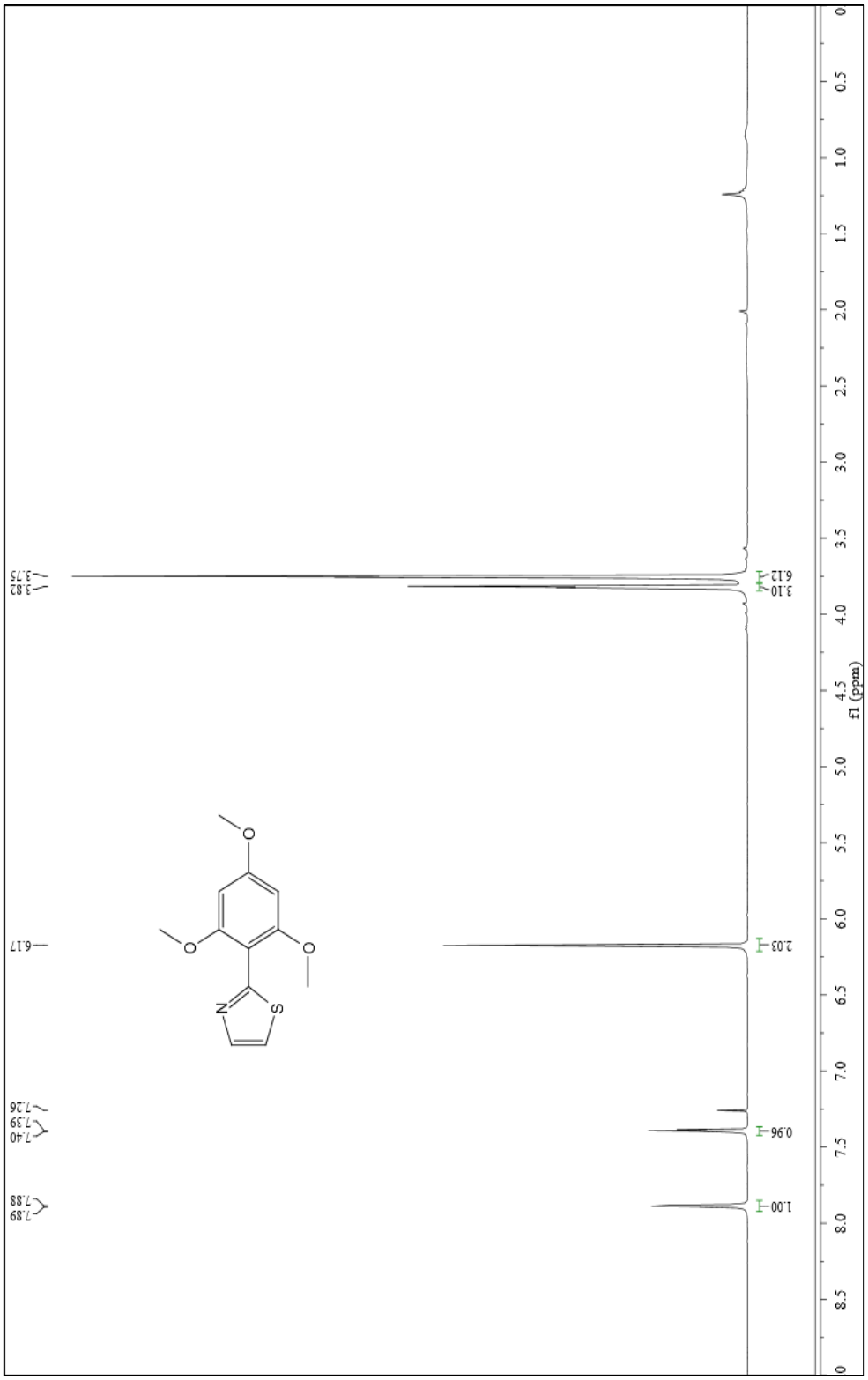
The **general procedure B** was followed using 6-bromonicotinonitrile (25 mg, 0.14 mmol), 1,3,5-trimethoxybenzene (117 mg, 0.70 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (16.6 mg, 0.07 mmol) and K_2CO_3 (38 mg, 0.28 mmol) and 2.8 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **37c** in 55% yield (21 mg, 0.077 mmol), rr 20:1 as a colorless solid. mp-165-167 ^oC The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.81 (dd, *J* = 8.0, 2.1Hz, 1H), 7.67 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.22 (s, 2H), 3.87 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 158.3, 153.7, 139.3, 134.3, 130.5, 127.5, 117.9, 106.7, 90.8, 55.8, 55.5. FT-IR (neat) cm^{-1} 790, 1117, 1583, 2228, 2841. Calculated HRMS[ESI] for $C_{15}H_{15}N_2O_3^+(M+H)^+$ is 271.1077 observed 271.1066.

37d) 2-(2,4,6-trimethoxyphenyl)pyrimidine-5-carbonitrile

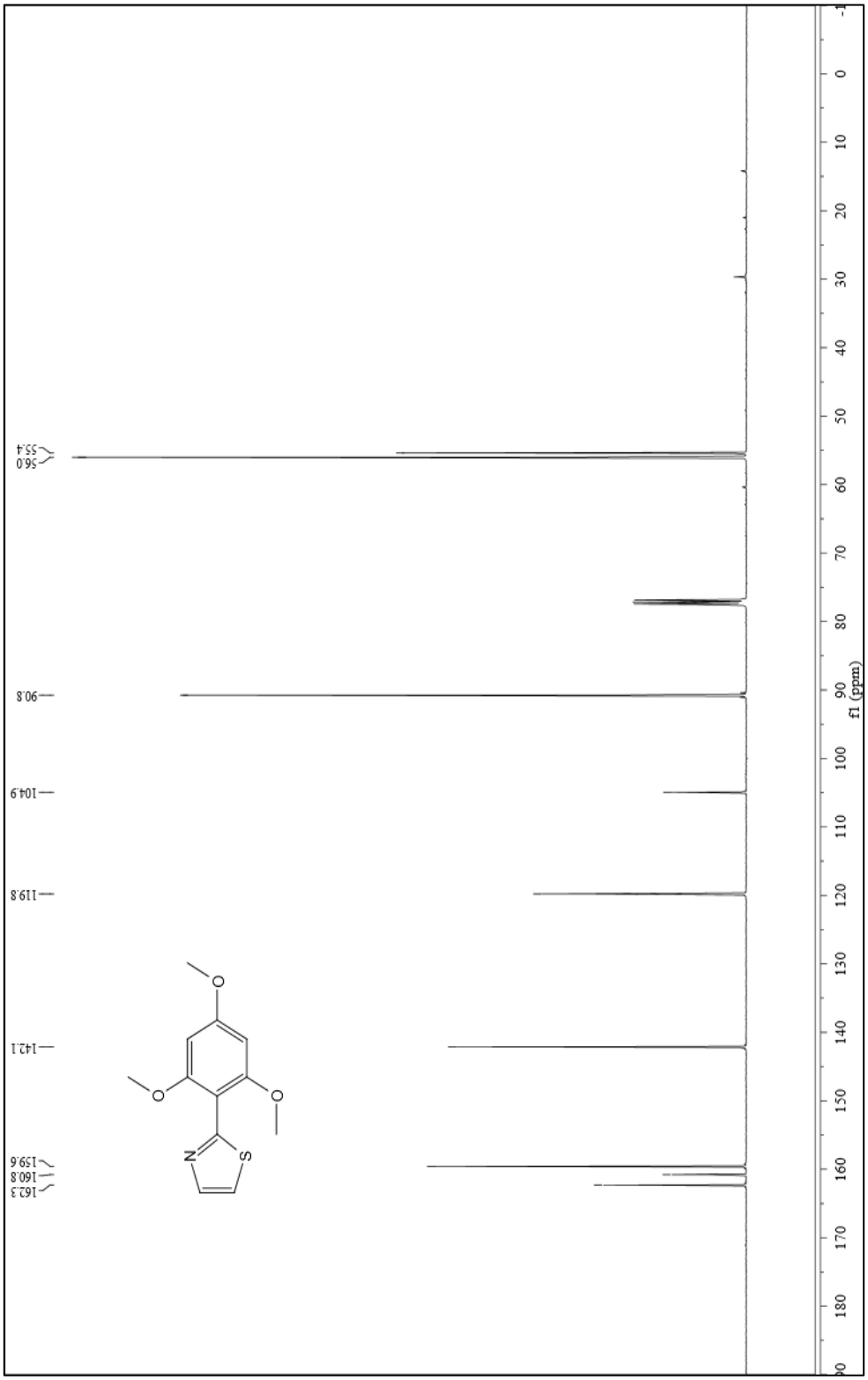


The **general procedure B** was followed using 2-bromopyrimidine-5-carbonitrile (25 mg, 0.14 mmol), 1,3,5-trimethoxybenzene (117 mg, 0.70 mmol), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (16 mg, 0.07 mmol) and K_2CO_3 (38 mg, 0.28 mmol) and 2 mL of stock solution of $Ir(ppy)_3$ in MeCN was used to afford **37d** in 61% yield (21 mg, 0.085 mmol), rr 20:1 as a white solid. mp-168-170 ^oC. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 12% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 2H), 6.25 (s, 2H), 3.91 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 159.5, 158.4, 141.7, 131.3, 116.2, 103.1, 90.8, 55.8, 55.5. FT-IR (neat) cm^{-1} 1166, 1598, 2300. Calculated HRMS[ESI] for $C_{14}H_{13}N_3NaO_3^+$ $(M+Na)^+$ is 294.0849 observed 294.084

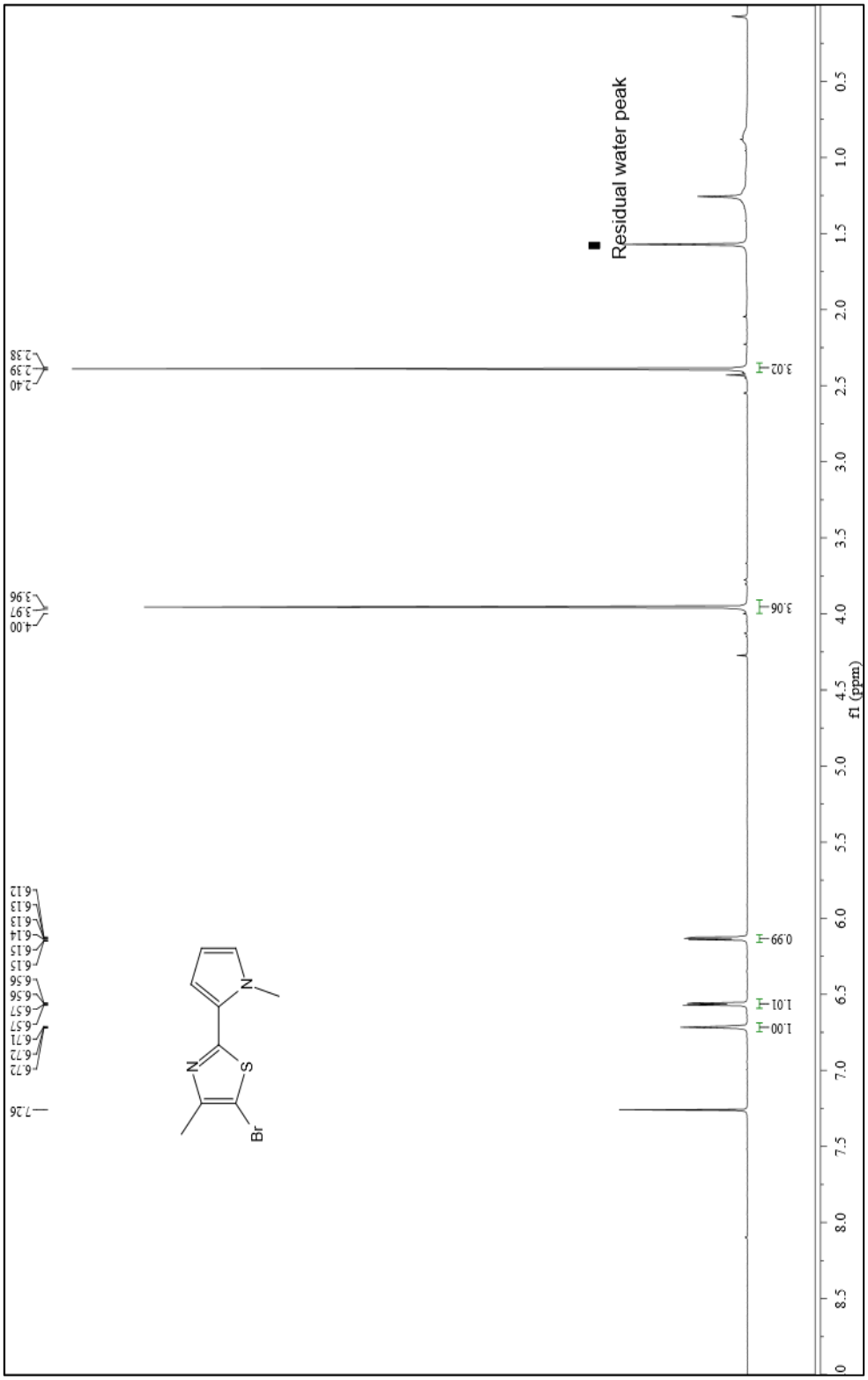
36a) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(2,4,6-trimethoxyphenyl)thiazole



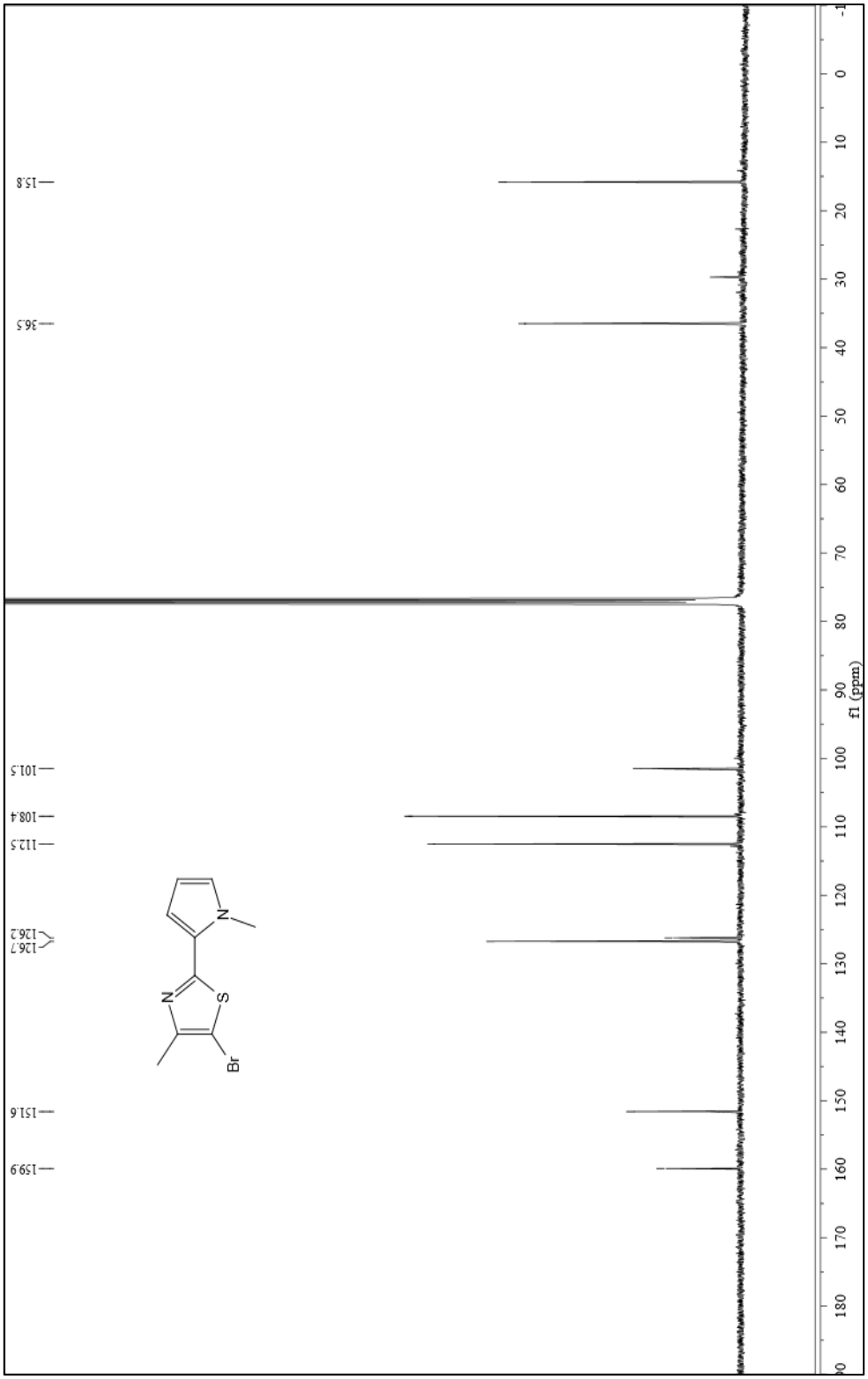
36a) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(2,4,6-trimethoxyphenyl)thiazole



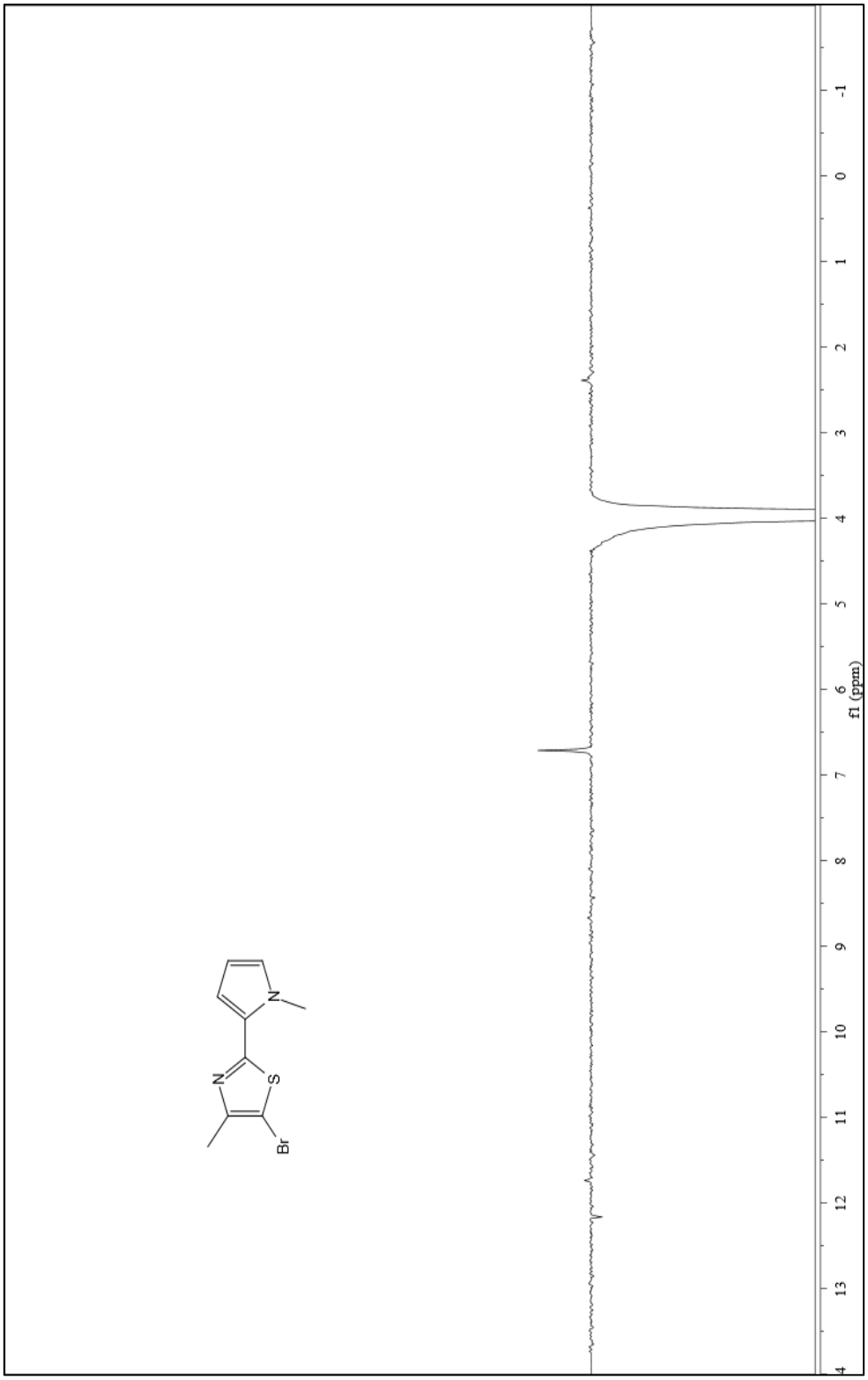
36b) ^{1}H NMR (400 MHz, $CDCl_3$) 5-bromo-4-methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole



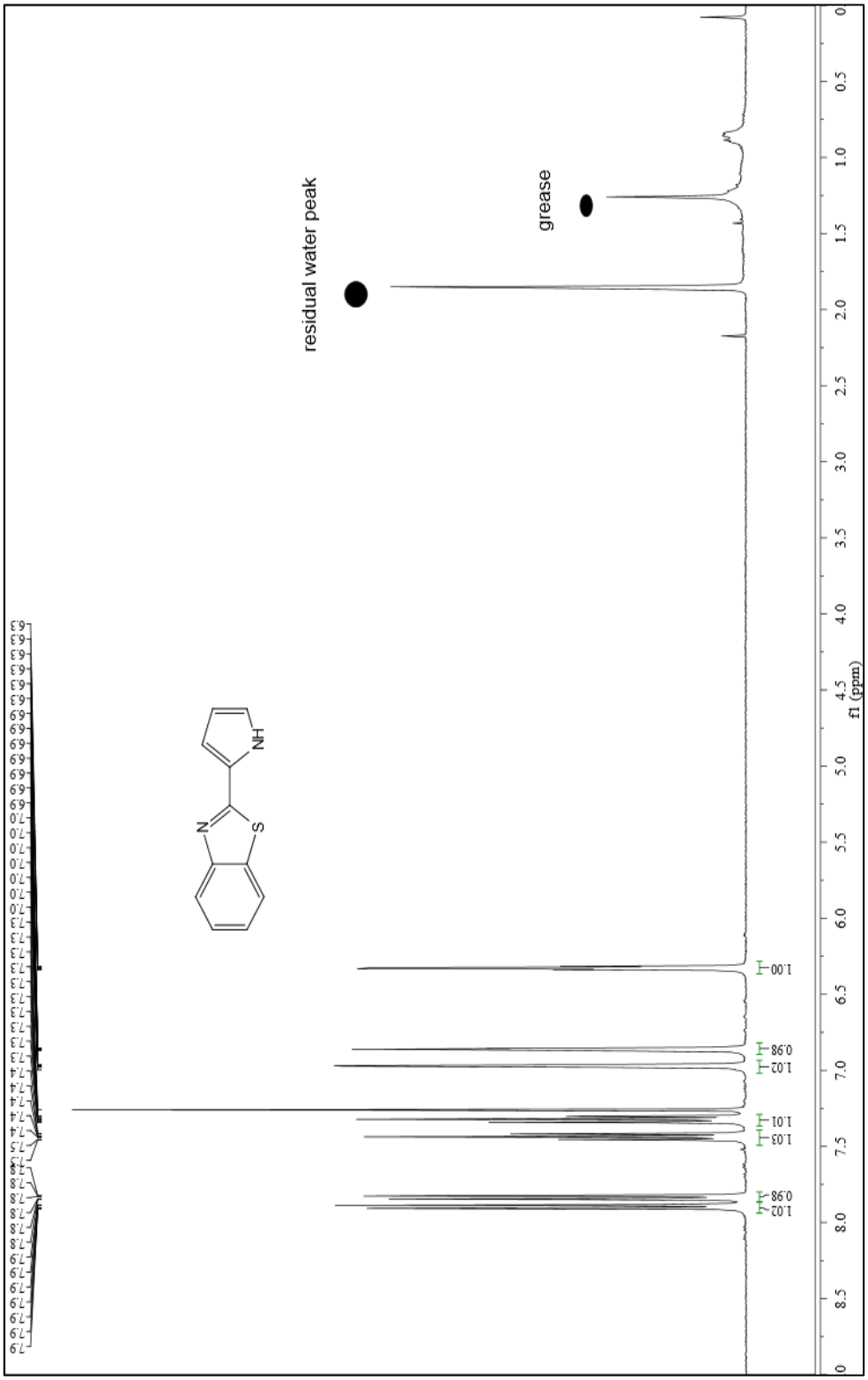
36b) ^{13}C NMR (101 MHz, $CDCl_3$) 5-bromo-4-methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole



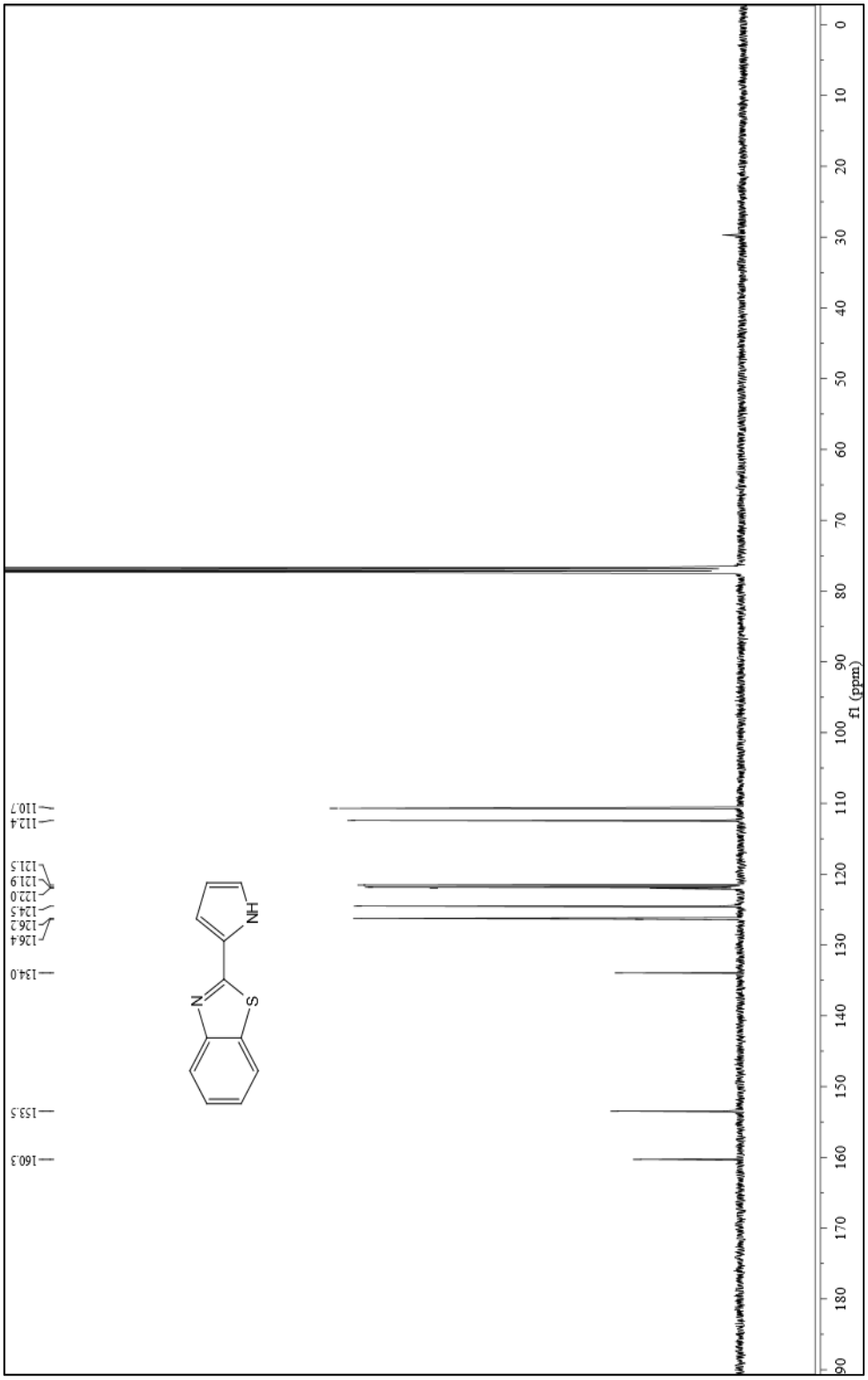
36b) NOE-1D (400 MHz $CDCl_3$) 5-bromo-4-methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole



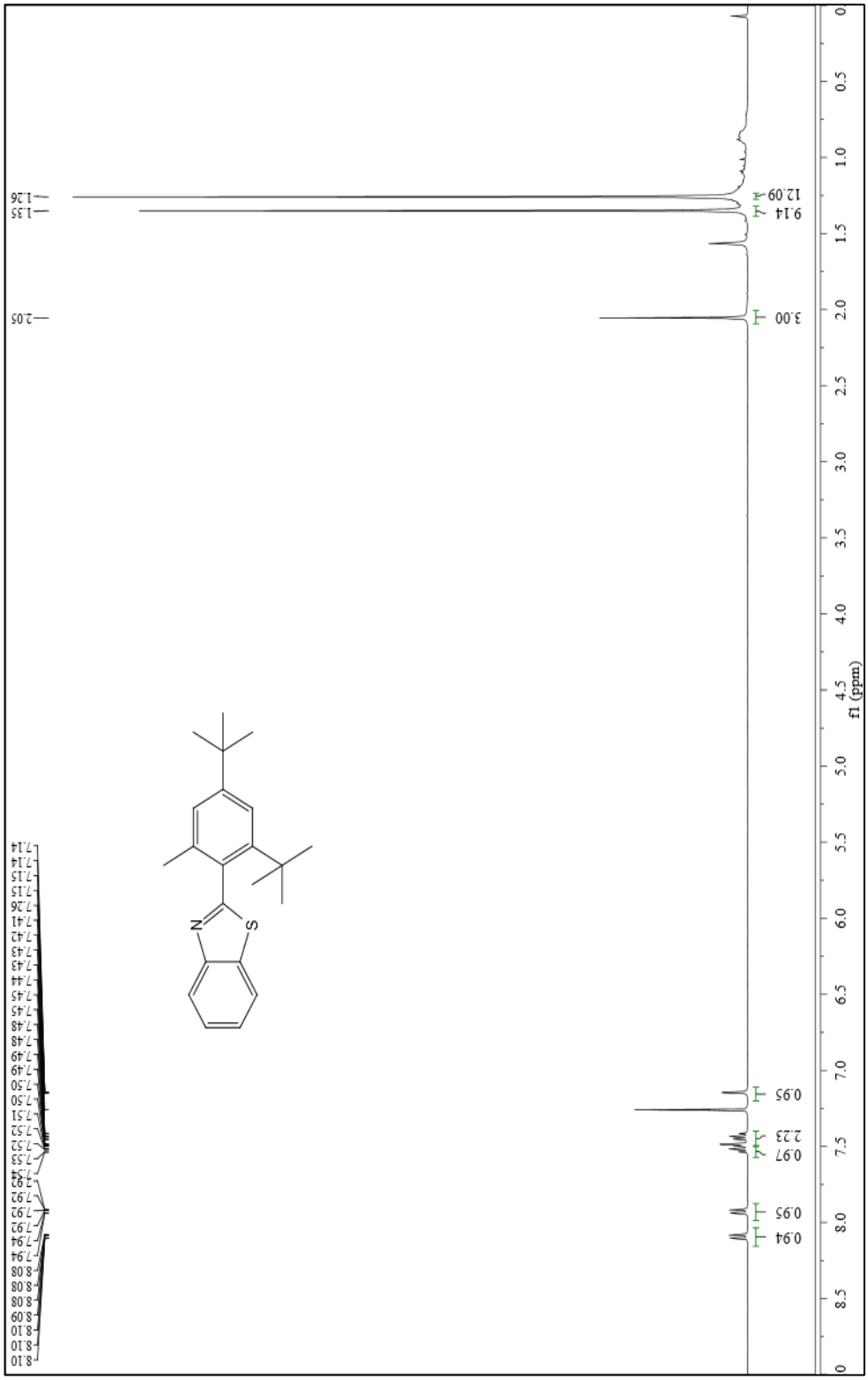
36c) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(1H-pyrrol-2-yl)benzo[d]thiazole



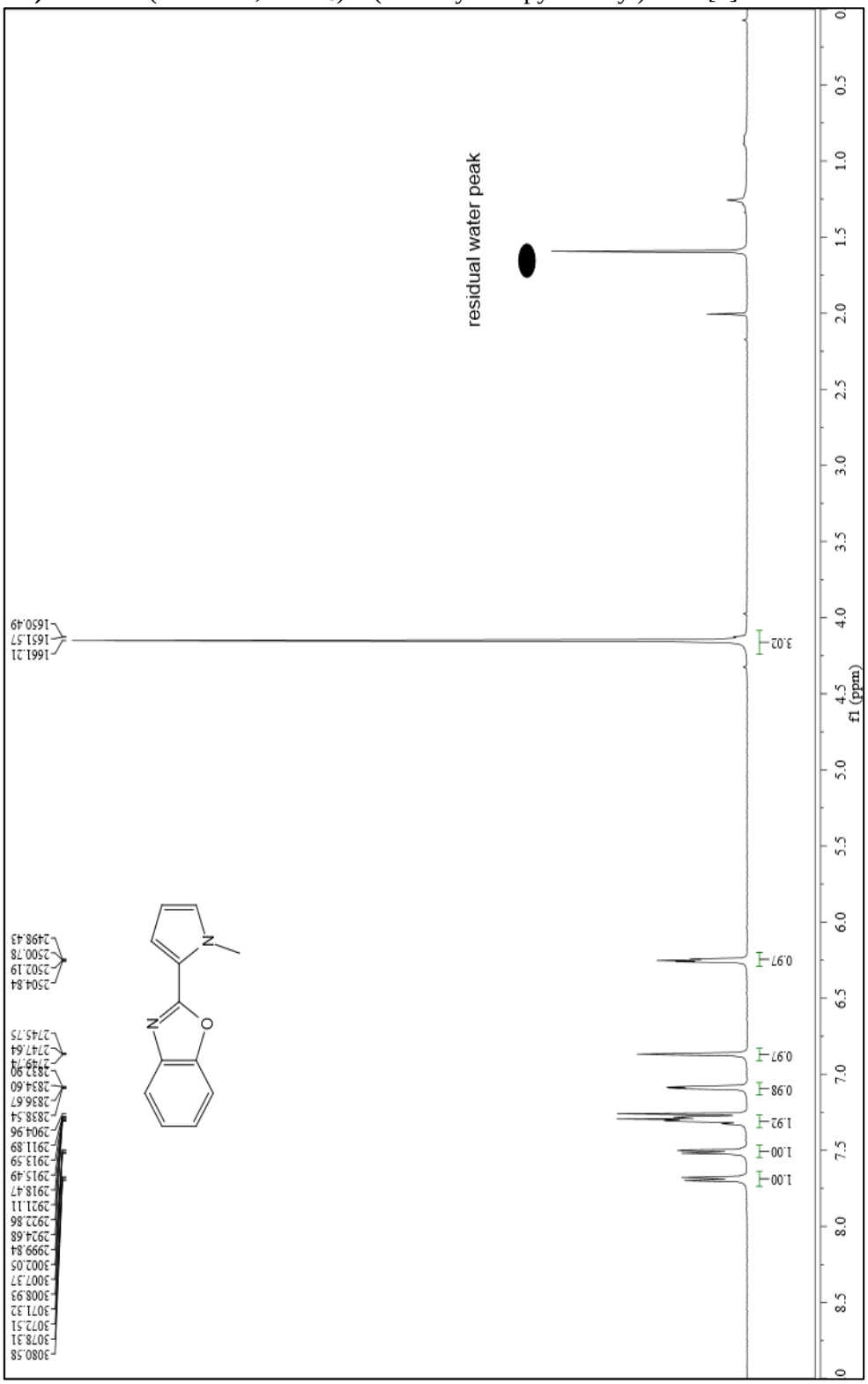
36c) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(1H-pyrrol-2-yl)benzo[d]thiazole



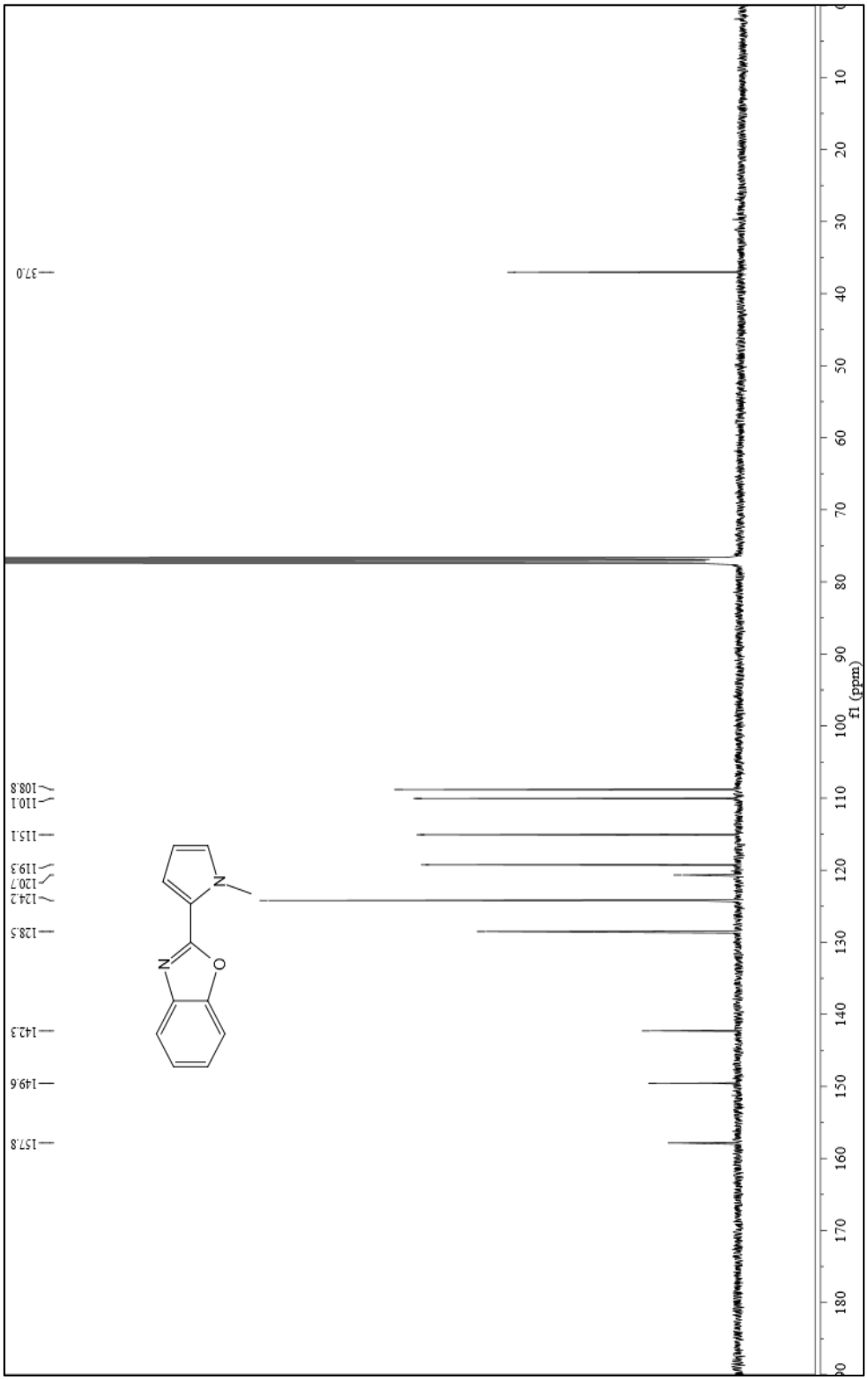
36d) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(2,4-di-tert-butyl-6-methylphenyl)benzo[d]thiazole



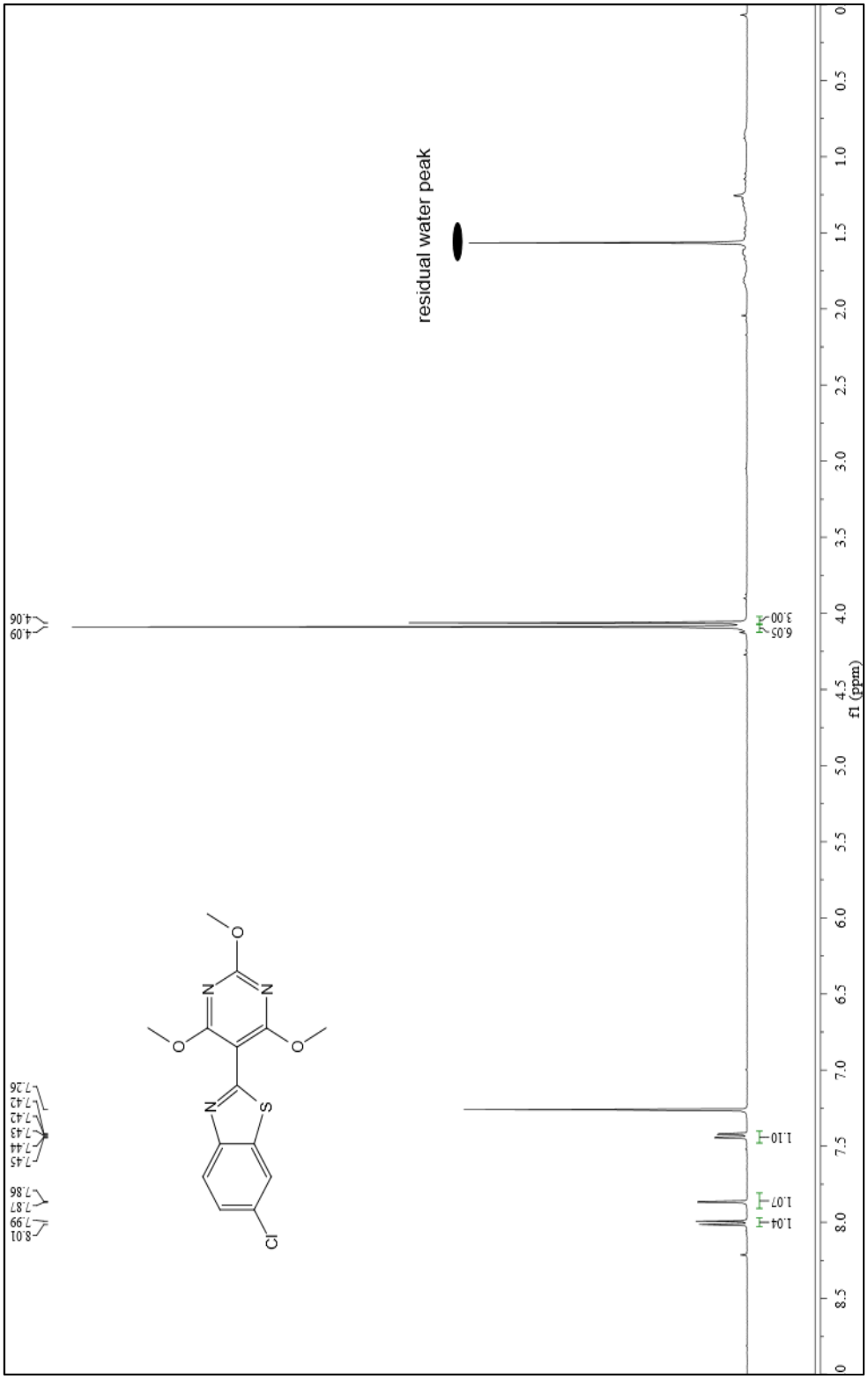
36f) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]oxazole



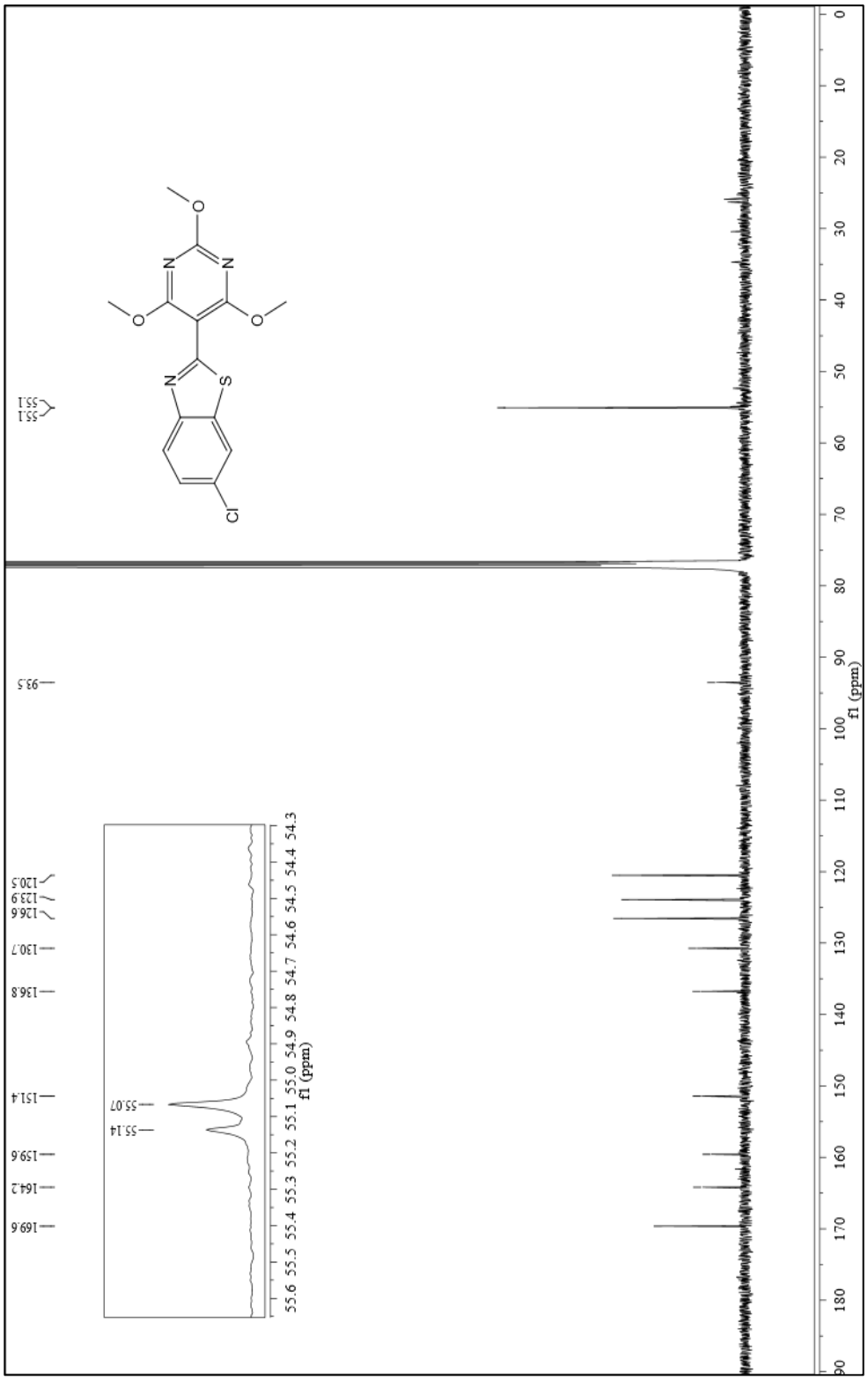
36f) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]oxazole



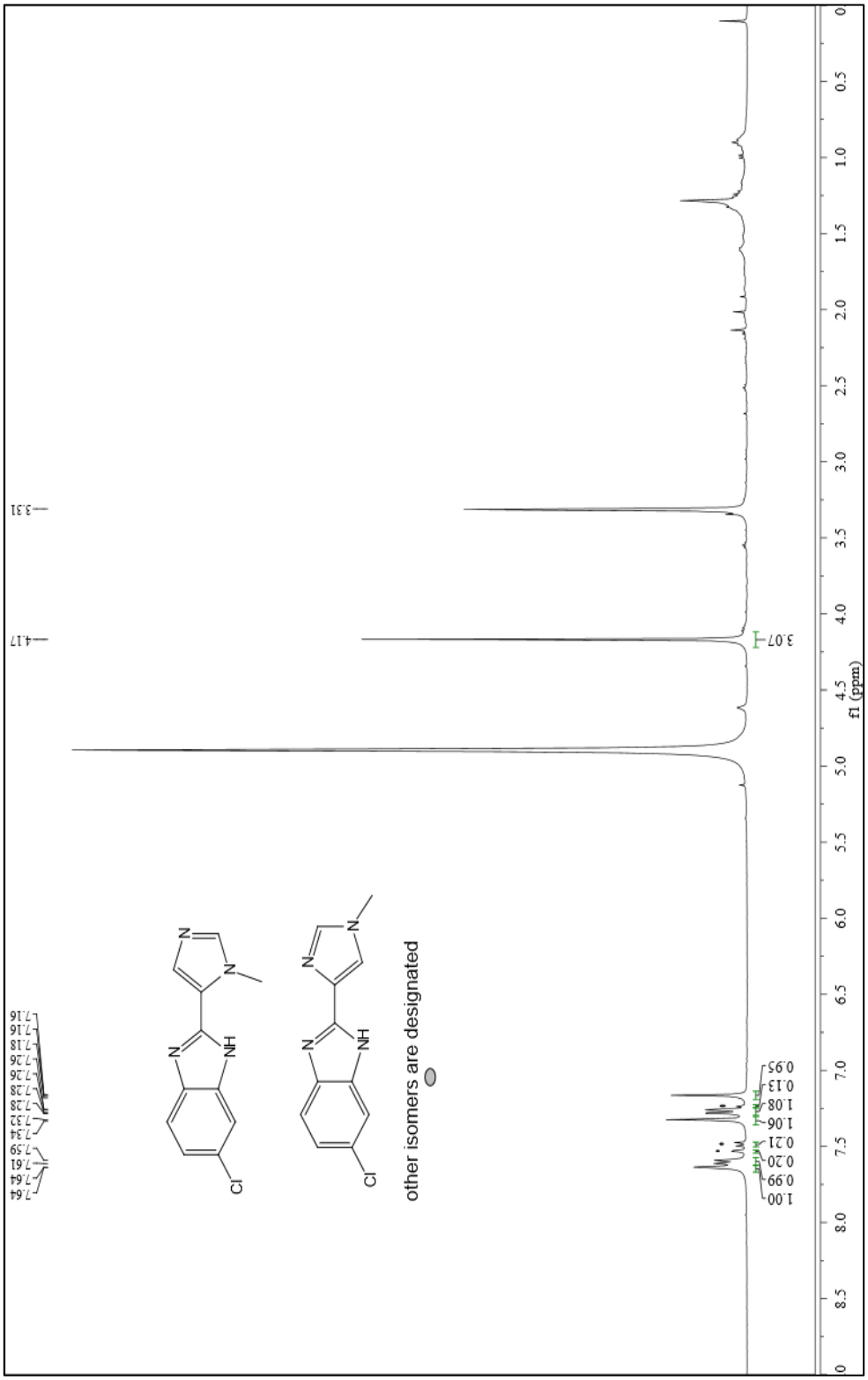
36g) ^{1}H NMR (400 MHz, $CDCl_3$) 6-chloro-2-(2,4,6-trimethoxypyrimidin-5-yl)benzo[d]thiazole



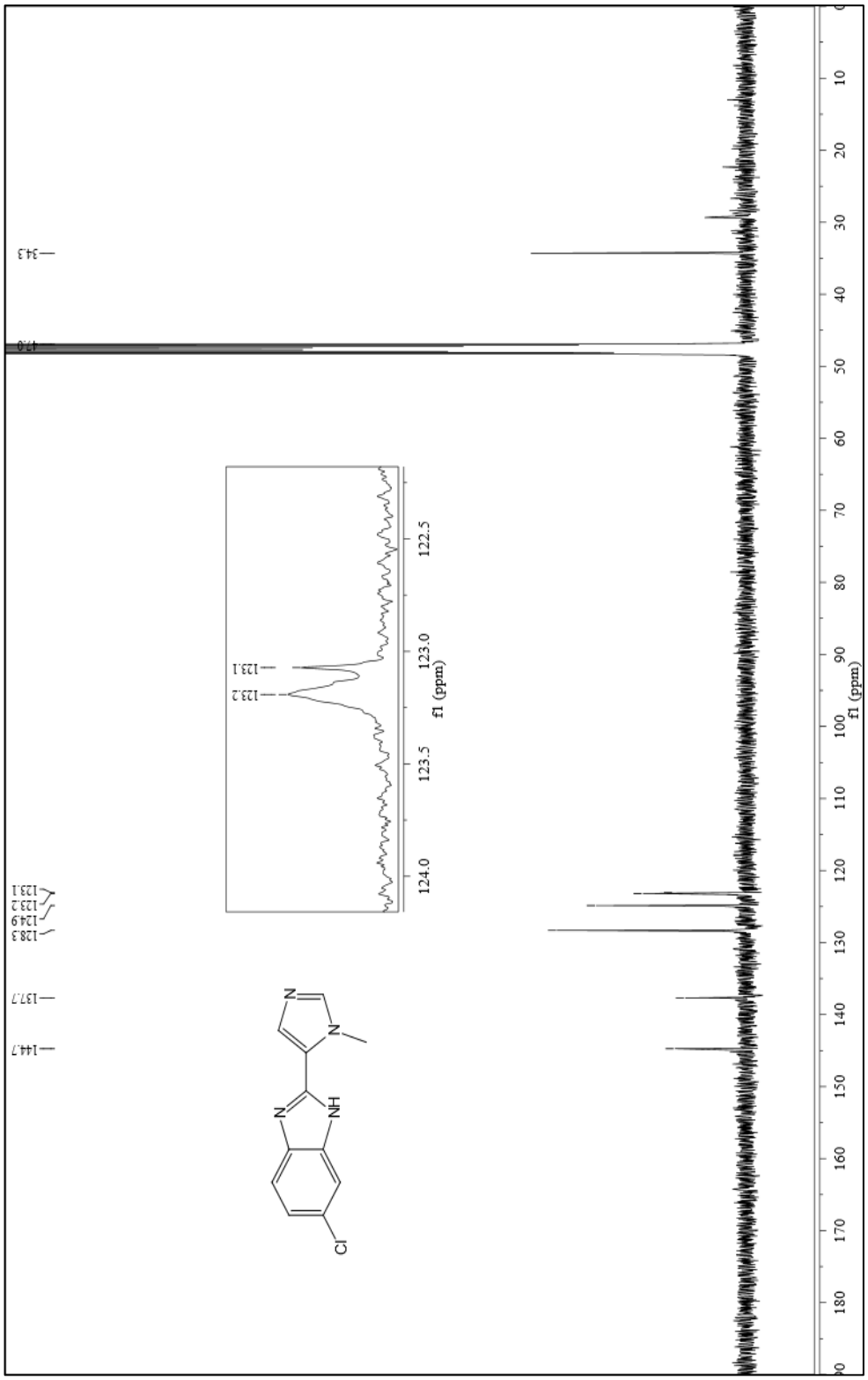
36g) ^{13}C NMR (101 MHz, $CDCl_3$) 6-chloro-2-(2,4,6-trimethoxypyrimidin-5-yl)benzo[d]thiazole



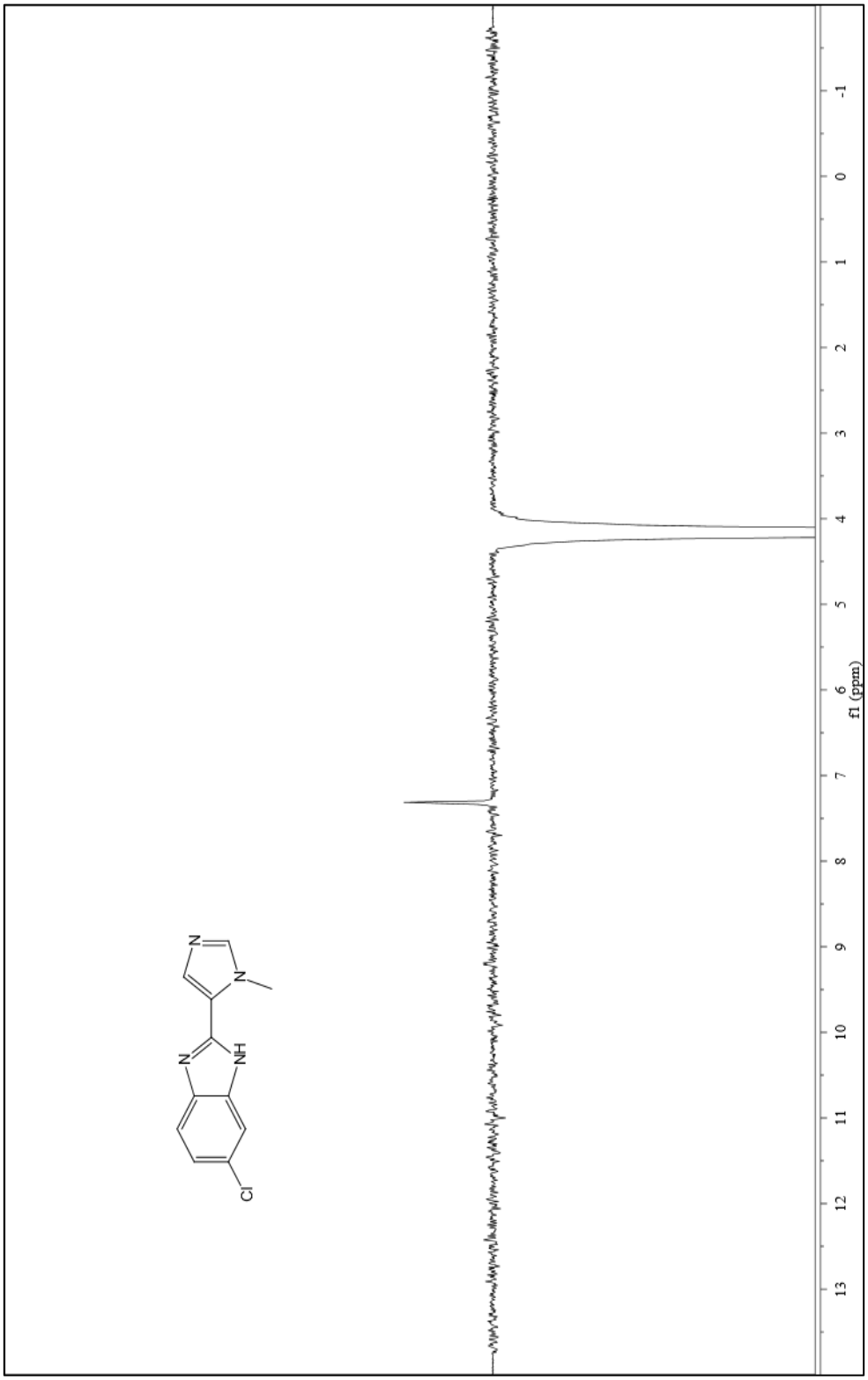
36h) ^{1}H NMR (400 MHz, CD_3OD) 6-chloro-2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



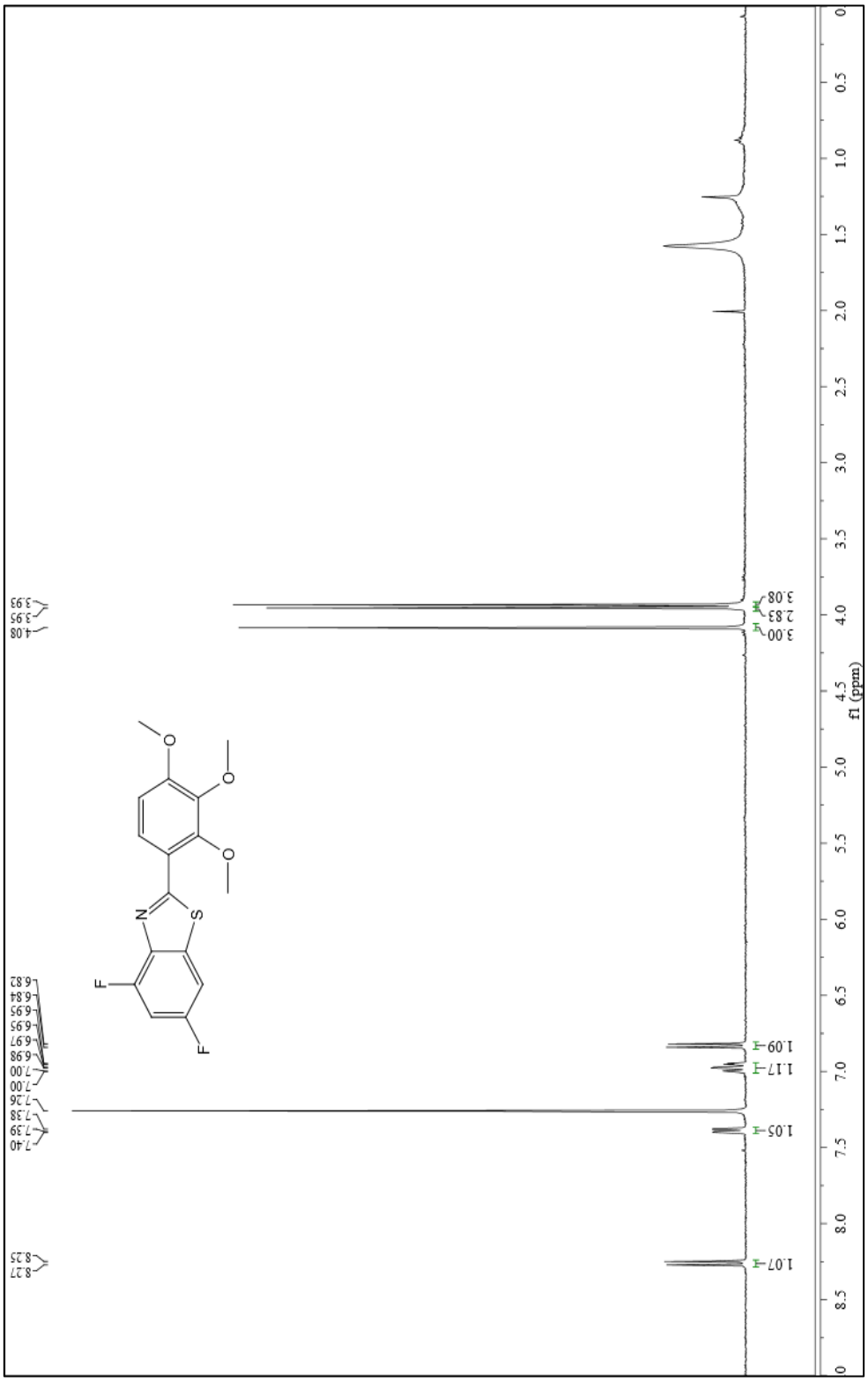
36h) ^{13}C NMR (101 MHz, CD_3OD) 6-chloro-2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



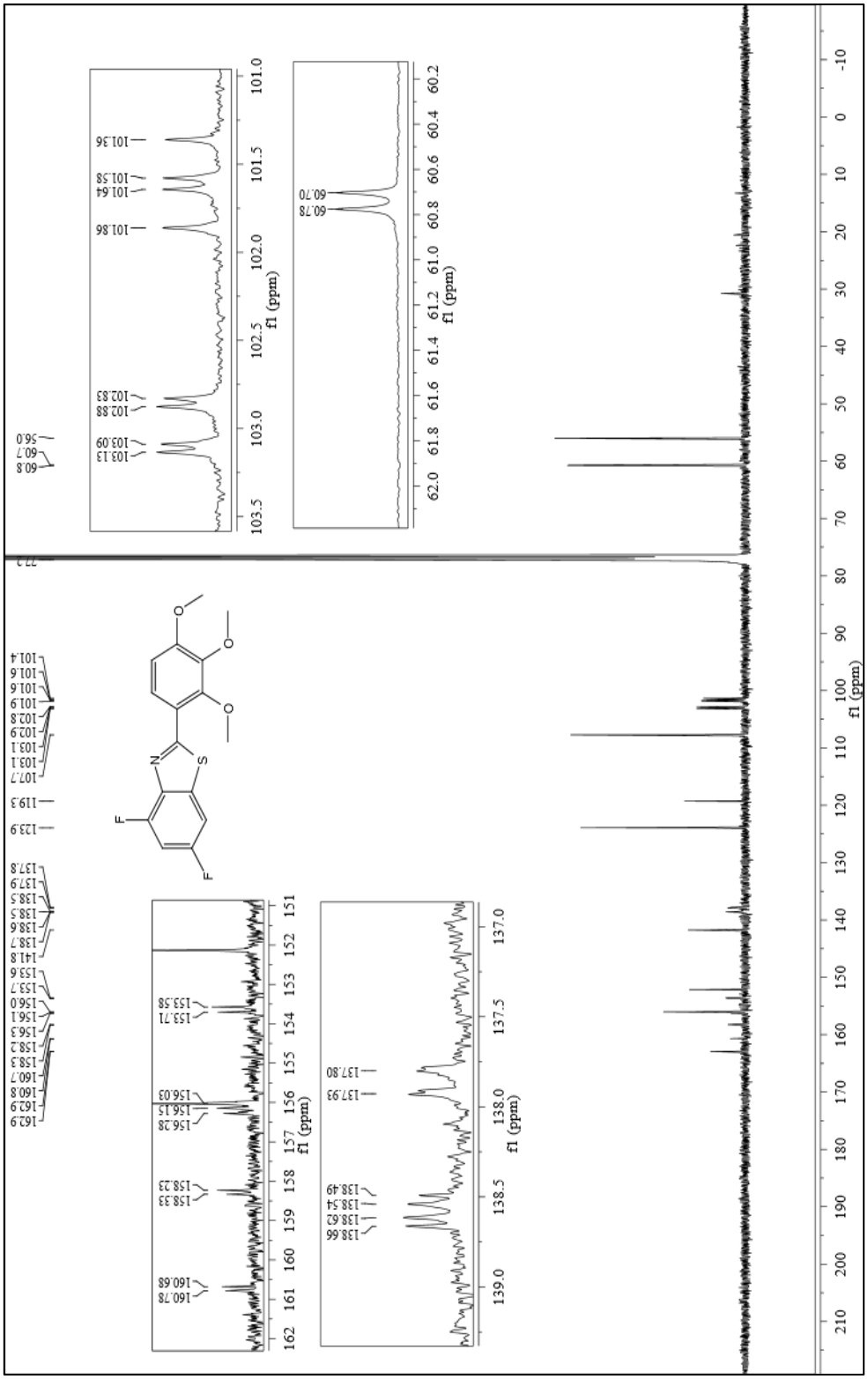
36h) NOE-1D (400 MHz, CD_3OD) 6-chloro-2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



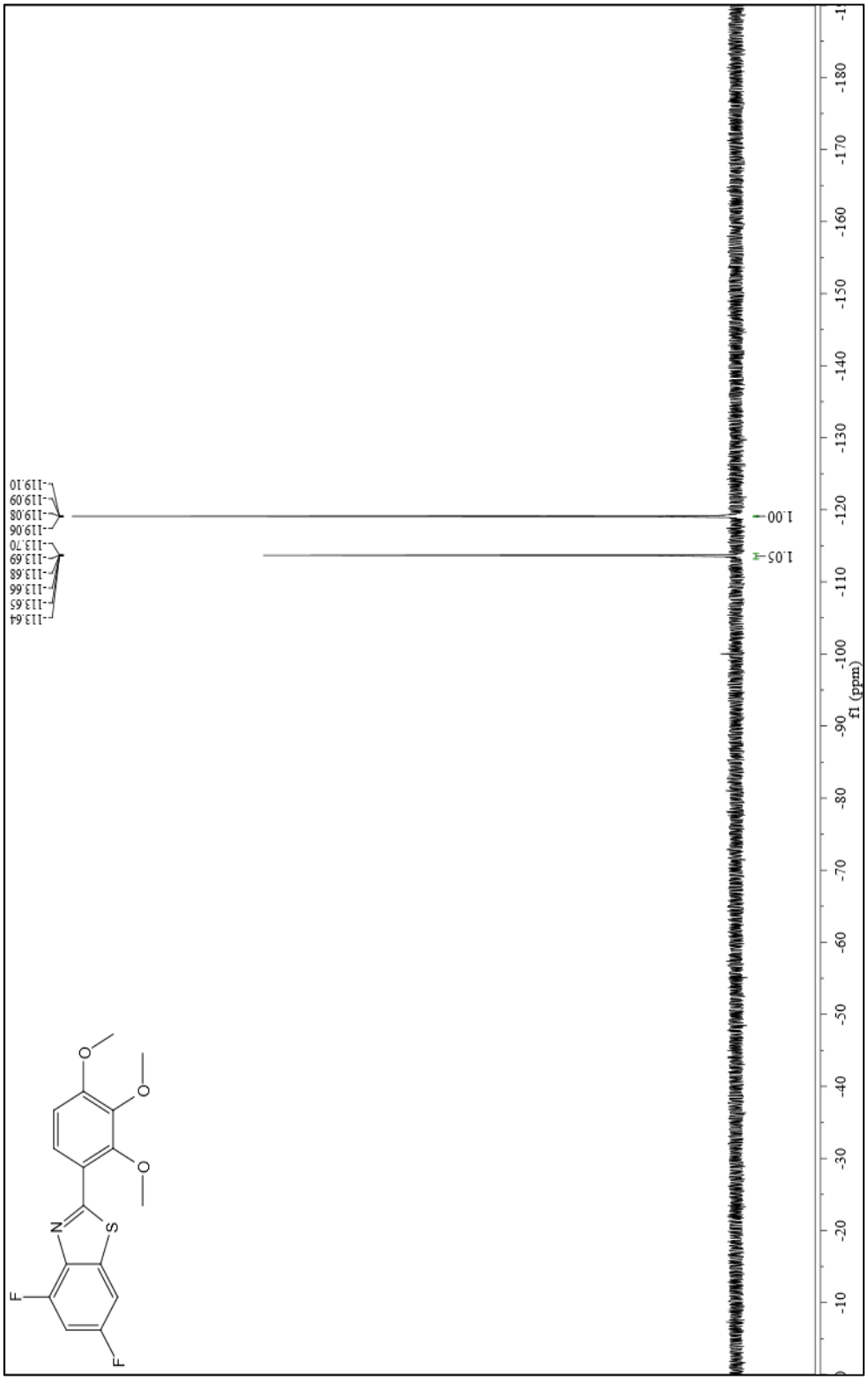
36i) ^{1}H NMR (400 MHz, $CDCl_3$) of 4,6-difluoro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



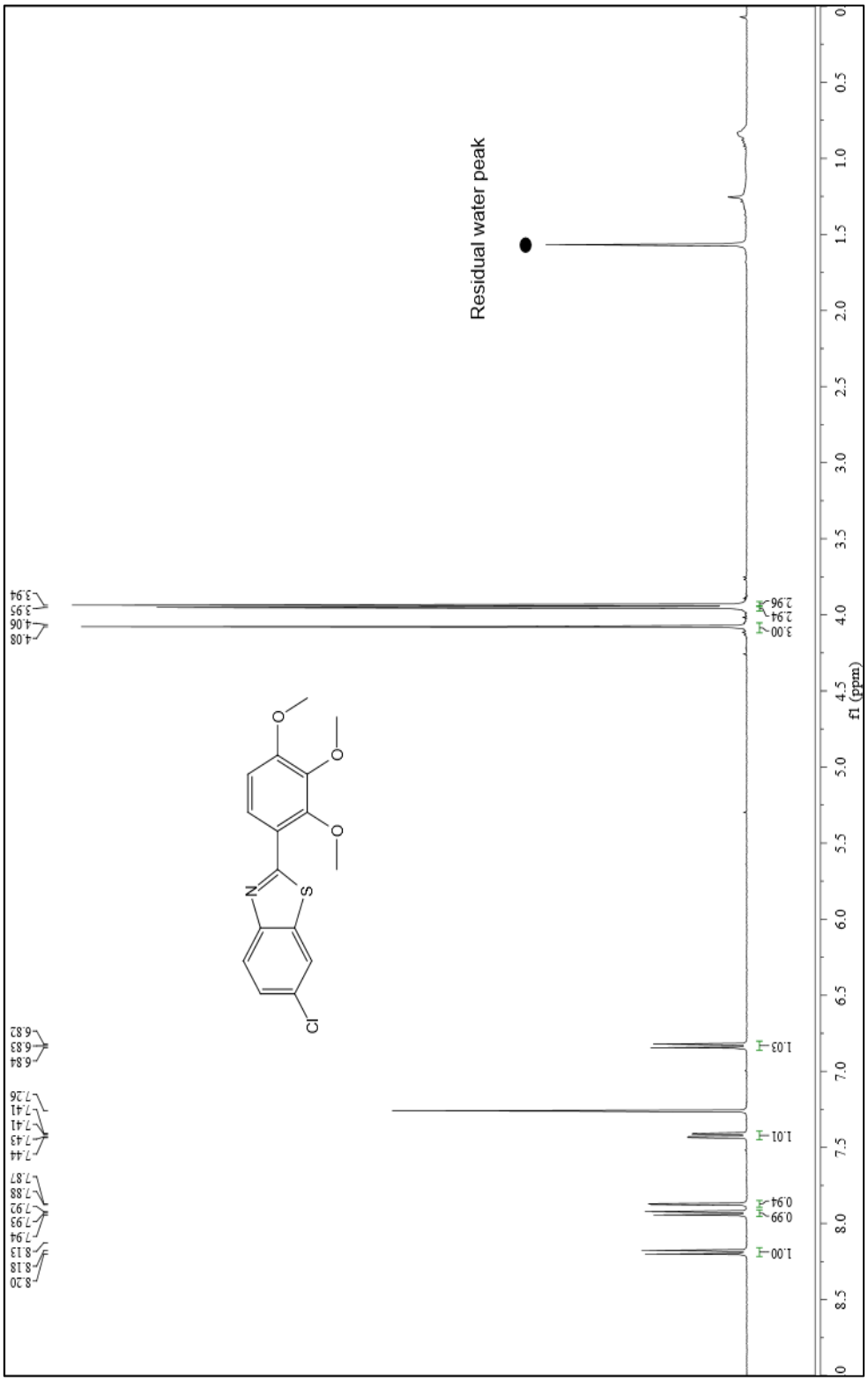
36i) ^{13}C NMR (101 MHz, $CDCl_3$) of 4,6-difluoro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



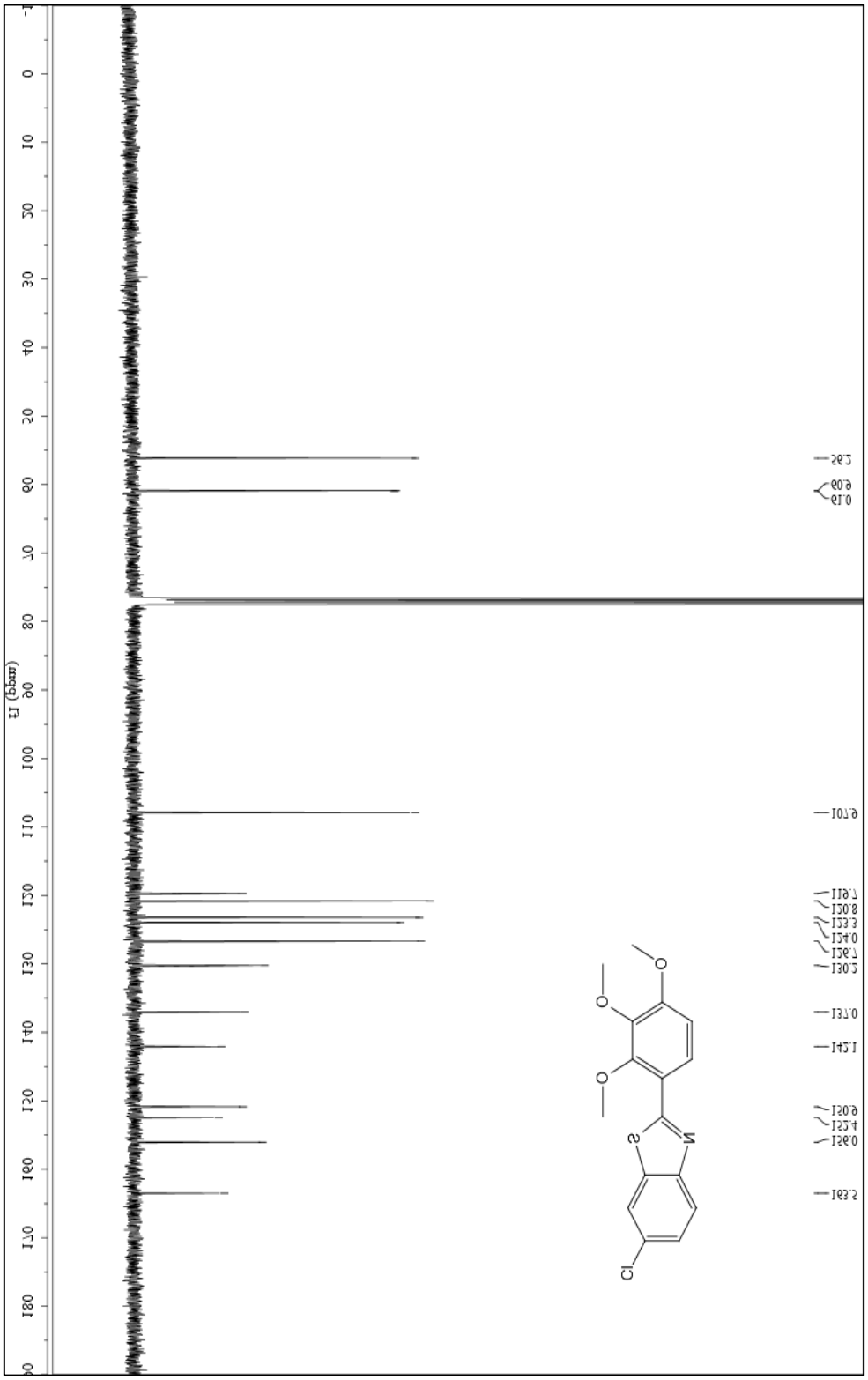
36i) ^{19}F NMR (376 MHz, $CDCl_3$) of 4,6-difluoro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



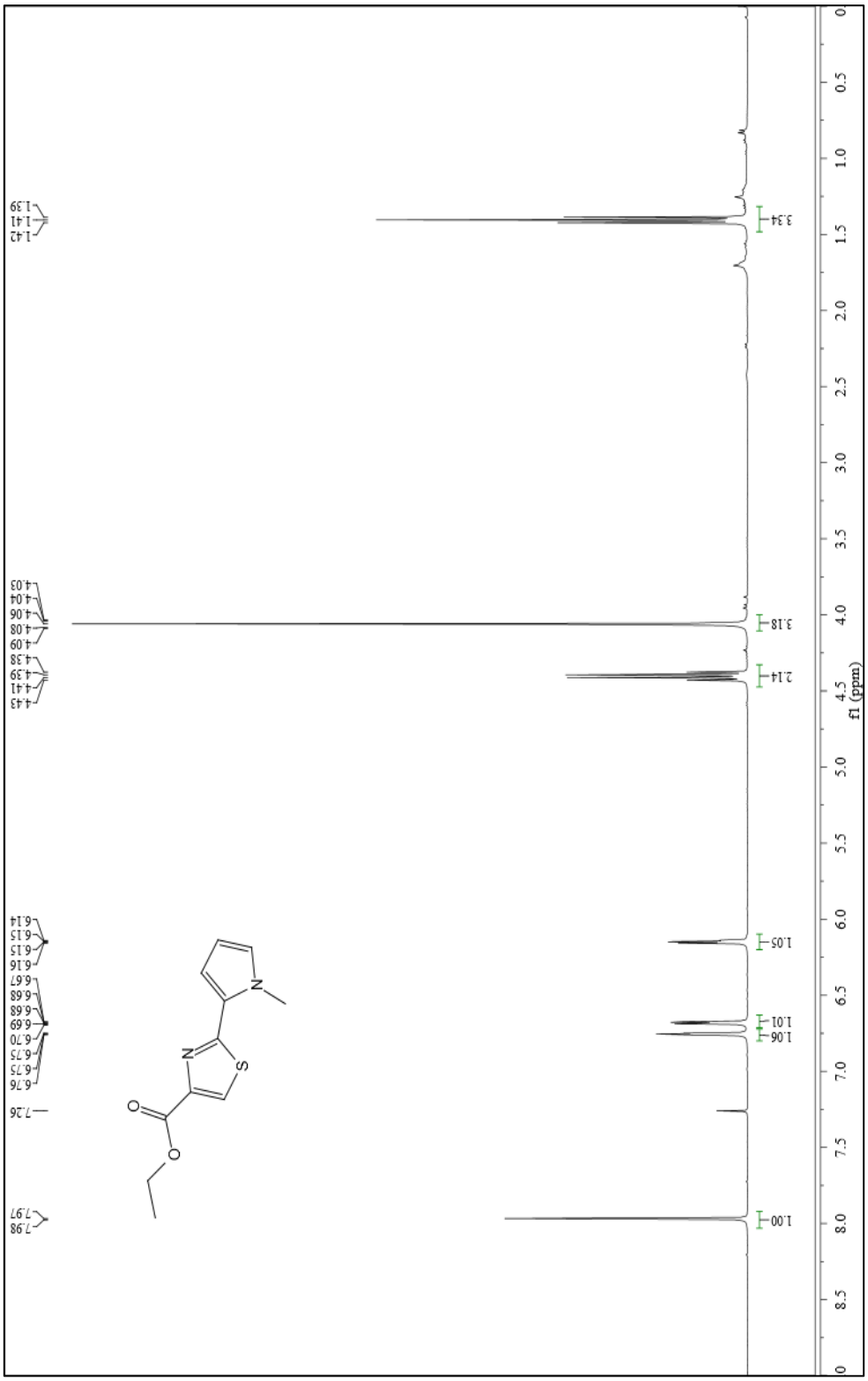
36j) ^{1}H NMR (400 MHz, $CDCl_3$) 6-chloro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



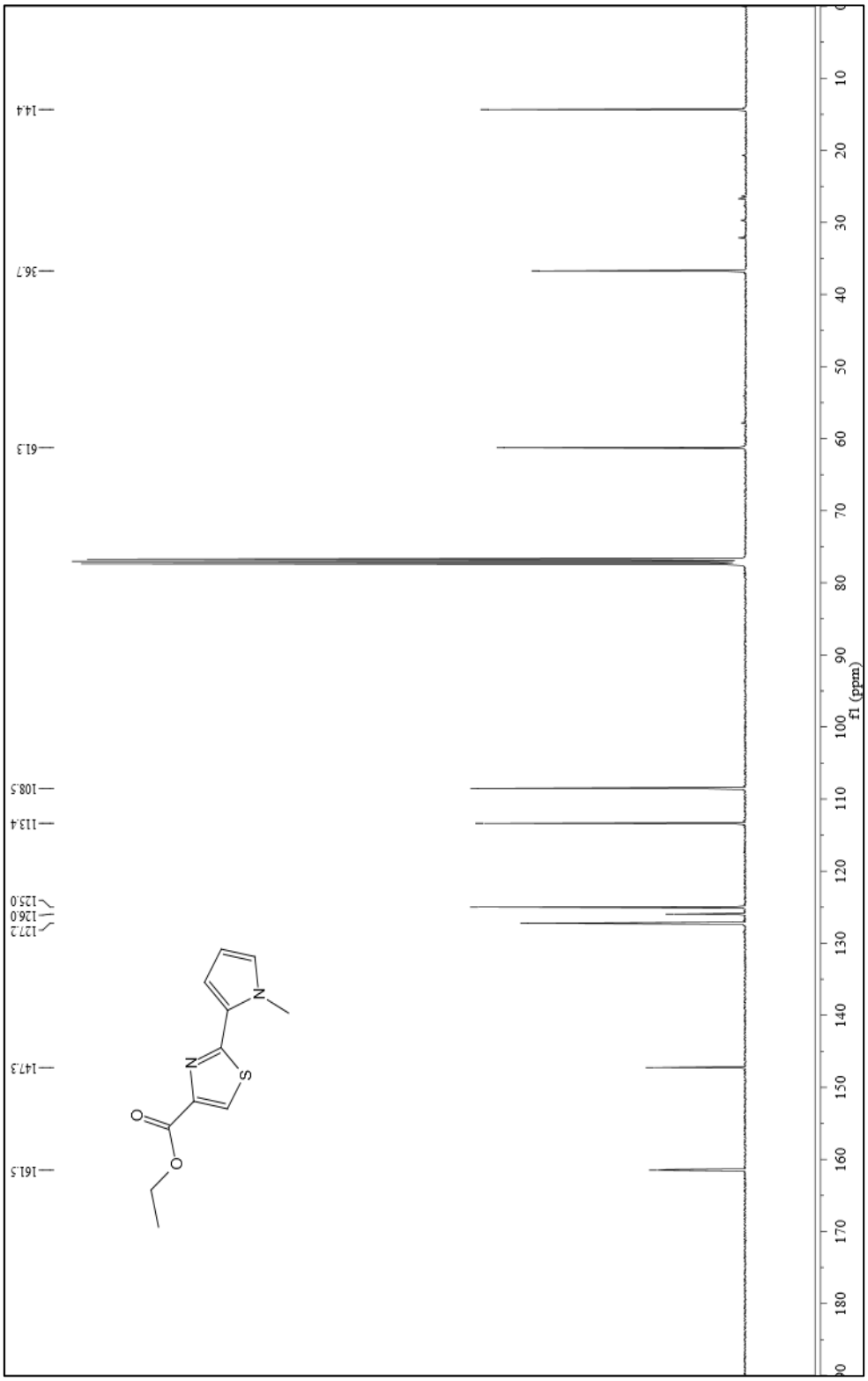
36j) ^{13}C NMR (101 MHz, $CDCl_3$) 6-chloro-2-(2,3,4-trimethoxyphenyl)benzo[d]thiazole



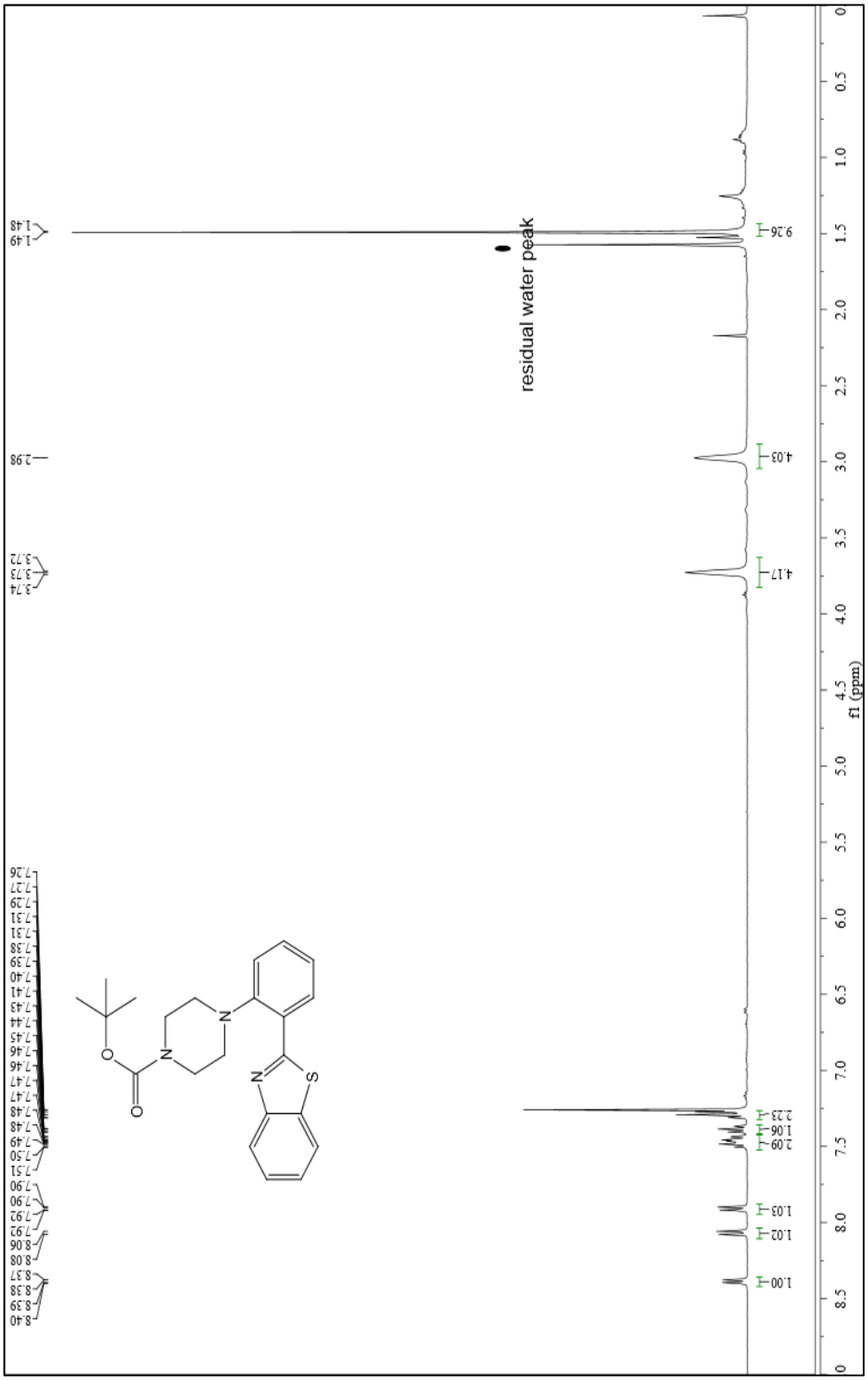
36k) ^{1}H NMR (400 MHz, $CDCl_3$) Ethyl 2-(1-methyl-1H-pyrrol-2-yl)thiazole-4-carboxylate



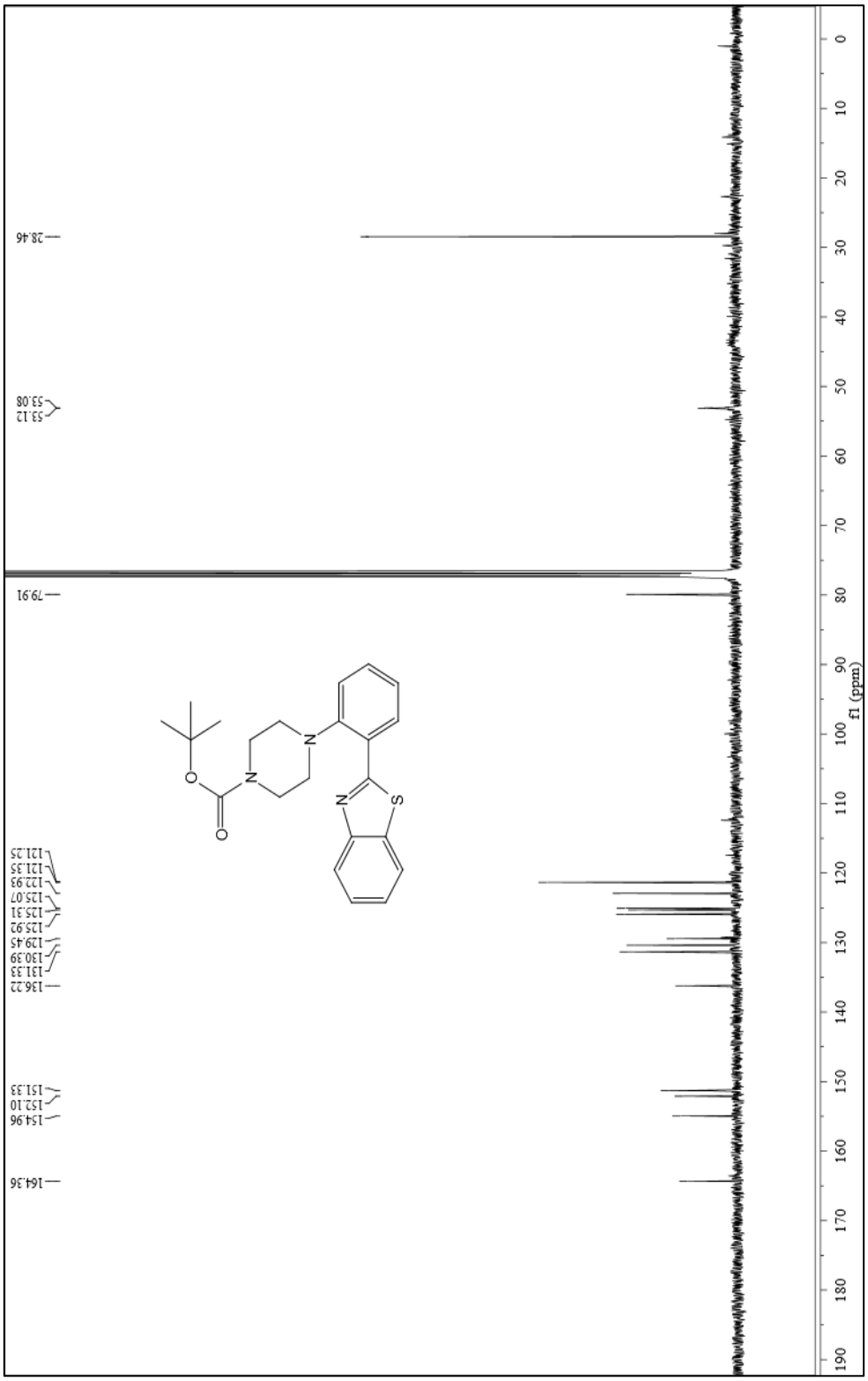
36k) ^{13}C NMR (101 MHz, $CDCl_3$) Ethyl 2-(1-methyl-1H-pyrrol-2-yl)thiazole-4-carboxylate



36l**)** ^{1}H NMR (400 MHz, $CDCl_3$)*tert*-butyl 4-(2-(benzo[d]thiazol-2-yl)phenyl)piperazine-1carboxyla

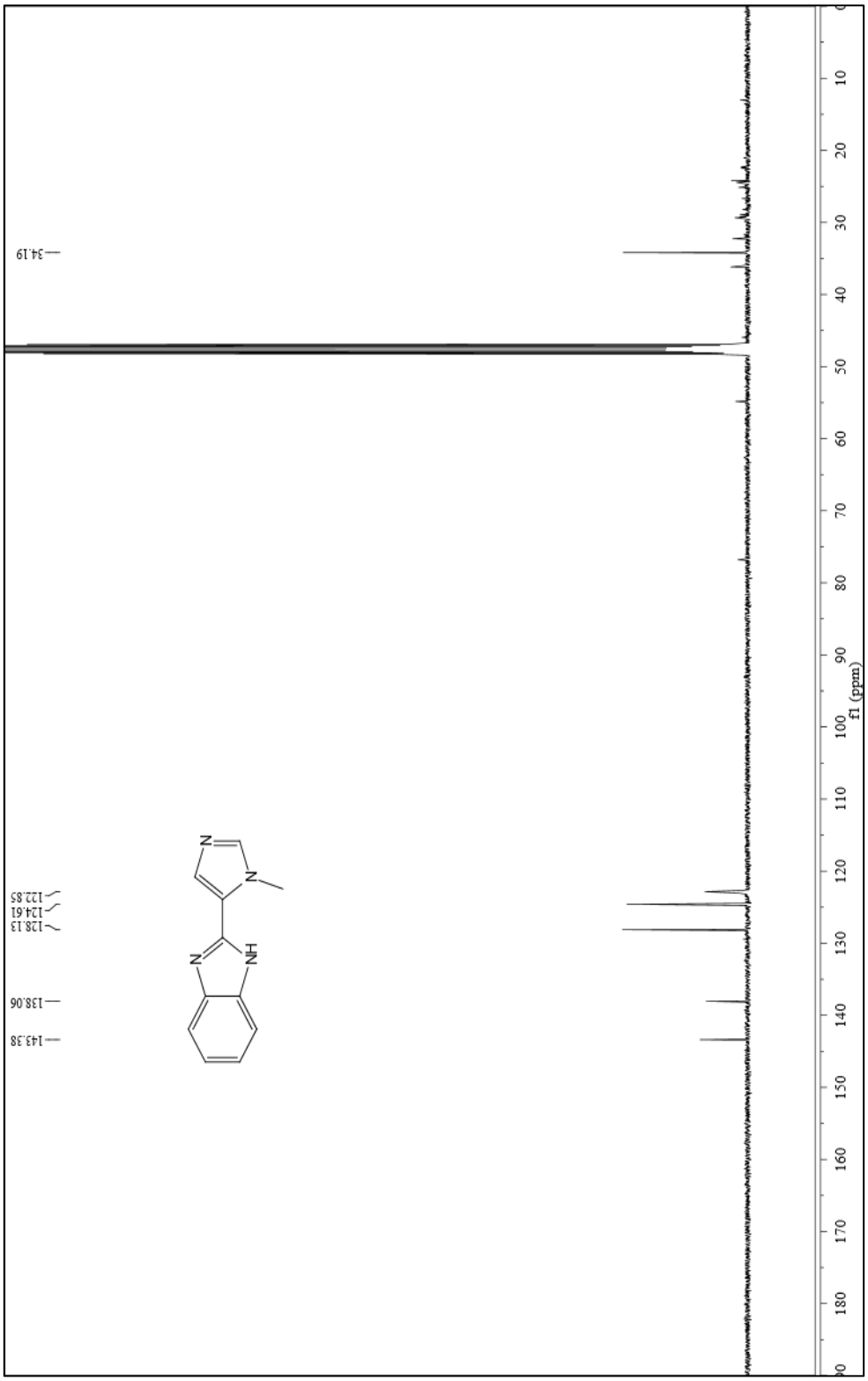


36l) ^{13}C NMR (101 MHz, $CDCl_3$)*tert*-butyl 4-(2-(benzo[d]thiazol-2-yl)phenyl)piperazine-1-carboxylate

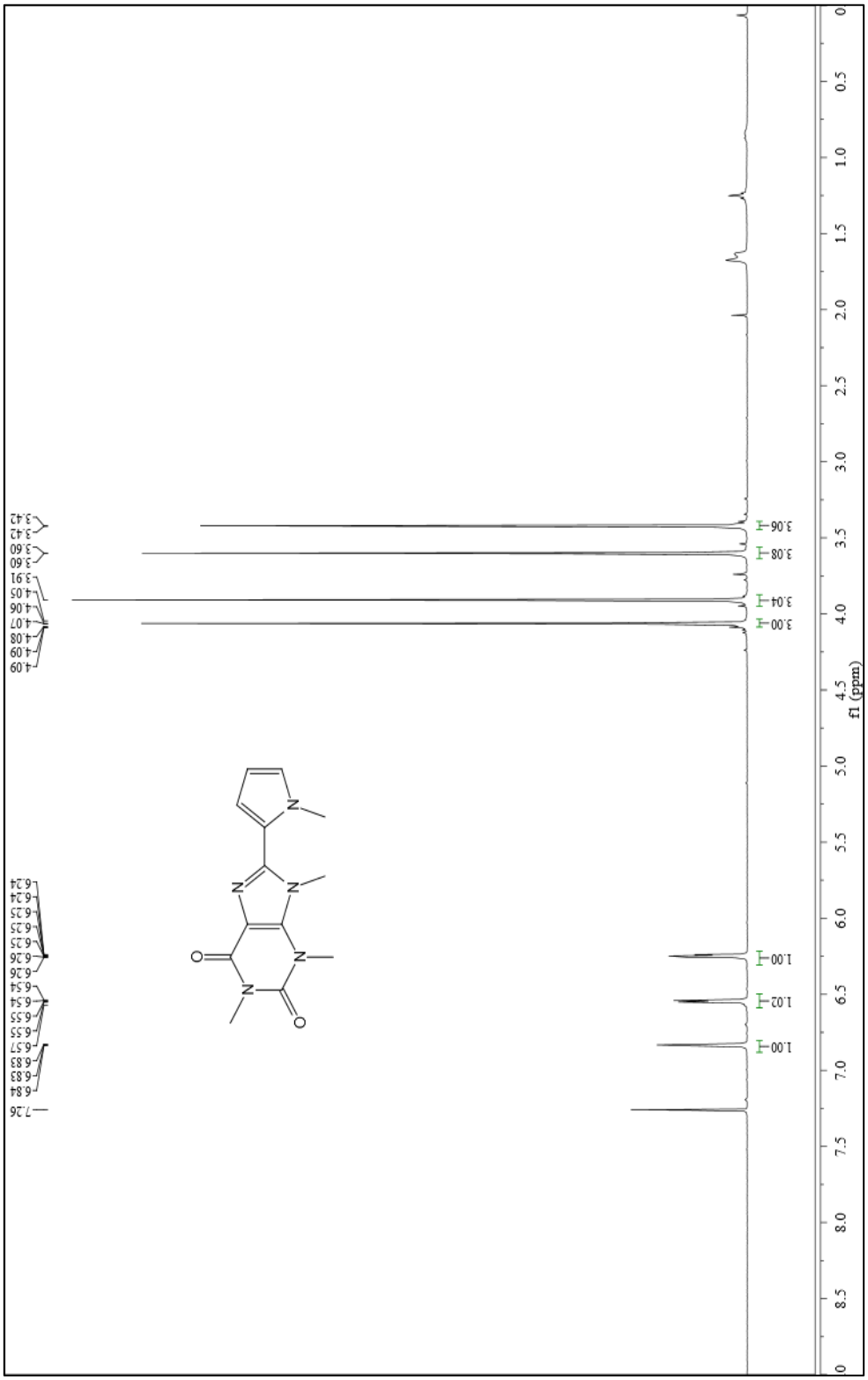


36m) ^{1}H NMR (400 MHz, CD_3OD) 2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole

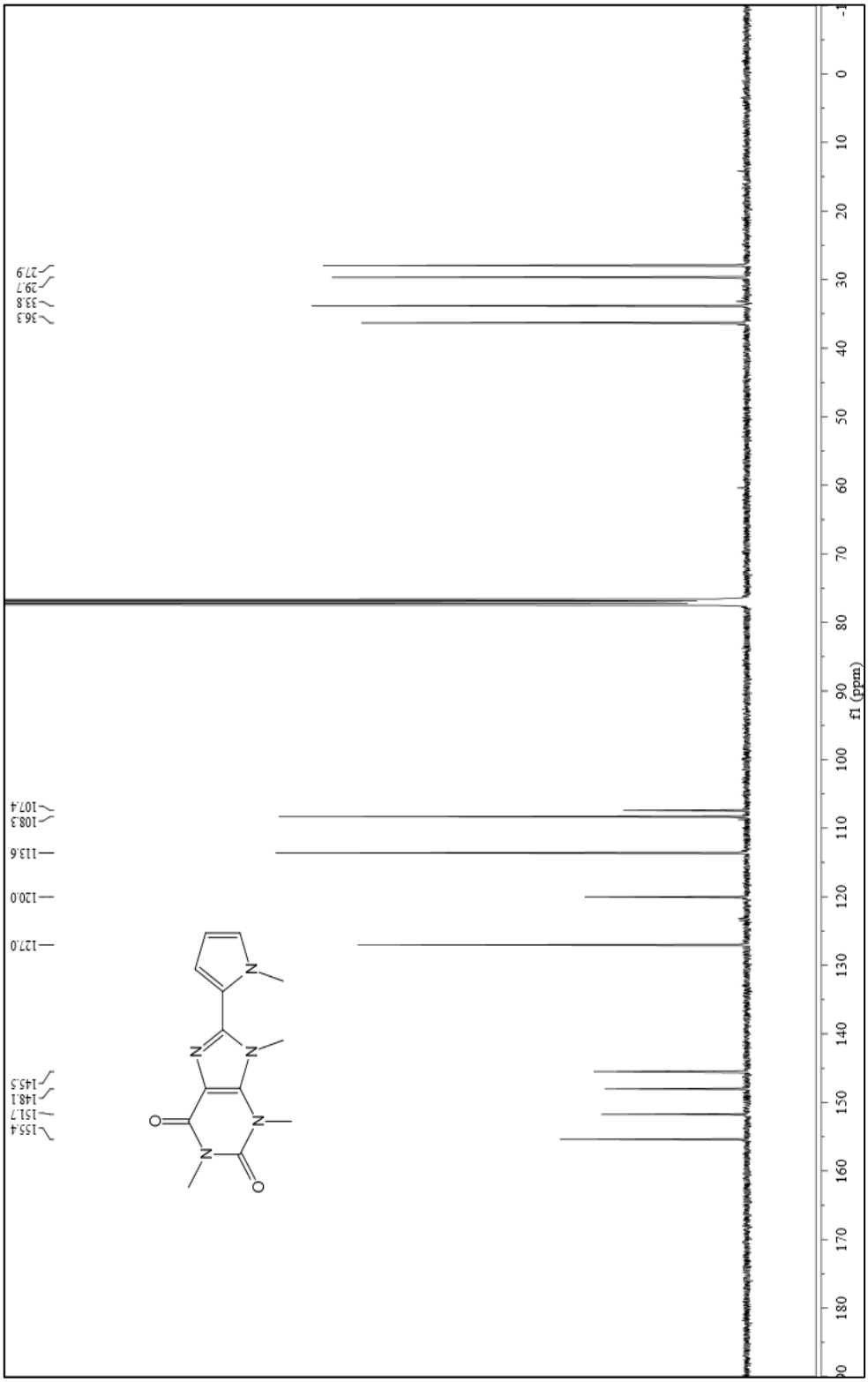
36m) ^{13}C NMR (101 MHz, CD_3OD) 2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazole



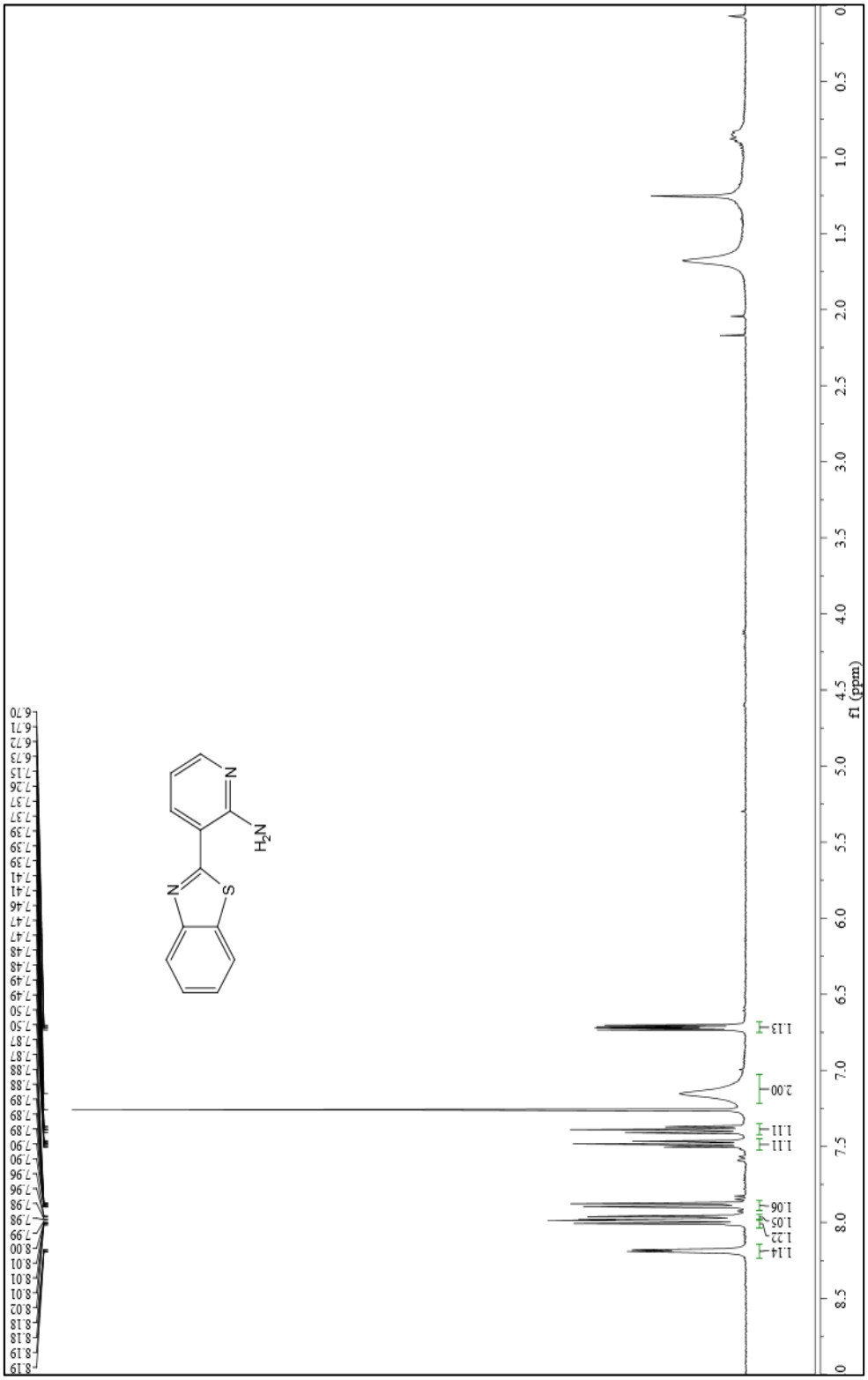
36n) ^{1}H NMR (400 MHz, $CDCl_3$) 1,3,9-trimethyl-8-(1-methyl-1H-pyrrol-2-yl)-3,9-dihydro-1H-purine-2,6-dione



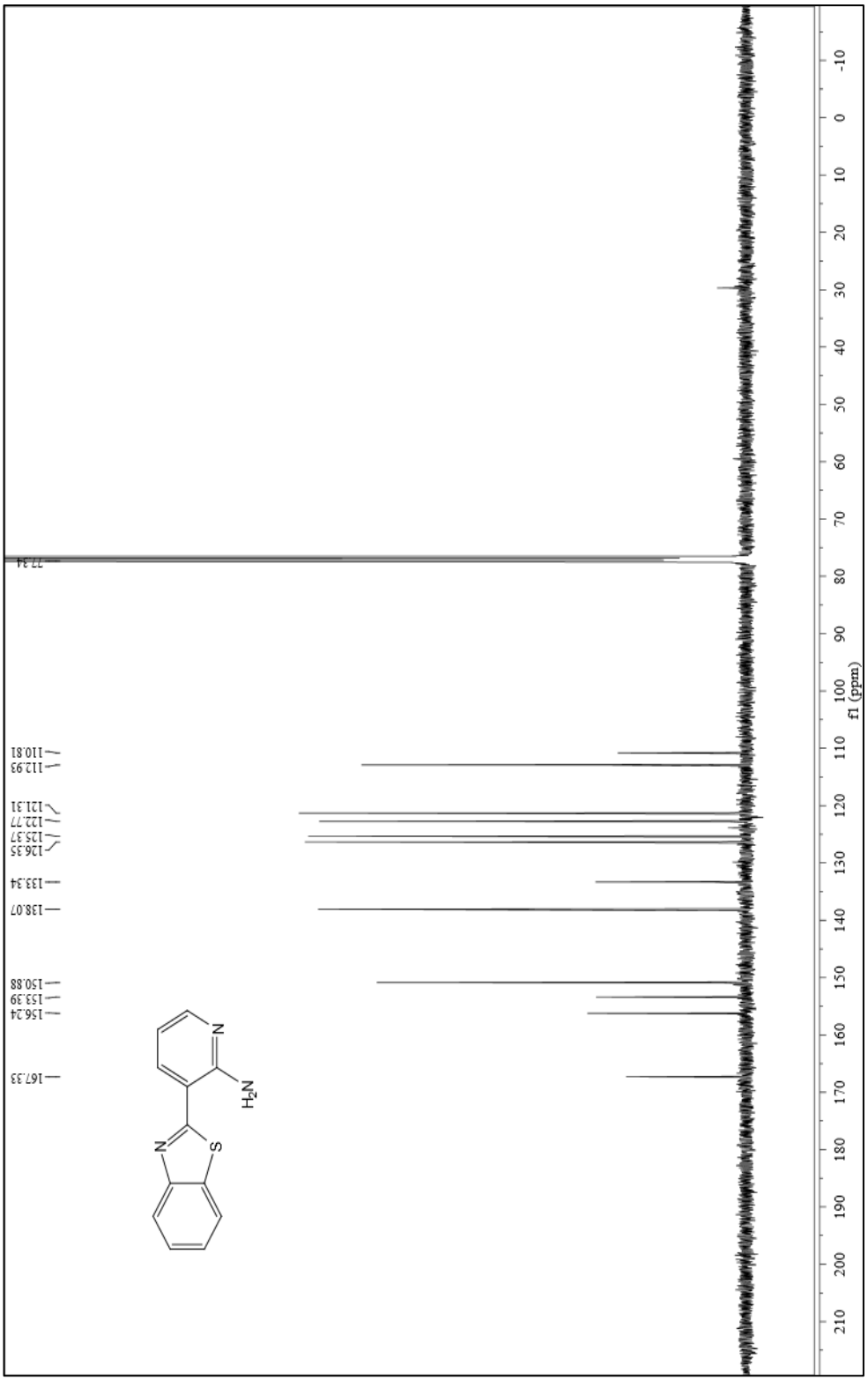
36n) ^{13}C NMR (101 MHz, $CDCl_3$) 1,3,9-trimethyl-8-(1-methyl-1H-pyrrol-2-yl)-3,9-dihydro-1H-purine-2,6-dione



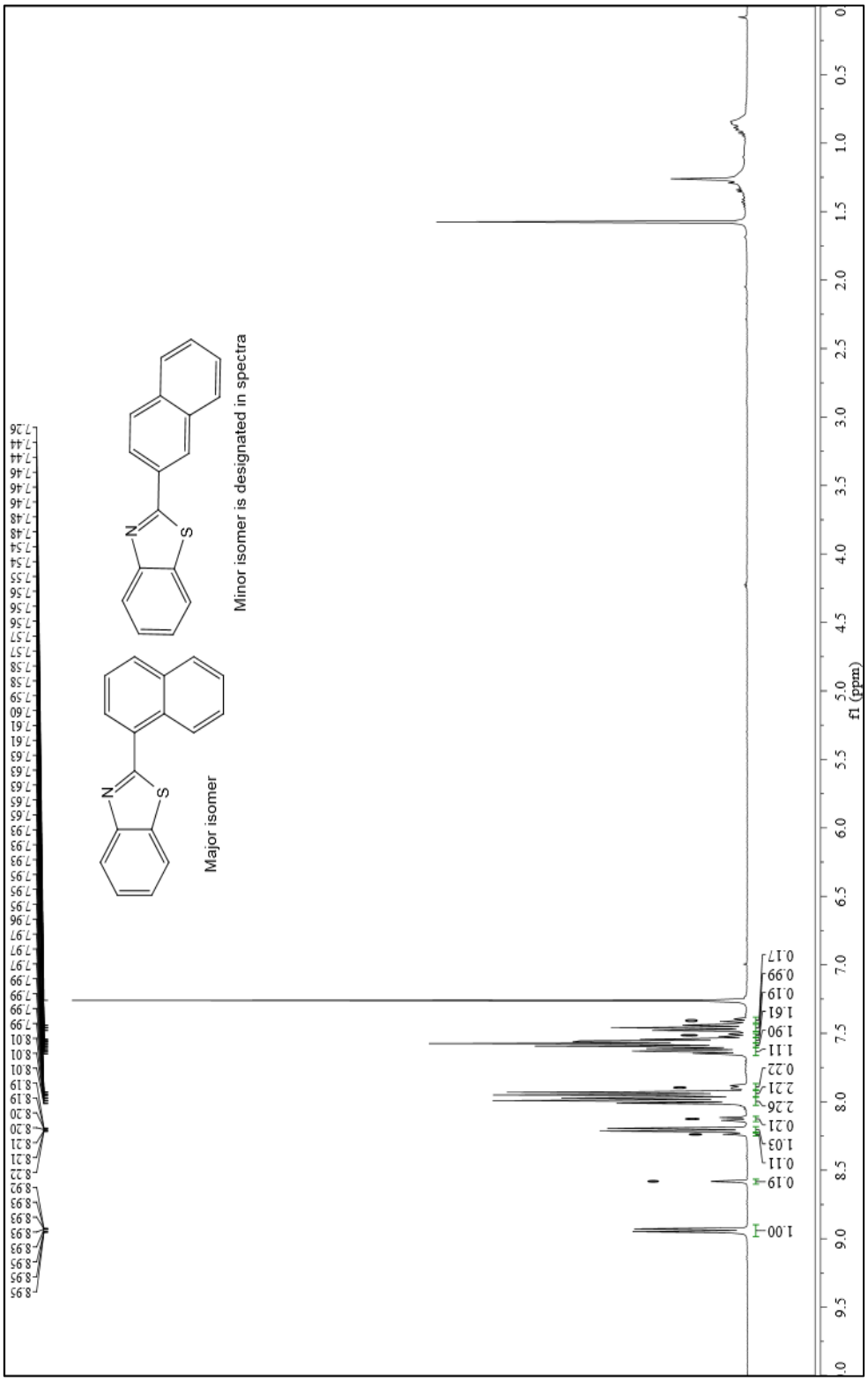
36o) ^{1}H NMR (400 MHz, $CDCl_3$) 3-(benzo[d]thiazol-2-yl)pyridin-2-amine



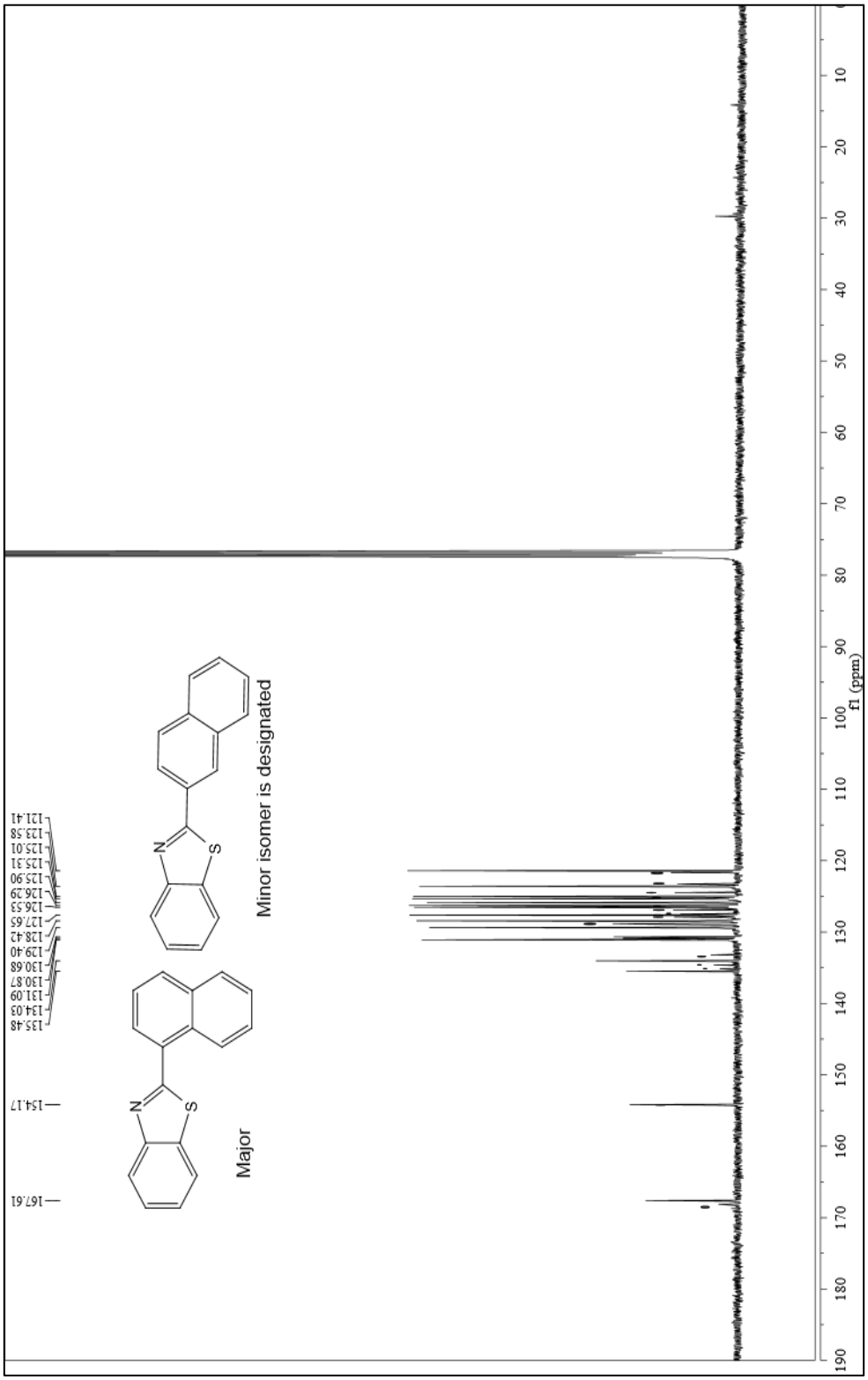
36o) ^{13}C NMR (101 MHz, $CDCl_3$) 3-(benzo[d]thiazol-2-yl)pyridin-2-amine



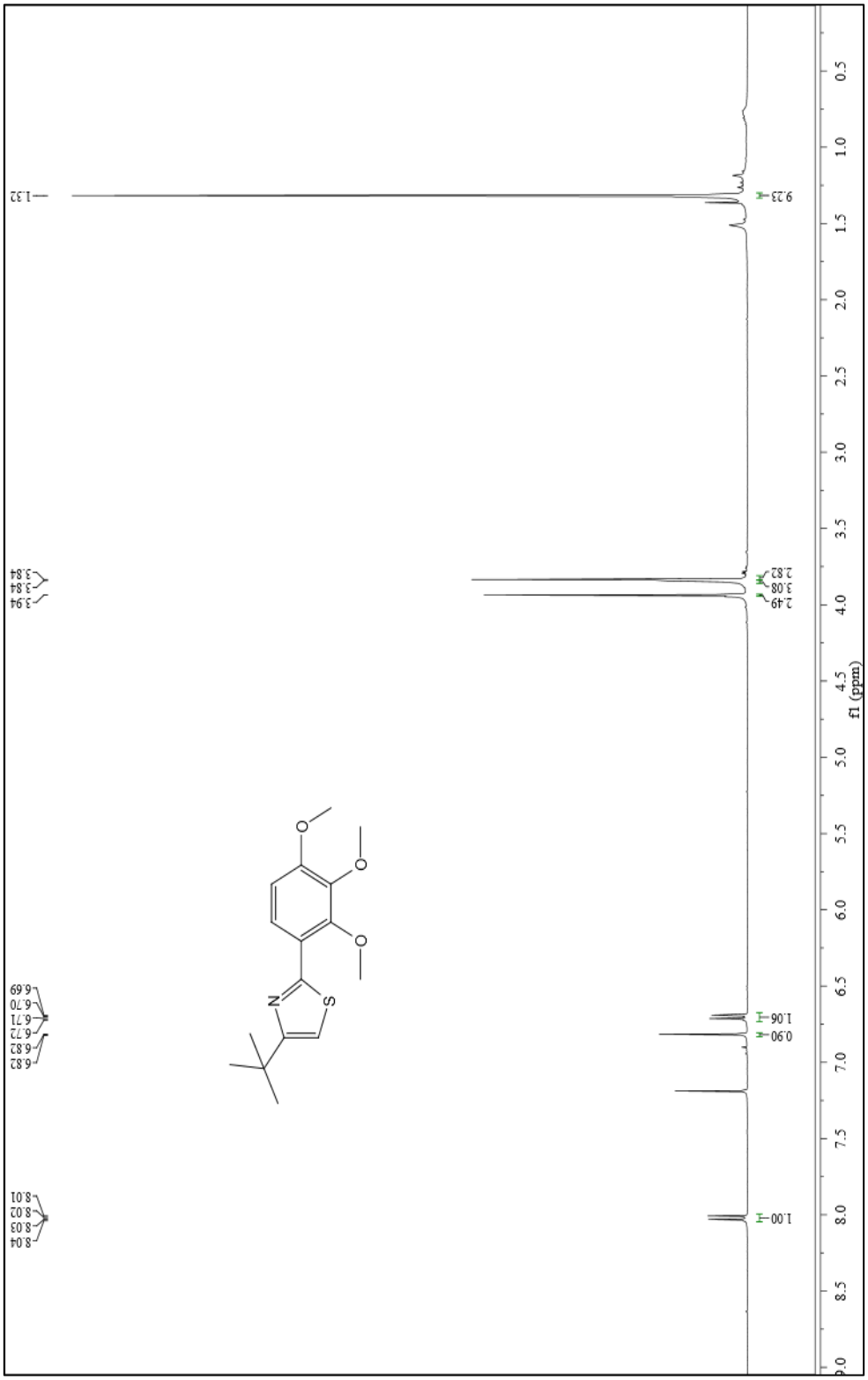
36p) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(naphthalen-1-yl)benzo[d]thiazole



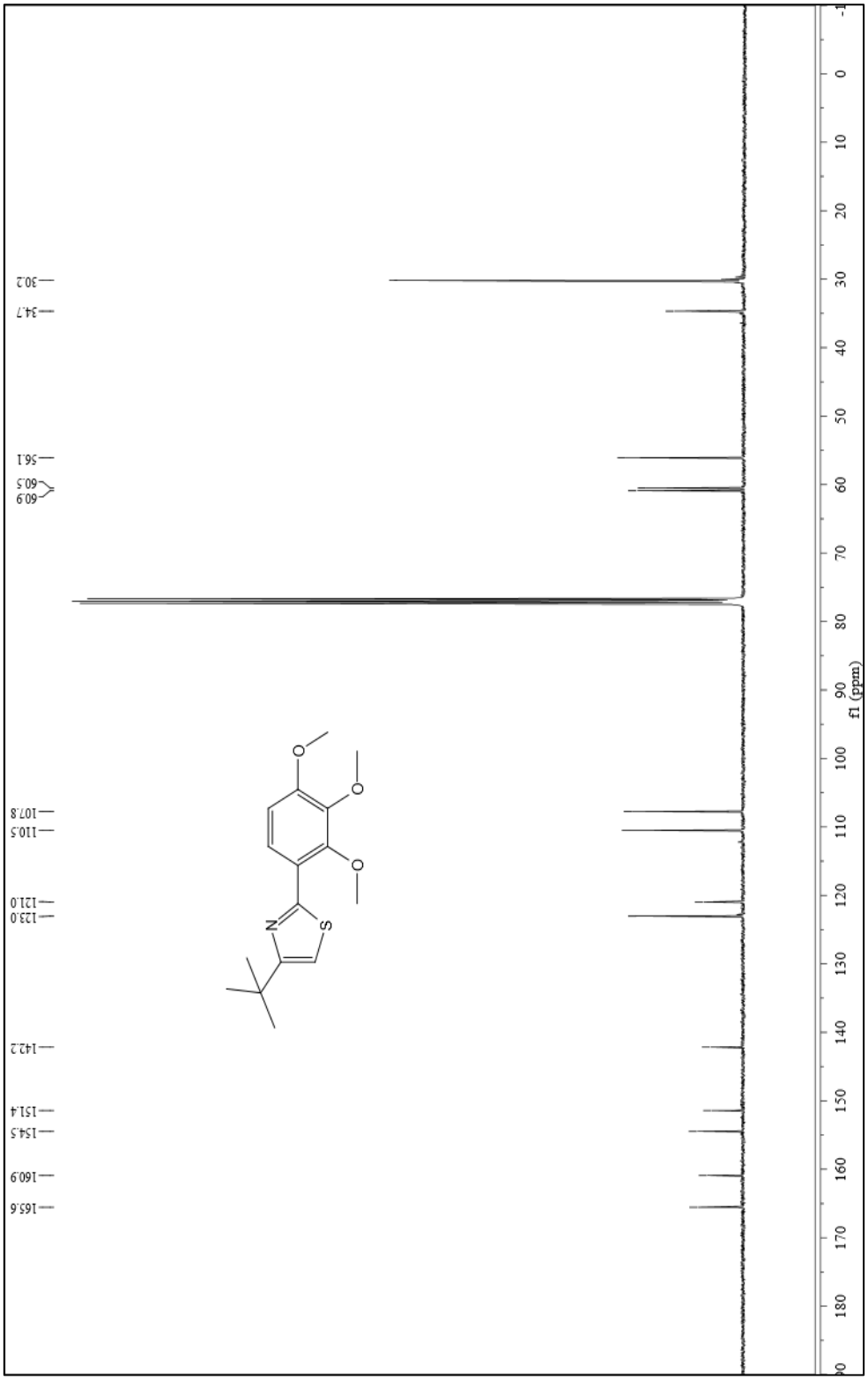
36p) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(naphthalen-1-yl)benzo[d]thiazole



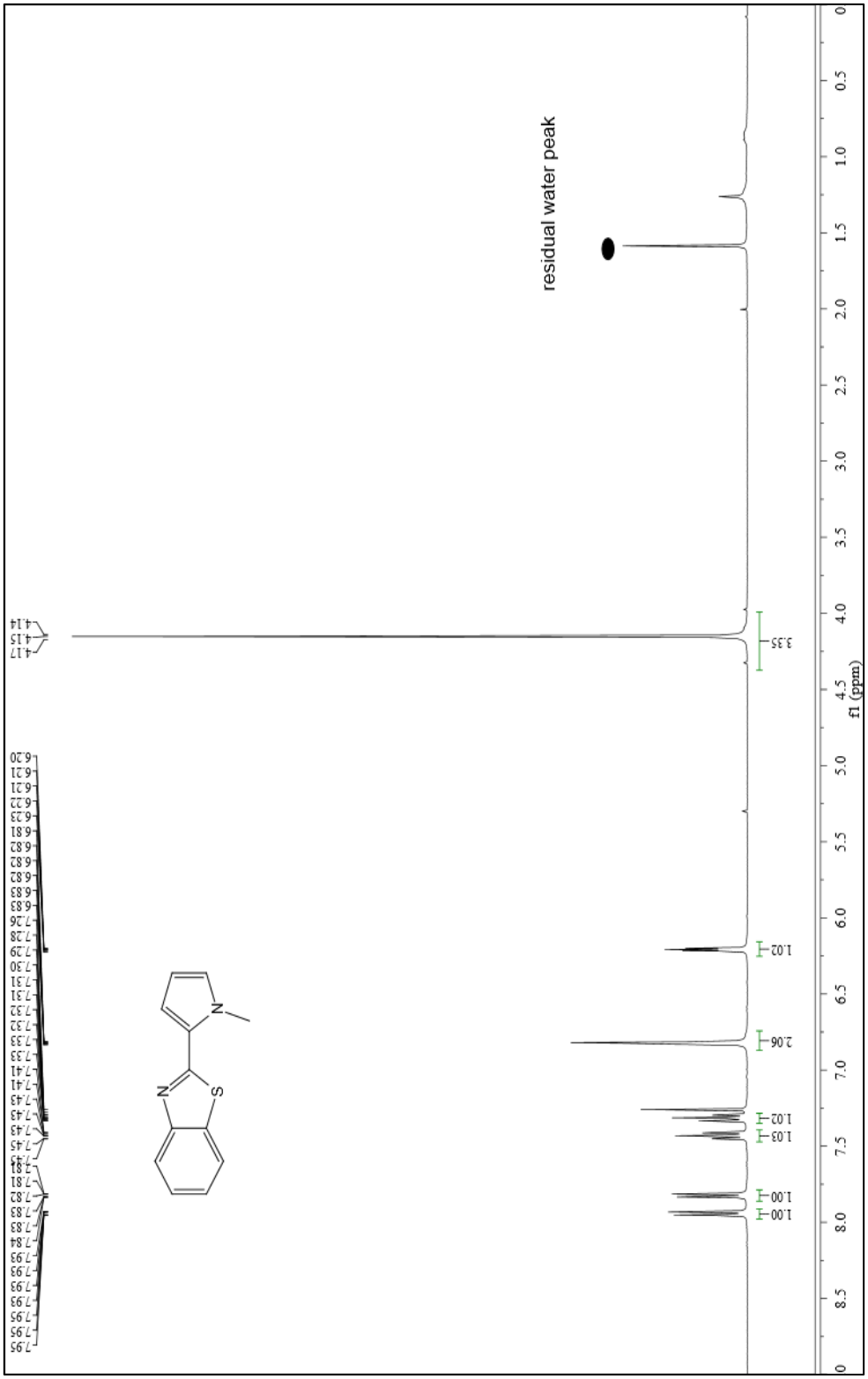
36q) ^{1}H NMR (400 MHz, $CDCl_3$) 4-(tert-butyl)-2-(2,3,4-trimethoxyphenyl)thiazole



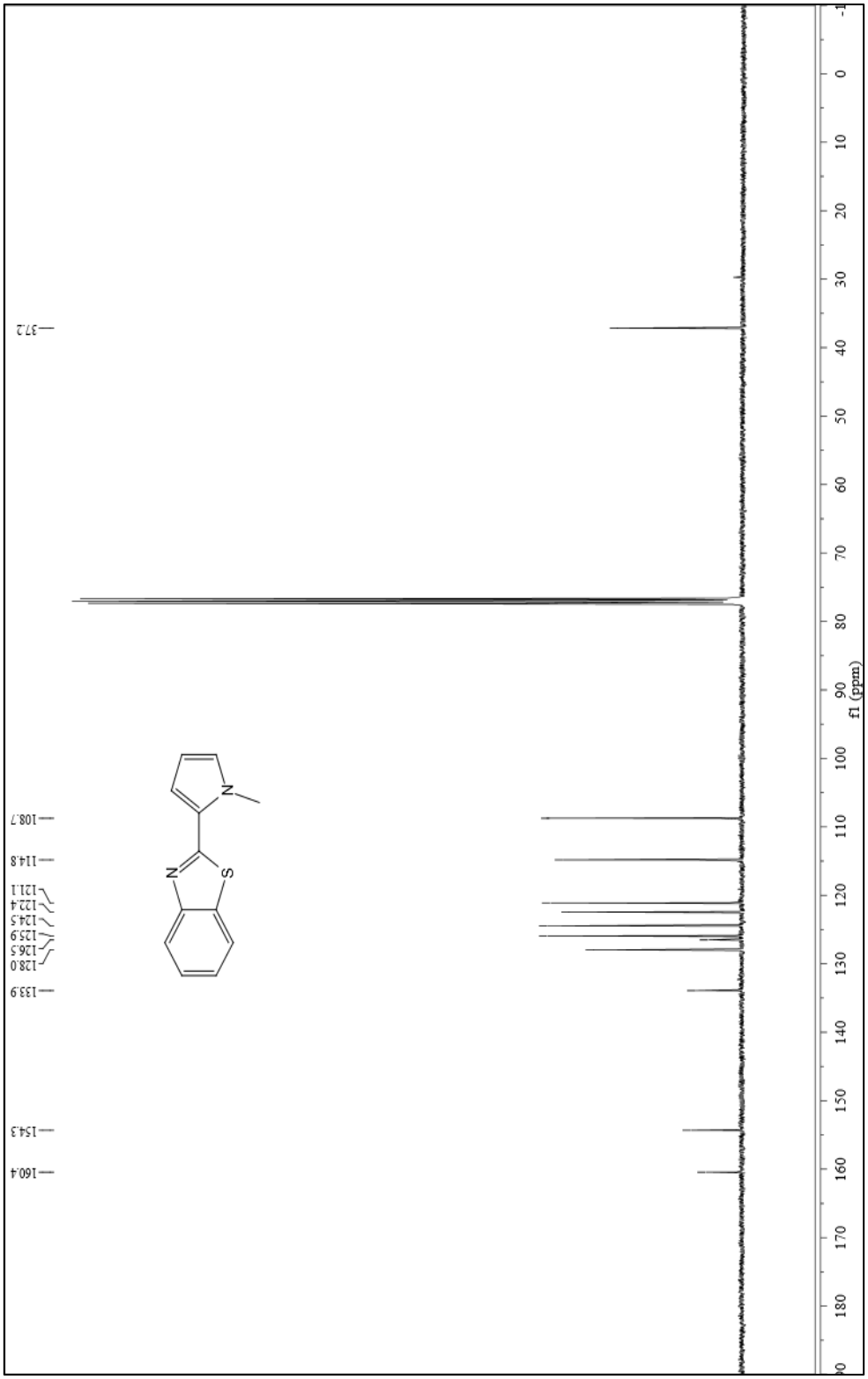
36q) ^{13}C NMR (101 MHz, $CDCl_3$) 4-(tert-butyl)-2-(2,3,4-trimethoxyphenyl)thiazole



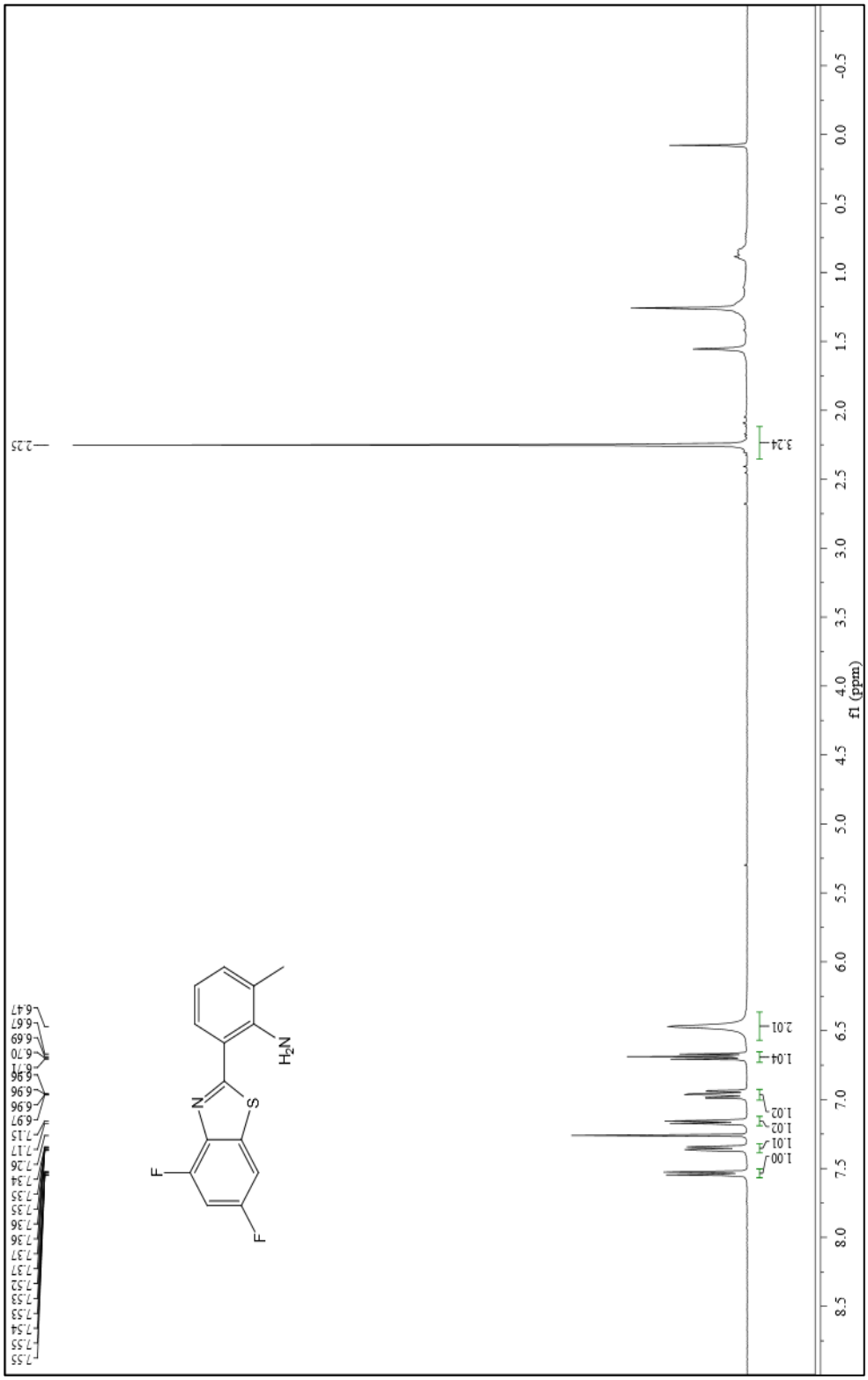
36r) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole



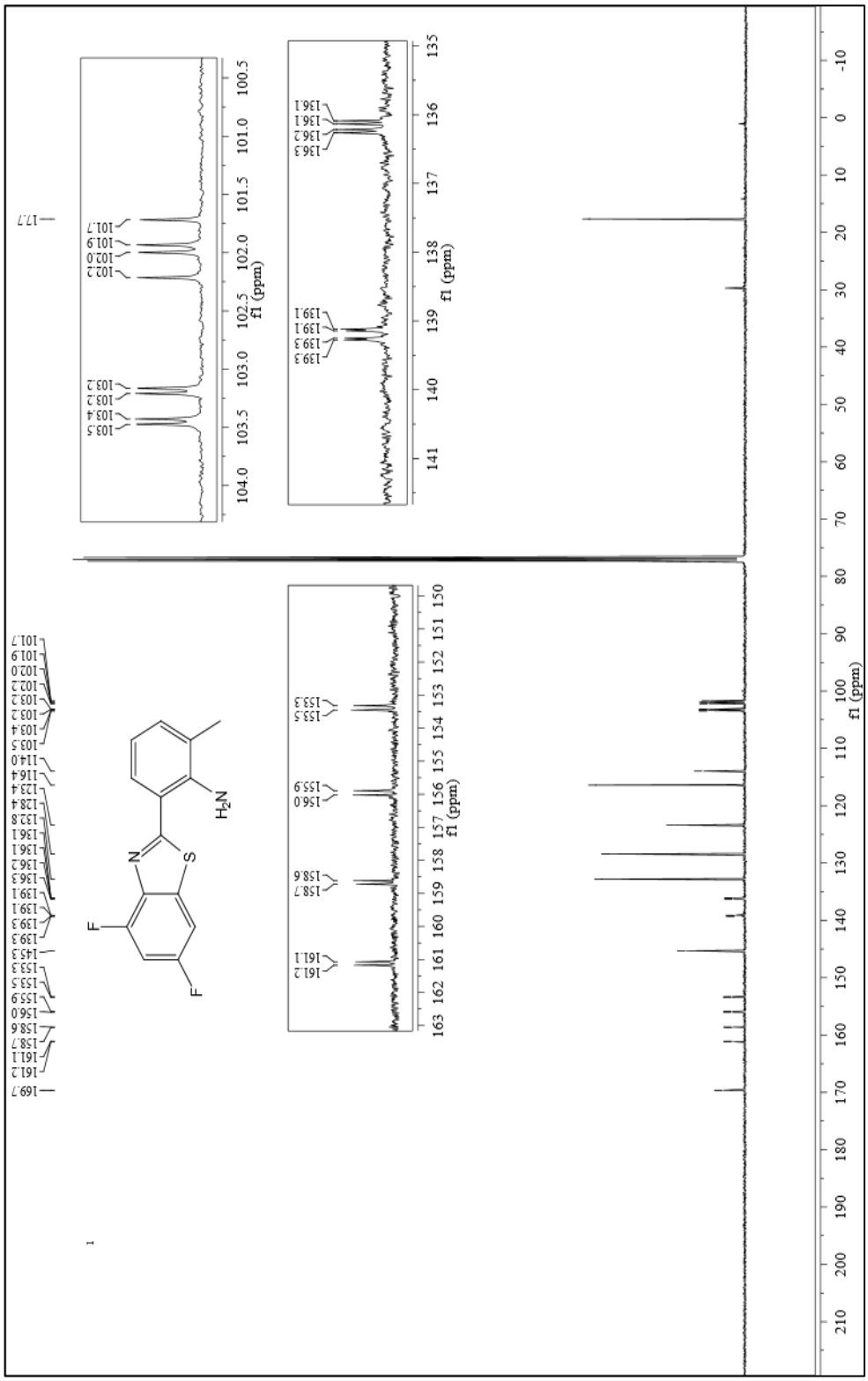
36r) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole



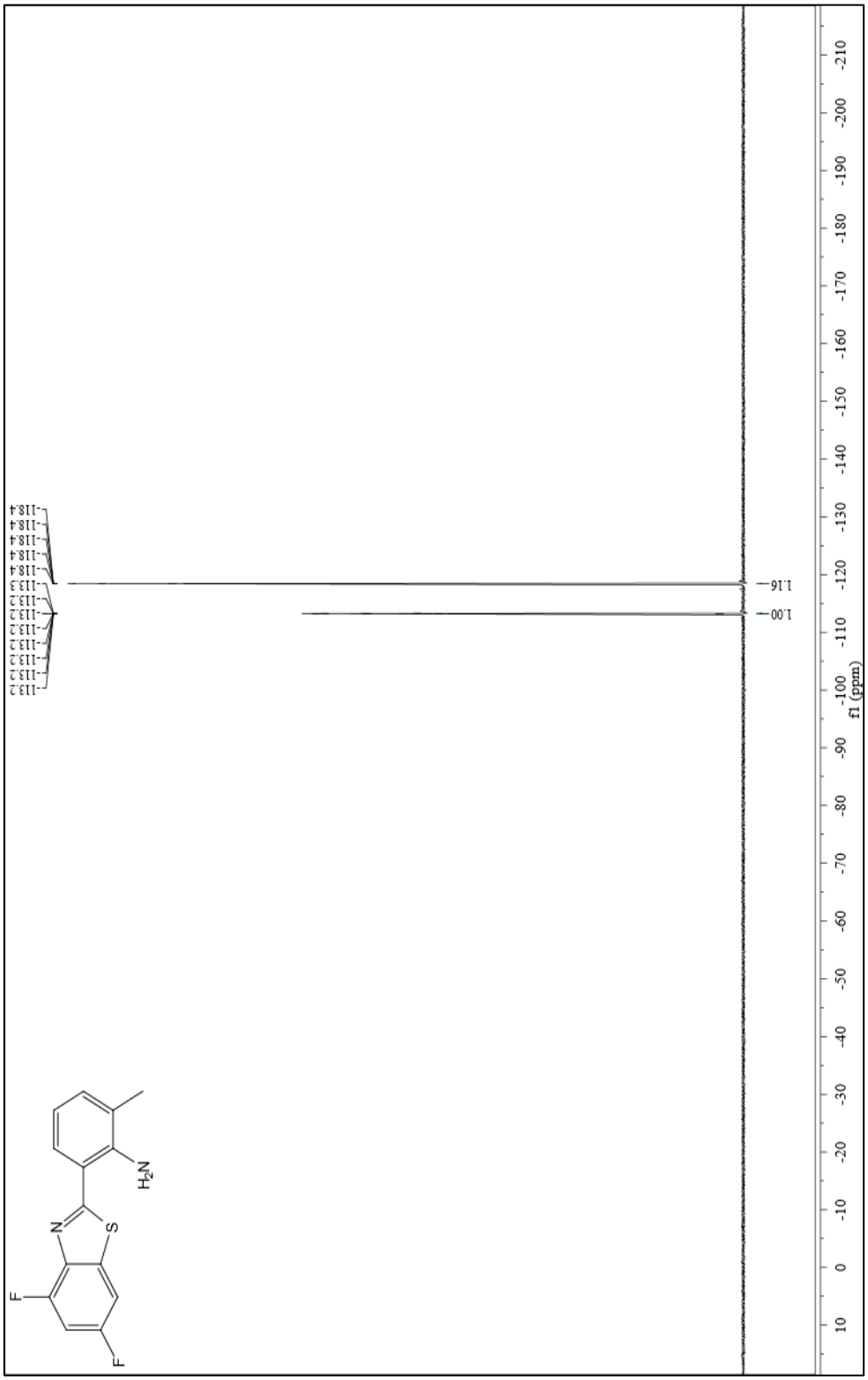
36s)- ^{1}H NMR (400 MHz, $CDCl_3$) 2-(4,6-difluorobenzo[d]thiazol-2-yl)-6-methylaniline(major)



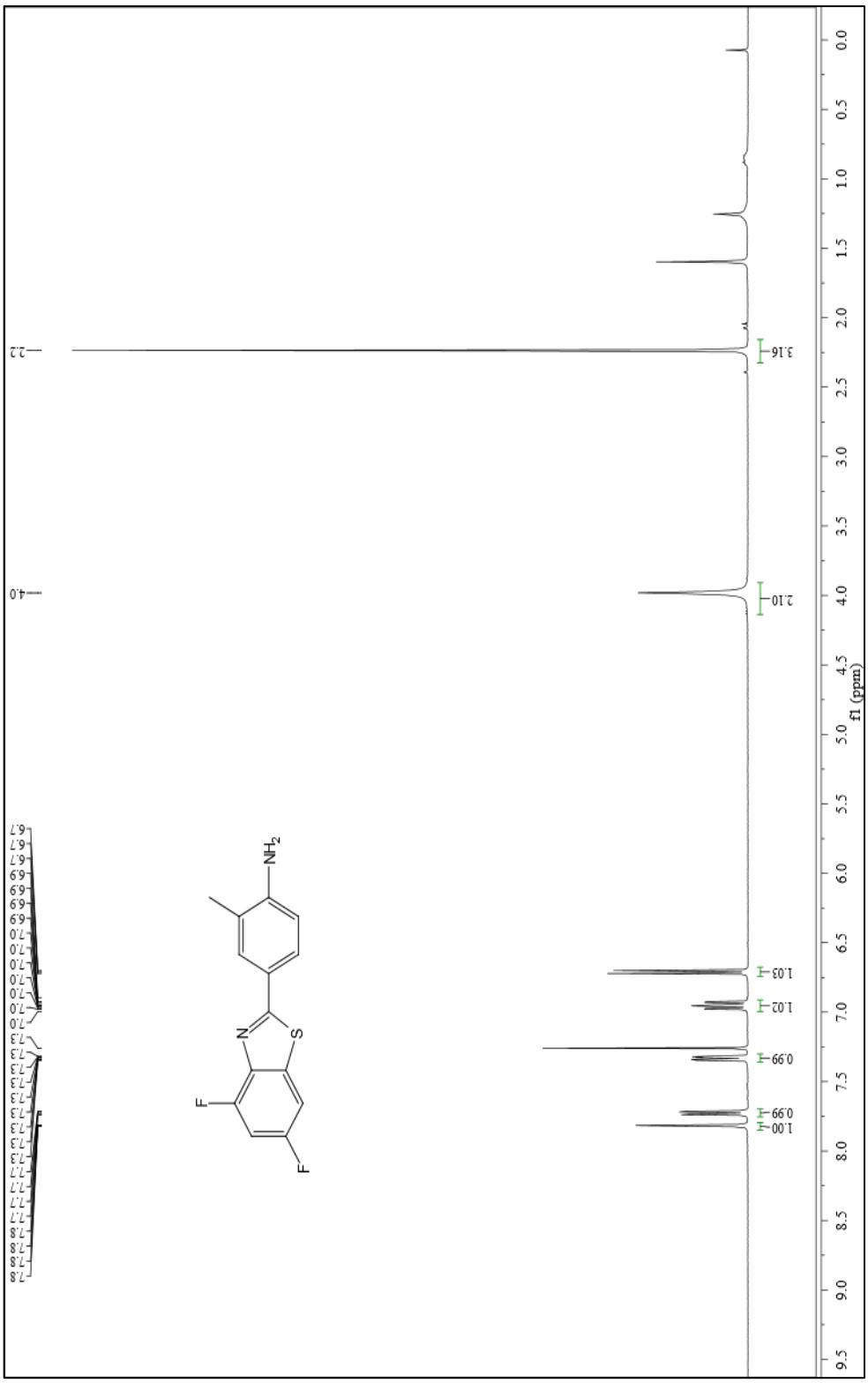
36s)- ^{13}C NMR (101 MHz, $CDCl_3$) 2-(4,6-difluorobenzo[d]thiazol-2-yl)-6-methylaniline(major)



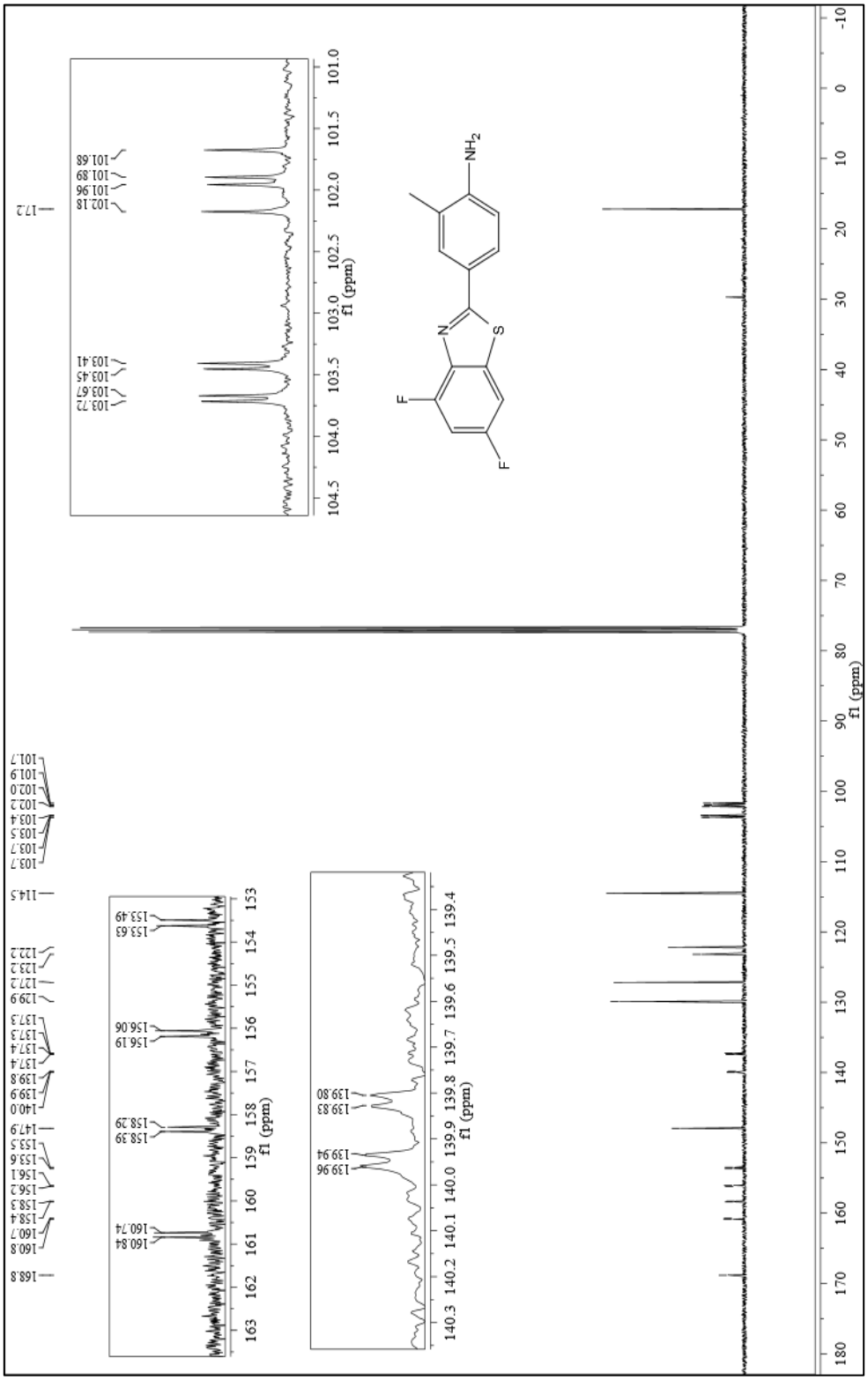
36s) ^{19}F NMR (376 MHz, $CDCl_3$) 2-(4,6-difluorobenzo[d]thiazol-2-yl)-6-methylaniline(major)



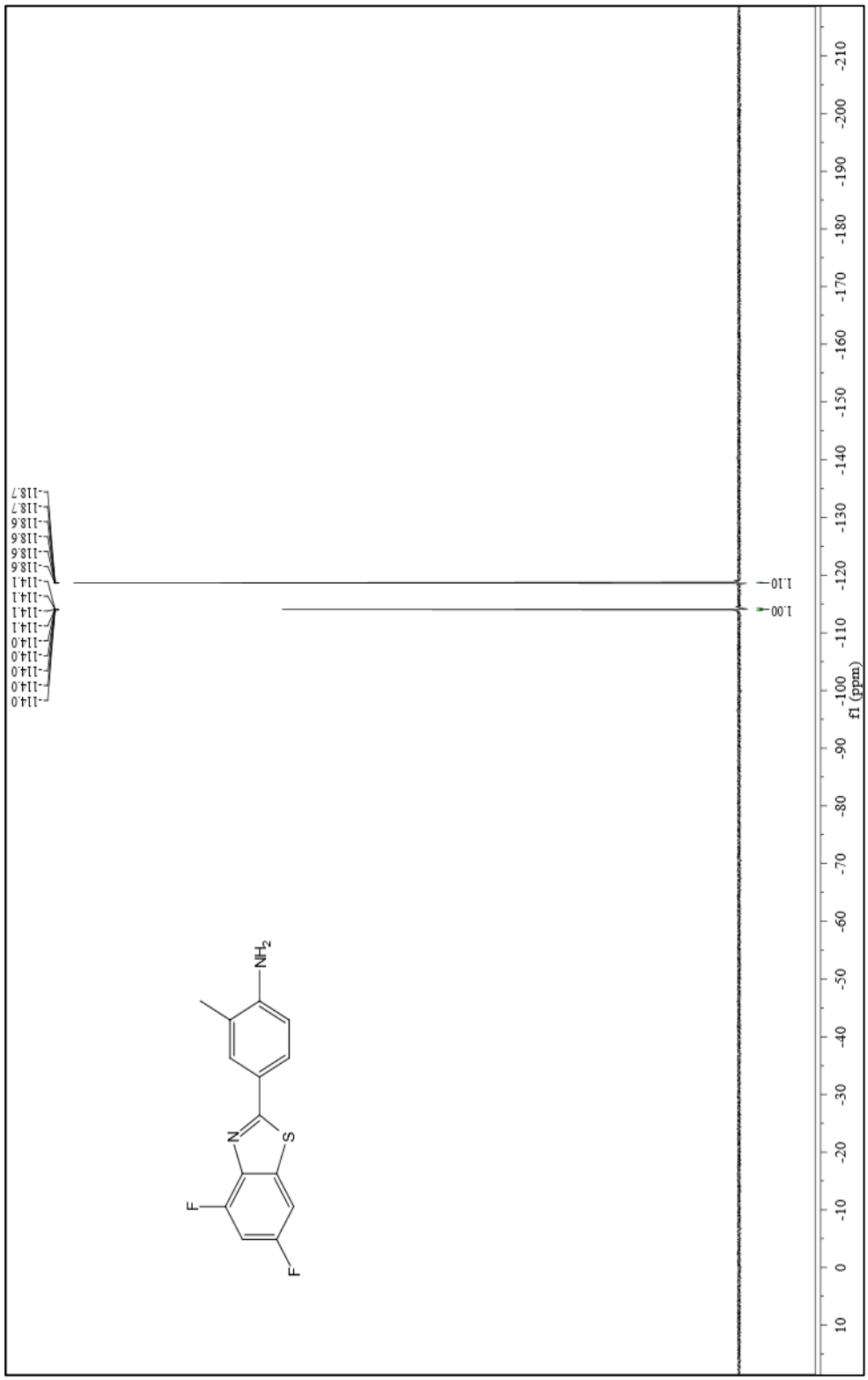
36sb) ^{1}H NMR (400 MHz, $CDCl_3$) 4-(4,6-difluorobenzo[d]thiazol-2-yl)-2-methylaniline(minor)



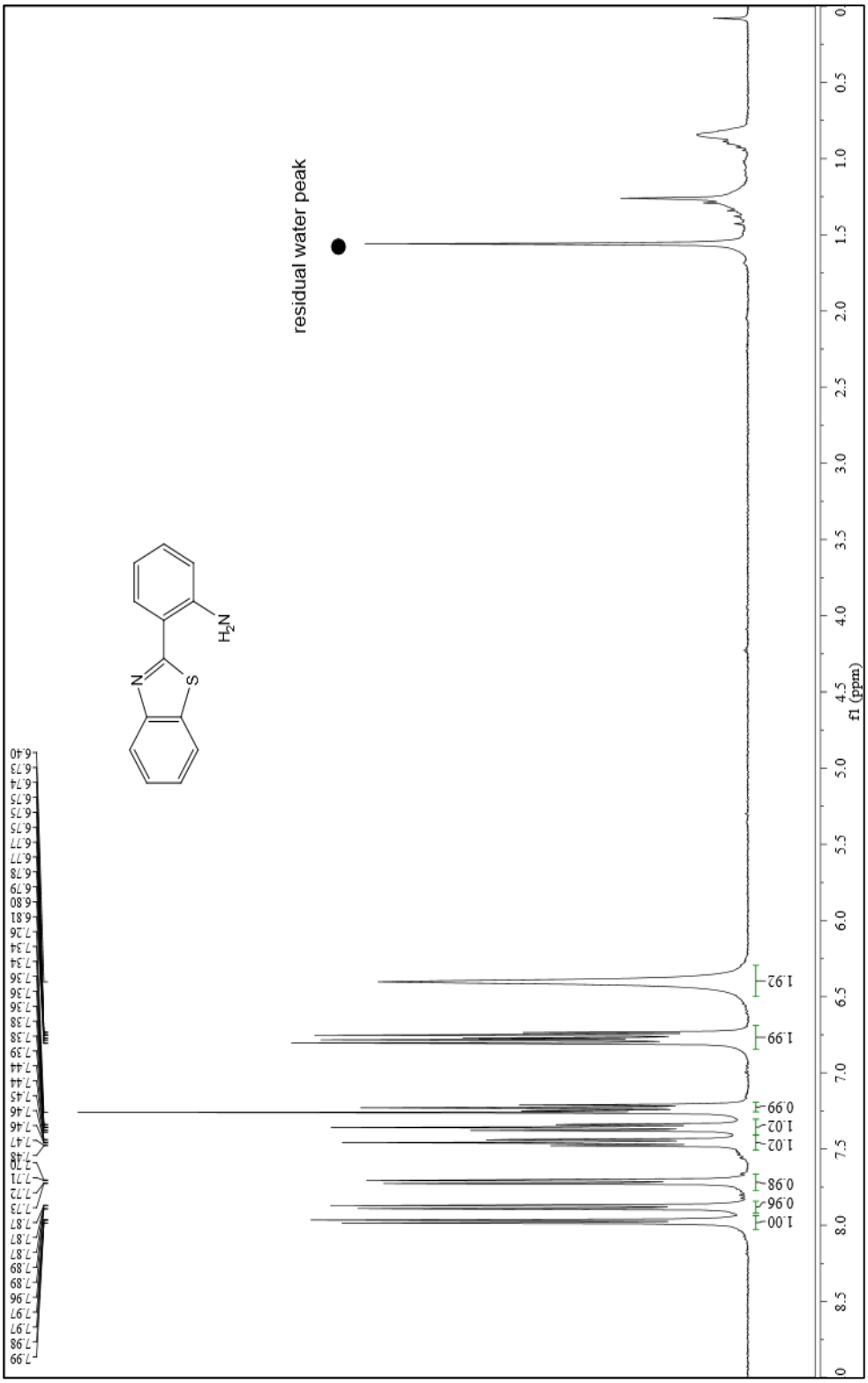
36sb) ^{13}C NMR (101 MHz, $CDCl_3$) 4-(4,6-difluorobenzo[d]thiazol-2-yl)-2-methylaniline(minor)



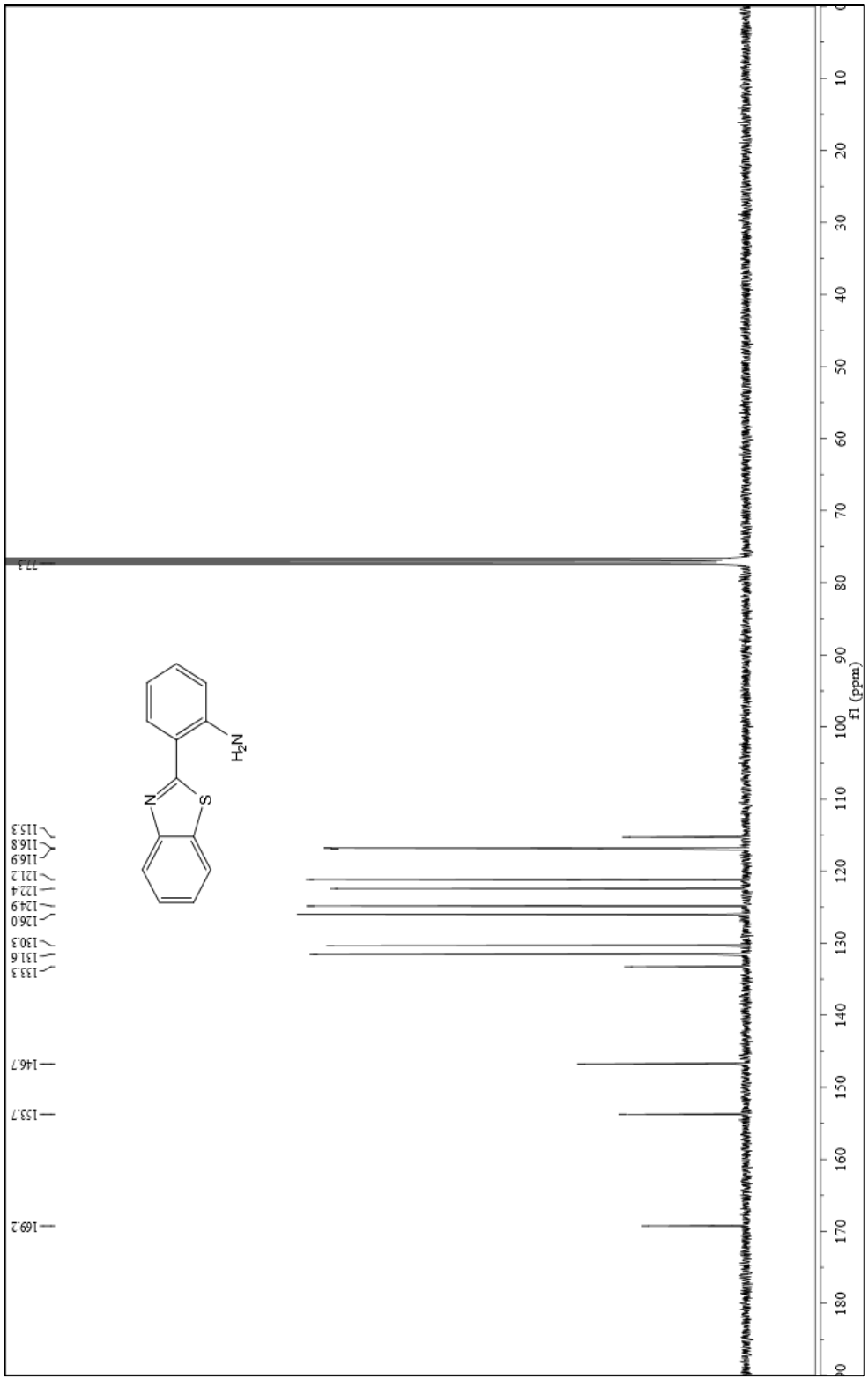
36sb) ^{19}F NMR (376 MHz, $CDCl_3$) 4-(4,6-difluorobenzo[d]thiazol-2-yl)-2-methylaniline(minor)



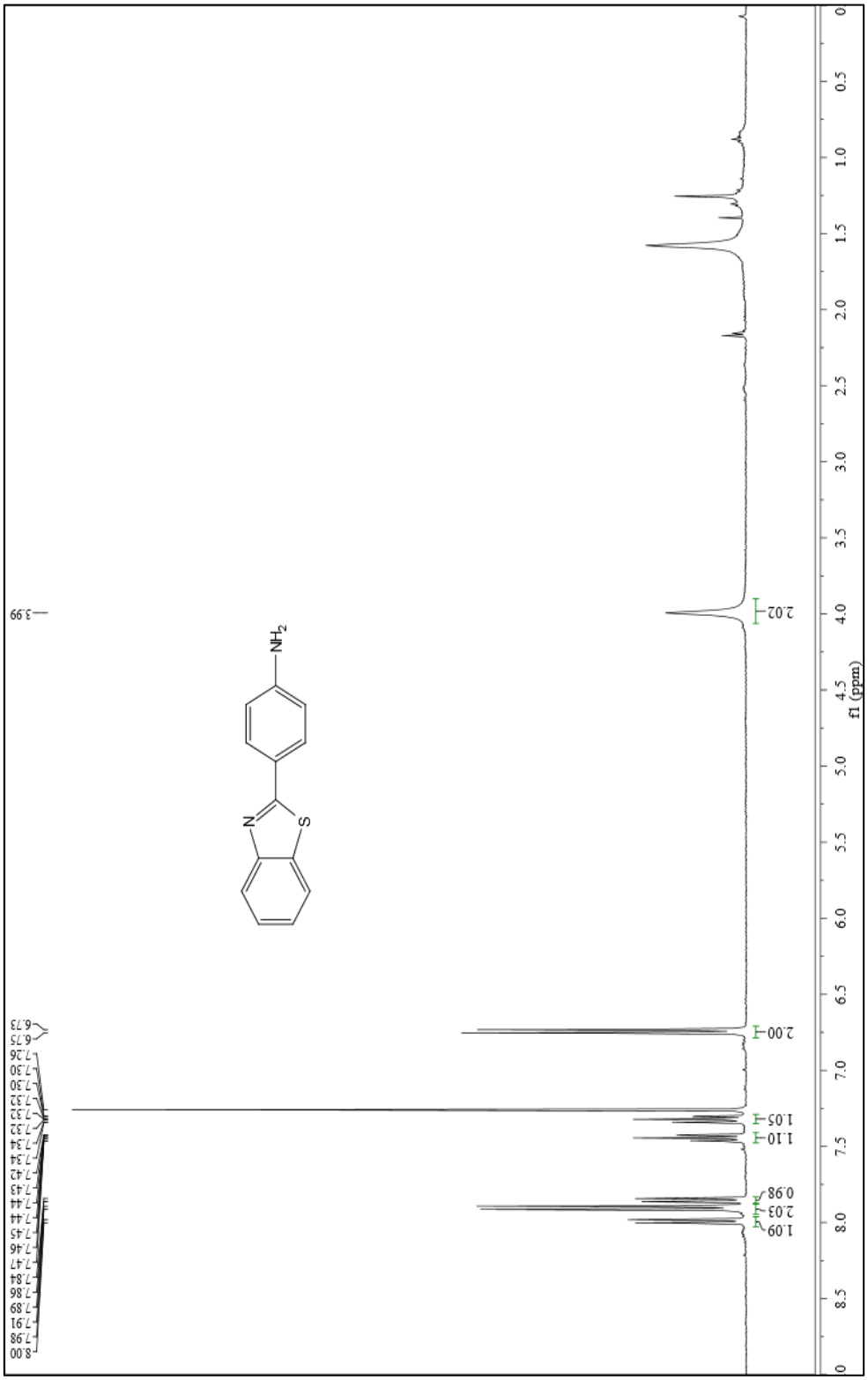
36t) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(benzo[d]thiazol-2-yl)aniline(Major)



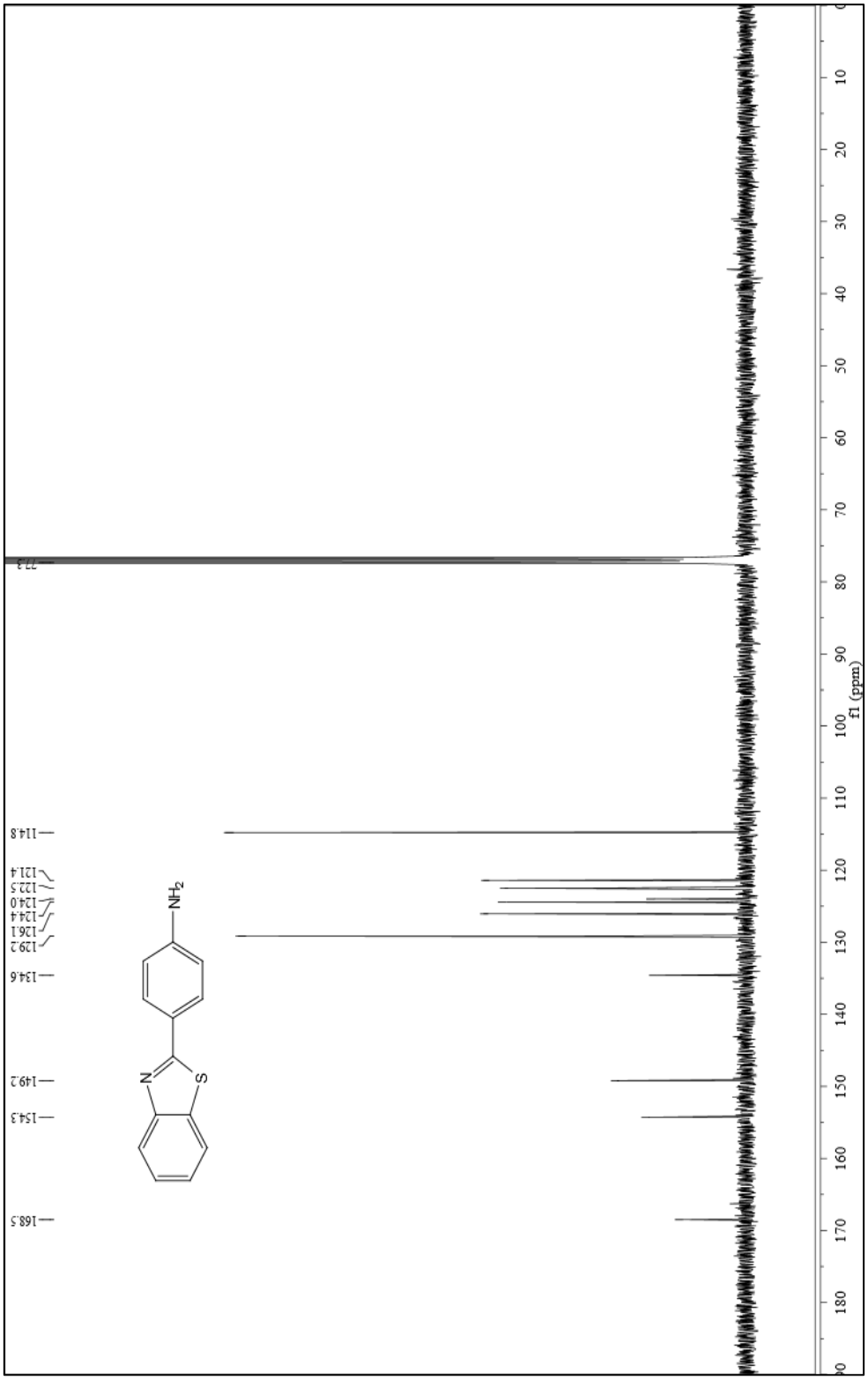
36t) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(benzo[d]thiazol-2-yl)aniline(Major)



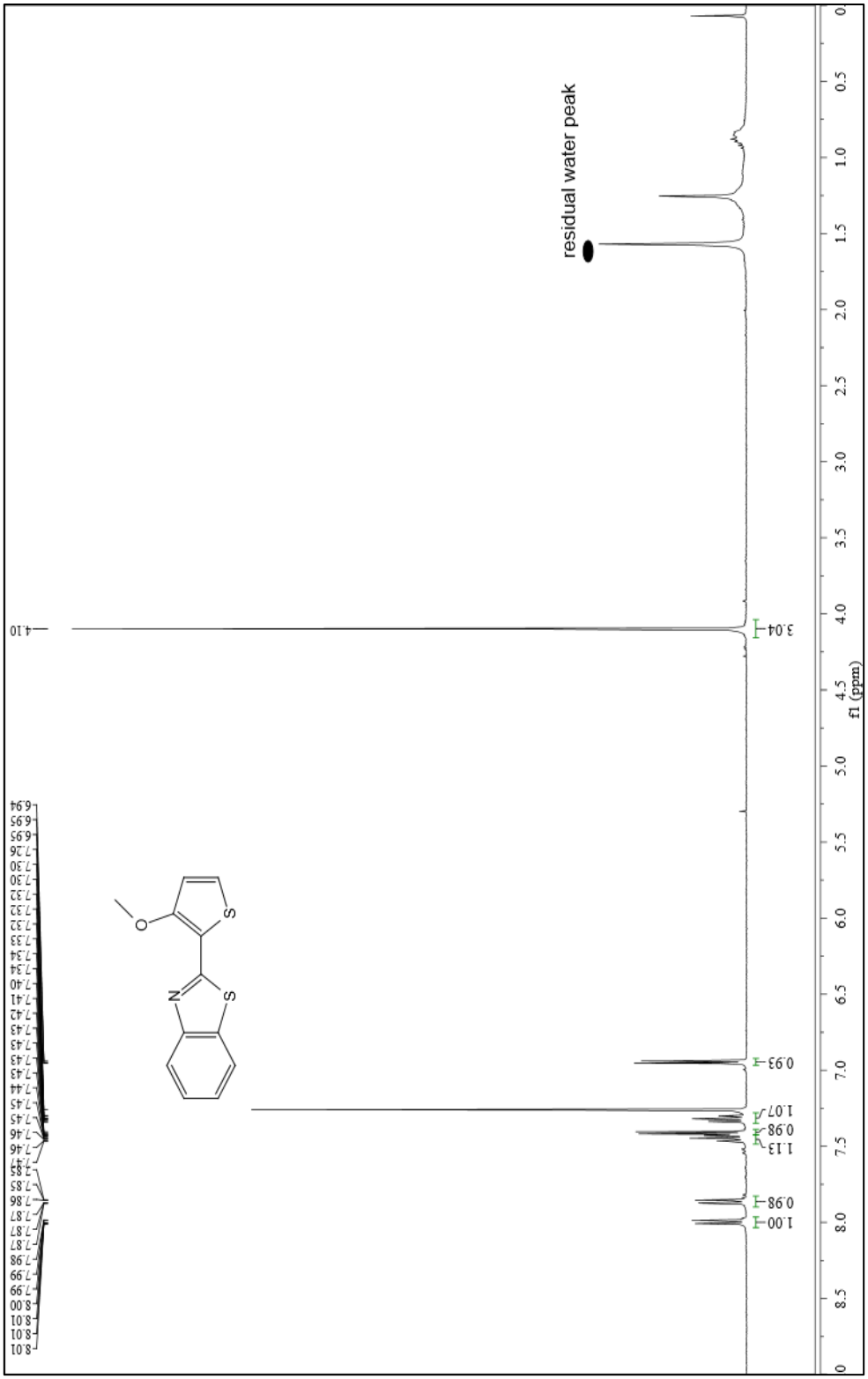
36tb) ^{1}H NMR (400 MHz, $CDCl_3$) 4-(benzo[d]thiazol-2-yl)aniline(minor)



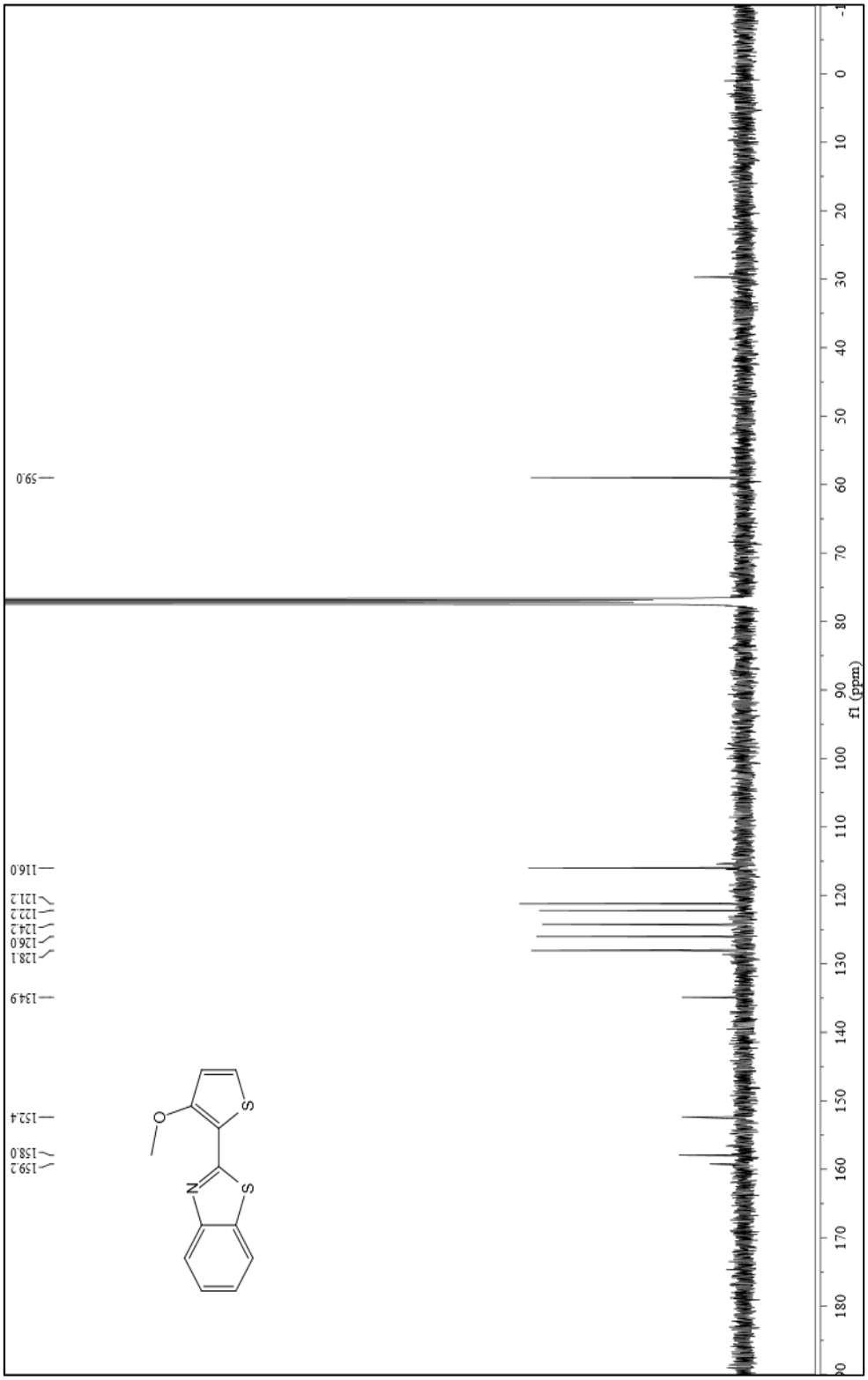
36tb) ^{13}C NMR (101 MHz, $CDCl_3$) 4-(benzo[d]thiazol-2-yl)aniline(minor)



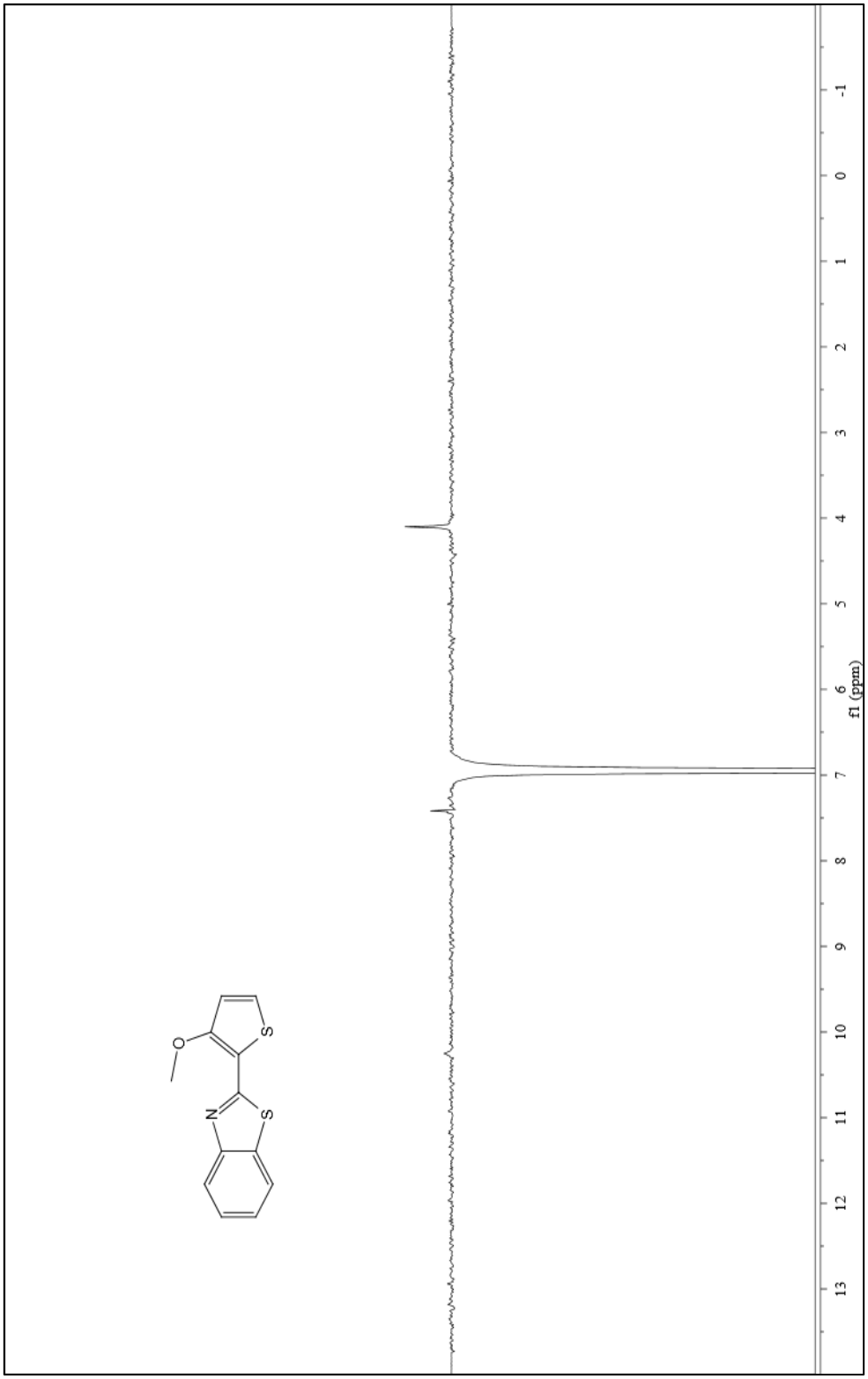
36u) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(3-methoxythiophen-2-yl)benzo[d]thiazole



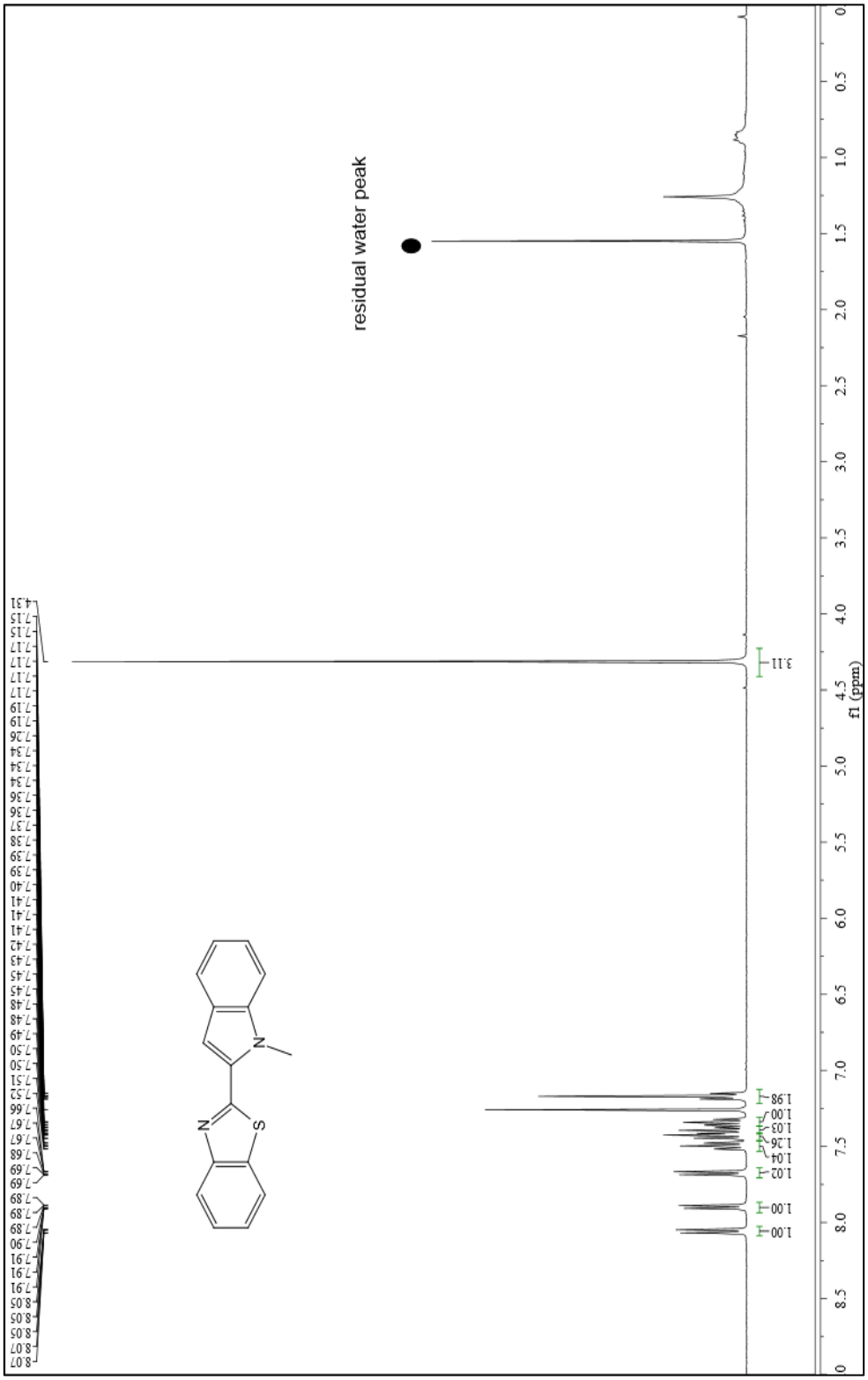
36u) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(3-methoxythiophen-2-yl)benzo[d]thiazole



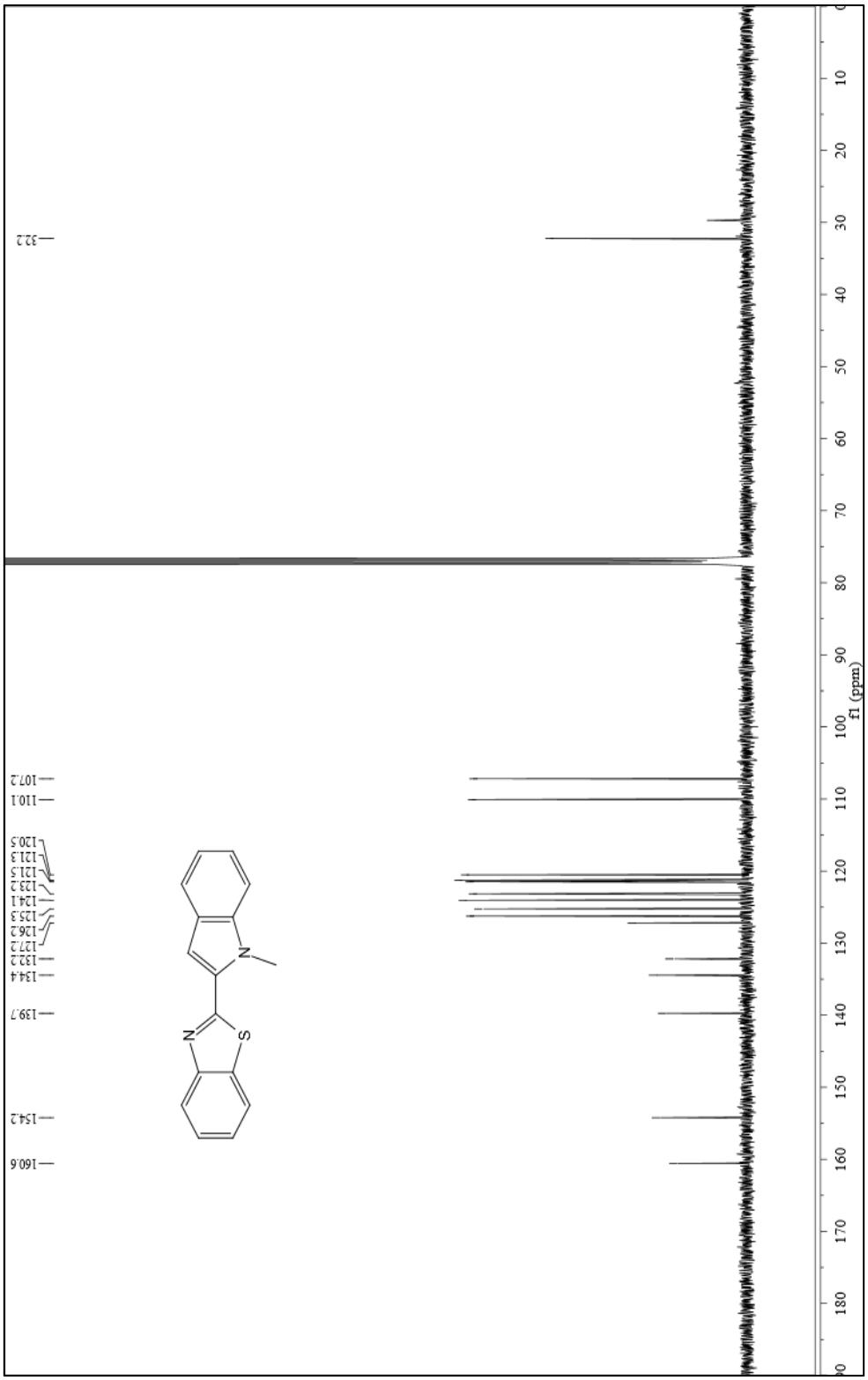
36u) NOE-1D (101 MHz, $CDCl_3$) 2-(3-methoxythiophen-2-yl)benzo[d]thiazole



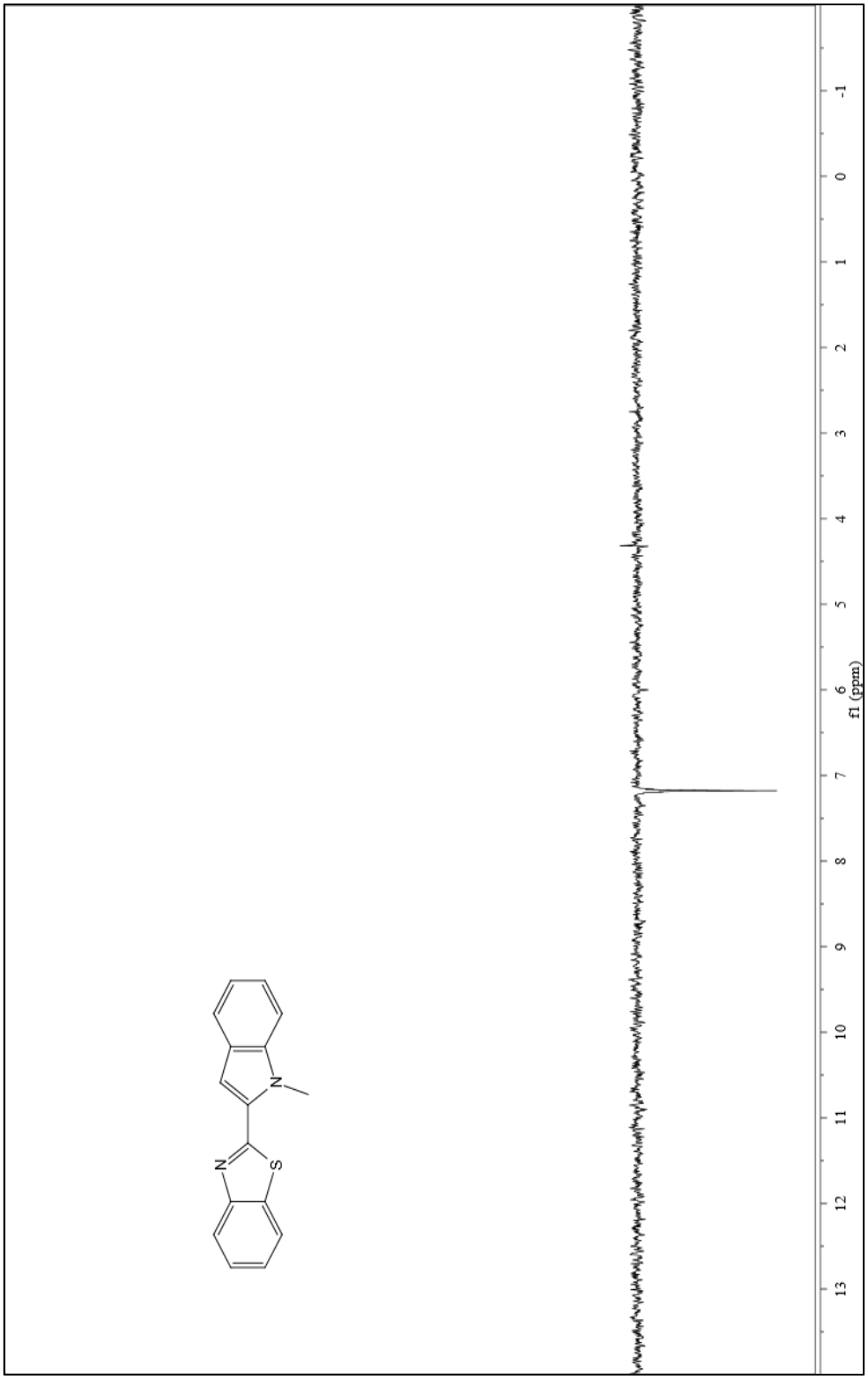
36v) ^{1}H NMR (400 MHz, $CDCl_3$) of 2-(1-methyl-1H-indol-2-yl)benzo[d]thiazole



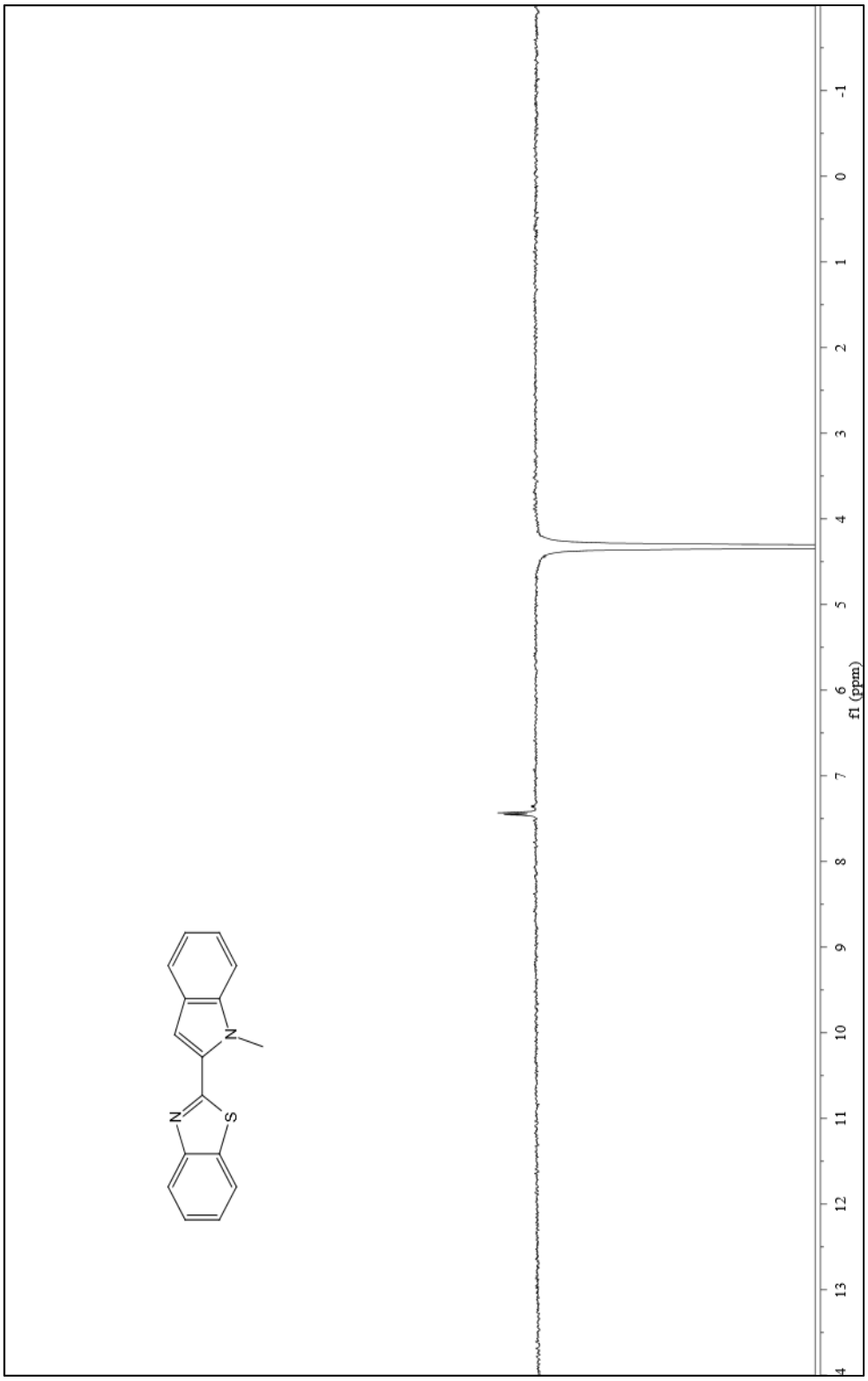
36v) ^{13}C NMR (101 MHz, $CDCl_3$) of 2-(1-methyl-1H-indol-2-yl)benzo[d]thiazole



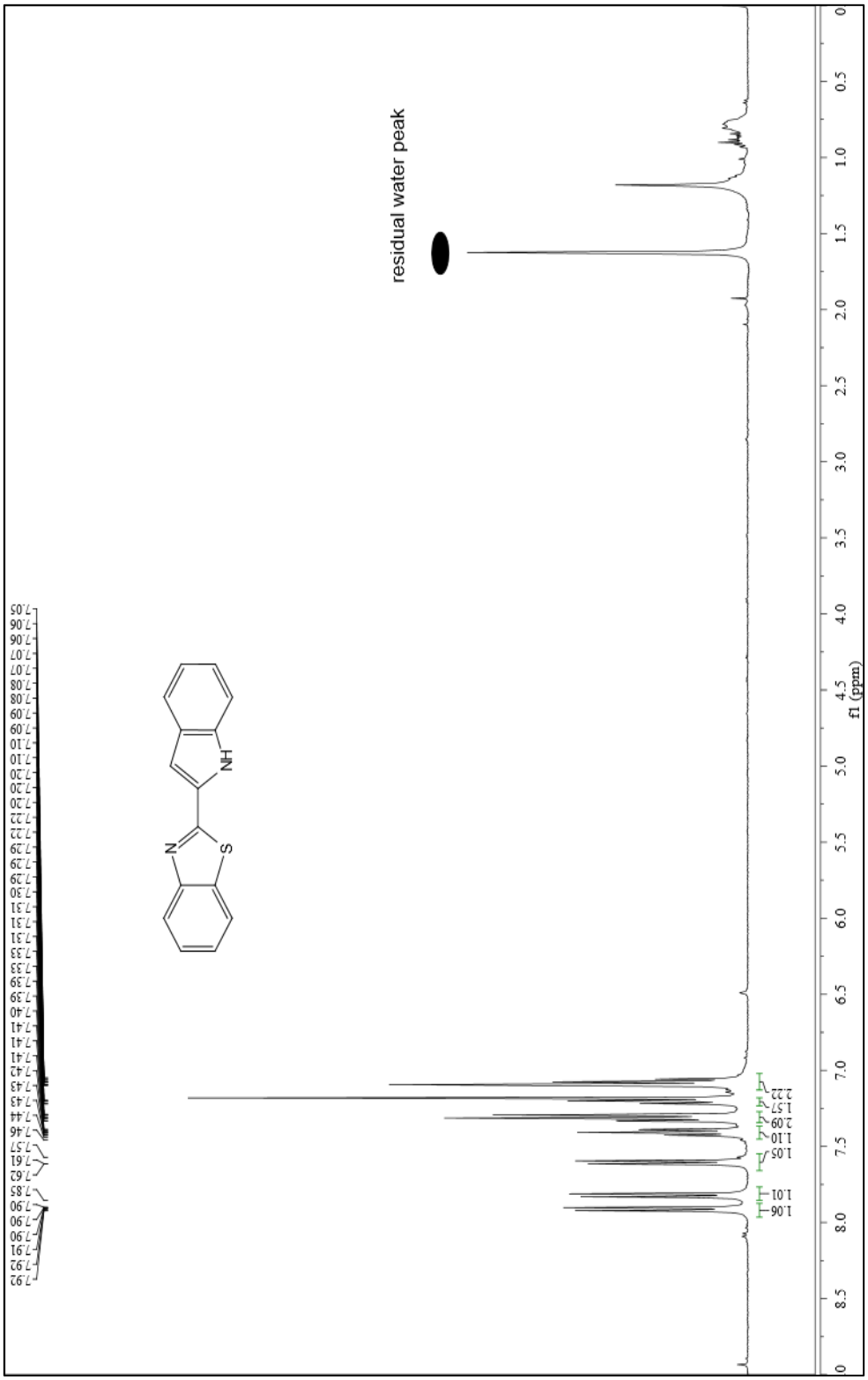
36v) NOE-1D (101 MHz, $CDCl_3$) of 2-(1-methyl-1H-indol-2-yl)benzo[d]thiazole



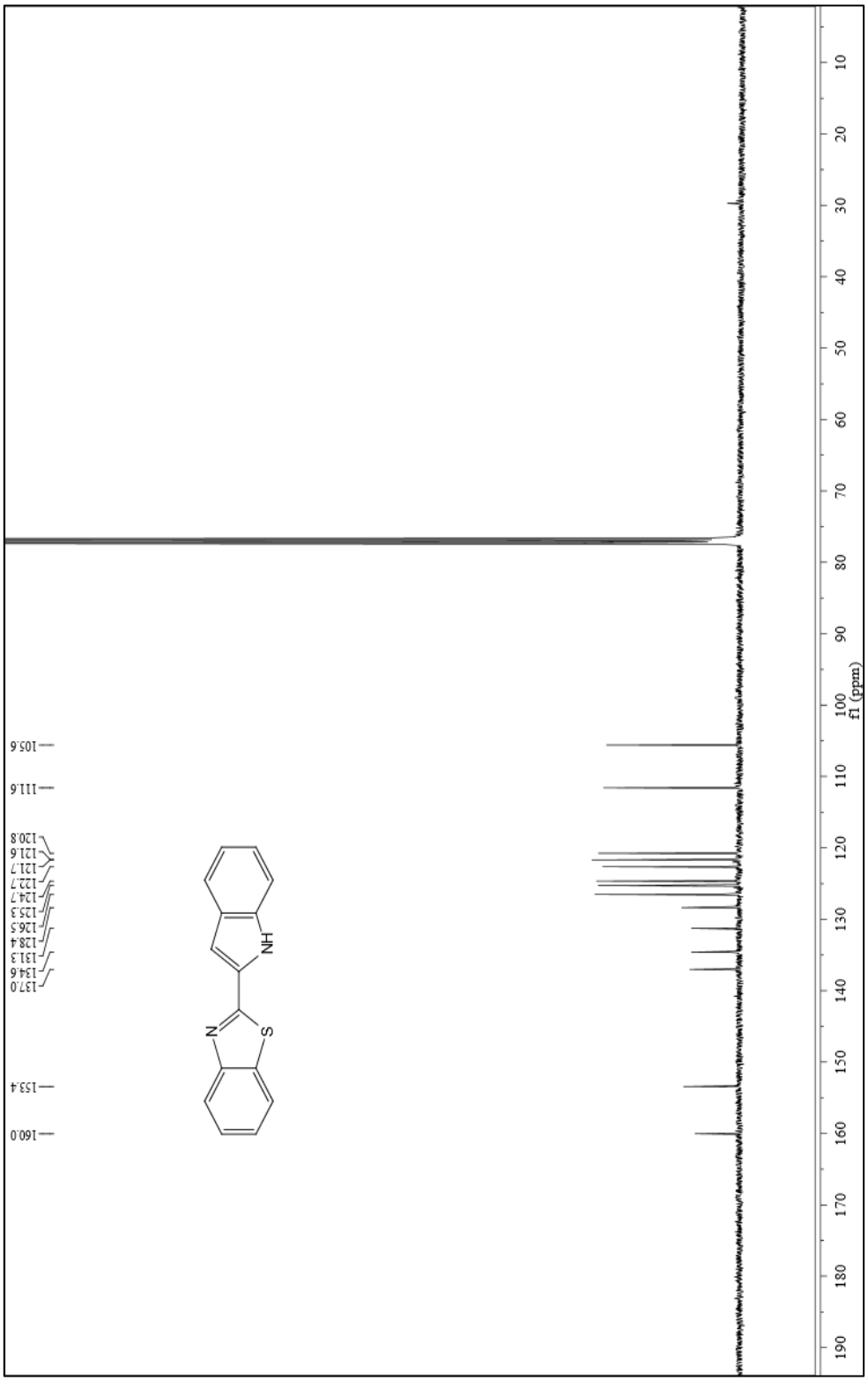
36v) NOE-1D (101 MHz, $CDCl_3$) of 2-(1-methyl-1H-indol-2-yl)benzo[d]thiazole



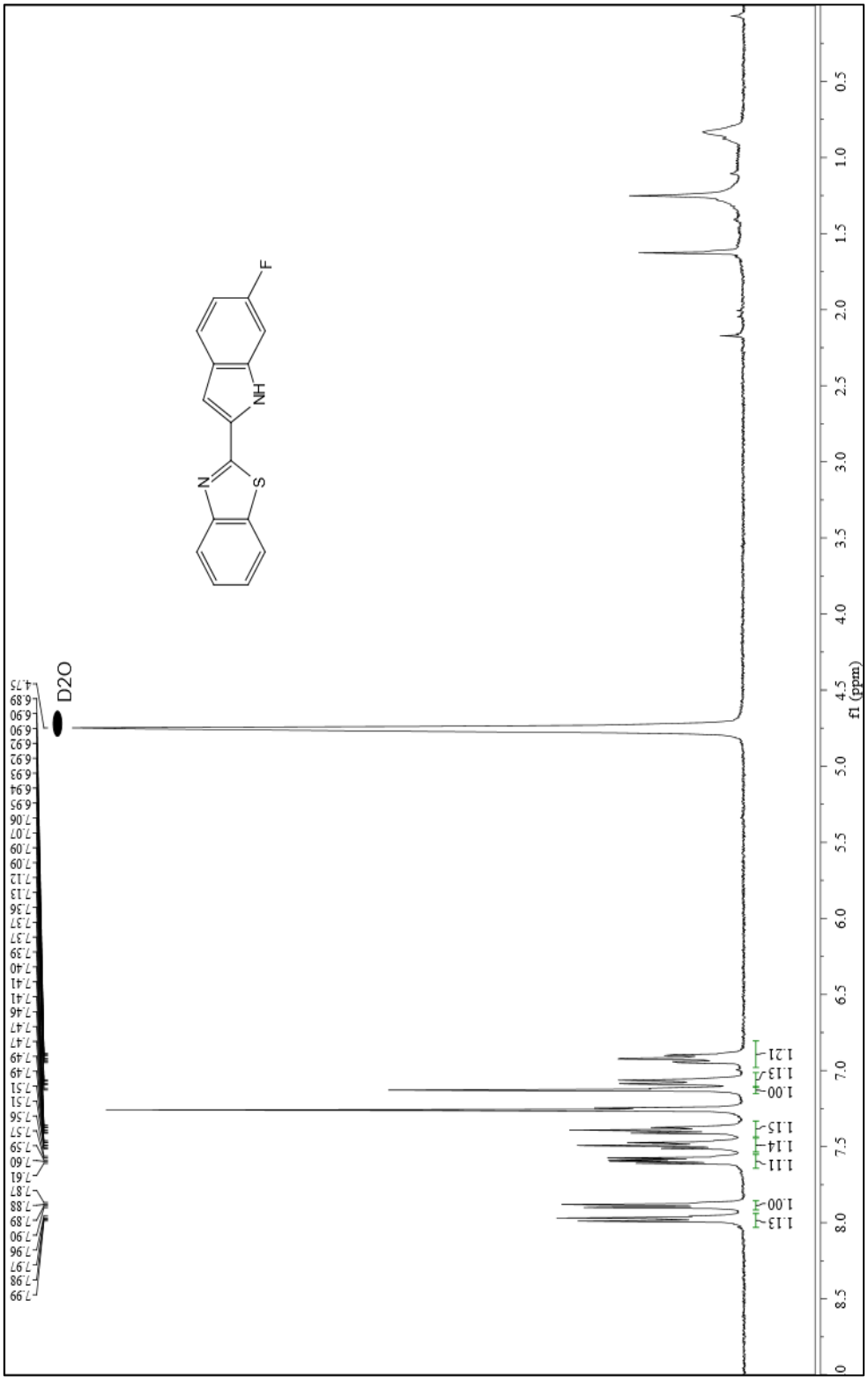
36w) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(1H-indol-2-yl)benzo[d]thiazole



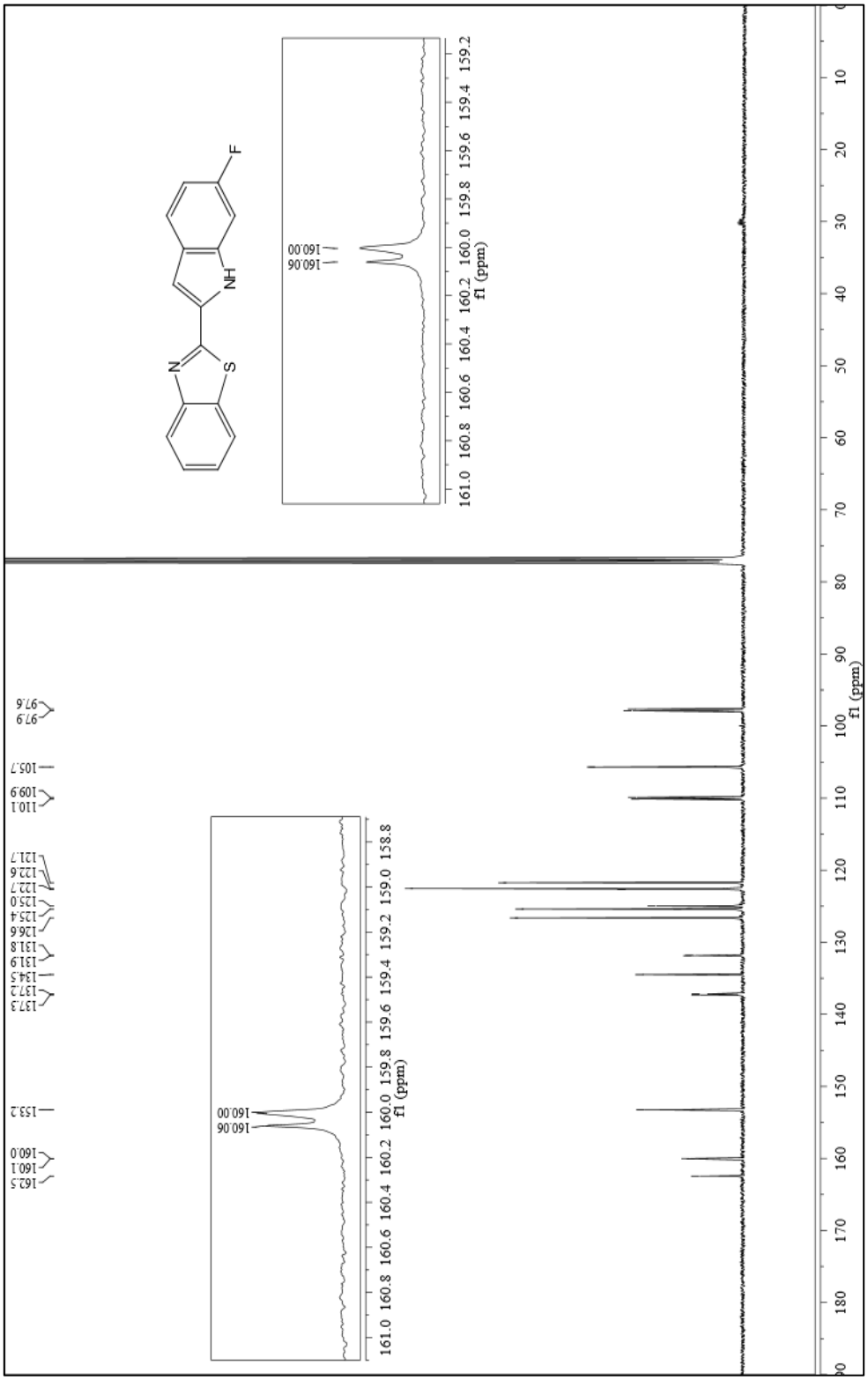
36w) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(1H-indol-2-yl)benzo[d]thiazole



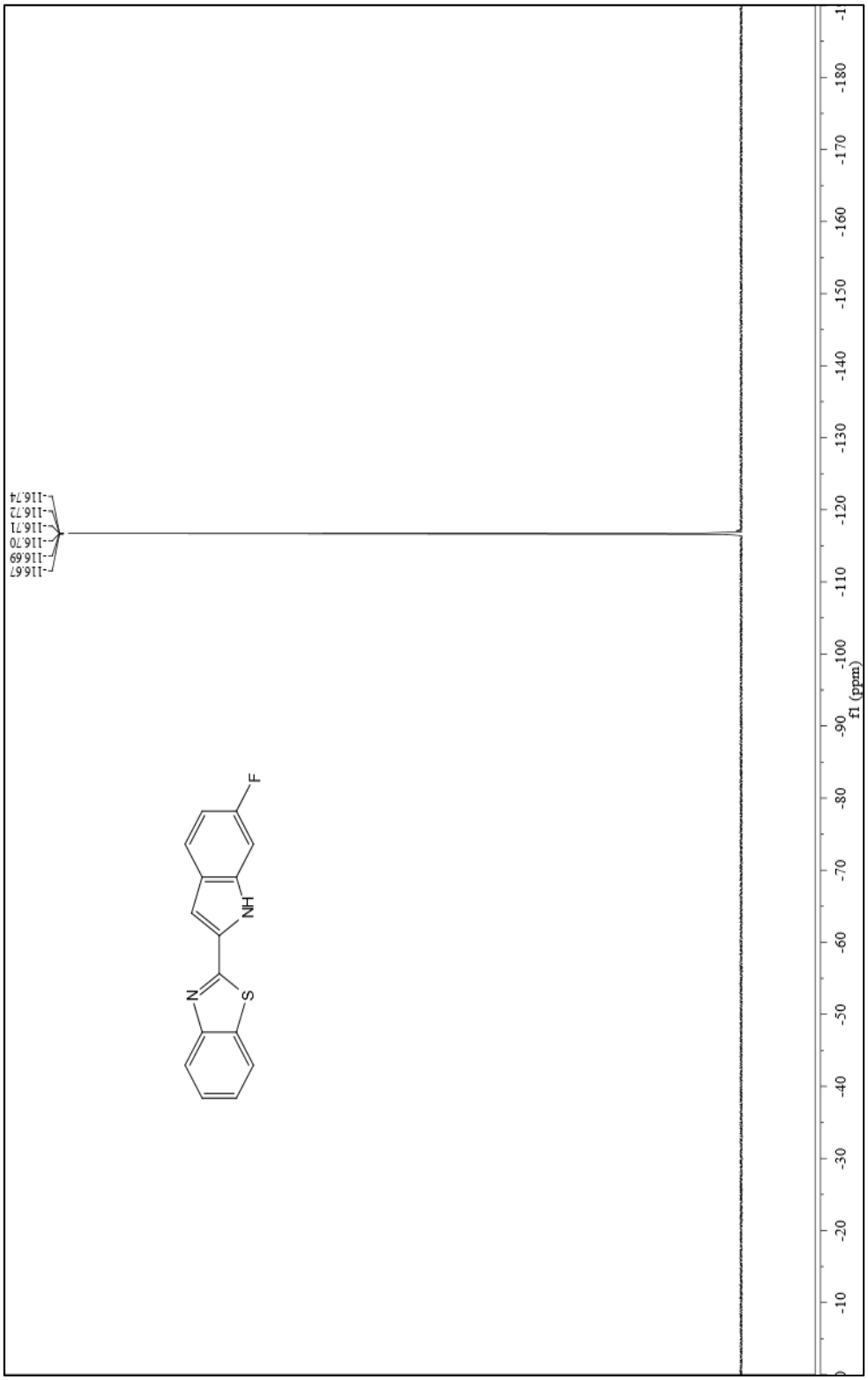
36x) ^{1}H NMR (400 MHz, $CDCl_3$ and D_2O) 2-(6-fluoro-1H-indol-2-yl)benzo[d]thiazole



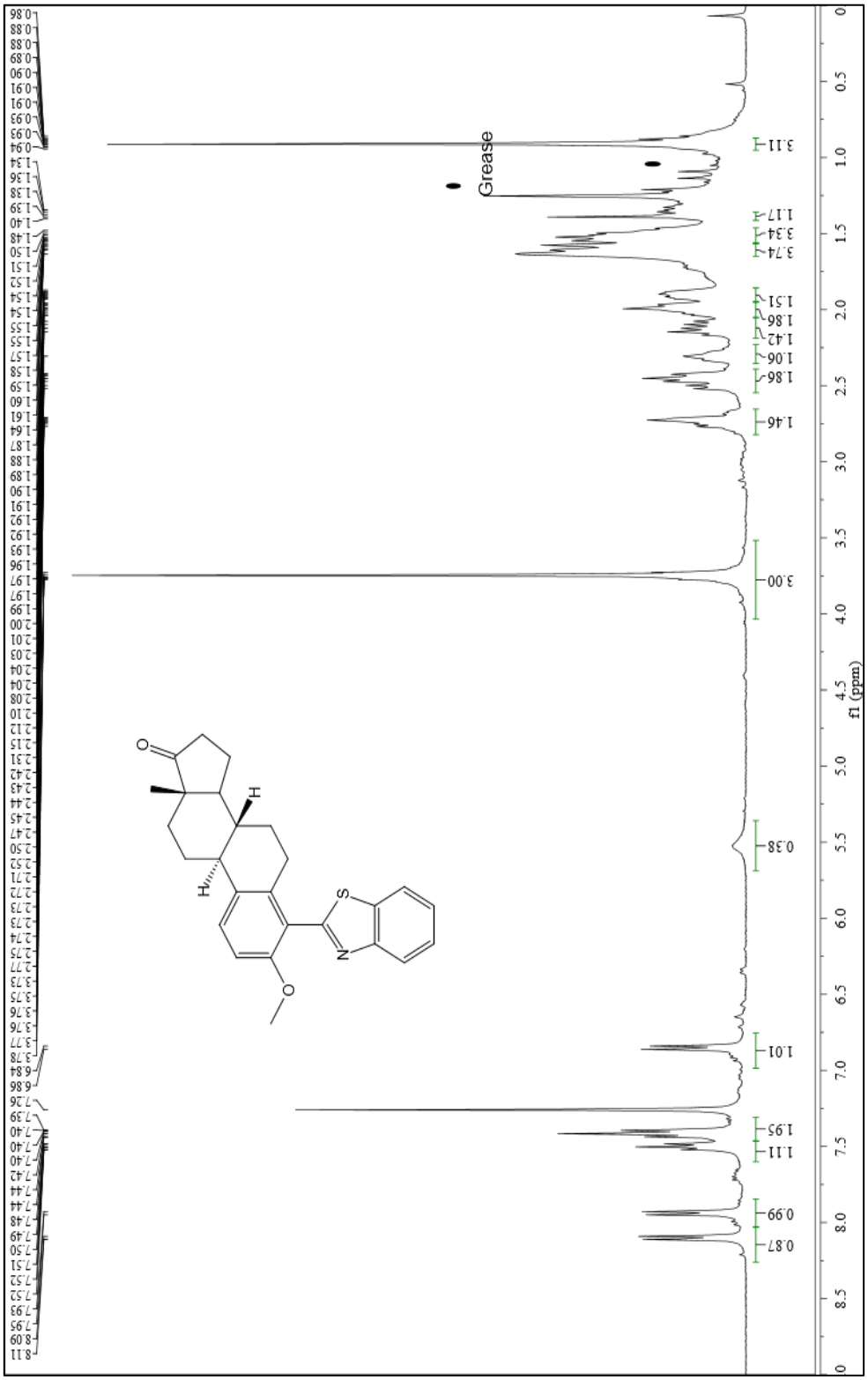
36x) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(6-fluoro-1H-indol-2-yl)benzo[d]thiazole



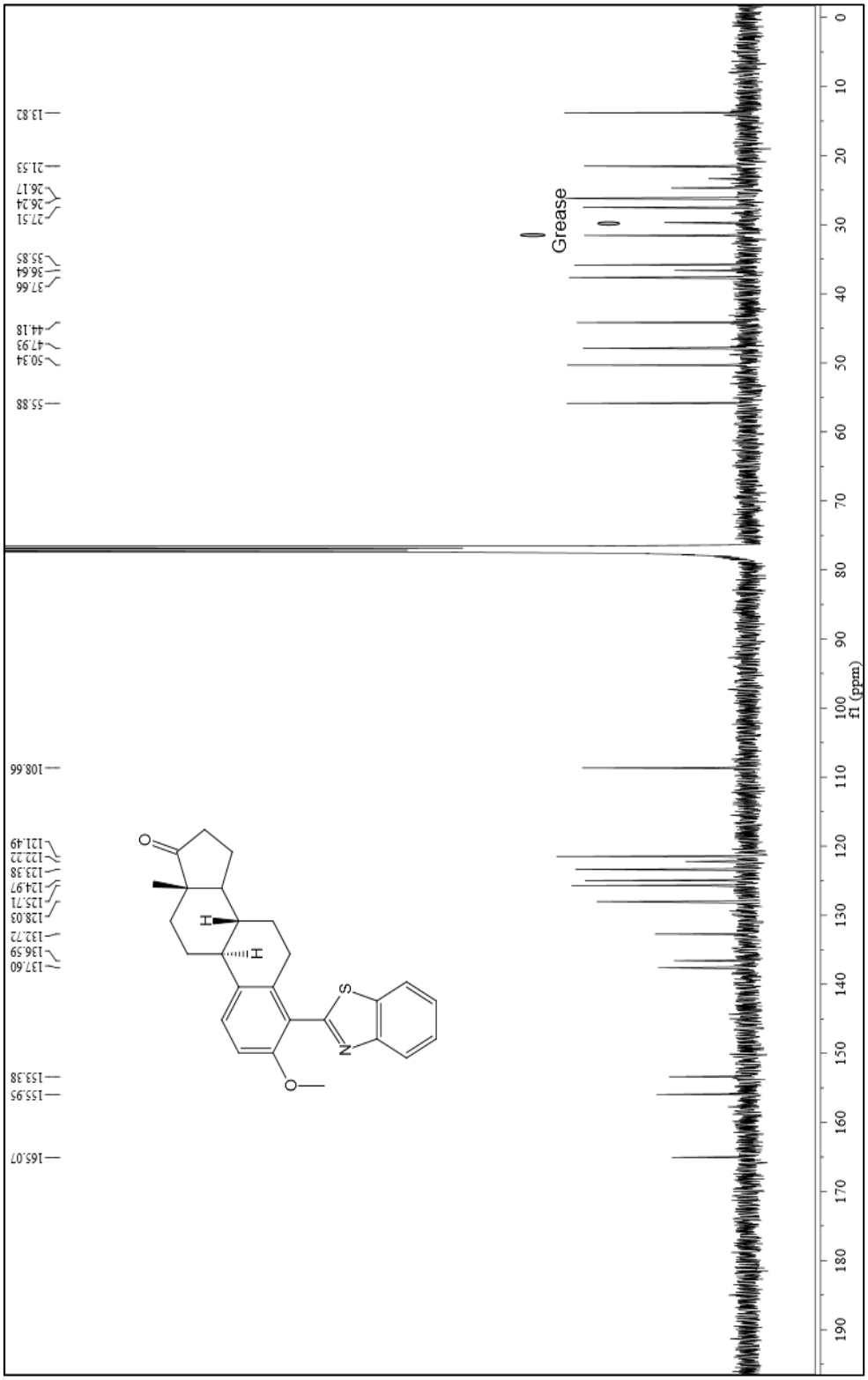
36x) ^{19}F NMR (376 MHz, $CDCl_3$) 2-(6-fluoro-1H-indol-2-yl)benzo[d]thiazole



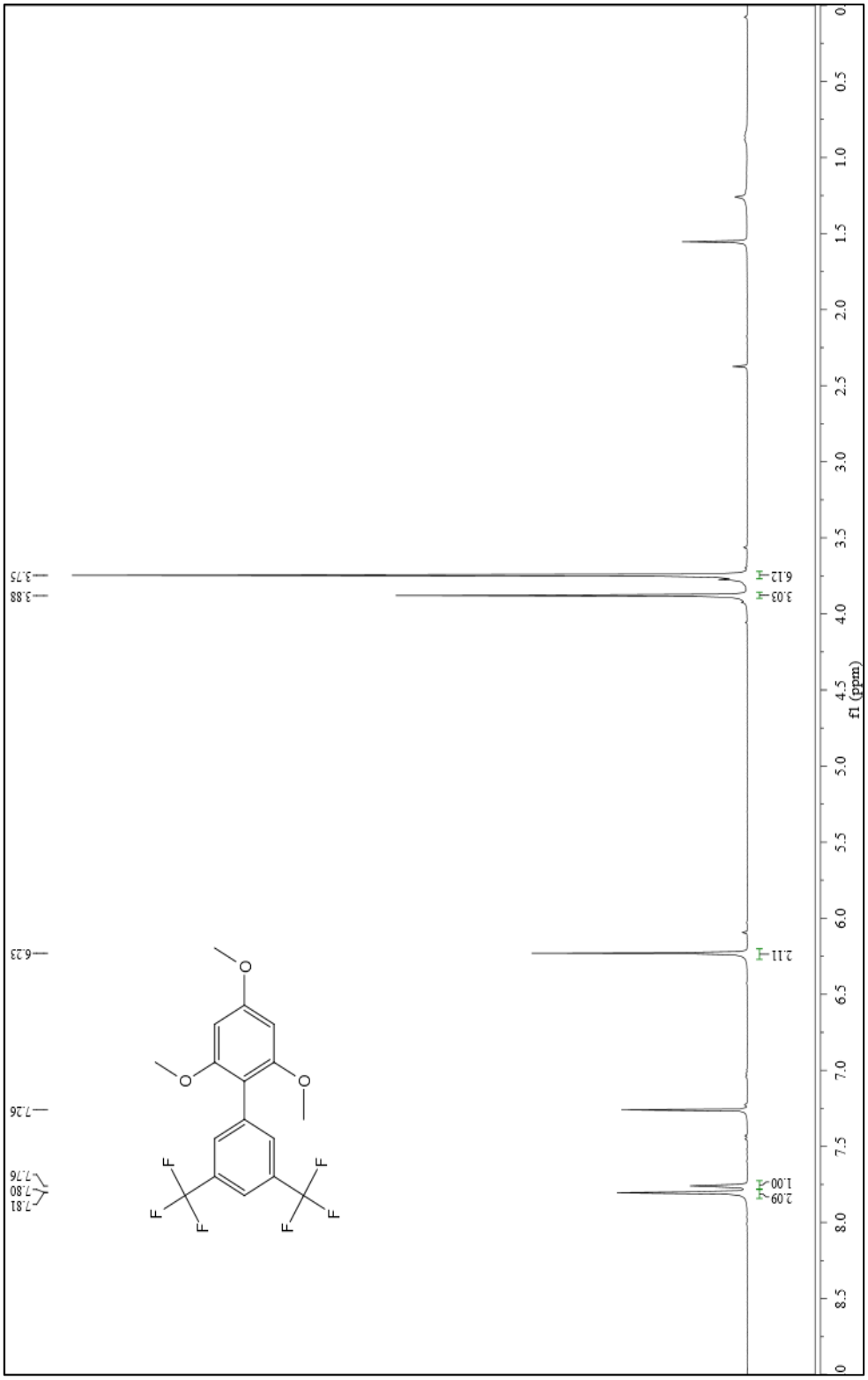
36y) ^{1}H NMR (400 MHz, $CDCl_3$) (8R,9S,13S)-2-(benzo[d]thiazol-2-yl)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one **(major)**



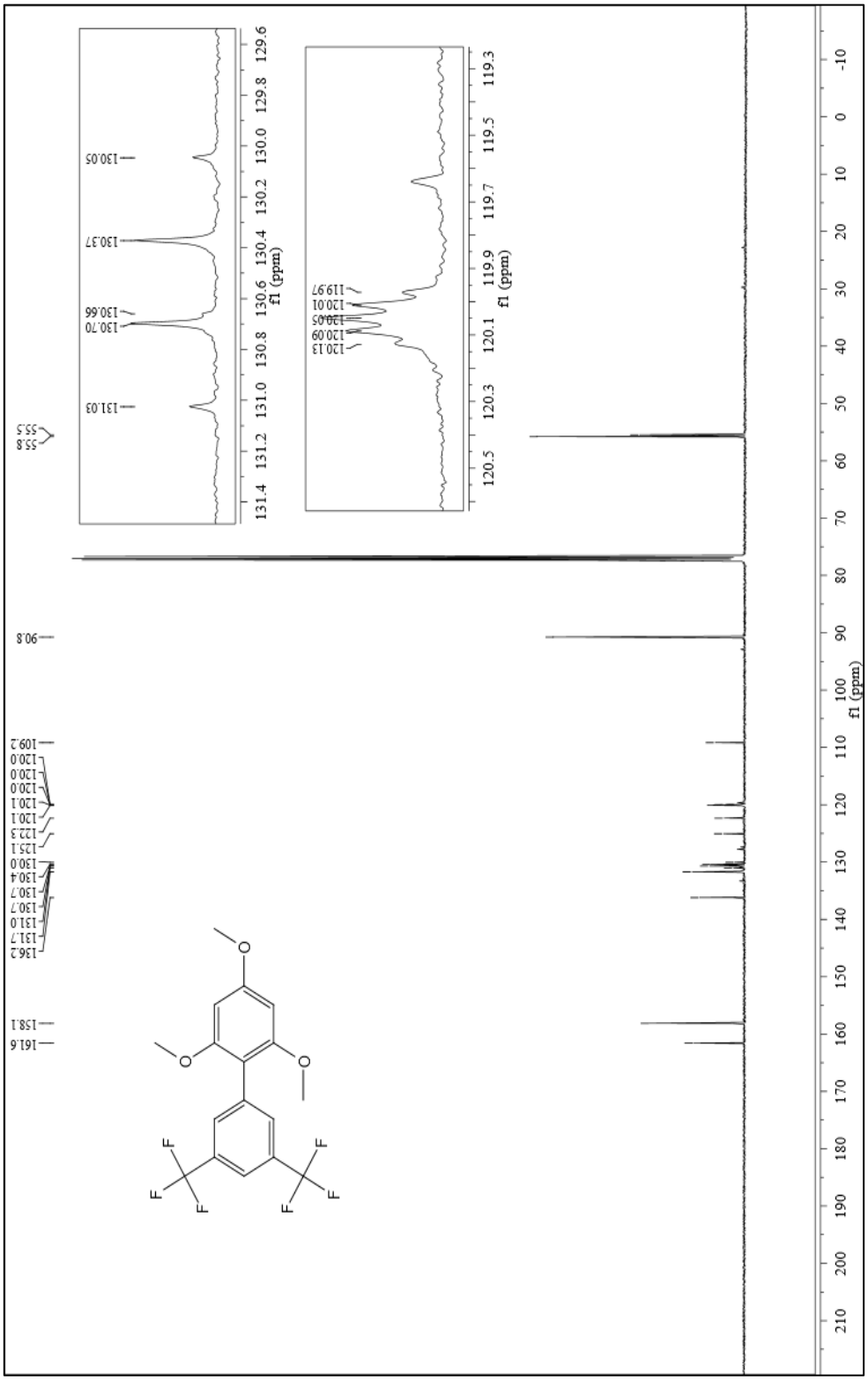
36y) ^{13}C NMR (101 MHz, $CDCl_3$) (8R,9S,13S)-2-(benzo[d]thiazol-2-yl)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one **(major)**



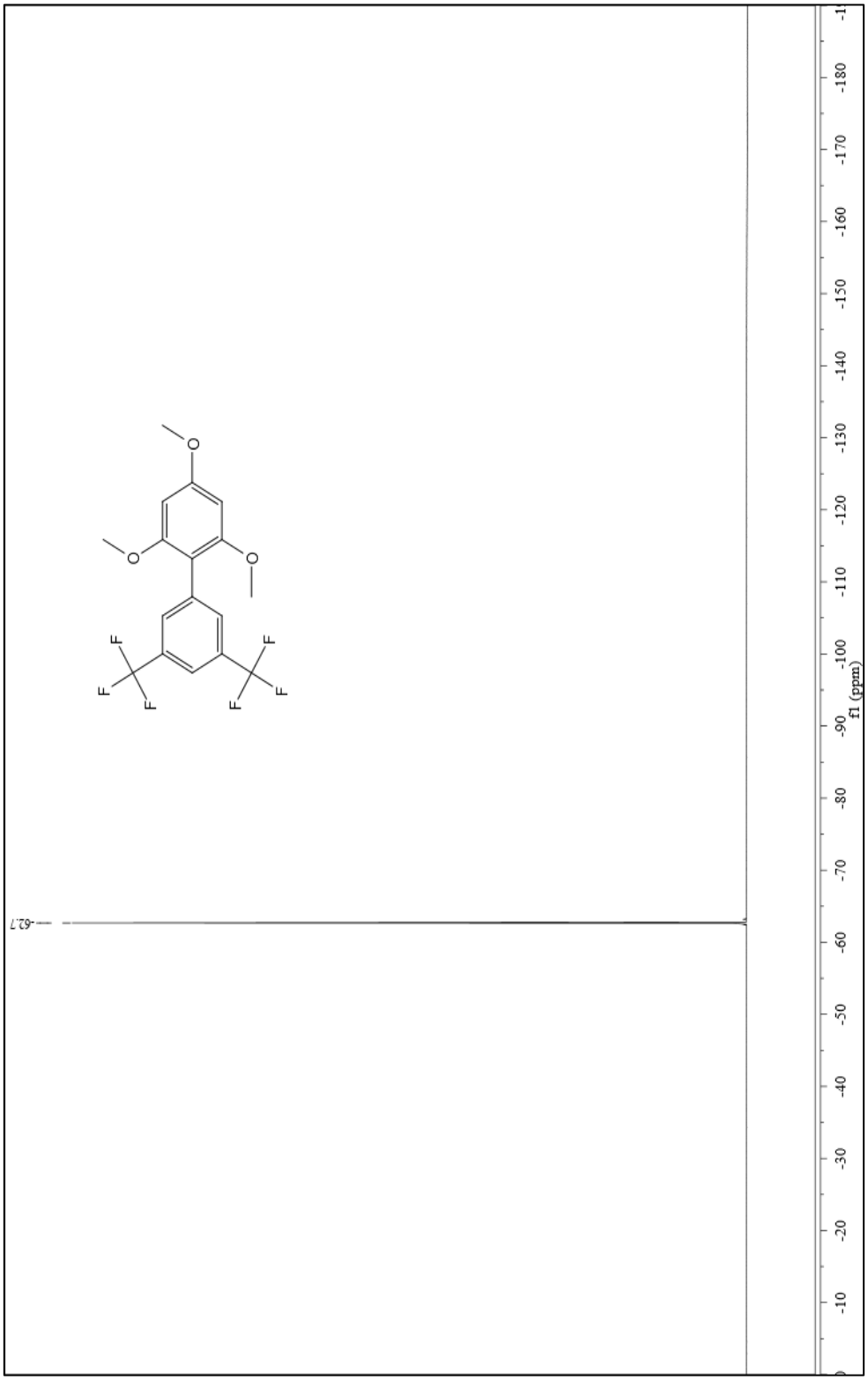
37a) ^{1}H NMR (400 MHz, $CDCl_3$) 2,4,6-trimethoxy-3',5'-bis(trifluoromethyl)-1,1'-biphenyl



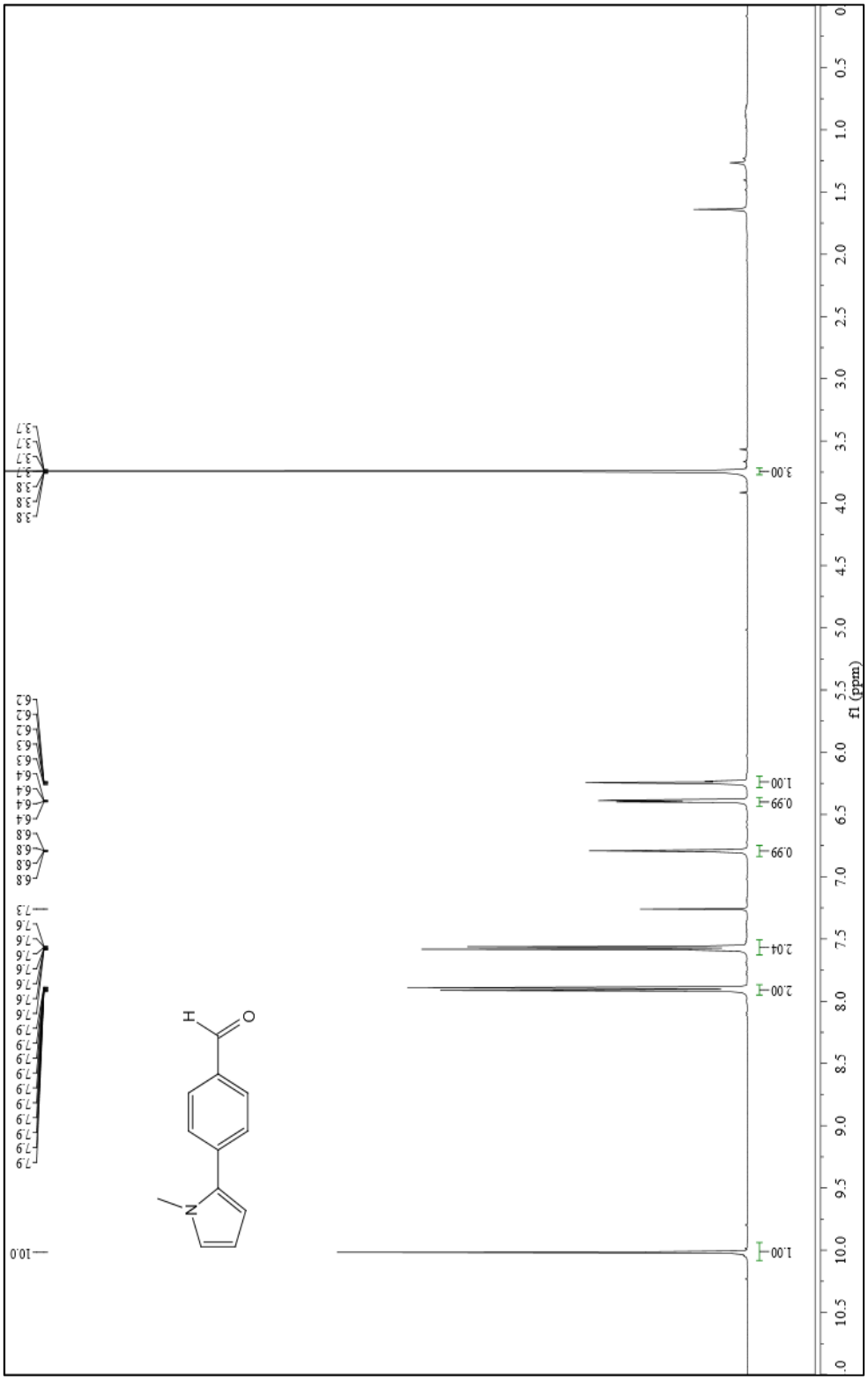
37a) ^{13}C NMR (101 MHz, $CDCl_3$) 2,4,6-trimethoxy-3',5'-bis(trifluoromethyl)-1,1'-biphenyl



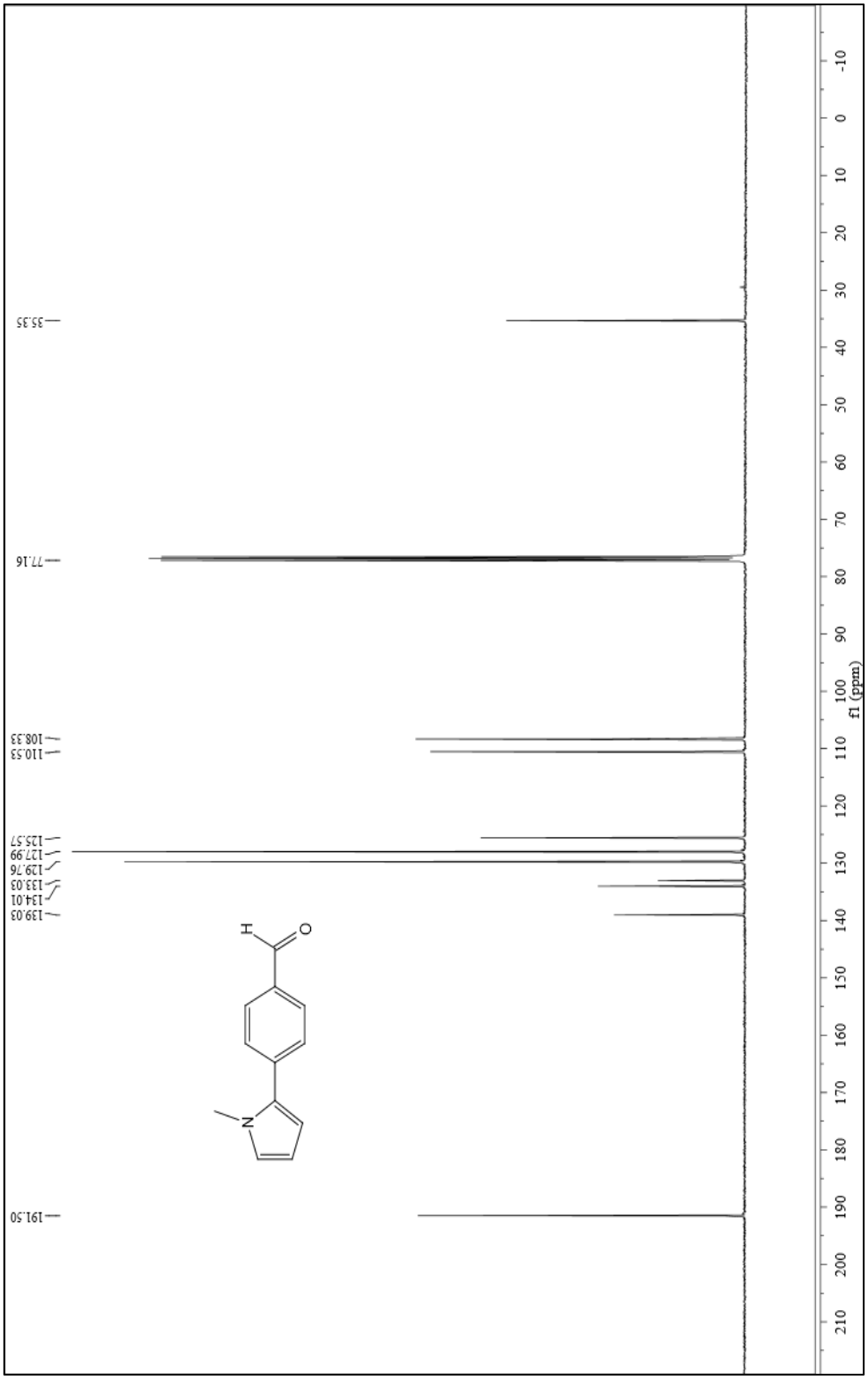
37a) ^{19}F NMR (376 MHz, $CDCl_3$**)** 2,4,6-trimethoxy-3',5'-bis(trifluoromethyl)-1,1'-biphenyl



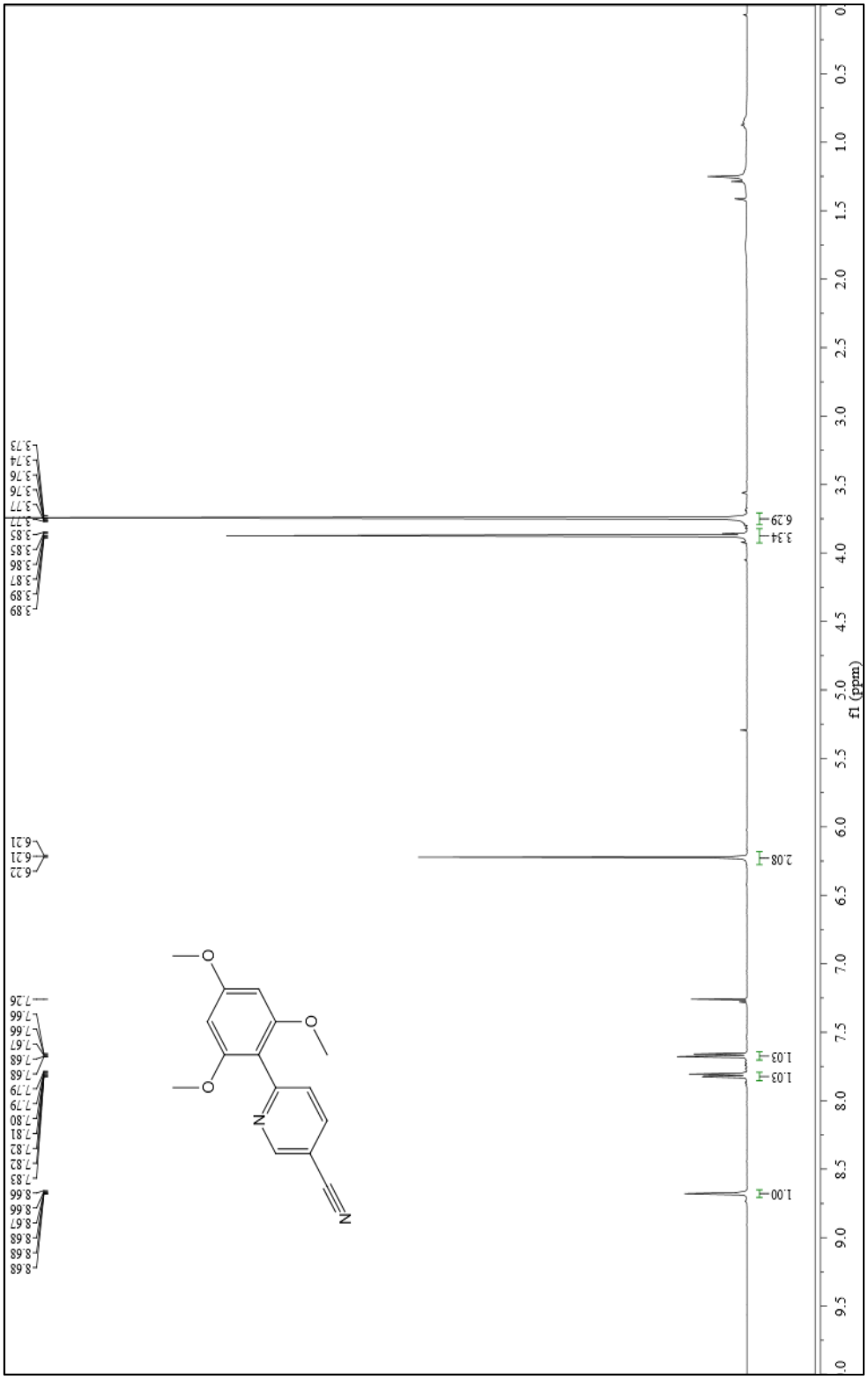
37b) ^{1}H NMR (400 MHz, $CDCl_3$) 4-(1-methyl-1H-pyrrol-2-yl)benzaldehyde



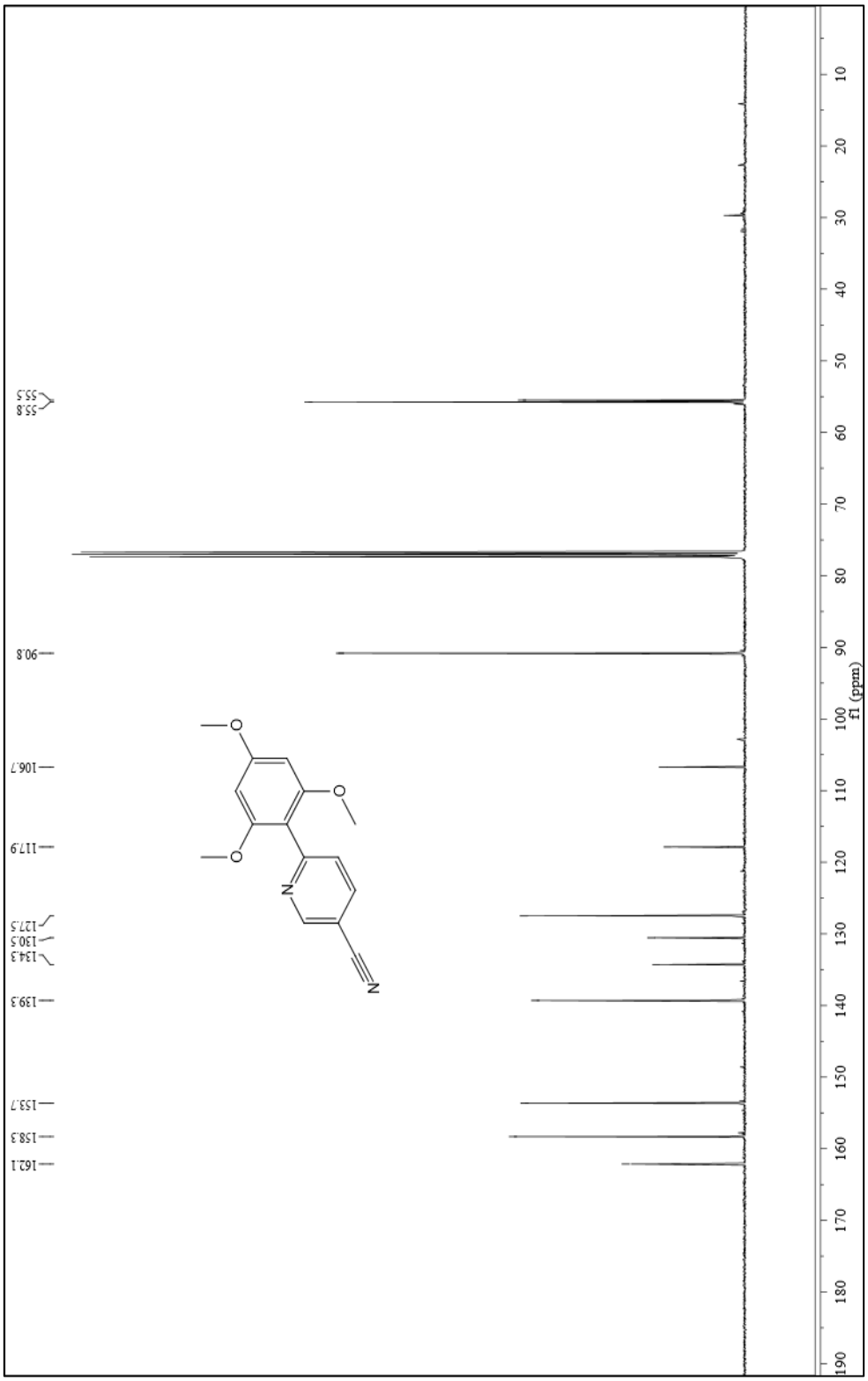
37b) ^{13}C NMR (101 MHz, $CDCl_3$) 4-(1-methyl-1H-pyrrol-2-yl)benzaldehyde



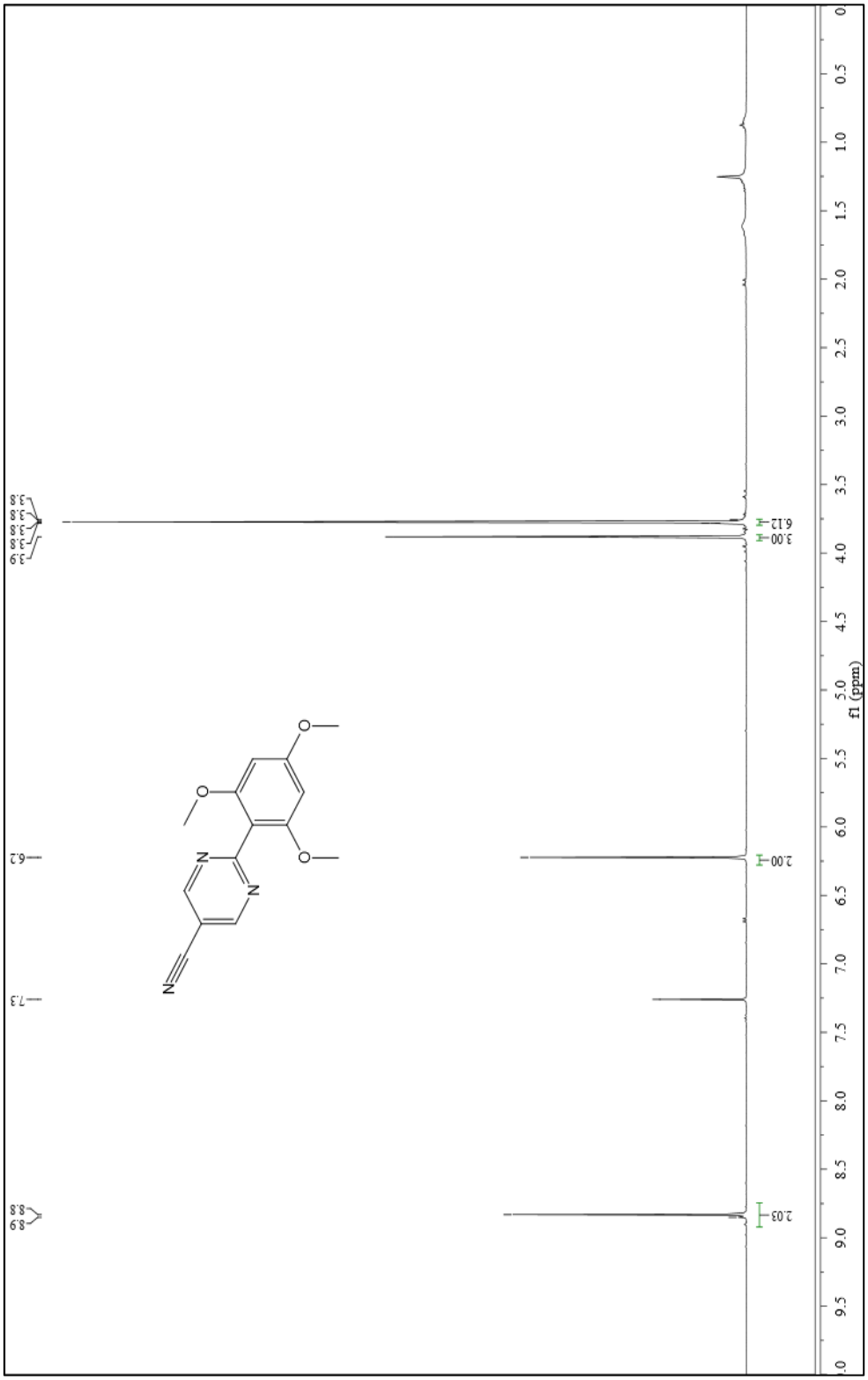
37c) ^{1}H NMR (400 MHz, $CDCl_3$) 6-(2,4,6-trimethoxyphenyl)nicotinonitrile



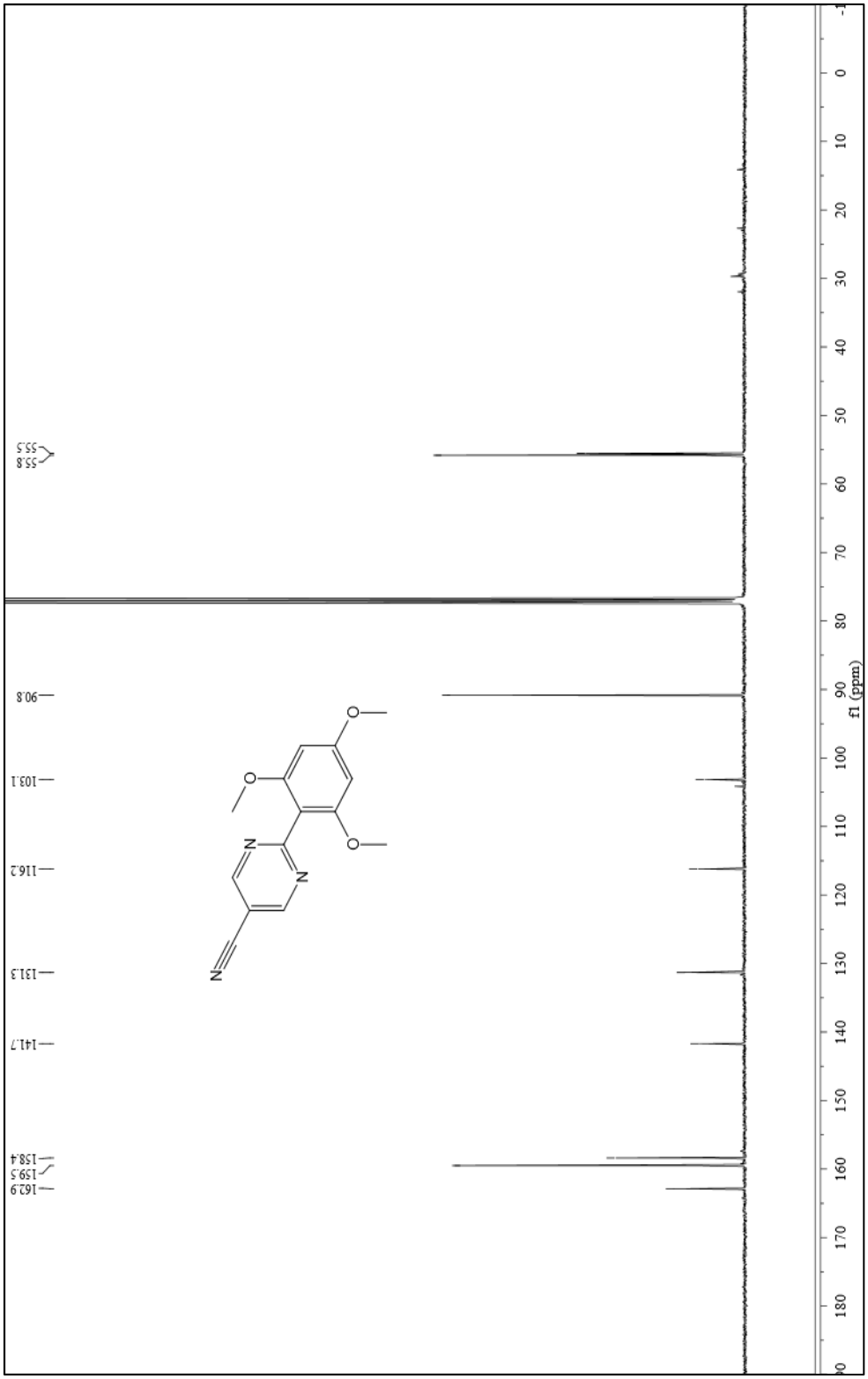
37c) ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) 6-(2,4,6-trimethoxyphenyl)nicotinonitrile



37d) ^{1}H NMR (400 MHz, $CDCl_3$) 2-(2,4,6-trimethoxyphenyl)pyrimidine-5-carbonitrile



37d) ^{13}C NMR (101 MHz, $CDCl_3$) 2-(2,4,6-trimethoxyphenyl)pyrimidine-5-carbonitrile



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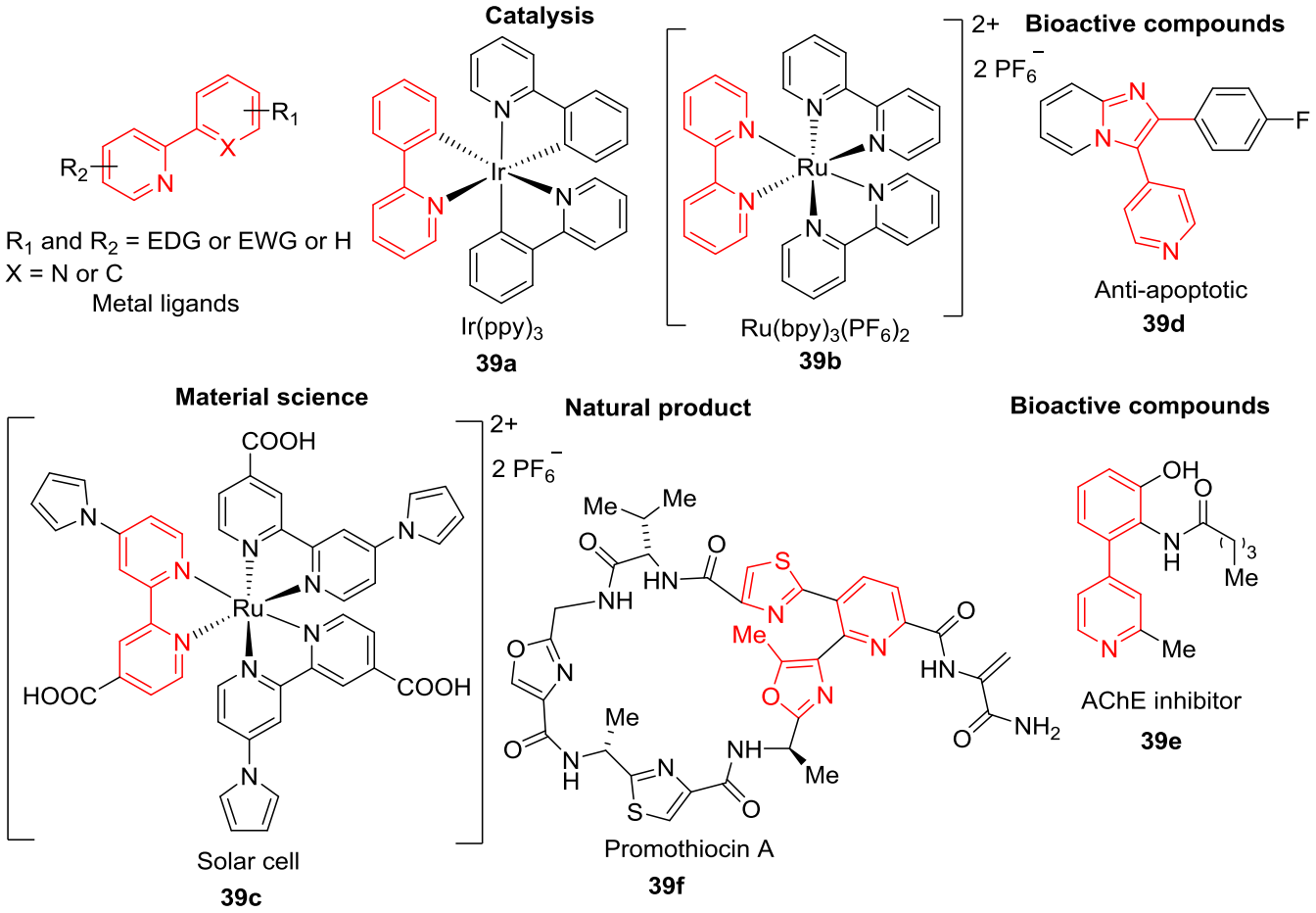
CHAPTER VI

DIRECT C–H ARYLATION OF ELECTRON DEFICIENT HETEROCYCLES

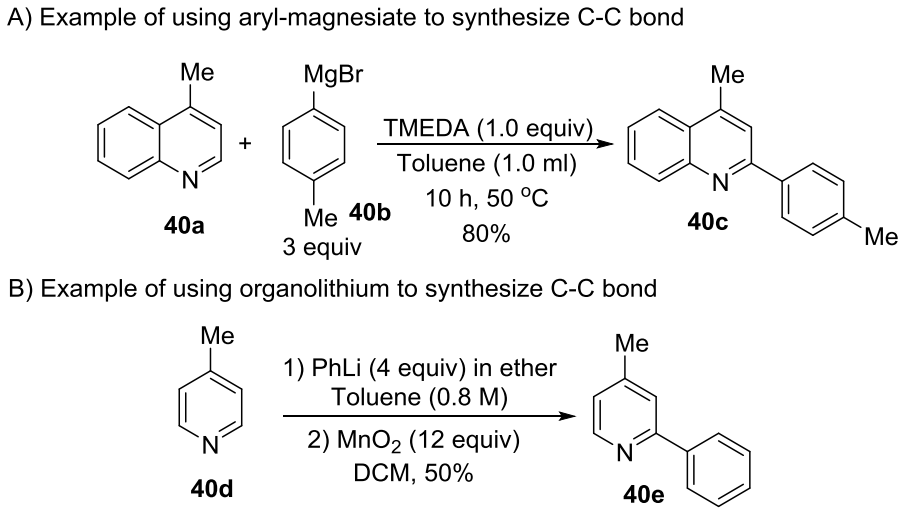
Expanding our efforts to study the intermediates that can be generated via the transfer of an electron to halogenated-, or pseudo halogenated-arenes, we turned our attention to aryl and heteroaryl diazonium salts. Aryl diazonium salts have attracted much interest over the years because of their applications in aromatic substitution reactions,[1] as well as precursors of aryl radicals.[2] In addition, diazonium salts are also highly useful in the dye and pigment industry for the preparation of azo-compounds.[3] The latter case is a little different because it is actually the nitrogen atom that is attacked to generate diazo compounds, whereas in the former the N_2 serves as a leaving group. The diazonium salts are generally prepared via nitrosation of primary aromatic amines with nitrous acid, which is generated *in situ* from sodium nitrite and a strong acid, such as hydrochloric, sulfuric acid, or HBF_4. The diazonium salt can be isolated if the counterion is non-nucleophilic, i.e. BF_4^-. One limitation to diazonium chemistry is that aliphatic and aryl diazonium salts are difficult to handle and store because of their reactive nature. In fact, this entire class of salts is often viewed to pose enough of a general explosion hazard that many industries will not use them on larger scale.[4] However, the use of flow chemistry, which can help mitigate the risks by keeping concentrations low, and on-demand synthesis has created some opportunity for diazonium chemistry on the industrial scale.[5] Nonetheless, often handling of isolated diazoniums can be tricky, because even when stored cold, and away from light, some decomposition is observed, which can make using them operationally difficult.

The target molecules of this chapter, which contain a pyridine core, are important because of their wide application in a number of chemical areas (Scheme 39). In the field of coordination chemistry, phenylpyridine **39a**, and bipyridines **39b** are prototypical ligands that can be used to chelate metal centers.[6] For example, these complexes have been widely used in the synthesis of photoredox catalysts by their coordination to Ir and Ru centers.[7] Additionally, these ligands have been studied for their ability to facilitate access to spin-crossover behavior in the *tris*-homoleptic Fe(II) complexes.[8, 9] Bipyridines are also involved in materials and supramolecular structures such as solar cells **39c**.[10] They also play an important role in biologicaly active molecules such as anti-apoptotic **39d**[11] and AChE inhibitor **39e**[12] and are also frequently observed in natural products **39f**.[13] Not surprisingly, due to their importance, there has been a good deal of effort to synthesize aryl pyridines.



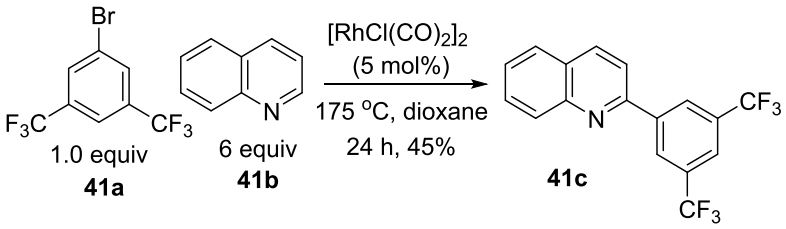
Scheme 39. Representative examples of important pyridine derivatives.

The most common method employed to synthesize these molecules is to arylate electron-deficient *N*-heterocycles *via* the direct addition of an aryl-magnesium (Scheme 40A),[14] or aryllithium reagents (Scheme 40B),[15] which add to the most electrophilic 2-(or 4)-position. This leads to a dearomatized species, which must be oxidized in order to achieve rearomatization.[16,17,18] However, while some exceptions exist, these methods often suffer from low to moderate yields, and have low functional group compatibility.



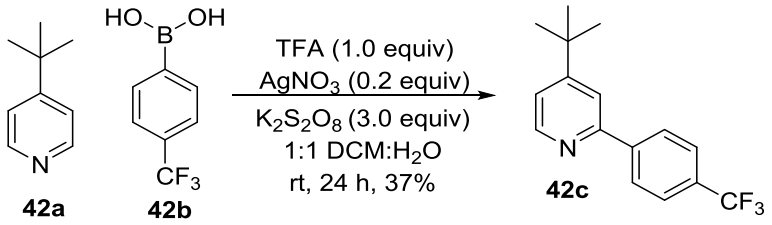
Scheme 40. Representative examples of using aryl-metallate to synthesize C–C bond in electron deficient heteroarenes.

More recently, efforts have been made to achieve a catalytic C–H arylation (Scheme 41).[19] Ellman and Bergman have shown that an aryl-bromide can be coupled to the 2-position of a quinoline **41b**. This process is thought to take place by insertion into the 2 C–H bond of the quinoline and oxidative addition of the bromoarene **41a**. However, the process is quite sluggish as it requires very high temperatures (175 °C), which results in some limitations to the scope.



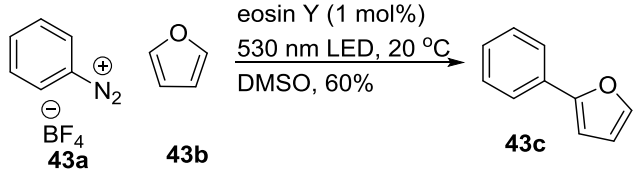
Scheme 41. Ellman and Bergmans' work on catalytic arylation.

In 2010, Baran demonstrated the direct arylation of electron-deficient heteroarenes **42a** (Scheme 42) with arylboronic acids **42b**.[20] The reaction proceeds at room temperature using catalytic silver (I) nitrate in the presence of a persulfate cooxidant. It was proposed that the aryl C–B was converted to an aryl radical as the intermediate. This method was tolerant to a variety of substituted heteroarenes as well as arylboronic acids. However, this method suffers from low to moderate yields, and modest selectivity, and is challenging to scale up. Despite the shortcomings, it does highlight the ability to couple the pyridine via a radical addition, similar to the Minisci reaction,[21] which typically involves the addition of alkyl radicals to electron deficient heteroarenes.



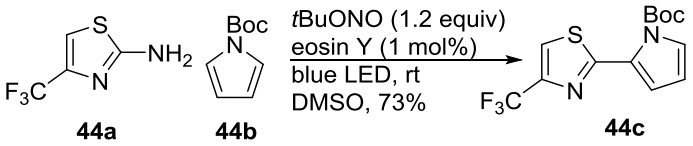
Scheme 42. Baran's work on C–H arylation of electron deficient heteroarenes with aryl boronic acids.

Recently, König has utilized pre-synthesized aryldiazonium salts **43a** (Scheme 43) to accomplish a photoredox mediated direct C−H arylation of electron-rich (hetero)arenes **43c**.[22] Presumably, this reaction begins by photocatalyzed electron transfer to the aryl diazonium, which results in extrusion of the N_2, and the formation of an aryl radical. The aryl radical then attacks the π-system of the electron rich arene to form a new C–C bond. The process of C–C bond formation dearomatizes the arene. Loss of an electron and a proton restores aromaticity, and provides the necessary electron for the next cycle. The scope of this reaction seems to be limited only to highly reactive electron rich arenes, i.e. furan, thiophene, pyrroles.



Scheme 43. König's work on C–H arylation.

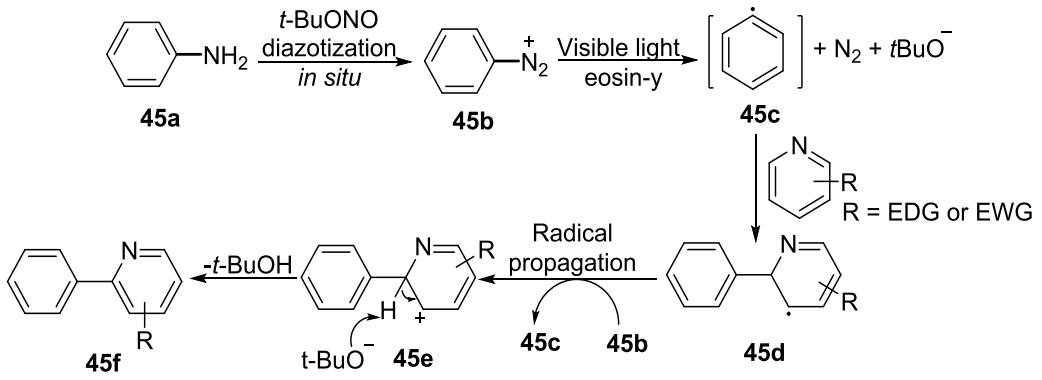
In general, diazonium salts are reactive in nature, and their handling and storage is not trivial. To circumvent this issue, Ranu[23] showed a method for the *in situ* diazotization of anilines **44a** to give diazoniums, that could be utilized with a photoredox catalyst to generate the aryl radical, and that this aryl radical was capable of subsequent addition to electron rich arene-Hs **44b**, analogous to König's work.



Scheme 44. Ranu's work on C–H arylation using *tert*-butylnitrite

However, with respect to electron-deficient *N*-heterocycles, very few methods for direct phototcatalytic C−H arylation are available.[24] Therefore, we sought to develop a mild C–H arylation of *electron deficient heterocycles* (Scheme 45) that would utilize *in situ* nitrosation of anilines as a facile route to generate aryl radicals **45b**.[23] Specifically, the mild and controlled generation of the aryl radical from widely available starting amines would be immensely enabling. At the outset, it was conceivable to use either the arene or the heteroarene as the radical, we ultimately chose the arene as the precursor to the aryl radical for two reasons. First, aryl amines are more widely available. Second, generally speaking the electronic difference between the C–Hs in arenes is small, whereas, in heteroarenes, the C–Hs are polarized by the presence of the heteroatom. Furthermore, protonation of the heterocycle can lead to even greater polarization and distinction of the C–Hs, which was expected to result in regioselective C–C bond formation.

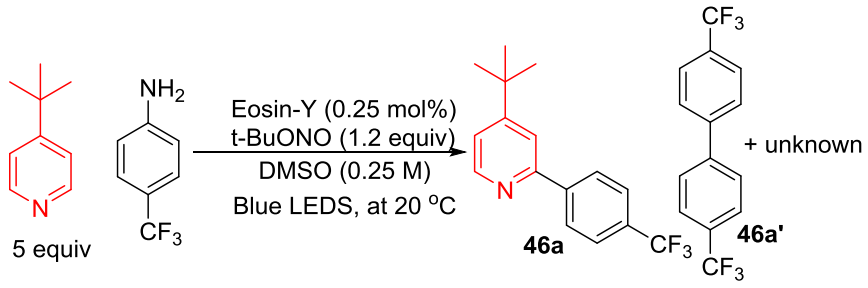
The use of the diazonium salts as precursors to radicals could be advantageous in terms of providing greater selectivity and functional group tolerance in the reaction, since a less reducing photocatalyst would be needed to reduce the diazonium. In addition, no amine reductant would be needed for the reaction, which in the case of aryl halides, often leads to competitive formation of undesired reduction products.



Scheme 45. Proposed strategy for C–H arylation of electron deficient heterocycles.

6.1. Optimization of the reaction conditions

We started our studies with 4-(trifluoromethyl)aniline, 4-*tert*-butylpyridine, *tert*-butyl nitrite (a nitrosating agent), and catalytic eosin-Y^{2-} (Scheme 46, entry 1). We found 47% NMR conversion to the desired product **46a**. The mass balance includes radical–radical homocoupled aniline **46a'**. Initial solvent screening (entry 2 to 4 *vs* 1) revealed that MeCN, and DCM gave low conversion (20%) to desired product **46a**, while polar protic MeOH, and polar aprotic DMF gave high conversions, but only to the reduced product of the starting aniline (i.e. trifluoromethyl toluene).[25] We did not observe any reaction in benzene and toluene. Thus, we chose DMSO as the solvent for further optimization. In addition to solvent, we explored the amount of arene-H required in the reaction. Consistent with a process in which there is a competition between radical-radical homocoupled product **46a'** and hetero-coupled desired product **46a**, increased concentration of heteroarene-H led to increased amount of desired product (entry 1 *vs* entries 5, 6 and 7). The effect of concentration on the outcome of the reaction was also evaluated. Decreasing the concentration from 0.25 M to 0.05 M (entry 8 *vs* entry 1) led to substantial decrease in the formation of desired product. However, further increase in the concentration of the reaction mixture showed little improvement (entry 9 vs entry 7). Using 0.25 mol% of eosin-y, 10 equiv of arene-H, and *t*BuONO (1.2 equiv) in DMSO (0.5 M), we obtained 49% yield of **46a**.



Entry	Modification	Conversion	Product (**46a**:**46a**':unknown)	Time (h)
1	None	100%	47:33:20	12
2	MeCN, DCM	20%	5:5:10	14
3	DMF, MeOH	100%	Reduction of aniline	14
4	Toluene, Benzene	0%	-	14
5	2.5 equiv of arene-H	100%	20:50:30	13
6	7 equiv of arene-H	100%	52:32:16	13
7	10 equiv of arene-H	100%	57:29:14	13
8	0.05 M conc.	100%	27:30:43	15
9[b]	0.5 M conc.	100%	58:25:17	15

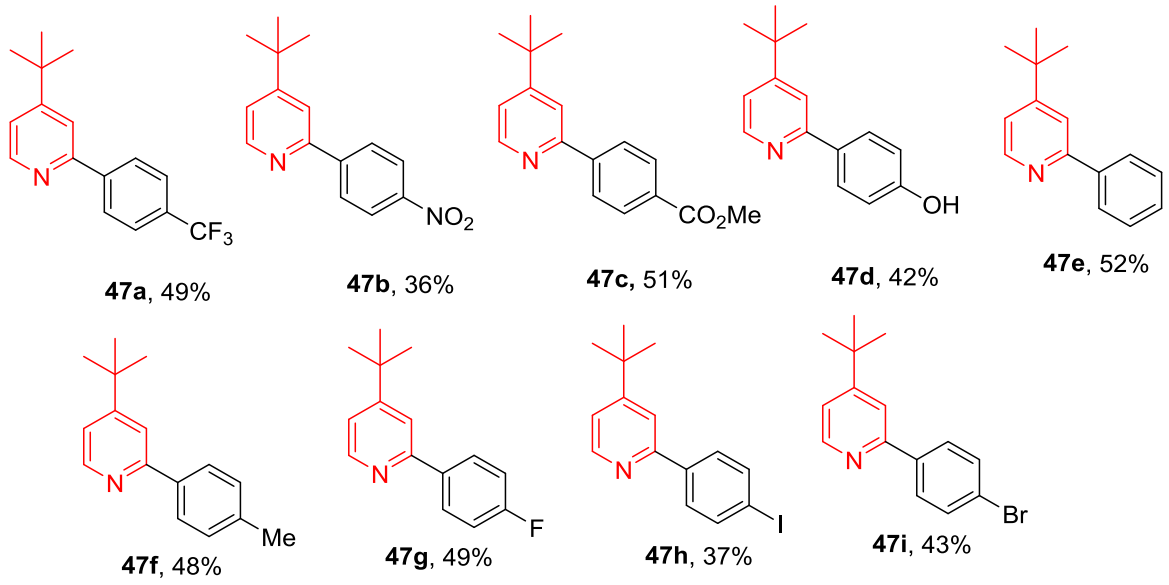
conversions are calculated by using ^{19}FNMR, [b]10 equiv of heteroarene-H was utilized.

Scheme 46. Determination of the optimal conditions**.**

6.2 Scope of the reaction

The relatively modest yield, 49%, for **47a** is less than ideal, but given the simplicity and ubiquity of the starting materials, we moved forward. With conditions in hand, we began to explore the scope of the reaction (Scheme 47). To our delight, reaction conditions worked well with aniline substrates containing an electron-donating methyl group **47f**, a neutral aniline **46e**, and an electron withdrawing groups CF_3, NO_2, and CO_2Me **47a**, **47b**, and **47c**, all resulting in moderate yields. Reaction conditions proved tolerant to a number of functional groups such as unprotected phenols **47d**, esters **47c**. Even aryl bromides **47i** and iodides **47h** which are prone to photocatalytic reduction[26] were well tolerated, and highlight the chemoselectivity of the reaction.

Initial scope of the reaction



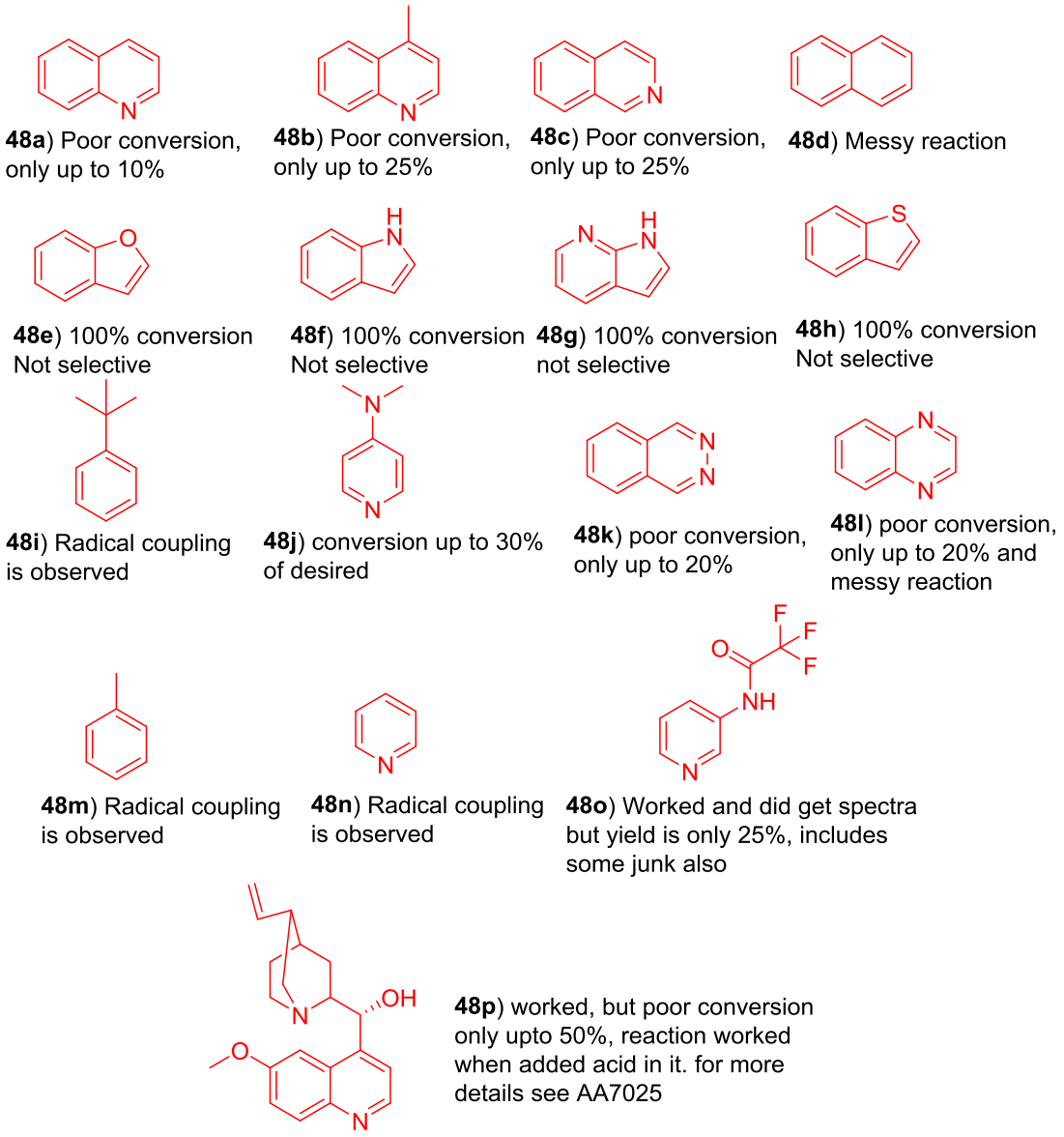
In all above case,yields are isolated and structures are confirmed by ^{1}HNMR, ^{13}CNMR and ^{19}FNMR

Scheme 47. Initial investigation of the scope of the reaction

6.3 List of poorly working substrates

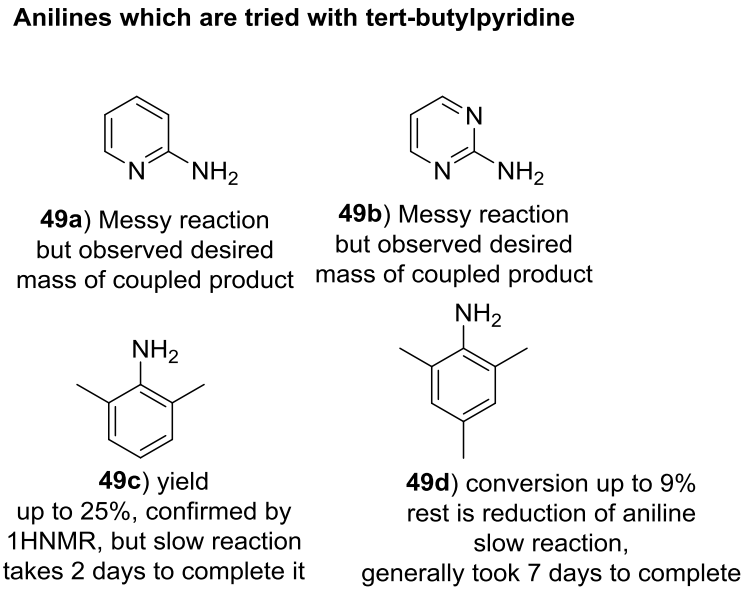
A variety of heteroarenes other than 4-*tert*-butylpyridine were tested under these reaction conditions (Scheme 48). In quinoline type substrates such as **48a**, **48b**, **48c**, **48k, 48l, 48j, 48o** and **48p** we observed desired product in a very low conversion. In the future, it will be worthwhile to try these reactions in the presence of an acid such as TFA, which is believed to activate basic heteroarenes.[24a] Other substrates such as **48i**, and **48m**, which do not contain any heteroatoms were also tried under the optimized reaction conditions. In these cases, only homocoupling of starting aniline was observed. Arguably, the exploration of the scope of this reaction is still in its infancy. It should be noted that, to date, no serious attempt has been made to improve, or understand, these poor-yielding reactions.

a) Other heteroarenes when tried with4-trifluoro-2-aminobenzene including poorly working or need to be isolated



Scheme. 48. List of other heteroarenes and anilines tried in the reaction.

Heteroaromatic amines such as **49a** and **49b** and electron rich aniline derivatives **49c**, and **49d** were also tried in the reaction conditions. In both of these cases, the desired coupled product was observed by compact mass spectrometer (CMS), but in the former, the reactions were not clean, and in the latter the reactions were very sluggish. In the future, it will be worthwhile to look at the quantification and isolation to confirm their desired structures.



Scheme 49. List of heteroaromatic and aromatic anilines tried in the reaction.

6.4 Future directions

This project is still ongoing within the lab, and future directions will look at more optimization reactions, including experiments aimed at understanding the effect of acid on the rate and conversion to the products. In this context, different acids with varying pK_a values and also various equivalents of the acid will be tested under the reaction conditions. Other future studies will be aimed at understanding the effect of the light source, i.e. blue LEDs vs. green LEDs. Eosin-Y^{2-} absorbs visible light in the green light region (λ_{max}=539 nm) as compared to the blue light region. It might be possible that changing the light source could further improve the conversion to desired product, as many of the diazonium salts are colored and could potentially engage in uncatalyzed photochemistry which might lead to undesired side reactions. Further, expanding the scope of the substrates to heteroarenes and heteroaromatic amines, characterizing the products, as well as further study of some of the reactions that are proving challenging are all experiments which are planned.

6.5 Acknowledgment

Undergraduate Ms. Rokaya El Mokadem has performed the synthesis and isolation of **47d**, **47f**, **47g** and **47h** in Scheme 47, and will continue to further investigations.

6.6 Experimental

Anilines and other arene-H utilized were purchased from Sigma-Aldrich, Oakwood Chemicals, VWR chemicals as well as from Fisher Scientific Ltd. *tert*-butylnitrite and eosin-Y was purchased from Sigma-Aldrich. Reactions were monitored by thin layer chromatography (TLC), on Sorbent Technology Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm and were visualized with ultraviolet light and ^{1}H NMR.

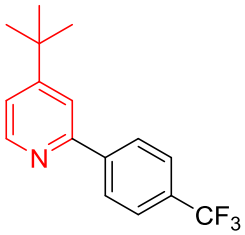
Photocatalytic reactions were set up in a light bath as described below. Blue LEDs (in the form of strips *i.e.*, 18 LEDs/ft from Solid Apollo) were wrapped around the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rest on the top was fashioned from cardboard and holes were made such that reaction tubes were held firmly in the cardboard lid which was placed on the top of bath. Water was added to the bath such that the tubes were submerged in the water which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat. Purifications were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and evaporative light scattering detection. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^{1}H, ^{13}C).

General procedure A for the photocatalytic reaction

A 12×75 mm borosilicate tube fitted with a rubber septum was charged with 2′,4′,5′,7′-tetrabromofluorescein, eosin-y (0.0025 equiv, X mL of 0.15 mM stock solution of catalyst in DMSO, where X mL of DMSO is used to make 0.5 M with respect to the aniline), aniline (1 equiv), arene-H (10 equiv) and *tert*-butylnitrite (1.2 equiv), and the reaction mixture was set up in the presence of air. The tube was placed in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 22 ^{o}C. The reaction was monitored by TLC, GC-MS and ^{1}H NMR. After the complete consumption of aniline, reaction mixture diluted with ethyl acetate (EtOAc) and washed with

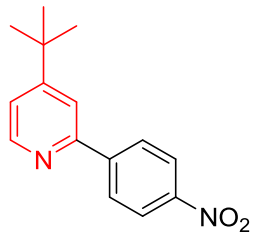
dI water (two times), then again reextracted the water layer with EtOAc (three times). In every step of workup, each layer is checked with CMS spectrometer to avoid the loss of the product in water layer. The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified via normal phase chromatography.

47a) 4-(tert-butyl)-2-(4-(trifluoromethyl)phenyl)pyridine



The **general procedure A** was followed using 4-(trifluoromethyl)aniline (40 mg, 0.25 mmol), *tert*-butylpyridine (337 mg, 2.5 mmol), *tert*-butylnitrite (31 mg, 0.3 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **47a** in 49% yield (33 mg, 0.12 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 5.2, 0.7 Hz, 1H), 8.15 – 8.03 (m, 2H), 7.75 – 7.69 (m, 3H), 7.30 (dd, *J* = 5.2, 1.8 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 156.1, 149.9, 143.5, 130.9, 130.6, 130.2, 127.5, 125.8 (q, *J* = 3.7 Hz), 123.0, 120.3, 118.2, 35.1, 30.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.53.

47b) 4-(tert-butyl)-2-(4-nitrophenyl)pyridine



The **general procedure A** was followed using 4-nitroaniline (100 mg, 0.72 mmol), tert-butylpyridine (979 mg, 7.24 mmol), *tert*-butylnitrite (89 mg, 0.864 mmol) and 1.4 mL of stock solution of eosin-y in DMSO was used to afford **47b** in 36% yield (66 mg, 0.26 mmol) as a yellow solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 20% on a 12 g silica column. ^{1}H NMR (400 MHz, CDCl3) δ 8.65 (d, J = 5.2 Hz, 1H), 8.33 (m, 2H), 8.17 (m, 2H), 7.78 (m, 1H), 7.35 (dd, J = 5.3, 1.8 Hz, 1H), 1.39 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.39, 154.94, 149.96, 148.02, 145.89, 127.81, 123.96, 120.75, 118.41, 35.01, 30.58.

47c) methyl 4-(4-(tert-butyl)pyridin-2-yl)benzoate

The **general procedure A** was followed using methyl 4-aminobenzoate (50 mg, 0.33 mmol), tert-butylpyridine (445 mg, 3.3 mmol), tert-butylnitrite (41 mg, 0.39 mmol) and 0.66 mL of stock solution of eosin-y in DMSO was used to afford **47c** in 51% yield (45 mg, 0.36 mmol) as oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 100% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.2 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.75 (s, 1H), 7.29 (dd, *J* = 5.3, 1.8 Hz, 1H), 3.95 (s, 3H), 1.38 (s, 9H).

47d) 4-(4-(tert-butyl)pyridin-2-yl)phenol

The **general procedure A** was followed using 4-aminophenol (50 mg, 0.45 mmol), tert-butylpyridine (607 mg, 4.5 mmol), tert-butylnitrite (55 mg, 0.54 mmol) and 0.9 mL of stock solution of eosin-y in DMSO was used to afford **47d** in 42% yield (43 mg, 0.189 mmol). The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.9 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 2H), 7.83 – 7.74 (m, 3H), 7.46 (d, *J* = 3.9 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 154.0, 148.0, 132.7, 128.0, 121.2, 119.1, 118.5, 113.2, 35.5, 30.5.

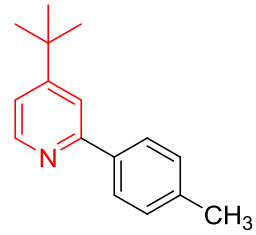
47e) 4-(tert-butyl)-2-phenylpyridine

The **general procedure A** was followed using aniline (50 mg, 0.54 mmol), tert-butylpyridine (729 mg, 5.4 mmol), tert-butylnitrite (67 mg, 0.65 mmol) and 1.1 mL of stock solution of eosin-y in DMSO was used to afford **47e** in 52% yield (59 mg, 0.28 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 100% on a 12 g silica column. ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.3 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.77 – 7.67 (m, 1H), 7.53 – 7.44 (m, 2H), 7.43 – 7.37 (m, 1H), 7.24 (dd, *J* = 5.3, 1.9 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.74, 157.55, 149.53, 140.03, 128.72, 128.68, 127.05, 119.34, 117.80, 34.88, 30.61.

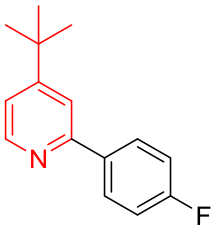
47f) 4-(tert-butyl)-2-(p-tolyl)pyridine

The **general procedure A** was followed using p-toluidine (50 mg, 0.45 mmol), tert-butylpyridine (607 mg, 0.46 mmol), tert-butylnitrite (55 mg, 0.54 mmol) and 0.9 mL of stock solution of eosin-y in DMSO was used to afford **47f** in 48 % yield (48.6 mg, 0.22 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 10% on a 12 g silica column. ^1H NMR (400 MHz, CDCl3) δ 8.57 (d, J = 4.0 Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.68 (dd, J = 1.9, 0.7 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.21 (dd, J = 5.3, 1.9 Hz, 1H), 2.41 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 160.8, 157.7, 149.5, 138.8, 137.3, 129.5, 127.0, 119.2, 117.6, 35.0, 30.7, 21.4.

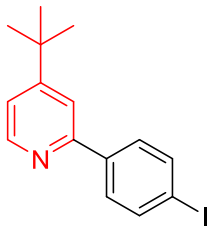


47g) 4-(tert-butyl)-2-(4-fluorophenyl)pyridine

The **general procedure A** was followed using 4-fluoroaniline (50 mg, 0.45 mmol), tert-butylpyridine (607 mg, 4.5 mmol), tert-butylnitrite (55 mg, 0.54 mmol) and 0.9 mL of stock solution of eosin-y in DMSO was used to afford **47g** in 49% yield (50.4 mg, 0.22 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 25% on a 12 g silica column. ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.3 Hz, 1H), 7.99 – 7.91 (m, 2H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.24 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.15 (t, *J* = 8.7, 8.7 Hz, 2H), 1.37 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.47.



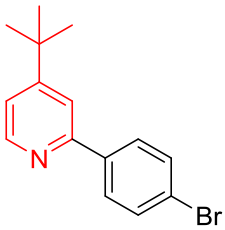
47h) 4-(tert-butyl)-2-(4-iodophenyl)pyridine



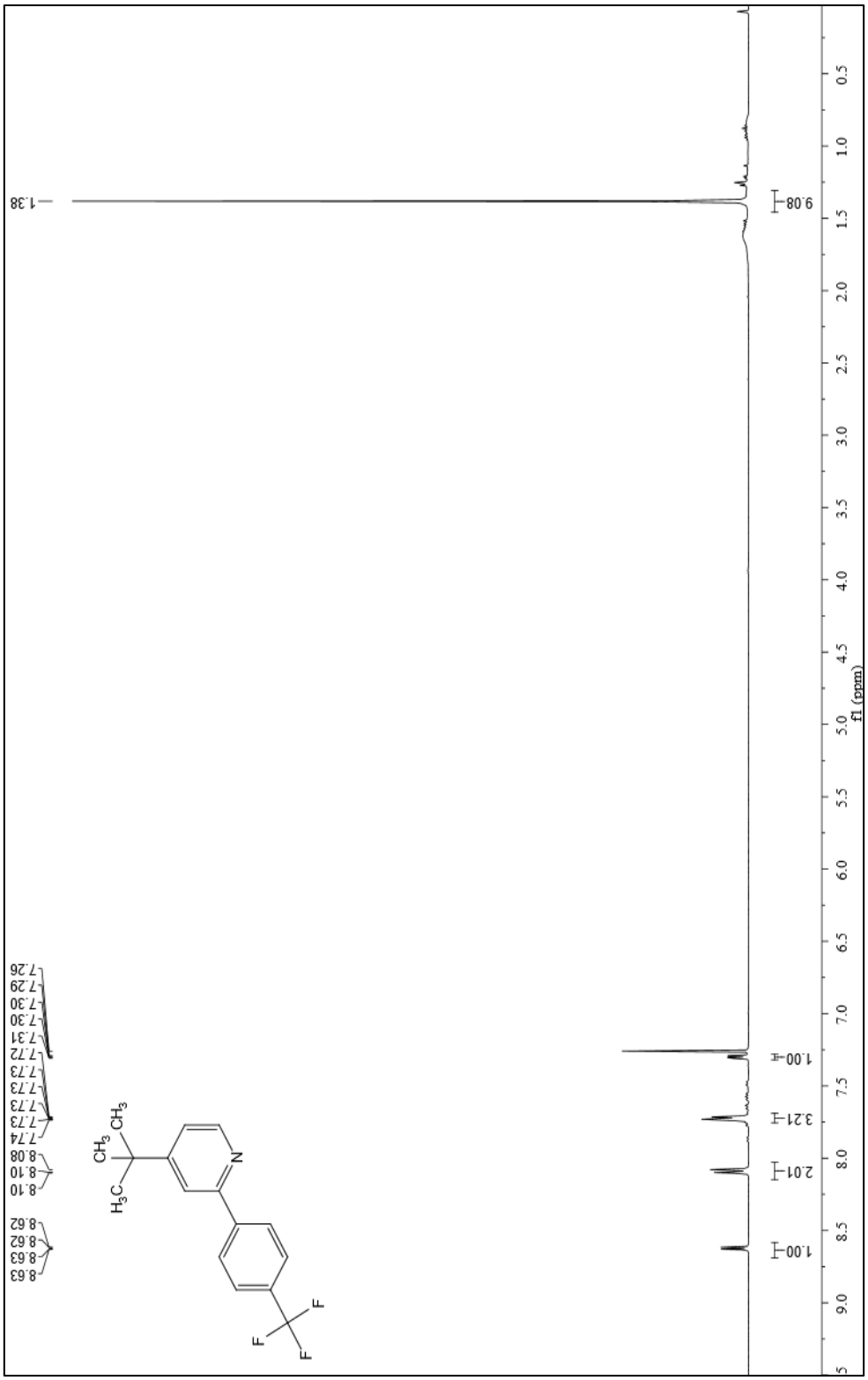
The **general procedure A** was followed using 4-iodoaniline (25 mg, 0.12 mmol), tert-butylpyridine (162 mg, 1.2 mmol), tert-butylnitrite (15 mg, 0.14 mmol) and 0.24 mL of stock solution of eosin-y in DMSO was used to afford **47h** in 37% yield (15 mg, 0.04 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 27% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 5.3 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 156.6, 149.8, 139.6, 137.9, 129.0, 119.9, 117.6, 95.2, 35.1, 30.7.

47i) 2-(4-bromophenyl)-4-(tert-butyl)pyridine

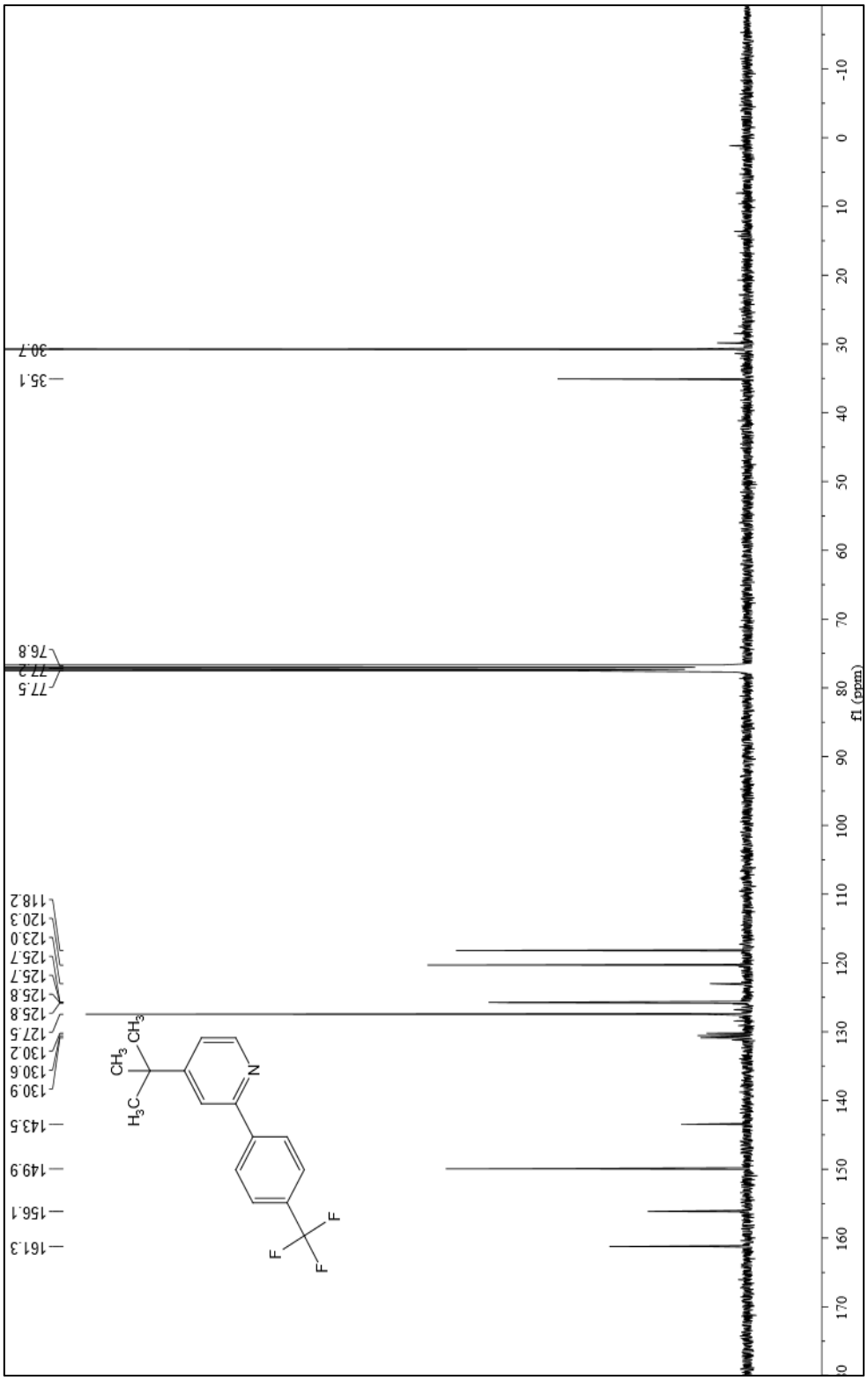
The **general procedure A** was followed using 4-bromoaniline (25 mg, 0.15 mmol), tert-butylpyridine (202 mg, 1.5 mmol), tert-butylnitrite (18 mg, 0.18 mmol) and 0.3 mL of stock solution of eosin-y in DMSO was used to afford **47i** in 37% yield (16 mg, 0.05 mmol) as a white solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 12 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.3 Hz, 1H), 7.93 – 7.82 (m, 2H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.33 – 7.27 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 156.1, 149.3, 138.4, 131.9, 128.7, 123.4, 119.8, 117.7, 35.0, 30.6.



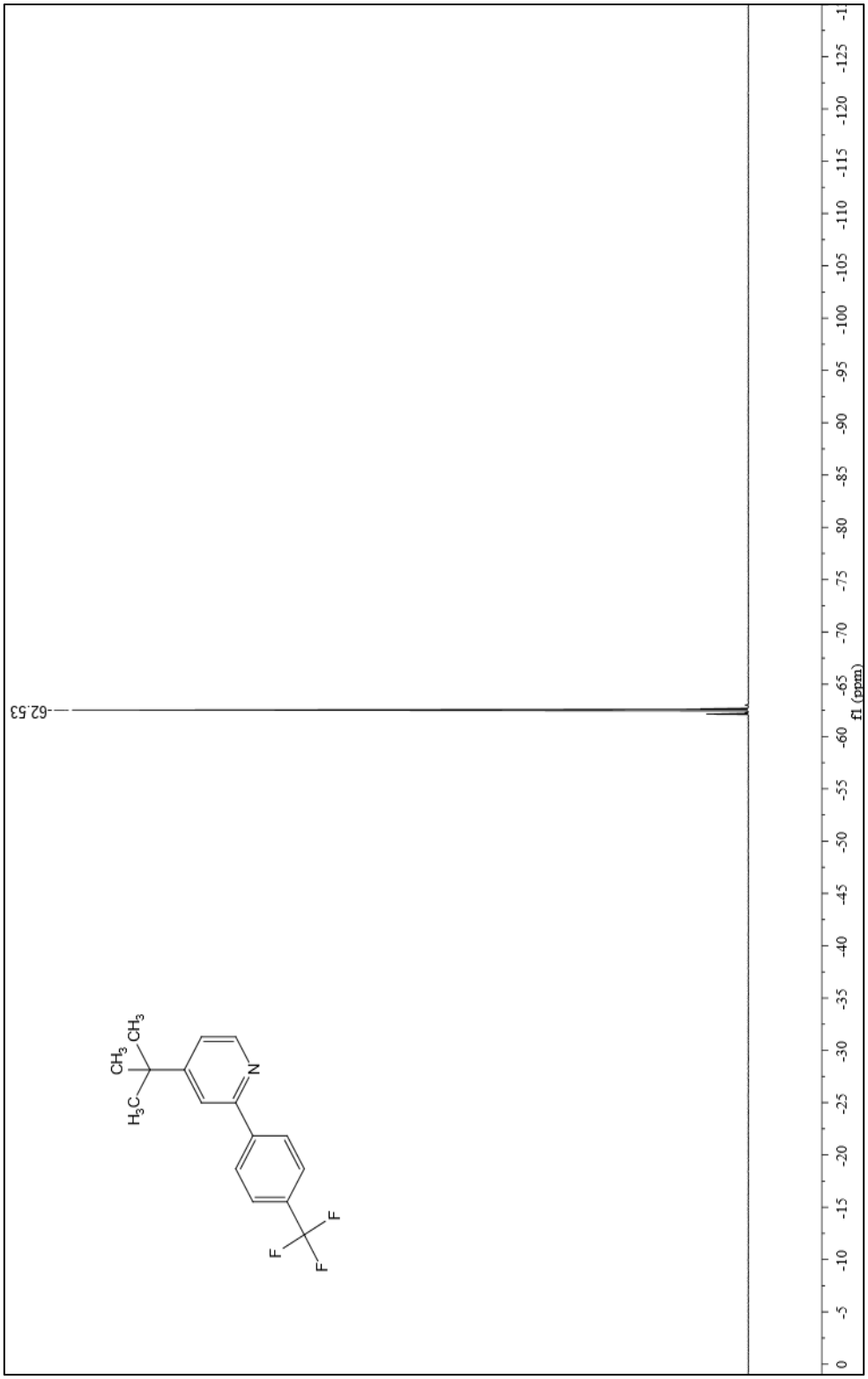
47a) 4-(tert-butyl)-2-(4-(trifluoromethyl)phenyl)pyridine



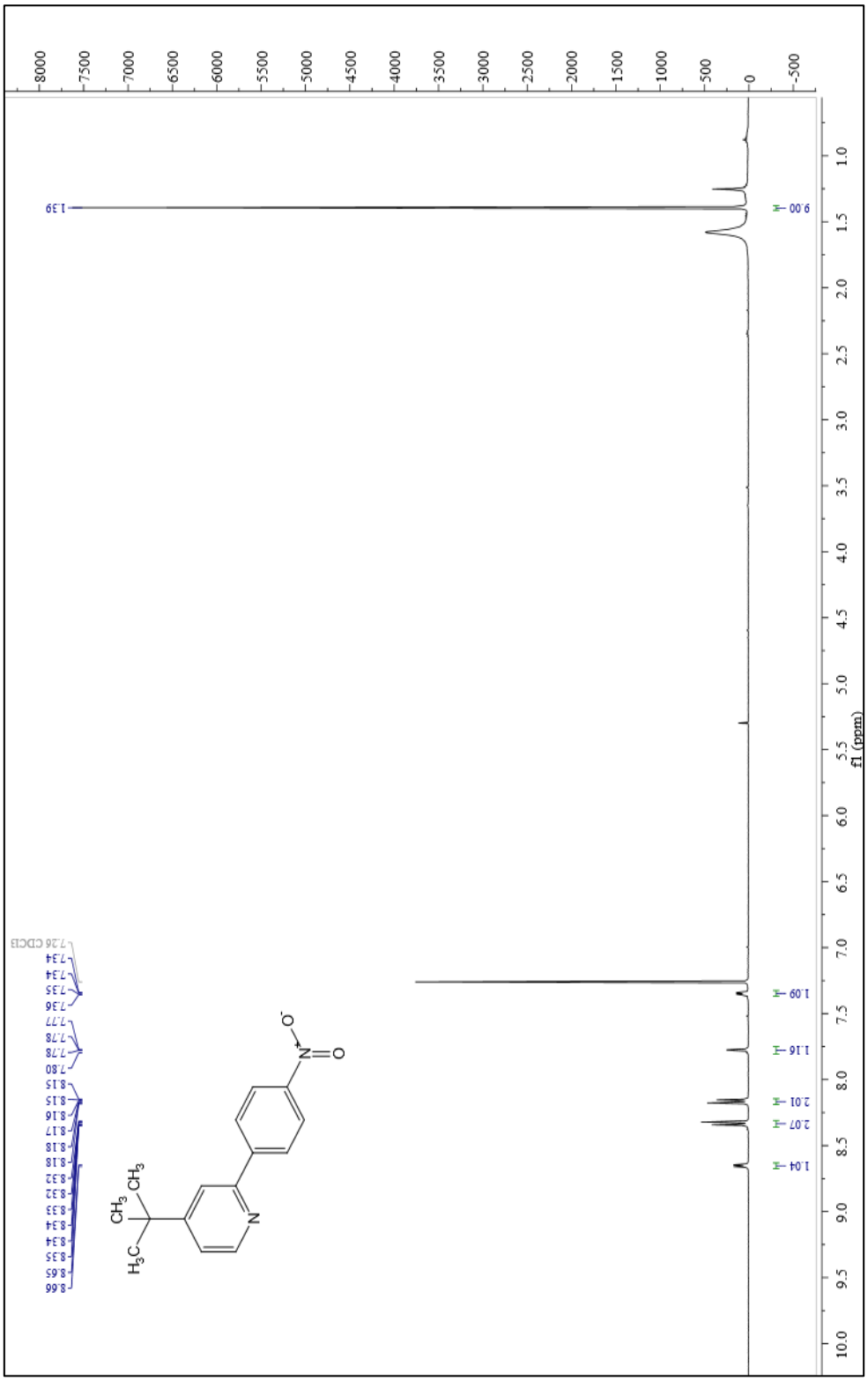
47a) 4-(tert-butyl)-2-(4-(trifluoromethyl)phenyl)pyridine



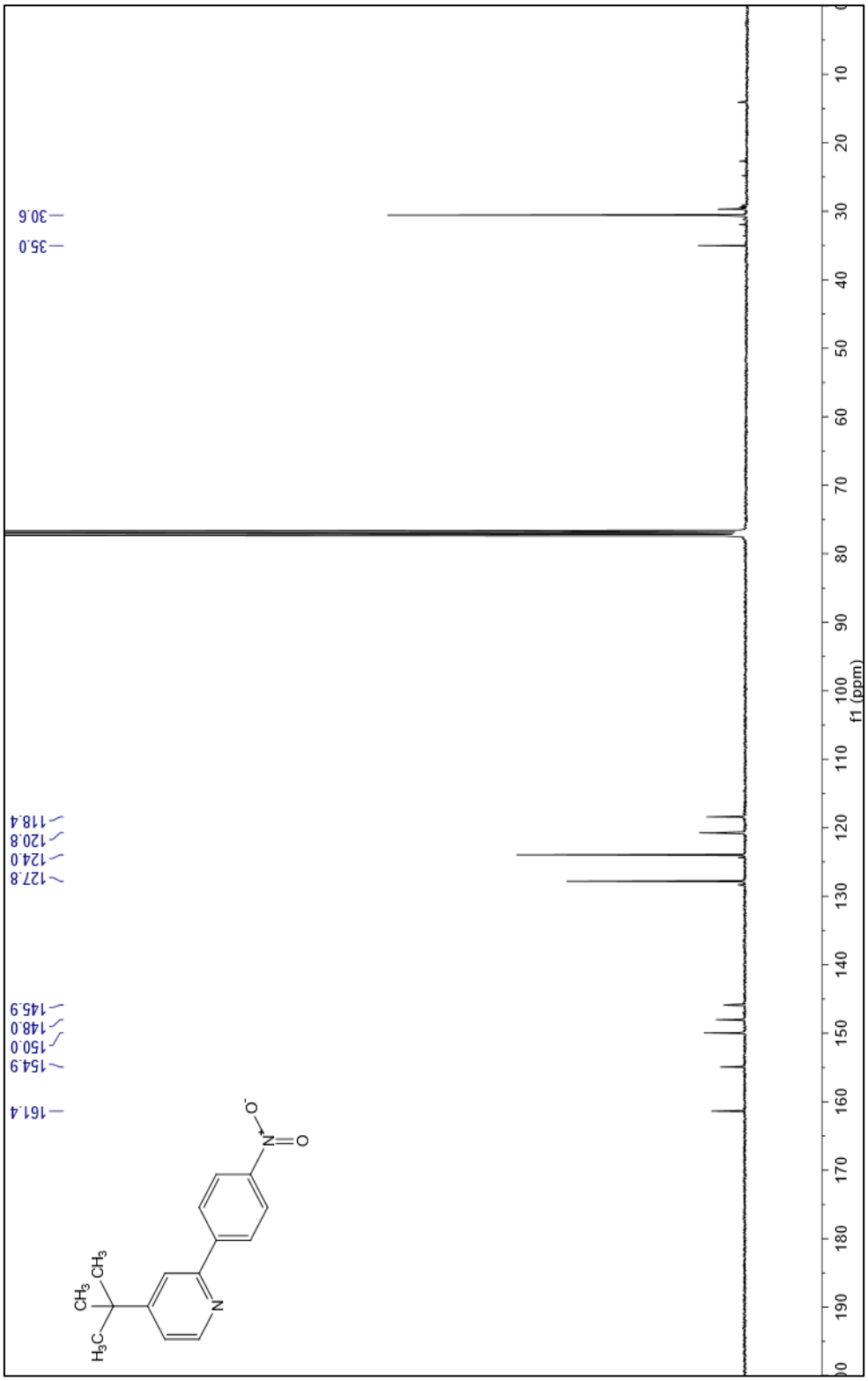
47a) 4-(tert-butyl)-2-(4-(trifluoromethyl)phenyl)pyridine



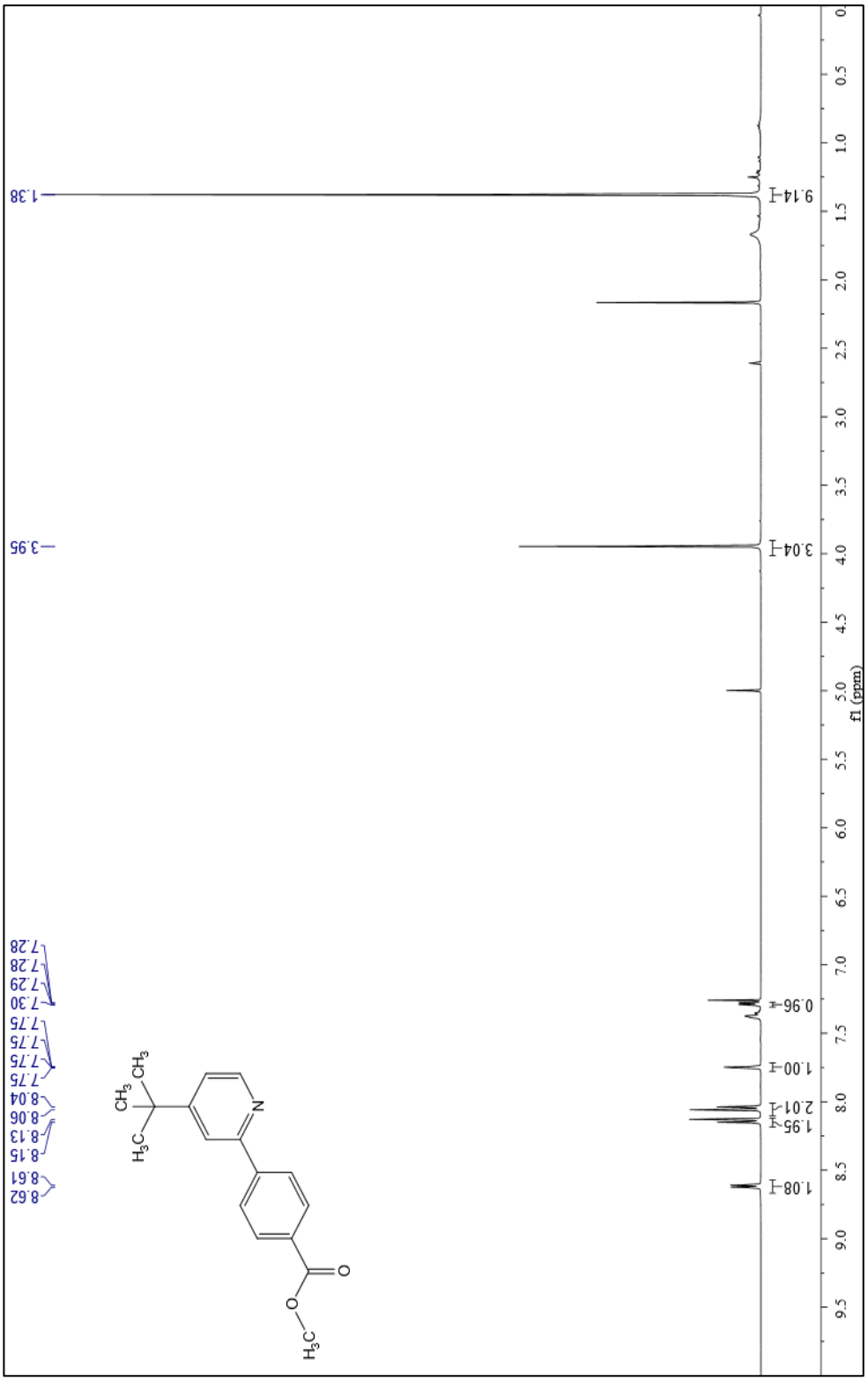
47b) 4-(tert-butyl)-2-(4-nitrophenyl)pyridine



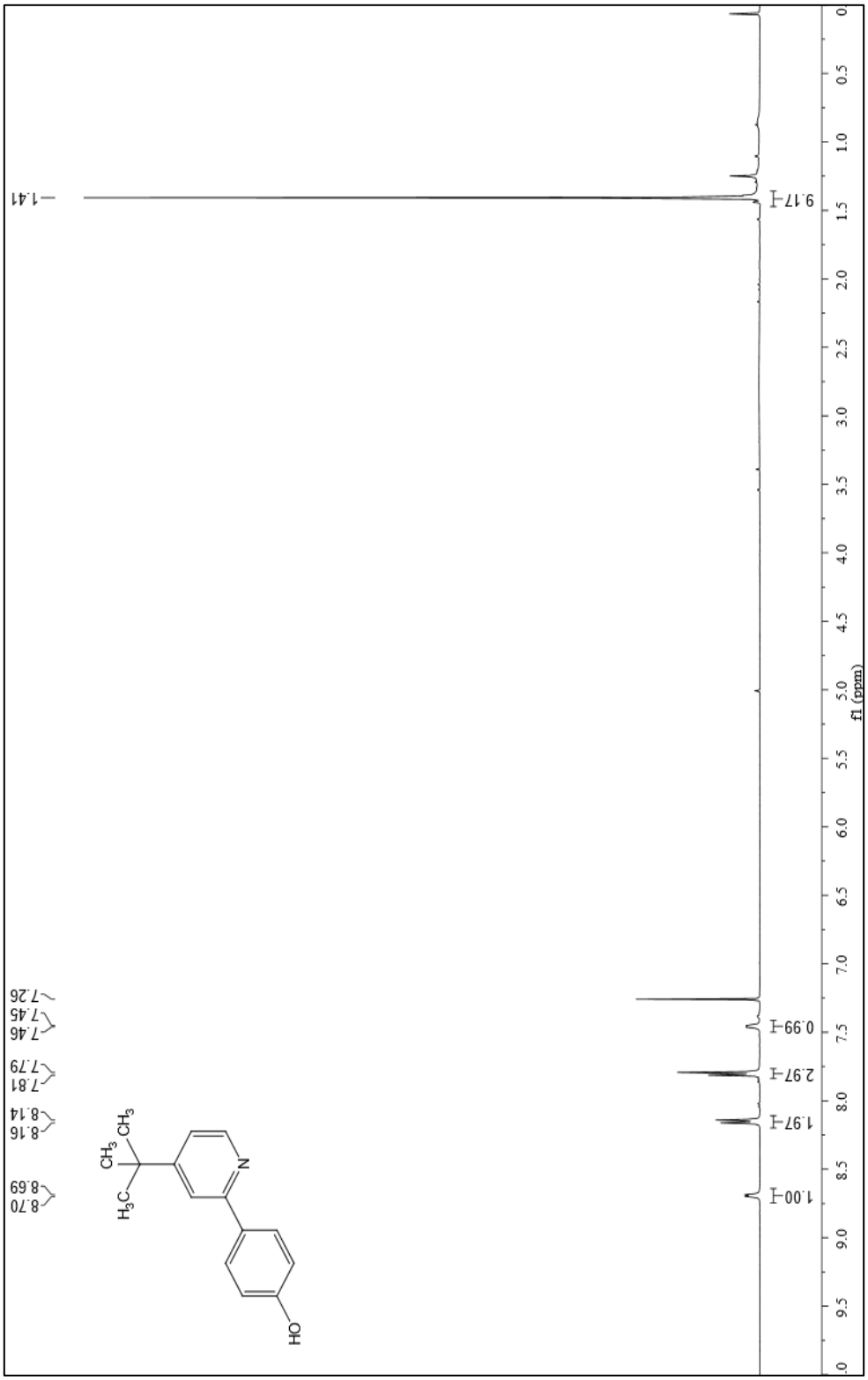
47b) 4-(tert-butyl)-2-(4-nitrophenyl)pyridine



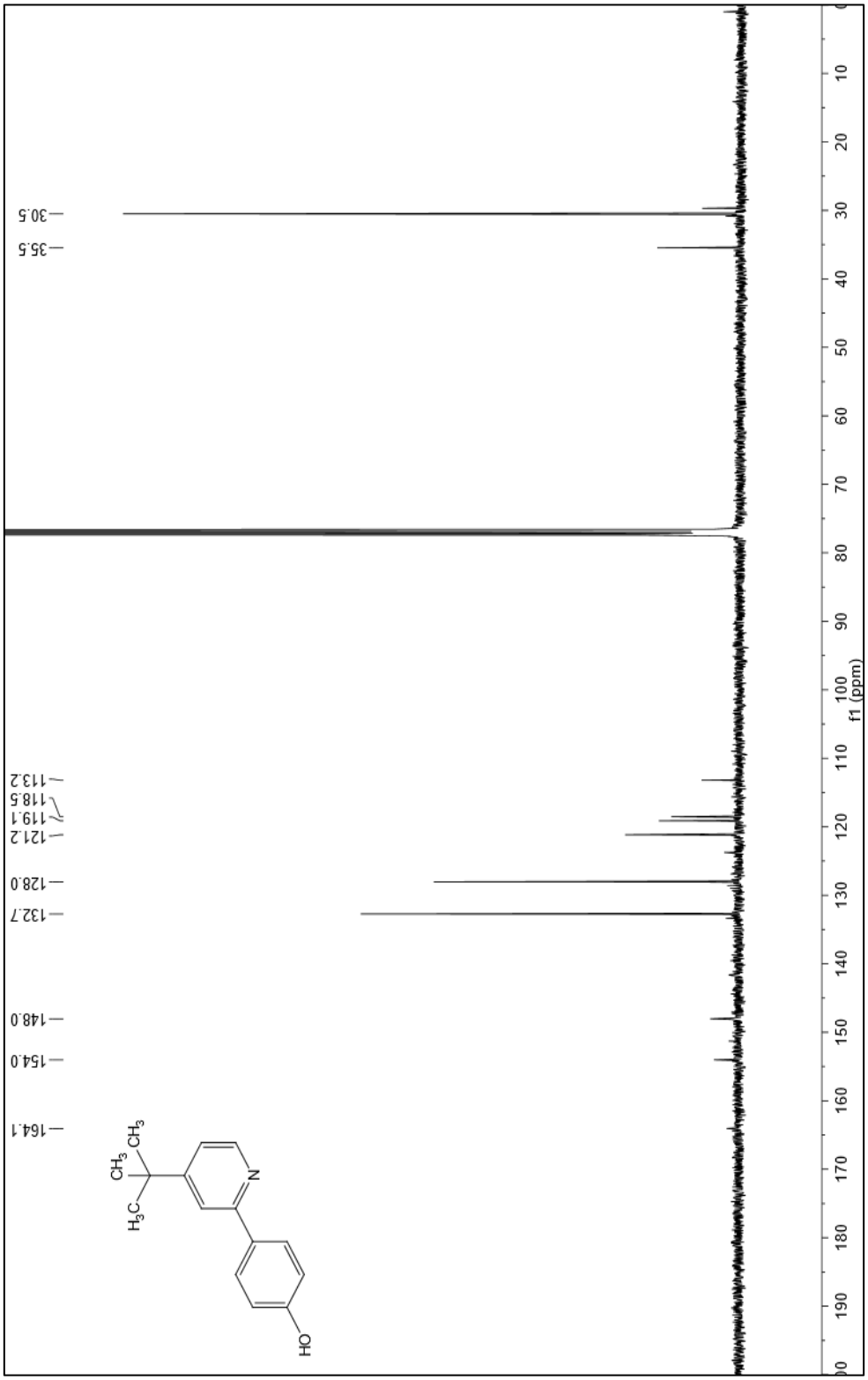
47c) methyl 4-(4-(tert-butyl)pyridin-2-yl)benzoate



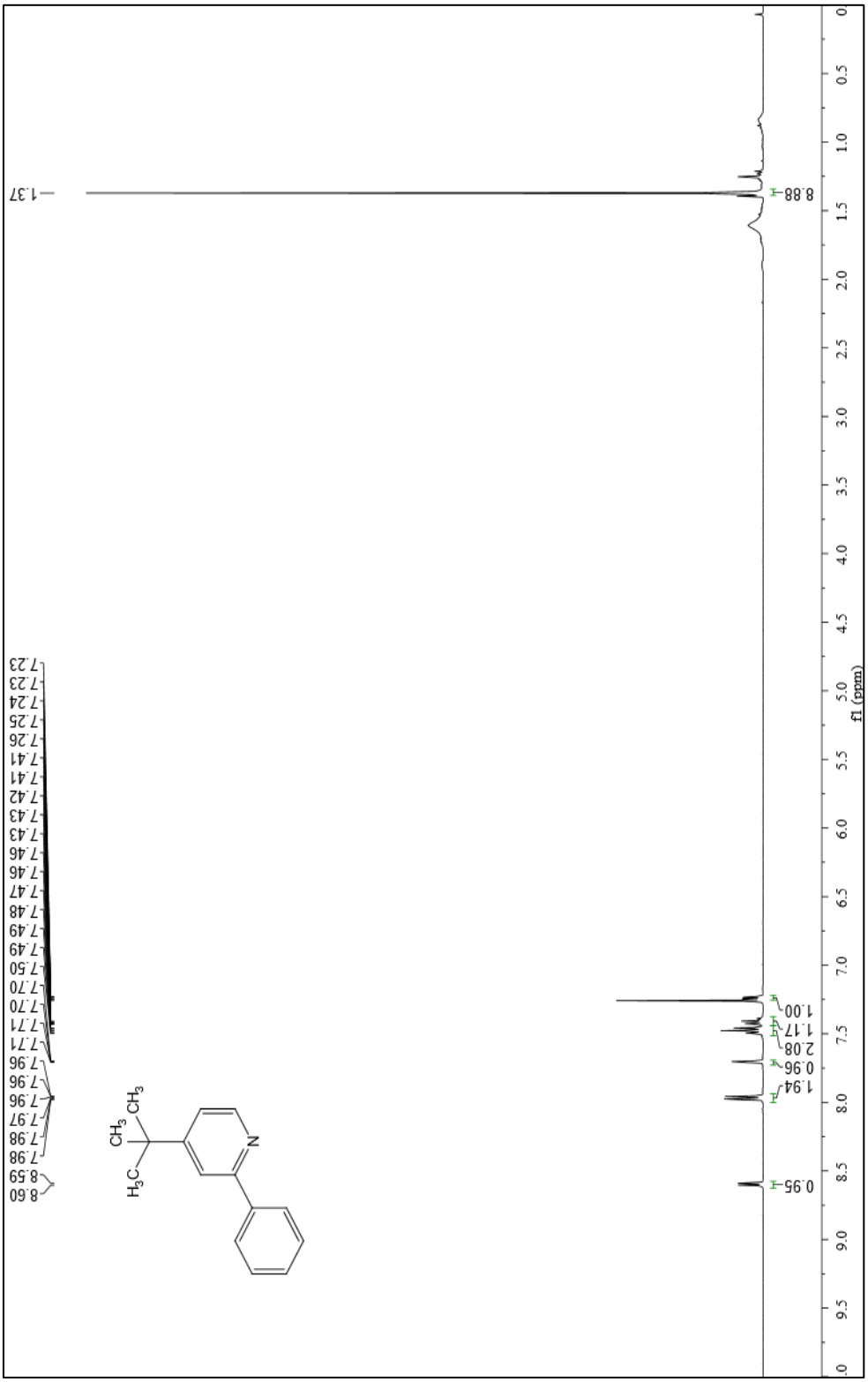
47d) 4-(4-(tert-butyl)pyridin-2-yl)phenol



47d) 4-(4-(tert-butyl)pyridin-2-yl)phenol



47e) 4-(tert-butyl)-2-phenylpyridine



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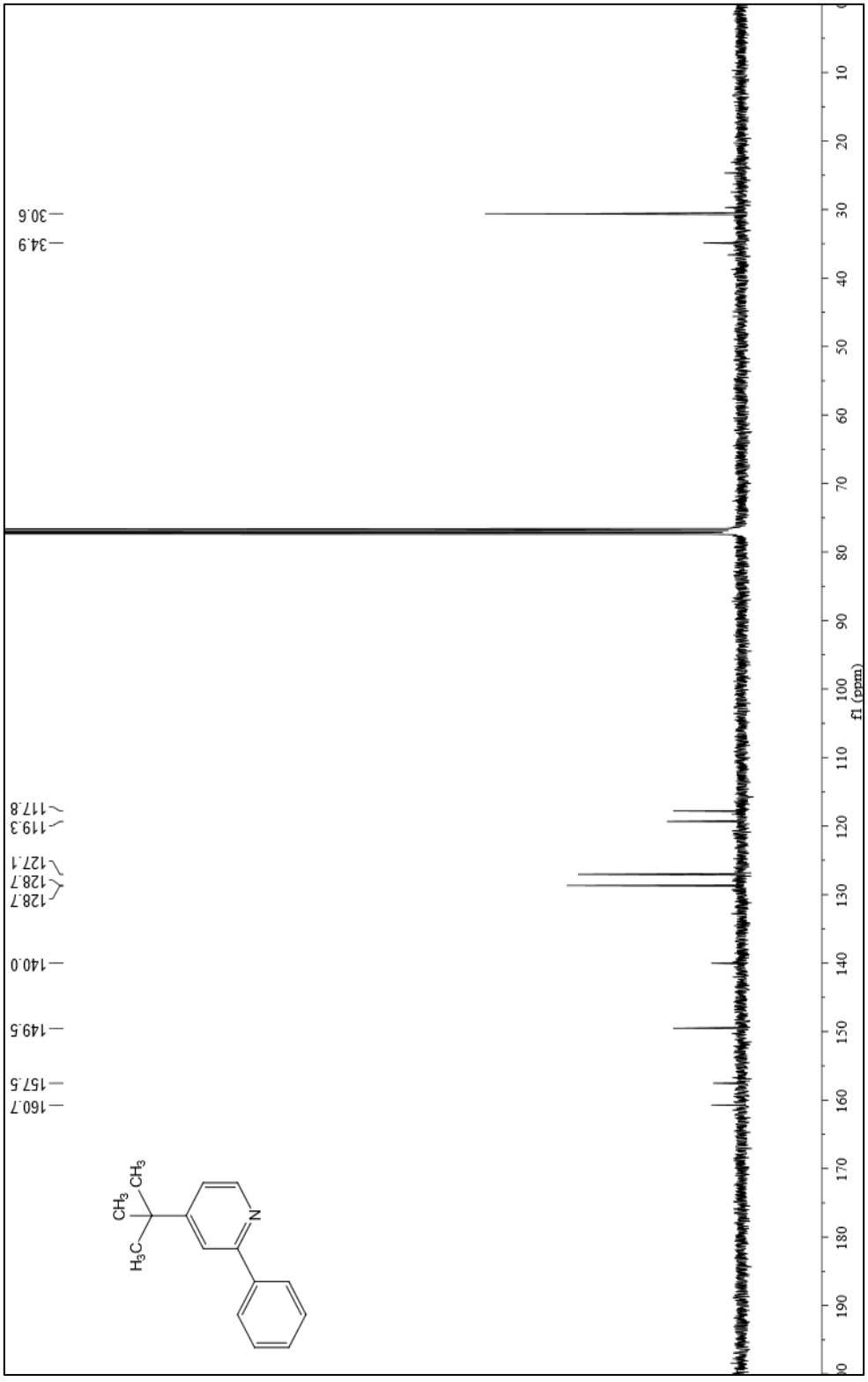
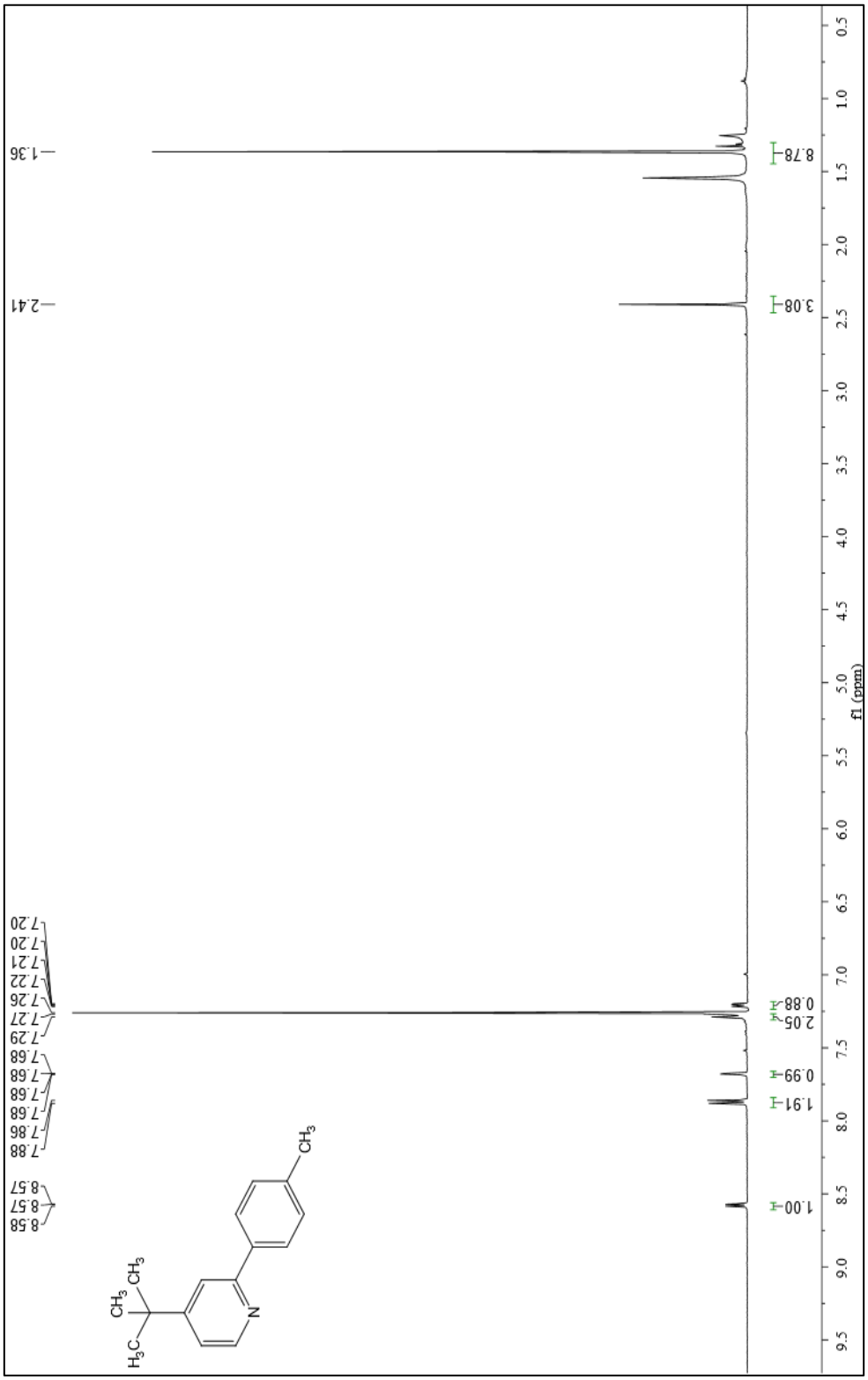
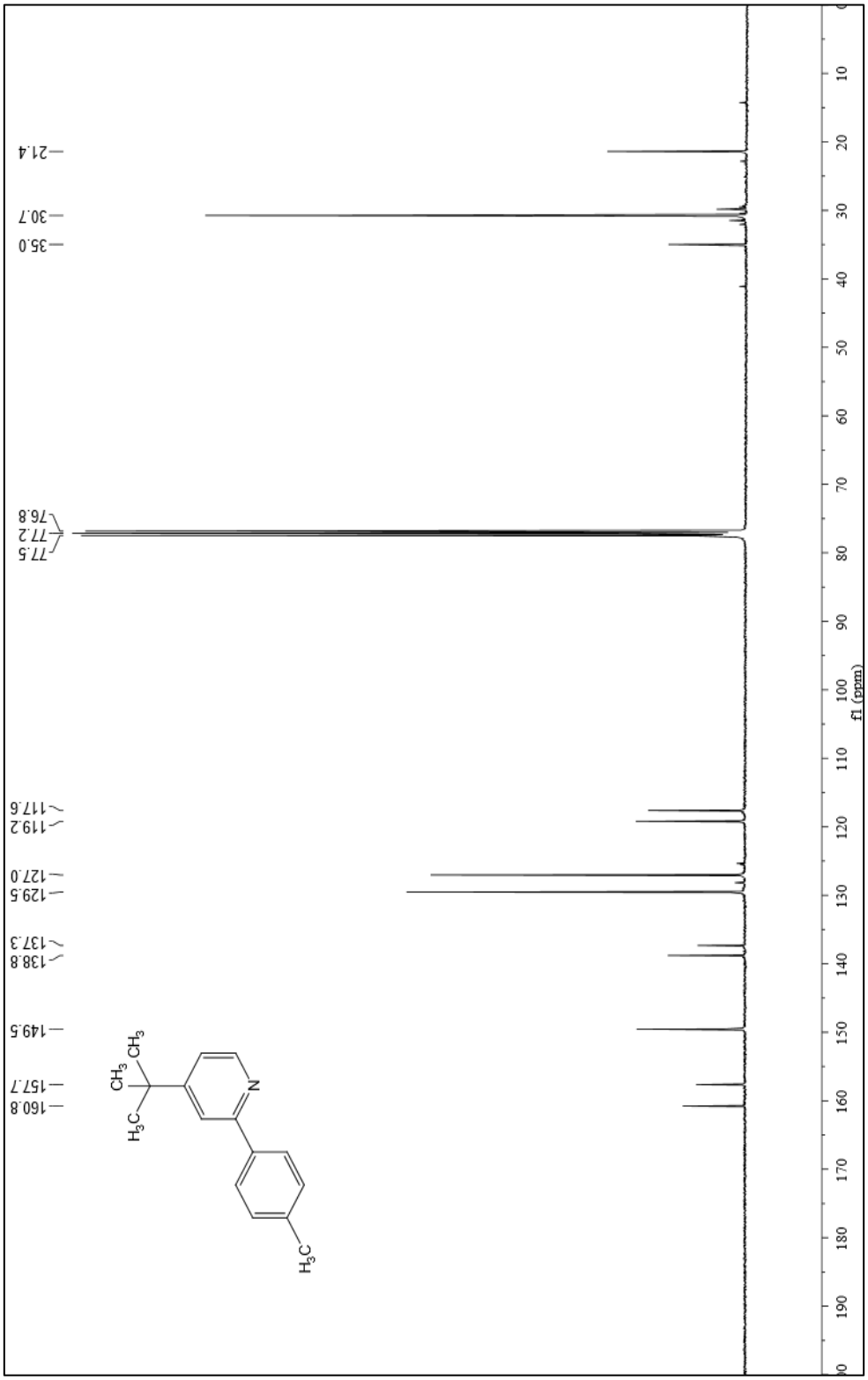


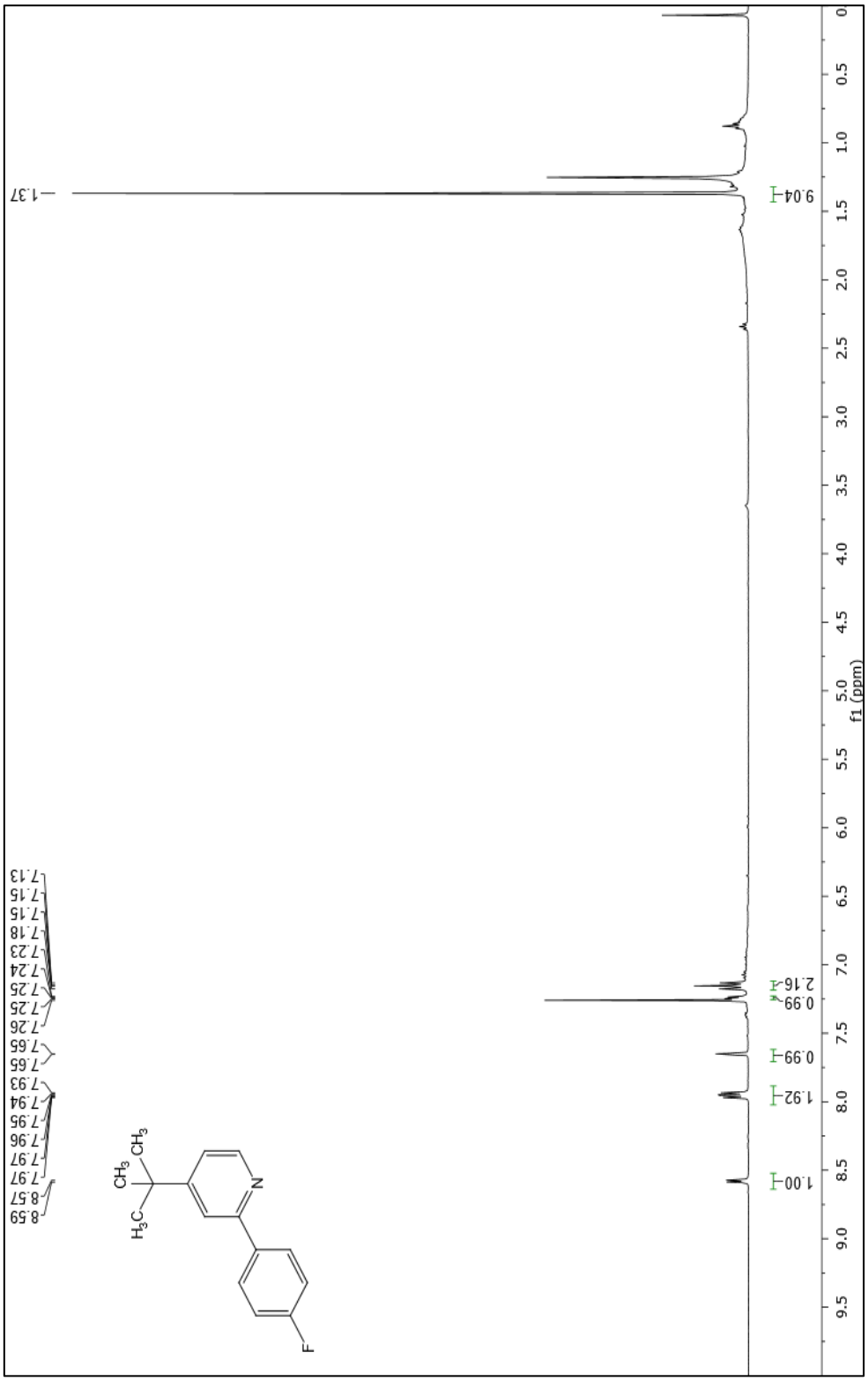
47f) 4-(tert-butyl)-2-(p-tolyl)pyridine



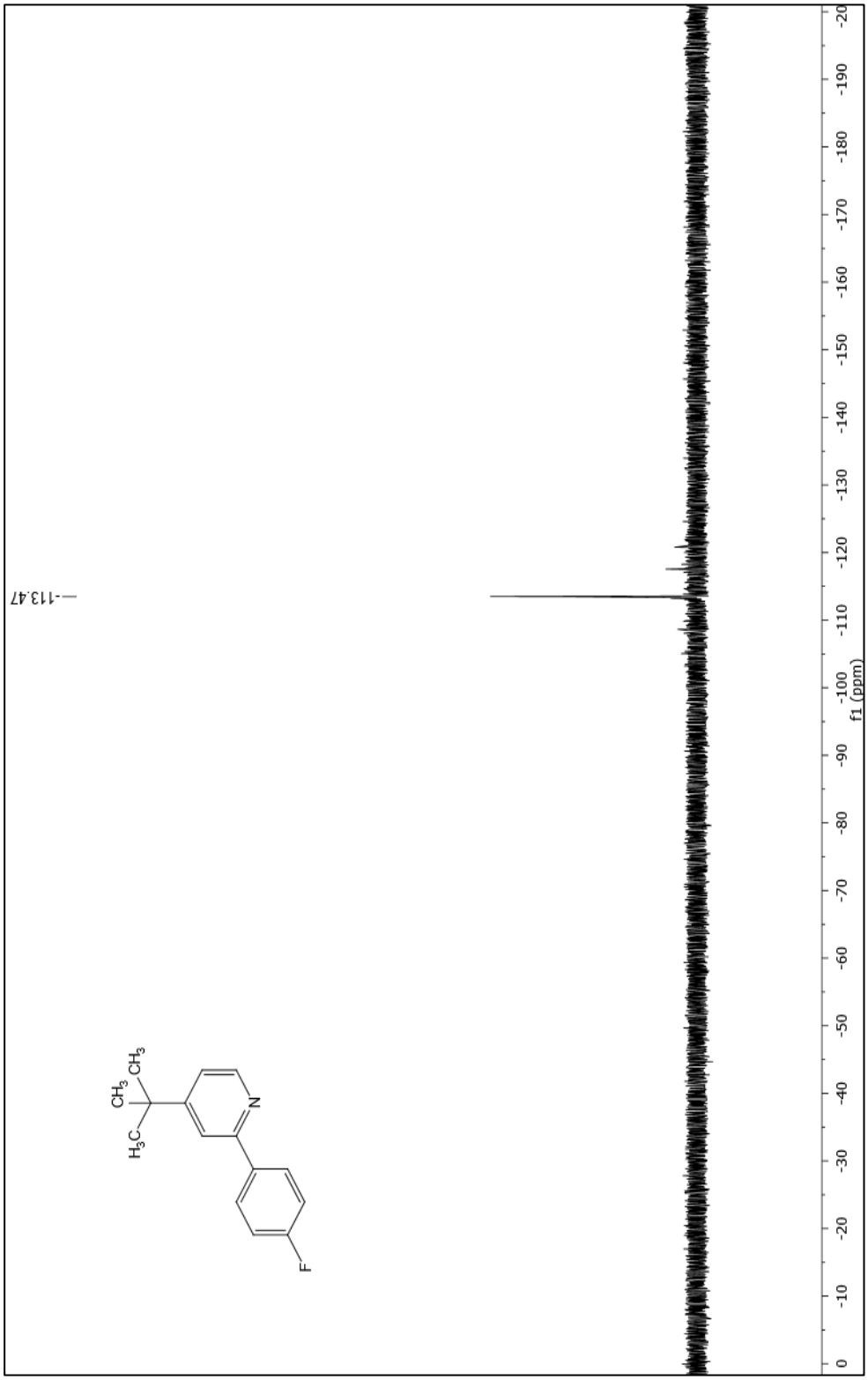
47f) 4-(tert-butyl)-2-(p-tolyl)pyridine



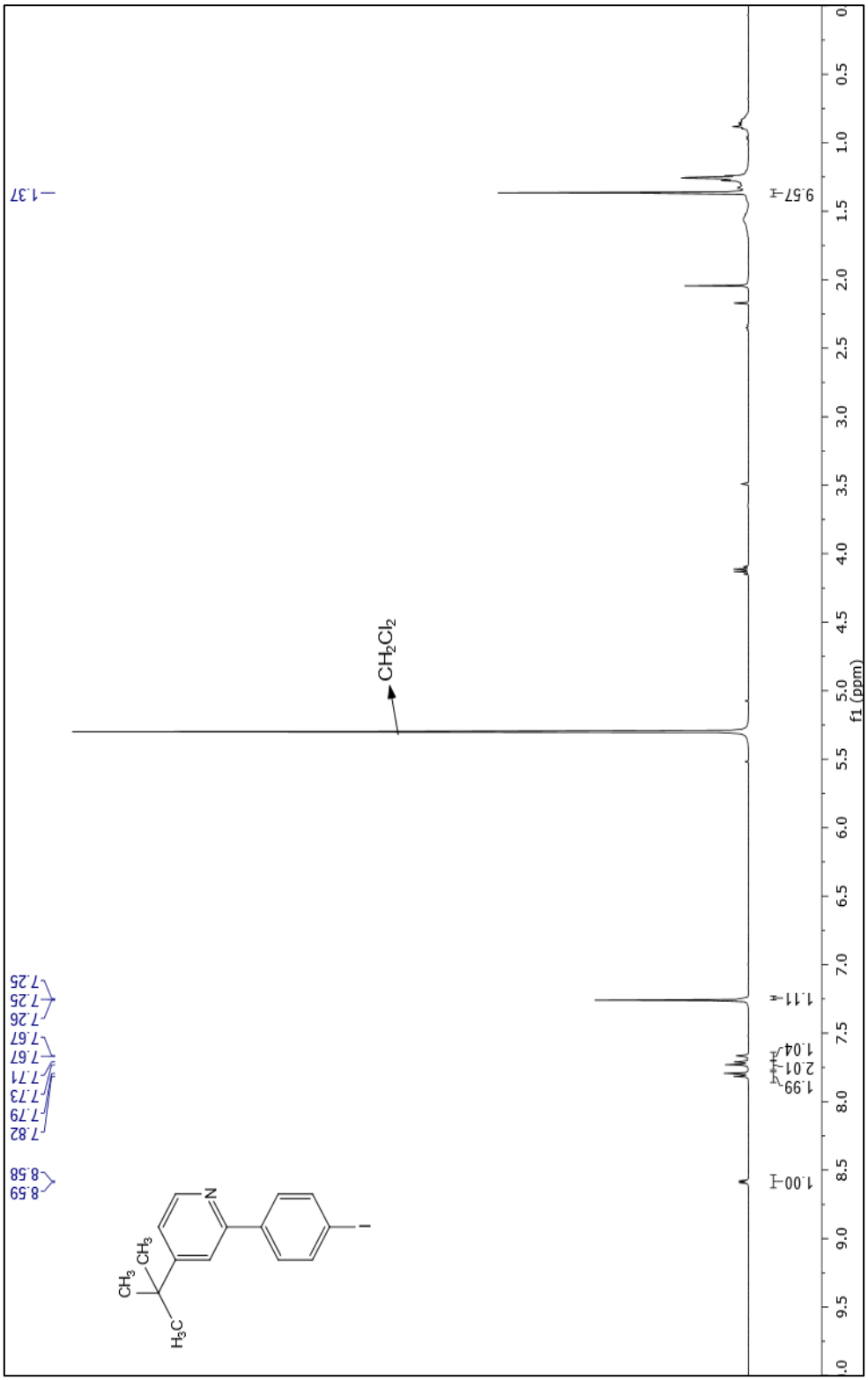
47g) 4-(tert-butyl)-2-(4-fluorophenyl)pyridine



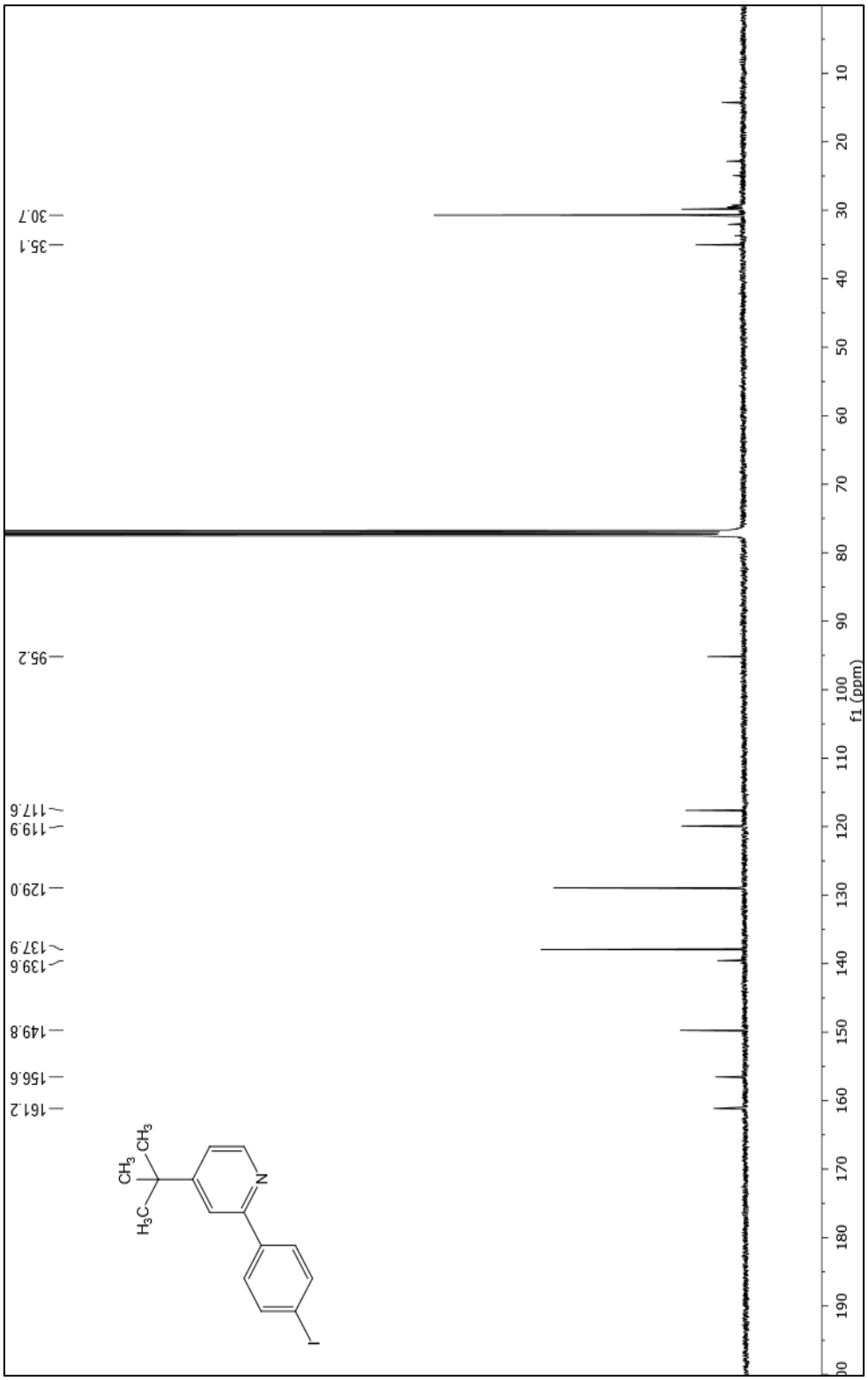
47g) 4-(tert-butyl)-2-(4-fluorophenyl)pyridine



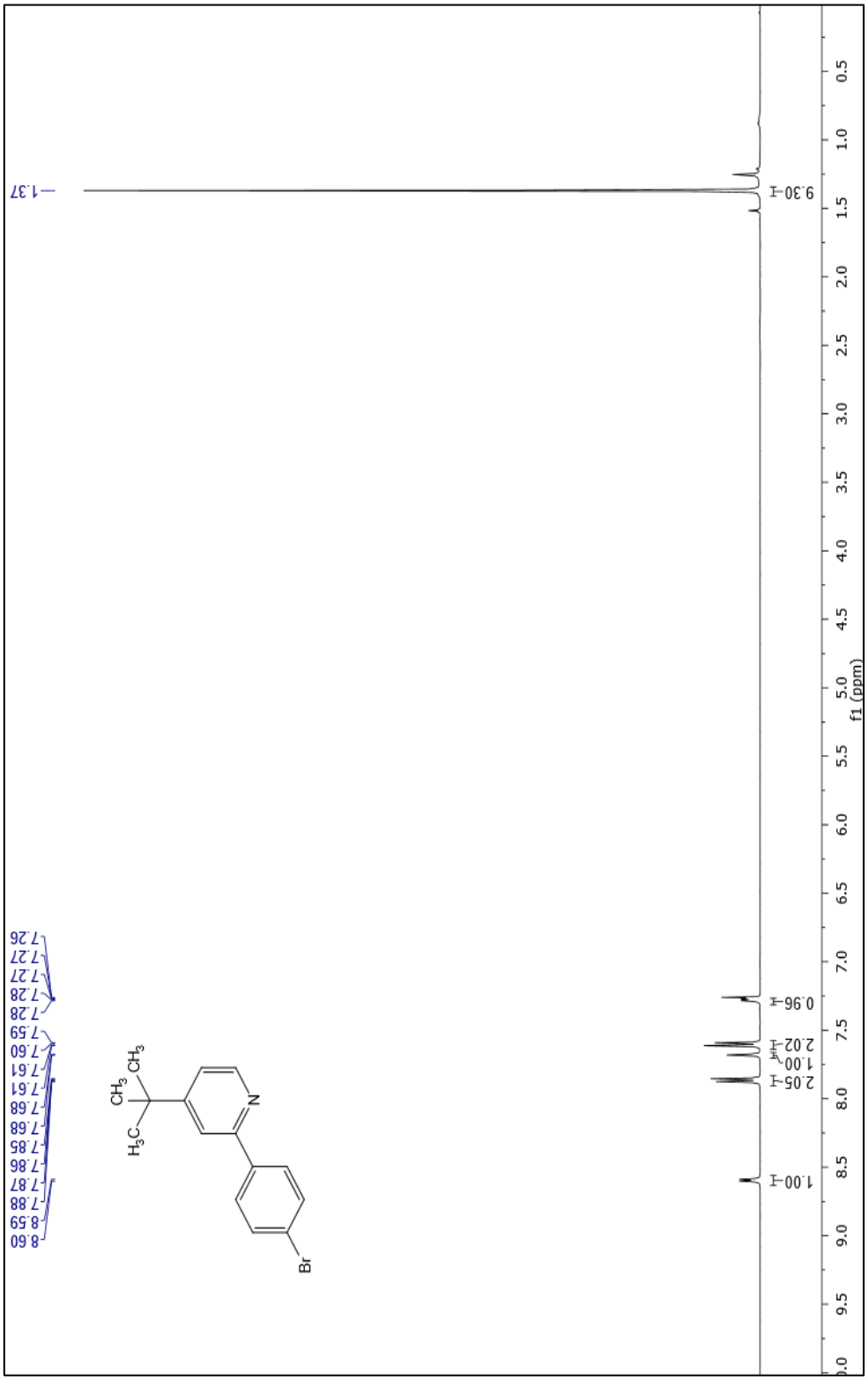
47h) 4-(tert-butyl)-2-(4-iodophenyl)pyridine



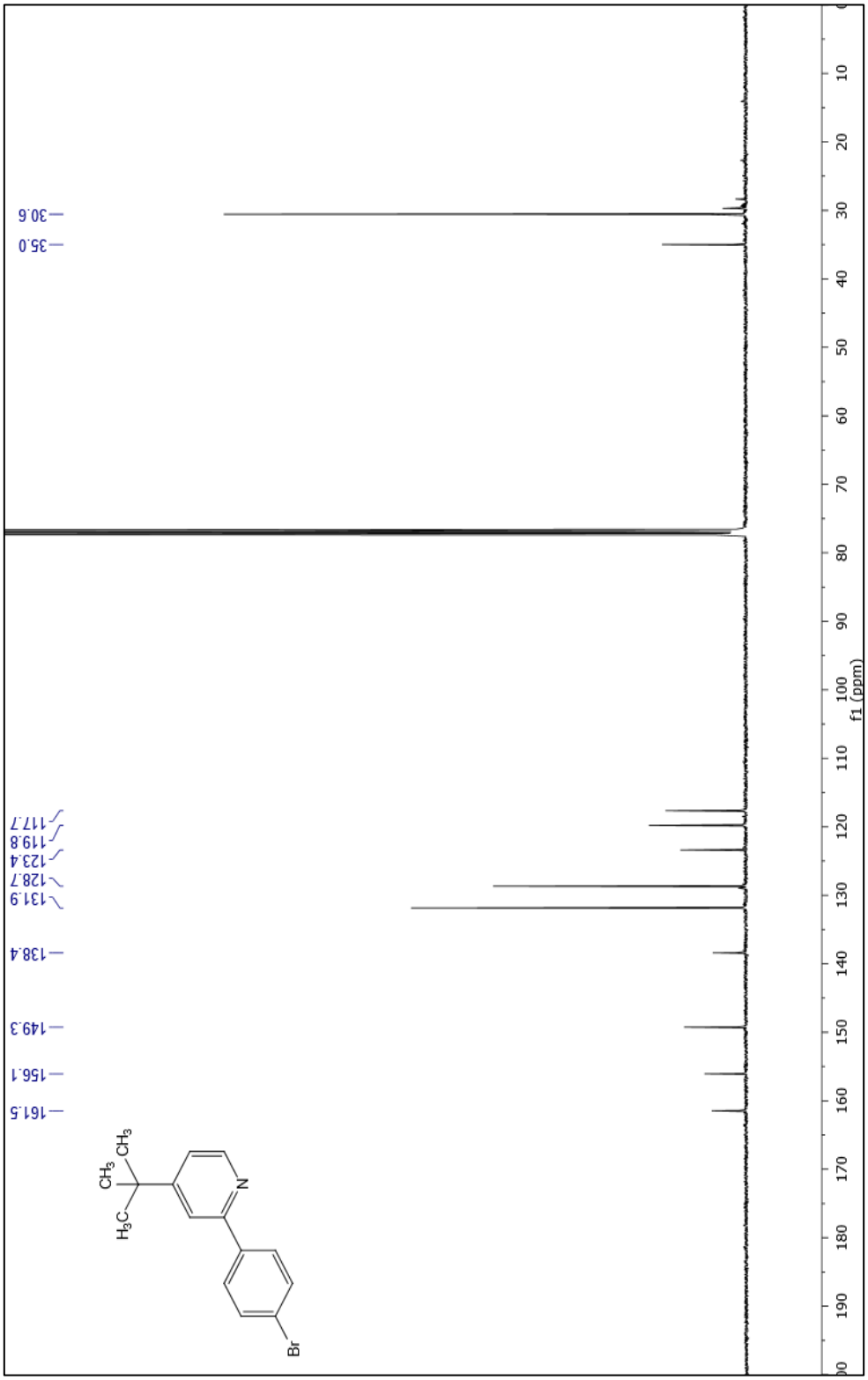
47h) 4-(tert-butyl)-2-(4-iodophenyl)pyridine



47i) 2-(4-bromophenyl)-4-(tert-butyl)pyridine



47i) 2-(4-bromophenyl)-4-(tert-butyl)pyridine



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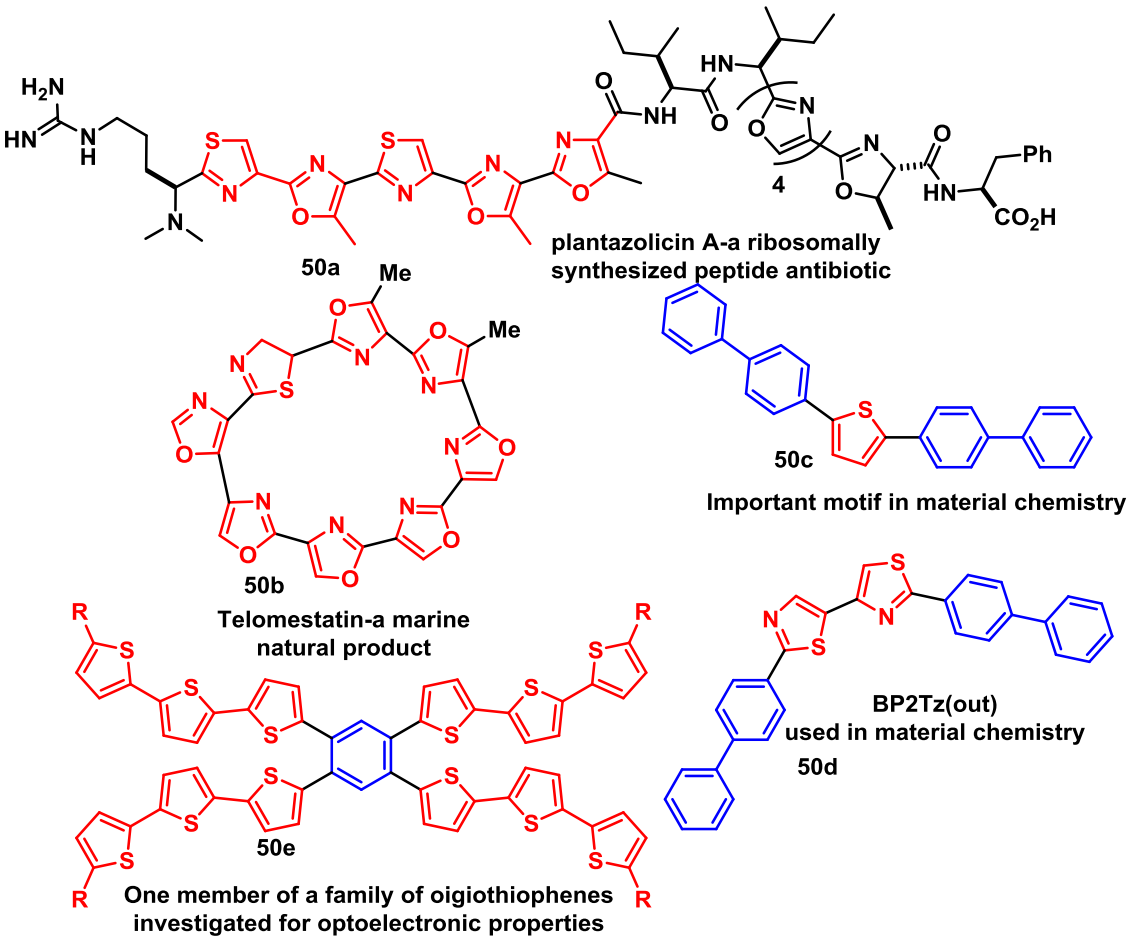
CHAPTER VII

PHOTOREDOX MEDIATED ITERATIVE SYNTHESIS OF OLIGOARENES

In chapter 6, we demonstrated that aryl radicals could be utilized for the direct C–H arylation of electron deficient heterocycles, and that these aryl radicals could be generated by starting with 2-amino arenes, and converting them, *in situ*, to the 2-diazonium arenes. We speculated that, with some clever substrate development, it might be possible to utilize this same type of reactivity to enable a completely novel type of iterative reaction sequence, which would enable the synthesis of oligoarenes.

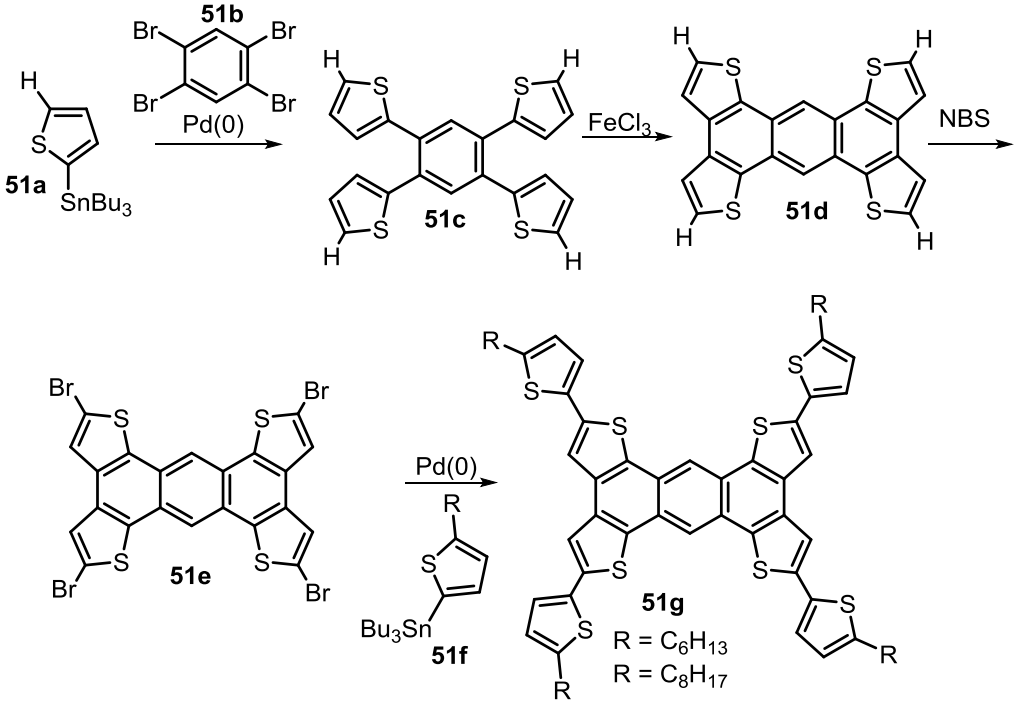
Conjugated oligoarenes are important structural motifs in natural products[1] **50a**, and **50b** (Scheme 50), photonic and optoelectronic materials[2] such as organic light emitting diodes, field-effect transistors, semiconductors, and fluorescent sensors[3] **50c**, **50d**, and **50e**. In each case, the nature of the arenes involved influence the properties of the materials. Thus, predictable and controllable syntheses of these types of molecules is an important objective for synthetic chemists.



Scheme 50. Representative examples of oligoarenes

Currently, cross-coupling reactions of an aryl halide and an organometallic is the most popular way to synthesize oligoarenes, which allows the direct connection of C(sp^2)-C(sp^2) bonds with high chemo-, stereo-, and regioselectivity.[4] In one example, Brusso and coworkers demonstrated the Stille coupling of tetrabromobenzene **51b** (Scheme 51) with stannylated oligothiophenes **51a**. This was followed by oxidative cyclodehydrogenation with $FeCl_3$.[5] This route was effective for the synthesis of alkylated thiophene substituted benzene *i.e.* in the preparation of **51g**.[5] However, in order to extend the cross-coupling sequence it was necessary to install a halogen on **51d**. Thus, selective oxidation (i.e. bromination of the C–H) of the substrate is needed to continue the sequence. [6] It is anticipated that such selectivity will become increasingly difficult as the molecule, and the number of C–H bonds, becomes larger, making this

approach fundamentally limited. Moreover, if we consider installing a different group at any other positions such as C-3 on the thiophene ring **51g** we realize this is not possible, since we cannot selectively oxidize this position. For example, if we attempted to extend the ring by one more thiophene unit **51g**, we would need to repeat the tetra-bromination step, which would likely not be nearly as selective as the first time when the molecule was smaller with fewer C–Hs. Alternatively, if we wanted to diversify the C-2 substituent we would have to begin the synthetic sequence again, using the appropriately substituted starting material for each substrate. Furthermore, the appropriately substituted starting material may not be available, or may not react well, which would pose a further limitation to the synthesis of oligoarenes derivative *via* cross-coupling reactions. In a situation, where studying the structure activity relationship of the desired oligoarenes is important in order to tune electric/optical properties, the cross-coupling approach is relatively uninspiring, as it requires substantial synthetic efforts, and careful planning to build the desired library.

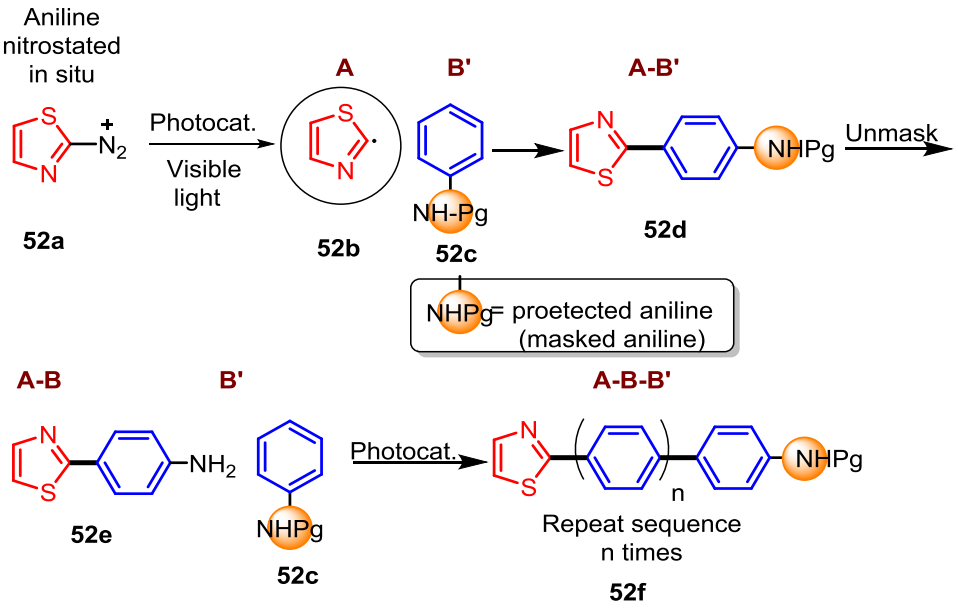


Scheme 51. Example of current synthetic method to synthesize oligoarenes

In contrast, general and automated platforms have been developed for making peptides,[7] oligonucleotides,[8] and oligosaccharides,[9] *via* the iterative assembly of a small set of building blocks.[10] Inspired by the way natural products are biosynthesized, namely the iterative reaction with a well-defined set of building blocks, we hypothesized that we could develop an analogous methodology for the synthesis of oligoarenes *via* the iterative coupling of (hetero)aromatic amines and protected (hetero)aromatic amines. We hypothesized that in order to carry out the iterative synthesis, one aromatic amine would need to be protected, and much of our objective has been to understand the role that this group has on the reaction outcome.

We speculated the utilization of an aryl radical, which could be formed *via* diazotization of aryl (heteroaryl)-NH_2, *in situ*,[11] could be used for the iterative synthesis of a wide range of functionalized oligoarenes, without the need to prefunctionalize the arene partner. Furthermore, the use of diazonium salts as precursors to radicals could be advantageous in terms of providing greater selectivity and functional group tolerance in the reaction, since a less reducing photocatalyst would be needed to reduce the diazonium.[12] In addition, no amine reductant would be needed for the reaction, which in the case of aryl halides, often leads to competitive formation of undesired reduction product.

Illustrating our proposed approach in Scheme 52, the synthesis of hypothetical biaryl A-B'**52d** takes place via photoredox mediated coupling of an aryl radical **A**, **52b**, and masked aniline **B'**, **52c**, *via* C–H functionalization. The coupled **A-B,' 52d** biaryl undergoes unmasking and the desired coupled product **A-B, 52e** is obtained. This coupled product **A-B, 52e** can undergo further diazotization to generate the new aryl radical, that can couple with **B'** a masked aniline, **52c** resulting in a oligoarene of type **A-B-B,' 52f**. This iterative photocatalyzed apporach will offer a new efficient route to synthesize oligoarene derivatives (e.g., **A-B-B'**). Of course, in this scenario **B'** can be varied, leading to a completely programmable and regio-regular synthesis of the oligoarene, which will allow rapid SAR about the oligoarene motif.

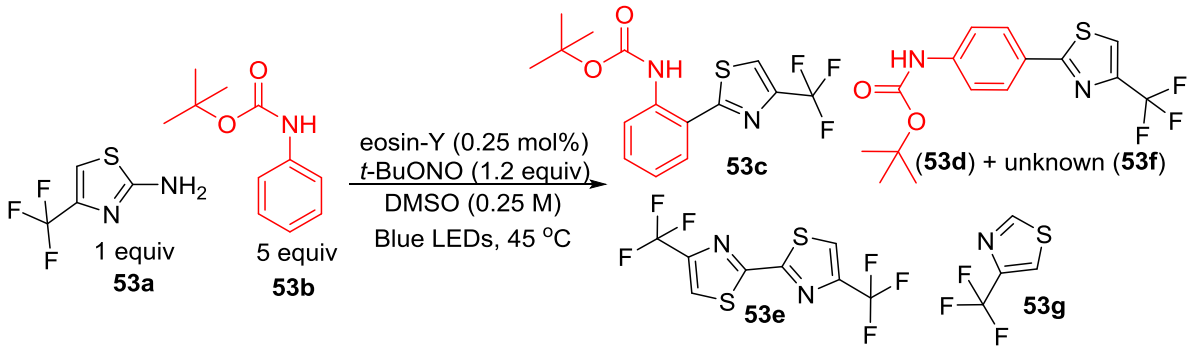


Scheme 52. Proposed iterative synthesis of oligoarenes.

7.1 Optimization of reaction conditions

To begin our study, we subjected 4-(trifluoromethyl)thiazol-2-amine and *N*-Boc-aniline using *tert*-butylnitrite, and catalytic eosin-Y to blue LEDs (Scheme 53, entry 1). We observed 100% NMR conversion, with 70% conversion to the desired product **53c** and **53d**. While *N*-Boc-aniline has three potential sites of reactivity, we observed product with an *ortho*:*para* ratio of (1.5:1), and the *meta* addition product was not observed at all. In addition, 30% of a side product whose structure was not determined **53f**. Initial solvent screen revealed that DMSO was the best solvent. In polar solvents such as MeCN and MeOH (entry 2), complete conversion to the **53f'** which while it gave a characteristic spectrum by mass on CMS mass spectrometer, its structure was never determined. In contrast, in non-polar solvents such as toluene and benzene (entry 4) no reaction was observed. The lack of reactivity, might simply be due to the low solubility of the photocatalyst, as well as *N*-Boc-aniline in these solvents. Interestingly, switching the solvent from DMSO to DMF (entry3), resulted only in the reduction of the azole **53g**.[13] Next, we screened the reaction conditions varying the equivalents of coupling reagent (entry 5 and 6). Increasing the equivalents of boc-aniline in the reaction, increased the conversion to desired product. We did observe an improvement in the overall conversion to the desired product (entry 1 *vs* 7 and 8) upon concentrating the

reaction mixture. Interestingly, the presence of air in the reaction did not seem to have a significantly detrimental effect on the reaction (entry 1 *vs* 9). Next, increasing the temperature of the reaction decreased the overall conversion to the desired product (entry 1 *vs* 10, 11, 12). We also employed other nitrosating reagents such as sodium nitrite with HCl as well as isoamyl nitrite (entry 13 and 14) in the reaction. However, we did not observe the desired product, rather unknown side products were formed in the reaction. Thus, we ultimately settled on running the reaction under air, at 20 °C, with 1.2 equivalents of *tert*-butylnitrite and 5.0 equivalents of Boc-protected aniline.



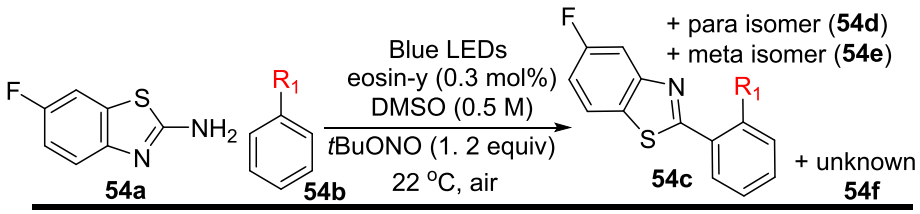
Entry	Modification	NMR conversion	**53c**+**53d** (*o*:*p*), **53f**	**53e**	**53g**	time
1.	None	100%	70 (1.5:1), 30	-	-	1:30 h
2.	MeCN, MeOH	100%	na, 100	-	-	1:30 h[a]
3.	DMF	100%	-	-	100	1:30 h
4.	Toluene, Benzene	-	-	-	-	1:30 h[b]
5.	2.5 equiv of arene-H	100%	60 (1.3:1), 40	-	-	
6.	7 equiv of arene-H	100%	78 (1.4:1), 22	-	-	1:30 h
7.	0.05 M Conc	100%	30 (1.6:1), 70	-	-	1:30 h
8.	0.5 M Conc	100%	80 (1.6:1), 20	-	-	1:30 h
9.	Entry 1 but in Ar condition	100%	72 (1.5:1), 28	-	-	1:30 h
10.	Entry 1 but at 20 °C	100%	85 (1.4:1), 15	-	-	1:30 h
11.	Entry 1 but at 30 °C	100%	80 (1.4:1), 20	-	-	1:30 h
12.	Entry 1 but at 60 °C	100%	60 (1.3:1), 40	-	-	1:30 h
13.	Entry 1 but using 1.2 equiv of $NaNO_2$/HCl	100%	na, 100	-	-	1 h/24 h[a]
14.	Entry 1 but using 1.2 equiv of isoamylnitrite	100%	na, 100	-	-	1 h/24 h[a]
15.	DMSO (0.5 M), 5 equiv of arene-H, *t*-BuONO (1.2 equiv) eosin-Y (0.25 mol%), 20 °C	100%	87 (1.5:1), 13	-	-	1:30 h

[a]No further investigation was done to characterize unknown product mass and spectra obtained was very messy. [b]eosin-y was not soluble

Scheme 53. Investigation of optimal conditions.

7.2 Investigation for the masking group

We continued investigating different protecting groups for the amine (Scheme 54). We wanted the chemistry to be operationally simple and highly functional, thus, we had several stipulations for the protecting group. First, we wanted it to survive the photocatalytic process. For example, it should not possess C–Hs susceptible to photocatalytic functionalization, or functional groups easily susceptible to redox chemistry. Second, it should be easily and quantitatively removed under conditions amenable to our oligoarene. While a softer requirement, if possible, it should positively influence the regioselectivity. Keeping these requirements in mind, we screened several protecting groups. We found that both the base sensitive trifluoroacetamide (entry 3) and the acid sensitive Boc group (entry 4) survived in the reaction conditions, and resulted in high NMR conversions to the desired products **54c** and **54d**. Whereas, in the presence of acyl (entry 1) and benzyl protecting group (entry 2), the reaction was very messy, and poor NMR conversions were obtained. We also employed nitro group in the reaction (entry 5), which could subsequently be hydrogenated to reveal the next amino group, however, in this case we observed all three possible regioisomers (*ortho*, *para*, and *meta* **54c**, **54d**, and **54e** respectively in very low isolated yields ~ 10% along with unknown side products **54f**).



entry	R_1	NMR conversion (**54c**+**54d**+**54e**)	(ortho/para/meta)	unknown (**54f**)	time
1.	NH-Acyl	40%	1.2/1/0	60%	24 h
2.	NH-Bn	<5%	na	94%	24 h
3.	$NH\text{-}COCF_3$	92%	2.5/1/0	8%	24 h
4.	NH-Boc	90%	1.3/1/0	10%	24 h
5.	NO_2	10% (isolated yield)	1.2/0.8/1	90%	24 h

Scheme 54. Investigation of potential protecting groups.

7.3 Investigation for the regioselective reaction conditions

At the outset, we realized for an iterative arylation to be useful, it must have near perfect regioselectivity. Anything less than this, would allow isomers to grow along with the desired product, and we anticipated that this would result in an ever increasingly difficult separation problem. Thus, we decided it was essential to address the modest regioselectivity that we were observing. In order to achieve regioselectivity in the reaction, we investigated severd strategies. We observed that replacing the H atom of N-Boc aniline with methyl group (Scheme 55, entry 1), resulted in selective formation of the *para* isomer **55c** in 30% isolated yield. While the yield left us wanting, we were pleased to see that no *ortho* or *meta* isomer was observed. This selectivity might be due to the steric hindrance generated by the methyl group located on the Boc-protected N-atom which shields the incoming azolyl radical from coupling at the *ortho* position. Given that the electronics of the ring are not expected to have changed substantially, it is not surprising that no *meta* addition product was observed. While this experiment was informative, removal of a methyl group is not a trivial feat, thus, it was not a general solution. Nonetheless, we utilized this finding to guide our next step.[14] We speculated that if we could replace the second H-atom of NH-Boc aniline with another acid-sensitive group such as MOM, Boc, or TMS, then we could remove both protecting groups using acidic conditions in one step. Along this line, we screened di-Boc aniline (entry 2). In this case, none of the desired product was formed, and complete conversion to an unknown side product was observed **55d**. We concluded that we probably did not want two electron withdrawing groups on the N-atom of aniline. Indeed, use of MOM/Boc protecting groups on N-atom of aniline (Scheme 55, entry 3), led to our desired *para* isomer in 62% (NMR conversion) along with unknown side products, but without other regioisomers was observed. The desired product was isolated (yield = 53%) and confirmed by ^{1}H NMR and ^{19}F NMR (entry 3). Other acid sensitive groups such as di-TMS aniline (entry 4) and mono-Boc and mono-TMS (entry 5) were tried under the reaction condition. However, we did not observe any reaction, and we recovered starting material at the end of the reaction. We also synthesized and tried di-Bn aniline (entry 6) under reaction conditions. In this case, none of the desired product was formed, but rather we

observed 100% conversion to a side product, whose structure was not determined. It is important to mention here that in each case, the unknown product of **55d** gave a mass spectrum by CMS, however, its structure was never determined.

An alternative strategy we investigated was to block the *ortho* position of the NH-Boc aniline, which would prevent access to the *ortho*-isomer. However, this strategy would add deblocking step. It is conceivable that this deblocking step could be done in a global fashion after all iterations are complete. Alternatively, if blocked with the right substituent (such as halogen) it might be possible to perform orthogonal chemistry after each iteration. In this case, we installed *ortho* methyls (entry 7) and observed a 52% isolated yield of the desired product. Ultimately, we have settled on utilizing the MOM and Boc protected aniline for accessing the *para* isomer selectively.

55a **55b** **55c** + unknown **55d**

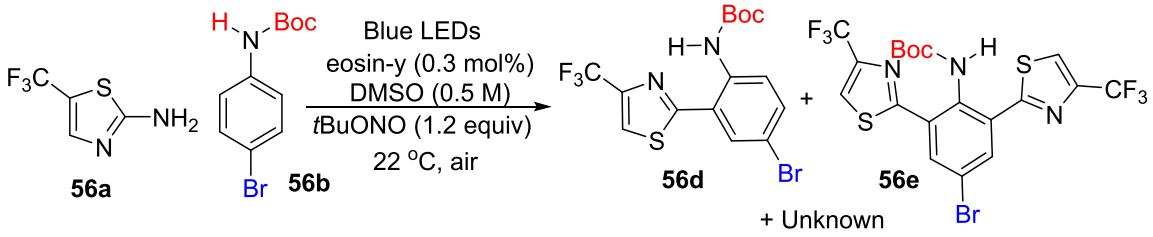
Entry	Modifications Pg_1	Pg_2	R_1	NMR conversion or yield	**Para 55c**	unknown **55d**	time
1.	Me	Boc	H	30% (isolated)	single isomer	70%	18 h
2.	Boc	Boc	H	na	na	100%	18 h
3.	Mom	Boc	H	62%	single isomer	38%	18 h
4.	TMS	TMS	H	na	na	na	18 h[a]
5.	TMS	Boc	H	na	na	na	18 h[b]
6.	Bn	Bn	H	na	na	100%	18 h[b]
7.	H	H	Me	52% (isolated)	single isomer	48%	18 h

[a]No reaction. [b]very messy spectra is obtained.

Scheme 55. Accessing the *para* isomer.

Next, we attempted to develop a strategy to obtain the *ortho* product selectively. Utilizing the blocking group strategy, we observed that by blocking the *para* position of N-Boc aniline with a bromine **56b**, (Scheme 56, entry 1) we were able to access *ortho* isomer **56d**, along with the di-*ortho* product **56e** in the ratio of (2:1) under the reaction conditions (entry 1). Thus, the use of bromine to block the *para* position

appears like a viable strategy to prevent *para* product, but introduces a greater tendency for over arylation. However, increasing further equivalents of **56b** from 5 equivalents to 10 equivalents improved the ratio to 5.3:1 (entry 2), suggesting that this is a solvable problem. In the future, it will be worthwhile to look at lower temperatures in order to increase the selectivity of the mono-arylated product. The bromo blocking group should be easily removed under Pd-catalyzed reaction conditions ultimately revealing the desired *ortho* isomer.[15] Alternatively, halogen-lithium exchange/protonation could potentially be used as well. In either case, this could be done at the end of the sequence to maximize the brevity of the sequence. Alternatively, the bromo group on oligoarenes provides opportunity for further elaboration of the products via more traditional cross-coupling methodologies, which would allow one to synthesize many biaryls from a rather simple one.



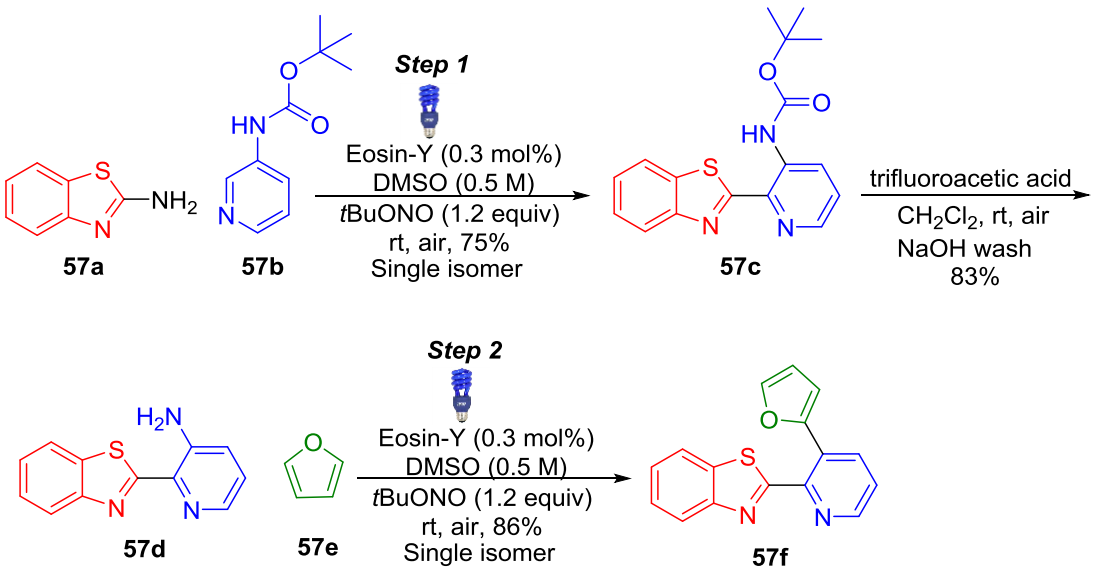
Entry	Equiv of **56b**	NMR conversion (**56d**+**56e**+ **unknown**)	**56d**	**56e**	Unknown	time
1	5 equiv	100%	53%	27%	20%	2 h
2	10 equiv	100%	69%	13%	18%	2 h

Scheme 56. Investigation for the conditions for the *ortho* isomer

7.4 Initial investigation for the scope of the reaction

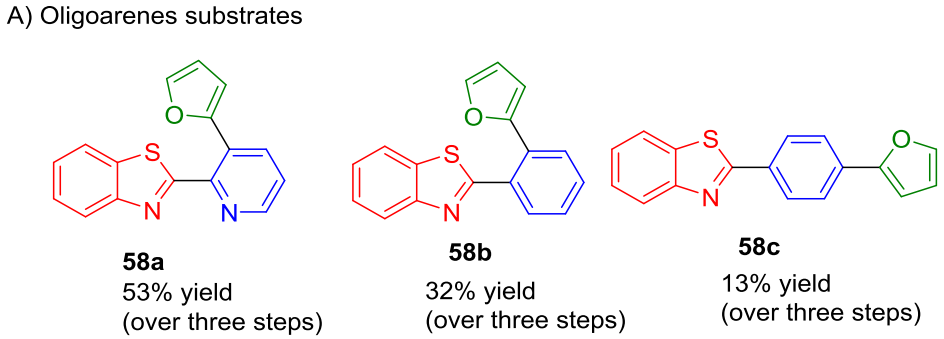
Having optimal conditions in hand, and a working strategy for controlling the regioselectivity, we started evaluating the scope of the reaction. We began our studies with 2-aminobenzothiazole **57a** with *tert*-butyl pyridin-3-ylcarbamate **57b** using *tert*-butylnitrite under eosin-Y catalyzed conditions and obtained the desired coupled product **57c** in 75% isolated yield as a single isomer (Step 1). Unmasking **57c** was accomplished with trifluoroacetic acid at room temperature, which was subsequently washed with 1 M sodium hydroxide to obtain neutral, coupled bi-heteroarene, **57d**. The unmasked **57d** (after

chromatographic isolation) was then subjected to the photocatalyzed conditions with furan **57e** (Step 2). The second coupling also proceeded efficiently, giving the desired oligoarene **57f** of type A-B-C in 86% yield.



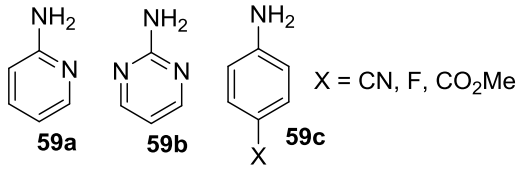
Scheme 57. Strategy for the synthesis of type (A-B-C) oligoarene

The first coupled *ortho* and *para* isomer products of **58b** and **58c** are derived from 2-aminobenzothiazole in one reaction. Both isomers were separated on coulmn. After deprotection step, they were coupled with furan separtely under photocatalyzed reaction conditions. The experimental details of synthesizing of other oligoarenes are discussed in the following experimental section (Section 7.6).



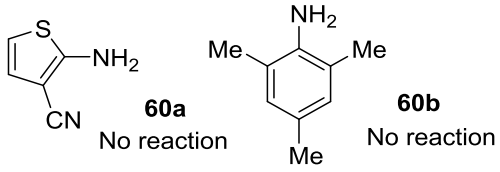
Scheme 58. Characterized oligoarene substrates

In addition to this, we tried other heteroarenes such as pyridine **59a**, pyrimidine **59b** and anilines substituted with electron withdrawing groups **59c**. We observed the mass for the desired coupled molecules (by mass on CMS). However, we have not yet isolated, quantified, or characterized these molecules.



Scheme 59. Other working anilines in the reaction conditions

We tried 2-amino thiophene **60a** and electron rich aniline **60b** under the reaction conditions. In both of these cases, we did not observe any reaction, and starting materials were recovered. This suggests that the diazotization may be problematic in highly hindered amines and certain thiophenes.



Scheme 60. (Hetero)aniline which did not result in diazotization in the reaction

7.5 Conclusion

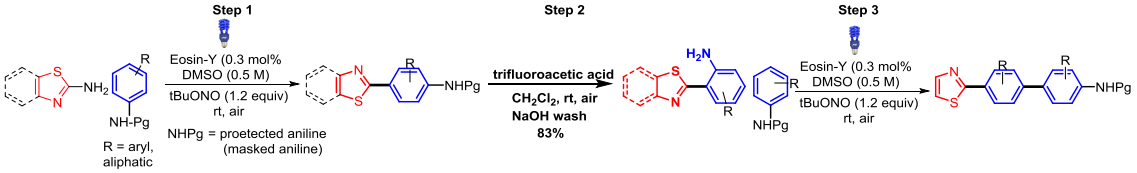
We have initiated the study of the iterative photocatalyzed (hetero)arylation of aryl amines, and have demonstrated the proof of concept. Key to the success is the use of an effective masking group for one of the N-atom of the amine group. Further studies are required before this technology is ready and in the future, we will investigate the directing ability of the N-protecting group during the addition. Additionally, future studies will also seek to increase the yield and streamline the sequence. If successfully completed, the applicability of this strategy for the iterative synthesis of oligoarene derivatives will be of interest, and highly enabling to a large community of scientists, who are interested in the SAR of materials.

7.6 Experimental

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Anilines and other arene-H utilized were purchased from Sigma-Aldrich, Oakwood, VWR as well as from Fisher Scientific Ltd. *tert*-butylnitrite and eosin-Y was purchased from Sigma-Aldrich. Reactions were monitored by thin layer chromatography (TLC) on Sorbent Technology Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm and were visualized with ultraviolet light.

Photocatalytic reactions were set up in a light bath as described below. Blue LEDs in the form of strips 18 LEDs/ft from Solid Apollo) were wrapped around the walls of glass crystallization dish and secured with masking tape and then wrapped with aluminum foil. A lid which rest on the top was fashioned from cardboard and holes were made such that reaction tubes were held firmly in the cardboard lid which was placed on the top of bath. Water was added to the bath such that the tubes were partially submerged in the water which was maintained at 45 ^{o}C with the aid of a sand bath connected to a thermostat. Isolations were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Redisep Rf normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and evaporative light scattering detection. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak.

General procedure A for the photocatalytic arylation of bromoazoles with Arene



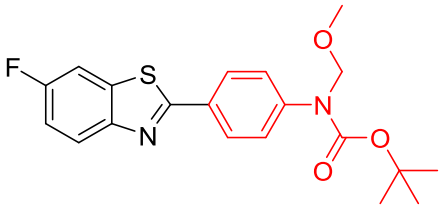
Step 1 - A 12×75 mm borosilicate tube fitted with a rubber septum was charged with 2′,4′,5′,7′-tetrabromofluorescein, eosin-y (0.0025 equiv, X mL of 0.15 mM stock solution of catalyst in DMSO, where X mL of DMSO is used to make 0.5 M with respect to the aniline), aniline (1 equiv), arene-H (5 equiv) and *tert*-butylnitrite (1.2 equiv), and the reaction mixture was set up in the presence of air. The tube was placed

in a light bath (description above) and the lower portion of the tube was submerged under the water bath which was maintained at 20 °C. The reaction was monitored by TLC and ^{1}H NMR. After the complete consumption of aniline, reaction mixture diluted with ethyl acetate (EtOAc) and washed with dI water (two times), then again reextracted the water layer with EtOAc (three times). In every step of workup, each layer is checked with CMS spectrometer to avoid the loss of the product in water layer. The organic portions were combined and dried over anhydrous $MgSO_4$. The crude product was concentrated *in vacuo* and purified via normal phase chromatography

Step 2 - A solution containing 1 equiv of the BOC-protected compound (from step 1) in 20 equiv of TFA (trifluoroacetic acid) was stirred at room temperature, until the starting material is consumed on tllc plate. Then, the solvent was eliminated under vacuum to generate the trifluoroacetate salt. This salt was redissolved in 10-20 mL of an aqueous solution of NaOH (2M), until the ph of the solution gets neutral on ph paper and then washed with DCM (3×15 mL). The organic layer was washed with brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give the corresponding free amine.

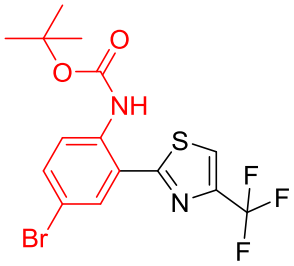
Step 3 – The procedure is identical to step 1

55c, entry 2) *tert*-butyl (4-(6-fluorobenzo[d]thiazol-2-yl)phenyl)(methoxymethyl)carbamate



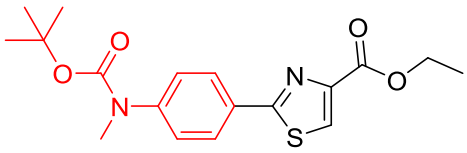
Step 1 The **general procedure A (step 1)** was followed using 6-fluorobenzo[d]thiazol-2-amine (25 mg, 0.15 mmol), *tert*-butyl (methoxymethyl)(phenyl)carbamate (280 mg, 0.90 mmol), *tert*-butylnitrite (18 mg, 0.18 mmol) and 0.3 mL of stock solution of eosin-y in DMSO was used to afford **55c, entry 2** in 53% yield (30 mg, 0.08 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 20% on a 24 g basic alumina column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 3H), 7.51 (dt, *J* = 8.1, 2.5, 2.5 Hz, 1H), 7.38 (dd, *J* = 7.9, 3.5 Hz, 2H), 7.15 (dt, *J* = 9.0, 2.3, 2.3 Hz, 1H), 4.97 (s, 2H), 3.38 (s, 3H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.72 (dtd, *J* = 61.1, 8.7, 8.6, 4.8 Hz).

56d) ethyl 2-(5-bromo-2-((ethoxycarbonyl)amino)phenyl)thiazole-4-carboxylate



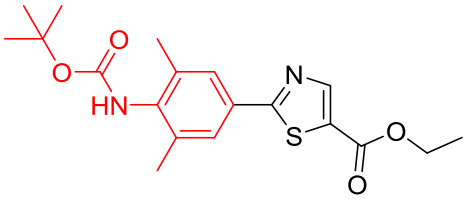
The **general procedure A (step 1)** was followed using 4-(trifluoromethyl)aniline (50 mg, 0.29 mmol), *tert*-butyl (4-bromophenyl)carbamate (404 mg, 1.48 mmol), *tert*-butylnitrite (36 mg, 0.35 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **56d** in 76% yield (100 mg, 0.22 mmol, includes both mono and di *ortho* isomers (5:1 (crude) and 5.3:1 (isolated) as a solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. Spectra of mono isomers - ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.39 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.77 (s, 1H), 7.51 (dd, *J* = 9.1, 2.3 Hz, 1H), 1.53 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.37.

55c, entry 1) ethyl 2-(4-((tert-butoxycarbonyl)(methyl)amino)phenyl)thiazole-4-carboxylate



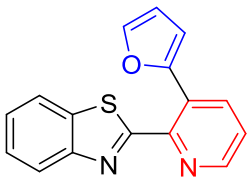
The **general procedure A (step 1)** was followed using ethyl 2-aminothiazole-5-carboxylate (50 mg, 0.29 mmol), *tert*-butyl methyl(phenyl)carbamate (301 mg, 1.45 mmol), *tert*-butylnitrite (36 mg, 0.35 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **55c,entry 1** in 30% yield (31.4 mg, 0.087 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 4.45 (td, *J* = 7.0, 6.8, 1.6 Hz, 2H), 3.30 (s, 3H), 1.47 (s, 9H), 1.43 (t, *J* = 7.1, 7.1 Hz, 3H). Spectra contains coupled N-methylaniline.

55c, entry 7) ethyl 2-(4-((tert-butoxycarbonyl)amino)-3,5-dimethylphenyl)thiazole-5-carboxylate



The **general procedure A (step 1)** was followed using ethyl 2-aminothiazole-5-carboxylate (50 mg, 0.29 mmol), *tert*-butyl (2,6-dimethylphenyl)carbamate (320 mg, 1.45 mmol), *tert*-butylnitrite (36 mg, 0.35 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **55c, entry 7** in 52% yield (57 mg, 0.15 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 1H), 4.44 (qd, *J* = 7.1, 7.1, 7.1, 3.0 Hz, 2H), 2.42 (s, 3H), 2.31 (d, *J* = 1.9 Hz, 3H), 1.50 (s, 9H), 1.43 (t, *J* = 3.7, 3.7 Hz, 3H).

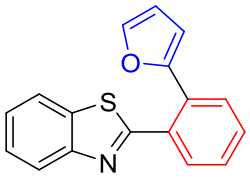
57a) 2-(3-(furan-2-yl)pyridin-2-yl)benzo[d]thiazole



The **general procedure A((step 1)** was followed using 2-amino benzothizole (50 mg, 0.33 mmol), *tert*-butyl pyridin-3-ylcarbamate (320 mg, 1.65 mmol), *tert*-butylnitrite (41 mg, 0.4 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **57a,** tert-butyl (2-(benzo[d]thiazol-2-yl)pyridin-3-yl)carbamate in 75% yield (81 mg, 0.25 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. (step 2) Next, using *tert*-butyl (2-(benzo[d]thiazol-2-yl)pyridin-3-yl)carbamate (81 mg, 0.25 mmol) in 20 equiv of TFA (trifluoroacetic acid) was stirred at room temperature, until the starting material is consumed on tlc plate. This salt was redissolved in 10-20 mL of an aqueous solution of NaOH (2M), until the ph of the solution gets neutral on ph paper and then washed with DCM (3×15 mL). The organic layer was washed with brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give the corresponding free amine, 2-(benzo[d]thiazol-2-yl)pyridin-3-amine (47 mg, 0.21 mmol). (Step 3) the general procedure A was repeated using 2-(benzo[d]thiazol-2-yl)pyridin-3-amine (47 mg, 0.21 mmol), furan (71.4 mg, 1.05 mmol), *tert*-butylnitrite (26 mg, 0.25 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **57a,** 2-(3-(furan-2-yl)pyridin-2-yl)benzo[d]thiazole in 86% yield (50.2 mg, 0.18 mmol) as a oil. The substrate

was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 5% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.6 Hz, 1H), 8.13 (dt, *J* = 8.0, 1.4, 1.4 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.46 (m, 4H), 6.82 (d, *J* = 3.4 Hz, 1H), 6.48 (dt, *J* = 3.1, 1.4, 1.4 Hz, 1H).

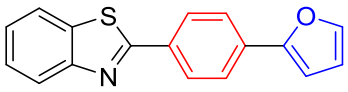
57b) a) 2-(2-(furan-2-yl)phenyl)benzo[d]thiazole



The **general procedure A((step 1)** was followed using 2-amino benzothizole (100 mg, 0.66 mmol), *tert*-butyl phenylcarbamate (636 mg, 3.3 mmol), *tert*-butylnitrite (82 mg, 0.80 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **57b,** tert-butyl (2-(benzo[d]thiazol-2-yl)phenyl)carbamate and tert-butyl (4-(benzo[d]thiazol-2-yl)phenyl)carbamate in 82% yield (176 mg, 0.54 mmol consists of both *ortho* 125 mg and 51 mg of *para* isomers) as a solid. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 8% *ortho* isomer and at 40% *para* isomer on a 24 g silica column. (step 2) Next, using tert-butyl (2-(benzo[d]thiazol-2-yl)phenyl)carbamate (125 mg, 0.38 mmol) in 20 equiv of TFA (trifluoroacetic acid) was stirred at room temperature, until the starting material is consumed on tlc plate. This salt was redissolved in 10-20 mL of an aqueous solution of NaOH (2M), until the ph of the solution gets neutral on ph paper and then washed with DCM (3×15 mL). The organic layer was washed with brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give the corresponding free amine, 2-(benzo[d]thiazol-2-yl)aniline (93 mg, 0.28 mmol). (Step 3) the general procedure A was repeated using 2-(benzo[d]thiazol-2-yl)aniline (93 mg, 0.28 mmol), furan (190 mg, 2.8 mmol), *tert*-butylnitrite (34 mg, 0.28 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **57b,** 22-(2-(furan-2-yl)phenyl)benzo[d]thiazole in 75% yield (59 mg, 0.21 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 15% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.77 – 7.71 (m, 1H), 7.58 – 7.53 (m, 1H), 7.53 – 7.48 (m,

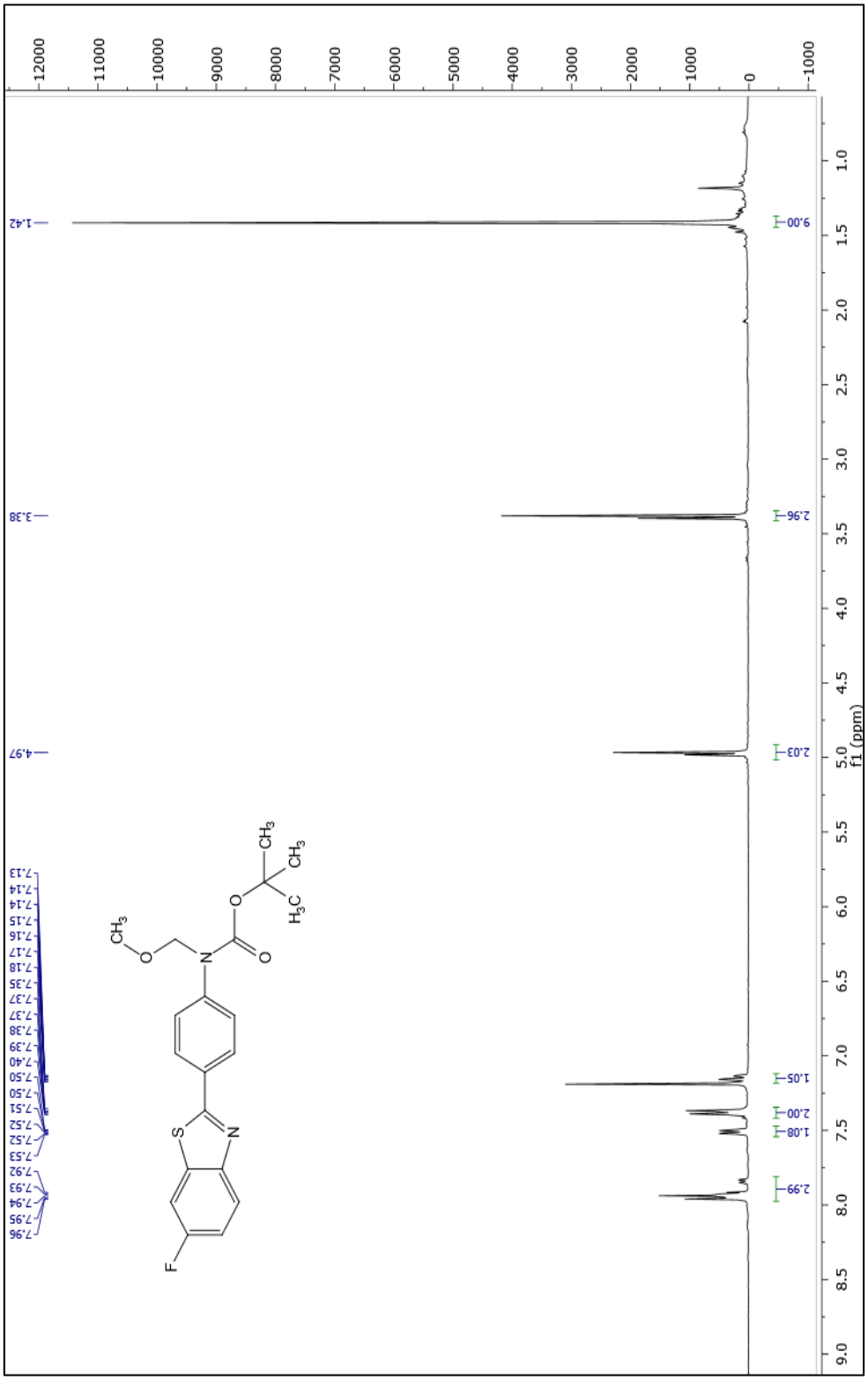
1H), 7.48 – 7.44 (m, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.41 – 7.36 (m, 1H), 6.37 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (d, *J* = 3.3 Hz, 1H).

57c) b) 2-(4-(furan-2-yl)phenyl)benzo[d]thiazole

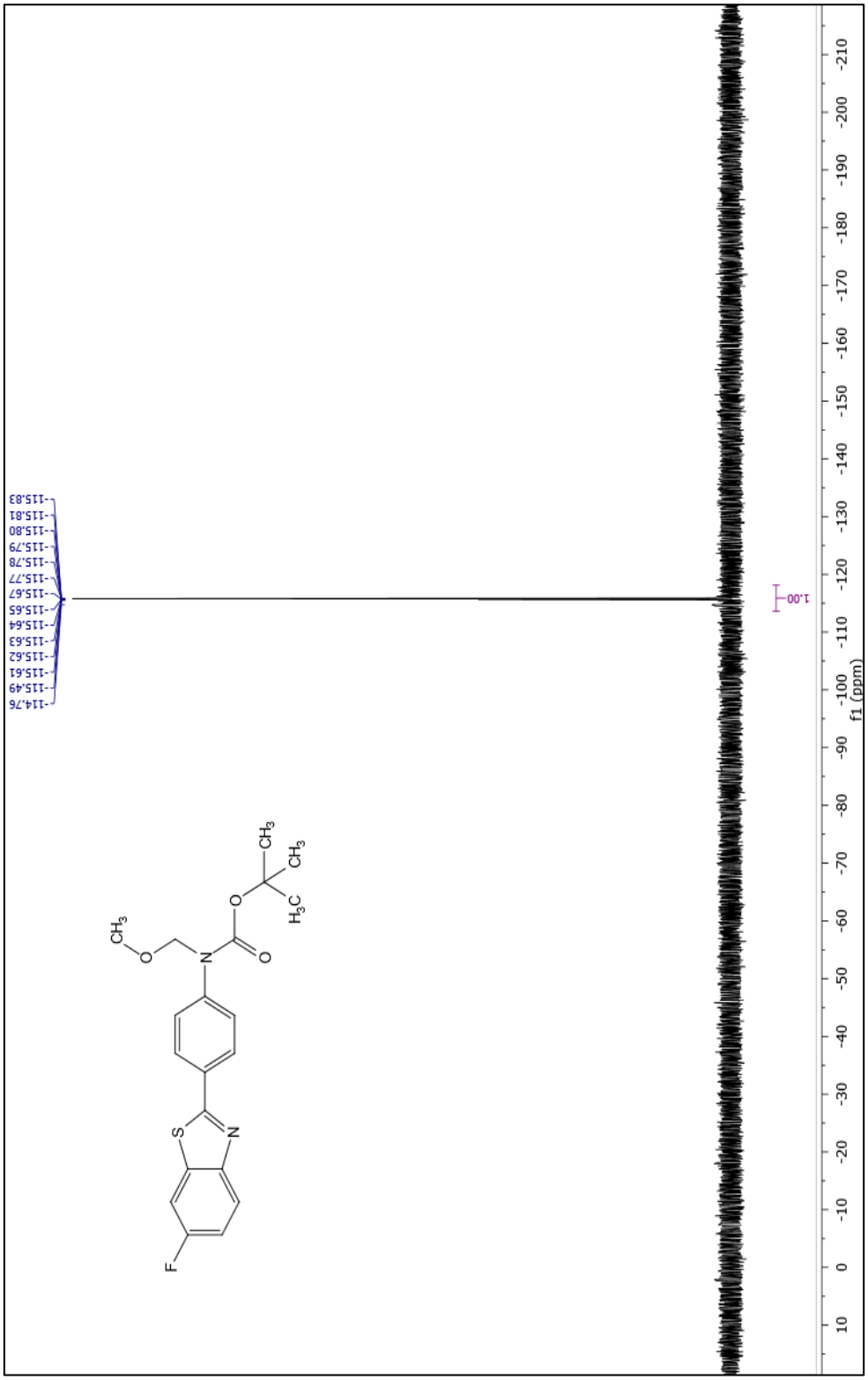


The general procdeure A (step 2) was performed using using tert-butyl (4-(benzo[d]thiazol-2-yl)phenyl)carbamate (51 mg, 0.16 mmol) in 20 equiv of TFA (trifluoroacetic acid) was stirred at room temperature, until the starting material is consumed on tlc plate. This salt was redissolved in 10-20 mL of an aqueous solution of NaOH (2M), until the ph of the solution gets neutral on ph paper and then washed with DCM (3×15 mL). The organic layer was washed with brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give the corresponding free amine, 4-(benzo[d]thiazol-2-yl)aniline (26 mg, 0.12 mmol). (Step 3) the general procedure A was repeated using 4-(benzo[d]thiazol-2-yl)aniline (26 mg, 0.12 mmol), furan (81 mg, 1.2 mmol), *tert*-butylnitrite (15 mg, 0.14 mmol) and 0.5 mL of stock solution of eosin-y in DMSO was used to afford **57c,** 2-(4-(furan-2-yl)phenyl)benzo[d]thiazole in 72% yield (24 mg, 0.086 mmol) as a oil. The substrate was purified via automated flash chromatography using EtOAc in hexanes (0% to 100%) with product eluting at 30% on a 24 g silica column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 2H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.56 – 7.47 (m, 2H), 7.40 (td, *J* = 7.7, 7.3, 1.2 Hz, 1H), 6.79 (d, *J* = 3.4 Hz, 1H), 6.60 – 6.48 (m, 1H).

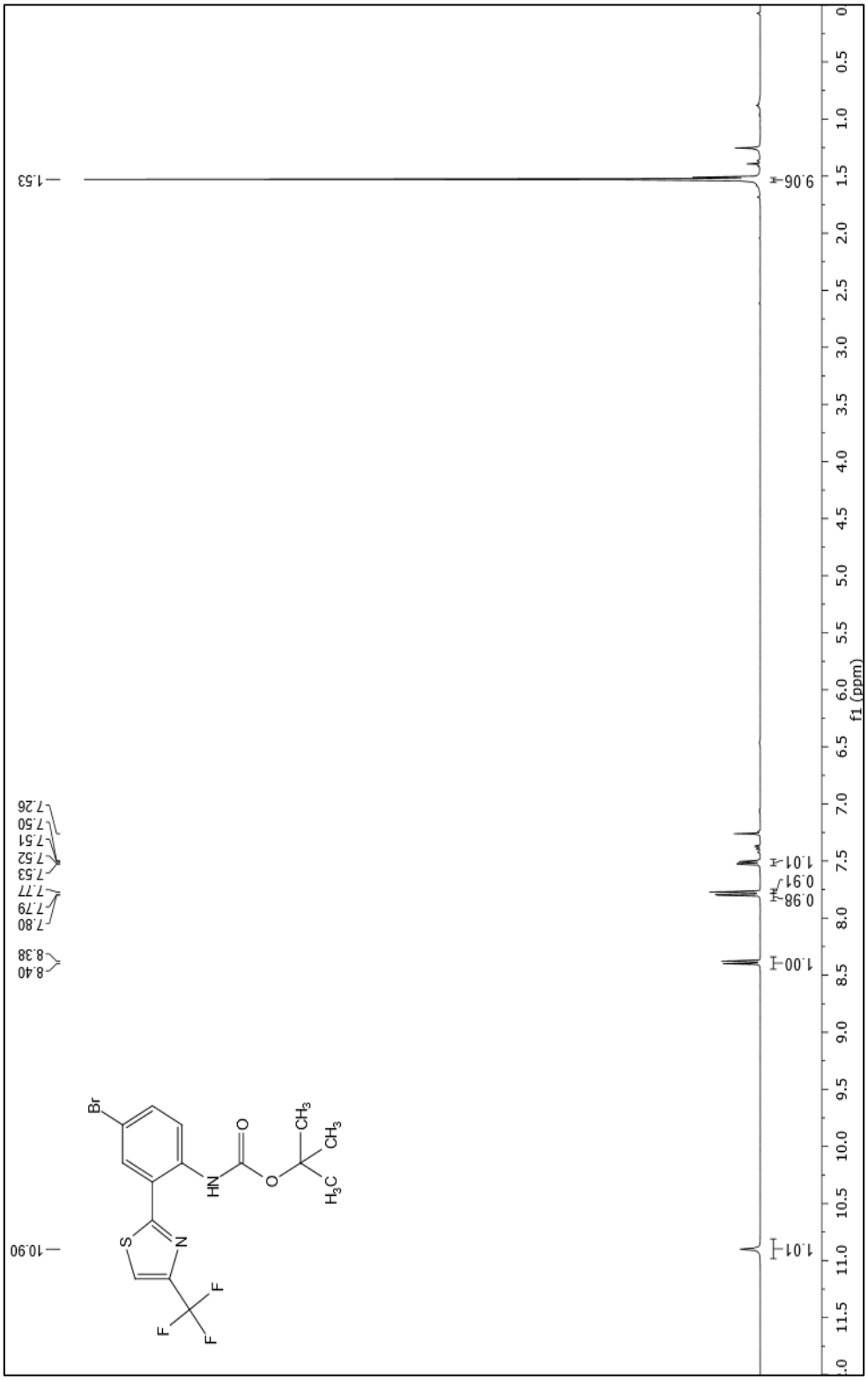
55c, entry 2) *tert*-butyl (4-(6-fluorobenzo[d]thiazol-2-yl)phenyl)(methoxymethyl)carbamate



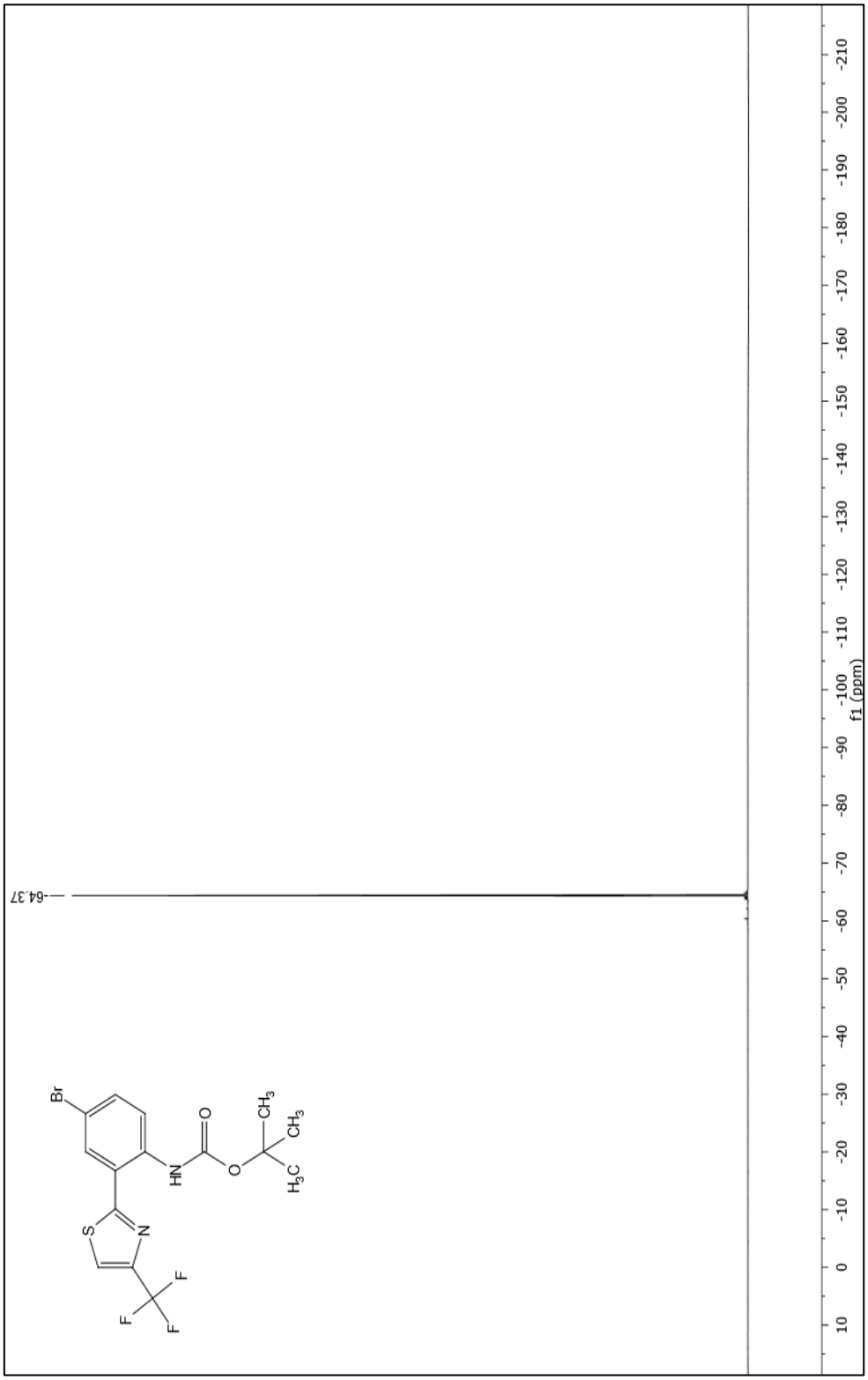
55c, entry 2) *tert*-butyl (4-(6-fluorobenzo[d]thiazol-2-yl)phenyl)(methoxymethyl)carbamate



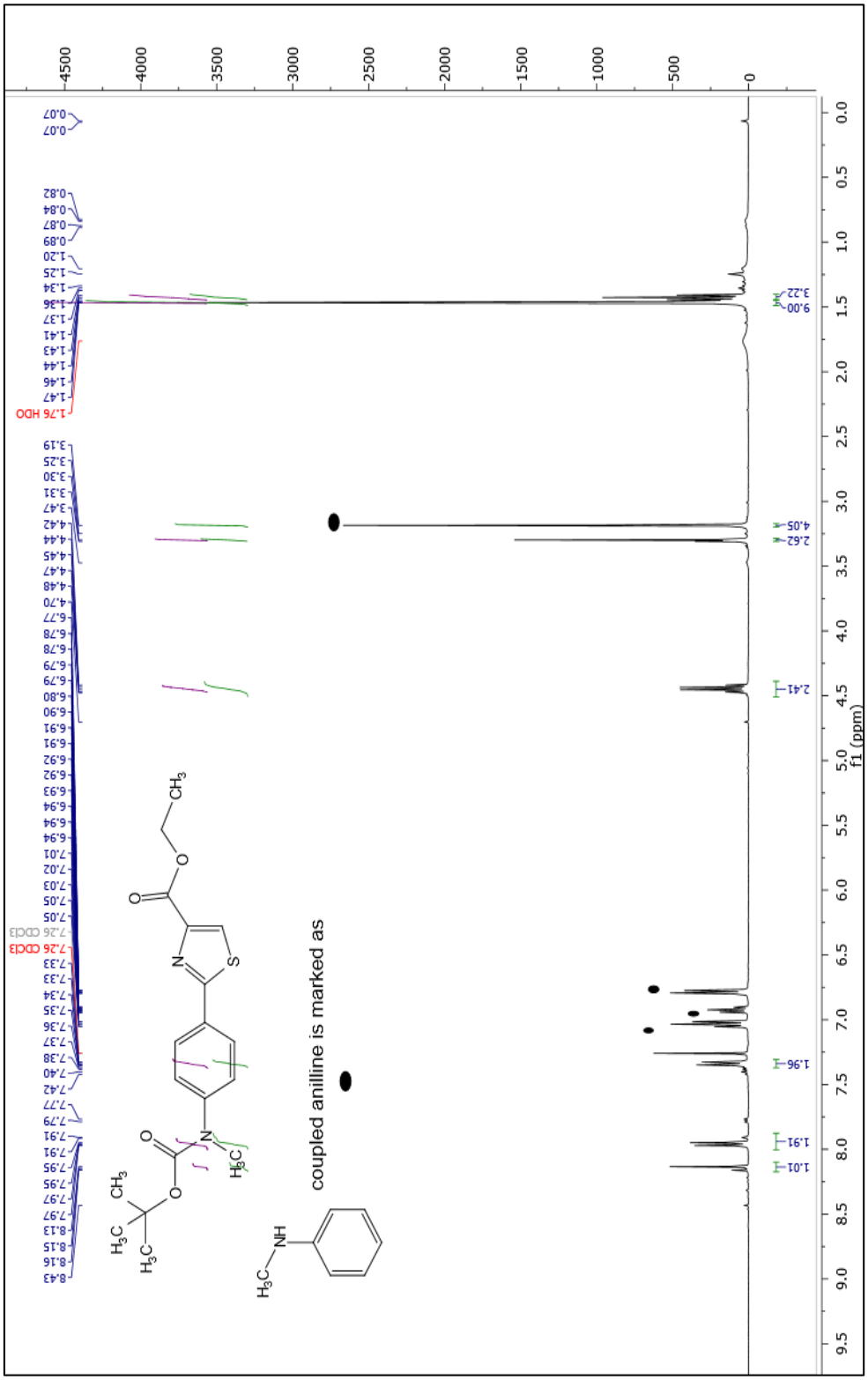
56d) ethyl 2-(5-bromo-2-((ethoxycarbonyl)amino)phenyl)thiazole-4-carboxylate



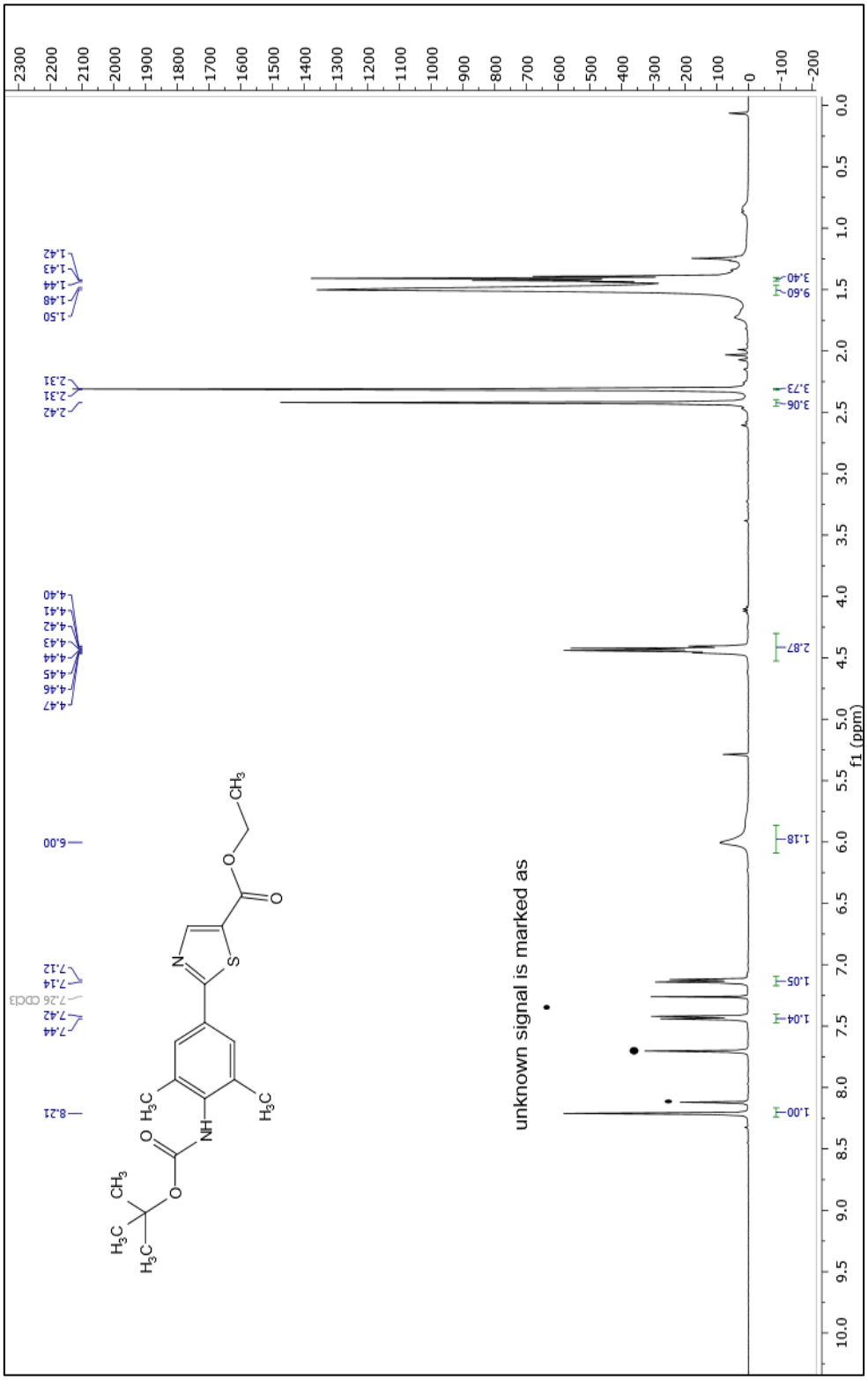
56d) ethyl 2-(5-bromo-2-((ethoxycarbonyl)amino)phenyl)thiazole-4-carboxylate



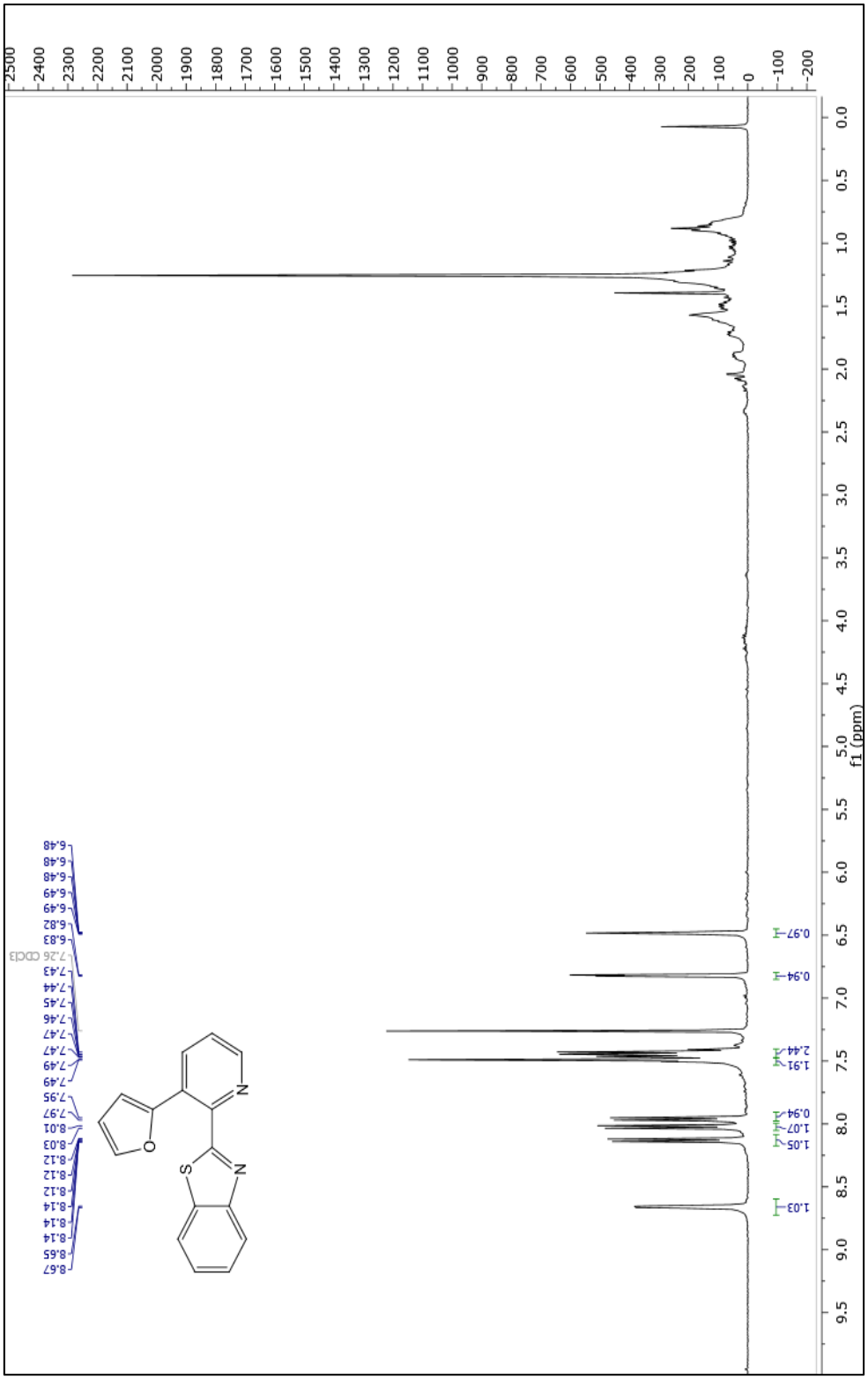
56d) ethyl 2-(4-((tert-butoxycarbonyl)(methyl)amino)phenyl)thiazole-4-carboxylate



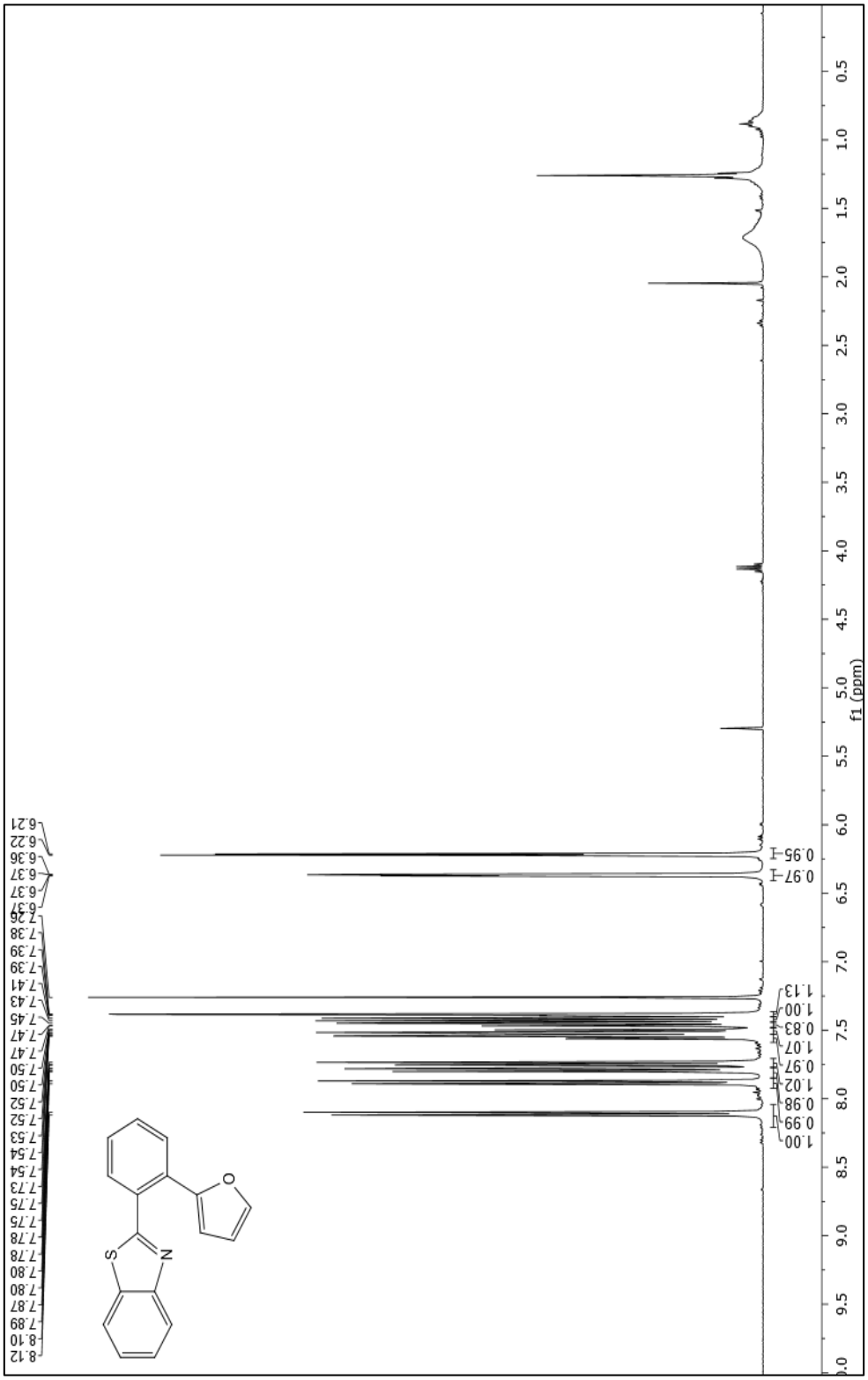
55c, entry 7) ethyl 2-(4-((tert-butoxycarbonyl)amino)-3,5-dimethylphenyl)thiazole-5-carboxylate



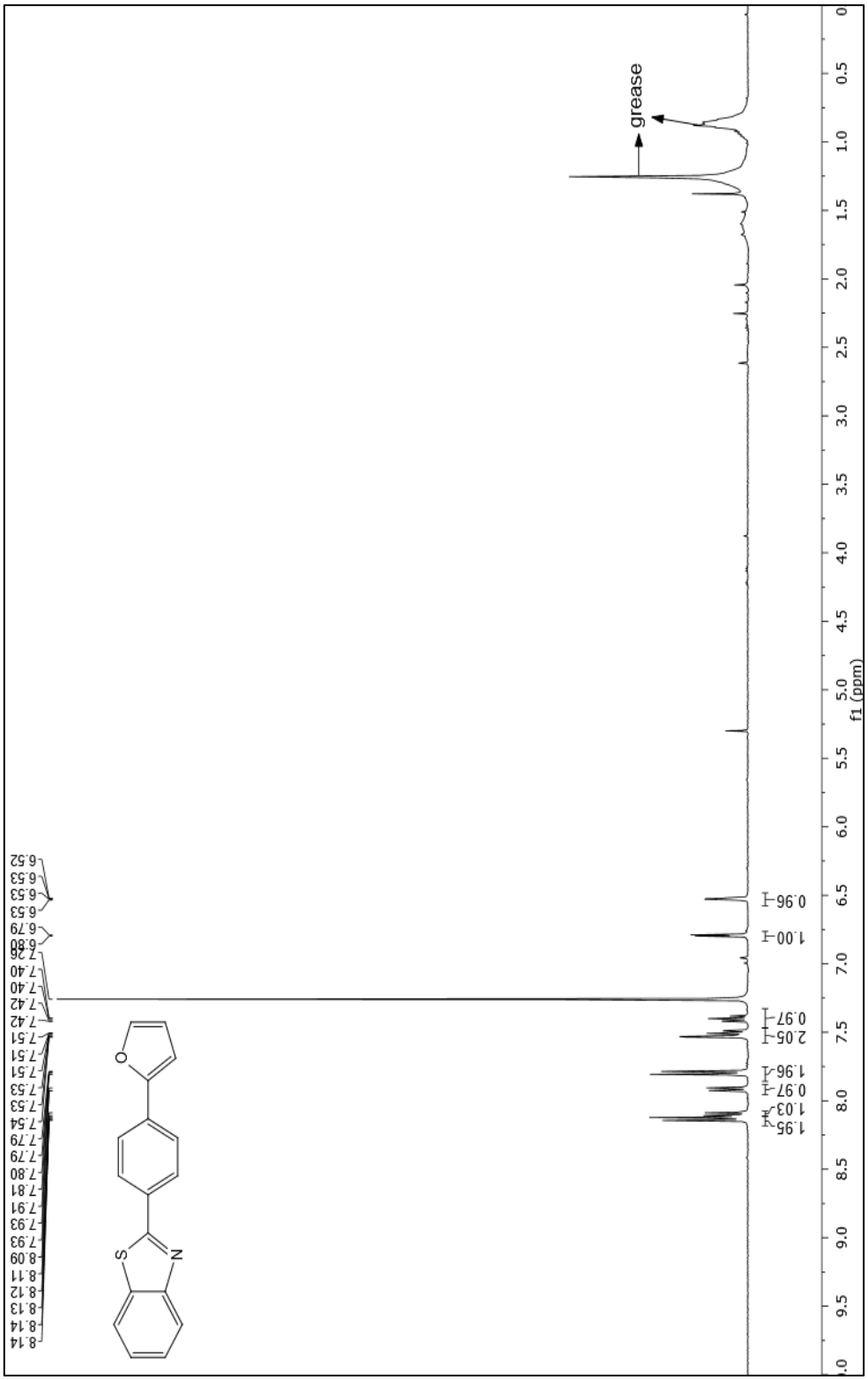
57a) 2-(3-(furan-2-yl)pyridin-2-yl)benzo[d]thiazole



57b) a) 2-(2-(furan-2-yl)phenyl)benzo[d]thiazole



57c) b) 2-(4-(furan-2-yl)phenyl)benzo[d]thiazole



7.7 References

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APPENDICES

Intersystem crossing (ISC).

Metal Ligand Charge Transfer (MLCT)

Single Electron Transfer (SET)

Regioisomeric ratio (rr)

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

Structure activity relationship (SAR)

Trimethylamine (TEA, Et_3N)

Di-isoprpylethylamine (DIPEA)

Dichloromethane (DCM)

Acetonitrile (MeCN)

Photoinduced electron transfer (PET)

Hydrogen atom transfer (HAT)

Methanol (MeOH)

N, N-Dimethylmethanamide (DMF)

Tetrahydrofuran (THF)

Thin layer chromatography (TLC)

Methanol (MeOH)

VITA

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