TOWARDS THE SYNTHESIS OF DI- AND TRI-PYRROLIC COMPOUNDS

By

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For Mom & Dad

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ABSTRACT

Dipyrrins and prodigiosenes are two classes of pyrrolic compounds. Dipyrrins consist of two pyrrole units linked by a methane bridge and prodigiosenes are a class of pyrrolyldipyrrins (a dipyrrin with a pyrrole substituent) containing a methoxy substituent. During this graduate work, two projects were undertaken to investigate these two classes.

The first project involved the development of a novel methodology for the synthesis of symmetric *meso*-H-dipyrrin hydrobromides. The reaction of 2-formylpyrroles in acidic methanol gives the corresponding symmetric, *meso*-H-dipyrrin hydrobromides in good yields. This convenient one-pot strategy involves initial deformylation under the acidic conditions, followed immediately by in situ reaction of the resulting α-free pyrrole with the remaining 2-formyl pyrrole in solution. However, there is evidence of some concerted character in this reaction mechanism and this is being investigated by isotopic labeling of a symmetric, α-free, 2-formyl pyrrole.

The second project involves the synthesis of a series of prodigiosenes in order to study their biological activity with respect to anticancer activity and leukemia selectivity. Acute myeloid leukemia (AML) accounts for the majority of adult leukemias and remains fatal for 40% of patients. Recently published work presented four new prodigiosenes featuring alkanoate substitution patterns, the first of their kind to be developed in the Thompson lab and the first to exhibit strong selectivity against leukemia cell lines. As such, a series of twelve new prodigiosenes have been designed and synthesized to probe the role of the alkyl ester substituent, the role of the ester moiety versus an amide moiety, the role of lipophilicity and the necessity of an alkyl ester over a conjugated ester regarding cell line selectivity.

LIST OF ABBREVIATIONS USED

δ	chemical shift
° C	degrees Celsius
Ac	acyl
AcOH	acetic acid
AML	Acute Myeloid Leukemia
Bn	benzyl
BnOH	benzyl alcohol
br	broad
Bu	butyl
CAN	ceric ammonium nitrate
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublets
dq	doublet of quartets
DCE	dichloroethane
DCM	dichloromethane

dec.	decomposition
DEPT-Q	Distortionless Enhancement by Polarization Transfer-Quaternary
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalents
ESI TOF	electrospray ionization time of flight
Et	ethyl
EtOAc	ethyl acetate
F-BODIPY	4,4'-diflouro-4-bora-diaza-*s*-indacenes
FDA	Food and Drug Administration
g	grams
h	hours
H_2O	water
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HSQC	Heteronuclear Single Quantum Coherence

Hz	Hertz
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
labeled DMF	*N,N*-dimethylformamide-(*carbonyl*-^{13}C)
M	molar
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minute
mL	milliliters
mmol	millimole
NCI/DTP	National Cancer Institute/Developmental Therapeutics Program
NMR	Nuclear Magnetic Resonance
O.N.	over night
PIG	phosphatidylinisitol glycan

q	quartet
quin	quintet
s	singlet
SAR	Structure-Activity Relationship
t	triplet
tBu	tert-butyl
TEG	triethyleneglycol
Tf	triflyl
TFA	triflouroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMOF	Trimethylorthoformate
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

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CHAPTER 1 INTRODUCTION

1.1 An Introduction to Pyrroles

Heterocycles are cyclic compounds where elements such as oxygen, sulfur or nitrogen, replace one or more of the carbon atoms in a ring.[1] Heterocyclic compounds represent a large group of biologically active compounds and they play a significant role in the pharmaceutical industry.[2] They are present within the structures of many active medicinal ingredients of drugs and also occur naturally in the nucleic acids and sugars which are fundamental to life, among other things.[3,4] Some common heterocyclic compounds include furan, pyridine and pyrrole (**Figure 1**).

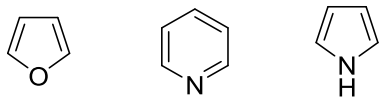


Figure 1: Common heterocyclic compounds; furan, pyridine and pyrrole (left to right).

Pyrroles and their derivatives are one of the most important classes of heterocyclic compounds.[5] **Figure 2** shows International Union of Pure and Applied Chemistry (IUPAC) numbering of the pyrrole ring as well as the common naming in which positions 2- and 5- are commonly referred to as α and α', and positions 3- and 4- as β and β', respectively. The pyrrole ring system is widely distributed in a variety of natural and biologically important molecules.[6] Many pyrrole-containing compounds have shown antioxidant, antibacterial, antitumor, antifungal, anti-inflammatory and immune suppressant activities. Functionalized pyrroles are sub-units of heme, chlorophyll, bile pigments, vitamin B12, porphyrins, coenzymes, naturally occurring drugs (Netropsin and Distamycin) and more.[5-7] As such, functionalized pyrroles are important synthetic targets.

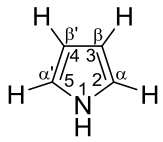
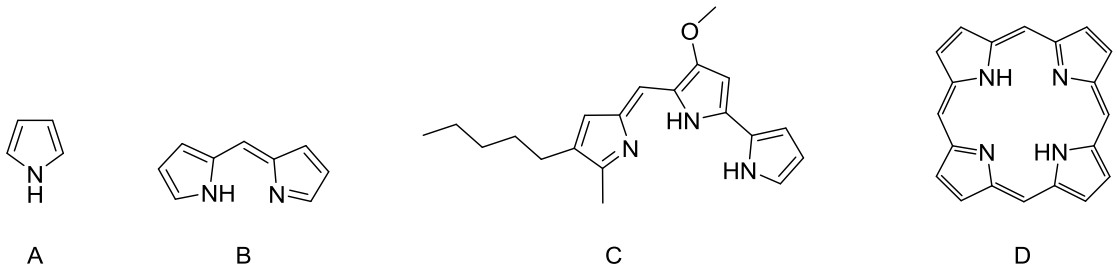


Figure 2: The IUPAC numbering and common nomenclature of the pyrrole ring system. Positions 2(5) referred to as α(α'), 3(4) as β(β').

Organic synthesis is a very important branch of organic chemistry that is concerned with the construction of organic compounds via organic reactions. This is an important field for many reasons. It makes natural products more accessible, provides routes to novel compounds, aids in structural identification, provides new methods and contributes to the field of organic chemistry as a whole. Many methods have been developed for the synthesis of pyrroles and their derivatives.[8-19] The development of new methodology is important for improving efficiency and for inventing new methods which are more affordable, more accessible, have better atom economy, employ green chemistry methods, provide routes to new skeletons and are scalable for industrial purposes.

The Thompson research group focuses on the synthesis and use of pyrrole-containing molecules. These can be divided roughly into four categories of pyrroles; mono-, di-, tri-, and tetra-pyrrolic compounds (**Figure 3**). Herein, the synthesis and applications of two classes, di-pyrrolic and tri-pyrrolic compounds, will be discussed.



A B C D

Figure 3: A) Pyrrole, B) dipyrrin, C) prodigiosin (tri-pyrrolic) and D) porphyrin (tetra-pyrrolic).

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CHAPTER 2 SYNTHESIS OF SYMMETRIC *MESO*-H DIPYRRIN HYDROBROMIDES

Excerpts from this chapter are taken from:

Lund, K. A. R.; Thompson, A. *Synlett* **2014**, *25*, 1142.

2.1 Introduction

The conjugated π-system of dipyrrins[1,2] consists of two pyrrolic units linked by a methene bridge. The structure and nomenclature of the dipyrrin skeleton, as recommended by IUPAC, is depicted in **Figure 4**.[3] The 1- and 9-positions are commonly referred to as the α-positions and the 2-, 3-, 7- and 8-positions as the β-positions, respectively. The 5-position is referred to as the *meso*-position.

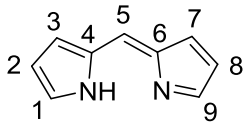


Figure 4: Dipyrrin skeleton and numbering system.

Fully unsubstituted dipyrrin (**Figure 4**) is not stable above – 40 °C.[4] Stability increases with substitution at the α- and β-positions (more substitution = more stable) and, in particular, aryl substitution at the *meso*-position greatly improves the stability of dipyrrins. Dipyrrins without a *meso*-substitution are generally isolated and stored as their more stable HBr or HCl salts.[5]

Traditionally of interest as a building block for porphyrins, the dipyrrinato unit is now appreciated as a useful chromophore by which to invoke desirable features such as

energy transfer and storage by the corresponding complexes (**Figure 5**).[6,7] Of the dippyrin complexes, borondiflouride complexes are the most thoroughly studied due to their high thermal and photochemical stability, chemical robustness, high fluorescence quantum yields and tuneable fluorescence properties. These complexes are formally known as 4,4'-diflouro-4-bora-diaza-s-indacenes and are commonly referred to as *F*-BODIPYs (**Figure 5**).

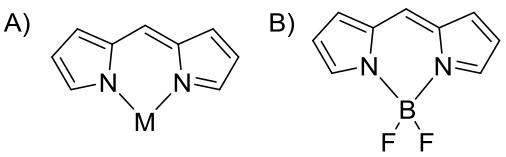
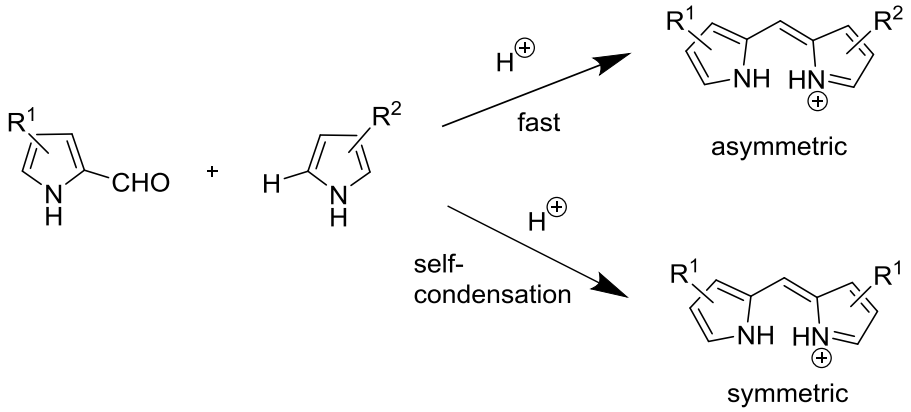


Figure 5: A) Dipyrrinato metal complex framework and B) an *F*-BODIPY.

Beyond the established utility of *F*-BODIPYs, i.e. $-BF_2$ complexes of dipyrrins,[8-11] the luminescence properties of these complexes and those of other metals[12] have fostered the recent use of this framework as a component of dye-sensitized solar cells.[13,14] Following earlier work regarding Ir and Rh dipyrrinato complexes as hydrogenation catalysts,[15] Fe and Co dipyrrinato complexes have recently been shown to catalyze the amination of C-H bonds.[16,17] There are numerous recent reports describing the use of dipyrrinato complexes in applications as diverse as biological stains/probes, light harvesters and anticancer agents,[18-23] all pointing towards a promising future for this underdeveloped ligand.

The most common synthetic route to dipyrrins is the MacDonald coupling,[24,25] an acid-catalyzed condensation of a 2-formyl pyrrole with a pyrrole that is unsubstituted in the 2-position, i.e. α-free (**Scheme 1**).[1,2] Upon the addition of aqueous HBr to a 2-formyl

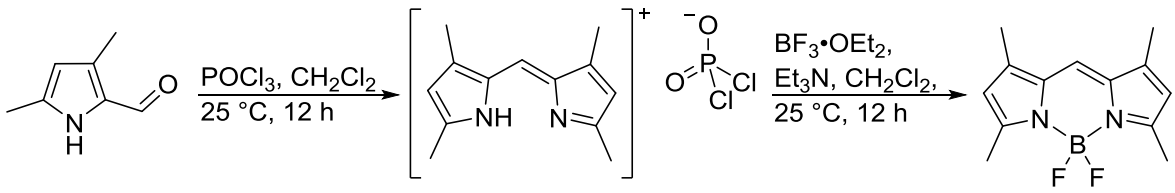
pyrrole and an α-free pyrrole, a dramatic colour change typically ensues, turning the solution an immediate orange/brown/brick-red colour, dependent upon the substituent patterns of the substrates, accompanied by rapid precipitation of the dipyrrin hydrobromides salt (**Scheme 1, top**). Both the colour change and the precipitation are delayed when the α-free pyrrole is electron-poor because the presence of electron-withdrawing substituents decreases the nucleophilicity of the pyrrole.[26] In some cases this leads to the formation of an undesired symmetric dipyrrin, resulting from competitive self-condensation of the 2-formyl pyrrole (**Scheme 1, bottom**).[2]



Scheme 1: MacDonald coupling to generate an asymmetric dipyrrin (top); when R^2 = electron-withdrawing group, the MacDonald coupling is uncompetitive and a symmetric dipyrrin forms (bottom).

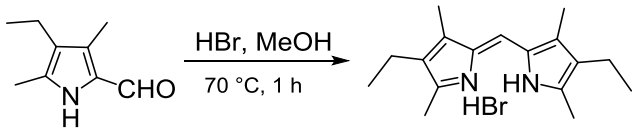
Symmetrical dipyrrins are usually prepared via: a) reacting two equivalents of an α-free pyrrole with formic acid; b) acid-catalyzed hydrolysis, decarboxylation and condensation of pyrrole-2-carboxylates in formic acid; or c) a MacDonald coupling in which the α-free component and the 2-formyl pyrrole have the same substitution

pattern.[27] Wu and Burgess reported the preparation of symmetric *F*-BODIPYs from 2-formyl pyrroles, eliminating the need to use an α-free pyrrole.[28] *F*-BODIPYs were isolated via an in situ trapping of the dipyrrin, demonstrating the one-pot synthesis of *F*-BODIPYs from 2-formyl pyrroles (**Scheme 2**). As such, just as α-free pyrroles can be generated via the acid-catalyzed decarboxylation of 2-carboxylate pyrroles, so too the precedent was demonstrated for the deformylation of 2-formyl pyrroles.



Scheme 2: One pot synthesis of an *F*-BODIPY by in situ trapping of dipyrrins.[28]

As such, the efficient synthesis and isolation of symmetric, *meso*-H-dipyrrins formed from 2-formyl pyrroles in the presence of acids was developed as part of the current thesis (**Scheme 3**). As well as being extremely convenient, this strategy complements existing methods by enabling the high-yielding synthesis of symmetrical dipyrrins where the α-free pyrrole has electron-withdrawing functional groups or may not be easily accessed.



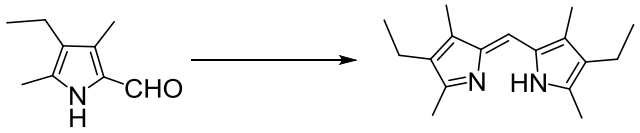
Scheme 3: Dipyrrin hydrobromides from 2-formyl pyrroles.

2.2 Results and Discussion

2.2.1 Optimization of 2-Formyl Pyrrole Synthesis

To investigate the formation of dipyrrins via acid-catalyzed deformylation (**Scheme 3**), 3,5-dimethyl-4-ethyl-2-formyl pyrrole (**1a**) was chosen as a test substrate (**Table 1**). First, a methanolic solution of **1a** and 48% aqueous HBr (1.1 equiv.) were stirred at room temperature. Although analysis using TLC indicated that some dipyrrin had formed after 48 hours, significant amounts of starting material remained (**entry 1**). Repeating the reaction using a temperature of 40 °C induced a gradual colour change, disappearance of starting material according to TLC analysis and the precipitation of the product after five hours (**entry 2**). However, performing the reaction at 70 °C for just two hours returned a 72% yield of the required dipyrrin hydrobromide (**entry 3**), and the yield was improved to 84% after just one hour with the use of excess HBr (27 equiv.) (**entry 4**). The use of AcOH, MeCN or DCE as the solvent, in place of MeOH, required longer reaction times and lower yields resulted (**entries 5-7**). The use of TFA as acid in place of HBr was effective (**entry 8**), but for convenience the more crystalline hydrobromide salts were pursued. After examining the effect of acid, temperature and solvent on dipyrrin formation, it was found that the optimal conditions were to react the 2-formyl pyrrole with excess HBr in MeOH at 70 °C for 1 h (**entry 4**).

Table 1: Examining the effect of acid, temperature and solvent on the conversion of **1a** into **2a**.



1a **2a**

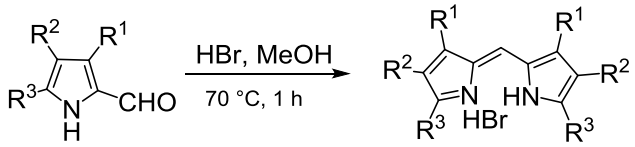
Entry	Solvent	Temp (°C)	Time (h)	Acid (equiv)	Isolated yield (%)
1	MeOH	r.t.	>48	HBr (1.1)	Reaction incomplete
2	MeOH	40	5	HBr (1.1)	70
3	MeOH	70	2	HBr (1.1)	78
4	MeOH	70	1	HBr (excess)	84
5	AcOH	70	4	HBr (excess)	67
6	MeCN	70	2.5	HBr (excess)	50
7	DCE	70	4.5	HBr (excess)	70
8	MeOH	70	24	TFA (excess)	74

2.2.2 A Look into Substrate Scope

A variety of 2-formyl pyrroles were then subjected to the optimized reaction conditions (**entry 4, Table 1**) to evaluate the scope of the methodology (**Table 2**). Analogues bearing alkyl (**2a-e**), keto (**2f-h**), alkanoate (**2i-j**) and conjugated ester (**2k, l**) substituents all reacted as expected to give the requisite dipyrrin salts. For the cases where yields are moderate, the microcrystallinity of these dipyrrins hampered isolation,

e.g. **2h**. Furthermore, the ethoxy groups of **1g** and **1h** inevitably underwent exchange in acidic methanol, and gave the Me ester-containing dipyrrins **2g** and **2h**, respectively.

Table 2: Dipyrrin hydrobromide salts from 2-formyl pyrroles.

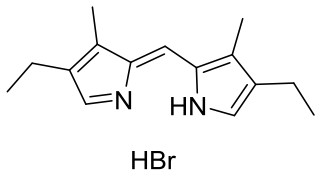


1a-l **2a-l**

Dipyrrin	R^1	R^2	R^3	Isolated yield (%)
2a	Me	Et	Me	84
2b	Me	Me	Me	72
2c	Me	Et	H	63[a]
2d	Me	$(CH_2)_4Me$	Me	79
2e	Me	$(CH_2)_6Me$	Me	75
2f	Me	Ac	Me	83
2g	Et	$COCH_2CH_2CO_2Me$	Me	79
2h	Et	$CO(CH_2)_4CO_2Me$	Me	50
2i	Me	CH_2CO_2Me	Me	65
2j	Me	$CH_2CH_2CO_2Me$	Me	84
2k	Me	CO_2Bu	Me	79
2l	Me	CO_2Bn	Me	90

[a]9:1 ratio of symmetric: asymmetric dipyrrins

Presumably,[28] the mechanism involves (some of) the 2-formyl pyrrole undergoing deformylation to give the α-free analogue which immediately undergoes rapid condensation, at 70 °C, with the remaining unreacted 2-formyl pyrrole. However, the regioselective formation of **2c** potentially points to some concerted character (**Figure 6**). Upon deformylation, pyrrole **1c** would have two unsubstituted α-positions, yet the major product (9:1 ratio) formed via nucleophilic attack from the α-position that had previously been substituted with the formyl group.



^{1}H NMR; 300 MHz, $CDCl_3$

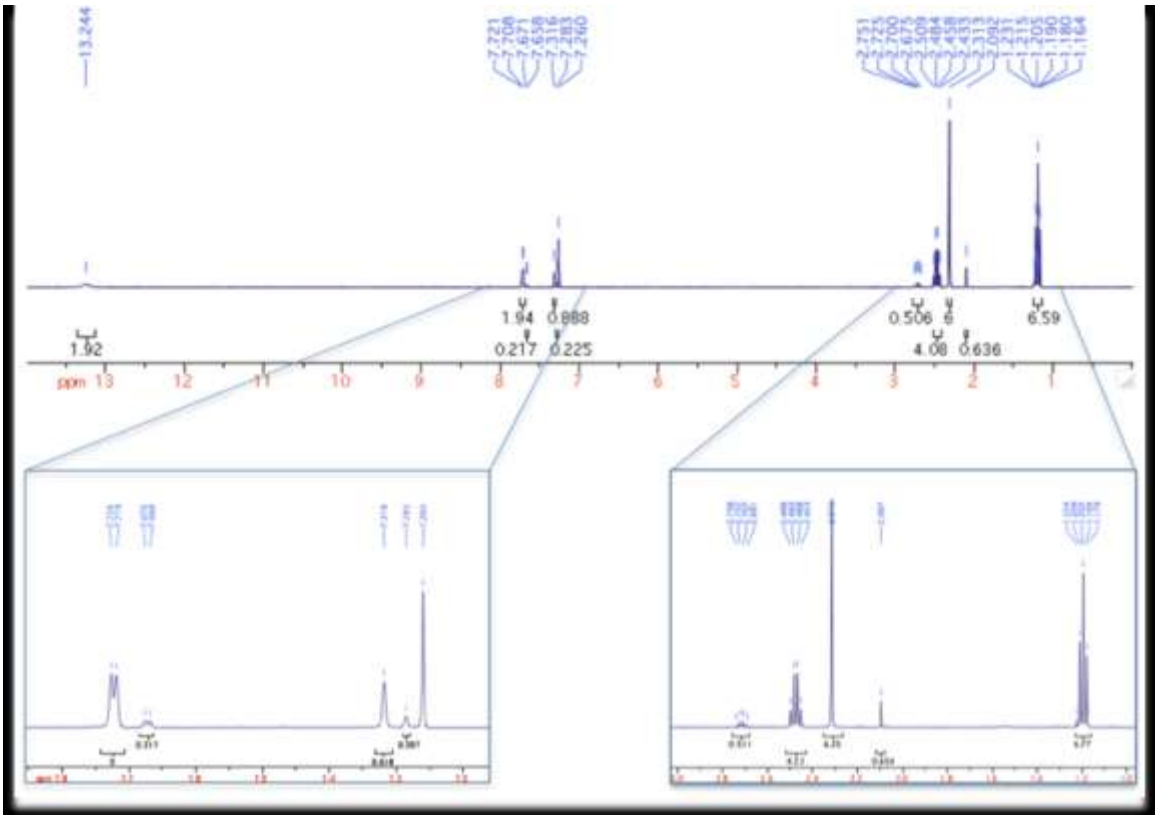
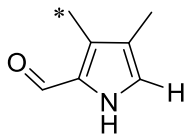


Figure 6: ^{1}H NMR spectrum of 2,3,7,8-Tetramethyl-4,6-dipyrrin hydrobromide (**2c**)
*note the presence of 10% of the dipyrrin salt isomer.

2.2.3 Mechanistic Studies – Synthesis of a Labeled 2-Formyl Pyrrole

In order to determine whether the mechanism has concerted character or is influenced by steric effects, isotopic labeling with carbon-13 (^{13}C) will be used to mark a symmetric pyrrole, and the fate of the labeled atom will be monitored using NMR spectroscopy. Having significant proportions of ^{13}C (an NMR active nucleus) at one of

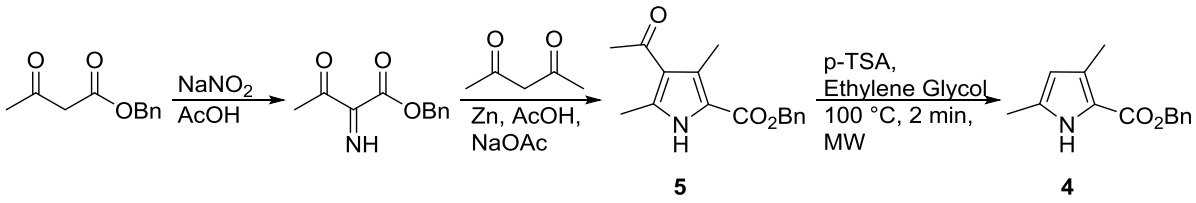
the substituent positions in the compound of interest will allow for location of the atom of interest in the final product, by NMR spectroscopy. To fit the needs of this experiment, the target 2-formyl pyrrole **3** (**Figure 7**) will be synthesized. This substrate is unsubstituted in the α'-position and the β and β'-substituents are Me groups (one of which contains the ^{13}C), eliminating any steric influence in the reaction to form the dipyrrin.



3

Figure 7: Target compound for studying the mechanism of dipyrrin formation using NMR spectroscopy. The ^{13}C labeled Me group is indicated by an asterisk (*).

Pyrrole **4** was chosen as the starting pyrrole for the synthesis of **3** in order to incorporate the ^{13}C label in a selective manner (**Scheme 4**). Pyrrole **4** was synthesized by combining benzyl benzoacetate and AcOH and adding a solution of $NaNO_2$ to generate the oxime which was then reacted with 2,4-pentanedione in AcOH with NaOAc and Zn while carefully monitoring the exothermic reaction and maintaining a temperature below 60 °C. When the reaction was complete, the product was precipitated through addition of the reaction mixture to iced-water. Crystallization of the crude product from a MeOH/H_2O mixture, gave the required pyrrole (**5**).[29] The next step involved de-acylation under microwave conditions to give pyrrole **4** (**Scheme 4**).[30]



Scheme 4: Synthesis of pyrrole **5.**[29,30]

Although unlabelled pyrrole **3** is generally synthesized through removing both the α and α' substituents and then formylating (**Figure 8**),[31] this method is not suitable for asymmetric pyrroles as it is not selective and would give a mixture of products with the label on both sides of the pyrrole. It was for this reason that the proposed alternative route to pyrrole **3** from pyrrole **4** was explored (**Scheme 5**).

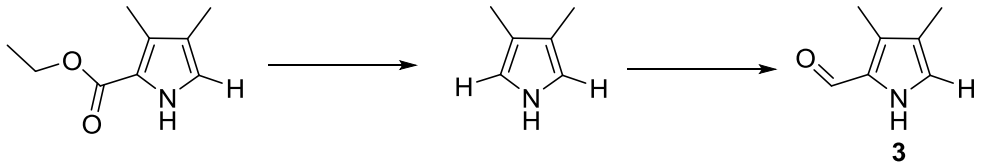
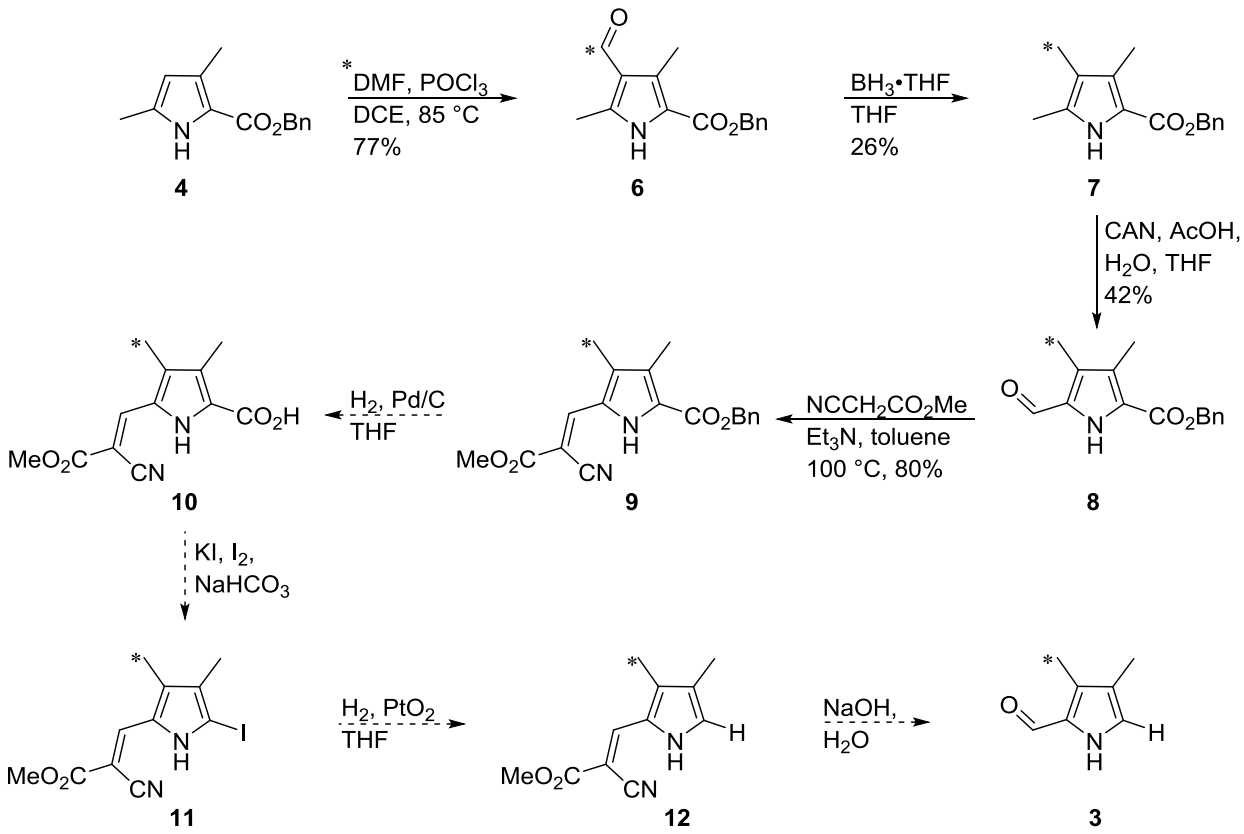


Figure 8: Reported synthesis of pyrrole **3**.[31]

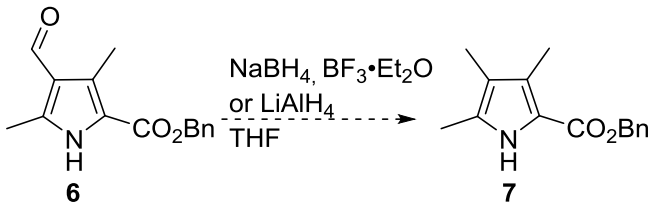


Scheme 5: Incorporation of ^{13}C label (*) and synthesis of pyrrole **3**.

Pyrrole **4**, with its Bn ester, was selected because the hydrogenation of Bn esters is well documented in the literature[32,33] and the aldehyde protecting group was predicted to survive these reaction conditions. With pyrrole **4** in hand, *N,N*-dimethylformamide-(*carbonyl*-^{13}C) (labeled DMF) can be incorporated through a Vilsmeier-Haack reaction. Quite often, Vilsmeier-Haack reactions are performed with a great excess of DMF and in the absence of any other solvent, with the pyrrole as the limiting reagent.[34] This would not be ideal as the labeled DMF is much more expensive than regular DMF and so it would be costly to synthesize the labeled pyrrole through this method. Due to the extra

expense of the labeled DMF, it was necessary to make DMF the limiting reagent in order to optimize the amount of **6** synthesized with the amount of DMF available at a reasonable price (1 g). When the reaction was first attempted according to the recommended literature amounts (19 equiv. of DMF)[34] only 70 mg of pyrrole **6** was synthesized from 0.5 g of DMF. When stoichiometric amounts of DMF and **4** (0.5 g, 1 equiv.) were used, 1.4 g of **6** was synthesized. Finally, when the Vilsmeier-Hack formylation was carried out with 1 g of ^{13}C labeled DMF it gave 2.55 g of **6** (77% yield).

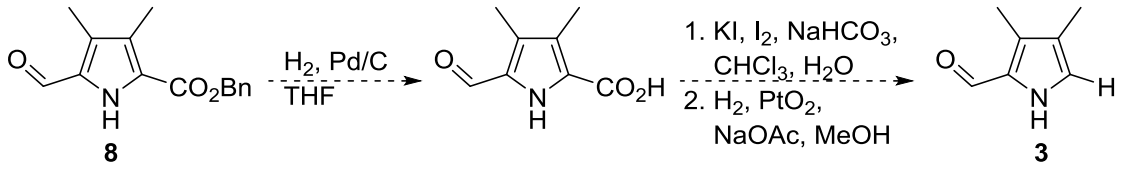
The next step involved reducing pyrrole **6** to give the trimethyl pyrrole **7**, containing the label. This reduction was attempted using a few different reducing agents. When $LiAlH_4$ was used,[35] a baseline spot and minimal amount of the expected product (**7**) was observed via TLC analysis (**Scheme 6**). The combination of $NaBH_4$ and $BF_3 \bullet Et_2O$[36] in THF successfully converted **6** to **7**, according to TLC analysis (**Scheme 6**). However, when the product was collected, the yield was only 12%. A reaction using $BH_3 \bullet THF$ as the reducing agent[37] was attempted multiple times with varying amounts of $BH_3 \bullet THF$ (2-3 equiv., added in portions/all at once), varying reaction times (up to 24 h) and varying reaction temperatures (0 °C to reflux temperature), yet the yields remained very poor (< 30%). However, this was still the best outcome and reduction with $BH_3 \bullet THF$ was focused on here forth. When the labeled pyrrole **6** was subjected to these conditions, it was reduced to **7** in a 26% yield (630 mg).



Scheme 6: Attempted alternative reduction of **6** with $NaBH_4$ with $BF_3 \bullet Et_2O$ as well as with $LiAlH_4$.[35,36]

Next, unlabelled pyrrole **7** was oxidized using CAN to give pyrrole **8** (**Scheme 5**).[38] This method proved most effective if, once any baseline material appeared and if the reaction was incomplete, another equivalent of CAN was added to increase the rate of the reaction, giving less opportunity for decomposition (baseline material). With the labeled substrate, pyrrole **7** was successfully oxidized to **8** in a 42% yield (279 mg).

First the series shown in **Scheme 7** with the unprotected aldehyde was investigated. This series has shown some success in the past, albeit always in poor yields.[39] This is presumably because the aldehyde is liable to reduction by H_2 or oxidation by halogen. However, this series would eliminate the need for additional protection and deprotection steps. Unlabeled pyrrole **8** was thus reacted with H_2 and Pd/C followed by KI, I_2 and finally H_2 and Pt_2O to result in only an 8% yield of pyrrole **3** as an off white solid. After obtaining an NMR spectrum in $CDCl_3$, the compound appeared to decompose or polymerize because the solution turned purple, presumably due to the slight acidity of $CDCl_3$.



Scheme 7: Synthesis of **3** without an aldehyde protecting group.

In order to avoid this, and hopefully improve the yield of this reaction, labeled pyrrole **8** was protected as pyrrole **9** as shown in **Scheme 5**. It was hypothesized that pyrrole **9** would eliminate the opportunity for polymerization due to the basic nature of the deprotection conditions. Labeled pyrrole **8** was thus protected to give pyrrole **9** in 80% yield.[40] The protecting group was expected to survive the hydrogenolysis step necessary to cleave the Bn ester.[40] However, when pyrrole **9** was reacted with H_2 and Pd/C, mass spectrometry and NMR spectroscopy revealed that the protecting group had been partially reduced in the process, and a complex mixture containing **10** and a reduced species was obtained. Despite the presence of the partly reduced compound, the next step was attempted using the crude material. This involved a decarboxylative iodination to give **11**, followed by subsequent dehalogenation to give **12**,[40] which resulted in none of the desired product **12** being isolated.

In order to confirm that the protecting group inevitably gets reduced, the hydrogenolysis experiment was repeated using unlabelled **9** to find that, this time, the protecting group was completely reduced. The mass spectrum of the crude material identified the mass of the isolated product to be 250 g/mol compared to the expected mass of 248 g/mol for **12**, indicating that there were two more protons than expected.

After the analysis of NMR spectra, it became apparent that the protecting group was indeed no longer intact. In the desired product **10** (**Figure 9**), one would expect an sp^2 CH peak and three sp^3 CH_3 peaks. However, the ^1H NMR spectrum was missing the sp^2 CH and instead showed that there was an sp^3 CH_2 in the product (**Figure 10, A**). This was supported by a DEPT-Q NMR experiment which showed the CH_2 phased opposite to the CH_3 carbons (^{13}C NMR spectra shown for comparison, **Figure 10, B**). An edited-HSQC NMR experiment showed the correlation of the observed CH_2 peak in the ^1H NMR spectrum to the CH_2 peak observed in the ^{13}C NMR spectrum, which was also phased opposite to the CH_3 signals (**Figure 10, C**). This led to the proposal of two alternate structures, **13** and **14**, with the protecting group reduced (**Figure 11**). The ^1H NMR spectra showed no evidence of the expected CH proton of **13** (**Figure 10, A**), supported by the COSY spectrum which showed no ^3J coupling, where it would be expected between a CH and CH_2 (**Figure 10, D**). This observation ruled out **13** as the structure observed. The potential structure **14** was also ruled out since the NH peak was not observed and the quartet coupling pattern could not be explained. The structure of the product observed (corresponding to a mass of 250 g/mol) was not elucidated yet there was enough evidence that pyrrole **10** was not obtained and so alternate routes towards the synthesis of **3** were explored.

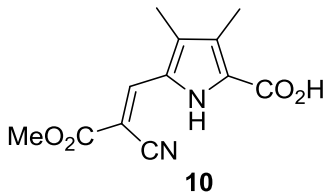


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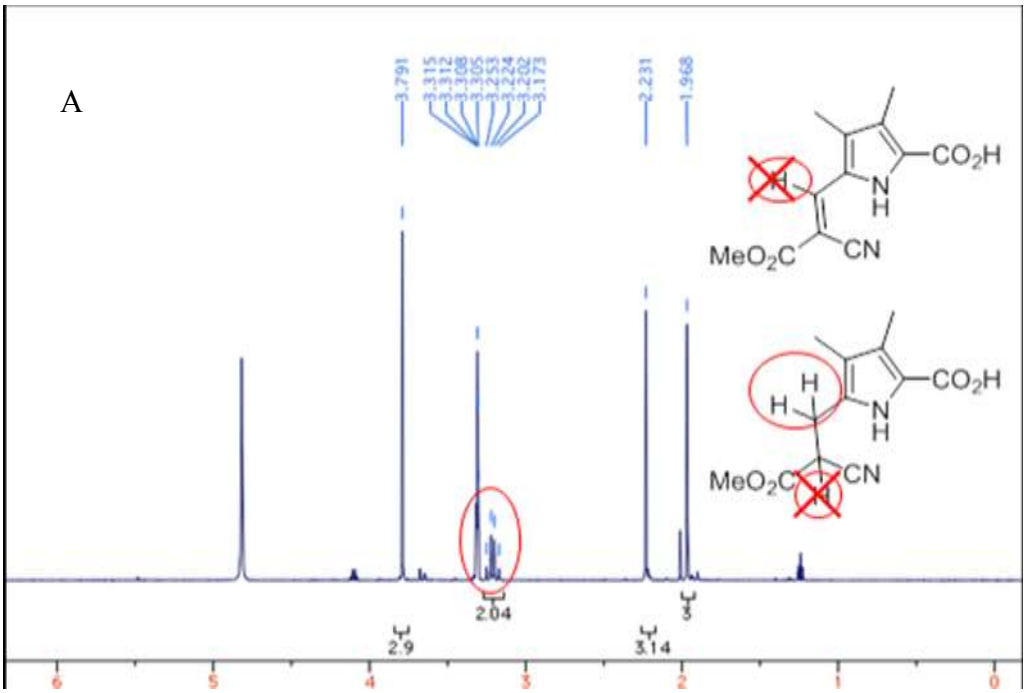
Figure 9: Desired pyrrole **10**.


A
3.791
3.315
3.312
3.308
3.305
3.253
3.224
3.202
3.173
2.231
1.968
CO2H
N
H
MeO2C
CN
H
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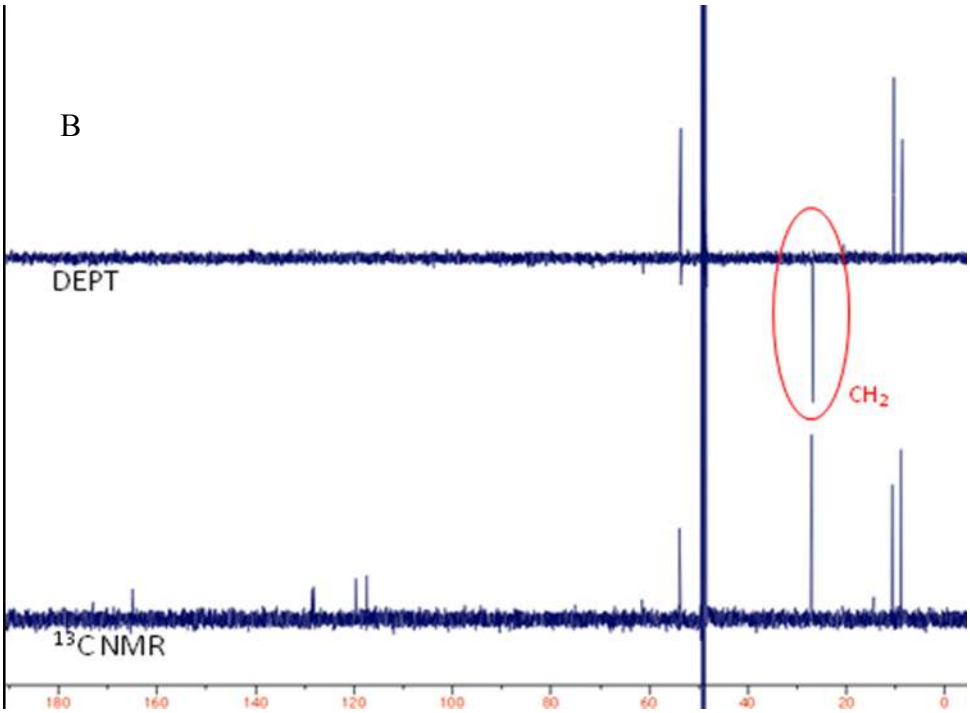
3
2
1
0


B
DEPT
CH2
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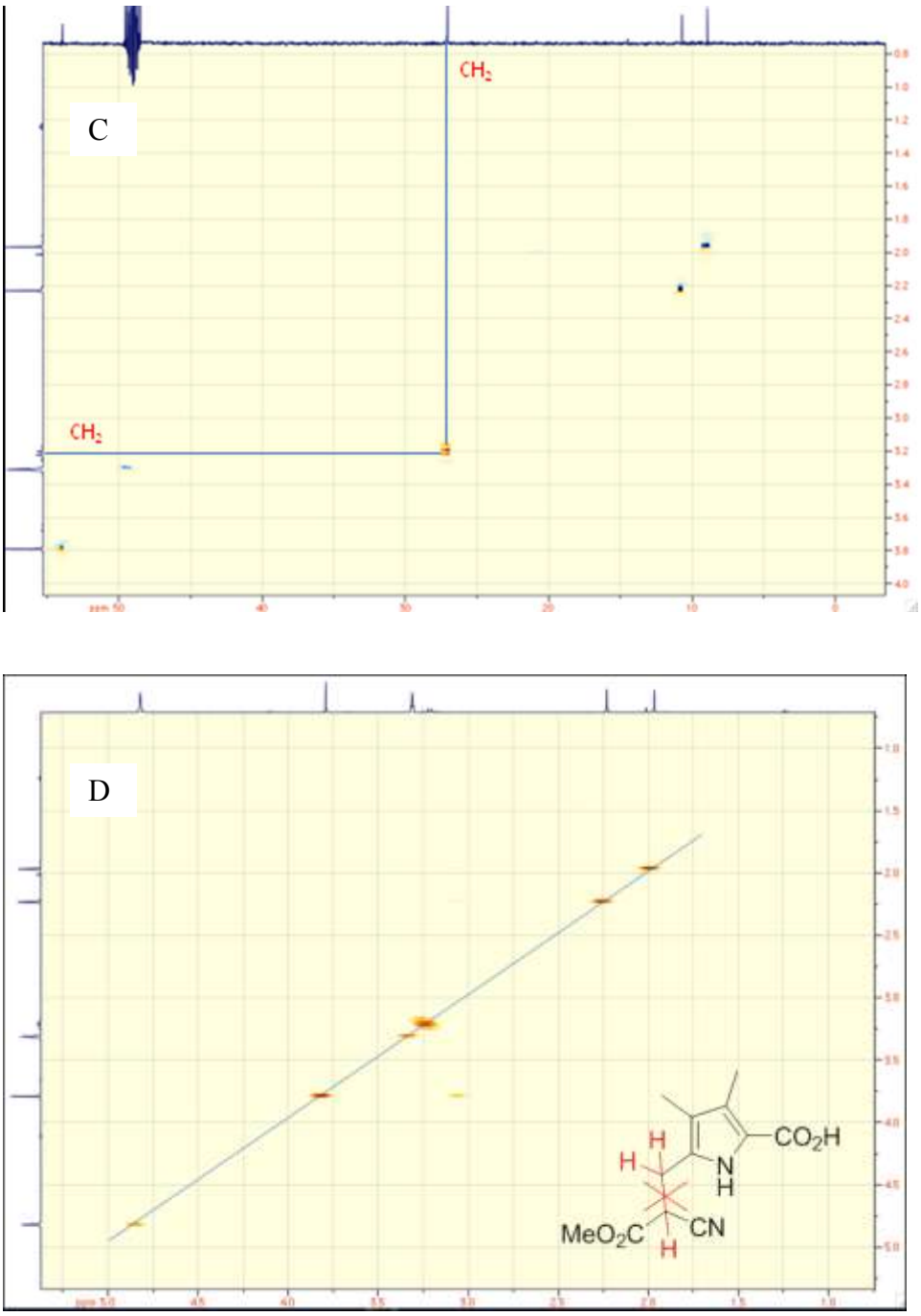


Figure 10: NMR spectra and analysis including A) ^{1}H, B) DEPT and ^{13}C, C) edited HSQC, and D) COSY.

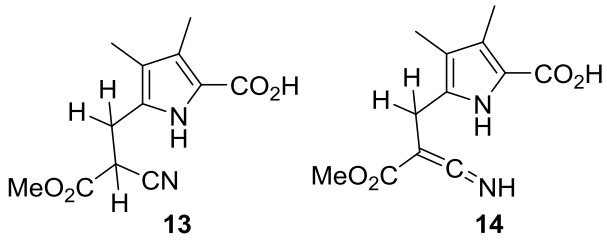


Figure 11: Proposed structures **13** and **14**.

Due to these results, it became apparent that a cleaner carboxylic acid **10** was required for the subsequent decarboxillative iodination and dehalogenation to be successful and so the Bn ester series (**4-8, Scheme 5**) was abandoned and different esters (i.e. Et and tBu) were explored. When examining the Et ester **15**, it was apparent that protecting the aldehyde was not a suitable strategy because the hydrolysis step required to remove the Et group is conducted under basic conditions and will therefore prematurely deprotect the aldehyde (**Figure 12**).

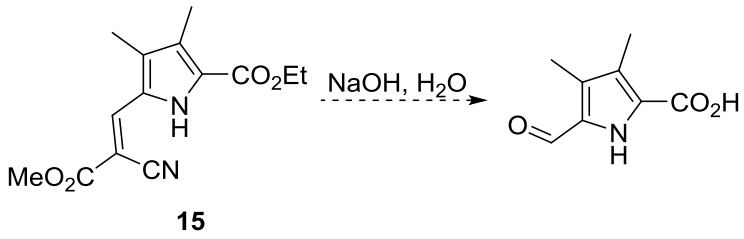
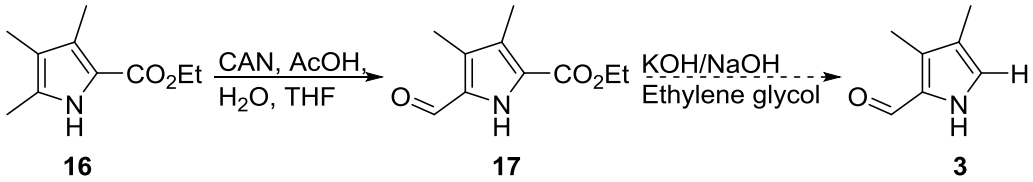


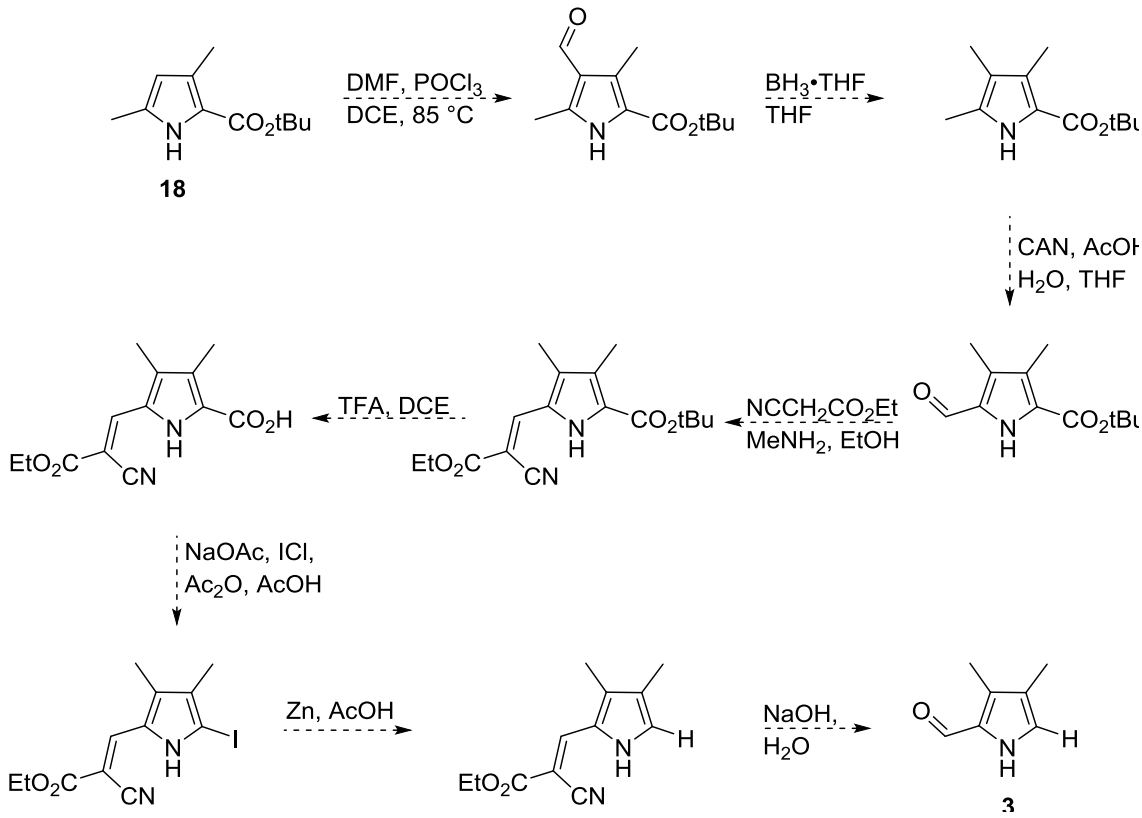
Figure 12: Hydrolysis and consequent deprotection of protected Et ester **15**.

Following the oxidation of the trimethyl ethyl ester **16** to give **17**, attempts to remove the Et ester without protecting the aldehyde were unsuccessful (**Scheme 8**). This was attempted first with NaOH in ethylene glycol and second, with KOH in ethylene glycol (**Scheme 8**), with neither strategy resulting in the isolation of **3**. These results were

not surprising as the conditions required to cleave the Et ester of **17** are quite harsh and the literature reports such reactions as "messy" and low-yielding.[32] As such, the use of the tBu ester **18** will be investigated (**Scheme 9**).



Scheme 8: Attempted synthesis of pyrrole **3** with an Et ester.



Scheme 9: Potential incorporation of ^{13}C label and synthesis of pyrrole **3** from **18**.

2.3 Conclusions and Future Work

Overall, a new convenient method for the synthesis of symmetric *meso*-H-dipyrrin hydrobromides has been developed. This method offers improvement over the existing literature by eliminating the use of a synthetic intermediate (the α-free pyrrole) and enabling the high yielding synthesis of symmetrical dipyrrins which may otherwise not be easily accessible. One interesting result while studying substrate scope revealed that the mechanism may have some concerted character. This is being investigated by the use of an isotopically labeled symmetric α-free, α'-formyl pyrrole in the coupling reaction. The synthesis of this pyrrole, with the ^{13}C incorporated, involves many steps and several routes were explored. Following the failure of the hydrogenolysis of Bn ester **8** and hydrolysis of Et ester **15**, next attempts will involve the t-Bu ester **18** according to **Scheme 9**. This pyrrole was carried through the series shown in **Scheme 9** with regular, unlabelled DMF by a fellow Thompson group member, Aleksandra Kajetanowicks, to test the validity of the series on this substrate. Pyrrole **3** was successfully synthesized and now the series will be repeated using labeled DMF and dipyrrin formation will be monitored and analyzed using NMR spectroscopy to determine the ratio of the two possible isomers. This future work will offer insight into the mechanism of dipyrrin formation.

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CHAPTER 3 PRODIGIOSENES AS POTENTIAL ANTI-LEUKEMIC AGENTS

3.1 Introduction

Prodigiosenes are a class of pyrrolyldipyrrins in which a pyrrole is joined to a dipyrrin through the 9-position. Each ring can be identified as the A-, B- or C-ring (**Scheme 13**).

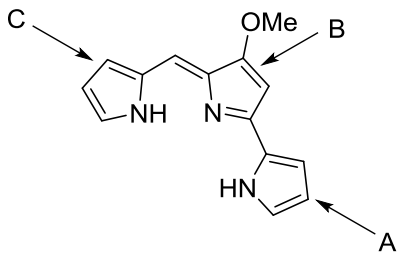


Figure 13: Prodigiosene skeleton.

Prodigiosin (**Figure 14**) is a bioactive secondary metabolite isolated from several Gram-positive and Gram-negative bacteria, including the bacterium *Serratia marcescens.*[1] The name prodigiosin is derived from the word prodigious meaning something marvelous or remarkable. Prodigiosin is the parent member of a class of red-pigmented compounds called prodigiosenes which are characterized by their 4-methoxypyrrolyldipyrrin framework (**Figure 14**). They possess immunosuppressive, anticancer and antimicrobial activities.[2-4]

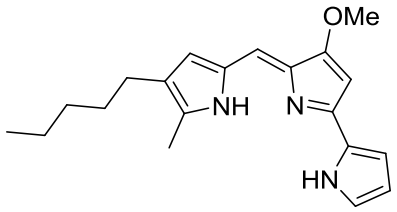


Figure 14: Prodigiosin.

Coley's toxin, an early chemotherapeutic, is a mixture of extracts containing prodigiosin which, before being withdrawn by the FDA due to toxicity, was used as a cancer treatment.[5] Prodigiosin itself exhibits systemic toxicity at effective cancer doses and as such it is not suitable for clinical development. Prodigiosenes exhibit significant activity against many cancerous cell lines and, given the expertise of the Thompson group regarding the synthesis of pyrrole-containing compounds, these analogues are of significant interest to the Thompson research group.

Obatoclax (GX15-070) (**Figure 15**) is an experimental drug candidate, developed by Gemin X, acquired by Cephalon. It is in phase II clinical trials for the treatment of leukemia, lymphoma, myelofibrosis and mastocytosis.[6] The structure of Obatoclax, as shown in **Figure 15** is very similar to prodigiosin (**Figure 14**) and is modified in the A-ring and the C-ring. Other SAR studies show that the B-ring (i.e. the methoxy) is essential for cytotoxicity.[7] This evidence suggests that further SAR studies should focus on the A- and/or C-ring.

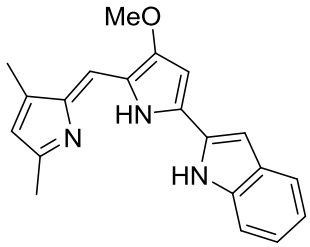


Figure 15: Obatoclax.

Previous work in the Thompson group focused on substituent modifications about the C-ring of prodigiosenes (**Figure 16**), and involved attempts to increase the stability of the synthetic intermediates and to facilitate the isolation of these compounds compared to the natural product.[8,9] It was discovered that prodigiosenes containing an extra methyl group on the C-ring, not present in the natural product, maintain the *in vitro* anticancer activity of prodigiosin and these derivatives are more readily available via synthetic strategies.[8] It was also discovered, by the Thompson group,[8,9] that ester or ketone linkages in the β-position of the C-ring serves two purposes. First, it makes for an easier synthesis, and second, provides opportunity for further functionalization of the prodigiosenes (**Figure 16**).

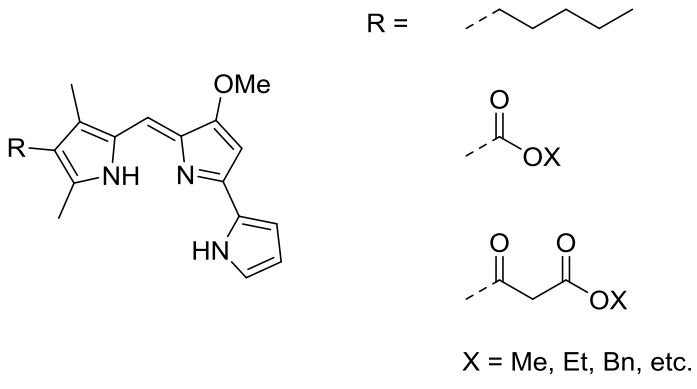


Figure 16: Synthetic prodigiosenes.[8,9]

Recently published work presented four new prodigiosenes featuring alkanoate substitution patterns (**19a-d, Figure 17**), designed and synthesized in the Thompson lab, which exhibited strong selectivity against leukemia cell lines compared to those representative of eight other human cancers.[10] Although many prodigiosenes have been synthesized in the Thompson lab, these are the first analogues to show such obvious selectivity for leukemia cell lines and they are also the first to bear an alkanoate substitution pattern.

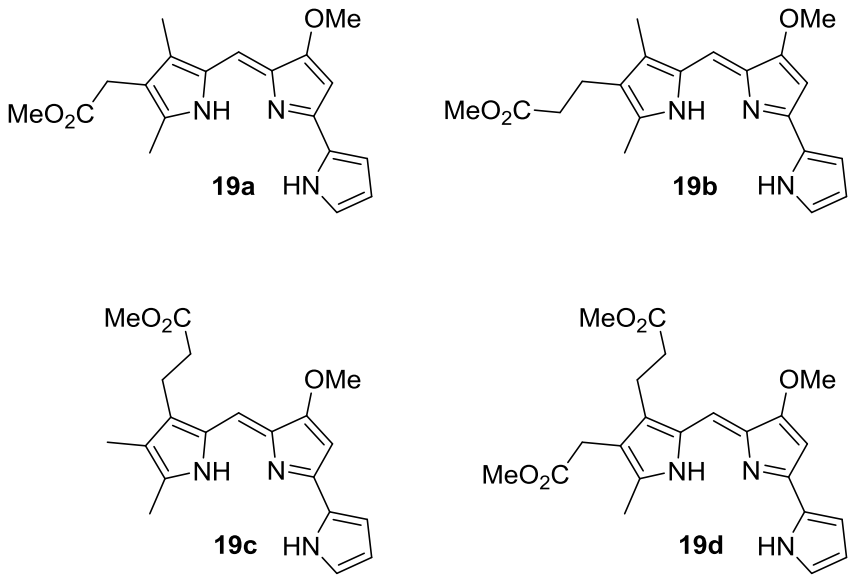


Figure 17: Synthetic prodigiosenes **19a-d** with alkanoate substitution pattern.[10]

Myeloid leukemias, among many other diseases, require new therapeutic agents. Acute myeloid leukemia (AML) accounts for approximately 20% of childhood leukemias and the majority of adult acute leukemias.[11] AML remains fatal for 40% of patients and is thought to have reached a "plateau" in efficacy of leukemia treatment.[11,12] Recent studies involving adults have shown improved remission rates upon the intensification of

anthracycline therapy.[13-15] However, the reported improvements were for younger adults or good risk patients suggesting that increasing doses of currently available agents is unlikely to benefit the majority of adult AML patients. Thus the need for new anti-leukemia agents is pressing.[13-15] Current leukemia therapeutic agents used for the treatment of leukemia include some anthracyclines (e.g. Doxorubicin and Imatinib) and Cytarabine (AraC) (**Figure 18**).[16,17]

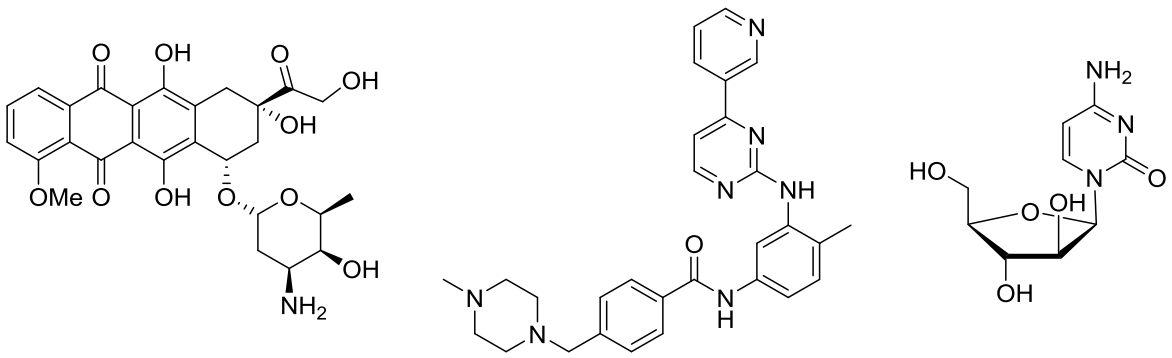
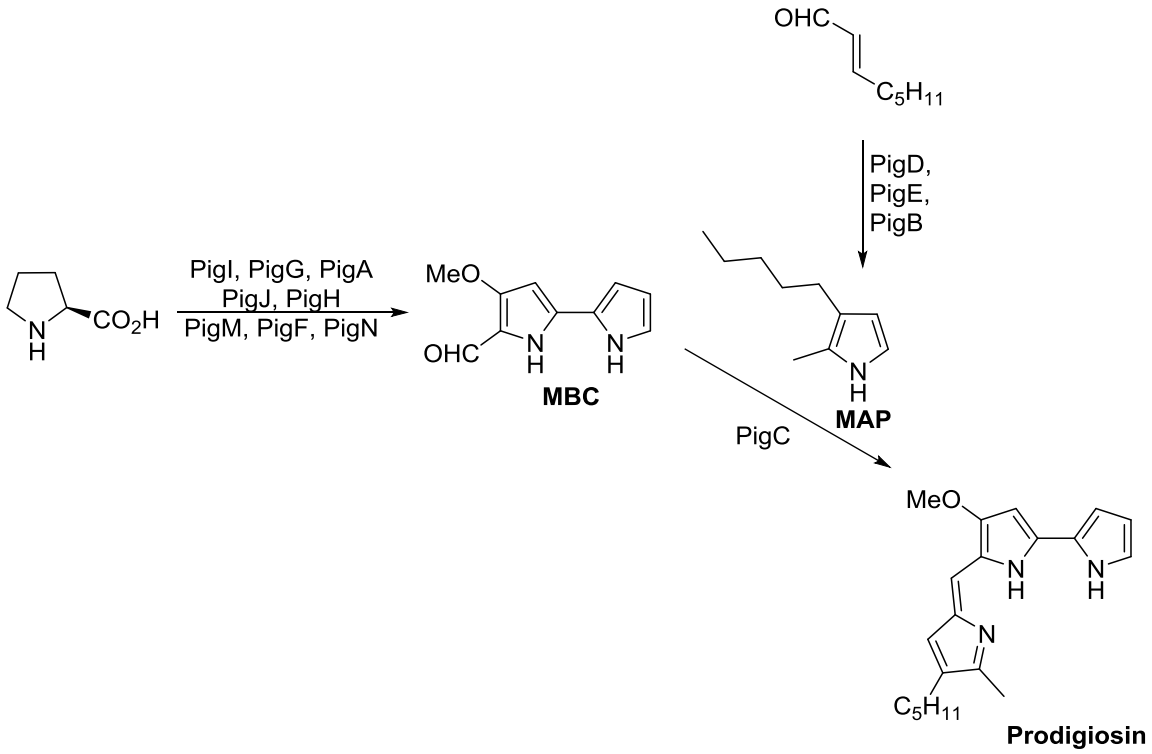


Figure 18: Examples of therapeutic agents used to treat leukemias.

The use of prodigiosenes as a potential leukemia treatment was first published in 1988 when variation of the B-ring substituents resulted in reduced cytotoxicity.[18,19] Other studies involving prodigiosenes and the potential to treat leukemia studies focused on signaling pathways, and the mechanism of action of apoptosis and prodigiosene was reported to induce apoptosis in human primary cancer cells.[20-24] Due to the different structural features and mechanisms of the anti-cancer activity of prodigiosenes, compared to AraC and anthracyclines, prodigiosenes are interesting targets in the development of leukemia therapeutics.

It was proposed that the biosynthesis of prodigiosin involves two separate enzymatic pathways leading to two late-stage intermediates, 3-methoxy-5,5'-bipyrrole-2-carbaldehyde (MBC) and 2-methyl-3-amylpyrrole (MAP) which come together in the last step, via an enzyme-catalyzed condensation reaction, to form prodigiosin (**Scheme 10**).[25]



Scheme 10: Biosynthesis of prodigiosin.[25]

There are two main retrosynthetic routes by which prodigiosenes have been synthesized in the laboratory. The first involves a biomimetic condensation between the bipyrrole carbaldehyde (A- and B-rings) and a monopyrrole (C-ring) as the final step (**A, Figure 19**). The second approach involves a cross-coupling between a dipyrrin unit (B- and C-rings) and a monopyrrole (A-ring) as the final step (**B, Figure 19**)

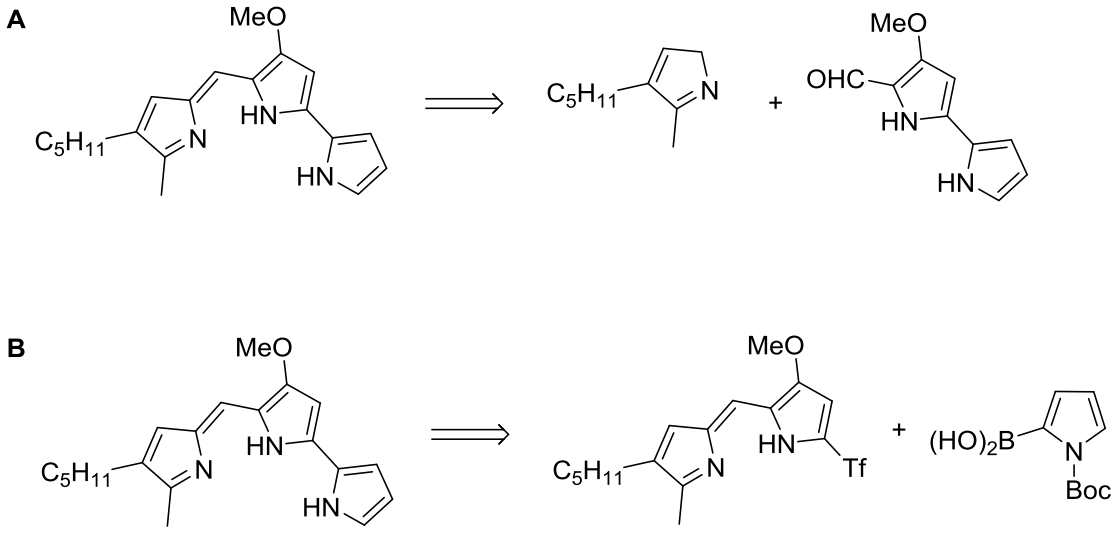
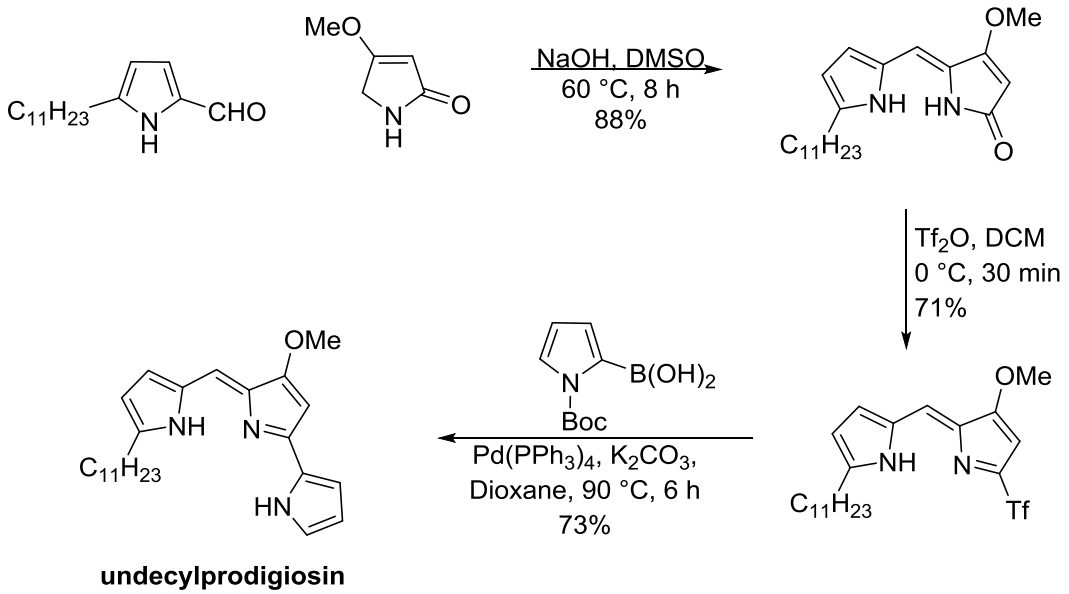


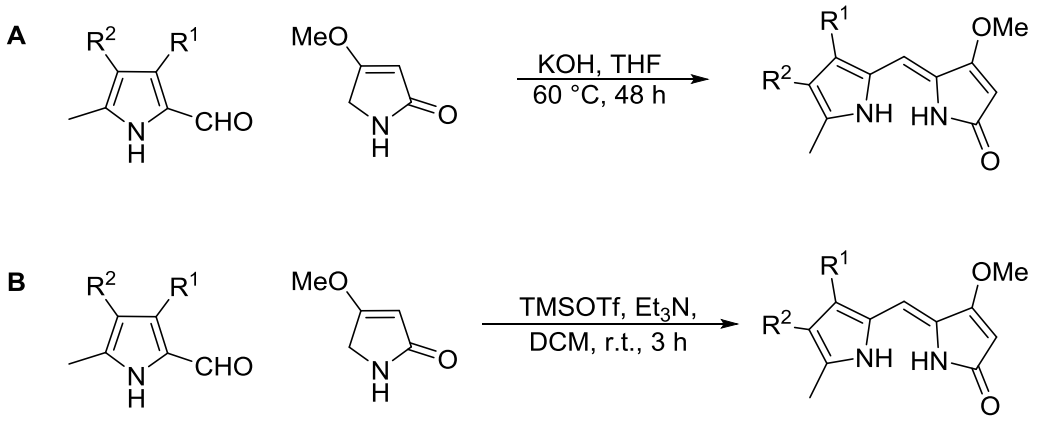
Figure 19: A) Biomimetic retrosynthetic approach to prodigiosene synthesis and B) alternative retrosynthetic approach to prodigiosene synthesis.

The biomimetic route to prodigiosenes was used in the first total synthesis of prodigiosin in 1962 and was quite popular for many years following.[26] It was not until 1996 when D'Alessio and co-workers reported an alternate synthetic route, avoiding the synthesis of the bipyrrole intermediate.[27] This method involves the condensation of a 2-formyl pyrrole, which would become the C-ring of the final prodigiosene, with a commercially available pyrrolinone (B-ring). The resulting dipyrrinone was then converted to its corresponding triflate which was then cross-coupled and the Boc group removed to give the final prodigiosene (**Scheme 11**). This method was an improvement over the literature at the time, because it was higher yielding as well as scaleable.



Scheme 11: D'Alessio and co-workers' synthesis of undecylprodigiosin.[27]

In the Thompson group, a modified version of the D'Alessio methodology has been implemented, resulting in higher and more consistent yields in prodigiosene synthesis. The first modification involves the base catalyzed condensation step in which KOH is used as the base and THF as the solvent (**A, Scheme 12**).[10] Alternatively, Et_3N and TMSOTf in DCM can be used to effect the same condensation (**B, Scheme 12**).[8]

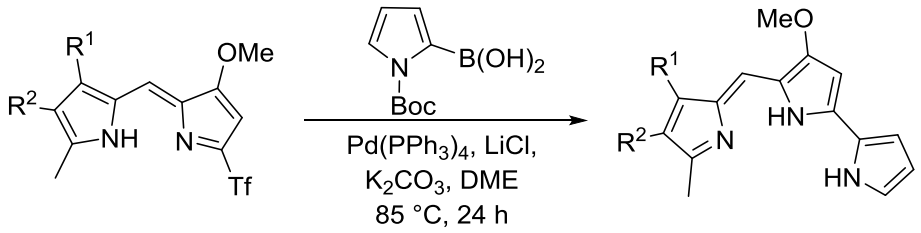


Scheme 12: Condensation of C-ring and B-ring in Thompson group prodigiosene syntheses.

Another modification by the Thompson group involves implementing bromination rather than triflation as the second-last step in the synthesis (**Scheme 13**). Although triflation is still commonly used, bromination has proven more successful than triflation when the C-ring bears an alkyl ester rather than a conjugated ketone/ester or alkyl substituents.[10]

Scheme 13: Bromination of dipyrrinone.

The final modification in prodigiosene synthesis, as used by the Thompson group, involves using LiCl as a base and DME as the reaction solvent for the final Suzuki cross-coupling, conducted in a closed system, to afford the synthetic prodigiosenes (**Scheme 14**). This is used for both the triflated and brominated derivatives.[8-10]



Scheme 14: Suzuki cross-coupling.

Most structure-activity relationship (SAR) studies concerning prodigiosenes have focused on the A-ring.[28-31] However, our proposed investigations concern structural modifications on the C-ring within the prodigiosene skeleton. To further investigate the role of the ester substitution pattern on the C-ring of the recently developed prodigiosenes **19a-d**,[10] Series 1 was developed (**Figure 20**). To probe the role of the alkoxy substituent (i.e. Me ester) regarding cell-line selectivity, compounds **20-23** (**Figure 20**) were designed to bear different esters in the same positions as **19a-d** (**Figure 17**). Compound **25** was designed in order to determine the necessity of an alkyl ester over a conjugated/aryl ester. Furthermore **24** and **26** were designed to allow for the identification of the role of lipophilicity of the alkanoate chain upon anti-leukemia activity (**Figure 20**).

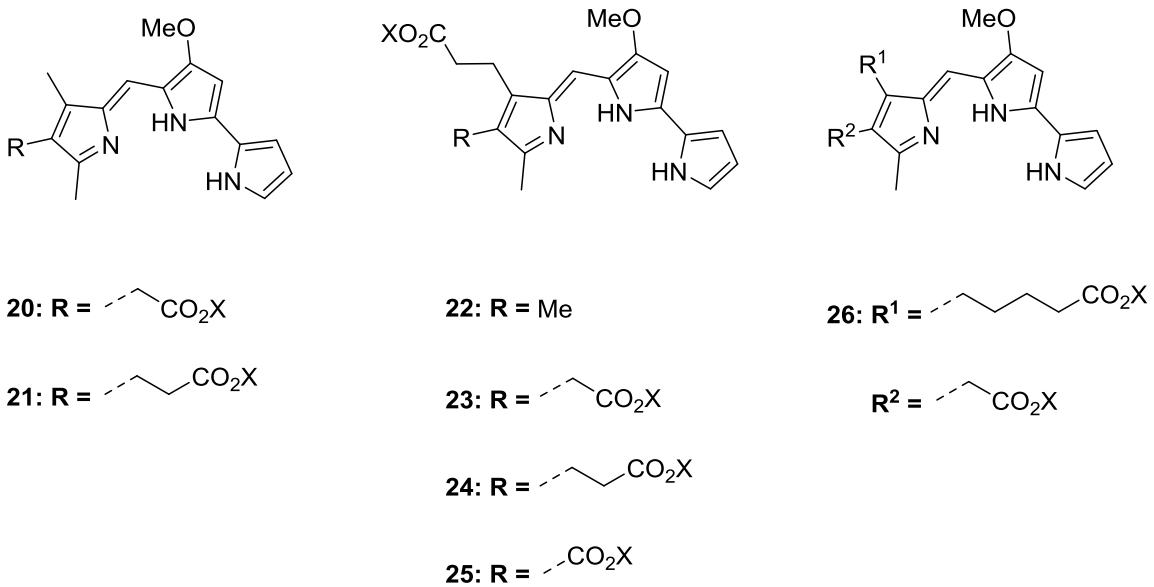


Figure 20: Proposed Series 1, developed to address the role of the ester substitution pattern in the C-ring.

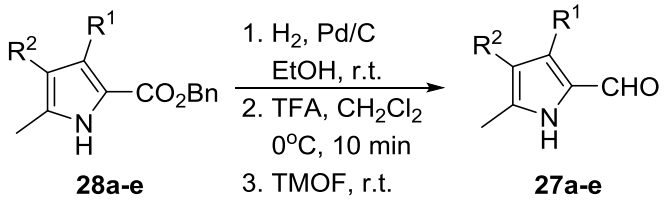
3.2 Results and Discussion

3.2.1 Synthesis of Prodigiosenes with C-ring Alkanoate Substitution Patterns

With the goal of synthesizing prodigiosenes **20-26** according to the modified D'Alessio methodology, the first synthetic task involved preparation of the 2-formyl pyrroles **27** that would constitute the C-ring of the target prodigiosenes. The synthetic strategy takes advantage of the ready availability of Knorr-type pyrroles **28** that can be transformed into the desired 2-formyl pyrroles shown in **Table 3**. The 2-formyl pyrroles **27a-e** were synthesized according to the literature procedure[10] which took advantage of the de-esterification of the 2-carboxylic acid benzyl esters **28a-e** through hydrogenolysis with Pd/C under H_2 atmosphere, followed immediately (carboxylic acid is not stable) by

decarboxylation with TFA and finally formylation with TMOF to give the corresponding 2-formyl pyrroles **27a-e** in good to moderate yields over the three steps (**Table 3**). The yields varied, presumably due to the stability of the carboxylic acid intermediate and how much decomposition occurred at that step. One can speculate that the lower yielding reactions had less stable carboxylic acid intermediates.

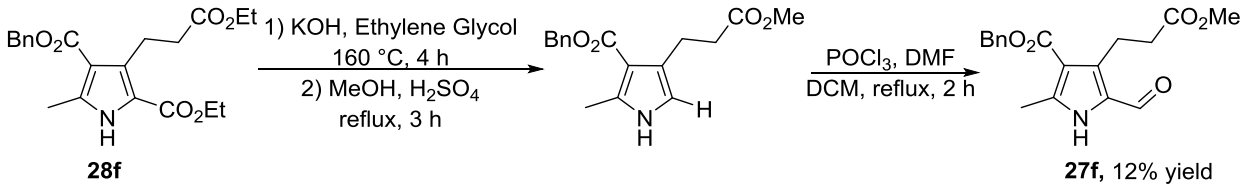
Table 3: Synthesis of 2-formyl pyrroles.



Pyrrole	R^1	R^2	Yield (%)
27a	Me	CH_2CO_2Me	60
27b	Me	$CH_2CH_2CO_2Me$	62
27c	$CH_2CH_2CO_2Me$	Me	71
27d	$CH_2CH_2CO_2Me$	CH_2CO_2Me	86
27e	$CH_2CH_2CO_2Et$	$CH_2CH_2CO_2Me$	77

Formyl pyrrole **27f** was synthesized from pyrrole **28f** (**Scheme 15**). Pyrrole **28f** was used due to the large stock available in the Thompson lab, rather than synthesizing the Bn ester pyrrole akin to **28a-e**. Hydrolysis of the Et ester, followed by decarboxylation is achieved through treatment with KOH and heating in ethylene glycol at 160 °C. Consequently, this resulted in the hydrolysis of the Et ester at the β-position

and so the acid was re-esterified using MeOH and 0.1 equiv. of H_2SO_4. A Vilsmeier-Haack reaction on the α-free pyrrole gave the corresponding formyl pyrrole **27f** in a 12% yield over three steps (**Scheme 15**).

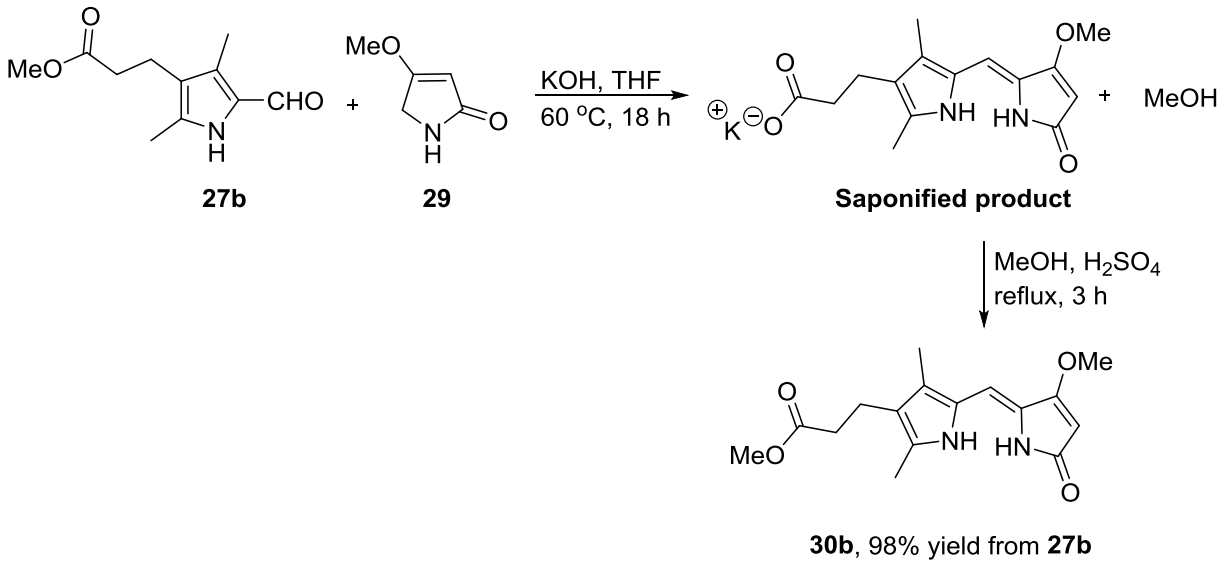


Scheme 15: Synthesis of 2-formyl pyrrole **27f**.

2-Formyl pyrrole **27a** would be transformed such as to prepare the prodigiosene **19a**, as previously reported, which would be modified further to prepare prodigiosene **20**. Pyrrole **27b** would be needed for the preparation of prodigiosenes **19b** and **21**. Pyrrole **27c** would be transformed into prodigiosenes **19c** and **22** and pyrrole **27d** would be needed to prepare prodigiosenes **19d** and **23**. Prodigiosene **24** would be prepared from pyrrole **27e** and prodigiosene **25** from pyrrole **27f**. Prodigiosene **26** was not prepared due to complications in synthesizing its corresponding Knorr-type pyrrole.

Subsequently, the appropriate 2-formyl pyrroles **27a-f** were reacted with 4-methoxy-1,5-dihydro-pyrrol-2-one (**29**) to form the consequent dipyrrinones **30a-f** (**Table 4**). Two methods are used in the Thompson group (**Scheme 12**). One literature method[8] involved reacting pyrrole **27b** with **29** in the presence of TMSOTf and Et_3N in DCM.[8] This reaction was incomplete after the suggested reaction time and the resulting mixture was impure and isolation of the desired product was unsuccessful. Alternatively, 4 M KOH was reacted with a solution of **29** in THF at 60 °C, followed by the addition of

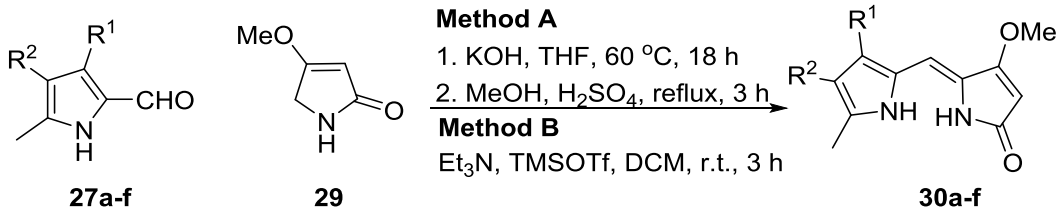
the 2-formyl pyrrole **27b** and then stirring for 48 h. According to the literature,[10] a precipitate should form after an acidic quench has been completed. However, during the first attempt using 2-formyl pyrrole **27b**, the formation of a precipitate was not observed and the crude material was a thick semi-solid that could not be purified via column chromatography, due to the crude material sticking to the baseline of the TLC plate even when eluted with MeOH, or by washing the residue with hexane or water. When this reaction was repeated with another portion of pyrrole **27b**, a precipitate formed as the reaction proceeded and the reaction was complete after stirring for 24 h. The change in how this reaction proceeded was potentially due to the dryness and quality of the starting aldehyde **28b** and dipyrrinone **29** used. However the source of precipitation (vs. no precipitation) could not be deduced. The crude material was collected and ^{1}H NMR spectroscopy was used to determine that this material was the saponified product (**Scheme 16**). As such, the crude was immediately re-esterified using MeOH and 2.1 equiv. of H_2SO_4 resulting in the desired dipyrrinone **30b** which was purified by washing the crude solid with water and Hexanes to remove any impurities (**Scheme 16**). This gave the desired product **30b** in a 98% yield compared to a 60% yield reported in the literature.[10]



Scheme 16: Saponification and esterification of **30b**.

The condensation using KOH was also successful in preparing substrates **30a, 30c** and **30f** (**Table 4, Method A**), and a precipitate was observed as each reaction proceeded. When substrates **27d** and **27e** were subjected to these conditions, the reaction was incomplete according to TLC analysis after 48 h. In these cases, the expected precipitate was not observed and so the reaction was quenched according to the literature procedure yet the product was difficult to isolate and purification was unsuccessful. Alternatively, the reaction was conducted using TMSOTf to achieve the condensation and the products **30d** and **30e** were successfully isolated (**Table 4, Method B**). These dippyrinones **30a-f** constitute the B- and C-rings of the target prodigiosenes **20-25**, respectively. The yields seemed to vary greatly for this reaction (compare **30b** and **30c**). The good yielding reactions had little decomposition and complete conversion to the ester whereas the lower yielding reactions had either more decomposition or incomplete conversion to the ester.

Table 4: Synthesis of dipyrrinones **30a-f**.



27a-f **29** **30a-f**

Dipyrrinone	Method	R^1	R^2	Yield (%)
30a	A	Me	CH_2CO_2Me	97
30b	A	Me	$CH_2CH_2CO_2Me$	98
30c	A	$CH_2CH_2CO_2Me$	Me	36
30d	B	$CH_2CH_2CO_2Me$	$CH_2CO_2CH_3$	83
30e	B	$CH_2CH_2CO_2Et$	$CH_2CH_2CO_2Me$	65
30f	A	$CH_2CH_2CO_2Me$	CO_2Bn	44

The next step involved bromination to afford the bromodipyrrins **31a-f** (**Table 5**). This involves reacting the corresponding dipyrrinone **30a-f** with $POBr_3$ in DCM for 5 days at 40 °C. According to the literature procedure,[10] when the reaction is complete, saturated $NaHCO_3$ (aq.) is to be added to the reaction mixture with stirring. In each case, this addition resulted in an emulsion that was very difficult to break and this problem was only minimized if the reaction mixture was instead added directly to a separatory funnel followed by saturated $NaHCO_3$ and gentle shaking of the funnel. Initially, dipyrrinones

30a-e were subjected to these conditions to successfully afford bromodipyrrins **31a-e**. Dipyrrinone **30f** was initially triflated, because previous Thompson group members have had more success with triflation over bromination when conjugated esters are installed in the dipyrrinone.[8] Triflation involved adding Tf_2O (2.8 equiv.) to a solution of **30f** in DCM at 0 °C with stirring for 4 h followed by quenching with saturated $NaHCO_3$ (aq.), and extracting with DCM. TLC analysis showed a yellow spot, assumed to be the product, at a much lower R_f then expected and when that fraction was collected after column chromatography and analyzed using ^1H NMR spectroscopy, the benzyl group was no longer intact and in fact, the product was the corresponding acid in only a 10% yield. This was deemed an ineffective strategy and so the dipyrrinone **30f** was brominated, like the other dipyrrinones, to afford the bromodipyrrin **31f** in 80% yield (**Table 5**). These bromodipyrrins **31a-f** are just one step away from the prodigiosenes **19a-d**, **24** and **25**. Prodigiosenes **19a-d** will then be used to prepare the target prodigiosenes **20-23** to complete Series 1 (**20-25**), with the potential to further derivatize these prodigiosenes (**Figure 20**).

Table 5: Synthesis of bromodipyrrins **31a-f**.

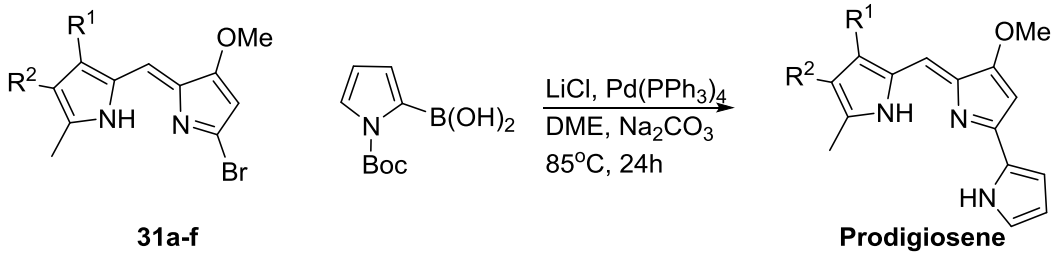
30a-f **31a-f**

Bromodipyrrin	R^1	R^2	Yield (%)
31a	Me	CH_2CO_2Me	50
31b	Me	$CH_2CH_2CO_2Me$	47
31c	$CH_2CH_2CO_2Me$	Me	75
31d	$CH_2CH_2CO_2Me$	CH_2CO_2Me	56
31e	$CH_2CH_2CO_2Et$	$CH_2CH_2CO_2Me$	33
31f	$CH_2CH_2CO_2Me$	CO_2Bn	35

Next, a Suzuki coupling[10] of bromodipyrrins **31a-f** with *N*-Boc-pyrrole-2-boronic acid (becoming the A-ring), in the presence of LiCl, $Pd(PPh_3)_4$, and Na_2CO_3 generated the corresponding prodigiosenes **19a-d, 24** and **25** (**Table 6).** The coupling reaction must be conducted in a sealed vessel, such as a microwave vial or a Schlenk flask, which can safely withstand being under pressure, and it must be properly degassed otherwise the reaction does not reach completion. When the reaction was complete, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed

with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was then purified via column chromatography on neutral alumina, eluting with a gradient of EtOAc/Hexanes increasing slowly from 0% EtOAc to 30%. In most cases, two columns were required to adequately purify the compound. When the prodigiosene was mostly pure, it was treated with HCl to generate the HCl salt of the prodigiosene which could be easily isolated using a Millipore filtration apparatus. The solid was washed with water and Hexanes to remove the remaining impurities. Yields were as expected, compared to the literature and the mass balance could be accounted for by some remaining starting material, remaining *N*-Boc protected prodigiosene, or decomposition. Bromodipyrrins **31a-d** were coupled with *N*-Boc-pyrrole-2-boronic acid to prepare the prodigiosenes **19a-d**, as previously reported. The next synthetic targets involved the incorporation of different ester substituents on these prodigiosenes to give the target compounds **20-23**. Coupling bromodipyrrins **31e** and **31f** to *N*-Boc-pyrrole-2-boronic acid gave prodigiosenes **24** and **25**, respectively. These were two new prodigiosenes making up a part of Series 1 and requiring no further derivitization. Prodigiosene **24** is different from the previously reported prodigiosenes **19a-d** in that it bears two longer chain alkyl esters on the C-ring, making it more lipophilic, which may have an effect on the biological activity. Prodigiosene **25** also bears two esters; however one is conjugated and the other is an alkyl ester. Both conjugated esters and alkyl esters show activity against cancer cell lines and no prodigiosene has been published bearing both.[8-10]

Table 6: Synthesis of prodigiosenes **19a-d, 24** and **25**.



Bromodipyrrin	Prodigiosene	R^1	R^2	Yield (%)
31a	**19a**	Me	CH_2CO_2Me	43
31b	**19b**	Me	$CH_2CH_2CO_2Me$	47
31c	**19c**	$CH_2CH_2CO_2Me$	Me	38
31d	**19d**	$CH_2CH_2CO_2Me$	CH_2CO_2Me	47
31e	**24**	$CH_2CH_2CO_2Et$	$CH_2CH_2CO_2Me$	18
31f	**25**	$CH_2CH_2CO_2Me$	CO_2Bn	27

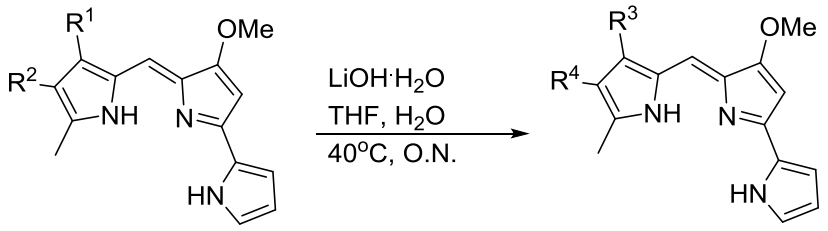
The first time bromodipyrrin **31f** was submitted to the Suzuki coupling, the isolation and purification of prodigiosene **25** was quite difficult. According to TLC analysis, the reaction did not reach completion and resulted in the generation of several impurities. The crude mixture was subjected to the reaction conditions once more, with little improvement. The crude material was twice purified using column chromatography on neutral alumina, eluting with a gradient of 0-50% EtOAc/Hexanes to collect a polar

red spot (and separate the yellow spot – presumed to be starting material – and other impurities) that appeared on the TLC plate. Little success was achieved, although there was evidence in the ^{1}H NMR spectrum that the prodigiosene **25** was the major product. At this point, only 5.8 mg of the impure material remained and so the synthesis of the prodigiosene was repeated from its corresponding 2-formyl pyrrole **27f**. In the mean time, preparative TLC was used for further purification. The material was dissolved in minimal MeOH and DCM and spotted across three 20x20cm glass-backed alumina TLC plates which were eluted with 40% EtOAc/Hexanes. The red spot corresponding to the prodigiosene was then collected and separated from the alumina. When this material was analyzed using ^{1}H NMR spectroscopy, it was dissolved in $CDCl_3$ and placed on the NMR queue overnight for the 500 MHz NMR spectrometer. When the ^{1}H NMR spectrum was obtained, it appeared as though the material had broken down and all of the impurities still remained (even amplified) according to NMR and TLC analysis. A second round of preparative TLC was done, the other major spots were also collected and this time the ^{1}H NMR spectrum of the prodigiosene was recorded in CD_3CN. This time, the spectrum appeared to be cleaner yet still not pure as it contained large peaks around 1-2 ppm. At this point, only ~1 mg of prodigiosene remained and no further purification was attempted. Once the bromodipyrrin **31f** had again been synthesized, the Suzuki coupling reaction was repeated. This time, although it appeared as though the reaction did not progress according to TLC analysis (two yellow, bromodipyrrin-like spots and no red spot), the fractions were separated and purified. As it turned out, the yellow spot that was presumed to be the bromodipyrrin was in fact the prodigiosene which was purified by

column chromatography and treated with HCl to generate the HCl salt as a nice stable red solid in a 27% yield.

3.2.2 Functionalization of Prodigiosenes with C-ring Alkanoate Substitutions

Next, prodigiosenes **19a-d** were required to prepare prodigiosenes **20-23**. This was achieved through hydrolysis of the existing ester and then coupling with the alcohol of choice, in this case benzyl alcohol, to give the corresponding ester. A strategy for the hydrolysis of prodigiosenes bearing esters involves the use of a large excess of KOH in THF and H_2O, with stirring at 70 ^oC.[9] To achieve the same hydrolysis, with less harsh conditions, 2.4 equiv. of $LiOH \bullet H_2O$ was used as base with heating at only 40 °C. The reaction was monitored using TLC analysis and the starting material **19a** was completely consumed after 24 h (**Scheme 17**). This ester was successfully converted into a material that appeared as a very polar purple spot, according to TLC analysis, indicating the hydrolyzed product **32a** was produced. At this point the strategy that proved most effective in isolating the product involved removing the THF and H_2O in vacuo, and then redissolving the crude material in H_2O, adding 1 M HCl and stirring for 2 h. The resultant fine precipitate was isolated via filtration using a Millipore filtration apparatus. When only partial amounts of the reaction solvent was initially removed (i.e. only the THF was removed) a sticky semi-solid resulted that was difficult to handle and as such the reaction mixture was concentrated to dryness before proceeding. Prodigiosenes **19b-d** were also subjected to these conditions to afford the saponified prodigiosenes **32b-d**, used in the next step with no further purification.



19a: R^1 = Me

R^2 = CO_2Me

19b: R^1 = Me

R^2 = CO_2Me

19c: R^1 = CO_2Me

R^2 = Me

19d: R^1 = CO_2Me

R^2 = CO_2Me

32a: R^3 = Me

R^4 = CO_2H

32b: R^3 = Me

R^4 = CO_2H

32c: R^3 = CO_2H

R^4 = Me

32d: R^3 = CO_2H

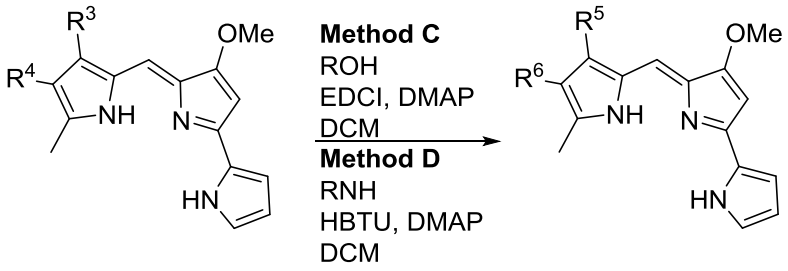
R^4 = CO_2H

Scheme 17: Procedure for the hydrogenolysis of prodigiosenes with alkanoate substituents.

With the intermediate prodigiosenes **32a-d** in hand, each one would be coupled to BnOH to prepare prodigiosenes **20a-23**. Prodigiosenes **20a**, **21**, **22** and **23** were successfully synthesized this way however, prodigiosene **21** contains some minor impurities, observed using NMR spectroscopy, yet more of this prodigiosene needs to be synthesized in order to obtain a sufficiently pure sample. The hydrolyzed prodigiosene **32a** would be subject to a wider variety of alcohols and amines to expand the series (**Figure 20, Table 7**). This coupling involved adding the corresponding hydrolysed prodigiosene **32a-d** to a solution of BnOH, EDCI and DMAP in DCM at r.t. for 3-5 d, monitoring consumption of starting material using TLC analysis.[9] The reaction mixture was diluted with H_2O, extracted with DCM and the organic layer was washed with brine.

The resulting material was purified via column chromatography and treated with HCl to afford prodigiosenes **20a-23**. With six of the initial targets now in hand, the hydrolyzed prodigiosene **32a** was then coupled with various alcohols to give a greater variety of prodigiosenes with varying esters **20b-d (Method C, Table 7)**. Prodigiosene **32a** was successfully coupled to BnOH (**20a**), hexyl alcohol (**20b**), and neopentyl alcohol (**20d**). Initially, a coupling with tBuOH was attempted to observe the effect of a more bulky alkyl ester however, this alcohol proved to be too bulky and the coupling did not occur. As such, neopentyl alcohol was used and the coupling proceeded nicely. A coupling was also attempted with TEG to make a more hydrophilic prodigiosene (**20c**) however, during purification of this prodigiosene it was converted to the HCl salt using MeOH as the solvent and during this process the TEG group underwent exchange with MeOH under the acidic conditions yielding a mixture of mostly the Me ester (**20a**) with trace amounts of the TEG ester (**20c**). Also, prodigiosene **32a** was coupled with various amines using an alternative set of coupling conditions (**Method D**) involving various amines, HBTU and DMAP in DCM at r.t. for 24 h to give the corresponding amide-substituted prodigiosenes **20e-g**, further improving the variety of prodigiosenes synthesized, allowing for a comparison of esters and amides regarding cell line activity (**Method D, Table 7**). Bn amine, Bu amine and diethyl amine were chosen to prepare prodigiosenes **20e-g**, respectively.

Table 7: Altering the alkyl esters of various prodigiosenes.



Prodigiosene	Method	R^5	R^6	Yield (%)
20a	C	Me	CH_2CO_2Bn	29
20b	C	Me	$CH_2CO_2(CH_2)_5CH_3$	17
20c	C	Me	CH_2CO_2TEG	Trace
20d	C	Me	$CH_2CO_2CH_2C(CH_3)_3$	46
20e	D	Me	$CH_2CONHBn$	55
20f	D	Me	$CH_2CONHBu$	68
20g	D	Me	$CH_2CON(Et)_2$	38
21	C	Me	$CH_2CH_2CO_2Bn$	13[a]
22	C	$CH_2CH_2CO_2Bn$	Me	29
23	C	$CH_2CH_2CO_2Bn$	CH_2CO_2Bn	13

[a]crude yield

3.3 Conclusions and Future Work

Overall, twelve new prodigiosenes were synthesized (**Figure 21**) bearing various alkyl esters. To complete series 1 (**Figure 19**), the synthesis of prodigiosene **20c** and **21** is being repeated in order to obtain a pure sample for complete characterization and prodigiosene **25** is being repeated on a larger scale and the final product will be isolated as its (hopefully) more stable HCl salt. Prodigiosene **26**, of the originally proposed series, was not synthesized in this work due to complications in synthesizing the C-ring. Following the development of Series 1 (**Figure 20**), an *in vitro* analysis of each new prodigiosene will involve one- and five-dose screening over four human leukemia cell lines maintained in the NCI-60 panel (http://dtp.cancer.gov).

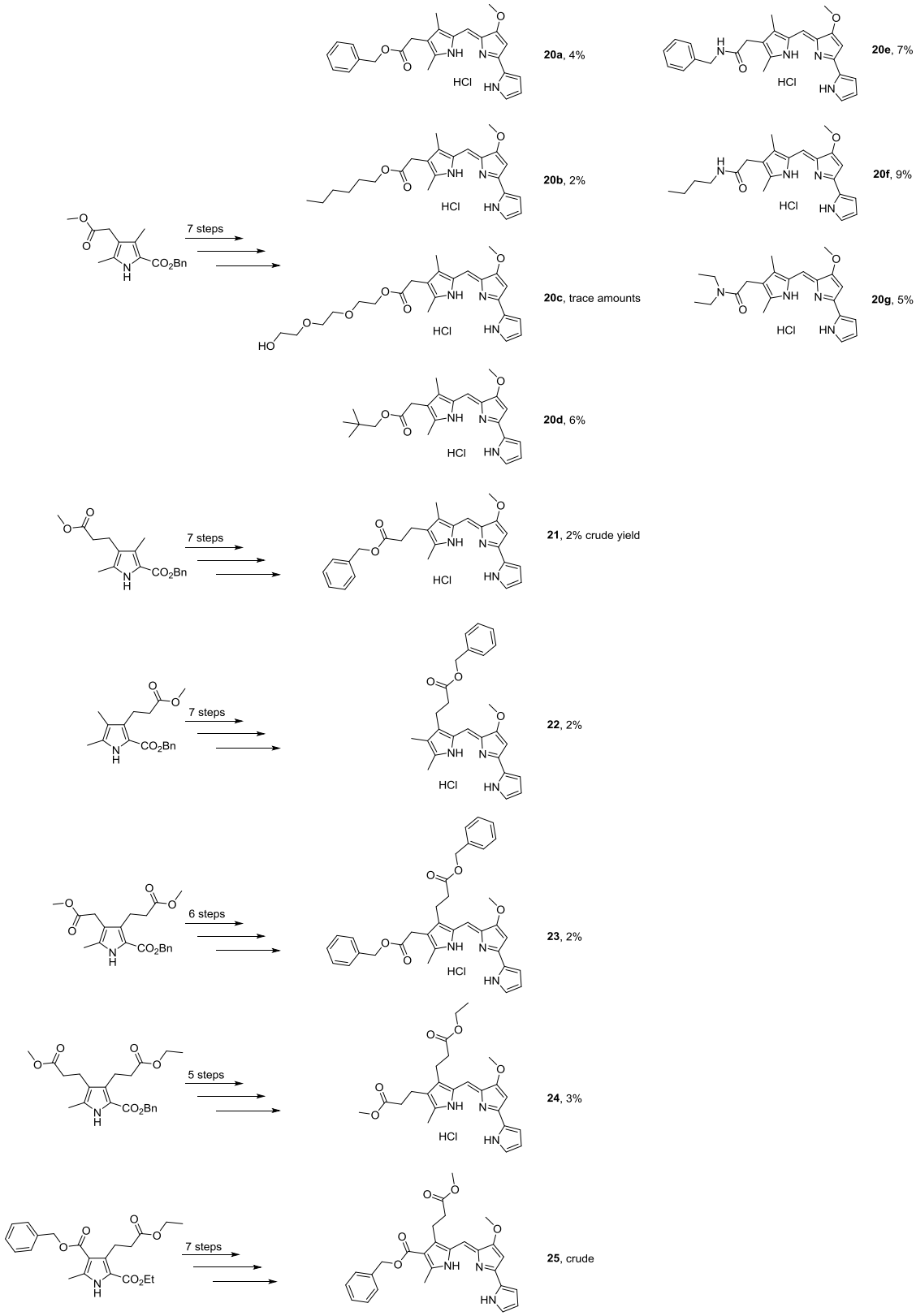
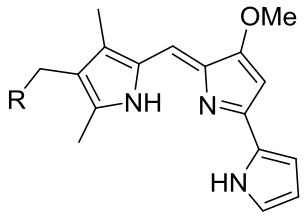


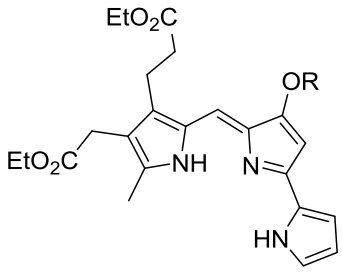
Figure 21: Twelve new prodigiosenes synthesized in this work (**20a-g, 21-25**).

Future work will involve developing Series 2 (**Figure 22**), focusing on varying the C-ring electronic properties, and Series 3 (**Figure 23**) focusing on varying the B-ring electronic properties. These routes will be developed based on the best emerging scaffolds from Series 1 and 2.

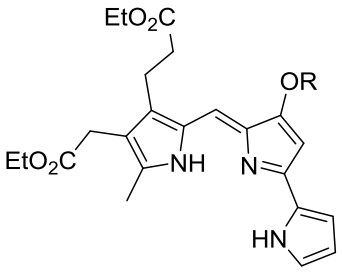


R = CO_2Me
R = OMe
R = CH_2OMe
R = SMe
R = COMe
R = C(=NR)Me

Figure 22: Series 2 prodigiosenes with varying electronic features on the C-ring.

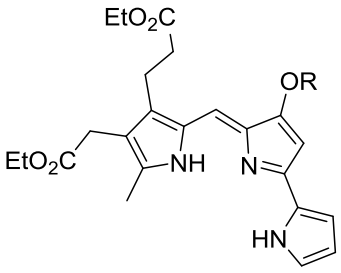


R = OMe
R = OPh



R = OC_6H_4CN
R = $OC_6H_4NO_2$
R = $OC_6H_4CF_3$

less electron donating through R



R = C_6H_4Me
R = C_6H_4OMe

more electron donating through R

Figure 23: Series 3 prodigiosenes with various B-ring substituents.

The most promising results identified via the NCI/DTP screen will be further evaluated in the Dellaire laboratory (department of pathology, Dalhousie University). Cytotoxicity of each compound at the IC50 using annexin V staining followed by Fluorescence Activated Cell Sorting (FACS) analysis will be evaluated after determining the IC50 using the MTT dye reduction assay. Finally, effectiveness against leukemia cell survival *in vivo* of the most promising leads will be investigated, using the zebrafish xenotransplantation platform.[9]

3.4 References for Chapter 3

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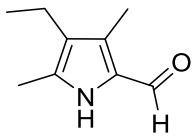
CHAPTER 4 EXPERIMENTAL

4.1 General Experimental

Commercial chemicals were used as received, unless otherwise stated. All ^{1}H NMR and ^{13}C NMR were recorded using a Bruker Avance AV-300 or AV-500 spectrometer. All chemical shifts are reported in parts per million (ppm) using the solvent signal [$CDCl_3$ (^{1}H 7.26 ppm; ^{13}C 77.16 ppm); MeOD (^{1}H 3.31 ppm; ^{13}C 49.00 ppm); CD_2Cl_2 (^{1}H 5.32 ppm; ^{13}C 53.84 ppm; DMSO (^{1}H 2.50 ppm; ^{13}C 39.52 ppm)] as the internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; dq, doublet of quartet; quin, quintet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained by Mr. Xiao Feng using an ion trap (ESI TOF) instrument. All dipyrrin hydrobromide mass spectra are recorded for M = [salt – HBr] and prodigiosene hydrochloride mass spectra are recorded for M = [salt – HCl]. All microwave-promoted reactions were performed using a Biotage Initiator 8 Microwave apparatus. The following compounds were synthesized by other Thompson group members: **1b-e**[1,2]**, 1g-l**[3-5]**, 28a-f**[19]**, 27c.**

4.2 Experimental Data and Procedures for Chapter 2

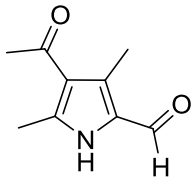
*4-Ethyl-3,5-dimethyl pyrrole-2-carboxaldehyde (**1a**)*



A) Under a N_2 atmosphere, 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylic acid tert-butyl ester[6] (8.4 mmol, 2.0 g) was dissolved in THF (100 mL) and 1 M $BH_3 \cdot THF$ (16.9 mmol, 16.9 mL) was added drop-wise at 0 °C. The reaction mixture was then allowed to warm to r.t. and stirred overnight at which point the reaction was quenched with H_2O (20 mL) drop-wise at 0 °C. When the reaction mixture was no longer evolving gas, 1 M HCl (~50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The organic fractions were combined and dried with Na_2SO_4, filtered and concentrated in vacuo to give 3,5-dimethyl-4-ethyl-1H-pyrrole-2-carboxylic acid tert-butyl ester which was carried on to the next step without further purification.[5]

B) The crude material was dissolved in DCM (50 mL) and, at 0 °C under a N_2 atmosphere, TFA (227 mmol, 17.4 mL) was added slowly and the reaction mixture was monitored using TLC analysis for the disappearance of starting material and the carboxylic acid intermediate (~15 min). Next, TMOF (42 mmol, 4.6 mL) was added drop-wise, with stirring, and the reaction mixture was warmed to r.t. and stirred for 30 min and monitored using TLC. When the reaction was complete, the reaction mixture was poured onto ice-water and 6 M NaOH (~20 mL) was added drop-wise, with stirring. The layers were separated and the aqueous was extracted with DCM (3 x 50 mL). The organic layers were combined and washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered and concentrated in vacuo.[7] The crude material was then purified via column chromatography on silica, eluting with a gradient of 10-20% EtOAc/Hexanes. The title compound was thus isolated as an off-white solid (0.4 g, 33% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.46 (s, 1H), 9.30 (br s, 1H), 2.38 (q, J = 7.6 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.06 (t, J = 7.6 Hz, 3H), in accordance with the literature.[8]

*4-Acetyl-3,5-dimethyl pyrrole-2-carboxaldehyde (**1f**)*

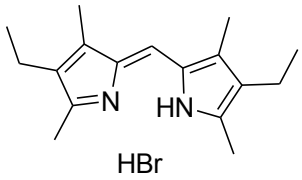


4-Acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylic acid tert-butyl ester[6] (2.11 mmol, 0.5 g) was dissolved in DCM (5 mL) and, at 0 °C under a N_2 atmosphere, TFA (57 mmol, 4.4 mL) was added slowly and the reaction mixture was monitored using TLC analysis for the disappearance of starting material and the carboxylic acid intermediate (~15 min). Next, TMOF (11 mmol, 1.2 mL) was added drop-wise, with stirring, and the reaction mixture was allowed to warm to r.t. and stirred for 30 min. When the reaction was complete, the reaction mixture was poured onto ice-water and 6 M NaOH (~10 mL) was added drop-wise, with stirring. The layers were separated and the aqueous was extracted with DCM (3 x 20 mL). The organic layers were combined and washed with saturated $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered and concentrated in vacuo.[8] The crude material was then purified via column chromatography on silica, eluting with a gradient of 10-20% EtOAc/Hexanes. The title compound was thus isolated as an off-white solid (0.3 g, 86% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.50 (br s, 1H), 9.63 (s, 1H), 2.60 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), in accordance with the literature.[9]

General procedure for the synthesis of meso-H-4,6-dipyrrin hydrobromides

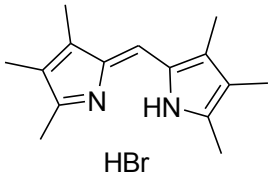
Aqueous HBr (48%, 1 mL) was added to a solution of the 2-formyl pyrrole (100 mg, 1 equiv.) in MeOH (2 mL). The reaction mixture was then heated at reflux temperature, with stirring, for 1 h or until all starting material was consumed, monitored using TLC (30% EtOAc/Hexanes). The precipitated product was collected using suction filtration and the residue was washed with Et_2O to yield the respective *meso*-H-4,6-dipyrrin hydrobromide.

1,3,7,9-Tetramethyl-2,8-diethyl-4,6-dipyrrin hydrobromide (2a)[10]



The title compound was synthesized according to the general procedure and was isolated as a red solid (93 mg, 84% yield): mp 225°C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.90 (br s, 2H), 7.01 (s, 1H), 2.65 (s, 6H), 2.41 (q, *J* = 7.6 Hz, 4H), 2.25 (s, 6H), 1.06 (t, *J* = 7.6 Hz 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.9, 141.4, 130.7, 126.3, 118.8, 17.4, 14.6, 13.0, 10.2; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{25}N_2$ 257.2012; found, 257.2018.

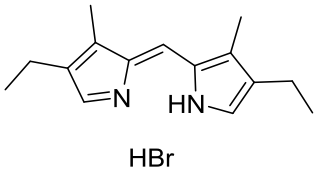
1,2,3,7,8,9-Hexamethyl-4,6-dipyrrin hydrobromide (2b)[10]



The title compound was synthesized according to the general procedure and was isolated as a red solid (80 mg, 72% yield): mp 240 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.94 (br s, 2H), 7.02 (s, 1H), 2.65 (s, 6H), 2.24 (s, 6H), 1.97 (s, 6H); ^{13}C NMR (125

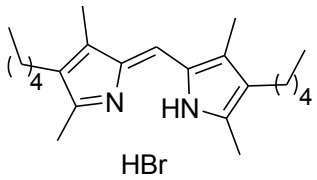
MHz, $CDCl_3$) δ: 154.2, 141.9, 126.2, 124.3, 118.7, 13.1, 10.5, 9.1; HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{15}H_{21}N_2$ 229.1699; found, 229.1697.

3,7-Dimethyl-2,8-diethyl-4,6-dipyrrin hydrobromide (2c)[11]



The title compound was synthesized according to the general procedure and was the main component of a mixture including 3,8-dimethyl-2,7-diethyl-4,6-dipyrrin hydrobromide (9:1 ratio, estimated using ^{1}H NMR), isolated as a green solid (72 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.24 (br s, 2H), 7.72 (d, *J* = 3.7 Hz, 4H), 7.32 (s, 1H), 2.47 (q, *J* = 7.6 Hz, 6H), 2.31 (s, 6H), 1.19 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.8, 141.6, 132.5, 128.5, 123.6, 18.4, 14.1, 10.4; HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{15}H_{21}N_2$ 229.1699; found, 229.1699. Data is given for **2c**; the NMR spectra reveal the 10% contribution from the scrambled analog.

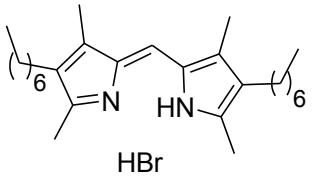
1,3,7,9-Tetramethyl-2,8-dipentyl-4,6-dipyrrin hydrobromide (2d)[12]



The title compound was synthesized according to the general procedure and was isolated as a red solid (84 mg, 79% yield): mp 190 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.93 (br s, 2H), 7.02 (s, 1H), 2.65 (s, 6H), 2.38 (t, *J* = 7.6 Hz, 4H), 2.25 (s, 6H), 1.43 (m, 4H), 1.35-1.25 (m, 8H), 0.89 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.2,

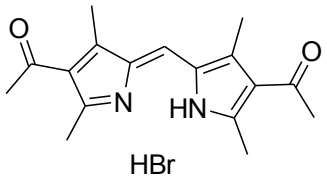
141.7, 129.4, 126.3, 118.8, 31.7, 29.9, 24.1, 22.7, 14.2, 13.1, 10.4; HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{23}H_{37}N_2$ 341.2951; found, 341.2941.

1,3,7,9-Tetramethyl-2,8-diheptyl-4,6-dipyrrin hydrobromide (2e)[12]



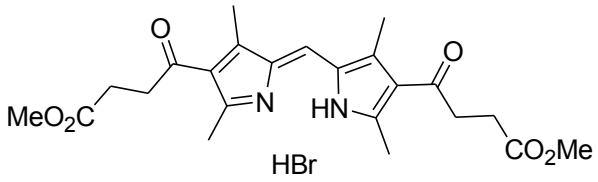
The title compound was synthesized according to the general procedure and was isolated as a red solid (81 mg, 75% yield): mp 175 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.93 (br s, 2H), 7.02 (s, 1H), 2.65 (s, 6H), 2.38 (t, *J* = 7.6 Hz, 4H), 2.25 (s, 6H), 1.44 (m, 4H), 1.35-1.25 (m, 16H), 0.88 (t, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.2, 141.7, 129.4, 126.3, 118.8, 32.0, 30.2, 29.6, 29.4, 24.2, 22.9, 14.3, 13.2, 10.4; HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{27}H_{45}N_2$ 397.3577; found, 397.3569.

1,3,7,9-Tetramethyl-2,8-diacetyl-4,6-dipyrrin hydrobromide (2f)[13]



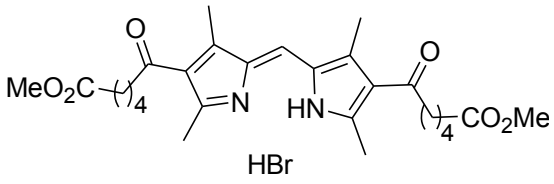
The title compound was synthesized according to the general procedure and was isolated as a brown solid (92 mg, 83 % yield): mp 200 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.83 (br s, 2H), 7.50 (s, 1H), 3.02 (s, 6H), 2.65 (s, 6H), 2.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 193.9, 159.2, 148.9, 128.7, 127.0, 123.5, 31.9, 16.2, 13.2; HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_2$ 285.1598; found, 285.1589.

1,3,7,9-Tetramethyl-2,8-di(4-methoxy-4-oxobutanoyl)-4,6-dipyrrin hydrobromide (2g)



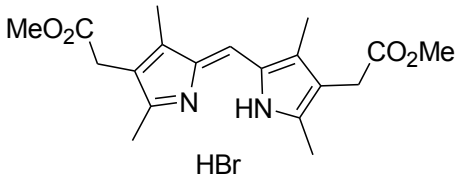
The title compound was synthesized according to the general procedure and was isolated as a yellow-brown solid (80 mg, 79% yield): mp 185 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.76 (br s, 2H), 7.51 (s, 1H), 3.71 (s, 6H), 3.07 (t, *J* = 6.3 Hz, 4H), 2.99 (s, 6H), 2.75 (t, *J* = 6.3 Hz, 4H), 2.66 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 194.6, 173.4, 159.1, 148.8, 128.3, 127.0, 123.6, 52.2, 38.2, 28.1, 16.2, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_6$ 429.2020; found, 429.2022.

1,3,7,9-Tetramethyl-2,8-di(6-methoxy-6-oxohexanoyl)-4,6-dipyrrin hydrobromide (2h)



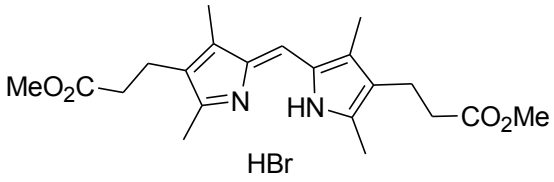
The title compound was synthesized according to the general procedure and was isolated as a brownish black solid (53 mg, 50% yield): mp 185 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 13.80 (br s, 2H), 7.47 (s, 1H), 3.67 (s, 6H), 2.99 (s, 6H), 2.79 (t, *J* = 6.8 Hz, 4H), 2.63 (s, 6H), 2.37 (t, *J* = 7.0 Hz, 4H), 1.74-1.72 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 174.0, 158.9, 148.4, 128.7, 127.0, 123.3, 51.8, 43.3, 34.1, 24.7, 23.5, 16.3, 13.2; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{37}N_2O_6$ 485.2646; found, 485.2647.

1,3,7,9-Tetramethyl-2,8-di(2-methoxy-2-oxoethyl)-4,6-dipyrrin hydrobromide (2i)



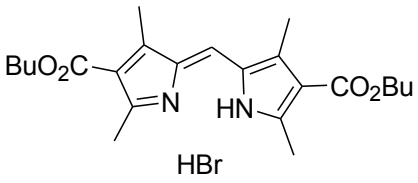
The title compound was synthesized according to the general procedure and was isolated as a orange solid (71 mg, 65% yield): mp 215 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.21 (br s, 2H), 7.12 (s, 1H), 3.69 (s, 6H), 3.43 (s, 4H), 2.69 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 155.2, 143.7, 126.4, 121.7, 120.2, 52.5, 30.0, 13.2, 10.6; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_4$ 345.1809; found, 345.1793.

1,3,7,9-Tetramethyl-2,8-di(3-methoxy-3-oxopropyl)-4,6-dipyrrin hydrobromide (2j)



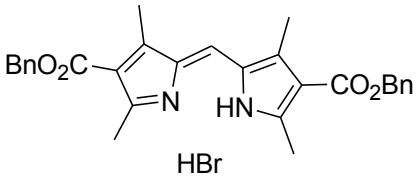
The title compound was synthesized according to the general procedure and was isolated as a orangey brown solid (91 mg, 85% yield): mp 170 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 13.06 (br s, 2H), 7.05 (s, 1H), 3.66 (s, 6H), 2.75 (t, J = 7.6 Hz, 4H), 2.68 (s, 6H), 2.46 (t, J = 7.6 Hz, 4H), 2.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.9, 154.5, 142.6, 127.1, 126.4, 119.4, 52.0, 34.0, 19.6, 13.1, 10.4; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{29}N_2O_4$ 373.2122; found, 373.2108.

1,3,7,9-Tetramethyl-2,8-dibutoxycarbonyl-4,6-dipyrrin hydrobromide (2k)



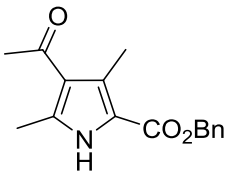
The title compound was synthesized according to the general procedure and was isolated as a orange solid (85 mg, 79% yield): mp 165 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.73 (br s, 2H), 7.47 (s, 1H), 4.30 (t, *J* = 6.6 Hz, 4H), 2.96 (s, 6H), 2.66 (s, 6H), 1.75 (m, 4H), 1.46 (m, 4H), 0.98 (t, *J* = 7.4 Hz 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.4, 160.2, 150.8, 126.8, 123.2, 120.0, 64.9, 30.9, 19.6, 15.7, 13.9, 12.6; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_4$ 401.2435; found, 401.2437.

1,3,5,7-Tetramethyl-2,8-dibenzyloxycarbonyl-4,6-dipyrrin hydrobromide (2l)



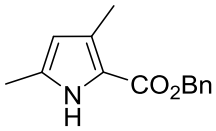
The title compound was synthesized according to the general procedure and was isolated as a yellow solid (99 mg, 90% yield): mp 185 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 13.78 (br s, 2H), 7.45 (s, 1H), 7.42-7.35 (m, 10H), 5.33 (s, 4H), 2.96 (s, 6H), 2.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.1, 160.4, 151.0, 135.7, 129.0, 128.8, 128.6, 126.9, 123.3, 119.7, 66.9, 15.8, 12.7; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_4$ 469.2122; found, 469.2119.

*4-Acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (**5**)*[14]



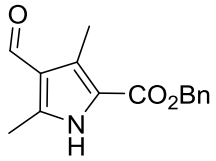
Benzyl acetoacetate (30.4 mL, 1 equiv.) and glacial acetic acid (35 mL, 3.5 equiv.) were combined in a three-necked round bottom flask with a stir bar. A previously prepared saturated solution of $NaNO_2$ (12.8 g, 1.05 equiv.) was then added drop-wise to the reaction mixture using a dropping funnel. The temperature of the reaction was monitored and kept below 60 ^{o}C, using an ice-bath and by amending the addition rate accordingly. Formation of the oxime was complete within 2 h and stirring was stopped to give the oxime intermediate. Glacial acetic acid (88 mL, 8.75 equiv.), 2,4-pentanedione (20 mL, 1.1 equiv.) and anhydrous NaOAc (crushed) (2.89 g, 0.2 equiv.) were combined in a three-necked round bottom flask and stirred. The oxime intermediate was added drop-wise using a dropping funnel alongside the addition of zinc dust (40.3 g, 3.5 equiv.), in portions. The temperature was monitored and kept below 70 ^{o}C using an ice-bath. Once addition was complete, the reaction mixture was stirred until reaching r.t. The mixture was then poured onto ice-water and the product precipitated overnight. The resulting precipitate was isolated using suction filtration, washed with water (to remove any excess acid) and Hexanes (to remove soluble impurities). The resulting solid was dissolved with DCM into a clean and dry suction flask. The solvent was concentrated in vacuo and the resulting crude solid was crystallized from MeOH/H_2O to yield the product as an off-white crystalline solid (17 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.39 (br s, 1H), 7.42-7.33 (apparent m, 5H), 5.32 (s, 2H), 2.61 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), in accordance with the literature.[14]

*3,5-Dimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (**4**)*[15]



The title compound was synthesized according to the literature procedure[15] and isolated as an off-white crystalline solid (1.4 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.06 (br s, 1H), 7.46-7.34 (apparent m, 5H), 5.83 (s, 1H), 5.34 (s, 2H), 2.36 (s, 3H), 2.25 (s, 3H), in accordance with the literature.[15]

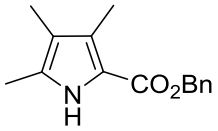
*4-Formyl-3,5-dimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (**6**)*[9]



Unlabeled DMF (0.5 g, 1 equiv.) was added to $POCl_3$ (0.43 mL, 1 equiv.), with stirring at 0 ^{o}C, forming the crystalline Vilsmeier reagent in solution. A solution of **4** (1 equiv.) in 1,2-DCE (22 ml) was then added drop-wise and the reaction mixture was heated at reflux temperature for 5 h. The reaction mixture was then slowly neutralized with saturated K_2CO_3, using an ice-bath. The reaction mixture was returned to 85 ^{o}C and stirred for 1 h. After cooling, the reaction mixture was extracted with $CHCl_3$ (2 x 15 mL), dried, concentrated and then crystallized from MeOH/H_2O to yield the product as an off-white crystalline solid. Unlabeled: (1.4 g, 83 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 9.27 (br s, 1H), 7.43-7.34 (apparent m, 5H), 5.33 (s, 2H), 2.58 (s, 3H), 2.53 (s, 3H), in accordance with the literature.[9] Labeled: (2.55 g, 77%) ^{1}H NMR (300 MHz, $CDCl_3$) δ:

10.00 (d, J = 168.6 Hz, 1H), 9.06 (br s, 1H), 7.43-7.34 (apparent m, 5H), 5.33 (s, 2H), 2.58 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.3, 161.5, 140.8, 135.9, 131.0, 128.8, 128.5, 128.3, 121.8 (d, J = 63.2 Hz), 118.4, 66.4, 12.7, 10.7; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{14}{}^{13}C\,H_{15}NO_3$ 281.0978; found, 281.0973.

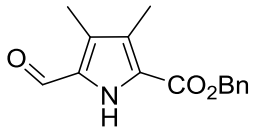
3,4,5-Trimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (7)



Pyrrole **6** (0.7 g, 1 equiv.) was dissolved in THF (35 mL) in a 100 mL two neck flask, under a N_2 atmosphere, and BH_3·THF (5.45 mL, 2 equiv.) was added drop-wise at 0° C. The reaction was warmed to r.t. and stirred overnight. The reaction mixture was cooled to 0° C and water (20 mL) was added until there was no more de-gassing. At this point, 1 M HCl was added (50 mL) and was extracted with EtOAc (3 x 60 mL). The organic fractions were combined and dried over Na_2SO_4, filtered and concentrated in vacuo.[1] The crude material was purified via column chromatography on silica eluting with 1% MeOH/DCM to afford the title compound as a white solid. Unlabeled: (198 mg, 30%) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (br s, 1H), 7.44-7.32 (apparent m, 5H), 5.29 (s, 2H), 2.27 (s, 3H), 2.18 (s, 3H), 1.91 (s, 3H), in accordance with the literature.[16] Labeled: (630 mg, 26%) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.59 (br s, 1H), 7.44-7.32 (apparent m, 5H), 5.29 (s, 2H), 2.27 (s, 3H), 2.18 (s, 3H), 1.91 (d, J = 125.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.4, 136.8, 129.9, 129.8, 128.5, 128.1, 128.0, 117.3 (d, J = 48.9 Hz), 116.3,

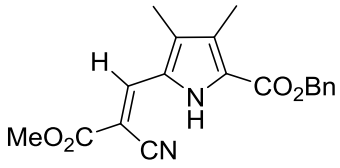
65.4, 11.5, 10.8, 8.8; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{14}{}^{13}C\,H_{17}NO_2$ 267.1186; found, 267.1185.

*5-Formyl-3,4-dimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (**8**)*



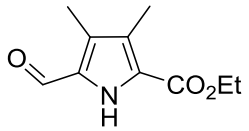
To a solution of pyrrole **7** (625 mg, 1 equiv.) in THF:AcOH:H_2O (26 mL:6.5 mL:26 mL) was added CAN (5.78 g, 4.1 equiv.) in one portion. The reaction mixture was stirred for 2 h at which point another portion of CAN (1.4 g, 1 equiv.) was added and the reaction mixture stirred for a further 1 h. The reaction mixture was poured onto water (~75 mL) and extracted with DCM (3 x 50 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated in vacuo.[17] The crude material was purified via column chromatography on silica, eluting with 20% EtOAc/Hexanes to afford the title compound as a white solid. Unabeled: (251 mg, 47%) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 9.57 (br s, 1H), 7.44-7.31 (apparent m, 5H), 5.33 (s, 2H), 2.27 (s, 6H), in accordance with the literature.[18] Labeled: (279 mg, 42%) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 9.39 (br s, 1H), 7.44-7.32 (apparent m, 5H), 5.33 (s, 2H), 2.27 (s, 3H), 2.27 (d, J = 127.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.3, 160.8, 135.6, 130.4 (d, J = 22), 130.1, 128.8, 128.6, 128.5, 127.6, 124.2, 66.8, 9.9, 8.6; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{14}{}^{13}C\,H_{15}NO_3$ 281.0978; found, 281.0984.

*Benzyl-5-[(E)-2-cyano-2-(methoxycarbonyl)ethynyl]-3,4-dimethyl-2-pyrrolecarboxaldehyde (**9**)*[18]



A mixture of pyrrole **8** (250 mg, 1 equiv.), methyl cyanoacetate (0.185 mL, 2 equiv.) and Et_3N (0.056 mL, 0.385 equiv.) was heated at reflux temperature in dry toluene (1.72 mL) for 3 h with stirring. The reaction mixture was cooled to room temperature and MeOH (~3 mL) was added. The resulting crystals were isolated via filtration to give the title compound as a yellow solid. Unlabeled: (261 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.24 (br s, 1H), 8.06 (s, 1H), 7.46-7.33 (m, 5H), 5.38 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H) in accordance with the literature.[18] Labeled: (261 mg, 80%). ^{1}H NMR[18] (300 MHz, $CDCl_3$) δ: 10.24 (br s, 1H), 8.06 (s, 1H), 7.46-7.33 (m, 5H), 5.38 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H), 2.18 (d, J = 127.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.6, 160.1, 139.6, 135.6, 128.8, 128.6, 128.3, 118.1, 94.4, 66.8, 53.3, 9.7, 9.5; pyrrolic peaks missing, expected at δ: 133.7, 127.5, 126.2, 125.7; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{18}{}^{13}C\,H_{18}N_2O_4$ 362.1193; found, 362.1189.

*5-Formyl-3,4-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (**17**)*[18]



To a solution of pyrrole **7** (240 mg, 1 equiv.) in THF:AcOH:H_2O (14 mL:3.5 mL:14 mL) was added CAN (3.10 g, 4.1 equiv.) in one portion. The reaction mixture was stirred for 2 h at which point another portion of CAN (0.75 g, 1 equiv.) was added and the reaction mixture stirred for a further 1 h. The reaction mixture was poured onto water (~30 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was recrystalized from MeOH:H_2O, filtered and dried to afford the title compound as a white solid (89 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 9.41 (br s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 2.27 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H) in accordance with the literature.[18]

4.3 Experimental Data and Procedures for Chapter 3

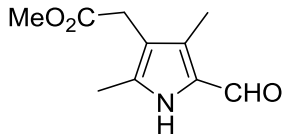
*General procedure for the synthesis of 2-formyl pyrroles (**27a-e**)*[4]

A) To the appropriate 2-carboxylic acid benzyl ester (**28**)[19] (4 mmol, 1 equiv.) in EtOH (65 mL), Et_3N (10 drops) was added and the mixture was degassed for 10 minutes. 10% Pd/C (10% by weight of **28**) was added and the reaction mixture was again degassed for 5 minutes before being placed under H_2 (balloon) and stirred overnight. The reaction mixture was filtered through Celite, washed with MeOH and the solvent was then removed in vacuo to give the crude carboxylic acid.

B) The crude carboxylic acid from step A was then dissolved in dry DCM (10 mL). TFA (44 mmol, 11 equiv.) was then added drop-wise at 0 °C, under N_2. The reaction was monitored using TLC and once there was no starting material left

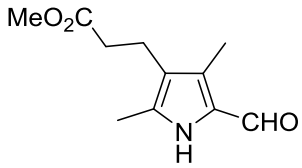
(~10 min), TMOF (20 mmol, 5 equiv.) was added drop-wise and the reaction mixture was warmed to r.t. and monitored using TLC (~15 min). The reaction mixture was poured onto ice-water and 6 M NaOH (32 mmol, 8 eauiv.) was added slowly. This mixture was extracted with DCM (2 x 80 mL). The combined organic fractions were washed with saturated $NaHCO_3$ (2 x 80 mL), H_2O (80 mL) and brine (80 mL), dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was then purified via column chromatography on silica eluting with 30% EtOAc/Hexanes to afford the resulting 2-formyl pyrrole.

4-[(Methoxycarbonyl)methyl]-3,5-dimethyl pyrrole-2-carboxaldehyde (27a)



The title compound was synthesized according to the general procedure[4] and was isolated as an off-white solid (775 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.87 (br s, 1H), 9.48 (s, 1H), 3.68 (s, 3H), 3.39 (s, 2H), 2.28 (s, 6H), in accordance with the literature.[20]

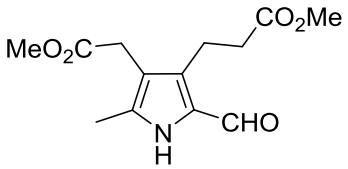
4-[2-(Methoxycarbonylethyl]-3,5-dimethyl pyrrole-2-carboxaldehyde (27b)



The title compound was synthesized according to the general procedure[4] and was isolated as an off-white solid (410 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.62 (br s, 1H), 9.46

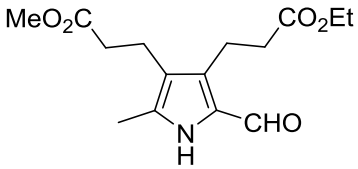
(s, 1H), 3.66 (s, 3H), 2.71 (t, J = 7.5 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.27 (s, 3H), 2.26 (s, 3H), in accordance with the literature.[19]

4-[(Methoxycarbonyl)methyl]-3-[2-(methoxycarbonyl)ethyl]-5-methyl pyrrole-2-carboxaldehyde (27d)



The title compound was synthesized according to the general procedure[4] and was isolated as an off-white solid (2.6 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.14 (br s, 1H), 9.50 (s, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.42 (s, 2H), 3.03 (t, J = 7.5 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 2.28 (s, 3H), in accordance with the literature.[19]

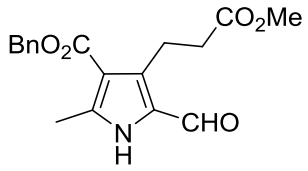
4-[(Methoxycarbonyl)ethyl]-3-[2-(ethoxycarbonyl)ethyl]-5-methyl pyrrole-2-carboxaldehyde (27e)



The title compound was synthesized according to the general procedure[4] and was isolated as an off-white solid (3.3 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.24 (br s, 1H), 9.46 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.65 (s, 3H), 3.01 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H), 2.45 (t, J = 7.8 Hz, 2H), 2.27 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.0, 173.2, 172.3, 136.5, 134.7, 127.5, 120.6, 60.6,

51.6, 36.7, 34.9, 34.9, 19.2, 14.2, 11.7; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{15}H_{21}NO_5$ 318.1312; found, 318.1297.

4-(Benzylmethanoate)-3[(methoxycarbonyl)ethyl]-5-methyl pyrrole-2-carboxaldehyde (27f)

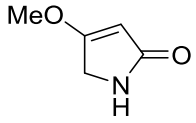


A) Pyrrole **28f** (10 g, 1 equiv.) was dissolved in ethylene glycol (20 mL) with stirring. KOH (2.88 g, 2 equiv.) was added and the reaction mixture was heated to reflux temperature and stirred for 4 h. The reaction mixture was then allowed to cool to r.t., diluted with H_2O (50 mL) and extracted with DCM (80 mL). The aqueous layer was acidified with 5 M HCl until just acidic, and extracted with DCM (3 x 80 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was dissolved in MeOH (500 mL). Concentrated H_2SO_4 (0.1 equiv.) was then added and the mixture was heated at reflux temperature for 3 h at which point it was allowed to cool to r.t. and the solvent was removed in vacuo.[21]

B) In a separate flask, $POCl_3$ (1.3 mL, 1.1 equiv.) was added drop-wise to DMF (1.1 mL, 1.1 equiv.) in DCM (4.5 mL) at 0 °C. This mixture was stirred for 15 min at r.t. and then added drop-wise to a solution of the preceding α-free pyrrole in DCM (14 mL) at 0 °C. The reaction mixture was heated to reflux temperature and stirred for 2 h. The reaction mixture was allowed to cool to r.t. and then 1 M

$NaHCO_3$ (5 equiv.) was added drop-wise at first, then rapidly. The reaction mixture was returned to reflux temperature for 1 h, before returning to r.t. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried with Na_2SO_4, filtered and concentrated in vacuo.[22] The crude material was crystallized from 70% EtOAc/Hexanes to give the title compound as an off-white solid (1.03 g, 12%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.95 (br s, 1H), 9.65 (s, 1H), 7.43-7.33 (m, 5H), 5.29 (s, 2H), 3.60 (s, 3H), 3.28 (t, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.3, 173.2, 164.4, 143.8, 137.7, 136.2, 128.8, 128.5, 128.4, 113.1, 66.1, 51.7, 35.4, 20.2, 14.7; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{18}H_{19}NO_5$ 352.1155; found, 352.1162.

*4-Methoxy-3-pyrolin-2-one (**29**)*[23]



A) To a stirred solution of methyl acetoacetate (280 mL, 1 equiv.) in TMOF (283 mL, 1 equiv.) was added concentrated H_2SO_4 (8 mL, 6.25 equiv.) drop-wise at 0 °C (exothermic) and the reaction mixture was stirred at r.t. for 30 minutes. Quinoline (12 mL, 4.25 equiv.) was added and the reaction mixture was heated to reflux temperature and stirred for 2 h before allowing the mixture to cool to r.t. The crude product was distilled at 130 °C at 1 atm. The aspirator was connected to a trap containing Drierite™, 6 mesh, to prevent the reverse reaction from

happening in the presence of water. The resulting enol ether was then subjected to part B) without any further purification.

B) NBS (175 g, 1.17 equiv.) was added to a stirred solution of the crude enol ether (124 g, 1 equiv.) and benzoyl peroxide (2.4 g, 1%) in DCM (1.3 L). The reaction mixture was then heated to reflux temperature and stirred, under a N_2 atmosphere, overnight. The reaction mixture was then cooled to room temperature and washed with water to remove the succinimide residue (a white, water-soluble product) and the organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo.

C) The crude allyl bromide (198 g, 1 equiv.) was added drop-wise to a stirred solution of 28% aqueous NH_4OH (160 g, 4.8 equiv.) at 65 °C and was stirred for 30 minutes, cooled to r.t. and then continuously extracted into DCM for 5 days using a continuous extraction apparatus. The solvent was then removed in vacuo and the crude product was crystallized from EtOAc (500 mL) to give the title compound as a pale yellow solid (30 g, 15%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.14 (br s, 1H), 5.06 (s, 1H), 3.91 (s, 2H), 3.80 (s, 3H), in accordance with the literature.[23]

General procedure A for the synthesis of dipyrrolinones[4]

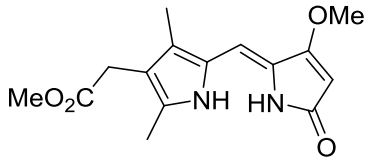
To a stirred solution of **29** (15.5 mmol, 1.55 equiv.) in THF (100 mL) was added 4 M KOH (20 mmol, 2 equiv), previously bubbled with N_2, and the resultant mixture was degassed (~ 15 minutes) and then placed under a N_2 atmosphere. The mixture was then heated to 60 °C with stirring for 1 h, before being cooled slightly and the appropriate 2-

formyl pyrrole (10 mmol, 1 equiv.) added in one portion. The resultant mixture was returned to 60 °C and stirred for 24 h whereby a yellow precipitate formed. The precipitate (saponified product) was collected via suction filtration, and washed with Hexanes. The crude yellow solid was then dissolved in MeOH and conc. H_2SO_4 (20 mmol, 2 equiv.) was added drop-wise and the mixture was then stirred at reflux temperature for 3 h, under N_2 atmosphere. The reaction mixture was then concentrated in vacuo and the crude product was washed with Hexanes and H_2O to give the desired dipyrrinone.

General procedure B for the synthesis of dipyrrolinones[1]

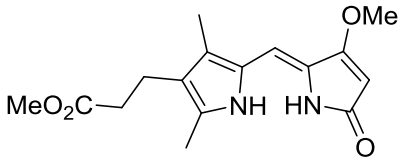
To a stirred solution of 4-methoxy-3-pyrolin-2-one (5.7 mmol, 2.2 equiv.), Et_3N (15.6 mmol, 6.0 equiv.) and DCM (55 mL) at 0 °C was added TMSOTf (7.8 mmol, 3.0 equiv.) and the mixture was stirred for 15 min. The appropriate 2-formyl pyrrole (2.6 mmol, 1.0 equiv.) in DCM (25 mL) was added drop-wise and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was then poured onto pH 7 phosphate buffer (150 mL), the organic phase was separated, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was diluted with THF (50 mL) and concentrated HCl (12 M, 7.8 mmol, 3 equiv.) was added and the mixture was stirred for 15 min at r.t. before being diluted further with DCM (50 mL) and poured onto saturated aq. $NaHCO_3$. The organic layer was separated and the aqueous was extracted with DCM (3 x 60 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was washed with Hexanes and H_2O to give the desired dipyrrinone.

(Z)-Methyl 2-(5-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1H-pyrrol-3-yl)actetate (30a)



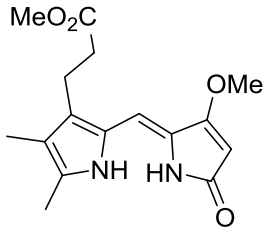
The title compound was synthesized according to general procedure A[4] and was isolated as a brown solid (3.57 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.87 (br s, 1H), 10.27 (br s, 1H), 6.36 (s, 1H), 5.08 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.40 (s, 2H), 2.37 (s, 3H), 2.13 (s, 3H), in accordance with the literature.[3]

(Z)-Methyl 3-(5-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1H-pyrrol-3-yl)propanoate (30b)



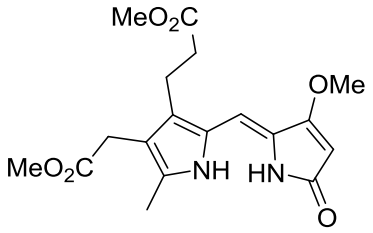
The title compound was synthesized according to general procedure A[4] and was isolated as a brown solid (3.58 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.89 (br s, 1H), 10.19 (br s, 1H), 6.34 (s, 1H), 5.09 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 2.72 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.12 (s, 3H), in accordance with the literature.[3]

(Z)-Methyl 3-(2-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-4,5-dimethyl-1Hpyrrol-3-yl) propanoate (30c)



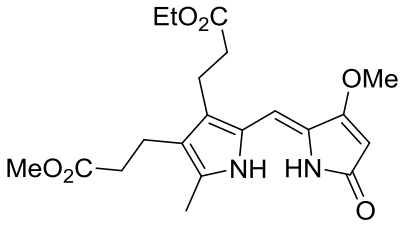
The title compound was synthesized according to general procedure A[4] and was isolated as a brown solid (0.9g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.91 (br s, 1H), 10.19 (br s, 1H), 6.34 (s, 1H), 5.09 (s, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H), 1.96 (s, 3H), in accordance with the literature. [4]

(Z)-Methyl 3-(4-(2-methoxy-2-oxoethyl)-2-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-5-methyl-1H-pyrrol-3-yl)propanoate (30d)



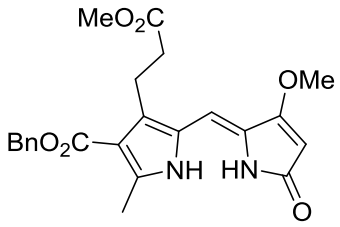
The title compound was synthesized according to general procedure B[1] and was isolated as a light brown solid (1.66 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.82 (br s, 1H), 10.31 (br s, 1H), 6.32 (s, 1H), 5.08 (s, 1H), 3.90 (s, 3H), 3.67 (s, 6H), 3.42 (s, 2H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), in accordance with the literature.[4]

(Z)-Ethyl 3-(4-(3-methoxy-3-oxopropyl)-2-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-5-methyl-1H-pyrrol-3-yl)propanoate (30e)



The title compound was synthesized according to general procedure B[1] and was isolated as a light brown solid (2.9 g, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.83 (br s, 1H), 10.22 (br s, 1H), 6.32 (s, 1H), 5.09 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.74 (t, *J* = 8.0 Hz, 2H), 2.49-2.44 (m, 4H), 2.35 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 173.7, 173.3, 173.1, 168.1, 132.5, 128.0, 122.5, 121.7, 118.8, 100.1, 89.9, 60.6, 58.3, 51.7, 36.7, 35.5, 20.0, 19.8, 14.3, 11.6; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_6$ 413.1689; found, 413.1685.

(Z)-Benzyl 4-(3-(3-methoxy-3-oxopropyl)-2-(3-methoxy-5-oxo-1H- pyrrole-2(5H)-ylidene)methyl)-5-methyl-1H-pyrrol-3-yl)formate (30f)



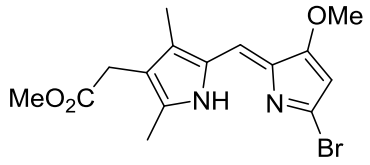
The title compound was synthesized according to general procedure A[4] and was isolated as a yellow-brown solid (681 mg, 59%): ^{1}H NMR (500 MHz, DMSO) δ: 10.96 (br s, 1H), 9.66 (br s, 1H), 7.43-7.33 (m, 5H), 6.06 (s, 1H), 5.28 (s, 1H), 5.22 (s, 2H) 3.86 (s, 3H), 3.51 (s, 3H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 2.41 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, DMSO); 172.5, 170.8, 166.9, 164.1, 139.7, 136.6, 128.4, 128.0, 127.9, 126.5,

126.0, 122.3, 110.3, 94.1, 91.6, 64.9, 58.5, 51.1, 35.0, 20.5, 13.8; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{23}H_{24}N_2O_6$ 447.1527; found, 447.1506.

General Method for the synthesis of bromodipyrrins[4]

To a solution of the appropriate dipyrrinone (2 mmol, 1 equiv.) in DCM (60 mL) under N_2 was added $POBr_3$ (4 mmol, 2 equiv.). The reaction mixture was heated to reflux temperature and stirred for 24 h. The reaction mixture was cooled slightly, by removing from the heat source, and $POBr_3$ (4 mmol, 2 equiv.) was then added before the mixture was returned to reflux temperature with stirring for 72 h. The reaction mixture was then cooled to r.t. and poured onto saturated $NaHCO_3$ (40 mL) and gently shaken in a separatory funnel. The organic layer was separated and the aqueous layer was extracted with DCM (4 x 50 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified via column chromatography over neutral alumina eluting with DCM to afford the pure bromodipyrrin as a yellow solid.

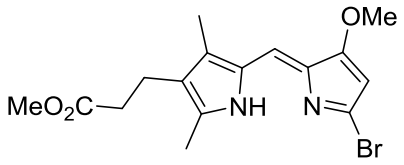
(Z)-Methyl 2-(5-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrol-3-yl)acetate (31a)



The title compound was synthesized according to the general procedure[4] and isolated as a yellow solid (200 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 5.58 (s, 1H),

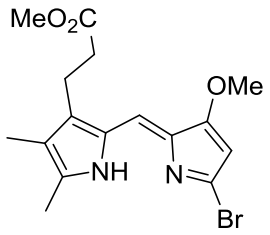
3.83 (s, 3H), 3.67 (s, 3H), 3.38 (s, 2H), 2.31 (s, 3H), 2.15 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(5-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrol-3-yl)propanoate (31b)



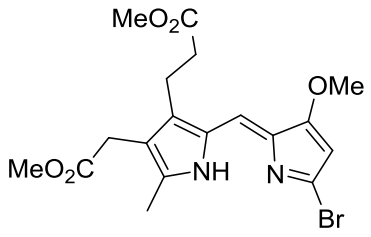
The title compound was synthesized according to the general procedure[4] and isolated as a yellow solid (170 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.87 (s, 1H), 5.58 (s, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 2.71(t, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 2.14 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-4,5-dimethyl-1Hpyrrol-3-yl) propanoate (31c)



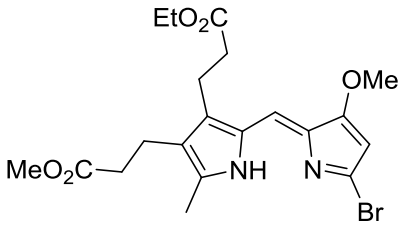
The title compound was synthesized according to the general procedure[4] and was isolated as a yellow solid (365 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.87 (s, 1H), 5.57 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 1.95 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-4-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrol-3-yl) propanoate (31d)



The title compound was synthesized according to the general procedure[4] and was isolated as a yellow solid (300 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.86 (s, 1H), 5.56 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.40 (s, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 2.30 (s, 3H), in accordance with the literature.[4]

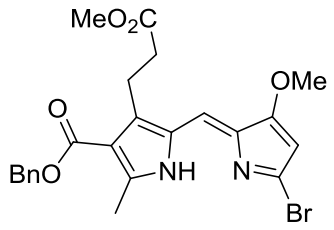
(Z)-Ethyl 3-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-4-(3-methoxy-oxopropyl)-5-methyl-1H-pyrrol-3-yl)propanoate (31e)



The title compound was synthesized according to the general procedure[4] and was isolated as a yellow solid (381 mg, 33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.86 (s, 1H), 5.57 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 3H), 2.89 (t, J = 7.9 Hz, 2H), 2.73 (t, J = 7.9 Hz, 2H), 2.51-2.43 (m, 4H), 2.29 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 173.4, 172.7, 167.1, 145.0, 137.6, 137.4, 133.5, 126.0, 121.1, 116.1, 99.6,

60.7, 58.6, 51.8, 36.7, 35.3, 20.0, 19.7, 14.3, 12.5; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{26}BrN_2O_5$ 453.1020; found, 453.1024.

(Z)-Benzyl 4-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-3-(3-methoxy-3-oxopropyl)-5-methyl-1H-pyrrol-3-yl)formate (31f)



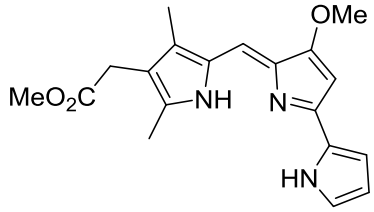
The title compound was synthesized according to the general procedure[4] and was isolated as a yellow solid (185 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44-7.33 (m, 5H), 6.97 (s, 1H), 5.58 (s, 1H), 5.28 (s, 2H), 3.86 (s, 3H), 3.60 (s, 3H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.58 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4, 167.8, 164.7, 148.3, 144.3, 140.2, 136.4, 135.7, 128.7, 128.5, 128.3, 126.4, 115.6, 112.9, 100.4, 66.0, 58.8, 51.6, 35.5, 21.2, 15.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for C_{23} $H_{24}BrN_2O_5$ 487.0863; found, 487.0846.

General Method for the synthesis of prodigiosenes[4]

To a solution of the appropriate bromodipyrrin (0.3 mmol, 1 equiv.) in DME (12 mL) was added commercially available *N*-boc pyrrole-2-boronic acid (0.36 mmol, 1.2 equiv.), LiCl (0.9 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (0.03 mmol, 0.1 equiv.), in a Schlenk flask. The reaction mixture was purged with N_2 for 15 min and placed under a N_2 atmosphere before adding a 2 M aqueous solution of Na_2CO_3 (1.2 mmol, 4 equiv.), previously purged with

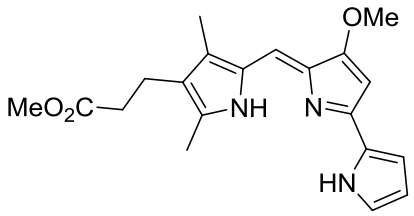
N_2, drop-wise to the reaction mixture. The Schlenk flask was sealed and the reaction mixture was heated to 85 °C and stirred for 24 h. The reaction mixture was cooled to r.t. and H_2O (30 mL) was added and extracted with EtOAc (4 x 30 mL). The organic layers were combined and washed with H_2O (60 mL) and brine (60 mL), dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via column chromatography on neutral alumina eluting with 0%-30% EtOAc/Hexanes. The product was then dissolved in MeOH:H_2O (1:1, 10 mL), 5 M HCl (0.3 mmol, 1 equiv.) was added drop-wise and the mixture was stirred for 3 h. The MeOH was removed in vacuo and the solid was isolated using Millipore filtration apparatus to give the pure prodigiosene as its HCl salt.

(Z)-Methyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate (13a)



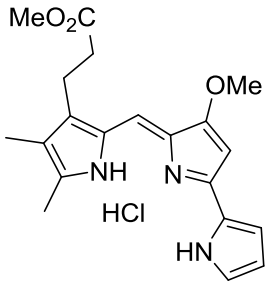
The title compound was synthesized according to the general procedure[4] and isolated as a red solid (186 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.87 (s, 1H), 6.70 (apparent s, 1H), 6.66 (apparent s, 1H), 6.17 (apparent s, 1H), 6.03 (s, 1H), 3.95 (s, 3H), 3.63 (s, 3H), 3.28 (s, 2H), 2.14 (s, 3H), 1.89 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)propanoate (13b)



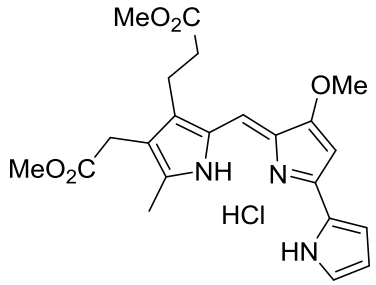
The title compound was synthesized according to the general procedure[4] and isolated as a red solid (181 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.89 (s, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.60 (apparent s, 1H), 6.11 (t, J = 2.5 Hz, 1H), 6.08 (s, 1H), 3.97 (s, 3H), 3.56 (s, 3H), 2.56 (t, J = 7.8 Hz, 2H), 2.32 (t, J = 7.8 Hz, 2H), 2.11 (s, 3H), 1.70 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4,5-dimethyl-2H-pyrrol-3-yl)propanoate hydrochloride (13c•HCl)



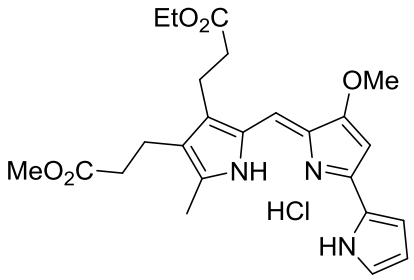
The title compound was synthesized according to the general procedure[4] and isolated as a red solid (119 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.70 (br s, 1H), 12.60 (br s, 2H), 7.22 (s, 1H), 7.04 (apparent s, 1H), 6.90 (apparent s, 1H), 6.35 (apparent s, 1H), 6.09 (s, 1H), 4.02 (s, 3H), 3.67 (s, 3H), 2.95 (t, J = 7.5 Hz, 2H), 2.53 (obscured s, 5H), 1.99 (s, 3H), in accordance with the literature.[4]

(Z)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4-(2-methoxy-2-oxoethyl)-5-methyl-2H-pyrrol-3-yl)propanoate hydrochloride (13d•HCl)



The title compound was synthesized according to the literature procedure[4] and isolated as a red solid (119 mg, 38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.79 (br s, 1H), 12.68 (br s, 1H), 12.62 (br s, 1H), 7.25 (s, 1H) 7.05 (apparent s, 1H), 6.95 (apparent s, 1H), 6.37 (apparent s, 1H), 6.10 (s, 1H), 4.04 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.46 (s, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.56 (obscured s, 5H), in accordance with the literature.[4]

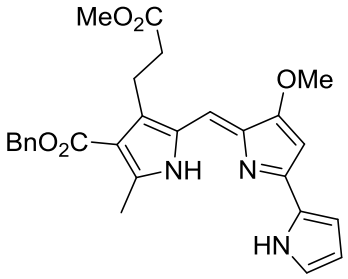
(Z)-Ethyl 3-(2-((4-methoxy-1H-1H'-[2,2'-bipyrrol]-5-yl)methylene)-4-(3-methoxy-3-oxopropyl)-5-methyl-2H-pyrrol-3-yl)propanoate hydrochloride (24•HCl)



The title compound was synthesized according to the general procedure[4] and isolated as a red solid (37 mg, 18%). ^{1}H NMR (500 MHz, $CDCl_3$); 12.75 (br s, 1H), 12.61 (br s, 2H), 7.23 (apparent s, 1H), 7.04 (s, 1H), 6.94-6.93 (m, 1H), 6.36-6.35 (m, 1H), 6.09 (d, J = 1.9 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.03 (s, 3H), 3.68 (s, 3H), 2.97 (t, J = 7.9 Hz, 2H), 2.77

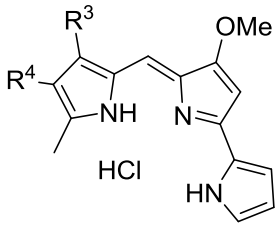
(t, *J* = 7.9 Hz, 2H), 2.56 (s, 3H), 2.51 (t, *J* = 7.9 Hz, 2H), 2.47 (t, *J* = 7.9 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR; 173.1, 172.4, 166.0, 148.1, 146.4, 139.4, 127.3, 124.0, 123.4, 122.4, 120.9, 117.4, 113.0, 112.0, 93.0, 60.9, 58.9, 51.9, 36.4, 34.7, 20.1, 19.6, 14.3, 12.6; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_5$ 440.2180; found, 440.2162.

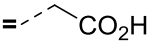
(Z)-Benzyl 4-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3-(3-methoxy-3-oxopropyl)-5-methyl-2H-pyrrol-3-yl)formate (25•HCl)

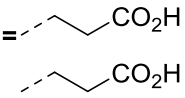


The title compound was synthesized according to the general procedure[4] and isolated as the crude, free base prodigiosene. Attempts at purification involved two columns on neutral alumina eluting with 0-50% EtOAc/Hexanes and preparative TLC eluting with 40% EtOAc/Hexanes. Complete purification was unsuccessful. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 13.04 (br s, 1H), 12.78 (br s, 1H), 12.75 (br s, 1H), 7.43-7.34 (m, 5H), 7.31 apparent s, 1H), 7.19 (s, 1H), 7.04 (apparent s, 1H), 6.42-6.40 (m, 1H), 6.11 (d, *J* = 1.4 Hz, 1H), 5.31 (s, 2H), 4.07 (s, 3H), 3.61 (s, 3H), 3.22 (t, *J* = 7.5 Hz, 2H), 2.81 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 167.2, 164.0, 151.0, 150.3, 141.8, 136.2, 129.2, 128.8, 128.5, 128.4, 123.5, 123.2, 122.1, 119.8, 114.7, 112.9, 112.8, 93.6, 66.2, 59.2, 51.8, 35.3, 21.2, 15.1; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{28}N_3O_5$ 474.2023; found, 474.2004.

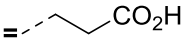
General procedure for the hydrolysis of prodigiosenes

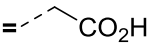


32a: R^3 = Me **R^4 =** 

32b: R^3 = Me **R^4 =** 

32c: R^3 = **R^4 =** Me

32d: R^3 = 

R^4 = 

$LiOH \cdot H_2O$ (0.62 mmol, 2.1 equiv.) was added to a stirred solution of the appropriate prodigiosene (0.30 mmol, 1 equiv.) in THF and H_2O (1:1, 17 mL). The reaction mixture was warmed to 40 ^oC and then stirred for 1.5 h at which point another portion of $LiOH \cdot H_2O$ (0.08 mmol, 0.25 equiv.) was added and stirring was continued overnight. The solvents were removed in vacuo and the resultant solid was dissolved in water (5 mL), 5 M HCl (1.20 mmol, 4 equiv.) was added drop-wise and the mixture was stirred for 2 h. The precipitate was collected via suction filtration using a Millipore filter to give the hydrolyzed prodigiosenes as a dark purple solid which were used without further purification.[24]

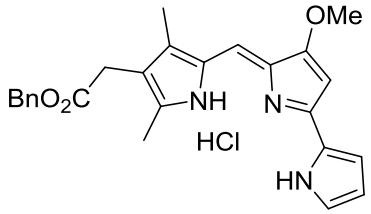
General procedure C for the coupling of prodigiosenes with various alcohols

The hydrolyzed prodigiosene (0.14 mmol, 1 equiv.) was added to a stirred solution of the appropriate alcohol (0.14 mmol, 1 equiv.), EDCI (1.1 mmol, 0.15 equiv.) and DMAP (0.29 mmol, 2.1 equiv.) in dry DCM (12 mL), under N_2. The reaction mixture was stirred at r.t. and monitored using TLC for up to 5 days. H_2O (15 mL) was then added and extracted with DCM (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude material was purified via column chromatography on neutral alumina eluting with 20% EtOAc/Hexanes. The prodigiosene was then dissolved in MeOH:CH_2Cl_2 (1:1, 10 mL). Concentrated HCl (0.14 mmol, 1 equiv.) was added drop-wise and the mixture was stirred for ~30 min. The DCM was removed in vacuo and the solid was isolated using Millipore filtration apparatus and washed with MeOH and ether to give the desired product as its HCl salt. [24]

*General procedure D for the coupling of prodigiosene **32a** with various amines*

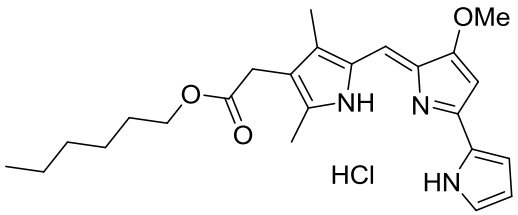
To a suspension of **32a** (0.17 mmol, 1 equiv.) in dry DCM (8.3 mL) was added the appropriate amine (0.17 mmol, 1 equiv.), DMAP (0.34 mmol, 2 equiv.) and HBTU (0.34 mmol, 2 equiv.) consecutively at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. When the reaction was complete, the reaction mixture was diluted with DCM (10 mL) and washed with saturated $NaHCO_3$ (aq.) (30 mL), 2% HCl (30 mL) and brine (30 mL) before being dried with Na_2SO_4. After filtration and removal of the solvemt in vacuo, the crude solid was recrystallized from a $CHCl_3$/Hexanes mixture.[25]

(Z)-Benzyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate hydrochloride (20a)



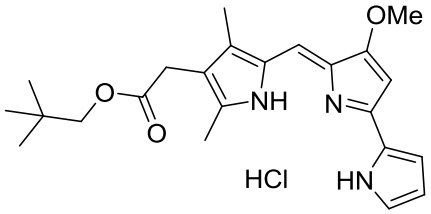
The title compound was synthesized according to the general procedure C[24] using benzyl alcohol and prodigiosene **32a**, and was isolated as a red solid (28 mg, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.74 (br s, 1H), 12.65 (br s, 1H), 12.58 (br s, 1H), 7.39-7.30 (m, 5H), 7.22 (apparent s, 1H), 7.04 (s, 1H), 6.91 (apparent s, 1H), 6.35 (apparent s, 1H), 6.08 (s, 1H), 5.12 (s, 2H), 4.01 (s, 3H), 3.46 (s, 2H), 2.54 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 165.8, 147.9, 146.9, 138.2, 135.8, 128.7, 128.5, 128.3, 127.1, 124.1, 122.4, 120.6, 118.5, 117.2, 113.3, 111.9, 93.0, 66.9, 58.9, 30.4, 12.5, 10.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$ 416.1969; found, 416.1978.

(Z)-Hexyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate (20b)



The title compound was synthesized according to the general procedure C[24] using hexyl alcohol and prodigiosene **32a**, and was isolated as a red solid (17 mg, 17%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.75 (br s, 1H), 12.66 (br s, 1H), 12.58 (br s, 1H), 7.23 (s, 1H), 7.06 (s, 1H), 6.92 (apparent s, 1H), 6.35 (apparent s, 1H), 6.09 (apparent s, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 4.02 (s, 3H), 3.41 (s, 2H), 2.57 (s, 3H), 2.26 (s, 3H), 1.63-1.55 (m, 2H), 1.34-1.25 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 165.7, 147.7, 147.0, 138.2, 126.9, 124.0, 122.3, 120.4, 118.7, 116.9, 113.3, 111.7, 92.8, 65.2, 58.7, 31.4, 30.3, 28.6, 25.5, 22.5, 14.0, 12.4, 10.2; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{32}N_3O_3$ 410.2438; found, 410.2446.

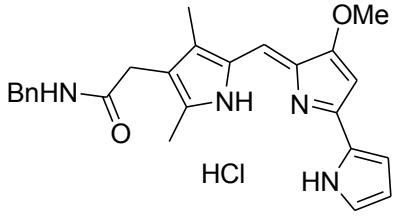
(Z)-Neopentyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate hydrochloride (20d)



The title compound was synthesized according to the general procedure C[24] using neopentyl alcohol and prodigiosene **32a**, and was isolated as a red solid (36 mg, 46%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.72 (br s, 1H), 12.64 (br s, 1H), 12.56 (br s, 1H), 7.22 (s, 1H), 7.05 (s, 1H), 6.91 (apparent s, 1H), 6.34 (apparent s, 1H), 6.08 (d, *J* = 3.5 Hz, 1H), 4.01 (s, 3H), 3.77 (s, 2H), 3.43 (s, 2H), 2.58 (s, 3H), 2.27 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0, 165.8, 147.8, 146.9, 138.2, 127.0, 124.1, 122.4, 120.6,

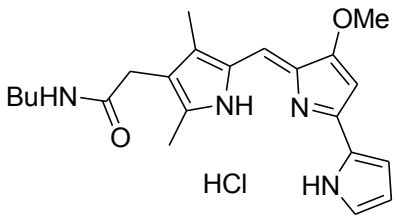
118.8, 117.1, 113.3, 111.9, 92.9, 74.4, 58.8, 31.5, 30.5, 26.5, 12.5, 10.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{30}N_3O_3$ 396.2282; found, 396.2270.

(Z)-Benzyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20e)



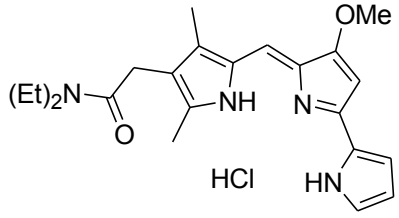
The title compound was synthesized according to the general procedure D[25] using Bn amine and prodigiosene **32a**, and was isolated as a red solid (37 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.78 (br s, 1H), 12.69 (br s, 1H), 12.59 (br s, 1H), 7.38-7.18 (m, 5H), 7.02 (s, 1H), 6.99-6.95 (m, 1H), 6.38-6.36 (m, 1H), 6.09 (d, *J* = 3 Hz, 1H), 5.84-5.80 (m, 1H), 4.41 (d, *J* = 9.5 Hz, 2H), 4.03 (s, 3H), 3.44 (s, 2H), 2.96 (br s, 1H), 2.53 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:170.2, 166.2, 148.7, 145.9, 138.1, 137.5, 129.3, 128.9, 127.8, 127.5, 124.2, 122.3, 121.3, 118.5, 118.0, 113.1, 112.2, 93.2, 58.9, 43.8, 31.1, 12.4, 10.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{27}N_4O_2$ 415.2129; found, 415.2124.

(Z)-Butyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20f)



The title compound was synthesized according to the general procedure D[25] using Bu amine and prodigiosene **32a**, and was isolated as a red solid (19 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.81 (br s, 1H), 12.71 (br s, 1H), 12.59 (br s, 1H), 7.06 (s, 1H), 6.97 (apparent s, 1H), 6.40-6.37 (m, 1H), 6.11 (d, *J* = 1.5 Hz, 1H), 5.48-5.47 (m, 1H), 4.04 (s, 3H), 3.38 (s, 2H), 3.22 (q, *J* = 7.0 Hz, 2H), 3.05 (br s, 1H), 2.54 (s, 3H), 2.22 (s, 3H), 1.42 (quin, *J* = 7.0 Hz, 2H), 1.27 (sex, *J* = 7.0 Hz, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 166.3, 148.8, 145.9, 137.5, 127.8, 124.2, 122.3, 121.4, 118.5, 118.0, 113.0, 112.3, 93.2, 59.0, 39.7, 31.8, 31.1, 20.1, 13.8, 12.4, 10.2 with acetone peaks at 207.0 and 31.1; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{29}N_4O_2$ 381.2285; found, 381.2269.

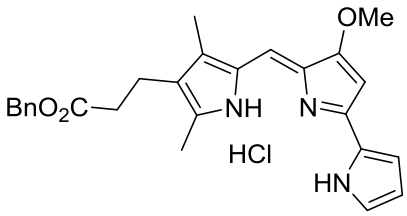
(Z)-N,N-Diethyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20g)



The title compound was synthesized according to the general procedure D[25] using diethylamine and prodigiosene **32a**, and was isolated as a red solid (21 mg, 38%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.71 (br s, 1H), 12.63 (br s, 1H), 12.56 (br s, 1H), 7.23-7.20 (apparent m, 1H), 7.05 (s, 1H), 6.92-6.89 (apparent m, 1H), 6.36-6.33 (apparent m, 1H), 6.09 (s, 1H), 4.02 (s, 3H), 3.46 (s, 2H), 3.37 (br q, *J* = 7 Hz, 4H), 2.54 (s, 3H), 2.23 (s, 3H), 1.15 (br t, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:169.1, 165.7, 147.5, 147.3, 138.5, 126.9, 124.3, 122.5, 120.4, 120.1, 116.9, 113.4, 111.8, 92.9, 58.8, 42.4, 40.8, 29.9,

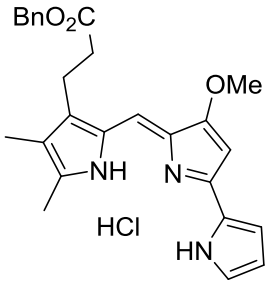
14.4, 13.2, 12.8, 10.5; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{29}N_4O_2$ 381.2285; found, 381.2278.

(Z)-Benzyl 3-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)propanoate hydrochloride (21)



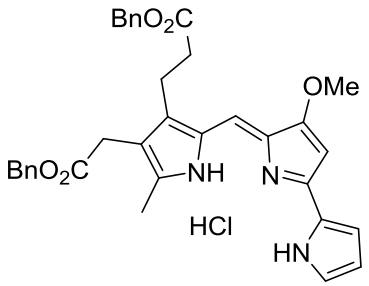
The title compound was synthesized according to the general procedure C^{24} using BnOH and prodigiosene **32b**, and was isolated as a red solid (mg, %): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.71 (br s, 1H); 12.58 (br s, 2H), 7.35-7.30 (m, 5H), 7.21 (s, 1H), 7.01 (s, 1H), 6.90 (s, 1H), 6.35 (s, 1H), 6.09 (s, 1H), 5.10 (s, 2H), 4.02 (s, 3H), 2.54 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.21 (s, 3H) with minor impurities; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 172.6, 165.6, 147.3, 147.1, 165.6, 147.3, 147.1, 137.9, 135.9, 128.7, 128.4, 126.8, 124.4, 124.3, 122.5, 120.2, 116.8, 113.3, 111.7, 92.9, 66.6, 58.8, 34.6, 19.7, 12.6, 10.1; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_3$ 430.2125; found, 430.2108.

(Z)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4,5-dimethyl-2H-pyrrol-3-yl)propanoate hydrochloride (22)



The title compound was synthesized according to the general procedure C[24] using benzyl alcohol and prodigiosene **32c**, and was isolated as a red solid (28 mg, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.68 (br s, 1H), 12.59 (br s, 2H), 7.37-7.29 (m, 5H), 7.22 (s, 1H), 7.03 (apparent s, 1H), 6.91 (s, 1H), 6.35 (apparent s, 1H), 6.08 (apparent s, 1H), 5.11 (s, 2H), 3.99 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.52 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.3, 165.7, 147.4, 147.2, 139.6, 135.9, 128.7, 128.5, 128.3, 126.8, 123.5, 122.5, 121.5, 120.4, 116.8, 113.0, 111.8, 92.9, 66.6, 58.8, 35.5, 20.3, 12.5, 9.0; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_3$ 430.2125; found, 430.2104.

(Z)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4-(2-methoxy-2-oxoethyl)-5-methyl-2H-pyrrol-3-yl)propanoate hydrochloride (23)



The title compound was synthesized according to the general procedure C^{24} using benzyl alcohol and prodigiosene **32d**, and was isolated as a red solid (12 mg, 13%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.79 (br s, 1H), 12.67 (br s, 2H), 7.38-7.23 (m, 10H), 6.85 (s, 1H), 6.68 (br s, 2H), 6.16 (apparent s, 1H), 6.04 (s, 1H), 5.08 (s, 2H), 5.02 (s, 2H), 3.95 (s, 3H), 3.31 (s, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.8, 171.5, 168.9, 159.8, 139.0, 136.7, 136.1, 136.0, 131.6, 128.7, 128.6, 128.6 (4C), 128.4, 128.3 (4C), 128.2, 127.1, 125.6, 122.7, 114.4, 112.7, 110.3, 95.6, 66.6, 66.4, 58.5, 36.2, 30.4, 20.1, 10.9; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{34}H_{34}N_3O_5$ 564.2493; found, 564.2467.

4.4 References for Chapter 4

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CHAPTER 5 CONCLUSIONS AND FUTURE WORK

Overall, two classes of pyrrolic compounds were investigated in this work; dipyrrins and prodigiosenes. Dipyrrins consist of two pyrrole units linked by a methane bridge and prodigiosenes are a class of pyrrolyldipyrrins (a dipyrrin with a pyrrole substituent) containing a methoxy substituent.

The goal of the first project, involving dipyrrins, was to develop a convenient and novel methodology for the synthesis of symmetric *meso*-H-dipyrrin hydrobromide. It was concluded that the reaction of 2-formyl pyrroles in acidic methanol gives the corresponding symmetric, *meso*-H-dipyrrin hydrobromides in good yields. As well as being convenient, this strategy complements existing methods by enabling the high-yielding synthesis of symmetrical dipyrrins where they might not be easily accessible.

Presumably, the mechanism involves initial deformylation under the acidic conditions, followed immediately by in situ reaction of the resulting α-free pyrrole with the remaining 2-formyl pyrrole in solution. However, the regioselectivity of **2c** potentially points to some concerted character. Upon finding these results, the synthesis of pyrrole **3** with significant portions of ^{13}C at one of the methyl substituents was proposed. This synthesis proved to have many limitations and continues to be being investigated. Following the successful synthesis of pyrrole **3**, its corresponding dippyrin hydrobromides salt will be synthesized according to the developed methodology and, by means of the ^{13}C label, the ratio of the two dipyrrin isomers will be analyzed using NMR spectroscopy.

The goal of the second project was to synthesize a series of novel prodigiosenes in order to study the effect of each of their unique C-ring substituent patterns on biological activity with respect to anticancer activity and leukemia selectivity. A series of prodigiosenes was developed in order to explore the role of the alkanoate substitution pattern present in four new prodigiosenes, designed and synthesized in the Thompson lab, which were the first of their kind and the first to exhibit strong selectivity against leukemia cell lines. In this work, twelve new prodigiosenes have been synthesized to probe the role of the alkyl ester substituent, the role of the ester moiety versus an amide moiety, the role of lipophilicity and the necessity of an alkyl ester over a conjugated ester regarding cell line selectivity.

Future work involves repeating the synthesis of prodigiosene **25** in order to isolate a larger quantity of pure material as its more stable hydrochloride salt. These twelve prodigiosenes with undergo *in vitro* analysis involving one- and five-dose screening over four human leukemia cell lines, plus cell lines representing eight other human cancer types, maintained in the NCI-60 panel (http://dtp.cancer.gov).

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APPENDICES

Appendix 1.

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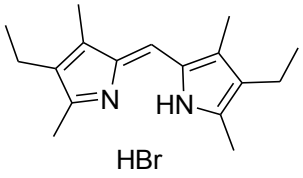
Appendix 2. NMR Spectra for Chapter 2

1,3,7,9-Tetramethyl-2,8-diethyl-4,6-dipyrrin hydrobromide (2a)



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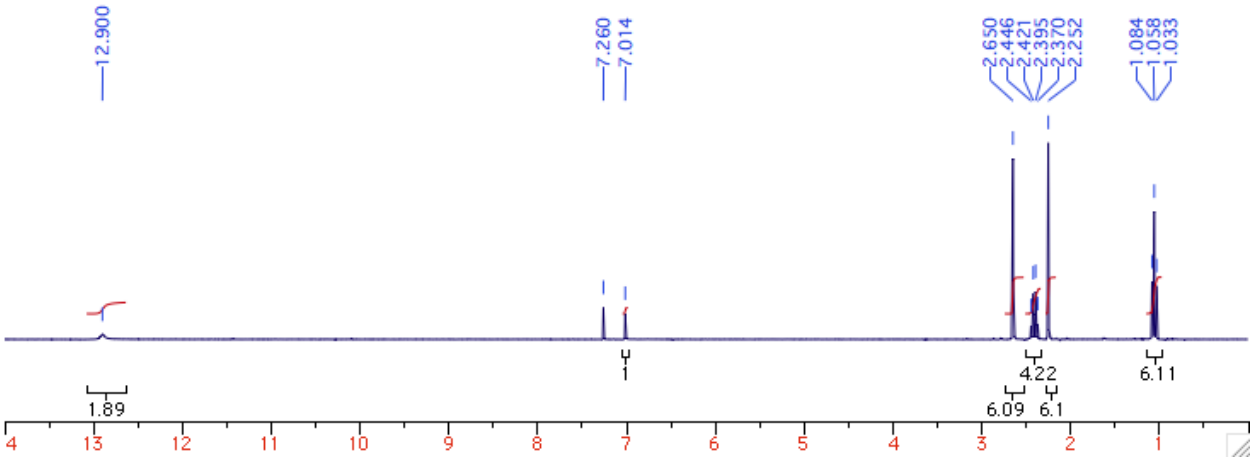

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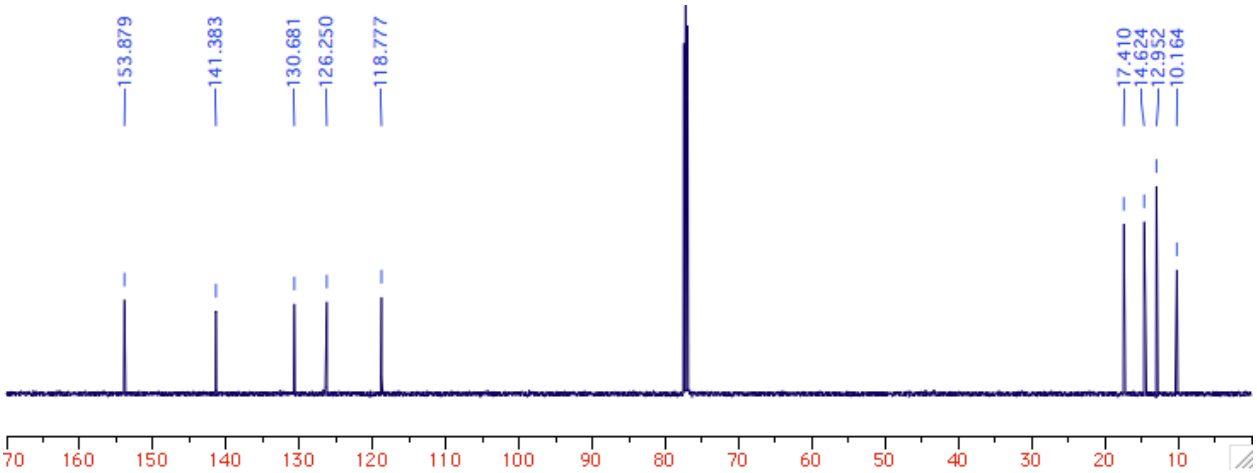
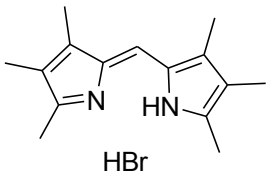


1,2,3,7,8,9-Hexamethyl-4,6-dipyrrin hydrobromide (2b)



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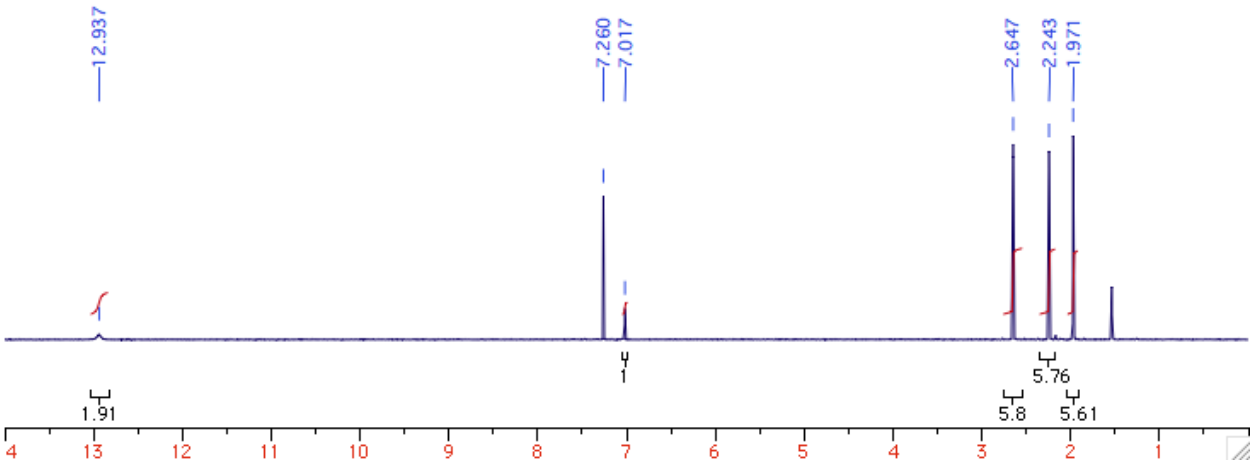

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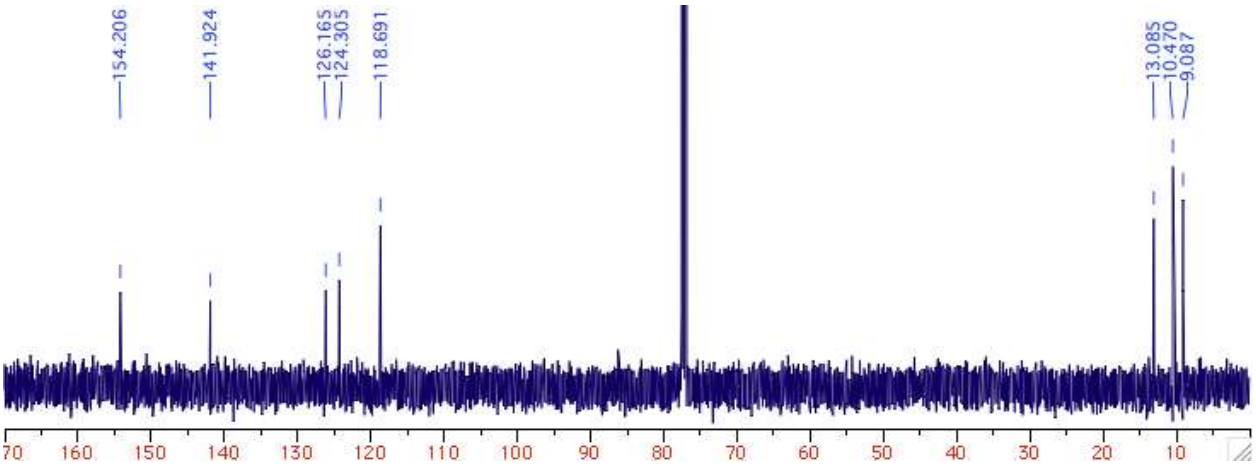
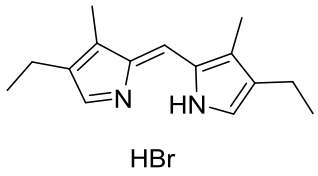
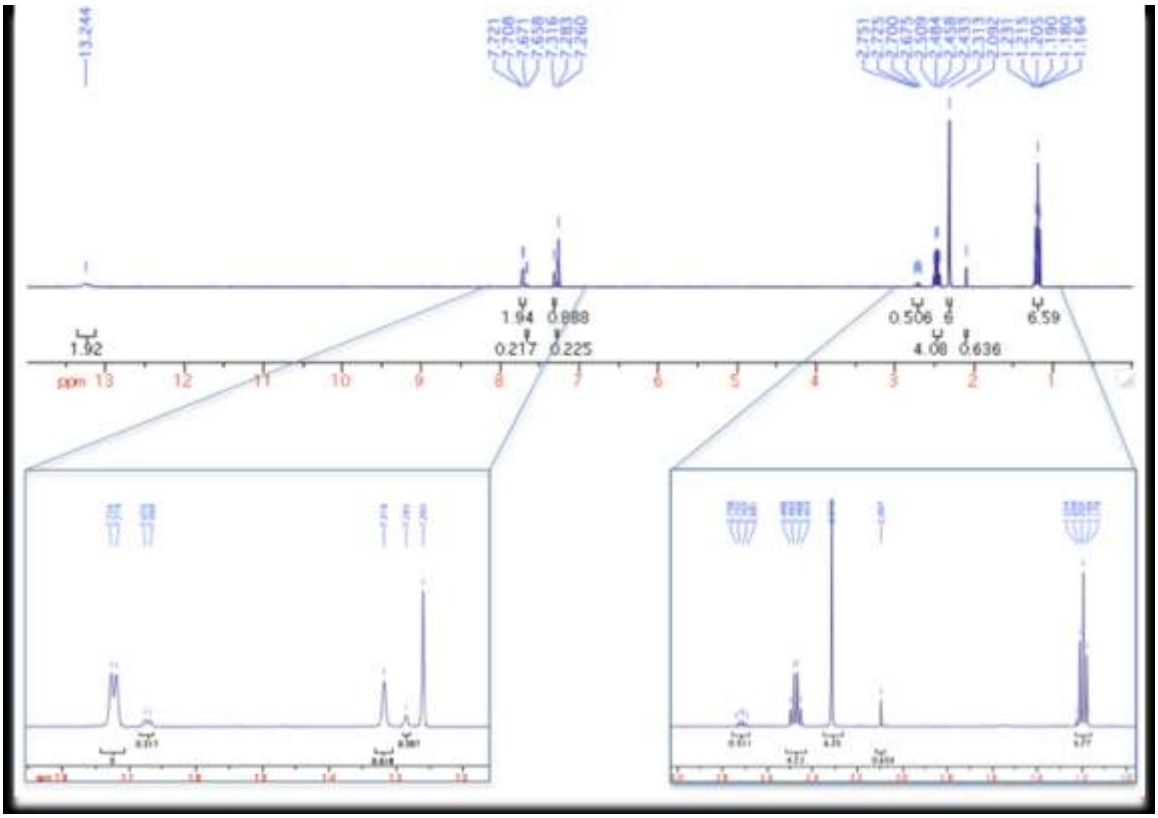


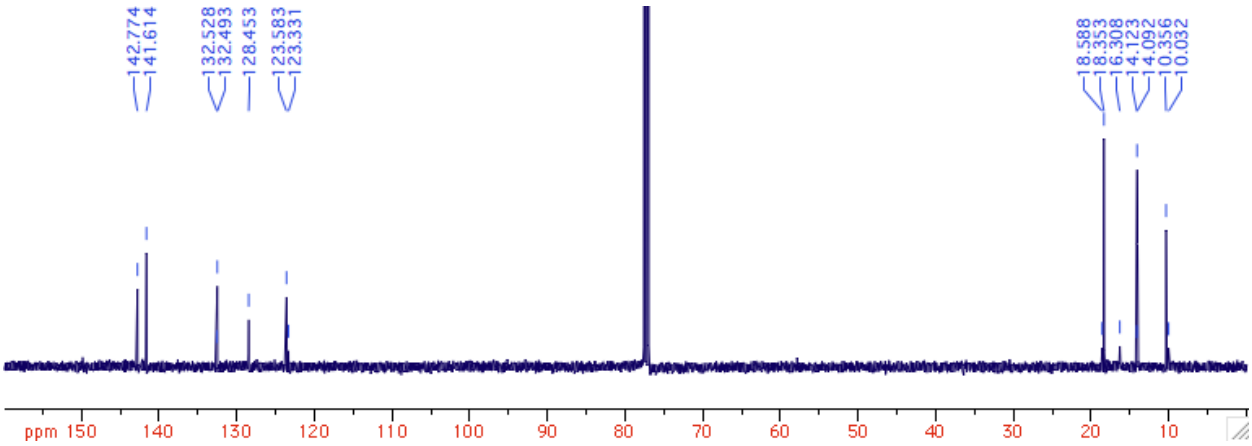
2,3,7,8-Tetramethyl-4,6-dipyrrin hydrobromide (2c)



^{1}H NMR; 300 MHz, $CDCl_3$

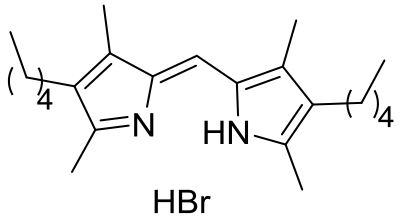


^{13}C NMR; 125 MHz, $CDCl_3$

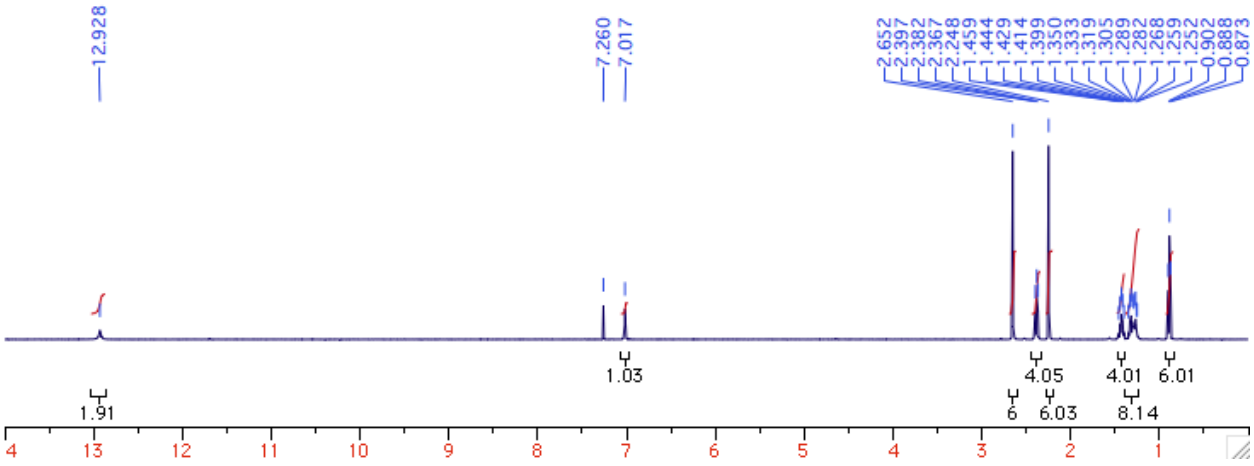


*note the presence of 10% of the dipyrrin salt isomer

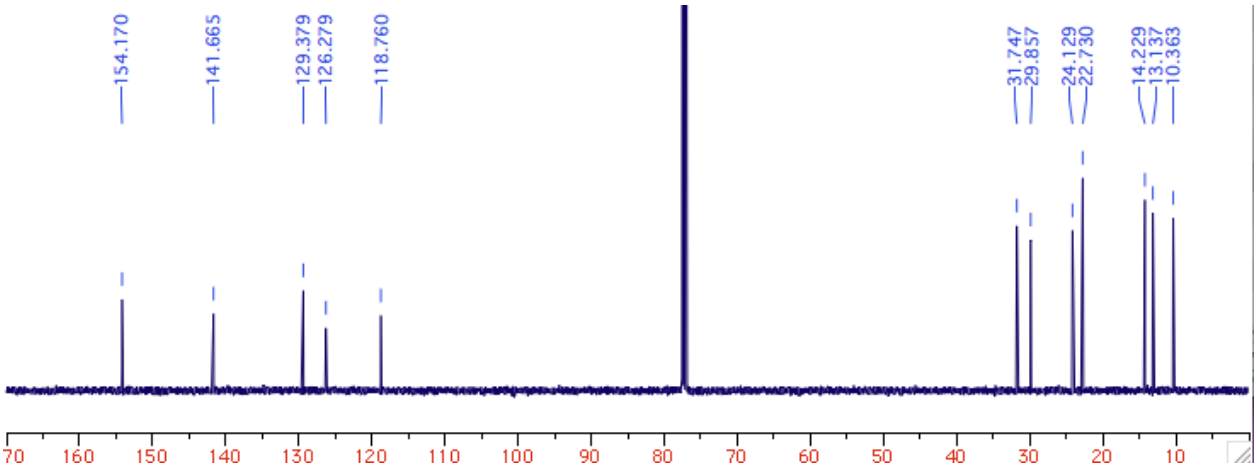
1,3,7,9-Tetramethyl-2,8-dipentyl-4,6-dipyrrin hydrobromide (2d)



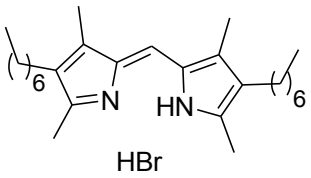
^{1}H NMR; 500MHz, $CDCl_3$



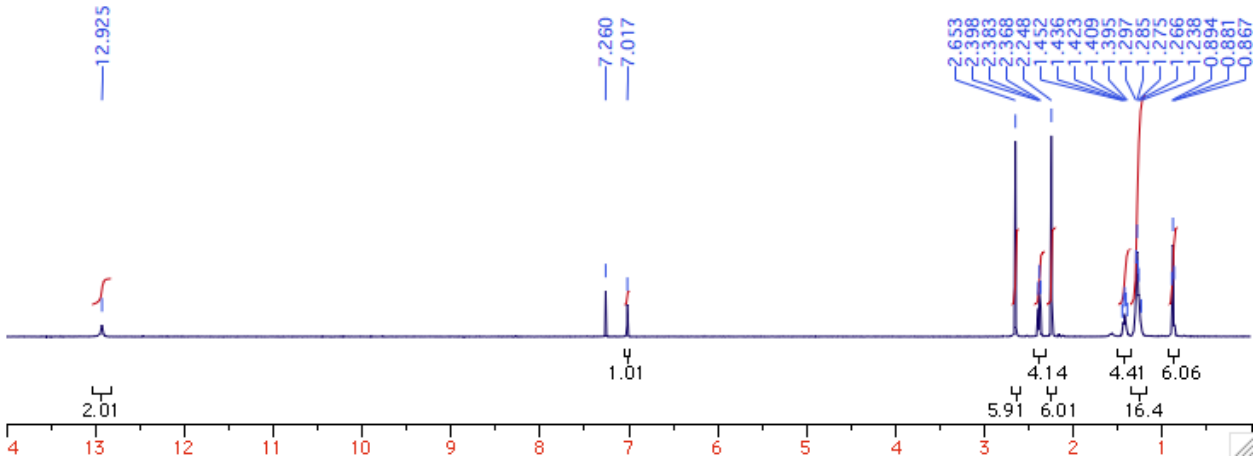
^{13}C NMR; 125 MHz, $CDCl_3$



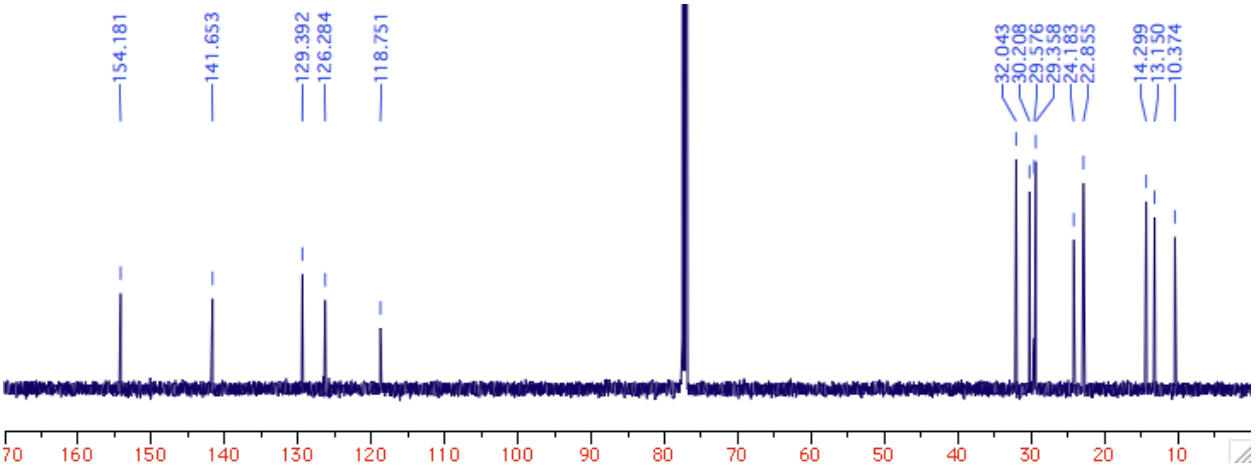
1,3,7,9-Tetramethyl-2,8-diheptyl-4,6-dipyrrin hydrobromide (2e)



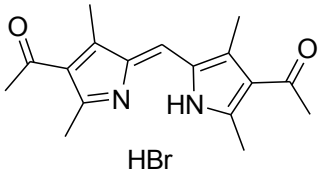
^{1}H NMR; 500 MHz, $CDCl_3$



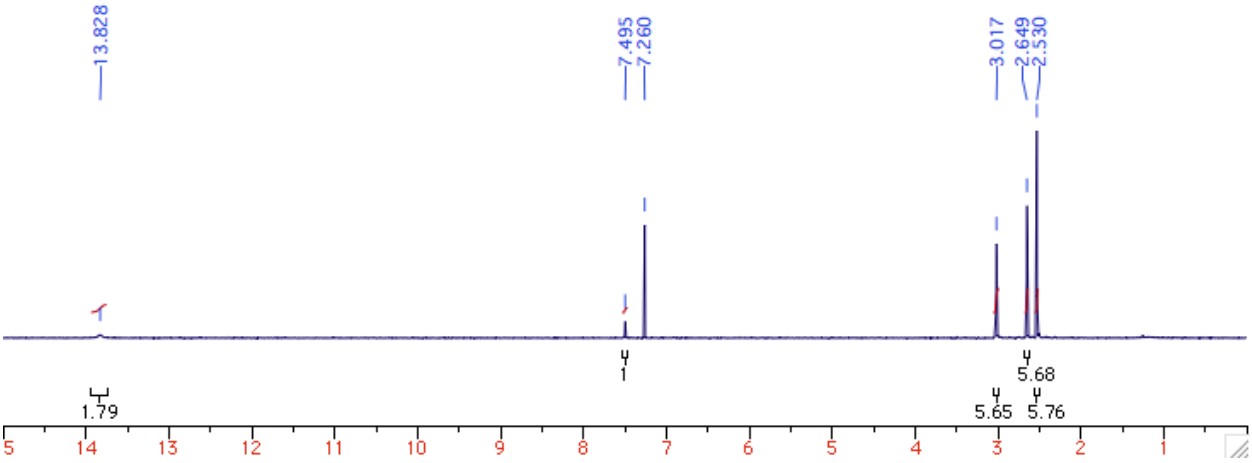
^{13}C NMR; 125 MHz, $CDCl_3$



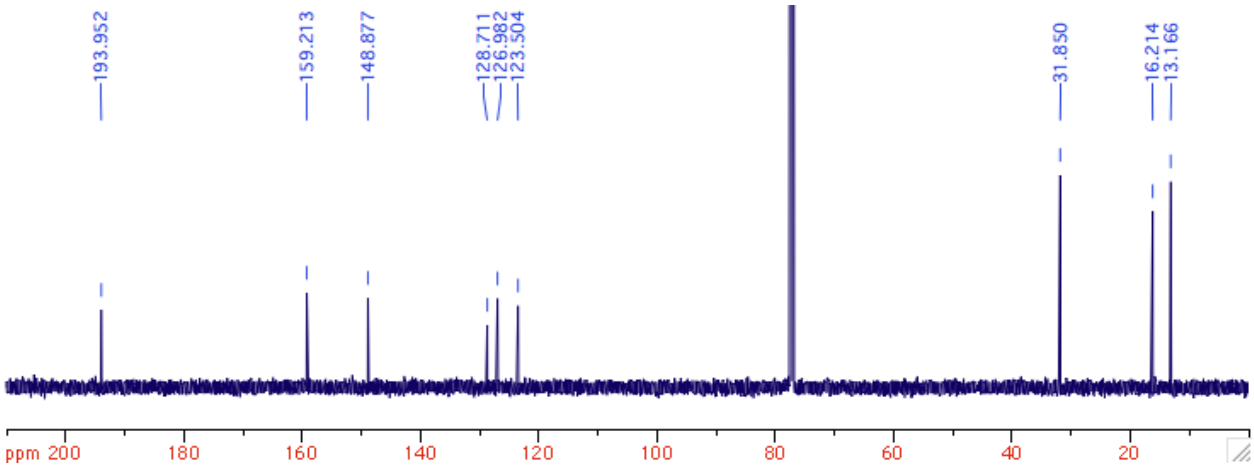
1,3,7,9-Tetramethyl-2,8-diacetyl-4,6-dipyrrin hydrobromide (2f)



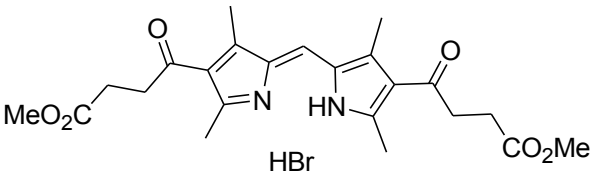
^{1}H NMR; 300 MHz, $CDCl_3$



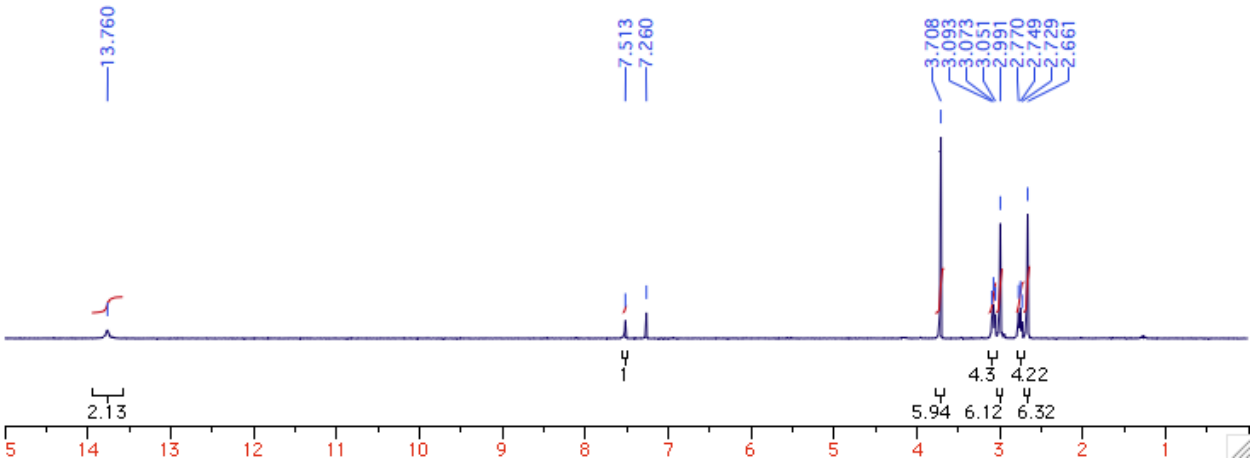
^{13}C NMR; 75 MHz, $CDCl_3$



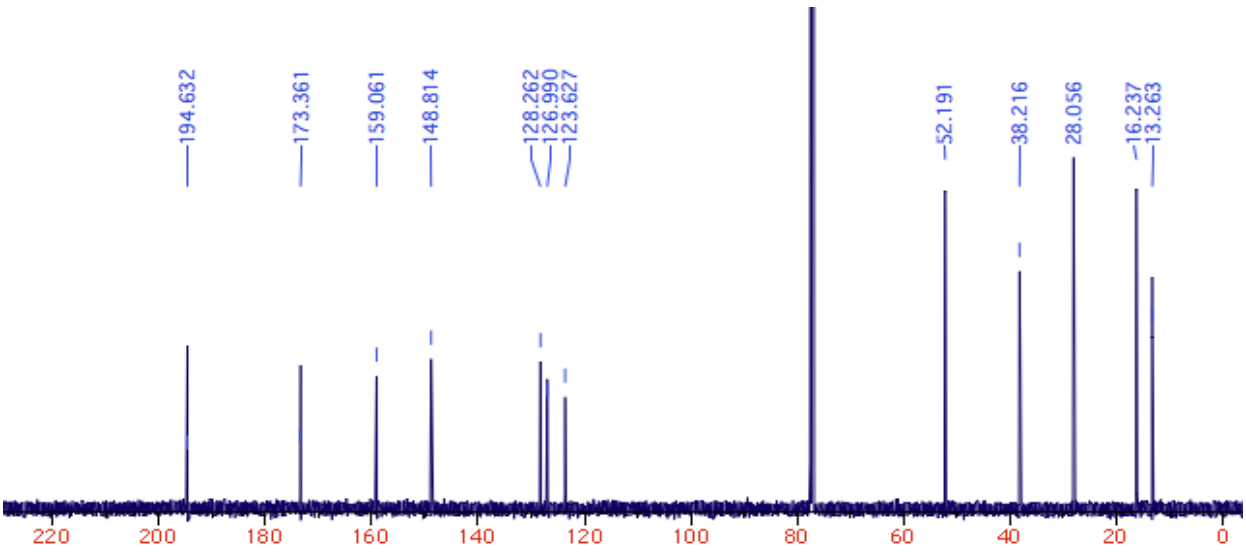
1,3,7,9-Tetramethyl-2,8-di(4-methoxy-4-oxobutanoyl)-4,6-dipyrrin hydrobromide (2g)



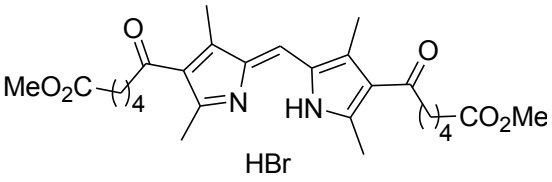
^{1}H NMR; 300 MHz, $CDCl_3$



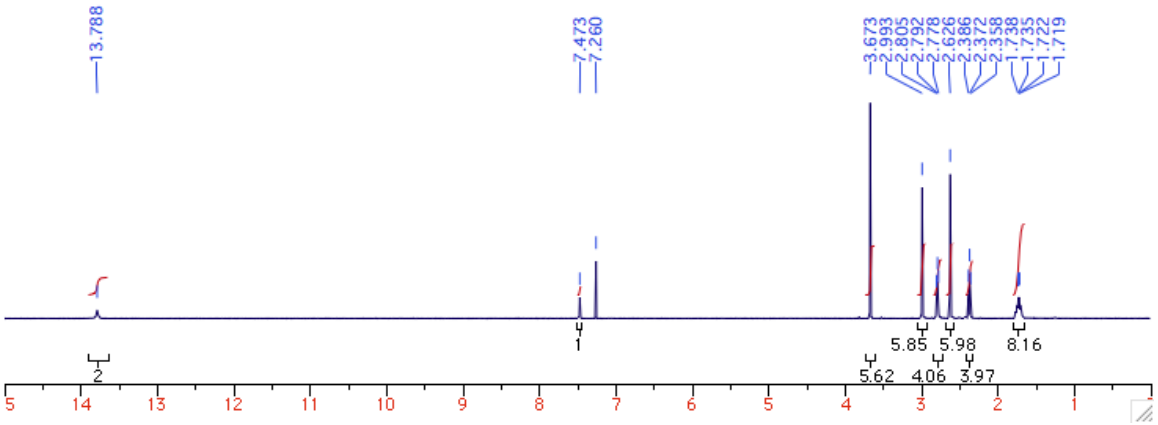
^{13}C NMR; 125 MHz, $CDCl_3$



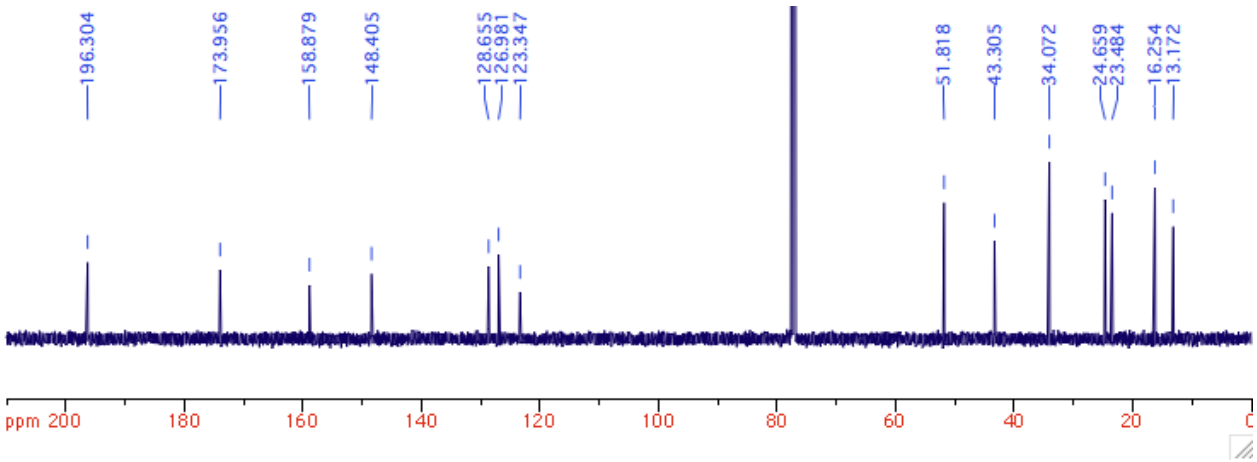
1,3,7,9-Tetramethyl-2,8-di(6-methoxy-6-oxohexanoyl)-4,6-dipyrrin hydrobromide (2h)



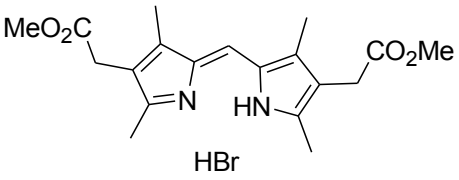
^{1}H NMR; 500 MHz, $CDCl_3$



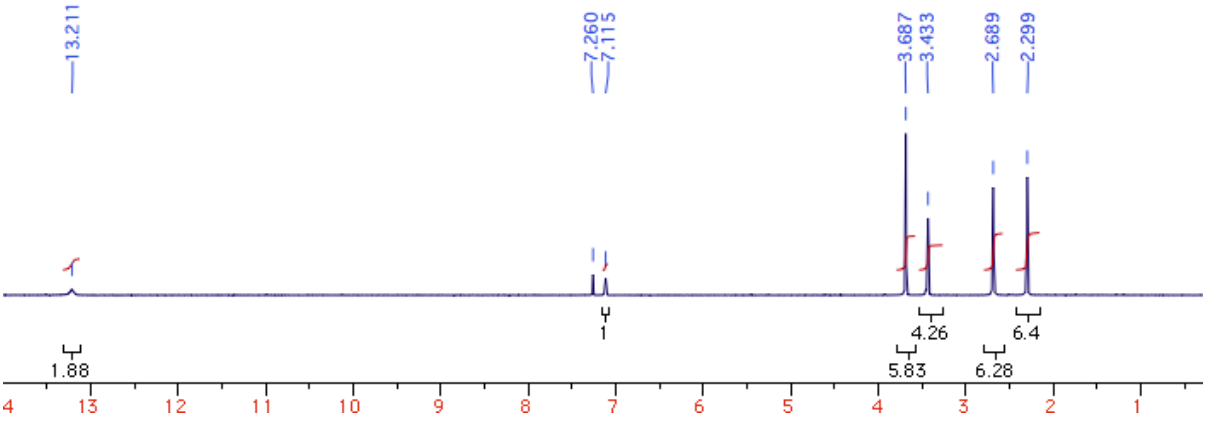
^{13}C NMR; 125 MHz, $CDCl_3$



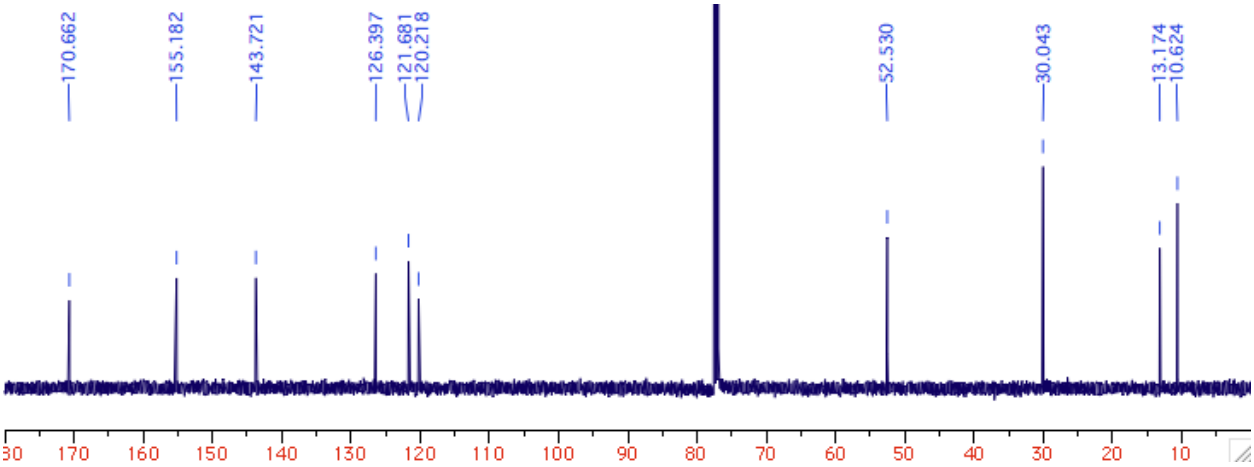
1,3,7,9-Tetramethyl-2,8-di(2-methoxy-2-oxoethyl)-4,6-dipyrrin hydrobromide (2i)



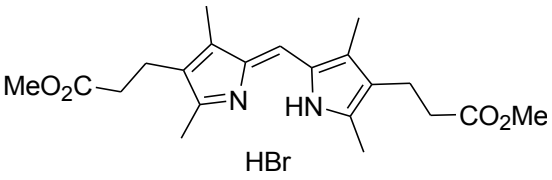
^{1}H NMR; 300 MHz, $CDCl_3$



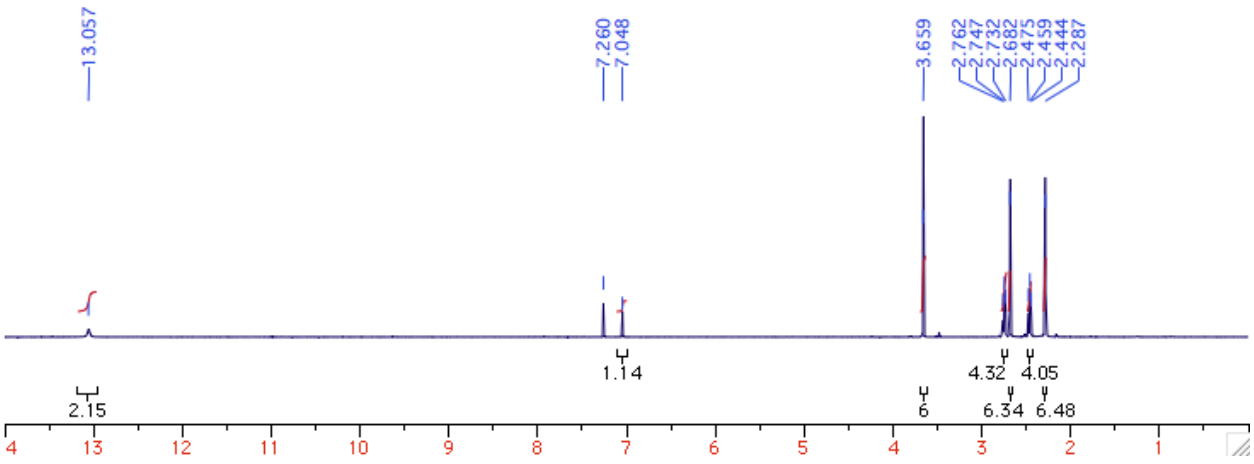
^{13}C NMR; 125 MHz, $CDCl_3$



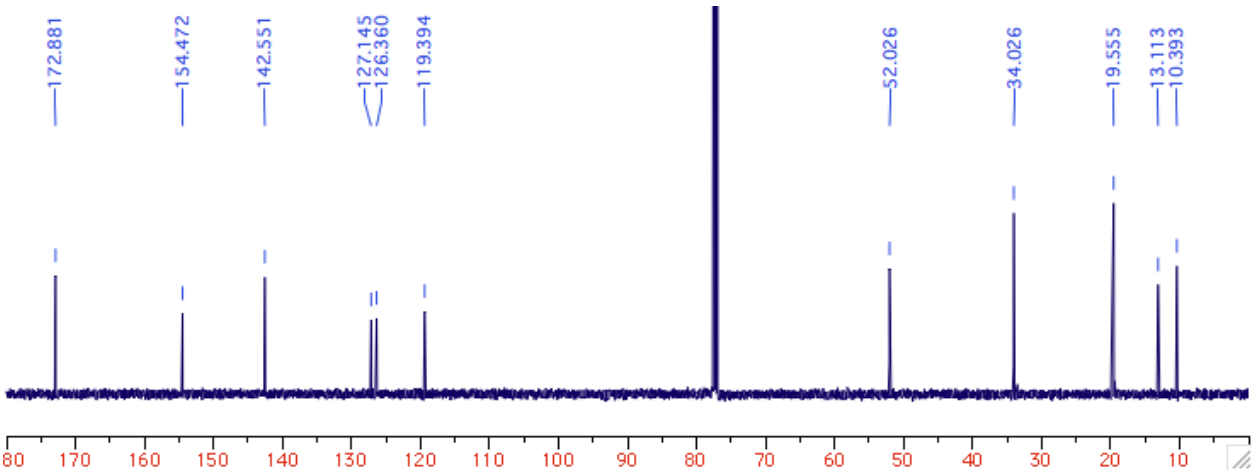
1,3,7,9-Tetramethyl-2,8-di(3-methoxy-3-oxopropyl)-4,6-dipyrrin hydrobromide (2j)



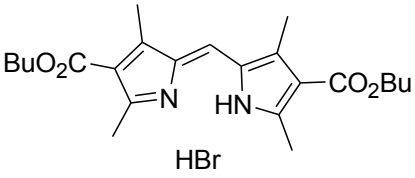
^{1}H NMR; 500 MHz, $CDCl_3$



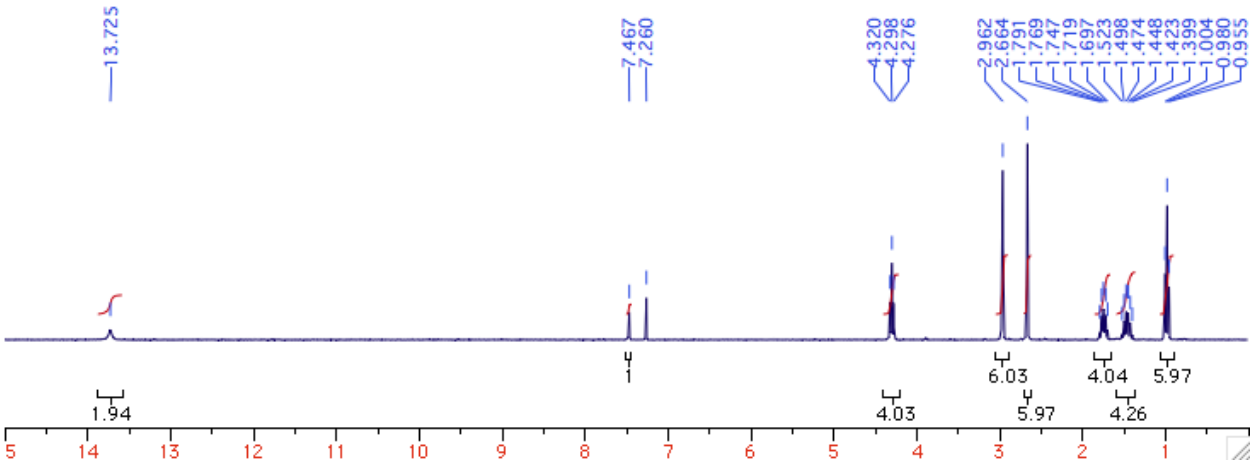
^{13}C NMR; 125 MHz, $CDCl_3$



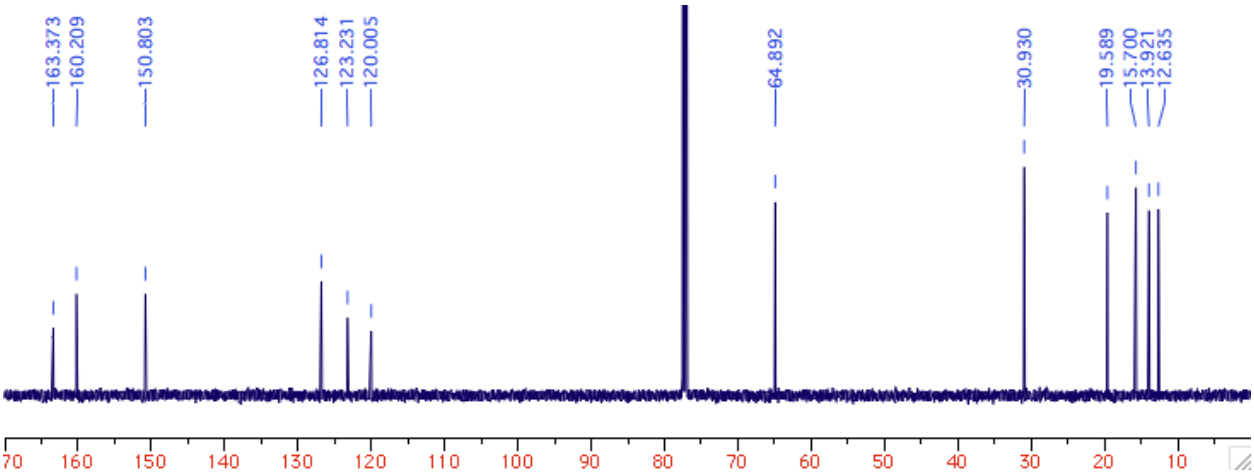
1,3,7,9-Tetramethyl-2,8-dibutoxycarbonyl-4,6-dipyrrin hydrobromide (2k)



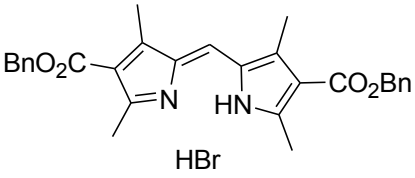
^{1}H NMR; 300 MHz, $CDCl_3$



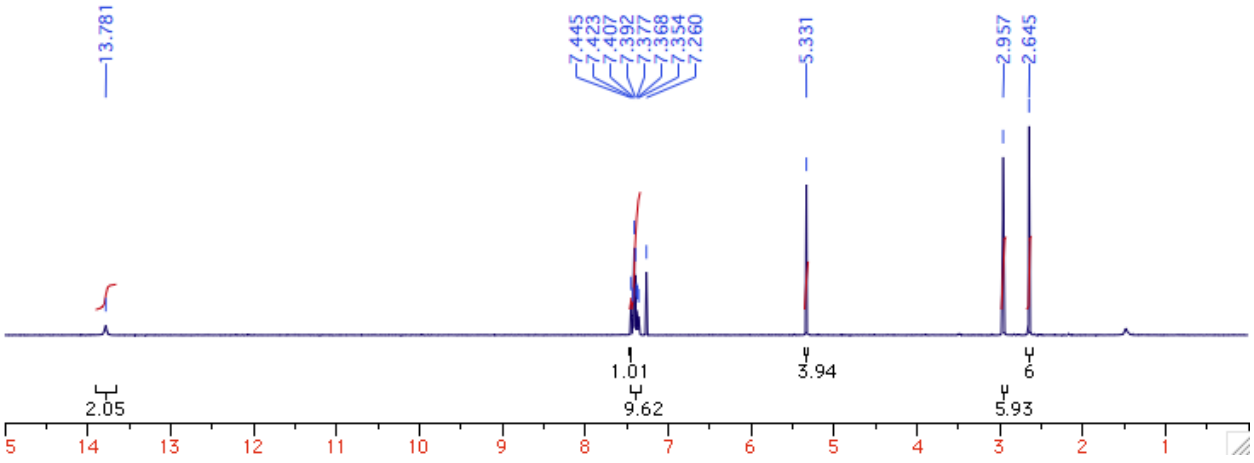
^{13}C NMR; 125 MHz, $CDCl_3$



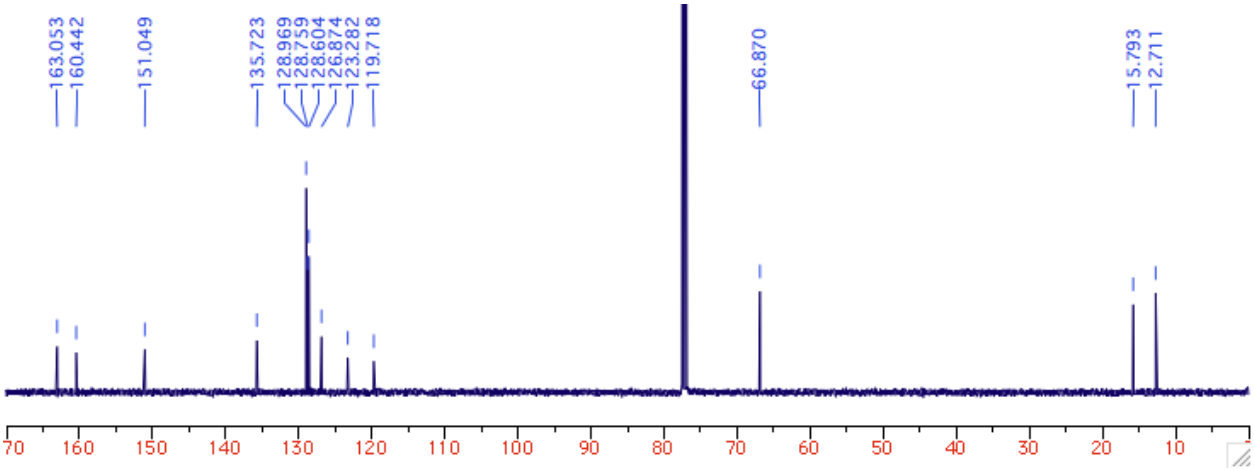
1,3,5,7-Tetramethyl-2,8-dibenzyloxycarbonyl-4,6-dipyrrin hydrobromide (2l)



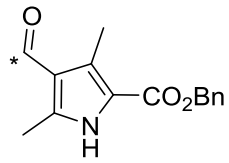
^{1}H NMR; 500 MHz, $CDCl_3$



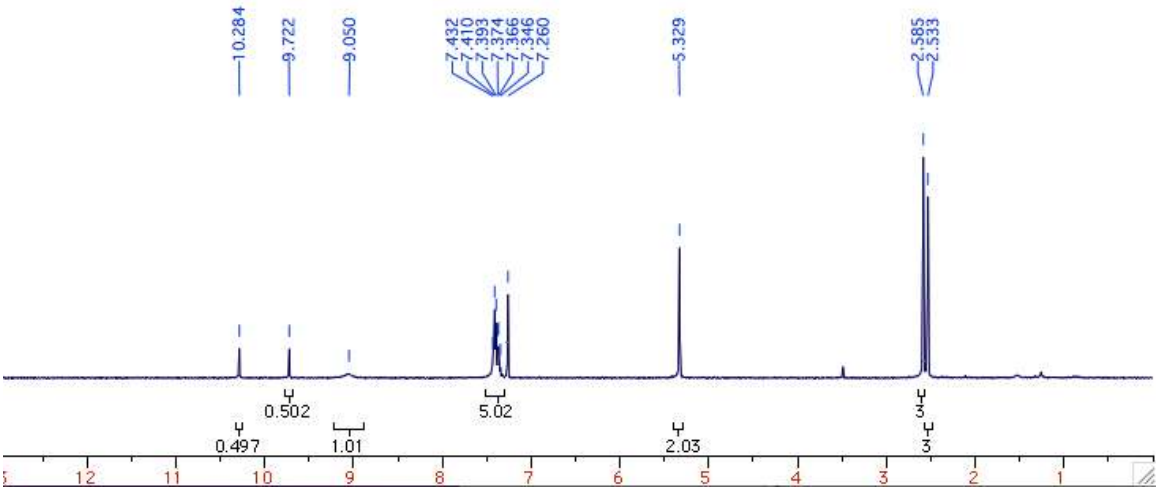
^{13}C NMR; 125 MHz, $CDCl_3$



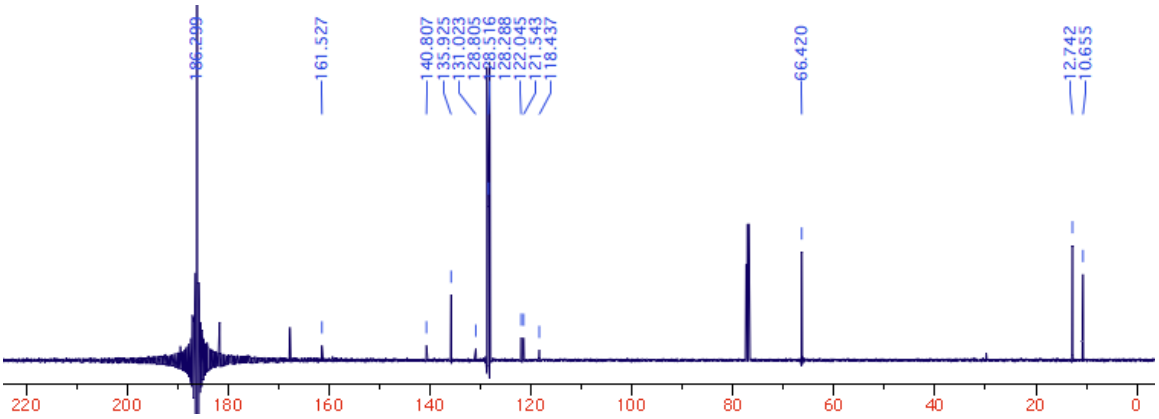
4-Formyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid benzyl ester (6)



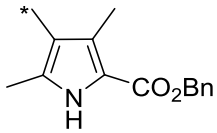
^{1}H NMR; 300 MHz, $CDCl_3$



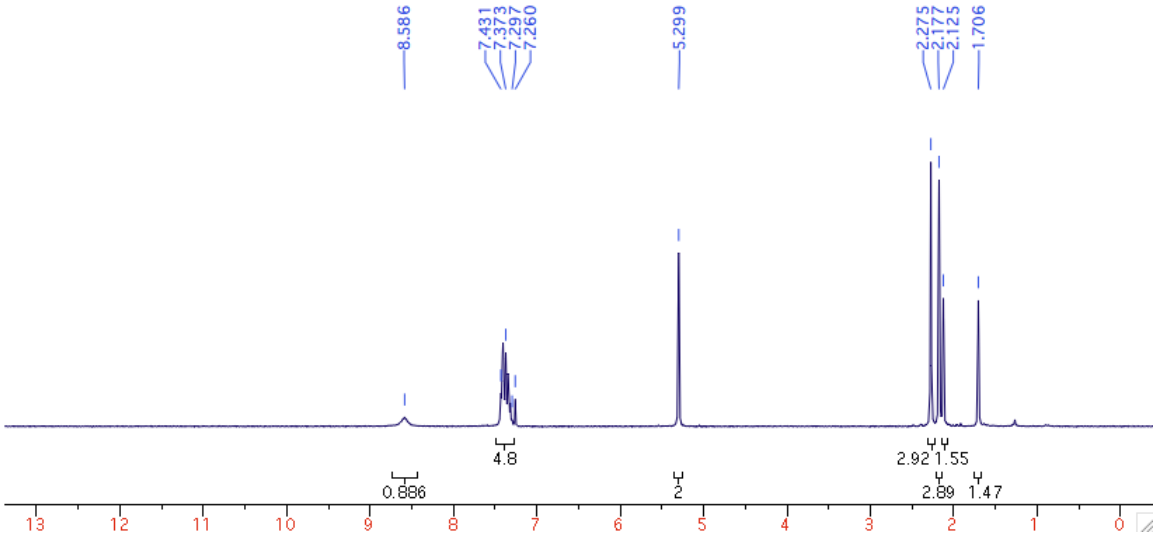
^{13}C NMR; 125 MHz, $CDCl_3$



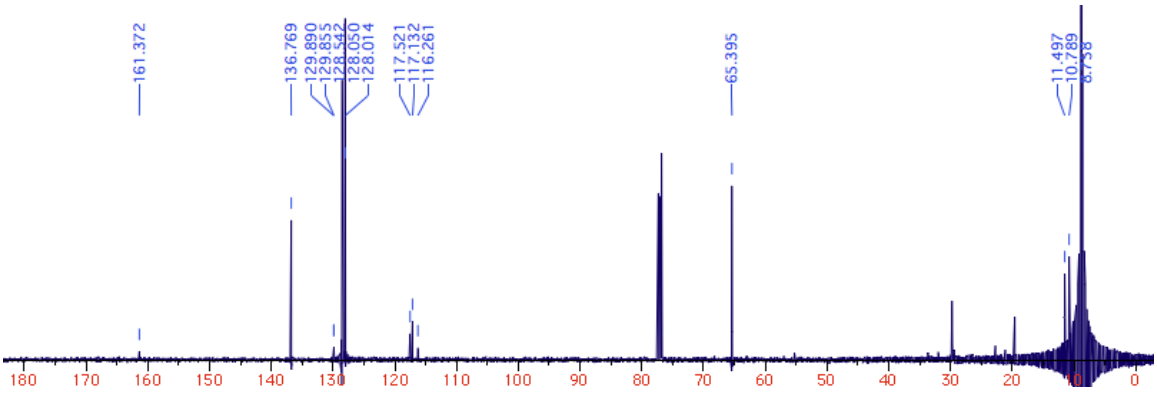
3,4,5-Trimethyl-1H-pyrrole-2-carboxylic acid benzyl ester (7)



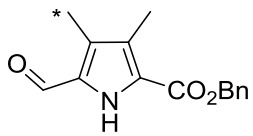
^{1}H NMR; 300 MHz, $CDCl_3$



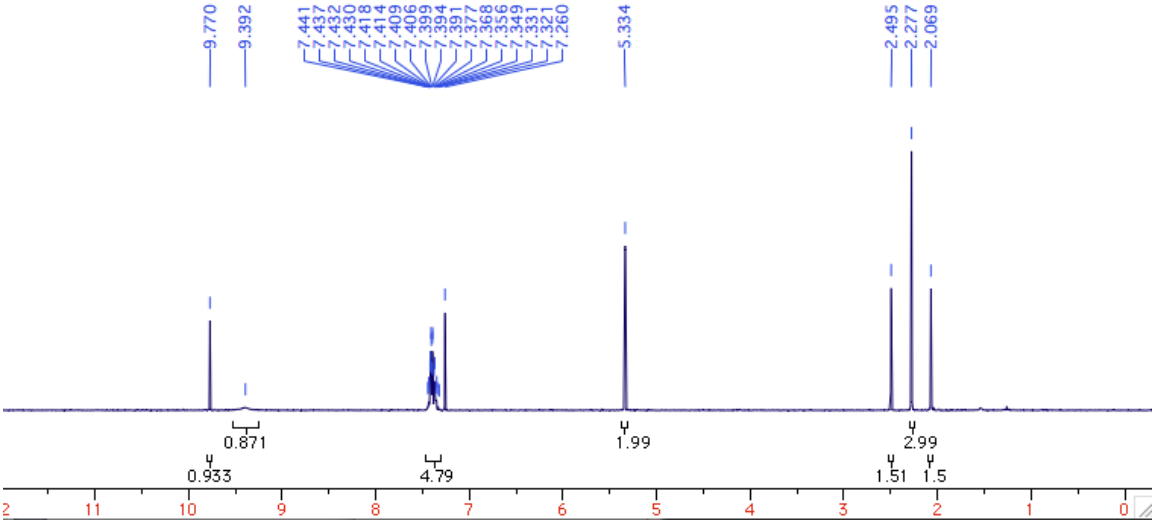
^{13}C NMR; 125 MHz, $CDCl_3$



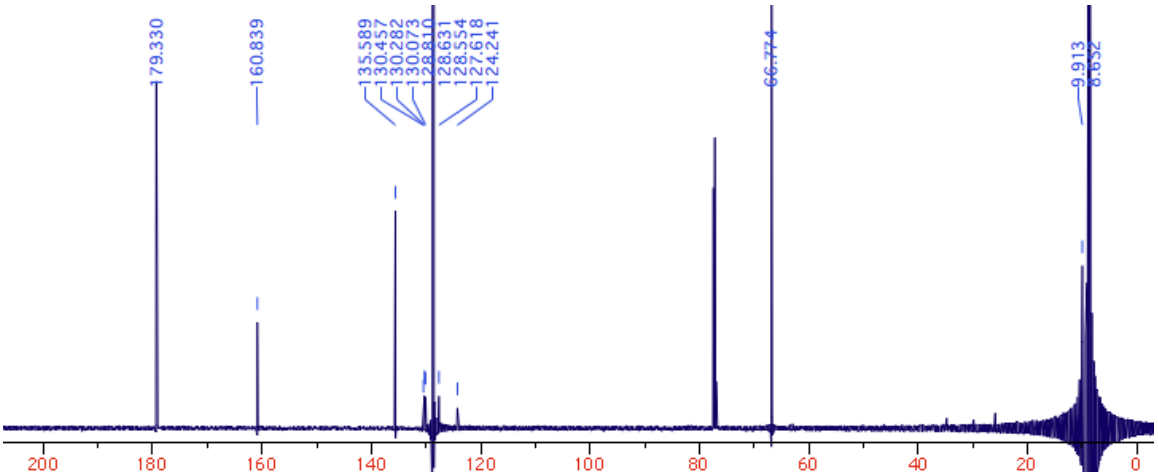
5-Formyl-3,4-dimethyl-1*H*-pyrrole-2-carboxylic acid benzyl ester (8)



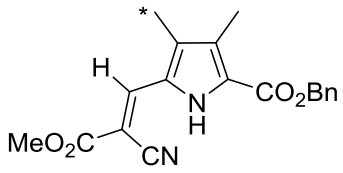
^{1}H NMR; 300 MHz, $CDCl_3$



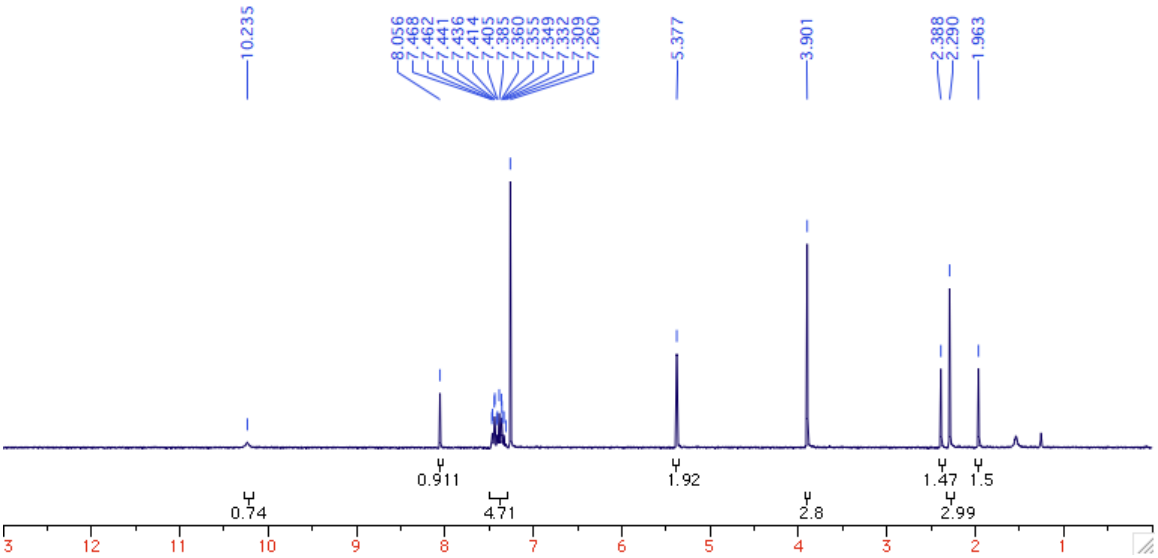
^{13}C NMR; 125 MHz, $CDCl_3$



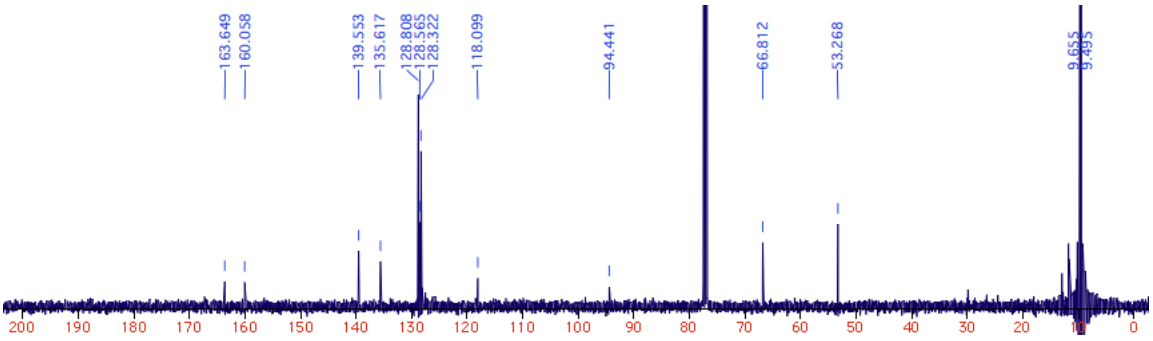
Benzyl-5-[(*E*)-2-cyano-2-(methoxycarbonyl)ethynyl]-3,4-dimethyl-2-pyrrolecarboxaldehyde (9)



^{1}H NMR; 300 MHz, $CDCl_3$

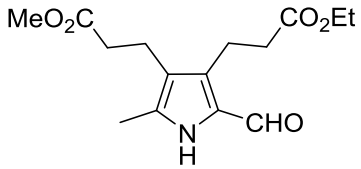


^{13}C NMR; 125 MHz, $CDCl_3$

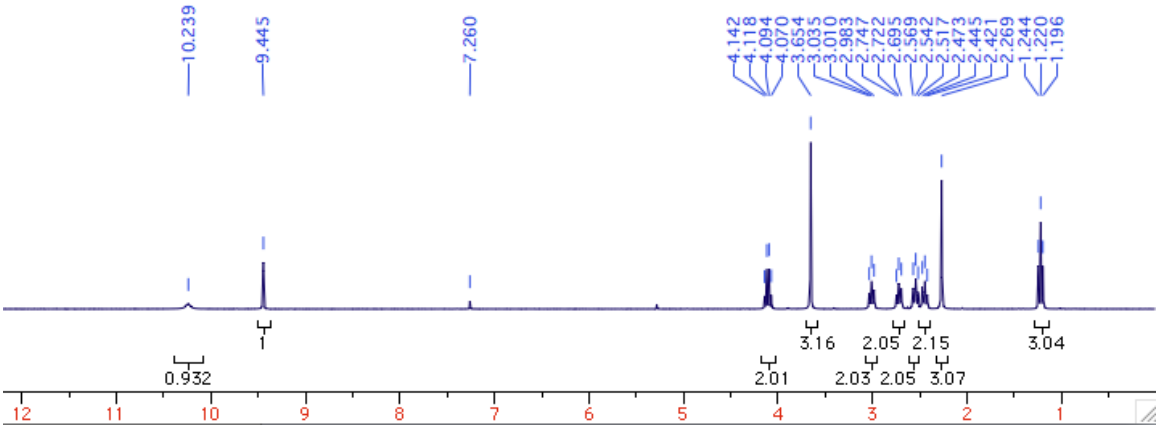


Appendix 3. NMR Spectra for Chapter 3

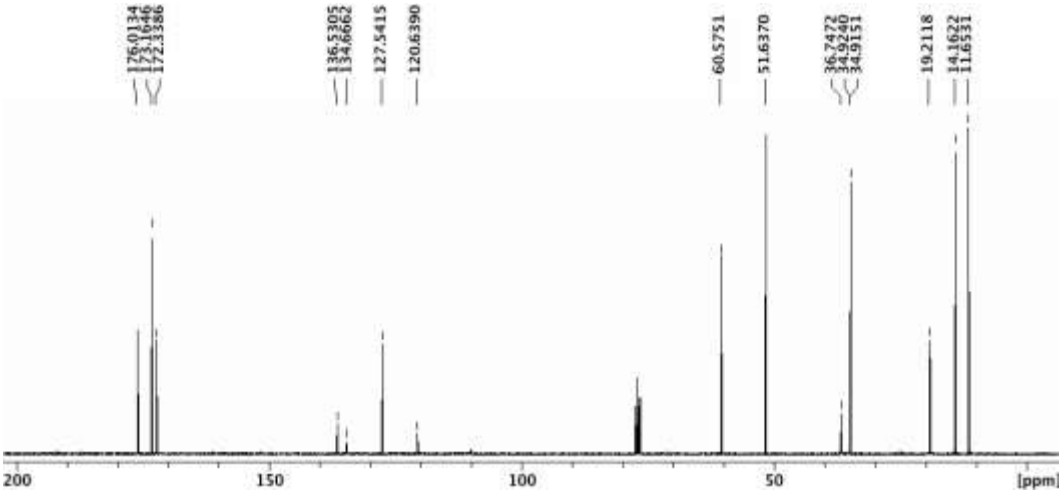
4-[(Methoxycarbonyl)ethyl]-3-[2-(ethoxycarbonyl)ethyl]-5-methyl pyrrole-2-carboxaldehyde (27e)



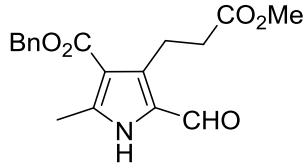
^{1}H NMR; 300 MHz, $CDCl_3$



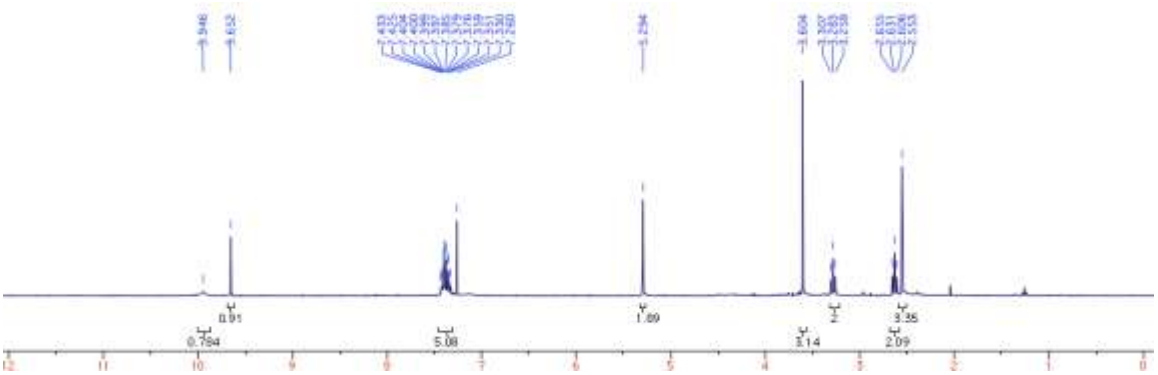
^{13}C NMR; 75 MHz, $CDCl_3$



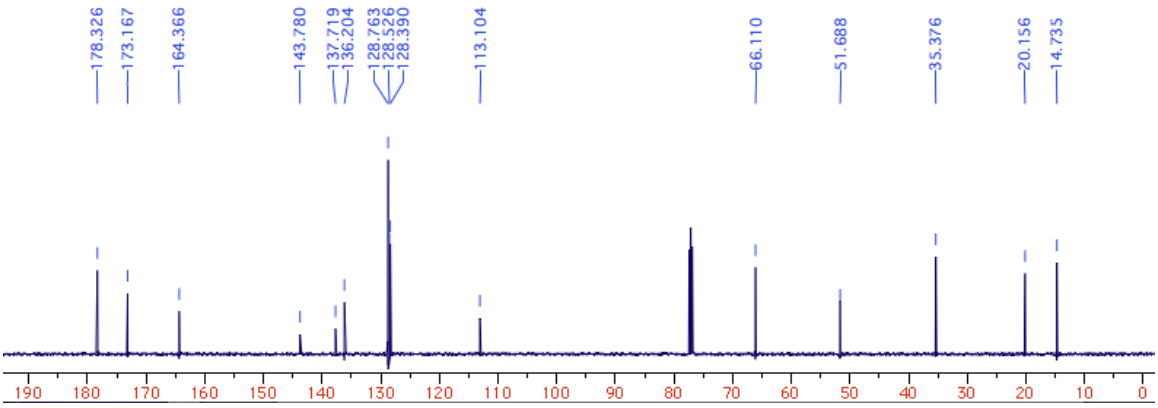
4-(Benzylmethanoate)-3[(methoxycarbonyl)ethyl]-5-methyl pyrrole-2-carboxaldehyde (27f)



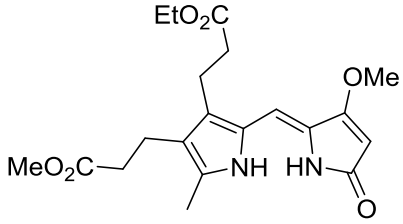
^{1}H NMR; 300 MHz, $CDCl_3$



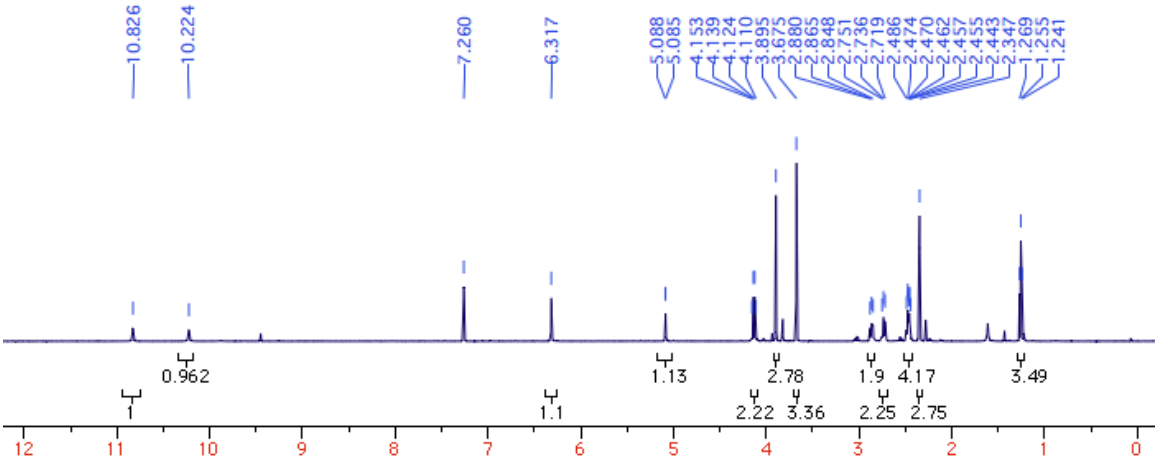
^{13}C NMR; 125 MHz, $CDCl_3$



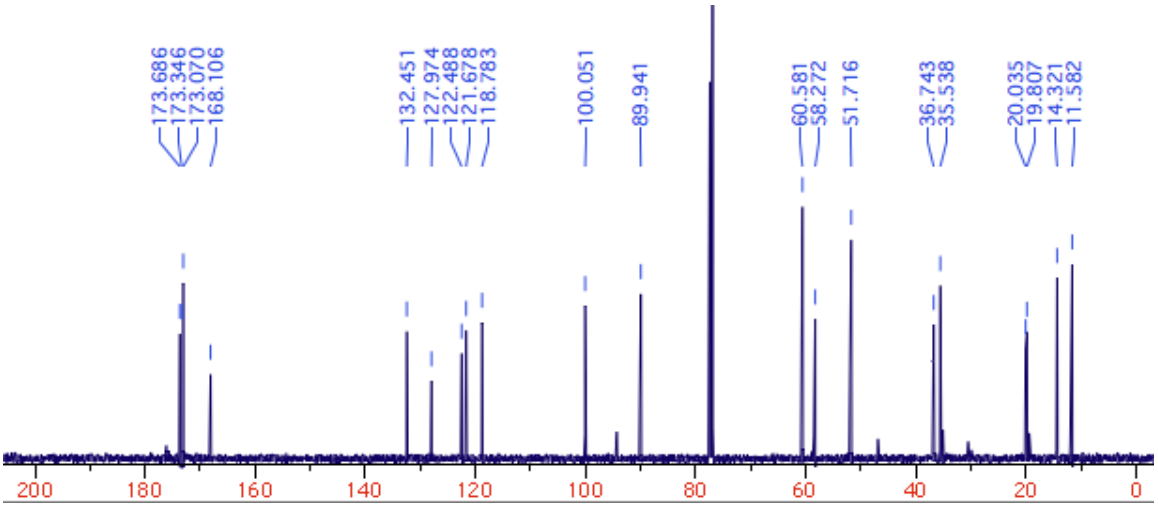
(*Z*)-Ethyl 3-(4-(3-methoxy-3-oxopropyl)-2-((3-methoxy-5-oxo-1H-pyrrol-2(5H)-ylidene)methyl)-5-methyl-1H-pyrrol-3-yl)propanoate (30e)



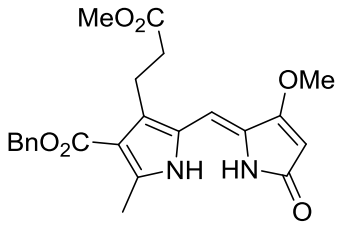
^{1}H NMR; 500 MHz, $CDCl_3$



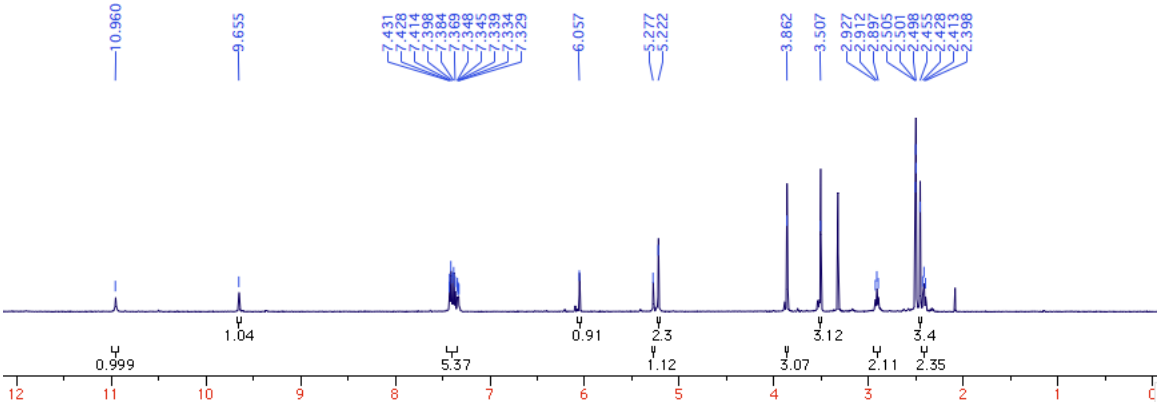
^{13}C NMR; 125 MHz, $CDCl_3$



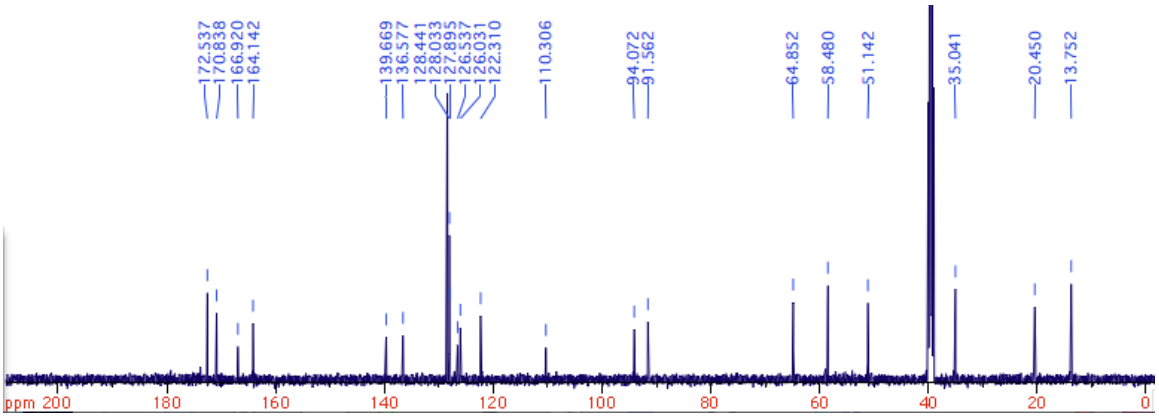
(*Z*)-Benzyl 4-(3-(3-methoxy-3-oxopropyl)-2-(3-methoxy-5-oxo-1H- pyrrole-2(5H)-ylidene)methyl)-5-methyl-1H-pyrrol-3-yl)formate (30f)



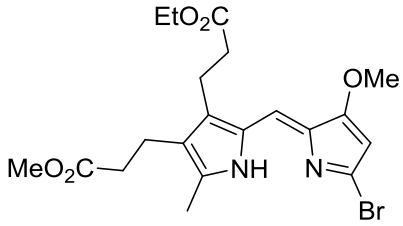
^{1}H NMR; 500 MHz, DMSO



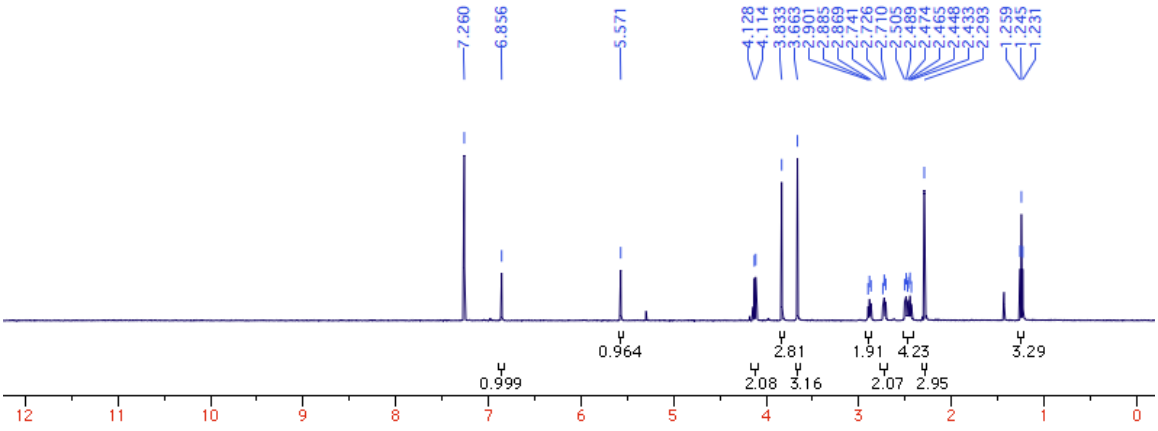
^{13}C NMR; 125 MHz, DMSO



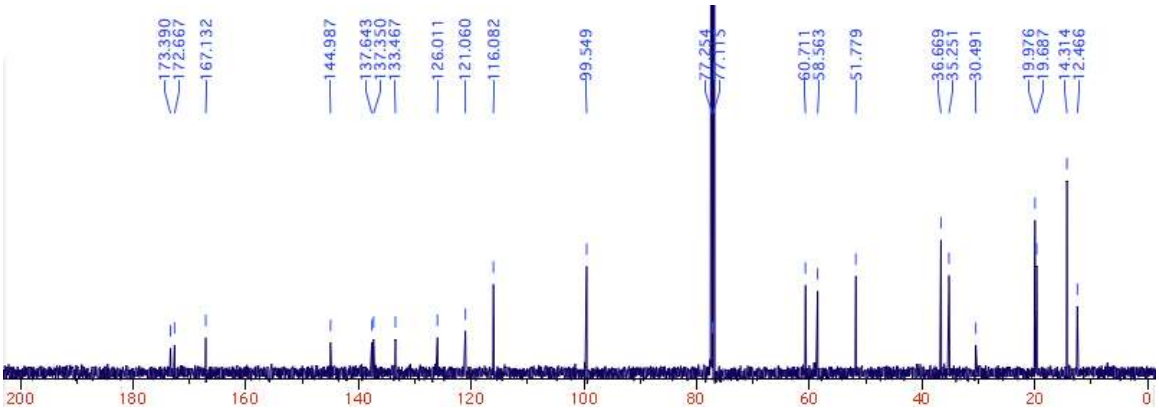
(*Z*)-Ethyl 3-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-4-(3-methoxy-oxopropyl)-5-methyl-1H-pyrrol-3-yl)propanoate (31e)



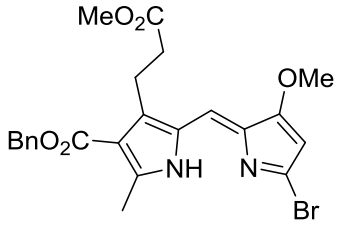
^{1}H NMR; 500 MHz, $CDCl_3$



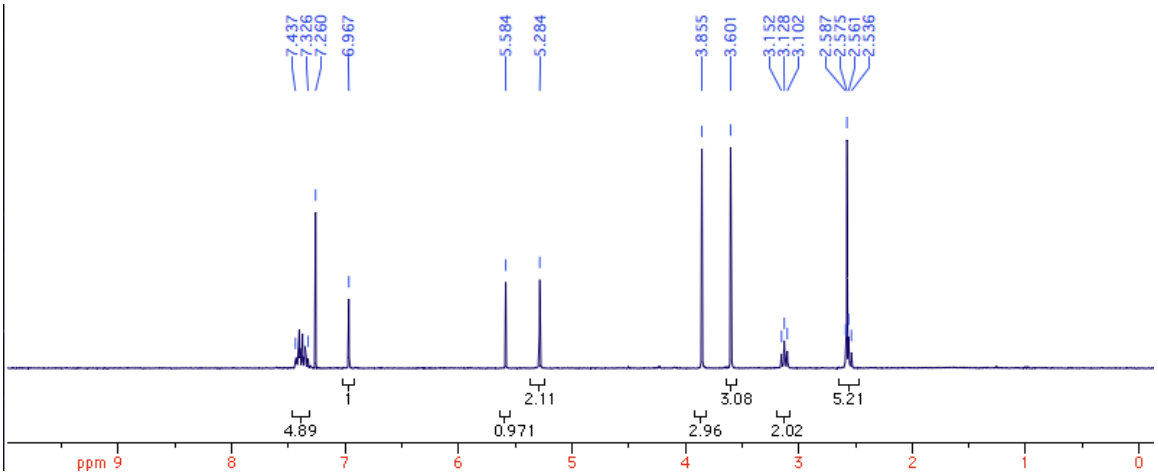
^{13}C NMR; 125 MHz, $CDCl_3$



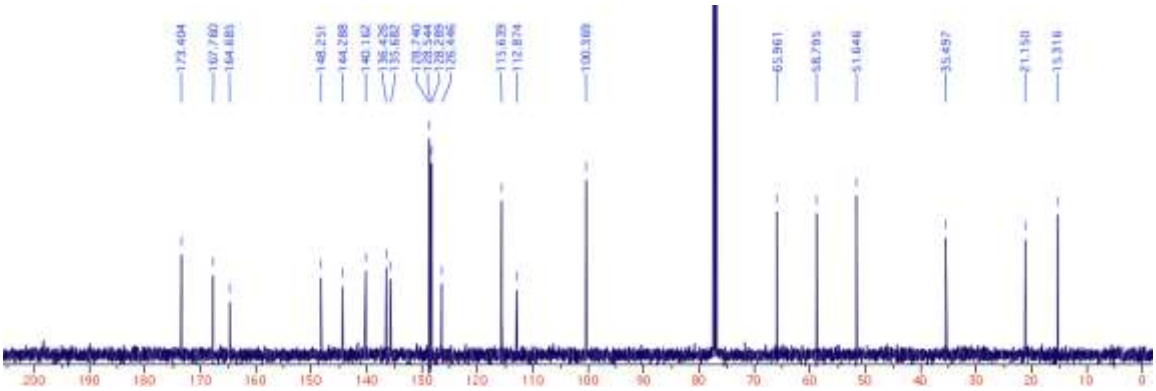
(*Z*)-Benzyl 4-(2-((5-bromo-3-methoxy-2H-pyrrol-2-ylidene)methyl)-3-(3-methoxy-3-oxopropyl)-5-methyl-1H-pyrrol-3-yl)formate (31f)



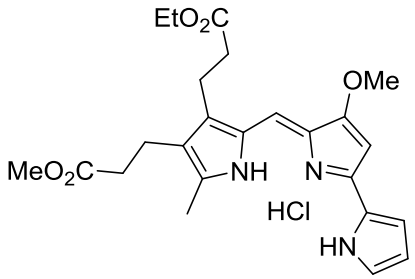
^{1}H NMR; 500 MHz, $CDCl_3$



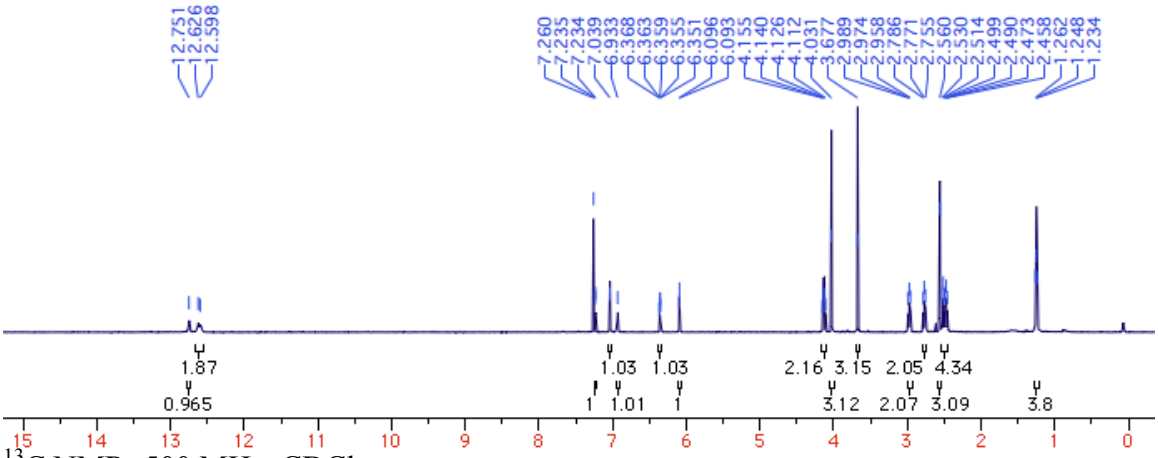
^{13}C NMR; 125 MHz, $CDCl_3$



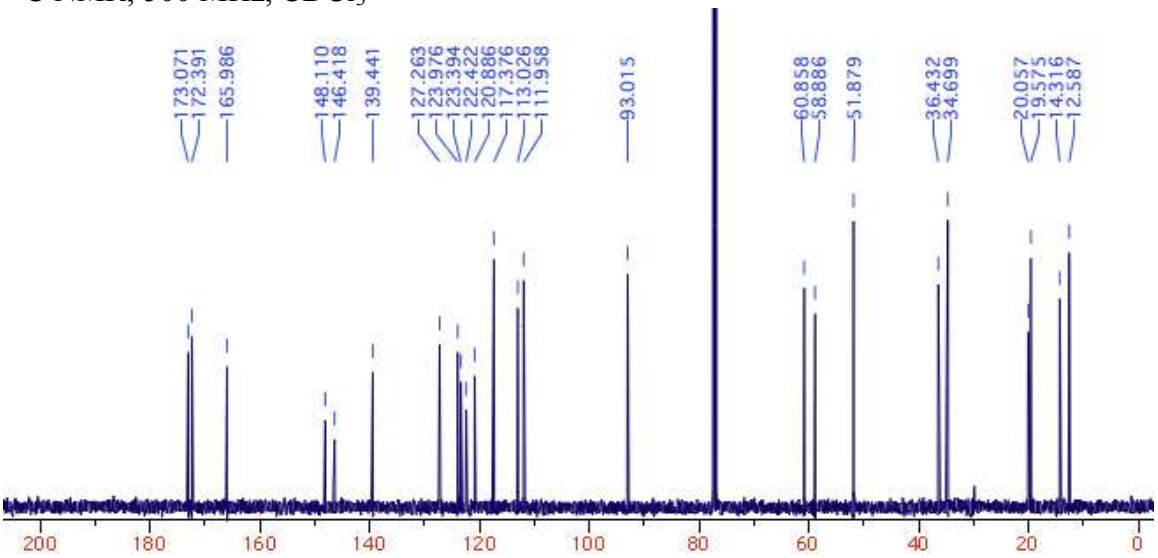
(*Z*)-Ethyl 3-(2-((4-methoxy-1H-1H'-[2,2'-bipyrrol]-5-yl)methylene)-4-(3-methoxy-3-oxopropyl)-5-methyl-2H-pyrrol-3-yl)propanoate hydrochloride (24•HCl)



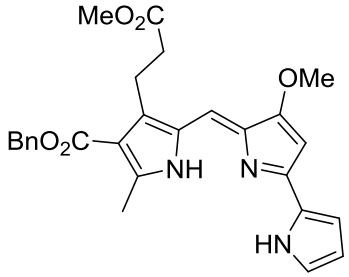
^{1}H NMR; 500 MHz, $CDCl_3$



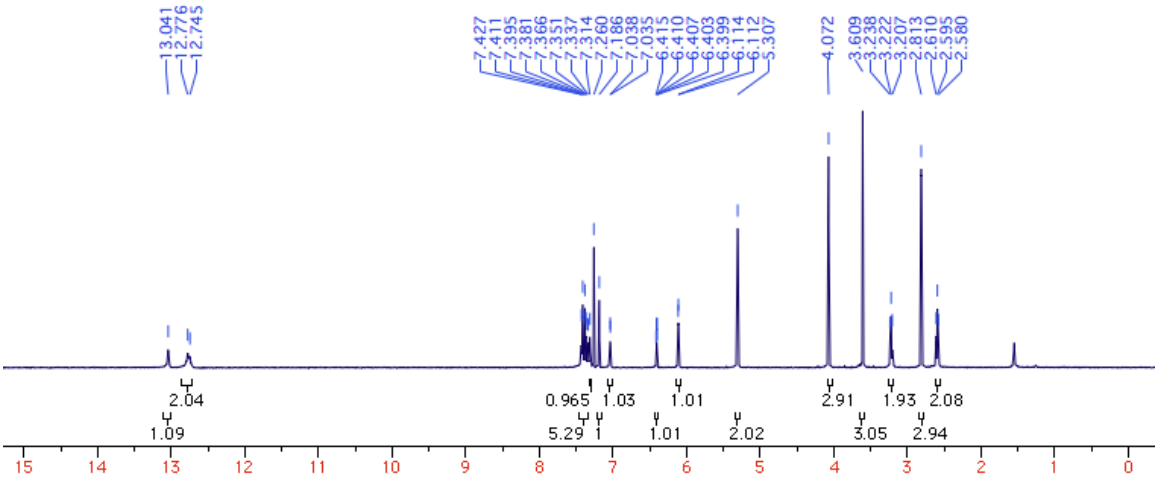
^{13}C NMR; 500 MHz, $CDCl_3$



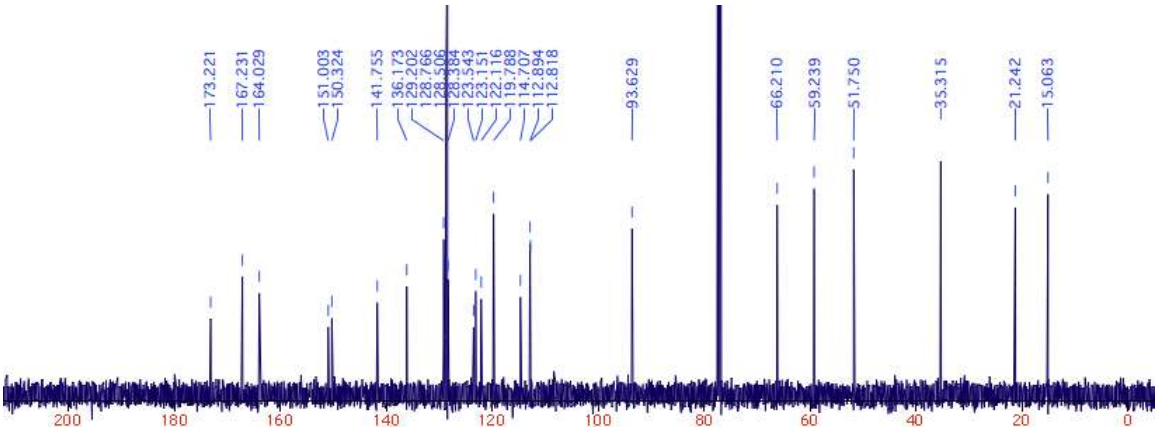
(*Z*)-Benzyl 4-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3-(3-methoxy-3-oxopropyl)-5-methyl-2H-pyrrol-3-yl)formate (25)



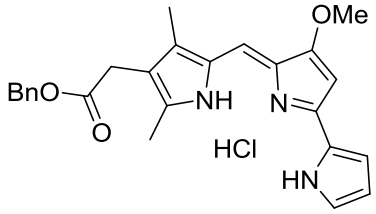
^{1}H NMR; 500 MHz, $CDCl_3$



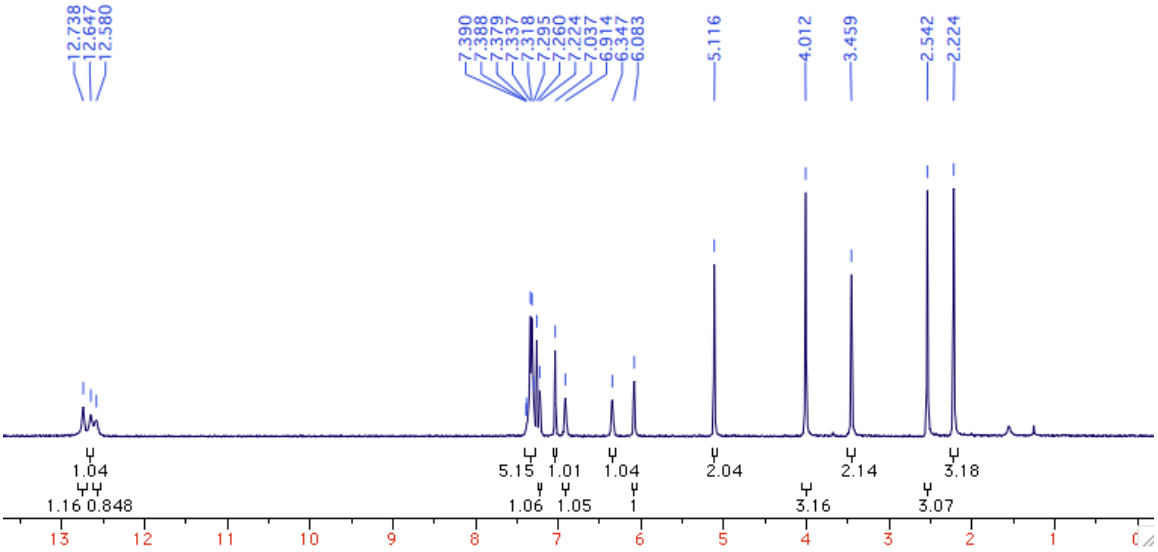
^{13}C NMR; 125 MHz, $CDCl_3$



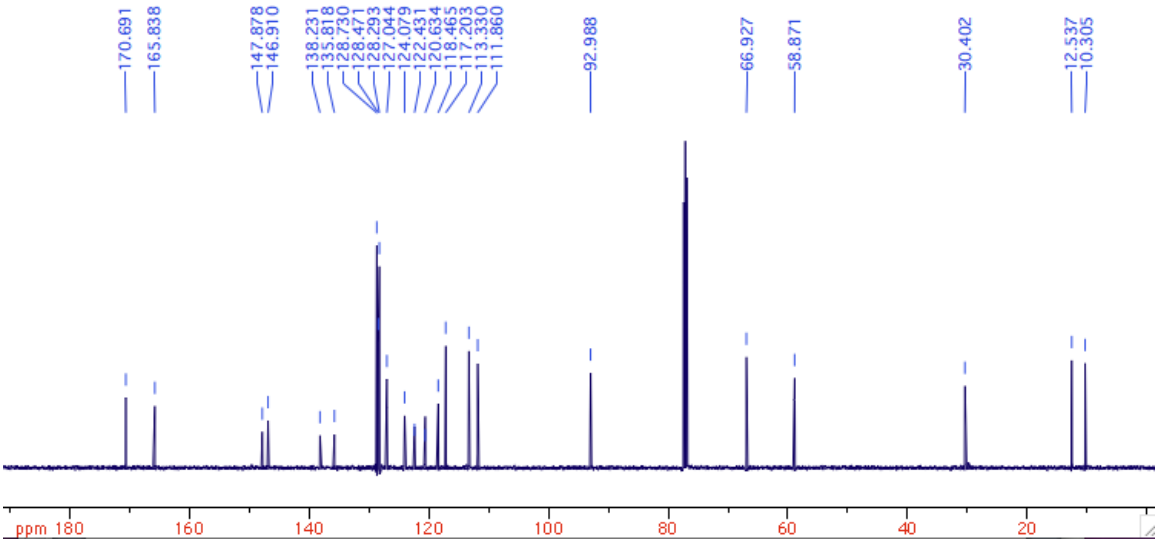
(*Z*)-Benzyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate (20a•HCl)



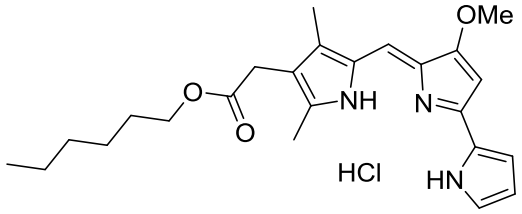
^{1}H NMR; 300 MHz, $CDCl_3$



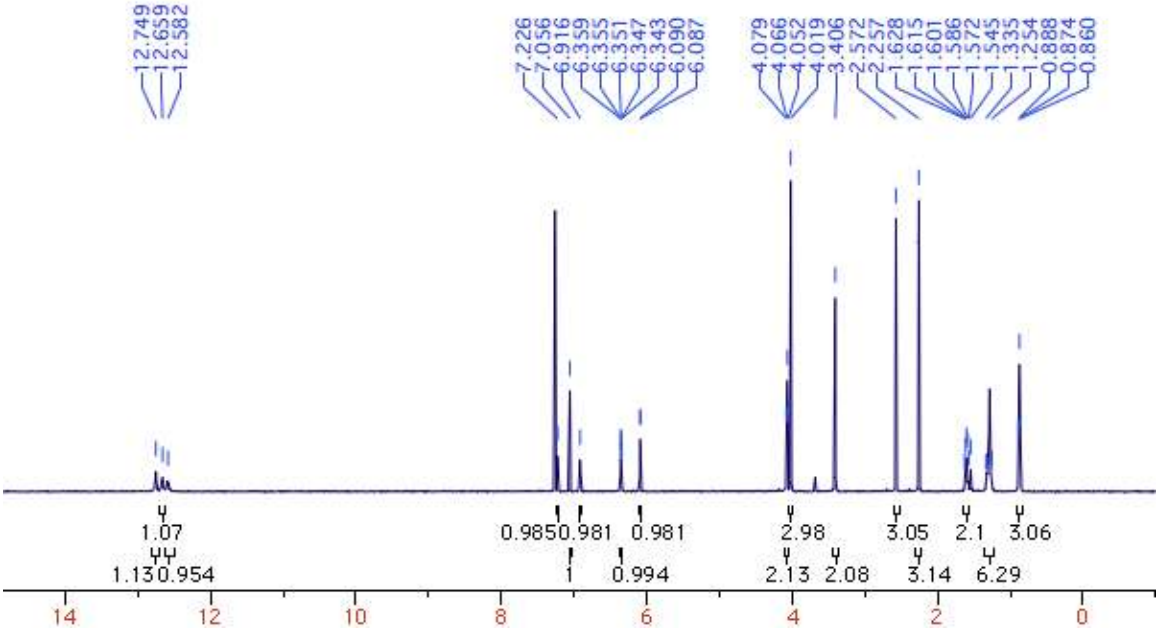
^{13}C NMR; 125 MHz, $CDCl_3$



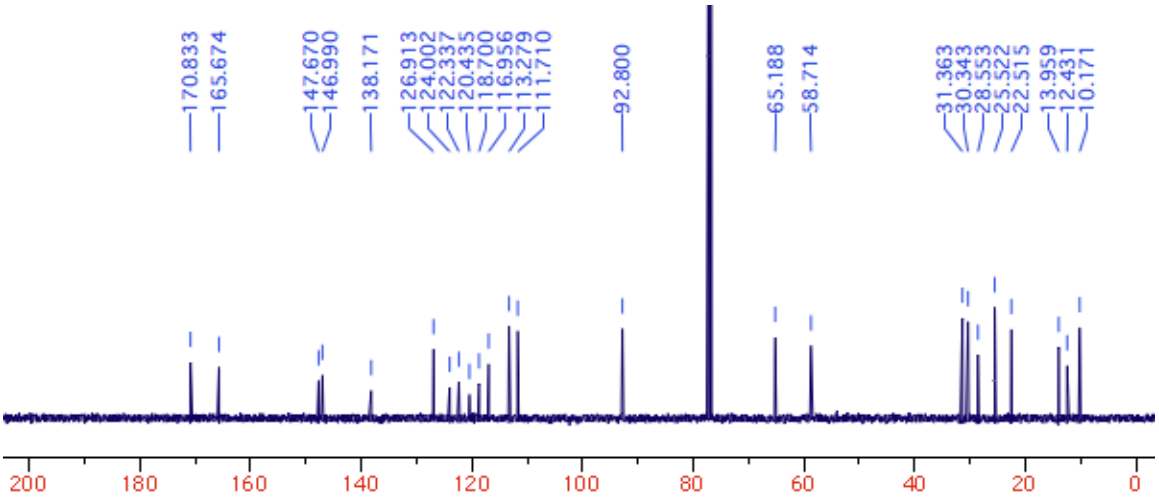
(*Z*)-Hexyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate (20b•HCl)



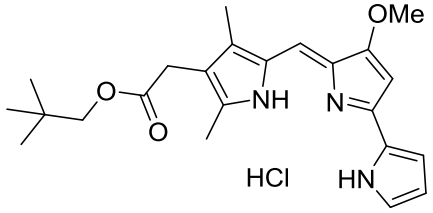
^{1}H NMR; 500 MHz, $CDCl_3$



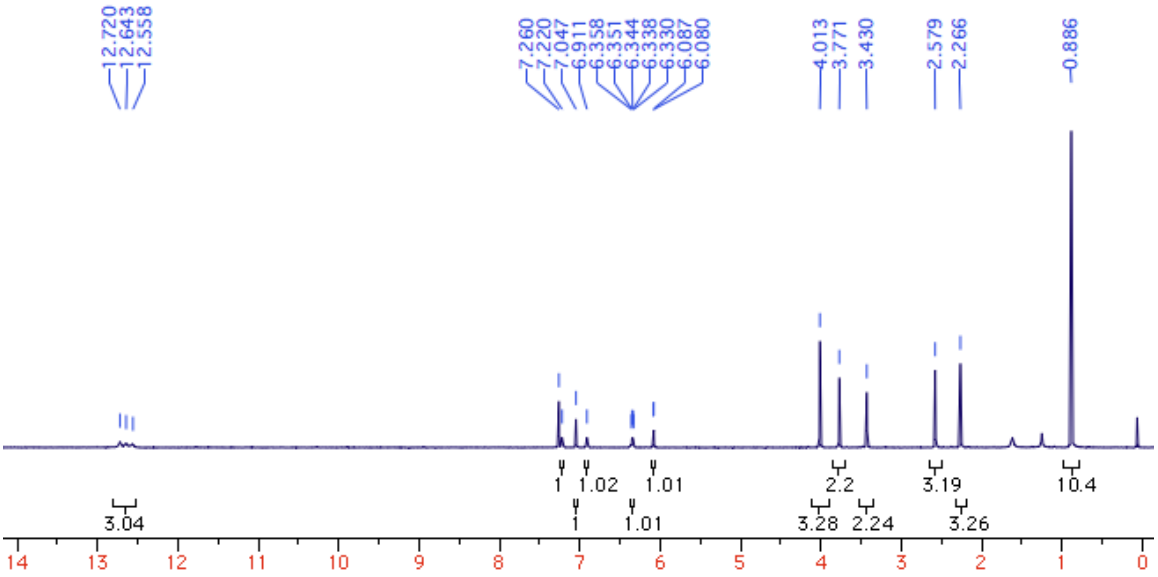
^{13}C NMR; 125 MHz, $CDCl_3$



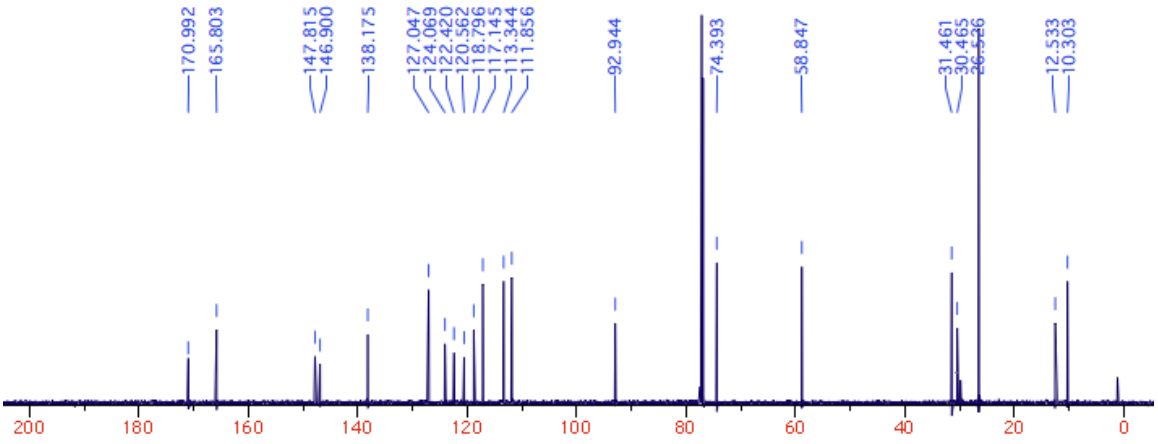
(*Z*)-Neopentyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetate hydrochloride (20d•HCl)



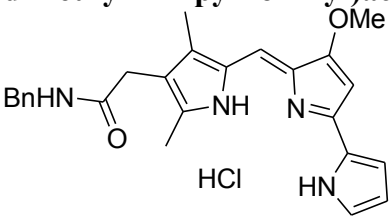
^{1}H NMR; 300 MHz, $CDCl_3$



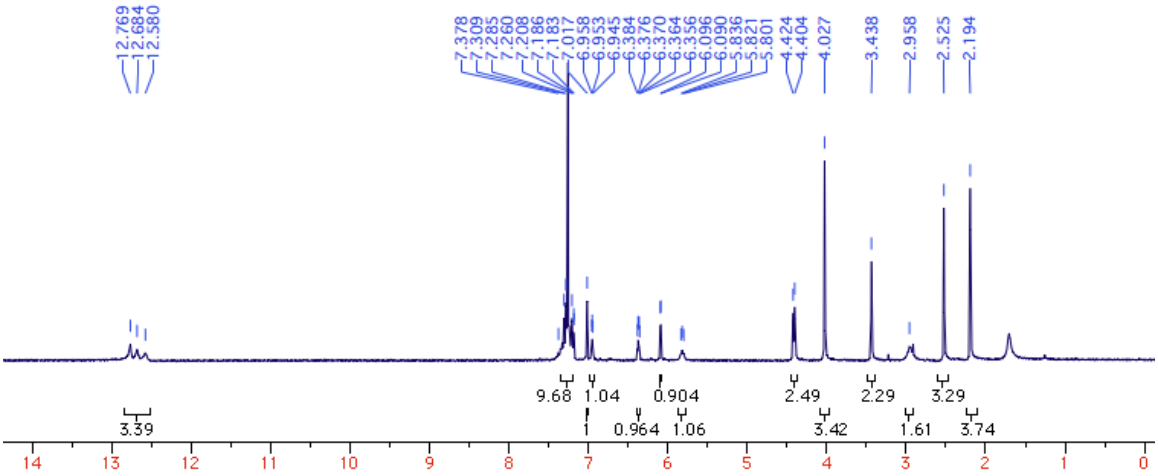
^{13}C NMR; 125 MHz, $CDCl_3$



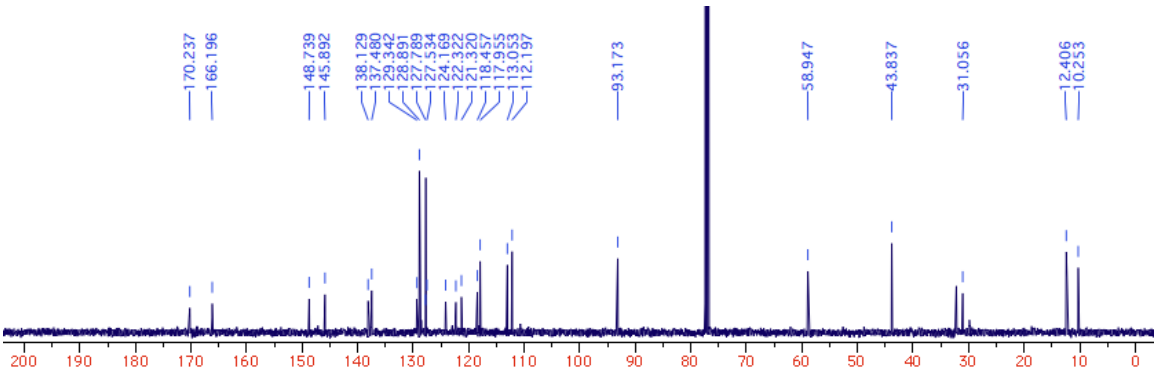
(*Z*)-Benzyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20e•HCl)



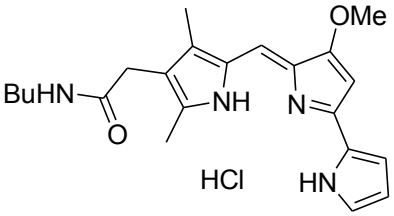
^{1}H NMR; 300 MHz, $CDCl_3$



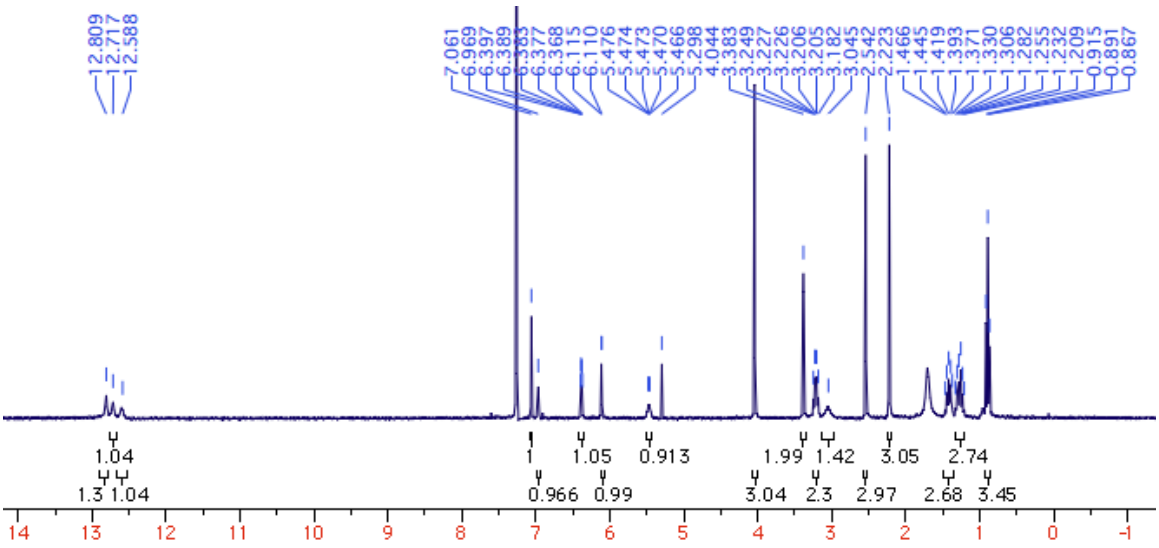
^{13}C NMR; 125 MHz, $CDCl_3$



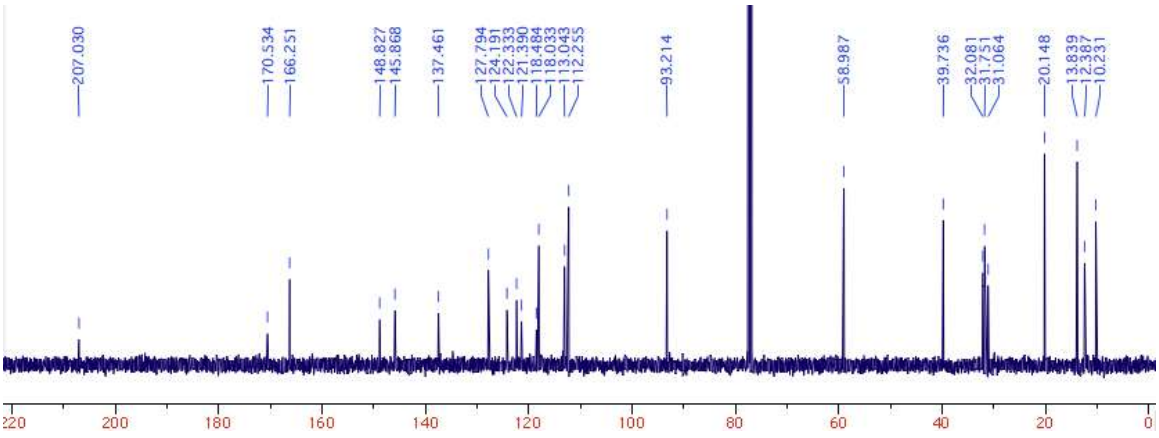
(*Z*)-Butyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20f•HCl)



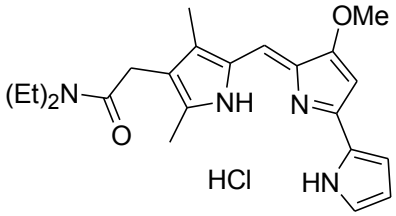
^{1}H NMR; 300 MHz, $CDCl_3$



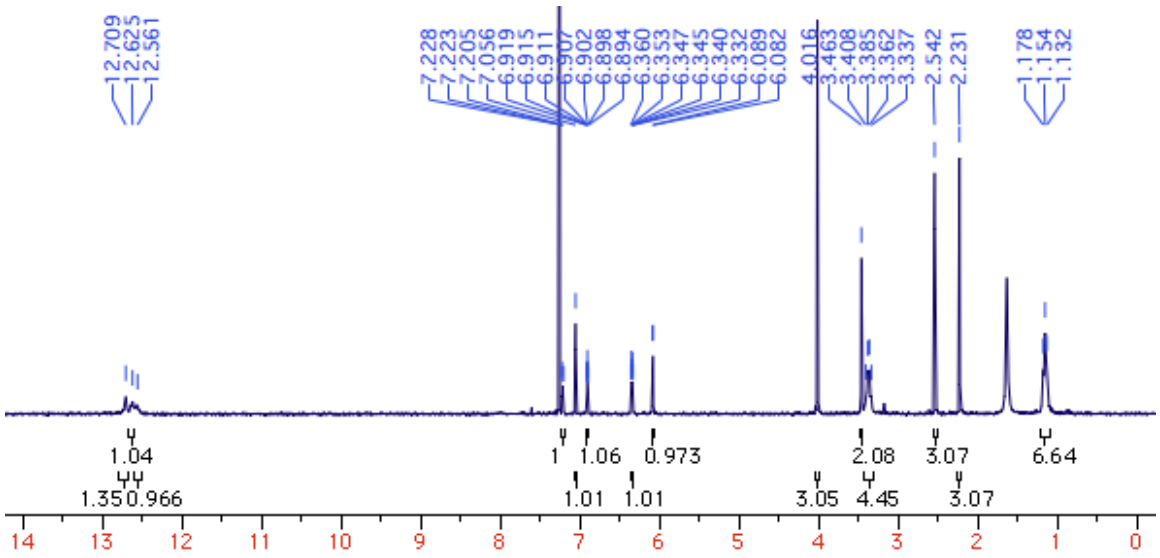
^{13}C NMR; 125 MHz, $CDCl_3$



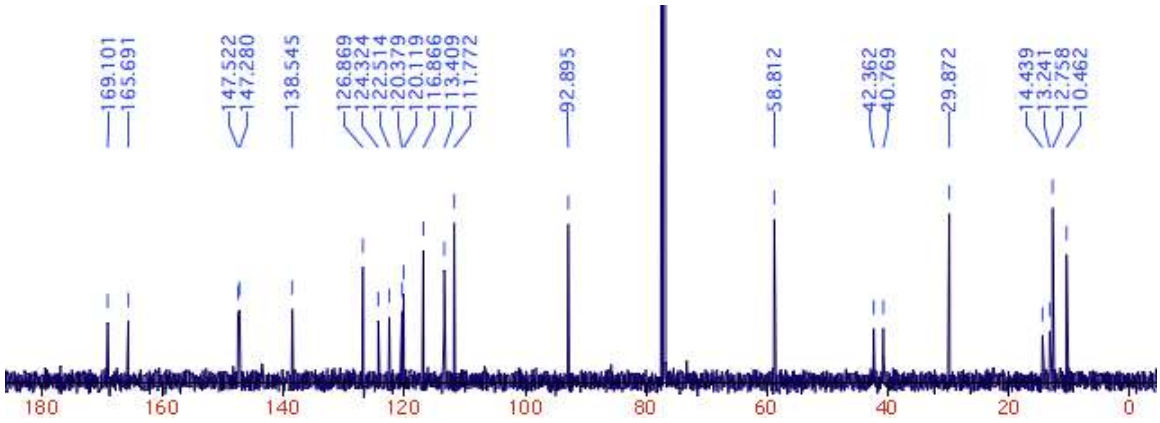
(*Z*)-N,N-Diethyl 2-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)acetamide hydrochloride (20g•HCl)



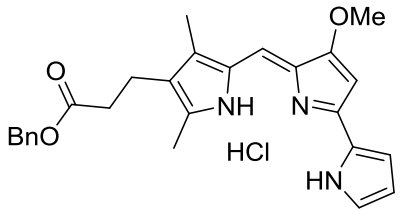
^{1}H NMR; 300 MHz, $CDCl_3$



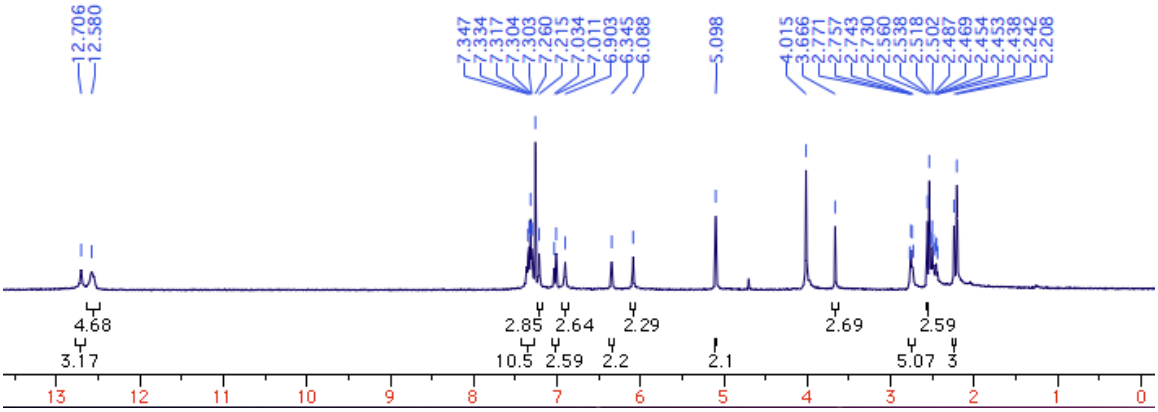
^{13}C NMR; 125 MHz, $CDCl_3$



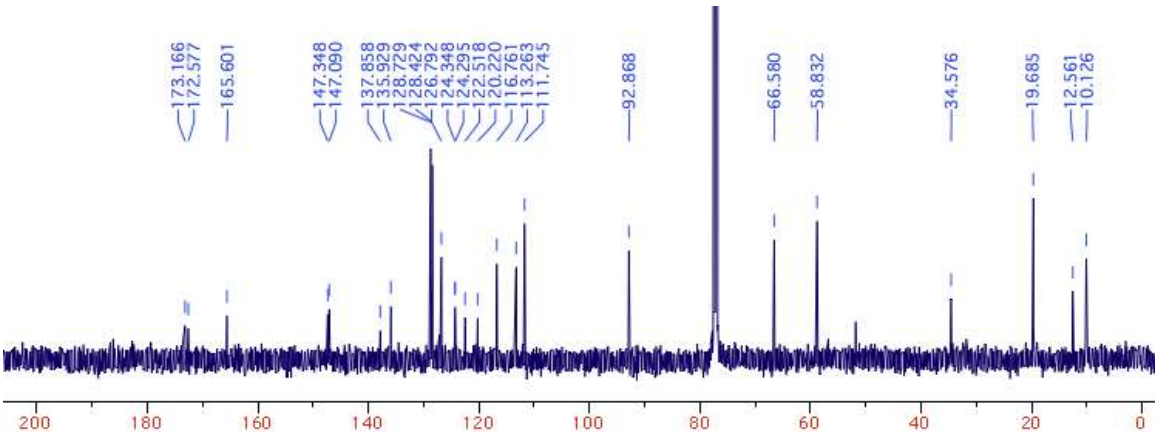
(*Z*)-Benzyl 3-(2-((4-methoxy-1H,1H'-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)propanoate (21•HCl)



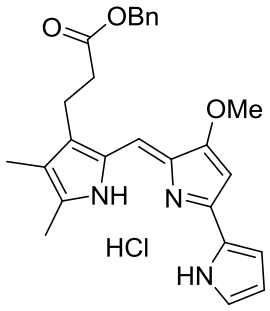
^{1}H NMR; 500 MHz, $CDCl_3$



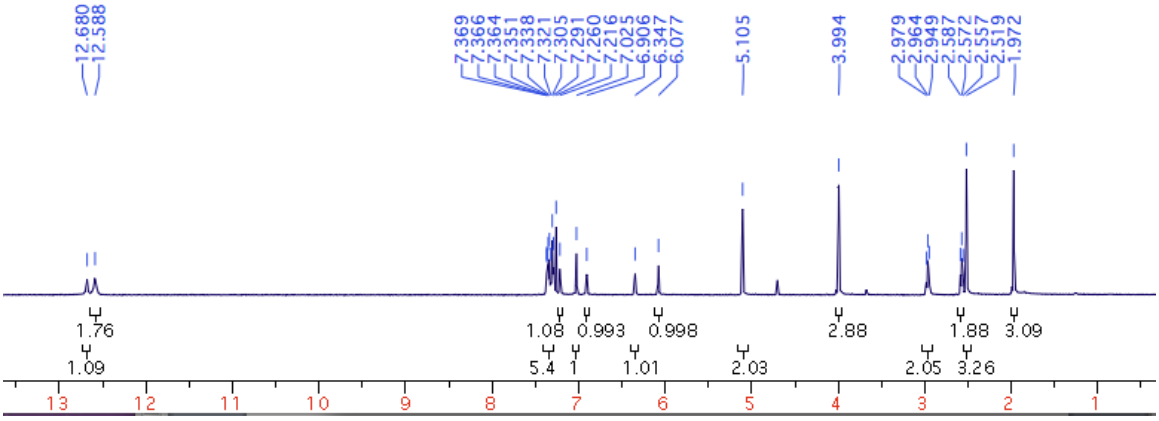
^{13}C NMR; 125 MHz, $CDCl_3$



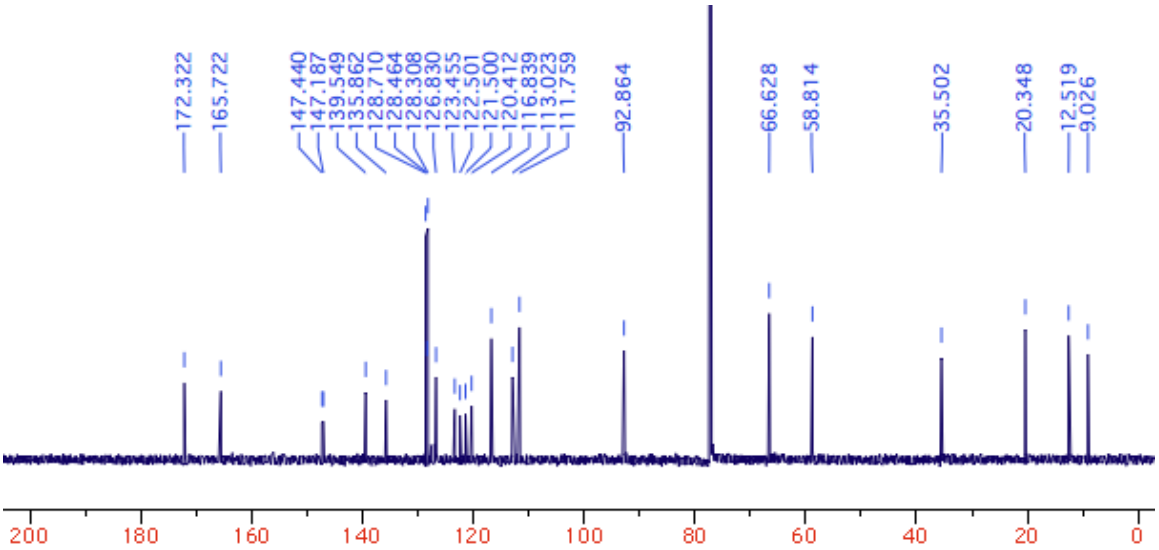
(*Z*)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4,5-dimethyl-2H-pyrrol-3-yl)propanoate (22•HCl)



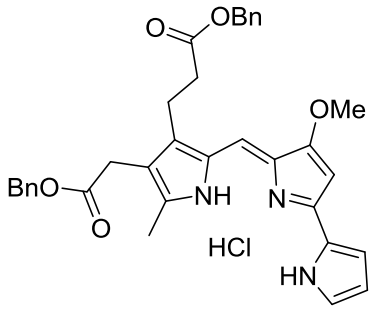
^{1}H NMR; 500 MHz, $CDCl_3$



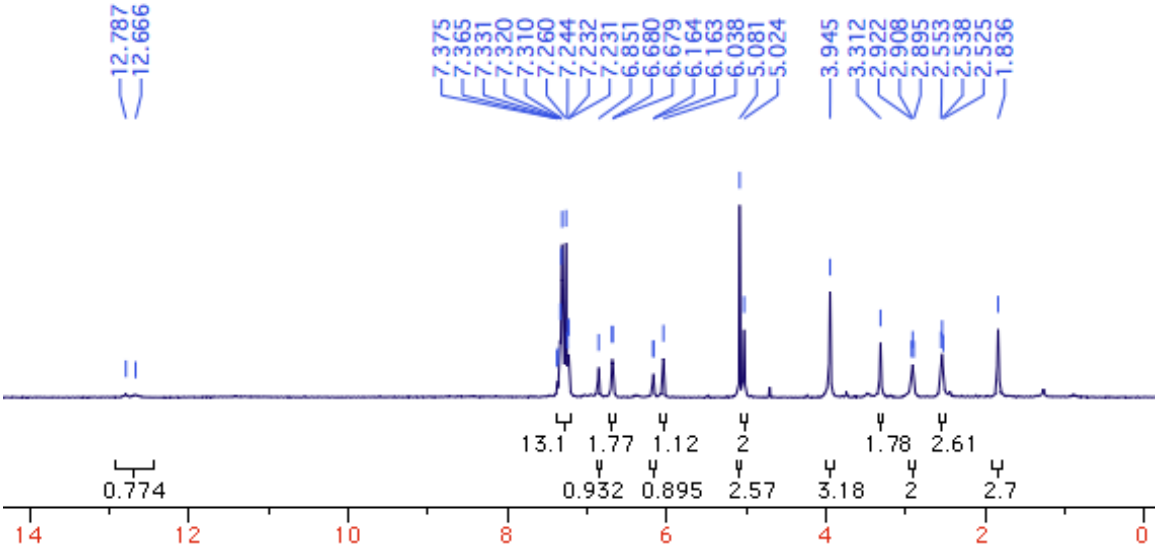
^{13}C NMR; 125 MHz, $CDCl_3$



(*Z*)-Methyl 3-(2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-4-(2-methoxy-2-oxoethyl)-5-methyl-2H-pyrrol-3-yl)propanoate (23•HCl)



^{1}H NMR; 500 MHz, $CDCl_3$



^{13}C NMR; 125 MHz, $CDCl_3$