DIMETHYL BILADIENE
DERIVATIVES AND THEIR
APPLICATION AS PHOTODYNAMIC
THERAPY PHOTOSENSITIZERS

by

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ABSTRACT

Photodynamic Therapy is an interesting and less invasive option for cancer treatment, and therefore it is an ongoing area of research. Photosensitizers capable of generating singlet oxygen are a required aspect of photodynamic therapy, however all currently known compounds possess certain undesirable traits which hinder their practical application and necessitates further efforts to develop improved photosensitizers with the optimal qualities for photodynamic therapy. We present the synthesis of a few different compounds inspired by the previously synthesized dimethyl biladiene framework, which efficiently produces singlet oxygen but fails to absorb sufficiently at long wavelengths of light. We synthesized and studied derivatives of this ligand designed to absorb deeper into the red and near IR regions of the spectrum. From the photophysical properties of these compounds we discuss their application as photosensitizers for photodynamic therapy.
Chapter 1

INTRODUCTION

1.1 Photodynamic Therapy

Each year almost 13 million cancer cases are newly diagnosed.\textsuperscript{1} With so many people affected, research has focused on finding treatments that are safer and more effective than the traditional surgical or chemotherapy options. Photodynamic Therapy (PDT) is a photochemistry-based treatment which has been approved to treat various cancers, such as skin, neck, head, ovary, bladder, and brain as well as many others.\textsuperscript{1,2,3,4} PDT consists of three components: a light activated compound, called a photosensitizer, light, and the utilization of oxygen present in tissue cells. The photosensitizer is introduced into the body and a specific wavelength of light that is efficiently absorbed by the photosensitizer illuminates the infected area. The photosensitizer absorbs the light, enters the excited singlet state and goes through intersystem crossing to the excited triplet state which reacts with ground state triplet oxygen (Figure 1.1) producing singlet oxygen (\textsuperscript{1}O\textsubscript{2}). This excited \textsuperscript{1}O\textsubscript{2} is toxic to nearby cells and therefore kills the tumorous cells.\textsuperscript{2}
Figure 1.1: Singlet Oxygen Generation

PDT has many advantages over other forms of cancer treatment. It is much less invasive than most surgical treatment options, since the photosensitizer is introduced either topically or intravenously, and therefore can be administered as an outpatient procedure. PDT is also more targeted because the ideal photosensitizer has low dark toxicity enabling treatment to be restricted to desired areas by selectively irradiating only cancerous tissues. PDT has also shown to be a more targeted treatment since the photosensitizer tends to accumulate at the tumor site, and singlet oxygen has approximately a 3 µs lifetime in biological systems, which limits cellular toxicity to within a 100 nm radius from the source. PDT also has fewer side effects compared to radiation and chemotherapy, as well as the added benefit that cancerous cells cannot become resistant. Another benefit is that PDT seems to stimulate the immune system when most other treatments suppress it.
1.1.1 **Optimal Qualities for Photodynamic Therapy Photosensitizers**

In order for photosensitizers to be effectively used in PDT they must possess certain optimal qualities. The compound should be easy to synthesize in large quantities as well as easy to purify, and needs to have a high purity quality in order to be reproduced and to be used as a drug. It also must be chemically stable for transport and storage. The best PDT photosensitizers also have high molar extinction coefficients and high quantum yields for singlet oxygen generation.¹

One of the most important qualities for PDT photosensitizers is the wavelength of light that they are excitable at. Blue light penetrates through tissue least effectively, whereas red and infrared light penetrates more deeply (Figure 1.2).⁴ The section of the electromagnetic spectrum between 600 and 1200 nm is usually referred to as the optimum window.¹ The wavelength of light must be longer than 600 nm in order to penetrate far enough into tissue; but only light with wavelengths up to about 800 nm can generate singlet oxygen. Light at wavelengths longer than 800 nm does not have enough energy to generate singlet oxygen⁴, making it useless for PDT. Photosensitizers with high extinction coefficients between 600 and 800 nm are the most effective for PDT.
1.1.2 Current Compounds used in Photodynamic Therapy

The first FDA approved photosensitizer for PDT, Photofrin, is the most widely used compound. Photofrin is used to treat lung, esophageal, bile duct, bladder, brain, and ovarian cancers.\(^1\) Photofrin, generally called a first generation photosensitizer, also has many drawbacks to its use. Patients show long-lasting skin photosensitivity and Photofrin is difficult to purify, which makes reproducibility problematic.\(^4\) Photofrin also has a low extinction coefficient in the red region of the spectrum. In order to achieve a suitable response the patient must be given a large dose of the drug.\(^1\)

With these drawbacks from first generation photosensitizers; research has focused on developing other compounds for PDT. Porphyrin or porphyrin-based macrocycles have been developed and are one class of second generation...
photosensitizers. Some of these second generation photosensitizers include Foscan, Talaporfin, and Verteporfin. These compounds were developed in order to improve the disadvantages in first generation photosensitizers, but they still cause unintentional photosensitivity for patients and have small extinction coefficients between 600 and 800 nm. Therefore, synthesizing enhanced photosensitizers is a prominent and ongoing area of research.

1.2 Dimethyl Biladiene Based Photosensitizers

1.2.1 The Dimethyl Biladiene Ligand

Our research lab has previously synthesized a series porphyrinoid compounds, which can act as photosensitizers of singlet oxygen. The lab synthesized the dimethyl biladiene (DMBil) ligand system (Figure 1.3), and studied its singlet oxygen sensitization. The free base DMBil only showed a singlet oxygen quantum yield of $\Phi_\Delta = 1.5 \times 10^{-2}$ in methanol upon irradiation at 500 nm. Other porphyrin based compounds have been shown to have singlet oxygen quantum yields near $\Phi_\Delta = 0.8$ in polar protic solvents. This shows that although the quantum yield of DMBil is only modest at best, this ligand system is able to generate singlet oxygen.
1.2.2 Metal Complexes of DMBil

With the free base form showing only modest sensitization for singlet oxygen, a variety of metallated versions were synthesized. We hoped that the addition of the metal center would facilitate intersystem crossing in the excited state and therefore more singlet oxygen would be produced. The first two metallated DMBil complexes studied were Zn-DMBil and Cu-DMBil. The addition of the metal center also changed the absorption profile of the compound; both metallated complexes now absorbed at longer wavelengths, which is important for PDT. The Zn-DMBil showed a slightly better singlet oxygen quantum yield $\Phi_\Delta = 2.6 \times 10^{-2}$ in methanol with irradiation at 550 nm. The Cu-DMBil showed negligible production of singlet oxygen. Since these compounds failed to give the desired singlet oxygen quantum yields, we decided to introduce a heavier atom to enhance spin-orbit coupling and in order to facilitate intersystem crossing and generate more singlet oxygen.

Figure 1.3: 10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (DMBil)
To test this, we synthesized DMBil with palladium (Pd-DMBil) and platinum (Pt-DMBil) centers, and tested them for singlet oxygen sensitization. Pd-DMBil and Pt-DMBil showed impressive singlet oxygen quantum yields of $8.0 \times 10^{-1}$ and $7.8 \times 10^{-1}$ respectively. This shows that a heavier atom does help facilitate intersystem crossing and these quantum yields are comparable to photosensitizers currently being used in PDT. While the Pd-DMBil and Pt-DMBil show impressive singlet oxygen quantum yields, they both only show appreciable absorption between 350 and 550 nm$^{13}$, which is outside the optimal therapeutic window for PDT.

1.3 Improvements on the Dimethyl Biladiene Ligand

After successfully synthesizing different metallated versions of the DMBil and discovering that the Pd-DMBil and Pt-DMBil versions have impressive quantum yields for singlet oxygen with irradiated light outside the optimal therapeutic window$^{13}$, we were interested in trying to modify the DMBil ligand. We sought to tune the absorption of the ligand by red-shifting it towards the therapeutic window between 600 and 800 nm. We were also interested in making a version of the DMBil ligand that would produce as much singlet oxygen as the palladium and platinum versions using less expensive metals which would be more suited for commercialization.

1.3.1 Brominated Dimethyl Biladiene

Previous research has shown that adding bromines to tetapyrrole systems can cause a red shift in the absorption spectra, as well as create a heavy atom effect that promotes intersystem crossing.$^{14,15,16}$ We were interested in replacing some of the hydrogen atoms on the pyrrole units in the DMBil ligand with bromine atoms in order
to take advantage of these benefits. We report in Chapter 2 the synthesis and characterizati
characterization of 1,2,3,7,8,12,13,17,18,19-decabromo-10,10-dimethyl-5,15-
dipentafluorophenylbiladiene, the palladium octabromo isocorrole, and attempts at synthesizing 2,3,17,18-tetrabromo-10,10-dimethyl-5,15-dipentafluorophenylbiladiene. We show an investigation into the photophysical properties of the newly developed compounds.

1.3.2 Dimethyl Biladiene with Extended Conjugation

Again, while the Pd-DMBil and Pt-DMBil complexes show impressive singlet oxygen quantum yields under irradiation outside of the optimum wavelength range, we thought it would be of interest to also synthesize a modified DMBil ligand with extended conjugation. Many tetrapyrrrole complexes with extended $\pi$-conjugation have previously been synthesized\textsuperscript{17,18,19}; and $\beta$-pyrrole substitution on the porphyrin leads to a strong bathochromic shift in the absorption spectrum.\textsuperscript{20} With this in mind we were interested in synthesizing a DMBil ligand with phenyl groups attached to two of the pyrrole units. We report in Chapter 3 the attempted synthesis of 2,3,17,18-tetra(4-methylphenyl)-10,10-dimethyl-5,15-dipentafluorophenylbiladiene. The phenyl substituted pyrrole starting material was successfully synthesized but the final product proved to be more challenging to produce.
Chapter 2

THE DEVELOPMENT OF BROMINATED DIMETHYL BILADIENE

2.1 Introduction

Developing efficient photosensitizers for photodynamic therapy is an interesting and prominent area of research today. Based on the previously synthesized DMBil ligand system and its extraordinary performance in singlet oxygen sensitization, we thought it would be of interest to synthesize and study a wide range of modified DMBil ligands for applications in PDT. The goal of these modified DMBil molecules would be to tune the photophysical properties of the DMBil ligand system to incorporate the optimum qualities for PDT. The first of these molecules is a DMBil with bromine atoms attached. Previous research has shown that the addition of bromine atoms to tetrapyrrole compounds can cause a red shift in the absorption profile\(^{14}\), which is needed for the DMBil ligand to function within the PDT window. The addition of the bromine atoms can also cause a heavy atom effect on the molecule and facilitate intersystem crossing\(^{14}\). This chapter will focus on the synthesis of different brominated DMBil molecules.

2.1.1 Synthesis of 1,2,3,7,8,12,13,17,18,19-Decabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (10Br-DM Bil)

We were able to successfully synthesize the 1,2,3,7,8,12,13,17,18,19-decabromo-10,10-dimethyl-5,15-dipentafluorophenylbiladiene (Figure 2.1). The 10Br-DM Bil ligand was easily synthesized by reacting the DMBil ligand with \(N\)-
bromosuccinimide at room temperature for three hours. After silica gel column purification we successfully obtained the compound and we studied its photophysical properties.

![Chemical Structure](image)

Figure 2.1: 1,2,3,7,8,12,13,17,18,19-Decabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene

### 2.2 Absorption Spectroscopy

The absorption profile of the 10Br-DMBil was recorded in CH$_2$Cl$_2$ and DMF, and the two profiles are overlaid and shown in Figure 2.2. The free base, 10Br-DMBil shows a single and wide absorption in the visible region from ~400 to 600 nm in CH$_2$Cl$_2$ and from ~400 to 650 nm in DMF. The maximum absorption in CH$_2$Cl$_2$ is at 541.5 nm ($\varepsilon = 49000 \text{ M}^{-1}\text{cm}^{-1}$) and there is a shift to longer a wavelength in DMF, with a maximum absorption at 559 nm ($\varepsilon = 75915 \text{ M}^{-1}\text{cm}^{-1}$). This is an interesting shift in the absorption profile and can be seen visually since the compound looks red
in CH$_2$Cl$_2$ and purple in DMF, this also suggests that the HOMO - LUMO gap is smaller in DMF.

The absorption profile of the DMBil free base was previously reported in CH$_2$Cl$_2$; and showed a wide absorption from ~325 to 525 nm. The absorption is composed of two close bands with maximum absorptions at 423 nm and 450 nm.$^{10}$ Comparing these values to the absorption maxima of 10Br-DMBil free base at 541.5 nm we successfully showed a red shift in the absorption profile with the addition of bromine atoms. While we were able to cause a bathochromic shift in the absorption profile with the addition of bromines, the compound still does not absorb strongly past 600 nm, which is important for PDT.
2.2.1 Fluorescence Spectroscopy

The 10Br-DMBil free-base was found to be fluorescent, with the emission spectra under air and nitrogen shown in Figure 2.3. Following excitation at 500 nm a solution of 10Br-DMBil in deaerated CH$_2$Cl$_2$ gave an emission feature at 586 nm. The 10Br-DMBil shows a single feature with a 44 nm Stoke’s Shift showing that 10Br-DMBil emits primarily fluorescence (Figure 2.4). When the experiment was repeated under air the compound gave a very similar spectrum. This is further proven by the fact that the fluorescence quantum yield under nitrogen and under air was calculated to
be $4.5 \times 10^{-3}$ for both experiments. We did not observe a phosphorescence peak in the emission spectrum under nitrogen.

Figure 2.3: Emission spectra recorded in nitrogen and air saturated CH$_2$Cl$_2$ for 10Br-DMBil
2.2.2 Singlet Oxygen Sensitization

The singlet oxygen quantum yield for the 10Br-DMBil ligand was measured. [Ru(bpy)$_3$]$^{2+}$ was used as the standard ($\Phi_\Delta = 0.57$ in DMF)$^{21}$ and 1,3-diphenylisobenzofuran was used as the trapping agent.$^{22,23}$ The $^1$O$_2$ sensitization quantum yield for 10Br-DMBil was measured to be $\Phi_\Delta = 4.92 \times 10^{-3}$ in DMF with irradiation at $\lambda_{irr} = 500$ nm. The DMBil ligand shows a $^1$O$_2$ sensitization quantum yield of $1.5 \times 10^{-2}$ in methanol with irradiation at $\lambda_{irr} = 500$ nm$^{10}$. The addition of bromine atoms on the ligand greatly reduces the amount of singlet oxygen the
compound produces resulting in a significantly lower singlet oxygen quantum yield, however $^1$O$_2$ quantum yields so vary from solvent to solvent therefore it is hard to compare these values; and due to the low solubility of the 10Br-DMBil free-base in methanol we could not perform the experiments in the same solvent as the DMBil free-base.

This decrease in the singlet oxygen sensitization could be a result of the decomposition of the compound. The compound seems to decompose in polar solvents. The 10Br-DMBil was dissolved in DMF in order to measure the singlet oxygen quantum yield and even after the short time required to conduct that experiment the solution had changed color. The two trials of singlet oxygen measurements showed two different values, 7.38 x 10$^{-3}$ and 2.45 x 10$^{-3}$, which shows a low reproducibility due to compound degradation. Additionally, $^1$H NMR of the compound after it was stirred for a few days in a polar solvent showed the emergence of multiple methyl peaks, instead of a single strong singlet as expected and initially observed for the 10Br-DMBil compound. This also indicates compound decomposition, therefore the instability of free-base 10Br-DMBil makes it a poor photosensitizer for singlet oxygen production.

2.3 Metallation of 10Br-DMBil

After obtaining the 10Br-DMBil we wanted to add a heavy metal center to hopefully create more singlet oxygen, as well as improve the stability of the compound. We tried metallating with zinc acetate, but the compound most likely decomposed to multiple byproducts after the reaction as indicated by $^1$H NMR, which showed two –NH proton peaks as well as multiple methyl peaks. We then performed the metallation with palladium; we carried out the reaction in a 1:1 mixture of CH$_2$Cl$_2$
and MeCN, since the 10Br-DMBil is only partially soluble in MeCN. The 10Br-DMBil ligand was dissolved in a 1:1 mixture of CH$_2$Cl$_2$ and MeCN and 1.2 equivalents of Pd(OAc)$_2$ were added. The reaction was stirred at room temperature overnight and surprisingly we did not produce the Pd(10Br-DMBil) as expected. The extra Pd(OAc)$_2$ present in the reaction facilitated a cross-coupling reaction between two bromine substituted carbon atoms at the 1 and 19 positions to close the ring, and creating the palladium isocorrole complex, 2,3,7,8,12,13,17,18,-octabromo-10,10-dimethyl-5,15-dipentafluorophenyl-isocorrole Pd(8Br-DMIC) (Figure 2.5). The high resolution mass spec data as well as the $^1$H, $^{13}$C, and $^{19}$F NMR all support the production of this palladium isocorrole compound. Previous research shows that bipyrrroles can be generated by catalysis from Pd(OAc)$_2$. We were very interested in studying the photophysical qualities of this new tetrapyrrrole complex.

Figure 2.5: 2,3,7,8,12,13,17,18-Octabromo-10,10-Dimethyl-5,15-Dipentafluorophenyl-isocorrole Pd(8Br-DMIC)
2.3.1 Absorption Spectroscopy

The absorption profile of the Pd(8Br-DMIC) was recorded in DMF and the profile is shown in Figure 2.6. The Pd(8Br-DMIC) shows multiple absorption bands across the entire visible region and into the infrared region from ~300 to 1000 nm. The first of these absorption bands has a maximum at 430 nm ($\varepsilon = 1530 \text{ M}^{-1}\text{cm}^{-1}$), the next major band has a maximum at 542 nm ($\varepsilon = 6140 \text{ M}^{-1}\text{cm}^{-1}$) and a shoulder at 566 nm ($\varepsilon = 5701 \text{ M}^{-1}\text{cm}^{-1}$), and the last band has a maximum at 829.5 nm ($\varepsilon = 3170 \text{ M}^{-1}\text{cm}^{-1}$). The Pd(8Br-DMIC) compound has a much broader absorption profile than the 10Br-DMBil, due to the extended conjugation.

With the addition of the palladium and the change from the DMBil ligand system to a closed ring, the Pd(8Br-DMIC) now absorbs more in the red portion of the visible region. The free base 10Br-DMBil does not absorb at wavelengths longer than 650 nm, so it is interesting that we were able to synthesize the Pd(8Br-DMIC) to give a compound that now absorbs in the 600 to 800 nm range, which is within the optimum window for PDT. However, the extinction coefficient is only about 2300 M$^{-1}$ cm$^{-1}$ at these wavelengths, which is lower than ideal for PDT. Compounds currently used in PDT have extinction coefficients that are multiple magnitudes higher.$^4$
2.3.2 Fluorescence Spectroscopy

The Pd(8Br-DMIC) was found to be fluorescent, with the emission spectra under air and nitrogen shown in Figure 2.7. Following excitation at 500 nm a solution of Pd(8Br-DMIC) in deaerated DMF gave an emission feature at 541 nm. The Pd(8Br-DMIC) shows a single feature with a 111 nm Stoke’s Shift (Figure 2.8). When the experiment was repeated under air the compound gave a very similar spectrum, suggesting that the complex emits primarily fluorescence. The fluorescence quantum yields under nitrogen and under air were calculated to be very similar values of $4.2 \times 10^{-4}$ and $4.5 \times 10^{-4}$ respectively.
Figure 2.7: Emission spectra recorded in nitrogen and air saturated DMF for Pd(8Br-DMIC)
2.3.3 Singlet Oxygen Sensitization

The singlet oxygen quantum yield for the Pd(8Br-DMIC) complex was measured. $[\text{Ru(bpy)}_3]^{2+}$ was used as the standard ($\Phi_\Delta = 0.57$ in DMF)\textsuperscript{21} and 1,3-diphenylisobenzofuran was used as the trapping agent.\textsuperscript{22,23} The $^1\text{O}_2$ sensitization quantum yield for Pd(8Br-DMIC) was measured to be $\Phi_\Delta = 1.0 \times 10^{-1}$ in DMF with irradiation at $\lambda_{\text{irr}} = 500$ nm. This value is much more impressive and two orders of magnitude larger than the 10Br-DMBil singlet oxygen quantum yield. This is likely due to the addition of the Pd$^{2+}$ center and the heavy atom facilitating intersystem
crossing to the triplet state. The Pd(8Br-DMIC) seems to be more stable over time than the 10Br-DMBil due to the minimum color change during the photolysis, which likely also contributes to the higher singlet oxygen quantum yield.

2.4 Attempted Synthesis of 2,3,17,18-Tetrabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (4Br-DMBil)

We were not able to successfully synthesize the 4Br-DMBil ligand, even with various different methods tried. The 1-(triisopropylsilyl)-3,4-dibromopyrrole starting material was first synthesized from commercially purchased N-(triisopropylsilyl)pyrrole and then was easily deprotected to give 3,4-dibromopyrrole. The 3,4-dibromopyrrole was then used in attempts to make the 4Br-DMBil. We tried using indium(III) chloride (InCl₃) and trifluoroacetic acid (TFA) as the catalyst. We also tried reacting different numbers of equivalents of N-bromosuccinimide with DMBil in order to produce the desired tetrabromo product.

2.4.1 Using 3,4-Dibromopyrrole

We first tried using 3,4-dibromopyrrole to synthesize 4Br-DMBil. We thought we could substitute 3,4-dibromopyrrole in place of pyrrole in the synthesis of DMBil in order to synthesize the 4Br-DMBil (Figure 2.9).

![Scheme of attempted synthesis of 2,3,17,18-Tetrabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (4Br-DMBil)](image)

Figure 2.9: Scheme of attempted synthesis of 2,3,17,18-Tetrabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (4Br-DMBil)
2.4.1.1 Using Indium(III) Chloride

Weak Lewis acid, indium(III) chloride was first used as the acid catalyst for the synthesis of 4Br-DMBil as similarly demonstrated in the synthetic procedure of DMBil. According to the general procedure used to prepare DMBil, \textsuperscript{10} diacyl was first reduced to the diol by NaBH\textsubscript{4}, the diol was dissolved in dichloromethane and InCl\textsubscript{3} and 2.8 equivalents of 3,4-dibromopyrrole were added and stirred at room temperature. After 15 minutes, DDQ was added as an oxidant and stirred for 5 min, then triethylamine was added and the solution was stirred for 30 minutes. The solvent was removed by rotary evaporation and the residue was then purified by silica gel column with a mixture of hexanes and ethyl acetate (10:1), the desired product was not produced.

Since the above procedure was unsuccessful in producing the desired product, we tried reacting the diol with InCl\textsubscript{3} and 3,4-dibromopyrrole under nitrogen as we thought that an inert atmosphere might aid in creating the desired product. The attempt under nitrogen was unsuccessful, various reaction times were also tried for this step both under nitrogen and under air, but these attempts were all unsuccessful in synthesizing the desired product. We thought that the reaction might need a great excess of the 3,4-dibromopyrrole but that was not economically feasible since the \textit{N}(triisopropylsilyl)pyrrole starting material is expensive.

2.4.1.2 Using Trifluoroacetic Acid

After the use of InCl\textsubscript{3} was not successful, we tried using TFA. We thought a Brönsted acid was needed in order to catalyze the reaction and produce the desired product. We used the same procedure substituting TFA for InCl\textsubscript{3}. Diacyl was reduced to the diol with NaBH\textsubscript{4}, the diol was dissolved in dichloromethane and TFA and 2.8
equivalents of 3,4-dibromopyrrole were added and stirred at room temperature. After 15 minutes, DDQ was added and stirred for 5 min, then triethylamine was added and the solution was stirred for 30 minutes. The solvent was removed by rotary evaporation and the residue was the purified by silica gel column with a mixture of hexanes and ethyl acetate (10:1), but the desired product was not produced. We then tried using a long reaction time between the diol, TFA, and 3,4-dibromopyrrole. This again was unsuccessful in producing 4Br-DMBil.

2.4.2 Using N-Bromosuccinimide (NBS)

After the methods with 3,4-dibromopyrrole were not successful, we tried reacting DMBil with N-bromosuccinimide in order to synthesize the 4Br-DMBil. This method was adapted from a literature method for brominating corroles. DMBil was dissolved in acetonitrile and a solution of 4.9 equivalents of N-bromosuccinimide in dichloromethane was added 1mL at a time over 5 min to the acetonitrile solution. The mixture was stirred at room temperature for 1 hour. The crude mixture was washed with water, saturated NaHCO₃, and brine. The solvent was removed by rotary evaporation. The residue was purified on a silica gel column with a mixture of hexanes and ethyl acetate (15:1) to give a red solid. This procedure gave a mixture DMBil derivatives with 4 or 5 bromines attached so we reduced the NBS equivalents to 4 to hopefully avoid over-bromination. The procedure was repeated with 4 equivalents of NBS. This was successful in producing 4Br-DMBil but multiple isomers were formed and could not be separated from one another.
2.5 Summary

There has been a lot of research on porphyrin compounds and their relationship to photodynamic therapy. After synthesizing the DMBil ligand and discovering its utility as a singlet oxygen sensitizer, we thought it would be interesting to investigate other derivatives of DMBil in an effort to tune the absorption properties to make more viable photosensitizers for PDT. A synthetic route to decabromodimethylbiladiene has been described, but the metallation of the compound led to another ligand system. While the isocorrole derivative is not what we were originally trying to produce, it proved to be an interesting molecule to study. The photophysics of both the free base 10Br-DMBil and Pd(8Br-DMIC) were studied. We were successful in red shifting the absorption of the DMBil ligand by adding the ten bromine atoms and induced an even larger red shift in the absorption spectrum with the formation of palladium isocorrole. Both compounds show singlet oxygen sensitization reactivity but the Pd(8Br-DMIC) shows a much higher quantum yield. We were not successful in synthesizing the 4Br-DMBil compound.

2.6 Experimental

2.6.1 General Synthetic Methods

All reactions were carried out under normal atmospheric conditions unless otherwise noted. Reagents and solvents were purchased from Sigma Aldrich, Acros, Fisher, Strem, Alfa Aesar, VWR, Synthonix, Matrix Scientific, Decon Lab, Inc., or Cambridge Isotopes Laboratories. The DMBil ligand was prepared using published methods. Solvents for synthesis were of reagent grade or better. Column chromatography was performed with 40-63 µm silica gel from Silicycle or 50-200 µm basic alumina from Acros Organics.
2.6.2 Spectroscopic Methods

$^1$H NMR and $^{13}$C NMR spectra were recorded at 25 °C on a Bruker 400 MHz or 600 MHz spectrometer. Proton spectra were referenced to the residual proton resonance of the deuterated solvent (CDCl$_3$ = $\delta$ 7.26) and carbon spectra were referenced to the carbon resonances of the solvent (CDCl$_3$ = $\delta$ 77.16).$^{25}$ $^{19}$F spectra were recorded at 25 °C on a Bruker 400 MHz spectrometer with a cryogenic QNP probe. Fluorine spectra were referenced to an external trifluoroacetic acid standard (TFA = $\delta$ -76.55 in CD$_3$CN).$^{26}$ All chemical shifts are reported using the standard $\delta$ notation in parts-per-million; positive chemical shifts are to higher frequency from the given reference. The Mass Spectrometry Laboratory in the Department of Chemistry and Biochemistry at the University of Delaware performed the high-resolution mass spectrometry analyses.

All UV/visible absorbance spectra were collected at room temperature on a StellarNet CCD array UV-vis spectrometer using quartz cuvettes (6Q) with a 1 cm path length from Starna Cells, Inc. Absorption was measured in dichloromethane or dimethylformamide containing 10Br-DMBIL or Pd(8Br-DMIC) at concentrations of 5, 10, 15, 20, and 25 µM.

Emission spectra were recorded on an automated Photon Technology International (PTI) QuantaMaster 40 fluorometer equipped with a 75-W Xenon arc lamp, an LPS-220B lamp power supply and a Hamamatsu R2658 photomultiplier tube. All samples were prepared in screw cap quartz cuvettes of 1 cm path length from Starna Cells, Inc. 8.6 µM solution of 10Br-DMBIL in CH$_2$Cl$_2$ and 25 µM solution of Pd(8Br-DMIC) in dimethylformamide were prepared under air and in a nitrogen-filled glovebox. The samples were excited at 500 nm and emission was
monitored from 510 – 1000 nm using a step size of 1 nm and an integration time of 0.25 s. Reported spectra are the average of at least 5 individual acquisitions.

Emission quantum yields were calculated using a 157 µM solution of [Ru(bpy)$_3$][PF$_6$]$_2$ in air-saturated acetonitrile ($\Phi = 0.018$)$^{27}$ as the reference and the expression below,

$$\Phi_s = \Phi_{ref} \left( \frac{I_s}{I_{ref}} \right) \left( \frac{A_{ref}}{A_s} \right) \left( \frac{\eta_s}{\eta_{ref}} \right)^2$$

where $\Phi_s$ and $\Phi_{ref}$ are the emission quantum yield of the sample and the reference, respectively, $I_s$ and $I_{ref}$ are the integrated emission intensities of the sample and reference, $A_s$ and $A_{ref}$ are the measured absorbance of the sample and reference at the excitation wavelength, and $\eta_s$ and $\eta_{ref}$ are the refractive indices of the solvents used for the sample and reference respectively.

2.6.3 Singlet Oxygen Experiments

Singlet oxygen sensitization was quantified by monitoring fluorescence from a singlet oxygen trapping agent, 1,3-diphenylisobenzofuran.$^{22,23}$ Measurements were recorded on an automated Photon Technology International (PTI) QuantaMaster 40 fluorometer equipped with a 75-W Xenon arc lamp, an LPS-220B lamp power supply and a Hammamatsu R2658 photomultiplier tube using quartz cuvettes (6Q) with a 1 cm path length from Starna Cells, Inc. Each cuvette contained 2 mL of a 10 µM solution of 10Br-DMBil, Pd(8Br-DMIC), or [Ru(bpy)$_3$][PF$_6$]$_2$ (used as a reference, $\Phi = 0.57$)$^{21}$ in dimethylformamide and 1 µM in 1,3-diphenylisobenzofuran. Along with another cuvette containing only dimethylformamide and 1 µM of 1,3-diphenylisobenzofuran, which acted as a blank. Consumption of 1,3-diphenylisobenzofuran was measured by observing the change in integrated emission
intensity from unreacted furan following irradiation with 500 nm light from an Intralux 9000 light source (Volpi) fitted with a 10 nm (fwhm) bandpass filter centered at 500 nm (Thor Labs, FB500-10). The cuvettes were irradiated for 10 sec or 30 sec intervals for a total of 150 seconds, and the experiment was repeated two or three times. Furan emission spectra were obtained by exciting at 405 nm and scanning from 400 to 600 nm using a step size of 1 nm and an integration time of 0.25 seconds.

Calibration curves of the integrated intensity of the emission spectra versus the concentration of unreacted 1,3-diphenylisobenzofuran remaining in solution were generated to correct for absorption of the photosensitizers between 400 and 600 nm. This was accomplished by collecting emission spectra from 10 µM solutions of 10Br-DMBil, Pd(8Br-DMIC), or [Ru(bpy)$_3$][PF$_6$]$_2$ which contained furan concentrations of 0, 0.25, 0.50, 0.75, 1, 1.25, or 1.50 µM. Linear regression lines were fit to the calibration data from each solution. The integrated intensity values obtained from the singlet oxygen experiments were then plugged in for the y values in the linear regression line equations enabling the corresponding concentrations of unreacted furan to be determined by calculation of the x values. A final plot of the concentration of unreacted furan versus irradiation time formed a straight line with slope, $m$, which was used in the following equation to calculate the singlet oxygen quantum yields:

$$\Phi_s = \Phi_{ref} \left( \frac{m_s}{m_{ref}} \right) \left( \frac{\varepsilon_{ref}}{\varepsilon_s} \right)$$

Where $\Phi_s$ and $\Phi_{ref}$ are the singlet oxygen quantum yields for the sample and for the reference, ([Ru(bpy)$_3$][PF$_6$]$_2$) respectively, $m_s$ and $m_{ref}$ are the slopes from the plots of the concentration of furan vs. irradiation time for the sample and reference, and $\varepsilon_s$ and
\( \varepsilon_{\text{ref}} \) are the extinction coefficients at the wavelength of irradiation (500 nm) for the sample and reference respectively.

### 2.6.4 Synthesis of 1,2,3,7,8,12,13,17,18,19-Decabromo-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (10Br-DMBil)

This compound was prepared by amending a literature method for brominating corroles.\(^{14}\) DMBil (0.110g, 0.17 mmol) was dissolved in acetonitrile (22.5mL). A solution of N-bromosuccinimide (0.444g, 2.5 mmol) in dichloromethane (18mL) was added 1mL at a time over 5 min to the acetonitrile solution. The mixture was stirred at room temperature for 3 hours. The crude mixture was washed with water, saturated NaHCO\(_3\), and brine. The solvent was removed by rotary evaporation. The residue was purified on a silica gel column with a mixture of hexanes and CH\(_2\)Cl\(_2\) (5:1) to give a pink red solid. Yield: 0.130g (54%) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 13.78 (s, 2H, -NH), 1.98 (s, 6H, -CH\(_3\)). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \( \delta \) 147.64, 146.60, 145.84, 141.56, 125.79, 122.92, 122.34, 121.05, 116.33, 106.47, 38.48, 29.85, 24.51. \(^{19}\)F NMR (400 MHz, CDCl\(_3\)) \( \delta \) -138.60 (m, 4F), -150.18 (t, \( J = 20.9 \) Hz, 2F), -160.45 (m, 4F). HR-LIFDI-MS: \([M^+] m/z\) calcd for C\(_{33}\)H\(_8\)N\(_4\)F\(_{10}\)\(^{79}\)Br\(_5\)\(^{81}\)Br\(_5\) 1449.2321; found: 1449.2325.

### 2.6.5 Synthesis of 2,3,7,8,12,13,17,18-Octabromo-10,10-Dimethyl-5,15-Dipentafluorophenylisocorrole Pd(8Br-DMIC)

10Br-DMBil (0.0572g, 0.037mmol) was dissolved in dichloromethane (10mL). Acetonitrile (10mL) was added to make a mixture of two solvents. Pd(OAc)\(_2\) (0.010g, 0.0445mmol) was added and the reaction was covered with a rubber septum and stirred overnight. The solvent was removed by rotary evaporation and the residue was dissolved in dichloromethane and then passed through a celite
pipet. The solvent was removed by rotary evaporation and the residue was purified on a silica gel column with a mixture of hexanes and CH₂Cl₂ (5:1) to give a dark red brown solid. Yield: 0.047g (92%) ¹H NMR (400 MHz, CDCl₃) δ 2.14 (s, 6H, -CH₃).

¹³C NMR (400 MHz, CDCl₃) δ 161.25, 128.73,127.96, 118.16, 115.26, 111.31, 45.06, 32.07, 29.85, 22.84, 16.68. ¹⁹F NMR (400 MHz, CDCl₃) δ -138.41 (dd, J = 23.8, 7.2 Hz, 4F), -150.46 (t, J = 20.0 Hz, 2F), -160.61 (dt, J = 21.8, 6.9 Hz, 4F). HR-LIFDI-MS: [M⁺] m/z: calcd for C₃₃H₆N₄F₁₀⁷⁹Br₄⁸¹Br₄Pd 1393.2853; found: 1393.2820.

2.6.6 Synthesis of 1-(Triisopropylsilyl)-3,4-Dibromopyrrole

This compound was prepared using a method from literature.²⁸,²⁹ N-(triisopropylsilyl)pyrrole (0.497g, 2.23mmol) was added to anhydrous tetrahydrofuran (10mL). The solution was cooled to -78 °C and N-bromosuccinimide (0.836g, 4.46mmol) was added. The solution was stirred for 1 hour and then warmed to room temperature. Hexane was added to the reaction mixture to precipitate the succinimide by-product, and the mixture was passed through a short neutral alumina plug using hexane as eluent. The solvent was removed by rotary evaporation and the residue was purified on a silica gel column with a mixture of hexanes and CH₂Cl₂ (15:1) to give a colorless gel. The product was recrystallized from pentane at 0 °C to give a colorless solid. Yield: 0.732g (46%) ¹H NMR (400 MHz, CDCl₃) δ 6.72 (s, 2H, α-H), 1.40 (septet, J = 7.5 Hz, 3H, -SiCH), 1.08 (d, J = 7.5 Hz, 18H, -CH₃).

2.6.7 Synthesis of 3,4-Dibromopyrrole

This compound was prepared using a method from literature.²⁹ 1-(Triisopropylsilyl)-3,4-dibromopyrrole (0.35g, 0.913mmol) was dissolved in anhydrous tetrahydrofuran (10mL). Tetra-n-butylammonium fluoride (0.913mL as a
1M solution in THF, 0.913mmol) was added to the pyrrole solution. The solution was stirred at room temperature for 10 minutes. The reaction mixture was diluted with ethyl ether and washed with water. The ethyl ether was dried with Na$_2$SO$_4$ and removed by rotary evaporation to give a dark liquid. Yield: Assumed Quantitative and carried to the next reaction $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 (s, 1H, -NH), 6.81 (d, $J$ = 3.00 Hz, 2H, $\alpha$-H).
Chapter 3

ATTEMPTED SYNTHESIS OF 2,3,17,18-TETRA(4-METHYLPHENYL)-10,10-DIMETHYL-5,15-DIPENTAFLUOROPHENYLBILADIENE

3.1 Introduction

Given that palladium and platinum DMBil were previously seen to give notable quantum yields for singlet oxygen sensitization when irradiated with light at wavelengths shorter than 600 nm\textsuperscript{13}, we thought it would be of interest to synthesize a DMBil with phenyl groups attached in order to red shift the absorption spectrum. Previous research has shown that the absorption of tetrapyrroles can be shifted to longer wavelengths by extending the $\pi$-conjugation.\textsuperscript{20} We wanted to achieve this extension of the conjugation by adding phenyl groups to two of the pyrrole units on the DMBil ligand to give 2,3,17,18-tetra(4-methylphenyl)-10,10-dimethyl-5,15-dipentafluorophenylbiladiene (Phenyl-DMBil). This would be achieved by first preparing the 3,4-bis(4-methylphenyl)pyrrole compound and substituting that in place of pyrrole in the DMBil synthesis. This Phenyl-DMBil would have extended conjugation and therefore could absorb within the optimum window for photodynamic therapy.

3.2 Attempts at Synthesizing 2,3,17,18-Tetra(4-methylphenyl)-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (Phenyl-DMBil)

We were not able to successfully synthesize the Phenyl-DMBil, but tried many different methods. The $N$-(benzenesulfonyl)-3,4-bis(4-methylphenyl)pyrrole starting material was successfully synthesized in a three step process starting from
commercially purchased pyrrole and then after easy deprotection to give 3,4-bis(4-methylphenyl)pyrrole. The 3,4-bis(4-methylphenyl)pyrrole was then used in attempts to make the Phenyl-DMBil. We tried using indium(III) chloride, (InCl$_3$), or trifluoroacetic acid, (TFA), as the catalysts (Figure 3.1).

![Figure 3.1: Scheme of attempted synthesis of 2,3,17,18-Tetra(4-methylphenyl)-10,10-Dimethyl-5,15-Dipentafluorophenylbiladiene (Phenyl-DMBil)](image.png)

3.2.1 Using Indium(III) Chloride

Indium(III) chloride was chosen as the acid catalyst first because we use this reagent in the synthesis of DMBil. InCl$_3$ is a relatively weak Lewis acid which we hoped would catalyze the condensation reaction between the diol and the 3,4-bis(4-methylphenyl)pyrrole. To prepare the Phenyl-DMBil, we first attempted to follow the general procedure used to prepare DMBil.$^{10}$ Diacyl was reduced to the diol with NaBH$_4$, the diol was dissolved in dichloromethane, InCl$_3$ and 2.8 equivalents of 3,4-bis(4-methylphenyl)pyrrole were added and stirred at room temperature. After 15 minutes, DDQ was added for oxidization and stirred for 5 min, then triethylamine was added and the solution was stirred for 30 minutes. The solvent was removed by rotary evaporation and the residue was purified by a silica gel column with a mixture of
hexanes and ethyl acetate (10:1). This procedure seemed promising from the NMR since it had the correct peaks in the aromatic region of the spectrum but the integration was not correct. The mass spec then gave 1510 m/z, which lead us to believe that the pyrrole over reacted and made an extended system with six pyrrole units, since the mass of the Phenyl-DMBil would be 1020 m/z, and 1510 corresponds to a six pyrrole unit system. We then decreased the number of equivalents of 3,4-bis(4-methylphenyl)pyrrole to 2 in order to reduce the chances of obtaining a hexapyrrole compound. This method was also not successful in producing the Phenyl-DMBil. We then tried adding a diluted solution of 3,4-bis(4-methylphenyl)pyrrole in CH₂Cl₂ dropwise with an addition funnel in an effort to prevent the pyrrole from reacting too many times. After many failed attempts at producing the Phenyl-DMBil with InCl₃, we determined that this method was not going to be successful.

3.2.2 Using Trifluoroacetic Acid

After the failed attempts using InCl₃ we switched to using TFA. We thought that using a Brönsted acid might help to catalyze the condensation reaction between the diol and 3,4-bis(4-methylphenyl)pyrrole to produce the desired product. Diacyl was reduced to the diol with NaBH₄, the diol was dissolved in dichloromethane and TFA was added. A solution of 2 equivalents of 3,4-bis(4-methylphenyl)pyrrole in CH₂Cl₂ was added dropwise and stirred at room temperature. After 15 minutes, DDQ was added and stirred for 5 min, then triethylamine was added and the solution was stirred for 30 minutes. The solvent was removed by rotary evaporation and the residue was then purified by silica gel column with a mixture of hexanes and ethyl acetate (10:1), but the desired product was not produced.
3.3 Summary

We were interested in synthesizing a DMBil with extended conjugation and red-shifted absorption features, but did not succeed in obtaining it. We tried the synthesis by varying the reaction conditions such as using different equivalents of 3,4-bis(4-methylphenyl)pyrrole, controlling the speed of addition of the phenyl substituted pyrrole, as well as using the Lewis acid indium(III) chloride or the Brönsted acid trifluoroacetic acid as the catalyst. The procedures were all chemically sound but the desired product could not be produced.

3.4 Experimental

3.4.1 General Synthetic Methods

General synthetic methods can be found on page 24.

3.4.2 Spectroscopic Methods

Spectroscopic methods can be found on page 25.

3.4.3 Synthesis of N-(Benzenesulfonyl)pyrrole

This compound was prepared using a method from the literature. A suspension was made of powdered NaOH (1.21g, 30mmol) and pyrrole (515µL, 7.4mmol) in dichloroethane (5.05mL) at 0°C. Benzenesulfonyl chloride (1.185mL, 9.3mmol) was added as a neat liquid and the solution was stirred for 30 min. The solution was allowed to warm to room temperature and continued to stir overnight. The solution was quenched with water and extracted twice with dichloromethane. The extract was washed three times with water, dried with Na₂SO₄, and the dichloromethane was removed by rotary evaporation. The product was recrystallized with methanol to give a white solid. Yield: 1.32g (86%) \(^1\)H NMR (400 MHz, CDCl₃)
δ 7.85 and 7.60 (m, 2H and m, 1H phenyl H), 7.50 (t, \( J = 7.7 \) Hz, 2H, phenyl H), 7.17 and 6.30 (t, \( J = 2.3 \) Hz, 2H and t, \( J = 2.3 \) Hz, 2H, pyrrole H).

3.4.4  Synthesis of \( N \)-(Benzenesulfonyl)-3,4-Dibromopyrrole

This compound was prepared using a method from the literature.\textsuperscript{30} \( N \)-(benzenesulfonyl)pyrrole (1.3294g, 6.4mmol) was dissolved in acetic acid (10mL). A solution of bromine (657µL, 13mmol) in acetic acid (8mL) was added drop wise to the \( N \)-(benzenesulfonyl)pyrrole solution and stirred for 1 hour at room temperature. The solution was then refluxed for 1.5 hours. The acetic acid was removed and a saturated solution of NaHCO\(_3\) was added to the residue. The product was extracted into dichloromethane then washed with a saturated solution of NaHCO\(_3\) and dried with Na\(_2\)SO\(_4\). The dichloromethane was removed by rotary evaporation and the residue was purified on a silica gel column with a mixture of hexanes and toluene (2:1) to give a white solid. Recrystallization with methanol gave colorless needle-like crystals.
Yield: 0.697g (30%) \( ^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.88 (d, \( J = 7.50 \) Hz, 2H, 2,6-benzeneylsulfonyl H), 7.68 (t, \( J = 7.50 \) Hz, 1H, 4-benzenesulfonyl H), 7.50 (t, \( J = 7.50 \) Hz, 2H, 3,5-benzeneylsulfonyl H) 7.20 (s, 2H, α-H).

3.4.5  Synthesis of \( N \)-(Benzenesulfonyl)-3,4-Bis(4-methylphenyl)pyrrole

This compound was prepared by amending a method from the literature.\textsuperscript{30} In a nitrogen atmosphere, \( N \)-(benzenesulfonyl)-3,4-dibromopyrrole (0.8314g, 2.3mmol), 4-methylphenyl boronic acid (0.9290g, 6.8mmol), and Pd(PPh\(_3\))\(_4\) (266mg, 0.023mmol) were dissolved in 1,2-dimethoxyethane (21mL). A degased solution of aqueous sodium carbonate (1.612g, 15mmol in 6mL of H\(_2\)O) was added to the reaction mixture and refluxed for 24 hours under nitrogen. The solution was cooled to room
temperature and the solvent was removed with rotary evaporation. The residue was dissolved in dichloromethane, washed with water and brine, dried with Na$_2$SO$_4$ and the solvent was removed by rotary evaporation. The residue was purified on a basic alumina column with a mixture of hexanes and ethyl acetate (15:1) to give a white solid. Yield: 0.668g (75%) $^1$H NMR (600 MHz, CDCl$_3$) δ 7.94 (m, 2H, 2,6-benzeneylsulfonyl H), 7.62 (t, $J = 7.50$ Hz, 1H, 4-benzenesulfonyl H), and 7.53 (t, $J = 7.90$ Hz, 2H, 3,5-benzeneylsulfonyl H), 7.22 (s, 2H, α-H), 7.07 (m, 8H, phenyl H), 2.32 (s, 6H, -CH$_3$).

### 3.4.6 Synthesis of 3,4-Bis(4-methylphenyl)pyrrole

This compound was prepared by amending a method from the literature. $^3$I $N$-(benzenesulfonyl)-3,4-bis(4-methylphenyl)pyrrole (0.200g, 0.52mmol) was dissolved in tetrahydrofuran (2mL). A solution of KOH (0.500g, 8.9mmol) in methanol (2mL) was added to the THF solution. The mixture was stirred at room temperature for 2 hours. The product was extracted into ethyl ether, washed with brine, and dried with Na$_2$SO$_4$. The ethyl ether was removed by rotary evaporation to give a yellow solid. Yield: Assumed Quantitative and carried into next step $^1$H NMR (600 MHz, CDCl$_3$) δ 8.25 (s, 1H, -NH), 7.19 and 7.08 (d, $J = 12.0$ Hz, 4H and d, $J = 12.0$ Hz, 4H, phenyl H), 6.89 (d, $J = 6.00$ Hz, 2H, α-H), 2.34 (s, 6H, -CH$_3$).
REFERENCES


Appendix

EXPERIMENTAL DATA

$^1$H NMR Data
$^{13}$C NMR Data
$^{19}$F NMR Data
Mass Spec Data