Synthesis of 2-aryl Pyrroles, Prodigiosene *F*-BODIPYs and B-ring Modified Prodigiosenes

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

ABSTRACT

Pyrrole constitutes the structural backbone of many natural products including heme and prodigiosin. This tripyrrolic natural product, and its synthetic analogues termed prodigiosenes, are reported to have an impressive array of biological activities including but not limited to immunosuppressive, antimalarial, anticancer, and antimicrobial effects. While the anticancer properties of these compounds are well known, the exact mechanism by which they impart such activity is unclear. When prodigiosene is protonated, is becomes an excellent ion transporter, and one proposed mechanism involves apoptosis of cancer cells induced via alteration of intracellular pH.

These tripyrrolic frameworks are not only effective at transporting ions, but also readily chelate to metals. When complexed with boron, a fluorescent dye known as a boron dipyrromethene (BODIPY) is formed. These dyes have attracted much attention due to their chemical robustness, large molar absorption coefficients, high fluorescence quantum yields and high photostability. These criteria are critical when developing dyes for fluorescence imaging and other biomedical applications.

The work presented herein focuses on the synthesis of pyrrolic compounds, specifically 2-aryl pyrroles, prodigiosene *F*-BODIPYs, and B-ring modified prodigiosenes. The first project involved the synthesis of a series of prodigiosene *F*-BODIPYs with varying substitution on each of the pyrrolic rings. This published work was the first of its kind to study how varying substitution about the prodigiosene core affects the photophysical properties of the corresponding *F*-BODIPYs. The second project, also published work, focused on the synthesis of 2-aryl pyrroles via decarboxylative cross-coupling. The final project involved the total synthesis of a series of prodigiosenes modified with thioether functionality on the B-ring in efforts to enhance its biological activity. Previous work in the synthesis and study of prodigiosenes has involved modifications to the A-ring, B-ring and C-ring. However, there have been no reported studies focused on modifying the ether functionality on the B-ring, which is known to be responsible for much of the biological activity of prodigiosin.

LIST OF ABBREVIATIONS AND SYMBOLS USED

abs	absorbance
bs	broad singlet
Boc	tert-butyloxycarbonyl
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	dichloromethane
1,2-DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformaide
DME	dimethoxyethane
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
em	emission
equiv	equivalent
F-BODIPY	difluoro-borondipyrromethene
FDA	Food and Drug Administration
GP	general procedure
h	hours
HRMS	high resolution mass spectrometry
J	coupling constant
LRMS	low resolution mass spectrometry
m	multiplet
M.p.	melting point
Ms	mesyl
NBS	N-bromosuccinimide
NIR	near infrared region
NMR	nuclear magnetic resonance
PDT	photodynamic therapy
PET	photo-induced electron transfer
q	quartet
R_f	retention factor
rt	room temperature

s	singlet
SEM	trimethylsilylethoxymethyl
t	triplet
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMOF	trimethyl orthoformate
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	tosyl
VEGF	Vascular Endothelial Growth Factor
δ	chemical shift
ε	extinction coefficient
Φ_F	fluorescence quantum yield
Δf	solvent orientation polarizability
μW	microwave

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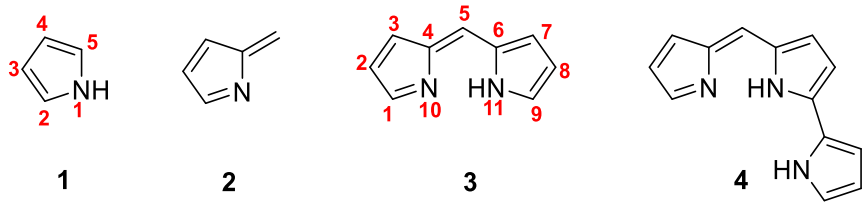
CHAPTER 1 - Introduction

1.1 Pyrrole and Pyrrolic Compounds

Pyrrole (**1**, Figure 1) was first discovered in coal tar by Runge in 1834.[1] Pyrrole is a planar, five-membered aromatic heterocycle containing a nitrogen atom. The aromaticity of pyrrole, like benzene, is due to the conjugation of six pi electrons within a planar cyclic structure. The biological importance of pyrrole is highly realized as this structural skeleton is found in an array of natural products including heme, chlorophyll, bile pigments and enzymes such as cytochromes.[2] When a pyrrolic unit is connected to an azafulvene (**2**) through the 2-position, a dipyrromethene, or dipyrrin (**3**), is created. The unsubstituted dipyrrin is highly unstable due to its susceptibility to be attacked by nucleophiles.[3] Stability of the dipyrrin core is improved via alkyl substitution at the 1-, 2-, 3-, 7-, 8-, and 9-positions or via aryl substitution at the 5-position. Pyrrolyldipyrrins (**4**) are a class of dipyrrins that feature a third pyrrolic unit attached to the 9-position. Building from one pyrrole unit to two (dipyrrin) and to three (pyrrolyldipyrrin) extends the pi conjugation. As a result, these chromophores have a multitude of uses in the life sciences and material chemistry.[4]



1 **2** **3** **4**

*Figure 1. Structure of pyrrole (**1**), azafulvene (**2**), dipyrrin (**3**) and pyrrolyldipyrrin (**4**)*

1.2 Dipyrrins and their Coordination Complexes

Deprotonation of the nitrogen atom of dipyrrins results in a monoanionic dipyrrinato ligand that is stabilized via resonance (Figure 2).[5] The nitrogen atoms of the dipyrrinato ligand readily donate electrons to metal ions forming stable metal coordinate complexes.[4] The literature reports coordination of dipyrrins to a variety metals including cadmium, cobalt, copper, iron, gallium, indium, nickel and zinc (Figure 3).[4, 6]

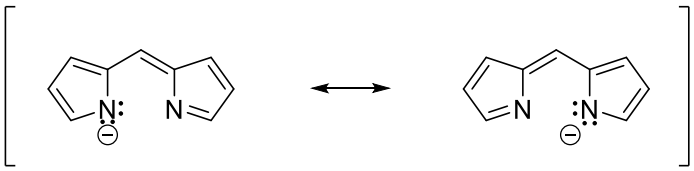


Figure 2. Resonance structures of the deprotonated dipyrrin framework

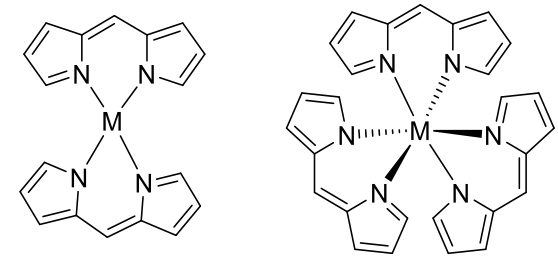


Figure 3. Metal complexes of dipyrrins

The most prominent type of dipyrrinato complex features coordination of the dipyrrinato ligand framework to a $–BF_2$ unit to a create 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (*F*-BODIPY), see Figure 4. Complexation of the dipyrrin with boron creates a fully conjugated, rigid structure. As a result, these complexes are highly fluorescent, with absorption and emission wavelengths typically centered around 530 nm.[7] *F*-BODIPYs are chemically robust, as well as thermally, photochemically and physiologically stable. They exhibit sharp fluorescence spectra, with high molar extinction coefficients and quantum yields, making them useful in a myriad of applications, including cell imaging, chemosensors and laser dyes.[7]

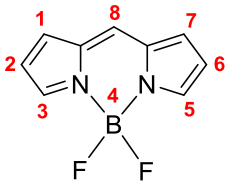


Figure 4. Skeletal structure of F-BODIPYs

1.3 Prodigiosin and Synthetic Derivatives

The pyrrolyldipyrrin structure constitutes the skeletal backbone of the natural product prodigiosin (**5**). This tripyrrolic red pigment is produced as a secondary metabolite from bacteria such as *Serratia marcesens*.[8-9] In the past few decades, prodigiosin has attracted much attention due to its potent biological activity and potential as an anticancer

agent.[10-11] However, despite the anticancer activity of the natural product, prodigiosin was not pursued as a drug candidate due to its cytotoxicity to healthy cells.[12] This led to further investigations and the synthesis of analogs of prodigiosin.[13] In the Thompson group, a series of prodigiosin analogues (termed prodigiosenes)[14] have been synthesized; differing structurally in the placement of an extra methyl group at the 4-position of the C-ring (Figure 5). Synthetic analogues of the natural product exhibit significant biological activity, including immunosuppressive,[15] anti-malaria,[16] anti-microbial[17] and anti-cancer activity.[18-19] In fact, the synthetic analogue Obatoclax (GX15-070), which differs structurally from prodigiosene via the presence of an indole moiety in lieu of the A-ring pyrrole, has been used in Phase I and Phase II clinical trials as an anticancer agent.[20] Unfortunately, all clinical trials involving Obatoclax were terminated by Teva Pharmaceuticals citing business decisions as the reason.[21]

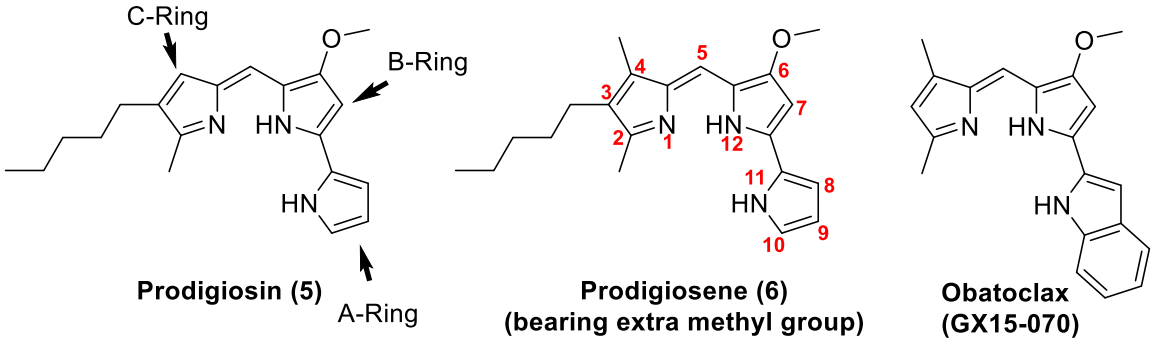


Figure 5. Natural product prodigiosin (5), synthetic analog (6) and Obatoclax

1.4 Chemistry of Prodigiosin

The structure of prodigiosin was first elucidated in the early 1960s through partial and total synthesis.[22-23] Conventionally, the rings of the pyrrolyldipyrrin are labelled as the A-, B-, and C- rings (Figure 5). The anticancer activity of prodigiosin has been attributed to a variety of mechanisms. One such mechanism is the ability of prodigiosin to transport ions such as H^+/Cl^-.[10, 24] This is due to the ability of prodigiosin to interconvert between its cis and trans rotamers, making it an effective ion transporter. When prodigiosin acts as an H^+/Cl^- symporter, all three pyrrolic nitrogens bind to the chloride ion (Figure 6).

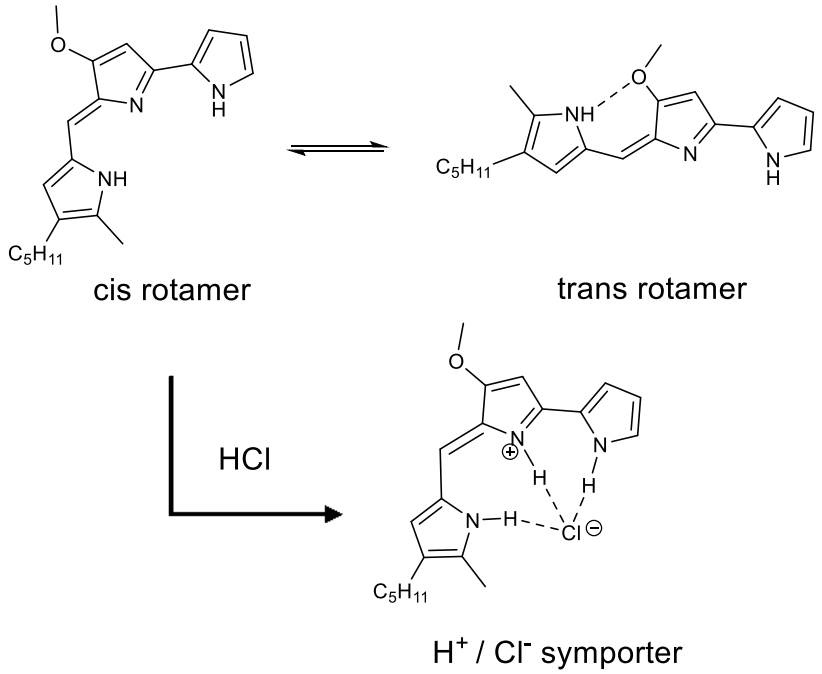


Figure 6. Cis and trans rotamers of prodigiosin; prodigiosin as an H^+/Cl^- symporter

1.5 Synthesis of Prodigiosene

Given the excellent biological profile of prodigiosin and synthetic analogs of the natural product, much effort has been invested to develop novel synthetic routes for these biologically important compounds. The prodigiosene core is assembled through two potential routes: by connecting the A- and B-rings followed by the C-ring, or alternatively, by connecting the C- and B- rings followed by the A-ring (Figure 7).

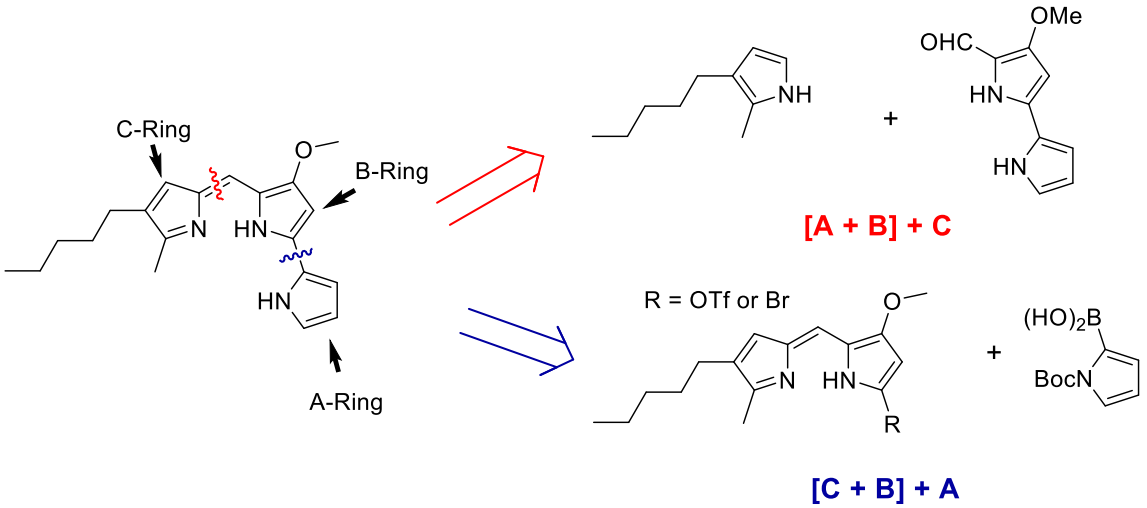
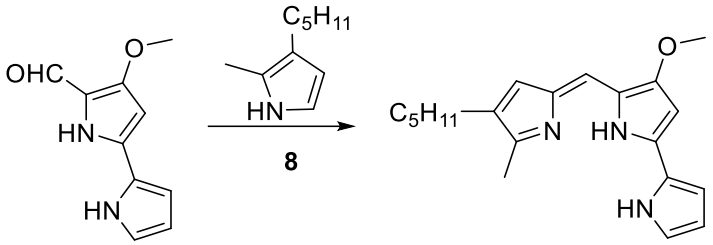


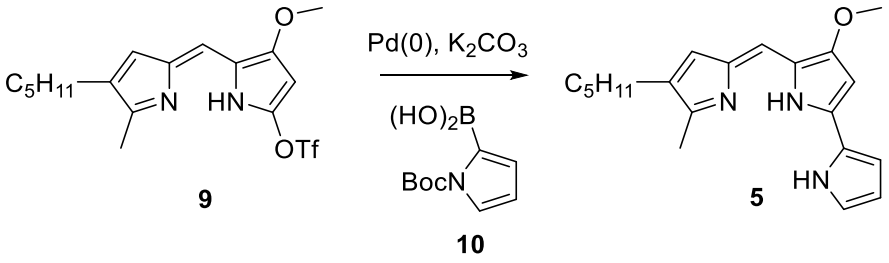
Figure 7. Retrosynthetic strategies towards prodigiosene

The first reported synthesis (Scheme 1) of prodigiosin (**5**) was developed by Rapoport and Holden in 1962 and involves the condensation of a bipyrrole aldehyde (**7**) and the pyrrole (**8**), which will become the C-ring (Scheme 1).[10, 13]



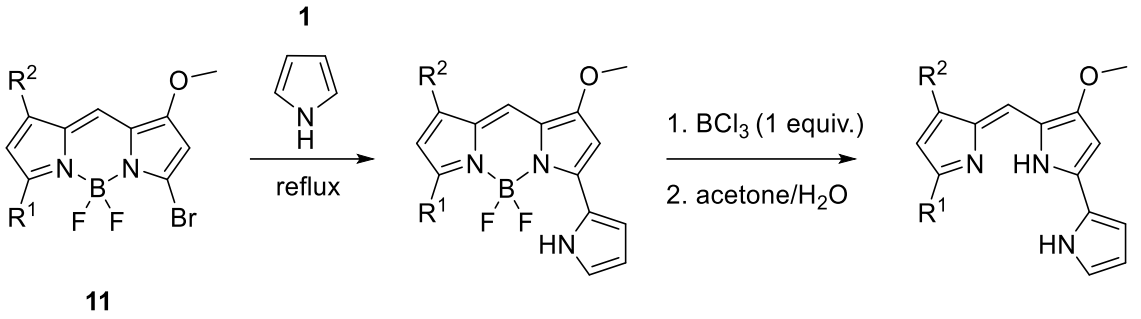
Scheme 1. Synthesis of Prodigiosin using [A+B]+C approach

Since this initial synthesis, several researchers have developed methods to synthesize the bipyrrole starting material. However, the drawback of these methods remains the use of the low-yielding McFadyen-Stevens reduction to obtain the bipyrrole aldehyde (**7**). D'Alessio and coworkers developed a much more convenient and scalable method (Scheme 2) to synthesize prodigiosenes via formation of a dipyrrin unit (**9**) and subsequent cross-coupling of the dipyrrin unit with the pyrrole (**10**), which will become the A-ring (Scheme 2).[10, 13]



Scheme 2: Synthesis of Prodigiosin using [C+B]+A approach

Recently, Li and coworkers developed a new metal-free route to synthetic prodigiosenes, by first forming the boron difluoro complex (**11**). This complex was then coupled under metal-free conditions with neat pyrrole (**1**, Scheme 3).[25] The boron difluoro moiety of the tripyrrolic structure was then deprotected via formation of the corresponding unstable boron dichloride complex, following methodology developed by the Thompson group. In this way a series of prodigiosenes was synthesized.[26]



Scheme 3. Synthesis of prodigiosenes via F-BODIPY protection/deprotection

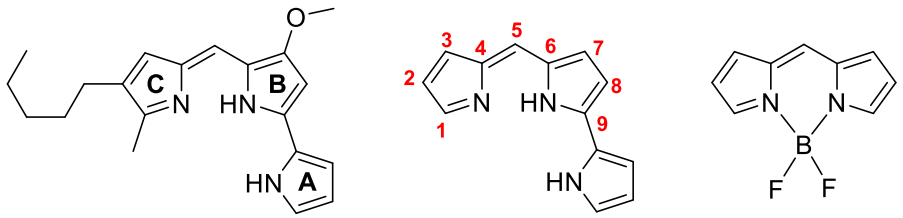
1.6 Thesis Overview

This thesis focuses on the synthesis of pyrrolic compounds, specifically 2-aryl pyrroles, prodigiosene *F*-BODIPYs, and B-ring modified prodigiosenes. As such, a chapter has been dedicated to each framework, followed by an experimental chapter for all synthesized compounds, and a conclusion chapter. Background information regarding each scaffold is included at the beginning of each chapter. In Chapter 2, the synthesis and characterization of prodigiosene *F*-BODIPYs is discussed. This published work is the first of its kind to study how changing the substituents about the prodigiosene core affects the photophysical properties of the corresponding *F*-BODIPYs. Chapter 3 also features published work and involves the decarboxylative arylation of SEM-protected pyrroles. Finally, Chapter 4 details the total synthesis of prodigiosenes bearing thioether functionality on the B-ring.

CHAPTER 2 - Prodigiosene *F*-BODIPYs

2.1 Background – Pyrrolyldipyrrin *F*-BODIPYs

As discussed in Chapter 1, a dipyrrin is formed when two pyrrolic units are connected through a methine, *CH*, bridge. Substituting a third pyrrolic unit in the 9-position of the dipyrrin forms a pyrrolyldipyrrin (Figure 8). Prodigiosin is a natural product and belongs to the pyrrolyldipyrrin family. The natural product and synthetic analogues (termed prodigiosenes)[14] exhibit significant biological activity including immunosuppressive,[15] anti-malaria,[16] anti-microbial,[17] and anti-cancer properties.[18-19]



prodigiosin **pyrrolyldipyrrin** ***F*-BODIPY**

Figure 8. Structure of prodigiosin, a pyrrolyldipyrrin, and an F-BODIPY

Coordination of dipyrrins to a variety metals[4, 6] has been reported, with the most prominent type of dipyrrinato complex featuring coordination of the ligand framework to a $–BF_2$ unit to create a 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (*F*-BODIPY, Figure 8). *F*-BODIPYs are chemically robust, as well as thermally, photochemically and physiologically stable. They exhibit sharp fluorescence spectra, with high molar extinction coefficients and quantum yields, making them useful in a myriad of applications, including cell imaging, chemosensors and laser dyes.[7]

Like dipyrrins, the nitrogen atoms of pyrrolyldipyrrins readily chelate metals. As such, several metal complexes of pyrrolyldipyrrins have been reported, including those of cobalt, copper, tin, zinc and boron (Figure 9).[16, 27-32]

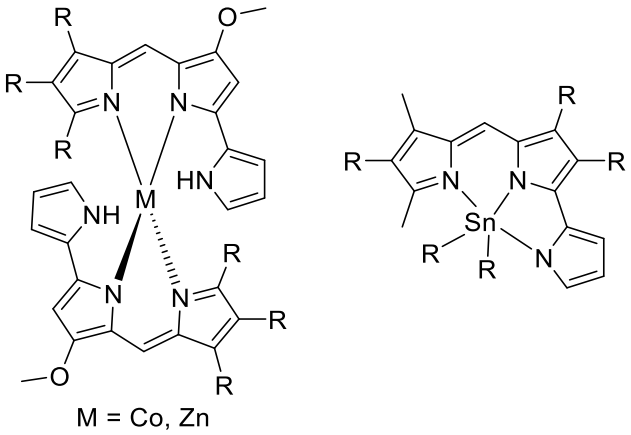


Figure 9. Metal complexes of pyrrolyldipyrrins

Compared to boron complexes of dipyrrins, pyrrolyldipyrrinato complexes absorb and emit light at much longer wavelengths, due to the extended π conjugation of the ligand. As a result, these highly fluorescent complexes are useful as probes in biological applications, for example, the commercially available fluorescent dyes BODIPY 576/589 and BODIPY 650/665 (see Figure 10).[32-36]

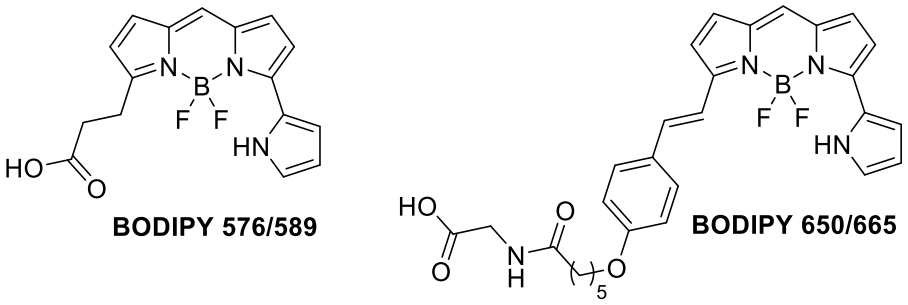


Figure 10. Commercially available pyrrolyldipyrrin F-BODIPYs

Other boron difluoro pyrrolyldipyrrinato complexes include those involving: the unsubstituted pyrrolyldipyrrin;[36] substituted aromatics,[27-28, 37-39] heterocycles[37] and alkyl groups[39] at the meso-position; phenyl substitution at the meso position with various functional groups present on the A-ring;[40-41] the presence of halogens about the pyrrolyldipyrrin core;[42-43] and replacement of the B-ring with an isoindolic unit (Figure 4).[32, 44]

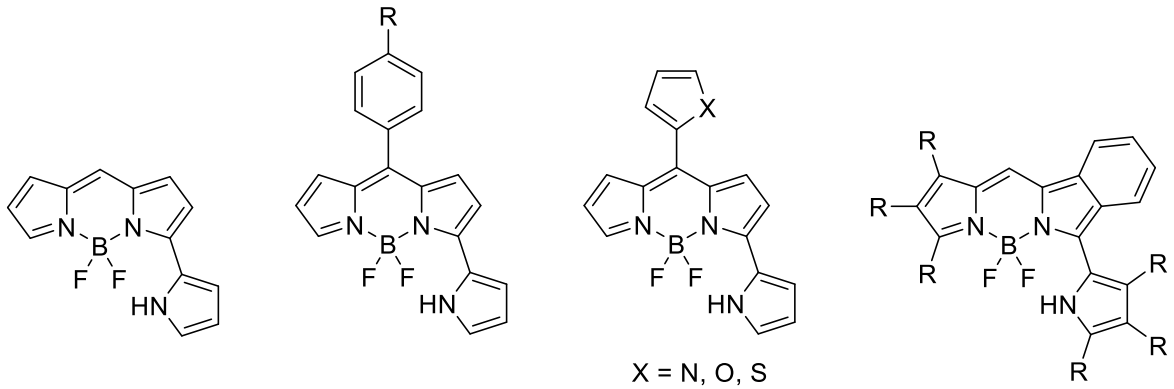


Figure 11. Pyrrolyldipyrrin F-BODIPYs

Boron difluoro complexes of prodigiosene have recently been reported.[25] However, the purpose of the synthesis was to afford the desired synthetic natural products in a facile manner by late-stage removal of the $–BF_2$ protecting group. Additionally, the Thompson group has reported the synthesis of two BF_2 complexes bearing ester functionality on the C-ring of prodigiosenes (Figure 12) .[16, 30, 45] Despite these examples, a thorough investigation of prodigiosene BF_2 complexes is lacking regarding how variation in the substituents about the pyrrolyldipyrrin core affects the photophysical properties.

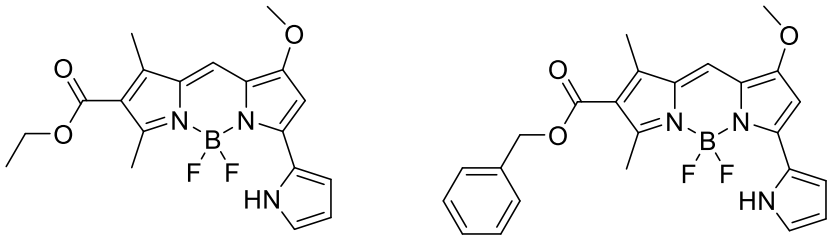


Figure 12. Prodigiosene F-BODIPYs prepared in the Thompson group

2.2 Project Goals

The goal of this project was to synthesize a series of prodigiosene *F*-BODIPYs with varying substituents on each of the pyrrolic rings, and then investigate the respective photophysical properties of these compounds.

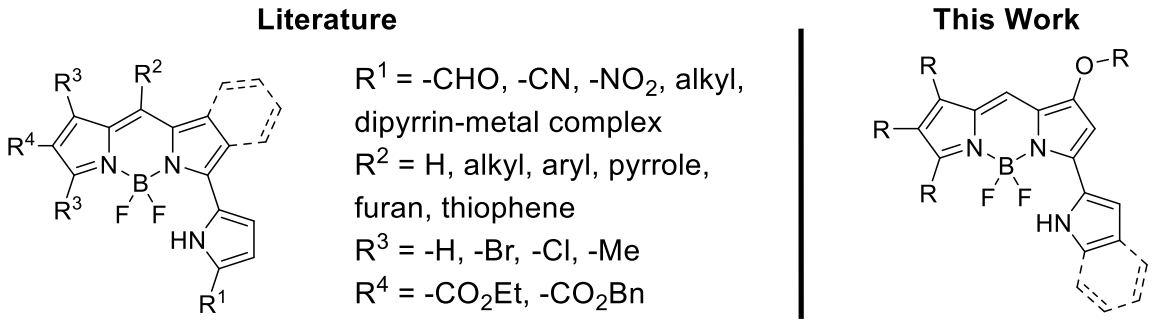


Figure 13. BF_2 complexes of pyrrolyldipyrrins

2.3 Results and Discussion

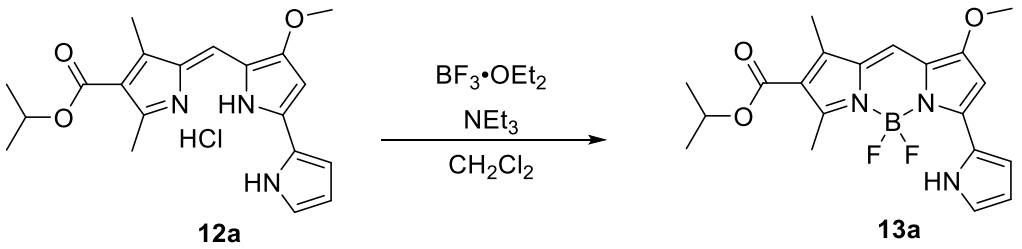
2.3.1 Synthesis and Characterization

In the Thompson group we have access to an extensive library of pyrrolic compounds made by previous group members. These compounds include a variety of prodigiosenes bearing modifications to the A, B, and C-rings and their syntheses have been reported.[16, 19, 46] Since the goal of this current work was to study the effects that different substituents have on the photophysical properties of prodigiosene *F*-BODIPYs, this library provided a wide substrate scope via which to achieve this goal.

Of the prodigiosenes available to the Thompson group, the compound bearing an isopropyl ester in the 3-position of the C-ring was chosen as a model substrate in order to explore the synthesis of prodigiosene *F*-BODIPYs (Scheme 4). Electron-withdrawing groups such as esters in this position improve the stability of the prodigiosene scaffold. Additionally, the ester functional group also offers a handle by which prodigiosenes can be further derivatized, as illustrated by reported conjugates of prodigiosene.[18]

The synthesis of prodigiosene *F*-BODIPY **13a** (Scheme 4) was attempted using traditional conditions that require treatment of the dipyrrin-containing species with 6 equivalents of triethylamine and 9 equivalents of boron trifluoride, over two hours of reaction time.[47] For this initial reaction, a scale of 0.13 mmol was utilized, corresponding

to 50 mg of the prodigiosene hydrochloride salt **12a**. The success of this reaction hinges on the availability of boron trifluoride in the reaction mixture which is readily quenched in the presence of water.[48]



*Scheme 4. Synthesis of F-BODIPY **13a***

Initial attempts to synthesize the *F*-BODIPY **13a** required subsequent additions of base and Lewis acid, along with extended reaction times up to three days. Indeed, after two hours, the reaction was analyzed via thin layer chromatography (TLC) which showed mostly starting material and the formation of a new pink, fluorescent spot. Following this, another 6 equivalents of base and 9 equivalents of Lewis acid were added. After an additional 3.5 hours of reaction time, the spot corresponding to the starting material appeared fainter while the pink fluorescent spot was more intensely colored. At this time, 5 equivalents of Lewis acid were added, and the reaction was stirred overnight. After a total of 20 hours, there was significantly less starting material present according to analysis via TLC. However, close consideration of the TLC also showed the presence of a new spot that did not correspond to the starting material or the fluorescent pink spot that was anticipated to be the desired *F*-BODIPY. The reaction was pushed to completion with another 3 equivalents of base and 6 equivalents of Lewis acid. Following washing with 1 M HCl, the compound was purified via column chromatography eluting with 5-10% ethyl

acetate in hexanes. However, this initial attempt to purify was unsuccessful, as both grease and plasticizer were observed in the ^{1}HNMR spectrum of the isolated material (Figure 14).

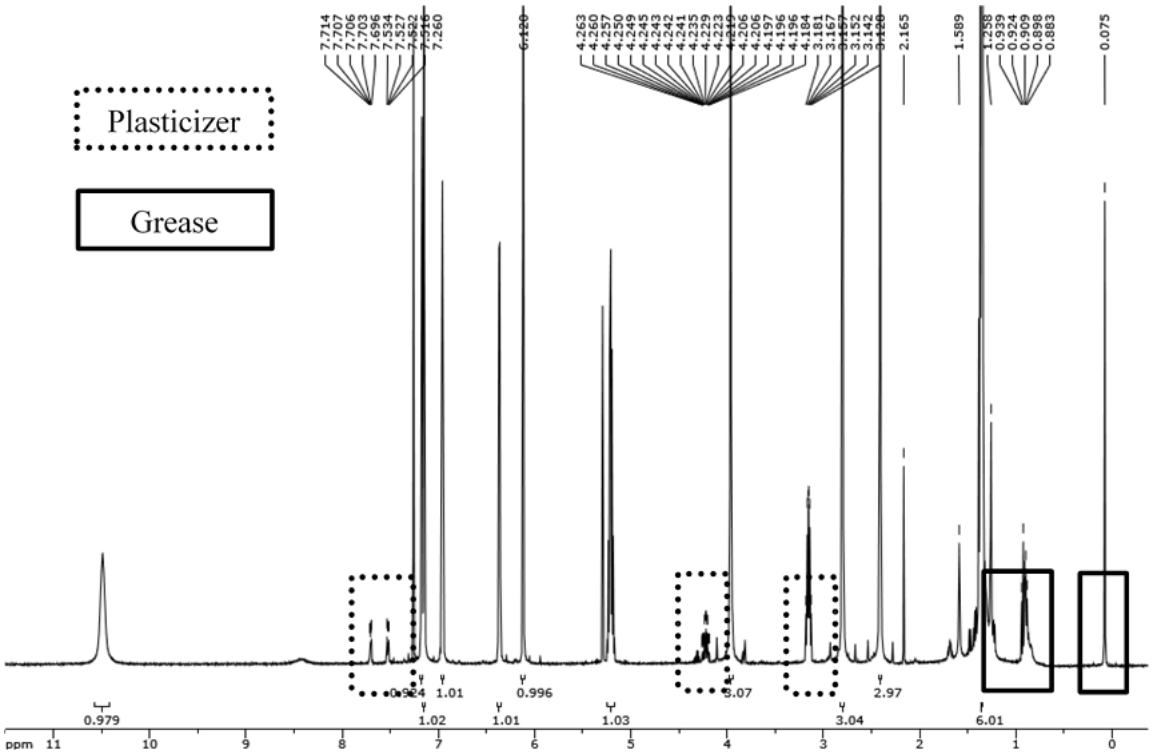


*Figure 14. ^{1}HNMR of **13a** with plasticizer and grease*

In addition to the extended reaction time, purification proved challenging for this compound due to its apparent affinity for grease. Multiple attempts to remove grease via column chromatography (flushing with hexanes) were unsuccessful. Realizing that the presence of grease would be an issue for this project at this scale, and as it was my first project working at this scale, much effort was put forth to identify the source of grease within our lab. It was found that if solvent vapors come into contact with rubber septa, a grease residue is left behind. Additionally, the potential sources of plasticizer were identified (i.e. pipet bulbs, gloves). As a result, lab techniques were optimized to prevent grease and plasticizer from contaminating the reaction mixtures.

With improved synthetic skills at hand, compound **13a** was successfully synthesized and purified, followed by characterization using ^{1}H, ^{13}C, ^{11}B, ^{19}F-NMR spectroscopy and high-resolution mass spectrometry (See Chapter 5). Coordination of the dipyrrin to $–BF_2$ is evident by the presence of a single –NH peak (~ 10 ppm) as opposed to two –NH signals (~ 12 ppm) in the ^{1}H-NMR spectrum of prodigiosene **12a** HCl salt (Figure

15). Using ^{11}B-NMR spectroscopy, isolation of the prodigiosene F-BODIPY **13a** was indicated by the presence of a triplet centered about 1.4 ppm with a coupling constant of 36 Hz. In the ^{19}F-NMR spectrum, an apparent quartet centered about -138 ppm (J = 36 Hz) was observed. Such splitting patterns, chemical shifts and coupling constants are observed in the spectra of other pyrrolyldipyrrin BF_2 complexes and are indicative of the complexed $–BF_2$ unit involving spin 3/2 ^{11}B (80% natural abundance) and spin 1/2 ^{19}F (100% natural abundance).[36]

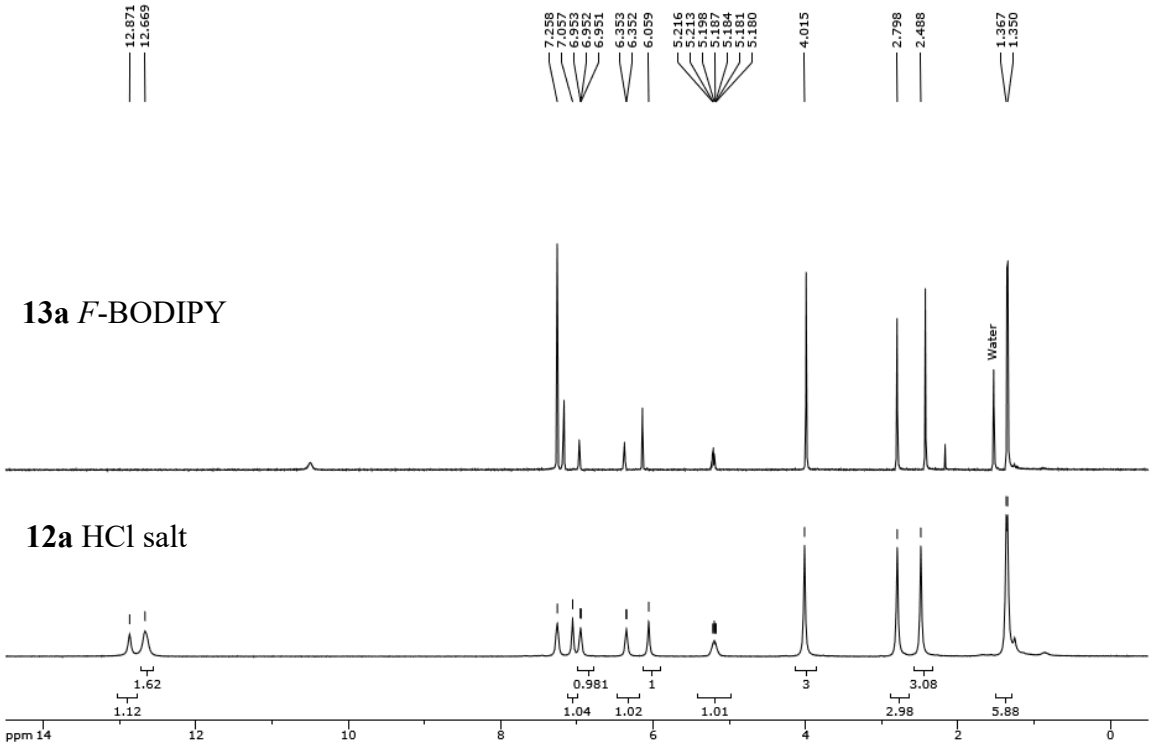


*Figure 15. [1]HNMR of prodigiosene F-BODIPY **13a** and prodigiosene HCl salt **12a***

A crystal of prodigiosene *F*-BODIPY **13a** suitable for X-ray analysis was obtained via the slow evaporation of a chloroform solution. The thermal ellipsoid diagram of **13a** (Figure 16, Side View**)** illustrates that the prodigiosene core of **13a** is virtually planar. However, the uncoordinated pyrrolic unit is slightly out of plane which may accommodate a hydrogen bond between the hydrogen atom of the pyrrolic nitrogen and a fluorine. The N-H…F hydrogen bond distance ranges from 2.05-2.53 Å. The prodigiosene core is also perpendicular to the plane of the coordinated F−B−F atoms. The B-N bond distances range from 1.54-1.56 Å, indicating electronic delocalization.

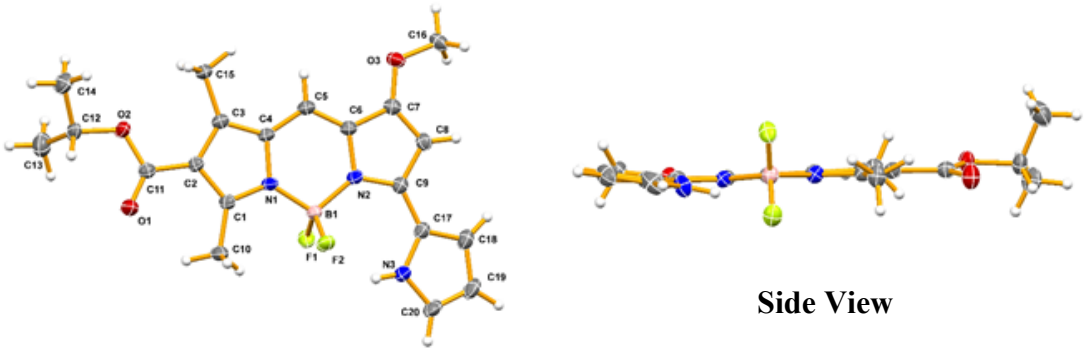
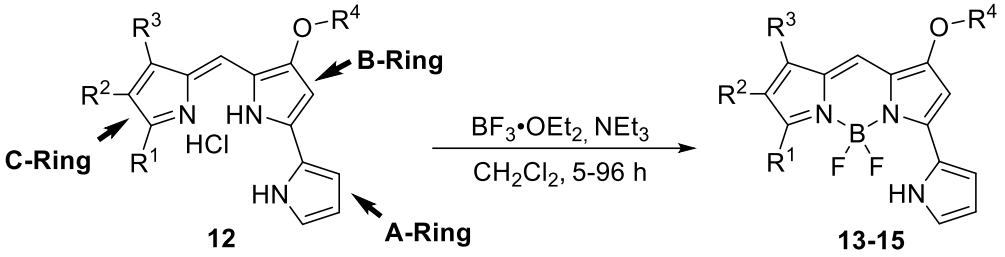


Figure 16. Thermal ellipsoid diagram of ***2d****. Selected bond distances (Å): B(1)-N(1), 1.5386(19); B(1)-N(2), 1.551(2); Selected bond angles (deg): N(1)-B(1)-N(2), 108.36(11); Selected torsional angles (deg): N(2)-C(9)-C(17)-N(3), -7.5(2); Hydrogen bond distance (Å): N(3)-H(3N)...F(1), 2.529(17), N(3)-H(3N)...F(2), 2.049(18).*

Since the goal of this work was to study the photophysical properties of prodigiosene *F*-BODIPYs, a series of prodigiosenes were selected to be complexed with $–BF_2$. As illustrated in Chapter 1, the synthesis of prodigiosene is a multi-step process that results in very low yields, long reaction times and challenging purification via column chromatography. Therefore, the amount of a given prodigiosene available for complexation was on the order of milligrams. Hence, simply selecting ready-made prodigiosenes from our inventory was not taken lightly.

Considering this, prodigiosene HCl salts were selected with variation of substituents on each of the pyrrolic rings. The respective prodigiosenes were then complexed with $–BF_2$ to create prodigiosene *F*-BODIPYs (Scheme 5). As illustrated with compound **13a**, the synthesis of prodigiosene *F*-BODIPYs would require careful monitoring, along with excessive amounts of base and Lewis acid, and extended reaction times.



Scheme 5. Synthesis of pyrrolyldipyrrin F-BODIPYs ***13-15***

2.3.2 C-ring Modifications of Prodigiosene *F*-BODIPYs

With a method in hand to coordinate prodigiosenes to $–BF_2$, a series of C-ring modified prodigiosene *F*-BODIPYs was synthesized (Figure 17). *F*-BODIPY **13c**, the unsubstituted prodigiosene bearing only the signature methoxy group on the B-ring, was chosen as a parent compound to which the properties of the C-ring substituted prodigiosene *F*-BODIPYs would be compared. Such substituents included a mimic of the natural product (**13b**), conjugated esters (**13a**, **13c-13f**), conjugated carbonyls (**13g-13i**) and derivatives of ethanoic acid (**13j** and **13k**). *F*-BODIPY **13l** completes the series, and bears both a conjugated benzyl ester and an alkanonate on the C-ring.

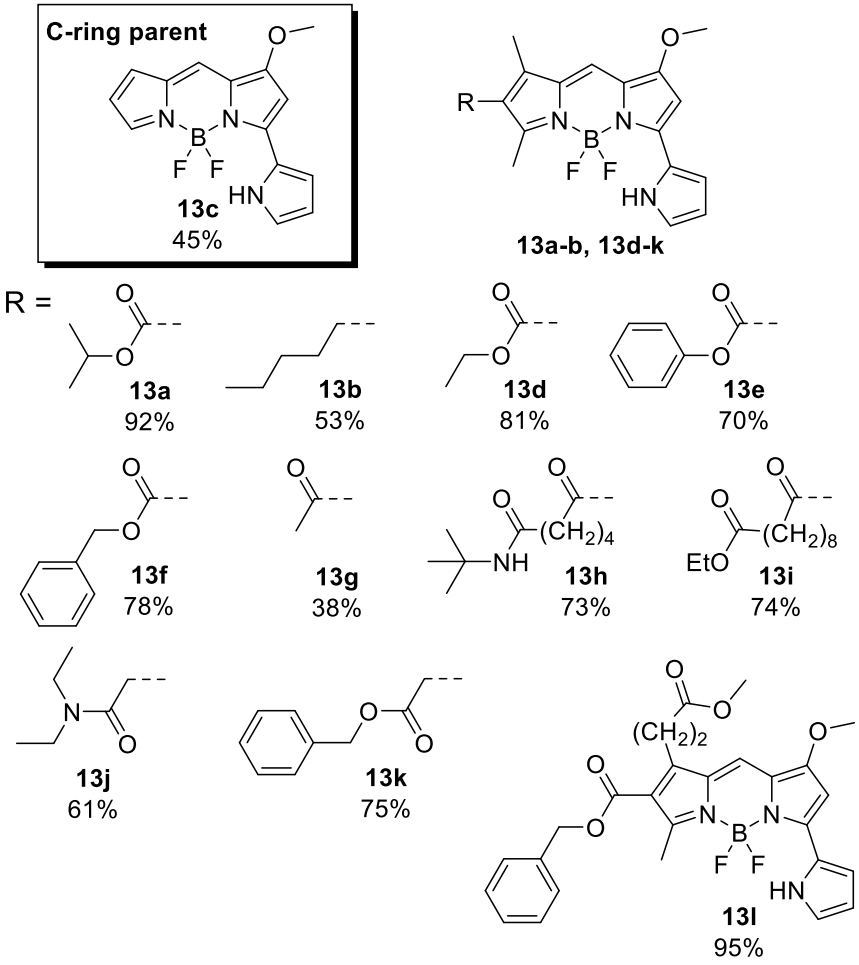


*Figure 17. Prodigiosene F-BODIPYs (**13a-13l**) with C-ring modifications*

These substituents were chosen to provide a wide scope by which to demonstrate the influence that C-ring substituents have on the photophysical properties of prodigiosene *F*-BODIPYs. Compounds **13a**-**13l** were synthesized in 45-95% yields through treatment of the prodigiosene hydrochloride salts **12** with excess boron trifluoride and triethylamine. All compounds were fully characterized.

2.3.3 A-ring Modifications of Prodigiosene *F*-BODIPYs

With prodigiosene *F*-BODIPYs with modifications to the C-ring in hand, attention was directed towards the synthesis of *F*-BODIPYs with non-pyrrolic A-rings. As such, the prodigiosene *F*-BODIPYs **14b** and **14f** featuring an indole moiety in lieu of the A-ring pyrrole (Figure 18), were prepared and characterized. The indole moiety further extends the π conjugation of the *F*-BODIPY core and as a result is expected to inherently absorb and emit at longer wavelengths. Compounds **13b** and **13f** (Figure 17) represent the parent compounds of the A-ring indole analogs **14b** and **14f**, respectively.

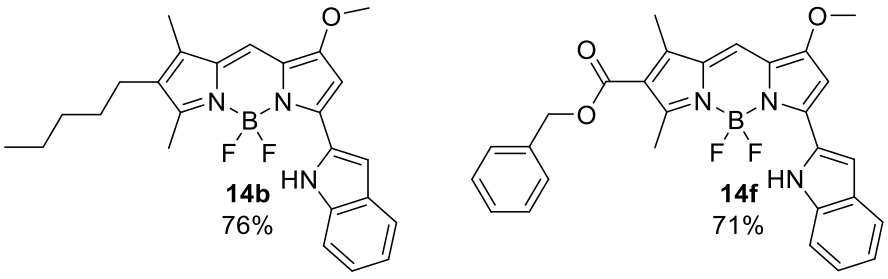


*Figure 18. Prodigiosene F-BODIPYs (**14b** and **14f**) A-ring (indole) modifications*

2.3.4 B-ring Modifications of Prodigiosene *F*-BODIPYs

All prodigiosene *F*-BODIPYs discussed thus far have featured a methoxy functional group on the B-ring. Initial reports indicate that this substituent contributes to the biological activity of prodigiosene, yet substituting the methoxy group for other -OR groups such as benzyl or phenyl does not diminish the anticancer properties of the compound.[19] Hence, prodigiosene *F*-BODIPYs **15m-p**, feature benzyl or phenyl substituents on the B-ring in lieu of the signature methoxy substituent (Figure 19) were synthesized in 50-92% yields. All compounds were fully characterized. Compound **13b** was selected as the parent compound to which all B-ring modified prodigiosene

F-BODIPYs would be compared. In this regard, the effect of the methoxy substituent has on the photophysical properties would be evaluated.

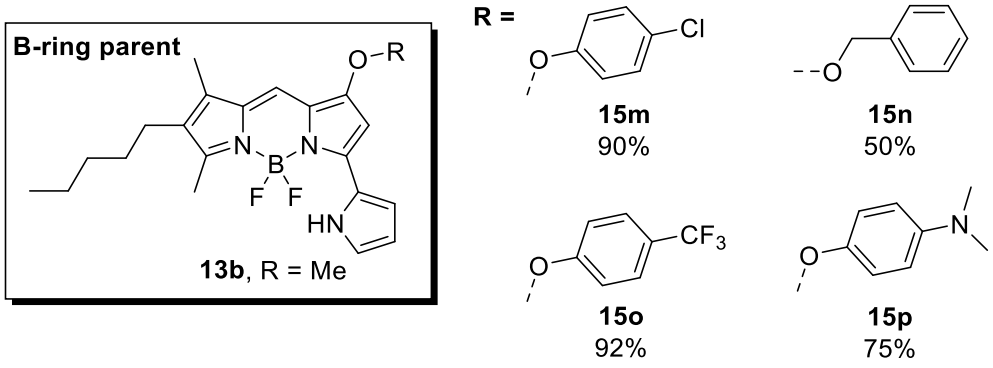


*Figure 19. Prodigiosene F-BODIPYs (**15m-p**) with B-ring modifications*

2.4 Photophysical Properties

2.4.1 *F*-BODIPY of the Synthetic Analogue of Prodigiosin

Complexation of the pyrrolyldipyrrinato ligand with a $–BF_2$ unit creates the rigid delocalized π-system of the *F*-BODIPY. As a result, these complexes absorb light at a longer wavelength compared to the prodigiosene HCl salt. This is evident when comparing the absorbance spectra of prodigiosene HCl salt **12b** and the prodigiosene *F*-BODIPY **13b** (Figure 20) with absorption occurring at a longer wavelength, red-shifted 24 nm, for the complex. Compound **13b** was selected for this analysis as it, amongst **13a-l**, most closely represents the natural product Prodigiosin.

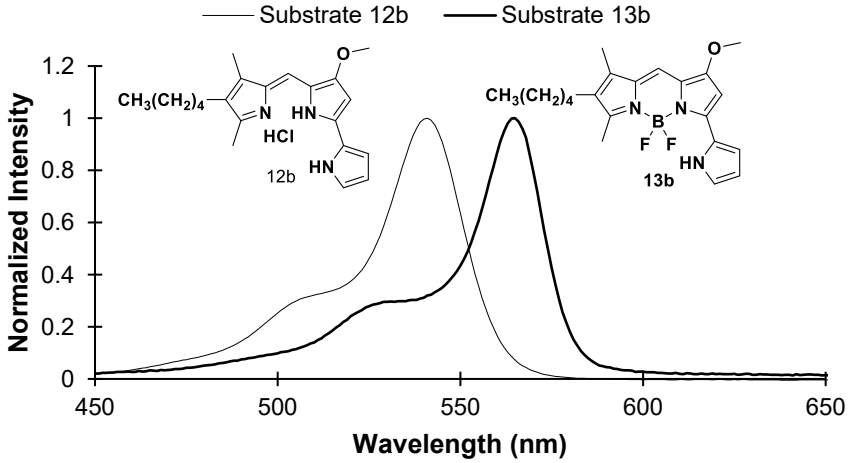


*Figure 20. Absorbance spectra of prodigiosene **12b** and BF_2 complex **13b***

The absorbance spectra of *F*-BODIPY **13b** over varying concentrations (4-21 μM) is shown in Figure 21. From this figure, we can see that the absorption maxima correlate in a linear fashion over the stated concentration range thus adhering to Beer's Law (Equation 1).

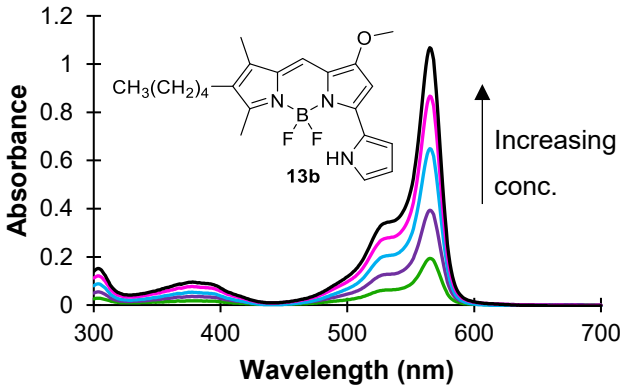


*Figure 21. Absorbance spectra of **13b** over varying concentrations (4-21 μM)*

$$\mathbf{A = \varepsilon cl}$$

Equation 1. Beer's Law: where A is the absorbance, ε is the molar extinction coefficient ($M^{-1}cm^{-1}$), c is the concentration (M) and l is the path length (cm).

To further demonstrate the absorption behavior of this compound, concentration (of a sample with a pathlength of 1 cm) was plotted against the corresponding absorbance maxima to produce the calibration curve shown in Figure 22.

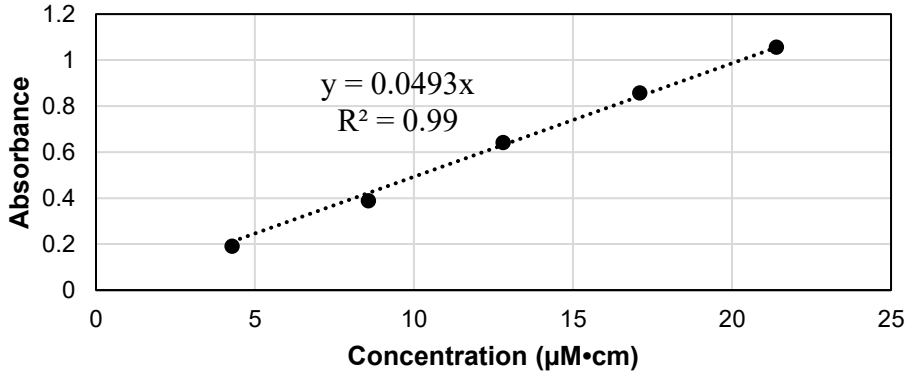


*Figure 22. Calibration curve of **13b** over varying concentrations (4-21 μM)*

Conforming to Beer's Law (Equation 1), the y-intercept of the generated trendline was set to zero and the slope of this trendline indeed corresponds to the extinction coefficient for a solution of **13b** in DCM. As illustrated by the plot, the experimental data has a linear

relationship demonstrating that *F*-BODIPY **13b** follows Beer's Law without deviation over concentrations of 4-21 μM. Calibration curves were generated for all *F*-BODIPYs synthesized (**13-15**) and the respective extinction coefficients determined (Table 1).

Prodigiosenes, in their neutral form, prior to deprotonation and complexation, do not display detectable fluorescence. This is evident visually, as solutions of the synthesized starting materials **12** are very weakly fluorescent under long-wave UV-light. However, all synthesized prodigiosene *F*-BODIPYs (**13-15**) exhibit considerable fluorescence with high relative quantum yields ($\Phi_F > 0.70$). The intense fluorescence upon BF_2 complexation is due to the creation of rigidity in the structure, and lack of rotation about the meso-position.[49] As shown in Figure 23, the normalized emission band of **13b** is approximately the mirror image of the normalized absorption band. However, the vibronic features are less prominent. All prodigiosene *F*-BODIPYs synthesized exhibit similar absorbance and emission spectra to those of the representative compound **13b**. Most emitting *F*-BODIPYs exhibit comparable fluorescence quantum yields.[7]

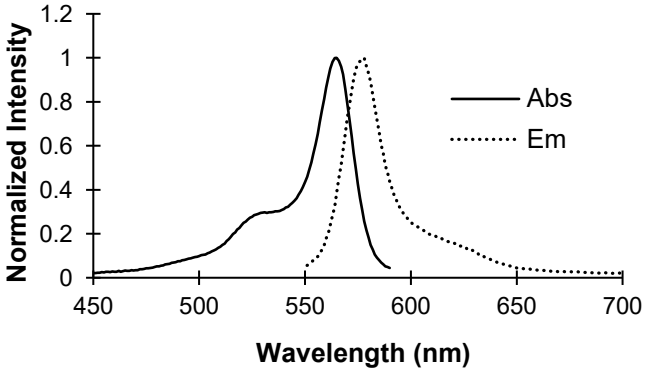


*Figure 23. Normalized absorbance and emission spectra of **13b***

To determine the relative quantum yield of *F*-BODIPYs **13-15**, first an appropriate reference standard to which each *F*-BODIPY would be compared was selected. Selection of the appropriate reference standard requires that the absorption profiles of the unknown compound overlap well with the reference dye. In addition, the quantum yield of the reference should match that of the unknown. As such, two reference standards (Rhodamine 6G, $\Phi_F = 0.94$ and Rhodamine 101, $\Phi_F = 0.96$ in EtOH) were selected based on these criteria. Dilute solutions of each prodigiosene *F*-BODIPY and reference standard were prepared (adjusted to an absorbance of ~ 0.1) in order to determine the relative quantum

yield for compounds **13-15**. The absorbance and emission spectra of each dilute sample was then acquired, and the relative quantum yield ($\mathbf{\Phi_F}$) was calculated using Equation 2: where Φ_{st} is the reported quantum yield of the standard, I is the area of the integrated emission spectra, A is the absorbance at the excitation wavelength and η is the refractive index of the solvent used. The subscripts "X" and "st" denotes the unknown and standard, respectively.

$$\mathbf{\Phi_X = \Phi_{st}} \left(\frac{\mathbf{I_X}}{\mathbf{I_{st}}}\right)\left(\frac{\mathbf{A_{st}}}{\mathbf{A_X}}\right)\left(\frac{\mathbf{\eta_X}^2}{\mathbf{\eta_{st}}^2}\right)$$

Equation 2. Relative quantum yield (Φ_X):

2.4.2 Prodigiosene *F*-BODIPYs with C-ring Modifications

The photophysical properties of prodigiosene *F*-BODIPYS (**13-15**) were evaluated in DCM and a summary of the results is presented in Table 1. All compounds have emission maxima in the range of 550-600 nm, display high extinction coefficients (11 000 – 127 000 M^{-1} cm^{-1}) and have Stokes shift in the range of 3-25 nm. To evaluate the effects of C-ring substituents on the absorption wavelength maxima, each *F*-BODIPY (**13a-b**, **13d-l**) was compared to the parent compound (**13c**) bearing only the methoxy substituent on the B-ring. *F*-BODIPY **13c** has a maximum absorbance wavelength of 530 nm, which is hypsochromically shifted by 44 nm from the unsubstituted pyrrolyldipyrrin *F*-BODIPY (i.e. **13c** without the methoxy substituent).[32] This indicates that the electron-donating methoxy group causes a blue-shift in absorption. All modifications to the C-ring (**13a-b**, **13d-l**) bathochromically shift the absorbance wavelength (9-35 nm) compared to the unsubstituted, methoxy bearing *F*-BODIPY **13c** (Figure 24). The greatest shift in absorption wavelength maxima of the C-ring modified prodigiosene *F*-BODIPYs occur with the alkyl and ethanoic acid derivative substituents **13b**, **13j** and **13k** bearing a $–(CH_2)CH_3$, $–CH_2CON(Et)_2$ and $–CH_2CO_2Bn$ group, respectively. This trend is in agreement with that laid out by Burgess in his comparison of *F*-BODIPYs. Burgess identified that as the core becomes more alkyl substituted, the fluorophore absorbs and therefore emits, at a longer wavelength.[7]

*Table 1. Photophysical Properties of F-BODIPYs **13-15** in DCM at 22 °C*

F-BODIPY	λ_{abs}(nm)	λ_{em} (nm)	Stokes shift (nm)	logε	Φ_F
13a	543	555	12	4.83	0.90[a]
13b	565	578	13	4.69	0.84[b]
13c	530	543	13	4.57	0.95[b]
13d[30]	542	555	13	4.81	0.85[a]
13e	539	555	16	4.80	0.90[a]
13f[16]	542	553	11	5.20	1.00[a]
13g	544	557	13	4.04	0.78[a]
13h	545	557	12	4.85	0.85[a]
13i	546	559	13	4.93	0.90[a]
13j	561	574	13	4.65	0.81[b]
13k	558	571	13	5.10	0.79[b]
13l	540	559	19	4.74	0.70[a]
14b	579	591	12	4.73	1.00[b]
14f	562	574	12	4.87	0.95[b]
15m	573	597	24	4.88	0.89[b]
15n	566	572	6	4.74	0.98[a]
15o	575	600	25	4.41	0.74[b]
15p	567	570	3	4.69	0.55[b,c]

[a]Relative to Rhodamine 6G in EtOH (ΦF = 0.94). [b]Relative to Rhodamine 101 in EtOH (ΦF = 0.96). [c]Hexanes used instead of DCM for quantum yield data.

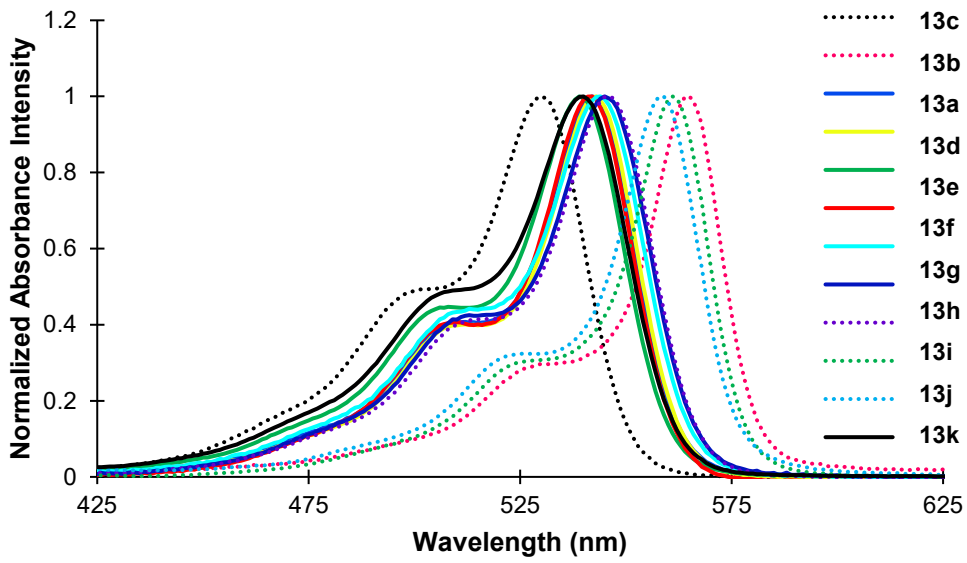


*Figure 24. Normalized absorbance spectra of **13a-13l***

2.4.3 Prodigiosene *F*-BODIPYs with A-ring Modifications

To study the effects of extending the pi conjugation would have on the photophysical properties of prodigiosene *F*-BODIPY core, two compounds were synthesized that featured an indole moiety in lieu of the A-ring (Figure 25).

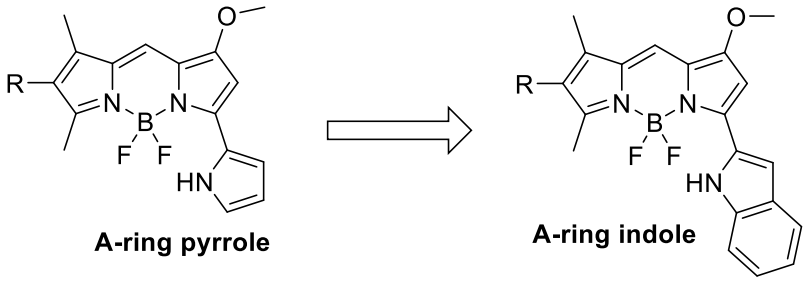


Figure 25. Prodigiosene F-BODIPY with a pyrrolic A-ring vs indolic A-ring

Both *F*-BODIPYS **14b** and **14f** (Figure 26) bearing the indole moiety in lieu of the pyrrolic A-ring exhibit red-shifted absorbance and emission maxima compared to the unsubstituted *F*-BODIPY **13c** (Table 1). Of the C-ring modified *F*-BODIPYs (**13a-k**), the alkyl substituted *F*-BODIPY **13b** exhibits the largest red-shift in absorption and emission wavelength maxima. This is also true for the comparison of **14b** and **14f**, the A-ring indole analogues of **13b** and **13f**, respectively. The alkyl substituted C-ring coupled with an indole moiety in lieu of the A-ring pyrrole exhibits the most redshifted compound of the eighteen

F-BODIPYs studied. These pi-extended fluorophores exhibit a red shift in absorption and emission of 14-21 nm of their A-ring pyrrole analogues, courtesy of the indole moiety (Figure 27 and Figure 28).

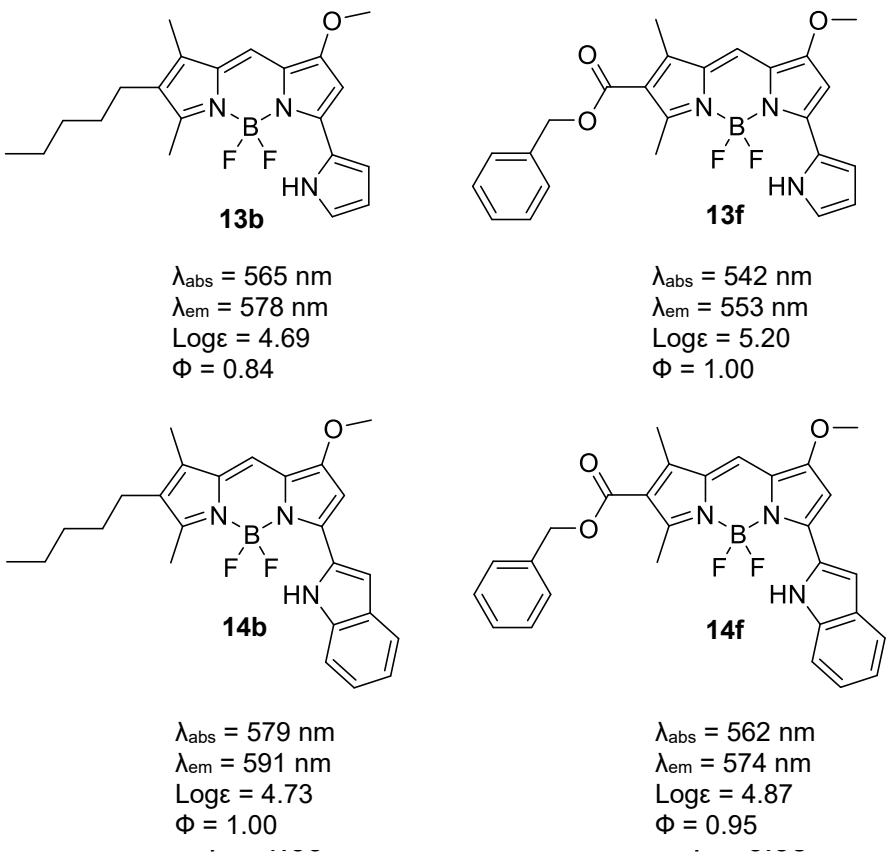


Figure 26. Photophysical properties of pyrrole-A-ring prodigiosene F-BODIPYs and their indole-A-ring analogues

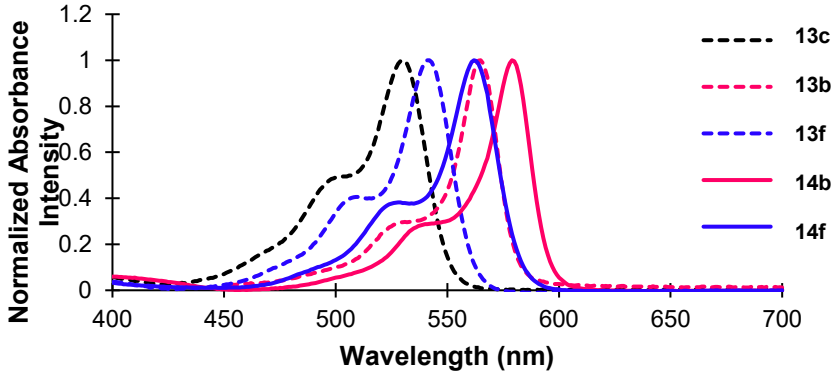


*Figure 27. Normalized absorbance spectra of **13c**, **13b**, **13f**, **14b** and **14f***

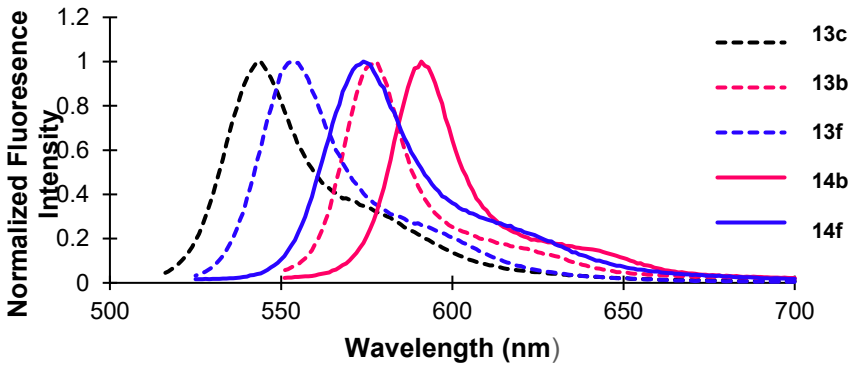


Figure 28. Normalized emission spectra of **13c**, **13b**, **13f**, **14b** and **14f**

2.4.4 Prodigiosene *F*-BODIPYs with B-ring Modifications

Now that the photophysical properties of C-ring and A-ring modifications of prodigiosene *F*-BODIPYS have been determined, attention was directed to derivatives with variation of the B-ring substituents. Specifically, the electron withdrawing/donating effects of these substituents was realized. The presence of electron-withdrawing groups on the B-ring (-p-C_6H_4Cl, **15m** or –p-$C_6H_4CF_3$, **15o**) results in a slight red-shift in absorption and emission wavelengths when compared to the parent compound **13b** (Figure 29). A similar trend has been reported for dipyrrin *F*-BODIPYs that contain electron-withdrawing groups in the meso-position.[50] In contrast, the presence of electron donating groups (–Bn or –p-$C_6H_4N(CH_3)_2$) on the B-ring do not result in a significant shift in absorbance wavelength maxima compared to **13b**. However, the presence of these groups results in much narrower Stokes shift (less than 6 nm). Furthermore, interesting solvatochromatic effects were observed for prodigiosene *F*-BODIPY **15p**.

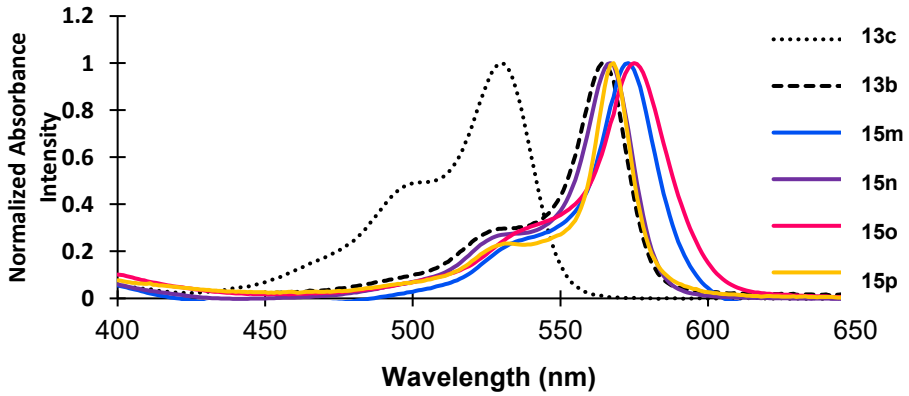


*Figure 29. Absorbance spectra of **13c**, **13b** and **15m-15p***

2.4.5 Solvatochromic Effects of Prodigiosene *F*-BODIPY 15p

Unlike their constituent ligands, prodigiosene *F*-BODIPYs (**13-15**) exhibit considerable fluorescence with excellent relative quantum yields ($\Phi_F > 0.70$), with the exception of *F*-BODIPY **15p**. Prodigiosene *F*-BODIPY **15p** did not fluoresce when dissolved in DCM (Figure 30a). However, when **15p** was dissolved in hexanes, an immediate display of fluorescence was evident (Figure 30b). The absorption and emission spectra of **15p** in DCM and hexanes are shown in Figure 31 and Figure 32. *F*-BODIPY **15p** exhibited a very narrow Stokes shift of 3 nm and much lower quantum yield of 0.55, as well as a broader band structure for the emission in hexanes (Figure 31) compared to that of **13c**.

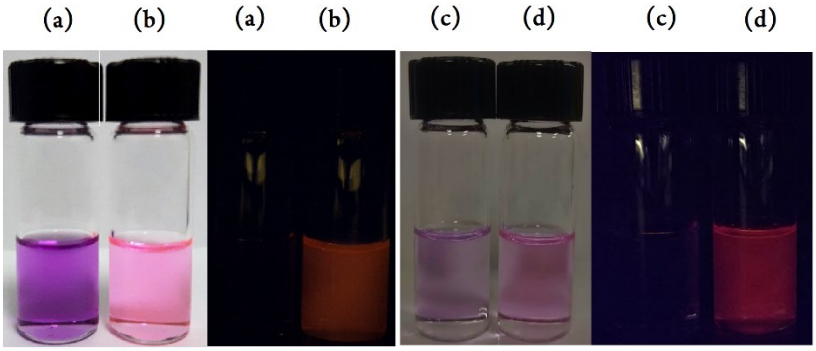


*Figure 30. (a) **15p** in DCM, (b) **15p** in hexanes, (c) DCM without 1 M HCl and (d) DCM with 1 M HCl (d) under ambient light and UV light.*

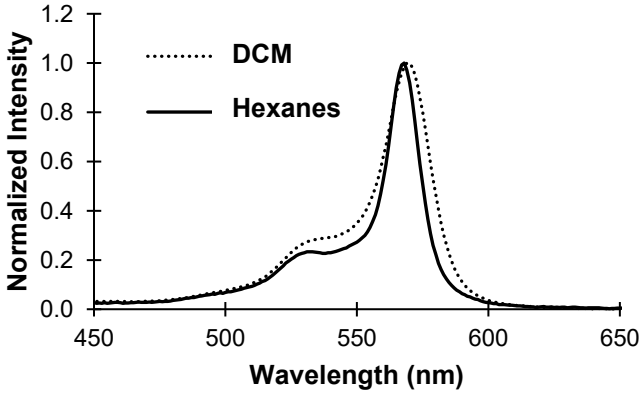


*Figure 31. Normalized absorption spectra of **15p** in DCM and hexanes*

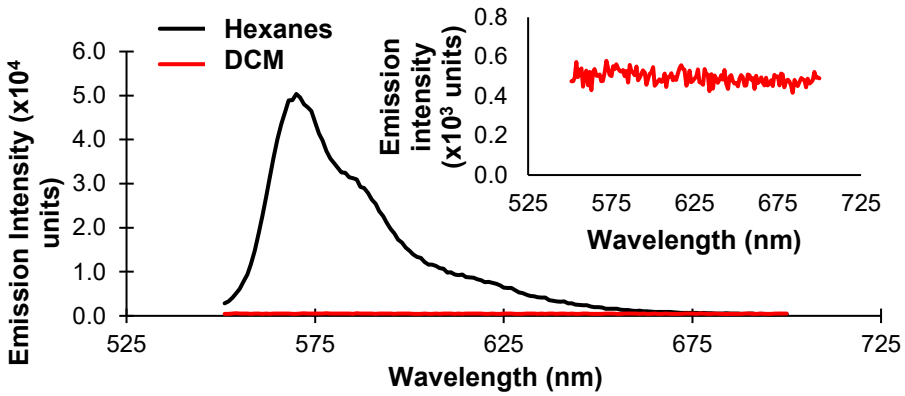


*Figure 32. Emission spectra of **15p** in hexanes and DCM*

The lack of emission of **15p** in DCM can be attributed to the lone pair of the amino substituent transferring an electron to the *F*-BODIPY fluorophore to quench its fluorescence through photo-induced electron transfer (PET).[51-52] This process can be effectively controlled by variation of the polarity of the solvent or by protonation of the amino substituent. To investigate the PET process observed for **15p**, a solution of this compound in hexanes was titrated with DCM and indeed fluorescence quenching was observed. Treatment of a DCM solution of **15p**, using 5 µL of 1 M HCl, restored fluorescence (Figure 30c-d and Figure 35). The maximum wavelength of emission for **15p** in DCM with the addition of 1 M HCl is 597 nm with a Stokes' shift of 28 nm and a quantum yield of 0.41. The absorbance spectra of **15p** in DCM shows a red-shift in the maximum wavelength of absorption (569 nm-574 nm) upon addition of 1 M HCl Figure 34. Additionally, the solvatochromatic effects on **13b** (Figure 36 and Figure 37), and **15n-p** were observed in hexane, toluene, dichloromethane, tetrahydrofuran, acetonitrile and methanol and are summarized in Table 2.

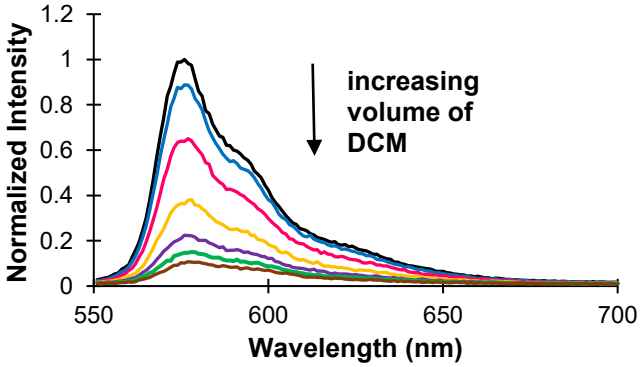


*Figure 33. Observed fluorescence quenching of **15p** in hexanes via titration with DCM*

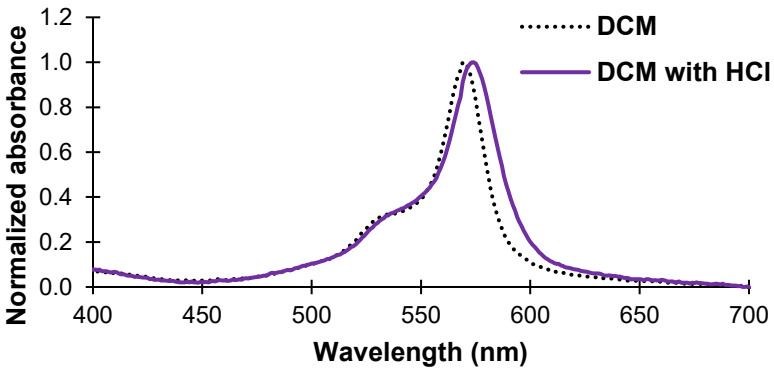


*Figure 34. Absorbance spectra of **15p** in DCM with and without the addition of 1 M HCl*

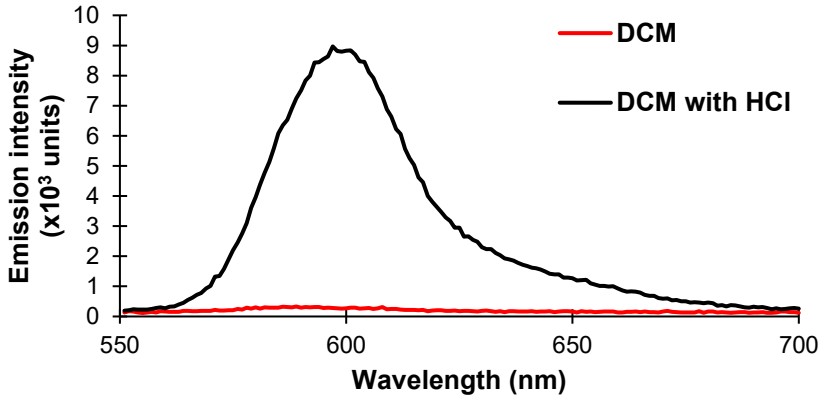


*Figure 35. Emission spectra of **15p** dissolved in DCM and in DCM with addition of 1 M HCl*

*Table 2. Maximum absorption/emission wavelengths and relative quantum yield of **13b** and **15m-15p** in various solvents*

Compound	Solvent	λ_{abs}(nm)	λ_{em} (nm)	Stokes' shift (nm)	Φ_F
13b	Hexanes	565	571	6	0.90
	Toluene	569	578	9	0.92
	DCM	565	578	13	0.84
	Tetrahydrofuran	565	575	10	0.95
	Acetonitrile	559	571	12	0.82
	Methanol	560	572	12	0.96
15m	Hexanes	572	589	17	0.99
	Toluene	577	594	17	0.79
	DCM	573	597	24	0.89
	Tetrahydrofuran	572	595	23	0.82
	Acetonitrile	567	586	19	0.81
	Methanol	568	590	22	0.78
15n	Hexanes	565	567	2	1.00
	Toluene	570	574	4	0.75
	DCM	566	572	6	0.98
	Tetrahydrofuran	565	570	5	0.82
	Acetonitrile	560	566	6	0.92
	Methanol	561	566	5	0.93
15o	Hexanes	575	589	14	0.78
	Toluene	581	597	16	0.60
	DCM	575	600	25	0.89
	Tetrahydrofuran	576	596	20	0.53
	Acetonitrile	569	592	23	0.68
	Methanol	570	592	22	0.52
15p	Hexanes	567	570	3	0.55
	Toluene	573	580	7	0.28
	DCM	569	-	-	-
	Tetrahydrofuran	569	591	22	0.27
	Acetonitrile	564	587	23	0.30
	Methanol	565	590	25	0.22

Interestingly, when **15p** was dissolved in polar solvents such as tetrahydrofuran, acetonitrile, and methanol, the Stokes shift was increased from 3 nm (in hexanes) to 22-25 nm, although with a much lower quantum yield ranging from 0.22-0.30. Such a profound effect was not observed for **13b** and **15m-15o**, where the Stokes shift and relative quantum yield did not vary amongst the different solvents. A slight blue-shift in absorption and emission wavelengths was observed for **13b** and **15m-15o** when dissolved in polar solvents (acetonitrile and methanol) compared to the wavelengths observed for these compounds dissolved in DCM.

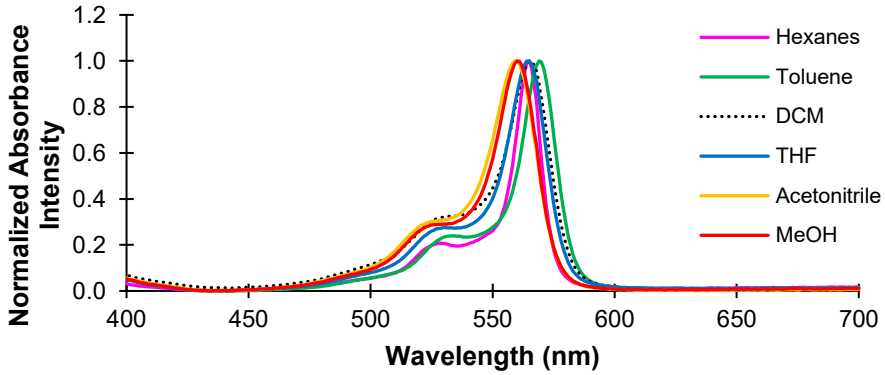


*Figure 36. Absorption spectra of **13b** in various solvents*

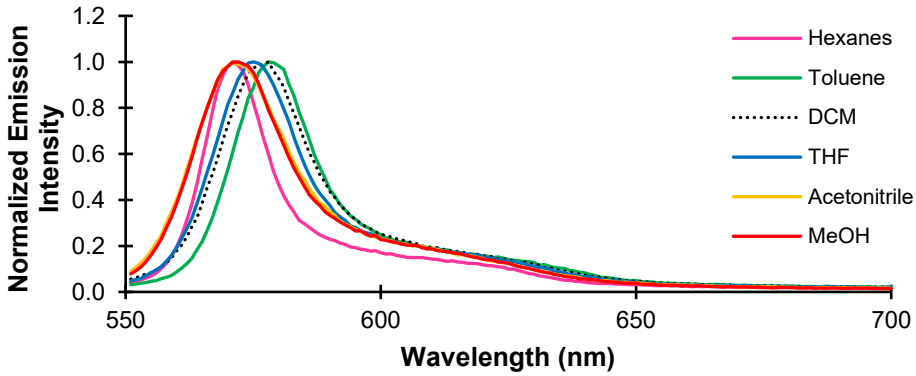


*Figure 37. Emission spectra of **13b** in various solvents*

The solvatochromatic effect on the emission of **15p** is illustrated by the Lippert-Mataga plot (Figure 38) of solvent orientation polarizability (Δf) versus Stokes Shift (in cm^{-1}). There is a linear correlation between the solvent polarizability and magnitude of the Stokes Shift, with high polarity solvents exerting the greatest effect. It should be noted that Lippert-Mataga plots for compounds **13b** and **15m-15o** (Figure 38) do not illustrate this strong correlation, suggesting that these compounds are not as sensitive to solvent polarity as **15p**. The larger Stokes shift observed for solutions of **15p** involving more polar solvents can be rationalized by the magnitude of the slope from the Lippert-Mataga plot, which gives an estimation of the change in dipole moment of the excited state and ground state of **15p**. In general, polar molecules can orient around the dipole of the excited state and thereby lower the energy of the excited state hence shifting emission maxima to longer wavelengths.

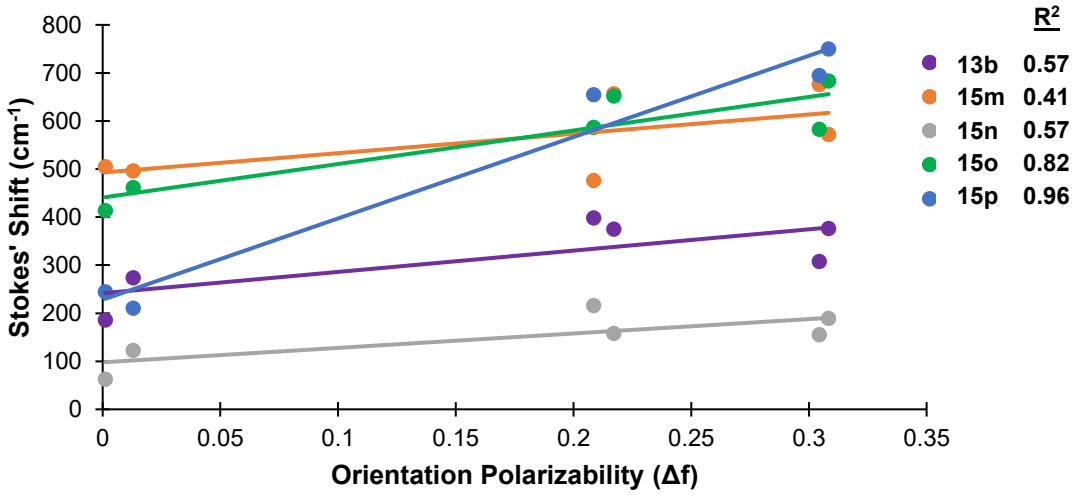


*Figure 38. Lippert-Mataga Plot illustrating Stokes' Shift as a function of solvent orientation polarizability (Δf) for **13b** and **15m-15p**. Solvents from left-right: hexane, toluene, tetrahydrofuran, dichloromethane, acetonitrile and methanol. Dichloromethane is not represented on the plot for **15p**, as there was no measurable emission maximum for the compound in this solvent.*

2.4.6 Conclusions

A series of prodigiosene *F*-BODIPYs with varying substituents on the A, B and C rings have been synthesized. All *F*-BODIPYs **13-15** have absorption and emission maxima in the range of 530-579 nm and 543-600 nm, respectively. The Stokes shift of all C-ring-modified and A-ring-modified *F*-BODIPYs (**13a-k**, **14b** and **14f**) are in the range of

11-13 nm while the Stokes shift of B-ring-modified *F*-BODIPYs varied depending on the nature of the substituent. When compared to the unsubstituted *F*-BODIPY **13c** (bearing only a methoxy substituent on the B-ring), all C-ring modified *F*-BODIPYs are red shifted, up to 35 nm for **13b**. Variation of substituents on the B-ring (compared to **13b**) and A-ring (compared to **13b** and **13f**) result in corresponding red-shifts in absorption, alongside emission reaching maximum wavelengths of 600 nm. Complexes bearing electron withdrawing substituents on the B-ring exhibited the largest Stokes shifts of 24-25 nm, while complexes bearing electron donating groups on the B-ring displayed the smallest Stokes shifts of only 3-6 nm. Extending the conjugation of the prodigiosene *F*-BODIPY core via placement of an indole substituent in lieu of the A-ring (**14b** and 1**4f**) results in a red-shift in absorption (562 for 14b and 579 nm for 14f) and emission (574 for **14b** and 591 nm for **14f**) wavelength, with Stokes shift comparable to that of any C-ring substituent. Prodigiosene *F*-BODIPY **15p** exhibited interesting photophysical properties where the fluorescence was influenced by the polarizing nature of the solvent. In hexanes, **15p** displayed appreciable fluorescence, while in DCM the fluorescence was effectively quenched. Additionally, the small Stokes shift observed for **15p** could be enhanced when dissolved in polar solvents such as tetrahydrofuran, acetonitrile and methanol.

CHAPTER 3 - Decarboxylative Arylation of N-SEM Pyrroles

3.1 Background

Discussions in Chapters 1 and 2 of this thesis have focused on the study of pyrrole-containing compounds. With a slight shift in focus this chapter is dedicated to N-protection and decarboxylative arylation of pyrroles. As described in Chapter 1, pyrrole is a natural product building block, and is found in a variety of biologically relevant compounds including prodigiosin and heme.[53] Functionalization of pyrroles at the 3-, 4-, and 5-positions is necessary for the synthesis of biologically relevant (poly)pyrrolic compounds such as prodigiosenes. Pyrrole is often described as "finicky", a description that is hard to appreciate unless you have worked with pyrrole and pyrrolic compounds. It is perhaps due to its finicky nature that pyrrole is frequently absent from the substrate scopes of cross-coupling studies, even those featuring heterocyclic substrates.[54-56] Studies where pyrrole has been included in the substrate scope tend to use N-methylated pyrrole, with no substituents at the 2- to 4-positions[57-60] Although this small heterocycle is commercially available from Millipore Sigma and relatively inexpensive ($0.50/g, half the cost per gram of N-H pyrrole), its success in demonstrating substrate scope is not representative of the likelihood of success of pyrroles bearing desired, and complex functionality. Furthermore, removal of the N-methyl group (i.e. deprotection) is challenging, and often requires very harsh reaction conditions that may be incompatible with sensitive substrates.[61]

3.1.1 N-Protection Strategies for Pyrrole

As outlined above, pyrrole is a very important heterocycle, but it can be challenging to work with. Members of the Thompson group have become experts in the synthesis and manipulation of pyrroles and pyrrolic compounds. In our group, we appreciate the need to synthesize pyrroles substituted in a manner such as to stabilize the electron-rich heterocycle and also provide handles for further functionalization. As such, these building blocks often require some sort of N-protection to achieve the desired reactivity.[61] While a full review of N-protecting groups is beyond the scope of this thesis, an overview of select groups for the protection of the pyrrolic nitrogen is necessary in this chapter. It should be noted that an ideal N-protecting group should be easy to install, promote or tolerate desired reactivity of the protected species, and be readily removed.

Common protecting groups for the pyrrolic nitrogen may be electron-withdrawing (i.e. sulfonyl, carbonyl) or electron-donating (i.e. alkyl, benzyl). Electron-withdrawing groups decrease the nucleophilicity of pyrrole, and thus promote controlled reactivity, and are among the most frequently employed protection strategies (Figure 39).

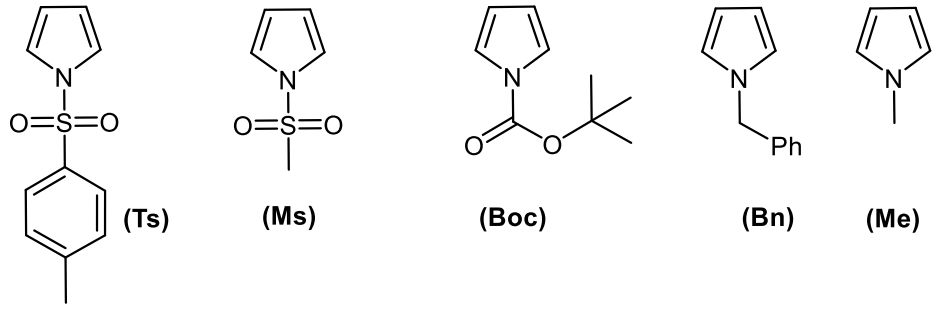


Figure 39. Common N-protecting groups for pyrrole: toluenesulfonyl (Ts), methanesulfonyl (Ms), tert-butoxycarbonyl (Boc), benzyl (Bn), methyl (Me)

Sulfonyl groups such as methanesulfonyl (mesyl, Ms) or toluenesulfonyl (tosyl, Ts) are attractive protecting groups due to their strong electron-withdrawing nature which results in a significant reduction of the reactivity of pyrrole.[61] However, deprotection is not facile and often requires harsh acidic conditions and high temperature, thereby limiting their utility.[62] Unlike sulfonyl groups, tert-butoxycarbonyl (Boc) can be installed and removed quite easily via a variety of acidic or basic conditions. This provides alternative protection strategies for the synthesis of less robust compounds, such as prodigiosenes. For example, the final step of one of the routes to prodigiosene involves the Suzuki-Miyaura cross-coupling of N-Boc-pyrrole-2-boronic acid and a 9-bromodipyrrin (Figure 40).[16, 19, 46, 63-64] However, the reactivity of N-Boc pyrroles to achieve deprotection also renders these species susceptible to premature, and unwanted deprotection.

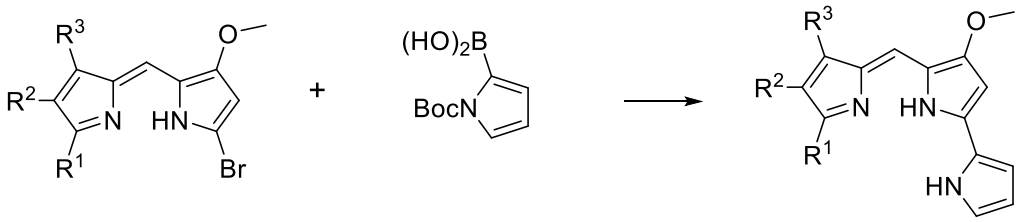
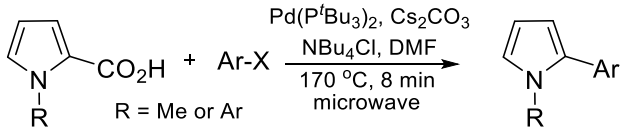


Figure 40. Suzuki-Miyaura cross-coupling of bromo-dipyrrins and N-Boc-pyrrole-2-boronic acid

3.1.2 Decarboxylative Arylation of Pyrroles

Metal-catalyzed decarboxylative cross-coupling has emerged as a synthetic strategy to form C-C bonds. The method employs carboxylic acids as coupling partners to be paired with aryl halides. The literature reports numerous examples of transition metal-mediated decarboxylative arylation using pyrroles and various transition metals.[57, 59-60] In this way, aryl groups have been efficiently adjoined to the 2-position of pyrroles. However, most methodologies focus on using the unsubstituted pyrrole unit, and do not embrace the necessity to work with pyrroles already bearing substituents on the 3-, 4- and/or 5-positions. Furthermore, these methodologies typically involve *N*-alkyl and *N*-aryl pyrroles,[65-75] thereby incorporating protecting groups that, courtesy of inherent challenges encountered in deprotection, are largely impractical for use in a synthetic sequence.[61] An exception to these generalities resulted in the first total synthesis of lamellarin L, and involved decarboxylative arylation of a pyrrole that is *N*-protected by an ethyl benzene derivative and that is highly substituted about the carbon atoms of the pyrrole.[76] The complex natural product bears *N*-substitution with features based on ethyl benzene, and thus deprotection was not required in this case.

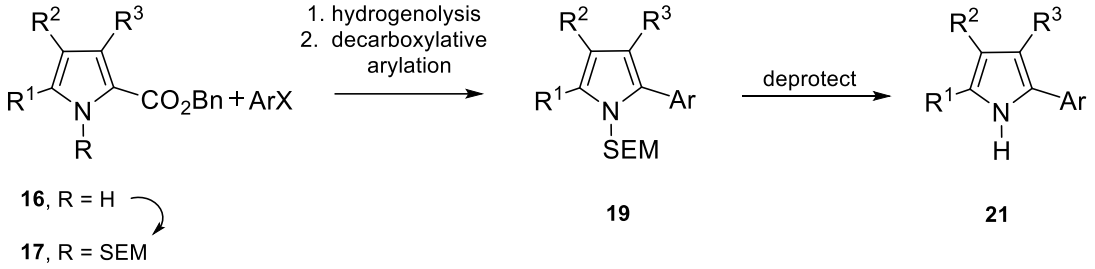
We were intrigued when Forgione and co-workers reported a comprehensive investigation of the reactivity of *N*-protected 2-pyrrole carboxylic acid in palladium-catalyzed decarboxylative arylation with Ar-X (X = iodide, chloride, bromide and triflate) affording the targeted biaryls (Scheme 6).[77] The pyrrolic nitrogen atom was protected with methyl or aryl groups to demonstrate that such species undergo decarboxylative arylation with higher efficiency than the corresponding *N*-aryl analogue.[77] However, despite significant success, this work was applied only to the unsubstituted and commercially available 2-pyrrole carboxylic acid (no further substituents about the pyrrolic core), and removal of these *N*-protecting groups is known to be challenging with pyrroles.[61]



Scheme 6. Palladium-catalyzed decarboxylative arylation by Forgione and co-workers

3.2 Project Goals

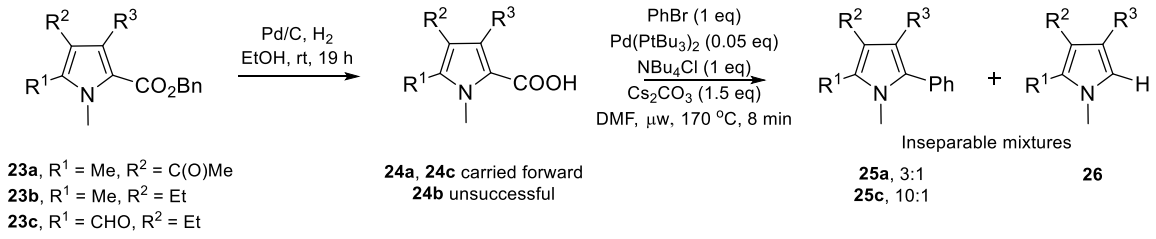
This chapter reports the synthesis of 2-aryl pyrroles achieved through protection of the pyrrolic nitrogen with 2-(trimethylsilyl)ethoxymethyl (SEM), followed by palladium-catalyzed decarboxylative arylation and subsequent deprotection. The use of 2-pyrrole carboxylic acids substituted in the 3-, 4- and 5-positions, which are necessary for the synthesis of many pyrrole-containing frameworks such as prodigiosene and *F*-BODIPYs, have not been used in such a transformation, until this published work.



Scheme 7. Decarboxylative arylation and the work reported herein

3.3 Results and Discussion

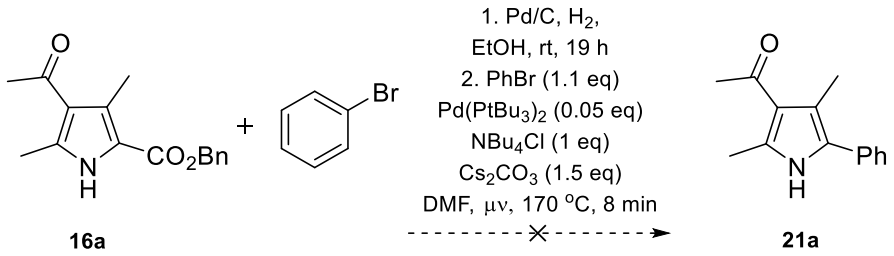
This published work was originally investigated by our post-doctoral fellow, Dr. Carlotta Figliola and a former graduate student, Dr. Brandon Groves.[78-79] My role involved expanding the substrate scope to include other coupling partners. To begin, Dr. Figliola and Dr. Groves repeated the work of Forgione and co-workers to involve N-methyl pyrroles substituted in the 3-, 4-, and 5- position. These pyrroles stem from Knorr-type reactions,[80] which place a benzyl ester in the 2-position. Hydrogenolysis of the benzyl ester provides easy access to the requisite carboxylic acid which is further subjected to cross-coupling conditions.



Scheme 8. N-methyl pyrroles subjected to Forgione's coupling conditions by Dr. Figliola

Given that the deprotection of *N*-methyl pyrroles is challenging,[61] efforts were then focused towards the synthesis of pyrroles amenable to decarboxylative arylation at the 2-position

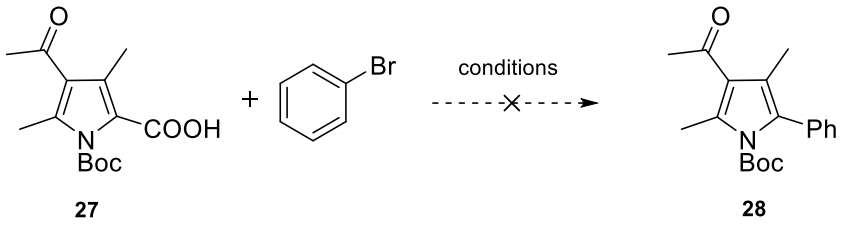
yet acquiescent to deprotection at the nitrogen atom. As palladium-catalyzed direct C-H arylation with *N*-unprotected pyrroles is known,[81] Brandon submitted the *N*-unprotected pyrrole **16a** to the decarboxylative arylation conditions (Scheme 9).



*Scheme 9. Attempted decarboxylative arylation of an N-unprotected pyrrole **16a***

However, ^{1}H-NMR spectroscopic analysis of the crude mixture showed only the two starting materials (PhBr and **16a**), as well as a significant amount of the corresponding α-free pyrrole. This result suggested that protection of the pyrrolic nitrogen atom is indeed required for decarboxylative arylation to proceed efficiently.

Cognizant that *N*-Boc pyrroles are facile to deprotect under mild conditions[61] and that direct C-H arylation involving *N*-Boc pyrroles has been reported,[82-83] Boc-protected **27** was submitted to hydrogenolysis followed by the conditions for palladium-catalyzed decarboxylative arylation (Scheme 10). Unfortunately, the desired phenyl pyrrole **28** was not isolated and the majority of the material was recollected as the corresponding *N*-deprotected α-free derivative.[84] *N*-Tosylation of pyrrole **16a** proved wholly unsatisfactory,[85-86] again demonstrating the fickle nature of *N*-protection of pyrroles.[61]



*Scheme 10. Attempted decarboxylative arylation using N-Boc pyrrole **27***

Attention was then turned to protecting groups that would mimic somewhat the methyl group of *N*-methyl pyrrole yet enable removal after the cross-coupling step. The 2-(trimethylsilyl)ethoxy methyl (SEM) protecting group (Figure 41) has been used to protect functionalities such as alcohols, imines, imidazoles and pyrroles. It is easily introduced, more selective than other protecting groups (*e.g.* methyl group), and most importantly, is removed under reaction conditions compatible with other functional

groups.[87-88] Furthermore, the SEM group has been shown to be effective as a protecting group for pyrazoles undergoing C−H arylation.[89]

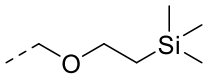
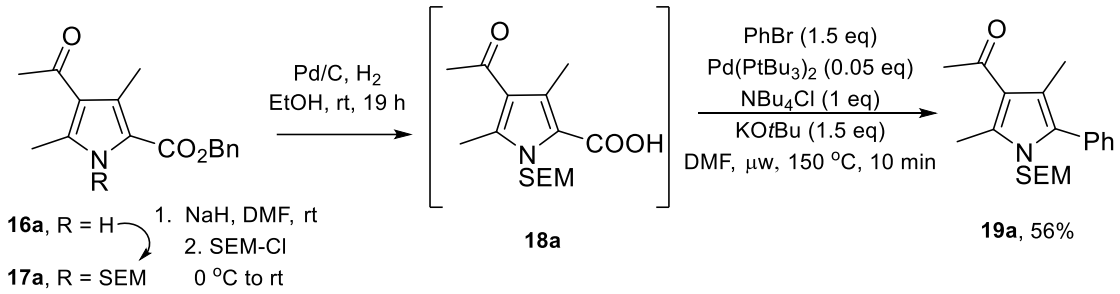


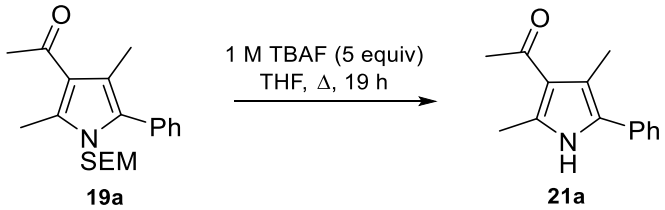
Figure 41. SEM protecting group

Pleasingly, reaction of the pyrrolide of **16a** with SEM-Cl gave the *N*-SEM pyrrole **17a**. Hydrogenolysis of the benzyl ester gave the acid **18a**, which was used in the subsequent palladium-catalyzed decarboxylative arylation step without isolation (Scheme 11). Optimization of this step by Dr. Figliola resulted in reaction conditions which required 1.5 equiv. of phenyl bromide, 0.05 equiv. of $Pd(P^tBu_3)_2$ as the transition metal catalyst, 1.0 equiv. of NBu_4Cl as the phase transfer catalyst, and 1.5 equiv. of potassium tert-butoxide as the base, to afford the desired SEM-protected 2-aryl pyrrole **19a** in a 56% isolated yield.



*Scheme 11. Decarboxylative arylation using SEM-protected pyrrole **18a***

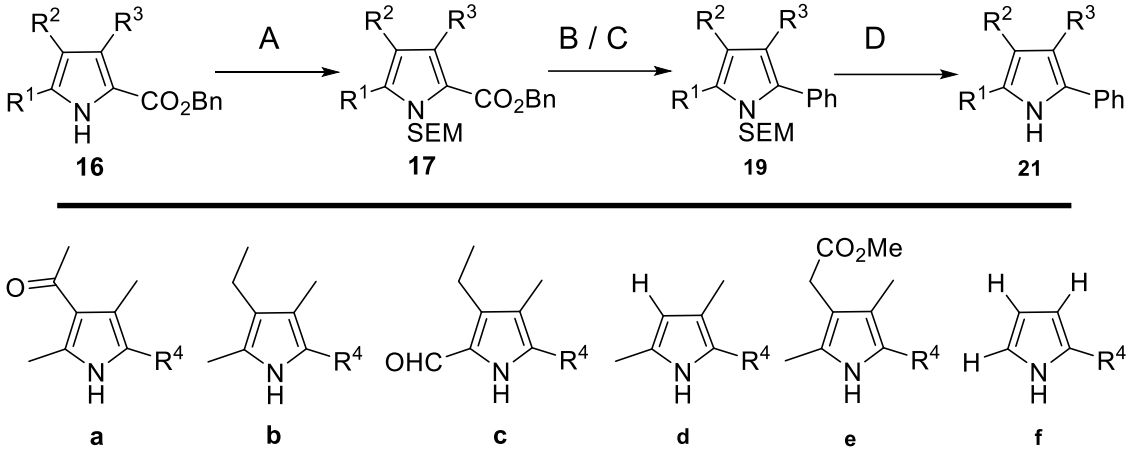
With **19a** in hand, the removal of the SEM-protecting group was successful following adaptation of a literature procedure,[88] wherein a solution of the SEM-protected pyrrole **19a** in THF was treated with 5 equiv. of TBAF as a 1 M solution and heated at reflux temperature for 19 hours (Scheme 12).



*Scheme 12. SEM-deprotection of pyrrole **19a***

In order to evaluate the feasibility of palladium-catalyzed decarboxylative arylation and *N*-deprotection involving substituted N-SEM pyrroles, Dr. Figliola explored the

substrate scope using pyrroles **16b-f**, which featured various functionalities about the pyrrolic core (Scheme 13).

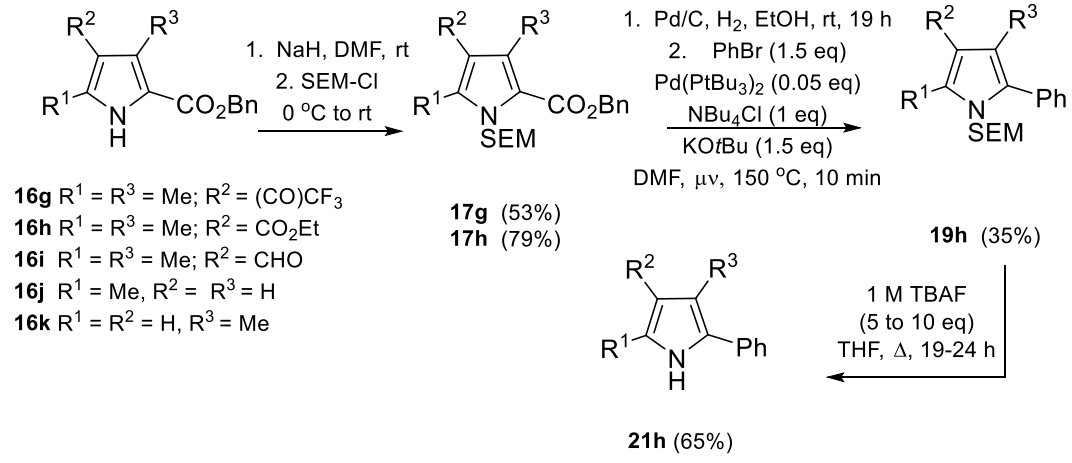


Scheme 13. Pyrroles investigated by Dr. Figliola; A. SEM protection, B. Hydrogenolysis, C. decarboxylative arylation, D. deprotection

Despite the different electronic nature of pyrroles **16b-f**, SEM-protection was consistent and high-yielding across all the investigated substrates. The SEM-protected pyrroles **17b-f** were submitted to hydrogenolysis and the resulting carboxylic acids reacted with PhBr under the optimized decarboxylative arylation reaction conditions. All substrates underwent successful hydrogenolysis and decarboxylative arylation except for pyrrole **17c**, which instead formed a mixture of deformylated products. Electron-rich pyrroles **19b** and **19e** were obtained successfully and in comparable isolated yields to that of **19a**. However, *N*-deprotection did not proceed and only resulted in decomposition of the starting materials. SEM-deprotection was also attempted on pyrrole **19b** and again decomposition of the starting material was observed. This suggests that removal of the SEM protecting group is challenging for electron-rich pyrroles.

The work completed by Dr. Figliola and Dr. Groves established the synthesis of 2-phenyl pyrroles (substituted in the 3-, 4-, and 5-positions) using decarboxylative arylation of SEM-protected pyrroles (Scheme 13). My role in this work involved further expanding the substrate scope to include other coupling partners as well as other substituted pyrroles. This work was requested by reviewers prior to publication.[79] First, attention was focused on the SEM-protection of other substituted pyrroles, both electron rich and electron deficient (Scheme 14). Of the substrates selected (**16g-k**) for SEM protection, only two pyrroles (**17g** and **17h**) were successfully prepared and isolated, each containing electron-

withdrawing groups (-(CO)CF_3 or -CO_2Et) in the 3-position. The pyrrole bearing a formyl group in the 3-position, like Dr. Figliola's example (Scheme 8, **23c**) with a formyl group in the 2-position was unsuccessful. After multiple additions of SEM-Cl and stirring at room temperature for two days, TLC analysis showed significant starting material still present and the formation of a new spot of higher R_f. The electron-rich pyrroles bearing a single methyl group in either the 2- or 3- position underwent successful SEM-protection. However, the desired products could not be isolated from other SEM-products found in the crude mixture. As a result, the two pyrroles **17g** and **17h** were carried forward and subjected to hydrogenolysis followed by decarboxylative arylation (Scheme 14). The 2-phenyl pyrroles **19g** and **19h** were successfully produced, but as the major component of an inseparable mixture containing multiple SEM products and the corresponding α-free (2- position) derivative. The electron-poor pyrrole, **19g** was subjected to multiple purification attempts via column chromatography, without success and therefore abandoned. Although, the pyrrole **19h** bearing an ethyl ester in the 3- position could not be isolated from its corresponding α-free derivative, the yield for **19h** was calculated based on the conversion of **17h** into **19h**, and the mass of the mixture. Upon deprotection, the unwanted α-free derivative **22h** was separated from the targeted **21h**, which was isolated in 65% yield.

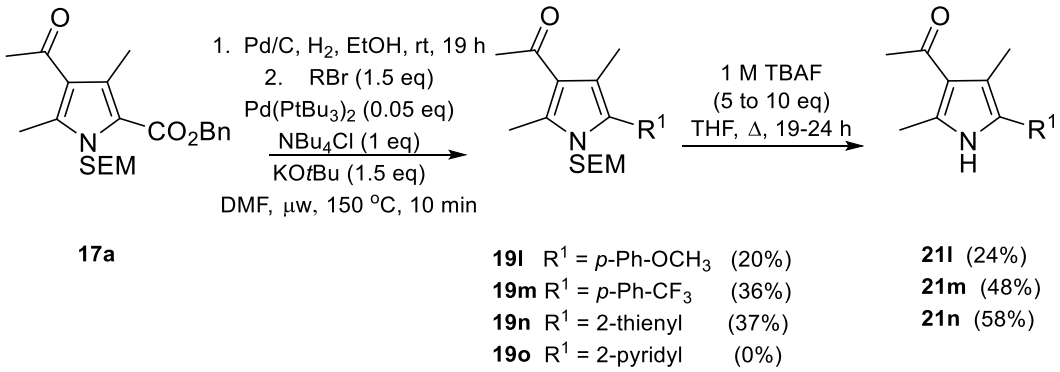


*Scheme 14. N-Protection of pyrroles with SEM followed by hydrogenolysis and decarboxylative arylation. Note: compound **20** and **22** are the α-free derivatives of compound **19** and **22**, respectively.*

During this work, I supervised a summer undergraduate research student, Connor Lamont. Under my guidance, Connor explored the reactivity of other aryl halides (besides

PhBr) in the decarboxylative arylation of the model substrate, **18a**. It was found that other phenyl halides (X = I, Cl, OTf) were not as successful as phenyl bromide when subjected to palladium-catalyzed decarboxylative cross-coupling. The use of phenyl chloride and phenyl triflate resulted in generation of only the α-free derivative. The use of phenyl iodide generated the desired pyrrole **19a**, in a lower yield of 25%. In this way, Connor demonstrated that aryl bromides are optimal for coupling to N-SEM protected pyrroles via decarboxylative arylation.

With this knowledge in hand, the feasibility of decarboxylative arylation and SEM deprotection involving the model substrate pyrrole **17a**, and various aryl bromide coupling partners, was explored (Scheme 15).



*Scheme 15. Palladium-catalyzed decarboxylative arylation and SEM-deprotection of **17a** with aryl bromides. Note: compound **20** and **22** are the α-free derivatives of compound **19** and **22**, respectively.*

The 2-aryl pyrroles **19l**-**19n** were successfully produced. However, **19l** and **19m** were the major component of an inseparable mixture containing the corresponding α-free derivative **20l** and **20m**, respectively. The yields are calculated based on the conversion of **18a** into the desired decarboxylative arylation product and the mass of the mixture. Upon deprotection, the unwanted α-free derivative was separated from the targeted **21l** and **21m** which were isolated in 24% and 48% yields, respectively. This suggests that the electron withdrawing nature of the aryl halide aids in the decarboxylative arylation compared to aryl halides bearing electron donating substituents. The 2-thienyl pyrrole **19n** was successfully produced in 37% yield and separable from the α-free derivative **20n** prior to the deprotection step. However, the 2-pyridyl pyrrole **19l** was not produced, with only the unwanted α-free derivative **20l** isolated.

3.4 Conclusions

This chapter describes the palladium-catalyzed decarboxylative arylation for heteroaryl-aryl C-C bond formation using substituted *N*-SEM pyrroles in stoichiometric amounts with aryl bromides. The influence of substituents about the pyrrole core, both electron-donating and electron-withdrawing, was investigated. The use of SEM as an *N*-protecting group enables both decarboxylative arylation and *N*-deprotection with select systems. Although SEM-deprotection of some electron-rich pyrroles was unsuccessful, the deprotection of pyrroles bearing a mixture of alkyl- and H-substitution, as well as acyl or pendant carbonyl functionality, proceeded well. Certainly, the fickle nature of pyrroles as regards to (de)protection means that protection strategies must be selected with care. Nevertheless, for certain systems, the use of *N*-SEM pyrroles provides a useful alternative when deprotection is required following decarboxylative arylation.

CHAPTER 4 - Thio-substituted Prodigiosenes

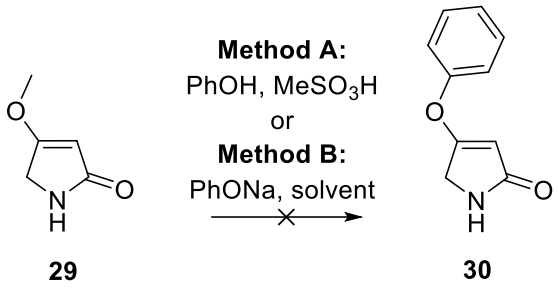
4.1 BackgroundProdigiosin as an Anticancer Agent

The study of prodigiosin as an anticancer agent dates back as far as 1893 when William Coley treated patients with a vaccine composed of inactivated bacteria, including *Serratia marcescens*.[90] Given the biological profile of prodigiosin (discussed in Chapter 1), especially its immunosuppressive activity, and the fact that Coley's Toxin contained killed bacterial strains known to produce prodigiosin, it is unsurprising that Coley's Toxin had been used successfully in the treatment of cancer over decades. Indeed, following treatment with Coley's Toxin, a bone cancer patient saw complete regression of a tumor and went on to live a long, normal life despite an initial prognosis of only 3 months survival.[91] This vaccine, known as Coley's Toxin, was used until the early sixties and is hailed as being the first example of immunotherapy for the treatment of cancer. While this treatment was in use until the early sixties, it became illegal following classification as a "new drug" by the FDA.[91] In 1962, the FDA passed an amendment to the Federal Food, Drug and Cosmetic Act which required that all "new drugs" must undergo rigorous clinical testing prior to approval. Drugs that had been already on the market and used for a long time, such as aspirin, were grandfathered in. However, in 1963, Coley's toxin was classified as a "new drug" despite have been used for over 60 years, hence rendering it illegal to use.

4.1.2 Synthesis of Prodigiosenes with B-ring Modifications

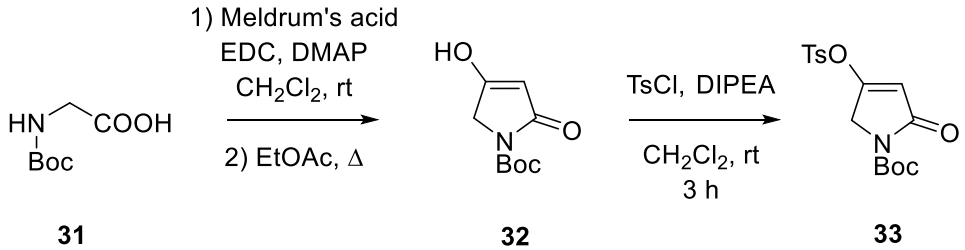
From Coley's Toxin to Obatoclax, the therapeutic potential of prodigiosin and synthetic derivatives (prodigiosenes) has captivated researchers for over a century. As discussed in Chapter 1, one mechanism by which prodigiosin can induce apoptosis of cancer cells is through altering intracellular pH via anion transport. When protonated, prodigiosin is one of the most effective anion transporters reported.[92] Previous work in the Thompson group by Dr. Estelle Marchal demonstrated that the basicity of prodigiosenes can be modulated through modifications to the B-ring with O-aryl substituents.[19] It was found that prodigiosenes with electron-donating substituents on the B-ring increase the basicity of the prodigiosene framework thereby improving anion transport efficiency. In order to study the anion transport efficiency of O-prodigiosenes, a method by which to

synthesize these compounds was needed. Using a patented procedure[93] for the substitution of pyrrolinone **29** with benzyl alcohol, Dr. Marchal attempted direct substitution of the methoxy substituent of pyrrolinone **29** using phenol or phenoxide as nucleophiles (Scheme 16). However, these attempts were unsuccessful in forming the desired pyrrolinone **30**.

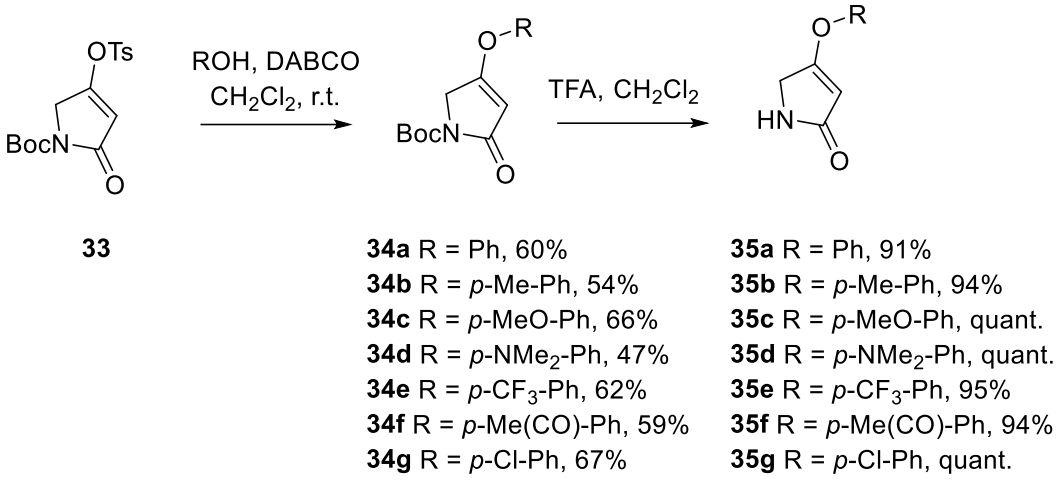


*Scheme 16. Attempts to synthesize -OPh pyrrolinone **30** using phenol or phenoxide as nucleophiles by Dr. Marchall[19]*

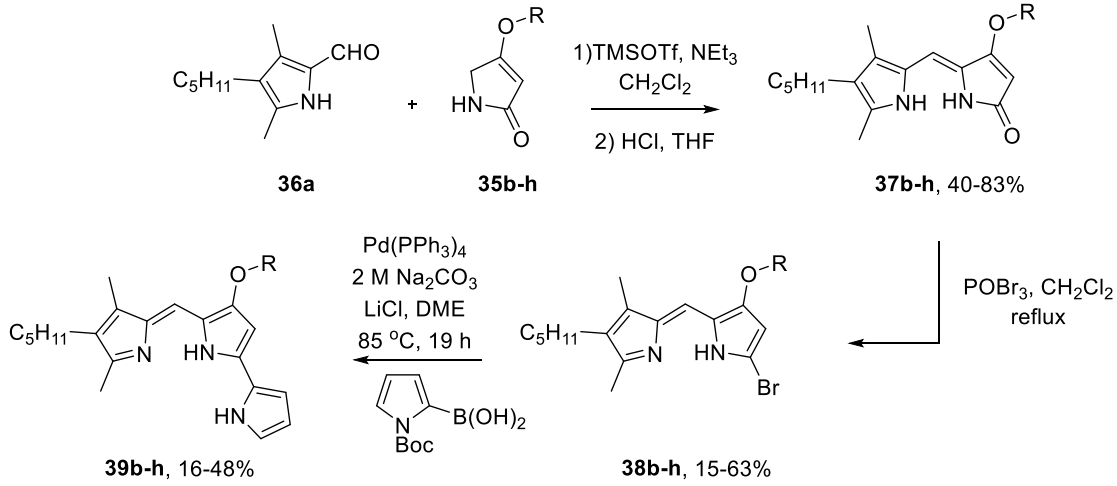
Adapting a literature procedure, Dr. Marchal then prepared 3-hydroxypyrrolinone **32** (Scheme 17) from the reaction of Boc-protected glycine **31**, Meldrum's acid, DMAP and EDC. The reaction mixture was subsequently heated in ethyl acetate at reflux temperature to induce intramolecular cyclization and decarboxylation. In order to achieve the desired O-aryl substitution at the 3-position, the hydroxyl group was activated with tosyl chloride to give the tosylated pyrrolinone **33**. With a better leaving group installed at the 3-position, O-aryl substitution was achieved across a variety of substituents (Scheme 18). Following N-Boc deprotection of the O-arylated pyrrolinone **34**, Dr. Marchal and co-workers generated seven O-aryl prodigiosenes (Scheme 19) and studied the anion transport efficiency of these compounds.[12]



Scheme 17. Synthesis of 3-hydroxypyrrolinone



Scheme 18. Synthesis of O-aryl pyrrolinones by Dr. Marchal[19]



Scheme 19. Synthesis of B-ring modified -OR prodigiosenes by Dr. Marchal[19]

4.1.3 Sulfur as a Scaffold for Drug Design

This published work[19] represented the first synthesis of a series of B-ring modified prodigiosenes. These B-ring derivatives proved to exhibit excellent anion transport efficiency, with the nature of the O-aryl B-ring substituent influencing this process. Cognizant that the nature of the O-substituent influenced biological properties in this manner, we became interested in introducing thio-based substituents onto the B-ring.

Sulfur has a variety of common oxidation states, and varied utility. It is found in many natural products and pharmaceuticals including the amino acid methionine, biotin and penicillin. As of December 2016, there were 249 US FDA-approved drugs containing sulfur atoms across a range of different functional groups.[94] The most common functional

groups found in these drugs were sulfonamides (72 drugs), B-lactams (36 drugs) and thioethers (32 drugs).

Sulfur has the ability to participate in non-covalent interactions, such as sigma-holes (σ-holes), which can influence conformational changes in a molecule.[95] Sigma-holes are formed when a region of positive electrostatic potential occurs along the extension of a covalent bond involving group IV-VII elements.[96-97] Hence, a σ-hole interaction is simply an electrostatic attraction between a positive site (σ-hole) of a molecule and a negative region (e.g. a lone pair of a Lewis base, or π electrons) of another. The polarization of covalent bonds between halogens and other atoms is well studied and is an example of a σ-hole. For sulfur, this interaction is similar to a hydrogen bond interaction, where the σ-hole of sulfur is analogous to those involving *NH* moieties.

Utilizing sulfur as an isostere for *NH* in drug design has been documented.[95] In a series of VEGF (Vascular Endothelial Growth Factor) kinase inhibitors (Figure 42), the parent compound **40** contains a fused-planar heterocyclic ring system.

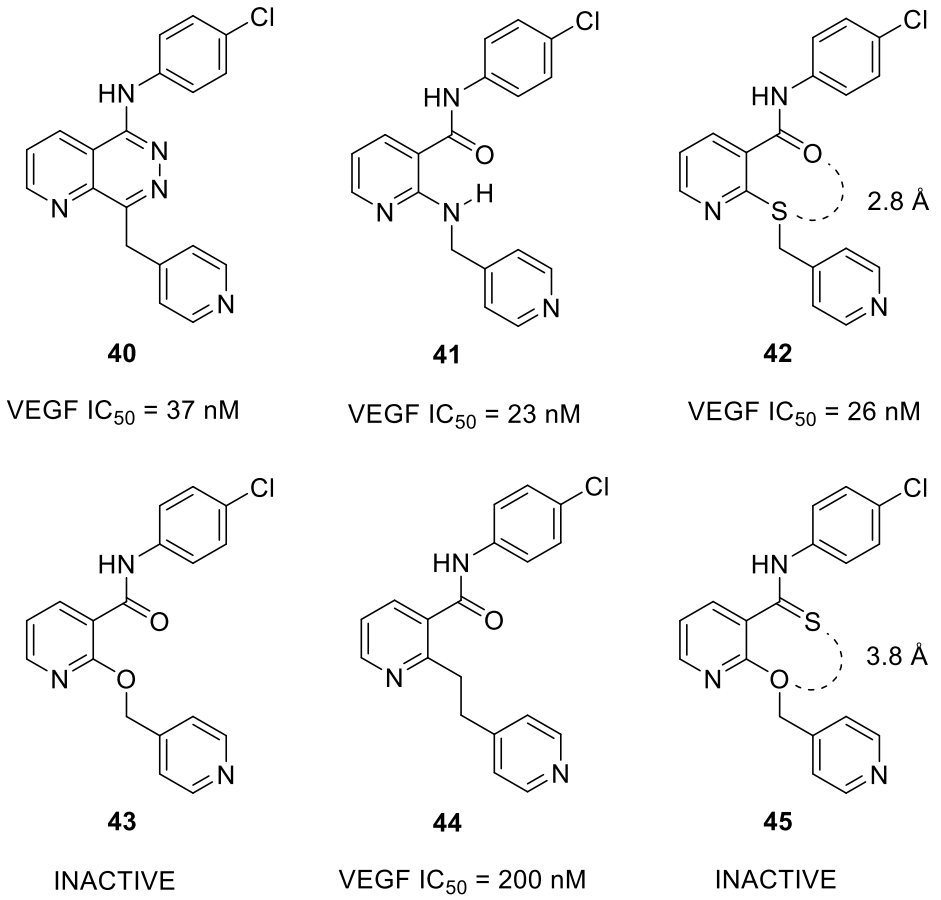


Figure 42. Structure activity relationships of a series of VEGF kinase inhibitors

Replacement of the pyridazine moiety of **40** with an amide and an amine (compound **41**) maintains planarity through hydrogen bonding of the amide oxygen atom and the *NH* unit of the amine. This change results in a slight improvement in activity when evaluated against compound **40**. In compound **42**, a thioether was incorporated to mimic the *NH* interaction with the oxygen of the carbonyl, resulting in a compound exhibiting similar activity. The electrostatic interaction between the carbonyl oxygen and the sulfur atom within **42** is supported with a S-O through-space distance of 2.8 Å. Meanwhile, when the thioether of **42** was replaced with an ether or alkyl moiety as in compounds **43** and **44**, much reduced activity was observed. Likewise, the incorporation of a thioamide **45** in lieu of the amide of **43**, resulted in a much weaker interaction between the sulfur and oxygen atoms (compared to **42**), and a distance of 3.8 Å between the oxygen and sulfur atoms. This highlights the ability of divalent sulfur to mimic hydrogen bonding between NH…O through σ-hole interactions.

4.2 Project Goals

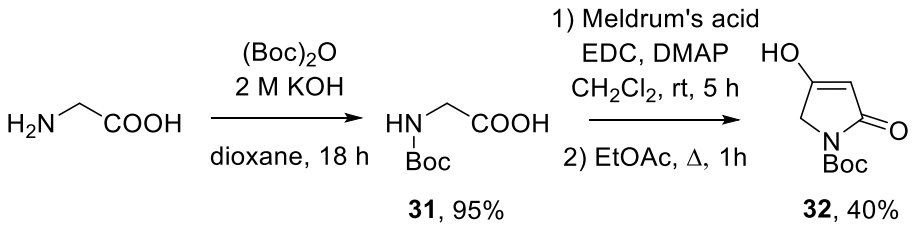
The goal of this thesis work was to synthesize derivatives of prodigiosin with thioether functionality on the B-ring, instead of the signature methoxy substituent of the natural product. This was achieved through substitution of the N-Boc-tosyl pyrrolinone **33** (Scheme 18) with various thiols. The synthesis and characterization of thio-substituted prodigiosenes is discussed herein.

4.3 Results and Discussion

4.3.1 Synthesis of B-ring Pyrrolinones with Thioether Linkages

The synthesis of prodigiosenes bearing modifications to the B-ring first required the preparation of 3-hydroxy pyrrolinone **32**, i.e. tetramic acid (Scheme 20). The amino acid glycine was reacted with $(Boc)_2O$ under basic conditions to install a Boc group. The N-protected amino acid was then reacted with Meldrum's acid (1.5 equiv), DMAP (1.5 equiv), and EDC (1.5 equiv) to give the final cyclized product, after heating at reflux temperature in ethyl acetate, with a yield of 40%. In the literature,[98] much higher yields are reported for this compound, yet, the patented procedure[99] reports a yield of only 56%.

Given that this is the first step of a 10-step synthesis, obtaining such a low yield in the beginning was not desirable. After analysis of the potential mechanism of the reaction, it was realized that the 1.5 equiv of coupling reagent (EDC) is inefficient for this reaction. As such, the equivalents of EDC was increased to 3 and the yield for this reaction was significantly improved (73%).



Scheme 20. Synthesis of 3-hydroxy pyrrolinone

Although this synthesis is widely used, it is met with some handling challenges that are not explicit within the published work. The reaction of Boc-glycine, Meldrum's acid, DMAP and EDC can take more than 5 hours to complete. After completion, ethyl acetate is added to form a precipitate which is then solubilized with the addition of 5% citric acid. Following

workup, cyclization is complete after 1 hour at reflux temperature in ethyl acetate. To conduct all of this in an 8-hour working day is not possible. Therefore, it was found that the first step could be set up in the evening and run overnight without impact to the outcome of the reaction.

It should also be noted that the first step of the reaction of Boc-glycine with Meldrum's acid was conducted in DCM and hence required an excess amount of ethyl acetate for extraction – limiting the scale at which this reaction could be conducted. For example, a 5 gram scale (29 mmol) of 3-hydroxypyrrolinone requires the use of 250 mL of DCM which would result in the use of 1 liter of extraction solvent. Hence, prior to precipitation with ethyl acetate, the reaction mixture was concentrated in vacuo, then the dark yellow oil was transferred with a minimal amount of DCM to the separatory funnel.

Another challenge lies in the purification of pyrrolinone **32**. The desired N-Boc-3-hydroxypyrrolinone (N-Boc tetramic acid) can exist in one of two tautomers (Figure 43), each with very different solubilities. The enol tautomer (Figure 43) is the most soluble of the two yet is only sparingly soluble in DCM; while the keto-tautomer is only somewhat soluble in methanol. Since Meldrum's acid is also soluble in DCM, this leads to difficulties in purification when more of the enol-tautomer is present. The desired pyrrolinone **32** could be obtained by suspending the crude solid in cold DCM and filtering through a Millipore filter. The solid was then washed with DCM to remove Meldrum's acid, followed by pentane. In some cases, this process had to be repeated multiple times, especially if more enol-tautomer was present.

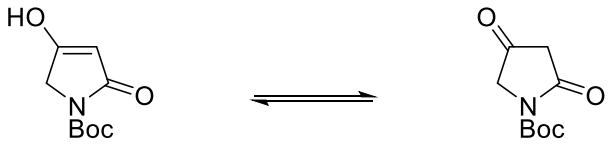
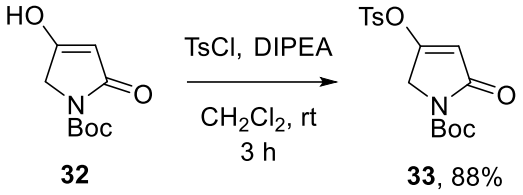


Figure 43. Tautomers of tetramic acid

Following optimization for the synthesis 3-hydroxy pyrrolinone **32**, attention was directed towards the synthesis of 3-tosylpyrrolinone **33** (Scheme 21). Following a literature procedure,[99] tosylation of 3-hydroxypyrrolinone **32** was met with variable success. In some cases, the reaction proceeded smoothly, changing from pale yellow to red, while in other

cases it would turn very dark, resulting in a black tar-like oil after workup and providing a much lower yield.

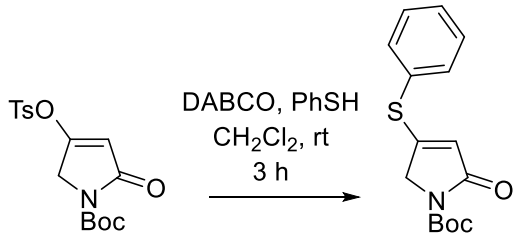


32 **33**, 88%

Scheme 21. Synthesis of 3-tosyl pyrrolinone

While the literature states[100] that 3-hydroxypyrrolinone **32** was used in the next step (tosylation) without further purification beyond workup, it was noticed that failure to remove excess Meldrum's acid (Scheme 20) results in a horrendous workup and required multiple purification attempts of 3-tosyl pyrrolinone **33** via column chromatography. After removal of Meldrum's acid, tosylation could be achieved without extensive purification. Pyrrolinone **33** was obtained by filtering over a short plug of silica to remove baseline material and washing with ethyl acetate/pentane (50/50 ratio). After removal of solvent, pyrrolinone **33** was precipitated using DCM/pentane resulting in a white solid (88%).

With improved procedures in hand to synthesize grams of the 3-tosyl pyrrolinone **33**, substitution with thiols could be conducted. For the synthesis of -OR pyrrolinones,[19] 3-tosyl pyrrolinone **33** was reacted with alcohols in the presence of DABCO for a reaction time of 16 hours at room temperature (Scheme 18). The reaction of 3-tosyl pyrrolinone **33**, thiophenol and DABCO resulted in complete conversion to pyrrolinone **46a** following just 3 hours of reaction time (Scheme 22). However, when other thiols such as 4-nitrobenzenethiol or 4-methoxybenzenethiol were used, the reaction did not reach completion, even after 24 hours and heating.



33 **46a**

Scheme 22. Synthesis of -SPh pyrrolinone

To facilitate the substitution, compound **33** was subjected to the reaction conditions as per Scheme 22, but with microwave irradiation rather than stirring at room temperature. Since

dichloromethane is transparent to microwaves, it would not be directly heated by microwave energy. However, a reaction conducted in a non-absorbing solvent will still heat if polar molecules (such as compound **33**) and/or ions are dissolved. Indeed, when the requisite 3-tosyl pyrrolinone **33** along with thiophenol (1.5 equiv) and DABCO (1.1 equiv) in DCM was subjected to microwave irradiation (P = 100 W), the temperature of the reaction reached up to 40 °C and the desired pyrrolinone **46a** formed after 10 minutes. After usual work up, pyrrolinone **46a** was purified via flash column chromatography using silica (0-25% EtOAc/hexanes). Upon removal of solvent via rotary evaporation, crystals formed inside the round bottom flask. A crystal suitable for x-ray analysis of pyrrolinone **46a** was selected and submitted to Dr. Katherine Robertson of Saint Mary's University, who conducted the analysis and solved the crystal structure. The crystal structure for compound **46a** is shown in Figure 44, illustrating incorporation of an -SPh moiety with bond distances of 1.74 and 1.78 for C(3)-(S1) and C(5)-(S1), respectively, and a bond angle of 101.6° for C(3)-S(1)-C(5).

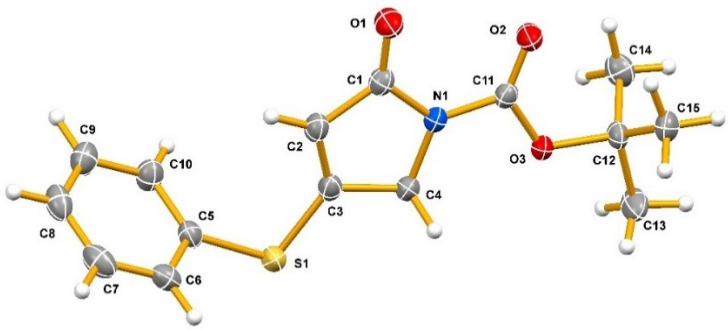
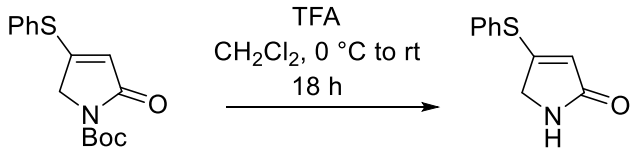


*Figure 44. Thermal ellipsoid diagram of NBoc-pyrrolinone **46a***

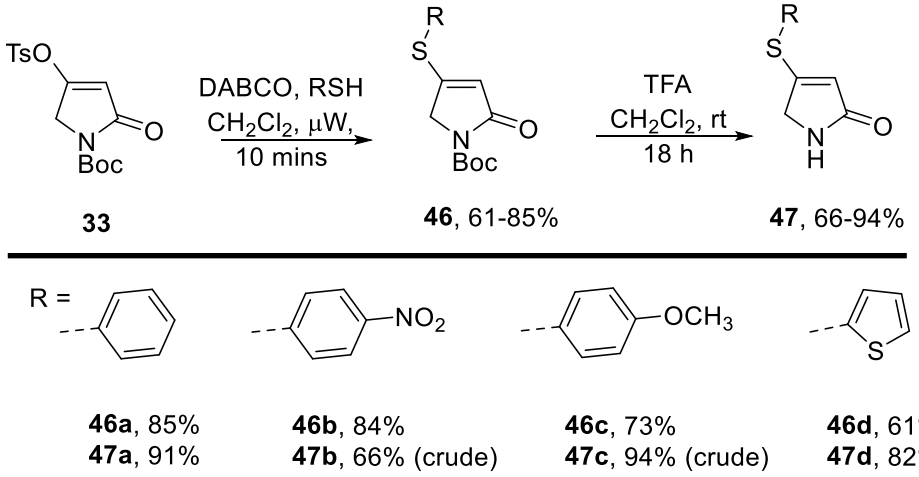
Following substitution of the tosyl group of pyrrolinone **33** with a -SPh moiety, the Boc group of **46a** was removed upon treatment with TFA (Scheme 23). The NH 3-thiophenyl pyrrolinone **47a** was obtained following workup and precipitation with DCM/pentane (91%).



46a **47a**, 91%

*Scheme 23. Deprotection of pyrrolinone **46a***

Using the modified conditions for the synthesis of pyrrolinone **47a**, three more pyrrolinones (**47b-d**) were successfully synthesized in overall modest yields following acid-catalyzed Boc-deprotection (Scheme 24). Substitution of the thiophenyl group with *p*-nitro and *p*-methoxy thiophenyl moieties would allow the effects of electron withdrawing and electron donating groups respectfully, to be assessed. Similarly, the incorporation of a thienyl group on the B-ring would enable the electronic effects of this aryl group to be evaluated.



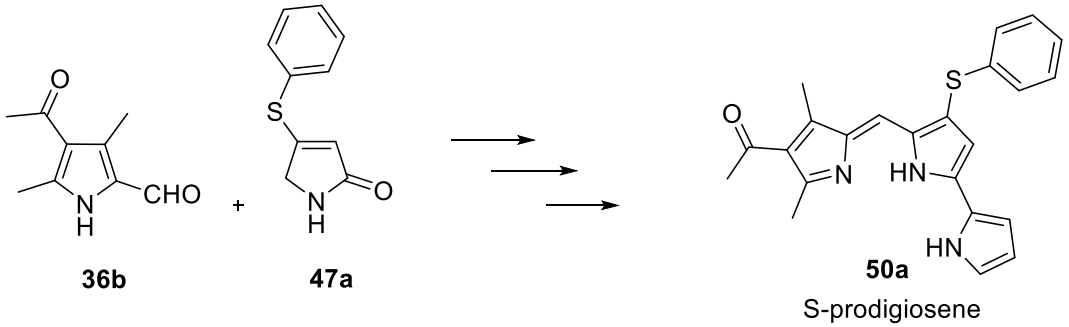
33 **46**, 61-85% **47**, 66-94%

46a, 85%	**46b**, 84%	**46c**, 73%	**46d**, 61%
47a, 91%	**47b**, 66% (crude)	**47c**, 94% (crude)	**47d**, 82%

*Scheme 24. Synthesis of thio-substituted pyrrolinones **46-47**. Microwave conditions: Power = 100 W; Absorbance = normal; T = off*

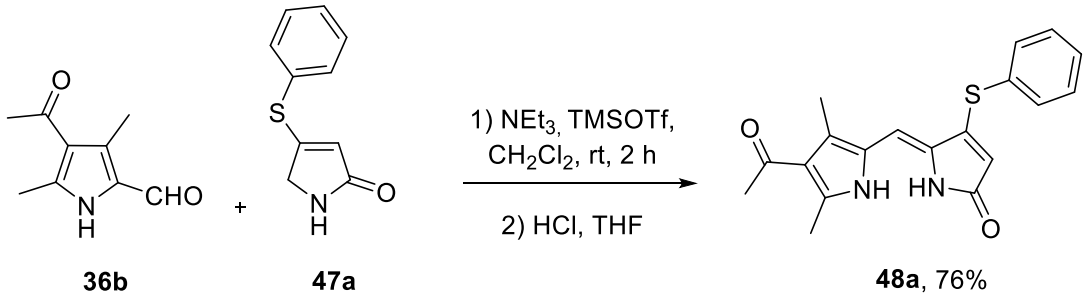
4.3.2 Synthesis of a Thio-substituted Prodigiosene

With a method to synthesize thio-substituted pyrrolinones, the synthesis of S-prodigiosenes could be pursued. To begin, the 2-formyl pyrrole **36b**, with electron-withdrawing functionality in the 4-position, and 3-thiophenoxy pyrrolinone **47a** were chosen as model substrates to explore the feasibility of this synthesis (Scheme 25).



Scheme 25. Model substrates for the synthesis of thio-substituted prodigiosenes

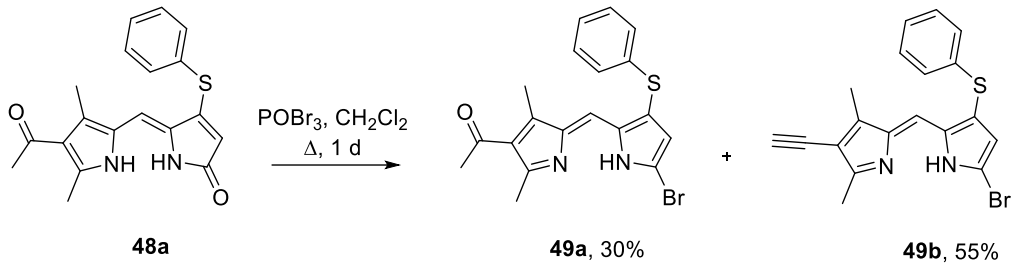
Using a [C+B]+A approach to the construction of the tripyrrolic skeleton, the C-ring 2-formyl pyrrole **36b** and B-ring 3-thiophenoxy pyrrolinone **47a** were condensed via Mukaiyama-type aldol conditions (Scheme 26). To achieve this, a solution of the requisite pyrrolinone **47a** was first activated with TMSOTf followed by dropwise addition of the 2-formyl pyrrole **36b**. The reaction mixture was then neutralized with phosphate buffer and extracted with DCM. Upon removal of the solvent, crude **48a** was dissolved in THF and treated with HCl to yield the final product as a yellow solid.



*Scheme 26. Synthesis of dipyrrinone **48a***

In order to install the final pyrrolic ring (the A-ring) through Suzuki cross-coupling conditions, the dipyrrinone **48a** was first activated at the 9-position. Dipyrrinones with -OR functionality on the B-ring can be derivatized to give dipyrrins with either a bromo or triflate substituent in the 9-position. Both methods have been used successfully in preparing -OR prodigiosenes. However, for this work, bromination was selected as bromo-dipyrrins

have been reported to be more stable than their triflate analogues.[64] As such, a solution of dipyrrinone **48a** in DCM was stirred overnight at reflux temperature, in the presence of $POBr_3$, to give the bromo-dipyrrin **49a** (Scheme 27).



*Scheme 27. Synthesis of bromo-dipyrrin **49b***

After 24 hours, analysis by TLC indicated consumption of starting material and the presence of two spots. The first spot (with a higher R_f relative to the second spot) appeared dark orange under ambient light, and of much darker intensity under short-wave UV light. Following quenching and workup, the compound corresponding to the second spot, which appeared yellow/orange under ambient light, was separated from the first via column chromatography. After analysis via ^{1}H-NMR spectroscopy, compound **49a** was identified as the "second spot" isolated from the column. However, the identity of the "first spot" was not obvious based on the ^{1}H-NMR alone. For compound **49a**, the chemical shift of the 2- and 4-position methyl groups are 2.41 and 2.46 ppm and integrate to 3 protons each. The chemical shift of the acyl -CH_3 group is slightly downfield at 2.63 and integrates to 3 protons. However, in the ^{1}H-NMR spectrum of the "first spot", there are only two singlets that each integrate to 3 protons, found at 2.24 and 2.44 ppm, respectively (Figure 45). The signal corresponding to the -CH_3 group of the acyl group (δ 2.63 ppm, 3H) is absent in the ^{1}H-NMR spectrum of the isolated material. A previously unobserved signal, integrating to 1 proton, was evident at 3.36 ppm.

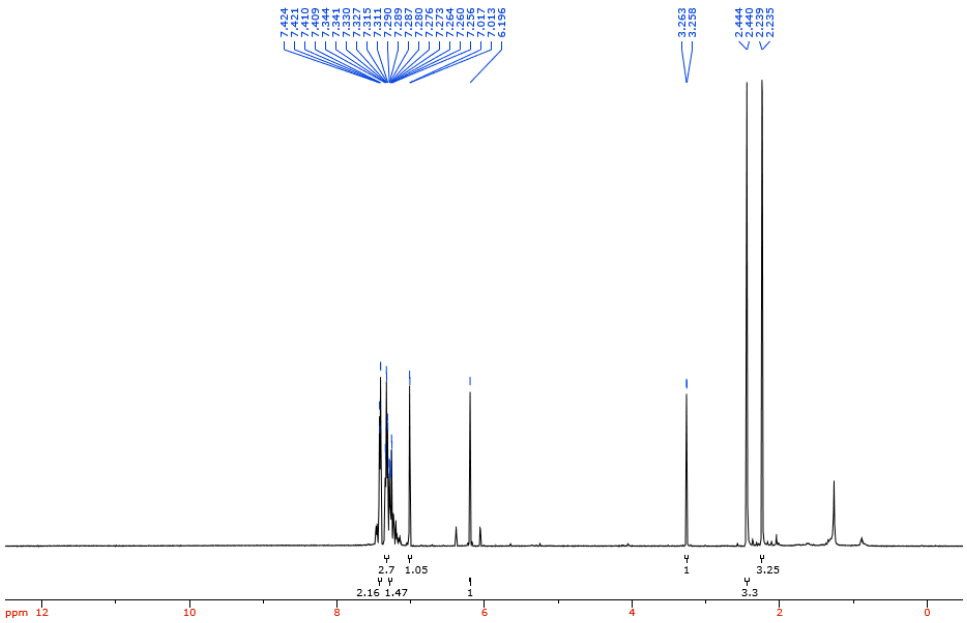
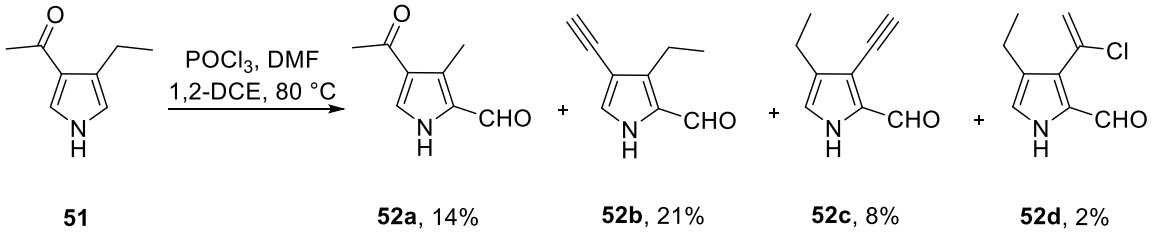


Figure 45. [1]H-NMR spectrum of "first spot"

Additionally, analysis of the ^{13}C-NMR spectrum (Chapter 5) did not reveal a signal in the carbonyl chemical shift region, thus indicating that the acyl functional group was no longer present. Previous work in the Thompson group by Dr. Figliola, demonstrated that when pyrrole **51** was subjected to Vilsmier-Haack conditions, many products were isolated, including 3-alkynyl pyrroles **52b** and **52d** (Scheme 28).[101]



Scheme 28. Byproducts isolated from Vilsmier-Haack reaction of 3-acyl pyrrole [101]

With this in mind, it was postulated that the same transformation occurred when the 3-acyl dipyrrinone **48a** was reacted with 2 equivalents of $POBr_3$. As such, a potential mechanism for the formation of the alkyne **49b** is shown in Figure 46. The desired 3-acyl bromo-dipyrrin **49a** is formed according to Figure 46, Steps 1-3. The 3-acyl group is then activated by $POBr_3$, forming an allene intermediate (Figure 46, Steps 4-6). The reaction is then quenched with saturated sodium bicarbonate to result in the formation of the alkyne **49b** (Figure 46, Step 7).

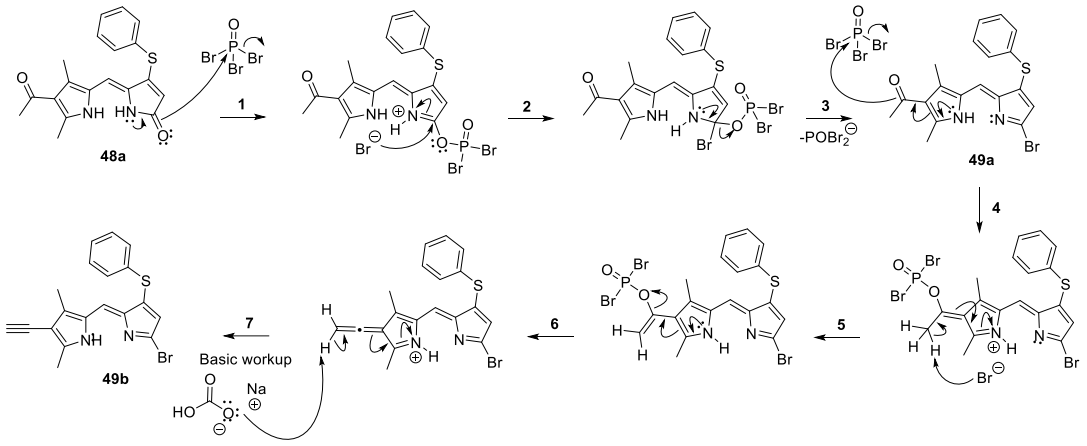


*Figure 46. Proposed mechanism for alkyne formation of **49a** during bromination step*

Further spectroscopic analysis of 1-D and 2-D NMR of the "first spot" along with MS analysis revealed that the "first spot" is indeed the bromo-dipyrrin **49b** with an alkyne in the 3-position. This material was isolated as the major product (55%).

Crystals suitable for x-ray analysis of both the acyl and alkynyl bromo-dipyrrins were obtained via a liquid-liquid diffusion method using a solution of the desired compound in chloroform and then layered with pentane on top. The resulting thermal ellipsoid diagram for the alkynyl bromo-dipyrrin **49b** is shown in Figure 47. Indeed, a triple bond between C(17) and C(18) is suggested, with a bond distance of 1.19 Å and a bond angle of 179° for C(18)-C(17)-C(8). The crystal structure for **49a** is shown in Figure 48. Two possible conformations arise from the rotation of the acyl moiety, both evident in the unit cell (Figure 48). In **C1** of **49a**, the oxygen atom of the carbonyl points in the direction opposite to the pyrrolic nitrogen atom N(2), with a dihedral angle of -168.4° for C(9)-C(8)-C(17)-O(1). In **C2** of **49a**, the oxygen atom of the carbonyl is pointing the same direction as the pyrrolic nitrogen N(2) with a dihedral angle of -8.1° for C(28)-C(27)-C(36)-O2. Non-covalent π-interactions between **C1** and **C2** or two **C2** molecules were observed within the unit cell, with contact distances of 3.74 Å and 3.93 Å, respectively (Figure 49).

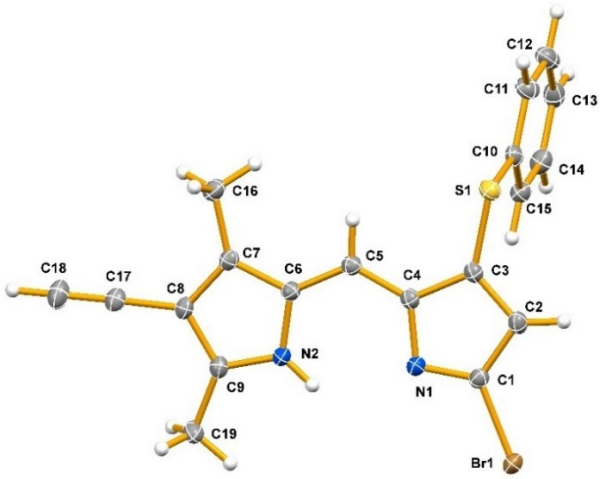


*Figure 47. Thermal ellipsoid diagram of alkynyl bromo-dipyrrin **49b**. Selected bond distances (Å): C(17)-C(18), 1.19; C(1)-Br(1), 1.88; C(3)-S(1), 1.75; C(10)-S(1), 1.78.*

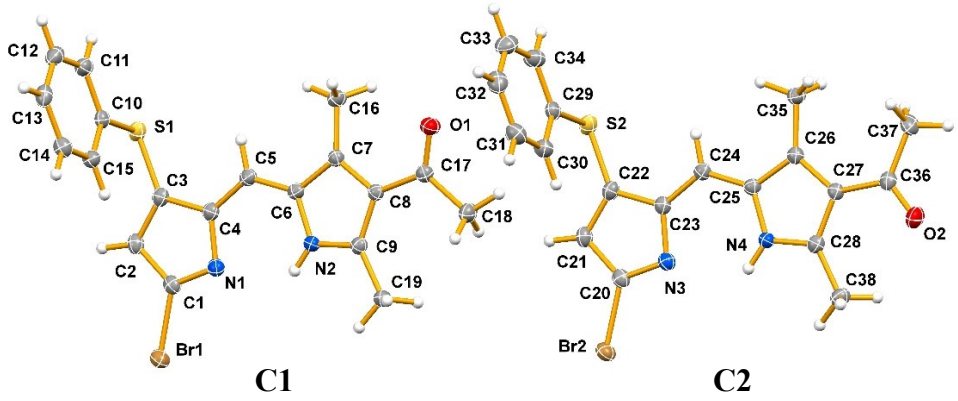


*Figure 48. Thermal ellipsoid diagram illustrating conformations **C1** and **C2** of bromo-dipyrrin **49a***

While the targeted compound was the bromo-dipyrrin **49a** bearing an acyl group in the 3-position, the presence of an alkyne in this position is attractive for further functionalization at a later synthetic step. Given this, future work in this project could focus on controlling the outcome of the bromination. Possible avenues would include varying the equivalents of $POBr_3$, the rate of addition and the concentration. Currently, $POBr_3$ is added as a solid, but perhaps adding it as a solution, dropwise, along with careful monitoring may be effective in controlling the formation of the undesired alkynyl unit.

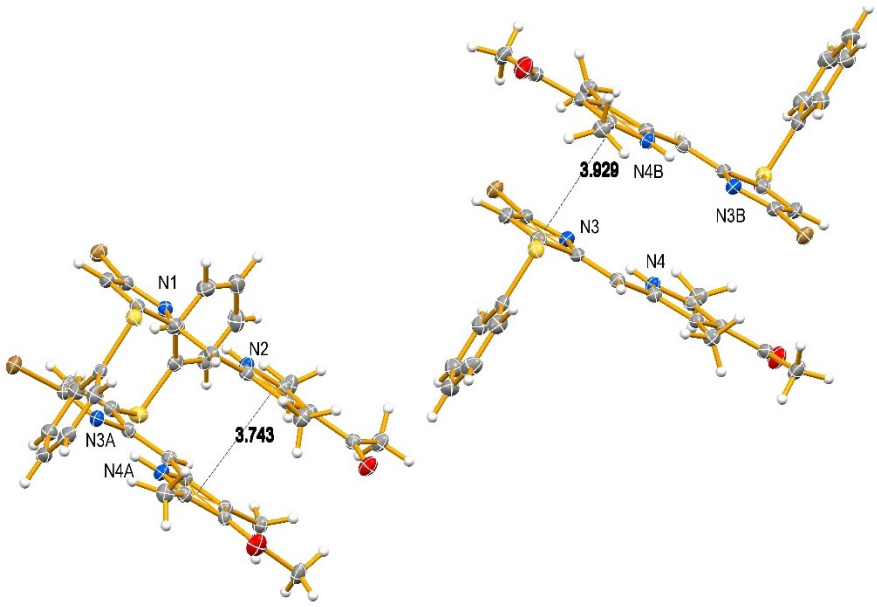
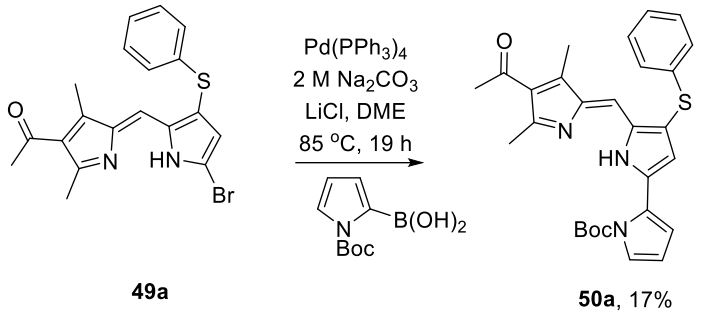


*Figure 49. Non-covalent interactions between **C1** and **C2 (a)** or **C2** and **C2 (b)***

With the successful preparation of bromo-dipyrrin **49a**, the final pyrrolic ring could now be installed as per Scheme 29. Fortunately, the N-Boc-2-pyrrole boronic acid is commercially available and was used without purification. Dipyrrin **49a** was subjected to Suzuki cross-coupling according to Scheme 29. Pleasingly, after just 5 hours of reaction time, the starting material was completely consumed according to TLC analysis. Following quenching of the reaction, workup and purification via column chromatography, the Boc-protected prodigiosene **50a** was isolated in an overall yield of 17% (17 mg). For O-prodigiosenes, the Boc-group is usually removed in-situ under the basic, heated conditions of the Suzuki coupling. However, this was not the case for the prodigiosene with a thiophenoxy substituent on the B-ring. Evidently, introducing sulfur to the prodigiosene scaffold imparts very different electronic effects, altering stability and reactivity.



Scheme 29. Suzuki cross-coupling of bromo-dipyrrin and N-Boc-2-pyrrole boronic acid

Efforts towards the removal of the Boc group from **50a** involved employing a variety of conditions (Table 3).[102-103] The Boc-group of the thio-substituted prodigiosene **50a** appeared to be quite stable under most conditions. Treatment with excess HCl in DCM, excess TFA in DCM, tosylic acid in THF/DCM, or iodine in DCM, were unsuccessful in removing the Boc group, as determined via TLC analysis. When HCl, TFA or TsOH were added to a solution of **50a** in DCM, an instant color change was observed, resulting in the appearance of a new pink spot with a lower R_f than Boc-protected **50a**. However, in all three cases (Table 3, Entries 1-2 and 5-6), the new spot corresponded to the respective salts of **50a** (confirmed via NMR). Upon washing each salt with water, an instant color change was observed and the resulting material corresponded to the "free-base" Boc-protected prodigiosene **50a**. In some instances, removal of the Boc group was successful (appearance of a new pink spot, with a R_f lower than that of **50a**), but also resulted in decomposition of the targeted prodigiosene (Table 3, Entries 3 and 8-9). Decomposition was visually evident when the orange/red colored solution turned dark purple followed by formation of a dark precipitate. Spectroscopic analysis of the resulting mixture did not reveal any signals that corresponded to **50a**. It was found that dissolving prodigiosene **50a** in a minimal amount of TFA successfully removed the Boc- group without destroying the prodigiosene core.

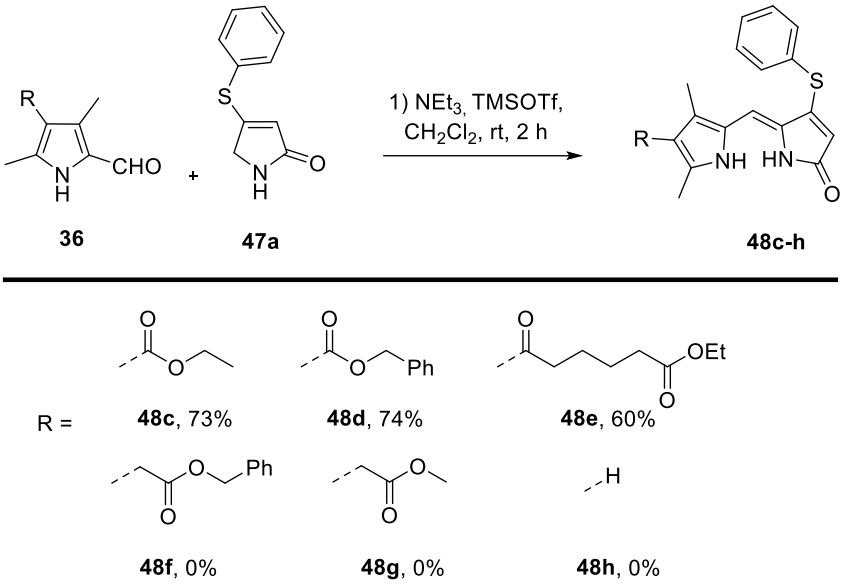
Table 3. Conditions used for Boc-removal attempts

Entry	Conditions	Time	Result
1	2M HCl in DCM	48 hrs	No reaction
2	7 eq (5 µL) of 12 M HCl in DCM	48 hrs	No reaction
3	2M HCl in ether	5-10 mins	Decomposition
4	1.5 eq TFA in DCM	5-10 mins	No reaction
5	8 eq TFA in DCM	5-10 mins	No reaction
6	2 eq TsOH in THF/DCM	5-10 mins	No reaction
7	1.1 eq iodine in DCM	24 hrs	No reaction
8	Reflux in DME	2-3 hrs	Decomposition
9	5 eq BF_3•OEt_2 w/ molecular sieves	5-10 mins	Decomposition
10	Neat TFA	5-10 minutes	Success

Prior to dissolving the Boc-protected prodigiosene **50a** in TFA, TLC analysis of **50a** in DCM showed a bright orange colored spot with a high R_f. After dissolving in TFA, the spot corresponding to the starting material was no longer present, but instead, a pink spot appeared slightly above the baseline. Given that O-prodigiosenes are usually isolated as their HCl salts (for added stability), the resulting prodigiosene-TFA salt was converted to its HCl salt. This was achieved via slow addition of sodium bicarbonate, extraction with DCM, washing with water followed by brine, a final wash with 1M HCl and then dried over sodium sulfate. TLC analysis showed the complete conversion of the TFA salt to the HCl salt with the appearance of a new spot with a higher R_f than the TFA salt, but lower than the Boc-protected prodigiosene.

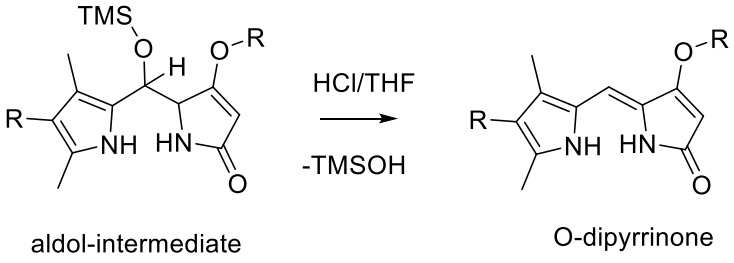
4.3.3 Synthesis of C-ring Modified S-prodigiosenes

With the successful synthesis of the "S-prodigiosene" **50a** bearing an acyl group in the 3-position, attention was directed to the synthesis of other S-prodigiosenes with various C-ring modifications. In the Thompson group, we have access to an extensive library of pyrroles, including Knorr-type pyrroles that bear a benzyl ester in the 2-position. These pyrroles can be readily transformed into 2-formyl pyrroles which are required to synthesize prodigiosenes in a [C+B]+A approach. First, the benzyl ester is cleaved via hydrogenolysis, forming a carboxylic acid. Decarboxylation of the acid is achieved through treatment with TFA generating an α-free pyrrole in-situ. Subsequent treatment with trimethyl orthoformate provides the requisite 2-formyl pyrrole to be condensed with a pyrrolinone. As such pyrroles **36c-h** were selected for the synthesis of S-dipyrrinones (Scheme 30).



Scheme 30. Synthesis of C-modified dipyrrinones

Condensation of 2-formyl pyrroles **36c-e** with pyrrolinone **47a** provided the respective dipyrrinones **48c-e** in good yields following filtration of the precipitate that formed upon quenching of the reaction. In the synthesis of O-dipyrrinones (-OR functionality on the B-ring), the aldol-like intermediate is treated with HCl in THF to eliminate the TMS group at the meso-position (Scheme 31). However, it was noticed that for S-dipyrrinones **48c-e**, this step was not necessary. After quenching with phosphate buffer, a yellow solid crashed out of solution. Isolation of this solid via filtration and washing with water yielded the desired thio-substituted dipyrrinones **48c-e**.

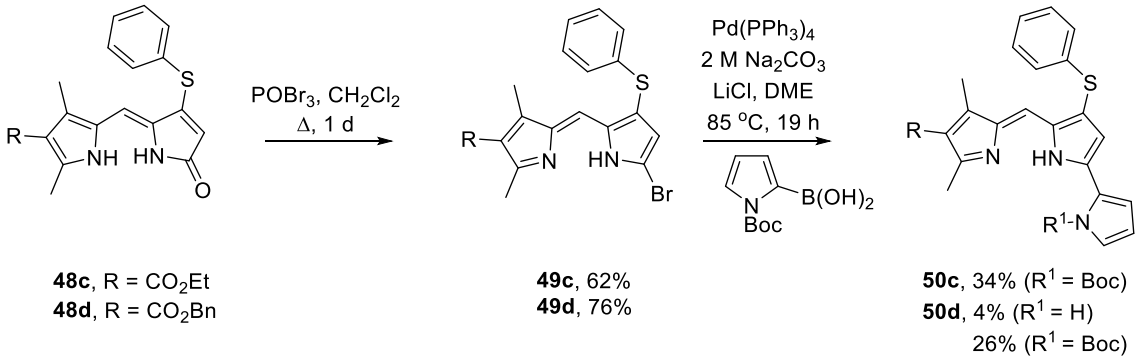


Scheme 31. Acid-promoted elimination of TMS group from aldol-intermediate of O-dipyrrinones

However, when pyrroles **36f-h** were subjected to the aldol reaction conditions, only unreacted starting material was collected, even when left to react overnight. Pyrroles **49f-h** do not have electron withdrawing groups in the 3-position and hence are less electrophilic.

With C-ring modified S-dipyrrinones in hand, transformation to the respective S-bromo-dipyrrins could proceed. As such, solutions of dipyrrinones **48c-e** in DCM were treated with $POBr_3$ and heated at reflux temperature for 1-2 days (Scheme 32). Although 1-2 days could be considered a long reaction time, bromination of S-dipyrrinones was considerably faster than compared to the bromination of O-dipyrrinones which can take up to 5 days. Following quenching with sodium bicarbonate, workup, and purification via column chromatography, bromo-dipyrrins **49c**-**d** were obtained in good yields.

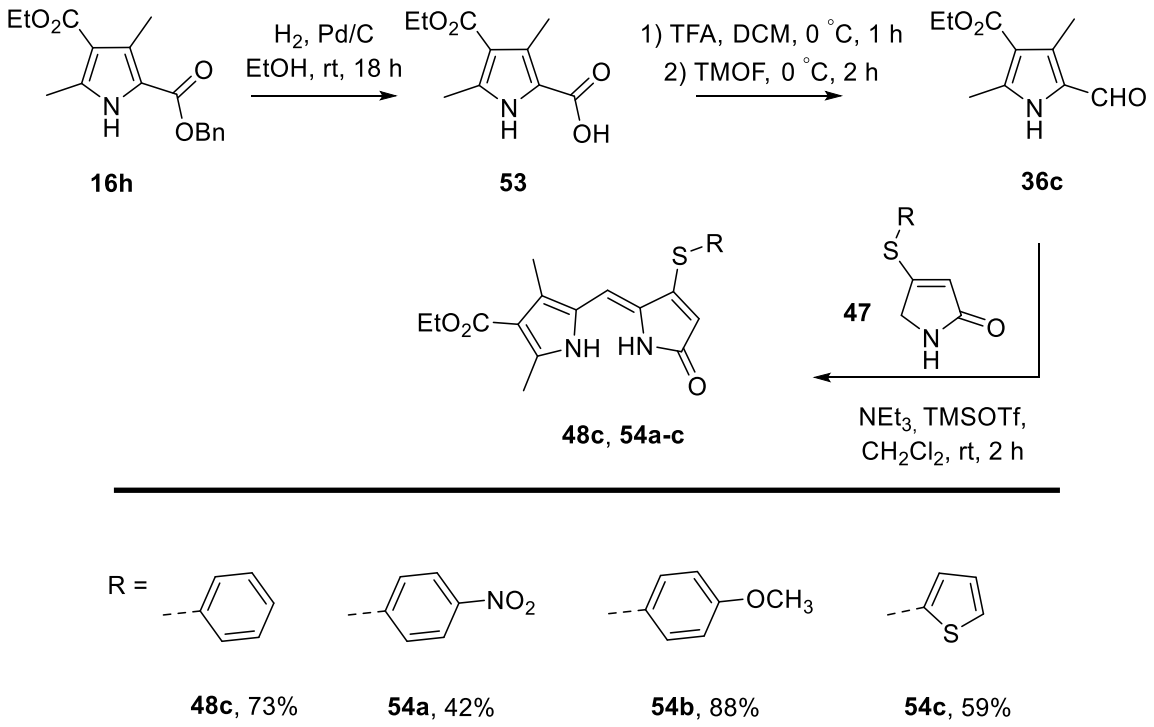
Following successful formation of bromo-dipyrrins bearing a -SPh moiety on the B-ring, the final A-ring of the prodigiosene core could now be installed. Proceeding with the conditions used to synthesize **50a**, the final A-ring was installed on **s**ubstrates **49c**-**d** via Suzuki-Miyaura cross-coupling (Scheme 32). In some cases, the target prodigiosene was isolated as either its -NH or -NBoc derivative. As discussed in Section 4.3.2, the stability of the Boc group and the nature of the prodigiosene core are intimately related. With the Boc group, the prodigiosene scaffold of **50a** remained intact under most conditions. However, once the Boc group was removed, the stability of the S-prodigiosene was significantly reduced. As such, compounds **50c-d** were isolated as their HCl salts. For prodigiosene **50d**, both its -NH and -NBoc derivative was isolated from the reaction mixture in low yields (-NH = 4%; -NBoc -26%). Possible reasoning for the poor outcome of this reaction could be attributed to the variable stability of each derivative (-NH or -NBoc) as demonstrated with **50a**. Attempts to remove the Boc-group of **50a** under heat (Table 3, Entry 8) resulted in decomposition. Hence, the low yield of this reaction could possibly be due to removal of the Boc-group under the heated, basic reaction conditions for Suzuki cross-coupling that also led to decomposition of the “free base” NH prodigiosene.



Scheme 32. Synthesis of C-ring modified S-prodigiosenes

4.3.4 Synthesis of S-aryl Prodigiosenes

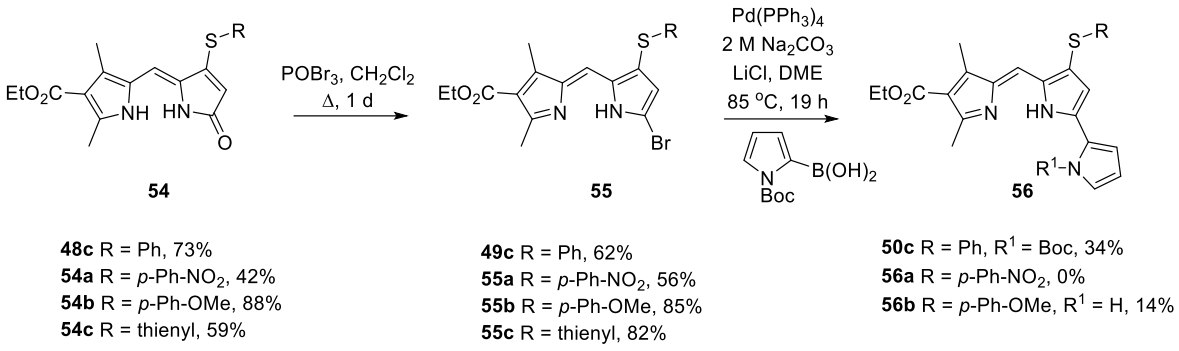
With a series of thio-substituted pyrrolinones (would-be B-rings) in hand and the successful synthesis of three prodigiosenes bearing an -SPh moiety, the synthesis of other -SR prodigiosenes was attempted. As discussed in Section 4.3.2, the 2-formyl pyrrole **36a** with an acyl moiety in the 3-position was problematic at the bromination step (undesired byproducts) and hence was not used as a model substrate to synthesize prodigiosenes with different -SR groups. Instead, the 2-formyl pyrrole bearing a 4-ethyl carboxylate was chosen as a model substrate to condense with various -SR pyrrolinones (Scheme 33). The Knorr-type pyrrole **16h** featuring a benzyl ester and an ethyl ester in the 2- and 3-position, respectively, is prepared in large quantities within the Thompson group, and hence readily available for use.[104-105] In order to prepare 2-formyl pyrrole **36c**, first the benzyl ester was cleaved to the carboxylic acid **53** via hydrogenolysis. Decarboxylation of **53**, facilitated by the treatment with TFA, generated the alpha-free pyrrole in-situ which was then formylated using TMOF to provide **36c**. Following this, the pyrrolinones **47a-d** discussed in Section 4.3.1 were each condensed with pyrrole **36c** to afford the respective dipyrrinones **48c** and **54a-c** as shown in Scheme 33.



Scheme 33. Synthesis of B-modified dipyrrinones

For the synthesis of S-dipyrrinones, the electron-donating pyrrolinone **47c** was condensed with pyrrole **36c** to give the dipyrrinone **54b** in a much higher yield than that observed for the case of the electron deficient **54a**. It appears that the pyrrolinone **47c** bearing an electron-donating group facilitates the nucleophilic attack upon the aldehyde, resulting in a higher yield than that of **48c** and **54a**. Conversely, pyrrolinone **47b** with an electron-withdrawing group decreases the nucleophilicity of the pyrrolinone. Work conducted previously in the Thompson group by post-doctoral fellow, Dr. Estelle Marchal, demonstrated this phenomenon with O-prodigiosenes. The condensation of pyrrolinones bearing strong electron withdrawing groups (*p*-$C_6H_4NO_2$ or *p*- C_6H_4CN) with a 2-formyl pyrrole were unsuccessful, while those with moderate electron-withdrawing groups (*p*-$C_6H_4CF_3$ or *p*-C_6H_4(CO)Me) were successful, albeit in a much lower yield relative to other dipyrrinones synthesized in the series.[19] The dipyrrinone **54c** bearing a thienyl moiety was also successfully prepared (Scheme 33). With S-dipyrrinones **48c** and **54a-c** in hand, the synthesis of S-bromo-dipyrrins could be attempted. As such, substrates **48c** and **54a-c** were treated with $POBr_3$ and heated at reflux temperature in DCM for 1-2 days. Following quenching and workup, and purification via column chromatography, bromo-dipyrrins **49c** and **55a-c** were isolated in good yields (56-85%). Onwards towards prodigiosene, utilizing

Suzuki cross-coupling, the final A-ring was successfully installed on substrates **49c** and **55c** (Scheme 34)**.**



Scheme 34. Synthesis of prodigiosenes with S-aryl groups on the B-ring

However, the electron deficient bromo-dipyrrin **55a** did not react during the final step towards prodigiosene. After 24 hours, TLC analysis indicated that much of the starting material was still present alongside a compound that gave a new pink spot of lower R_f. Following workup and purification via column chromatography, only starting material was collected. Given that this was the only substrate to not undergo cross-coupling and it is the last step of a lengthy synthesis, and thus only a small amount of this material was available, the synthesis of prodigiosene **56a** was abandoned. An attempt to synthesize the model substrate **56b** was attempted using microwave-promoted conditions for the Suzuki cross-coupling. As such, 50 mg (0.11 mmol) of bromo-dipyrrin **55b** was subjected to microwave heating at 80 °C for 30 minutes. However, this attempt was also unsuccessful, with only unreacted starting material observed via TLC analysis.

4.3.5 Synthesis of S-methyl Prodigiosene, the Natural Product Analogue

With a method to synthesize prodigiosenes featuring thioethers on the B-ring, attention was turned towards the synthesis of the -SMe analogue of the -OMe natural product (Figure 50).

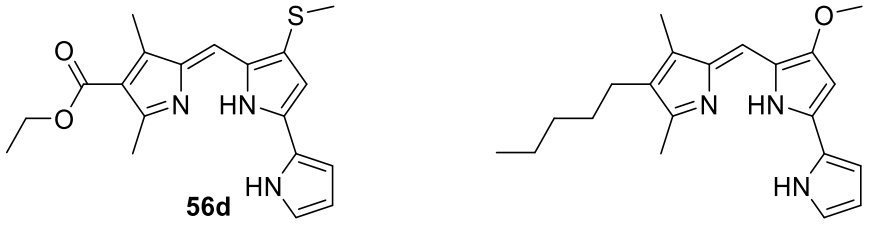
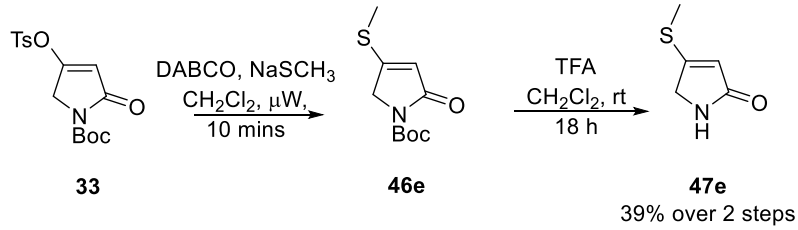


Figure 50. S- and O- prodigiosene

Reaction of the requisite N-Boc-3-tosyl pyrrolinone with thiols under microwave irradiation affords the desired thio-substituted pyrrolinones. In order to use this method for the synthesis of the -SMe derivative, it would require the use of methanethiol, a highly flammable gas at room temperature. Methanethiol is sold compressed and only available in a small lecture bottle. The cost to purchase 224 g of this highly flammable gas (e.g. from Millipore-Sigma) is over $1000, an order of magnitude more expensive than a standard hydrogen tank. The substantial cost coupled with the extra precautions required for safe handling made the use of methanethiol impractical for this synthesis. However, the sodium salt of methanethiol is commercially available and was purchased from Millipore-Sigma for use in this synthesis.

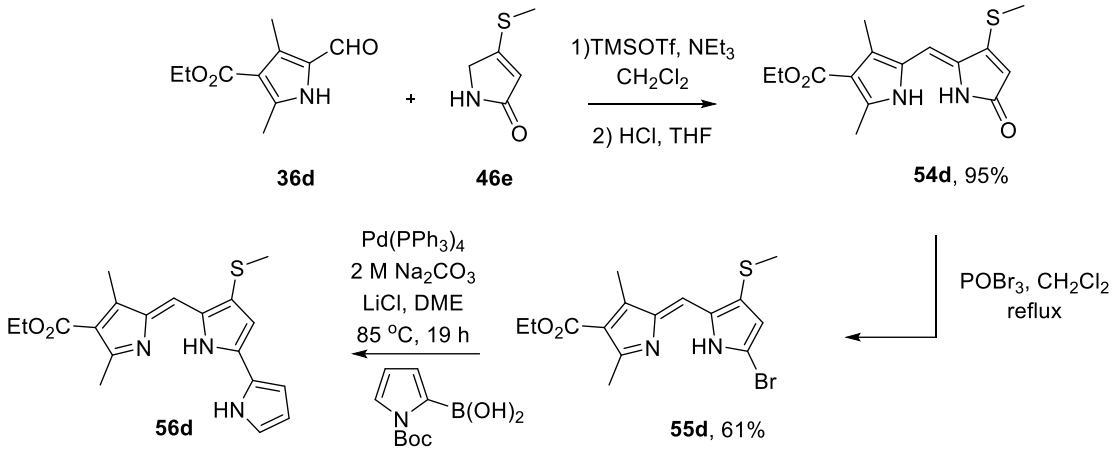
Previous work in the Thompson group by an undergraduate honours student, Natasha Milosevich, attempted to synthesize a S-ethyl pyrrolinone using ethanethiol, without success. Given that microwave irradiation proved successful in facilitating the substitution of pyrrolinone **33** with S-aryl groups, it was envisioned that non-aromatic thiols/thiolates could also be used. All thio-substituted pyrrolinones discussed thus far feature S-aryl substituents. Hence, to investigate the utility of sodium methanethiolate for the substitution of the tosyl group of pyrrolinone **33**, first the reaction was conducted on a 100 mg scale. Pyrrolinone **33** was reacted with 2.5 equiv. of $NaSCH_3$ in the presence of DABCO (1.1 equiv) for 10 mins in the microwave as per Scheme 35. Analysis of the

reaction mixture via TLC indicated the presence of a new spot with a lower R_f than that of the starting material. TLC analysis also indicated the presence of a faint spot corresponding to the starting material. Hence, the reaction was subjected to microwave irradiation for an additional 5 minutes. Analysis by TLC revealed complete consumption of the starting material. The reaction was then quenched with dilute HCl (0.5 M). Extraction with DCM followed by washing with dilute NaOH (0.5 M) and brine yielded a crude oil after drying with anhydrous sodium sulfate. The N-Boc-3-thiomethoxy pyrrolinone **46e** was then embedded on silica and eluted with EtOAc to remove baseline impurities followed by drying under vacuum for two hours. Following this, removal of the N-Boc group was achieved through treatment of pyrrolinone **46e** with TFA and stirring overnight. The reaction mixture was then quenched with saturated sodium bicarbonate, followed by workup and purification via precipitation with DCM/hexanes resulting in a yield of 39% (over two steps) for **47e**.



*Scheme 35. Synthesis of S-alkyl pyrrolinone **47e***

With the successful synthesis of 3-thiomethoxy pyrrolinone in hand, the condensation of this substrate with a 2-formyl pyrrole was attempted. Given the successful condensation of pyrrole **36d** and other -SR pyrrolinones, this pyrrole was chosen as a model substrate to react with pyrrolinone **46e**. Indeed, condensation was successful, forming the desired -Sme dipyrrinone in quantitative yield (Scheme 36). Bromination of the dipyrrinone **54d** occurred smoothly, after 2 days of reaction time, to yield **55d**. The crude reaction mixture was purified by filtration of the crude reaction mixture through a small plug of alumina to remove baseline impurities.



Scheme 36. Synthesis of S-alkyl prodigiosene

Although compound **55d** was successfully synthesized as indicated by the ^{1}HNMR spectrum, a final yield was not obtained due to the persistence of plasticizer in the obtained sample of this compound. In order to obtain an accurate yield for this reaction, more -SMe starting material would have to be prepared. However, since all substrates discussed so far have had aromatic groups appended to the sulfur atom of the B-ring, not alkyl, this impure bromo-dipyrrin was carried forward. Gratifyingly, the -SMe bromo-dipyrrin successfully coupled to the N-Boc-2-pyrroleboronic acid resulting in 24 mg of NH prodigiosene, and 19 mg of NBoc prodigiosene, both isolated as their HCl salts. Despite the success in synthesizing **56d**, a final yield could not be obtained due to the persistence of plasticizer, which had been carried forward from the bromo-dipyrrin **55d**. Prodigiosene **56d** (without Boc group) was characterized via ^{1}HNMR spectroscopy and mass spectrometry (see Chapter 5). A crystal suitable for x-ray analysis of prodigiosene HCl salt **56d** (without Boc group) was obtained via a liquid-liquid diffusion method using DCM/pentane.

In the thermal ellipsoid diagram of **56d** (Figure 51), all pyrrolic nitrogens of the salt are protonated and coordinate to the chloride ion via hydrogen bonding with bond distances ranging from 2.27-2.31 Å. As illustrated in Figure 52, intermolecular π-interactions occur between salt molecules of **56d** with a contact distance of 3.47 Å.

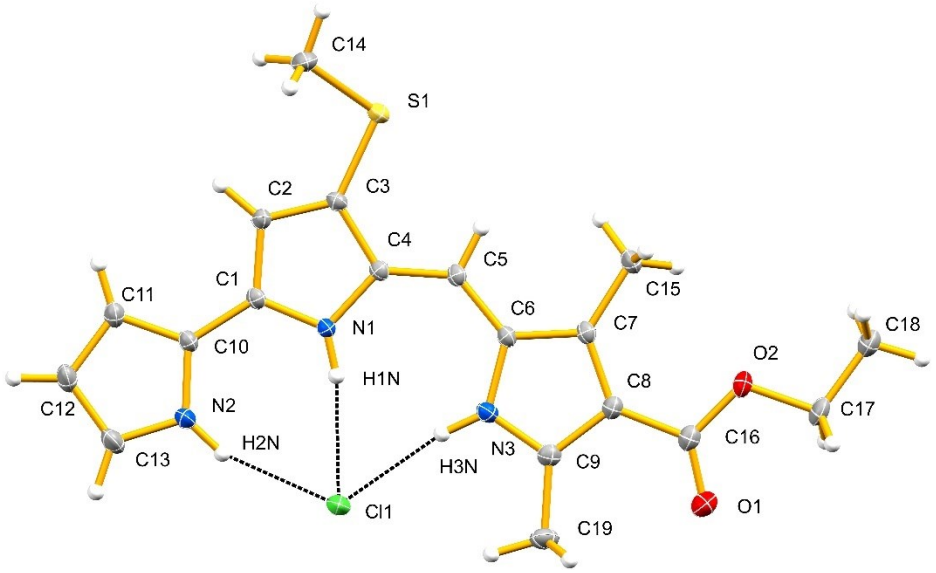


Figure 51. Thermal ellipsoid diagram of -SMe prodigiosene hydrochloride salt ***56d****. Selected bond distances (Å): C(3)-S(1), 1.74; C(14)-S(1), 1.80.*

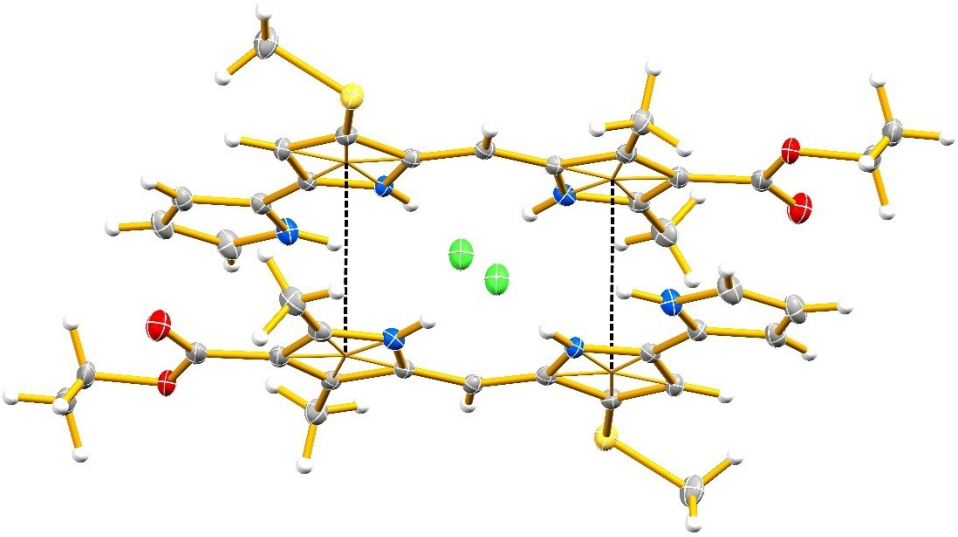


Figure 52. Non-covalent π-interactions observed for ***56d•HCl***

4.4 Conclusions

The work presented in this chapter describes the total synthesis of prodigiosenes bearing modified B-rings containing aryl and alkyl thioethers. This builds upon previous work in this area involving the synthesis of B-ring modified prodigiosenes with aryl ethers (not alkyl ethers). Prior to developing methodology to synthesize thio-substituted prodigiosenes, first the reaction conditions, and purification procedures were optimized to achieve maximal availability of starting materials for the synthesis. With starting materials in hand, the N-Boc tosylpyrrolinone underwent successful introduction of aryl- and methyl-thioether functionalities to produce five new thio-substituted pyrrolinones **47a-e**. Following N-Boc deprotection, pyrrolinones **47a-e** were successfully condensed with aldehyde **36c** to give dipyrrinones **48c** and **54a-d**. Additionally, the pyrrolinone **47a** with an -SPh substituent was reacted with other 2-formyl pyrroles to explore the feasibility of dipyrrinone formation with various C-ring substituents. All dipyrrinones **48a-e** and **54a-d** were successfully transformed into their respective bromo-dipyrrins **49a-e** and **55a-d** in moderate yields via reaction with $POBr_3$, except for substrate **48a** bearing an acyl group in the 3-position. This dipyrrinone was isolated in only 30% yield from a mixture that contained compound **50a** and the alkyne **50b**. Utilizing traditional Suzuki-Miyaura cross-coupling conditions, all bromo-dipyrrins (except **55c**) were coupled with 2-formyl pyrroles to give N-Boc or N-H prodigiosenes that were isolated as their HCl salts. In total, five new prodigiosenes bearing aryl and alkyl thioethers on the B-ring were synthesized (Figure 53).

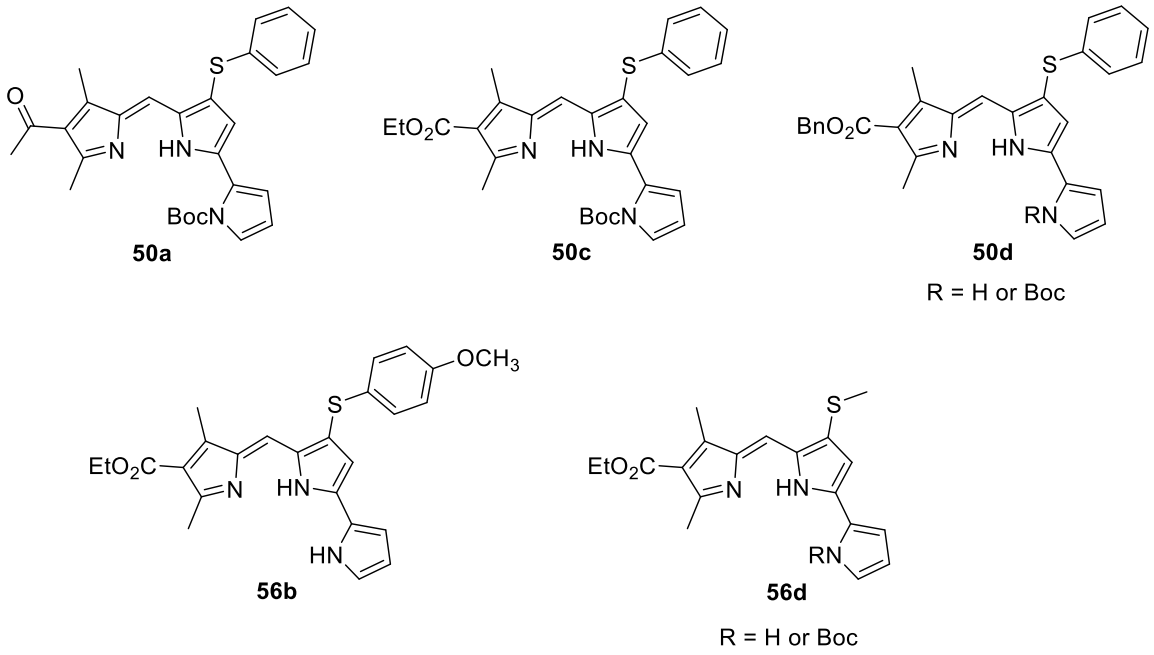


Figure 53. S-prodigiosenes synthesized in this work

Introducing sulfur to the prodigiosene scaffold imparts new electronic properties, as evident by the different reactivity observed in synthesizing S-prodigiosenes compared to O-prodigiosenes. As such, future work will involve evaluation of these compounds in terms of pKa determination and anion transport assays. Additionally, compounds will be submitted to the National Cancer Institute for testing against various human cancer cell lines.

CHAPTER 5 - Experimental Section

5.1 General Experimental

All chemicals, including anhydrous solvents and reagents, were obtained from commercial sources and used as received unless otherwise noted. DCM and hexanes for chromatography were obtained crude and distilled under air at 1 atm pressure before use. Column chromatography was performed using 150 mesh Brockman III basic or neutral aluminum oxide, or 230-400 mesh silica. NMR spectra were obtained using a 500 MHz or 300 MHz instruments using $CDCl_3$ or DMSO-D_6 as solvent. Chemical shifts are reported in part per million (ppm) using the solvent signals at 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C as an internal reference. ^{11}B and ^{19}F chemical shifts were referenced using BF_3•Et_2O (15% in $CDCl_3$) and CCl_3F defining the 0 ppm position as per the absolute referencing procedure standard for Bruker digital spectrometers. Coupling constants (*J*) are reported in Hertz. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in $ESI^{+/-}$ mode or APCI, as indicated. UV-Vis and emission analyses were performed using a Varian CARY 100 Bio UV-Visible spectrophotometer and PTI spectrofluorometer, respectively. X-ray crystallography measurements were made on a Bruker APEXII CCD equipped diffractometer (30 mA, 50 kV) using monochromated Mo Kα radiation (λ = 0.71073 Å) at 125 K.[106] Compounds **12a**-**12r** were prepared according to literature procedures.[16, 19, 46]

5.1.1 General Procedure for Absorbance and Emission Measurements

In all measurements, a 10 mm quartz cuvette (with screw cap) was used. For fluorescence experiments, a slit width of 3 nm was used for both excitation and emission. Each compound of interest was dissolved in DCM and absorbance and emission measurements obtained at room temperature. Calibration curves were generated for each with concentrations corresponding to absorbance values below 1.0. Emission measurements were obtained from concentrations corresponding to an absorbance value of ~ 0.3.

5.1.2 Fluorescence Quantum Yield

Relative fluorescence quantum yields were obtained by comparing the area under the emission spectrum of the compound of interest to that of the standard, rhodamine 6G

(ϕ=0.94 in ethanol) or rhodamine 101 (ϕ=0.96 in ethanol).[107] The excitation wavelength was 520 nm for rhodamine 6G and 546 nm for rhodamine 101. The excitation wavelength was 520 nm for **13d-13i**, **13l** and **15n** and compared to rhodamine 6G excited at 520 nm. The excitation wavelength for **13a**, **13b**, **13j**, **13k**, **14b**, **14f**, **15m** and **15o-15p** was 546 nm and compared to rhodamine 101 excited at 546 nm. Each compound was dissolved in DCM with a concentration corresponding to an absorbance of less 0.1. Relative quantum yields were determined using equation 1[108], where Φ_{st} is the reported quantum yield of the standard, I is the area of the integrated emission spectra, A is the absorbance at the excitation wavelength and η is the refractive index of the solvent used. The subscripts "X" and "st" denote the unknown and standard, respectively.

$$\boldsymbol{\Phi_X = \Phi_{st}} \left(\frac{\boldsymbol{I_X}}{\boldsymbol{I_{st}}}\right)\left(\frac{\boldsymbol{A_{st}}}{\boldsymbol{A_X}}\right)\left(\frac{\boldsymbol{\eta_X}^2}{\boldsymbol{\eta_{st}}^2}\right)$$

Equation 1. Relative quantum yield (Φ_X)

5.2 Chapter 2 Experimental

5.2.1 General Procedure 1 (GP1) for BF_2 Complexation of Prodigiosenes

The corresponding prodigiosene HCl salt **12** (1 equiv.) was dissolved in dry DCM under a nitrogen atmosphere. Triethylamine (6 equiv.) was added and the reaction mixture then stirred for 10 minutes. $BF_3 \cdot OEt_2$ (9 equiv.) was then added slowly, over a period of a few minutes. The reaction mixture was stirred until complete conversion was visualized using thin layer chromatography (TLC) analysis. Subsequent additions of base (6 equiv.) and $BF_3 \cdot OEt_2$ (9 equiv.) occurred after a period of 8 hours. Reaction time and total amount of base and $BF_3 \cdot OEt_2$ varied (5-96 h) depending upon the substrate. Upon completion, the reaction mixture was quenched via addition to 1 M HCl (15 mL) and then extracted with DCM (25 mL). The organic phase was washed with 1 M HCl (1x15 mL) and brine (2x15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting crude solid was purified via column chromatography on basic or neutral alumina eluting with 5-20% ethyl acetate in hexanes, unless otherwise stated.

5.2.2 Synthesis of *F*-BODIPYs 13-15

Boron, difluoro[isopropyl 2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)-methylene]-3,5-dimethyl-2*H*-pyrrole-4-carboxylate] (13a)

Following GP1, over a 72 hour period a solution of **12a** (23 mg, 0.08 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (133 μL, 1.08 mmol) and NEt_3 (100 μL, 0.72 mmol) to form *F*-BODIPY **13a** (22 mg, 92% yield). The product was purified using column chromatography on neutral alumina eluting with 5%, 10% and then 25% ethyl acetate in hexanes. M.p. 191-193 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 10.50 (br s, 1H), 7.18-7.16 (m, 1H), 7.15 (s, 1H), 6.97-6.94 (m, 1H), 6.38-6.36 (m, 1H), 6.12 (s, 1H), 5.21 (sep, J = 6.2 Hz, 1H), 3.97 (s, 3H), 2.80 (s, 3H), 2.41 (s, 3H), 1.35 (d, J = 6.3 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 165.0, 164.4, 153.0, 151.4, 136.7, 129.5, 129.4, 126.4, 123.7, 118.6, 118.3, 115.1, 111.8, 97.3, 67.1, 58.8, 22.5, 14.5, 12.0; ^{11}B-NMR ($CDCl_3$, 160 MHz): 1.38 (t, J = 36 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz): -138 (q, J = 34 Hz); UV/vis (DCM) λ_{max} (nm): 543, ε 68000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 555, Φ_F: 0.90; LRMS: 424.2 $(M+Na)^+$; HRMS: 424.1607 Found, 424.1614 Calculated for $C_{20}H_{22}BF_2N_3NaO_3$.

Boron, difluoro[5-[(3,5-dimethyl-4-pentyl-2H-pyrrol-2ylidene)methyl]-4-methoxy-1H,1'H-2,2'-bipyrrole] (13b)

Following GP1, over a 4 day period a solution of **12b** (18 mg, 0.05 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (278 μL, 2.25 mmol) and NEt_3 (167 μL, 1.20 mmol) to form *F*-BODIPY **13b** (10 mg, 53% yield). The product was purified using column chromatography on neutral alumina eluting with 1%, 3%, 5% and then 10% ethyl acetate in hexanes. M.p. 124-126 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.43 (br s, 1H), 7.08-7.07 (m, 1H), 7.05 (s, 1H), 6.84 (m, 1H), 6.33-6.31 (m, 1H), 6.10 (s, 1H), 3.95 (s, 3H), 2.49 (s, 3H), 2.37 (t, J = 7.7 Hz, 2H), 2.15 (s, 3H), 1.48-1.41 (m, 2H), 1.37-1.30 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 162.6, 150.2, 147.8, 134.3, 130.7, 129.5, 126.2, 124.2, 124.1, 115.6, 114.8, 110.8, 96.5, 58.4, 31.9, 30.2, 24.3, 22.7, 14.2, 12.6, 9.7; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.41 (t, J = 36 Hz); ^{19}F-NMR (235 MHz, $CDCl_3$) -139 (q, J = 33 Hz); UV/vis (DCM) λ_{max} (nm): 565, ε 49000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 578, Φ_F: 0.84; LRMS: 408.2 $(M+Na)^+$; HRMS: 408.2031 Found, 408.2029 Calculated for $C_{21}H_{26}BF_2N_3NaO$.

Boron, difluoro[[(2H-pyrrol-2-ylidene)methyl]-4-methoxy-1H, 1'H-2,2'-bipyrrole] (13c)

Following GP1, over a 72 hour period a solution of **12c** (20 mg, 0.07 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (233 µL, 1.89 mmol) and NEt_3 (176 µL, 1.26 mmol) to form *F*-BODIPY **13c** (9 mg, 45% yield). The product was purified using column chromatography on basic alumina eluting with 10-25% DCM in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.61 (br s, 1H), 7.51 (s, 1H), 7.20-7.18 (m, 1H), 7.13 (s, 1H), 7.01-6.99 (m, 1H), 6.77-6.76 (m, 1H), 6.42-6.37 (m, 2H), 6.12 (s, 1H), 3.98 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 165.3, 152.7, 134.1, 131.3, 130.5, 126.9, 123.5, 121.7, 119.2, 117.8, 114.9, 111.8, 97.1, 58.8; ^{11}B-NMR ($CDCl_3$, 160 MHz): 1.23 (t, J = 35 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz) -139 (q, J = 34 Hz); UV/vis (DCM) λ_{max} (nm) 530, ε 37000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{ex} (nm), 543, Φ_F: 0.95; LRMS: 310.1 $(M+Na)^+$; HRMS: 310.0925 Found, 310.0934 Calculated for $C_{14}H_{12}BF_2N_3NaO$. Despite extrinsic purification, analysis of the ^{13}C-NMR spectrum showed an extra carbon signal in the aromatic region. HSQC spectra indicated that the aromatic signals were indeed quaternary carbons, with no $^1J_{HC}$ coupling. HMBC correlations were inconclusive, as there was significant overlap of the signals at 131.3, 131.0, and 130.5 ppm. Hence, a semi-selective HMBC experiment was performed and it was determined that the signal at 131.0 ppm did not correlate to any protons in the aromatic region.

Boron, difluoro[ethyl 2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)-methylene]-3, 5-dimethyl-2H-pyrrole-4-carboxylate] (13d)[30]

Following **GP1**, over a 24 hour period a solution of **12d** (50 mg, 0.13 mmol) in DCM (6 mL) was reacted with $BF_3 \cdot OEt_2$ (610 µL, 4.94 mmol) and NEt_3 (544 µL, 3.90 mmol) to form *F*-BODIPY **13d** (42 mg, 81% yield). The reaction mixture was quenched via addition of 5% citric acid and extracted with 20 mL of diethyl ether. The product was purified using column chromatography on neutral alumina eluting with 75% DCM in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.50 (br s, 1H), 7.19-7.18 (m, 1H), 7.17 (s, 1H), 6.97-6.96 (m, 1H), 6.39-6.37 (m, 1H), 6.14 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.81 (s, 3H), 2.43 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{11}B-NMR (160 MHz, $CDCl_3$) 1.39 (t, J = 36 Hz); ^{1}HNMR and ^{11}B-NMR chemical shifts were in agreement with literature values.[30] UV/vis (DCM) λ_{max} (nm): 542, ε 64000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 555, Φ_F: 0.85.

Boron, difluoro[phenyl 2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)-methylene]-3,5-dimethyl-2H-pyrrole-4-carboxylate] (13e)

Following GP1, over a 24 hour period a solution of **12e** (50 mg, 0.12 mmol) in DCM (6 mL) was reacted with $BF_3 \cdot OEt_2$ (267 µL, 2.16 mmol) and NEt_3 (201 µL, 1.44 mmol) to form *F*-BODIPY **13e** (37 mg, 70% yield). The product was purified using column chromatography on neutral alumina eluting with 60% DCM in hexanes. M.p. 248-250 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.52 (br s, 1H), 7.41 (t, J = 7.93 Hz, 2H), 7.25-7.23 (m, 1H), 7.21-7.20 (m, 3H), 7.19 (s, 1H), 7.01-7.00 (m, 1H), 6.40-6.39 (m, 1H), 6.17 (s, 1H), 4.01 (s, 3H), 2.88 (s, 3H), 2.52 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 164.6, 163.6, 153.4, 152.0, 150.9, 136.4, 129.9, 129.6, 126.8, 125.6, 123.5, 122.2, 119.1, 114.8, 111.9, 97.4, 58.8, 14.6, 12.0; ^{11}B-NMR (160 Hz) 1.41 (t, J = 36 Hz); ^{19}F-NMR (235 Hz) -138 (q, 34 Hz); UV/vis (DCM) λ_{max} (nm): 539, ε 63000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 555, Φ_F: 0.90; LRMS: 458.1 $(M+Na)^+$; HRMS: 458.1459 Found, 458.1458 Calculated for $C_{23}H_{20}BF_2N_3NaO_3$.

Boron, difluoro[benzyl 2-[(4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)-methylene]-3,5-dimethyl-2*H*-pyrrole-4-carboxylate] (13f)[64]

Following GP1, over a 24 hour period a solution of **12f** (22 mg, 0.05 mmol) in DCM (8 mL) was reacted with $BF_3 \cdot OEt_2$ (56 µL, 0.45 mmol) and NEt_3 (42 µL, 0.30 mmol) to form *F*-BODIPY **13f** (6 mg, 26 % yield). The product was purified using column chromatography on neutral alumina eluting with 25% DCM in hexanes. ^{1}H-NMR (500 MHz, $CDCl_3$) 10.49 (br s, 1H), 7.45-7.34 (m, 1H), 7.20-7.17 (m, 1H), 7.16 (s, 1H), 6.99-6.96 (m, 1H), 6.40-6.36 (m, 1H), 6.14 (s, 1H), 5.32 (s, 2H), 3.99 (s, 3H), 2,81 (s, 3H), 2.42 (s, 3H); ^{11}B-NMR (160 MHz, $CDCl_3$) 1.35 (t, J = 36 Hz). ^{1}H and ^{11}B-NMR chemical shifts were in agreement with literature values.[64] UV/vis (DCM) λ_{max} (nm): 542, ε 156000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 553, Φ_F: 1.00.

Boron, difluoro[1-[2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3,5-dimethyl-2*H*-pyrrol-4-yl]ethanone] (13g)

Following GP1, over a 48 hour period a solution of **12g** (13 mg, 0.04 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (99 µL, 0.80 mmol) and NEt_3 (84 µL, 0.60 mmol) to form *F*-BODIPY **13g** (5 mg, 38% yield). The product was purified using column chromatography on basic alumina eluting with 25% ethyl acetate in hexanes. ^{1}H-NMR (500 MHz, $CDCl_3$) 10.50 (br s, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 6.99 (s, 1H), 6.39 (s, 1H),

6.15 (s, 1H), 4.00 (s, 3H), 2.80 (s, 3H), 2.48 (s, 3H), 2.44 (s 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 195.4, 164.4, 152.1, 151.8, 134.3, 129.5, 127.2, 126.7, 123.5, 118.9, 115.01, 114.84, 111.8, 97.4, 58.8, 31.7, 15.2, 12.5; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.41 (t, J = 36 Hz); ^{19}F-NMR (235 MHz, $CDCl_3$) -138 (q, J = 29 Hz); UV/vis (DCM) λ_{max} (nm): 544, ε 11000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 557, Φ_F: 0.78; LRMS: 380.1 $(M+Na)^+$; HRMS: 380.1363 Found, 380.1352 Calculated for $C_{18}H_{18}BF_2N_3NaO_2$.

Boron, difluoro[N-tert-butyl-6-[2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3,5-dimethyl-2H-pyrrol-4-yl]-6-oxohexanamide] (2h)

Following GP1, over a 60 hour period a solution of **12h** (21 mg, 0.04 mmol) in DCM (3 mL) was reacted with $BF_3{\cdot}OEt_2$ (74 µL, 0.60 mmol) and NEt_3 (50 µL, 0.36 mmol) to form *F*-BODIPY **13h** (16 mg, 73% yield). The product was purified using column chromatography on neutral alumina eluting with 40% ethyl acetate in hexanes. M.p. 214-216 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.49 (s, 1H), 7.19-718 (m, 1H), 7.16 (s, 1H), 7.00-6.97 (m, 1H), 6.39-6.37 (m, 1H), 6.14 (s, 1H), 5.44 (br s, 1H), 3.99 (s, 3H), 2.79-2.76 (m, 5H, overlapping CH_3 and CH_2), 2.42 (s, 3H), 2.15 (t, J = 7.0 Hz, 2H), 1.73-1.68 (m, 4H), 1.35 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 197.9, 172.2, 164.4, 151.9, 151.7, 133.8, 129.7, 129.5, 127.3, 126.6, 123.5, 118.9, 114.8, 111.8, 97.3, 58.8, 51.3, 42.9, 37.8, 29.0, 25.6, 23.8, 15.2, 12.6; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.41 (t, J = 32 Hz); ^{19}F-NMR (235 MHz, $CDCl_3$) -138 (q, J = 34 Hz); UV/vis (DCM) λ_{max} (nm): 545, ε 71000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 557, Φ_F: 0.85; LRMS: 521.3 $(M+Na)^+$; HRMS: 521.2517 Found, 521.2506 Calculated for $C_{26}H_{33}BF_2N_4NaO_3$.

Boron, difluoro[ethyl 10-[2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3,5-dimethyl-2H-pyrrol-4-yl]-10-oxodecanoate] (13i)

Following GP1, over a 72 hour period a solution of **12i** (24 mg, 0.05 mmol) in DCM (4 mL) was reacted with $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol) and NEt_3 (77 µL, 0.55 mmol) to form *F*-BODIPY **13i** (20 mg, 74% yield). The product was purified using column chromatography on basic alumina flushing first with 100% hexanes and then eluting compound with DCM. M.p. 138-140 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 10.50 (br s, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 6.98 (s, 1H), 6.38 (s, 1H), 6.14 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 2.78 (s, 3H), 2.74 (t, J = 7.4 Hz, 2H), 2.42 (s, 3H), 2.28 (t, J = 7.6 Hz, 2H), 1.72-1.54 (m, 4H), 1.33 (s, 8H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 198.5, 174.1, 164.4, 151.9, 151.6, 134.0, 129.7, 129.6, 127.6, 126.6, 123.6, 118.8, 114.9,

111.8, 97.3, 60.3, 58.8, 43.3, 34.6, 29.6, 29.4, 29.3, 25.2, 24.5, 15.2, 14.5, 12.5; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.41 (t, J = 30 Hz); ^{19}F-NMR (235 MHz, $CDCl_3$) -138, (q, J = 36 Hz); UV/vis (DCM) λ_{max} (nm): 546, ε 85000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 559, Φ_F: 0.90; LRMS: 550.3 $(M+Na)^+$; HRMS: 550.2661 Found, 550.2659 Calculated for $C_{28}H_{36}BF_2N_3NaO_4$.

Boron, difluoro[N,N-diethyl-2-[2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3,5-dimethyl-2H-pyrrol-4-yl]acetamide] (13j)

Following GP1, over a 72 hour period a solution of **12j** (17 mg, 0.04 mmol) in DCM (4 mL) was reacted with $BF_3{\cdot}OEt_2$ (89 µL, 0.72 mmol) and NEt_3 (67 µL, 0.48 mmol) to form *F*-BODIPY **13j** (11 mg, 61% yield). The product was purified using column chromatography on basic alumina eluting with 25% and then 50% ethyl acetate in hexanes. ^{1}H NMR ($CDCl_3$, 500 MHz): 10.44 (br s, 1H), 7.09 (s, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 6.33 (s, 1H), 6.10 (s, 1H), 3.95 (s, 3H), 3.44 (s, 2H), 3.34-3.44 (m, 4H), 2.49 (s, 3H), 2.17 (s, 3H), 1.12-1.17 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 169.3, 162.9, 149.1, 148.4, 134.4, 130.1, 126.7, 124.4, 123.8, 121.8, 116.1, 114.7, 110.8, 96.4, 58.2, 42.1, 40.4, 30.1, 14.1, 13.0, 12.5, 9.7; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.40 (t, J = 36 Hz); ^{19}F-NMR (235 MHz, $CDCl_3$) -139 (q, J = 34 Hz) UV/vis (DCM) λ_{max} (nm): 561,ε 45000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 546 (nm); λ_{max} (nm), 574, Φ_F: 0.81; LRMS: 451.2 $(M+Na)^+$; HRMS: 451.2081 Found, 451.2087 Calculated for $C_{22}H_{27}BF_2N_4NaO_2$.

Boron, difluoro[benzyl 2-[2-[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3,5-dimethyl-2*H*-pyrrol-4-yl]acetate] (13k)

Following GP1, over a 48 hour period a solution of **12k** (12 mg, 0.03 mmol) in DCM (4 mL) was reacted with $BF_3{\cdot}OEt_2$ (100 µL, 0.81 mmol) and NEt_3 (75 µL, 0.54 mmol) to form *F*-BODIPY **13k** (9 mg, 75% yield). The product was purified using column chromatography on basic alumina eluting with DCM. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.46 (br s, 1H), 7.35-7.30 (m, 5H), 7.11-7.10 (m, 1H), 7.08 (s, 1H), 6.89-6.88 (m, 1H), 6.35-6.33 (m, 1H), 6.11 (s, 1H), 5.13 (s, 2H), 3.96 (s, 3H), 3.46 (s, 2H), 2.49 (s,*3*H), 2.17 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 171.0, 163.3, 149.1, 136.0, 135.3, 134.5, 131.0, 128.7, 128.2, 127.2, 124.9, 124.0, 120.5, 116.7, 115.0, 111.1, 106.1, 96.7, 66.8, 58.5, 30.6, 12.6, 9.8; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.39 (t, J = 36 Hz); ^{19}F (235 MHz, $CDCl_3$) -139 (q, J = 35 Hz); UV/vis (DCM) λ_{max} (nm): 558, ε 127000 mol L^{-1} cm^{-1}. Fluorescence (DCM)

λ_{exci}, 546 (nm); λ_{max} (nm), 571, Φ_F: 0.79; LRMS: 486.2 $(M+Na)^+$; HRMS: 486.1778 Found, 486.1771 Calculated for $C_{25}H_{24}BF_2N_3NaO_3$.

Boron, difluoro[benzyl 2[(4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene]-3-(3-methoxy-3-oxopropyl)-5-methyl-2H-pyrrole-4-carboxylate] (13l)

Following GP1, over a 48 hour period a solution of **12l** (19 mg, 0.04 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (89 µL, 0.72 mmol) and NEt_3 (67 µL, 0.48 mmol) to form *F*-BODIPY **13l** (18 mg, 95% yield). The product was purified using column chromatography on basic alumina eluting with 2%, 4%, 8%, 10% and then 25% ethyl acetate in hexanes. ^{1}H-NMR ($CDCl_3$, 300 MHz): 10.50 (s, 1H), 7.44-7.32 (m, 5H), 7.23-7.17(m, 2H), 6.99 (s, 1H), 6.38 (s, 1H), 6.12 (s, 1H), 5.30 (s, 2H), 3.98 (s, 3H), 3.61 (s, 3H), 3.12 (t, J = 7.5 Hz, 2H), 2.80 (s, 3H), 2.56 (t, J = 7.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 173.4, 164.7, 152.7, 152.3, 137.6, 136.5, 130.3, 129.0, 128.7, 128.5, 128.2, 127.0, 123.4, 119.3, 114.9, 111.9, 97.4, 65.9, 58.8, 51.7, 35.4, 21.3, 14.6; ^{11}B-NMR (160 MHz, $CDCl_3$) 1.34 (t, J = 36 Hz); ^{19}F (235 MHz, $CDCl_3$) -138 (q, J = 35 Hz); UV/vis (DCM) λ_{max} (nm): 540, ε 55000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 559, Φ_F: 0.70; LRMS: 544.2 $(M+Na)^+$; HRMS: 544.1825 Found, 544.1826 Calculated for $C_{27}H_{26}BF_2N_3NaO_5$.

Boron, difluoro[4-(4-chlorophenoxy)-5-[(3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl]-1H,1'H-2,2'-bipyrrole] (15m)

Following GP1, over a 72 hour period a solution of **12m** (20 mg, 0.04 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (148 µL, 1.2 mmol) and NEt_3 (109 µL, 0.78 mmol) to form *F*-BODIPY **15m** (18 mg, 90% yield). The product was purified using column chromatography on basic alumina eluting with 20% DCM in hexanes. M.p. °C 135-137 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.35 (br s, 1H), 7.40-7.38 (m, 2H), 7.19-7.16 (m, 3H), 7.07-7.05 (m, 1H), 6.70-6.68 (m, 1H), 6.29-6.27 (m, 1H), 5.98 (s, 1H), 2.53 (s, 3H), 2.38 (t, J = 7.7 Hz, 2H), 2.18 (s, 3H), 1.46-1.41 (m, 2H), 1.35-1.30 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 158.3, 154.7, 153.3, 146.0, 136.2, 131.7, 130.7, 130.2, 130.1, 125.9, 124.1, 124.0, 120.9, 115.5, 115.4, 110.8, 100.4, 31.8, 30.1, 24.2, 22.7, 14.3, 12.9, 9.8; ^{11}B-NMR ($CDCl_3$, 160 MHz): 1.37 (t, J = 31 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz): -140 (q, J = 33Hz); UV-vis (DCM) λ_{max} (nm): 573, ε 75000 mol L^{-1} cm^{-1}; Fluorescence (DCM) λ_{exci}, 546 (nm); λ_{max} (nm), 597, Φ_F: 0.89; LRMS: 504.2 $(M+Na)^+$; HRMS: 504.1793 Found, 504.1796 Calculated for $C_{26}H_{27}BClF_2N_3NaO$.

Boron, difluoro[4-(benzyloxy)-5-[(3,5-dimethyl-4-pentyl-2H-pyrrol-2-ylidene)methyl]-1H,1'H-2,2'-bipyrrole] (15n)

Following GP1, over a 96 hour period a solution of **12n** (16 mg, 0.04 mmol) in DCM (8 mL) was reacted with $BF_3{\cdot}OEt_2$ (160 µL, 1.3 mmol) and NEt_3 (120 µL, 0.86 mmol) to form *F*-BODIPY **15n** (9 mg, 50% yield). The product was purified using column chromatography on basic alumina eluting with 2%, 4%, 6% and then 8% ethyl acetate in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.42 (br s , 1H), 7.46-7.38 (m, 5H), 7.10 (s, 1H), 7.07 (s, 1H), (6.81 (s, 1H), 6.33-6.31 (m, 1H), 6.14 (s, 1H), 5.16 (s, 2H), 2.49 (s, 3H), 2.36 (t, 2H, J = 6.90 Hz), 2.14 (s, 3H), 1.48-1.40 (m, 2H), 1.37-1.29 (m, 4H), 0.90 (t, 3H, J = 7.64 Hz); ^{13}C-NMR ($CDCl_3$, 126 MHz): 161.4, 156.5, 147.6, 135.7, 134.6, 130.8, 129.6, 128.9, 128.8, 128.0, 126.4, 124.2, 124.1, 115.6, 115.0, 110.8, 97.4, 73.2, 31.9, 30.2, 24.3, 22.7, 14.2, 12.7, 9.7; ^{11}B-NMR ($CDCl_3$, 160MHz): 1.41 (t, J = 36 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz): -139 (q, J = 34 Hz); UV/vis (DCM) λ_{max} (nm): 566, ε 55000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 520 (nm); λ_{max} (nm), 572, Φ_F: 0.98. LRMS: 484.2 $(M+Na)^+$; HRMS: 484.2339 Found, 484.2342 Calculated for C_{27} $H_{30}BF_2N_3NaO$.

Boron, difluoro[5-[(3,5-dimethyl-4-pentyl-2H-pyrrol-2-ylidene)methyl]-4-[4-(trifluoromethyl)phenoxy]-1H,1'H-2,2'-bipyrrole] (15o)

Following GP1, over a 48 hour period a solution of **12o** (12 mg, 0.02 mmol) in DCM (8 mL) was reacted with $BF_3{\cdot}OEt_2$ (54 µL, 0.44 mmol) and NEt_3 (42 µL, 0.30 mmol) to form *F*-BODIPY **15o** (12 mg, 92% yield). The product was purified using column chromatography on basic alumina eluting with 5% ethyl acetate in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.34 (br s , 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.32 (J = 8.6 Hz, 2H), 7.13 (s, 1H), 7.07-7.05 (m, 1H), 6.72-6.70 (m, 1H), 6.30-6.28 (m, 1H), 6.11 (s, 1H), 2.54 (s, 3H), 2.39 (t, J = 7.7 Hz, 2H), 2.18 (s, 1H), 1.49-1.41 (m, 2H), 1.38-1.31 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 126 MHz): 159.2, 154.5, 145.8, 136.8, 131.2, 130.0 (q, $^1J_{Cl\text{-}F}$ = 331 Hz), 124.2, 124.0, 119.0, 115.7, 115.4, 110.9, 110.1, 101.6, 68.3, 31.9, 30.0, 24.3, 22.7, 14.2, 13.0, 9.8; ^{11}B-NMR ($CDCl_3$, 160 MHz): 1.27 (t, J = 35 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz): -62 (s, CF_3), -140 (q, J = 35 Hz); UV/vis (DCM) λ_{max} (nm): 575, ε 26000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 546 (nm); λ_{max} (nm), 600, Φ_F: 0.74. LRMS: 516.2 $(M+Na)^+$; HRMS: 516.2262 Found, 516.2240 Calculated for $C_{27}H_{28}BF_5N_3NaO$. Missing three carbon signals.

Boron, difluoro[4-[5-((3,5-dimethyl-4-pentyl-2H-pyrrol-2-ylidene)methyl)-1H,1'H-2,2'-bipyrrol4-yloxy]-N,N-dimethylaniline] (15p)

Following GP1, over a 48 hour period a solution of **12p** (16 mg, 0.03 mmol) in DCM (8 mL) was reacted with $BF_3 \cdot OEt_2$ (67 μL, 0.54 mmol) and NEt_3 (50 μL, 0.36 mmol) to form *F*-BODIPY **15p** (12 mg, 75% yield). The product was purified using column chromatography on basic alumina eluting with 2%, 4%, 6%, and then 8% ethyl acetate in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.38 (br s, 1H), 7.21 (s, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.04 (t, *J* = 1.8 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.67 (t, *J* = 1.8 Hz, 1H), 6.26-6.25 (m, 1H), 5.87 (s, 1H), 2.98 (s, 6H), 2.51 (s, 3H), 2.38 (t, *J* = 7.7 Hz, 2H), 2.18 (s, 3H), 1.49-1.43 (m, 2H), 1.36-1.31 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{11}B-NMR ($CDCl_3$, 160MHz): 1.41 (t, *J* = 35 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz): -139 (q, *J* = 35 Hz); UV/vis (DCM) λ_{max} (nm): 569, ε 55000 mol L^{-1} cm^{-1}. LRMS: 491.3 $(M+H)^+$; HRMS: 491.2803 Found, 491.2788 Calculated for $C_{28}H_{34}BF_2N_4O$.

Boron, difluoro[2-[5-((3,5-dimethyl-4-pentyl-2H-pyrrol-2-ylidene)methyl)-4-methoxy-1H-pyrrol-2-yl]-1H-indole] (14b)

Following GP1, over a 5-day period a solution of **12q** (28 mg, 0.07 mmol) in DCM (15 mL) was reacted with $BF_3 \cdot OEt_2$ (273 μL, 2.21 mmol) and NEt_3 (205 μL, 1.47 mmol) to form *F*-BODIPY **14b** (22 mg, 76% yield). The product was purified using column chromatography on basic alumina eluting with 0%, 1%, 2% and then 4% ethyl acetate in hexanes. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.19 (br s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.28-7.24 (m, 1H), 7.13-7.09 (m, 3H), 6.30 (s, 1H), 3.95 (s, 3H), 2.56 (s, 3H), 2.39 (t, J = 7.7 Hz, 2H), 2.17 (s, 3H), 1.49-43 (m, 2H), 1.38-1.32 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 126 MHz): 161.8, 153.5, 146.4, 138.2, 136.3, 131.8, 130.7, 129.5, 128.1, 126.0, 124.4, 121.2, 120.6, 116.0, 112.2, 107.9, 98.0, 58.4, 31.9, 30.0, 24.3, 22.7, 14.2, 13.0, 9.7; ^{11}B-NMR ($CDCl_3$, 160 MHz): 1.39 (t, *J* = 35 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz) -138 (q, *J* = 35 Hz); UV/vis (DCM) λ_{max} (nm): 579, ε 54000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 546 (nm); λ_{max} (nm), 591, Φ_F: 1.0; LRMS: 458.2 $(M+Na)^+$; HRMS: 458.2183 Found, 458.2186 Calculated for $C_{25}H_{28}BF_2N_3NaO$.

Boron, difluoro[benzyl 2-[(5-(1H-indol-2-yl)-3-methoxy-1H-pyrrol-2-yl)methylene]-3,5-dimethyl-4-pentyl-2H-pyrrol-4-carboxylate] (14f)

Following GP1, over a 5 hour period a solution of **12r** (14 mg, 0.03 mmol) in DCM (4 mL) was reacted with $BF_3 \cdot OEt_2$ (48 μL, 0.39 mmol) and NEt_3 (38 μL, 0.27 mmol) to form

F-BODIPY **14f** (10 mg, 71% yield). The product was purified using column chromatography on basic alumina eluting with DCM. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.24 (br s, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 7 Hz, 2H), 7.43 (t, *J* = 7 Hz, 2H), 7.39-7.304 (m, 2H), 7.31 (s, 1H), 7.25 (s, 1H), 7.17 (t, *J* = 8 Hz, 1H), 6.38 (s, 1H), 5.37 (s, 2H), 4.05 (s, 3H), 2.90 (s, 3H), 2.49 (s, 3H); ^{13}C-NMR ($CDCl_3$, 126 MHz): 164.8, 164.0, 155.3, 151.1, 139.1, 139.0, 136.6, 130.3, 130.2, 129.3, 128.7, 128.4, 18.2, 127.9, 125.9, 121.7, 121.2, 117.0, 112.5, 111.1, 98.6, 65.9, 58.8, 14.8, 12.1; ^{11}B-NMR ($CDCl_3$, 160MHz): 1.39 (t, *J* = 36 Hz); ^{19}F-NMR ($CDCl_3$, 235 MHz): -137 (q, *J* = 31 Hz); UV/vis (DCM) λ_{max} (nm): 562, ε 74000 mol L^{-1} cm^{-1}. Fluorescence (DCM) λ_{exci}, 546 (nm); λ_{max} (nm), 574, Φ_F: 0.95; LRMS: 522.2 $(M+Na)^+$; HRMS: 522.1762 Found, 522.1771 Calculated for $C_{28}H_{24}BF_2N_3NaO_3$.

5.3 Chapter 3 Experimental

5.3.1 General Procedure 2 (GP2) for SEM-protection of Pyrrole 16

Adapting a literature procedure,[88] pyrrole **16** (1.0 equiv) was added in one portion to a stirred solution of NaH (60% dispersion in mineral oil, 1.1 equiv) in DMF (0.4 M) at room temperature under a nitrogen atmosphere. When the evolution of H_2 ceased, 2-(trimethylsilyl)ethoxymethyl chloride (1.1 equiv) was added dropwise at 0 ºC. The reaction mixture was allowed to warm to room temperature, then stirred until complete consumption of the starting material (according to TLC analysis) and poured into a saturated solution of $NaHCO_3$ at 0 ºC. The crude mixture was extracted with EtOAc (x3) and the combined organic fractions washed with water (x2) and brine, dried over Na_2SO_4 and concentrated under reduced pressure.

5.3.2 General Procedure 3 (GP3) for the Decarboxylative Pd-coupling of Pyrrole 17

Adapting literature procedures,[77, 87] a solution of pyrrole **17** (1 equiv), 10 mol% Pd/C (10% of the mass of **17**) and NEt_3 (few drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times with nitrogen before the introduction of a H_2 atmosphere. After stirring the reaction micture for 19 h, N_2 atmosphere was introduced and the reaction mixture was filtered through a plug of Celite® and rinsed with MeOH. Removal of the

solvent under reduced pressure gave pyrrole **18**, which was used in the next step without further purification. Pyrrole **18** (1 equiv), ArBr (1.5 equiv), NBu_4Cl (1 equiv), KO*t*Bu (1.5 equiv), and $Pd(P(tBu)_3)_2$ (0.05 equiv) were combined in an open microwave vial. The vessel was crimped through the use of a septum cap, a nitrogen atmosphere introduced and anhydrous DMF was added (0.1 M). Alternatively, pyrrole **18** was added to a microwave vial which was subsequently sealed with a rubber septum and a nitrogen atmosphere introduced. The vial was then brought into a glovebox, septum removed, remaining reagents and solvent were added and then the vessel was re-sealed. The mixture was stirred for 30 s, brought out of the glovebox and then submitted to microwave-promoted heating conditions (150 °C, 10 min, high absorption). The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated solution of $NaHCO_3$ (x3) and water (x2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

5.3.3 General Procedure 4 (GP4) for the Deprotection of Pyrrole 19 and 21

Adapting literature procedures,[88] TBAF (1 M solution in THF, 5 equiv.) was added dropwise to a solution of pyrrole **19** (1 equiv.) in THF (0.1 M) at room temperature under a nitrogen atmosphere. The reaction mixture was heated to reflux temperature for 19 h. If TLC analysis still showed starting material, TBAF (1 M solution in THF, 5 equiv.) was added and the reaction mixture was heated at reflux temperature for an additional 10 h. Water was added to the reaction mixture and the two layers were separated. The aqueous layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

5.3.4 Synthesis of Pyrroles 17, 19 and 21

Benzyl 3,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (17g)

Pyrrole **17g** was obtained according to **GP2**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **17g** as a pale yellow oil (53%). ^{1}H-NMR ($CDCl_3$, 500 MHz): -0.04 (s, 9H), 0.86 (t, J = 8.1 Hz, 2H), 2.44 (s, 3H), 2.51 (s, 3H), 3.51 (t, J = 8.1 Hz, 2H), 5.33 (s, 2H), 5.72 (s, 2H), 7.43-7.34 (m, 5H) ppm. ^{19}F-NMR (471 MHz; $CDCl_3$) -74 ppm. ^{13}C-NMR ($CDCl_3$, 126 MHz): -1.3, 12.2, 18.1, 12.72, 12.74, 66.2, 66.6, 73.6, 117.7, 121.5, 128.50, 128.56, 128.8, 131.3, 135.8, 144.2, 161.6,

179.2, 179.5 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{28}F_3NNaO_4Si$, 478.1632; found, 478.1631.

Benzyl 4-ethyl 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2,4-dicarboxylate (17h)

Pyrrole **17h** was obtained according to **GP2**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **17h** as a pale yellow oil (79%). ^{1}H-NMR ($CDCl_3$, 500 MHz): -0.04 (s, 9H), 0.85 (t, *J* = 8.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 2.53 (s, 3H), 2.58 (s, 3H), 3.49 (t, *J* = 8.1 Hz, 2H), 4.29 (q, J =7.1 Hz, 2H), 5.32 (s, 2H), 5.72 (s, 2H), 7.39-7.31 (m, 3H), 7.42 (d, *J* = 7.1 Hz) ppm. ^{13}C-NMR ($CDCl_3$, 126 MHz): -1.3, 12.0, 13.1, 14.5, 18.1, 59.8, 65.7, 66.1, 73.2, 76.9, 77.2, 77.4, 114.1, 120.1, 128.29, 128.33, 128.7, 132.2, 136.3, 142.8, 161.9, 165.6 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{33}NNaO_5Si$, 454.2020; found, 454.2001.

Ethyl 2,4-dimethyl-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl) -pyrrole-3-carboxylate (19h)

Pyrrole **19h** was obtained according to **GP3**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give a colorless oil containing both the product **19h** (35%, based on the amount of **19h** in the isolated mixture) and the decarboxylated derivative **20h** in a 3:1 ratio. ^{1}H-NMR (300 MHz; $CDCl_3$) -0.06 (s, 9H, TMS of **19h**), -0.02 (s, 9H, TMS of **20h**), 0.77 (t, *J* = 8.4 Hz, 2H, C*H*$_2$-TMS of **19h**), 0.88 (t, *J* = 8.2 Hz, 2H, C*H*$_2$-TMS of **20h**), 1.34-1.39 (m, 6H, C*H*$_3$CH$_2$O(CO) of **19h** and **20h**), 2.15 (s, 3H, C*H*$_3$ of **19h**), 2.21 (s, 3H, C*H*$_3$ of **20h**), 2.53 (s, 3H, C*H*$_3$ of **20h**), 2.63 (s, 3H, *CH*$_3$ of 19h), 3.25 (t, *J* = 8.4 Hz, 2H, C*H*$_2$CH$_2$-TMS of **19h**), 3.46 (t, *J* = 8.4 Hz, 2H, C*H*$_2$CH$_2$-TMS of **20h**), 4.24-4.34 (m, 4H, CH$_3$C*H*$_2$O(CO) of **19h** and **20h**), 5.04 (s, 2H, C*H*$_2$O of 19h), 5.010 (s, 2H, C*H*$_2$O of **20h**), 6.38 (s, 1H, Ar-*H* of **20h**), 7.27-7.28 (m, 2H, Ar-*H* of **19h**), 7.38-7.45 (m, 3H, Ar-*H* of **19h**) (significant overlap between ^{1}H-NMR signals of **19h** and **20h** in spectrum) ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) -1.3, -1.2, 11.8, 11.9, 12.2, 14.4, 17.9, 18.0, 65.0, 65.3, 73.0, 75.7, 109.8, 116.4, 118.0, 118.9, 126.8, 128.3, 129.4, 130.8, 130.9, 133.2 (significant overlap between ^{13}C-NMR signals of **19h** and **20h** in spectrum) ppm. HRMS-ESI (*m/z*) for **19h**: $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3Si$, 396.1965; found, 396.1982. HRMS-ESI (*m/z*) for **20h**: $[M+Na]^+$ calcd for $C_{15}H_{27}NNaOSi$, 320.1652; found, 320.1640.

1-(5-(4-methoxyphenyl)-2,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrol-3-yl)ethanone (19l)

Pyrrole **19l** was obtained according to **GP3**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give a white solid containing both the product **19l** (20%, based on the amount of **19l** in the isolated mixture) and the decarboxylated derivative **20a** in a 6:1 ratio. ^{1}H-NMR ($CDCl_3$, 500 MHz): -0.04 (s, 9H, TMS of **19l**), -0.01 (s, 9H, TMS of **20a**), 0.79 (t, *J* = 8.3 Hz, 2H, C*H*$_2$-TMS of **19l**), 0.89 (t, *J* = 8.1 Hz, 2H, C*H*$_2$-TMS of **20a**), 2.14 (s, 3H, C*H*$_3$ of **19l**), 2.25 (s, 3H, C*H*$_3$ of **20a**), 2.43 (s, 3H, C*H*$_3$ of **20a**), 2.48 (s, 3H, C*H*$_3$ of **19l**), 2.52 (s, 3H, *CH*$_3$ of **20a**), 2.60 (s, *CH*$_3$ of **19l**), 3.29 (t, *J* = 8.3 Hz, 2H, C*H*$_2$CH$_2$-TMS of **19l**), 3.47 (t, *J* = 8.1 Hz, 2H, C*H*$_2$CH$_2$-TMS of **20a**), 3.86 (s, 3H, Ar-O*CH*$_3$ of **19l**), 5.01 (s, 2H, C*H*$_2$O of **19l**), 5.11 (s, 2H, C*H*$_2$O of **20a**), 6.39 (s, 1H, Pyrrole-*H* of **20a**), 6.96 (d, *J* = 8.7 Hz, 2H, Ar-*H* of **19l**), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-*H* of **19l**) ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) -1.3, 12.2, 12.4, 12.9, 13.7, 17.9, 18.0, 31.4, 31.6, 55.4, 65.6, 65.9, 72.8, 75.7, 113.9, 116.6, 119.2, 120.3, 122.7, 122.9, 124.0, 131.6, 132.7, 135.7, 136.3, 159.4, 196.1, 196.5 ppm. HRMS-ESI (*m/z*) for **19l**: $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3Si$, 396.1965; found, 396.1971. HRMS-ESI (*m/z*) for **20i**: $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2Si$, 290.1547; found, 290.1545.

1-(2,4-dimethyl-5-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-3-yl)ethanone (19m)

Pyrrole **19m** was obtained according to **GP3**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give a white solid containing both the product **19m** (36%, based on the amount of **19m** in the isolated mixture) and the decarboxylated derivative **20a** in a 6:1 ratio. ^{1}H-NMR ($CDCl_3$, 300 MHz): -0.04 (s, 9H, TMS of **19m**), -0.02 (s, 9H, TMS of **20a**), 0.1 (t, *J* = 8.3 Hz, 2H, C*H*$_2$-TMS of **19m**), 0.89 (t, *J* = 8.2 Hz, 2H, C*H*$_2$-TMS of **20a**), 2.17 (s, 3H, C*H*$_3$ of **19m**), 2.25 (s, 3H, C*H*$_3$ of **20a**), 2.43 (s, 3H, C*H*$_3$ of **20a**), 2.49 (s, 3H, C*H*$_3$ of **19m**), 2.52 (s, 3H, *CH*$_3$ of **20a**), 2.61 (s, *CH*$_3$ of **19m**), 3.33 (t, *J* = 8.3 Hz, 2H, C*H*$_2$CH$_2$-TMS of **19m**), 3.46 (t, *J* = 8.2 Hz, 2H, C*H*$_2$CH$_2$-TMS of **20a**), 5.01 (s, 2H, C*H*$_2$O of **19m**), 5.11 (s, 2H, C*H*$_2$O of **20a**), 6.39 (s, 1H, Pyrrole-*H* of **20a**), 7.44 (d, *J* = 7.9 Hz, 2H, Ar-*H* of **19m**), 7.69 (d, *J* = 8.0 Hz, 2H, Ar-*H* of **19m**) ppm. ^{19}F-NMR (471 MHz; $CDCl_3$) -63 ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) -1.3, 12.2, 12.4, 12.8, 13.7, 17.9, 18.0, 31.4, 31.7, 65.8, 65.9, 72.9, 75.7, 110.1, 117.8, 119.2, 120.3, 123.1, 125.4, 129.8, 130.1, 130.4, 131.6, 135.7, 136.7, 196.1, 196.3 ppm. HRMS-ESI (*m/z*) for

19m: $[M+Na]^+$ calcd for $C_{21}H_{28}F_3NNaO_2Si$, 434.1734; found, 434.1731. HRMS-ESI (*m/z*) for **20a**: $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2Si$, 290.1547; found, 290.1551.

1-(2,4-dimethyl-5-(thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-3-yl)ethanone (19n)

Pyrrole **19n** was obtained according to **GP3**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **19n** (37%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): -0.03 (s, 9H), 0.81-0.84 (m, 2H), 2.20 (s, 3H), 2.47 (s, 3H), 2.60 (s, 3H), 3.34-3.37 (m, 2H), 5.10 (s, 2H), 7.00 (dd, J = 3.5 and 1.1 Hz, 1H) 7.12 (dd, J = 5.2 and 3.5 Hz, 1H), 7.44 (dd, J = 5.2 and 1.1 Hz, 1H) ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) -1.3, 12.5, 13.1, 18.0, 31.6, 65.8, 72.8, 120.0, 122.9, 123.6, 127.2, 127.7, 130.4, 132.2, 136.9, 196.2 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{27}NNaO_2SSi$, 372.1424; found, 372.1414.

Ethyl 2,4-dimethyl-5-phenyl-1H-pyrrole-3-carboxylate (21h)

Pyrrole **21h** was obtained according to **GP4**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **21h** as a pale yellow solid (65%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.37 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 2.55 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 7.28-7.29 (m, 1H), 7.36-7.42 (m, 4H), 8.06 (br s, 1H) ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) 12.0, 14.3, 14.7, 59.3, 112.6, 118.1, 126.8, 127.4, 127.4, 128.9, 133.0 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}NNaO_2$, 266.1151; found, 266.1148.

1-(5-(4-methoxyphenyl)-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (21l)

Pyrrole **21l** was obtained according to **GP4**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **21l** as a brown solid (24%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.34 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 3.84 (s, 3H), 6.96 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 8.04 (br s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 126 MHz): 12.78, 15.28, 31.20, 55.50, 110.14, 114.36, 116.16, 125.28, 127.72, 129.19, 134.41, 158.86, 195.80 ppm.HRMS-APCI (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1332; found, 244.1324.

1-(2,4-dimethyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)ethanone (21m)

Pyrrole **21m** was obtained according to **GP4**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **21m** as a pale beige solid (48%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.38 (s, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 7.46 (d, J = 8.2 Hz,

2H), 7.64 (d, J = 8.2 Hz, 2H), 8.33 (br s, 1H) ppm. ^{9}F-NMR (471 MHz; $CDCl_3$) -63 ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) 12.8, 15.3, 31.3, 118.6, 123.2, 125.4, 125.9, 126.5, 127.6, 128.6, 135.8, 136.2, 195.8 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{14}FNNaO$, 304.0920; found, 304.0926.

1-(2,4-dimethyl-5-(thiophen-2-yl)-1H-pyrrol-3-yl)ethanone (21n)

Pyrrole **21n** was obtained according to **GP4**. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 85/15) to give **21n** as a pale beige solid (58%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.41 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 7.02 (dd, J = 3.5 and 0.9 Hz, 2H), 7.08 (dd, J = 5.1 and 3.6 Hz, 2H), 7.28 (dd, J = 5.a and1.0 Hz), 8.08 (br s, 1H) ppm. ^{13}C-NMR(125 MHz; $CDCl_3$) 12.7, 15.1, 31.1, 118.1, 122.8, 124.2, 124.3, 127.5, 133.3, 134.2, 134.9, 195.5ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{13}NNaOS$, 242.0610; found, 242.0615.

5.4 Chapter 4 Experimental

5.4.1 General Procedure 5 (GP 5) for Synthesis of Pyrrolinone 32

Adapting reported procedures,[98-99] Boc-protected glycine (29 mmol) was suspended in 250 mL of anhydrous DCM under a positive pressure of nitrogen. Meldrum's acid (44 mmol) and DMAP (44 mmol) were added. The reaction mixture was cooled to 0°C using an ice bath, and EDC (88 mmol) was added in 3-4 portions and stirred overnight. Following this, the reaction mixture was concentrated under reduced pressure, and the resulting dark yellow oil was transferred with a minimum amount of DCM to a separatory funnel. Ethyl acetate was added until a precipitate formed, and then an additional 50-100 mL of ethyl acetate was added. The resulting mixture was then washed with 5% citric acid (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting mixture was then re-dissolved in 200 mL ethyl acetate and heated at reflux temperature for 1 hour. Solvent was removed in vacuo, resulting in a light yellow/orange solid which was subsequently suspended in cold DCM, isolated via filtration, and washed with DCM followed by pentane to give **32** as white solid (4.2 g, 73%).

5.4.2 General Procedure 6 (GP 6) for Synthesis of Pyrrolinone 33

To a suspension of **32** (2.5 g, 12.6 mmol) in DCM (100 mL, 0.1 M) under a positive pressure of nitrogen, tosyl chloride (2.6 g, 13.4 mmol) was added. DIPEA (2.2 mL, 12.6 mmol) was added dropwise, and the resulting mixture was stirred for 2-3 hours. The reaction mixture was then washed with 0.5 M HCl (10 mL x 3). The aqueous layer was extracted with DCM (10 mL x 3) and the combined organic layers were washed with saturated $NaHCO_3$ (10 mL x 3), and brine, then dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude **33** as a brown oil. The crude product was embedded on silica with a minimum amount of DCM, and then eluted with ethyl acetate/hexanes (50/50 v/v). After removal of solvent under reduced pressure, pyrrolinone **33** was dissolved in a small amount of DCM, precipitated with pentane, and then isolated via filtration to give a white solid (3.9 g, 88%).

5.4.3 General Procedure 7 (GP 7) for Synthesis of N-Boc Pyrrolinones 46

In a microwave vial, pyrrolinone **33** (500 mg, 1.42 mmol) and DABCO (175 mg, 1.56 mmol) were combined. The vial was sealed, degassed 3 times and placed under a positive pressure of nitrogen. Anhydrous DCM (15 mL, 0.09M) was added, followed by liquid RSH (2.84 mmol). If solid RSH, 2 equiv. of thiol was added prior to sealing of the microwave vial. The reaction mixture was then subjected to microwave irradiation (power = 100 W, normal absorbance) for 10-15 minutes. HCl (0.5 M, 10 mL) was added and the two layers separated. The aqueous layer was extracted with DCM (20 mL x 3) and the combined organic layers were washed with NaOH (5% aqueous solution, 10 mL x 3) and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

5.4.4 General Procedure 8 (GP 8) for Synthesis of N-H Pyrrolinones 47

To a solution of pyrrolinone **46** (613 mg, 2.1 mmol) in DCM (10.0 mL), TFA (0.32 mL, 4.2 mmol) was added and the reaction mixture was stirred overnight at room temperature. H_2O (5 mL) was then added and the two layers separated. The organic layer was washed with $NaHCO_3$ (saturated aqueous solution, 5 mL x 3). The organic layer was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

5.4.5 General Procedure 9 (GP 9) for Synthesis of Dipyrrinones 48 and 54

To a solution of pyrrolinone **47** (682 mg, 3.08 mmol) in anhydrous DCM (52 mL), NEt_3 (0.65 mL, 4.62 mmol) and TMSOTf (1.7 mL, 9.24 mmol) were added at 0 °C under a nitrogen atmosphere. After 15 minutes a solution of aldehyde **36b** (300 mg, 1.54 mmol) in anhydrous DCM (26 mL) was added to the reaction mixture, which was stirred at 0 °C under a nitrogen atmosphere for an additional 2 hours.

5.4.6 General Procedure 10 (GP 10) for Synthesis of Bromo-dipyrrins 49 and 55

To a solution of dipyrrinone **48** or **54** (350 mg, 0.88 mmol) in anhydrous DCM (24 mL), $POBr_3$ (305 mg, 1.76 mmol) was added at room temperature under a nitrogen atmosphere. The temperature was increased to 40 ºC using an oil bath and the reaction stirred for 1 day. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture and the two layers separated. The aqueous layer was extracted with DCM (20 mL x 5). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

5.4.7 General Procedure 11 (GP 11) for Synthesis of Prodigiosenes 50 and 55

A solution of LiCl (47 mg, 1.10 mmol), dipyrrin **49** or **55** (169 mg, 0.37 mmol) and *N*-Boc-pyrrole-2-boronic acid (93 mg, 0.44 mmol) in DME (0.04 M wrt dipyrrin) was degassed (x 3) and placed under nitrogen. $Pd(PPh_3)_4$ (27 mg, 0.02 mmol) was added to the solution and the resulting reaction mixture degassed (x 2) and placed under a positive pressure of nitrogen. A solution of 2 M Na_2CO_3 (0.750 mL, 1.47 mmol) was added and the resulting reaction mixture degassed (x 2), placed under a positive pressure of nitrogen and stirred at 85 °C for 19 h. The reaction mixture was poured into water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude product, which was purified using flash chromatography on neutral alumina.

5.4.8 General Procedure 12 (GP 12) for Synthesis of HCl Salts of Prodigiosenes

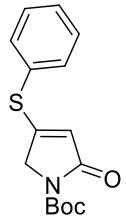
Solutions of prodigiosene **50** or **56** were dissolved in DCM (5 mL) and 1M HCl (1 mL) was added at room temperature and stirred for a few minutes. The organic layer was separated, washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure affording the HCl salt of **50** or **56** as a dark red solid in quantitative yield.

5.4.9 General Procedure 13 (GP 13) for Boc Removal of 50a

Prodigiosene **50a** (0.01 mmol) was dissolved in TFA (~ 1 mL) under a positive pressure of nitrogen. After 5 minutes, the resulting mixture was then quenched via addition of $NaHCO_3$. DCM (5 mL) was added and the organic layer was washed with water, brine and 1M HCl (1x 5 mL each), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure affording the Boc-deprotected HCl salt of **50a** as a pink film in quantitative yield.

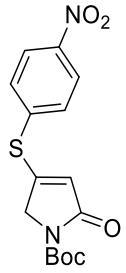
5.4.10 Synthesis of Compounds 46-50 and 54-56

Tert-butyl 2-oxo-4-(phenylthio)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (46a)



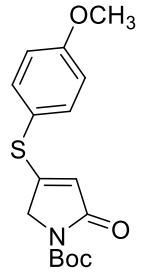
This compound was obtained according to **GP 7**. The crude product was embedded on silica with a minimum amount of DCM, and then washed with pentane and eluted with 20% ethyl acetate in hexanes to give compound **46a** as a white solid (1.76 g, 85%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.52 (s, 9H), 4.29 ($^4J_{H-H}$ ~ 0.9 Hz, 2H), 5.48 (s, 1H), 7.46-7.42 (m, 3H), 7.54-7.52 (m, 2H). ^{13}C-NMR and HRMS were not obtained for this compound.

Tert-butyl 4-(4-Nitrophenylthio)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (46b)



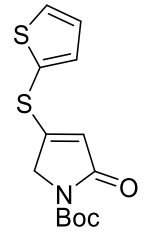
This compound was obtained according to **GP 7**. After removal of solvent under reduced pressure, crude pyrrolinone **46b** was dissolved in a small amount of DCM, precipitated with pentane, and then isolated via filtration to give compound **46b** as a pale yellow solid (1.91 g, 84%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.53 (s, 9H), 4.35 (s, 2H), 5.64 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 8.28 (d, J = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 28.2, 52.7, 83.5, 120.1, 125.0, 135.0, 136.4, 148.9, 149.2, 157.5, 166.8. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{16}N_2NaO_5S$, 359.0672; found, 359.0658.

Tert-butyl 4-(4-methoxyphenylthio)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (46c)



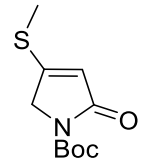
This compound was obtained according to **GP 7**. The crude mixture was purified by flash column chromatography using SiO_2 (6% - 50% EtOAc in hexanes) to give compound **46c** as a pale-yellow oil (700 mg, 73%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.52 (s, 9H), 3.84 (s, 3H), 4.26 (s, 2H), 5.44 (s, 1H), 6.95 (d, 2H, J = 8.9 Hz), 7.44 (d, 2H, J = 8.9 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): 28.3, 52.6, 55.6, 83.0, 115.7, 117.6, 118.0, 136.6, 161.5, 162.4, 167.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{19}NNaO_4S$, 344.0927; found, 344.0913.

Tert-butyl 2-oxo-4-(thiophen-2-ylthio)-2,5-dihydro-1H-pyrrole-1-carboxylate (46d)



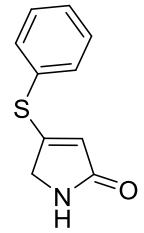
This compound was obtained according to **GP 7**. The crude mixture was purified by flash column chromatography using SiO_2 (6% - 50% EtOAc in hexanes) to give compound **46d** as a pale brown oil (521 mg, 61%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.52 (s, 9H), 4.27 (d, $^4J_{H\text{-}H}$ ~ 1.2 Hz, 2H), 5.63 (t, $^4J_{H\text{-}H}$ ~ 1.1 Hz, 1H), 7.12 (dd, J = 5.4, 3.6 Hz, 1H), 7.31 (dd, J = 3.6, 1.1 Hz, 1H), 7.58 (dd, J = 5.4, 1.1 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 28.2, 52.2, 83.1, 118.8, 124.2, 128.5, 133.2, 137.5, 149.4, 161.1, 167.2 HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NNaO_3S_2$, 320.0386; found, 320.0380.

Tert-butyl 4-(methylthio)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (46e)



This compound was obtained according to **GP 7**. The crude product was embedded on silica with a minimum amount of DCM, and then washed with pentane and eluted with 20% ethyl acetate in hexanes to give compound **46e** (611 mg, 86%) as a pale beige oil after removal of solvent in vacuo, which was used in the next step without characterization.

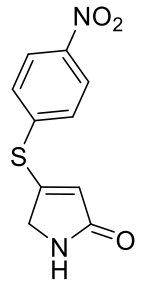
4-(Phenylthio)-1*H*-pyrrol-2(5*H*)-one (47a)



This compound was obtained according to **GP 8**. After removal of solvent under reduced pressure, crude pyrrolinone **47a** was dissolved in a small amount of DCM, precipitated with pentane, and then isolated via filtration to give compound **47a** as a white solid (486 mg, 91%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 3.99 (s, 2H), 5.57 (s, 1H), 7.40-7.45 (m, 3H),

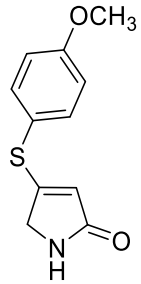
7.54-7.55 (m, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 50.4, 118.6, 128.8, 130.0, 130.1, 134.8, 160.6, 174.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_9NNaOS$, 214.0297; found, 214.0291.

4-(4-Nitrophenylthio)-1H-pyrrol-2(5H)-one (47b)



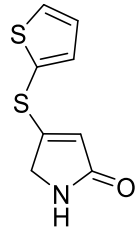
To a solution of pyrrolinone **46** (1.5 g, 4.5 mmol) in DCM (74 mL, 0.06 M), TFA (685 µL, 9 mmol) was added at 0°C and the reaction mixture was stirred overnight at room temperature. Following quench with $NaHCO_3$, compound **47b** crashed out of solution which was then isolated via filtration and washed with water followed by ether. The crude mixture (730 mg, 66%) was not further purified and it was used directly into the next step without characterization.

4-(4-Methoxyphenylthio)-1H-pyrrol-2(5H)-one (47c)



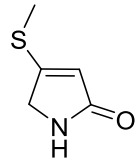
This compound was obtained according to **GP 8**. After removal of solvent under reduced pressure, crude pyrrolinone **47c** was dissolved in a small amount of DCM, precipitated with pentane, and then isolated via filtration to give compound **47c** as a white solid (408 mg, 94%) which was used in the next step without characterization via NMR. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{11}NNaO_2S$, 244.0403; found, 244.0407.

4-(Thiophen-2-ylthio)-1H-pyrrol-2(5H)-one (47d)



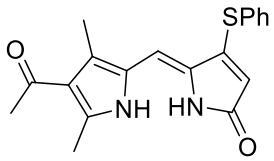
This compound was obtained according to **GP 8**. After removal of solvent under reduced pressure, crude pyrrolinone **47d** was dissolved in a small amount of DCM, precipitated with pentane, and then isolated via filtration to give compound **47d** as a light brown solid (270 mg, 82%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 3.95 (s, 2H), 5.68 (d, $^{4}J_{H\text{-}H}$ ~ 1.1 Hz, 1H), 7.09 (dd, J = 5.3, 3.7 Hz, 1H), 7.29 (dd, J = 3.5, 0.8 Hz, 1H), 7.33 (s, 1H), 7.54 (dd, J = 5.4, 0.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 126 MHz): 49.9, 119.3, 125.6, 128.3, 132.7, 137.1, 160.3, 174.1; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_8H_7NNaO_1S_2$, 219.9861; found, 219.9853.

4-(Ethylthio)-1H-pyrrol-2(5H)-one (47e)



This compound was obtained according to **GP 8**. The crude mixture was purified by flash column chromatography using SiO_2 (0% - 5% MeOH in DCM) to give compound **47e** as a beige solid (155 mg, 39% over two steps) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.42 (s, 3H), 4.05 (s, 2H), 5.72 (s, 1H), 7.14 (s, 1H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 15.1, 50.4, 116.5, 161.1, 174.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for C_5H_7NNaOS, 152.0141; found, 152.0140.

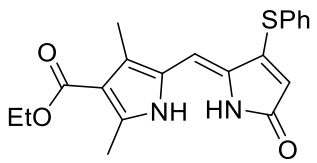
(Z)-5-((4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)methylene)-4-(phenylthio)-1H-pyrrol-2(5H)-one (48a)



This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and the two layers separated. The organic layer was washed with H_2O (100 mL x 2)

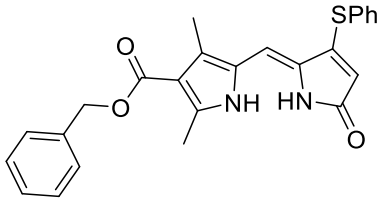
and the combined aqueous layers extracted with DCM (50 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in THF (100 mL), 12 M HCl (100 µL) was added and then was stirred for 5 minutes at room temperature. The reaction was then quenched with saturated $NaHCO_3$, the resulting layers were separated and then the aqueous layer was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. Following removal of solvent under reduced pressure, **48a** crashed out of solution, which was isolated via filtration and washed pentane to give compound **48a** as a bright yellow solid (297 mg, 83%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.39 (s, 3H), 2.44 (s, 3H), 2.57 (s, 3H), 5.50 (s, 1H), 6.50 (s, 1H), 7.43-7.44 (m, 3H), 7.56-7.58 (m, 2H), 10.58 (s, 1H), 11.38 (s, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 12.3, 15.3, 31.4, 103.1, 114.6, 122.8, 123.2, 128.7, 129.0, 129.5, 130.0, 130.5, 133.8, 141.9, 152.7, 172.8, 195.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{18}N_2NaO_2S$, 361.0981; found, 361.0977.

(Z)-Ethyl-2,4-dimethyl-5-((5-oxo-3-(phenylthio)-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrole-3-carboxylate (48c)



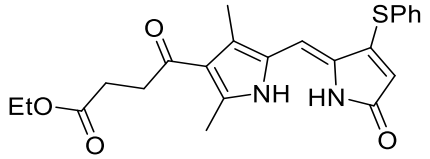
This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and the two layers separated. The organic layer was washed with H_2O (100 mL x 2) and the combined aqueous layers extracted with DCM (50 mL x 5). The combined organic layers were were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was then triturated with cold methanol and isolated via filteration to give **48c** as a bright yellow solid (267 mg, 73%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.36 (t, J = 7.1 Hz, 3H), 2.37 (s, 3H), 2.54 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 5.50 (s, 1H), 6.50 (s, 1H), 7.42-7.43 (m, 3H), 7.56-7.57 (m, 2H), 10.60 (s, 1H), 11.39 (s, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 11.5, 14.4, 14.6, 59.6, 103.4, 113.3, 114.7, 122.7, 128.3, 129.4, 130.0, 130.7, 130.7, 133.7, 142.8, 152.3, 165.6, 172.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{21}N_2O_3S$, 369.1267; found, 369.1266.

(Z)-Benzyl 2,4-dimethyl-5-((5-oxo-3-(phenylthio)-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrole-3-carboxylate (48d)



This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and the two layers separated. The organic layer was washed with H_2O (100 mL x 2) and the combined aqueous layers extracted with DCM (50 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in THF (100 mL), 12 M HCl (100 µL) was added and then was stirred for 5 minutes at room temperature. The reaction was then quenched with saturated $NaHCO_3$, the resulting layers were separated and then the aqueous layer was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. The organic solvent was concentrated to 1/5 of the original volume and **48d** crashed out of the solution. The precipitate was isolated via filtration and washed with pentane to afford **48d** as a bright yellow solid (249 mg, 74%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.38 (s, 3H), 2.54 (s, 3H), 5.29 (s, 2H), 5.50 (s, 1H), 6.49 (s, 1H), 7.33-7.30 (m, 1H), 7.35-7.38 (m, 2H), 7.44-7.41 (m, 5H), 7.55-7.57 (m, 2H), 10.58 (s, 1H), 11.31 (s, 1H). ^{13}C-NMR was not obtained for this compound. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{23}N_2O_3S$, 431.1424; found, 431.1435.

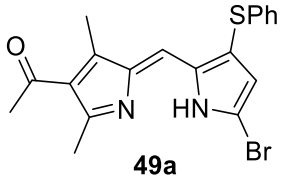
(Z)-Ethyl 4-(2,4-dimethyl-5-((5-oxo-3-(phenylthio)-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrol-3-yl)-4-oxobutanoate (48e)



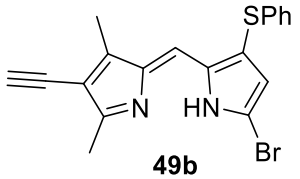
This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and the two layers separated. The organic layer was washed with H_2O (100 mL x 2) and the combined aqueous layers extracted with DCM (50 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in THF (100 mL), 12 M HCl (100 µL) was added and then was stirred for 5 minutes at room temperature. The reaction was then

quenched with saturated $NaHCO_3$, the resulting layers were separated and then the aqueous layer was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent under reduced pressure, crude dipyrrinone **48e** was dissolved in a small amount of DCM, precipitated with ether, and then isolated via filtration to give compound **48e** as a yellow solid (136 mg, 60%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.27 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 2.57 (s, 3H), 2.70 (t, J = 6.6 Hz, 2H), 3.04 (t, J = 6.6 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 5.49 (d, J = 0.7 Hz, 1H), 6.49 (s, 1H), 7.43-7.44 (m, 3H), 7.58-7.56 (m, 2H), 10.59 (s, 1H), 11.37 (s, 1H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 12.5, 14.4, 15.4, 28.5, 37.5, 60.7, 103.0, 114.6, 122.5, 122.9, 128.7, 128.9, 129.5, 130.0, 130.4, 133.8, 141.8, 152.7, 172.7, 173.5, 195.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{24}N_2NaO_4S$, 447.1349; found, 447.1352.

(Z)-1-(2-((5-Bromo-3-(phenylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)ethanone (49a and 49b)



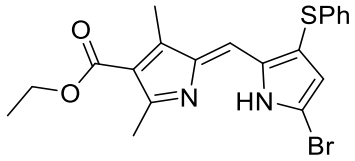
49a



49b

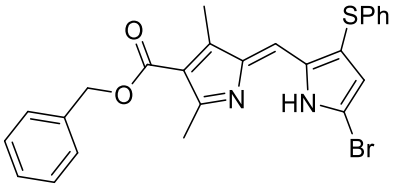
These compounds were obtained according to **GP 10**. The crude mixture was purified by flash column chromatography using neutral Al_2O_3 (0-70% DCM in hexanes) to afford **49a** as a bright orange/red solid (85 mg, 30%) and **49b** as a yellow/orange solid (156 mg, 55%) after removal of solvent in vacuo. Data for **49a**: ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.41 (s, 3H), 2.46 (s, 3H), 2.63 (s, 3H), 6.16 (s, 1H), 7.10 (s, 1H), 7.32-7.35 (m, 3H), 7.43-7.47 (m, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 12.6, 16.2, 31.4, 119.6, 124.5, 125.2, 127.5, 128.1, 129.6, 131.5, 133.9, 135.2, 144.8, 145.6, 145.9, 146.1, 194.7. LRMS: 401.1 $(M+H)^+$; HRMS: 401.0308 Found, Calculated for 401.0318 $C_{19}H_{18}BrN_2O_1S$. Data for **49b**: ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.24 (s, 3H), 2.44 (s, 3H), 3.26 (s, 1H,), 6.19 (s, 1H), 7.02 (s, 1H), 7.30-7.33 (m, 3H), 7.40-7.44 (m, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 10.7, 13.4, 76.7, 82.1, 107.9, 120.1, 125.0, 127.7, 127.8, 129.5, 131.0, 134.7, 138.1, 142.8, 144.0, 145.0, 146.2. HRMS: 383.0218 Found, Calculated for 383.0212 $C_{19}H_{16}BrN_2S$.

(Z)-Ethyl 2-((5-bromo-3-(phenylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (49c)



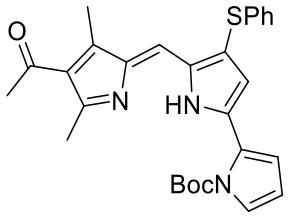
This compound was obtained according to **GP 10**. The crude mixture was purified by flash column chromatography using neutral Al_2O_3 (12-100% DCM in hexanes) to afford **49c** as a bright orange/red solid (180 mg, 62 %) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.37 (t, 3H, J = 7.1 Hz), 2.40 (s, 3H), 2.62 (s, 3H), 4.31 (q, 2H, J = 7.1 Hz), 6.17 (s, 1H), 7.10 (s, 1H), 7.28-7.36 (m, 3H), 7.43-7.45 (m, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 11.8, 14.6, 15.3, 59.9, 115.2, 124.6, 120.0, 125.2, 127.6, 128.0, 129.6, 131.4, 134.1, 137.4, 144.4, 145.6, 146.5, 165.1. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{20}BrN_2O_2S$, 431.0423; found, 431.0424.

(Z)-Benzyl 2-((5-bromo-3-(phenylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (49d)



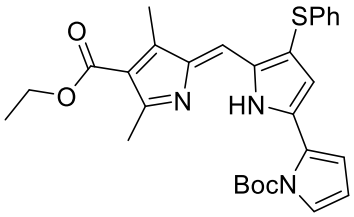
This compound was obtained according to **GP 10**. Following workup, the crude mixture was dissolved in a small amount of DCM, filtered over a short plug of neutral Al_2O_3 eluting with DCM to afford **48d** as a red solid (176 mg, 77%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.40 (s, 3H), 2.61 (s, 3H), 5.31 (s, 2H), 6.17 (s, 1H), 7.09 (s, 1H), 7.30-7.46 (m, 10H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 11.9, 15.4, 65.8, 114.7, 119.8, 125.2, 127.6, 128.1, 128.2, 128.3, 128.7, 129.6, 131.5, 134.0, 136.5, 137.3, 144.5, 145.7, 145.8, 146.5, 164.7; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{22}BrN_2O_2S$, 493.0580; found, 493.0568.

(Z)-Tert-butyl 5'-((4-acetyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-4'-(phenylthio)-1H,1'H-2,2'-bipyrrole-1-carboxylate (50a)



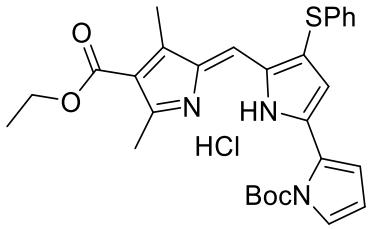
This compound was obtained according to **GP 11**. The crude mixture was purified using flash chromatography on neutral Al_2O_3 (0-30% EtOAc in hexanes) affording **50a** as a dark red/orange film (17 mg, 17%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.54 (s, 9H), 2.42 (s, 3H), 2.46 (s, 3H), 2.60 (s, 3H), 6.27 (t, 1H, J = 3.4 Hz), 6.63 (s, 1H), 6.70 (dd, 1H, dd, J = 3.5 and 1.7 Hz), 7.15 (s, 1H), 7.18-7.21 (m, 1H), 7.27-7.29 (m, 2H), 7.34-7.37 (m, 2H), 7.40 (dd, 1H, J = 3.2 and 1.7). ^{13}C-NMR ($CDCl_3$, 125 MHz): 12.7, 17.9, 28.0, 31.4, 84.9, 111.5, 117.91, 119.3, 123.6, 125.4, 126.7, 128.1, 128.6, 129.2, 129.3, 133.4, 136.6, 136.8, 140.2, 141.9, 149.3, 154.6, 195.4. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_3S$, 488.2002; found, 488.2021.

(Z)-Ethyl 3,5-dimethyl-2-((4-(phenylthio)-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-2H-pyrrole-4-carboxylate (50c)



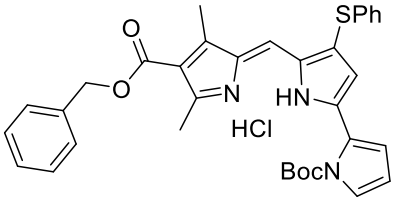
This compound was obtained according to **GP 11**. The crude mixture was purified using flash chromatography on neutral Al_2O_3 (6-50% EtOAc in hexanes) affording **50c** as a dark red/orange film (68 mg, 33%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.47 (t, 3H, J = 7.1 Hz), 1.66 (s, 9H), 2.54 (s, 3H), 2.72 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 6.38 (t, 1H), 6.75 (s, 1H), 6.80-6.81 (m, 1H), 7.15 (s, 1H), 7.18-7.20 (m, 1H), 7.29-7.31 (m, 2H), 7.37-7.40 (m, 2H), 7.47-7.49 (m, 1H), 11.41 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 11.9, 14.5, 16.9, 27.9, 59.7, 84.7, 111.5, 117.7, 118.7, 119.3, 123.5, 125.2, 126.5, 128.6, 129.1, 129.2, 133.2, 136.3, 136.8, 141.7, 142.6, 149.17, 149.21, 154.7, 165.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_4S$, 518.2102; found, 518.2108.

(Z)-Ethyl 3,5-dimethyl-2-((4-(phenylthio)-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-2H-pyrrole-4-carboxylate hydrochloride (50c•HCl)



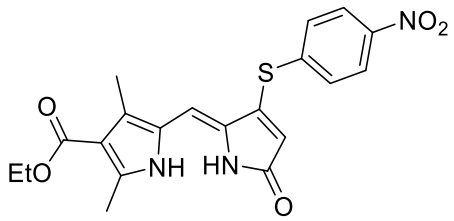
The HCl salt of **50c** was obtained according to **GP 12**. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.39 (3H, *J* = 7.1 Hz), 1.49 (s, 9H), 2.56 (s, 3H), 2.88 (s, 3H), 4.34 (q, 2H, *J* =7.1), 6.33-6.35 (m, 1H), 6.42 (s, 1H), 7.34-7.52 (m, 8H), 14.10 (bs, 1H), 14.60 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 12.2, 14.5, 15.5, 27.9, 60.5, 85.4, 112.6, 118.6, 119.7, 120.4, 123.1, 124.3, 126.7, 128.6, 128.7, 128.9, 129.9, 132.2, 132.3, 145.7, 148.0, 148.2, 148.4, 157.3, 163.9.

(Z)-Benzyl 3,5-dimethyl-2-((4-(phenylthio)-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-2H-pyrrole-4-carboxylate (50d•HCl)



The free-base of compound **50d** was obtained according to **GP 11**. The crude mixture was purified using flash chromatography on neutral Al_2O_3 (2-20% EtOAc in hexanes). The resulting freebase **50d** was then converted to the HCl salt according to **GP 12** to afford **50d•HCl** as a dark red/orange film (R = Boc, 44 mg) after removal of solvent in vacuo. ^{1}H-NMR was obtained for this compound, however chemical signals could not be assigned due to presence of impurities. ^{13}C-NMR was not obtained for this compound.

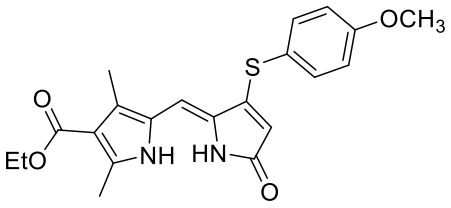
(Z)-Ethyl 2,4-dimethyl-5-((3-(4-nitrophenylthio)-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrole-3-carboxylate (54a)



This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and a yellow precipitate formed, which was subsequently isolated via filtration, washed with THF and then pentane to give compound **54a** as a yellow solid (260 mg, 42%).

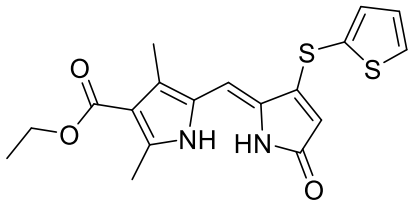
^{1}H-NMR (DMSO-d6, 500 MHz) 1.26 (t, *J* = 7.1 Hz, 3H), 2.15 (s, 3H), 2.47 (s, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.19 (s, 1H), 6.26 (s, 1H), 7.67 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H). ^{13}C-NMR (DMSO-d_6,126 MHz): 10.8, 13.7, 14.3, 58.9, 99.8, 109.5, 112.0, 123.3, 124.5, 126.7, 129.5, 129.8, 140.7, 142.6, 142.8, 146.3, 164.4, 169.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{20}N_3O_5S$, 414.1118; found, 414.1115.

(Z)-Ethyl 5-((3-(4-methoxyphenylthio)-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (54b)



This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and the two layers separated. The organic layer was washed with H_2O (100 mL x 2) and the combined aqueous layers extracted with DCM (50 mL x 5). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was then triturated with cold methanol and **54b** was isolated via filtration as a bright yellow solid (133 mg, 40%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.36 (t, *J* = 7.1 Hz, 3H), 2.39 (s, 3H), 2.53 (s, 3H), 3.86 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 5.32 (s, 1H), 6.44 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 10.59 (s, 1H), 11.30 (s, 1H); ^{13}C-NMR ($CDCl_3$, 126 MHz): δ 11.5, 14.4, 14.6, 55.6, 59.5, 102.7, 113.0, 113.1, 115.6, 120.1, 122.7, 128.1, 129.9, 136.2, 142.6, 154.5, 161.0, 165.7, 172.8; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{21}N_2O_4S$, 397.1228; found, 397.1212.

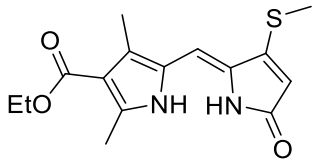
(Z)-Ethyl 2,4-dimethyl-5-((5-oxo-3-(thiophen-2-ylthio)-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrole-3-carboxylate (54c)



This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and a yellow precipitate formed, which was subsequently isolated via filtration, washed with methanol and then pentane to give compound **54c** as a yellow solid (227 mg, 59%). ^{1}H-NMR (DMSO-d_6, 500 MHz): 1.28 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 2.47 (s, 3H),

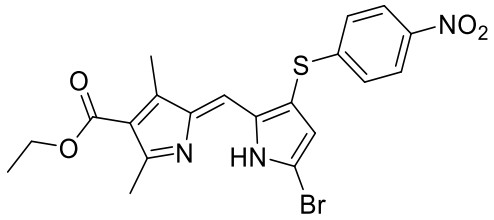
4.19 (q, J = 7.0 Hz, 2H), 5.42 (s, 1H), 6.13 (s, 1H), 7.22 (t, J = 4.3 Hz, 1H), 7.51-7.51 (m, 1H), 7.91-7.90 (m, 1H), 10.21 (s, 1H), 11.05 (s, 1H). ^{13}C-NMR and HRMS were not obtained for this compound.

(Z)-Ethyl 2,4-dimethyl-5-((3-(methylthio)-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-1H-pyrrole-3-carboxylate (54d)



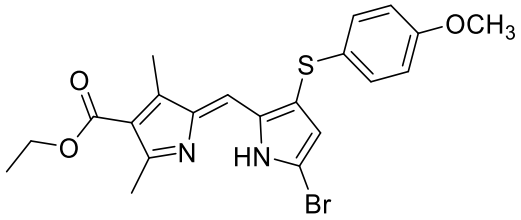
This compound was obtained according to **GP 9**. Phosphate buffer (pH = 7.2, 80 mL) was added and a yellow precipitate formed, which was subsequently isolated via filtration, washed with methanol followed by pentane to give compound **54d** as a yellow solid (158 mg, 95%). ^{1}H-NMR (DMSO-d_6, 500 MHz) 1.27 (t, J = 7.1 Hz, 3H), 2.23 (s, 3H), 2.46 (s, 3H), 2.49 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 5.88 (s, 1H), 5.95 (s, 1H), 10.01 (s, 1H), 10.99 (s, 1H). ^{13}C-NMR was not obtained for this compound. HRMS-APCI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{19}N_2O_3S$, 307.1111; found, 307.1106.

(Z)-Ethyl 2-((5-bromo-3-(4-nitrophenylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (55a)



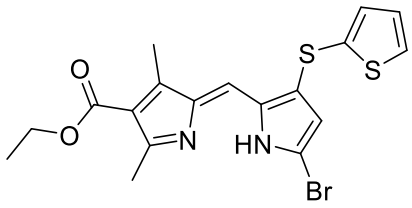
This compound was obtained according to **GP 10**. The crude mixture was purified by flash column chromatography using neutral Al_2O_3 (0-100% DCM in hexanes) to afford **55a** as an orange solid (90 mg, 56%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.37 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 2.65 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 6.64 (s, 1H), 7.14 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 11.9, 14.6, 15.5, 60.1, 116.1, 121.8, 124.4, 127.2, 128.3, 130.2, 135.6, 140.2, 144.2, 145.8, 145.9, 147.0, 148.5, 164.7. LRMS: 498.0 $(M+Na)^+$; HRMS: 498.0109 Found, Calculated for 498.0094 $C_{20}H_{18}BrN_3O_4SNa$.

(Z)-Ethyl 2-((5-bromo-3-(4-methoxyphenylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (55b)



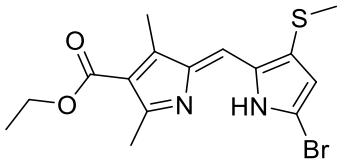
This compound was obtained according to **GP 10**. Following workup, the crude mixture was dissolved in a small amount of DCM, filtered over a short plug of neutral Al_2O_3, and eluted with DCM to afford **55b** as a red solid (148 mg, 85%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.37 (t, J = 7.1 Hz, 3H), 2.42 (s, 3H), 2.61 (s, 3H), 3.83 (s, 3H), 4.31 (q, J = 7.1 Hz, 2H), 5.90 (s, 1H), 6.93-6.91 (m, 2H), 7.05 (s, 1H), 7.46-7.45 (m, 2H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 11.8, 14.6, 15.3, 55.6, 59.8, 114.9, 115.4, 119.0, 122.7, 122.8, 127.4, 135.0, 136.5, 145.2, 145.9, 146.1, 148.2, 160.4, 165.1. LRMS: 461.0 $(M+H)^+$; HRMS: 461.0547 Found, Calculated for 461.0529 $C_{21}H_{22}BrN_2O_3S$.

(Z)-Ethyl 2-((5-bromo-3-(thiophen-2-ylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (55c)



This compound was obtained according to **GP 10**. Following workup, the crude mixture was dissolved in a small amount of DCM, filtered over a short plug of neutral Al_2O_3, and eluted with DCM to afford **55c** as a red solid (182 mg, 82%). LRMS: 461.0 $(M+H)^+$; HRMS: 436.993 Found, Calculated for 436.998 $C_{18}H_{18}BrN_2O_3S_2$. This compound was carried forward without further characterization.

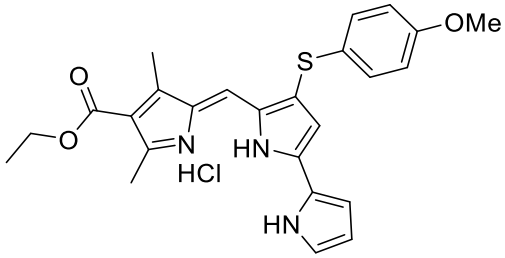
(Z)-Ethyl 2-((5-bromo-3-(methylthio)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (55d)



This compound was obtained according to **GP 10**. Following workup, the crude mixture was dissolved in a small amount of DCM, filtered over a short plug of neutral Al_2O_3, and

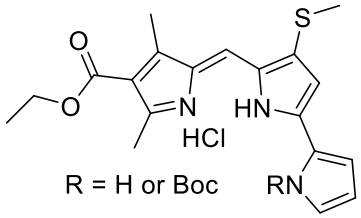
eluted with DCM to afford **55d** as a bright orange/red solid (91 mg, 61%) after removal of solvent in vacuo. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.37 (t, J = 7.1 Hz, 4H), 2.43 (s, 3H), 2.49 (s, 3H), 2.60 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 6.12 (s, 1H), 6.97 (s, 1H). ^{13}C-NMR was not obtained for this compound. LRMS: 369.0 $(M+H)^+$; HRMS: 369.0260 Found, Calculated for 369.0267 $C_{15}H_{18}BrN_2O_2S$.

(Z)-Ethyl 2-((4-(4-methoxyphenylthio)-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (56b•)



This compound was obtained according to **GP 11**. The crude mixture was purified using flash chromatography on neutral Al_2O_3 (0-50% EtOAc in hexanes). The resulting freebase **56b** was then converted to the HCl salt according to **GP 12** to afford **56b•HCl** as a dark red/orange film (R = H, 25 mg, 14%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.39 (t, J = 7.1 Hz, 3H), 2.55 (s, 3H), 2.84 (s, 3H), 3.87 (s, 3H), 4.33 (q, J = 7.1 Hz, 2H), 6.21 (s, 1H), 6.32 (s, 1H), 6.83 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.23 (s, 1H), 7.25 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 12.62 (s, 1H), 13.04 (s, 1H), 13.24 (s, 1H). ^{13}C-NMR ($CDCl_3$, 126 MHz): 12.1, 14.5, 15.1, 55.6, 60.2, 112.5, 114.1, 115.3, 115.8, 118.9, 120.1, 121.6 124.7, 128.7, 129.1, 135.9, 142.9, 148.9, 152.1, 152.5, 161.2, 164.4. Missing one carbon signal.

(Z)-Tert-butyl 5'-((4-(ethoxycarbonyl)-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-4'-(methylthio)-1H,1'H-2,2'-bipyrrole-1-carboxylate hydrochloride (56d)



The free-base of compound **56d** was obtained according to **GP 11**. The crude mixture was purified using flash chromatography on neutral Al_2O_3 (0-100% DCM in hexanes). The resulting freebase **56d** was then converted to the HCl salt according to **GP 12** to afford **56d•HCl** as a dark red/orange film (R=Boc, 24 mg, R=H, 19 mg). Plasticizer and grease

could not be removed from these compound, however crude ^{1}H-NMR spectra were obtained for **56d•HCl** (R=Boc and H). Crude ^{1}H-NMR of **56d•HCl** (R=H): ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.38 (t, J = 7.1 Hz, 3H), 2.52 (s, 3H), 2.62 (s, 3H), 2.81 (s, 3H), 4.31 (q, J = 7.1 Hz, 2H), 6.37 (s, 1H), 6.55 (s, 1H), 7.00 (s, 1H), 7.08 (s, 1H), 12.67 (s, 1H), 12.96 (s, 1H), 13.21 (s, 1H). See page 177 for crude ^{1}H-NMR spectrum of **56d•HCl** (R=Boc).

CHAPTER 6 - Conclusions

6.1 Conclusions

Discussions pertaining to Chapter 2, 3 and 4 were individually summarized at the end of each respective chapter. As such, the final chapter of this thesis consists of a compilation of conclusions from each chapter.

6.1.1 Chapter 2 Conclusion

A series of prodigiosene *F*-BODIPYs with varying substituents on the A, B and C rings have been synthesized. All *F*-BODIPYs **13-15** have absorption and emission maxima in the range of 530-579 nm and 543-600 nm, respectively. The Stokes shift of all C-ring-modified and A-ring-modified *F*-BODIPYs (**13a-k**, **14b** and **14f**) are in the range of 11-13 nm while the Stokes shift of B-ring-modified *F*-BODIPYs varied depending on the nature of the substituent. When compared to the unsubstituted *F*-BODIPY **13c** (bearing only a methoxy substituent on the B-ring), all C-ring modified *F*-BODIPYs are red shifted, up to 35 nm for **13b**. Variation of substituents on the B-ring (compared to **13b**) and A-ring (compared to **13b** and **13f**) result in corresponding red-shifts in absorption, alongside emission reaching maximum wavelengths of 600 nm. Complexes bearing electron withdrawing substituents on the B-ring exhibited the largest Stokes shifts of 24-25 nm, while complexes bearing electron donating groups on the B-ring displayed the smallest Stokes shifts of only 3-6 nm. Extending the conjugation of the prodigiosene *F*-BODIPY core via placement of an indole substituent in lieu of the A-ring (**14b** and 1**4f**) results in a red-shift in absorption (562 for 14b and 579 nm for 14f) and emission (574 for **14b** and 591 nm for **14f**) wavelength, with Stokes shift comparable to that of any C-ring substituent. Prodigiosene *F*-BOIPY **15p** exhibited interesting photophysical properties where the fluorescence was influenced by the polarizing nature of the solvent. In hexanes, **15p** displayed appreciable fluorescence, while in DCM the fluorescence was effectively quenched. Additionally, the small Stokes shift observed for **15p** could be enhanced when dissolved in polar solvents such as tetrahydrofuran, acetonitrile and methanol.

6.1.2 Chapter 3 Conclusion

This chapter describes the palladium-catalyzed decarboxylative arylation for heteroaryl-aryl C-C bond formation using substituted *N*-SEM pyrroles in stoichiometric amounts with aryl bromides. The influence of substituents about the pyrrole core, both electron-donating and electron-withdrawing, was investigated. The use of SEM as an *N*-protecting group enables both decarboxylative arylation and *N*-deprotection with select systems. Although SEM-deprotection of some electron-rich pyrroles was unsuccessful, the deprotection of pyrroles bearing a mixture of alkyl- and H-substitution, as well as acyl or pendant carbonyl functionality, proceeded well. Certainly, the fickle nature of pyrroles as regards to (de)protection means that protection strategies must be selected with care. Nevertheless, for certain systems, the use of *N*-SEM pyrroles provides a useful alternative when deprotection is required following decarboxylative arylation.

6.1.3 Chapter 4 Conclusion

The work presented in this chapter describes the total synthesis of prodigiosenes bearing modified B-rings containing aryl and alkyl thioethers. This builds upon previous work in this area involving the synthesis of B-ring modified prodigiosenes with aryl ethers (not alkyl ethers). Prior to developing methodology to synthesize thio-substituted prodigiosenes, first the reaction conditions, and purification procedures were optimized to achieve maximal availability of starting materials for the synthesis. With starting materials in hand, the N-Boc tosylpyrrolinone underwent successful introduction of aryl- and methyl-thioether functionalities to produce five new thio-substituted pyrrolinones **47a-e**. Following N-Boc deprotection, pyrrolinones **47a-e** were successfully condensed with aldehyde **36c** to give dipyrrinones **48c** and **54a-d**. Additionally, the pyrrolinone **47a** with an -SPh substituent was reacted with other 2-formyl pyrroles to explore the feasibility of dipyrrinone formation with various C-ring substituents. All dipyrrinones **48a-e** and **54a-d** were successfully transformed into their respective bromo-dipyrrins **49a-e** and **55a-d** in moderate yields via reaction with $POBr_3$, except for substrate **48a** bearing an acyl group in the 3-position. This dipyrrinone was isolated in only 30% yield from a mixture that contained compound **50a** and the alkyne **50b**. Utilizing traditional Suzuki-Miyaura cross-coupling conditions, all bromo-dipyrrins (except **55c**) were coupled with 2-formyl pyrroles

to give N-Boc or N-H prodigiosenes that were isolated as their HCl salts. In total, five new prodigiosenes bearing aryl and alkyl thioethers on the B-ring were synthesized (Figure 53).

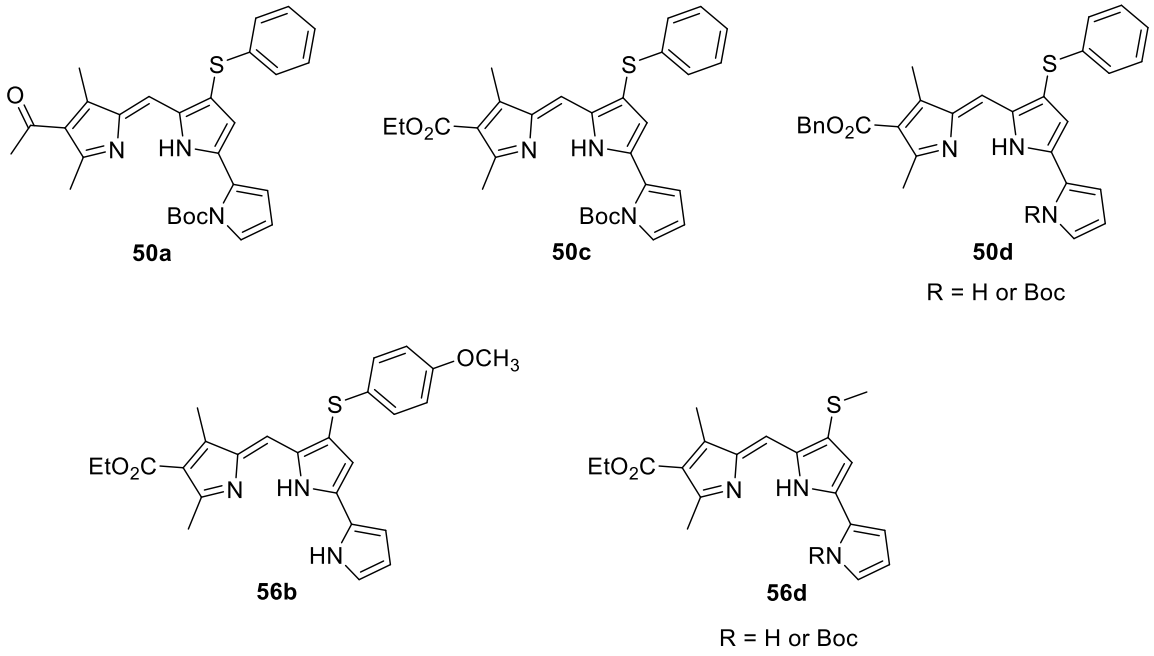


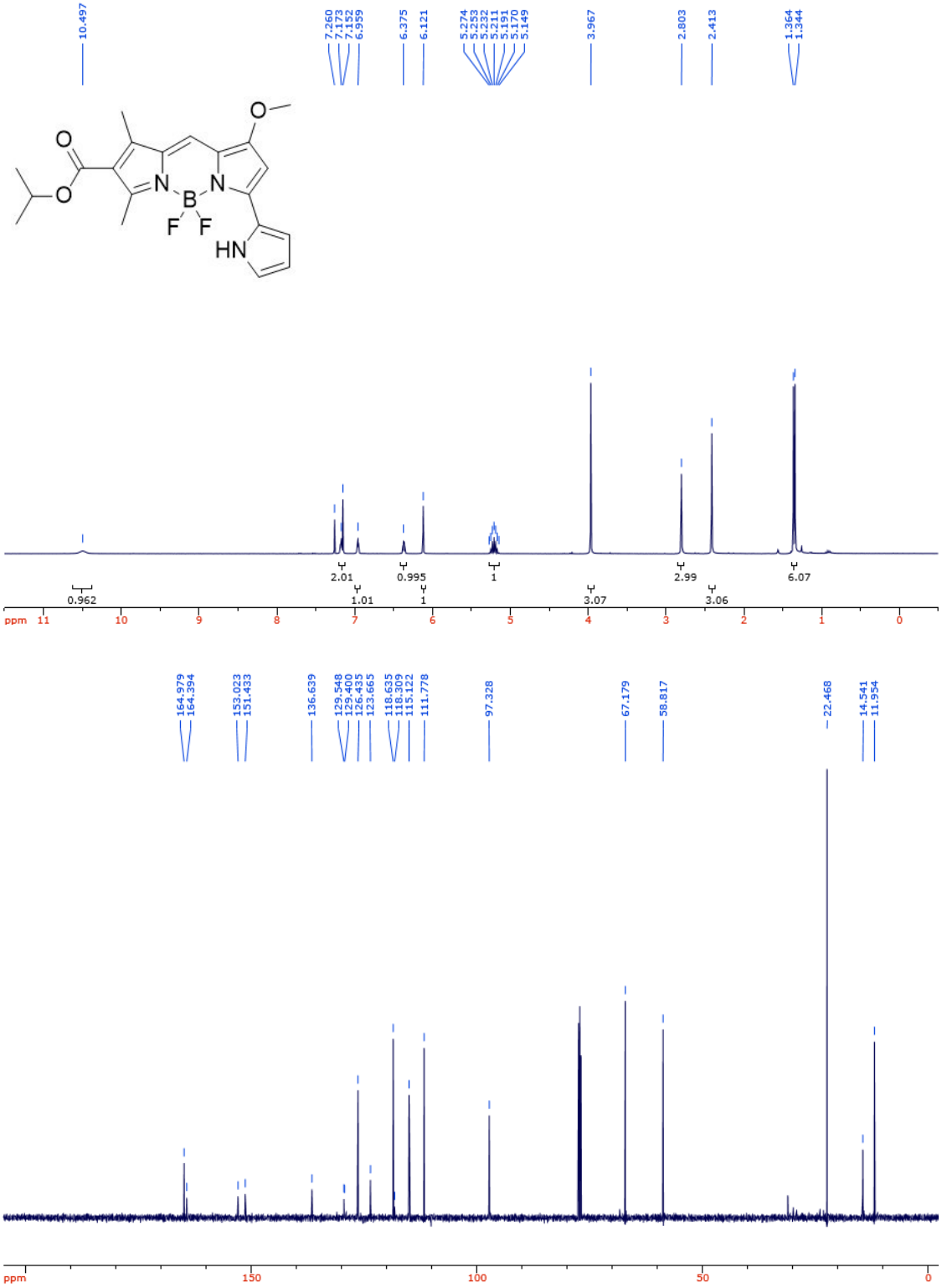
Figure 54. S-prodigiosenes synthesized in this work

Introducing sulfur to the prodigiosene scaffold imparts new electronic properties, as evident by the different reactivity observed in synthesizing S-prodigiosenes compared to O-prodigiosenes. As such, future work will involve evaluation of these compounds in terms of pKa determination and anion transport assays. Additionally, compounds will be submitted to the National Cancer Institute for testing against various human cancer cell lines.

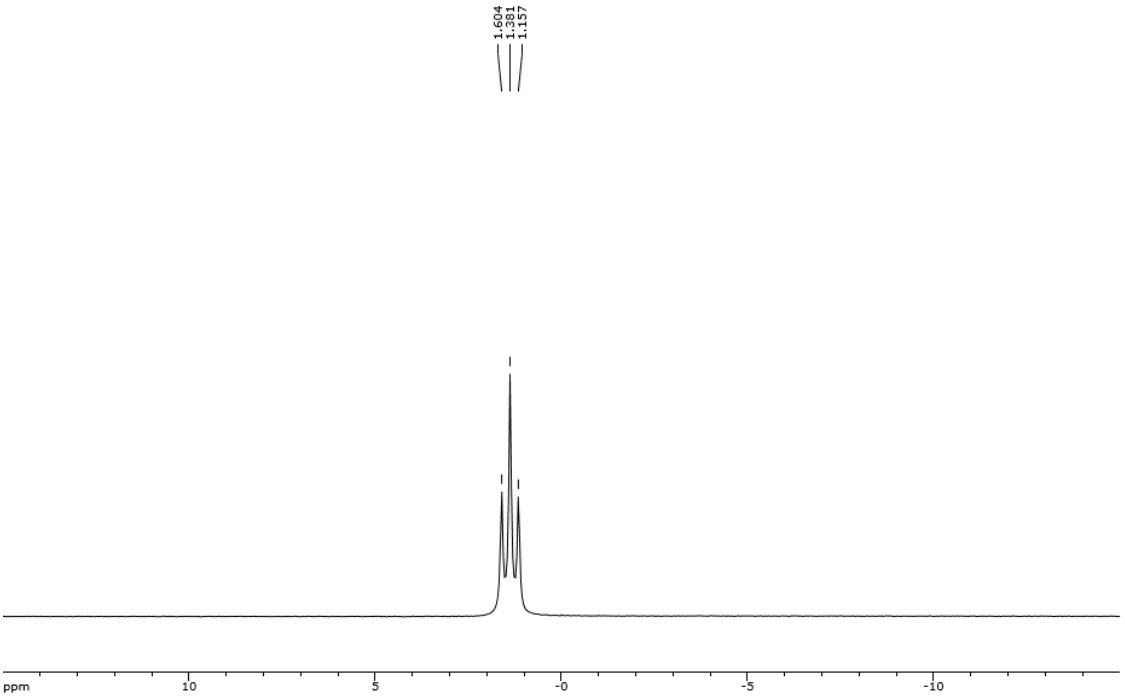
Appendix

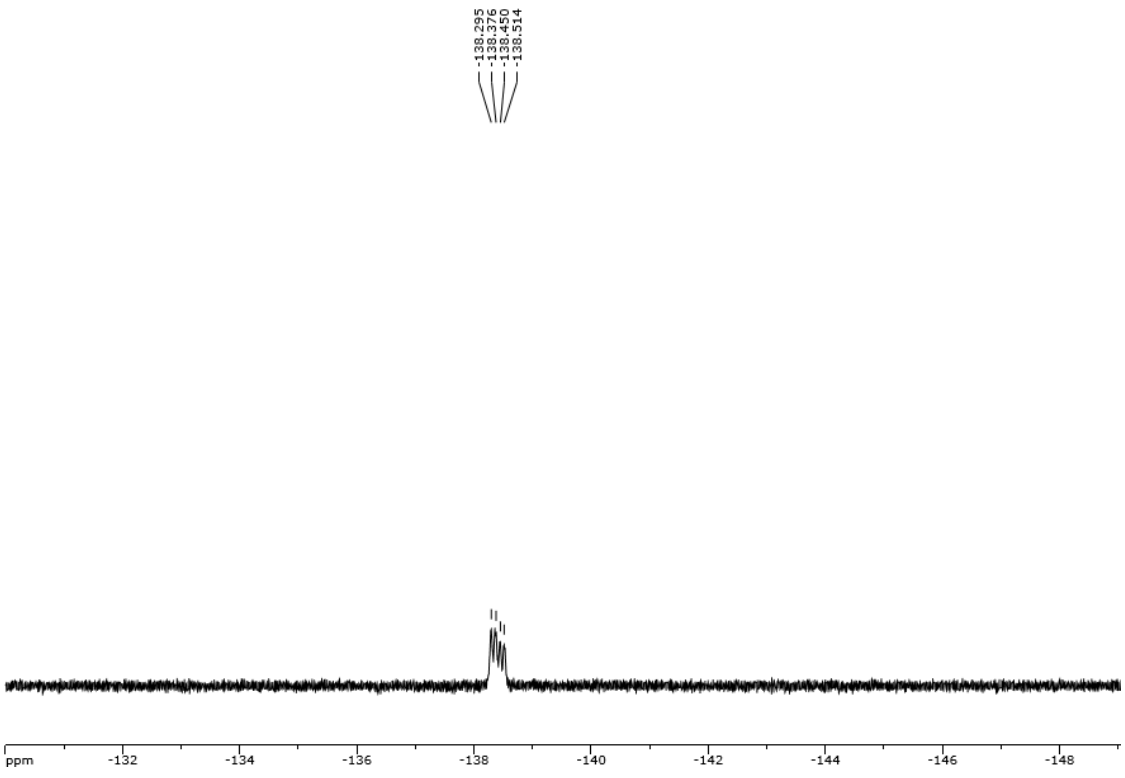
NMR Spectra of *F*-BODIPYs 13-15

^{1}H and ^{13}C-NMR of 13a in $CDCl_3$:

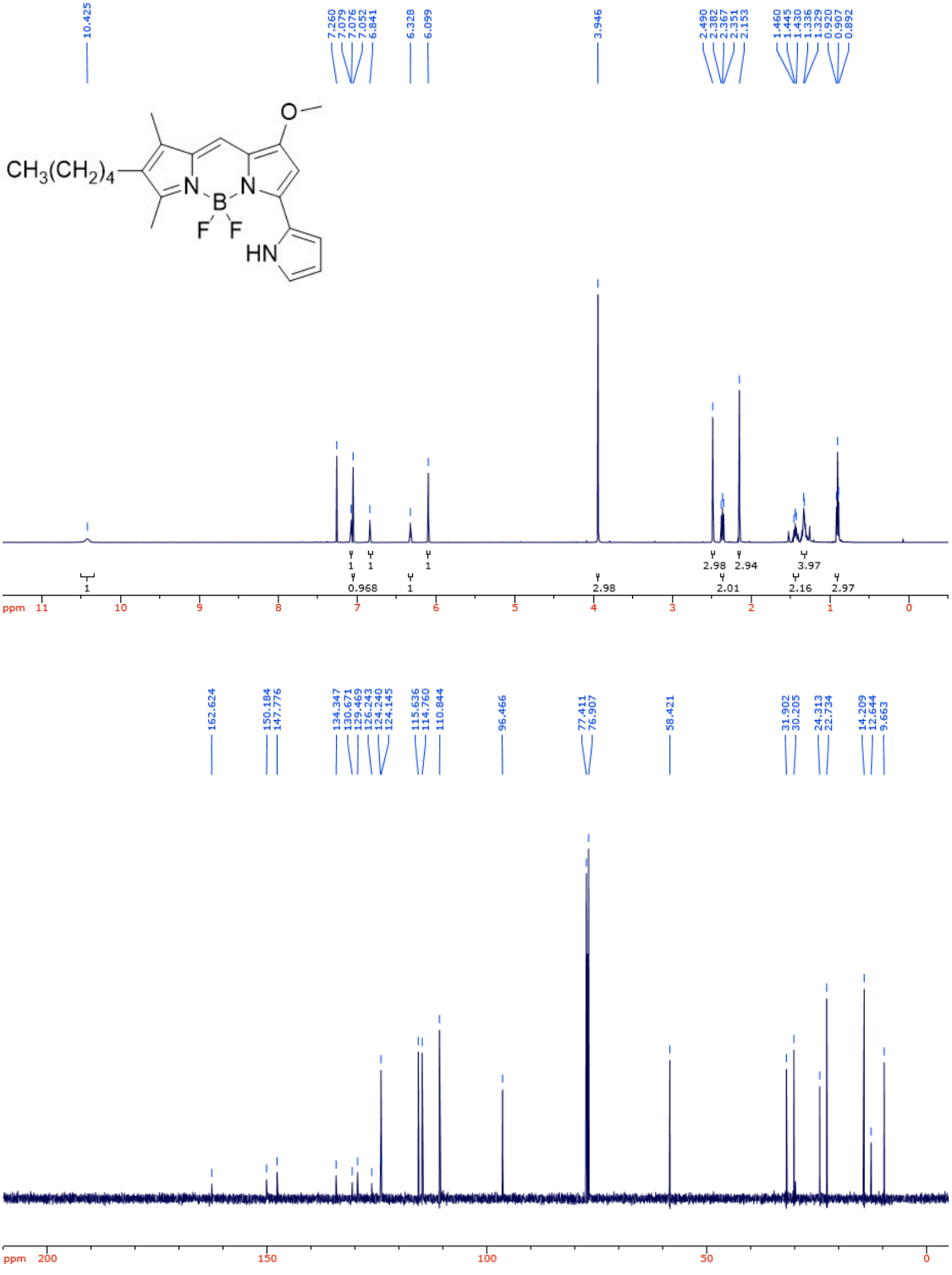


^{11}B and ^{19}F-NMR of 13a in $CDCl_3$:

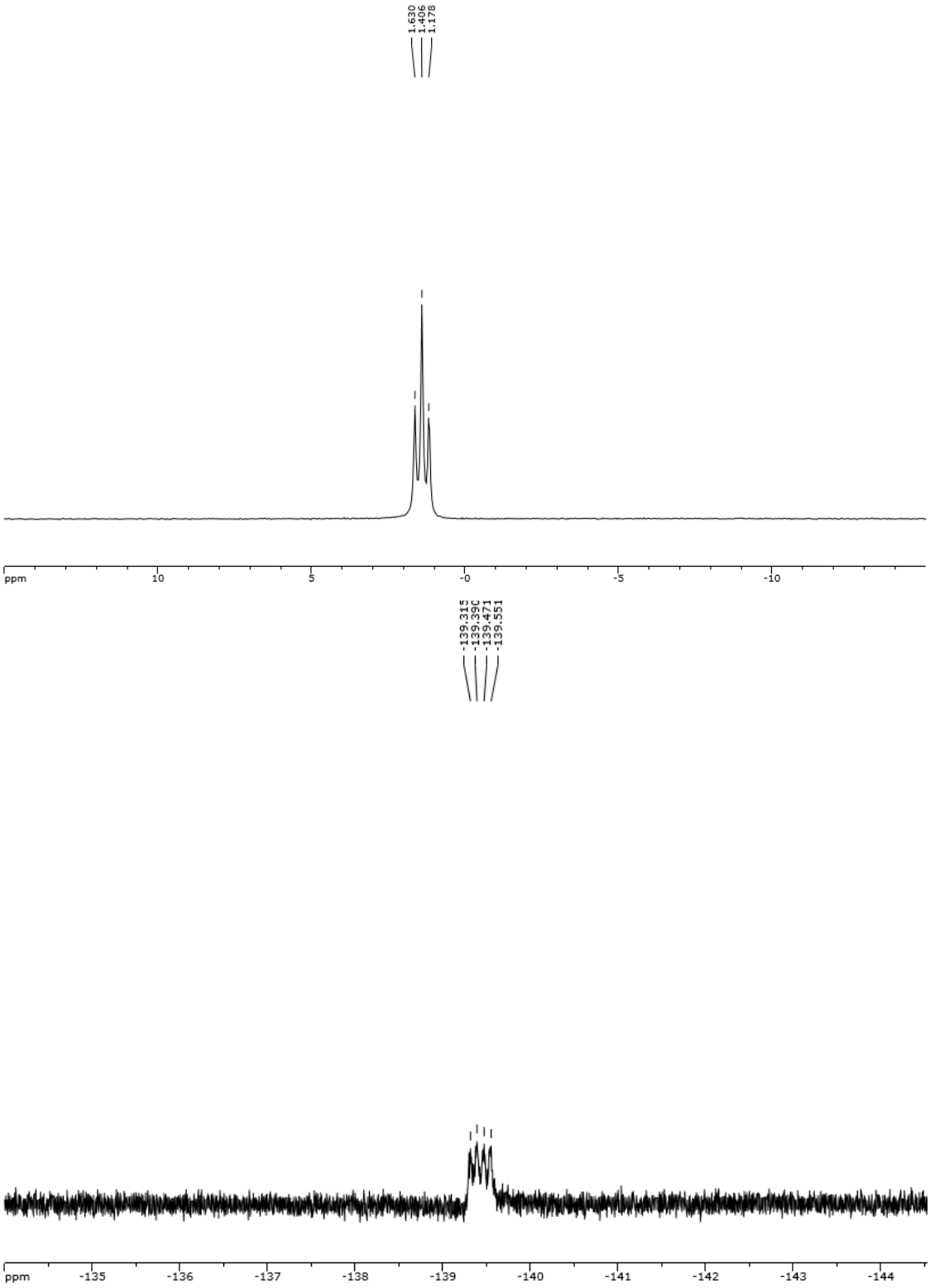




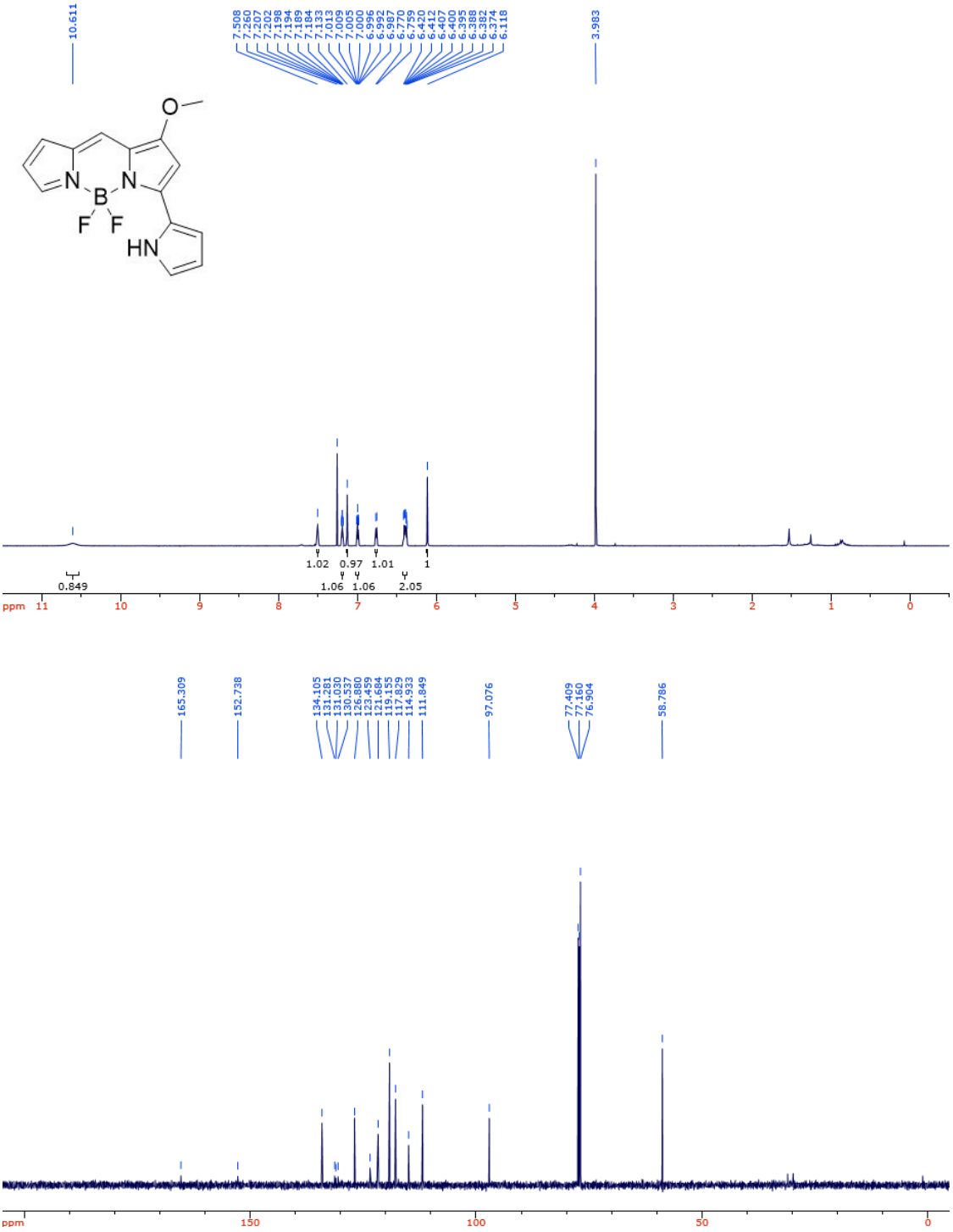
^{1}H and ^{13}C-NMR of 13b in $CDCl_3$:



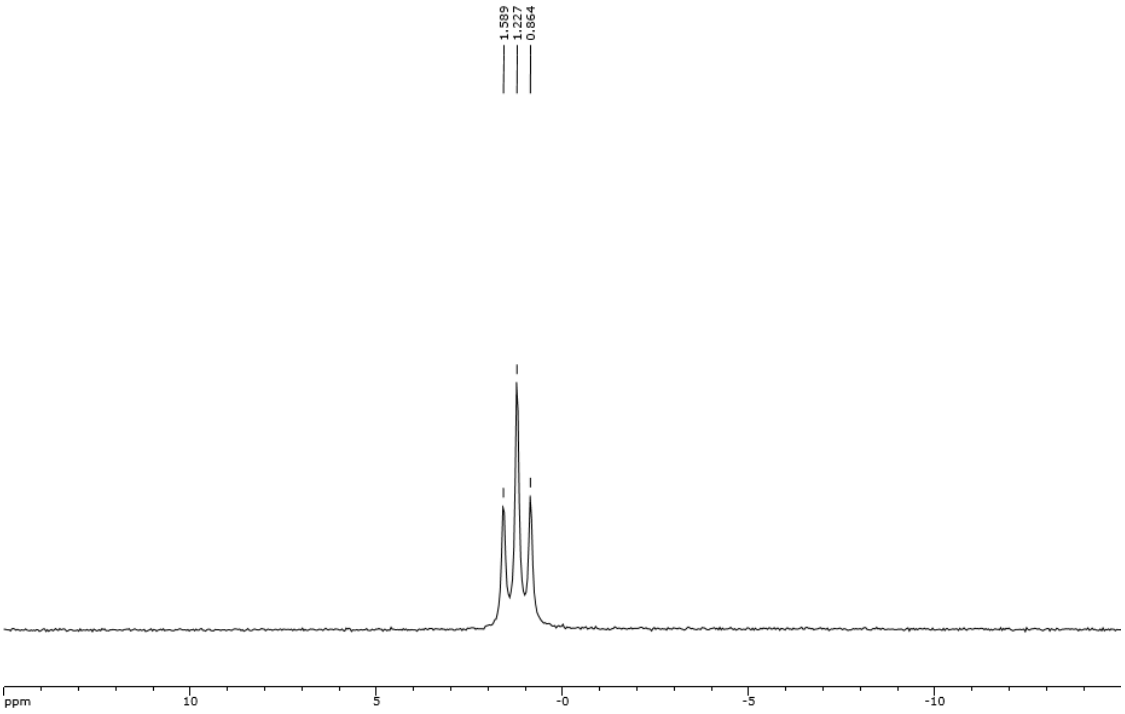
^{11}B and ^{19}F-NMR of 13b in $CDCl_3$:

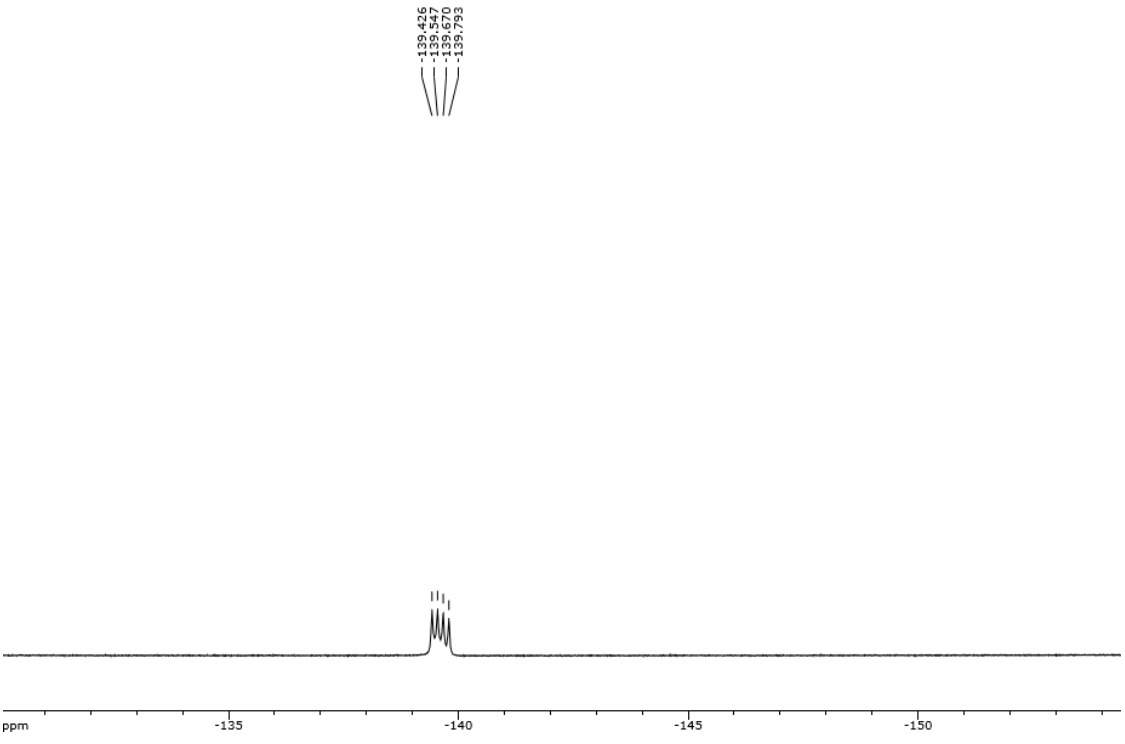


^{1}H and ^{13}C-NMR of 13c in $CDCl_3$:

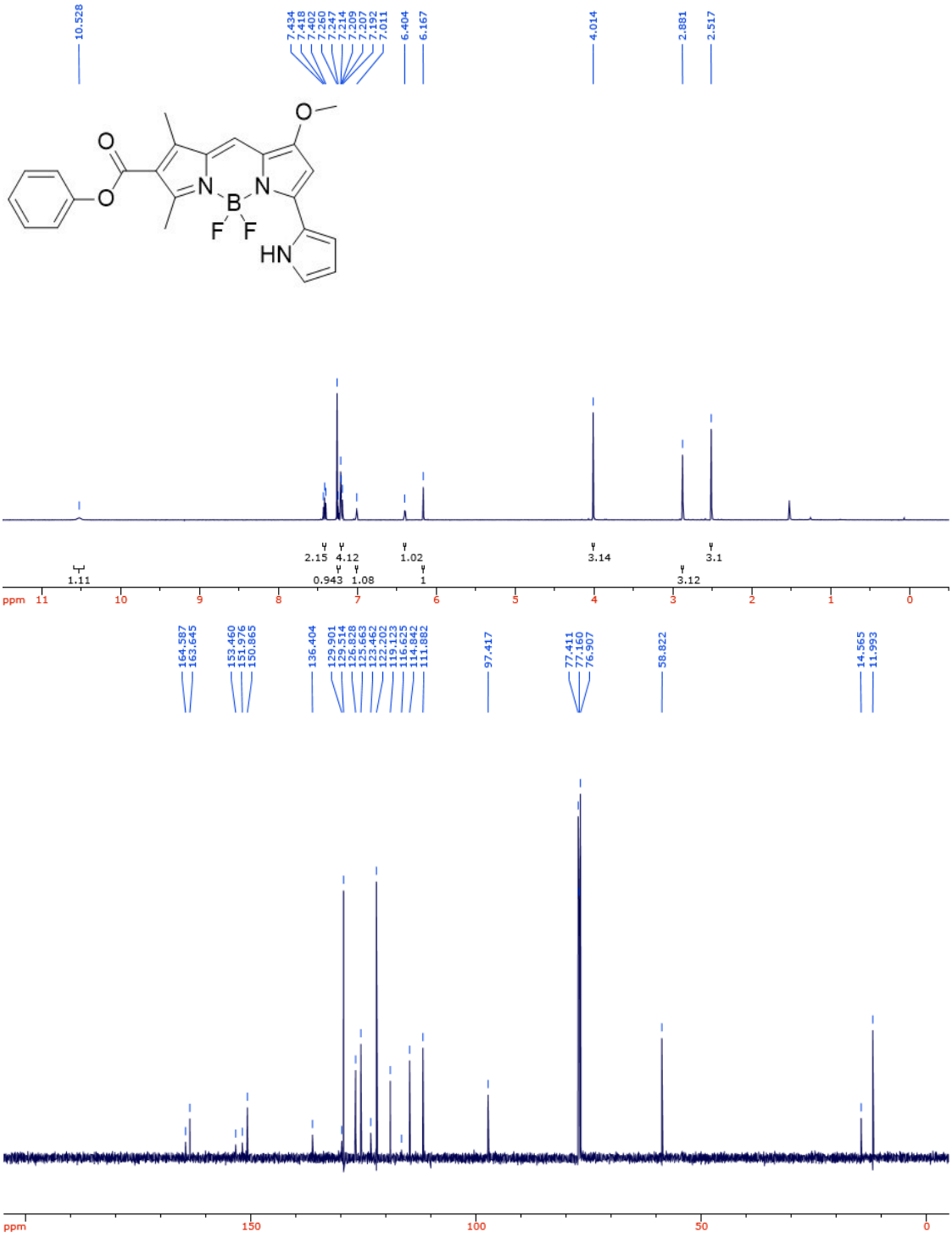


^{11}B and ^{19}F-NMR of 13c in $CDCl_3$:

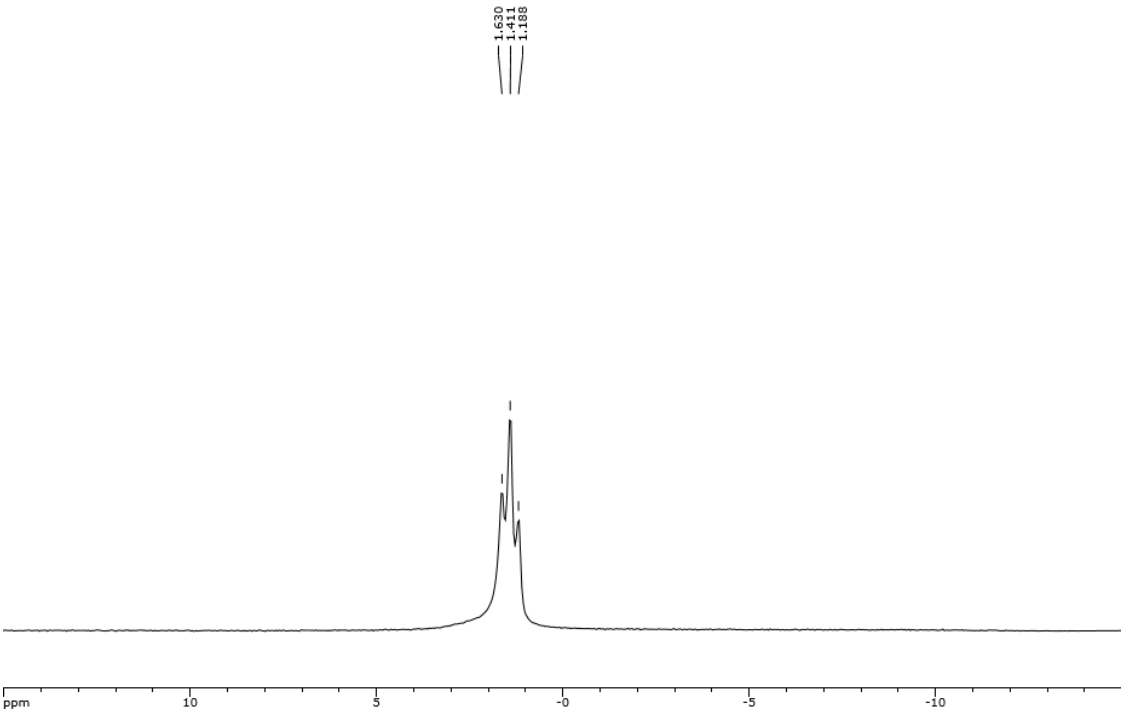


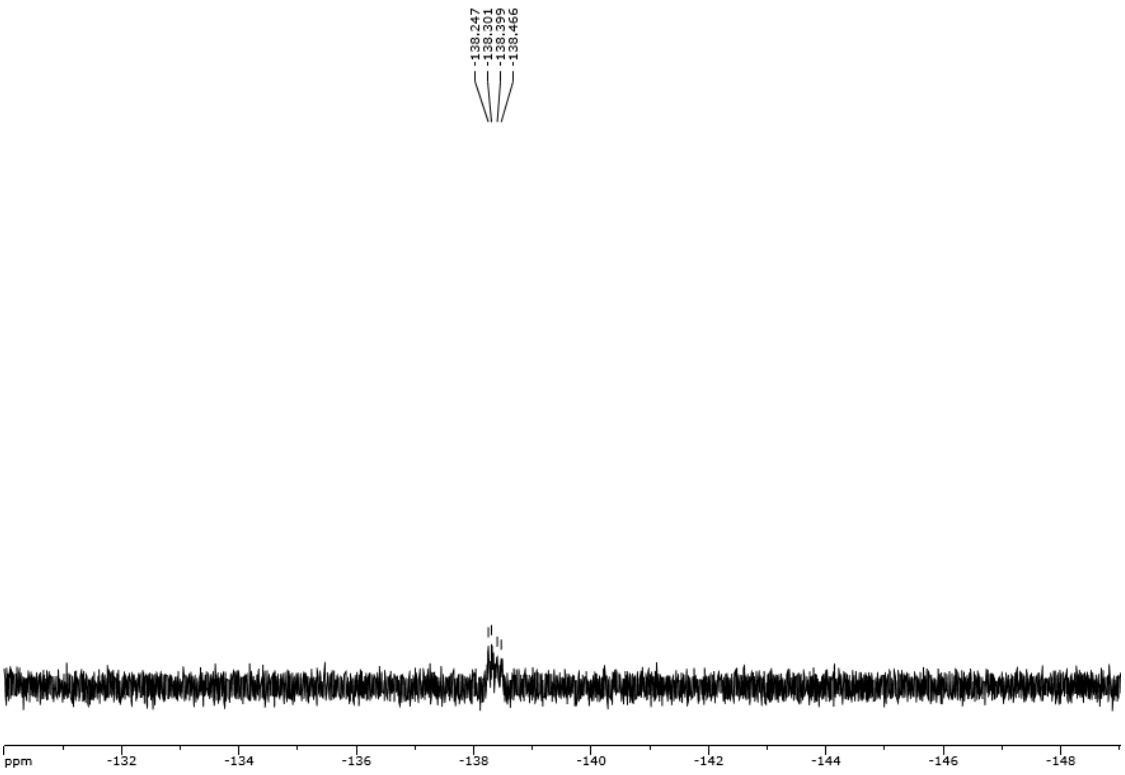


^{1}H and ^{13}C-NMR of 13e in $CDCl_3$:

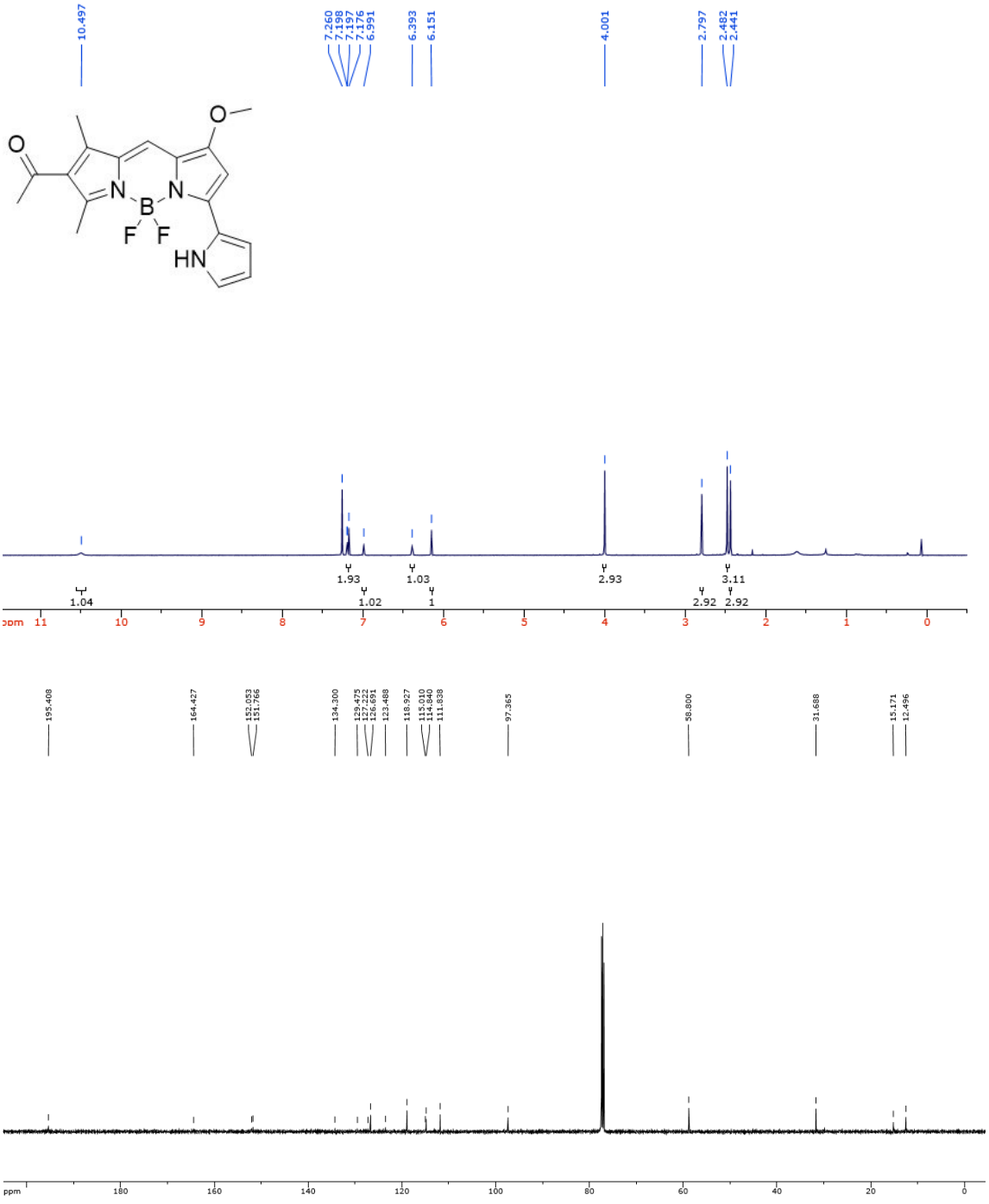


^{11}B and ^{19}F-NMR of 13e in $CDCl_3$:

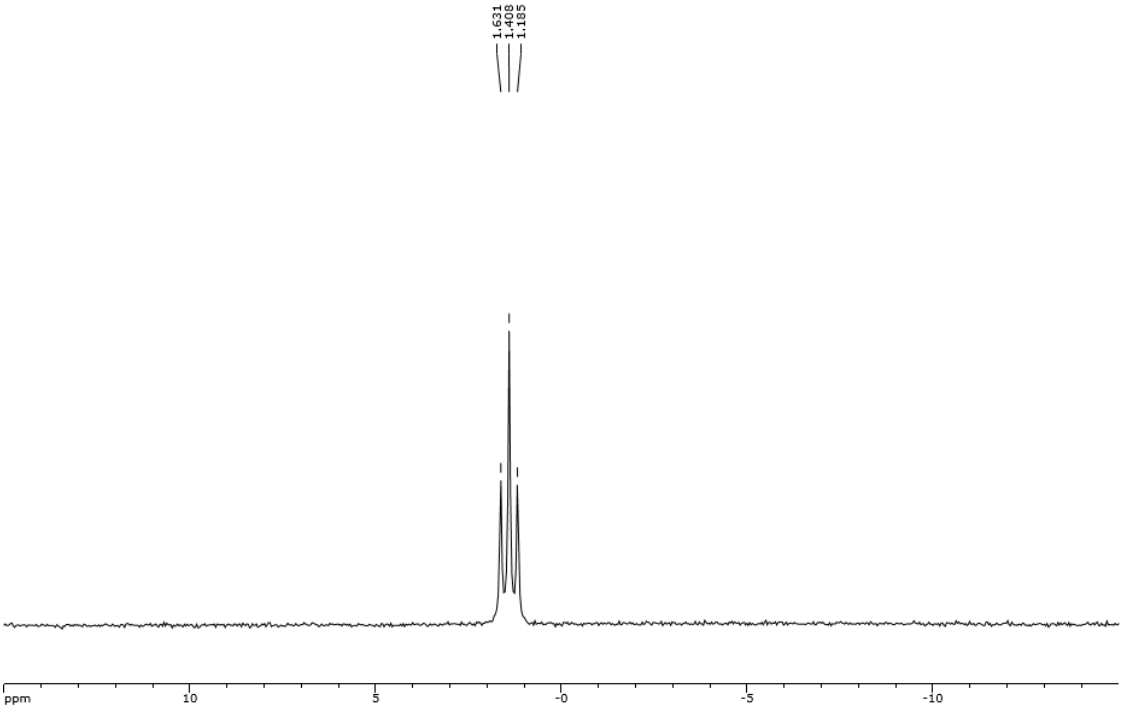


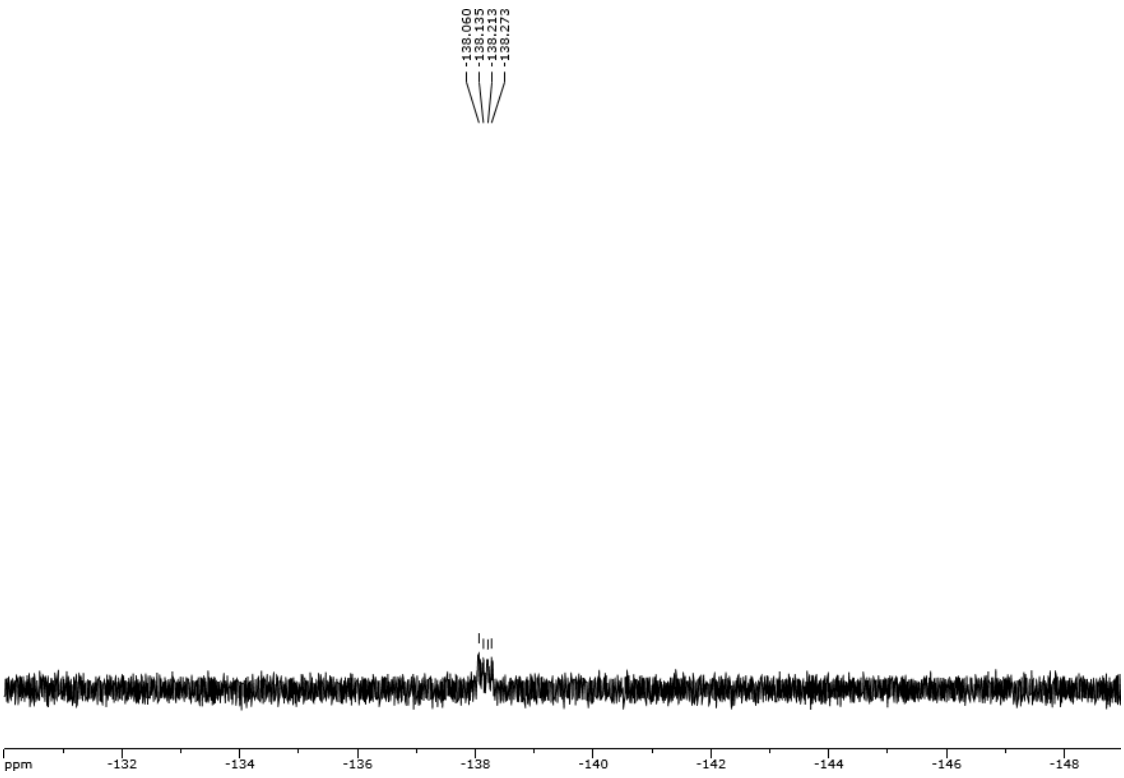


^{1}H and ^{13}C-NMR of 13g in $CDCl_3$:

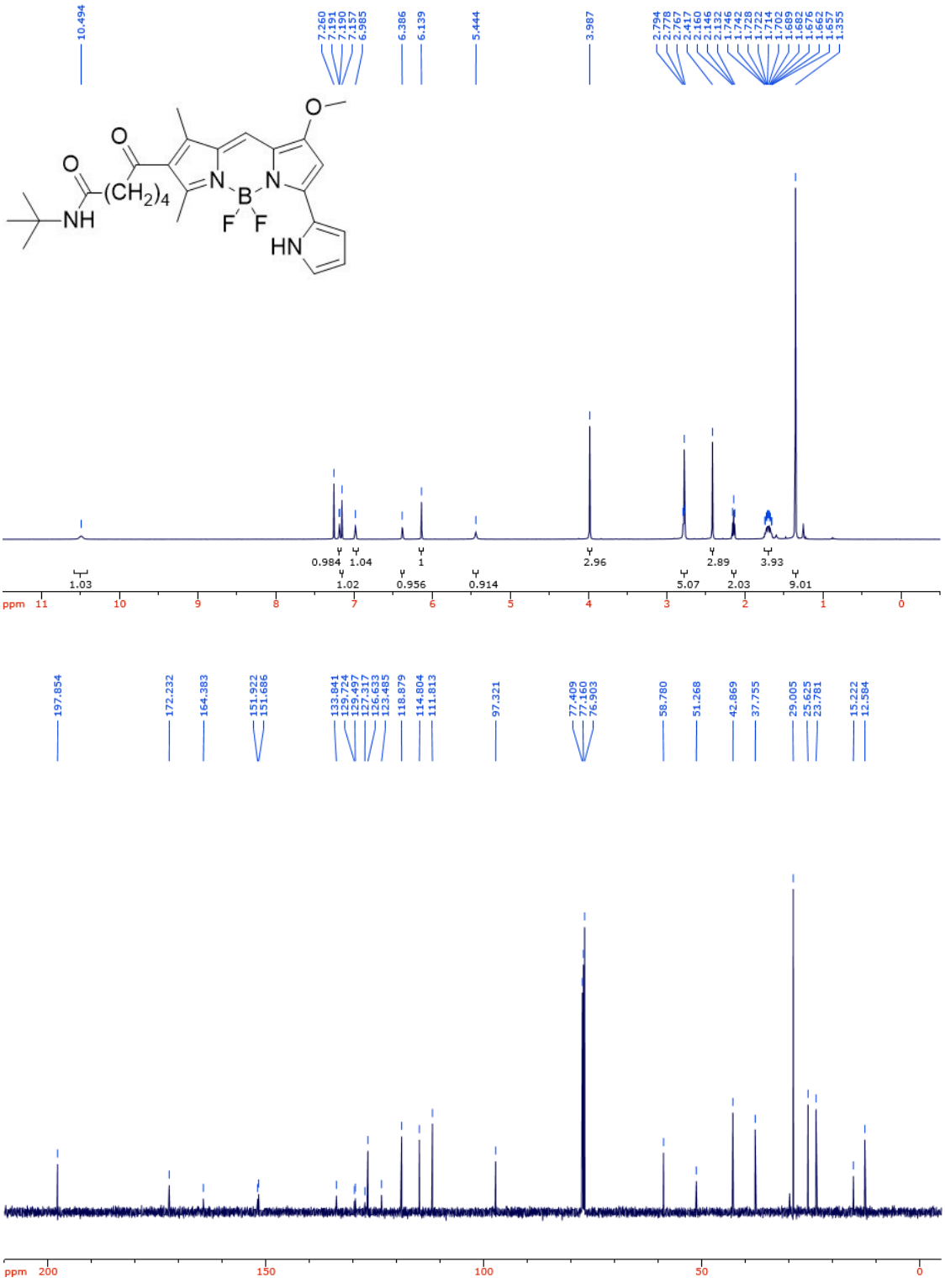


^{11}B and ^{19}F-NMR of 13g in $CDCl_3$:

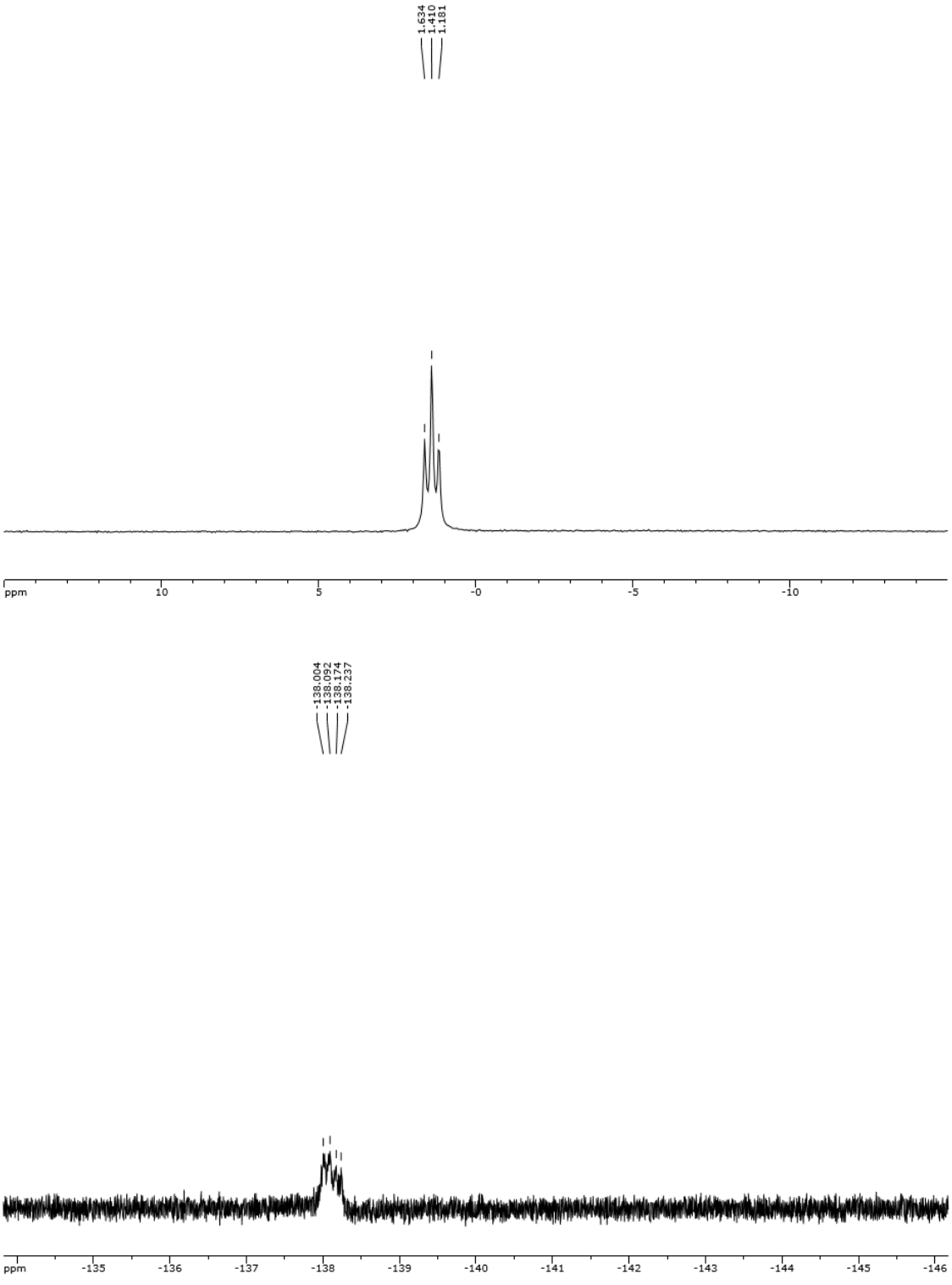




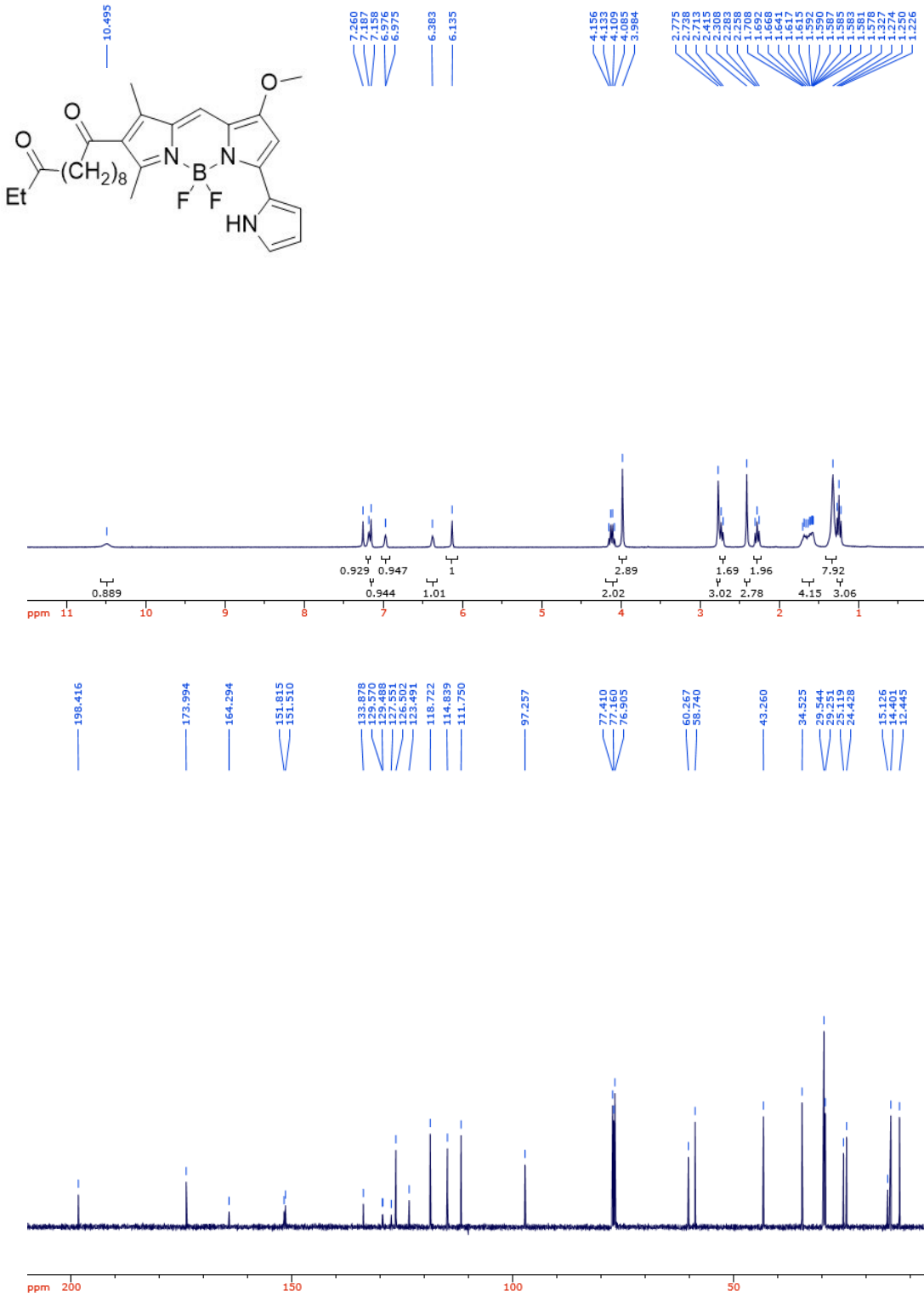
^{1}H and ^{13}C-NMR of 13h in $CDCl_3$:



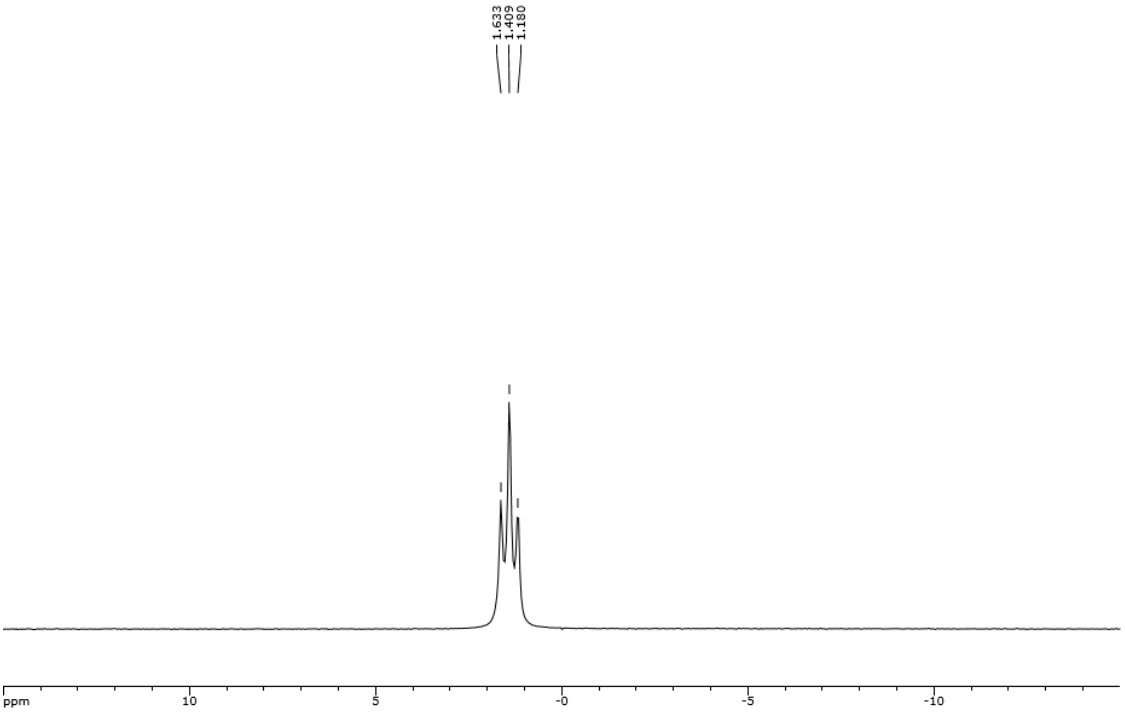
^{11}B and ^{19}F-NMR of 13h in $CDCl_3$:

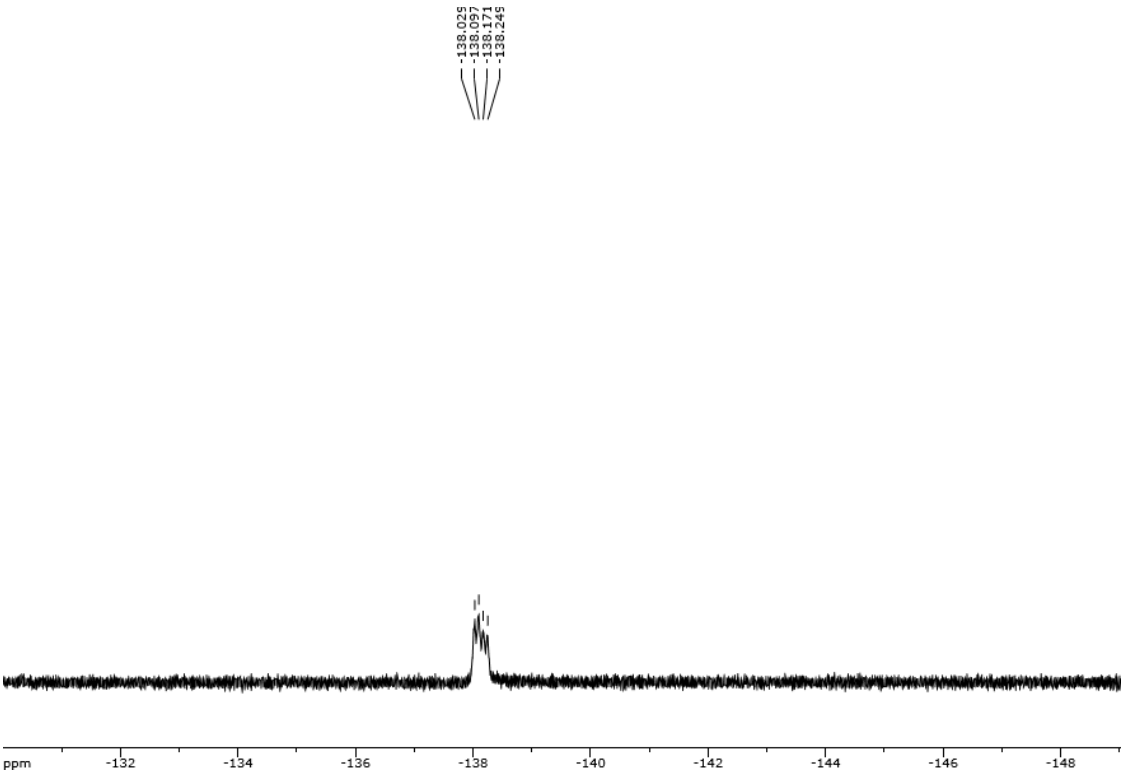


^{1}H and ^{13}C-NMR of 13i in $CDCl_3$:

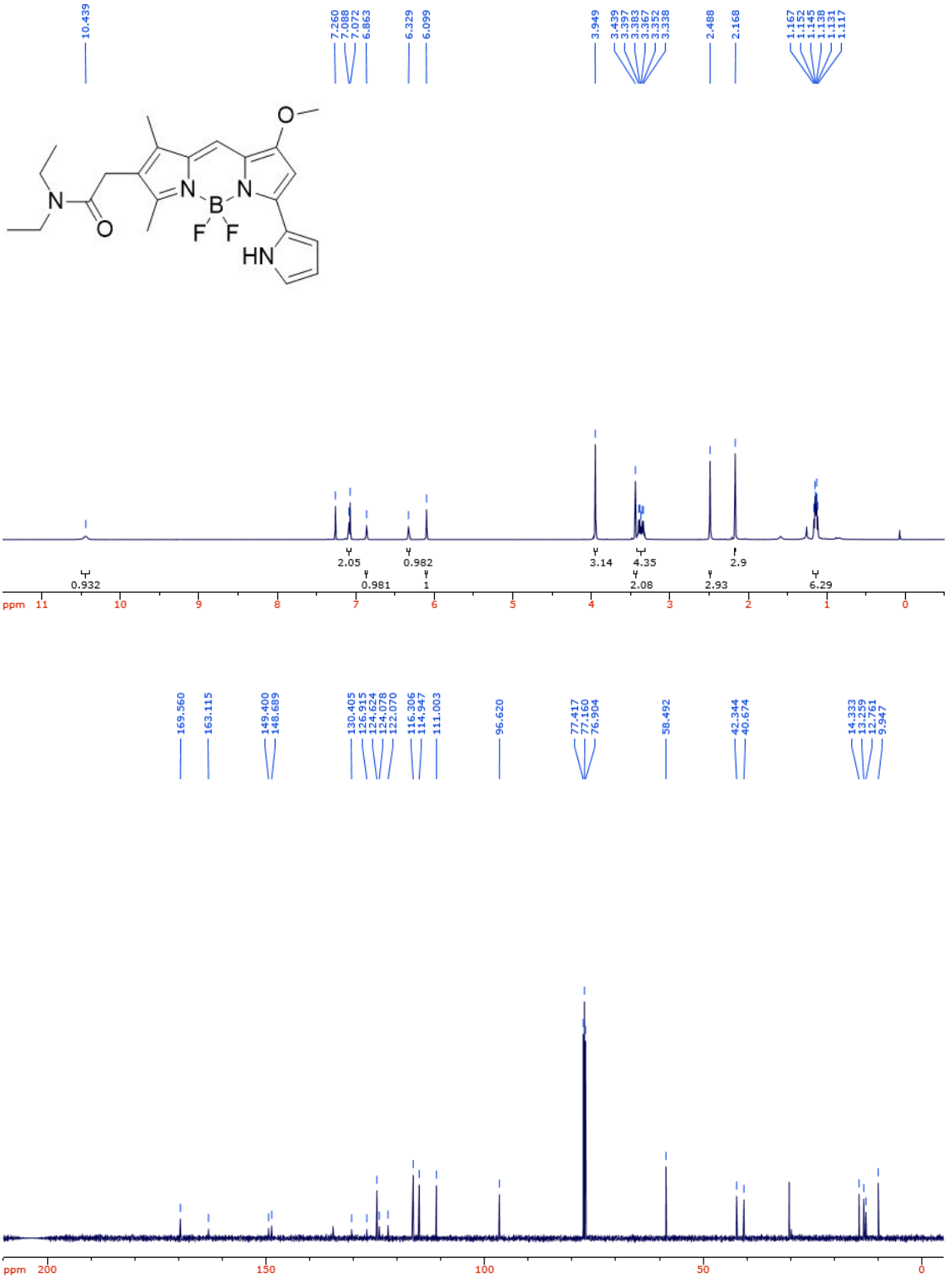


^{11}B and ^{19}F-NMR of 13i in $CDCl_3$:

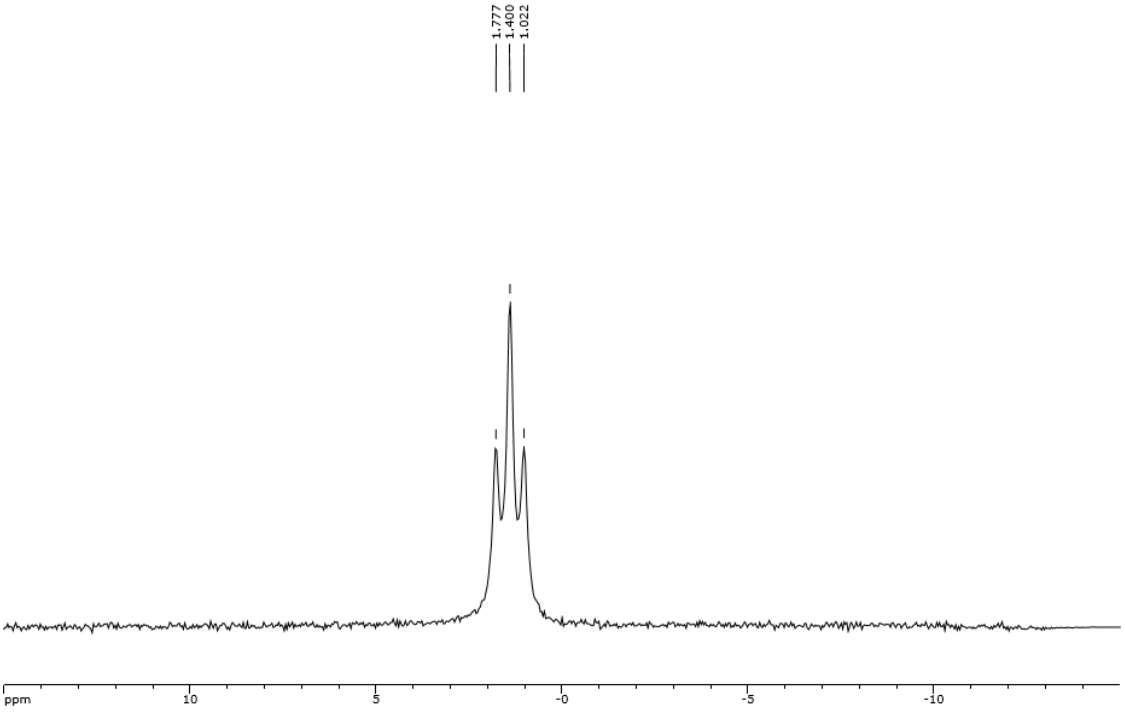


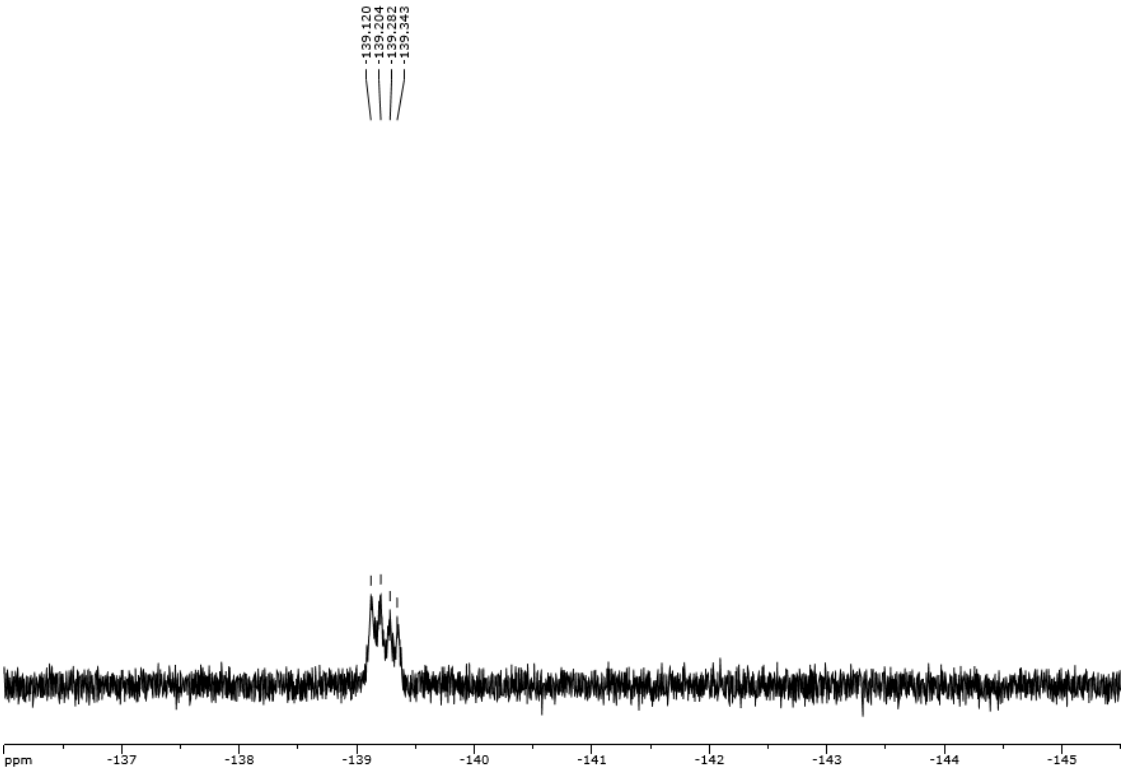


^{1}H and ^{13}C-NMR of 13j in $CDCl_3$:

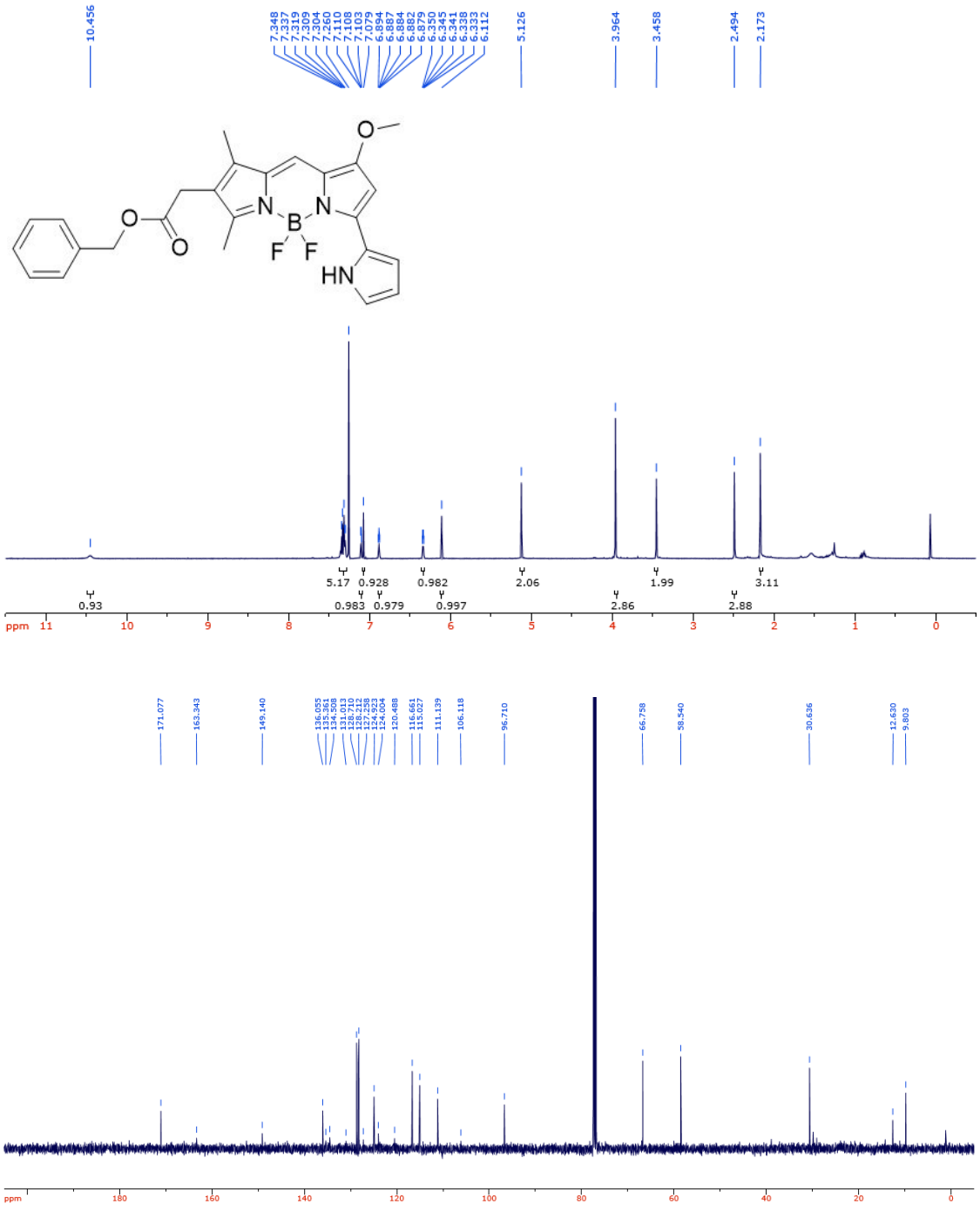


^{11}B and ^{19}F-NMR of 13j in $CDCl_3$:

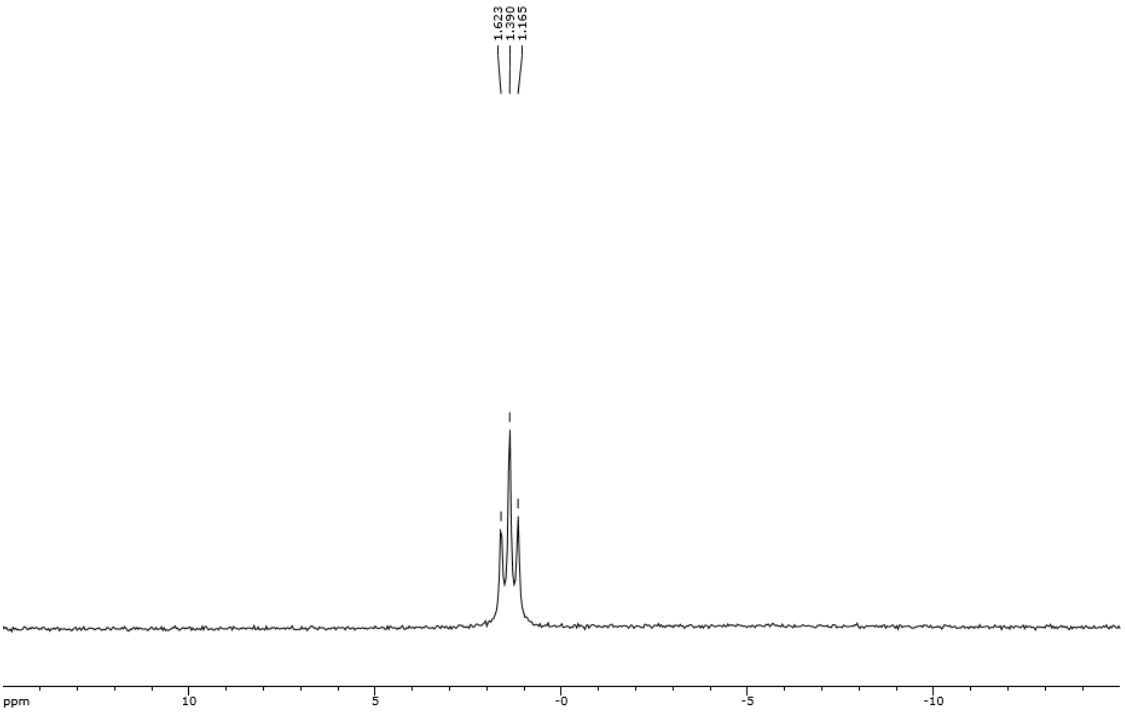


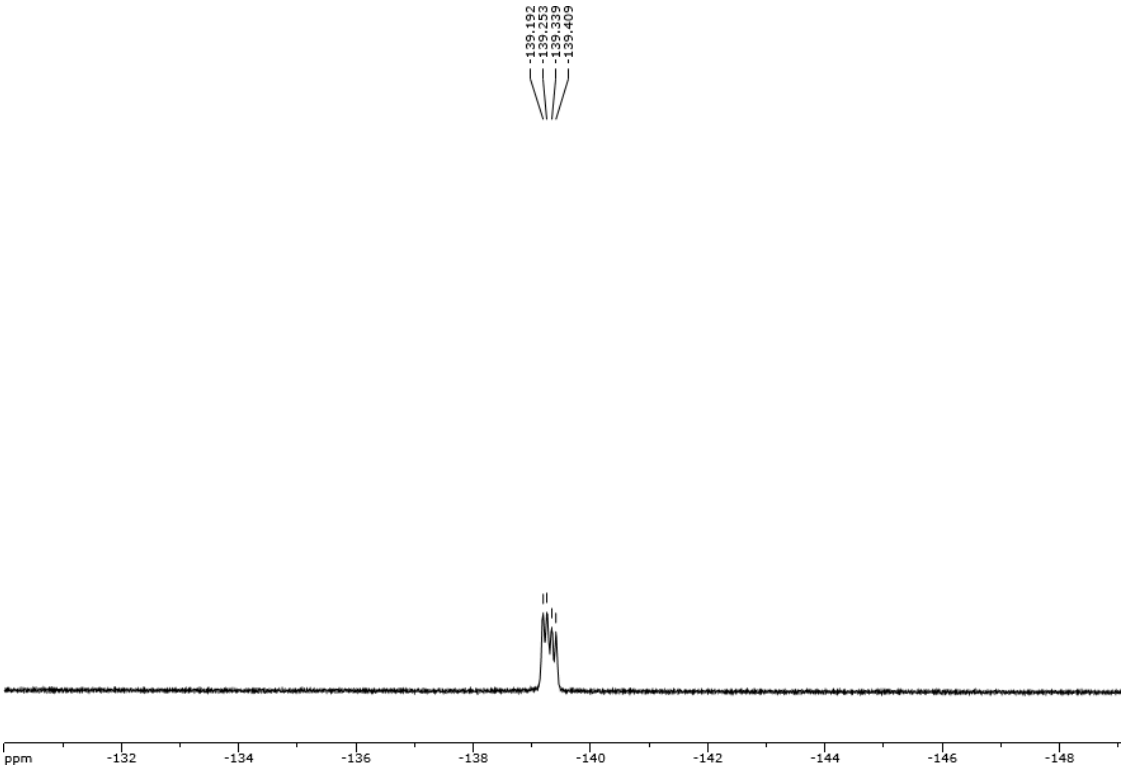


^{1}H and ^{13}C-NMR of 13k in $CDCl_3$:

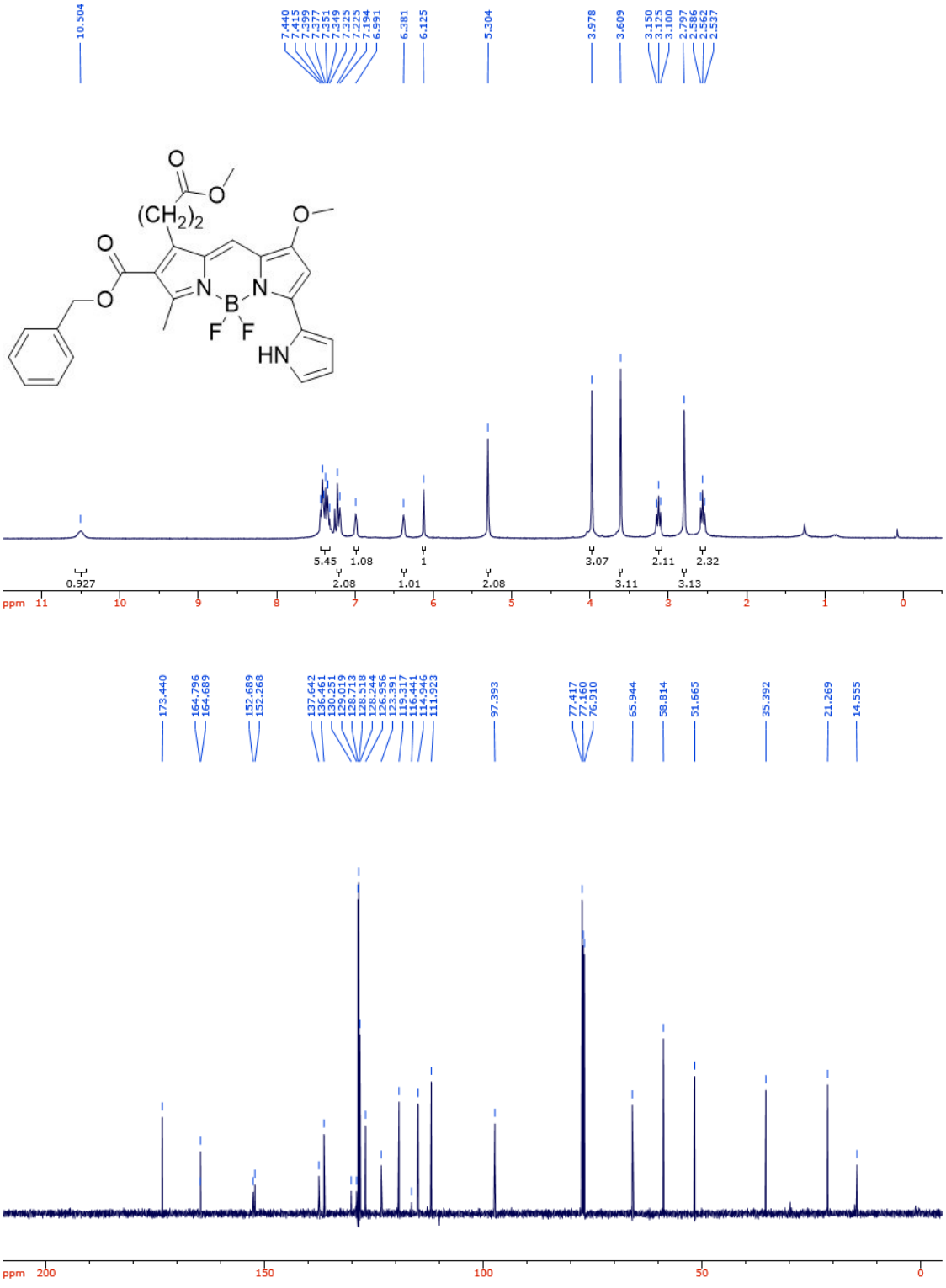


^{11}B and ^{19}F-NMR of 13k in $CDCl_3$:

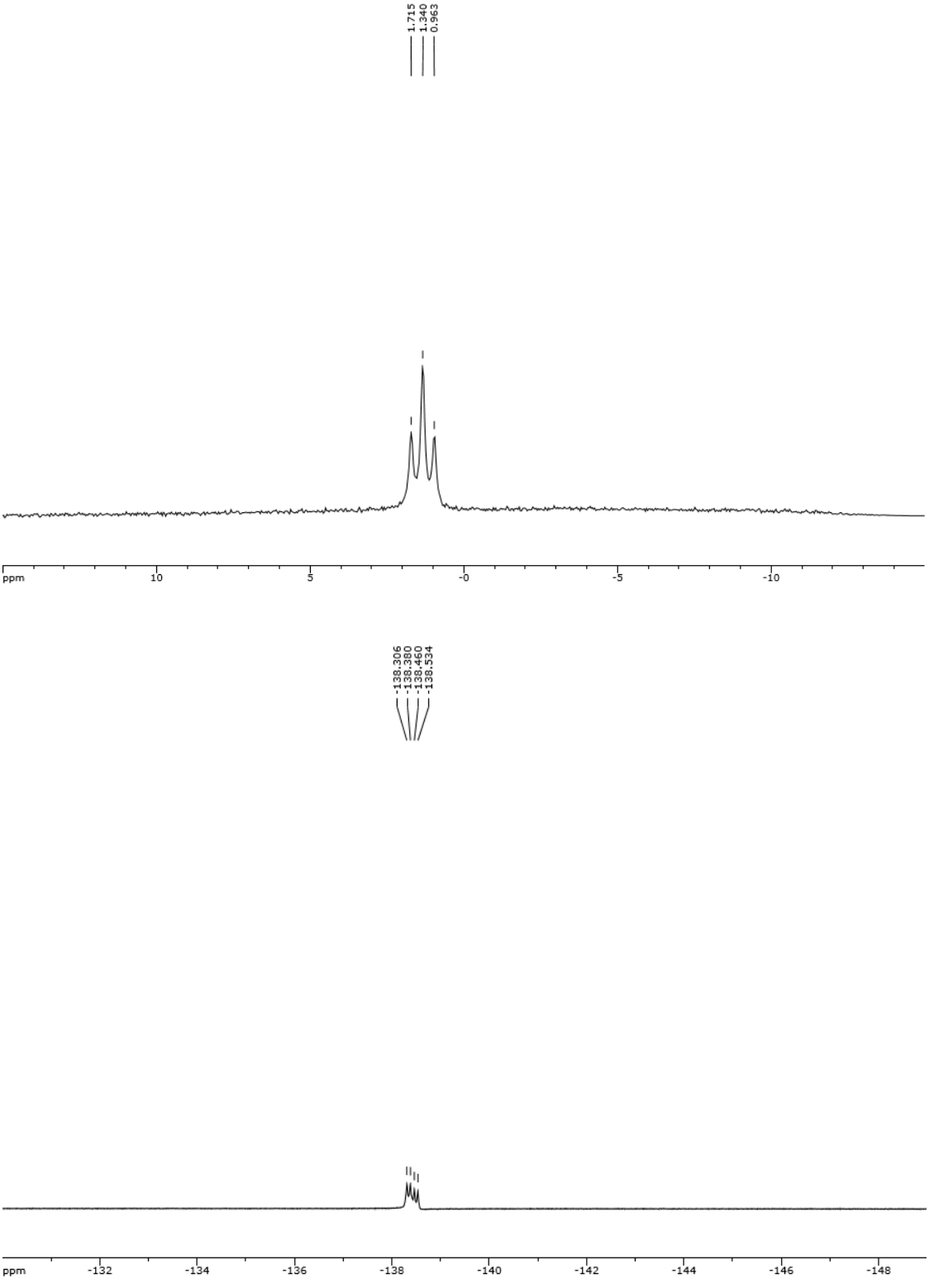




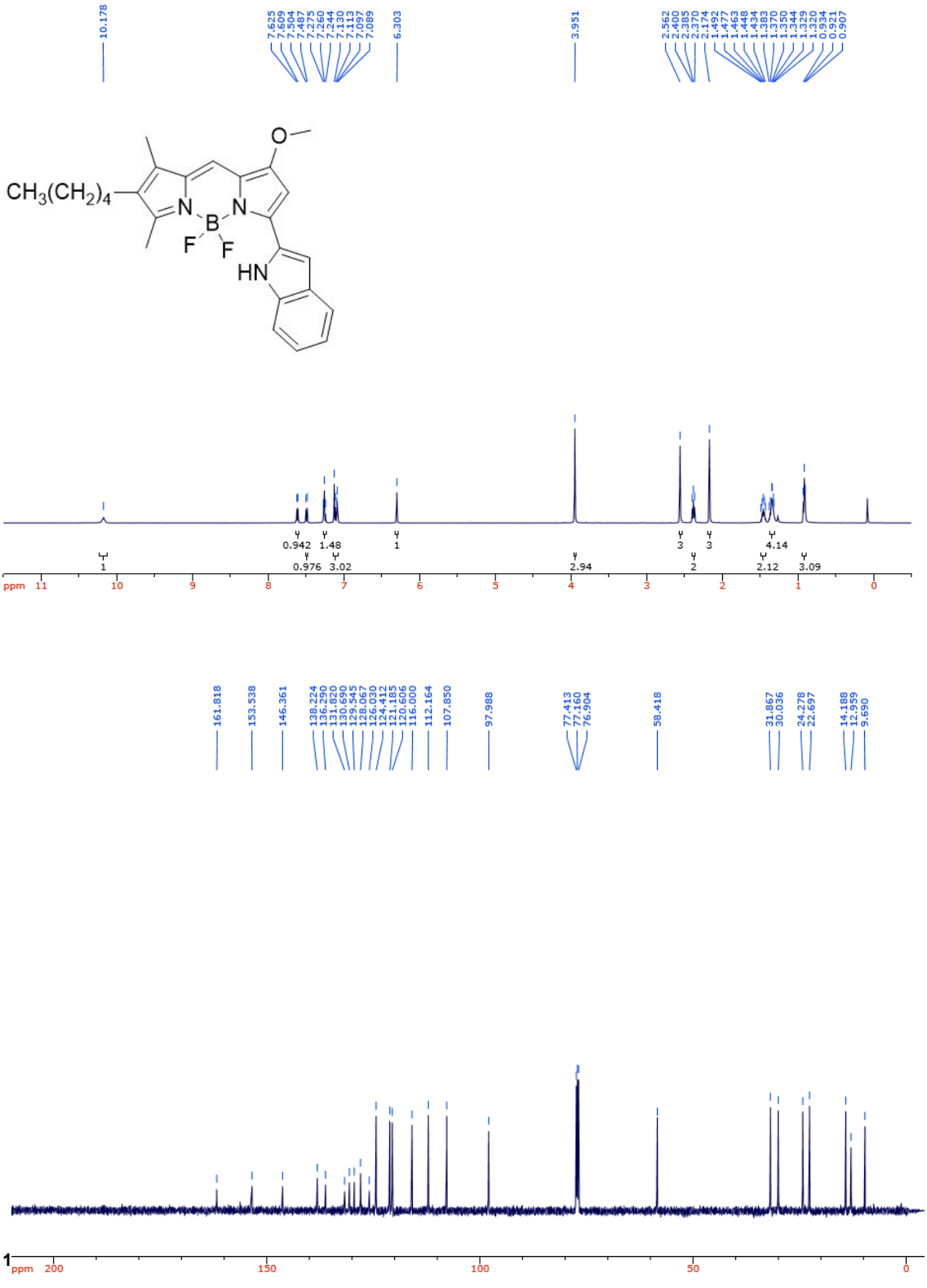
^{1}H and ^{13}C-NMR of 13l in $CDCl_3$:



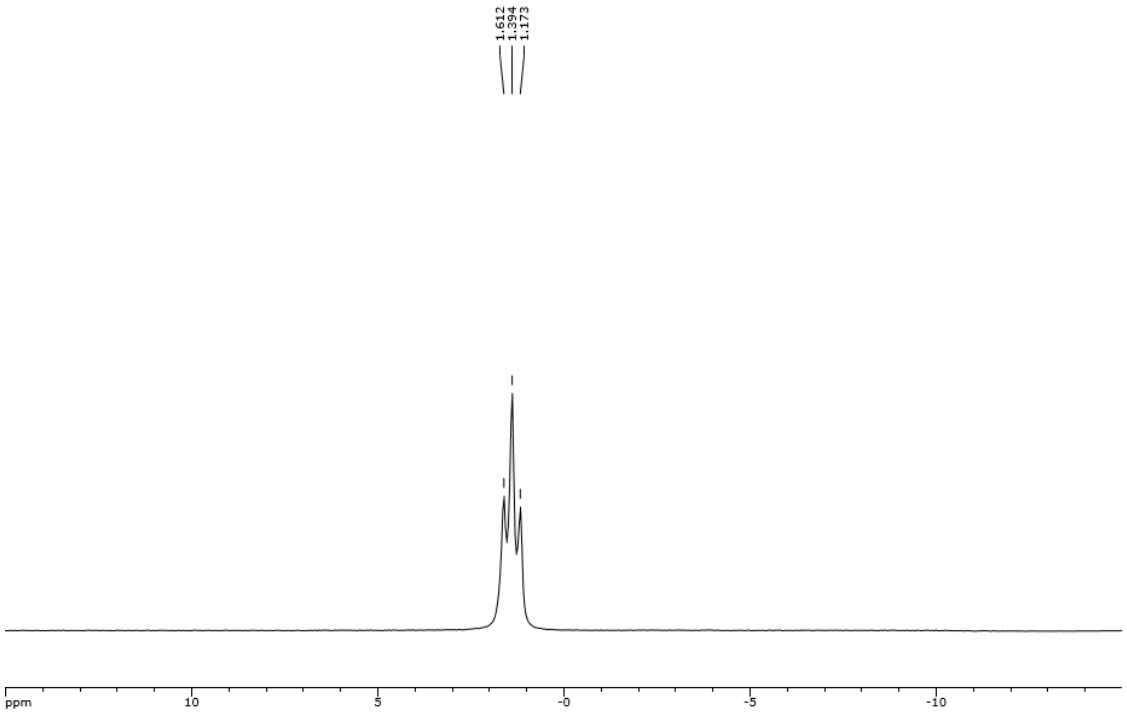
^{11}B and ^{19}F-NMR of 13l in $CDCl_3$:

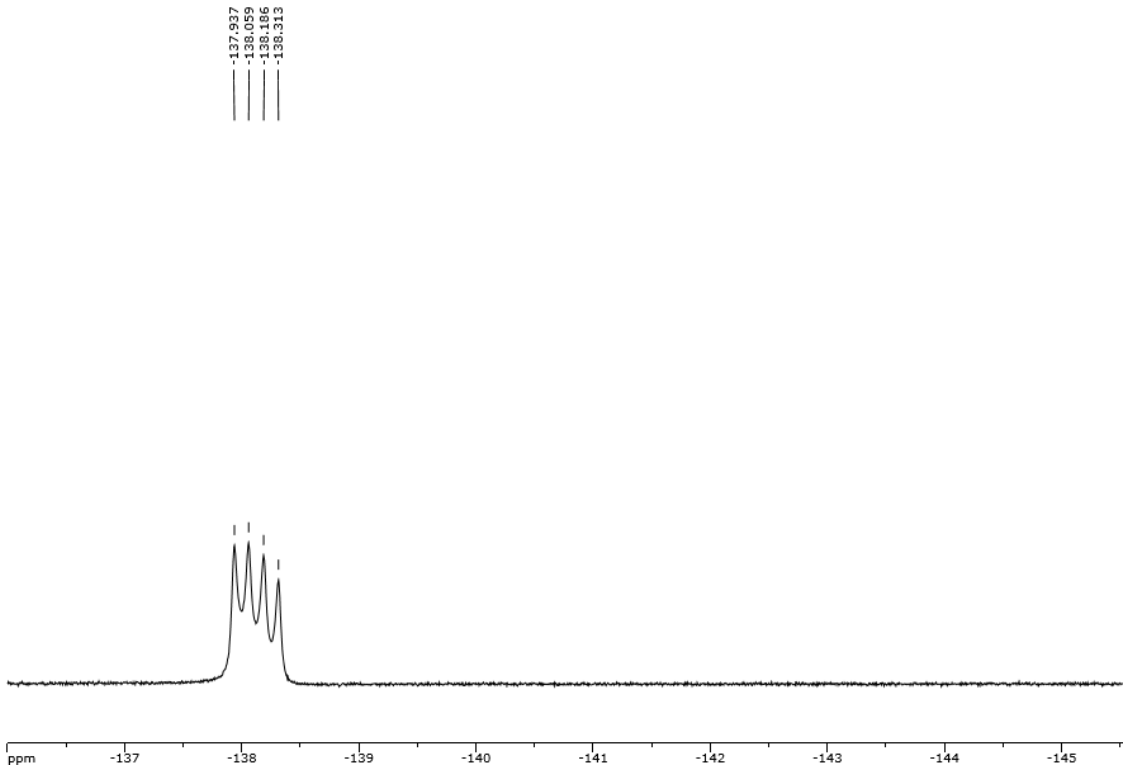


^{1}H and ^{13}C-NMR of 14b in $CDCl_3$:

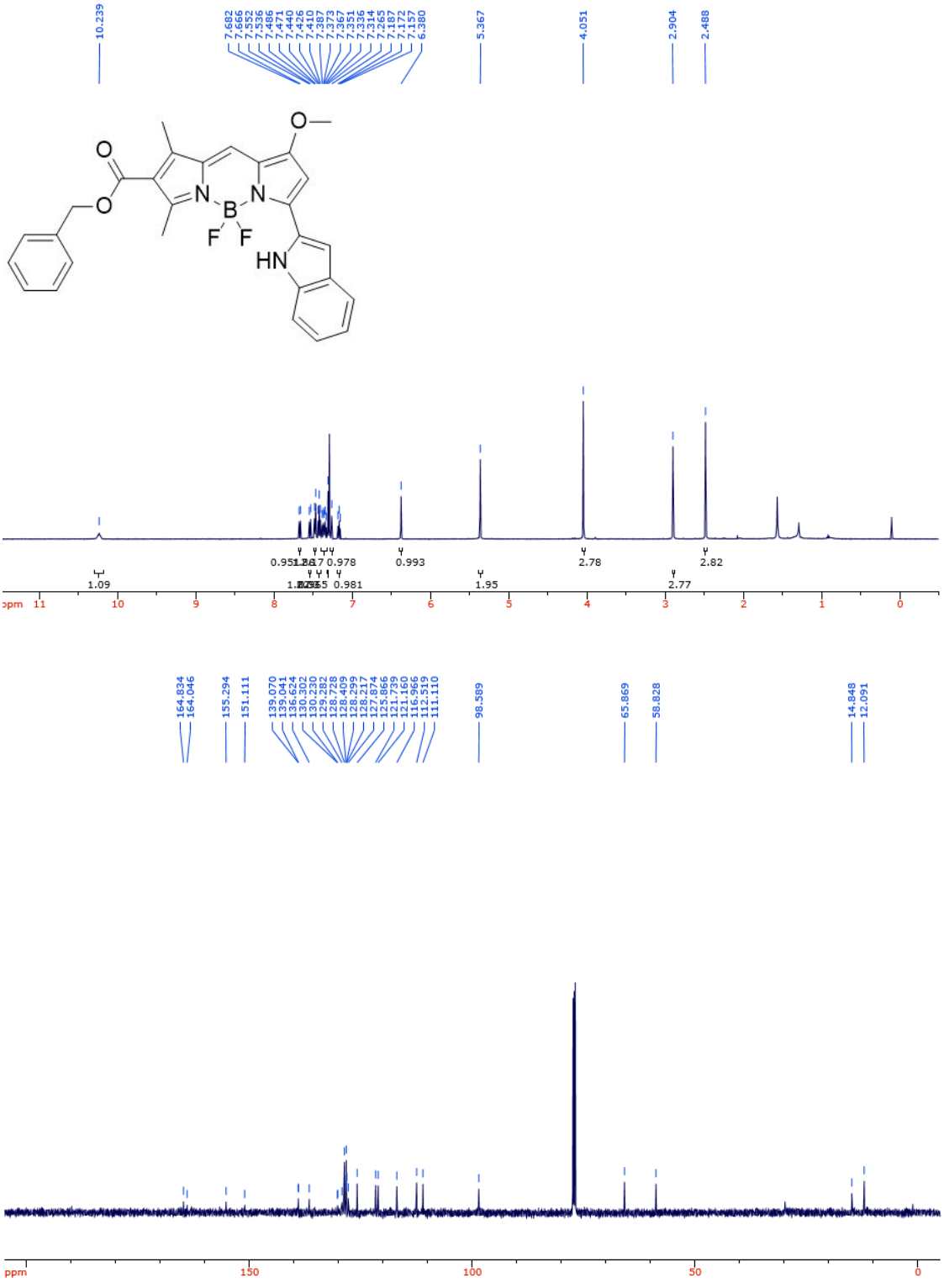


^{11}B and ^{19}F-NMR of 14b in $CDCl_3$:

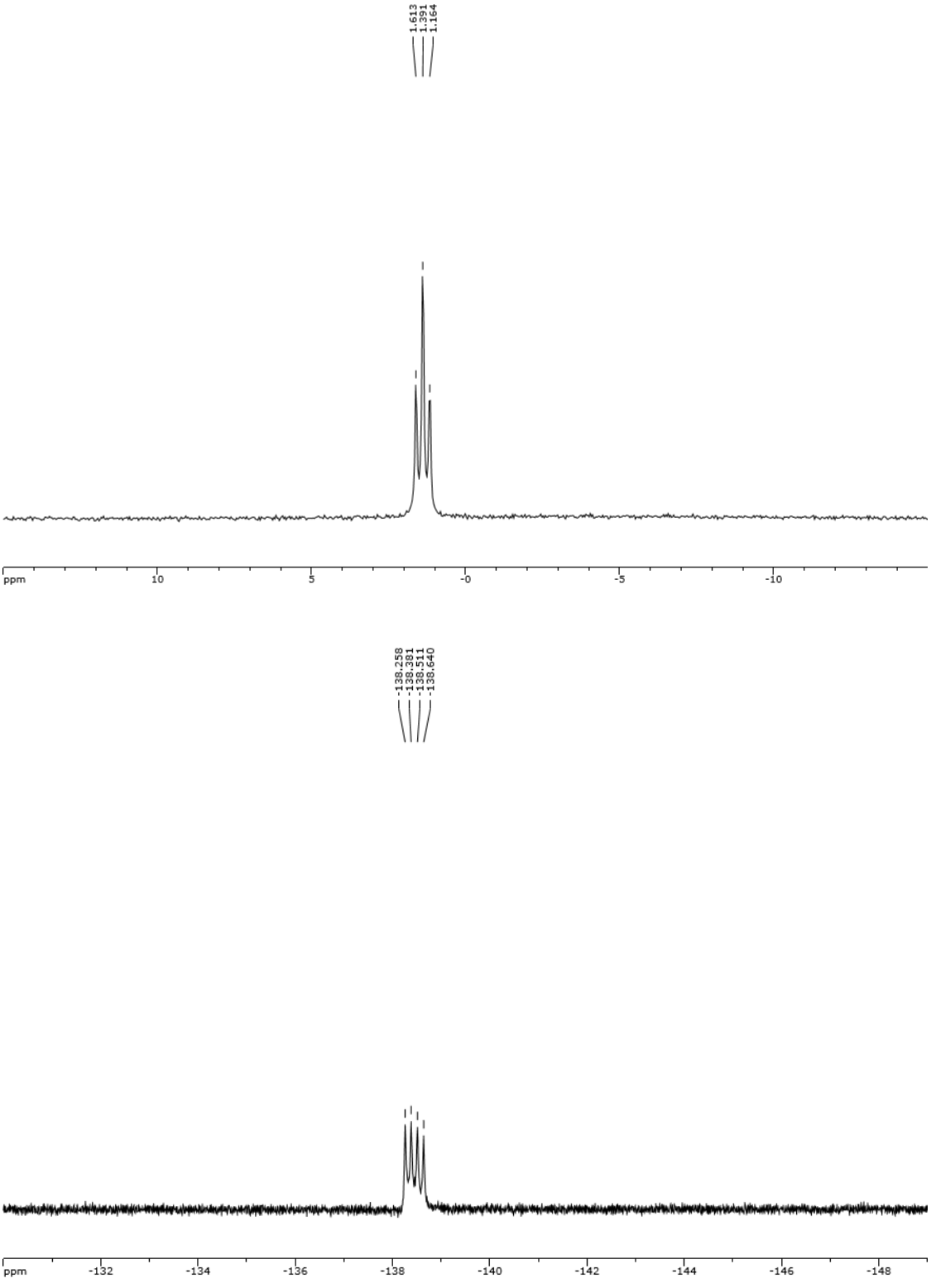




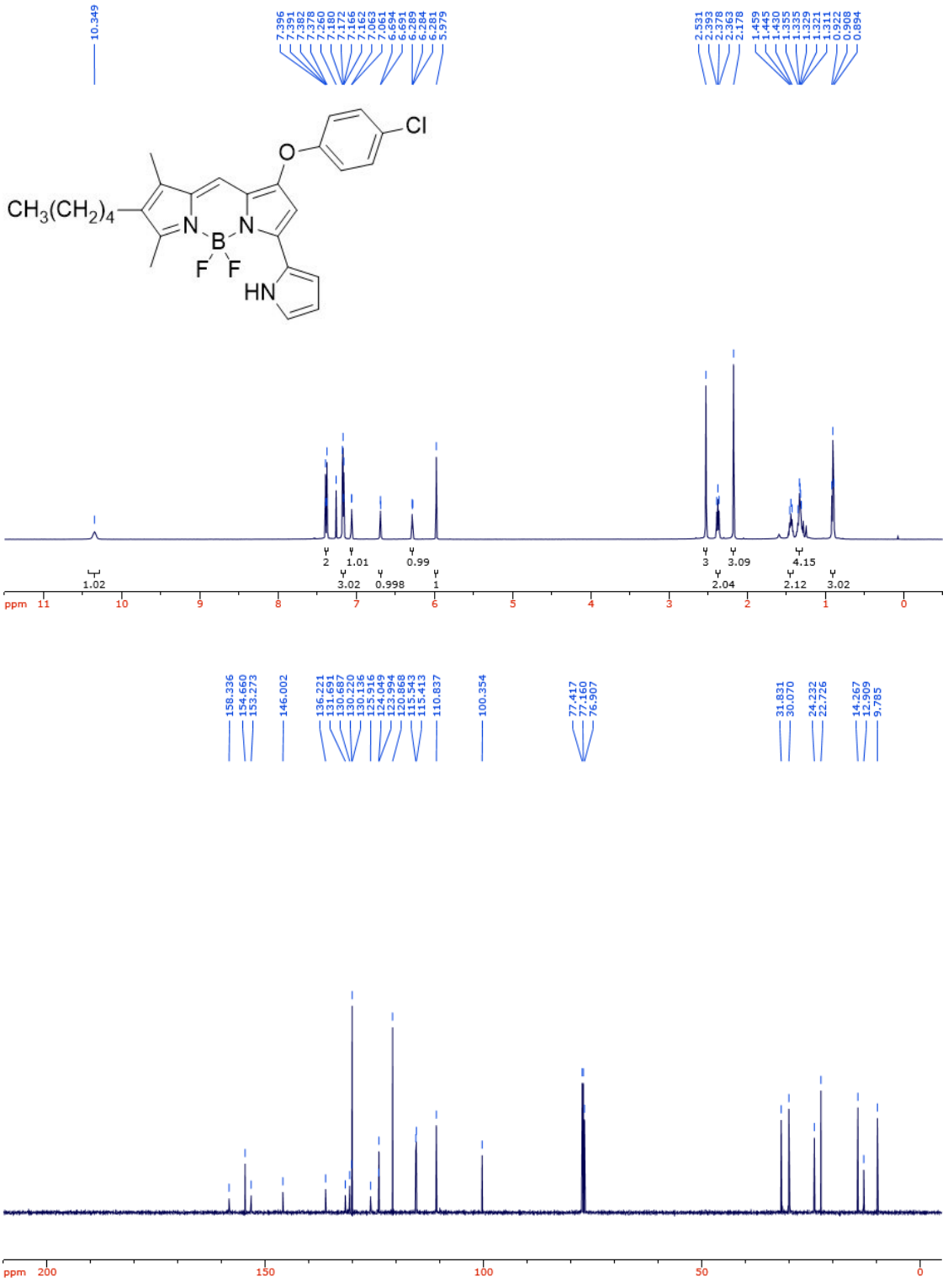
^{1}H and ^{13}C-NMR of 14f in $CDCl_3$:



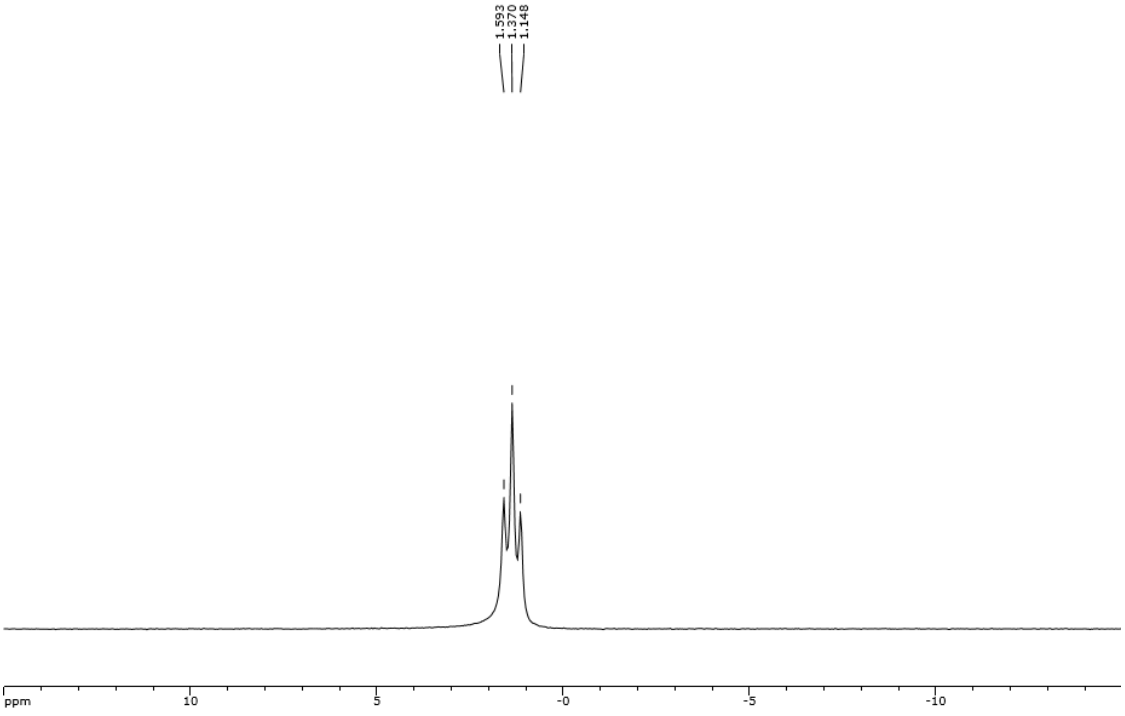
^{11}B and ^{19}F-NMR of 14f in $CDCl_3$:

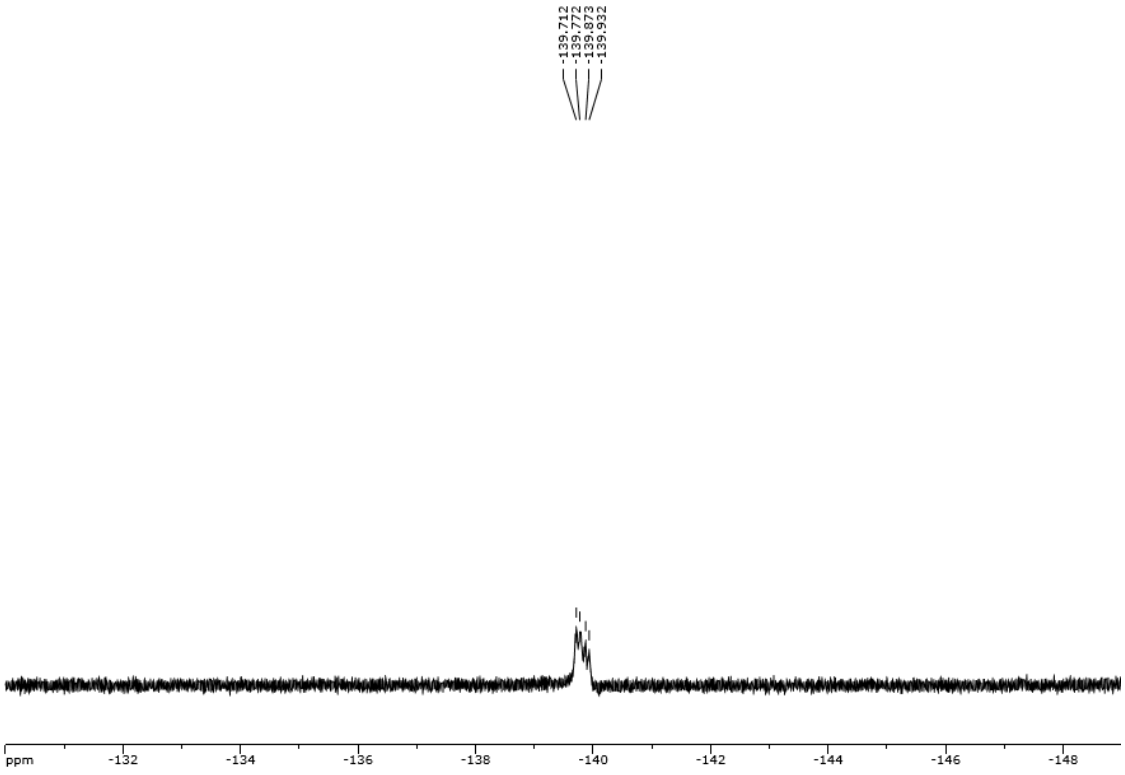


^{1}H and ^{13}C-NMR of 15m in $CDCl_3$:

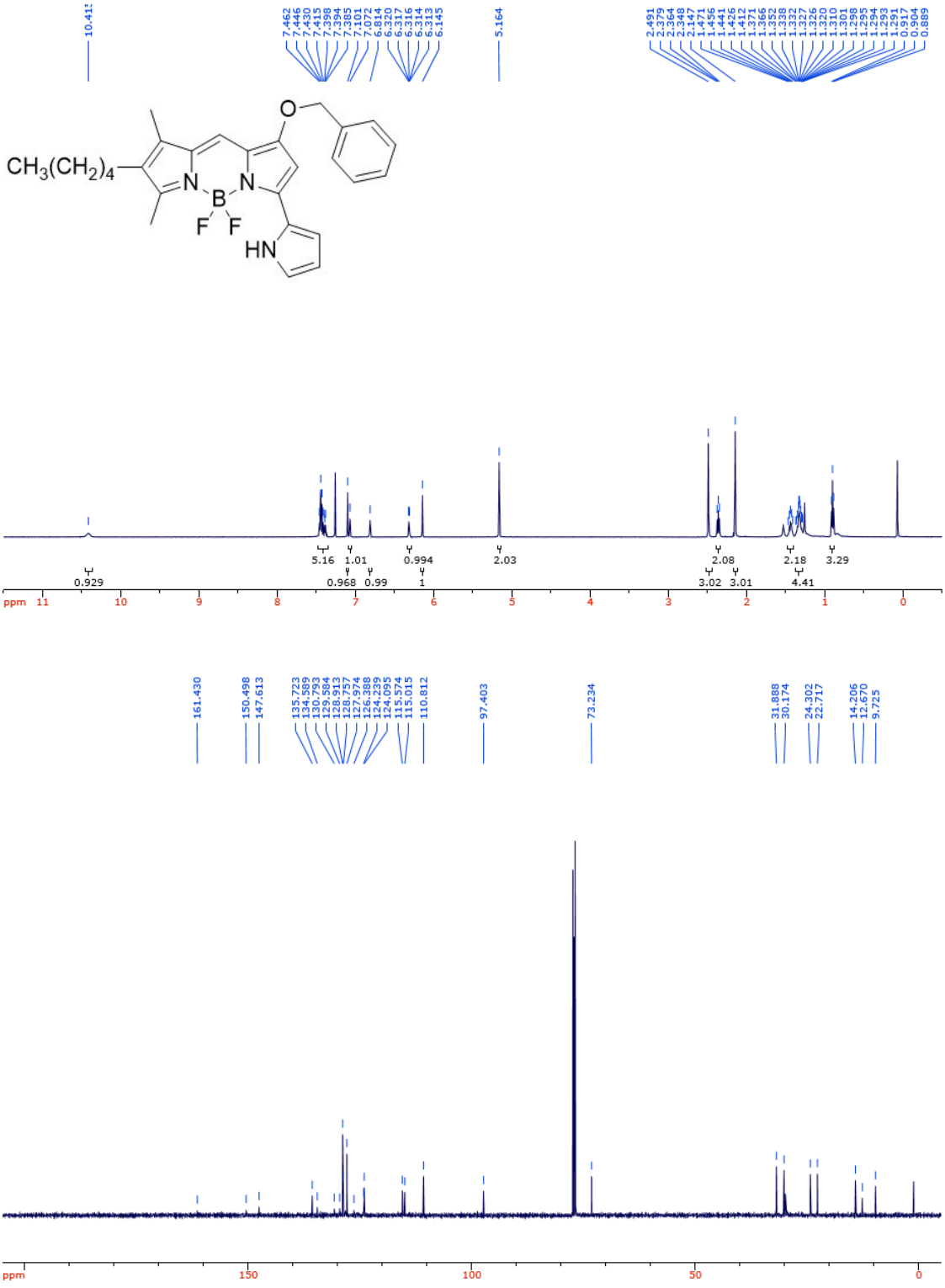


^{11}B and ^{19}F-NMR of 15m in $CDCl_3$:

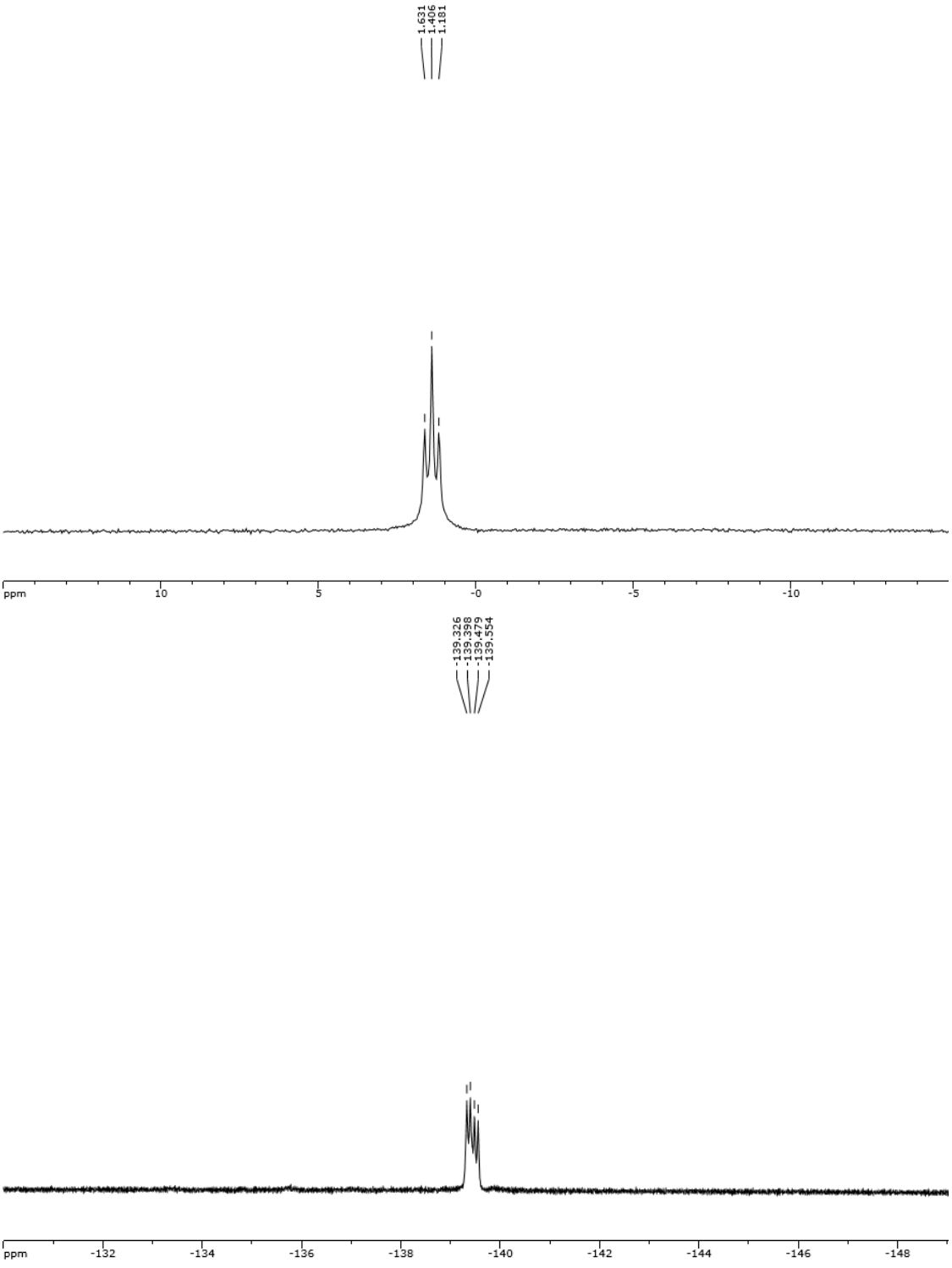




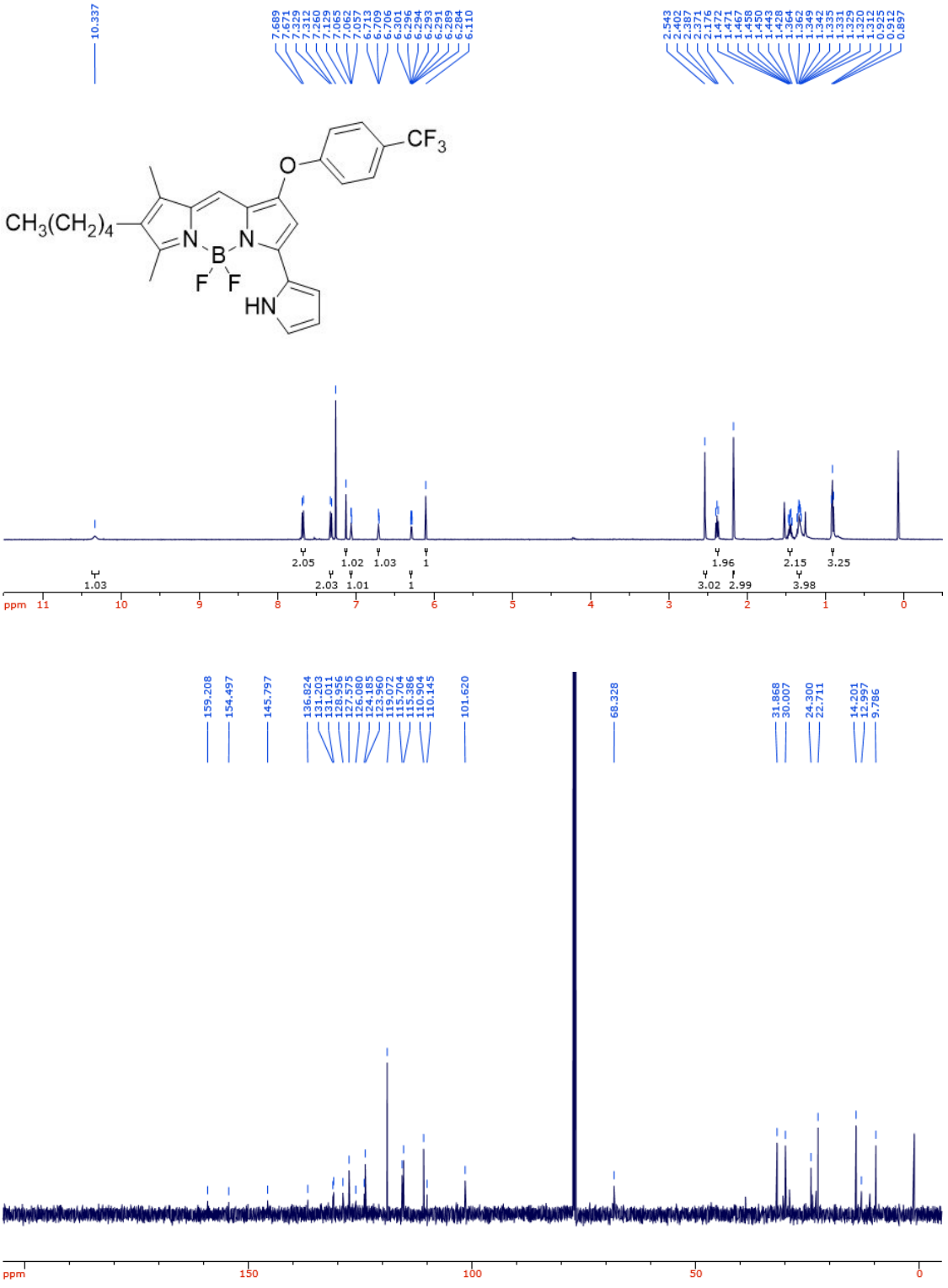
^{1}H and ^{13}C-NMR of 15n in $CDCl_3$:



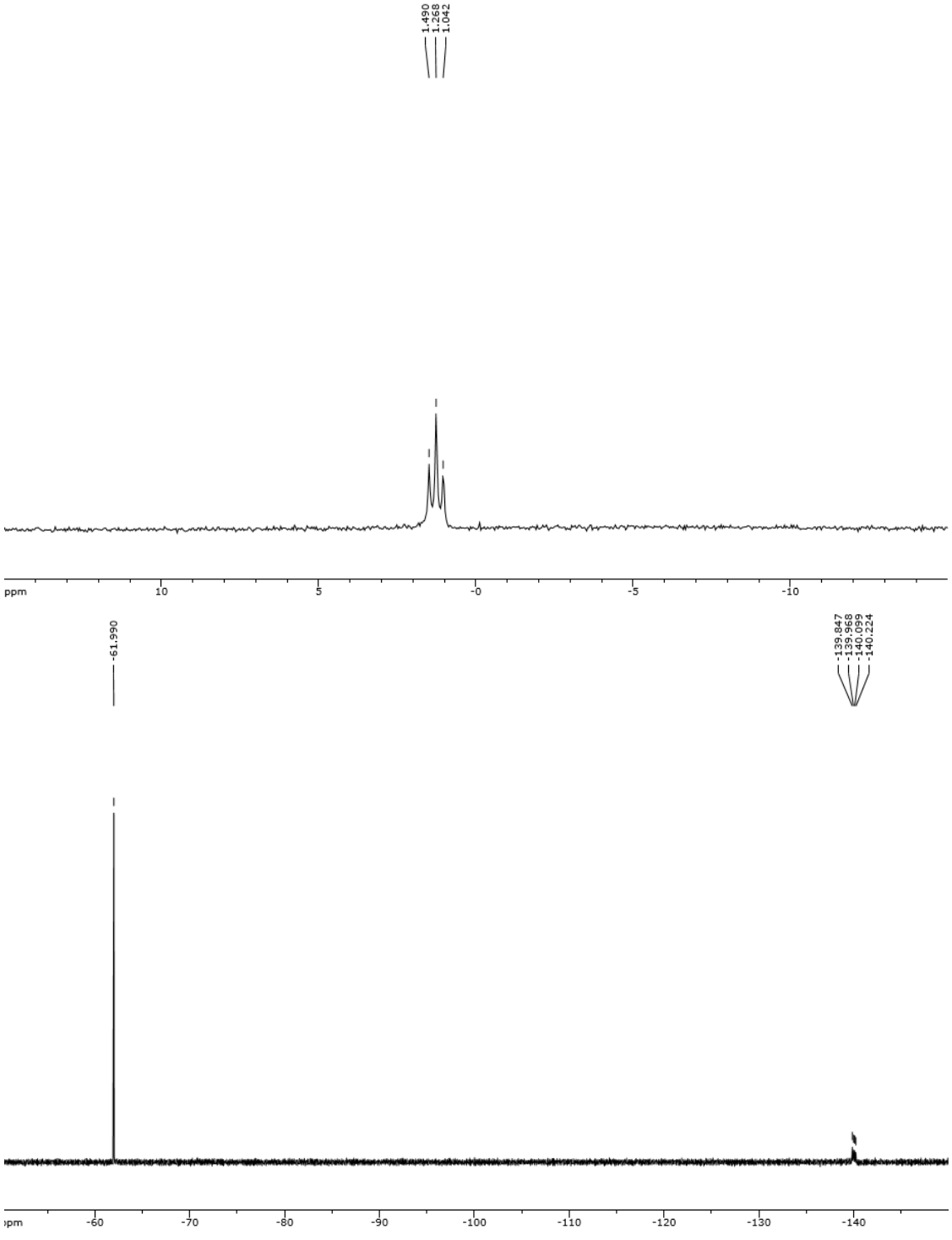
^{11}B and ^{19}F-NMR NMR of 15n in $CDCl_3$:



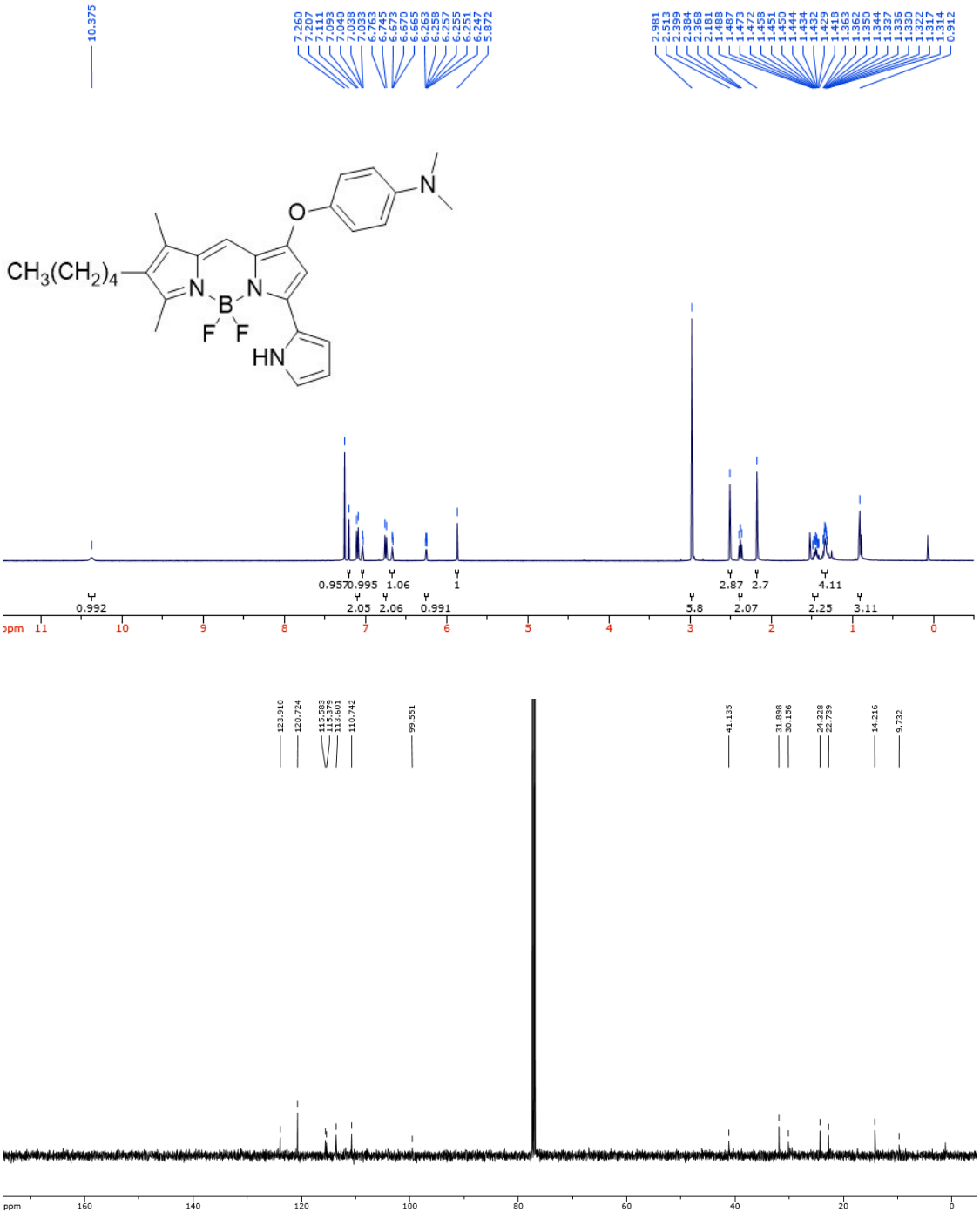
^{1}H and ^{13}C-NMR of 15o in $CDCl_3$:



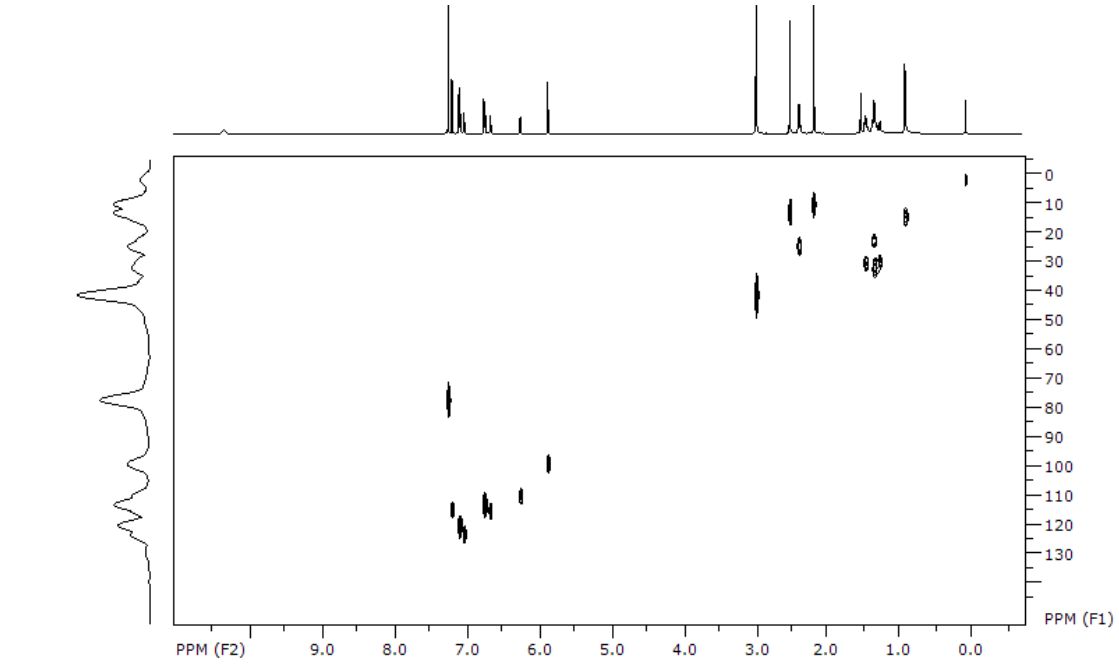
^{11}B and ^{19}F-NMR of 15o in $CDCl_3$:



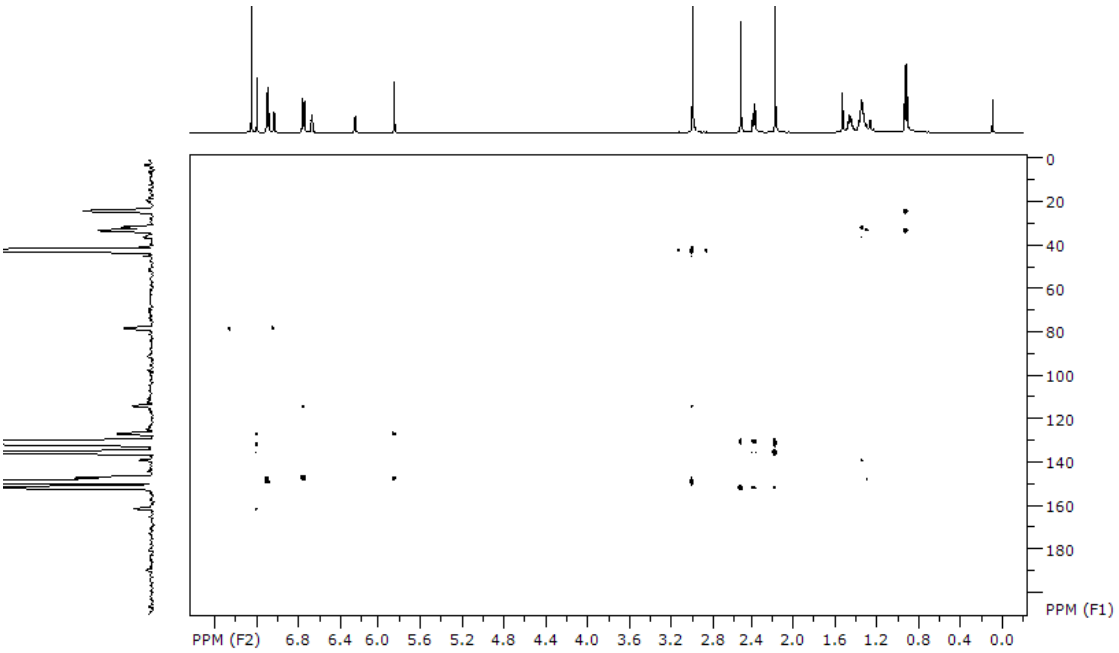
^{1}H and ^{13}C-NMR of 15p in $CDCl_3$:



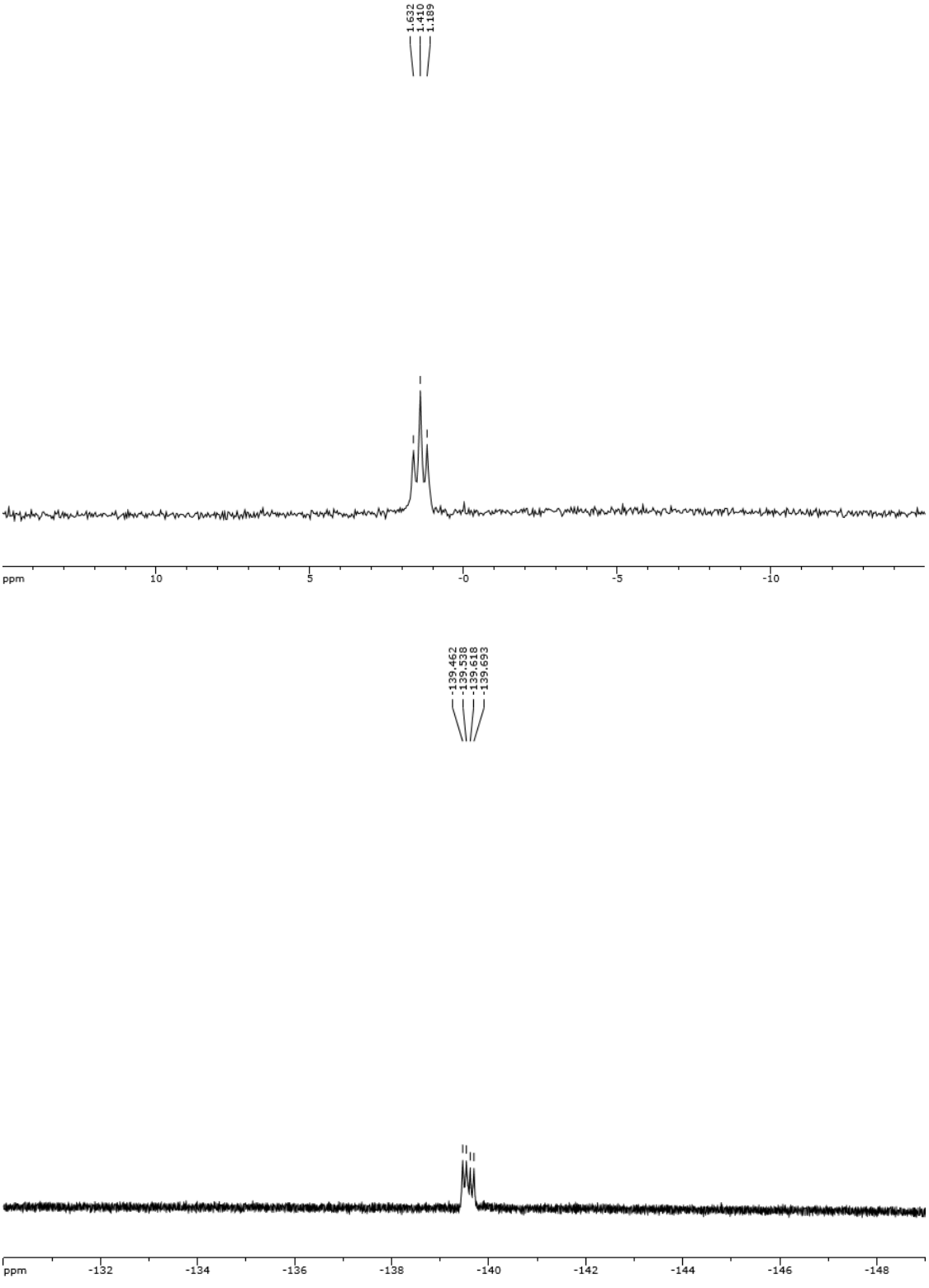
^{1}H-^{13}C-HSQC-NMR of 15p in $CDCl_3$:



^{1}H-^{13}C-HMBC-NMR of 15p in $CDCl_3$:

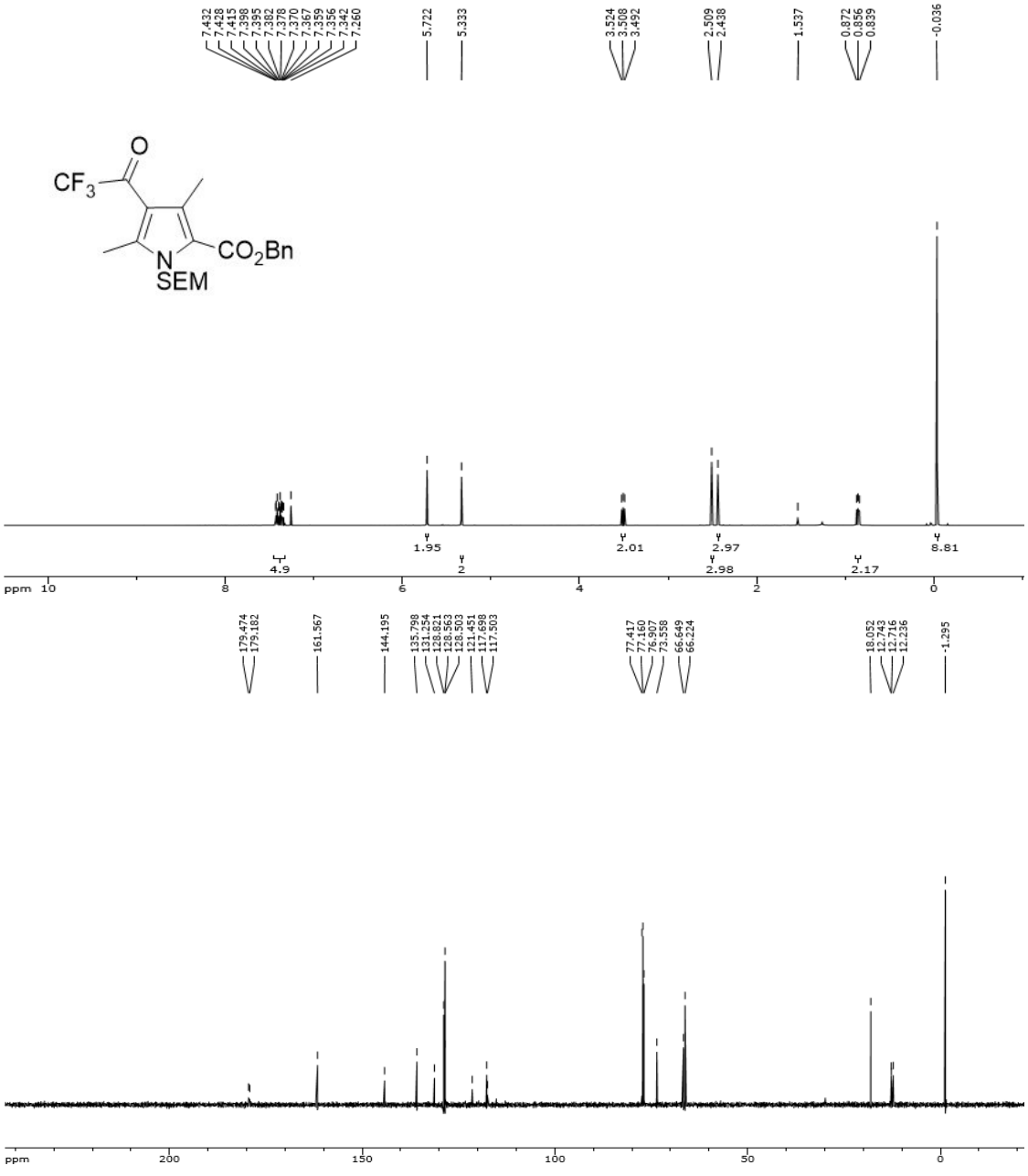


^{11}B and ^{19}F-NMR of 15p in $CDCl_3$:

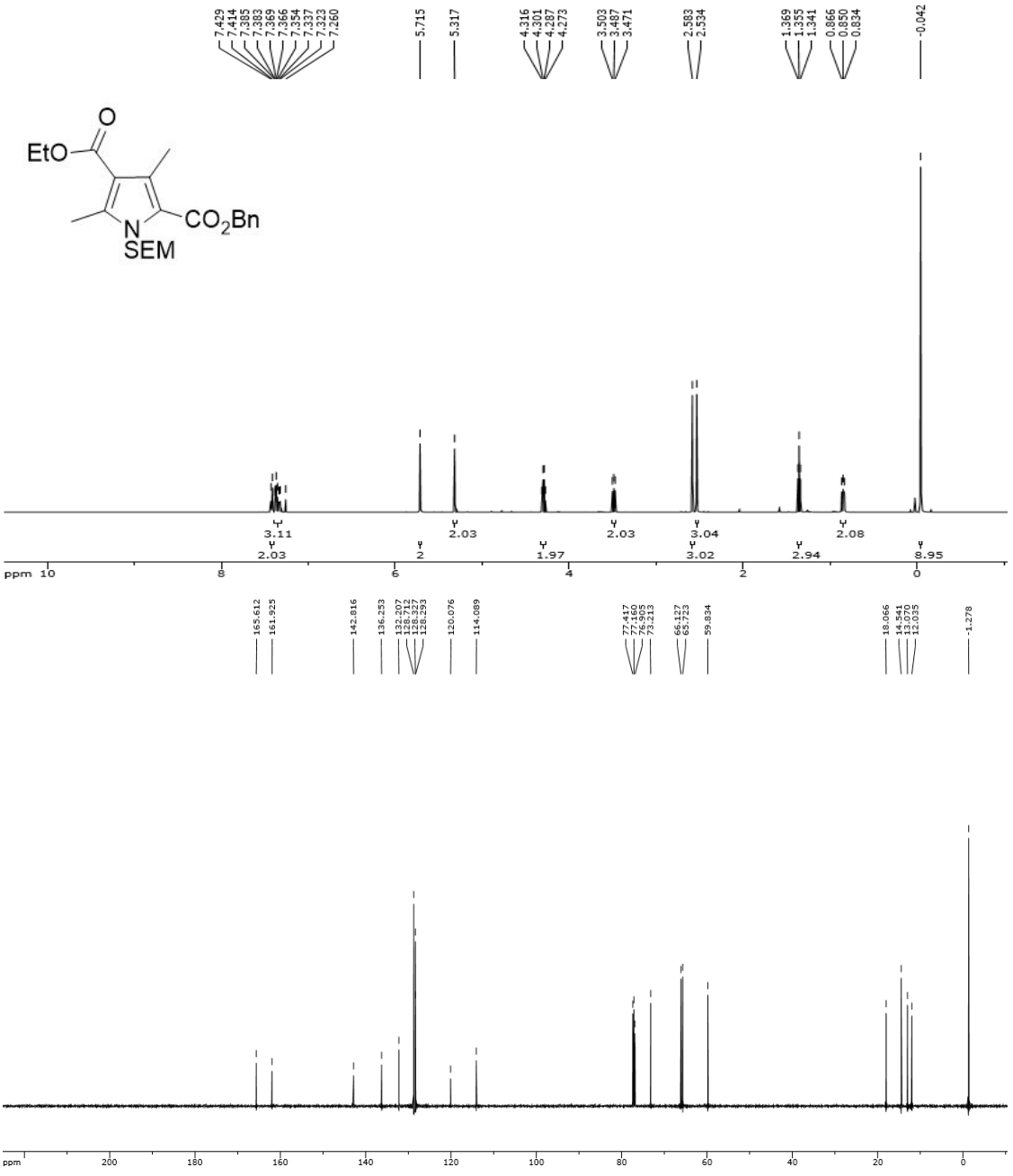


NMR Spectra of Pyrroles 17, 19 and 21

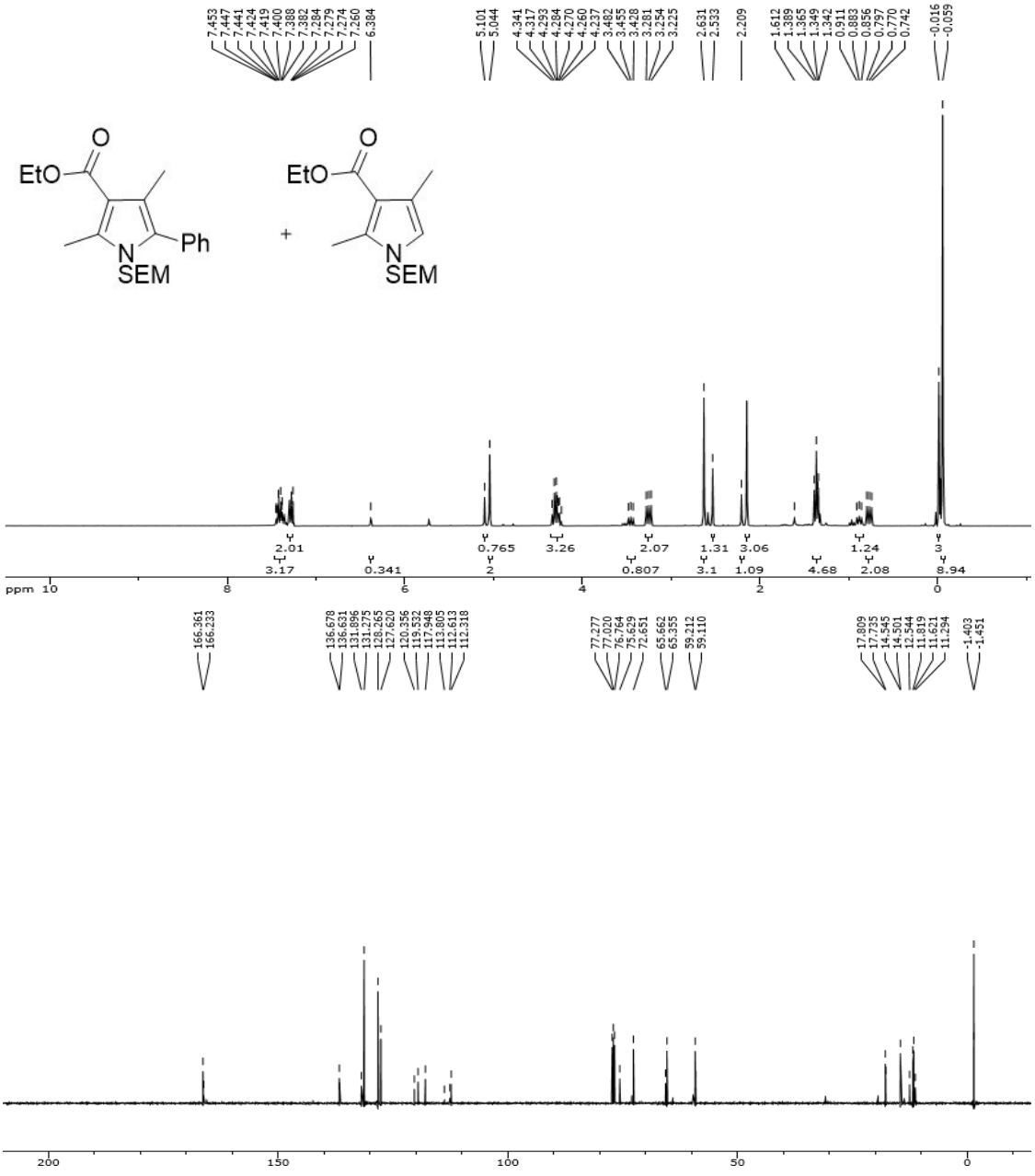
^{1}H and ^{13}C-NMR of 17g in $CDCl_3$



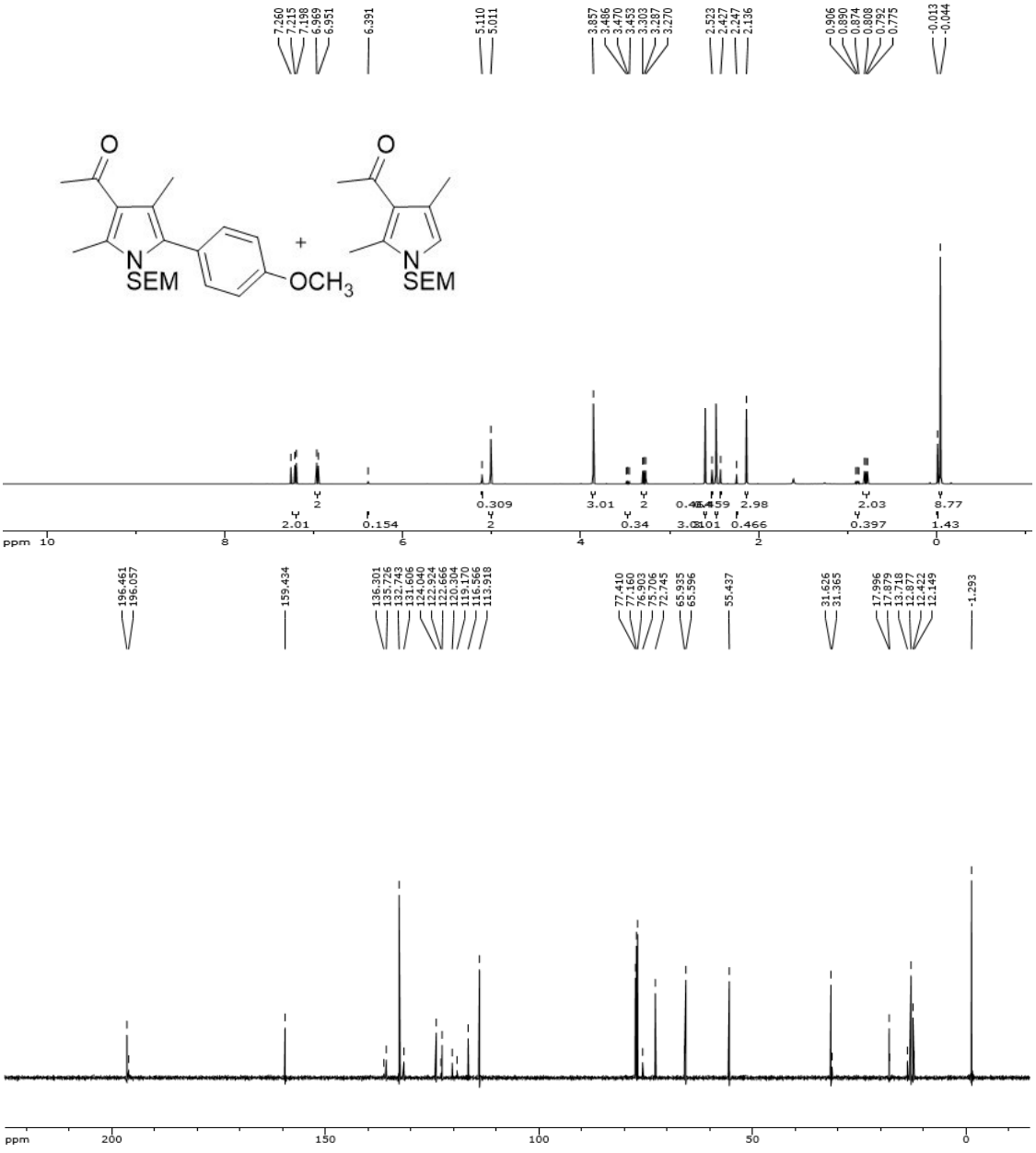
^{1}H and ^{13}C-NMR of 17h in $CDCl_3$



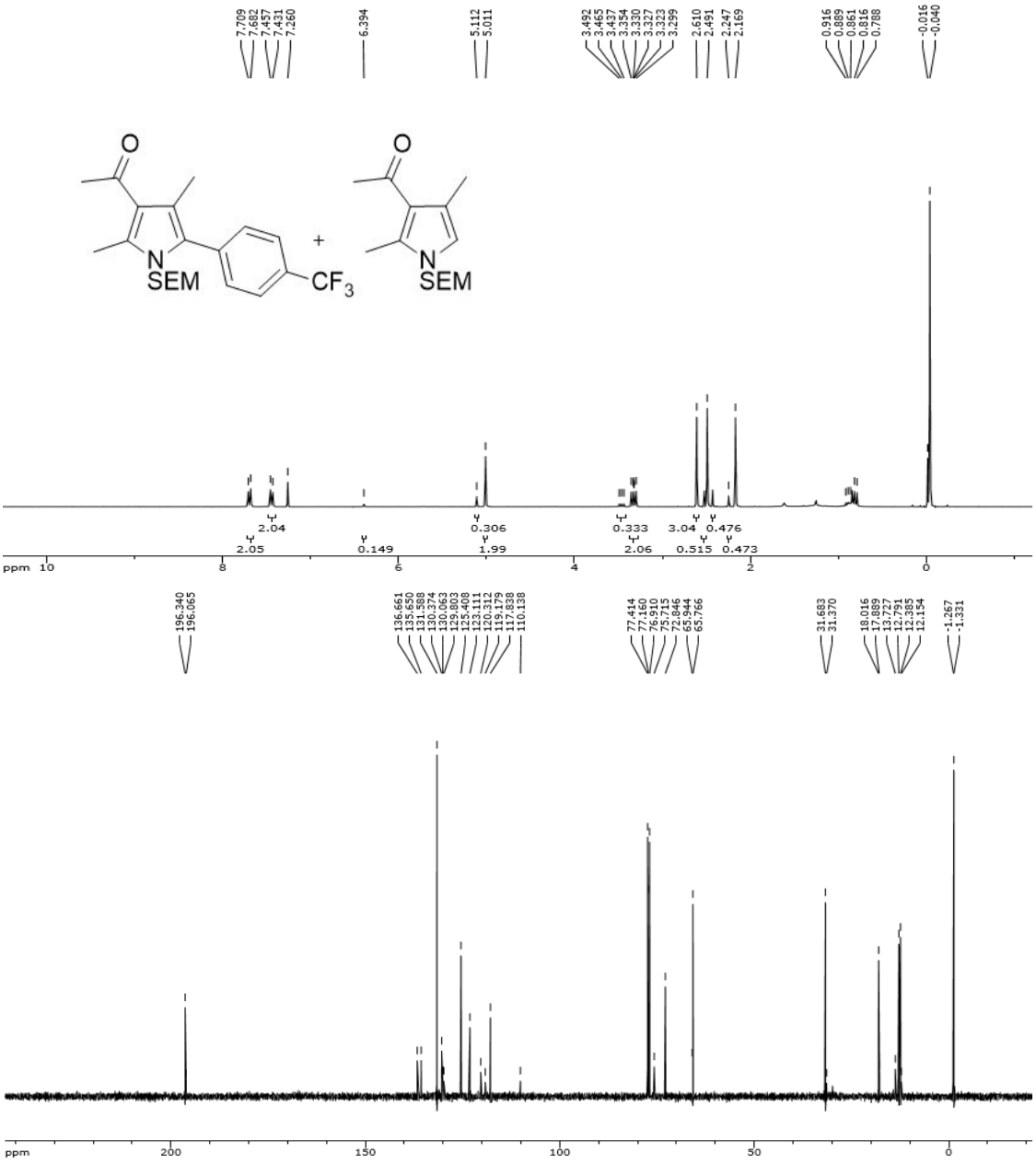
^{1}H and ^{13}C-NMR of 19h + 20h in $CDCl_3$



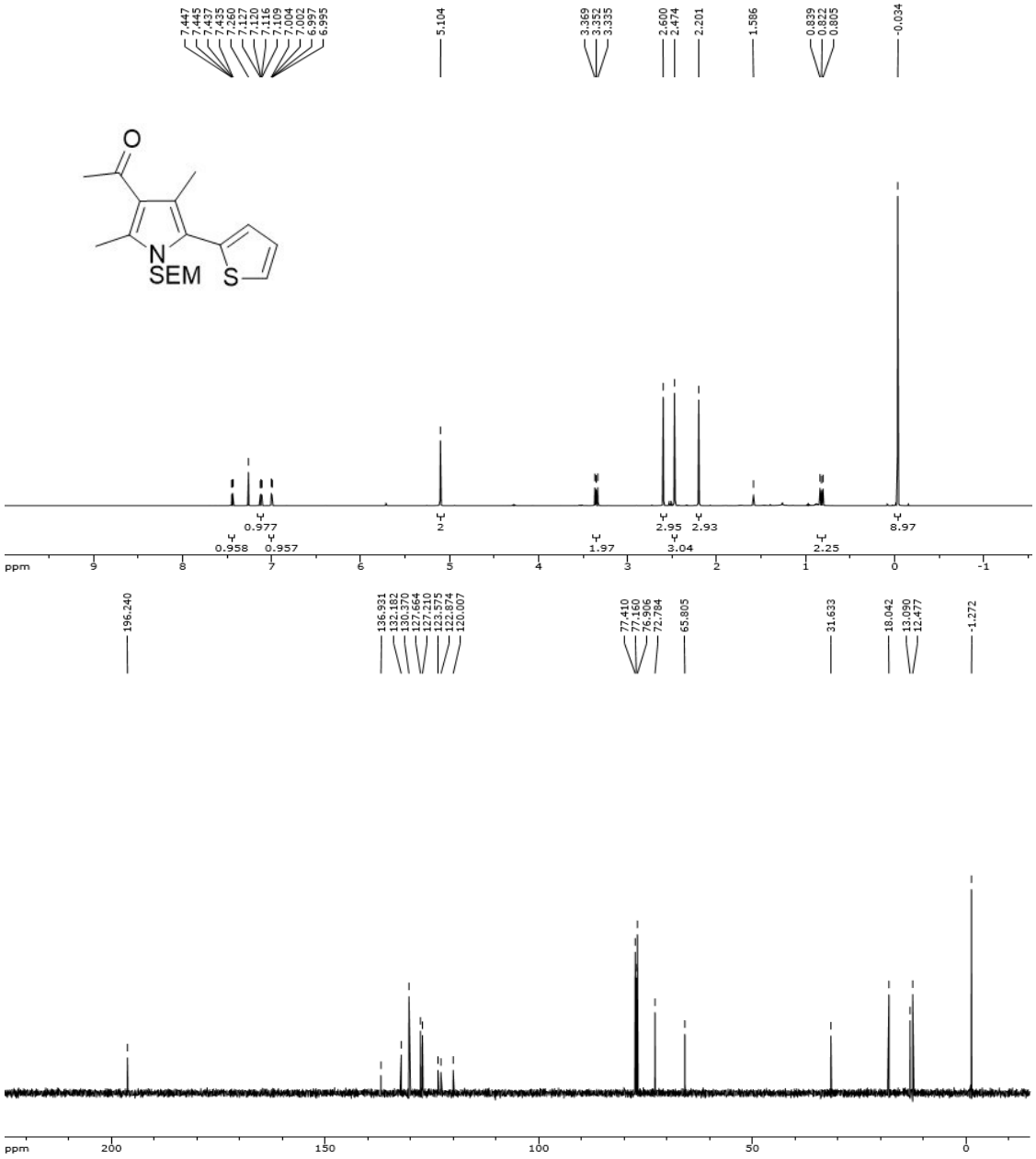
^{1}H and ^{13}C-NMR of 19l + 20a in $CDCl_3$



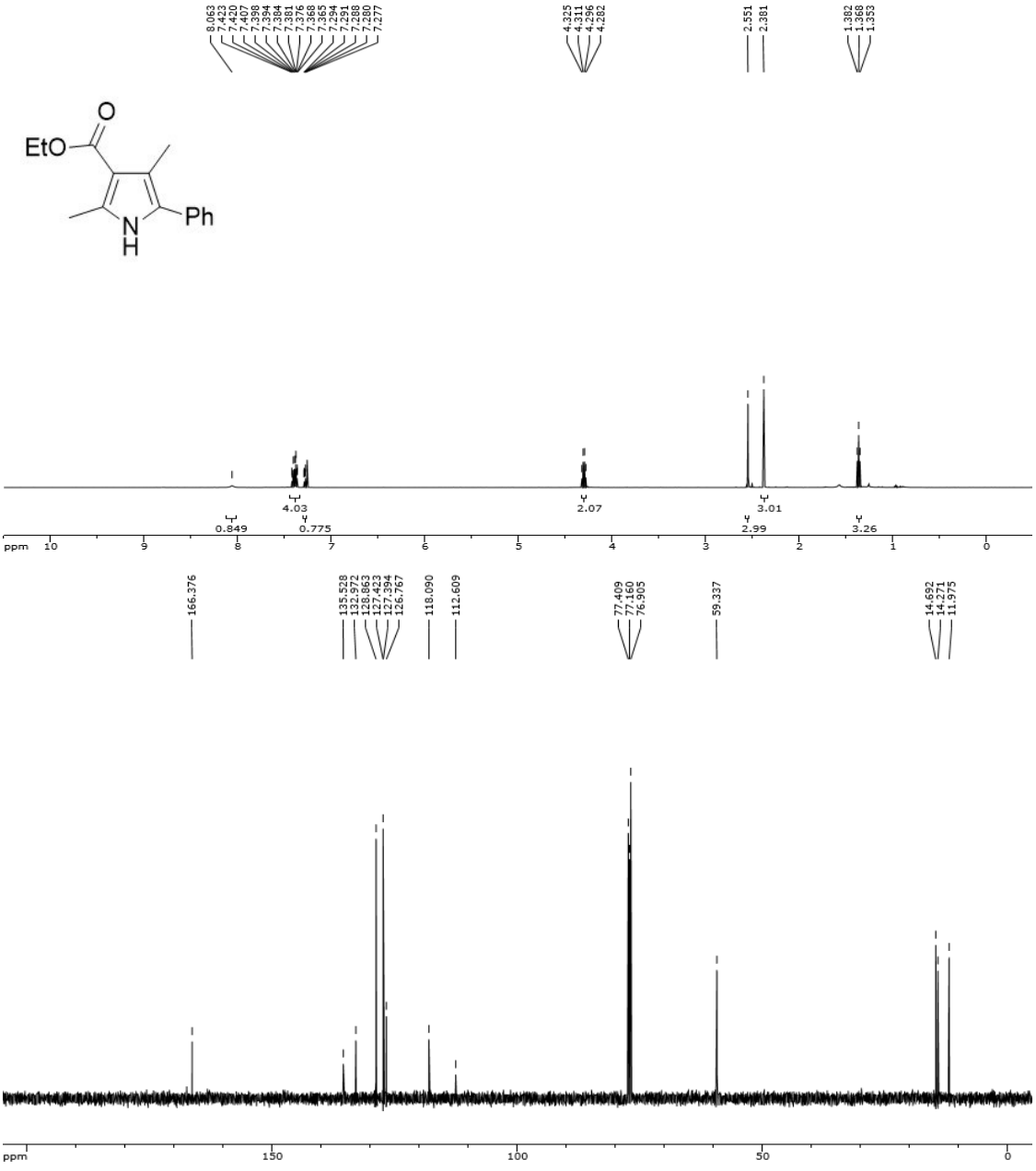
^{1}H and ^{13}C-NMR of 19m + 20a in $CDCl_3$



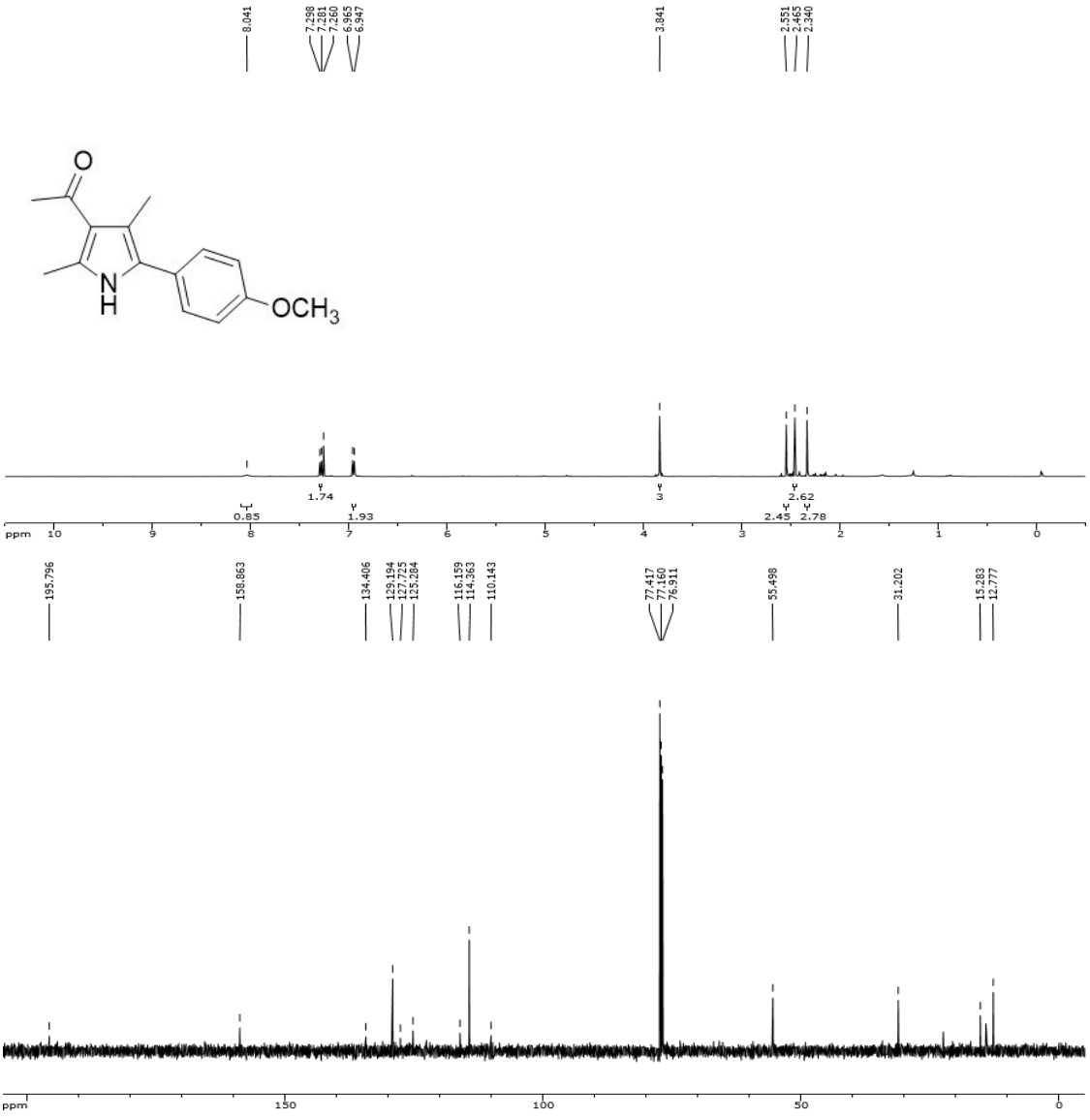
^{1}H and ^{13}C-NMR of 19n in $CDCl_3$



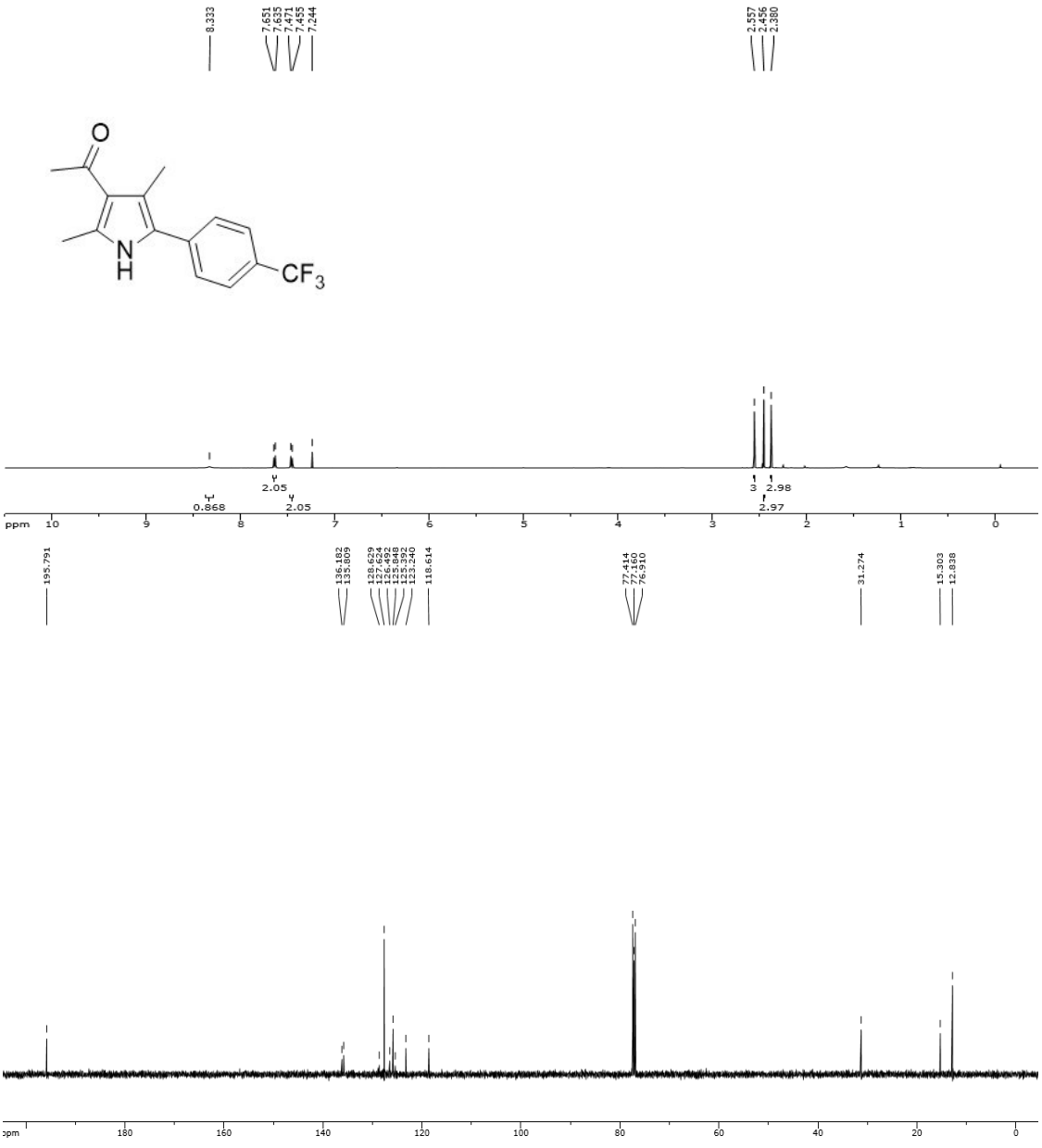
^{1}H and ^{13}C-NMR of 21h in $CDCl_3$



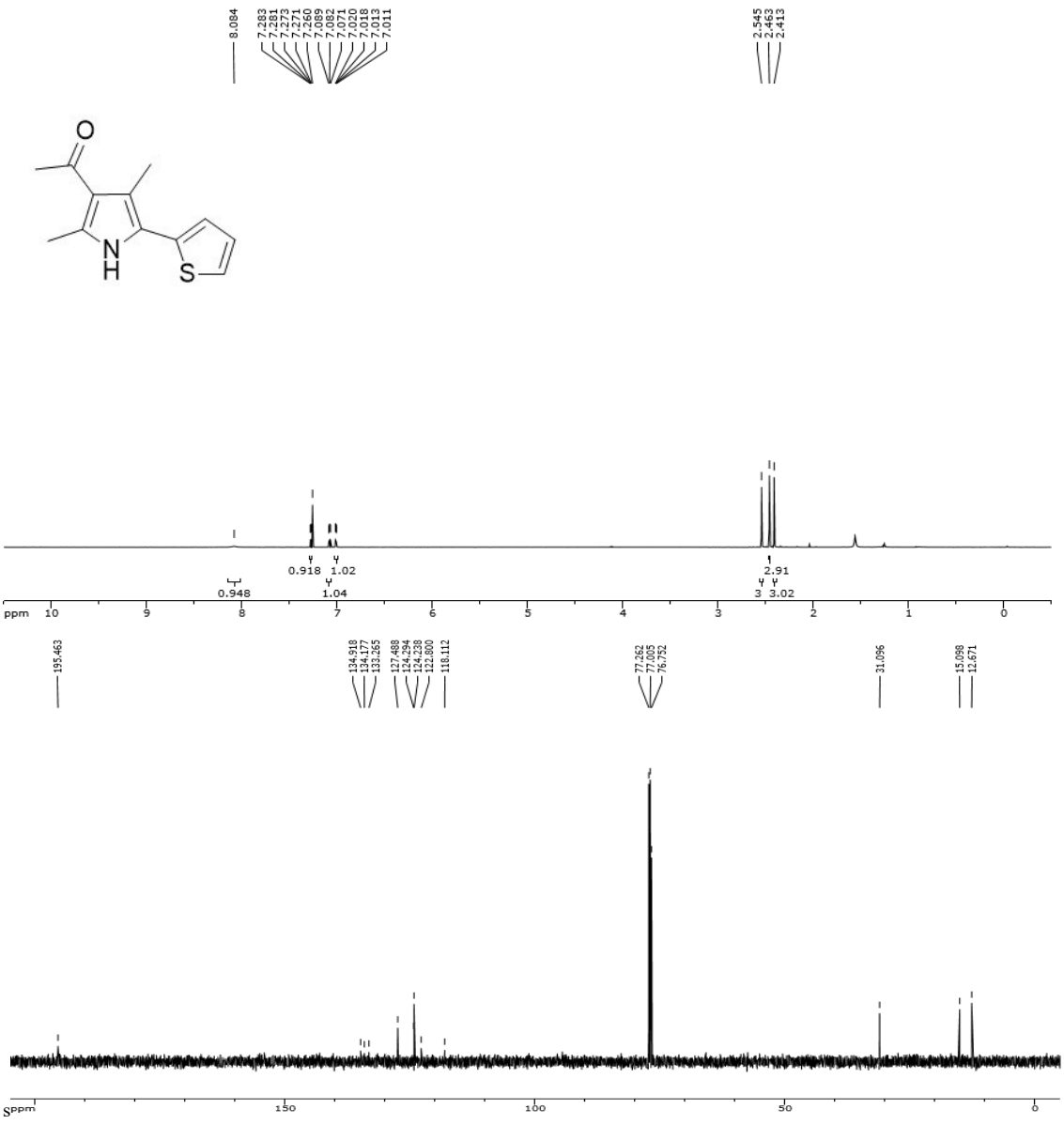
^{1}H and ^{13}C-NMR of 21l in $CDCl_3$



^{1}H and ^{13}C-NMR of 21m in $CDCl_3$

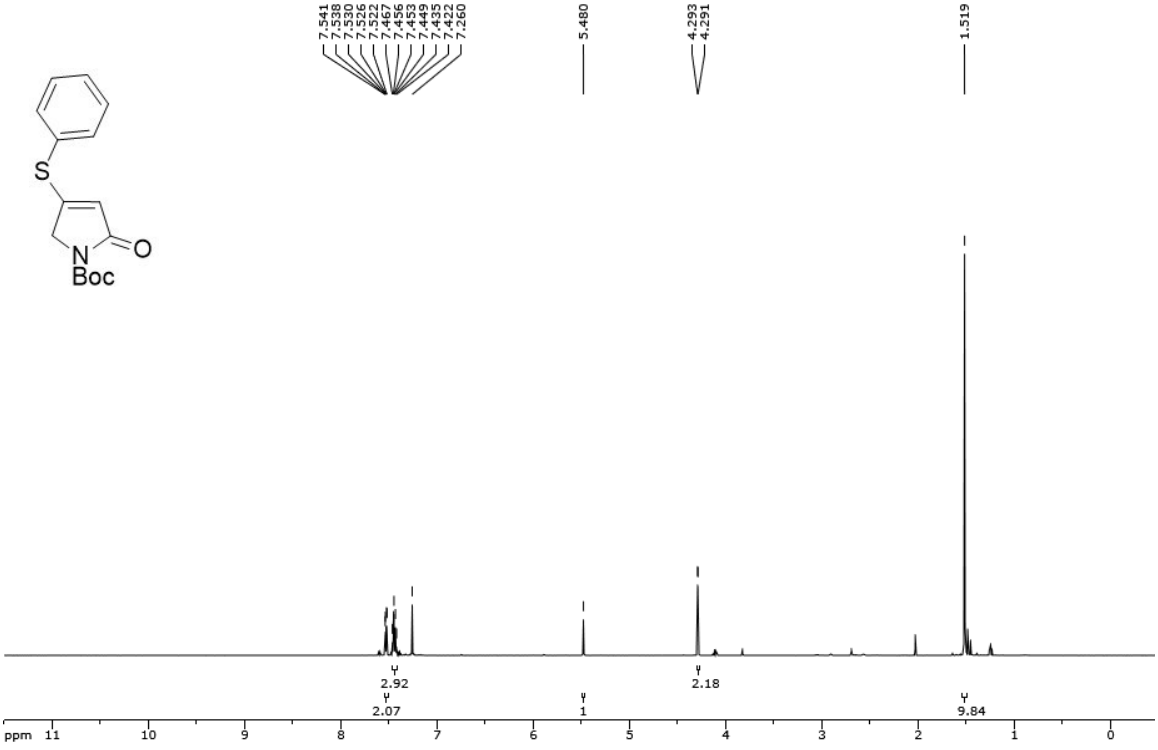


^{1}H and ^{13}C-NMR of 21n in $CDCl_3$

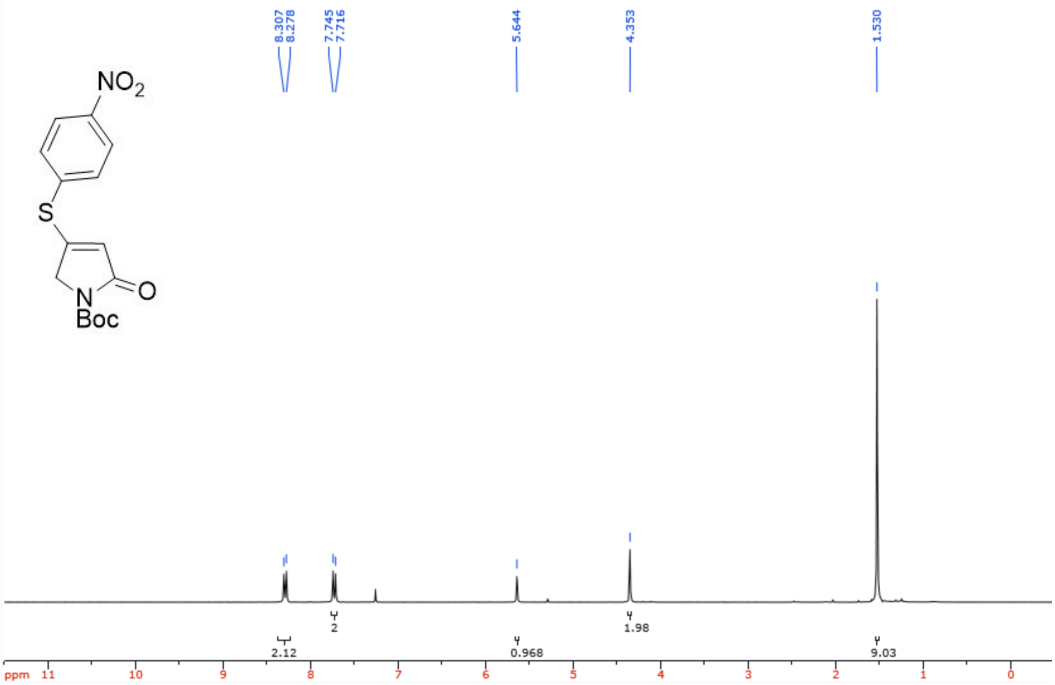


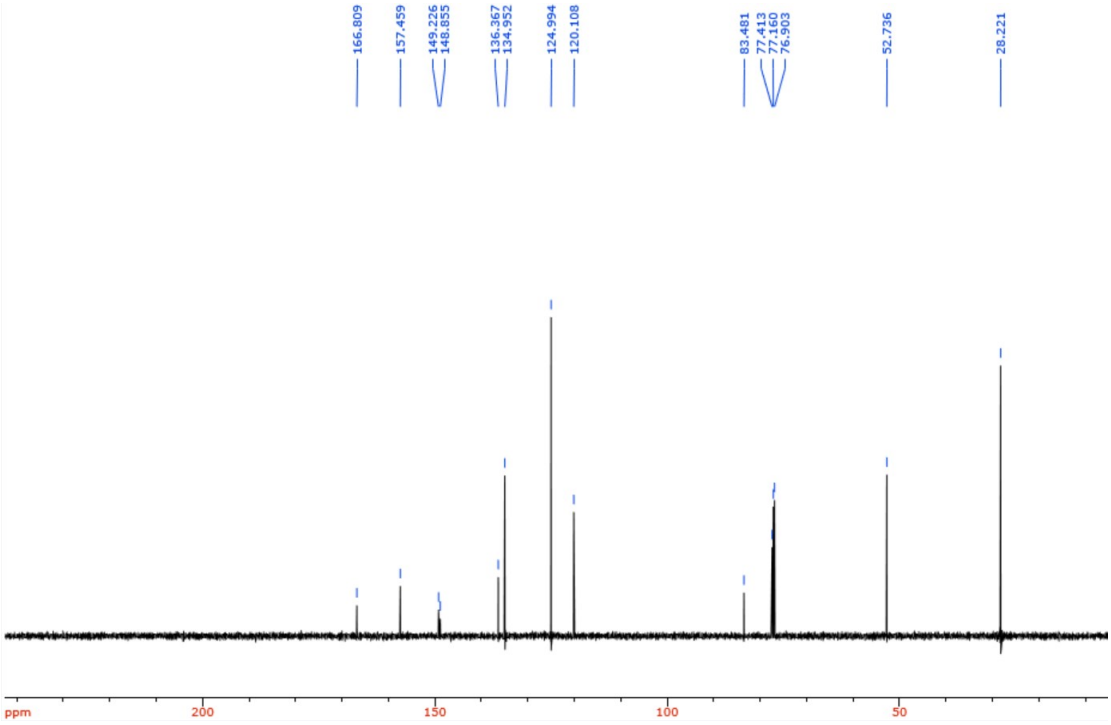
NMR Spectra of Compounds 46-50 and 54-56

^{1}H-NMR of 46a in $CDCl_3$:

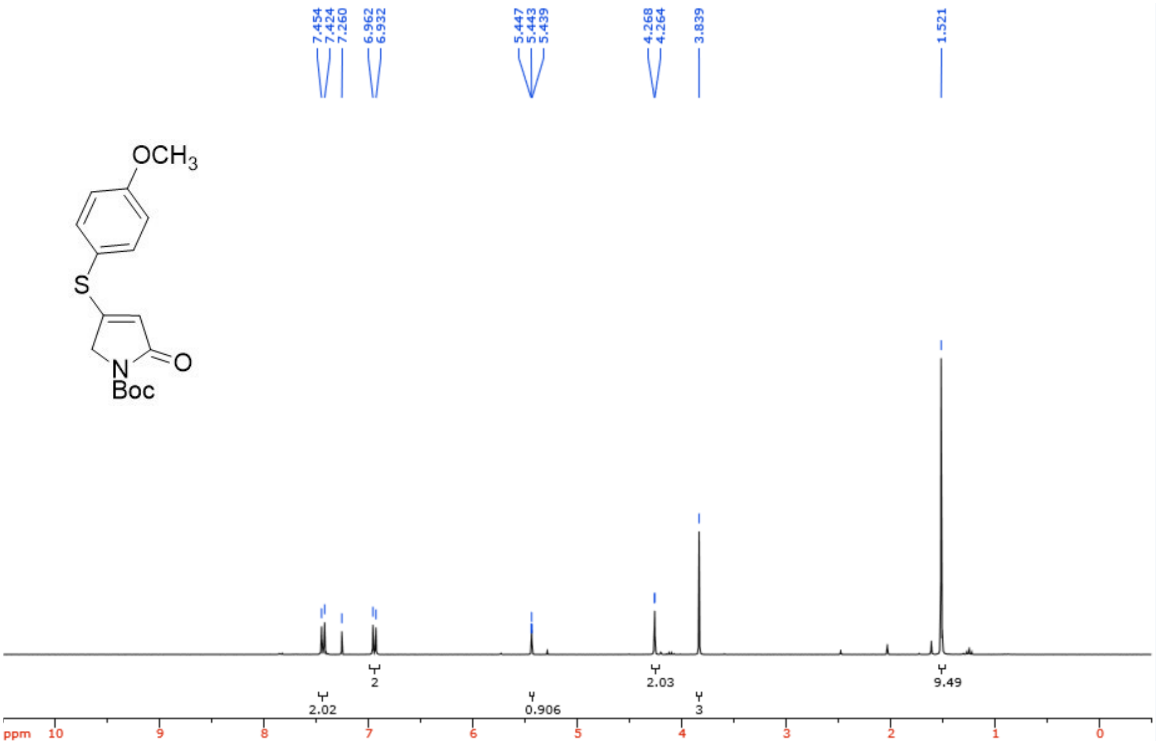


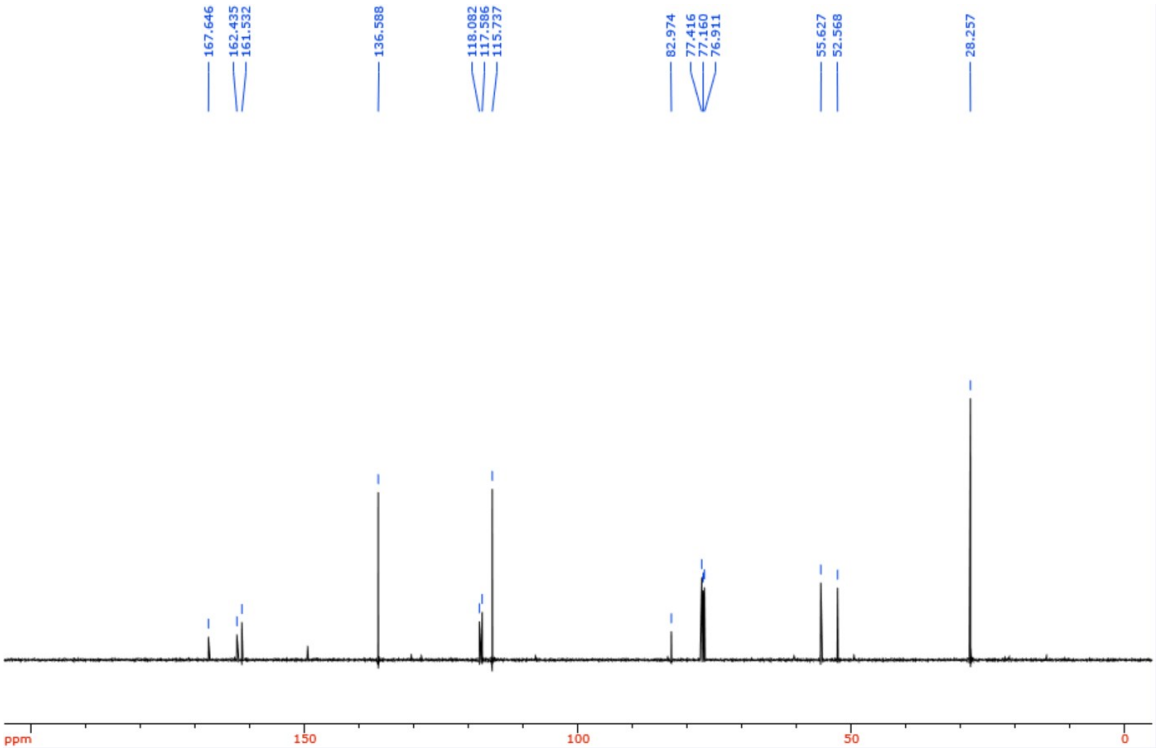
^{1}H and ^{13}C-NMR of 46b in $CDCl_3$:



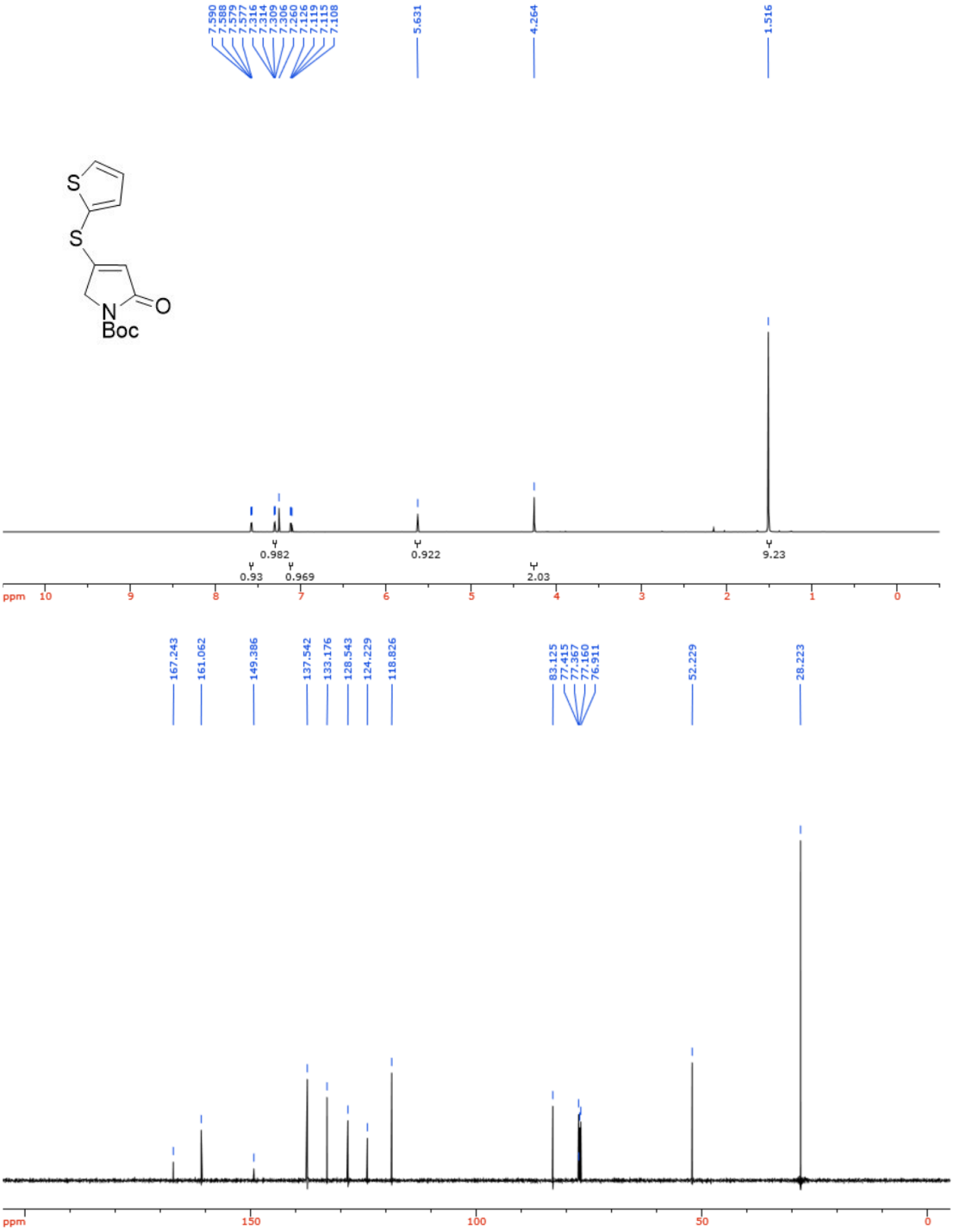


^{1}H and ^{13}C-NMR of 46c in $CDCl_3$:

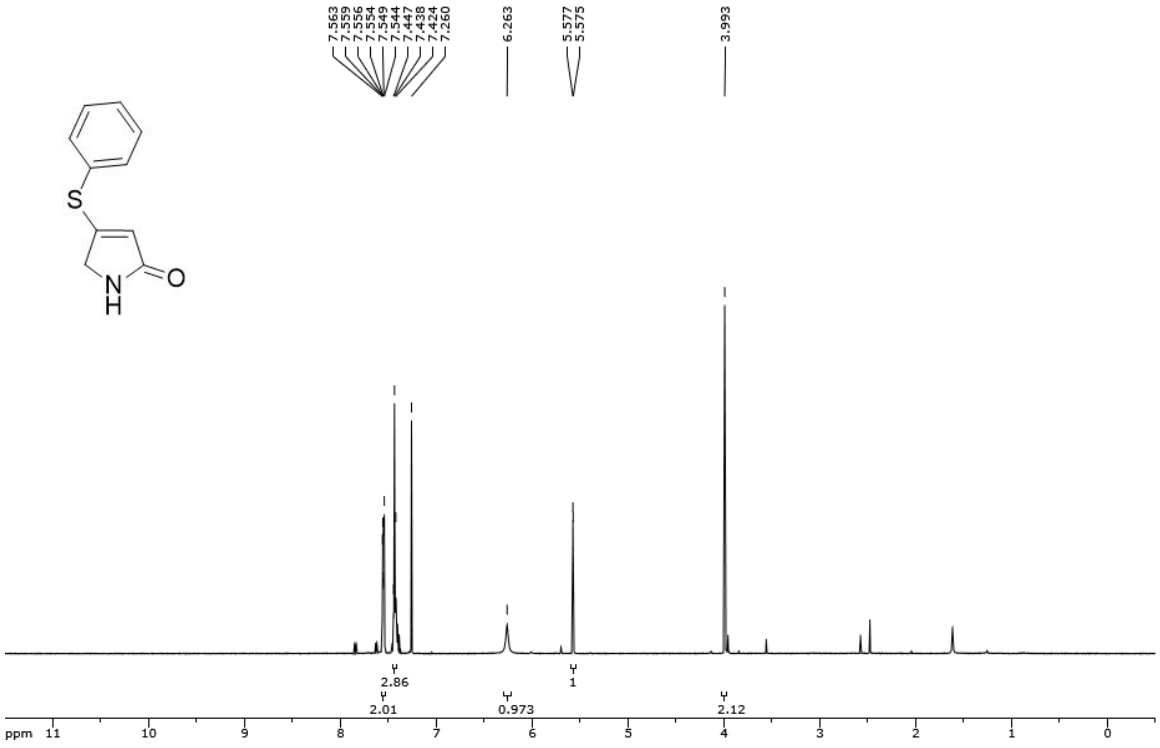




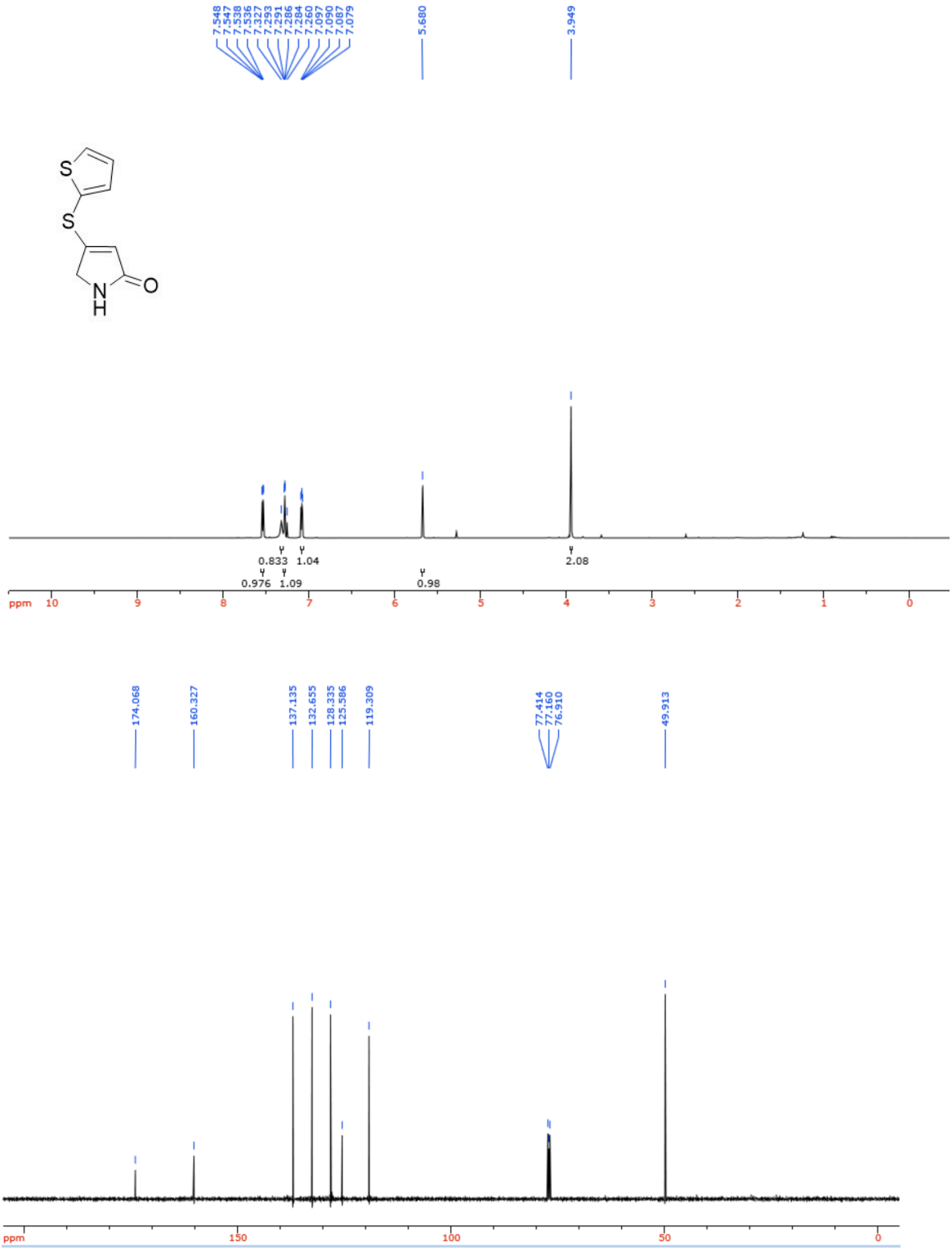
^{1}H and ^{13}C-NMR of 46d in $CDCl_3$:



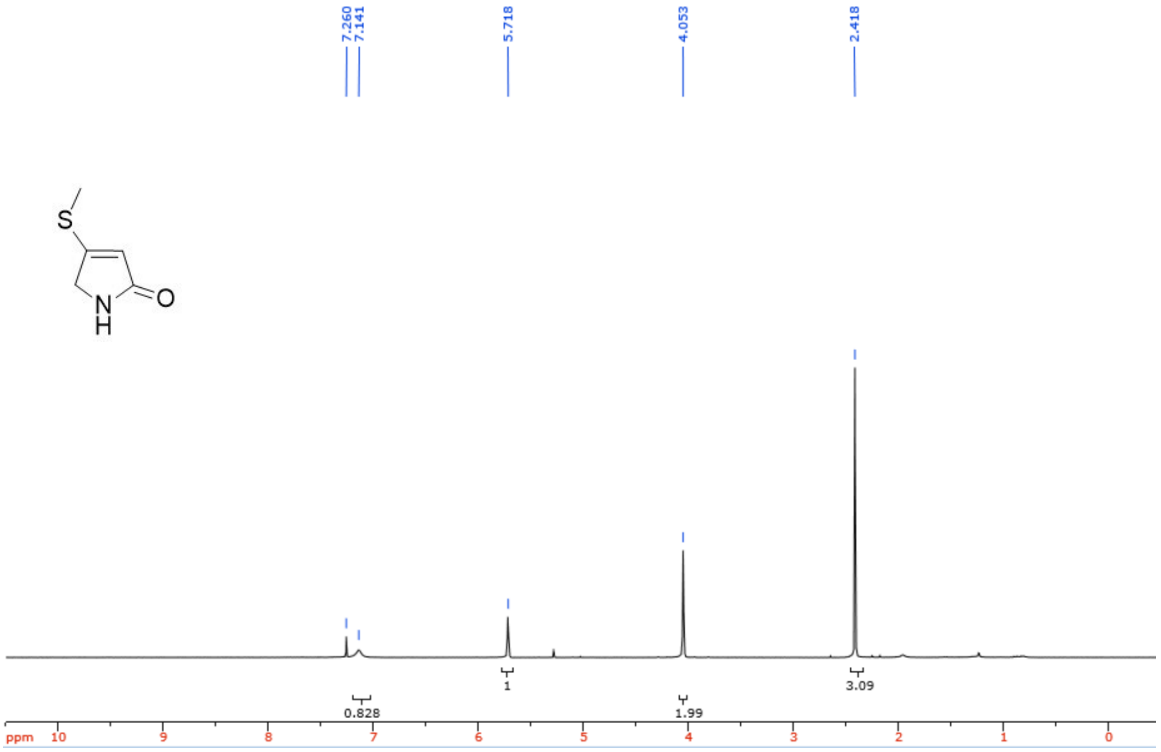
^{1}H-NMR of 47a in $CDCl_3$:

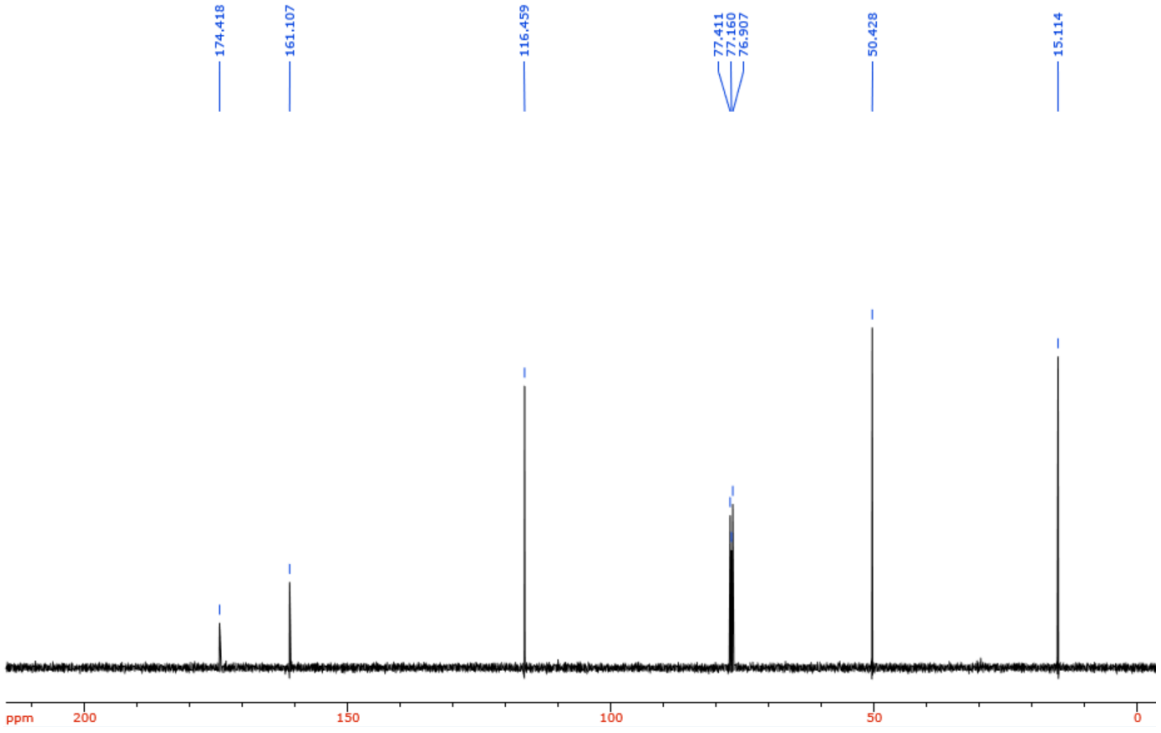


^{1}H and ^{13}C-NMR of 47d in $CDCl_3$:

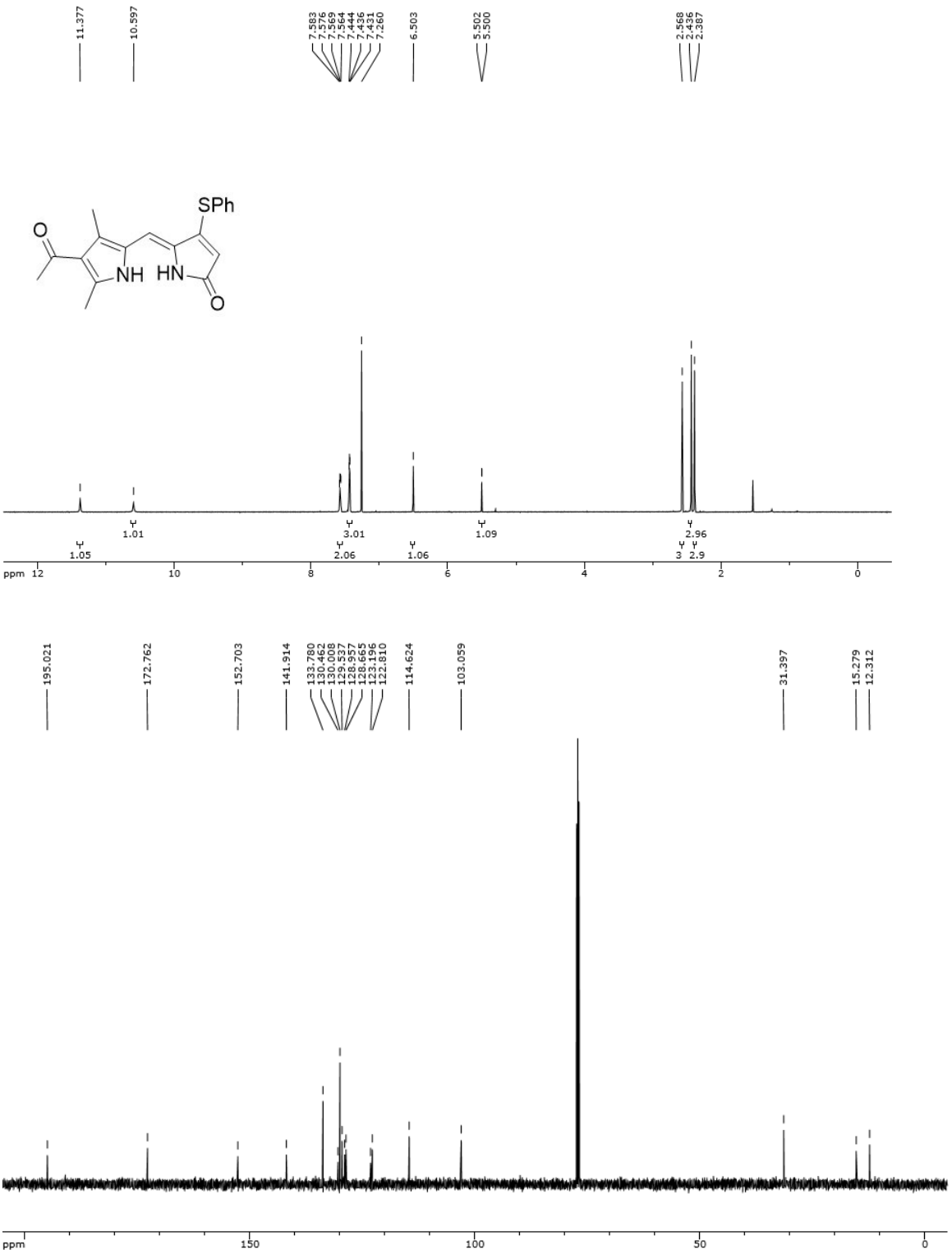


^{1}H and ^{13}C-NMR of 47e in $CDCl_3$:

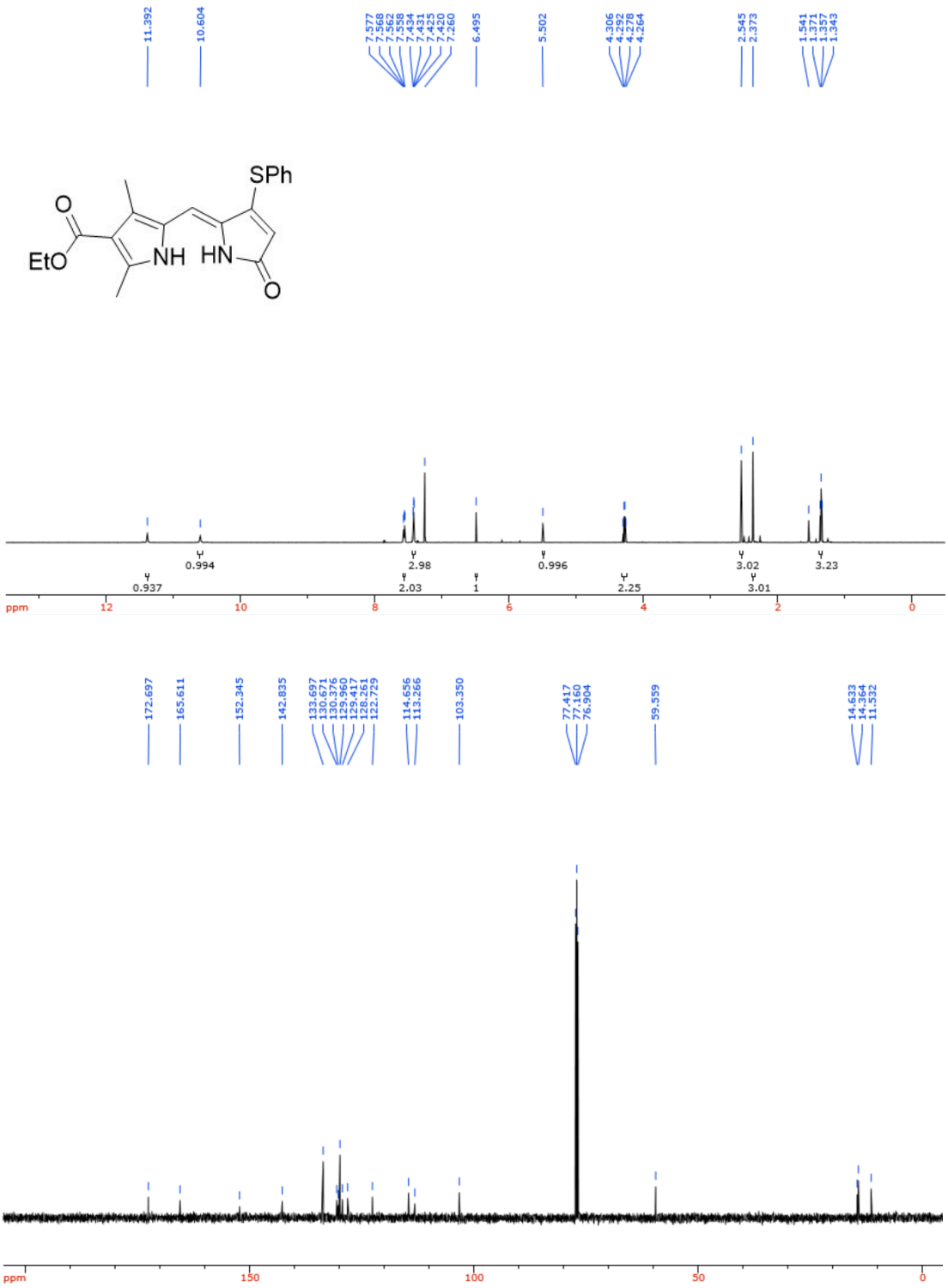




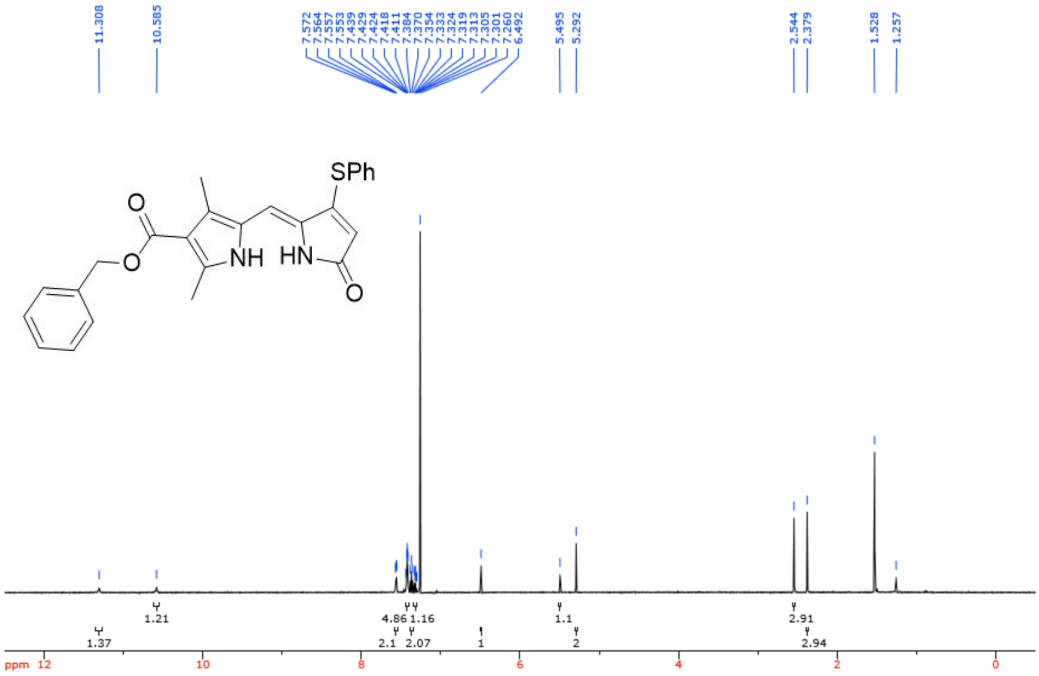
^{1}H and ^{13}C-NMR of 48a in $CDCl_3$:



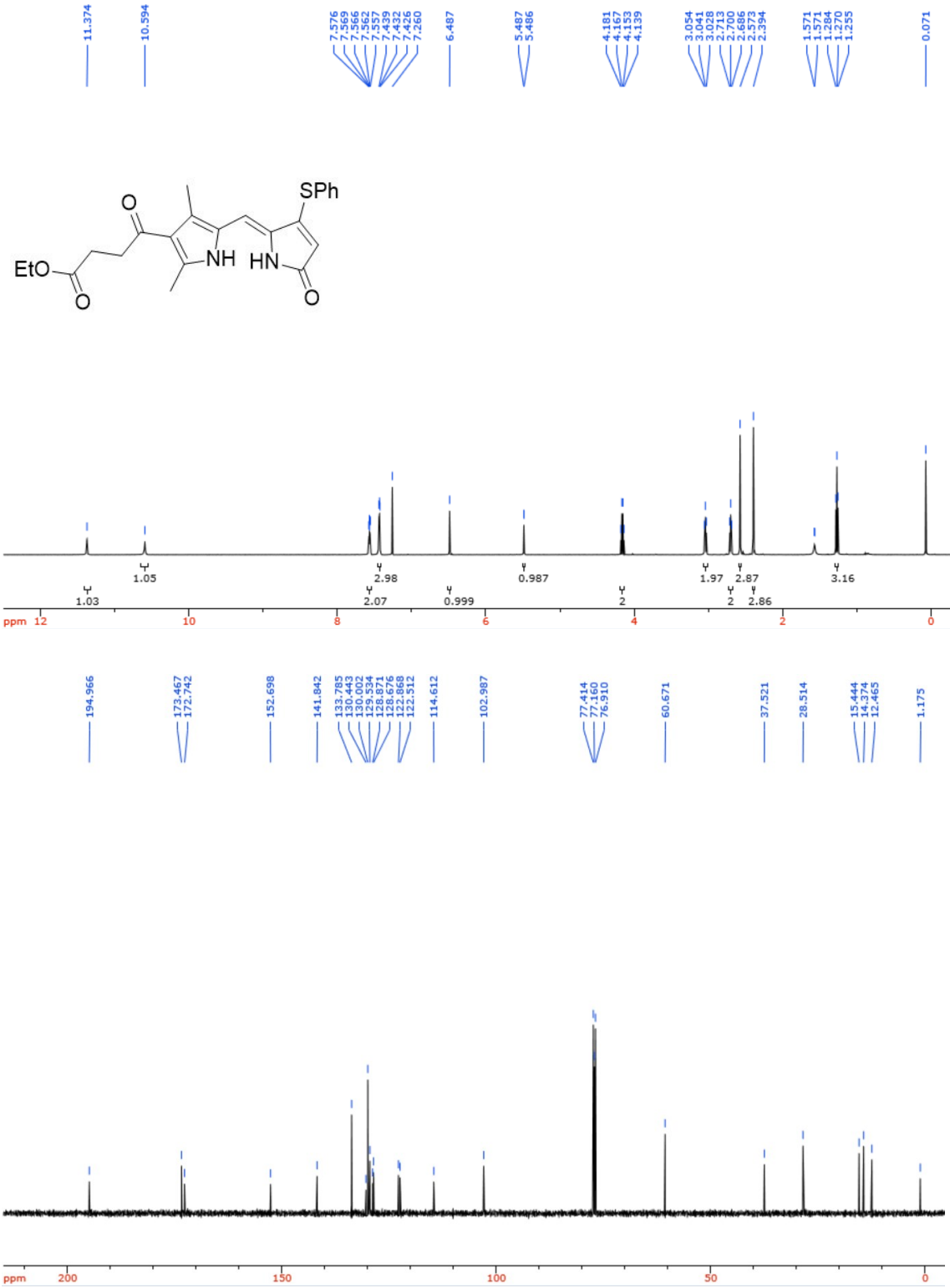
^{1}H and ^{13}C-NMR of 48c in $CDCl_3$:



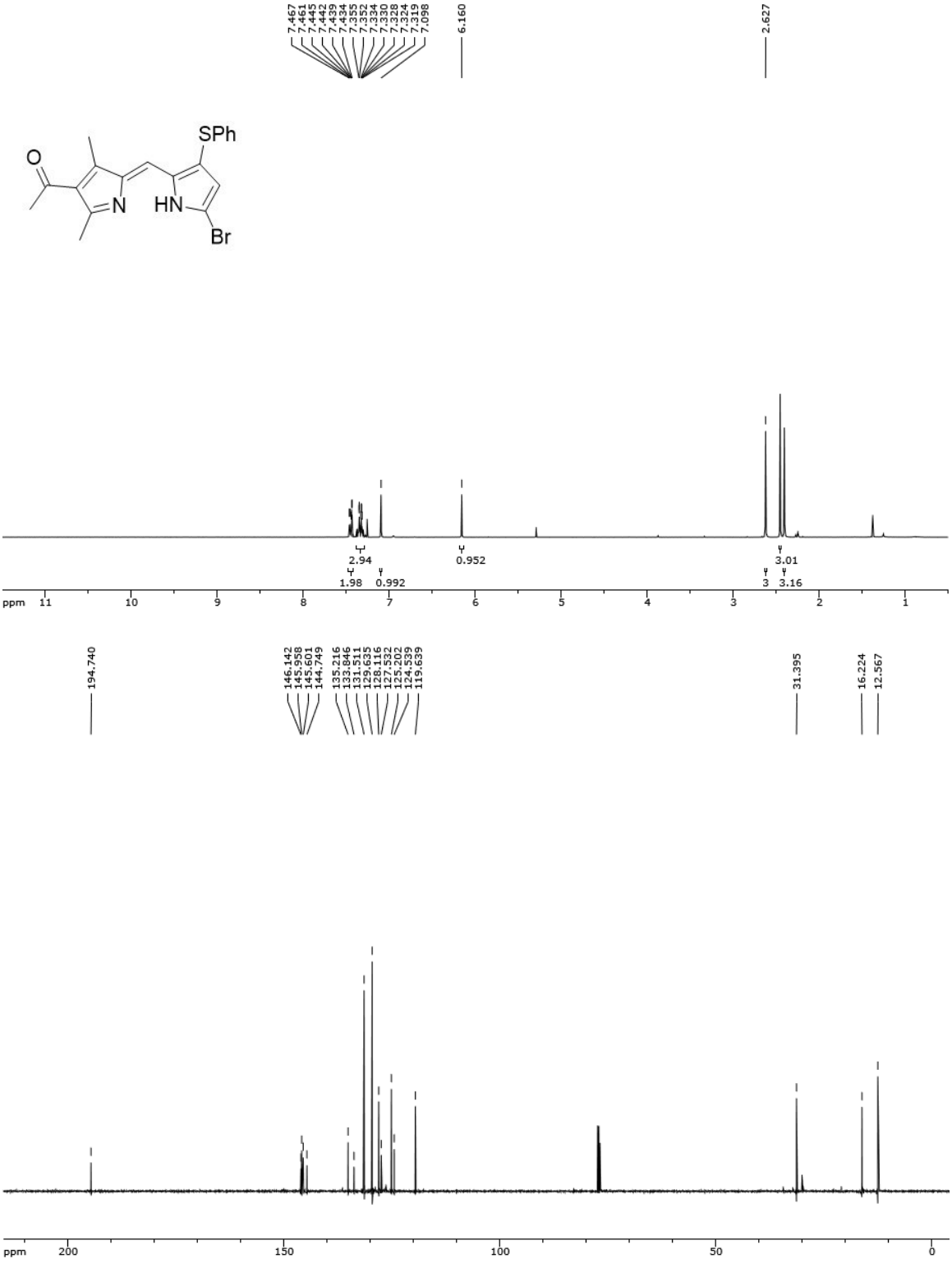
^{1}H-NMR of 48d in $CDCl_3$:



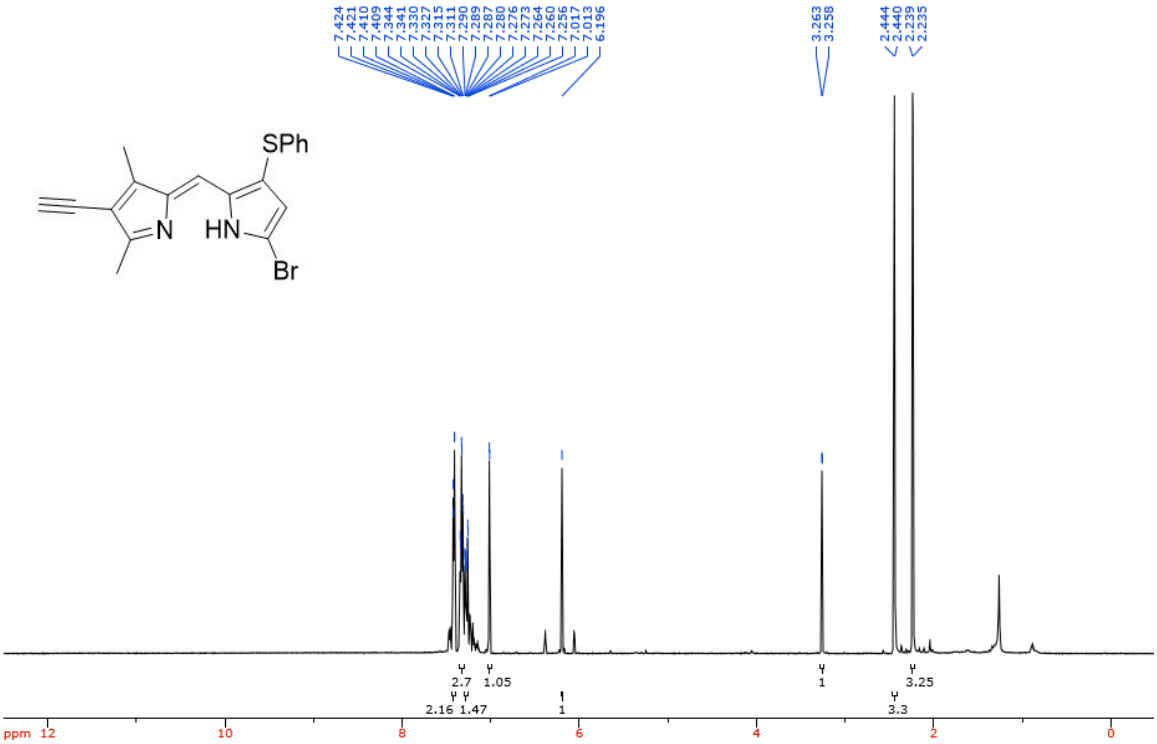
^{1}H and ^{13}C-NMR of 48e in $CDCl_3$:

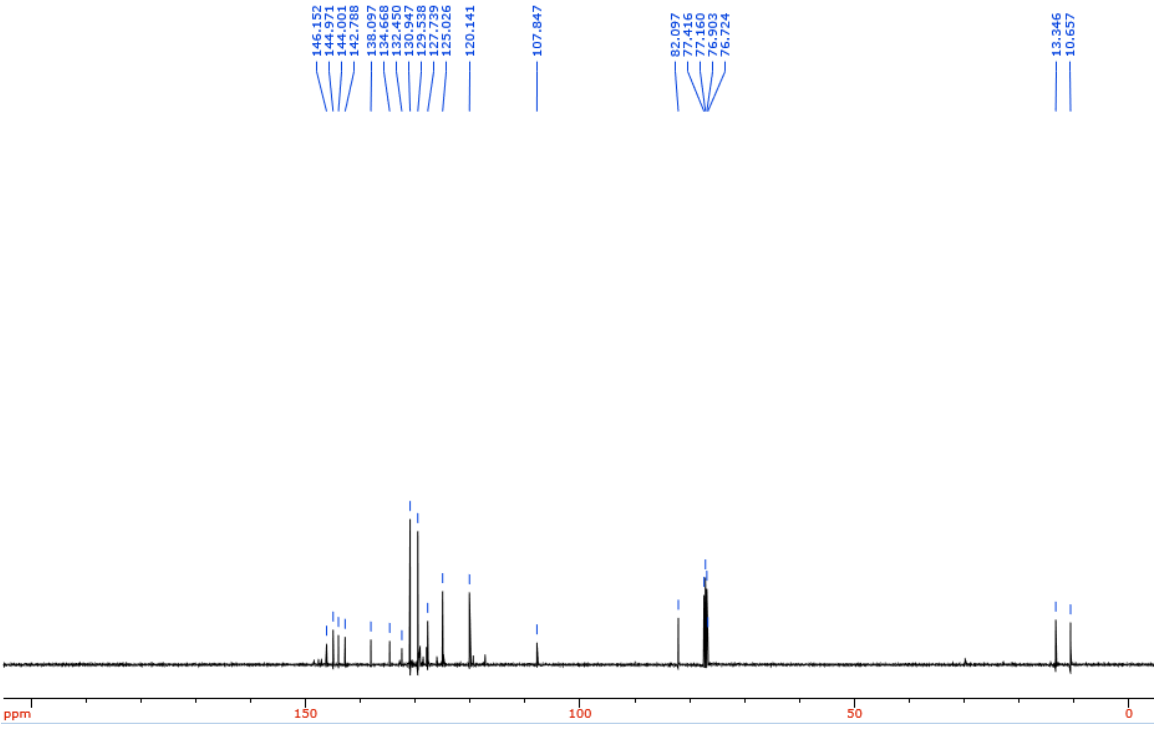


^{1}H- and ^{13}C-NMR of 49a in $CDCl_3$:

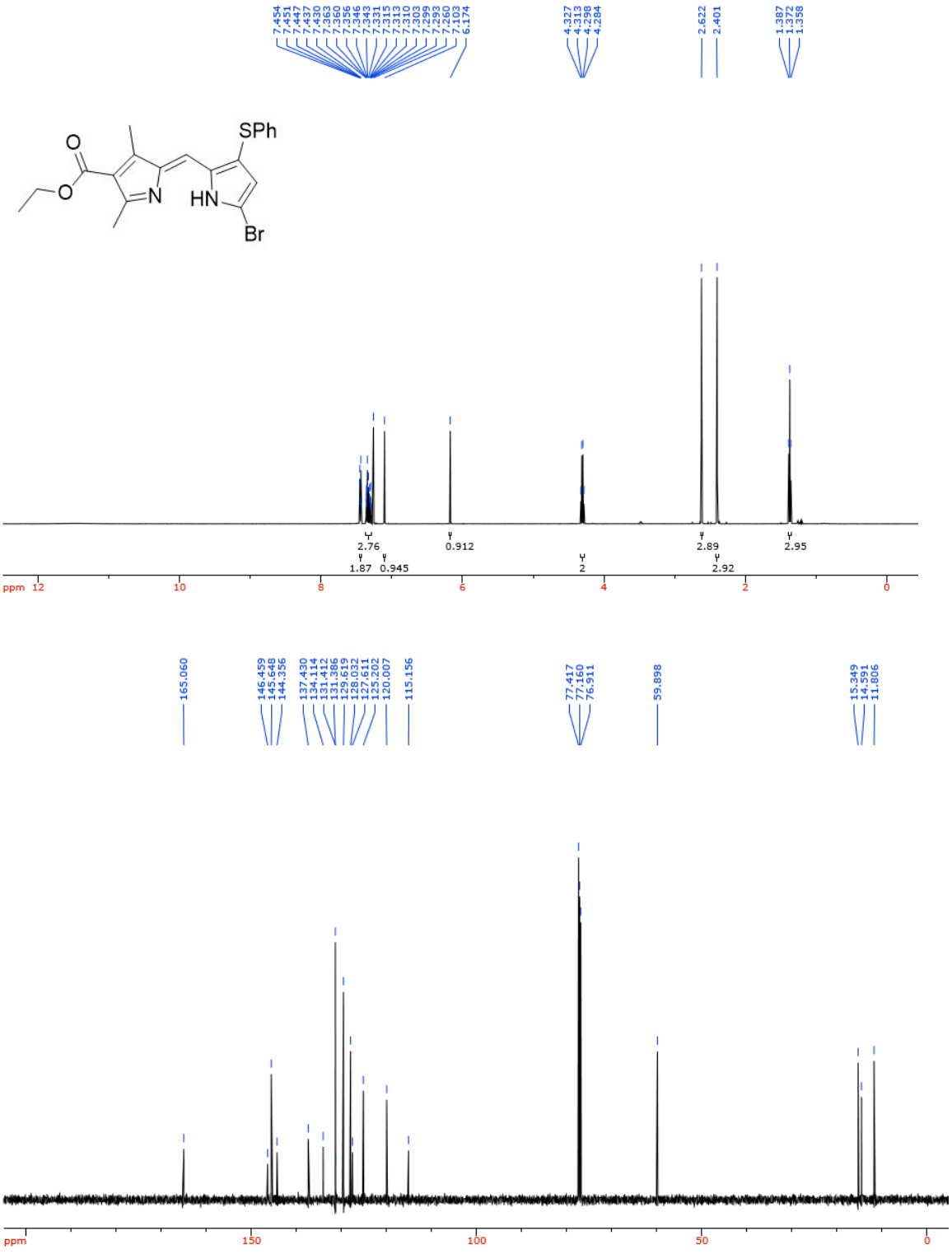


^{1}H and ^{13}C-NMR of 49b in $CDCl_3$:

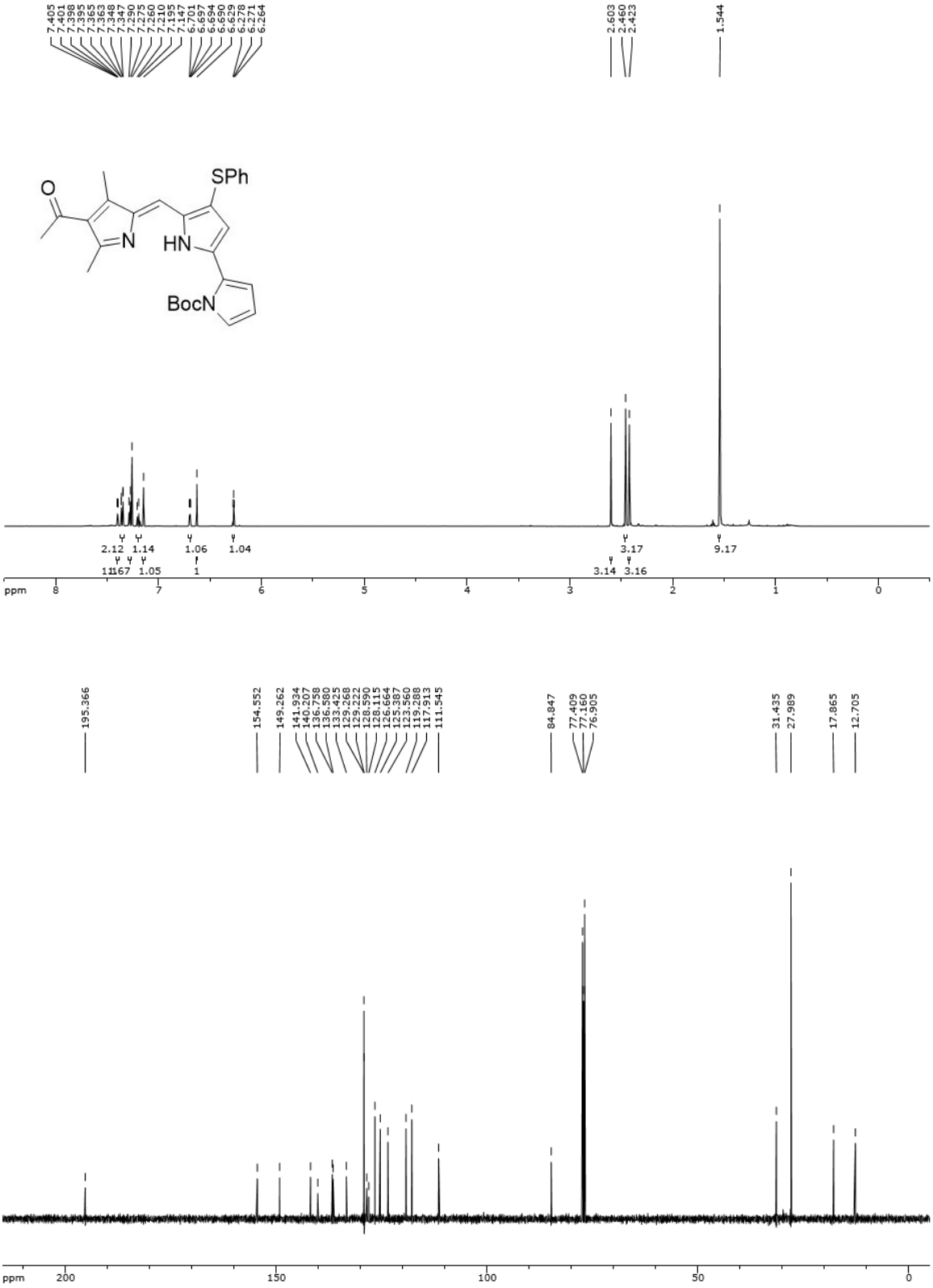




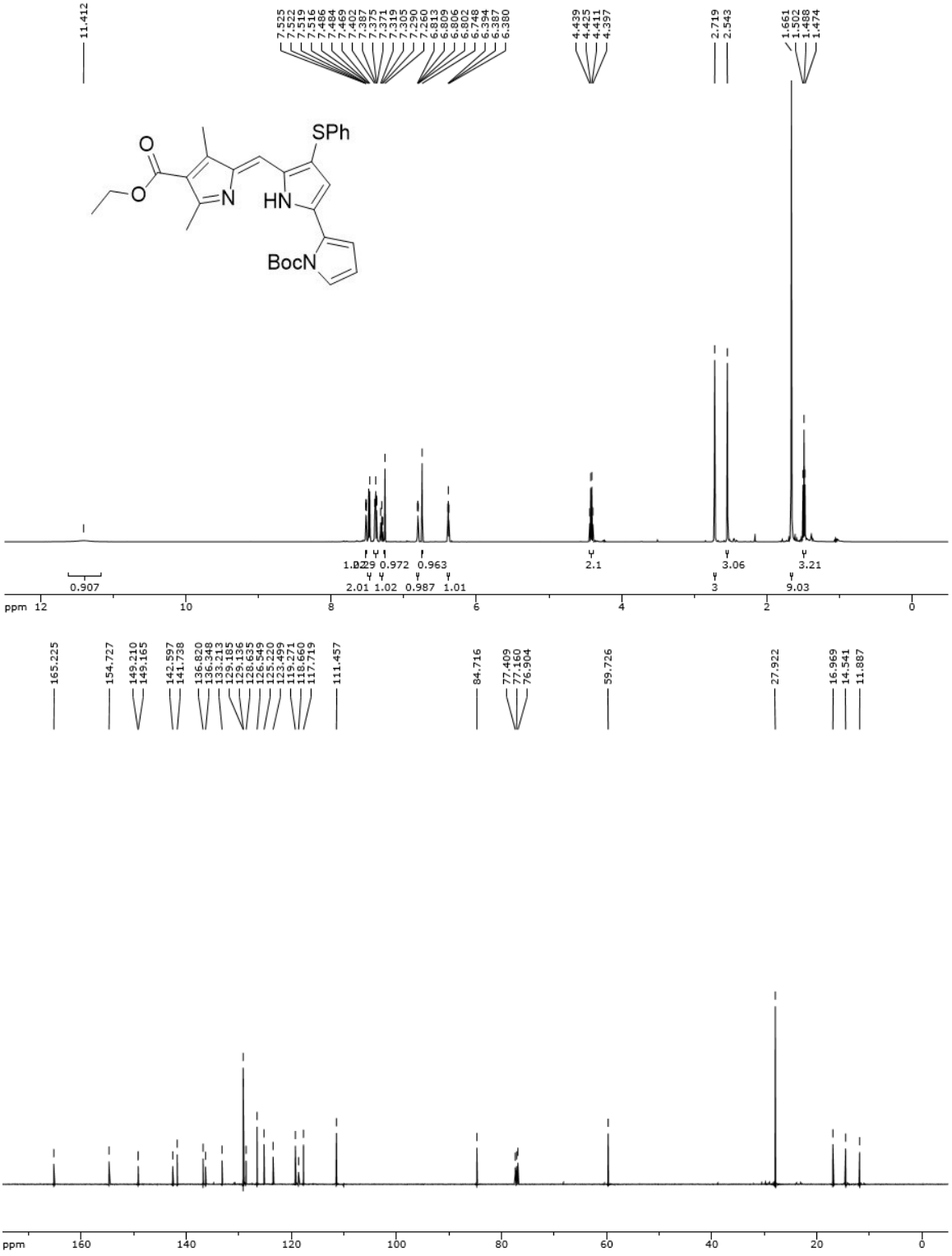
^{1}H and ^{13}C-NMR of 49c in $CDCl_3$:



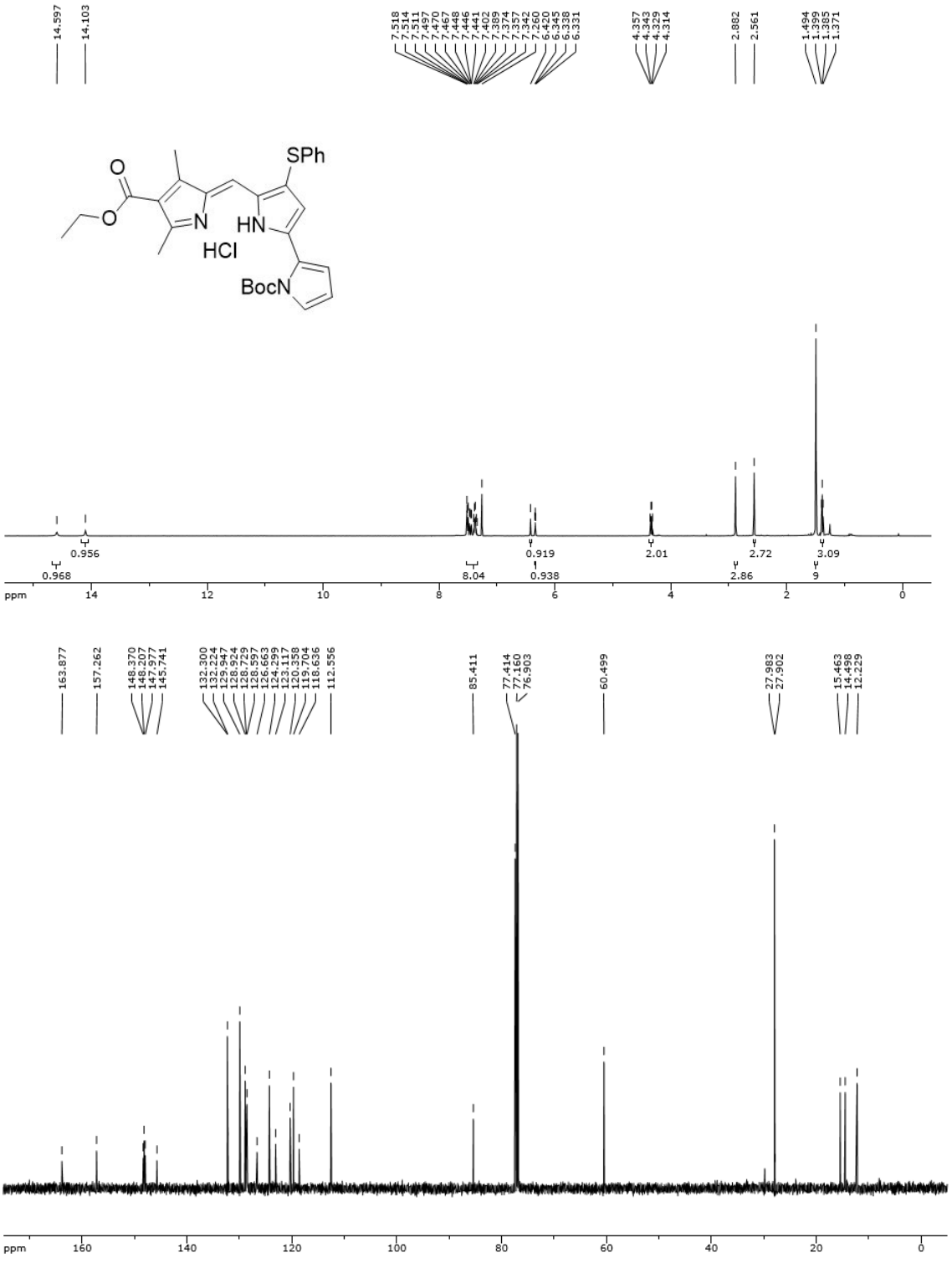
^{1}H and ^{13}C-NMR of 50a in $CDCl_3$:



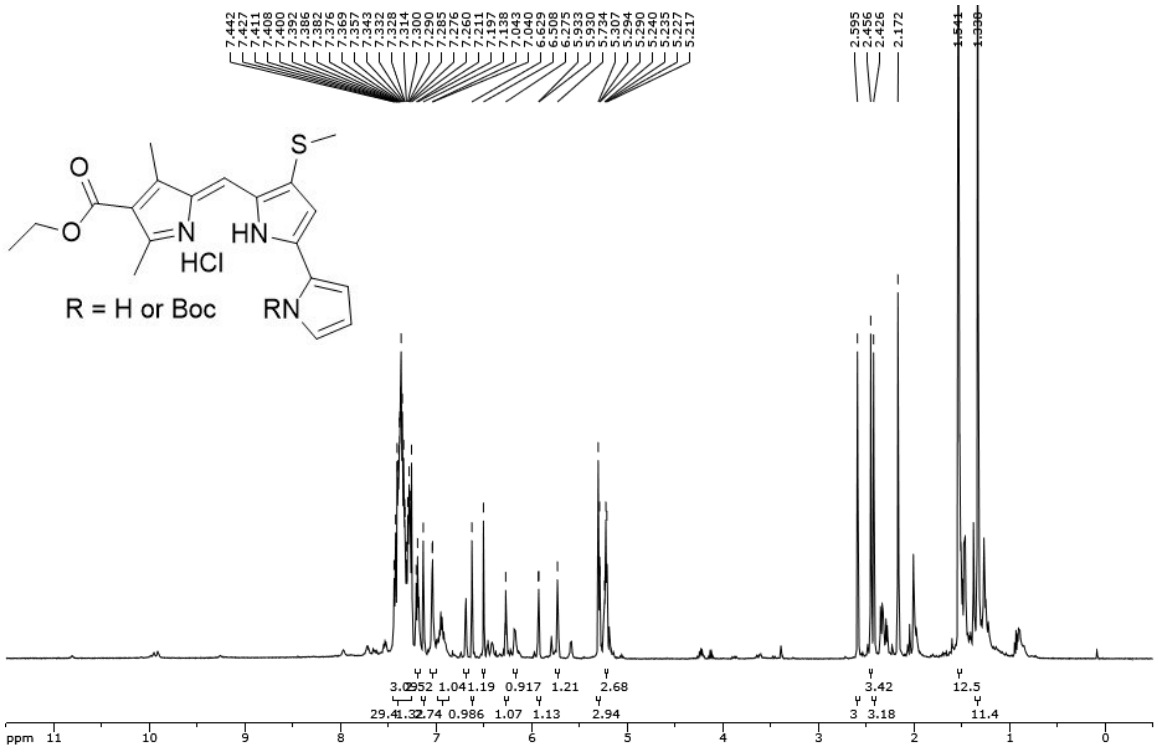
^{1}H and ^{13}C-NMR of 50c in $CDCl_3$:



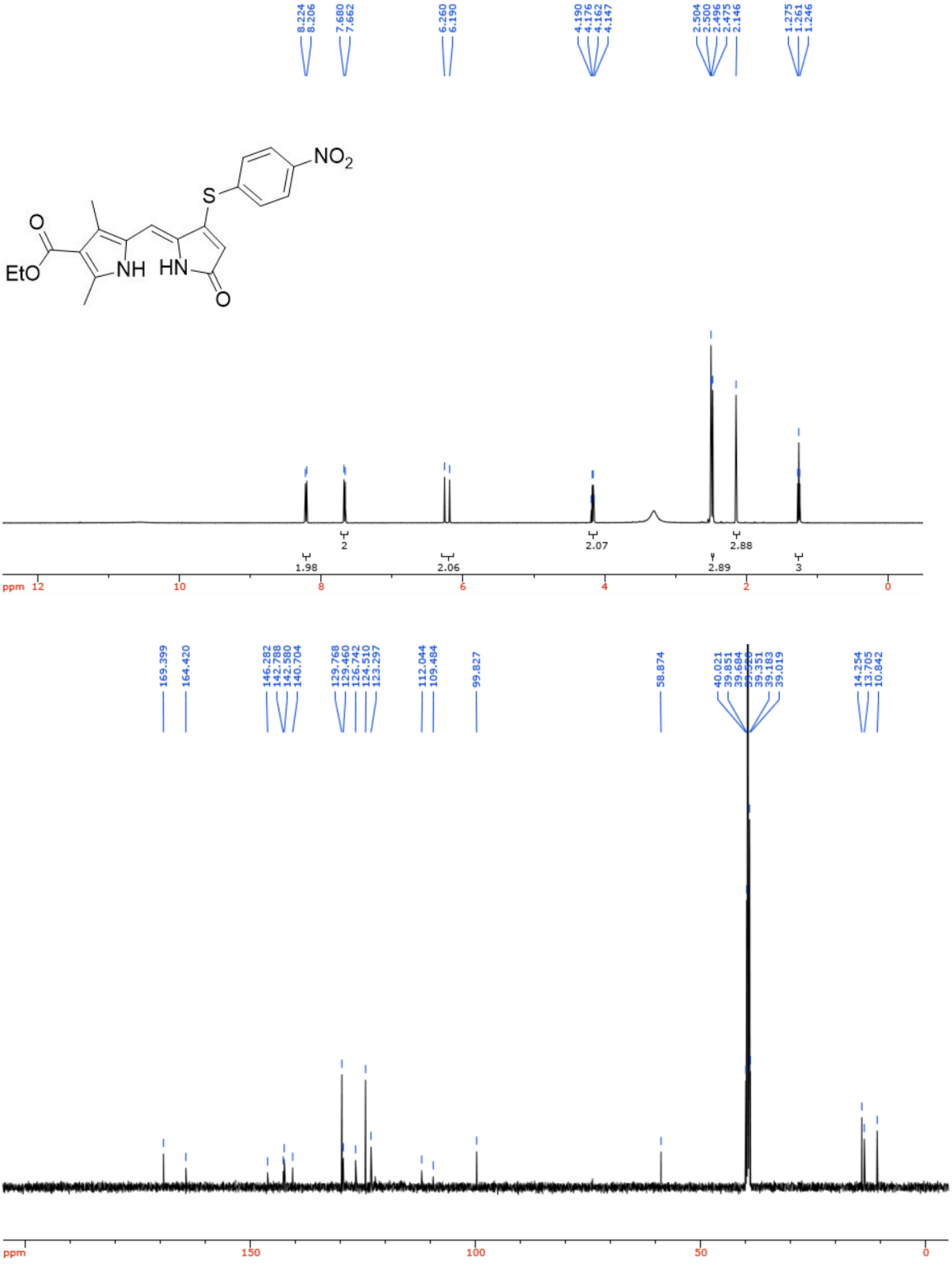
^{1}H and ^{13}C-NMR of 50c•HCl in $CDCl_3$:



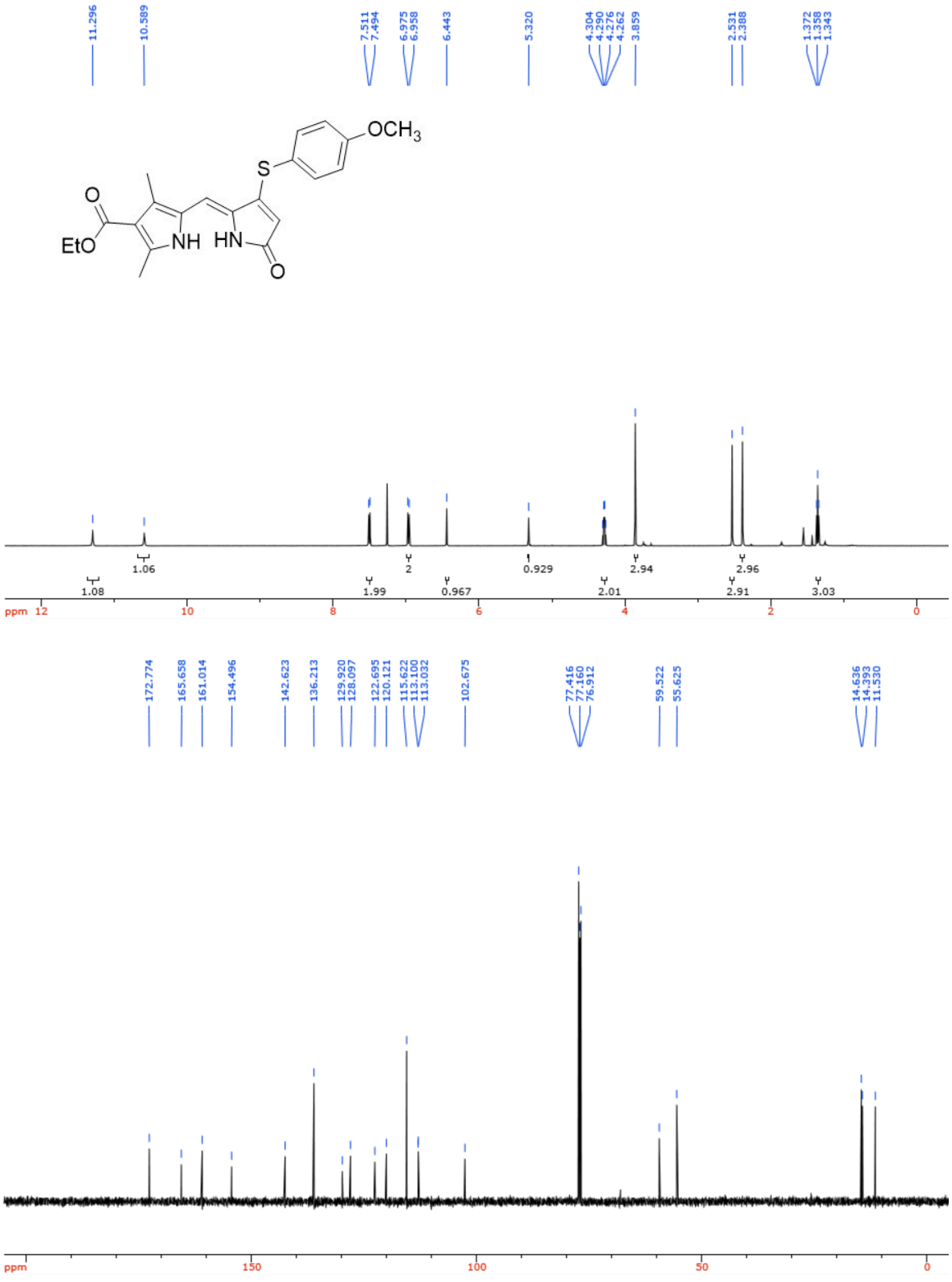
^{1}H-NMR of 50d•HCl in $CDCl_3$:



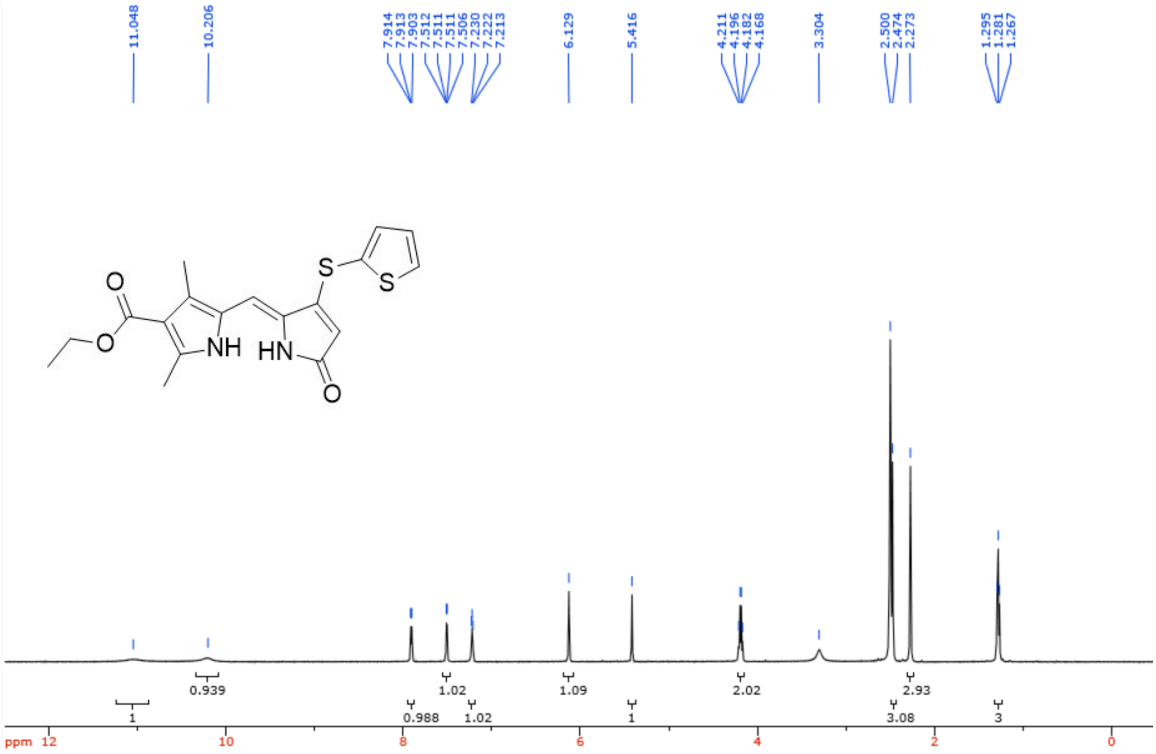
^{1}H and ^{13}C-NMR of 54a in $CDCl_3$:



^{1}H and ^{13}C-NMR of 54b in $CDCl_3$:



^{1}H-NMR of 54c in $CDCl_3$:



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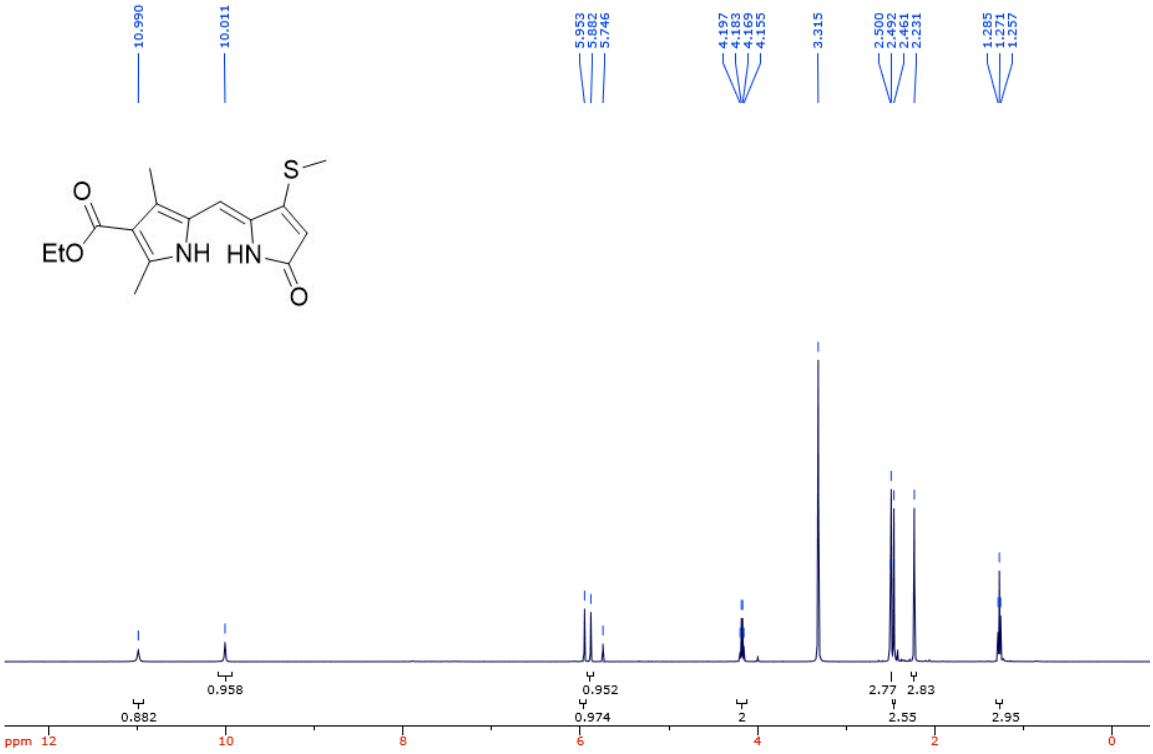

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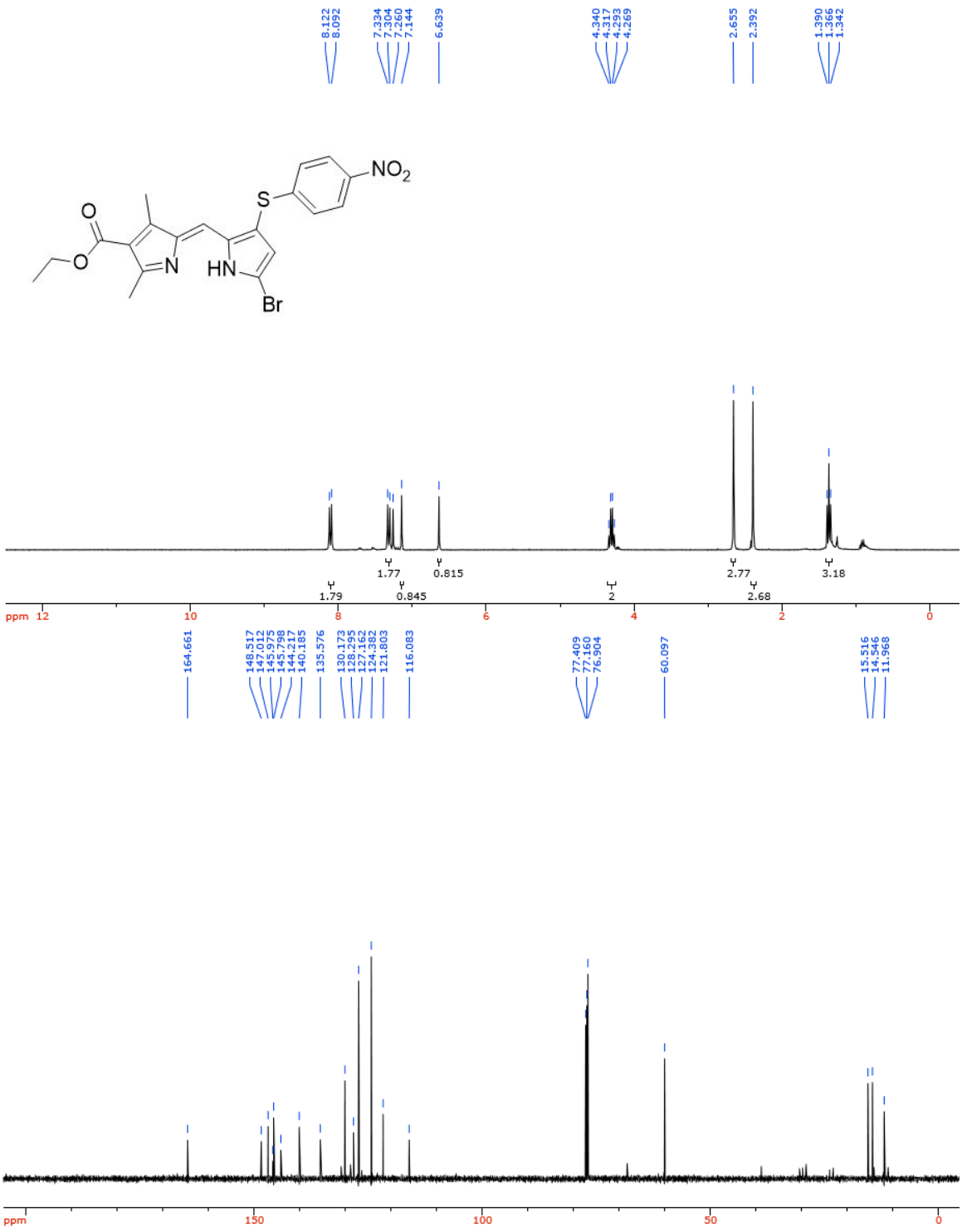

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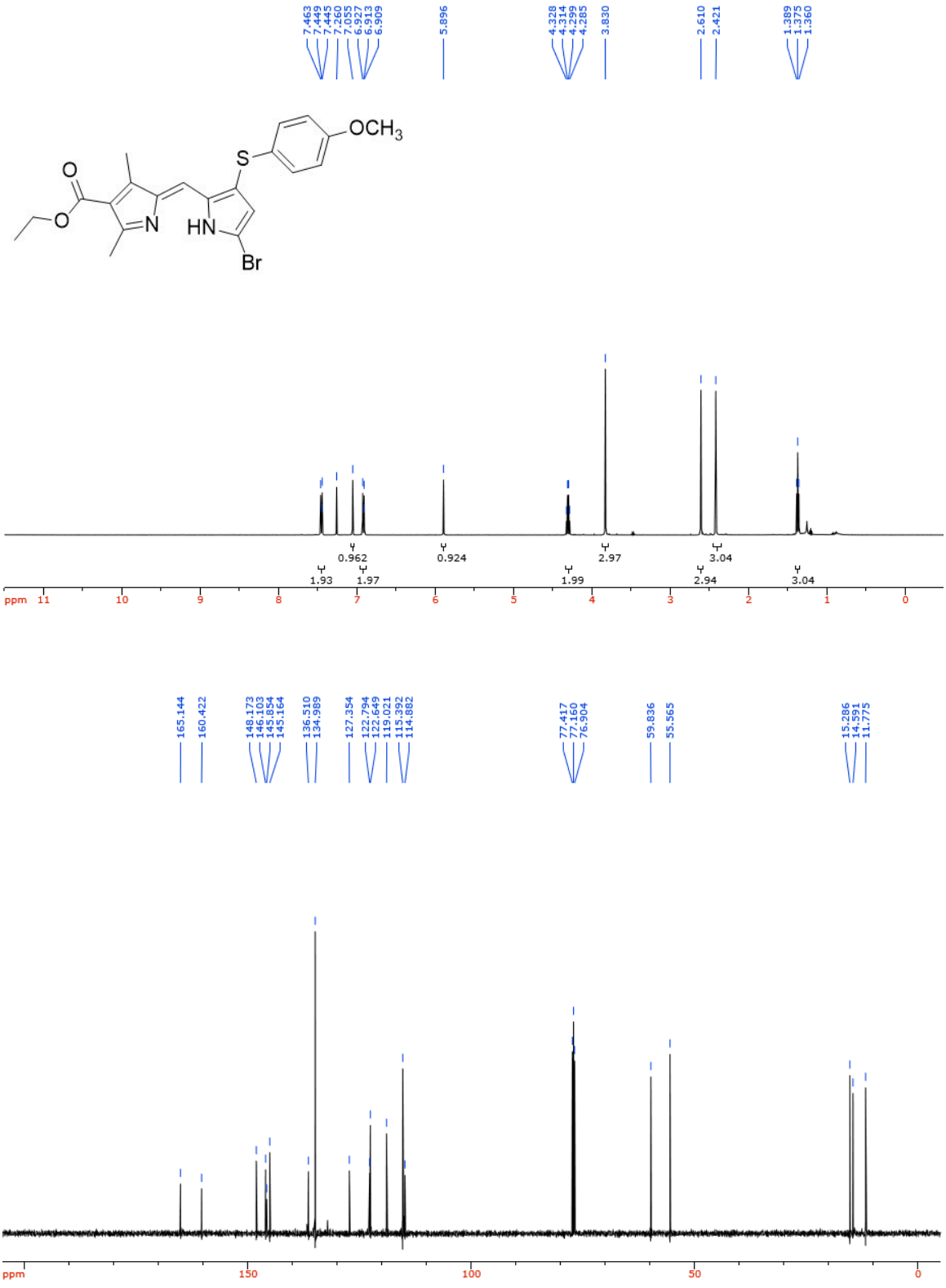

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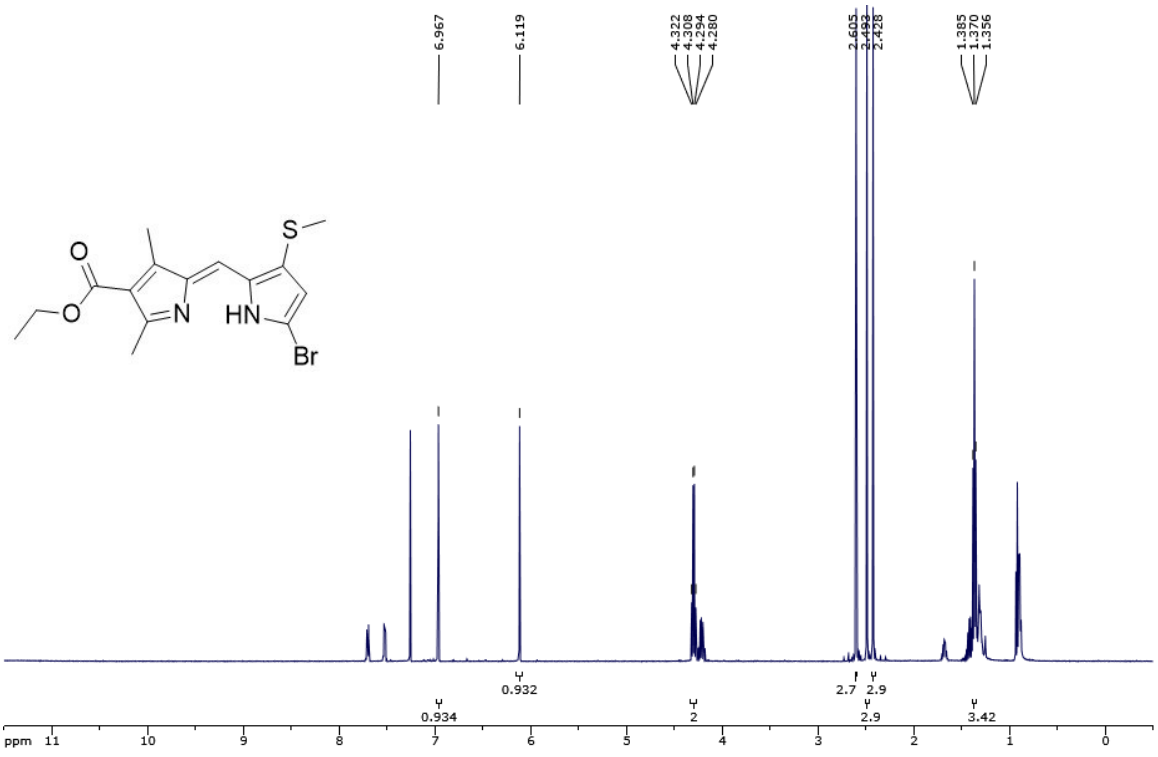
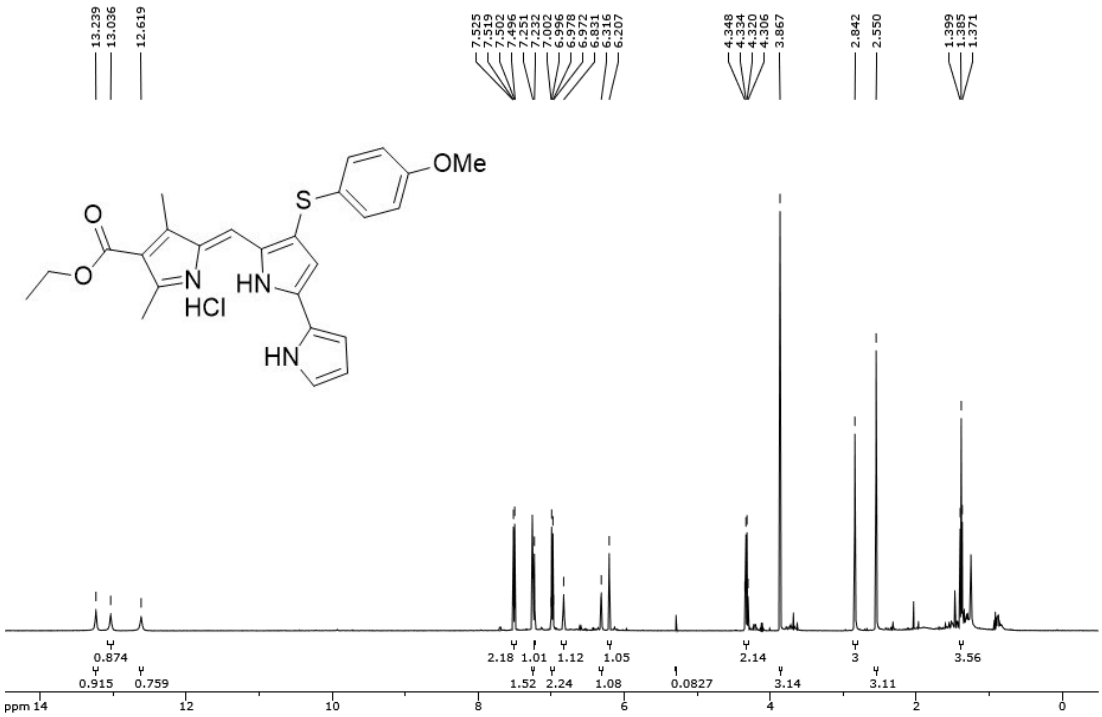
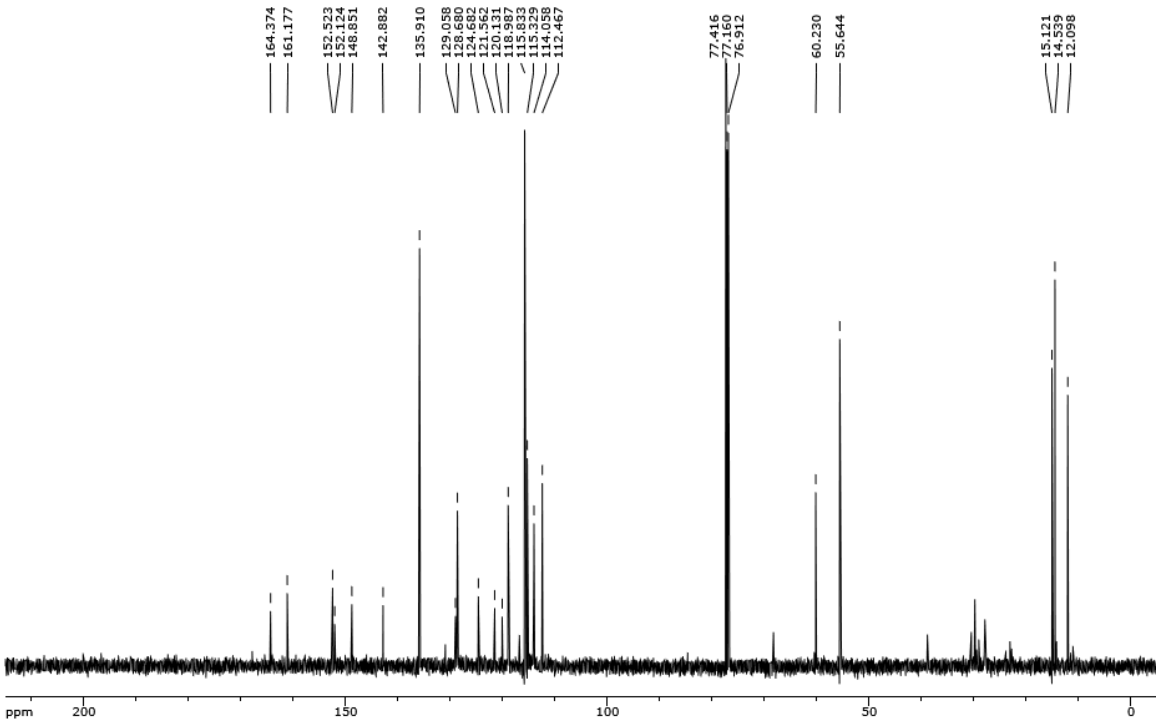


^{1}H and ^{13}C-NMR of 56b•HCl in $CDCl_3$:





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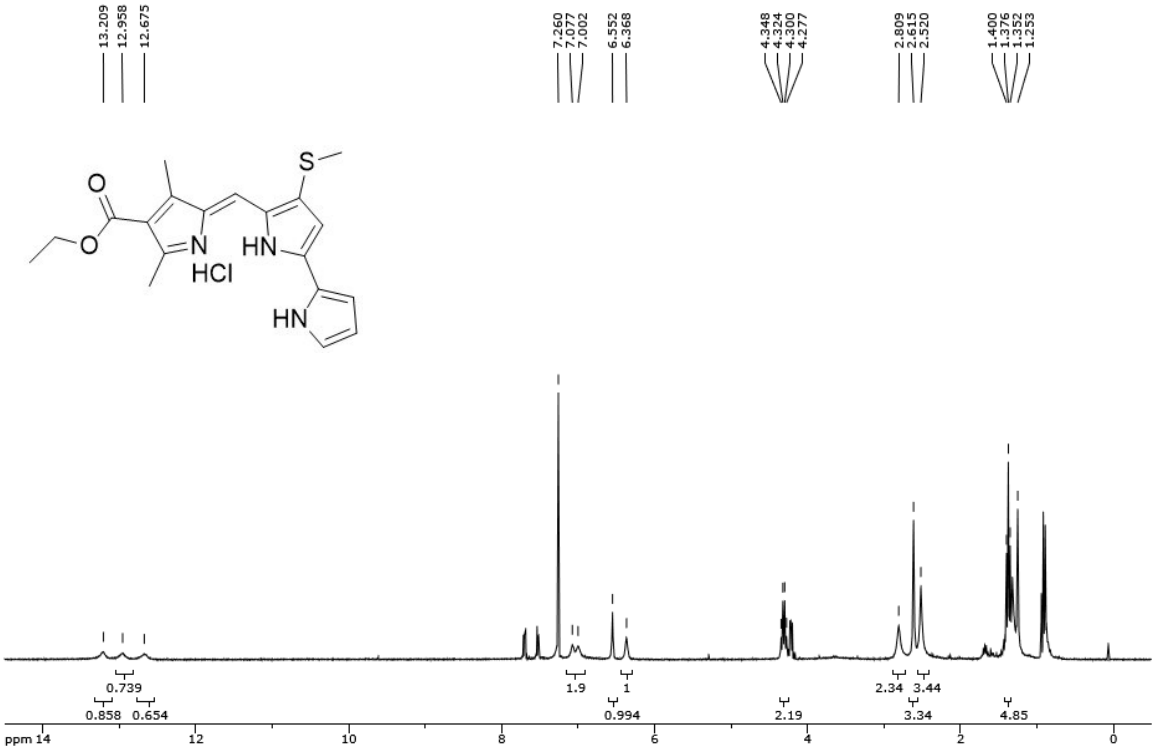

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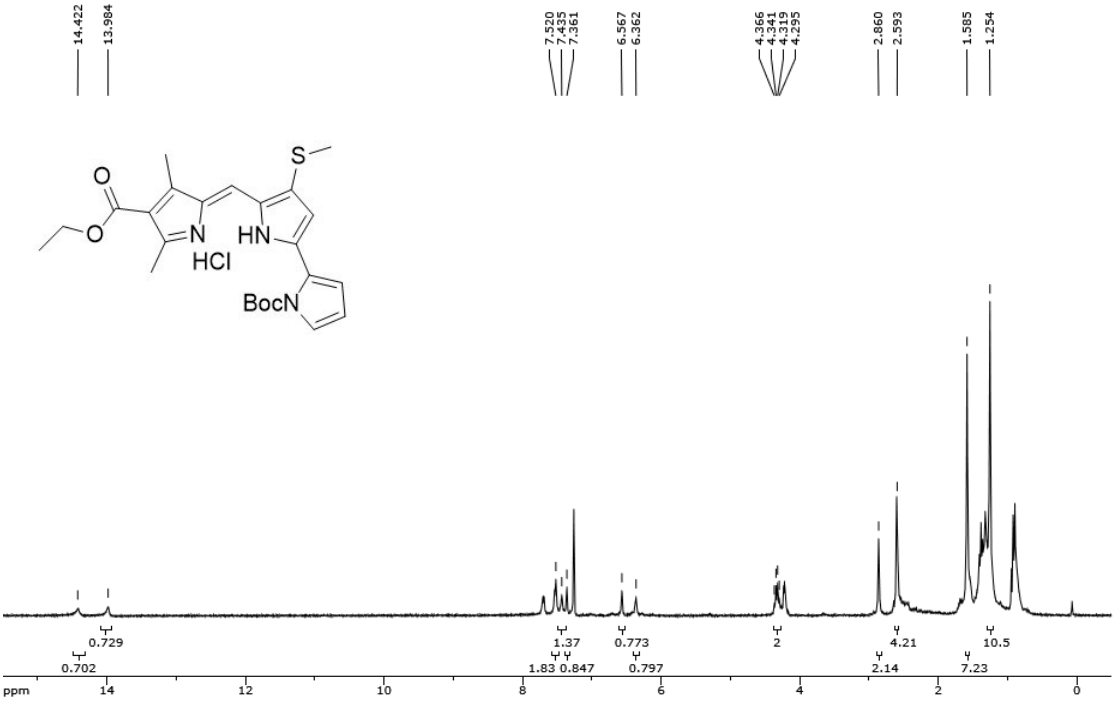

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