SYNTHESIS OF NEW PORPHYRINOIDS FOR BIOMEDICAL AND MATERIALS APPLICATIONS

by

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ABSTRACT

SYNTHESIS OF NEW PORPHYRINOIDS FOR BIOMEDICAL AND MATERIALS APPLICATIONS

by

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The facile synthesis of three non-hydrolysable thioglycosylated porphyrinoids is reported. Starting from meso perfluorophenylporphyrin ($TPPF_{20}$), the non-hydrolysable thioglycosylated porphyrin ($PGlc_4$), chlorin ($CGlc_4$), isobacteriochlorin ($IGlc_4$), and bacteriochlorin ($BGlc_4$) can be made in 2-3 steps. The ability to append a wide range of targeting agents onto the perfluorophenyl moieties, the chemical stability, and the ability to fine-tune the photophysical properties of the chromophores make this a suitable platform for development of biochemical tags, diagnostics, or as photodynamic therapeutic agents. With reduction of one or two pyrrole double bonds, there is a red shift in the lowest energy absorption band and a significant increase in intensity. The fluorescence of these porphyrinoids is in the order $PGlc_4$ = $BGlc_4$ < $CGlc_4$<$IGlc_4$ and there is a corresponding decrease in the amount of triplet formed. Fluorescence micrographs of cells after treatment with these four porphyrinoids indicate they are taken up. The $CGlc_4$ and $IGlc_4$ may be dual function agents that can detect cancer by luminescence, and treat cancer by photodynamic therapy (PDT).

Porphyrins appended with four rigid hydrogen bonding motifs on the *meso* positions were synthesized and self-assembled into a cofacial cage with four complementary bis-(decyl)melamine units in dry solvents, these hydrogen-bonded cages were analysed by diffusion-ordered spectroscopy (DOSY) in solution. The hydrocarbon chains on the melamine mediate the formation of nanofilms on surfaces as the solvent slowly evaporates.

A water soluble zinc (II) phthalocyanine symmetrically appended with eight thioglucose units was synthesized from commercially available hexadecafluoro-phthalocyaninato zinc(II) by controlled nucleophilic substitution of the peripheral fluoro groups by thio-sugars. The photophysical properties and cancer cell uptake studies of this nonhydrolyzable thioglycosylated phthalocyanine are reported. The new compound has amphiphilic character, is chemically and photochemically stable, and can potentially be used as a photosensitizer in photodynamic therapy.

A porphyrin bearing pyridyl groups at the meso positions was synthesized using 2,6-diacetamido-4-formylpyridine. A new method has been developed for the synthesis of the precursor aldehyde that avoid much of the problems associated with the earlier synthesis. With this porphyrin it is possible to build hetero-complementary rigid, multi-porphyrin supramolecular arrays via hydrogen bonds. For example, when using naphthalenediimide (NDI) units a checkerboard pattern is expected to be formed using this porphyrin as a donor and NDI as an acceptor where triple hydrogen bond is formed between the diimide and pyridyl units. Energy transfer can be studied through this hydrogen bonded supramolecular assembly.

The synthesis of a triply bridged diporphyrin appended with six thioglucose units is reported. The electronic spectrum of this triply bridged porphyrin has enhanced intensity at low-

energy wavelengths that reaches the near infrared region. The goal of this project is to create tumor targeting dyes that can be activated with red wavelengths of light that penetrate deeper into tissues. This new compound is amphiphilic in nature, chemically and photochemically stable, expected to have unusual photophysical and electrochemical properties, and can potentially be used as a photosensitizer in photodynamic therapy.

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I dedicate my thesis to my husband Amit Aggarwal and to my Parents Mr. Jagjit Singh and Mrs. Amarjit Kaur for their encouragement and belief in me.

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Abbreviations

AFM	Atomic Force Microscopy
ESI-MS	Electrospray Mass Spectrometry
GC-MS	Gas Chromatography-Mass Spectrometry
UV-Vis	Ultraviolet-visible spectroscopy
NMR	Nuclear Magnetic Resonance
DOSY	Diffusion ordered spectroscopy
PDT	Photodynamic Therapy
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
ROS	Reactive Oxygen Species
PBS	Phosphate Buffer Saline
THF	Tetrahydrofuran
DMF	Dimethylformamide
ITO	Indium Tin Oxide
$TPPF_{20}$	5,10,15,20-tetrakis-(2,3,4,5,6-pentafluorophenyl)porphyrin
$PGlc_4$	Thioglycosylated Porphyrin Conjugate
$CGlc_4$	Thioglycosylated Chlorin Conjugate
$IGlc_4$	Thioglycosylated Isobacteriochlorin Conjugate
$BGlc_4$	Thioglycosylated Bacteriochlorin Conjugate
m-THPC	meso-tetrakis(3'-hydroxyphenyl) chlorin
TPP	5,10,15,20-tetraphenyl porphyrin
ZnTPP	5,10,15,20-tetraphenyl porphyrinato Zinc(II)
PIFA	Phenyliodine bis(trifluoroacetate)
$ZnP2\text{-}F_{15}$	5,10,15-Tris(pentafluorophenyl)porphyrinatozinc(II)

NDI	Naphthalene diimide
$ZnPcF_{16}$	Hexadecafluoro-phthalocyaninatozinc(II)
$ZnPcGlc_8$	Octathioglycosylated Zn (II) phthalocyanine

CHAPTER 1

COMBINATORIAL LIBRARIES OF PORPHYRINS: CHEMISTRY AND APPLICATIONS[1]

1.1 Introduction

1.1.1 Porphyrins

Porphyrins and related macrocycles have staggeringly diverse roles as cofactors in biological systems – from reduction and oxidation catalysts such as cytochrome P_{450}, to carriers of small molecules such as dioxygen, to solar energy harvesting systems that provide most of the free energy on earth.(*2*) With nature as inspiration, there is a more diverse array of synthetic porphyrinic systems designed to understand the structure-function relationships of the natural systems, to understand the mechanisms of porphyrin related diseases, to be effective reagents in organic synthesis such as oxidations, to be effective photonic materials for dye-base solar energy utilization, to perform as sensors elements, to be efficacious therapeutics.(*3*) These properties and functions derive from several factors that are unique to these macrocycles. The porphyrin core can be modified to tune the electronic properties and conformational flexibility. The macrocycle can bind nearly every metal ion in the periodic table. The exocyclic organic moieties can fine tune the electronic and structural properties, provide an appropriate environment, and at the same time serve to organize the chromophores into functional materials.(*4, 5*) Although there are many possible isomers of the natural porphyrinoid systems, only a few are routinely found as

[1]This chapter is adapted from reference 1. Drain, C. M., and Singh, S. (**2010**) Combinatorial Libraries of Porphyrins: Chemistry and Applications, In *The Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* (Kadish, K. M., Smith, K. M., and Guilard, R., Eds.), pp 485-537, World Scientific Publisher, Singapore.

cofactors. For example, there are 60 possible isomers for protoporphyrin due to the four methyl, two vinyl, and two propionate groups on the eight pyrrolepositions,(*6*) yet protoporphyrin IX is most often found in nature. The reasons for this are both enzymatic and thermodynamic. Thus, the design of new porphyrinic materials for the array of applications in the aforementioned areas remains a tremendously active research endeavor. Rational design of target compounds can be complimented by the use of combinatorial chemistry to discover leads that can be further developed into functional materials. The aim of the present chapter is the discussion of the synthesis and applications of the combinatorial porphyrin libraries.

1.1.2 Overview of Combinatorial Chemistry

Combinatorial chemistry uses one or more high yield reactions to generate a library of compounds, and is used as a means to significantly accelerate the discovery of active compounds.(*7-10*) Combinatorial chemistry has in many ways changed the way in which chemists approach the discovery, design, and optimization of a variety of chemical systems such as drugs that inhibit target enzymes,(*11*) molecular catalysts,(*12, 13*) and other materials.(*14, 15*) Systematic combinatorial mixtures of inorganics have been used to discover new materials such as ceramic superconductors,(*16, 17*) and band gap materials for solar energy harvesting. The formation of libraries of polypeptides, DNA, RNA, sugars, and other polymers most often use Merrifield's approach(*18*) to systematically build the polymers on a solid support such as a bead, or more recently planar platforms with grids.(*11, 14, 18-20*) The solid phase, pool and split approach has the advantage of being able to track and identify the chemical composition of each member of the library via a number of strategies such as IR, Raman, and other tags on the bead or by the position on a grid. The solid phase synthesis of very large organic-chemical libraries with high structural diversity has evolved towards a knowledge based approach that aims to

make smaller but more directed libraries based on the known or desired properties of the target.(*12*) The formation of solution phase libraries can have the advantage of higher yielding reactions, but needs chromatography and mass spectrometry to assure the expected chemical diversity is present in the mixture.(*21, 22*) Efficient selection of the winning or active compounds from both solid phase and solution phase libraries is required if the combinatorial strategy is to be effective.

Combinatorial libraries have proven to be an efficient method to examine structure-function relationships.(*23, 24*) Though some of the early expectations have not come to full fruition, the rapid growth in combinatorial approaches in last few years in the development of chemically diverse libraries of molecules remains an important strategy for drug discovery. Solid phase and solution phase methods have been employed to synthesize and characterize combinatorial libraries of porphyrins. Combinatorial synthesis allows for the efficient formation of large collections of porphyrins with diverse chemical properties that heretofore have targeted biological activity such as for photodynamic therapeutic (PDT) discovery for treatment of various diseases and antimicrobial agents. Three general approaches are reported for porphyrin combinatorial library formation: (1) solution phase formation of the macrocycle by adding a mixture of reagents such as aldehydes followed by purification of the porphyrins from the side products of the reaction, (2) solution phase derivatization of a core porphyrin platform bearing highly reactive functional groups, (3) formation of the macrocycle on a solid support or making derivatives of the porphyrin appended to a solid support. Large excesses of the reagents can be used to drive the reactions on pre-formed core porphyrinoid platforms to completion, which assures diversity of the library and simplifies the work up and purification steps.

In general, the motivating factors for the design and synthesis of combinatorial libraries of porphyrins have been in the arenas of supramolecular chemistry, materials discovery, and therapeutics discovery. In terms of supramolecular chemistry and materials discovery, small six-member libraries of *meso* substituted porphyrins are predominantly made with exocyclic ligands and/or H-bond groups. See Table 1 for a survey of porphyrins made from condensation reactions employing two different aldehydes. The supramolecular chemistry of porphyrins has been extensively reviewed.(*5, 25-44*)

This chapter focuses on the synthesis of porphyrin libraries rather than on a collection of individually synthesized porphyrins. Over the years, many laboratories have developed a large collection of porphyrins that can be screened for a given functional or photophysical property, e.g. metalloporphyrins for electrocatalysts.(*45*) Perhaps a data base or reported porphyrins, phthalocyanines and other macrocycles can be developed to facilitate discovery of new materials, therapeutics, and photonics by correlating known structure property relationships.

1.1.3 Porphyrin Synthesis

There are numerous strategies to make porphyrins that range from simple one pot, one step reactions, to complex multistep procedures. The choice of procedure depends on a variety of factors, including (1) overall yield, (2) ease of synthesis and purification, (3) availability of reagents, (4) product distributions, (6) overall scale of the reaction, (7) costs, (8) organic chemistry skills. Yields based on the commercially available starting materials of elegant, directed synthetic procedures are oftentimes similar to the less elegant approaches wherein several possible products need to be separated to obtain the desired compounds. Since most of the combinatorial chemistry of porphyrins is base on the meso substituted derivatives, we will focus on the synthesis of these compounds. Further discussion is provided below.

1.2 Solution Phase Combinatorial Libraries of Porphyrins

Solution phase combinatorial libraries of porphyrins can be made by either formation of the macrocycle using a mixture of reagents, e.g. aldehydes and/or pyrroles, or by using high yield reactions to modify the pre-made macrocycle.

1.2.1 Mixed Reactant Approaches

The strategy of forming solution phase combinatorial libraries that build the core platform requires high-yielding reactions or the unwanted byproducts need to be separated from the library. Since the porphyrin forming reaction does not go in high yields by any method reported to date, the library must be separated from the unwanted polymeric side products. This can be achieved using several chromatographic steps when the members of the library have similar polarities, but risks losing some of the compounds. Thus, the chemical diversity of porphyrin libraries formed in this way must be assured.

Characterization of solution phase libraries is essential to assure that the expected diversity is present otherwise the selection of winning compounds may yield skewed results. The ^{1}H NMR can be used to look for the presence of different functional groups, and in some cases correlations can be made between line widths, e.g. of isolated methyl peaks, and library size.(*46*) With porphyrins, the UV-visible spectra of libraries are also broadened relative to the spectrum of a single compound. Both MALDI(*47*) and ESI(*48*) mass spectrometry techniques are useful to characterize combinatorial libraries, provided that the molecular weights of the individual compounds are non-identical (not isobaric), as they produce essentially fragmentation-free spectra with a pseudo molecular ion peak for every component. MALDI is good at providing a fingerprint of the mass profile of the library because most of the members ionize similarly. Thus MALDI gives an indication of the diversity of the library by comparison to a calculated mass

profile and can be done with or without a supporting matrix.(*47*) Since these are core-centered libraries (C_4 symmetry for *meso* aryl porphyrin cores, not including the pyrrole N-H), the peaks in the mass spectra will generally be centered around an average mass/charge, such that many of the individual members of large libraries will not be discernable. Because of differences in ionization by ESI, the mass profile of the libraries may not correspond well to the calculated profiles when injected directly into the MS. Nonetheless, HPLC can fractionate the library into various overlapping mixtures that feed into the ESI-MS thereby enabling identification of (nearly) every member of the solution phase library.(*48*)

Libraries of six compounds/isomers resulting from mixing two different symmetric pyrroles, R_a=$R_{a'}$ and R_b=$R_{b'}$ range from porphyrins with only one type of pyrrole R_a to those with only the other R_b. When two pyrroles are combined where $R_a \neq R_{a'}$ and $R_b \neq R_{b'}$ the number of isomers increases rapidly to 43. (B) Libraries of six compounds/isomers result from mixing two different aldehydes, but when there are 10 aldehydes there are 1540 members of the library. Increasing the number of pyrroles or aldehydes increases the combinations available in the libraries, but are governed by the C_4 symmetry of the macrocycle. Porphyrins bearing two or more substituents with significant rotational barriers, such as ortho substituted aromatics, also have atropisomers, e.g. for *meso* tera ortho-subtituted aryl derivatives αααα, ααβ, ααββ, αβαβ. Since atropisomers can have significantly different polarities, these can add to the chemical diversity of the libraries.

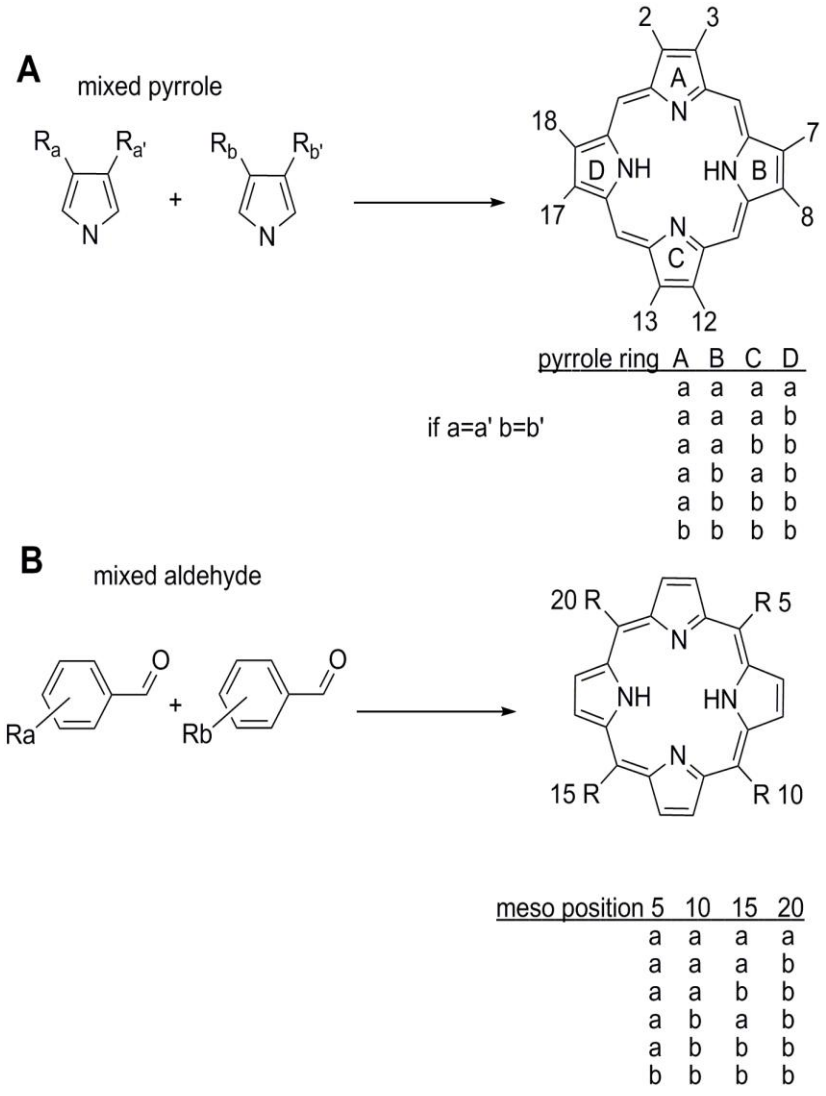

Figure 1.1 (A) Libraries of six compounds/isomers resulting from mixing two different symmetric pyrroles, $R_a=R_{a'}$ and $R_b=R_{b'}$. When $R_a \neq R_{a'}$ and $R_b \neq R_{b'}$ the number of isomers is 43. (B) Libraries of six compounds/isomers result from mixing two different aldehydes.

1.2.1.1 Mixed pyrroles: from natural products to drug discovery

Early studies of why specific isomers of naturally occurring porphyrins are found in nature,(*49, 50*) concluded that without enzymatic constraints and reactivities being equal, entropy plays an important role in skewing the expected statistical distributions.(*2, 51-54*) There is some confusion in the literature between the possible isomers found in nature versus those statistically possible. Secondly, the statistics are quite different if one considers the combination of four pyrroles with given substituents or each of the eight pyrrole β positions independently. The reaction of two different, symmetrically substituted pyrroles (both β positions have the same substituent) results in six compounds (Figure1.1). There are four possible isomers of uroporphyrin when considering one type of non-symmetrical pyrrole is used (each with acetic and propionic groups) as proposed by Fischer and summarized by Moss,(*55, 56*) versus the 13 theoretically possible compounds when four copies of two different substituents are found on the eight β pyrrole positions.(*6, 57*) The 13 possible compounds when there are 4-A-type and 4-B-type substituents is itself a limiting case. All possible combinations of A and B substituents in the eight positions – from all A to all B – results in 43 possibilities (see Tapscott and Marcovich for a complete list of possible pyrrole substitution patterns,(*6*) Table 1). There are 5040 isomers when there are eight different substituents on the pyrroles.(*6*) Given the present state of the art in porphyrin synthesis, mixing four different pyrroles, each with two different β substituents, can be done; but this would result in a staggering number of possible products because each of the 55 combinations of pyrroles would have positional isomers for the β positions.

Beyond examination of the natural systems, there is little in terms of using a mixed pyrrole strategy for material or drug discovery. One advantage of pyrrole based combinatorial libraries is that the substitutents are attached directly to the macrocycle so that they can have a strong influence on the photophysical properties. The photophysical properties can be tuned by the number, position, and electronic properties of the exocyclic groups that dictate HOMO – LUMO gaps, symmetry, polarity, and polarizability.(*58*) Small nonaromatic substituents minimizes steric encumbrance, thereby allowing molecules such as octaethylporphyrin to lay flat on surfaces and to maximize π-π interactions in solid state materials for photonics applications.(*59-68*) Despite the potential to discover interesting materials, there are no reports on the construction of combinatorial libraries using a mixed pyrrole approach beyond probes into the natural systems; perhaps because of the of the isomer problem arising from the substitution patterns on the pyrrole β position and the fact that number of isobaric isomers is so large even for simple A_4B_4 systems. There are small libraries available that are based on the natural products.

Table 1.1 Possible combinations of A and B pyrrole substituents on porphyrins coming from reactions with three pyrroles: AA, BB, and AB. (Adapted from reference (1).)

Pyrrole substituent A+B=8	# isomers
A_8	1
A_7B	1
A_6B_2	6
A_5B_3	7
A_4B_4	13
A_3B_5	7
A_2B_6	6
A_1B_7	1
B_8	1
total	43

1.2.1.2 Two Mixed Aldehydes

There are several methods to make meso-substituted porphyrins, and all of them have the potential to be used in combinatorial chemistry.

a. Adler-type reactions

The various modifications of the Adler synthesis(*69*) have yielded a staggering variety of *meso*-aryl, aromatic, and alkyl-substituted porphyrins.(*3, 54, 70, 71*) Some of the common variations in the Adler synthesis include lower concentrations, addition of metal ion templates, rate of addition of the two reagents, addition of nitrobenzene or other oxidants, and use of cosolvents with the acetic acid or propionic acid. Many simple *meso*-aryl porphyrins can be made in solventless reactions by mixing the reagents in a closed vial and heating to ca. 180^{o}C,(*72*) and this reaction is now used in an undergraduate laboratory as an example of green chemistry.(*73*) Because the oxidations in Adler-type reactions occur at various stages of macrocycle formation, the intermediates and products are kinetically trapped during the course of the reaction, and any equilibria along the way are fleeting.(*54*) Symmetric (wherein all *meso* substituents are the same) tetra- meso aryl porphyrins (TAPs) are readily available, easy to make, and have a plethora of applications. Unsymmetrical TAPs also have applications in optoelectronics, sensors, therapeutics, and materials chemistry.(*3, 74*)

With variations, this mixed aldehyde strategy based on the Adler synthesis has been exploited by numerous groups to prepare small libraries of porphyrins when two or more of the six compounds are needed.(*26, 28, 75-80*) The relative yields of the six compounds depend on a variety of factors including the stoichiometry of the reagents, the relative reactivity of the aldehydes, and the solubility of the intermediates under the reaction conditions. The mixed aldehyde approach results in lower yields of the individual compounds compared to those using

one aldehyde and requires additional chromatography to separate the six compounds, nonetheless the overall yields can be comparable to directed synthesis of each compound separately.(*53, 54, 81, 82*) Lower concentrations and template reactions are often used to mitigate the diminished solubility of intermediates derived from polar aldehydes such as pyridyls and uracyls.(*83, 84*)

Five of the six compounds formed in a mixed aldehyde synthesis using pyridine-4-carboxaldehyde and an aryl aldehyde, often with an alkane to increase solubility, can be used to organize the porphyrins into a variety of structures. Both coordination polymers and designed supramolecular systems are formed from stoichiometric reactions with porphyrin tectons bearing 4-pyridyl and 4-tert-butylphenyl moieties in specified geometries and topologically complementary metal ions.

In addition to coordination chemistry, formation of multiple hydrogen bonds between complementary molecular components is widely used in the fabrication of supramolecular assemblies because of their strength, directionality, specificity, and reversibility. The mode of assembly modulates the materials properties in chromophoric systems because electron and energy transfer are exquisitely sensitive to the intervening structure and dynamics. For example, porphyrin squares formed by metal ion coordination(*85*) have substantially different photophysical properties than porphyrin squares formed via hydrogen bonding.(*83, 84, 86*) While there are an ever increasing number of discrete arrays mediated by metal ion coordination, there are fewer discrete arrays mediated by hydrogen bonding. Nonetheless, porphyrin systems with rigidly attached *meso* H-bond motifs can be used to form linear, square, and junction structures in a predefined geometry, and each subunit with a specific metalation state-the caveat being that the yield of the desired system varies substantially because of the equilibria with other structures.

A large variety of aldehydes can be used in mixed condensation porphyrin-forming reactions. Reactions with aldehyde a : aldehyde b : pyrrole in 2:2:4 ratios favor formation of the a,a,b,b and a,b,a,b substituted products, but adjusting the stoichiometry can significantly increase the yield the products with one a,b,b,b (1:3:4) or three a,a,a,b (3:1:4) of a given substituent (see Figure 1.1). Adjustments in concentration and small excesses of less reactive aldehydes further improve the yields of target compounds. An example of using Lindsey's approach to mixed aldehyde synthesis of porphyrins(*87*) used a 1:3.2:4 mixture of 4-nitrobenzaldehyde:benzaldehyde:pyrrole where the desired 5-(4'-nitrophenyl)-10,15,20-triphenylporphyrin was the major product.(*88*) The nitro group was then reduced and the porphyrin metallated with zinc to increase macrocycle stability and the nucleophilicity of the amino group. Heating this compound with 2-amino-4,6-dichloro-1,3,5-triazine in dioxane yields a triaminotriazine appended with two porphyrins. Three of the bisporphyrin triaminotriazines self-assembles into a circular rosette upon addition of three equivalents of 5,5-di(butyl)barbituric acid via complementary hydrogen bonding interactions.(*88*) At the time this supramolecular array was designed, it was thought that it would resemble the disposition of B850 chlorophylls in photosynthetic antenna complexes(*89*) wherein the slipped cofacial dimers arising from the formation of the rosette were similarly oriented. Fluorescence anisotropy and quenching studies indicated energy transfer among the porphyrins, and there is also possible electron transfer to the barbiturate components.

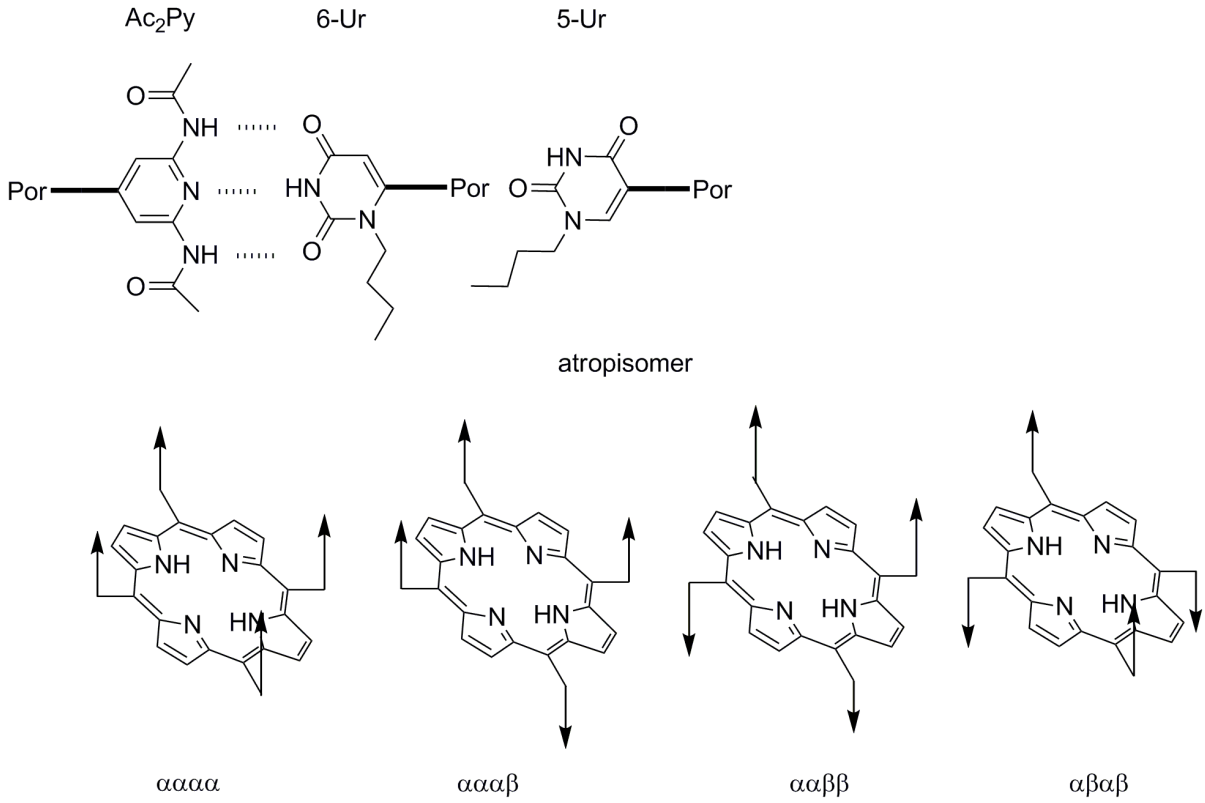

Figure 1.2. Top: H-Bond moieties rigidly appended to the porphyrin *meso*-position can afford supramolecular assemblies. Bottom: There are four possible aptropisomers when all the meso-positions bear groups that are rotationally asymmetric about the bond connecting them to the porphyrins; e.g. the uracyl (Ur) moieties. (Adapted from reference (1).)

Mixing two aryl aldehydes, one bearing H-bonding groups and the other an alkane, results in a set of building blocks to construct supramolecular arrays of porphyrins akin to the more often studied metal ion assembled systems (Figure 1.2).(*83*) Atropisomers results when more than one of the *meso* substituents has no rotational axis about the bond attaching it to the macrocycle, e.g. the uracyl (Ur) moieties, there are atropisomers. When all four *meso* positions bear rotationally asymmetric groups there are four possible atropisimers. Each atropisomer affords different geometrical possibilities for self-assembly into three-dimensional materials, and adds to the diversity of libraries containing these compounds.

The use of a mixed aldehyde synthesis for the formation of six-member libraries of porphyrins bearing H-bond groups, for example uracils and diacetamidopyridyls, has been reported.(*83, 84*) The non-aromatic, nonsymmetric uracil is attached to the *meso*-position such that there are atropisomers for the compounds bearing two or more. Thus, the symmetry depends on both the disposition of the uracils and on the relative orientation of these groups (Figure 1.2). The mixed aldehyde approach enables the porphyrin analogues to self-assemble into one-, two,- and three-dimensional arrays of porphyrins via complementary H-bonding. Topologies can be achieved that are analogous to the metal ion assembled arrays, but these supramolecular structures are generally less robust.(*26*) These constructs allow studies of electron and energy transfer across H-bond assembled systems as well as antenna effects. For example, using the zinc complexes as donor and free bases as acceptors, it was found that there is an asymmetry in the efficiency of energy transfer across the uracyl-diacetamidopyridyl motifs depending on the direction.(*76*) There are now many hundreds of papers that use the Adler-type mixed aldehyde route to derive a set of porphyrins for the formation of supramolecular structures, crystal engineering,(*28, 33, 35, 39, 44*) and for studies of the biological properties of the various compounds for therapeutics or diagnostics.(*90*).

b. Dynamic libraries based on H-Bonds

The mixed aldehyde condensation approach to the synthesis of a small cadre of porphyrins is often used to make components of supramolecular multiporphyrin arrays. Thus, porphyrins bearing hetero-complementary and self-complementary hydrogen bond motifs can be used to make squares, rosettes, tapes and other structures. The degree to which any of these constructs form is highly dependent on the conditions used because of the diverse equilibria

involved. Thus, oligomers, self-complementary, and hetero-complimentary supramolecular constructs are found to various degrees in each system (Figures 1.3-1.6). The percentage of each depends on the formation conditions, and what is observed depends on how the system is probed. For example, NMR can detect everything in solution but will miss precipitates, and crystals for X-ray analysis may represent a minority product. These equilibria and populations need to be considerations for metal ion coordination assemblies as well.

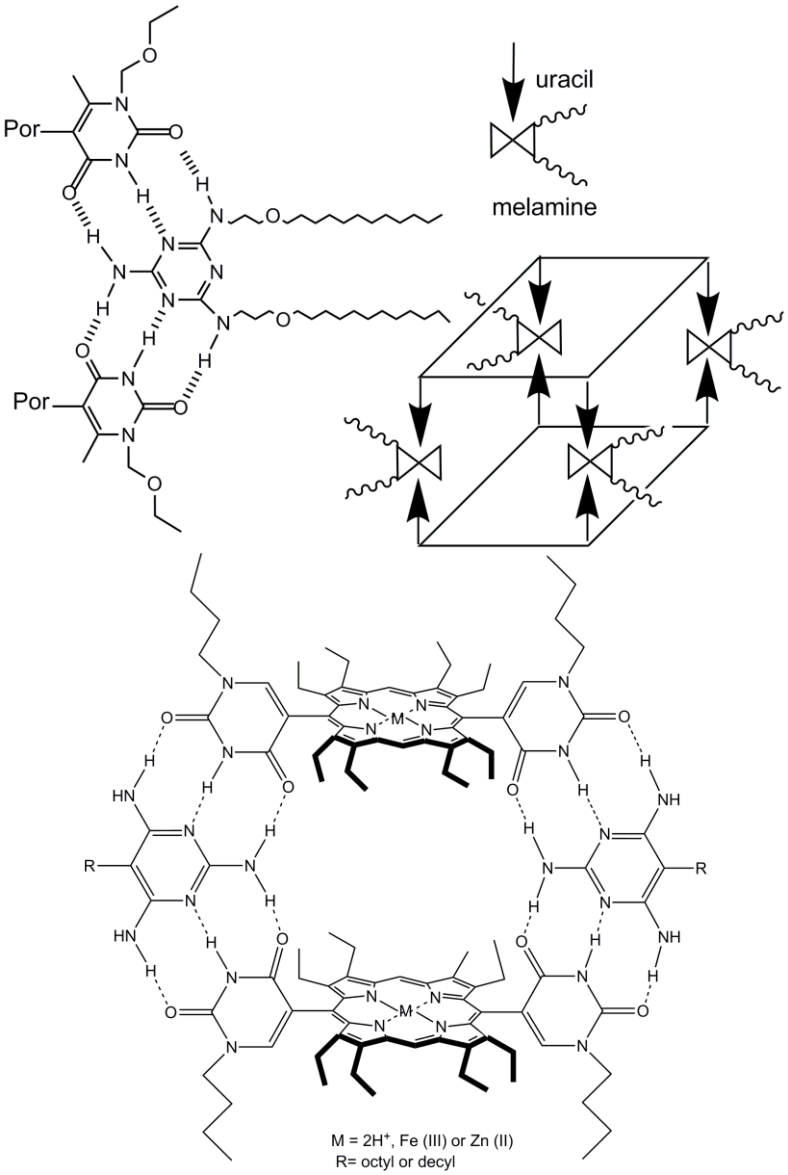

Figure 1.3 Top: *Meso* tetrauracylporphyrin can be used to form a bisporphyrin cage upon addition of the four equivalents of the complementary H-bond triaminotriazine. Bottom: the same strategy can be used with the 5,15-uracyl substituted porphyrins (Adapted from reference (*91*)).

Two equivalents of a mixture of the atropisomers of a meso-tetrauracyl porphyrin can be used to form a bisporphyrin cage upon addition of the four equivalents of the complementary H-bond triaminotriazine. The same strategy can be used with the 5,15-uracyl substituted porphyrins.(*91*) In both cases, because the mixtures of atropisomers are used, the solutions containing both component molecules are heated to more rapidly equilibrate the system; the αααα atropisomer and αα atropisomer, respectively, are obtained and the desired structure forms by stabilization of these atropisomers (Figure 1.3). Formation of discrete arrays is indicated by the increased solubility of the supramolecular constructs compared to the components, substantial shifts in the H-bond protons in the NMR, and electrospray ionization mass spectrometry.

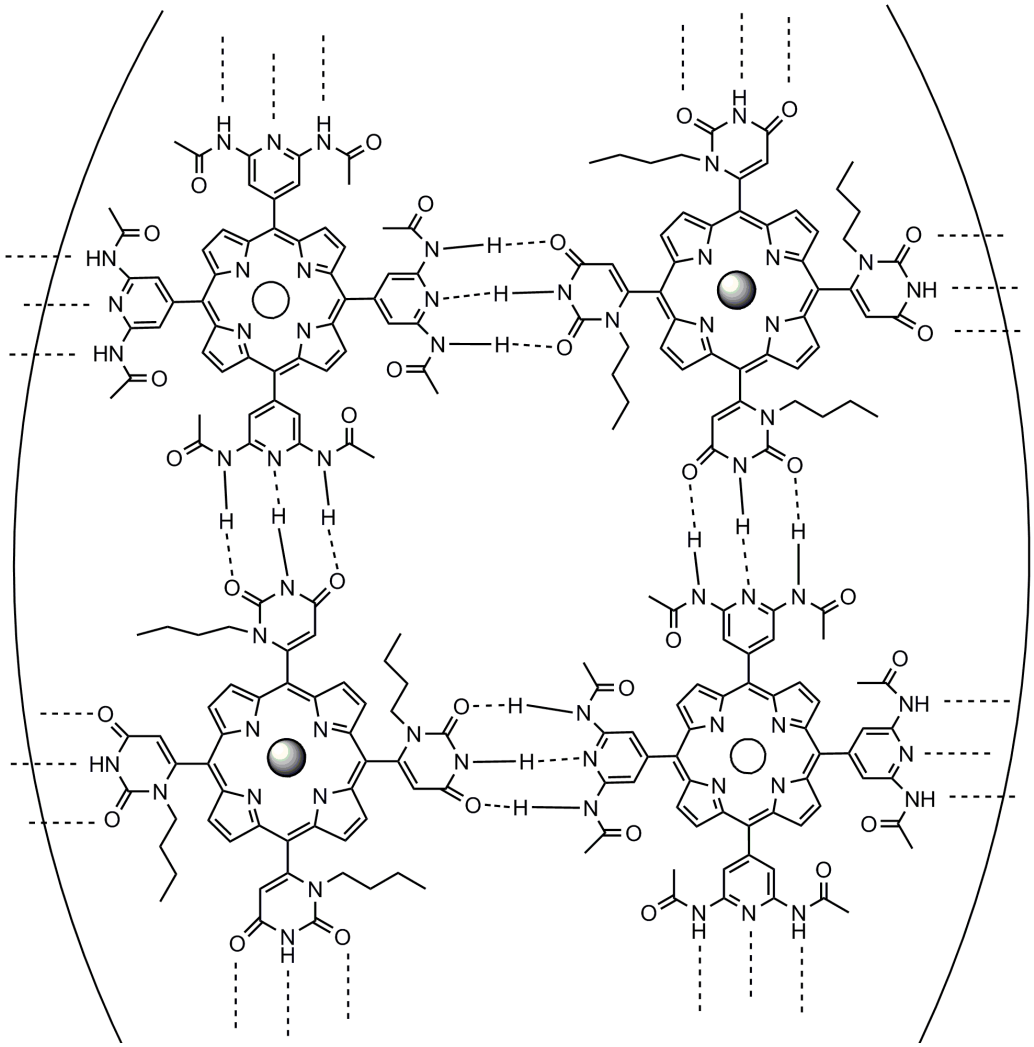

Figure 1.4. 5, 10, 15, 20-tetrakis(3, 5-diacetamido-4-pyridyl) porphyrin and 5, 10, 15, 20-tetrakis(1'-butyl-6'-uracyl) porphyrin (Zn) in different organic solvents can result in the tessellation of arrays of various sizes when cast onto glass, quartz and mica surfaces (Adapted from reference (*26*)).

The tessellation of 2-dimensional arrays mediated by complementary H-bond groups on two different porphyrins results in a checkerboard pattern wherein donor chromophores and acceptor chromophores alternate (Figure 1.4). Here, 5, 10, 15, 20-tetrakis(3, 5-diacetamido-4-pyridyl)porphyrin serves as an acceptor and 5, 10, 15, 20-tetrakis(1'-butyl-6'-uracyl) porphyrin Zn(II) serves as the donor. Arrays of various sizes can be deposited on the surfaces wherein the

surface energetics, solvent, and rate of solvent evaporation strongly influence the domain size and defect density. The orthogonal recognition groups still allow for energy transfer from the Zn(II) complex to one of the four surrounding free bases (Adapted from reference (*26*)).

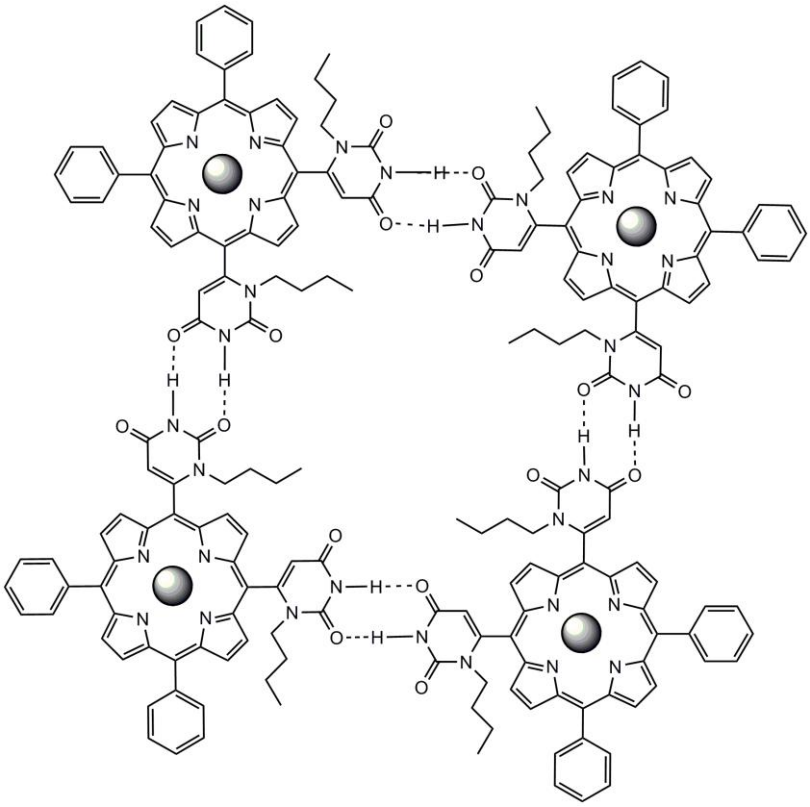

Figure 1.5. A closed tetrameric square assembles via self-complementary H-bond interactions between 5,10-bis(1'-butyl-6'-uracil)-15,20-bis(4-tert-butyl phenyl) porphyrins in THF-d_8. (Adapted from references (*83*, *84*)).

Several NMR and mass spectrometry experiments indicate that a closed tetrameric square assemblies via self-complementary H-bond interactions between 5,10-bis(1'-butyl-6'-uracil)-15,20-bis(4-tert-butyl phenyl) porphyrins in THF-d_8 (Figure 1.5). The porphyrin is synthesized by a mixed aldehyde approach using pyrrole: 1-butyl-6-formyluracil: 4-*tert*-butylbenzaldehyde in 2:1:1 ratio, respectively, in refluxing propionic acid. Supramolecular squares are formed also

in 1:1 mixtures of this compound with the complementary H-bond compound, *meso*-tetrakis(3,5-diacetamido-4-pyridyl)porphyrin. As with all self-assembled systems, the degree to which these are formed in solution depends on a variety of factors that influence H-bond equilibria.

The complex equilibriums of supramolecular constructs that are self-assembled and/or self-organized by weak H-bond interactions in solution can be considered a virtual combinatorial library of possible oligomers between the components.(*92, 93*) This property can be exploited to form adaptive systems wherein the porphyrin serves as a reporter of supramolecular structure and supramolecular dynamics. Solvent, temperature, analytes, concentration, and other factors that influence equilibriums can be probed. In the case of a two porphyrin system containing *meso*-tetra(uracyl)porphyrin and *meso*-terta(3,5-diacetamido-4-pyridyl)porphyrin, the hetero-complementary interactions compete with the self-complementary interactions (Figure 1.3-1.5).(*83, 84*)

The goal of forming 2-dimensional molecular and supramolecular systems impacts an array of technologies because this approach can be used as a method for surface modification, and functional materials formation. Nonetheless, the formation of ordered 2-dimensional materials is complicated by kinetics in terms of covalent systems, and thermodynamics for self-organized films.

c. Small Libraries for Therapeutic Discovery

Porphyrins can act as PDT (photodynamic therapy) agents for the treatment of cancer, wet macular degeneration, periodontal disease, antimicrobials, and antivirals.(*94-98*) The dyes can sensitize the formation of singlet oxygen via a transfer of energy from the triplet excited state

of the porphyrin to ground state triplet oxygen, and/or generate reactive oxygen species directly. The resulting oxidative damage causes necrosis or can induce apoptosis, weaken biofilms, or effect membrane stability. The photophysical properties of the chromophore and the specific localization of the porphyrin in the cell or tissue determine the mechanism of action of the PDT agents. Since currently approved PDT agents lack targeting motifs that specifically direct the chromophore to the target tissue or cells, appending different chemical entities to the macrocycle is an active area of research. The rational design of new chromophores by known structure-function relationships has yielded a large number of compounds with varying degrees of efficacy. Secondly, adjusting the chemical stability and photophysical properties of the porphyrin can improve efficacy. For example, increasing the absorptivity in the red region of the spectrum will facilitate treatments deeper into tissues and tumors.

Exogenous porphyrins are known to interact with variety of cell structures such as membranes, DNA, and proteins; therefore, studies to identify new combinations of functional groups that enhance porphyrin uptake into cells and binding to biomolecules is an active area of research.(*74, 90, 99-104*) The overarching hypothesis is that multiple types of substitutents will target different tissues better than the homosubstituted parent molecules. Illumination of light on cells or tissues containing the multisubstituent porphyrins will cause damage to a variety of cellular components simultaneously, thereby more effectively eliciting cell death. Since cells have an array of mechanisms to sequester therapeutic agents and to repair damaged components, this multipronged attack may provide a better strategy towards development of new therapeutics.

Though formation and separation of the six compounds results in low yields,(*69, 82*) varying the stoichiometry of the reagents can increase yields of target compounds. The mixed aldehyde approach has been used to examine the uptake and efficacy of the N-methylpyridinium

derivatives of the five pyridyl compounds in the Fleisher library in terms of DNA binding, cell uptake, photodynamic therapy (PDT) of cancer, and PDT treatment of microbial infections.(*105*) Results from the last few years have shown hydroxynitrophenyl porphyrins, 5,10,15,20-tetrakis(2-hydroxy-5-nitrophenyl)porphyrin and 5-mono(carboxy-phenyl)-10,15,20-tris(2-hydroxy-5-nitrophenyl)-porphyrin can be considered as promising photosensitizers in PDT and are being prepared by the mixtures of two aldehydes using Adler's method.(*106, 107*) Similarly, the number and disposition of sugars around the macrocycle has a profound effect on the PDT activity of these compounds.(*90*)

1.2.1.3 Equilibrium Reactions

Building on an understanding of both natural and synthetic porphyrin forming reactions, Lindsey and coworkers reported the synthesis of *meso* substituted porphyrins from pyrrole and aryl aldehydes in a reaction that initially forms the porphyrinogen in an equilibrium reaction catalyzed by Lewis acids and salts.(*54, 87, 108*) The porphyrinogen is subsequently oxidized by organic soluble reagents such as dichlorodicyanobenzoquinone to yield the porphyrin. While initially reported for the formation of symmetrically substituted porphyrins, it was quickly realized that the use of two aldehydes results in a mixture of the possible compounds but there can be differences in the relative ratios compared to the Adler synthesis. Secondly, the equilibrium method is not usually amenable to syntheses with aldehydes bearing polar Lewis bases such as the pyridyl aldehydes. Directed synthesis of porphyrins bearing different *meso* substitutents can be accomplished with MacDonald 2+2 coupling and 3+1 coupling reactions.(*54, 82, 109, 110*) Of the various incarnations of these methods, deliberate formation of solution phase combinatorial libraries has not been a specified goal.

The directed synthesis of porphyrins with a variety of substitution patterns under Lindsey-type conditions, e.g. mono-substituted, A_3, AB, A_2B, A_2BC, A_2B_2 ABCD, still often results in some amounts of the scrambled and statistical products depending on the reactants and the conditions used (Figure 1.6).(*111, 112*) However, the equilibrium methods are amenable to functional groups that are not tolerant of the conditions used in the Adler synthesis, such as the use of alkynes to form multiporphyrin arrays that have enhanced two-photon absorption cross sections relative to the meso tetraaryl porphyrins.(*113, 114*) In terms of porphyrins for solar energy harvesting, both the mixed aldehyde and equilibrium reactions have been used to make a large variety of porphyrins to examine binding geometries, chromophore properties, and organization onto surfaces such as ITO and TiO_2.(*115-120*)

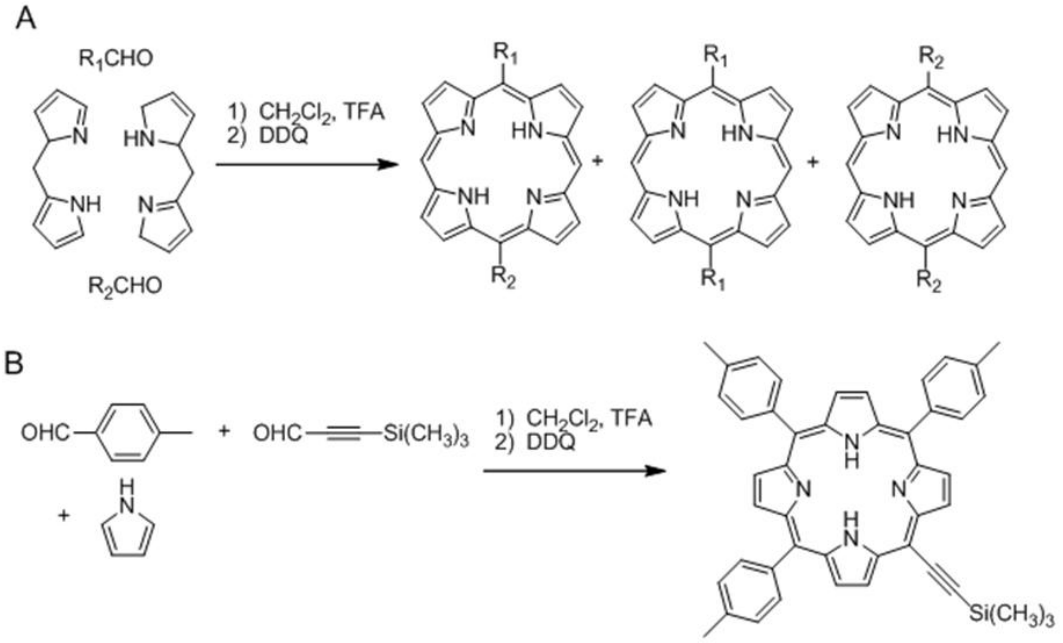

Figure 1.6. (A) Combinatorial synthesis of 5,15 AB porphyrins from mixing two different aldehydes with two equivalents of dipyrromethane, as found with other systems that rely on aldehyde condensation reactions, results in mixtures that depend both on statistical probability and on the reactivity of the reagents. (B) Similar reaction conditions allow for the formation of porphyrins that cannot be made by Adler methods (Adapted from reference (*113*)).

1.2.2 Modification of the Porphyrin Macrocycle

High-yielding reactions on commercially available porphyrins can be used to generate combinatorial libraries. Also, to eliminate the tedious purification and the potential to lose members of the family from porphyrin-forming reactions, it is desirable to add substituents to pre-formed macrocycles with readily functionalizable groups as an avenue to combinatorial porphyrin libraries.

The four *para* fluoro groups on 5,10,15,20-tetrakis-(2,3,4,5,6-pentafluorophenyl) porphyrin ($TPPF_{20}$), or other porphyrins with the pentafluorophenyl group, are known to react with a variety of nucleophiles.(*121, 122*) Thus *meso*-$TPPF_{20}$ can be used as an efficient platform to generate a variety of solution-phase combinatorial libraries as long as the nucleophilicity of the reagents is similar, 1:1 stoichiometric mixtures result in the expected distribution of compounds.(*48*) The reactivity is: thiolate > amine > alkoxide. For example, primary amines react with $TPPF_{20}$ in high yields in a microwave reaction that uses N-methylpyrrolidine; an environmentally acceptable solvent. Thus, amino poly(ethyleneglucol)s, poly(ethylenediamine)s and lysine can be substituted for the F moiety at the para position of $TPPF_{20}$.(*27*) These groups are known to impart cancer cell selectivity and permeability.(*99, 102, 104*) Similarly, thioglucose addition results in non-hydrolysable sugar coated porphyrins that exhibit good selectivity toward MDA-MB-231 breast cancer cells, good uptake, and good PDT activity.(*123, 124*)

A combinatorial approach exploiting the reactivity of $TPPF_{20}$ allows the mild, room temperature reaction of a variety of thiols to produces a set of combinatorial libraries (Figure 1.7).(*48*) A cell-based selection assay was developed whereby a solution of combinatorial library was incubated with the MDA-MB-231 breast cancer cells for 24 hours. After rinsing the unbound materials from the cell culture, the cells were lysed, centrifuged, and the members of

the porphyrin library that were taken up identified by MALDI-MS and ESI-MS. Though this method may miss molecules that have been conjugated to cellular components, no fluorescence was detected in the cell detritus. These studies suggested that two sugars and two pyridinium moieties were take up by these cells to the greatest extent. However, PDT assays indicate that these compounds are not as active as the tetraglycosylated derivative studied previously(*123*) likely because they partition into the cells differently. For example, the tetraglycosylated porphyrin tends to localize in the endoplasmic reticulum and cause necrosis or apoptosis.(*124*) Because of the stronger red absorption band, glycosylated chlorins are emerging as synthetic targets for PDT.(*125*)

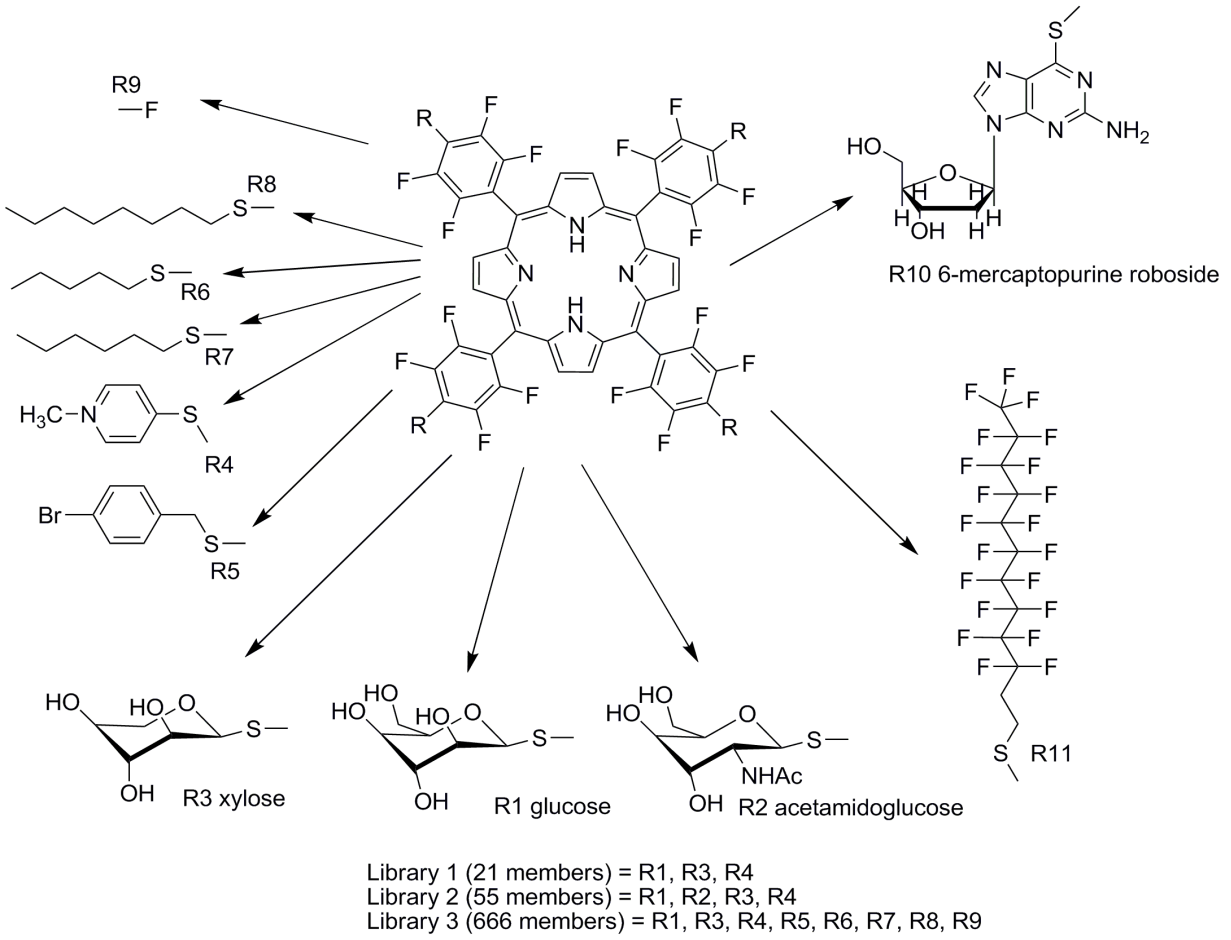

Figure 1.7. A series of combinatorial libraries base on the $TPPF_{20}$ platform can be formed. Cell-based selection assays on Library 1 and Library 2 found that two sugar groups and two pyridinium groups were taken up to the greatest extent into MDA-MB-231 breast cancer cells, but these were not the most active compounds because they localize in different parts of the cell than the most active tetraglycosylated derivative. (Adapted from reference (*48*).)

1.3 Combinatorial Libraries of Other Porphyrinoids

Because of their different metal ion binding chemistry, their different photonic properties, and their photophysical properties, the other porphyrinoids have been widely studied for diverse applications. Using the aforementioned chemistries and other strategies, other porphyrinoids such as the corroles, porphyrazines, and phthalocyanines, as well as those with other atoms replacing the pyrrole nitrogen, can serve as core platforms for the formation of combinatorial

libraries. Both expanded porphyrins(*126*) and contracted phthalocyanines, i.e. subphthalocyanines, are prime candidates as core platforms. Similarly, libraries of chlorins, bacteriochlorins, and isobacteriochlorins are possible. The statistical distribution of products in a give library depends on the symmetry of the core and/or the relative reactivity of different positions in these systems. As with any library developed around a core chemical entity, the presence of numerous isobaric isomers can significantly complicate the characterization of the library and identification of the selected compounds. Nonetheless, this strategy may be employed for both biological and materials applications. Below are a couple of examples where libraries are the targets of the synthetic strategies.

Phthalocyanines

For just over 100 years phthalocyanines have found uses as dyes, and later as functional materials, and photonics.(*3, 127, 128*) Metallated phthalocyanines have properties that combine the chromophore with the metal ion, e.g. the diamagnetic Zn(II), Al(III), Ga(III) complexes have good triplet quantum yields in the excited state with long lifetimes;(*129*) therefore, are efficient photosensitisers for the formation of singlet oxygen.(*130*) Phtahlocyanines can be more efficient in generating reactive oxygen species than porphyrins, and generally have better light absorbing properties for therapeutic applications because of the strong electronic bands greater than 600 nm.(*131*) In general, *vide infra*, the activity of phototherapeutics also depends on the uptake by cells and tissues, as well as where they are localized. Uptake and distribution are a function of degree of hydrophobicity, specific targeting motifs appended to the dye, and degree of aggregation. Water solubility of phthalocyanines can be achieved by ionic substitutents present on the macrocycle such as sulfonic groups,(*132*) quaternarized amino(*133*) or pyridyl

groups,(*134, 135*) whereas water soluble neutral Pc can be made by appending polyethylene glycol(*136*) or hydroxyl groups.(*137*) Carbohydrate substituted Pcs are of great interest since these groups increase water solubility due to the presence of multiple hydroxyl groups and the propensity of cancer cells to express large numbers of glucose receptors. However, to date only a few of the carbohydrate substituted Pcs have been reported.(*129, 138-140*)

The synthesis of carbohydrate-appended phthalocyanines is generally achieved by cyclotetramerization of the corresponding phthalonitriles, which can be prepared by Ziegler-Hannack's glycosylation procedure using 4- or 3-nitrophthalonitrile, 4-hydroxyphthalonitrile and the selected carbohydrate.(*129*) Similar derivative have also been made by other groups.(*141*) The zinc(II) phthalocyanines are formed in 42–54% yields. Some of different types of glycosylated phthalocyanines which can be prepared by this method are shown in Figure 1.8.

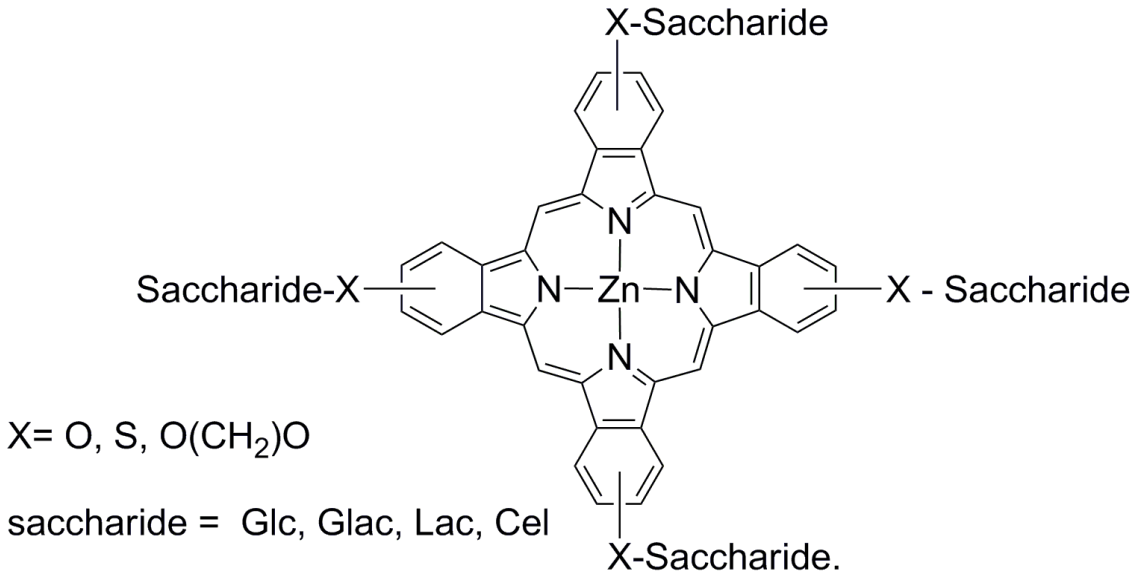

Figure 1.8. Some glcosylated phthalocanines. (Adapted from reference (*129*).)

Phthalocyanine derivatives with one substituent per isoindole group have several positional isomers (Figure 1.8) that are difficult to separate, and complicate the characterization of combinatorial libraries by mass spectrometry because these are isobaric. In principle, a variety of combinatorial libraries can be built upon phthalocyanine platforms bearing clickable, or other highly reactive groups. Nonetheless, small phthalocyanine libraries may yield important information about the types and number of targeting motifs, uptake, and selectivity for a given biomedical application. Similarly, for the formation of photonic materials, the modulation of the photo-physical properties, and the directed self-organization of phthalocyanines into materials can be discovered using a targeted combinatorial approach.

The commercially available perfluorophthalocyanine derivative, PcF_{16}, can serve as a model core platform, wherein the derivatives with 16 or eight substituents can be pure compounds without isomers, and the photo-physical properties are systematically modulated by the number and type of substituent. From one perspective, the isomer "problem" that arises from the synthesis of substituted phthalocyanines may in fact be turned to an advantage. In this case a family of related compounds, each with somewhat different chemical and photophysical properties, may be used for applications in photonics such as solar energy conversion. For example, the photonic properties of perfluorophthalocyanine systematically changes as the fluoro groups are replaced with thioalkanes.(*142*) This is made possible by the fact that substituents on the phthalocyanine core are linked to the pi systems and exert strong effects on the HOMO-LUMO energy gap.

1.4 Conclusions and Outlook

The combinatorial chemistry of porphyrins is a burgeoning and fertile area of research that has the potential to identify new structural motifs for a diverse array of applications – from biological to materials. The focus to date has largely been on clinical and diagnostic applications, thus the development of libraries with a diversity of exocyclic organic motifs that render the system biocompatible or serve as biomolecular recognition or targeting functions. Most, libraries developed to date have the diverse organic groups appended to the *meso* positions, especially on aryl groups derived from using different aldehydes. This strategy is well developed and convenient, yet yields libraries with specific steric properties around the porphyrin. An alternative is to use a variety of pyrroles and with unsubstituted meso positions to yield porphyrins that are better suited to tessellation on surfaces, intercalate into DNA, or π-stack. One could envision combinatorial libraries with the same porphyrin but an array of metal ions. Small libraries of compounds wherein the porphyrin core is modified, thus having significantly different photophysical properties, can be made; for example, perfluorophenylcorroles.(*48*) Core chlorin, isobacteriochlorin, and bacteriochlorin platforms with reactive exocyclic groups can be used, but nonsymmetric or non-coplanar moieties that stabilize the reduced pyrrole(s)(*96, 143*) can result in sets of diasteromers on the pyrrolic positions when appended with chiral groups at other positions of the macrocycle.

As with all combinatorial approaches, the key is to develop an assay that effectively selects compounds from the library with desired functions or properties. Selection assays can be, for example, to DNA, lipid vesicles, proteins (and *vice versa*) or other properties. HPLC of solution phase libraries, which separates large numbers of compounds into smaller fractions, can be coupled to a variety of functional assays such as fluorescence, UV-visible absorbance, and

affinity to a molecule on a secondary support. Cultured cells can be used as a means to select porphyrins from solution phase libraries that bind and/or are taken up by a particular cell types.(*48*) Small, targeted libraries can be designed to answer specific questions or address specific hypotheses. Chromatographic separation of the members of small libraries is a viable alternative and has significant advantages over making the compounds one at a time. Thus, the combinatorial chemistry will continue to provide insights into the design and applications of ever more sophisticated porphyrinoid systems.

1.5 References

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CHAPTER 2

SYNTHESIS AND PHOTOPHYSICAL PROPERTIES OF THIOGLYCOSYLATED-CHLORINS, ISOBACTERIOCHLORINS AND BACTERIOCHLORINS FOR BIOIMAGING AND DIAGNOSTICS[1]

Abstract

The facile synthesis of three non-hydrolysable thioglycosylated porphyrinoids is reported. Starting from meso perfluorophenylporphyrin ($TPPF_{20}$), the non-hydrolysable thioglycosylated porphyrin ($PGlc_4$), chlorin ($CGlc_4$), isobacteriochlorin ($IGlc_4$), and bacteriochlorin ($BGlc_4$) can be made in 2-3 steps. The ability to append a wide range of targeting agents onto the perfluorophenyl moieties, the chemical stability, and the ability to fine-tune the photophysical properties of the chromophores make this a suitable platform for development of biochemical tags, diagnostics, or as photodynamic therapeutic agents. With reduction of one or two pyrrole double bonds, there is a red shift in the lowest energy absorption band and a significant increase in intensity. The fluorescence of these porphyrinoids is in the order $PGlc_4$ = $BGlc_4$ < $CGlc_4$<$IGlc_4$ and there is a corresponding decrease in the amount of triplet formed. Fluorescence micrographs of cells after treatment with these four porphyrinoids indicate they are taken up. The $CGlc_4$ and $IGlc_4$ may be dual function agents that can detect and treat cancer by photodynamic therapy (PDT)

[1] Adapted from reference 1. Singh, S., Aggarwal, A., Thompson, S., Tomé, J. P. C., Zhu, X., Samaroo, D., Vinodu, M., Gao, R., and Drain, C. M. (2010) Synthesis and photophysical properties of thioglycosylated- chlorins, isobacteriochlorins and bacteriochlorins for bioimaging and diagnostics, *Bioconjugate Chem. 21*, 2136-2146.

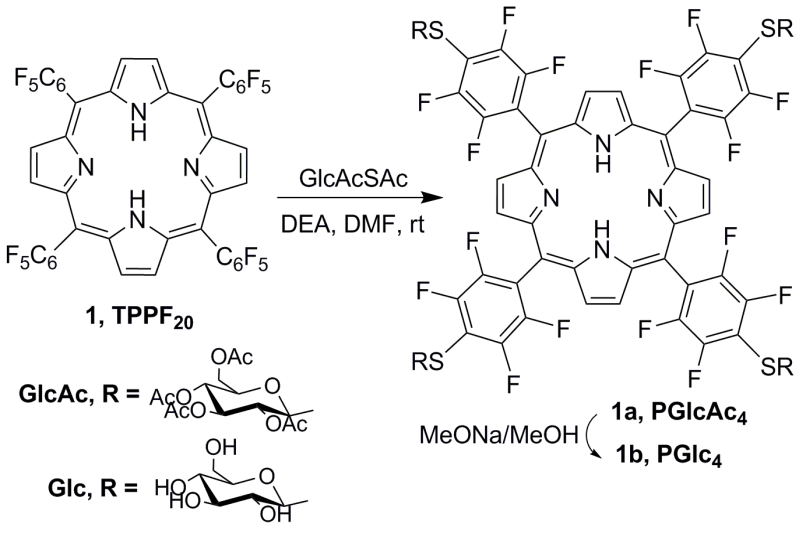
2.1 Introduction

Chlorins are porphyrinoids with one pyrrole double bond missing. Isobacteriochlorins and bacteriochlorins are porphyrinoids with two pyrrole double bonds missing on adjacent or opposite pyrroles, respectively. Oxidative or reductive transformations of porphyrins can yield these chromophores. Porphyrins, chlorins, bacteriochlorins, and isobacteriochlorins each have unique photophysical properties and are being studied for several applications.(*2, 3*) The intensity of the lowest energy UV-visible absorption band near 650 nm is about 20 fold greater for the present chlorins, and about 5-fold greater for the isobacteriochlorins compared to the parent tetraphenylporphyrin derivative,. For bacteriochlorins there is additional high intensity absorption band appears near 730 nm. The focus of this chapter is on the synthesis of the glycosylated compounds, and the photophysical properties of these macrocycles(*4, 5*) will be described in detail elsewhere.

For diagnostic and photodynamic therapeutic (PDT) applications, the increased intensity of the low energy absorption bands allows more efficient use of wavelengths of light that penetrate further into tissues.(*6-9*) An example of a chlorin PDT photosensitizer is meso-tetrakis(3'-hydroxyphenyl)chlorin (m-THPC) and its derivatives.(*10*) Other water soluble chlorins are reported.(*11-13*) For therapeutic uses of PDT agents, high triplet quantum yields are desirable to photosensitize the formation of singlet oxygen and other reactive oxygen species, which then cause damage to diverse cellular components. For diagnostics the dyes appended with appropriate targeting motifs need to have greater fluorescence quantum yields for use as fluorescent tags or trackers.(*14*) Fluorescent dyes with targeting motifs can be used in fluorescence guided surgery.(*15*)

Porphyrins, chlorins, isobacteriochlorins, bacteriochlorins, and phthalocyanines with 1-8 appended sugar moieties can have cytotoxic activity because the sugars can direct the chromophore to some cancer cells.(*16-28*) However, most reported compounds have O-glyco linkages where hydrolysis may diminish in vivo effectiveness compared to corresponding non-hydrolysable derivatives. The number, type, and position of the sugar moieties have long been known to effect cell uptake and photochemical properties.(*17, 22, 29*) The synthesis of a polyglycerol dendrimer with a porphyrin core is reported (*30*), click reactions have been use to glycosylate chlorin e_6 (*31*), and polysaccharides have been appended to porphyrins.(*32*)

The non-hydrolysable tetra-thioglycosylated tetraarylporphyrin $PGlc_4$, (Scheme 2.1 **1b**) is selective and effective PDT agent in vitro using MDA-MB-231 human breast cancer cells, whereas the galactose derivative is much less effective.(*33*) Also the $PGlc_4$ was taken up by transformed $3Y1^{vSrc}$ cells but not taken up by normal fibroblast cells.(*33, 34*) Our initial report on the formation of the tetra-thioglycosylated chlorin $CGlc_4$ outline our overall strategy (Scheme 2.1).(*35*)



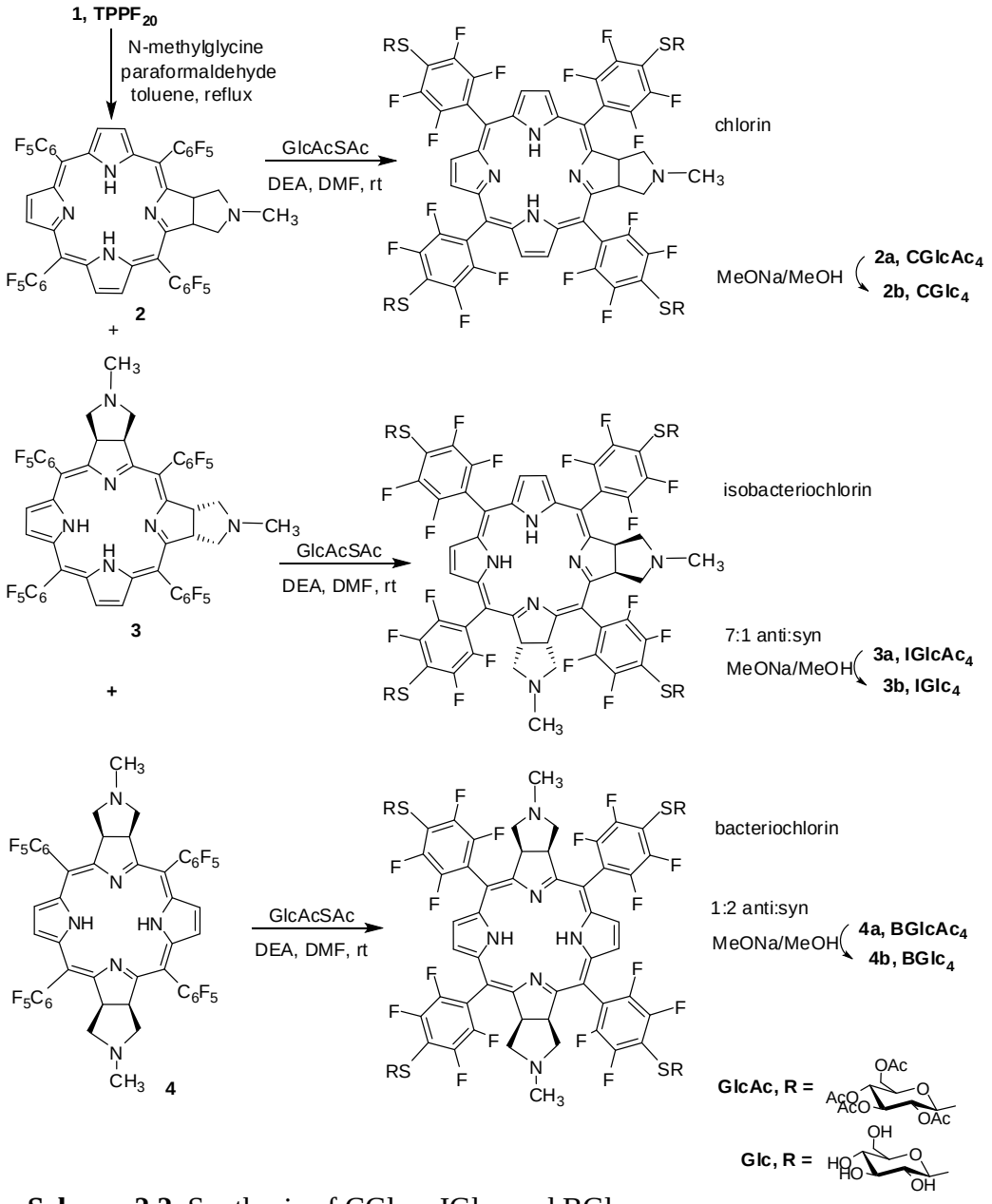
Scheme 2.1. Synthesis of $PGlc_4$ from tetra(pentafluorophenyl)porphyrin ($TPPF_{20}$)

One advantage of using the perfluorophenylporphyrin ($TPPF_{20}$) is that it can serve as a core platform for a host of materials (*36, 37*) and biochemical applications because the para fluoro group can be routinely substituted with a variety of nucleophiles to form bioconjugates, biocompatible compounds, and combinatorial libraries.(*34, 38-42*) For example, we have appended ethyleneglycols, polyamines, lysines, alkanes, fluorous alkanes, sugars and nucleotides using both primary amines and thiols. Subsequently, glycols with an oxygen linkage were also reported.(*43*) The PDT activity of many of these derivatives has been studied with a variety of cell lines, and the glycosylated compounds effect apoptosis in several cases.(*23, 43-45*) Also, the 16 fluoro groups make this compound amenable for in vivo ^{19}F NMR studies of localization.(*46*)

Given the diversity of the targeting moieties on the core platform, it is desirable to be able to tune the photophysical properties of the chromophore for these assorted applications, and an obvious means to accomplish this is to adjust the number of double bonds in the macrocycle and by metal ion chelation as is done in nature.(*47*) There are many strategies to make porphyrins lacking one or two double bonds using oxidative and reductive strategies.(*6, 48*) The formation of the perfluorophenylchlorin (CF_{20}), perfluorophenylisobacteriochlorin (IF_{20}), and perfluorophenylbacteriochlorin (BF_{20}) by 1,3-dipolar additions was reported by the Cavaleiro group.(*49-53*) This synthetic method doesn't use toxic reagents and the products are stable chemically and to photobleaching. Vicente and coworkers exploited the thio coupling chemistry on CF_{20} to append carboranyl groups (*54*) and Hirohara has appended sugars to free base and Pt derivatives (*55, 56*) for potential therapeutic applications.

The synthesis of the glycosylated chlorin **2b** ($CGlc_4$), isobacteriochlorin **3b** ($IGlc_4$) and bacteriochlorin **4b** ($BGlc_4$) analogues (Scheme 2.2) is reported in this chapter and the

photophysical properties, and relative cell uptake summarized, but the details reported elsewhere.[2]



Scheme 2.2. Synthesis of $CGlc_4$, $IGlc_4$ and $BGlc_4$

[2] The photophyiscal properties of these compounds were evaluated by Amit Aggarwal.

2.2 Experimental Procedure

Materials and methods:

General

^{1}H and ^{13}C NMR spectra were recorded in a Brüker Avance 500 MHz spectrometer and the ^{19}F spectra in a JEOL 400 MHz spectrometer. Electrospray ionization mass spectrometric analyses were performed at the CUNY Mass Spectrometry Facility at Hunter College using an Aligent Technologies HP-1100 LC/MSD instrument. The Electrospray ionization was run in methanol, with 0.1% formic acid. UV-visible spectra were recorded on a Varian Bio3 spectrophotometer. All reagents were obtained from commercial sources and used without further purification. $TPPF_{20}$ porphyrin was obtained from Frontier Scientific. Dulbecco's Modified Eagle Medium (DMEM), trypsin-EDTA and antimycotic for cell culture were obtained from GibcoBRL. Hanks' balanced salt solution was obtained from Cellgro (Mediatech). Bovine calf serum was obtained from HyClone. Phosphate buffered saline (PBS) was purchased from Invitrogen. Flash column chromatography was performed using silica gel-60, and the analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick) both from Sorbent Technologies. Adapted from reference 1.

Quantum yield of singlet oxygen production (Φ_Δ)[3]

Φ_Δ were determined on a relative basis by using *meso*-tetra(4-sulfonatophenyl)porphine dihydrochloride (TSPP) as a reference sensitizer ($\Phi_{\Delta,TSPP}$ = 0.7 in methanol) (*57*). A time-resolved Nd:YAG laser (Polaris II, Electro Scientific Industries, Inc.) equipped with low temperature cooled Ge detector (Applied Detector Corporation) was employed as an excitation

[3] Singlet oxygen production measurements were done by X. Zhu in the laboratory of Prof. R. Gao, Department of Chemistry and Biochemistry, Jackson State University.

source at 532 nm. All of the experiments were carried out in deuterium methanol-d_1. The absorbances from samples and TSPP at 532 nm were controlled between 0.1-0.5. $^1O_2$ luminescence was monitored as a function of sensitizer absorbance. Slopes were analyzed from a plot of $^1O_2$ intensity via absorbance. Φ_Δ can be calculated according to following equation.

$$\Phi_{\Delta\ \text{sample}}/\Phi_{\Delta\ \text{reference}} = \text{slope}_{\ \text{sample}} / \text{slope}_{\ \text{reference}}$$

Synthesis

Improved synthesis PGlcAc$_4$ (1a)

To a solution of $TPPF_{20}$, **1** (50 mg, 51 μmol) and 2,3,4,6-tetra-*O*-acetyl-glucosylthioacetate (90 mg, 233 μmol, 4.6 equiv) in DMF (5 mL) were added diethyl amine (1 mL). The reaction mixture was stirred at room temperature for 1.5 h. Then the product was precipitated with MeOH/H_2O and the solid filtered through a short column of Celite and washed with water. The crude mixture was recovered in dichloromethane (DCM) and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/hexanes (3:1) as eluent. The glycoporphyrin **1a** (110 mg, 92%) was obtained after crystallization in dichloromethane/hexane, as a red powder.

Synthesis of Porphyrin PGlc$_4$, (1b)

Porphyrin **1a** (50 mg, 21 μmol) was dissolved in methanol/dichloromethane (3:1, 8 mL) and treated with sodium methoxide (0.5 M solution in methanol, 1 mL). The reaction mixture was stirred at room temperature for 1.5 h and then neutralized by an aqueous citric acid solution. The mixture is filtered through a Waters Sep-Pak C_{18} 35cc reverse phase prep column and washed with water. The deprotected glycoporphyrin **1b** was then purified on flash chromatography (silica gel) eluted using a mixture of ethyl acetate/methanol (3:1) and

crystallized in methanol/DCM (33.5 mg, 96%). Mp > 250 ºC. ^{19}F NMR (DMSO-d_6): δ -133.82 to -132.57 (m, 8F, Ar-*m*-F), -139.75 to -139.50 (m, 8F, Ar-*o*-F). ^{1}H NMR (DMSO-d_6): δ 9.33 (bs, 8H, pyrrolic β-H), 5.78 (bs, 4H, Glc-H), 5.10-5.29 (m, 13H, Glc-H), 4.72 (bs, 4H, Glc-H), 3.82-3.84 (m, 5H, Glc-H), 3.52-3.55 (m, 6H, Glc-H), 3.18-3.23(m, 12H, Glc-H), -3.17 (s, 2H, NH).

Synthesis of protected thioglycosylated chlorin, CGlcAc$_4$ (2a)

Chlorin **2** was prepared as previously reported method (*49, 50*). To a solution of chlorin **2** (25 mg, 24 μmol) and 2,3,4,6-tetra-*O*-acetyl-glucosylthioacetate (42 mg, 109 μmol, 4.5 equiv) in DMF (2.5 mL) was added diethyl amine (0.5 mL). The reaction mixture was stirred at room temperature for 1h. Then the reaction mixture was precipitated with MeOH/H_2O and the solid was filtered through a short column of Celite and washed with water. The crude mixture was recovered in DCM and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/hexanes (3:2) as eluent. Chlorin **2a** (48 mg, 82%) was obtained after crystallization in DCM/hexanes, as a green powder. Because the *N*-methylpyrrolidine points to one face of the chlorin and the stereo centers on the sugars, **2a** is made as a mixture of diastereomers at the β pyrrole positions bearing the N-methyl pyrrolidine moieties. These are seen in some of the resonances in the ^{1}H NMR and especially the complexity of the phenyl region of the ^{13}C NMR, which show the coupling to ^{19}F and the diastereomers. The peaks in the ^{19}F NMR spectrum are somewhat broader than the achiral starting material. Mp > 250 ºC. ^{19}F NMR (DMSO-d_6): δ -130.09 to -129.81, -130.56 to -130.25 (2m, 4F, Ar-*m*-F), -131.69 to -131.54 (m, 4F, Ar-*m*-F), -137.10 to -136.78 (m, 2F, Ar-*o*-F), -138.98 to -138.82 (m, 6F, Ar-*o*-F). ^{1}H NMR ($CDCl_3$): δ 8.82-8.84, 8.55-8.57, 8.48-8.50 (3m, 6H, pyrrolic β-H), 5.11-5.40 (3m, 18H, 2H β-H [C (sp^3)]

and 16H, Glc-H), 4.26-4.35 (m, 8H, Glc-H), 3.88-3.91 (m, 4H, Glc-H), 2.58 and 3.16 (2t, 4H, pyrrolidine-H), 2.22 (s, 3H, NCH_3), 2.07-2.10 (m, 48H, acetyl-H), –1.74 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 20.6 and 20.7 (CH_3CO_2), 41.2 (NCH_3), 53.1 and 53.2 (C2 and C3), 61.7 and 61.9 (Glc), 63.0 (CH_2), 68.0, 68.1, 70.7, 73.9, 84.5 and 84.6 (Glc), 97.5, 106.7, 106.8, 111.6, 111.8, 122.1, 122.4, 124.0, 124.3, 128.2, 128.3, 132.5, 134.9, 135.0, 140.0, 141.1, 144-149 (C_6F_4), 152.3, 168.6, 168.8, 169.4 (CH_3CO_2), 170.2 and 170.7 (CH_3CO_2). HRMS calcd for $C_{103}H_{95}F_{16}N_5O_{36}S_4$ $(M+2H)^+$ 2409.4384, found 2409.4318.

Synthesis of thioglycosylated chlorin, CGlc$_4$ (2b)

This details what we previously reported (*35*), and later modified by Hirohara et al.(*55*) Glycochlorin **2a** (30 mg, 12.4 μmol) was dissolved in methanol/DCM (3:1, 4 mL) and treated with sodium methoxide (0.5 M solution in methanol, 1 mL). The reaction mixture was stirred at room temperature for 1 h and then neutralized by an aqueous citric acid solution. The mixture is filtered through Waters Sep-Pak C_{18} 35cc reverse phase prep column and washed with water. The deprotected glycochlorin **2b** was then eluted with methanol and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/methanol (3:2) as eluent. Chlorin **2b** (20 mg, 93%) was obtained after crystallization in methanol/DCM, as a green powder. **2b** is also a mixture of diastereomers. These are not well resolved in the ^{1}H NMR but are observed especially the complexity of the phenyl region of the ^{13}C NMR which show the coupling to ^{19}F and the diastereomers. Mp > 250 ºC. ^{19}F NMR (DMSO-d_6): δ -132.67 to -132.28 (m, 4F, Ar-*m*-F), -133.79 to -133.64 (m, 4F, Ar-*m*-F), -137.90 to -137.53 (m, 2F, Ar-*o*-F), -139.93 to -139.82 (m, 6F, Ar-*o*-F). ^{1}H NMR (DMSO-d_6): δ 9.14, 8.81 and 8.74 (3bs, 6H, pyrrolic β-H), 5.02-5.10, 5.28 and 5.75 (1m and 2bs, 18H, 2H β-H [C (sp^3)] and 16H, Glc-H), 4.55-4.68 (m, 4H, Glc-H), 4.10 (m, 2H, Glc-H), 3.73-3.78, 3.51, 3.18 and 3.04 (1m and 3bs, 26H, 4H pyrrolidine-H and

22H Glc-H), 2.05 (s, 3H, NCH_3), -1.97 (s, 2H, NH). ^{13}C NMR (DMSO-d_6): δ 41.0 (NCH_3), 49.1 and 53.1 (C2 and C3), 61.7, 61.71 and 61.9 (Glc), 62.9 (CH_2), 70.57, 70.60, 70.68, 70.78, 70.8, 75.1, 75.2, 78.51, 78.54, 78.6, 79.6, 82.2, 82.3, 84.9, 85.0 and 85.2 (Glc), 97.8, 106.8, 113.8, 113.9, 114.1, 114.2, 119.5, 119.6, 119.8, 120.0, 120.2, 126.6, 129.8, 133.5, 135.1, 140.3, 143-149 (C_6F_4), 152.4, 170.2. HRMS calcd. for $C_{71}H_{62}F_{16}N_5O_{20}S_4$ $(M+H)^+$ 1736.2615, found 1736.2603.

Synthesis of isobacteriochlorin (3) and bacteriochlorin (4)

This compound is made using modifications of the previously reported procedure (*50*) and scaled up. A toluene (20 mL) solution of 5,10,15,20-tetrakis-(pentafluorophenyl)porphyrin (100 mg, 0.1 mmol), *N*-methylglycine (30 mg, 1 mmol) and paraformaldehyde (20 mg, 0.22 mmol) was heated at reflux for ca. 12 h under a nitrogen atmosphere. Further portions of N-methylglycine (30 mg) and paraformaldehyde (20 mg) were again added and the resulting mixture was refluxed for a total of 24 h (2 x 12 h). The compounds were separated by flash chromatography (silica gel) using hexane/DCM (50:50 v/v) to elute the negligible amount of unreacted porphyrin **1**, followed by DCM to get the chlorin **2** (45 mg, 42%) and then DCM/acetone (95:5) to get the isobacteriochlorin **3** (40 mg, 34%). However, we found that a small amount (ca. 10-15%) of the bacteriochlorin consistently elutes with the isobacteriochlorin under these conditions. Thus, compounds **2, 3** and **4** were separated using a petroleum ether/ethylacetate gradient on a flash silica gel column. From 100 mg $TPPF_{20}$ (102.6 μmol) is obtained 70 mg of the chlorin compound **2** (67.89 μmol, 66 % yield), 15 mg of the anti isobacteriochlorin compound **3** (13.77 μmol, 13 % yield), and 5 mg of both the syn and anti bacteriochlorin compound **4** (4.6 μmol, 5 % yield). The diastereomeric anti form of compound **3** is preferentially formed, conversely the syn form of compound **4** is the major product (3:2

syn:anti), and the NMR, HRMS, and UV-visible spectra for **3** and **4** were consistent with previous the report.(*50*)

Synthesis of protected thioglycosylated isobacteriochlorin, IGlcAc$_4$ (3a)

To a solution of isobacteriochlorin **3** (25 mg, 23 μmol) and 2,3,4,6-tetra-*O*-acetyl-glucosylthioacetate (40 mg, 103 μmol, 4.5 equiv) in DMF (2.5 mL) was added diethyl amine (0.5 mL). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was precipitated with MeOH/H_2O and the solid filtered through a short column of Celite and washed with water. The crude mixture was recovered in DCM and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/hexanes (3:1) as eluent. Isobacteriochlorin **3a** (49 mg, 86%) was obtained after crystallization in DCM/hexanes, as a pink powder. Because the *N*-methylpyrrolidines points to opposite faces of the isobacteriochlorin and of the stereo centers on the sugars, **3a** is made as a mixture of two sets of diastereomers on the four β pyrrole positions bearing the N-methyl pyrrolidine moieties. These are seen in some of the resonances in the ^{1}H NMR and especially the complexity of the phenyl region of the ^{13}C NMR, which shows the coupling to ^{19}F and the multiplicity due to the adjacent pair of diastereomers. Mp > 250 ºC. ^{19}F NMR (DMSO-d_6): δ -128.46 to -128.35, -128.81 to -128.70 (2m, 2F, Ar-*m*-F), -130.11 to -129.88, -130.45 to -130.35, -130.91 to -130.81 and -131.62 to -131.41 (4m, 6F, Ar-*m*-F), -136.79 to -136.64, -137.35 to -137.17, -139.42 to -139.23 and -140.04 to - 139.94 (4m, 8F, Ar-*o*-F). ^{1}H NMR ($CDCl_3$): δ 7.64, 7.63, 7.22, 7.17 (4d, *j*= 5 Hz, 4H, pyrrolic β-H), 5.03-5.32 (m, 16H, Glc-H), 4.45-4.50 and 4.16-4.25 (2m, 14H, 4H β-H [C (sp^3)], 2H NH and 8H Glc-H), 3.83(d, *j*= 5 Hz, 4H, Glc-H), 2.70 and 2.88 (2t, *j*= 8.2 Hz, 4H, pyrrolidine-H), 2.06-2.31 (m, 58H, 4H pyrrolidine-H, 6H NCH_3, 48H, acetyl-H). ^{13}C NMR ($CDCl_3$): δ 20.6 ($\underline{C}H_3CO_2$), 41.0 (NCH_3), 47.8 and 51.7 (C2, C3, C7 and C8), 61.4, 61.8, 62.5

(CH_2 and Glc), 68.0, 70.2, 70.5, 73.81, 73.83, 76.3, 84.5 and 84.6 (Glc), 92.2, 98.2, 111.0, 111.1, 111.3, 113.6, 121.4, 121.5, 121.6, 128.5, 128.6, 144.4-148.7 (C_6F_4), 169.37, 169.38, 169.41, 170.16 and 170.62 ($CH_3\underline{C}O_2$). HRMS calcd. for $C_{106}H_{100}F_{16}N_6O_{36}S_4$ $(M)^{+\bullet}$ 2464.4806, found 2464.4700.

Synthesis of thioglycosylated isobacteriochlorin, IGlc$_4$ (3b)

Isobacteriochlorin **3a** (30 mg, 12.1 μmol) was dissolved in methanol/DCM (3:1, 4 mL) and treated with sodium methoxide (0.5 M solution in methanol, 1 mL). The reaction mixture was stirred at room temperature for 1 h and then neutralized by an aqueous citric acid solution. The mixture was filtered through Waters Sep-Pak C_{18} 35cc reverse phase prep column and washed with water. The deprotected chlorin **3b** was eluted with methanol and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/methanol (3:2) as eluent. Isobacteriochlorin **3b** (19 mg, 88%) was obtained after crystallization in methanol/DCM, as a pink powder. **3b** is likewise a mixture of two sets of diastereomers. These are not resolved in the ^{1}H NMR, but are observed especially in the complexity of the phenyl region of the ^{13}C NMR which shows the coupling to ^{19}F and the multiplicity due to the adjacent pair of diastereomers. Mp > 250 ºC. ^{19}F NMR (DMSO-d_6): δ -131.31 to -131.01, -132.98 to -132.25 and -133.68 to -133.43 (3m, 8F, Ar-*m*-F), -138.2 to -137.59, -140.13 to -140.04, -140.37 to -140.31 and -140.89 to -140.79 (4m, 8F, Ar-*o*-F). ^{1}H NMR (DMSO-d_6): δ 7.78 and 7.30 (2s, 4H, pyrrolic β-H), 5.67 (m, 4H, Glc-H), 5.21-5.24, 5.02-5.06 and 4.91-4.95 (3m, 12H, Glc-H), 4.40-4.44 and 4.05- 4.13 (2m, 12H, 4H β-H [C (sp^3)], 2H NH, 8H Glc-H), 3.16-3.26 (m, 20H), Glc-H), 2.70, 2.57, 2.19 and 2.18 (4bs, 8H, pyrrolidine-H), 2.01 (s, 6H, NCH_3). ^{13}C NMR (DMSO-d_6/methanol-d_4): δ 40.6 (NCH_3), 47.7, 49.06 (C2, C3, C7 and C8), 61.5, 61.6, 61.7, 62.5, 70.48, 70.52, 75.0, 75.1, 78.44, 78.46, 78.48, 84.8, 85.0 (CH_2 and Glc), 92.2, 97.8 113.2, 113.3, 113.36, 113.38, 113.61,

119.0, 119.2, 146.0-148.6 (C_6F_4). HRMS calcd. for $C_{74}H_{69}F_{16}N_6O_{20}S_4$ $(M+H)^+$ 1793.3194, found 1793.3197.

Synthesis of protected thioglycosylated bacteriochlorin, BGlcAc$_4$ (4a)

To a solution of bacteriochlorin **4** (7 mg, 6.4 μmol) and 2,3,4,6-tetra-*O*-acetyl-glucosylthioacetate (12 mg, 29 μmol, 4.5 equiv) in DMF (0.5 mL) was added diethyl amine (0.1 mL). The reaction mixture was stirred at room temperature for 4h. Then the reaction mixture was precipitated with MeOH/H_2O and the solid was filtered through a short column of Celite and washed with water. The crude mixture was recovered in DCM and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/hexanes (3:1) as eluent. Bacteriochlorin **4a** (13 mg, 86%) was obtained after crystallization in DCM/hexanes, as a green powder. Because of the stereo centers on the sugars, **4a** is made as a mixture of two sets of diastereomers. Mp > 250 ºC. ^{19}F NMR ($CDCl_3$): δ -129.05 to -128.15 (4m, 8F, Ar-*m*-F), -132.80 to -132.40 (m, 4F, Ar-*o*-F), -134.95 to -134.45 (m, 4F, Ar-*o*-F). ^{1}H NMR ($CDCl_3$): δ 8.30 (m, 4H, pyrrolic β-H), 5.12-5.23 (m, 20H, 16H Glc-H, 4H, β-H [C (sp^3)]), 4.15-4.30 (m, 8H Glc-H), 3.88 (m, 4H, Glc-H), 3.05-3.10 (m, 4H, pyrrolidine-H), 2.45-2.46 (m, 4H pyrrolidine-H), 2.06-2.31 (m, 54H, 6H NCH_3, 48H, 48H, acetyl-H), -1.75 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 20.6 (CH_3CO_2), 41.2 (NCH_3), 52.4 and 52.5 (C2, C3, C7 and C8), 61.7, 61.8 (CH_2 and Glc), 68.0, 70.6, 73.88, 76.70, 77.0, 77.3, 84.6 and 84.7 (Glc), 92.2, 99.7, 107.7, 111.4, 111.5, 115.5, 115.6, 122.6, 122.7, 136.0, 136.1, 144.4-148.7 (C_6F_4), 164.0, 169.38, 169.40, 170.19 and 170.64 (CH_3CO_2). HRMS calcd. for $C_{106}H_{100}F_{16}N_6O_{36}S_4$ $(M)^{+\bullet}$ 2464.4806, found 2464.4813.

Synthesis of thioglycosylated bacteriochlorin, $BGlc_4$ (4b)

Bacteriochlorin **4a** (10 mg, 4.0 μmol) was dissolved in methanol/DCM (3:1, 1.5 mL) and treated with sodium methoxide (0.5 M solution in methanol, 0.2 mL). The reaction mixture was stirred at room temperature for 1 h and then neutralized by an aqueous citric acid solution. The mixture is filtered through Waters Sep-Pak C_{18} 35cc reverse phase prep column and washed with water. Though **4** have a plane of symmetry, because of the chiral centers on the sugars on **4a** and **4b**, these are prepared as a set of two diastereomers. The deprotected bacteriochlorin **4b** was eluted with methanol and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/methanol (3:2) as eluent. Bacteriochlorin **4b** (6.5 mg, 88%) was obtained after crystallization in methanol/DCM, as a green powder. Mp > 250 ºC. ^{19}F NMR (MeOD): δ -134.0 to -132.5 (4m, 8F, Ar-*m*-F), -137.2 to -136.0 (m, 4F, Ar-*o*-F), -140.0 to -139.0 (m, 4F, Ar-*o*-F). ^{1}H NMR (MeOD): δ 8.42 (bs, 4H, pyrrolic β-H), 5.30-5.45 (m, 4H, Glc-H), 5.05-5.14 (m, 4H, β-H [C (sp^3)]), 3.73-3.74 and 3.63-3.65 (2m, 8H, Glc-H), 3.49-3.54 and 3.41-3.43 (2m, 16H, 8H and 8H Glc-H), 3.15-3.18 (m, 4H, pyrrolidine-H), 2.79-2.82 (m, 4H, pyrrolidine-H), 2.28 (s, 6H, NCH_3). ^{13}C NMR (MeOD): δ 39.8 (NCH_3), 51.8, 51.9 (C2, C3, C7 and C8), 61.6, 70.5, 74.57, 74.59, 78.3, 81.36, 81.37, 84.9, 85.12 (CH_2 and Glc), 99.91, 99.94 100.0, 103.9, 113.32, 113.34, 113.45, 113.50, 120.86, 121.0, 136.2, 136.3, 136.4, 146.0-148.6 (C_6F_4). HRMS calcd. for $C_{74}H_{69}F_{16}N_6O_{20}S_4$ $(M+H)^+$ 1793.3194, found 1793.3179.

UV-visible, fluorescence spectroscopy and quantum yield calculations

UV-visible and fluorescence measurements were performed on dilute solutions, typically ~2 μM, of compounds in ethanol, phosphate buffered saline and ethyl acetate. The UV-visible spectra were obtained from 330 nm to 800 nm using 1 cm quartz cuvettes. For steady state fluorescence spectroscopy, samples were excited at 509 nm for ethyl acetate, 512 nm for PBS

and ethanol where absorbencies ≤ 0.1. For emission spectra both the excitation and detection monochromators had a band pass of 1 nm. The corrected emission (for instrument response) and absorption spectra were used to calculate the quantum yield. Fluorescence quantum yields were determined for chlorin, isobacteriochlorin, and bacteriochlorin solutions relative to TPP in toluene, which has a fluorescence quantum yield of 0.11 (*58, 59*). The quantum yields were measured indirectly using TPP, thus these values may have some systematic error. All experiments were carried out on the same day, using identical concentrations to minimize any experimental errors. These three glycosylated conjugates are quite stable towards photobleaching. When ethanolic solution of $IGlc_4$ is exposed to sunlight with a power of ca 40-80 W/m^2 for ca. 2 hours we found only 10.5% of the compound decomposed.

Cell Culture

3T3 NIH cells maintained in DMEM, 10% BCS, 1% antimycotic at 37 ºC and in 5% CO_2 atmosphere were plated onto coverslips in cell culture dishes. Porphyrins, chlorins and isobacteriochlorins dissolved in methanol were added to the cultures to a final concentration of 1 or 2.5 μM such that there was never more than 0.5% methanol in the solution. After 20 h incubation, cells were washed with PBS 3 – 5 times and fixed in 4% paraformaldehyde solution for 10 min at room temperature. The cells were then washed with PBS 3 times. The cells were visualized using a Nikon Optiphot 2 fluorescence microscope. Images were captured as JPEG files at 10x magnification, with a 505 – 565 nm excitation band pass filter and a 565 – 685 nm emission band pass filter. For each set of experiments, cells were cultured and the fluorescence images were taken under identical culture and microscopic conditions.

2.3 Results and Discussion

The reduction of $TPPF_{20}$ is carried out by modifications of a reported 1,3-dipolar cycloaddition reaction of an azomethine ylide with $TPPF_{20}$, **1** to produce chlorin **2**, isobacteriochlorin **3**, and bacteriochlorin **4** (Scheme 2.2).(*49, 50, 52*) The reaction is scaled up by 5-fold, and the chlorin, bacteriochlorin and isobacteriochlorin products separated by column chromatography using a petroleum ether/ethylacetate gradient as eluent. When compound **3** is the target, the products are formed in yields of ca. 66% for **2**, 13% yield of the anti isomer of **3**, and 5% yields for the syn and anti isomers of the bacteriochlorin **4**. These yields are somewhat different from those reported, and reflect the yield of the isobacteriochlorin to the bacteriochlorin is ca. 3:1 rather than a few % of the latter.

The mechanism of these dipolar additions has been discussed.(*52*) Interestingly, chiral HPLC assays and CD spectra indicate that a trace quantity of what is likely the product of a non-concerted addition reaction in the crude reaction mixture in the synthesis of the chlorin. This may arise because of the stability of an intermediate conferred by the macrocycle (*60, 61*), but we did not pursue this. Statistically, the second dipolar addition reaction should prefer the adjacent pyrrole 2:1 over the opposite pyrrole, but IF_{20} is formed 3:1. As with previous reports, for IF_{20} the anti structure (Scheme 2.2) forms predominantly by ca. 8-fold (*49, 50*), and our preliminary dynamics calculations indicate steric crowding between the N-methylpyrrolidine methylenes and adjacent fluorophenyls results in distortion of the macrocycle and somewhat blocking the syn face. In the case of the BF_{20} the syn isomer is the major product. The dipolar addition mechanism in terms of MO calculations was discussed.(*52*)

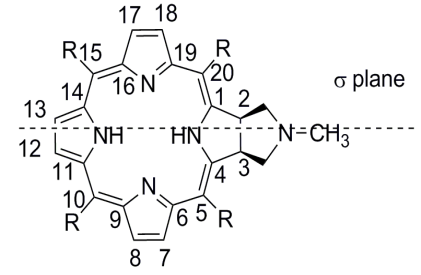
The principal goal was to obtain the four compounds in one-step and in sufficient quantity for the next reactions. NMR and mass spectrometry are consistent with the previous

report and attest to the purity of these porphyrinoid-F_{20} intermediates. The nucleophilic substitution of the thioglucose at the para position of the perfluorophenyl substituents of these porphyrinoids is a modification of that previously reported (*34*). Specifically, 4.5 equivalents of 1-thioacetate-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose, a greater quantity of diethylamine (DEA), in 1 h reactions yield $PGlcAc_4$ **1a**. Thus, **2a** ($CGlcAc_4$), **3a** ($IGlcAc_4$) and **4a** ($BGlcAc_4$), are obtained from **2**, **3**, and **4** respectively (Scheme 2.2). More than four thiosugars can be added with greater equivalents and longer reaction times. Flash chromatography yields the protected glycosylated derivatives as the mixture of diastereomers in ca. 85% yields. The carbohydrate protection groups were removed by treating **1a**, **2a**, **3a**, and **4a** with sodium methoxide in dry methanol to obtain the glycoporphyrinoids **1b**, **2b**, **3b**, and **4b** in ca. 95-98% yield (Scheme 2.2)

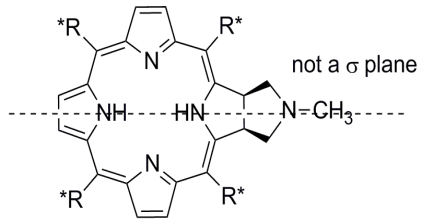
Since the N-methylpyrrolidine points toward one face of the macrocycle, addition of moieties with chiral centers such as the sugars to chlorin **2** results in diastereomers at the N-methylpyrrolidine β-carbons for **2a**, **2b**, even though **2** has a plane of symmetry. Thus **2a** and **2b** are 2R,3S diastereomers, which was not previously recognized. As pointed out in the synthesis (*52*), there is a set of enantiomers at the β-carbons for the anti conformer of **3** thus the addition of the sugars further differentiates these in **3a** and **3b**. into diastereomers 2R,3S,7S,8R and 2S,3R,7R,8S. Both the syn and anti forms of bacteriochlorin **4** have a plane of symmetry, but addition of the sugars results in a set of diastereomers, 2R,3S,12S,13R and 2S,3R,12R,13S as shown in scheme 2.3 and figure 2.1.

The structures of all porphyrinoids were confirmed by NMR, UV–visible, mass spectrometry and HRMS analysis. The ^{1}H NMR spectra of **2a**, **3a** and **4a** show the porphyrinoid core pyrrole β protons near 8.9 ppm and the pyrrole NH protons near -2 ppm. The ^{1}H NMR spectrum of all three compounds show resonance at 2.1 and 2.3 ppm, due to the acetyl protons, and the resonances of the other protons of the carbohydrate unit appear between 4 and 6 ppm. The resonances of the anomeric protons appear as doublets at 5.03 ppm to 5.40 ppm. The N-methyl groups are observed in the 2.22 ppm for **2a** and are obscured by the acetyl groups in **3a** and **4a**. While the diastereomers are observed for some resonances for the protected derivatives, they are not well resolved for **2b**, **3b,** and **4b**.

The ^{19}F NMR spectra confirm the substitution of the para-fluorine atom by the sugar unit; showing the disappearance of the resonances due to the para-fluorine atoms in **2**, **3** and **4** at -150 ppm. An important diagnostic is the signal due to the meta-fluorine atoms shifts from -160



1 (2*R*,3*S*) - meso when R is achiral



2 (2*R*,3*S*) - one optically active diastereomer when R* is chiral

Scheme 2.3. $CGlc_4$ diastereomers

ppm in **2**, **3**, and **4** to -130 ppm for **2a**, **3a** and **4a**. The ortho-fluorine atoms resonances remain near -140 ppm. The ^{19}F NMR spectra do not exhibit marked differences between **2a** and **2b**, **3a** and **3b,** or **4a** and **4b**, though these peaks are broadened due to the diastereomeric centers. The ^{13}C NMR clearly indicates the multiple resonances arising from the diastereomers, especially for the phenyl carbons, which remain coupled to the F, and are closest to the chiral centers of **2a**, **2b**, **3a**, **3b**, **4a**, and **4b**.

Since the photophysical properties of polar chromophores depend on the solvent and the temperature, a self-consistent set of data is needed. The photophysics were assayed in three different solvents: phosphate buffered saline PBS at pH = 7.4, ethanol, and ethylacetate. The partition coefficients and are in Tables 2.1. A summary of the photophysical properties are in Table 2.2. Initial association with the cell is believed to be mediated by glucose receptors binding one of the four glycosyl groups on the chromophore, and some non-specific partition into the membrane is also indicated. The size of the molecules prevent uptake by active or passive transporters, but the high local concentration around the cell increases diffusion. In this scenario, uptake depends on the relative hydrophobicity of the compounds.(*62*) The octanol/water partition coefficient and R_f for the glycoslyated compounds are listed in Table 2.1.

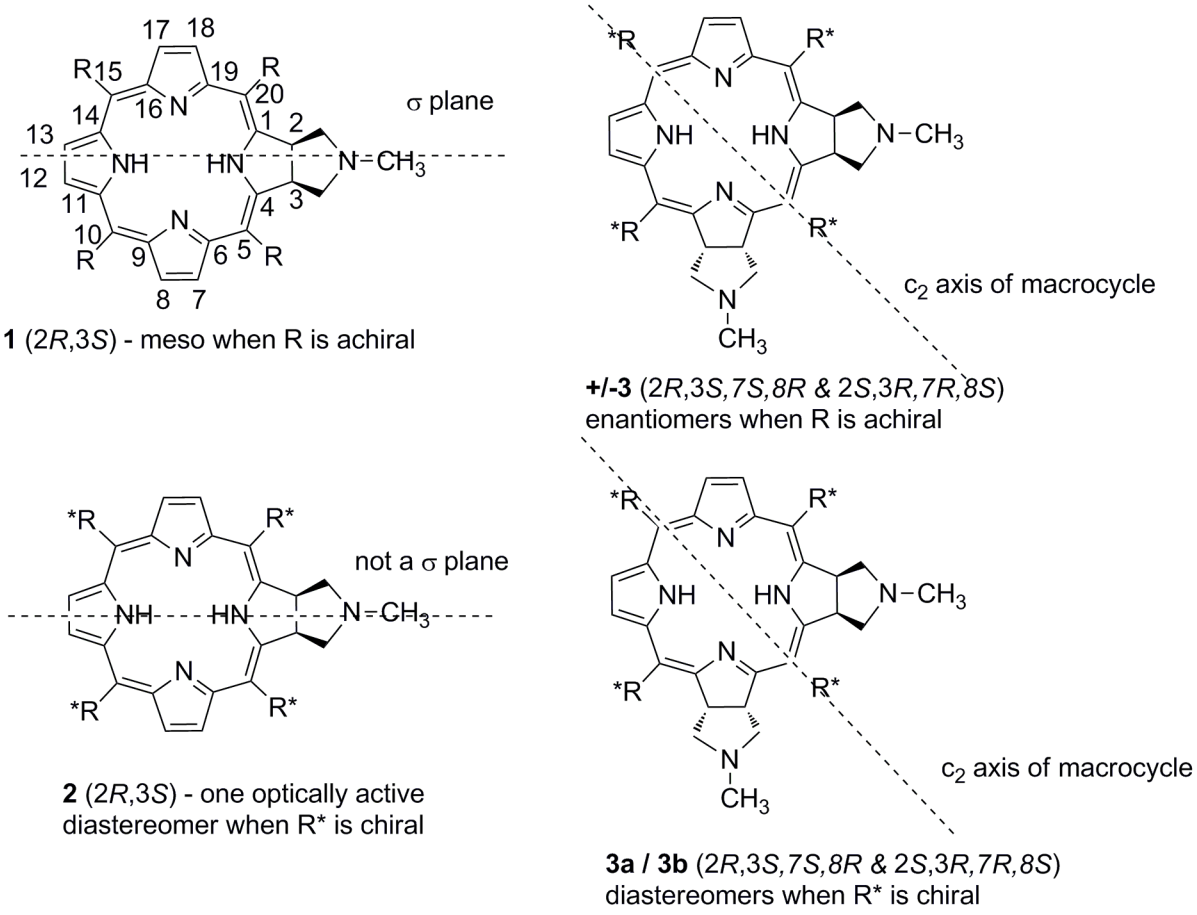


Figure 2.1. Formation of diastereomers. The diastereomers of IF_{20} can be separated on a chiral HPLC column.

Table 2.1. partition coefficients & R_f		
Cpd.	octanol/water	R_f[a]
$PGlc_4$	43.9 (4.8)	0.6 (5.5)
$CGlc_4$	28.5 (3.13)	0.37 (3.4)
$IGlc_4$	9.1 (1)	0.11 (1)
$BGlc_4$	12.7 (1.4)	0.13 (1.2)

[a] normalized values in parentheses, see experimental section. Partition coefficient data from Amit Aggarwal.

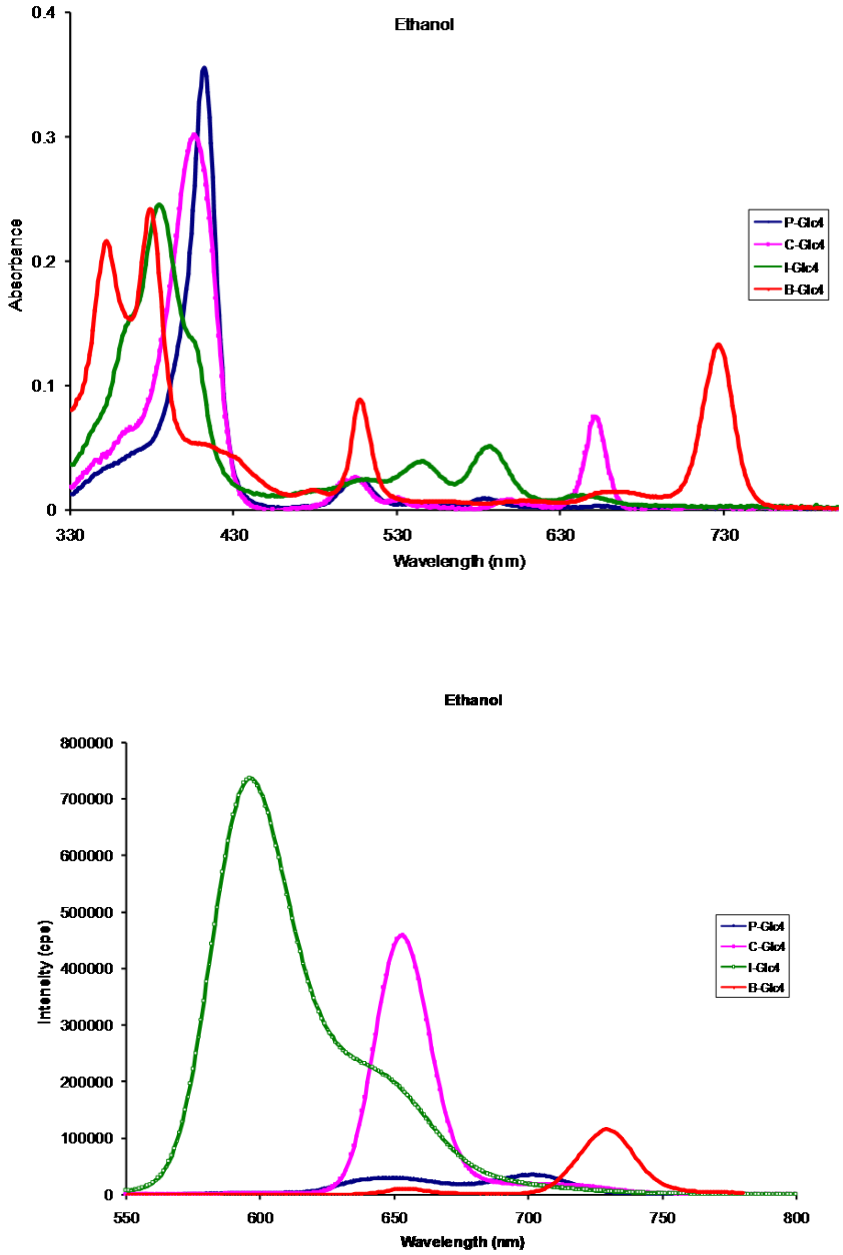


Figure 2.2. Top: UV spectra of the compounds, 2 μM in ethanol. Bottom: emission spectra of the compounds in ethanol; excitation at 512 nm where the absorbance is ca. 0.05 for each compound. Taken from reference (*1*). Data from Amit Aggarwal.

The UV-visible and fluorescence spectra of the parent $TPPF_{20}$ and the glycosylated derivatives are in Table 2.2. Several features are noteworthy. (1) The lowest energy Q band of chlorin, $CGlc_4$ at 649 nm has about 25-fold greater intensity than corresponding Q band of porphyrin $PGlc_4$ at 645 nm. For $BGlc_4$ the strong lowest energy peak is located at 730 nm. The fluorescence emission spectra for the four glycosylated porphyrinoids are correspondingly different and have a strong solvent dependence (Table 2.2).

Table 2.2. Photophysical Properties of Glycosylated Porphyrinoid Derivatives.

Cpd.	Solvent	UV-visible[a]	Emission λ_{max}	Φ_F [b]	$^1O_2$ Φ_Δ
$TPPF_{20}$	DMSO	412, 504, 538, 580, 632	637, 702	--	
CF_{20}	DMSO[c]	408, 504, 536, 598, 652	656	--	
THPC	methanol[d]		653, 720	0.09	0.43
THPBC	methanol[d]		612, 653, 746	0.11	0.43
$PGlc_4$	ethanol	412, 505, 535, 586, 653	653, 702	0.05	0.85[f]
	PBS buffer	410, 510, --- 576, 646(1)[a]	646, 692	0.03	
	ethylacetate	412, 507, 450, 583, 655	649, 701	0.05	
	DMSO[c]	415, 507, 539, 581, 636	640, 705	0.06	
$CGlc_4$	ethanol	408, 507, 534, 599, 653	653, 715	0.43	0.32[f]
	PBS buffer	409, 506, 533, 597, 649(25)[a]	649, 707	0.17	
	ethylacetate	406, 504, 531, 597, 651	653, 712	0.39	
	DMSO[e]	412, 506, 537, 598, 652	652	--	0.28
$BGlc_4$	Ethanol	353, 374, 505, 732	729	0.047	--
	PBS buffer	357, 508, 730	725	0.03	
	ethylacetate	352, 379, 508, 730	730	0.055	
$IGlc_4$	ethanol	385, 513, 548, 588, 643	596, 646, 705	0.70	0.59[f]
	PBS buffer	385, 513, 548, 593, 645(5)[a]	606, 650, 711	0.36	
	ethylacetate	384, 510, 548, 589, 653	596, 646, 700	0.60	

[a]relative intensity of lowest energy Q bands, [b]fluorescence experiments done in air, [c]taken from reference (*56*), [d]mTHPC and the bacteriochlorin mTHPBC taken from reference (*14*), [e]taken from reference (*55*), [f]excited at 532 nm in methanol d_1. Data from Amit Aggarwal.

There are negligible Stokes shifts.(*63*) The 0.17 and 0.36 fluorescence quantum yields for $CGlc_4$ and for $IGlc_4$ in PBS are 6 times and 12 times respectively that of the porphyrin analogue $PGlc_4$ while for $BGlc_4$ is 0.03, similar to the $PGlc_4$. The fluorescence quantum yield of **2b** is greater than m-THPC (*14*) or a water soluble di-meso substituted chlorin (*11, 64*); however this is similar to (*65*) and other meso aryl chlorins.(*66*)

The quantum yields of singlet oxygen formation for three of the compounds in methanol d_1 are listed in Table 2.2. The Φ_Δ data dovetails with the observe fluorescence yields, but the Φ_Δ for $IGlc_4$ in methanol is more consistent with the PBS buffer data.

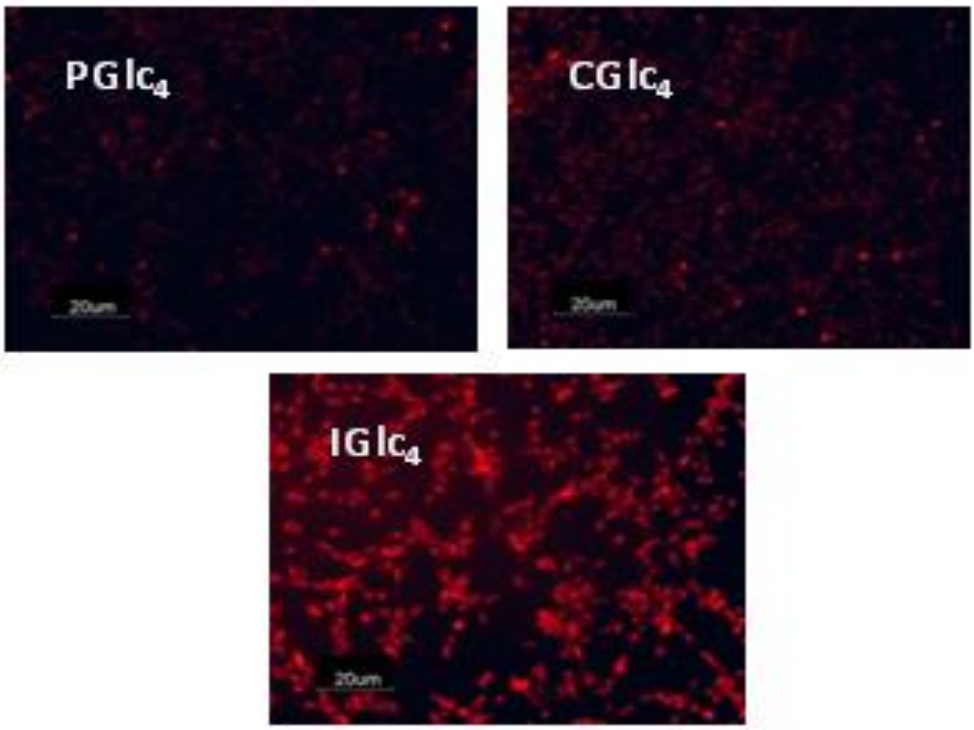


Figure 2.3. Fluorescence microscopy of 3T3 cells treated with 2.5 μM **$PGlc_4$** (**1b**), **$CGlc_4$** (**2b**), and **$IGlc_4$** (**3b**). K:Molv NIH 3T3 cells were incubated for 20 hrs with porphyrinoid, followed by removal of unbound dye from the cell culture by repeated rinsing with PBS, and the cells were imaged under idential microscope settings and not enhanced; magnification 10X. Data from Amit Aggarwal and Sebastian Thompson.

Because our previous studies with thioglycosylated porphyrin $PGlc_4$ indicated good uptake and photodynamic effects on several cancer cell lines, K:Molv NIH 3T3 mouse fibroblasts (Figure 2.3) and MDA-MB-231 breast cancer cell line were used to evaluate the cellular uptake of the glycosylated derivatives. The N-methylpyrrolidine moieties of the chlorin, bacteriochlorin, and isobacteriochlorin (as well as the stereo centers at the β positions) was expected to have small effects on cell uptake, since these are between the glycosylated tetrafluorophenyl groups. K:Molv NIH 3T3 cells were incubated with 2.5 μM concentrations of $PGlc_4$, $CGlc_4$, $IGlc_4$, and $BGlc_4$, rinsed with buffer, and the relative uptake was quantified by comparison of the images (*39*). For $BGlc_{4\ a}$ confocal microscope was used (Figure 2.4). These compounds are robust to photobleaching, which may be a functional role of the 16 F groups.

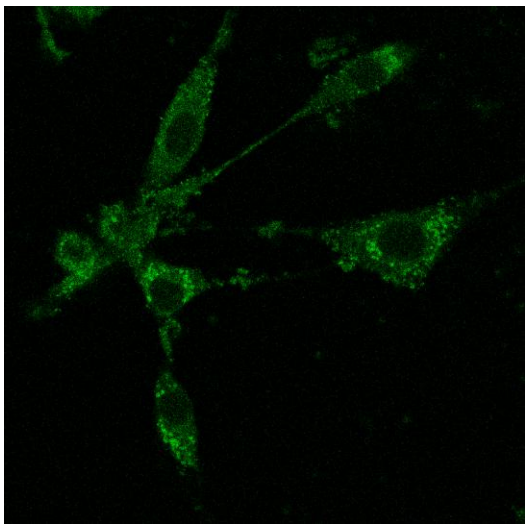


Figure 2.4. K:Molv NIH 3T3 cells were incubated with 10 μM $BGlc_4$ for 24 hours, rinsed three times with PBS buffer, and fixed with 4% paraformaldehyde solution. Confocal microscope excitation at 514 nm, emission monitored with a 710-750 band pass filter. No images are observed using a 610-650 nm emission band pass filter, so fluorescence does not arise from the one of the other dye systems. The image is not enhanced, magnification is 60x. Data from Amit Aggarwal.

The propensity of aggregation inside the cell may also vary.(*18*) Also, some diastereomers may be taken up preferentially over others. The mechanism of uptake and photodynamic effects in this and other cell lines will be reported elsewhere.

$PGlc_4$ compound localizes in the endoplasmic reticulum because of the metabolic needs of this organelle (*44*). The ~15% fluorescence quantum yield of the $IGlc_4$ allow low concentrations (<25 nM) to be used to follow receptors and/or glycolysis processes in the cell (Figure 2.5). The optical cross section of $CGlc_4$ in the red region is significantly larger than the porphyrin or isobacteriochlorin analogues. $BGlc_4$, may be the best photosensitizer for PDT of the compounds described herein because of its strong 730 nm absorption where tissues are more transparent, but a better synthesis and separation of the isomers and diastereomers needs to be developed.

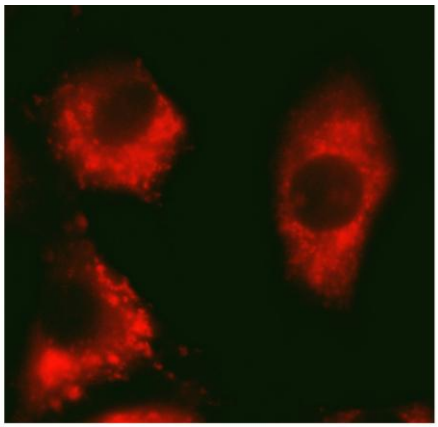


Figure 2.5. Fluorescence image of a MDA-MB-231 breast cancer cell treated with 25 nM $IGlc_4$, and rinsed three times with BPS buffer to remove unbound dye. Data from Sebastian Thompson and Amit Aggarwal.

These compounds can be used as dual function agents that both locate and treat cancerous cells. Our Group previously made the chlorin via a gemdiol on one pyrrole unit of $TPPF_{20}$ and the corresponding tetraglycosylated derivative (*48, 67*), but the yield and stability are not as good as the compounds described herein. Similar to the parent PF_{20}, preliminary studies indicate the same high yield substitution chemistry can yield an array of conjugates on these core platforms to target various tissues (*3, 35, 39*), cell types, and cellular structures.(*68*)

2.4 Conclusions

We have developed the $TPPF_{20}$ as a platform for the synthesis of a variety of conjugates that target cancer and bacteria, and as a starting point to form new chromophores with tuned photophysical properties.(*69*) These compound may serve as effective probes for fundamental biochemical/biophysical studies (*45, 70*) because $CGlc_4$ and $IGlc_4$ have significantly greater fluorescence quantum yields compared to the $PGlc_4$.

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2.6 Appendix

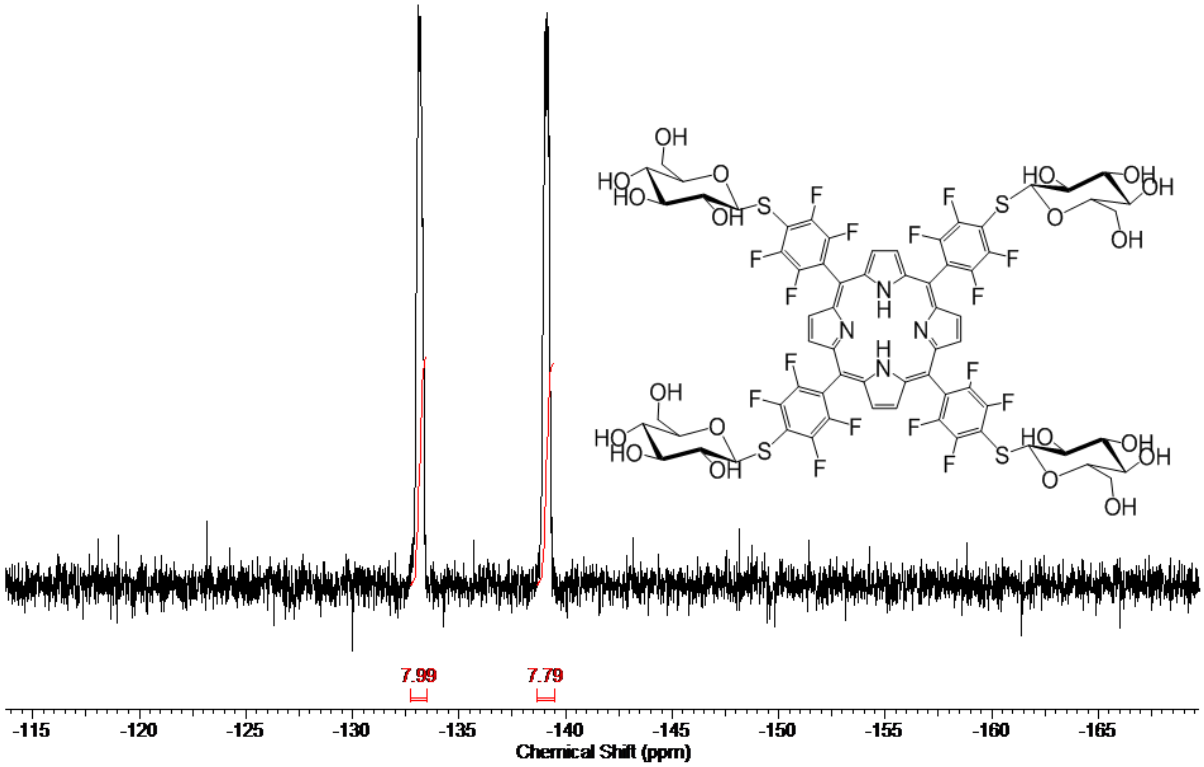


Figure A2.1. Porphyrin 1b ($PGlc_4$) ^{19}F NMR (DMSO-d_6).

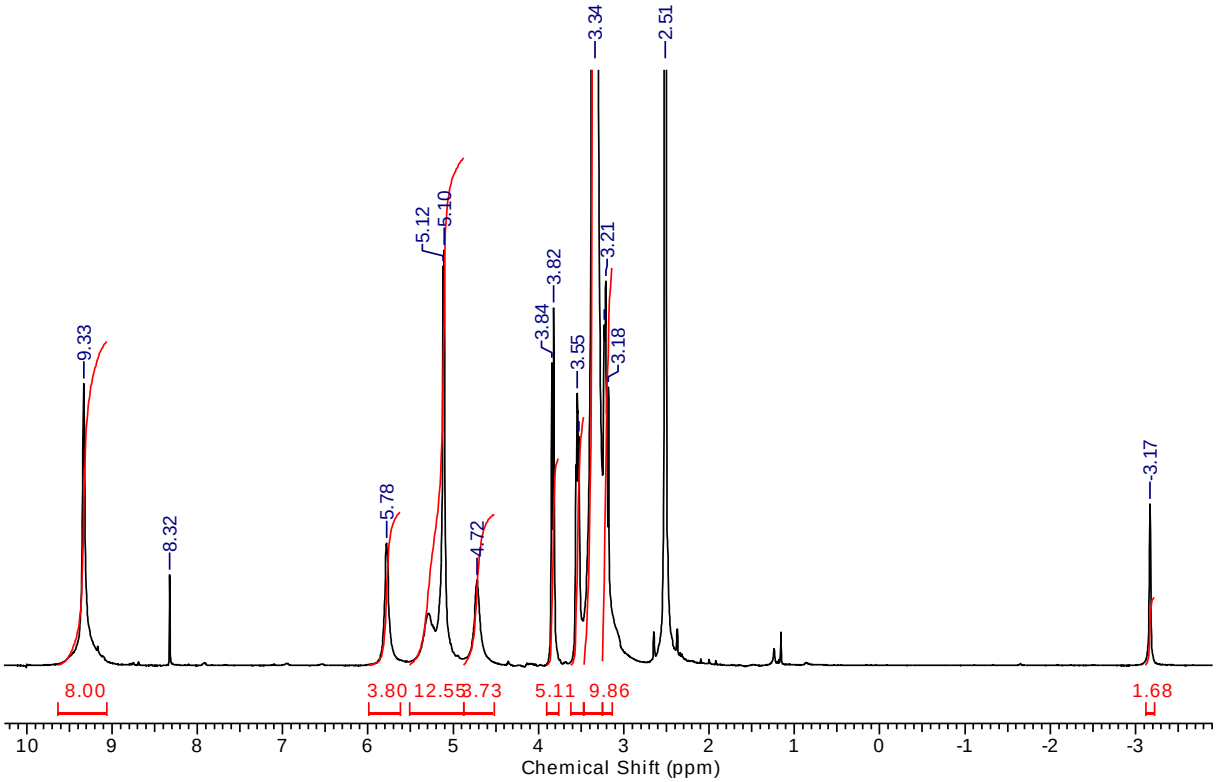


Figure A2.2. Porphyrin 1b ($PGlc_4$) ^{1}H NMR (DMSO-d_6 3.34 ppm, 2.51 water ppm).

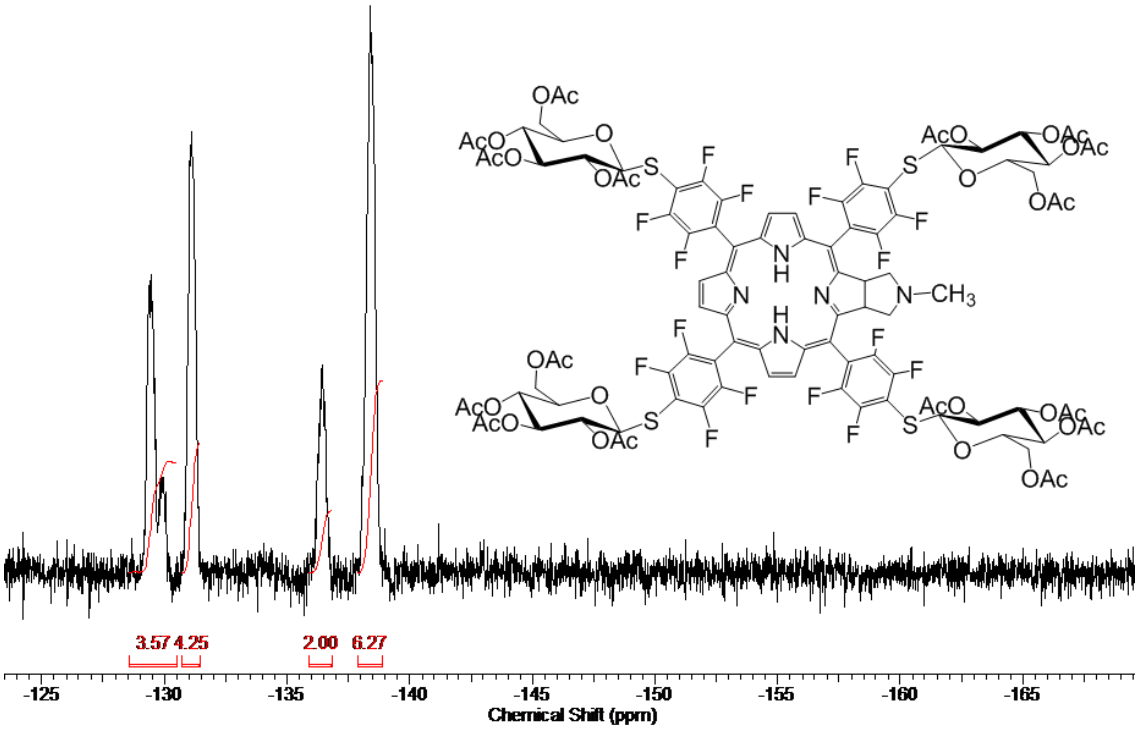


Figure A2.3. Chlorin 2a ($CGlcAc_4$) ^{19}F NMR (DMSO-d_6).

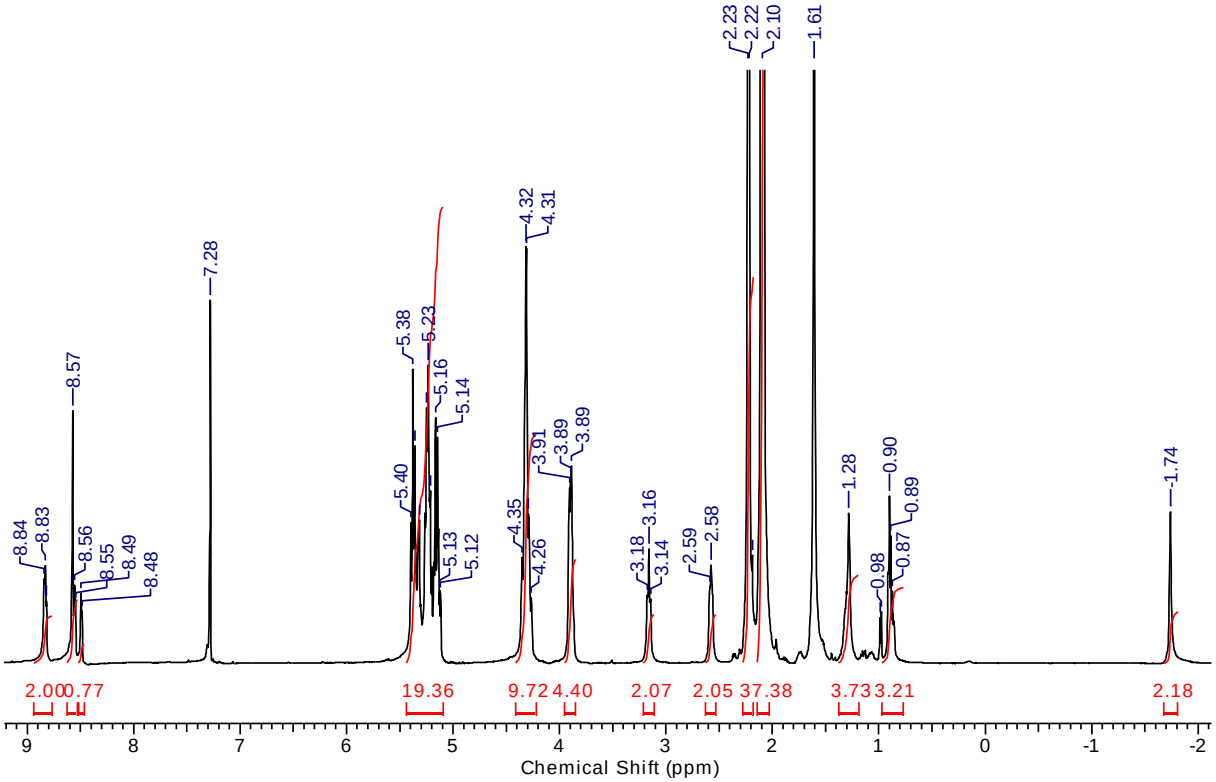


Figure A2.4. Chlorin 2a ($CGlcAc_4$) ^{1}H NMR ($CDCl_3$ 7.28 ppm, water 1.61 ppm).

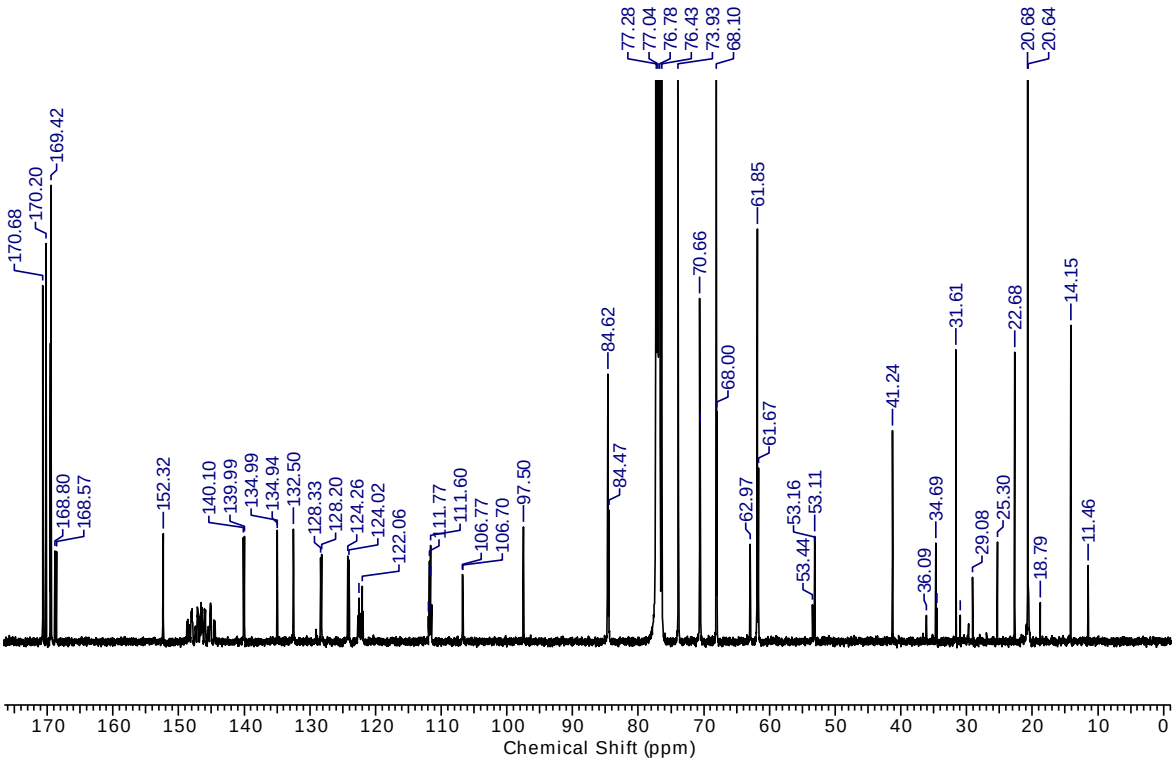
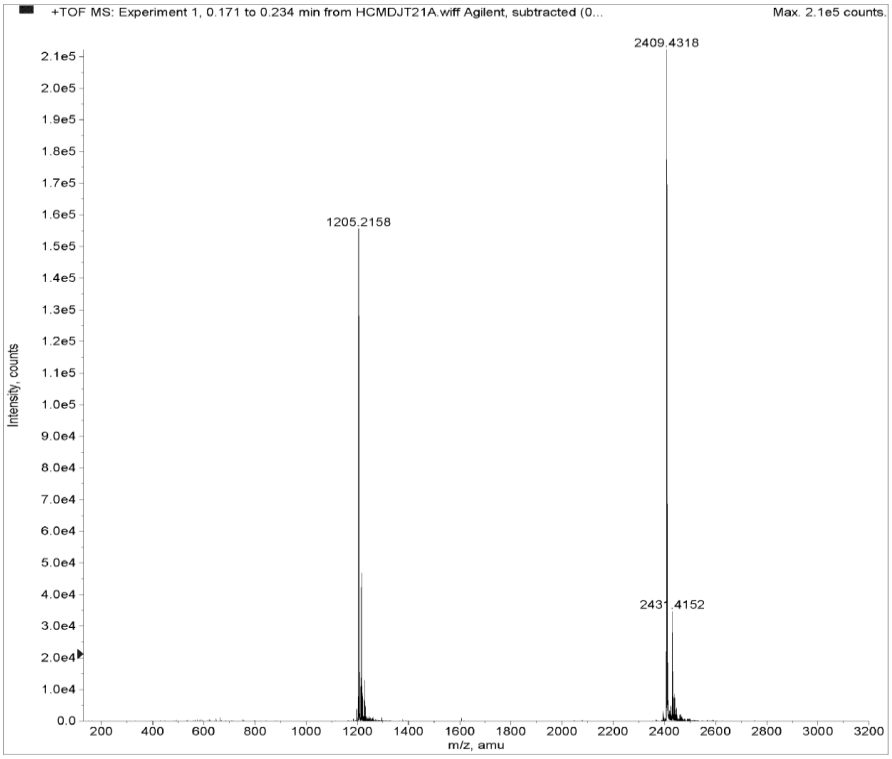


Figure A2.5. Chlorin 2a ($CGlcAc_4$) ^{13}C NMR ($CDCl_3$ 77 ppm).



The peak at 2431 is the sodium ion adduct, and the peak at 1205 is the doubly charged M/2 ion.

	Formula	Calculated m/z (amu)	mDa Error	PPM Error	DBE
1	C101 H95 N5 O36 F16 Na S4	2408.4276	0.0638	0.0264	48.5
2	C103 H94 N5 O36 F16 S4	2408.4300	-2.3414	-0.9721	51.5
3	C104 H82 N5 O36 F16 S4	2408.3361	91.5590	38.0160	58.5
4	C100 H107 N5 O36 F16 Na S4	2408.5215	-93.8366	-38.9617	41.5
5	C102 H83 N5 O36 F16 Na S4	2408.3337	93.9642	39.0147	55.5
6	C102 H106 N5 O36 F16 S4	2408.5239	-96.2419	-39.9604	44.5

Figure A2.6. Chlorin 2a ($CGlcAc_4$) HRMS.

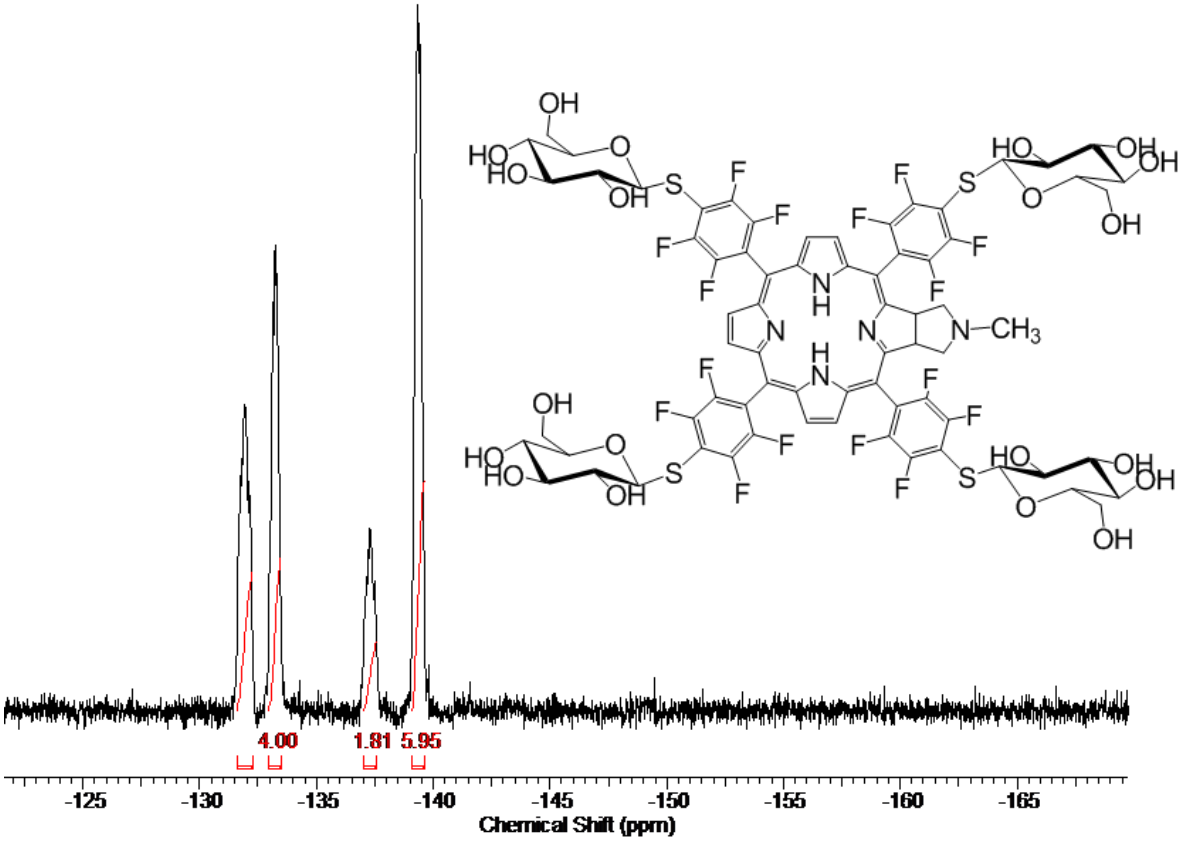


Figure A2.7. Chlorin 2b ($CGlc_4$) ^{19}F NMR ($DMSO\text{-}d_6$).

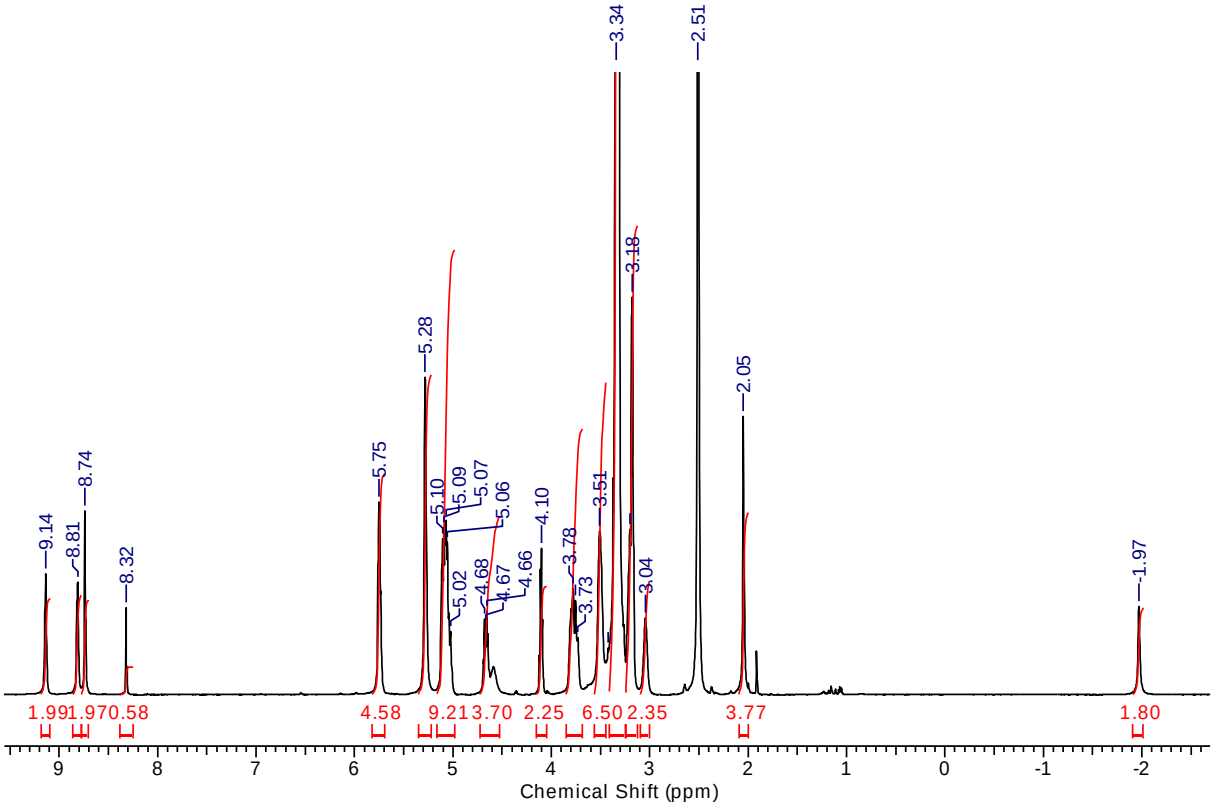


Figure A2.8. Chlorin 2b ($CGlc_4$) ^{1}H NMR (DMSO-d_6 3.34 ppm, 2.51 water ppm)

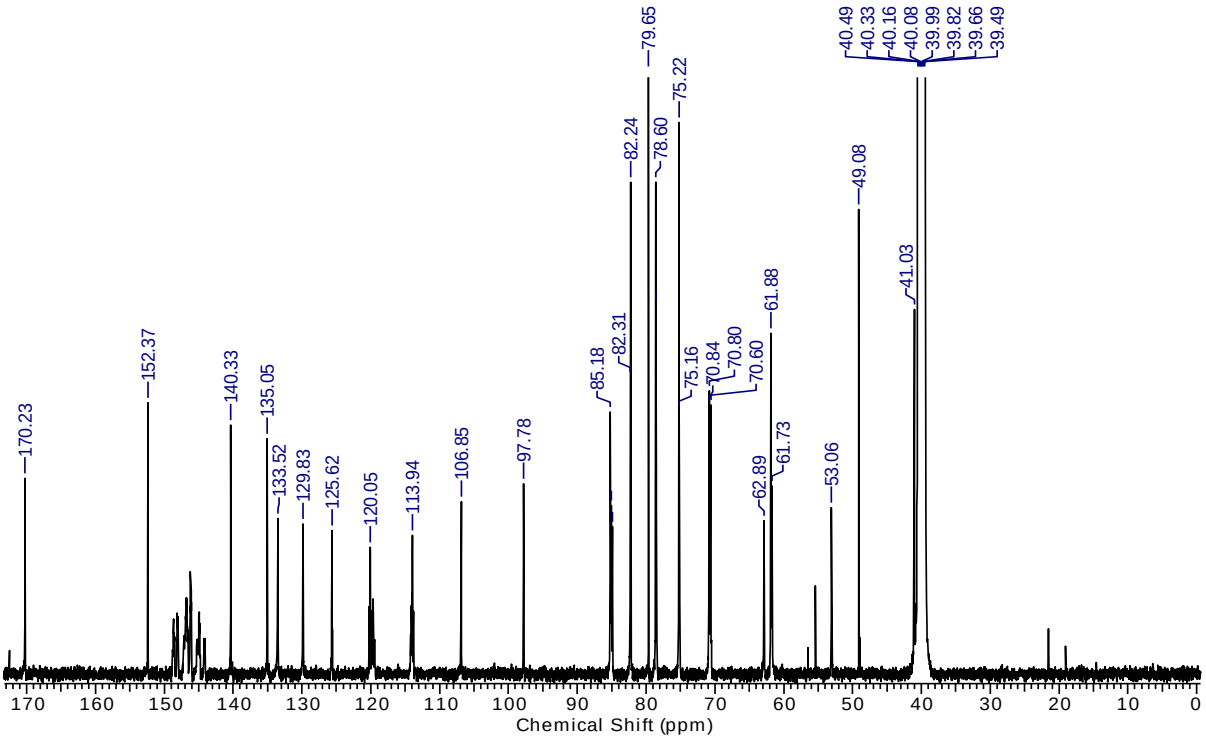
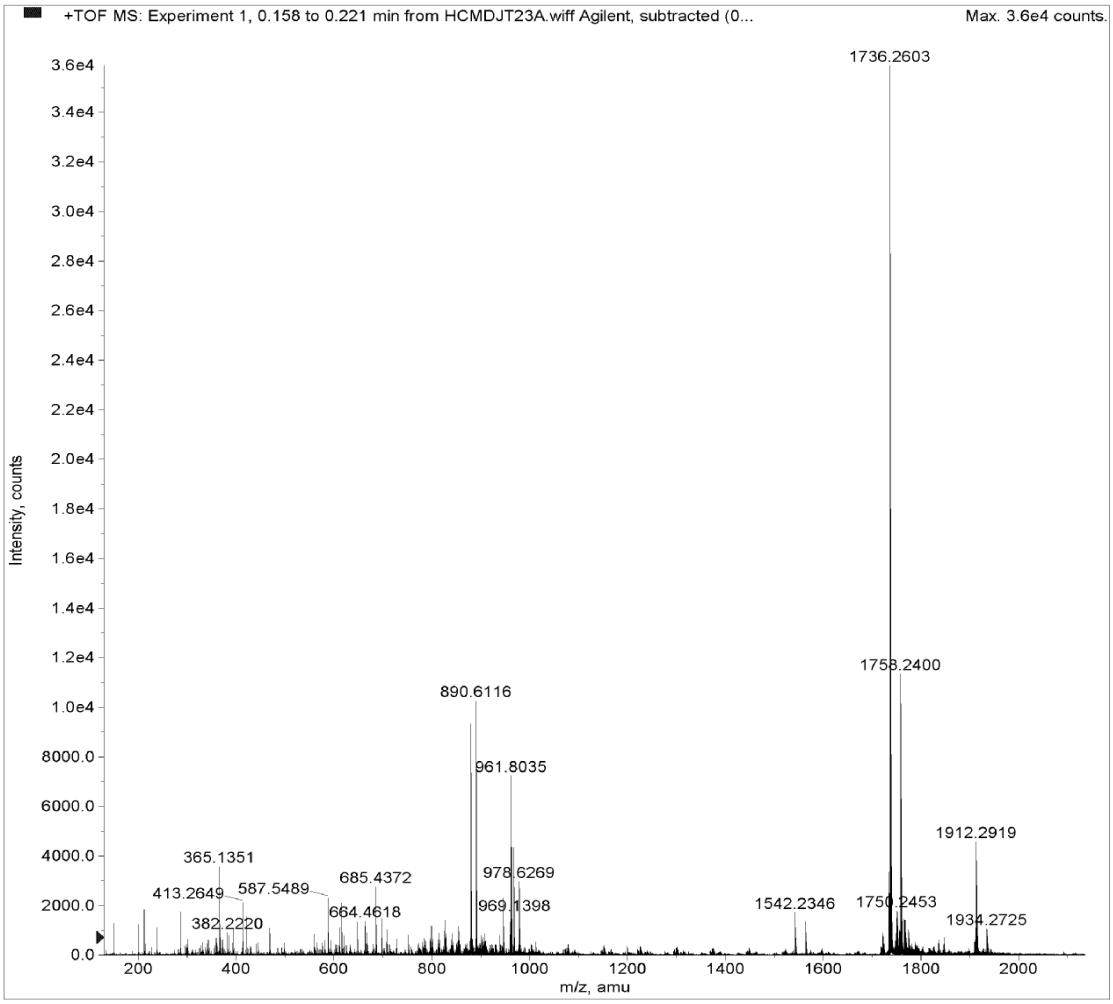


Figure A2.9. Chlorin 2b ($CGlc_4$) ^{13}C NMR (DMSO-d_6 40 ppm), some acetic acid is present in this sample.



	Formula	Calculated m/z (amu)	mDa Error	PPM Error	DBE
1	C71 H62 N5 O20 F16 S4	1736.2610	-1.1059	-0.6369	35.5

Figure A2.10. Chlorin 2b ($CGlc_4$) HRMS.

The ESI of chlorin **2b** ($CGlc_4$) was run in methanol, with 0.1% formic acid. M/z peak at 1736 is for (M+H), 1758 is for (M + Na), 1542 is for M - SGlc, 1575 for M - Glc, and 1912 is M + Na + 2,5-dihydroxybenzoic acid (calibration matrix)

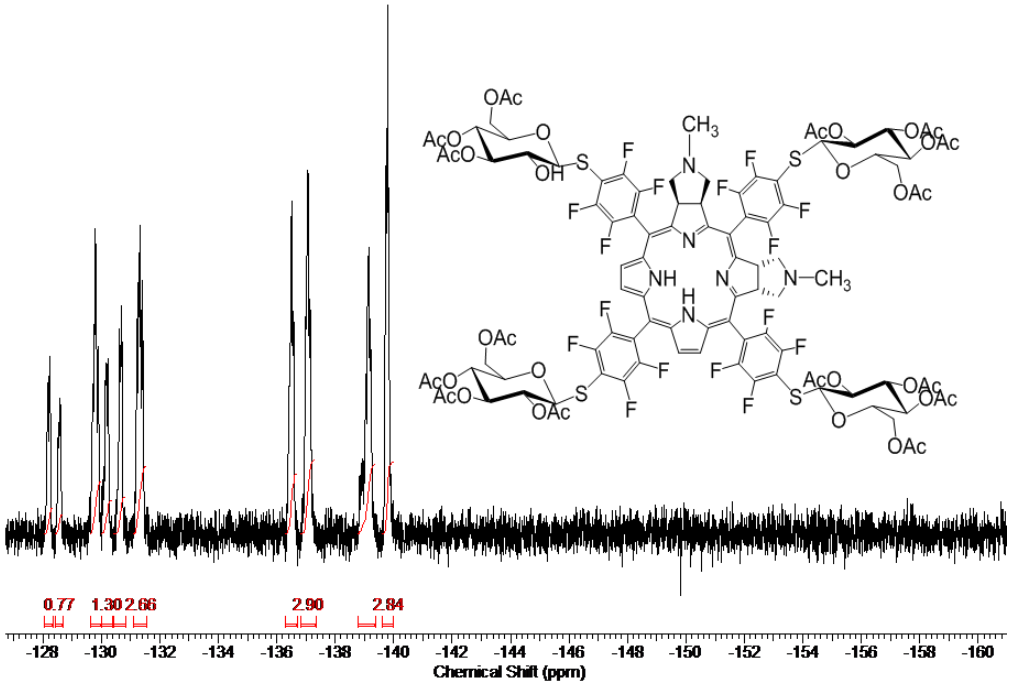


Figure A2.11. Isobacteriochlorin 3a ($IGlcAc_4$) ^{19}F NMR (DMSO-d_6).

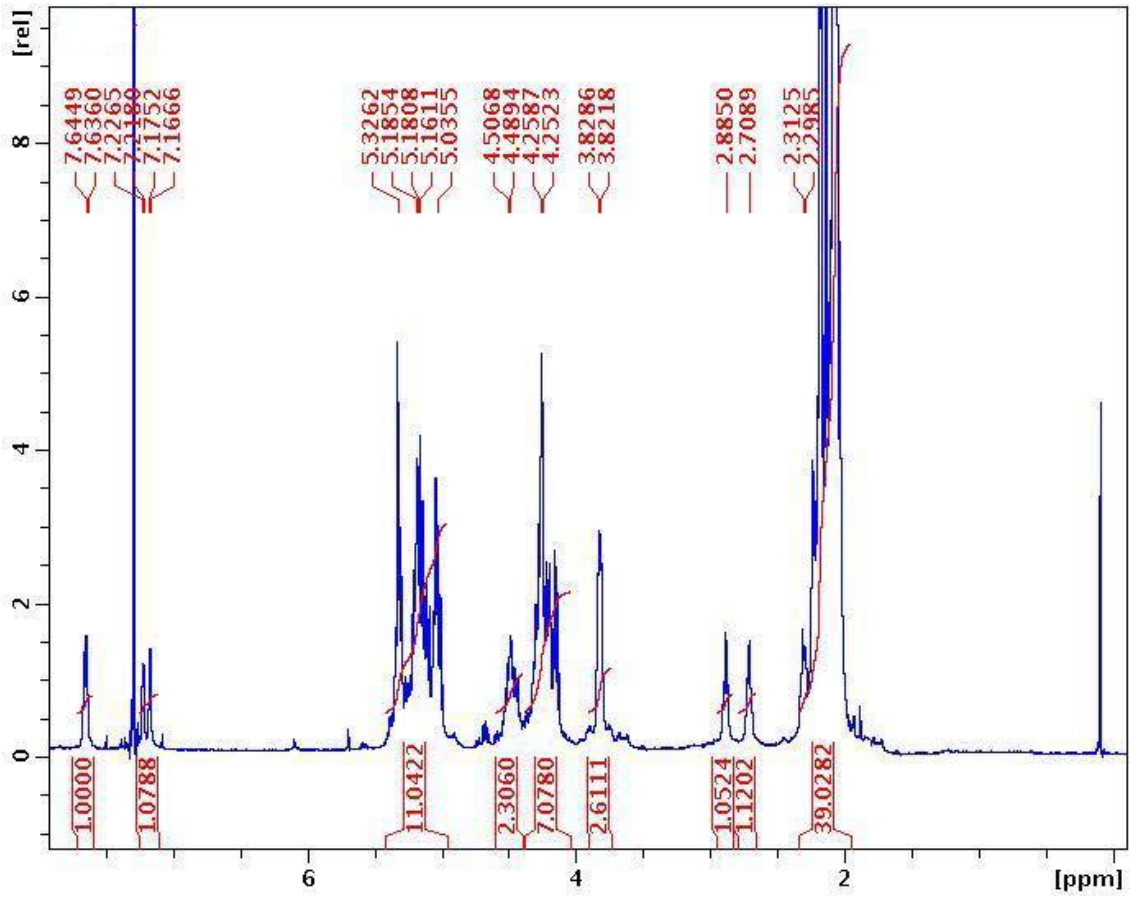


Figure A2.12. Isobacteriochlorin 3a ($IGlcAc_4$) ^{1}H NMR ($CDCl_3$ 7.29 ppm

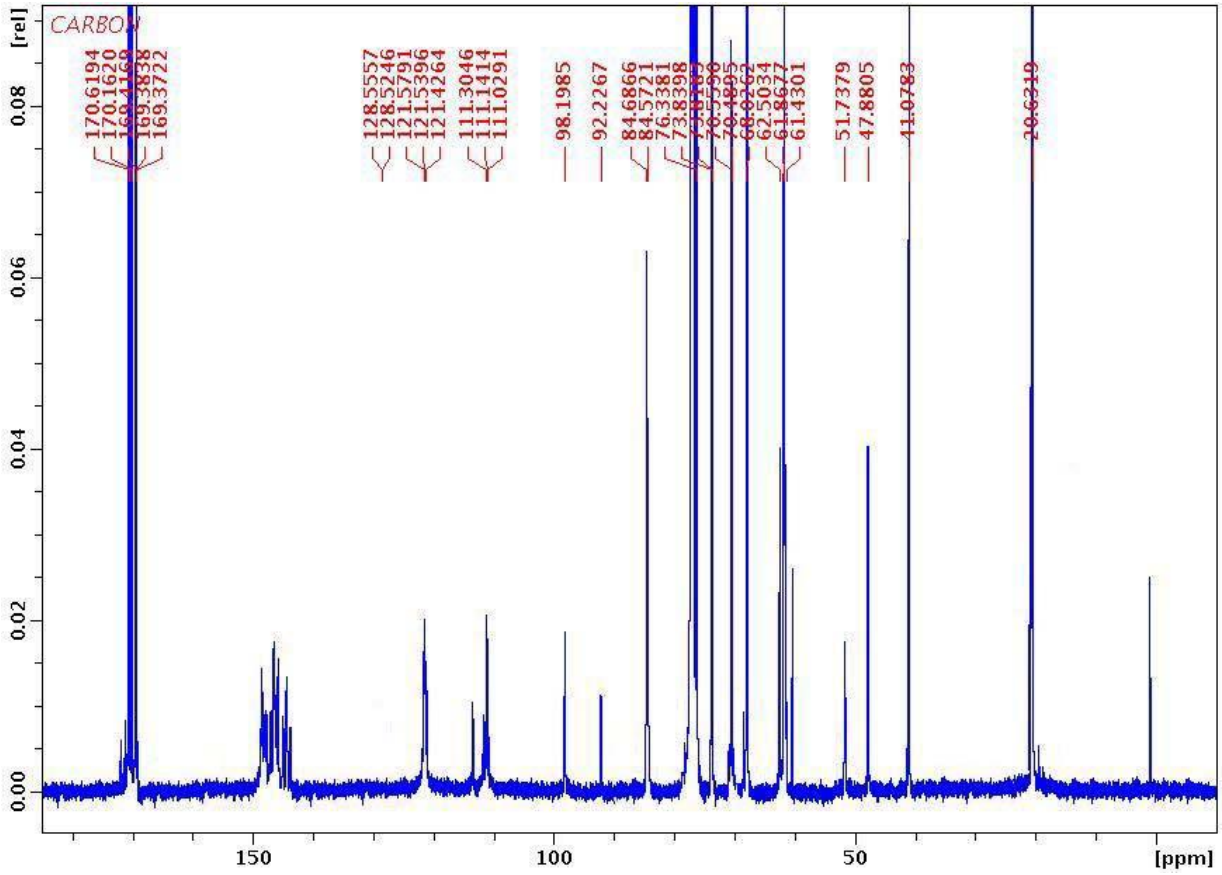
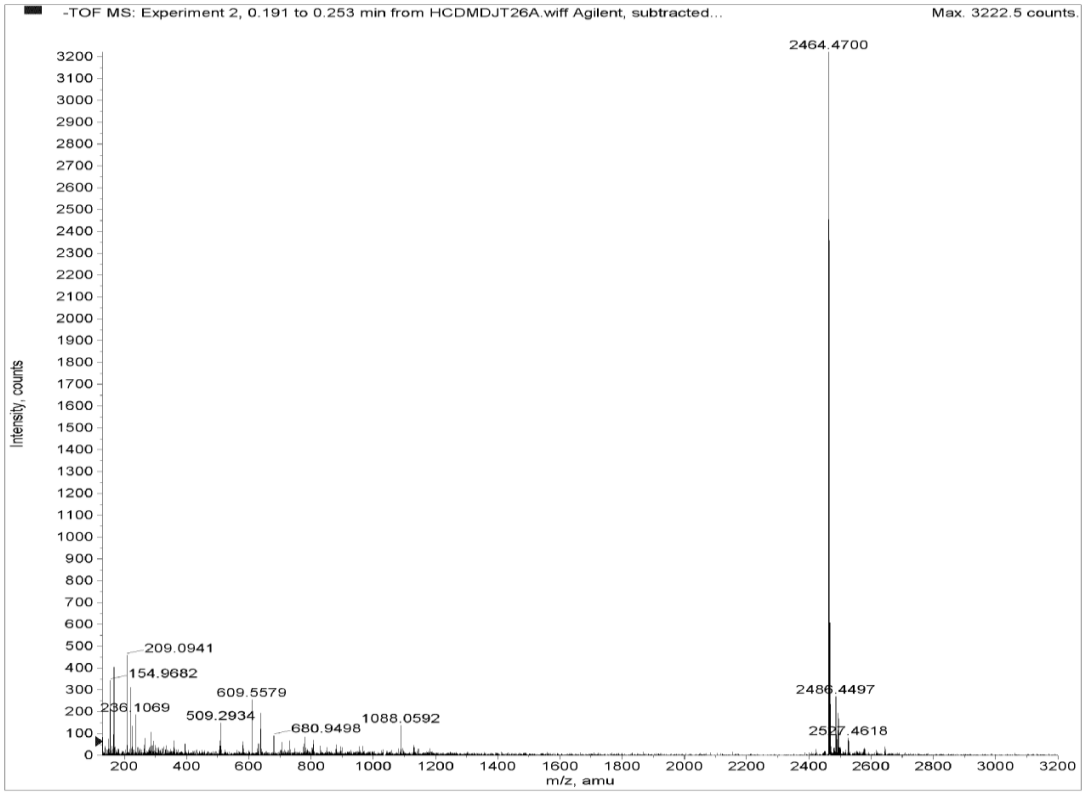


Figure A2.13. Isobacteriochlorin 3a ($IGlcAc_4$) ^{13}C NMR ($CDCl_3$ 76 ppm).



The peak at 2486 is the sodium ion adduct.

Elemental composition calculator

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Tolerance: +3.0000 ppm
Result type: Elemental
Max num of results: 100
Min DBE: -0.5000 Max DBE: +100.0000
Electron state: Even
Num of charges: -1
Add water: N/A
Add proton: N/A
File Name: HCDMDJT26A.wiff

	Elements	Min Number	Max Number
1	C	106	106
2	Cl	0	0
3	F	16	16
4	H	98	105
5	K	0	0
6	N	6	6
7	Na	0	0
8	O	36	36
9	P	0	0
10	S	4	4

	Formula	Calculated m/z (amu)	mDa Error	PPM Error	DBE
1	C106 H99 N6 O36 F16 S4	2463.4733	-6.7378	-2.7351	52.5

Figure A2.14. Isobacteriochlorin 3a ($IGlcAc_4$) HRMS.

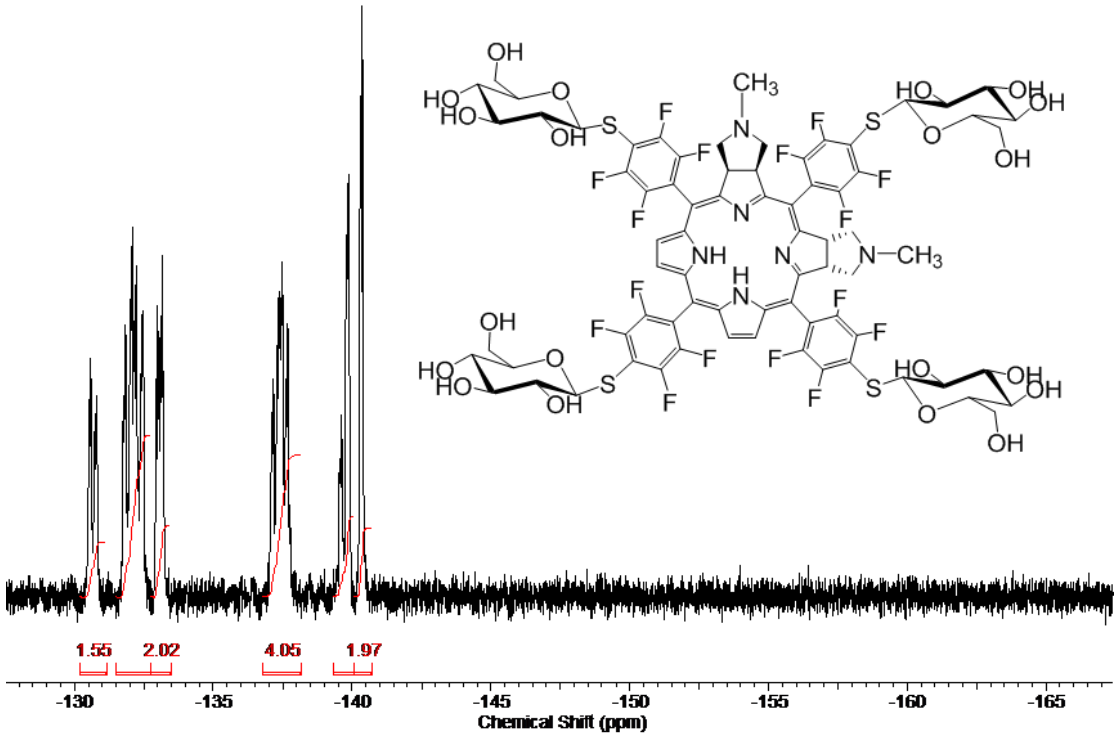


Figure A2.15. Isobacteriochlorin 3b ($IGlc_4$) ^{19}F NMR (DMSO-d_6).

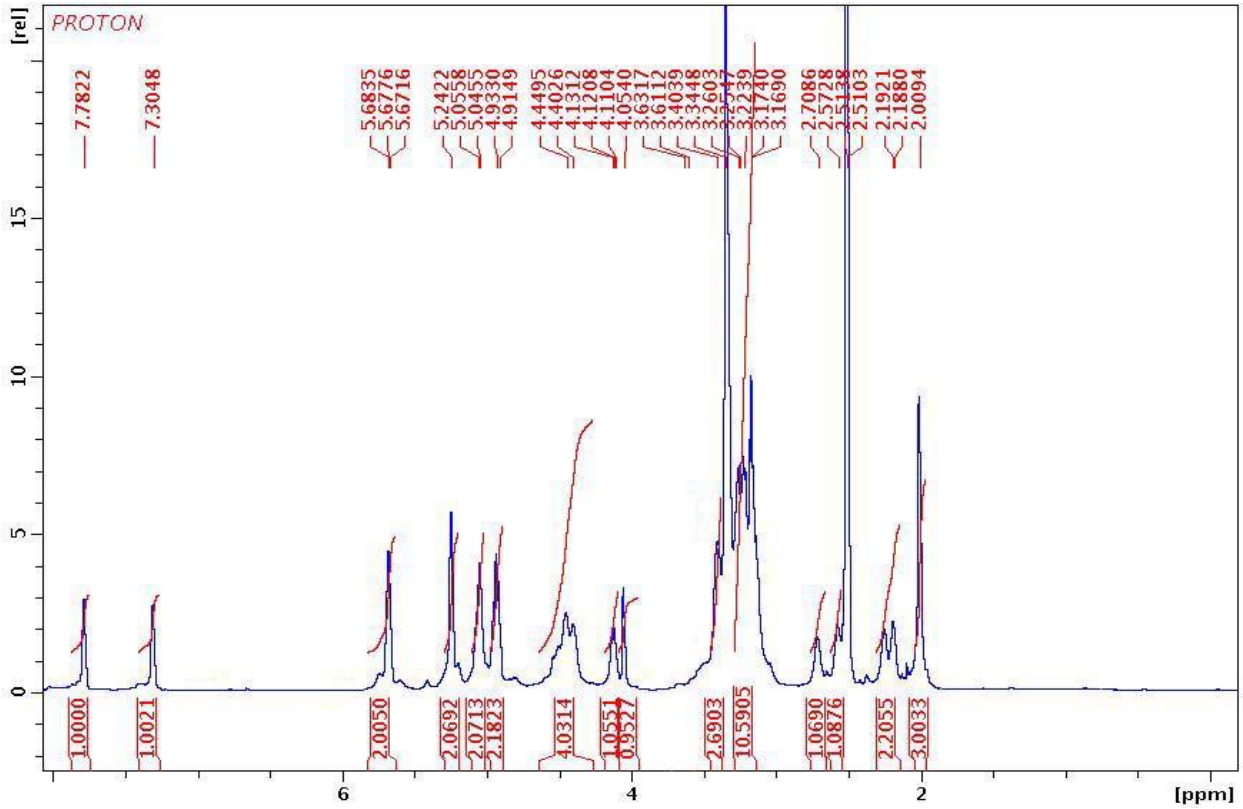


Figure A2.16. Isobacteriochlorin 3b ($IGlc_4$) ^{1}H NMR (DMSO-d_6 2.51 ppm, water 3.3 ppm)

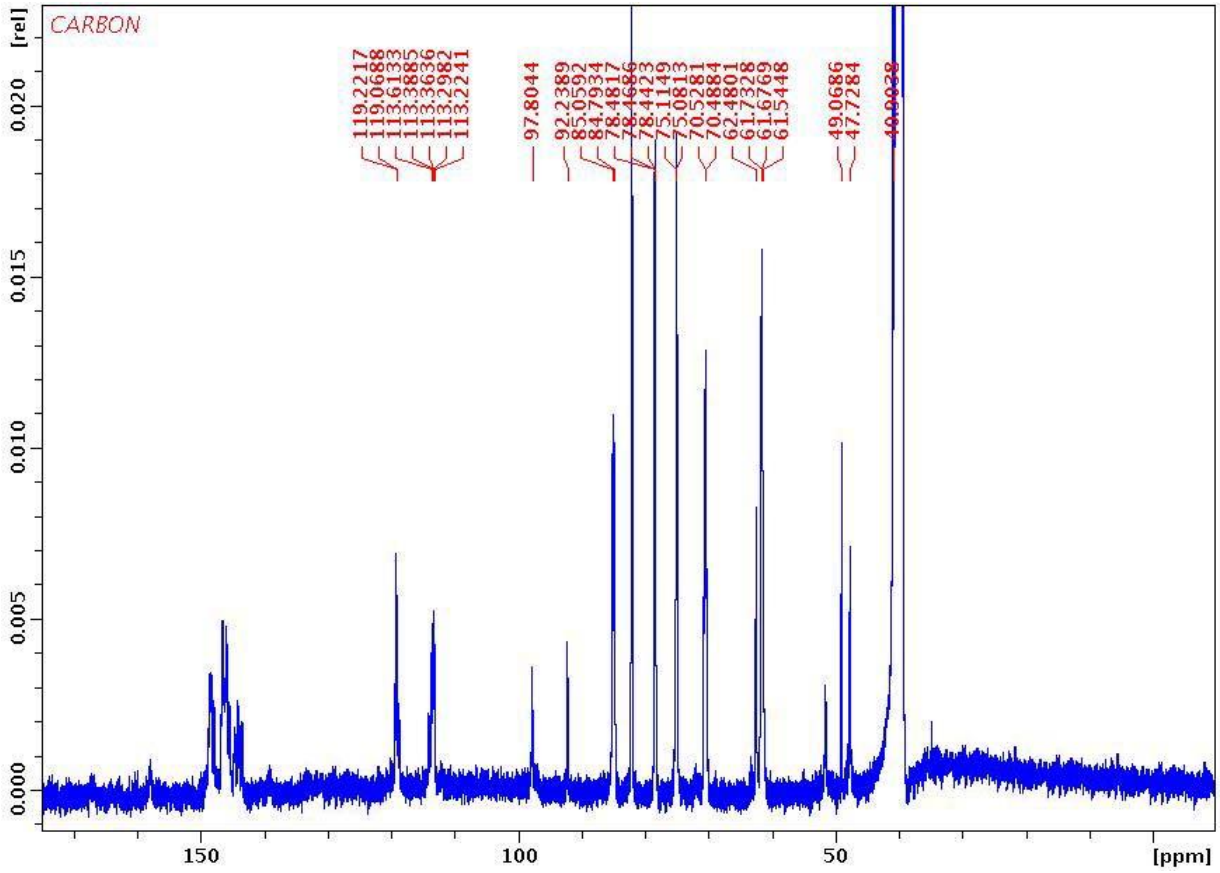
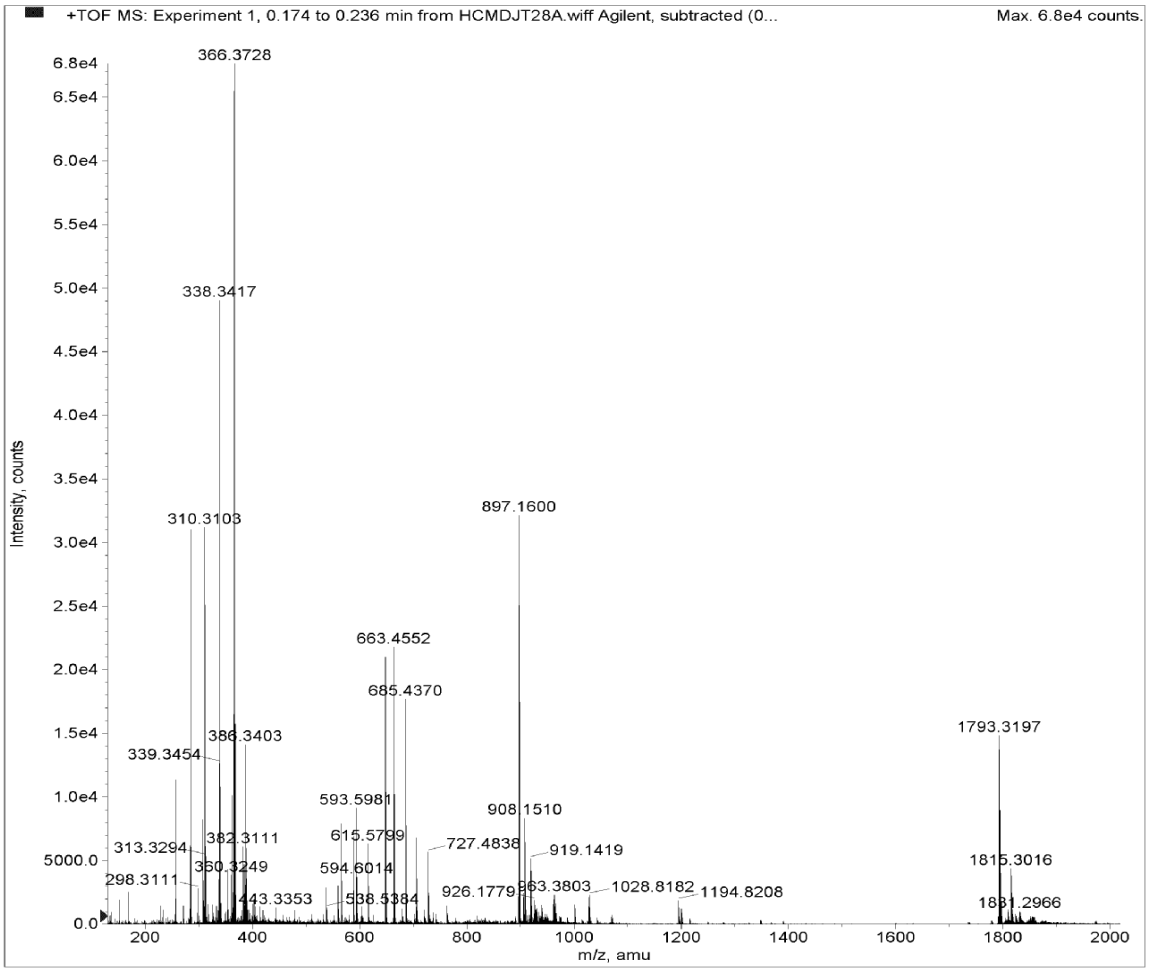


Figure A2.17. Isobacteriochlorin 3b ($IGlc_4$) ^{13}C NMR (DMSO-d_6 40 ppm).



	Formula	Calculated m/z (amu)	mDa Error	PPM Error	DBE
1	C74 H69 N6 O20 F16 S4	1793.3188	0.8447	0.4710	35.5

Figure A2.18a. Isobacteriochlorin 3b ($IGlc_4$) HRMS.

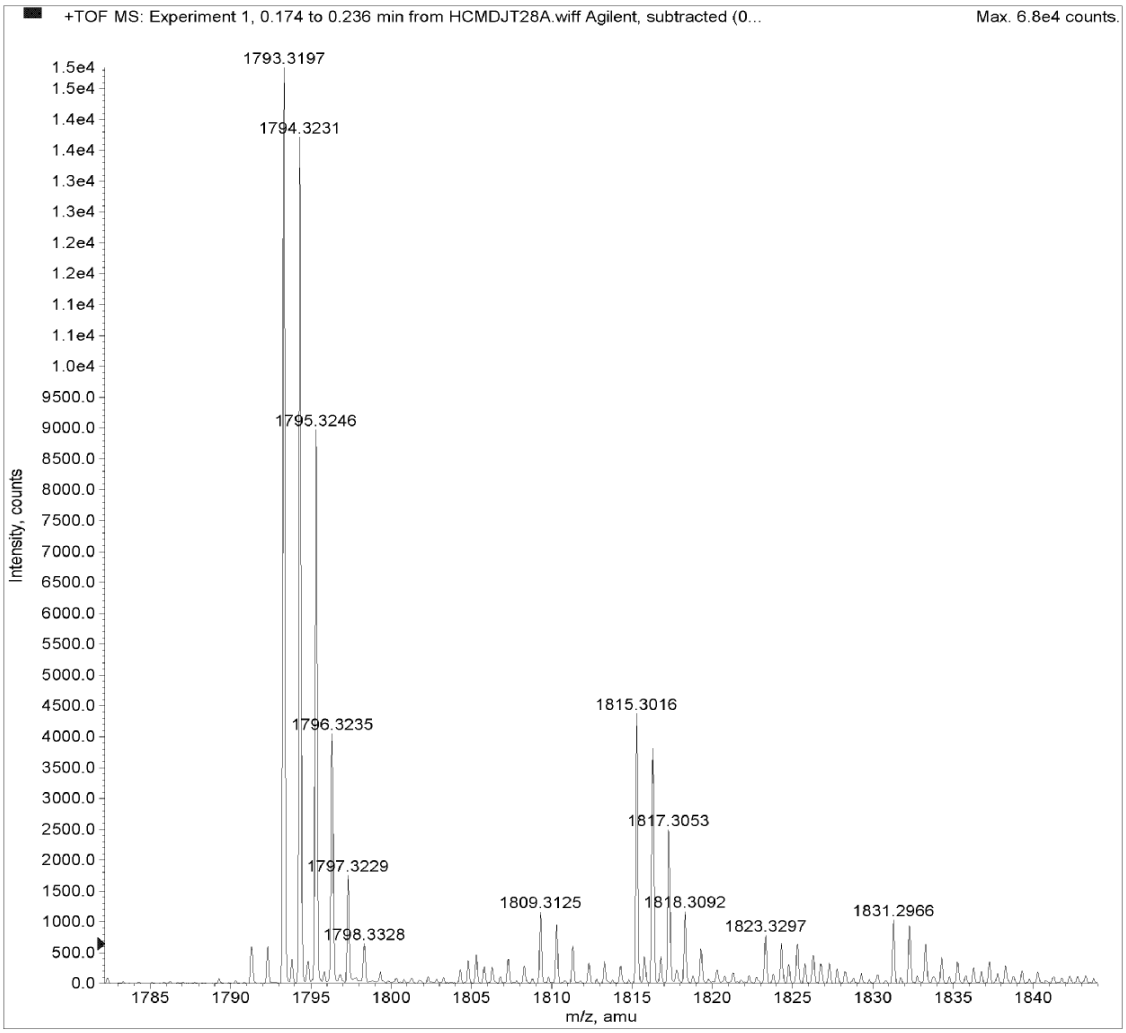


Figure A2.18b. Isobacteriochlorin 3b ($IGlc_4$) HRMS. The peak at 1815 is the sodium ion adduct, and the peak at 797 is the doubly charged M/2 ion.

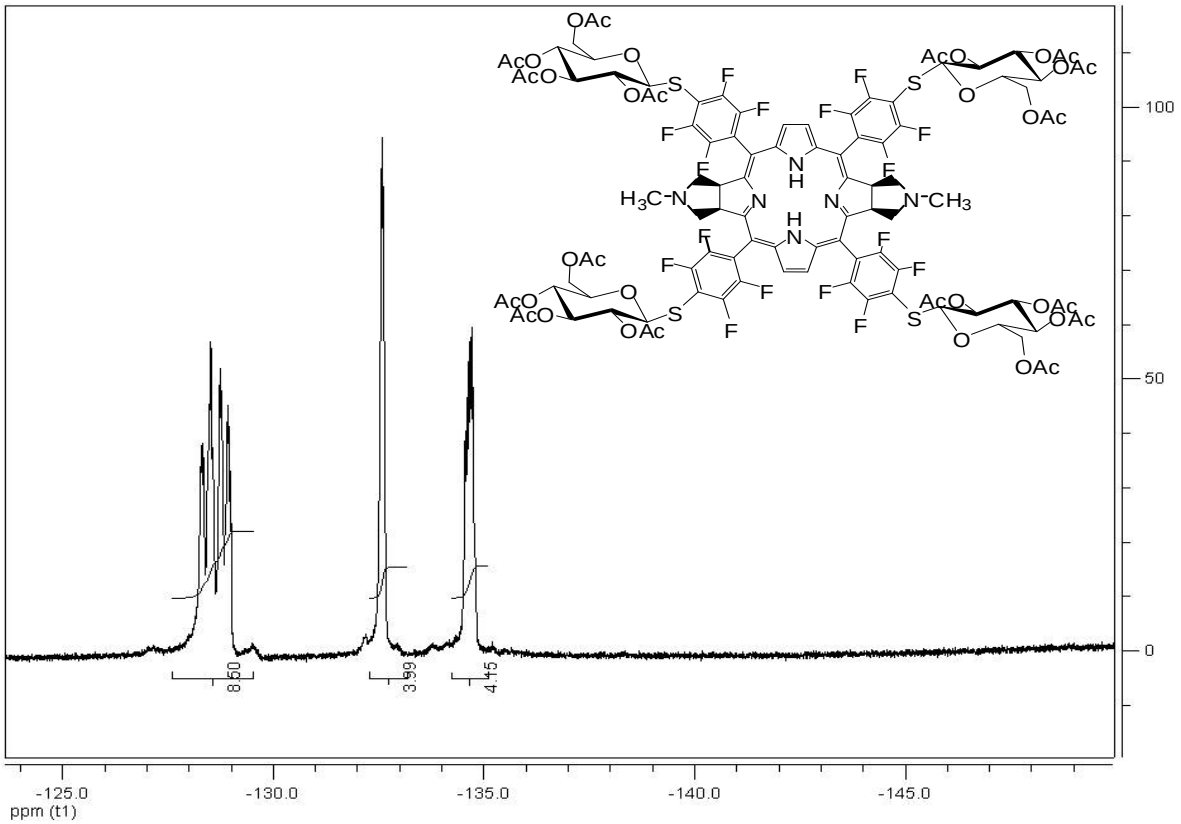


Figure A2.19. Bacteriochlorin 4a ($BGlcAc_4$) ^{19}F NMR ($CDCl_3$)**.**

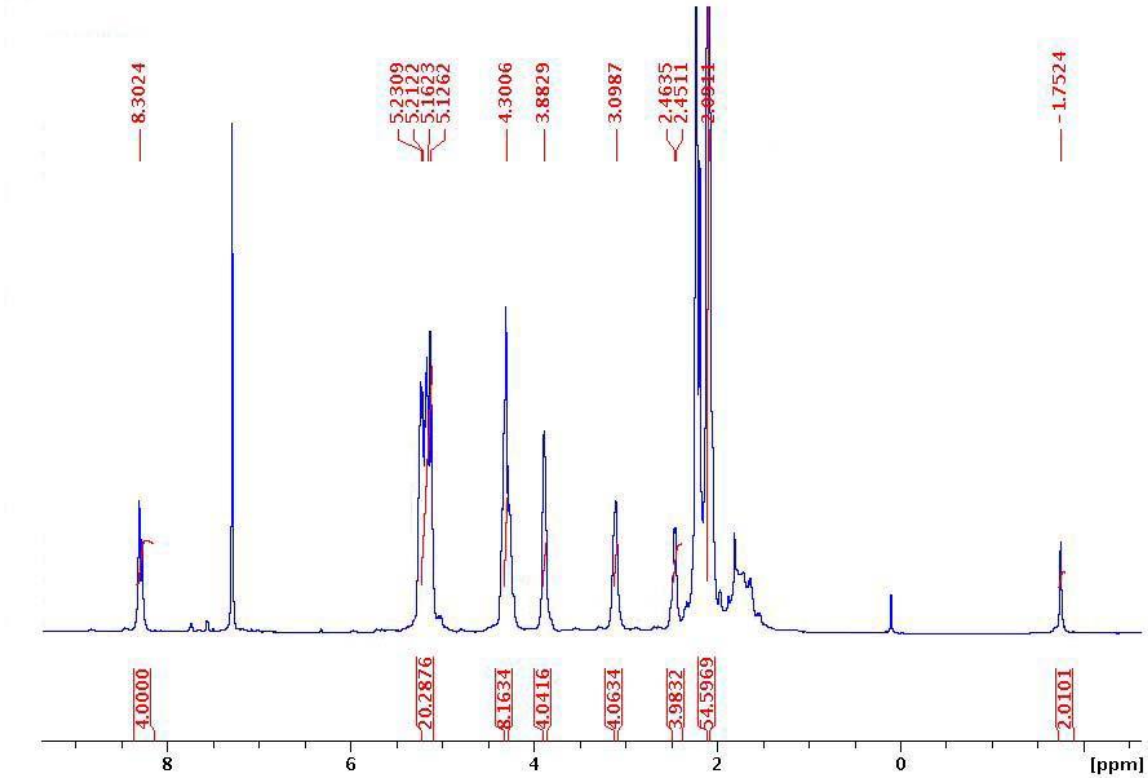


Figure A2.20. Bacteriochlorin 4a ($BGlcAc_4$) ^{1}H NMR ($CDCl_3$ 7.29 ppm

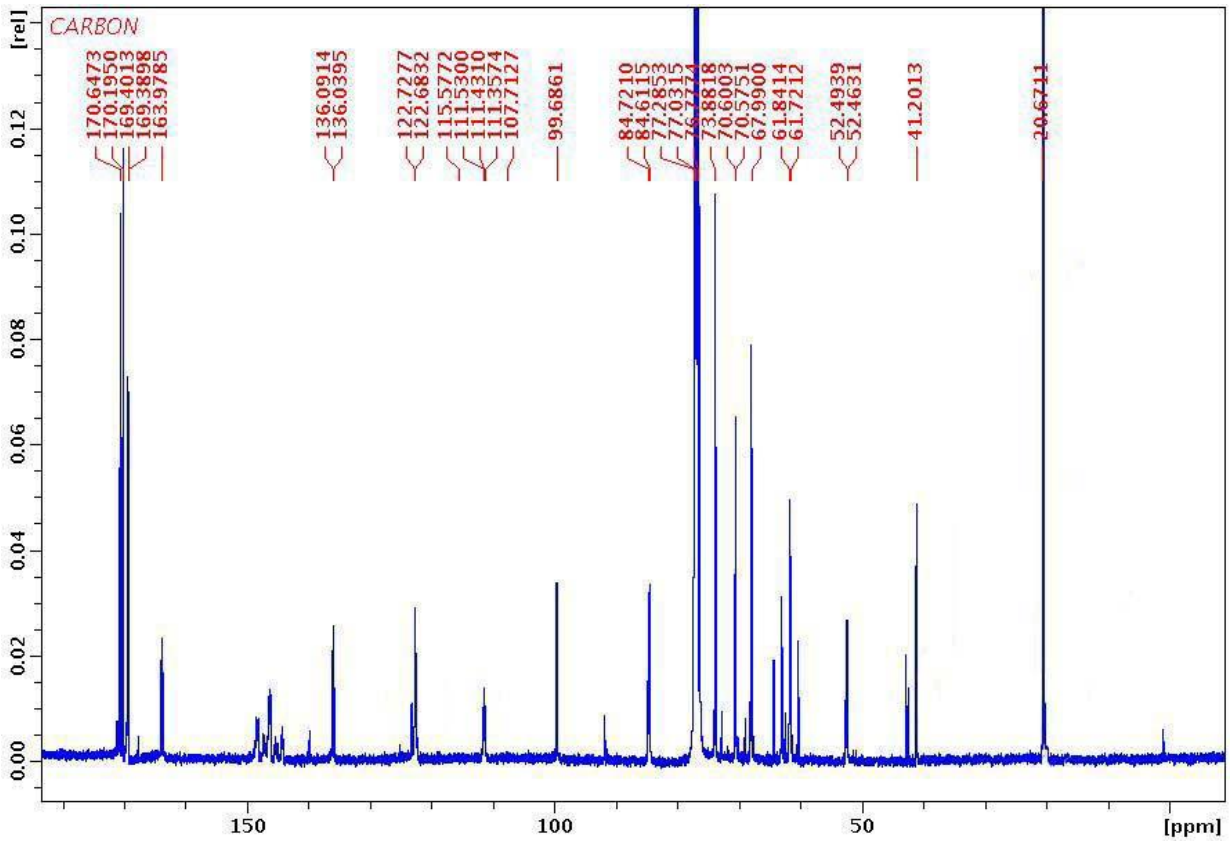


Figure A2.21. Bacteriochlorin 4a ($BGlcAc_4$) ^{13}C NMR ($CDCl_3$ 76 ppm).

Qualitative Compound Report

Data File	HCSS200900629_002.d	**Sample Name**	BGlac4
Sample Type	Sample	**Position**	P1-C1
Instrument Name	Instrument 1	**User Name**	Mahen
Acq Method		**IRM Calibration Status**	Success
DA Method	MahenFI.m	**Comment**	Sample M - Flow injection, ACN% MeOH

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C106 H100 F16 N6 O36 S4	0.2	2464.4813	11551	C106 H100 F16 N6 O36 S4	2464.4806	0.3

Compound Label	RT	Algorithm	Mass
Cpd 1: C106 H100 F16 N6 O36 S4	0.2	Find By Formula	2464.4813

MS Spectrum

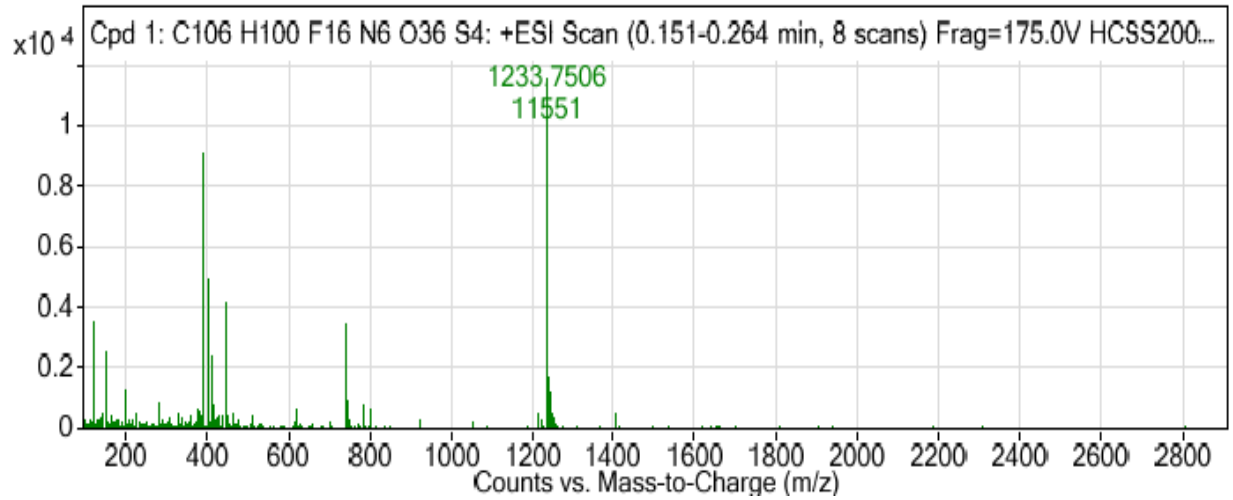


Figure A2.22. Bacteriochlorin 4a ($BGlcAc_4$) HRMS, the peaks at 1233 are the doubly charged species.

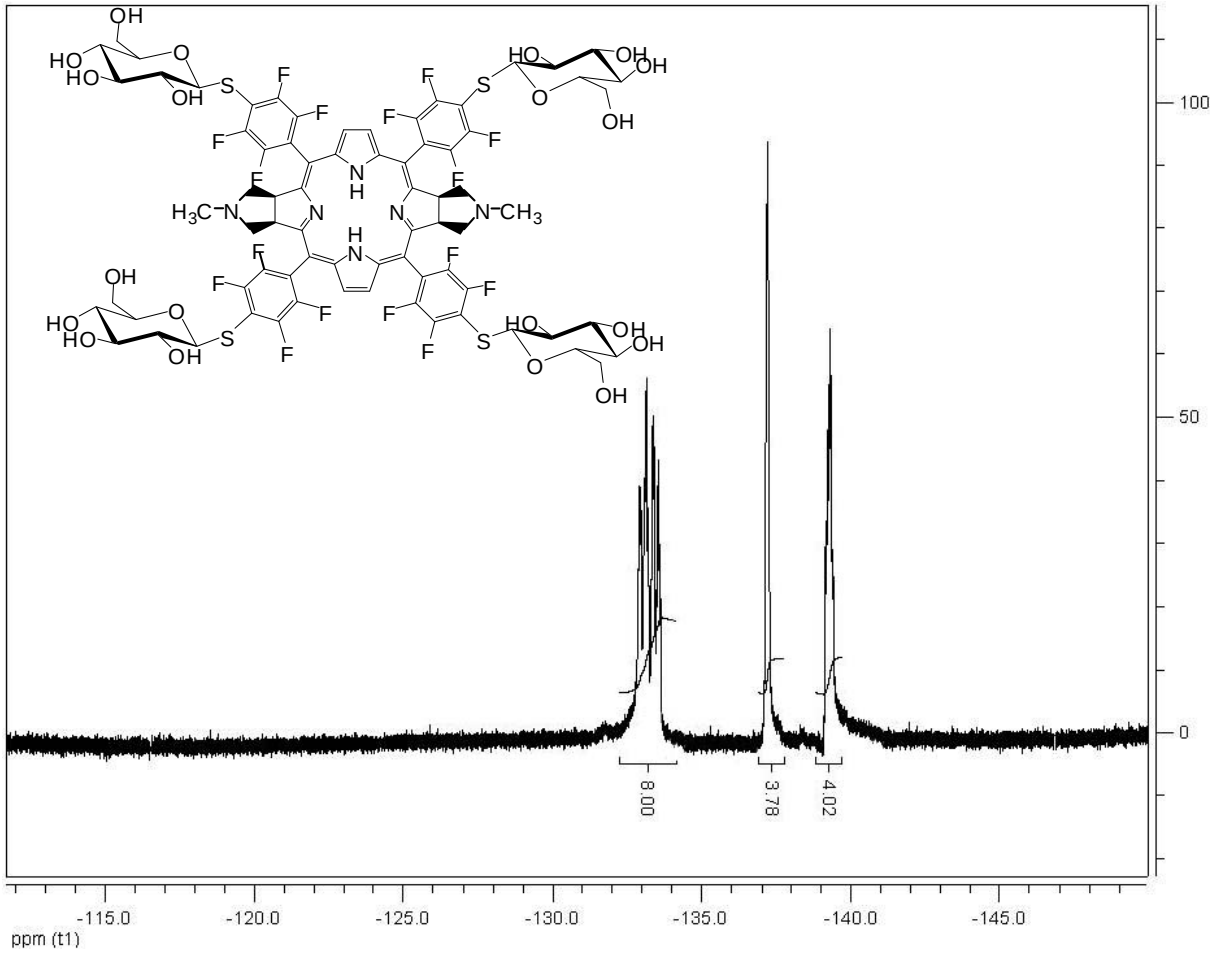


Figure A2.23. Bacteriochlorin 4b ($BGlc_4$) ^{19}F NMR (MeOD).

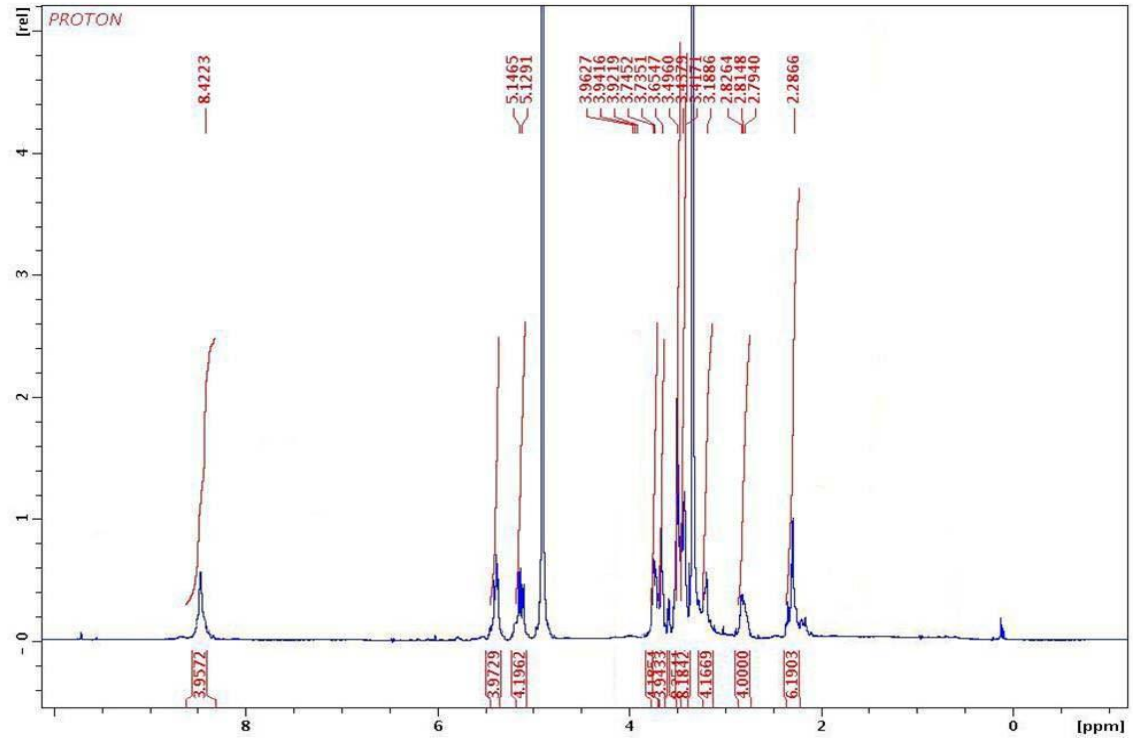


Figure A2.24. Bacteriochlorin 4b ($BGlc_4$) ^{1}H NMR (MeOD 4.87 and 3.31 ppm, water 4.9 ppm).

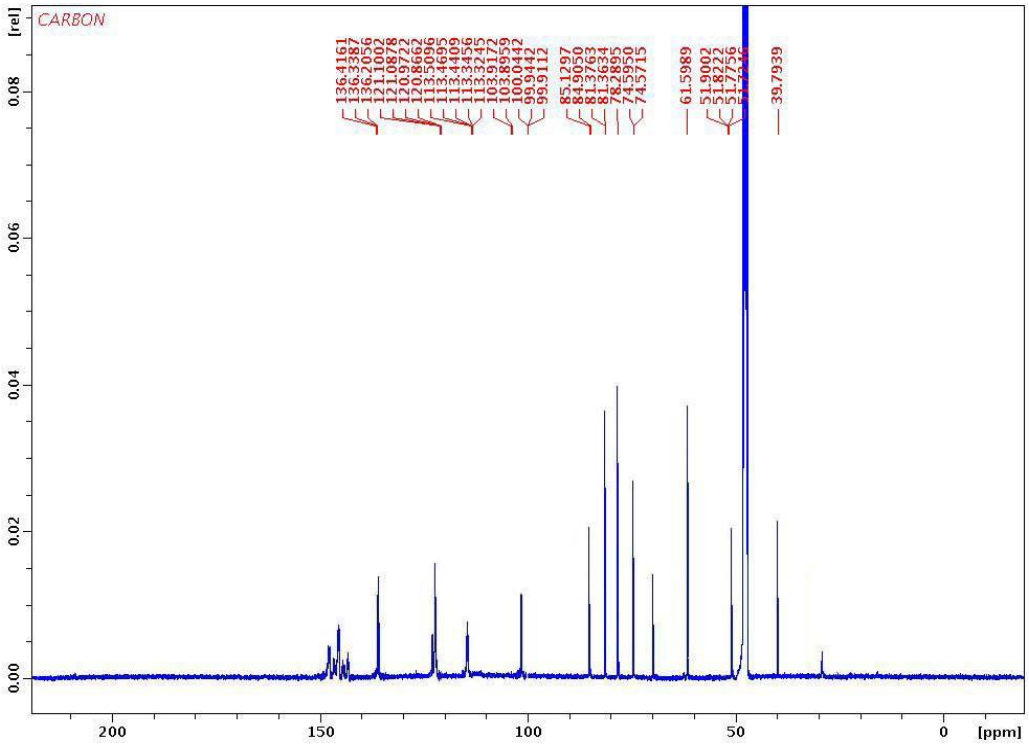


Figure A2.25. Bacteriochlorin 4b ($BGlc_4$) ^{13}C NMR (MeOD 49.15 ppm).

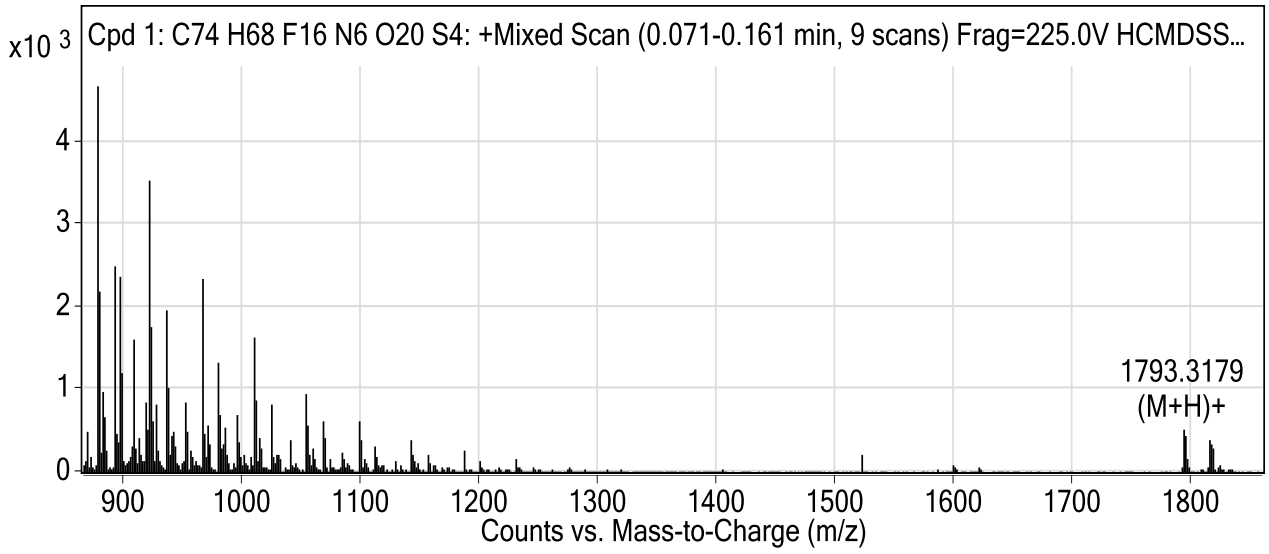


Figure A2.26. Bacteriochlorin 4b ($BGlc_4$) HRMS.

CD spectra

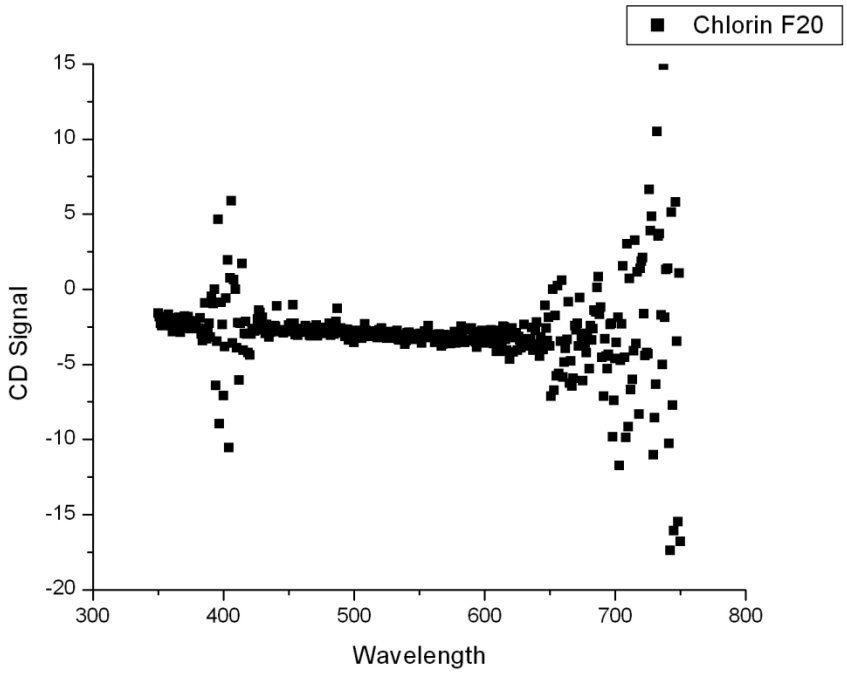


Figure A2.27a. CD spectra of CF_{20} in chloroform.

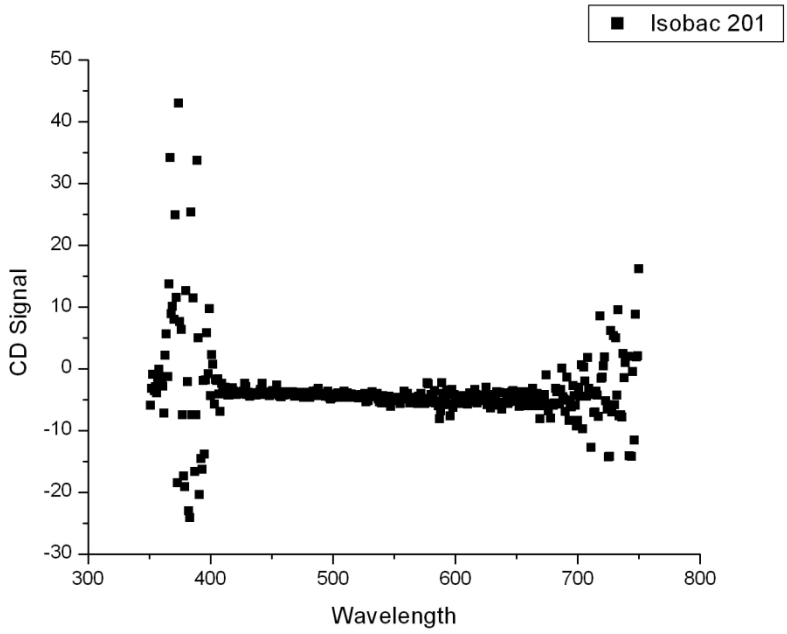


Figure A2.27b: CD spectra of *anti* IF_{20} in chloroform.

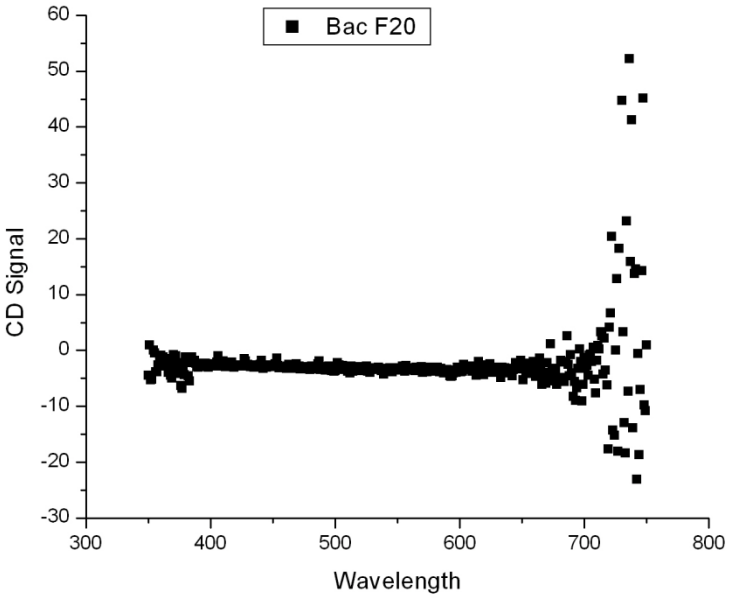


Figure A2.27c. CD spectra of *syn* BF_{20} in chloroform**.**

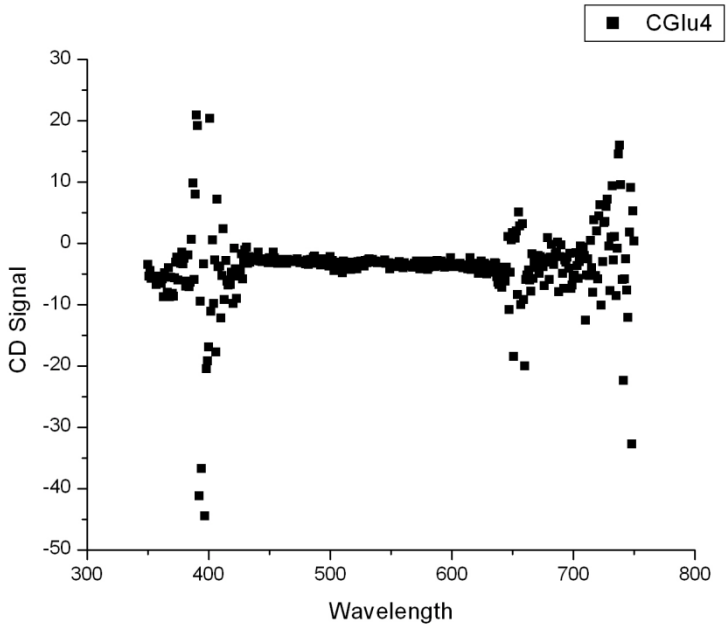


Figure A2.27d: CD spectra of $CGlc_4$ in methanol.

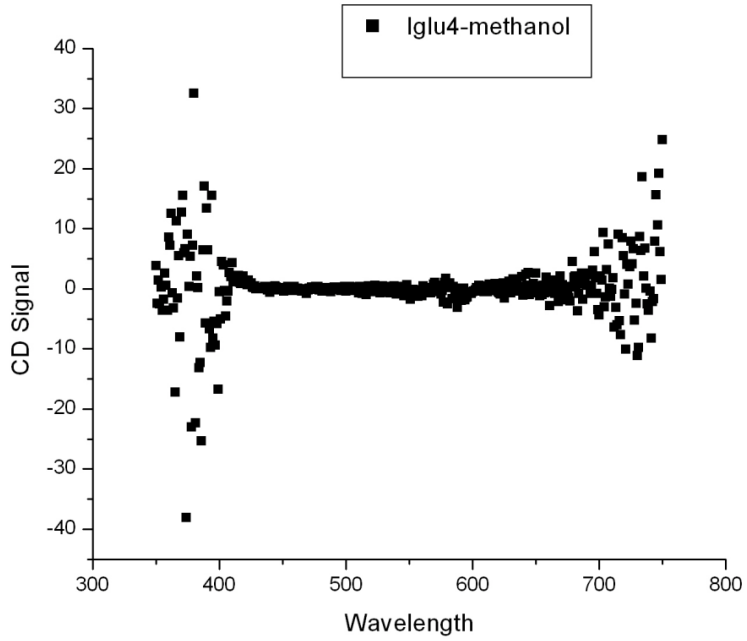


Figure A2.27e: CD spectra of $IGlc_4$ in methanol.

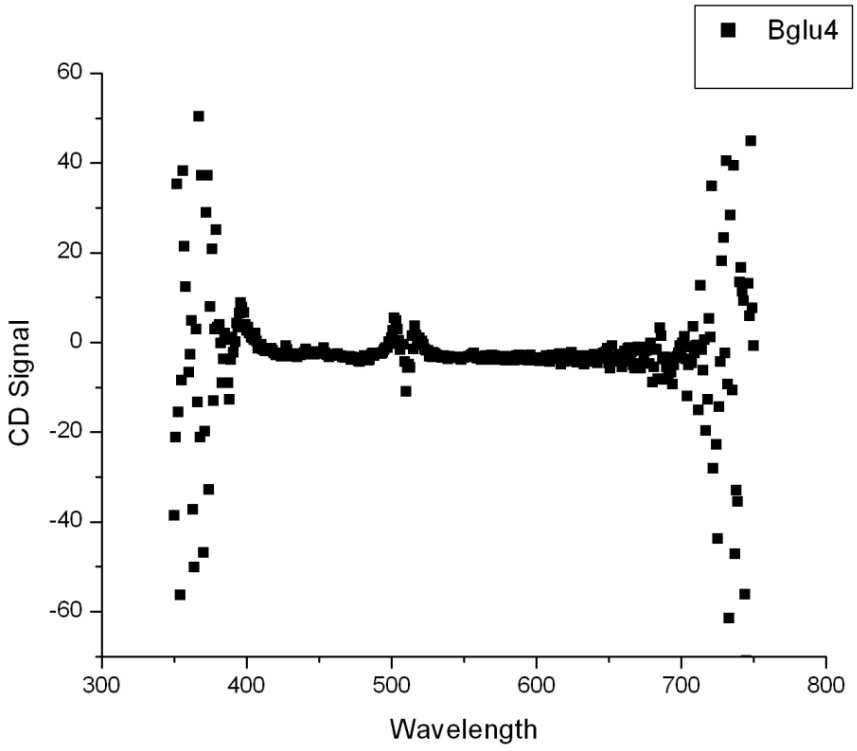


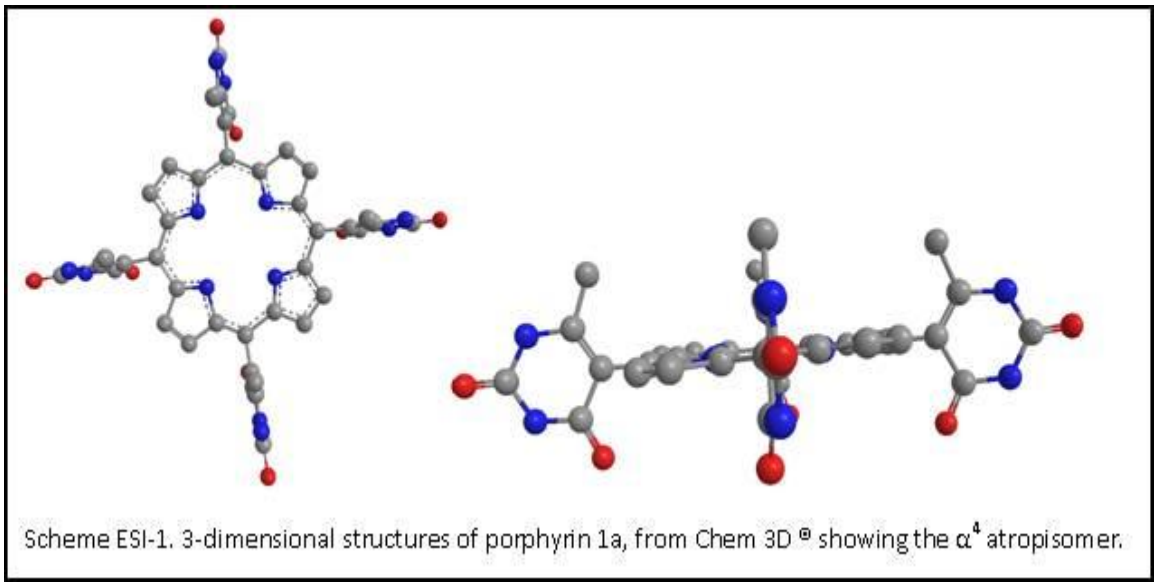
Figure A2.27f: CD spectra of $BGlc_4$ in methanol.

CHAPTER 3

HIERARCHICAL ORGANIZATION OF A ROBUST PORPHYRIN CAGE SELF-ASSEMBLED BY HYDROGEN BONDS[1]

Abstract

Porphyrins appended with four rigid hydrogen bonding motifs on the *meso* positions were synthesized and self-assembled into a cofacial cage with four complementary bis-(decyl)melamine units in dry solvents, these hydrogen-bonded cages were analysed by diffusion-ordered spectroscopy (DOSY) in solution. The hydrocarbon chains on the melamine mediate the formation of nanofilms on surfaces as the solvent slowly evaporates.



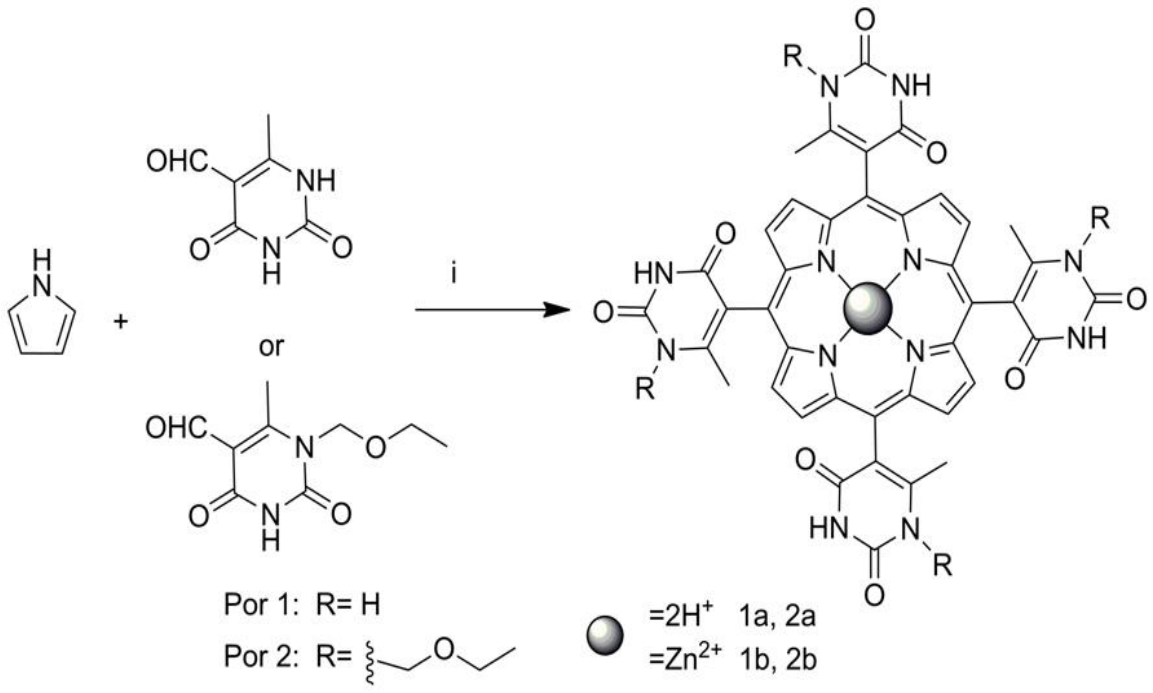
Scheme ESI-1. 3-dimensional structures of porphyrin 1a, from Chem 3D ® showing the α^4 atropisomer.

[1]This chapter is adapted from reference: 1. Singh, S., Aggarwal, A., Farley, C., Hageman, B. A., Batteas, J. A., and Drain, C. M. (2011) Hierarchical Organization of a Robust Porphyrin Cage Self-Assembledby Hydrogen Bonds, *Chem. Commun. 47*, 7134-7136.

3.1 Introduction

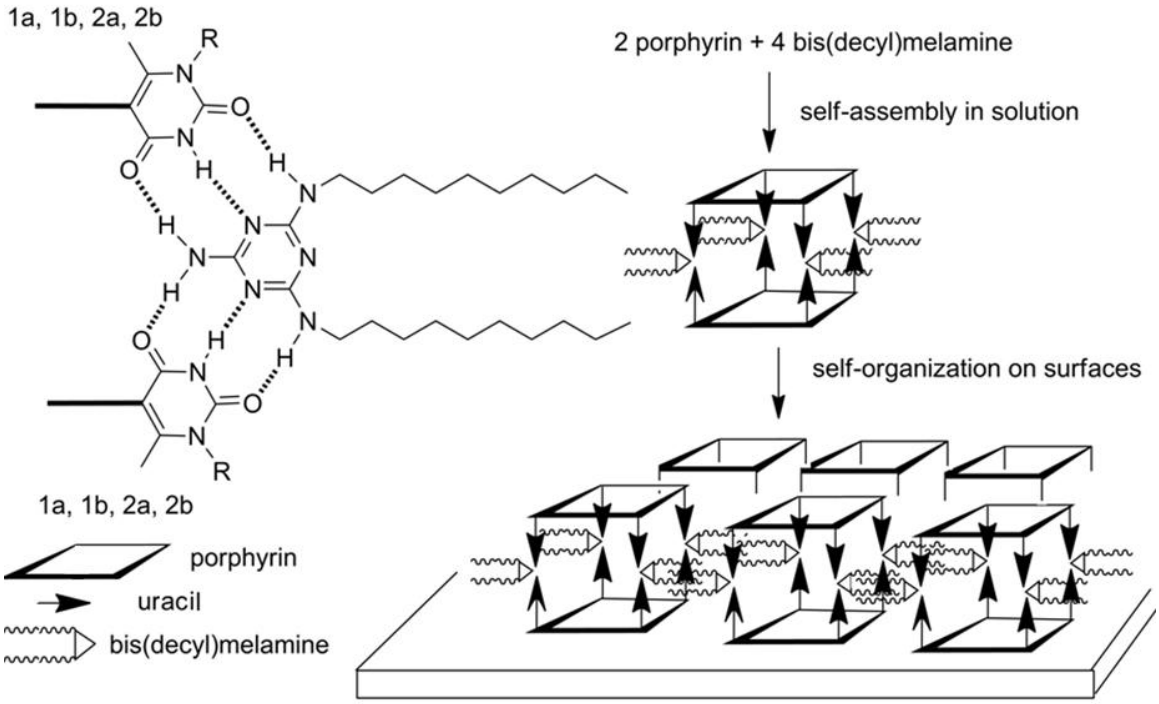
Self-assembly and self-organization of porphyrinoids(*6-8*) continue to produce functional materials with applications ranging from electronics(*9*) to catalysis.(*10*) Both coordination bonds and H-bonds can mediate formation of supramolecular porphyrinic materials. Porphyrinoids appended with H-bond motifs can assemble into diverse arrangements such as rosettes, squares, tapes, and nanoparticles for materials for solar energy harvesting, photonic devices, sensors, catalysts, and understanding biological electron transport.(*5, 11-16*) In addition to directing supramolecular architectures, the functional groups on the macrocycle and mode of assembly can modulate photophysical and chemical properties of chromophoric arrays. Responsive H-bond materials, whereby the supramolecular structure can be modulated by environmental conditions such as temperature or solvent, can find applications as catalytic hosts for specific guests, or control of electronic communication between subunits.(*17-20*) While functional materials of porphyrins self-assembled by hydrogen bonding have demonstrated utility, (*14*) porphyrins bearing hydrogen bonding motifs rigidly attached can be difficult to synthesize.(*11-13*)

Herein we report the synthesis of porphyrins possessing four rigid uracylic hydrogen bonding units on the meso positions (Scheme 3.1) and characterization of the self-assembly of these subunits into robust cage structures mediated by complementary 2,4-di(*n*-decylamino)-6-amino-1,3,5-triazine, bis(decyl)melamine, units.



Scheme 3.1 (i) reflux 10 h in 10% nitrobenzene in acetic acid with 0.05 M $Zn(OAc)_2$. The porphyrin is prepared as a mixture of the four atropisomers (α^4, $\alpha^3\beta$, $\alpha^2\beta^2$, $\alpha\beta\alpha\beta$) since the uracyl moieties are nominally orthogonal to the macrocycle plane.

Two notable features are: the porphyrins are made in one step, and the supramolecular dynamics are significantly reduced because all four meso positions participate in the assembly instead of two.(*5*, *11-16*) The free base and zinc complexes of two different macrocycles are used to form the cages (Scheme 3.2), where interconversion of the atropisomers of the uracylporphyrins is required. NMR, light scattering, and photophysical properties in solution indicate formation of the cages, and atomic force microscopy (AFM) elucidates the self-organization of the materials cast onto mica.



Scheme 3.2 Prolonged heating of two equivalents of one of the porphyrins in the presence of four equivalents of the H-bond complimentary bis(decyl)melamine (left) results in formation of and the α^4 atropisomer and self-assembly of the cage in solution, and the decyl groups mediate formation of monolayer films of the cage on surfaces (right).

Uracylporphyrin **1b** and *N*-alkyluracyl porphyrin **2b** are synthesized from 5-formyl-6-methyluracil and 1-ethoxymethyl-5-formyl-6-methyluracil(*5*, *15*-*21*) using Adler conditions with $Zn(OAc)_2$ (Scheme 3.1). *N*-alkylation of the uracil inhibits tautomerization at this position, diminishes unproductive H-bond formation, and improves solubility. Thus, we focus on these porphyrins herein. The free bases, **1a** and **2a**, are formed by demetalation reactions. The 2,4-di(*n*-decylamino)-6-amino-1,3,5-triazine was prepared similarly to previous reports.(*22, 23*)

3.2 Experimental Procedure

Materials and Instrumentation

^{1}H and ^{13}C spectra were recorded in a Brüker Avance 500 MHz spectrometer. Mass spectrometry analyses were performed at the CUNY Mass Spectrometry Facility at Hunter College by electrospray ionization on an Agilent Technologies G6520 Q-TOF instrument and Agilent 1200 HPLC system. The electrospray ionization was done in methanol, with 0.1% formic acid. UV-visible spectra were recorded on a Varian Bio3 spectrophotometer. Emission spectra and steady state fluorescence lifetimes were measured with a Fluorolog τ3 TCSPC (time correlated single photon counting) from Jobin-SPEX Instrument S. A., (Horiba Scientific. Inc.). To determine the size of the aggregates and cages, Dynamic light scattering (DLS) was performed using a Precision Detector PD2000DLS Cool-Batch instrument in batch mode at 25 ^{o}C. All reagents were obtained from commercial sources and used without purification. 5-Formyl-6-methyluracil (1) and 1-ethoxymethyl-5-formyl-6-methyluracil (2) were synthesized according to the previous literature(*5*, *21*, *24*). Variable temperature NMR measurements were performed from the range 279 K to 323 K.

Synthesis of Porphyrin 1b

Pyrrole (69.5 µL, 1.0 mmol) and 5-Formyl-6-methyluracil **1** (158 mg, 1.0 mmol) and zinc acetate (109.8 mg, 0.50 mmol) were added to a boiling mixture of acetic acid (7.5 mL) and nitrobenzene (5.0 mL). The reaction mixture was refluxed for 10 h while monitoring the yields spectroscopically, and then taken to dryness under vacuum. The resulting solid was purified by column chromatography, eluting with ethyl acetate/

methanol/ acetic acid (7:3:1) to yield 17 mg (8 %) of **1**. Chromatographic purification enriches the α^4 and $\alpha^3\beta$ atropisomers. ^{1}H NMR (DMSO-d_6) δ11.5 (br, d, 8H), 9.50 (s, 8H), 2.50 (s, 12 H); ^{13}C (DMSO-d_6) δ 41.84, 110.60, 113.38, 113.41, 131.70, 150.77, 150.81, 152.26, 166.25. HRMS calcd. for $C_{40}H_{28}N_{12}O_8Zn$ (M+H)+ 869.1523, found 869.1514.

Synthesis of Porphyrin 2b

Aldehyde **4** was synthesized according to the previous literature. Pyrrole (69.5 µL, 1.0 mmol) and 1-Ethoxymethyl-5-formyl-6-methyluracil **4** (212 mg, 1.0 mmol) and zinc acetate (109.8 mg, 0.50 mmol) were added to a boiling mixture of acetic acid (7.5 mL) and nitrobenzene (5.0 mL). The reaction mixture was refluxed for 10 h while monitoring the yields spectroscopically, and then taken to dryness under vaccum. The resulting solid was purified by column chromatography, eluting with ethyl acetate/ methanol (9:1) to yield 15 mg (5 %) of **2**. Chromatographic purification enriches somewhat the α^4 and $\alpha^3\beta$ atropisomers. ^{1}H NMR (MeOD-d_4) δ 9.22 (s, 8H), 5.65 (m, 8H), 3.86 (m, 8H), 2.51 (m, 12H), 1.31(m, 12H). ^{13}C NMR (MeOD-d_4) δ 12.83, 14.48, 54.63, 63.24, 71.86, 129.61, 149.23, 163.24, 189.5. HRMS calcd. for $C_{52}H_{52}N_{12}O_{12}Zn$ $(M)^+$ · 1100.3119, found 1100.3112.

Free base porphyrins 1a and 2a.

Porphyrin 2b (15 mg, 13 µmol) were dissolved in a THF, water and conc. HCl. The mixture was stirred for 30 min, the mixture was poured into water and $(NH_4)_2CO_3$ was added until the pH is 6, the porphyrin products were extracted with ethylacetate. The combined organic extract was washed with water and brine and dried over Na_2SO_4 and then porphyrin was precipitated with ethylacetate/hexane to give the free base porphyrin

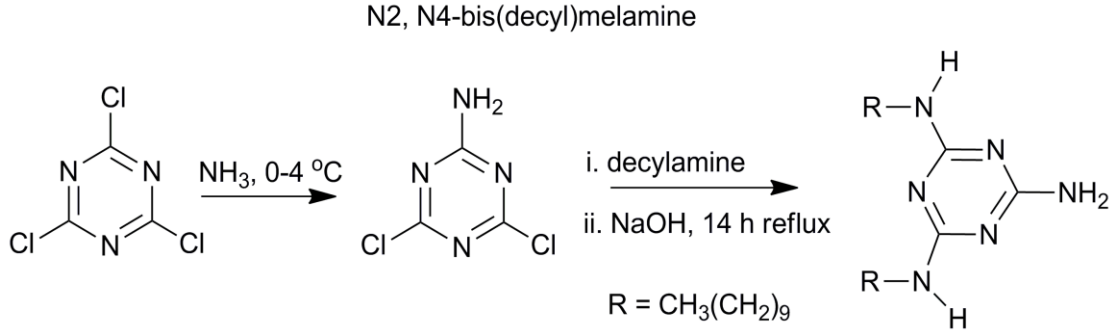
2a (12 mg, 90 % yield). Porphyrin 1b (15 mg, 17 μmol) were dissolved in a THF, acetic acid and conc. HCl. The mixture was stirred for 30 min, the mixture was poured into water and $(NH_4)_2CO_3$ was added until the pH is 6. The porphyrin was precipitated from solution to give 1a (12 mg, 90% yield).

Atropisomers

Porphyrins **1** and **2** shows atropisomerism because of the steric hindrance to rotation of the uracyl-porphyrin bond due to interactions between the uracyl 2-carbonyl and 6-methyl groups and the pyrrole βH. The thermodynamics of atropisomerization was determined for **2b** in MeOD-d_4. The ^{1}H NMR spectra of porphyrin **2** has distinct resonances for the uracyl 6-methyl due to ring current effects and the 1-N methylene groups. There should be six resonances for both the 6-methyl near 2 ppm, and the 1-N methylene group, observed as complex multiplets near 5 ppm. The ratio of the resonances for the 6-methyl group was used to determine the ratio of the four rotamers; which in the initially prepared porphyrin was approximately the expected 1:4:2:1 for αααα, αααβ, ααββ, and αβαβ. The rotational barrier was determined for porphyrin **2b** by doing the variable temperature NMR from 5 ^{o}C to 50 ^{o}C in MeOD-d_4.(*25*) The value of K was determined by shift in the (N-CH_2-O) protons. The equilibrium constant was determined by a Van't-Hoff plot (ln K versus 1/T) and the $\Delta G^{\#}$ was found to be about 123 kJ/mol for **2b**.(*2, 4*) The $\Delta G^{\#}$ for the free base is typically less by about 20 kJ/mol because the metalloporphyrin is more rigid. The poor solubility of porphyrins **1a** and **1b** made similar analysis difficult, but the barriers should be about the same. MALDI mass spectrometry reveals the starting components but not the cages. Note that one uracyl methyl resonance is observed for the cages (see appendix).

2,4-di(*n*-decylamino)-6-amino-1,3,5-triazine

bis(decyl)melamine, was prepared similarly to literature methods(*22, 23, 26*) from 2-Amino-4,6-dichloro-1,3,5-triazine, which was prepared from cyanuric chloride (*27*)



Scheme 3.3: Synthesis of bis(decyl)melamine

3.3 Results and Discussion

For **2b** the free energy barrier for atropisomer interconversion was determined by a van't Hoff plot (ln K versus 1/T) and the $\Delta G^{\#}$ was found to be about 123 kJ/mol in CD_3OD. This is consistent with earlier results, which proposed the increased rigidity of the macrocycle when complexed to a metal ion raises the rotational barrier by about 20 kJ/mol. Therefore, the $\Delta G^{\#}$ for **2a** is estimated to be about 102 kJ/mol.(*2, 4, 28*) Similarly, $\Delta G^{\#}$ values for atropisomerization of **1a** and **1b** are expected. The porphyrins are poorly soluble in dry THF-d_8 but slowly become more soluble upon addition of the melamine and heating between 40-50 ^{o}C for greater than four days for **1a** and **1b** and two days for **2a** and **2b**. The formation of the cage removes the α^4 atropisomer from the equilibrating solution thereby increasing the yield of the cage.(*29*) The self-assembled cage is characterized by the NMR chemical shifts of the

uracil and melamine NH protons in the H-bonds (Table 3.1).

Table 3.1

Compound	NH proton porphyrin	NH proton melamine
Porphyrin I	11.5 ppm	NA
Porphyrin II	12 ppm	NA
Melamine	NA	4.5-5 ppm
Porphyrin I + Melamine	14 ppm	5.5-6.7 ppm
Porphyrin II + Melamine	13.8 ppm	5.5-6.1 ppm

Diffusion ordered spectroscopy (DOSY) allows the molecular weights of the assemblies to be determined.(*5*, *15-20*, *30-33*) The DOSY experiments used a Bruker 500 MHz instrument and the normalized diffusion coefficient (D_{norm}) was measured as the ratio of the observed value (D_{obs}) to $D_{\beta\text{-CD}}$, where $D_{\beta\text{-CD}}$ is the diffusion coefficient for the internal standard, heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (β-CD). The molecular weight could be calibrated by D_{norm} of a series of polystyrene standards (Figure 3.1). The value of D_{norm} for Por **1b** + melamine was 0.64, which indicates a **1b**-**1b** cage with a *m* of 3360 (calculated 3295), and D_{norm} for Por **2b** + melamine was 0.60 which indicates the formation of a cage with a *m* of 3820 (calculated 3717).

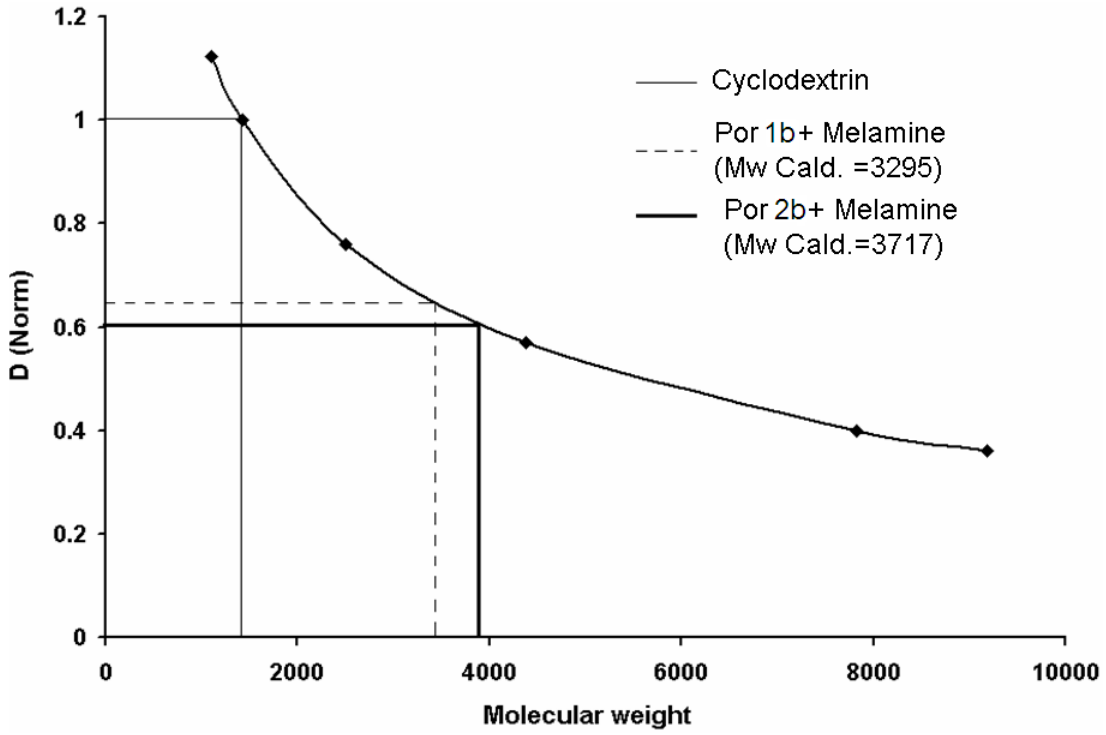


Figure 3.1. The five points on the curve are D_{norm} of polystyrene standards versus molecular weight, and the D_{norm} of the two cages to yield estimates of the molecular weights. (10 mM in THF-d_8)

The photophysical properties correlate with the NMR results.(*34*)[†] UV-visible spectra of the **2a-2a** and **2b-2b** (Figure 3.2) cages (38 µM - 42µM in porphyrin) with bis(decyl)melamine in dry THF were recorded. For the first several days at room temperature, there was no or little change in the intensity of the UV-visible bands but on heating at 45-47 ^{o}C for ~ 2 days causes an increase in the intensities of these bands indicating increased solubilty of porphyrins due to complexation with melamine units and also shift in the equilibrium towards the formation of the α^4 atropisomer and the cages. The emission spectra of the **2a-2a** and **2b-2b** cage solutions, exciting in the Soret or Q bands, are consistent with the UV-visible results. Due to formation of the porphyrin aggregates, there was initial decrease in the intensity of the signals

followed by increase in fluorescence intensity upon heating indicating increased solubility and the cage formation.

Dynamic light scattering data reveals the hydrodynamic radius of the initially formed aggregates formed for the **2a-2a, 2b-2b**, and for **2a-2b** cages to be about 42 nm, and after heating the average particle size is between 7-9 nm. Assuming extended decyl groups, an estimation of the cage dimensions from Chem 3D© is about 5.2 nm from terminal methyl to terminal methyl on opposite sides of the cage and about 2 nm perpendicular to the porphyrin planes.

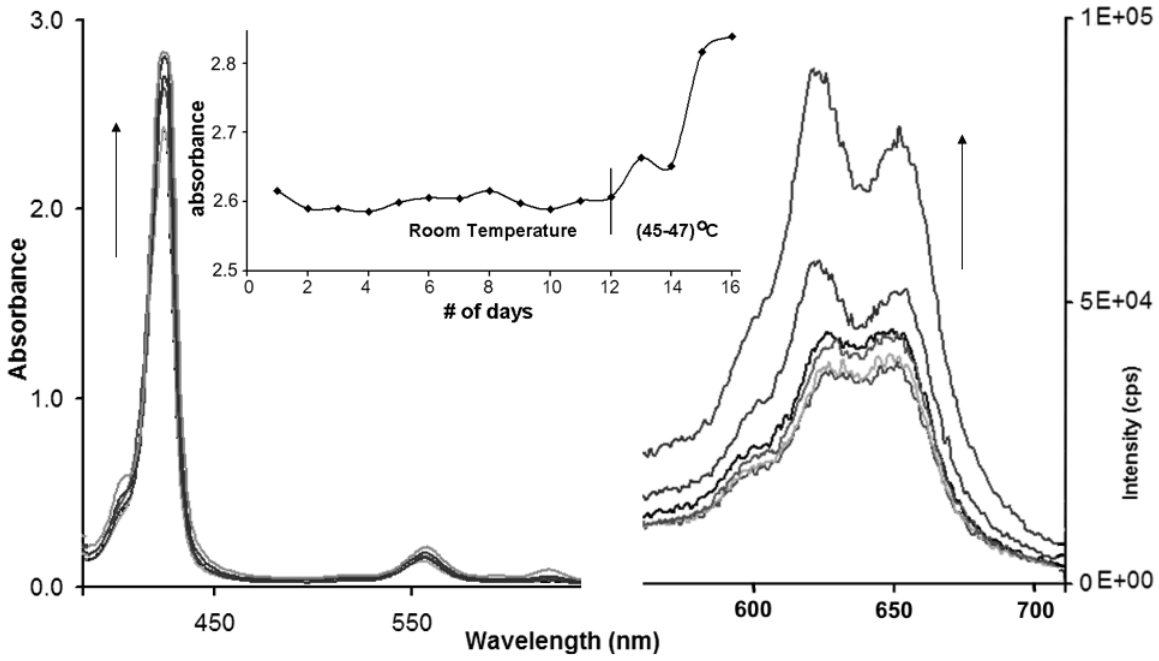


Figure 3.2: After somewhat decreasing initially due to aggregation, the intensity of the UV-visible and fluorescence spectra increases with time and heating as the amount of the self-assembled **2b-2b** cage increases. (Photophysics done by Amit Aggarwal and Christopher Farley)

Time correlated single photon counting experiments on these self-assembled cages were carried out in dry THF under N_2 at the same concentration used for the UV-visible studies, and 408 nm excitation (Table 3.2).

Table 3.2: Fluorescence Life time of Porphyrins and Cages

Compound	τ1 (ns)	τ2 (ns)
1a	2.2 (19%)*	8.8 (81%)
1b	2.5	----------
2a	1.8 (5%)*	8.6 (95%)
2b	3.76	----------
1a-1a cage	2.8 (20%)	10.2 (80%)
1b-1b cage	2.9	----------
2a-2a cage	3.64 (11%)	9.6 (89%)
2b-2b cage	2.4	----------

*some metalloporphyrin present, 408 nm excitation, 200 ps instrument response time
Data from Amit Aggarwal.

The two lifetimes for 1a and 2a is indicative of incomplete demetalation of porphyrins 1b and 2b respectively. The lifetimes for **1a**, **2a**, **1b**, **2b** are somewhat shorter than standard tetraphenylporphyrin (TPP, 11 ns) and ZnTPP (2.7 ns) under similar conditions(*35*) because of some aggregation. However, disaggregation of the aggregates in solutions for the cage formation, brings the lifetime closer to those for other meso aryl porphyrins.

For self-assembled materials to be used in optical devices, the interaction between the material and surfaces is necessary, we examined the self-organization of the cages into films. Drop cast method was used to deposit a 30-40 μM solution of supramolecular cage in THF onto freshly cleaved mica and imaged with AFM. The

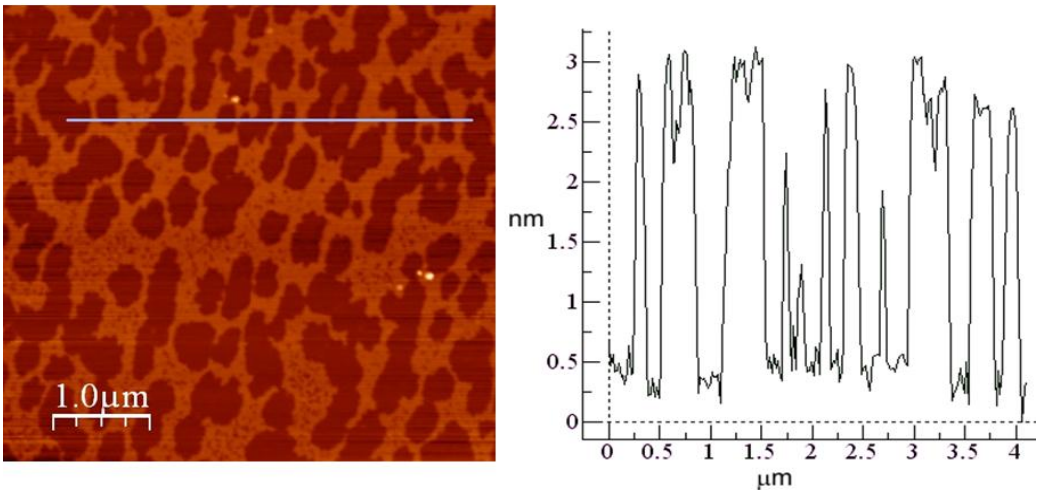


Figure 3.3A: AFM of the **2a-2a** cage on mica (left) and height profile (right). (AFM was done by Brian A. Hageman)

mica was placed in closed cell culture dishes and the evaporation rate was retarded by adding the solvent to the space surrounding the sample. A film corresponding to a single layer of the cage structures is observed when **2a-2a** is cast onto the mica. (Figure 3.3A). In this film, the self-assembled cage is hierarchically organized by interactions between the protruding hydrocarbon chains on the four bis(decyl)melamine units.(*36*) Friction images show no indication of separation of the porphyrin and the melamine components. When the **2b-2b** cage is cast onto mica, somewhat thicker 12 nm films are observed, with root-mean-square roughness of about 4 nm. More complex patterns on the surface were observed when the three different cages resulting from the mixture of **2a** and **2b** were used. This hierarchical self-organization into films is analogous to those observed for squares of porphyrins self-assembled by coordination chemistry.(*37*)

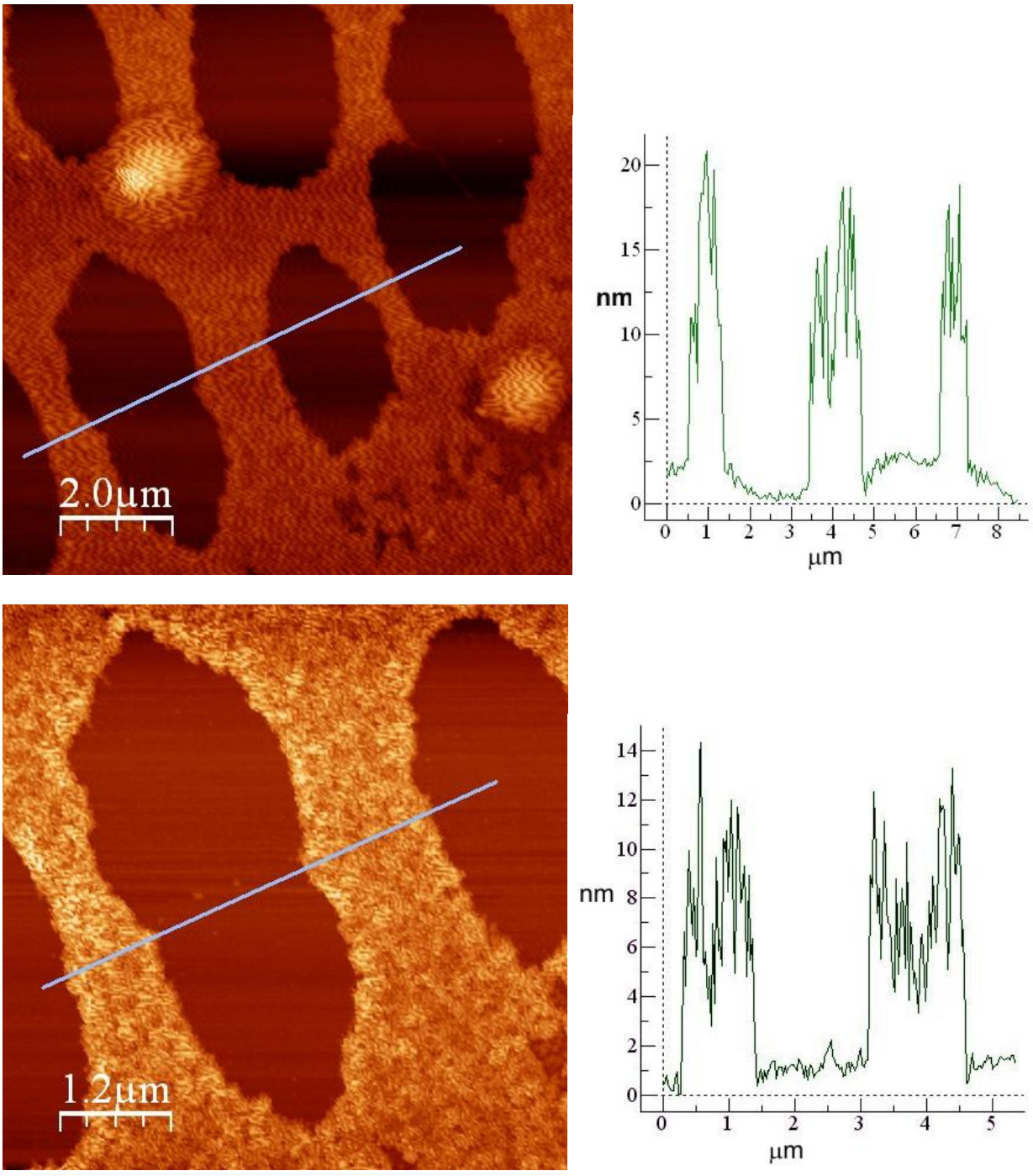


Figure 3.3B: AFM of the cage formed from **2b**. Image taken by Brian A. Hagemann.

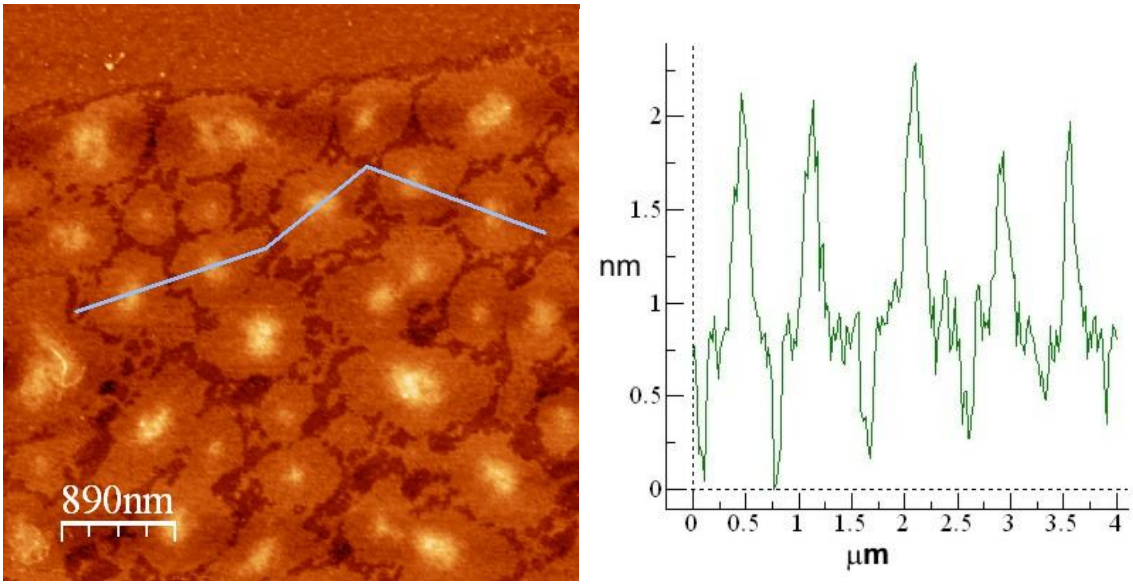


Figure 3.3C AFM of the 1:2:1 mixture of **2a-2a**, **2a-2b**, **2b2b** cages formed from the mixture of **2a** and **2b** with the bid(decyl)melamine. Image taken by Brian A. Hageman.

3.4 Conclusions

The synthesis of the porphyrins and aldehydes is straight forward. The cooperative self-assembly of the porphyrin cages mediated by four rigid meso uracil groups and the bis(decyl)melamine form a stiff cage robust enough to allow organization on surfaces driven by the long hydrocarbon chains into nm thick films on mica. Assembly, in this case, turns off electronic communication between chromophores.

3.5 References

1. Singh, S., Aggarwal, A., Farley, C., Hageman, B. A., Batteas, J. A., and Drain, C. M. (2011) Hierarchical Organization of a Robust Porphyrin Cage Self-Assembledby Hydrogen Bonds, *Chem. Commun. 47*, 7134-7136.
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3.6 Appendix

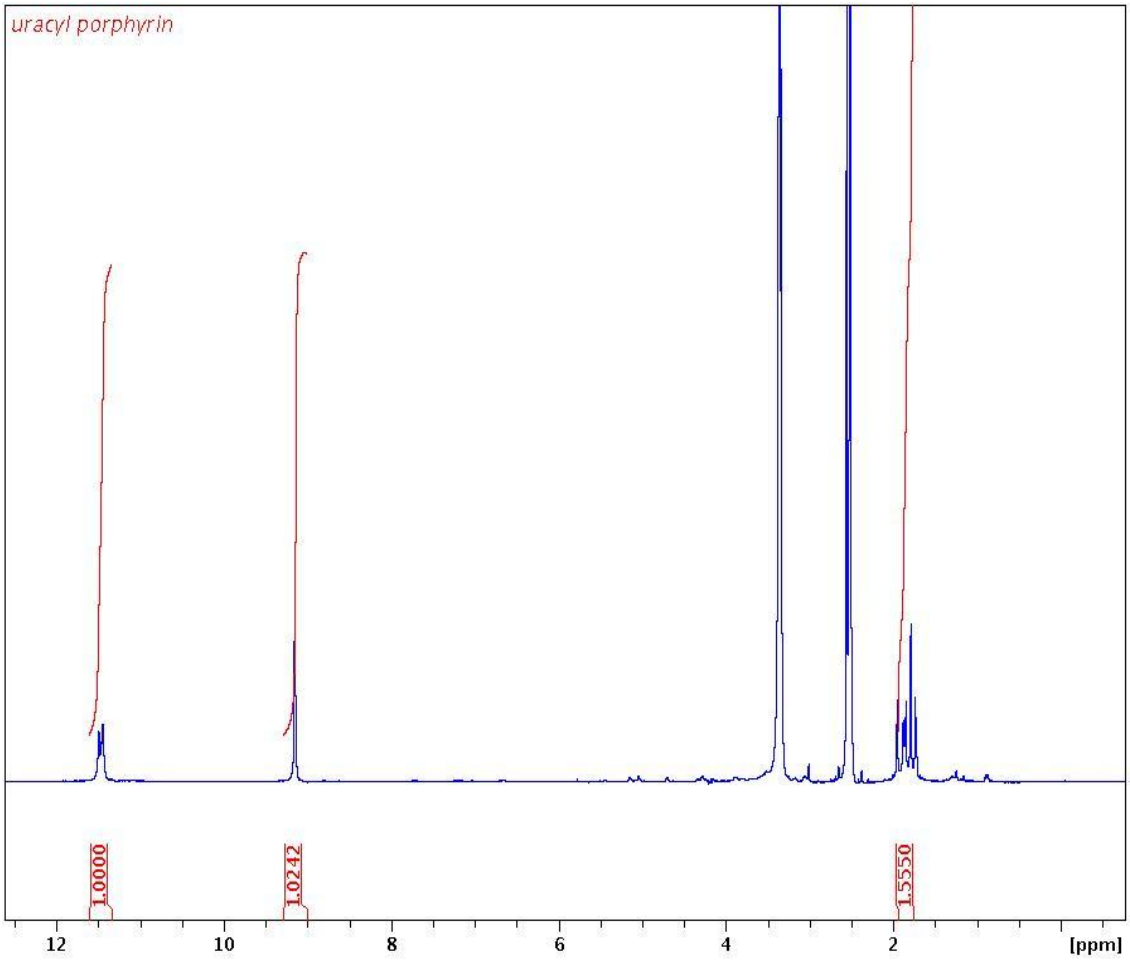


Figure A3.1. ^{1}H NMR of porphyrin **1b** in DMSO-d_6**.**

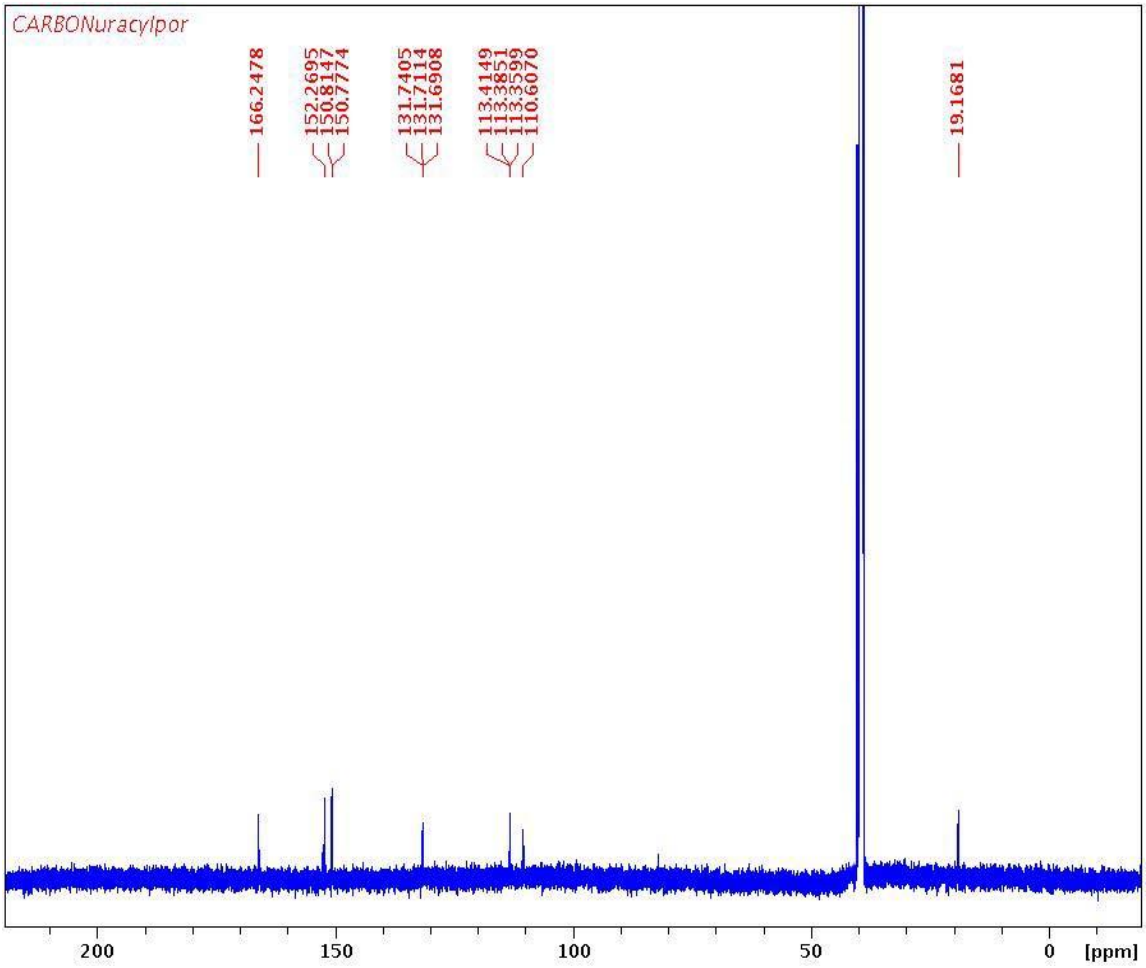


Figure A3.2. ^{13}C NMR of Porphyrin **1b** in DMSO-d_6

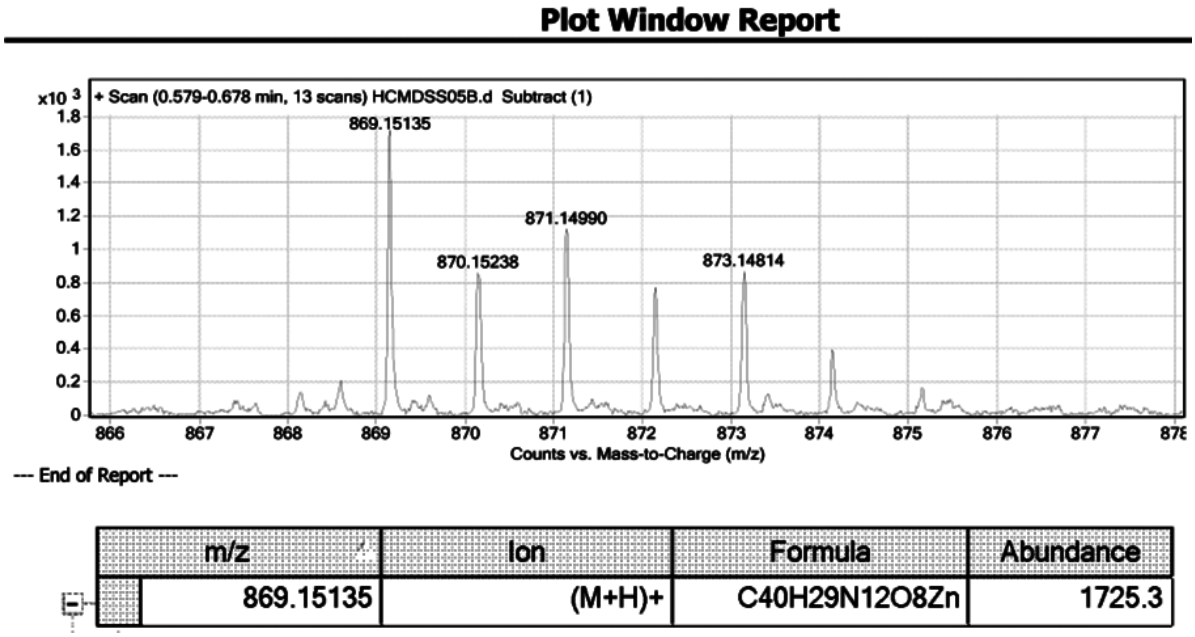


Figure A3.3. Mass spectrum of Porphyrin **1b**

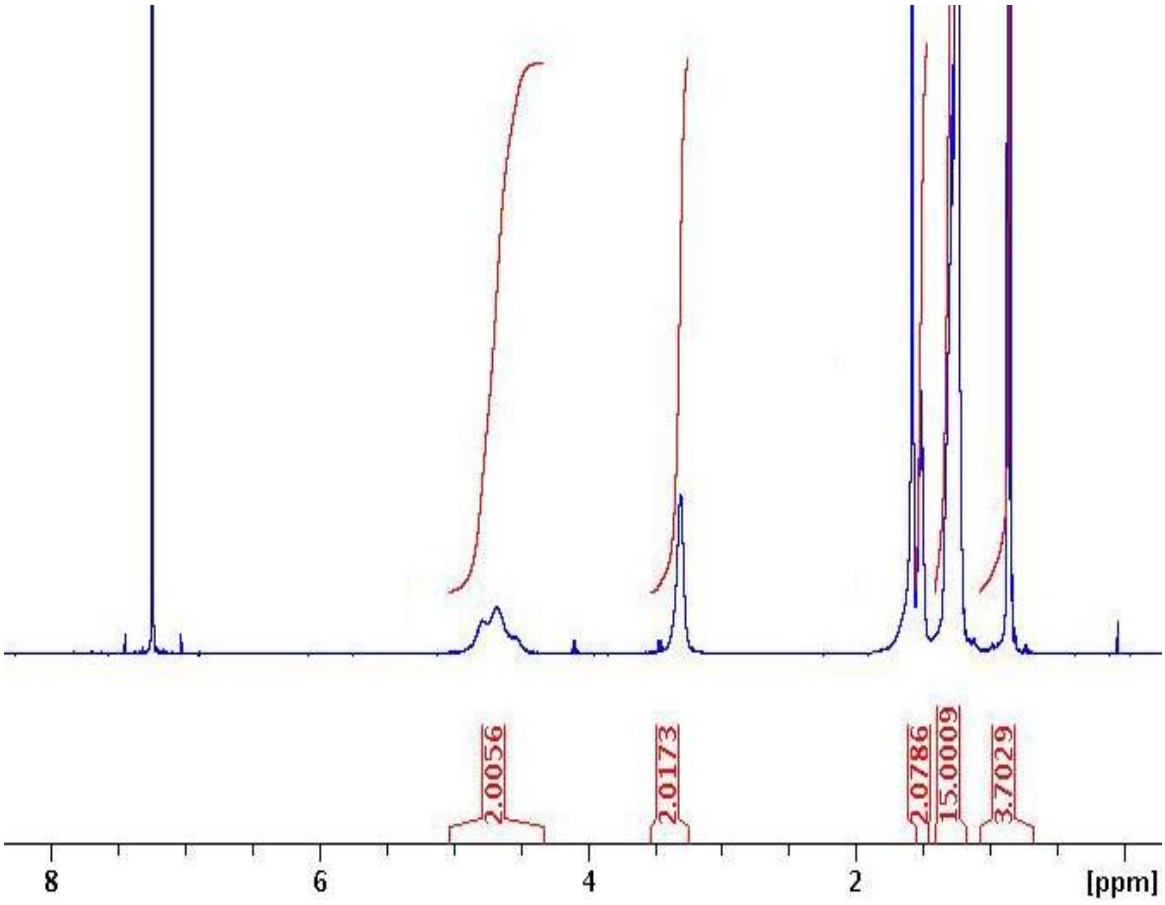


Figure A3.4. ^{1}H NMR of bis(decyl)melamine in $CDCl_3$

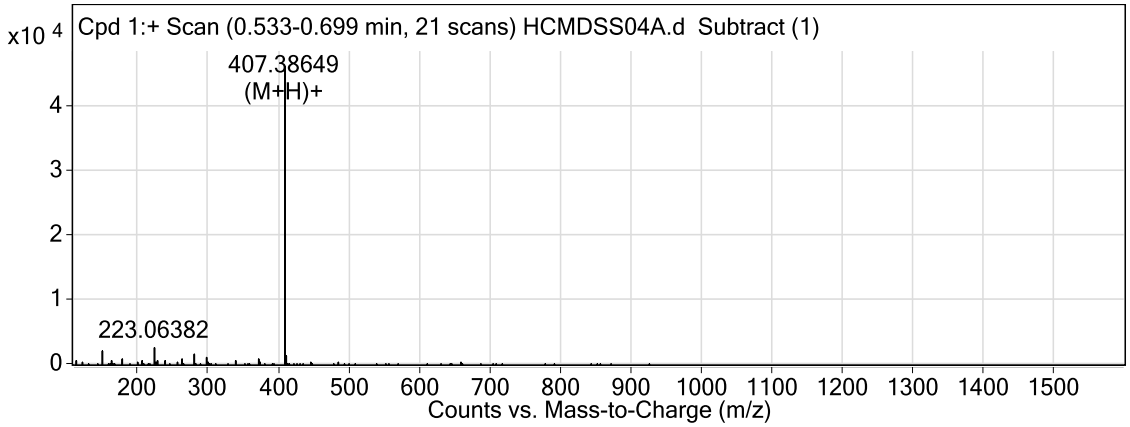
Data Filename	HCMDSS04A.d	**Sample Name**	Alkylated Melamine
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
Acq Method	HC ESI Pos Small Molecule No HPLC.m	**IRM Calibration Status**	Success
DA Method	HCEmpirical1.m	**Comment**	EM=406.38 M=HC ESI Pos Small Molecule No HPLC.m

Compound Table

Name	RT	Mass	Abund.	Formula	Tgt Mass
Compound 1	0.6	406.37921	46202	C23H46N6	406.3784

Compounds

Name	RT	Algorithm	Mass
Compound 1	0.583	Find By Formula	406.37921



MS Spectrum Peak List

m/z	z	Abund.	Formula	Ion	Diff(ppm)
223.06382		2821			
407.38649	1	47484	C23H47N6	(M+H)+	2.01
408.38908	1	11471			

Figure A3.5. Mass spectrum of bis(decyl)melamine.

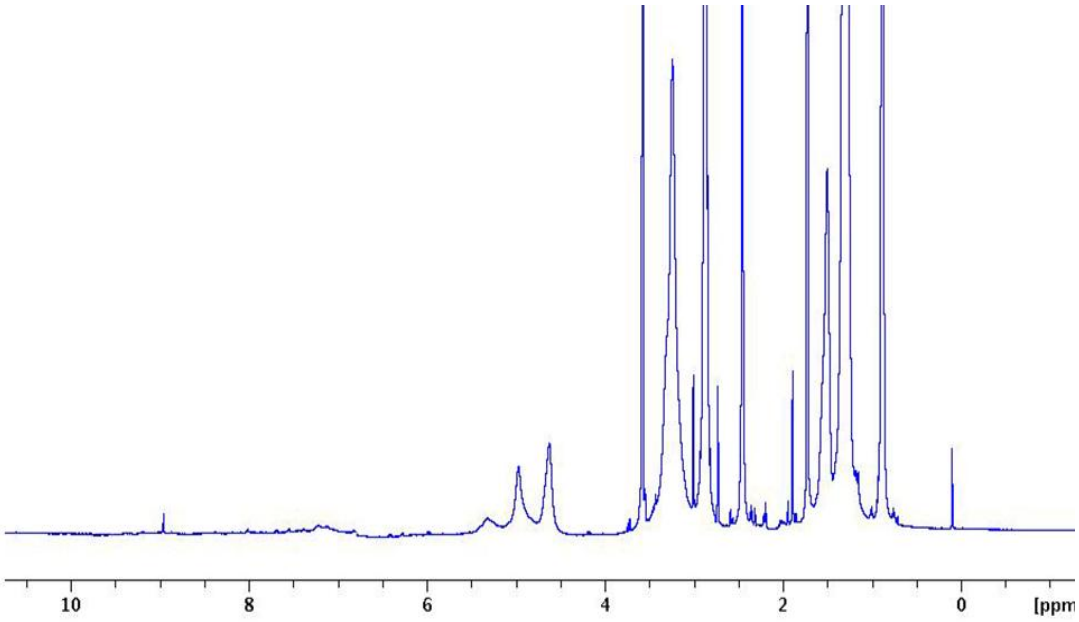


Figure A3.6. Day 1 NMR of melamine and porphyrin **1b** in dry THF in ratio 4:2 respectively

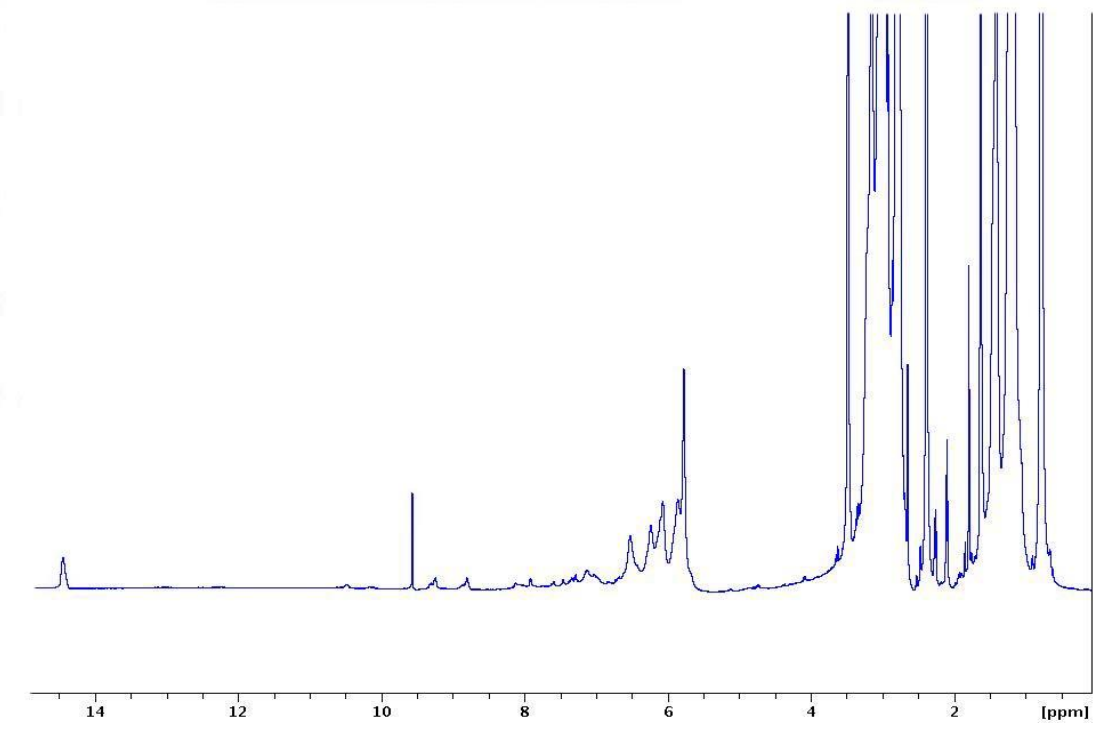


Figure A3.7. Day 14 NMR of melamine and porphyrin **1b** in dry THF in ratio 4:2 respectively.

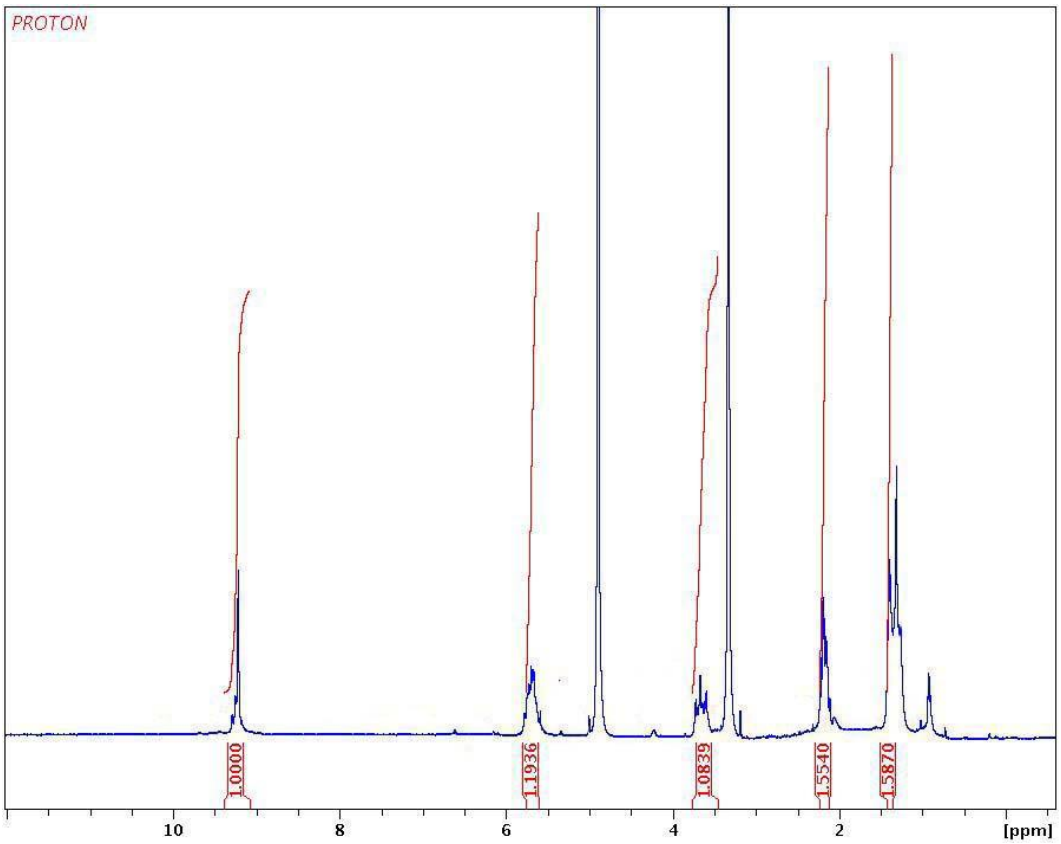


Figure A3.8. ^{1}H NMR of porphyrin **2b** in MeOD-d_4 solvent

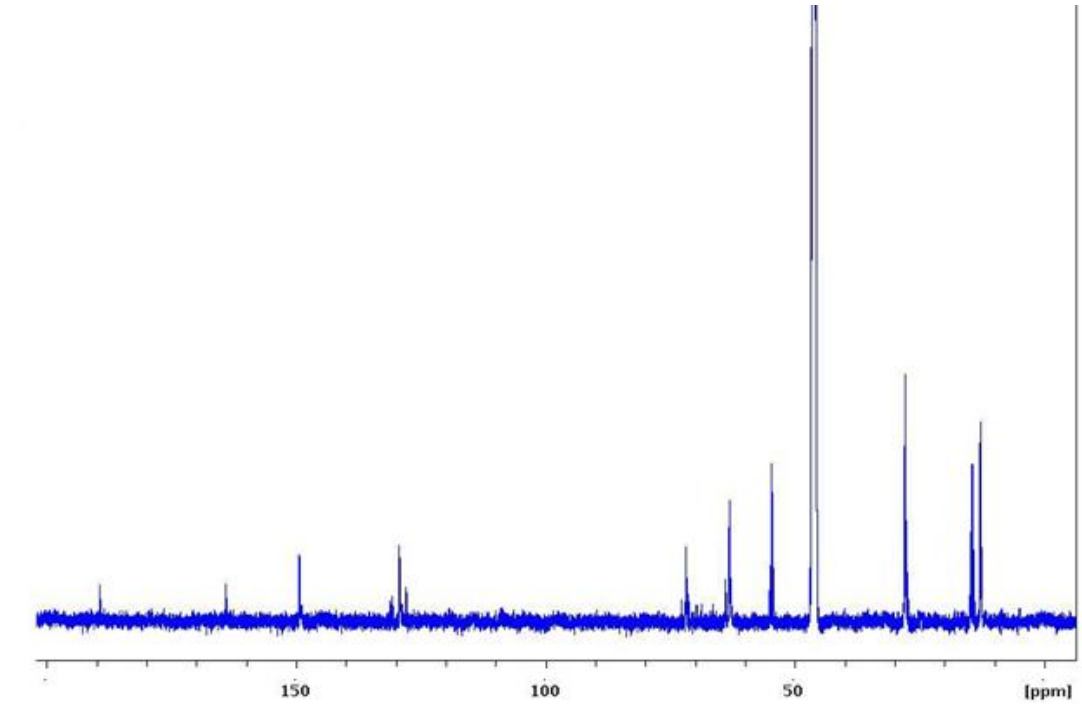


Figure A3.9. ^{13}C NMR of porphyrin **2b** in MeOD-d_4 solvent

Data File	HCMDSS54A.d	**Sample Name**	EthoxyZnPor
Sample Type	Sample	**Position**	P1-A2
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	9/17/2010 7:28:46 PM
IRM Calibration Status	Some Ions Missed	**DA Method**	HCEmpirical1.m
Comment	EM=1100.3119 EM=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C52H52N12O12Zn	**0.264**	**1100.3122**	**2913**	**C52H52N12O12Zn**	**1100.3119**	**0.24**

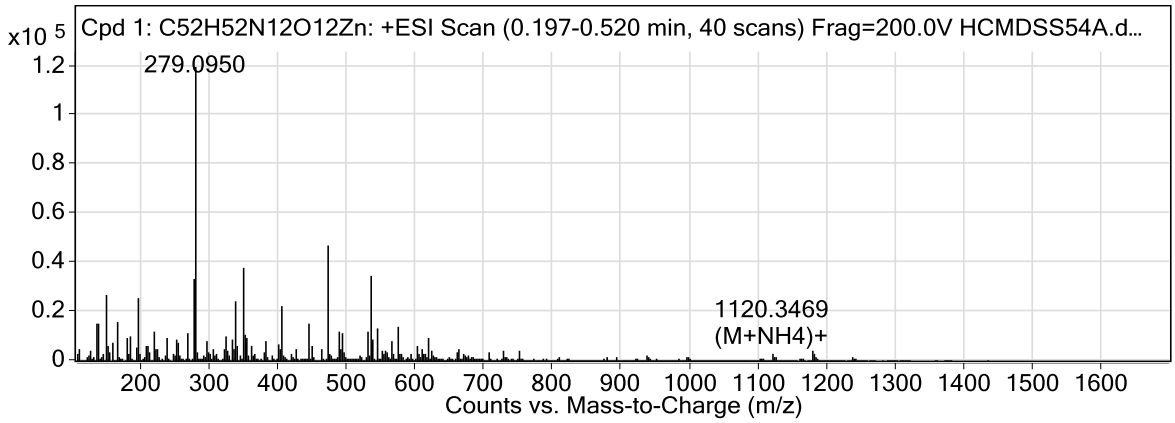


Figure A3.10. Mass spec of porphyrin **2b**.

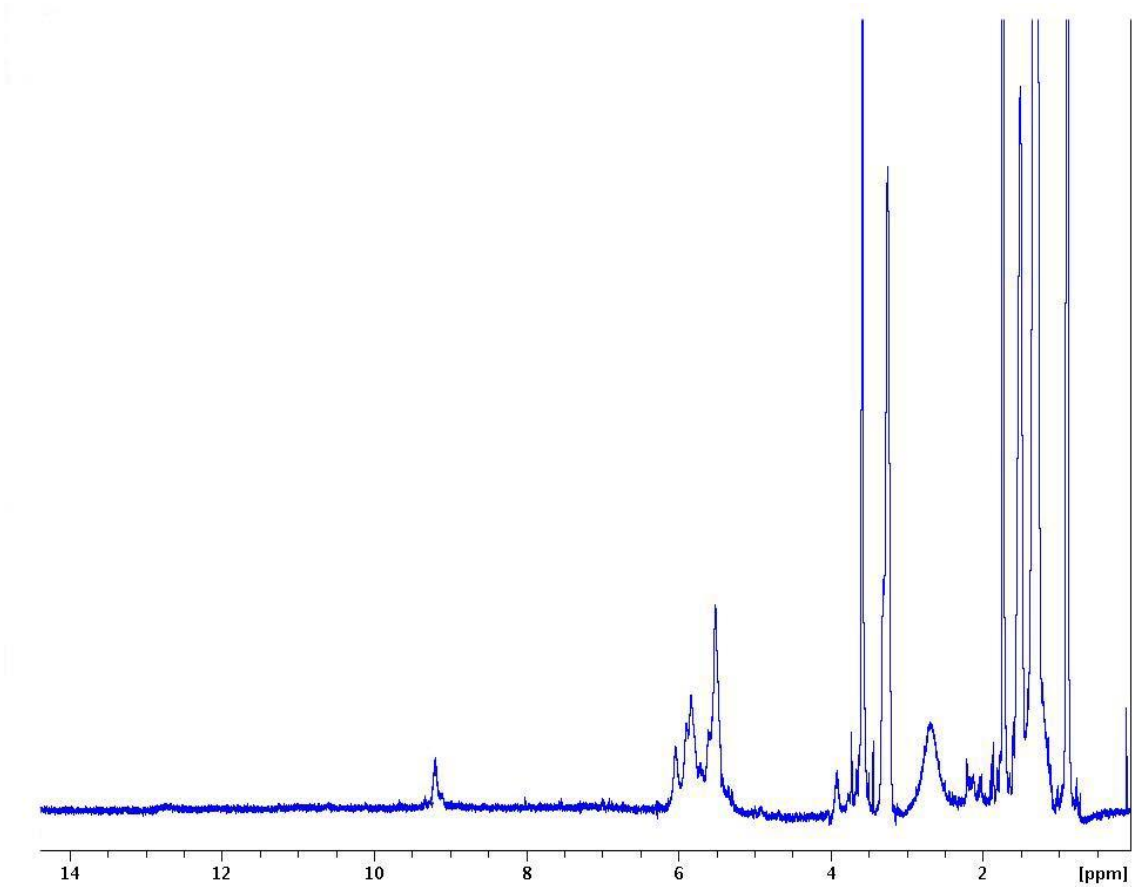


Figure A3.11. ^{1}H NMR of Porphyrin **2b** + melamine; day 1 in THF-d_8

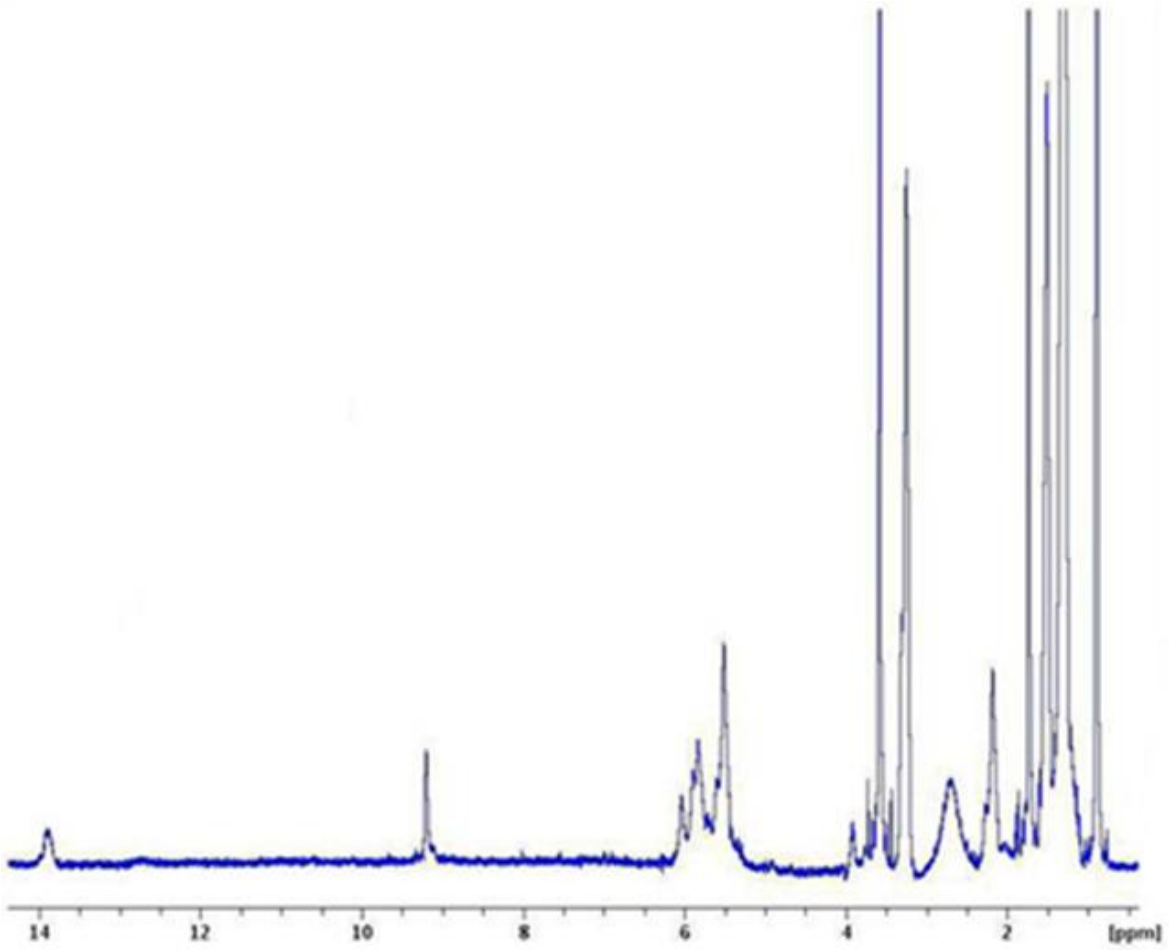


Figure A3.12. ^{1}H NMR of Porphyrin **2b** + melamine; day 10 in THF-d_8

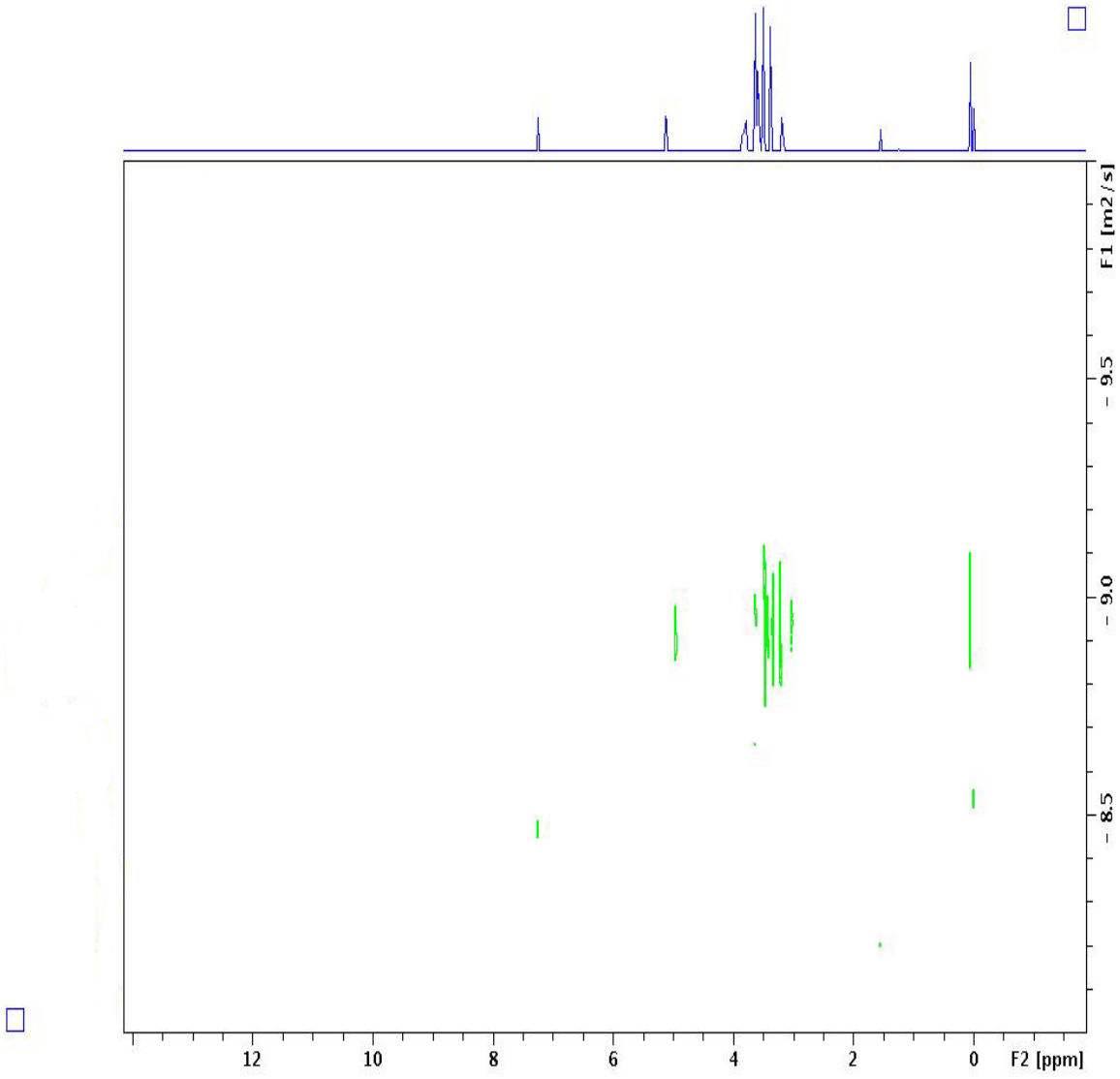


Figure A3.13. 2D DOSY spectrum of cyclodextrin in $CDCl_3$

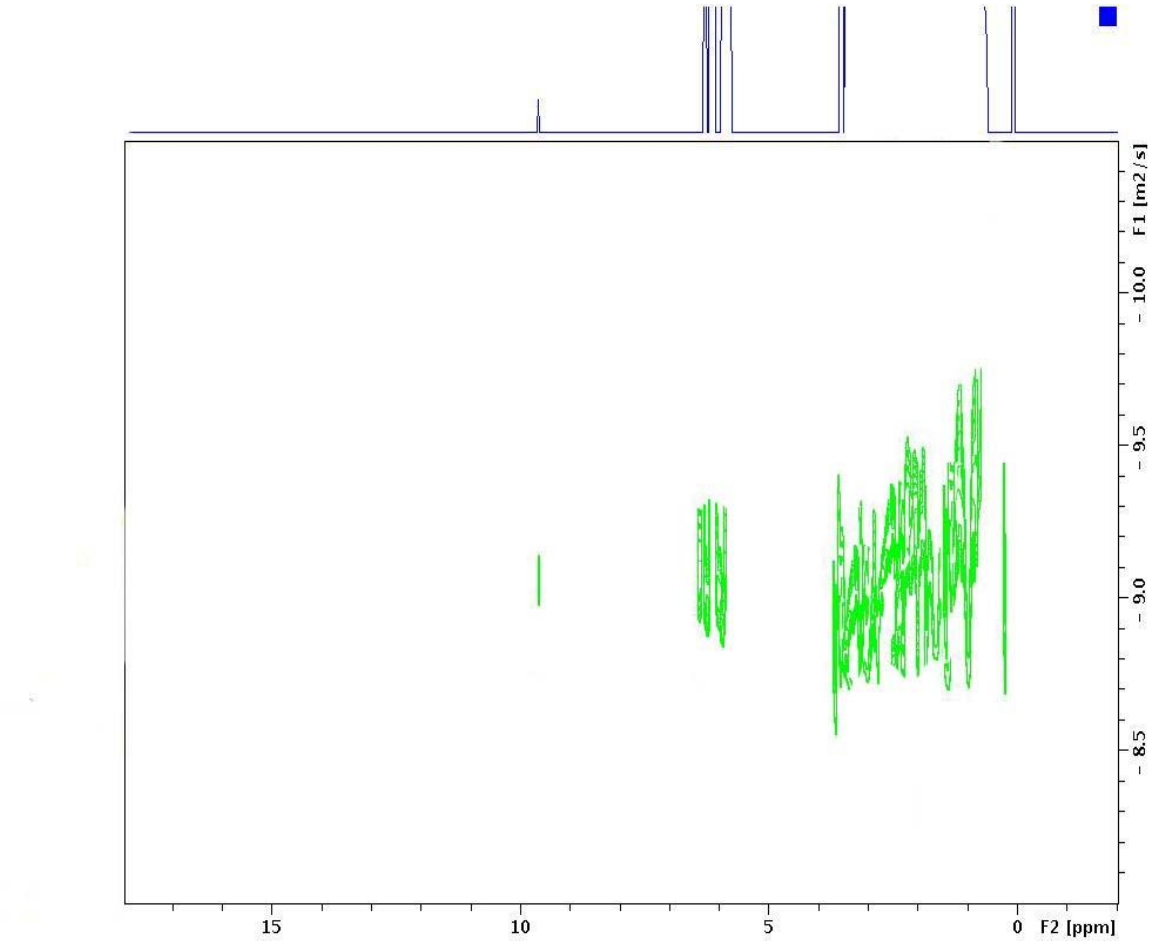


Figure A3.14. 2D DOSY spectrum of porphyrin **1b** + melamine in THF-d_8 as solvent

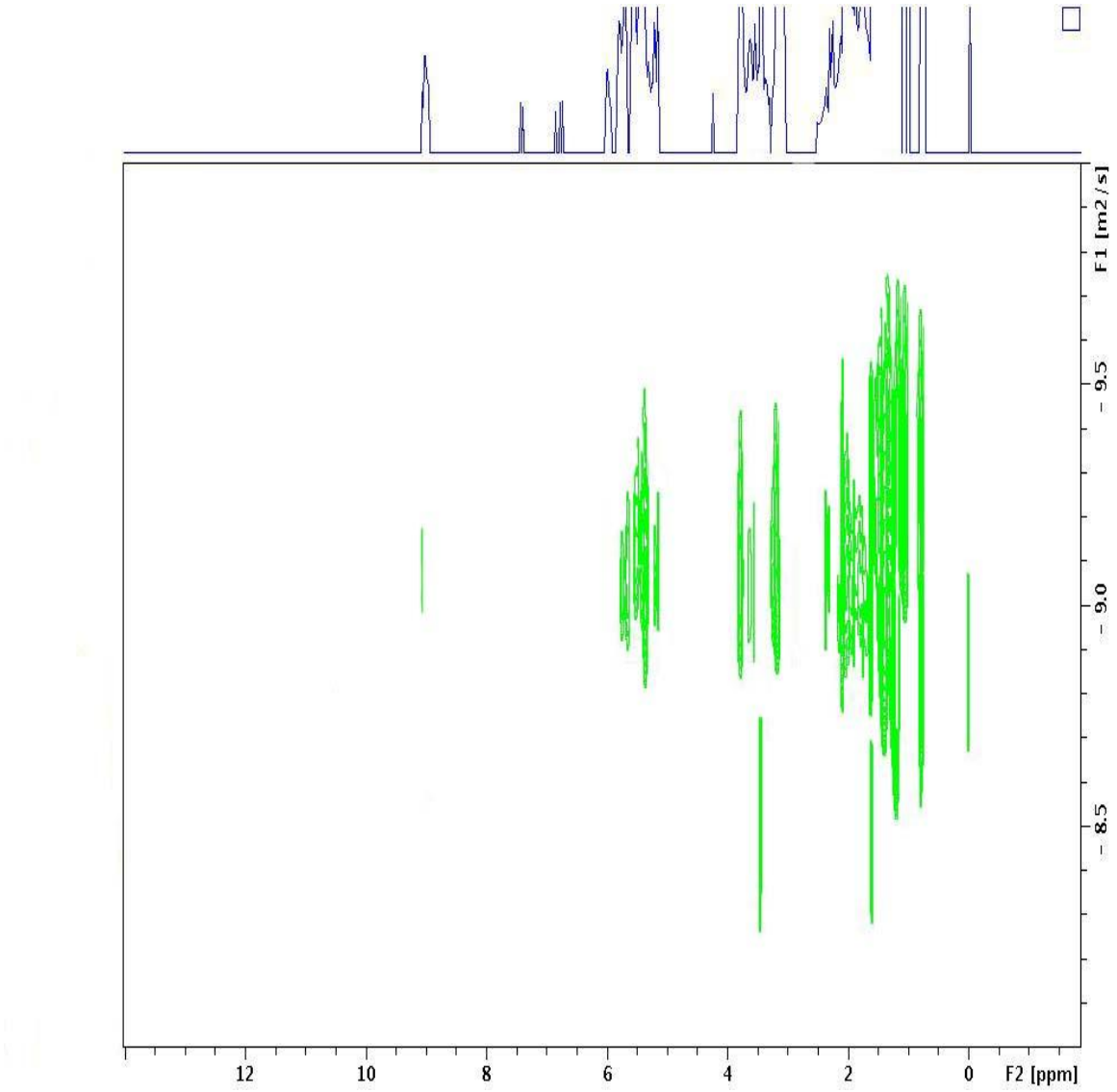


Figure A3.15. 2D DOSY spectrum of Porphyrin **2b** + melamine in THF-d_8 as the solvent.

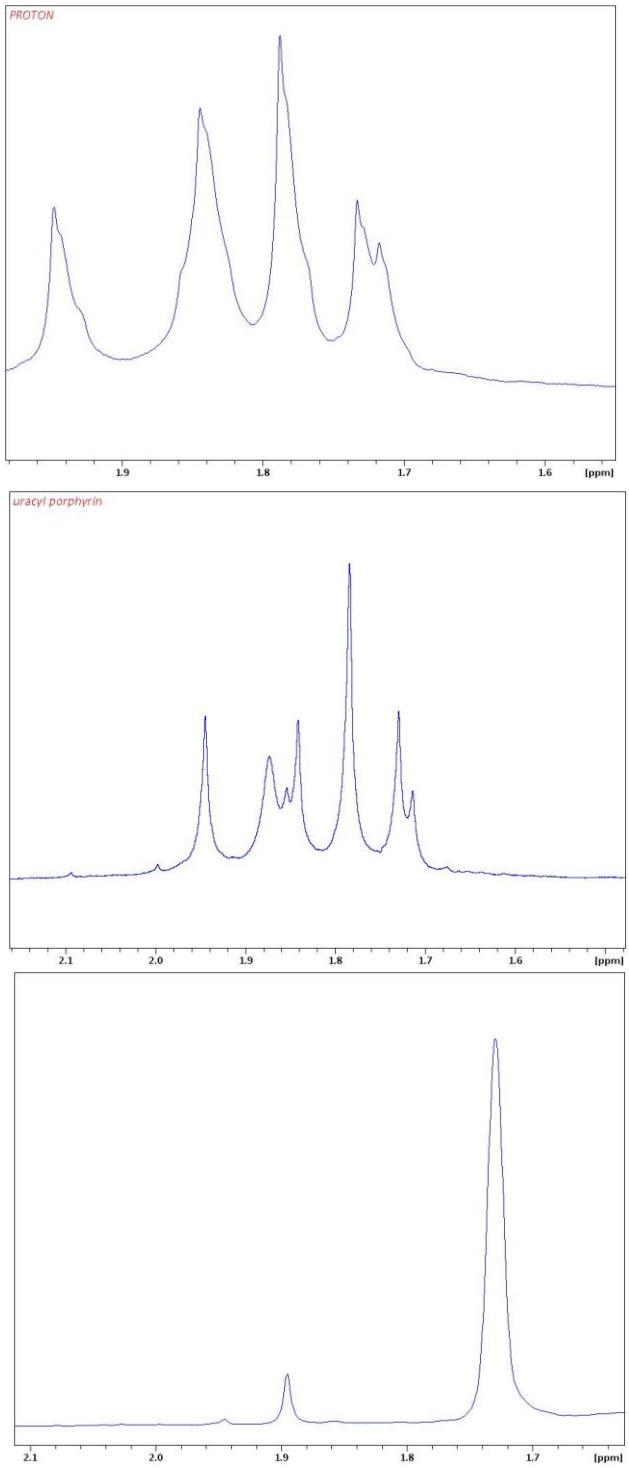


Figure A3.16. Expansion of ^{1}H NMR of the 6-methyl uracyl resonance for (A) the statistical mixture of atropisomers of porphyrin **1b** after one column purification in DMSO-d_6; (b) **1b** in DMSO-d_6 after complete purification. (c) After formation of the cage, there is only one uracyl methyl resonance at 1.88 ppm in THF-d_8 which is consistent with formation of the α^4 atropisomer. The resonance at 1.74 is the THF solvent. The resonance for the methyl uracyl on the cage in THF-d_8 is shifted by ~0.1 ppm, from where this peak shows up for the non-assembled compounds in DMSO-d_6. (*2-5*)

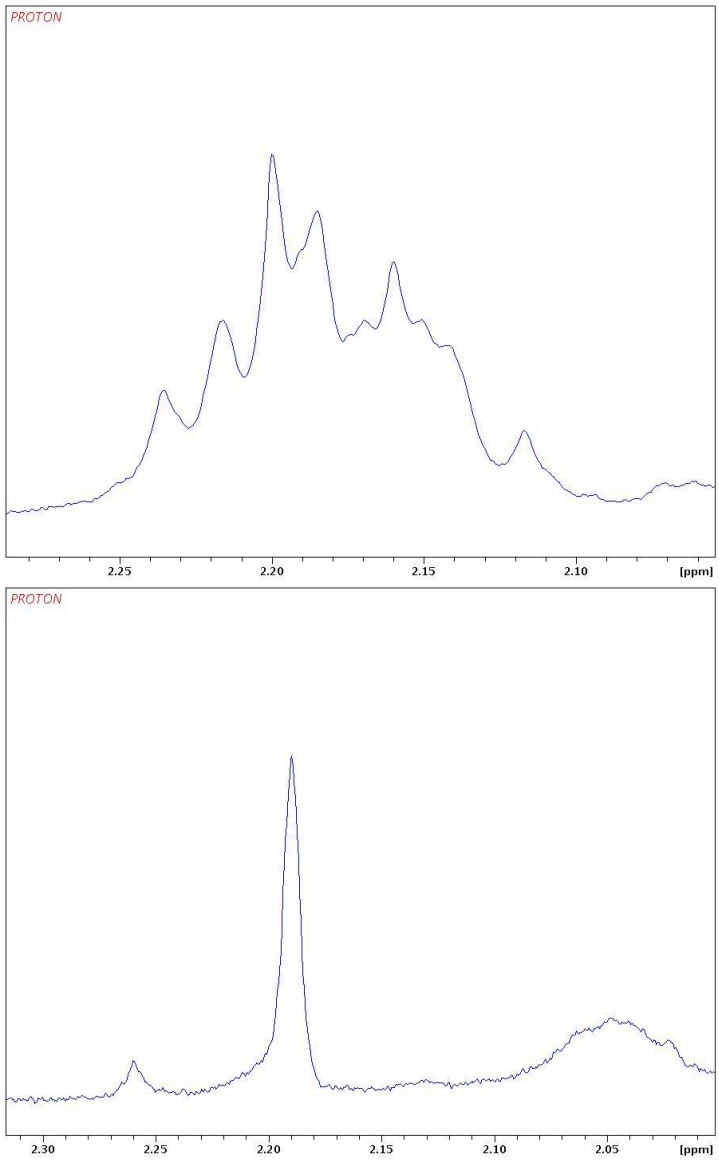


Figure A3.17. Expansion of ^{1}H NMR of the 6-methyl uracyl resonance for (A) the statistical mixture of atropisomers of porphyrin **2b** in methanol-d_4 after one column purification; (b) After formation of the cage, there is only one uracyl methyl resonance at 2.19 ppm in THF-d_8. Residual solvent at 2.05 ppm.

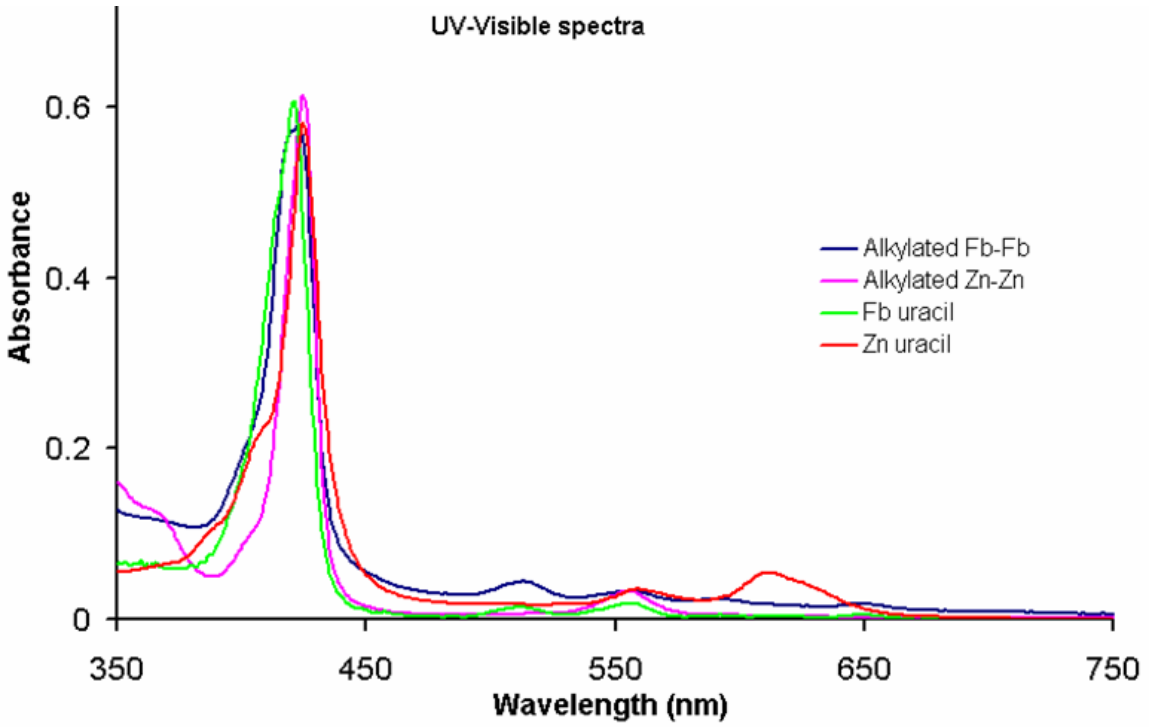


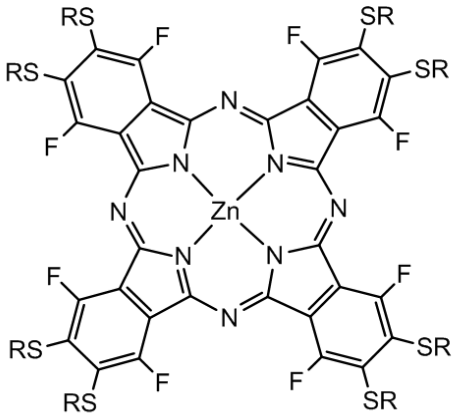
Figure A3.18. UV-visible spectra of porphyrins (**1a, 1b, 2a** and **2b**) in THF.

CHAPTER 4

SYNTHESIS AND PHOTOPHYSICS OF AN OCTATHIOGLYCOSYLATED ZINC(II) PHTHALOCYANINE[1]

Abstract

A water soluble zinc (II) phthalocyanine symmetrically appended with eight thioglucose units was synthesized from commercially available hexadecafluoro-phthalocyaninatozinc(II) by controlled nucleophilic substitution of the peripheral fluoro groups. The photophysical properties and cancer cell uptake studies of this nonhydrolyzable thioglycosylated phthalocyanine are reported. The new compound has amphiphilic character, is chemically and photochemically stable, and can potentially be used as a photosensitizer in photodynamic therapy.



[1] Adapted from Reference 1. Aggarwal, A., Singh, S., Zhang, Y., Anthes, M., Samaroo, D., Gao, R., and Drain, C. M. (2011) Synthesis and photophysics of an octathioglycosylated zinc(II) phthalocyanine, *Tetrahedron Lett. 52*, 5456-5459.

4.1 Introduction

Free base phthalocyanines (Pcs) and their diamagnetic metalated complexes, e.g. Zn(II), Al(III), Ga(III), can be efficient photosensitisers for photodynamic therapeutics (PDT) because they can photosensitize the formation of singlet oxygen. Highly reactive singlet oxygen is formed upon energy transfer from the triplet excited state of the dye to ground state triplet oxygen.(*2-5*). Since red light penetrates deeper into tissues, Pcs can be more efficient PDT agents than the well studied porphyrins because the electronic bands of Pcs in the red spectral region are about two orders of magnitude stronger than the porphyrins. Pcs are also extraordinary stable(*6, 7*). Zinc metallophthalocyanines are of interest because of their high triplet quantum yield and appreciably long triplet lifetimes(*8*). Long lived triplet states are advantageous since this increases the probability of a diffusional encounter between the excited triplet state of the photosensitizer with the ground triplet state of the molecular oxygen to produce singlet oxygen. Significant research directed at improving the selectivity of the Pcs towards malignant tissues has resulted in limited success because of poor solubility in physiological fluids(*9*).

In general, amphiphilic porphyrinoid photosensitizers are taken up by cells and tissues better than water soluble derivatives(*10*). Uptake and distribution are also a function of specific targeting motifs appended to the dye, and degree of aggregation(*7, 10*). Appending ionic groups on the Pc macrocycle such as sulfonic groups(*11*), quaternary amino or pyridino groups(*12, 13*) makes them water soluble but the purification of these compounds can be a problem. Neutral, polar Pcs can be prepared by attaching hydroxyl groups(*14*). Appending carbohydrates to porphyrinoids is of great interest because: (1) these impart amphipathic properties, and (2) many cancer cells over express carbohydrate receptors (*15*) since they have a greater metabolic rate (*16*). The increased levels of glucose uptake and glycolysis may promote the uptake of

glycosylated photosensitizers. There are several examples of porphyrin-carbohydrate conjugates(*17-20*), and a few examples of carbohydrate substituted Pcs are reported(*21-25*). The Pc compounds are generally prepared by cylcotetramerisation of the glycosylated phthalonitrile, e.g. from the phthalonitrile by Ziegler-Hannack's glycosylation procedure(*26*)

In addition to the inherently stronger red absorption bands, several important considerations distinguish the Pcs from the porphyrins. Mono substitution of the four isoindoles results in a mixture of isomers(*27*). The nature and number of functional groups appended to any position of the Pc macrocycle can have marked effect on the photophysical properties because they are attached directly to the chormophore. There are also strong solvent and aggregation effects on the electronic properties of Pcs(*28*). In contrast the photophysical properties are minimally affected in most glycol-porphyrin conjugates, which have the sugar appended to the meso aryl moieties of tetraphenyl-porphyrins. The number and position of functional groups on porphryinoids has been discussed in terms of PDT effects(*29*). O-glycoside attached sugars can be hydrolysed off of conjugates enzymatically, lysosomal degradation (*30, 31*), and the decreased pH surrounding cancer cells and tissues due to the Warburg effect(*32*). Therefore, non-hydrolysable attachments may be more effective as therapeutics and for other applications (*33, 34*).

Herein we report the facile, one step, formation of a metallophthalocyanine appended with non-hydrolysable thioglucose units (Figure 4.1) that takes advantage of the different reactivities of fluoro groups on the α and β positions. This work is the first example of base-promoted substitution of phthalocyanines with thioglucose that takes advantage of the excellent leaving group character of fluoride. This straightforward strategy allows commercially available

zinc perfluorophthalocyanine, $ZnPcF_{16}$, to serve as a core platform to rapidly make derivatives to assess the effectiveness of a broad array of biotargeting motifs for diverse applications.

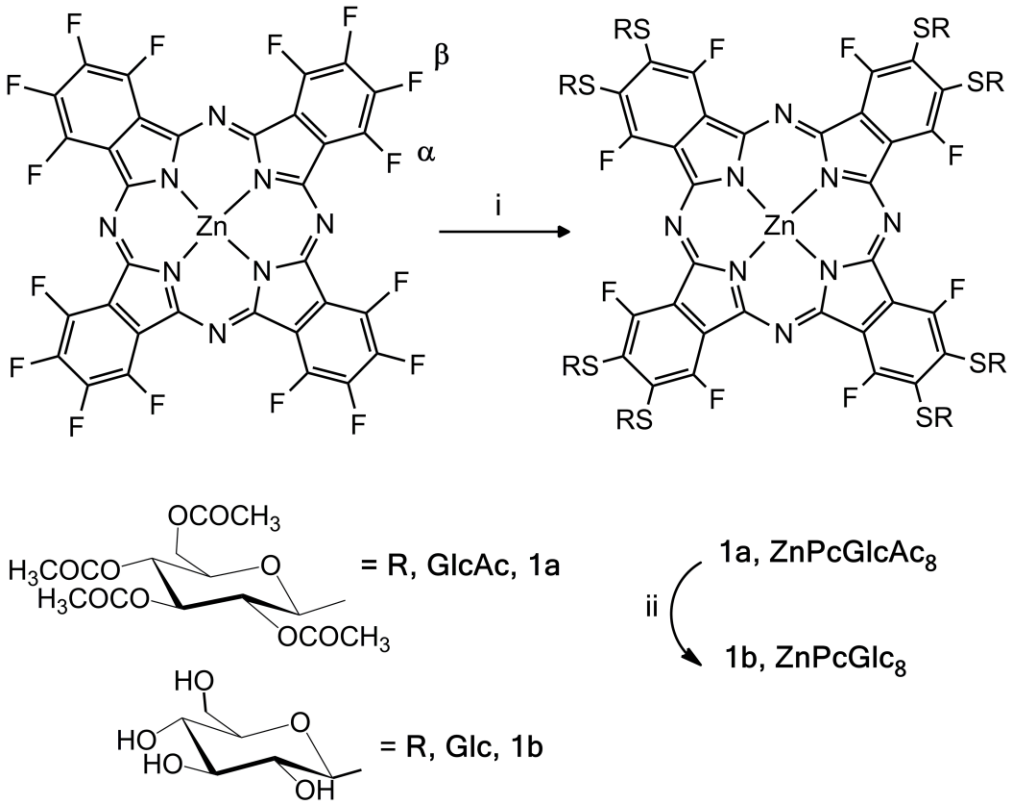


Figure 4.1. Synthesis of ZnPcGlc8. (i) 8.5 eq. $GlcAc_4SAc$, K_2CO_3 in THF at 40-50 ^oC for three days; (ii) CH_3ONa in CH_2Cl_2/CH_3OH. The isolated yield of **1b** = 72%. The α and β positions on the phthalocyanine are indicated on the starting $ZnPcF_{16}$.

Though mixtures of compounds and/or isomers or atropisomers may have advantages in terms of PDT, because each may partition or localize in different parts of a tissue or cell resulting in oxidative damage is at multiple sites, mixtures should be designed rather than accidental. For Pcs, derivatives with 16 or eight substituents can be pure compounds without isomers. The electronic absorption and luminescence properties of $ZnPcF_{16}$ systematically changes as the fluoro groups are replaced with thioglucose(*35, 36*). We focus on the octa-thioglycosylated compound since the remaining fluorine atoms can help protect the chromophore from oxidation

(*37*). The main objective of this work was to synthesize $ZnPcGlc_8$ in reasonable yields, study the photophysical properties, and examine cancer cell uptake.

4.2 Experimental Procedure

Materials and methods:

General

^{1}H and ^{13}C NMR spectra were recorded in a Brüker Avance 500 MHz spectrometer and the ^{19}F spectra in a JEOL 400 MHz spectrometer. UV-visible spectra were recorded on a Varian Bio3 spectrophotometer. Steady-state fluorescence (emission) spectra were measured with a Fluorolog τ3, Jobin-SPEX Instruments S.A., Inc. All reagents were obtained from commercial sources and used without further purification. $ZnPcF_{16}$ phthalocyanine was obtained from Sigma Aldrich. Dulbecco's Modified Eagle Medium (DMEM), trypsin-EDTA and antimycotic for cell culture were obtained from GibcoBRL. Hanks' balanced salt solution was obtained from Cellgro (Mediatech). Bovine calf serum was obtained from HyClone. Phosphate buffered saline (PBS) was purchased from Invitrogen. Flash column chromatography was performed using silica gel-60, and the analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick) both from Sorbent Technologies.

SYNTHESIS

Synthesis of Protected Thioglycosylated Phthalocyanine, $ZnPcGlcAc_8$ (**1a**). To a solution of 2,3,4,6-tetra-O-acetyl-glucosylthioacetate (60 mg, 139.04 μmol, 8 equiv) in THF (2 mL) was added K_2CO_3 (25 mg), the mixture was stirred for 10 min and then zinc perfluorophthalocyanine, $ZnPcF_{16}$ (15 mg, 17.38 μmol) was added. The reaction mixture was stirred at 40-50^{o}C for 48 h and then additional 2 equiv of 2,3,4,6-tetra-O-acetyl-glucosylthioacetate and K_2CO_3 dissolved in

THF was added and the reaction mixture was stirred at 40-50^{o}C for additional 24 h with total reaction time of 3 days. The reaction mixture was then precipitated with water and the solid was filtered through a short column of Celite and washed with water. The crude mixture was recovered in CH_2Cl_2 and purified by flash chromatography (silica gel) using a mixture of Toluene/acetone as a gradient. Compound **1a** (47 mg, 75%) was obtained after crystallization in CH_2Cl_2/hexanes, as a green powder. Peaks in the spectrum are broader due to aggregation. ^{19}F NMR ($CDCl_3$): δ -109. ^{1}H NMR ($CDCl_3$): δ 3.7-5.5 (m, 56H, Glc-H), 1.90-2.36 (m, 96H, acetyl-H). ^{13}C NMR ($CDCl_3$): δ 20.6 (CH_3CO_2), 61.85, 68.32, 71.10, 73.84, 75.70, 85.15 (Glc), 127.28-127.94, 151.42, 151.53, 154.13, 154.22, 156.24, 156.28, 156.31, 169.35(Pc-C), 169.90, 170.04, 170.71(CH_3CO_2). MALDI Calcd for $C_{144}H_{152}F_8N_8O_{72}S_8Zn$ M^+: 3620.67 found 3620.33

Synthesis of Thioglycosylated Phthalocyanine, $ZnPcGlc_8$ (**1b**). Phthalocyanine **1a** (20 mg, 8.8 μmol) was dissolved in methanol/CH_2Cl_2 (3:1, 2 mL) and treated with sodium methoxide (0.5 M solution in methanol, 0.4 mL). The reaction mixture was stirred at room temperature for 2 h and then neutralized by an aqueous citric acid solution. The mixture is filtered through Waters Sep-Pak C_{18} 35 cm^3 reverse-phase prep column and washed with methanol. The deprotected Phthalocyanine **1b** was eluted with water/methanol mixture. Phthalocyanine **1b** (12 mg, 96 %) was obtained after crystallization in water/methanol as a green powder. mp> 250^{o}C. ^{19}F NMR (DMSO-d_6): δ -108.3. ^{1}H NMR (DMSO-d_6): δ 3.18-5.79 (m, 56H, Glc-H) ^{13}C NMR (DMSO-d_6): δ 61.13, 70.48, 75.23, 78.57, 81.60, 86.48 (Glc), 125.56, 128.67, 151.55, 153.28, 155.32 (Pc-C). MALDI Calcd for $C_{80}H_{88}F_8N_8O_{40}S_8Zn$ $(M+H)^+$: 2276.49 found 2276.44.

PHOTOPHYSICAL STUDIES (done by Amit Aggarwal):

Photophysical properties of $ZnPcGlc_8$ involve the measurement of their absorption and emission spectra, fluorescence quantum yield and fluorescence life time in different solvents including dry DMSO, Ethanol, toluene, phosphate buffer saline (PBS) and ethylacetate. All experiments were done under similar experimental and instrumental conditions and in air. ZnPc, Φ_F = 0.20, in DMSO (*38*) was used as standard to measure the fluorescence quantum yield. The detailed phtophysical data of $ZnPcGlc_8$ is shown in table 4.1.

Emission spectroscopy, fluorescence quantum yield, and fluorescence life time measurements:

Steady-state fluorescence (emission) spectra and fluorescence life time were measured with a Fluorolog τ3, Jobin-SPEX Instrument S.A., Inc. For ZnPc and $ZnPcF_{16}$ emission spectra were recorded in DMSO, whereas for $ZnPcGlc_8$ spectra were recorded in DMSO, toluene, ethylacetate, ethanol, phosphate buffer saline (PBS) and 1:1 DMSO: H2O mixture solvent.

Dynamic Light Scattering (DLS) for particle size measurement:

A solution of $ZnPcGlc_8$ was found to aggregates in various studied solvents. A Precision Detector PD2000DLS Cool-Batch dynamic light scattering (DLS) instrument was used in batch mode at 25 ^oC to determine particle size.

Octanol/Water partition coefficient:

For octanol/water partition coefficient, a saturated solution of $ZnPcGlc_8$ was prepared in 1:1 (V/V) mixture of these two solvents. The mixture solution was shaken vigorously and then waited for 8-10 to separate the two layers and UV-Visible spectra were recorded for the two

layers. The partition coefficient for this compound was calculated by measuring its Soret band and Q-Band intensities in two solvents. We know that the compound aggregates in water. So, to ensure our results a 50 uL of each layer of the above saturated solution of $ZnPcGlc_8$ in mixture solvent (1:1=octanol:water) were withdrawn and were mixed again and diluted with 1 mL of DMSO, to break any aggregates formed (if there), and then the spectra were recorded to calculate the partition coefficient.

Photo bleaching of $ZnPcGlc_8$ in sunlight:

5 µM solution of $ZnPcGlc_8$ in DMSO was exposed to sunlight (on a full sunny day) over a time period of 2 hr and 30 min and absorption and emission spectra were recorded at different interval of times. The power of sunlight was measured to be 60-95 W/m^2.

Cell uptake studies: (done by Mariah Anthes)

Two different cell lines Murine bladder tumor cells MBT2 and Human breast cancer cells MDA-MB-231 were used to study the uptake of the chromophore. MBT2 cells were sustained in RPMI-1640 Medium containing 10% fetal bovine serum and 1% antimycotic. MDA-MB-231 cells were sustained in DMEM medium containing 10% fetal Bovine serum and 1% antimycotic. Cells were kept in an incubator set at 37 °C with a 5% CO_2 atmosphere. Cells were seeded at 2 x 10^5 cells/mL at 2mL per well. Incubation of Zinc Phthalocyanine was done at approximately 80% cell confluency 24hrs prior to fixing and mounting cells onto glass slides. Fluorescence images were captured as JPEG files.

4.3 Results and Discussion

Figure 4.1 shows the synthetic route for the octa-glycosylated substituted $ZnPcGlc_8$. $ZnPcF_{16}$ was treated with 8.5 equivalents of thioglucose in presence of K_2CO_3 as a base and dry THF as the solvent. The reaction was done under argon for about three days at 40-50 ^oC. The type of the solvent and the base used for this reaction play an important role. No substitution reaction took place when solvents such as diglyme or DMF were used along with bases such as diethylamine, triethylamine, pyridine, Na/MeOH, or t-butylammonium hydroxide. The acetate deprotection was done using a mixture of dichloromethane and methanol as solvent and sodium methoxide; using a slight excess of sodium methoxide relative to the equivalents of Ac. Similar procedures using 4.5 equivalents of the thioglucose starting material yields the four isomers of the tetraglycosylated Pc where in each isoindole has one thioglucose unit. The water soluble Pc (**1b**) was purified by precipitation with water/methanol mixture. The reactivity of the $ZnPcF_{16}$ progresses from a single substituent on one β position on each isoindole, to substitution of each β position, to substitution of the α positions. The diminished reactivity with succeeding additions is due to both thermodynamic effects from the exchange of an F for an S atom on the macrocycle,(*27*) and kinetic effects from steric hindrance.

The compounds were characterized by ^1H, ^{13}C, ^{19}F NMR, UV-visible spectra and MALDI-TOF. In the ^1H NMR of compound **1a**, acetyl peaks appear at 1.90-2.34 ppm, and resonances of the other protons of the carbohydrate units appear as two multiplets at 3.7-4.2 ppm and 5.2-5.5 ppm. The ^1H NMR of compound **1b** in DMSO-d_6 is well resolved and confirms the deprotection of the carbohydrate units (disappearance of the signals due the acetyl protecting groups). The resonances of the anomeric protons appear as doublets between 5.2 to 5.6 ppm. The

^{13}C NMR displays the typical chemical shifts for Pcs but multiple resonances are observed near 125 to132 ppm for the α position carbons that remain coupled to the F atoms. The ^{19}F NMR of the compound shows a singlet around -109 and disappearance of the peak at around -85 indicating that the β-F is substituted by the thioglucose.

The UV-visible spectra of compound **1b** in different solvents are shown in figure 4.2. Notably, the spectra in DMSO shows defined peaks and no apparent aggregation, but the marked decrease in intensity and broadening of the Q-band at 727 nm in both less polar solvents and phosphate buffered saline (PBS) indicates significant aggregation of this compound. Similarly, there is a gradual decrease and broadening of this Q band with increasing amounts of water in the DMSO solution. The nearly 60 nm blue shift of both the Q bands, and somewhat small blue shift in the B bands in the optical spectra in these solvents indicates the $ZnPcGlc_8$ aggregates are generally in a cofacial arrangement (H-aggregates)(*23, 39*). This aggregation behavior has been observed with other glycosylated Pcs(*2, 14*).

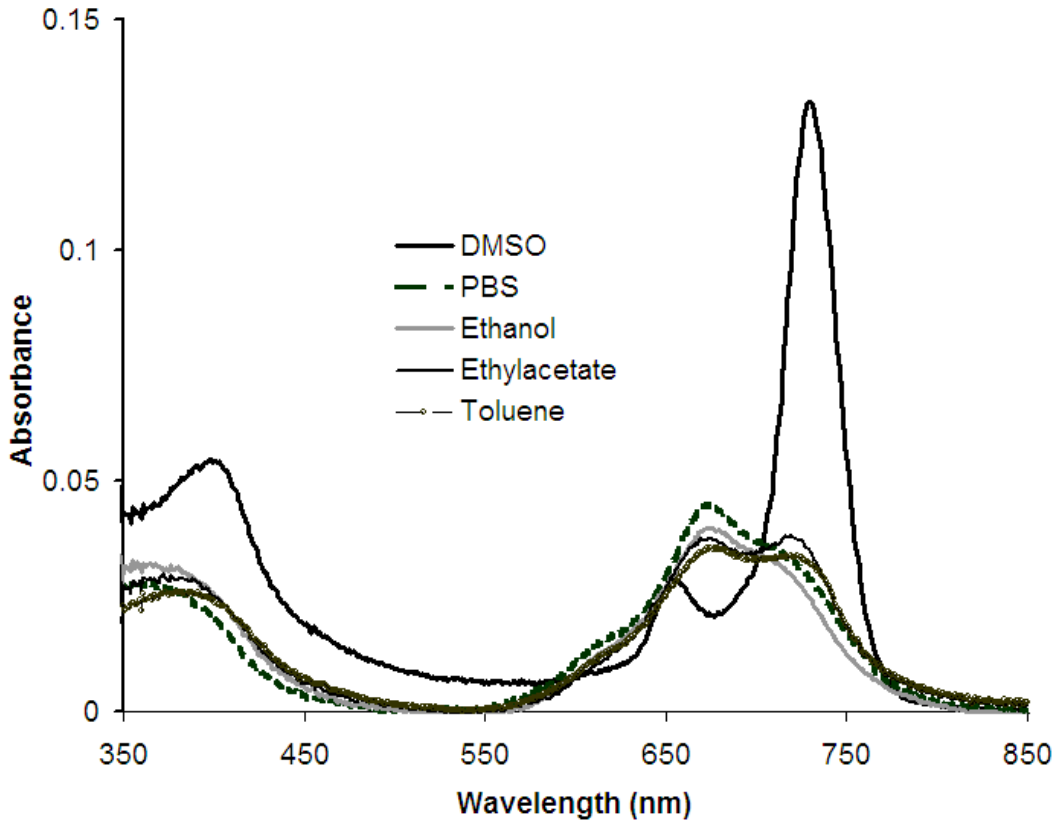


Figure 4.2. UV-Visible spectra of $ZnPcGlc_8$ compound in different solvents. 1mM $ZnPcGlc_8$ in DMSO was used as stock solution to prepare these solutions. The final concentration of the compound in each solution was 2uM.

The detailed photophysical data of $ZnPcGlc_8$ was measured in dry DMSO, PBS, and 1:1 mixture solvent of DMSO:H_2O and is summarized in Table **4.1**. The UV-visible spectra of $ZnPcGlc_8$ is significantly different than the starting $ZnPcF_{16}$ compound. The Q-band at 727 nm of $ZnPcGlc_8$ is red shifted by ~55 nm compared to the 672 nm Q-band for $ZnPcF_{16}$ and other ZnPc compounds. The systematic red-shift with successive exchange of the F for the S attached to the macrocycle arises from the decrease in the optical band gap as reported earlier(*40*).

The nanoarchitecture of the component molecules and the size of organic nanoparticles depends on a variety of factors such as concentration, solvent, solute and method of formation.

Table 4.1. Photophysical properties $ZnPcGlc_8$ measured in air. (Photophysics done by Amit Aggarwal, Φ_Δ by Prof. Roumie Gao)

Compound	Solvent	Absorption, λ (log ε)	Emission, λ	Φ_F air	Φ_F N_2	τ_F, ns (air)	Φ_Δ
ZnPc	DMSO	360, 605, 641, 672	679, 747	0.20	-------	3.1	0.67
$ZnPcF_{16}$	DMSO	356, 636, 672 (5.2)	686	0.01	0.013	2.7	0.13
$ZnPcGlc_8$	DMSO	397, 650, 727 (5.2)	740	0.06	0.064	2.1	0.41
	PBS	358, 671, 711	727	0.0021	0.0026	T_1=0.3 (17%) T_2=2.1 (83%)	0.41 D_2O Tris buffer
	DMSO:H_2O (1:1)	376, 672, 719	738	------	-----	------	-------

The fluorescence quantum yield, Φ_F, was measured by exciting the molecule at 647 nm where all the compounds have an absorbance 0.027. Both quantum yield and singlet state life time was measured in air and under N_2 by purging N_2 gas through the solution for 10 min. Time correlated single photon counting measurements of the singlet state life time used a 401 nm laser to excite the molecule and emission decay was recorded at 740 nm, and band pass = 3 nm. The instrument response time is ~200 ps. [a] $\Phi_F = 0.18$, $\tau_F = 1.2$ ns.

For example in PBS, dynamic light scattering (DLS) measurements shows two different sized aggregate populations with diameters of 40±6 nm and 265±25 nm after stirring in **1b**. After sonication of this solution for about 15 minutes, the organic nanoparticles reorganize to yield only particles that were 65±8 nm in diameter.

The fluorescence life time for the chromophore in DMSO was measured to be 2.1 ns. These are consistent with other ZnPc derivatives(*38, 41*). Photobleaching of the chromophore was measured by exposing a 5 μM solution of compound in DMSO to sunlight with a power of about 60-95 W/m^2. The photodegradation was measured by taking UV-visible and emission

spectra after different interval of time. After 5 minutes exposure ca. 26 % compound decomposed and after 2 hours almost complete photo degradation was observed. The photodecomposition product(s) of the chromophore were not explored.

The mechanism of cancer cell uptake of nonhydrolysable thioglycosylated porphyrinoids is not well understood. Our hypothesis is that the glucose receptors on the cell surface bind the chromophore, thereby increasing its concentration around the cell, but these are unable to transport the large conjugate inside the cell. The amphipathic properties of the molecule allow diffusion across the cell membrane. Additionally, nano-aggregates less than ca. 50 nm can be endocytosed into the cell. Fluorescence microscopy indicates that $ZnPcGlc_8$ is taken up by MDA-MB-231 breast cancer cells mostly as poorly fluorescent nano-aggregates (Figure 4.3) because initially small, diffuse spots are just visible. Four days after fixing the cells the cell morphology remains, but the nanoparticles of $ZnPcGlc_8$ have disaggregated; therefore the fluorescence significantly increases.

Direct observation of $^1O_2$ luminescence kinetics at 1270 nm after irradiation of $ZnPcGlc_8$ at 532 nm in pH 7.4 D_2O Tris buffer was done as previously described (*42*).

4.4 Conclusions

A new method has been developed to synthesize non-hydrolysable thioglycosylated Pc from commercially available $ZnPcF_{16}$ in high yields. The amphiphilic character of **1b** provides an useful for drug administration since carbohydrate units have specific affinity for cancer cells(*43*). The chromophore was found to aggregate in water resulting in quenching of the fluorescent signal, but uptake and disaggregation in breast cancer cells indicates this may be a viable strategy for new PDT agents.

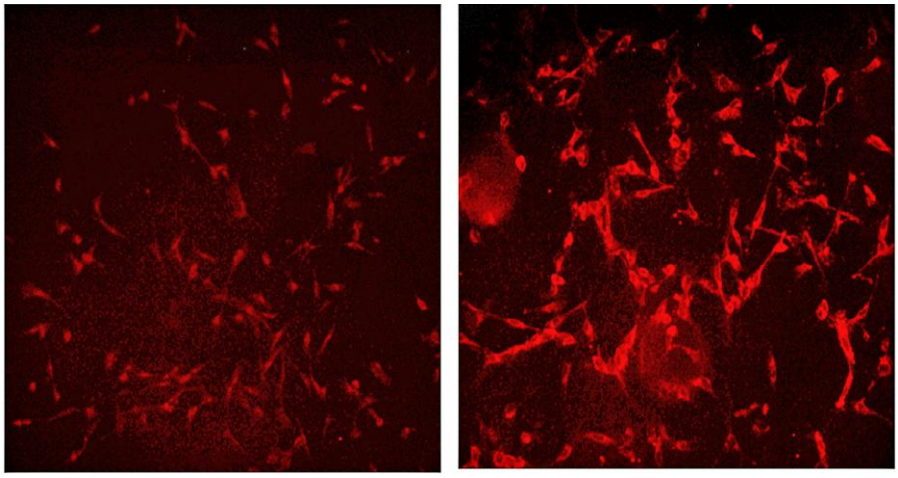


Figure 4.3. MDA-MB-231 cells were incubated overnight with 50 nM $ZnPcGlc_8$ for 24 h, rinsed three times with PBS buffer to remove unbound dye and fixed with 4% paraformaldehyde solution. Fluorescence images were captured by exciting at 540-580 nm, magnification 10x under identical conditions. (a) Just after preparation of the fixed cells slide (b) 4 day after later. The contrast was enhanced by 80% for publication (Cell incubation studies done by Amit Aggarwal and Mariah Anthes).

4.5 References

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4.6 APPENDIX

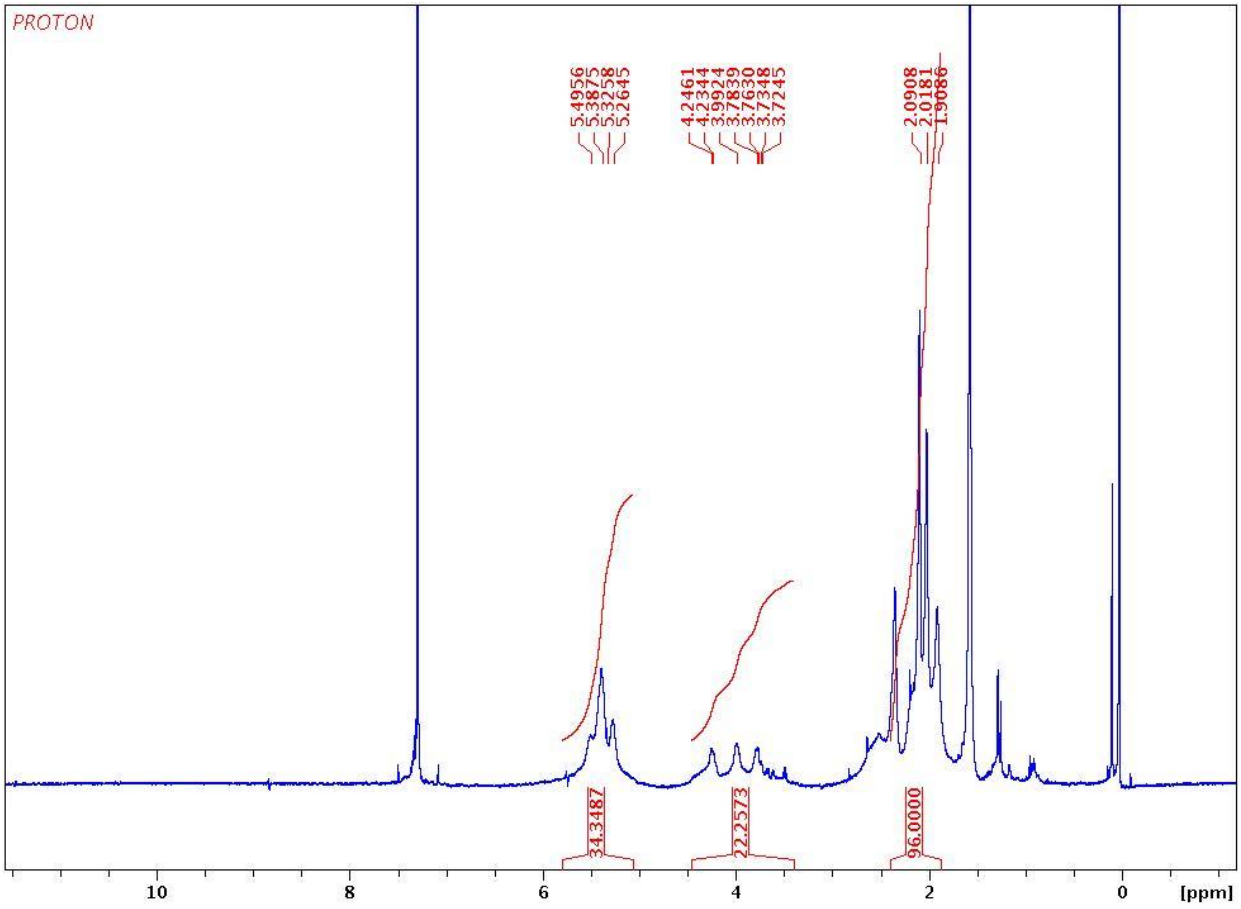


Figure A4.1: ^{1}H NMR of Compound 1a ZnPcGlcAc$_8$ ($CDCl_3$7.28 ppm, water 1.6 ppm)

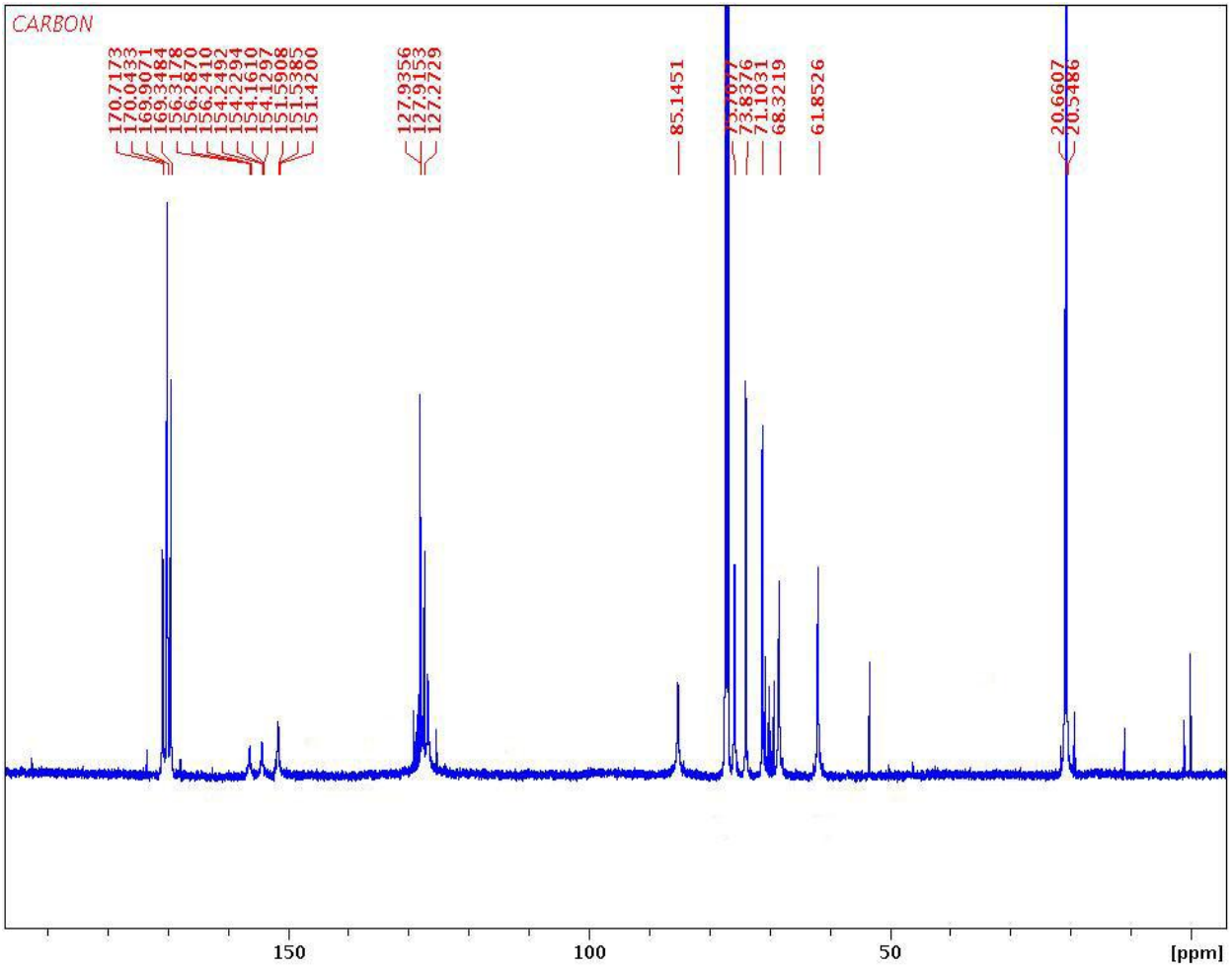


Figure A4.2: ^{13}C NMR of Compound 1a ZnPcGlcAc$_8$ (CDCl$_3$ 77 ppm)

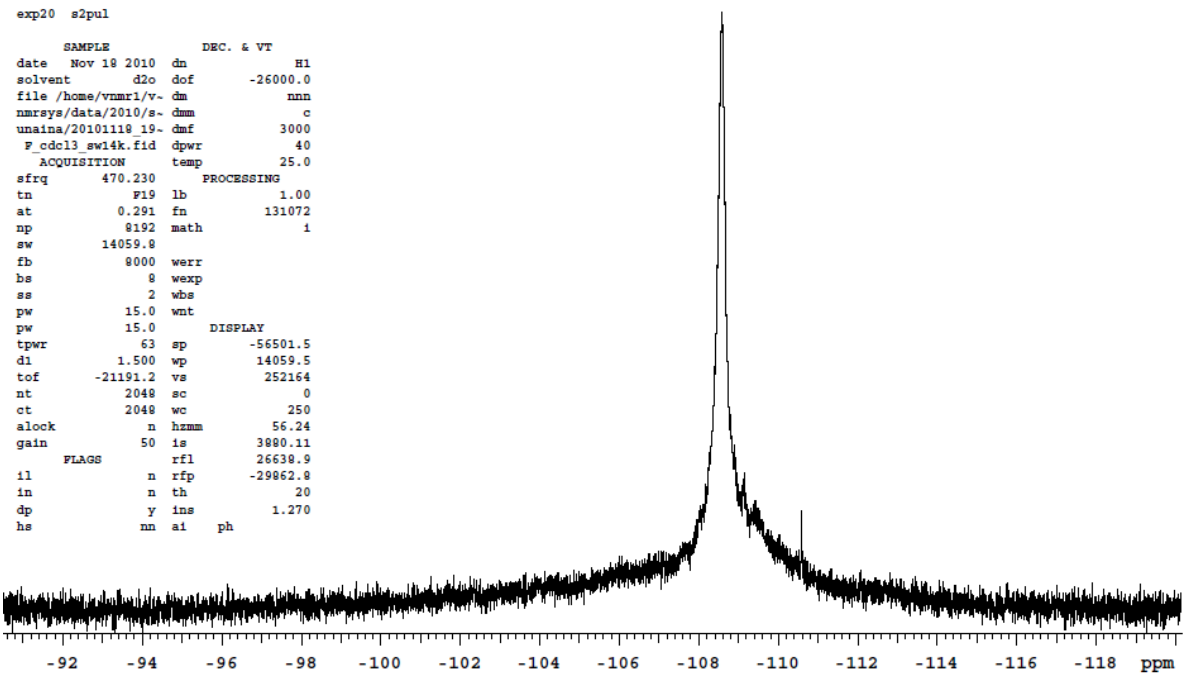


Figure A4.3: ^{19}F NMR of compound 1a ZnPcGlcAc$_8$ (CDCl$_3$)

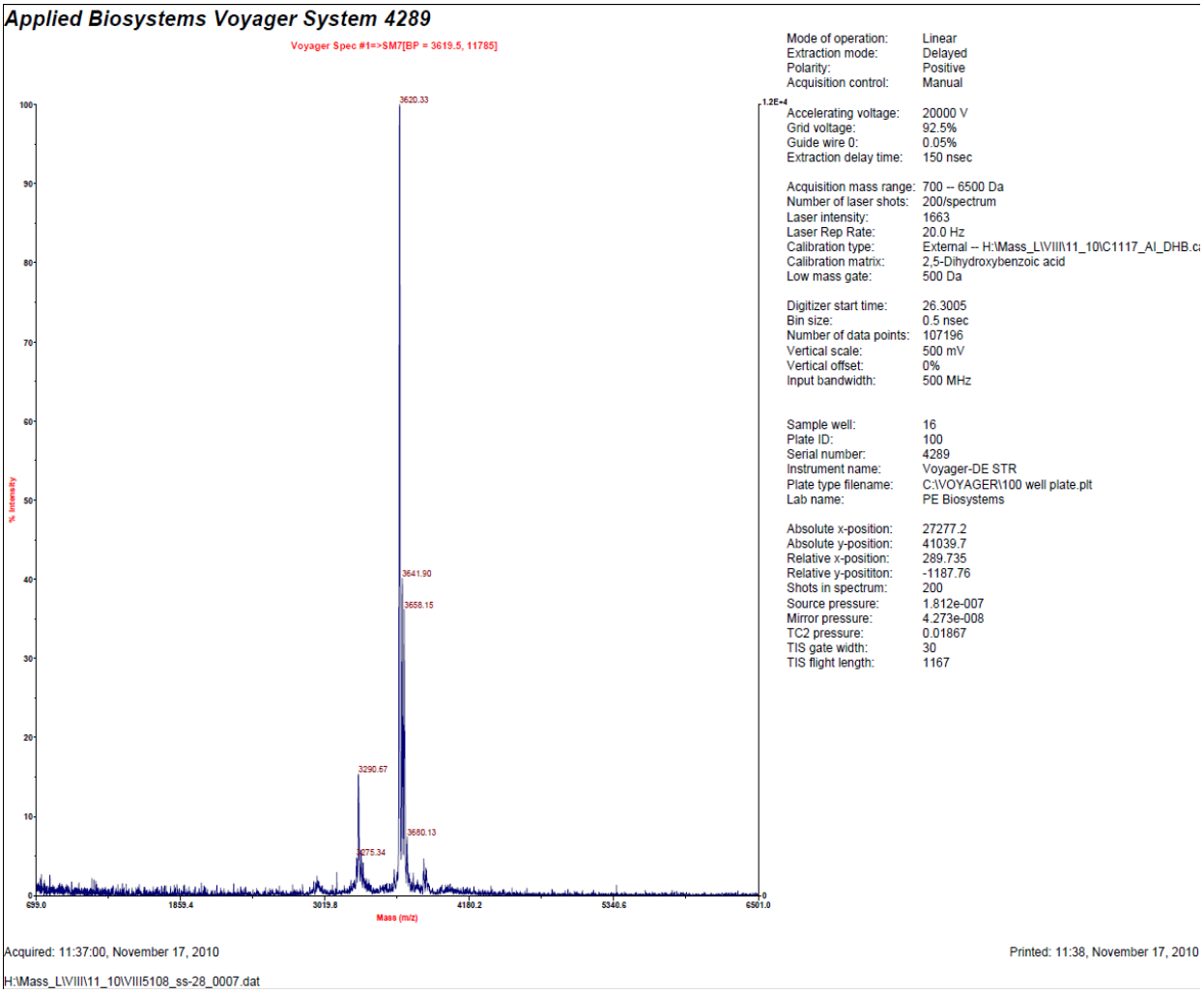


Figure A4.4: MALDI of 1a

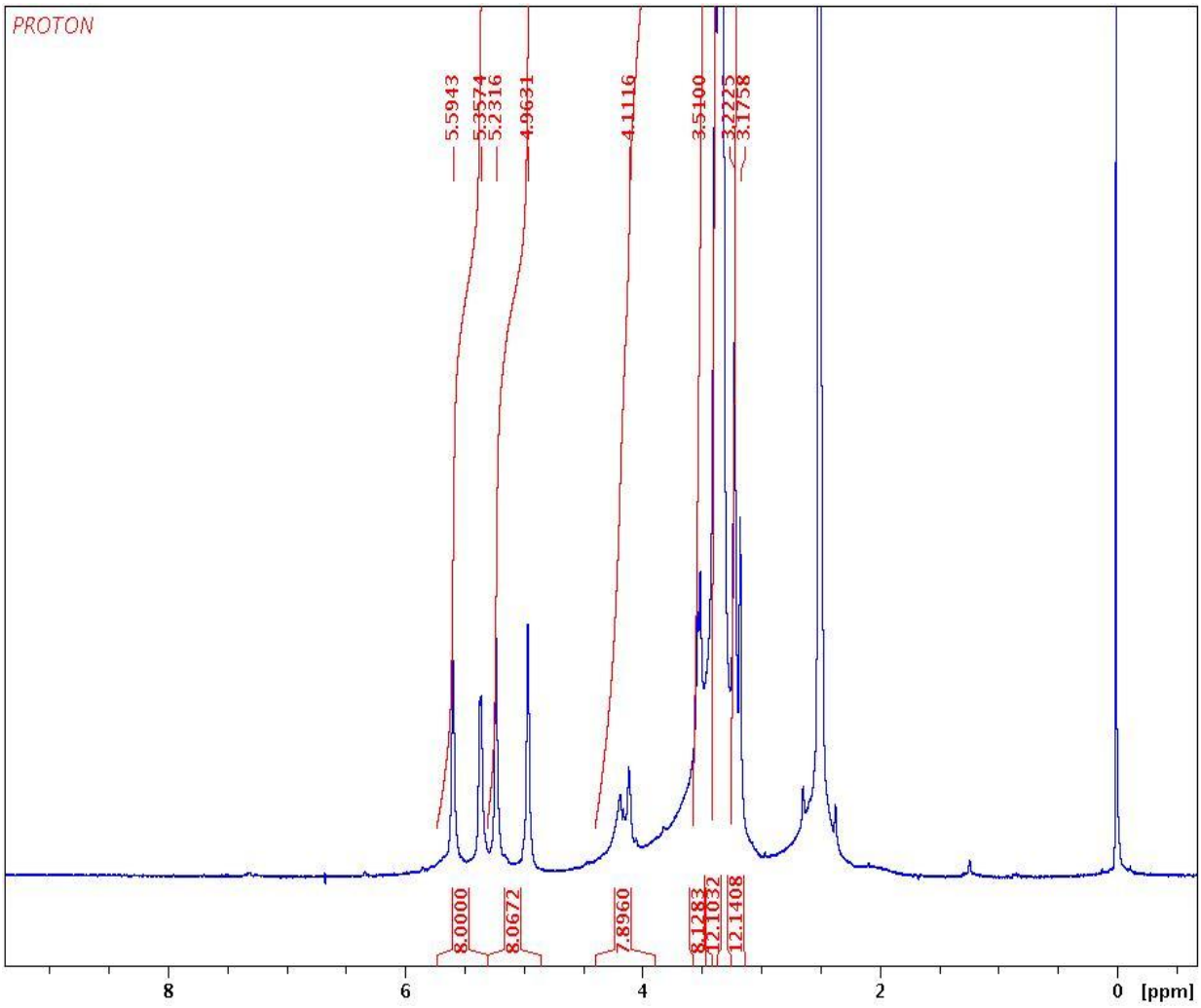


Figure A4.5: ^{1}H NMR of compound 1b ZnPcGlc$_8$ (DMSO-d$_6$ 2.5 ppm, water 3.3 ppm)

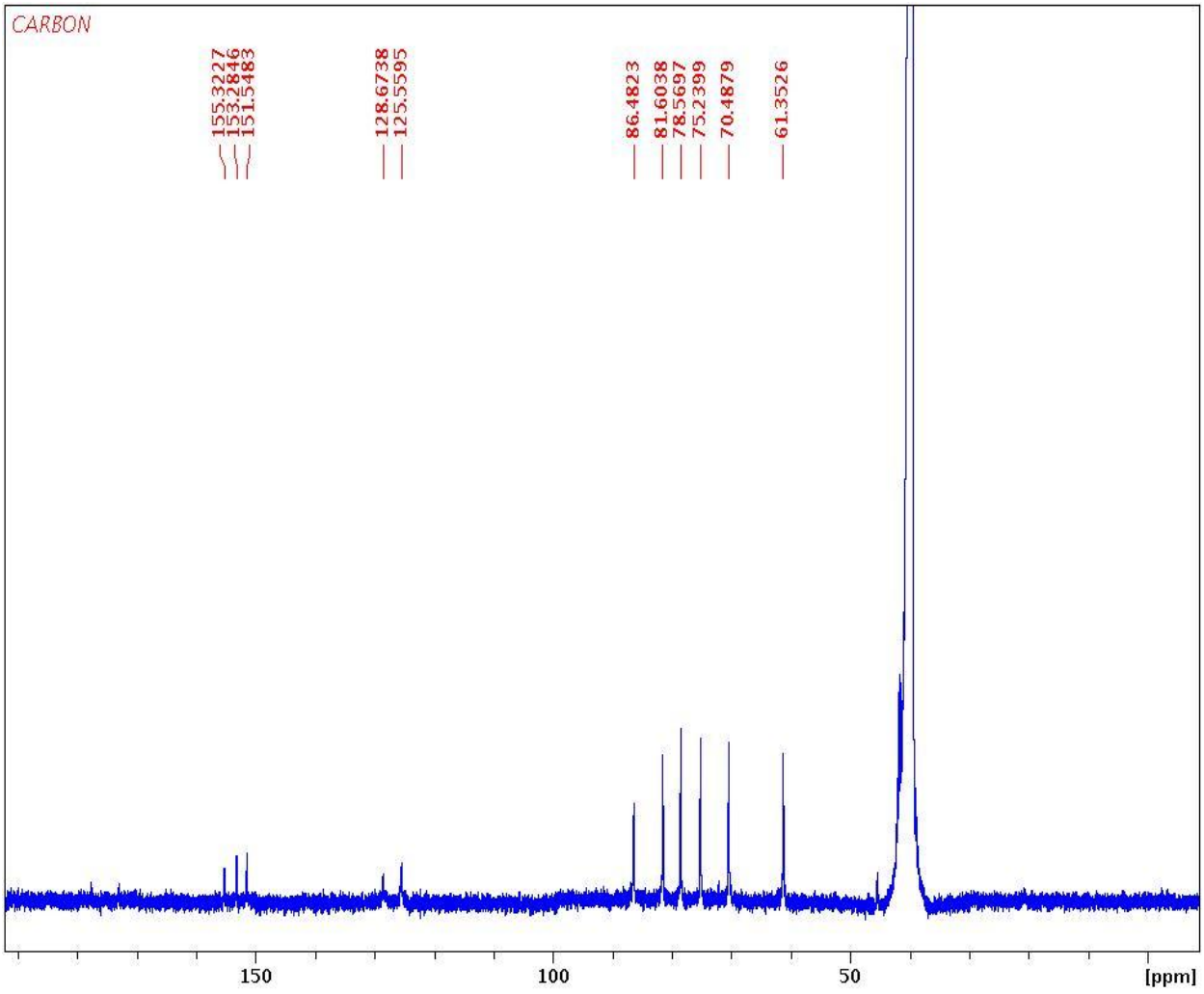


Figure A4.6: ^{13}C NMR of Compound 1b ZnPcGlc$_8$ (DMSO 40 ppm)

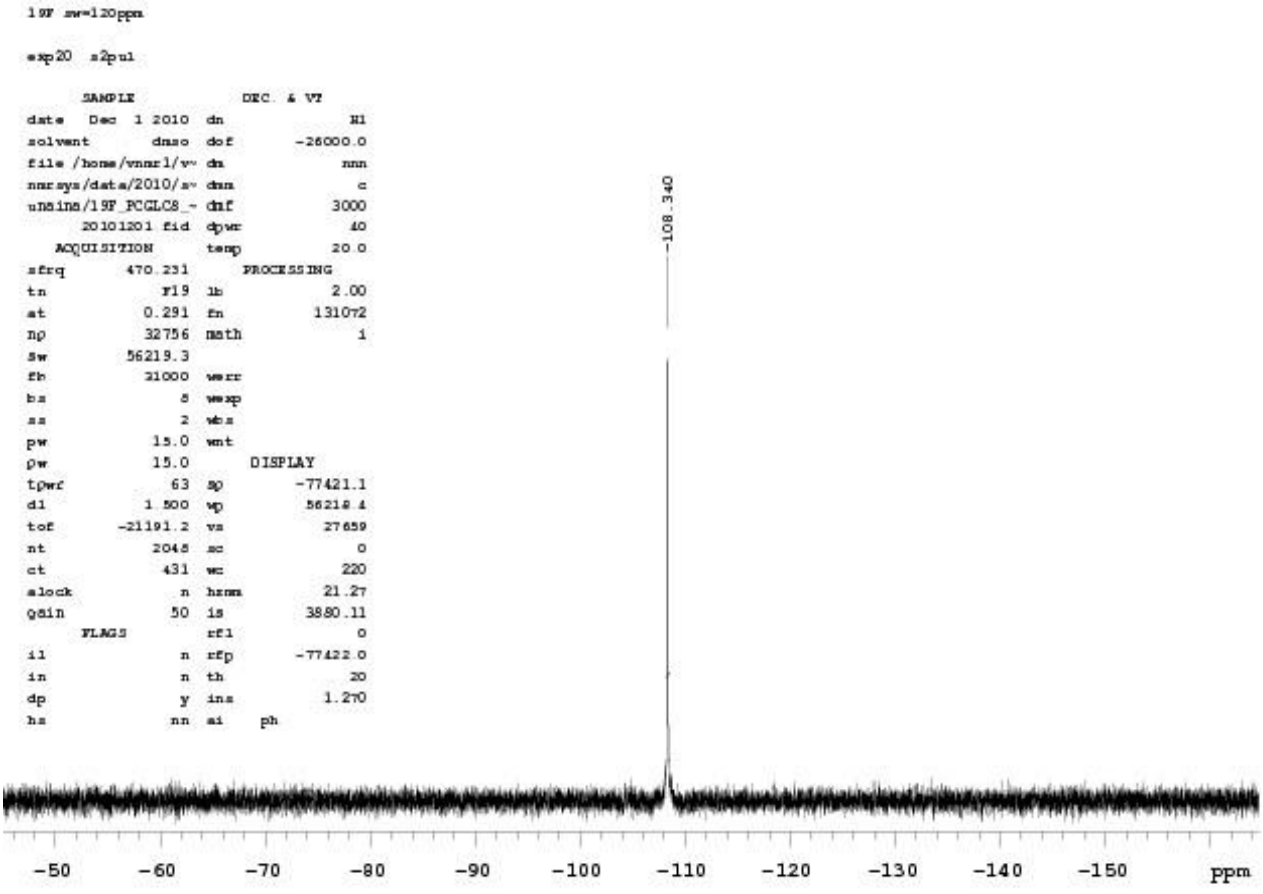


Figure A4.7. ^{19}F NMR of compound 1b ZnPcGlc$_8$ (DMSO-d$_6$)

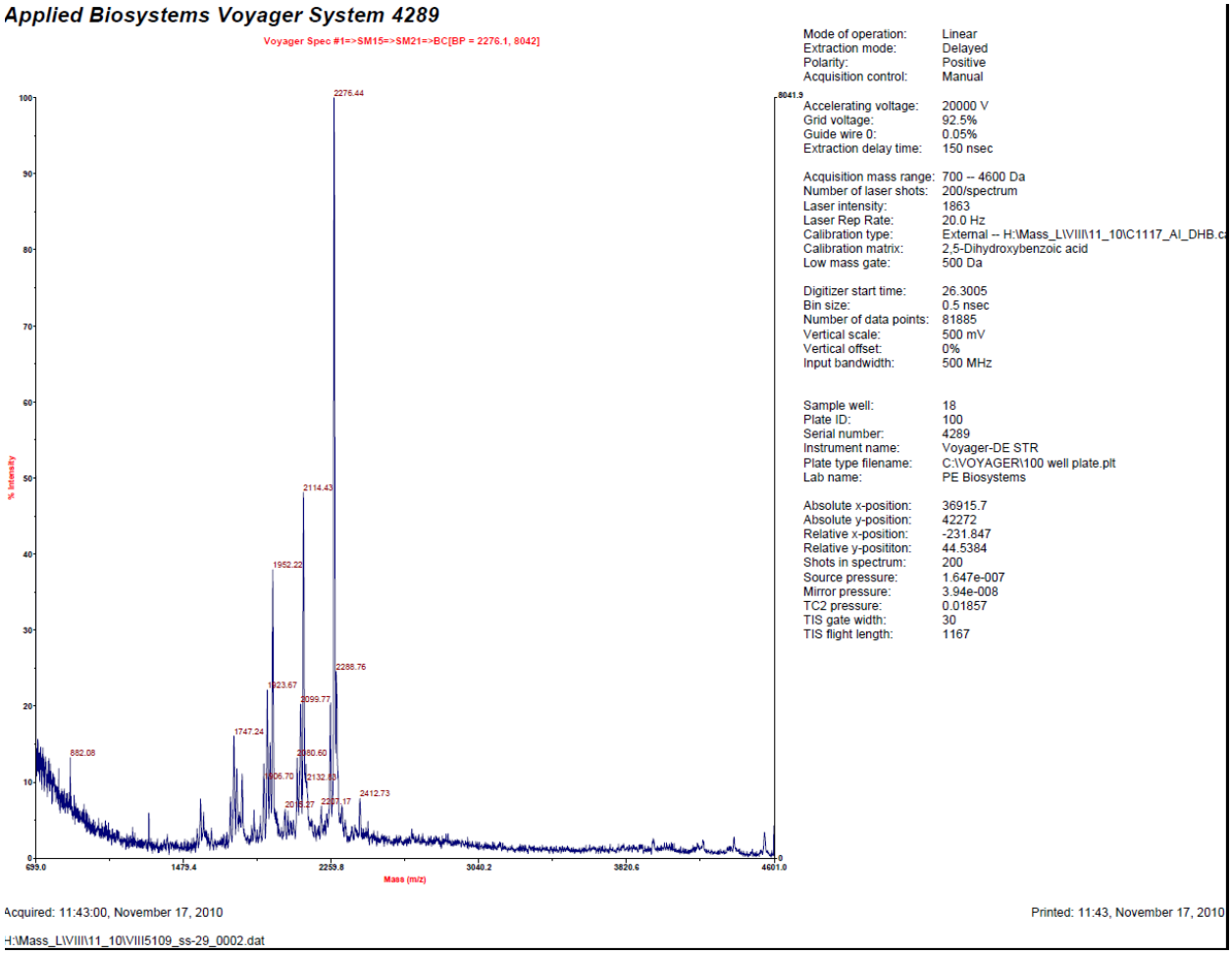


Figure A4.8: MALDI of compound 1b $ZnPcGlc_8$

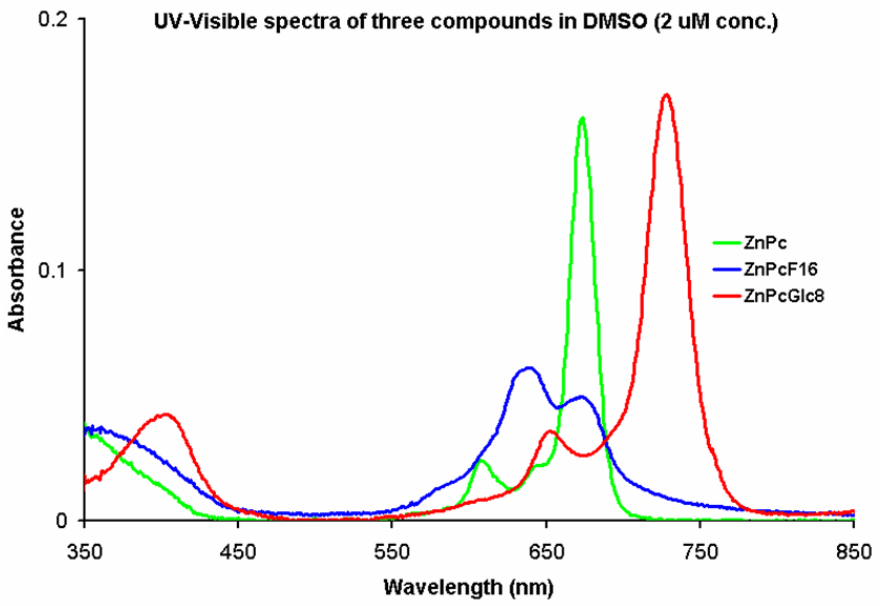


Figure A4.9: UV- Visible spectra of three compounds ZnPc, $ZnPcF_{16}$ and $ZnPcGlc_8$ in DMSO. The concentration of each solution was 2 µM. The blue shift in the Q-band for $ZnPcF_{16}$ is because of the electron withdrawing effect of the F atoms where as in case of $ZnPcGlc_8$ a strong red shift was observed because of the electron donating effect of S-atoms in thioglucose moieties.

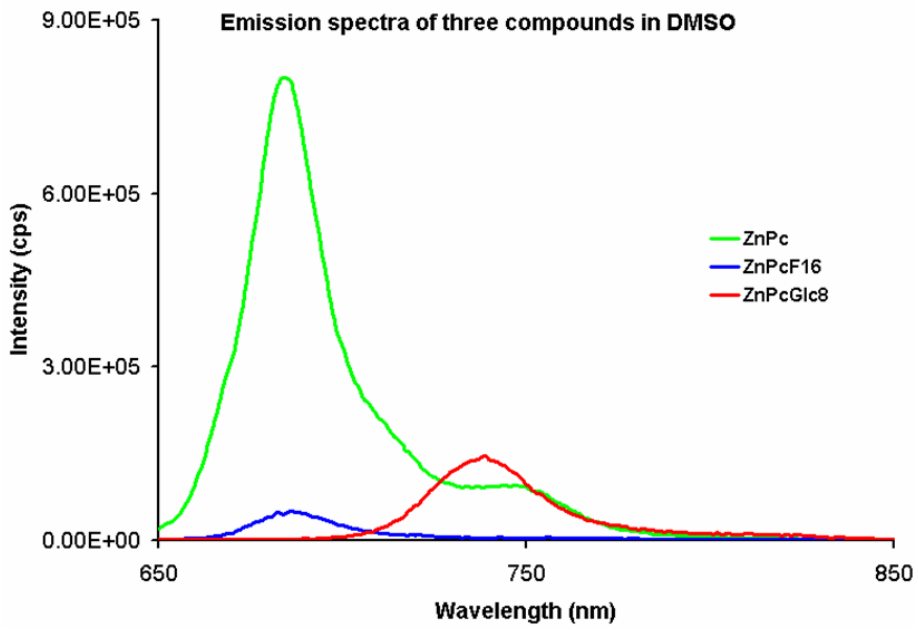


Figure A4.10: Emission spectra of three compounds ZnPc, $ZnPcF_{16}$, and $ZnPcGlc_8$ in DMSO. The three compounds were excited at 646 nm where absorbance of each compound was 0.027. The band pass for both emission and excitation mono-chromators were 2 nm.

CHAPTER 5

IMPROVED METHOD FOR THE SYNTHESIS OF 5,10,15,20-TETRAKIS(3,5-DIACETAMIDO-4-PYRIDYL)PORPHYRIN

Abstract

Porphyrin bearing pyridyl group at the meso positions is synthesized using 2,6-diacetamido-4-formylpyridine. New method has been developed for the synthesis of precursor aldehyde. With this porphyrin, it is possible to build hetero-complementary rigid multi-porphyrin hydrogen bonded supramolecular arrays with differently designed spatial relationships using napthalenediimide (NDI) units. Rigid, coplanar hydrogen bonded dyad can be formed using this porphyrin as a donor and NDI as an acceptor where triple hydrogen bond is formed between the diimide and pyridyl units. Energy transfer can be studied through this hydrogen bonded supramolecular assembly.

5.1 Introduction

The supramolecular arrays formed by porphyrins bearing multiple H-bonding donor and acceptor groups that can mimic the photosynthetic antenna complexes, have been studied as model systems for light harvesting, and have diverse potential applications such as for sensors, and catalysis. Supramolecular assembly formed by these porphyrins through hydrogen bonds can be tuned by adjusting the number of H-bonds and their relative orientation.(*1-4*) For these reasons, 5,10,15,20-Tetrakis(3,5-diaceatmido-4-pyridyl)porphyrin (**I**) (Figure 5.1) is an interesting compound to study the supramolecular design, principles, and photonic properties such as the extent of electron and energy transfer in supramolecular systems.

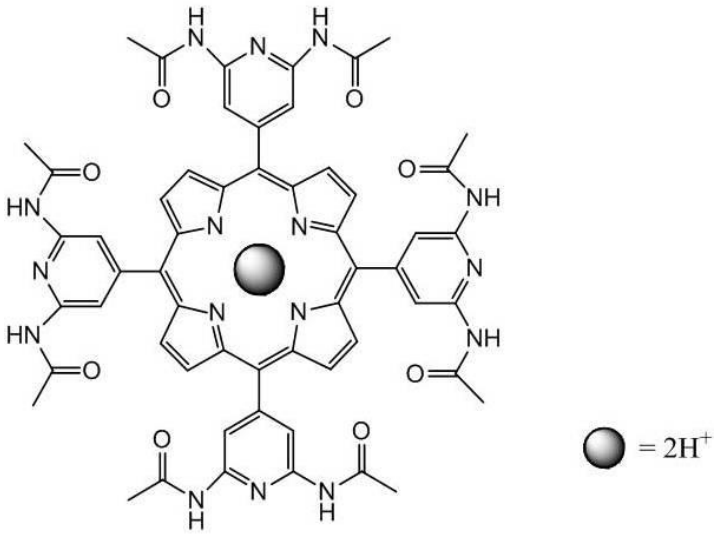


Figure 5.1. 5,10,15,20-Tetrakis(3,5-diacetamido-4-pyridyl)porphyrin (**I**).

This porphyrin, when mixed with complementary porphyrins bearing uracil groups at the meso positions with the correct orientation in an aprotic solvent results in the self assembly of these porphyrin analogs into one-, two-, and three-dimensional arrays via complementary H-bonding (Figure 5.2).

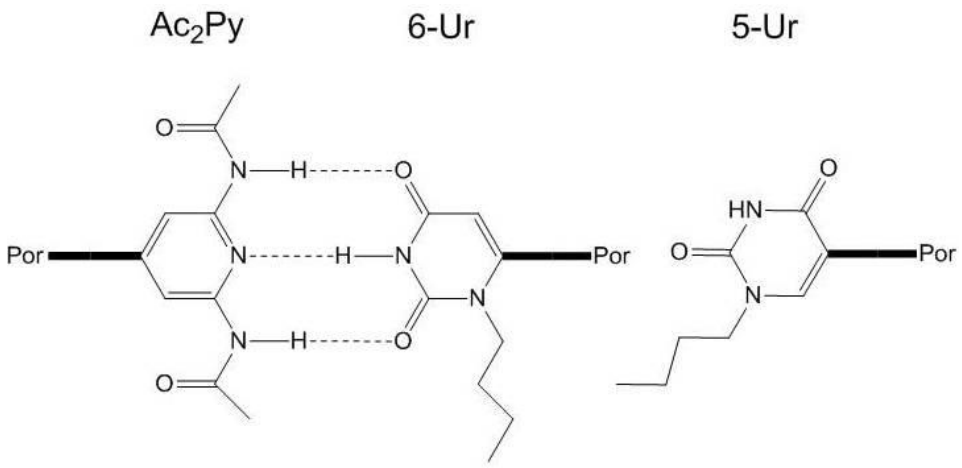


Figure 5.2. Interactions between two porphyrin building blocks via complementary hydrogen bonding can afford supramolecular assemblies.

The tessellation of 2-dimensional arrays mediated by complementary H-bond groups on two different porphyrins results in a checkerboard pattern wherein donor chromophores and acceptor chromophores alternate (Figures 5.3 and 5.4). These types of systems promote electron transfer and are of particular interest because of their relevance to light harvesting arrays. Here, 5, 10, 15, 20-tetrakis(3, 5-diacetamido-4-pyridyl)porphyrin serves as an acceptor and 5, 10, 15, 20-tetrakis(1'-butyl-6'-uracyl) porphyrin Zn(II) serves as the donor. Arrays of various sizes can be deposited on the surfaces wherein the surface energetics, solvent, and rate of solvent evaporation strongly influence the domain size and defect density. The orthogonal recognition groups still allow for energy transfer from the Zn(II) complex to one of the four surrounding free bases.(*5*, *6*)

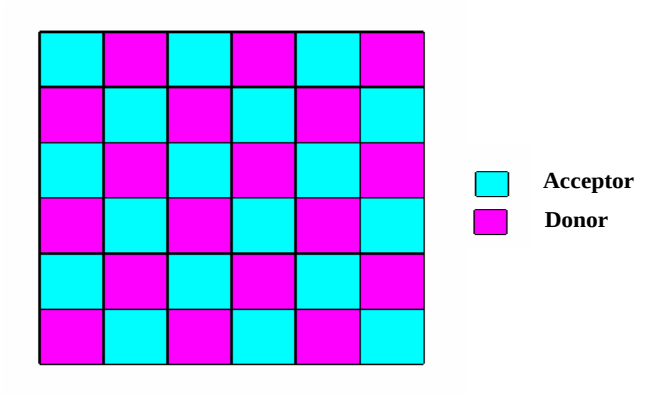


Figure 5.3a. In this pattern each acceptor is surrounded by four donor or vice-versa. The ratio of metalated porphyrin: freebase porphyrin is 1:1.

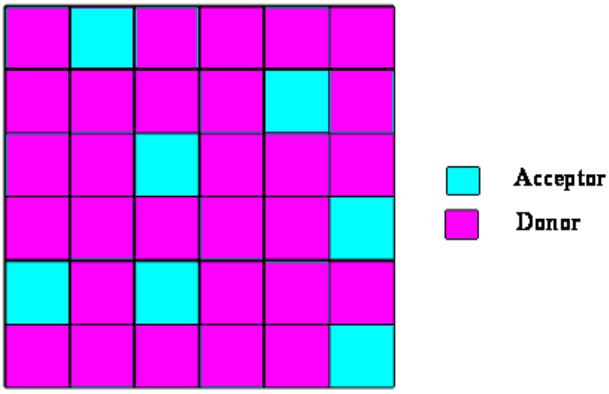


Figure 5.3b. In this pattern each acceptor is surrounded by 8 energy donors or the antenna.

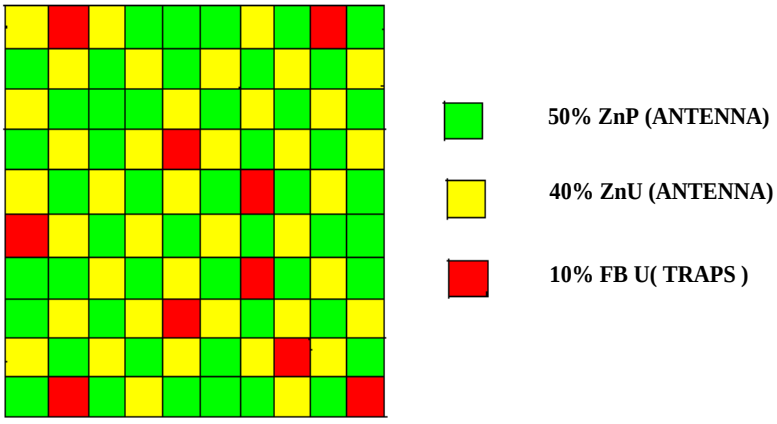


Figure 5.3c. Random arrangement where the excited state energy goes to the nearest trap.

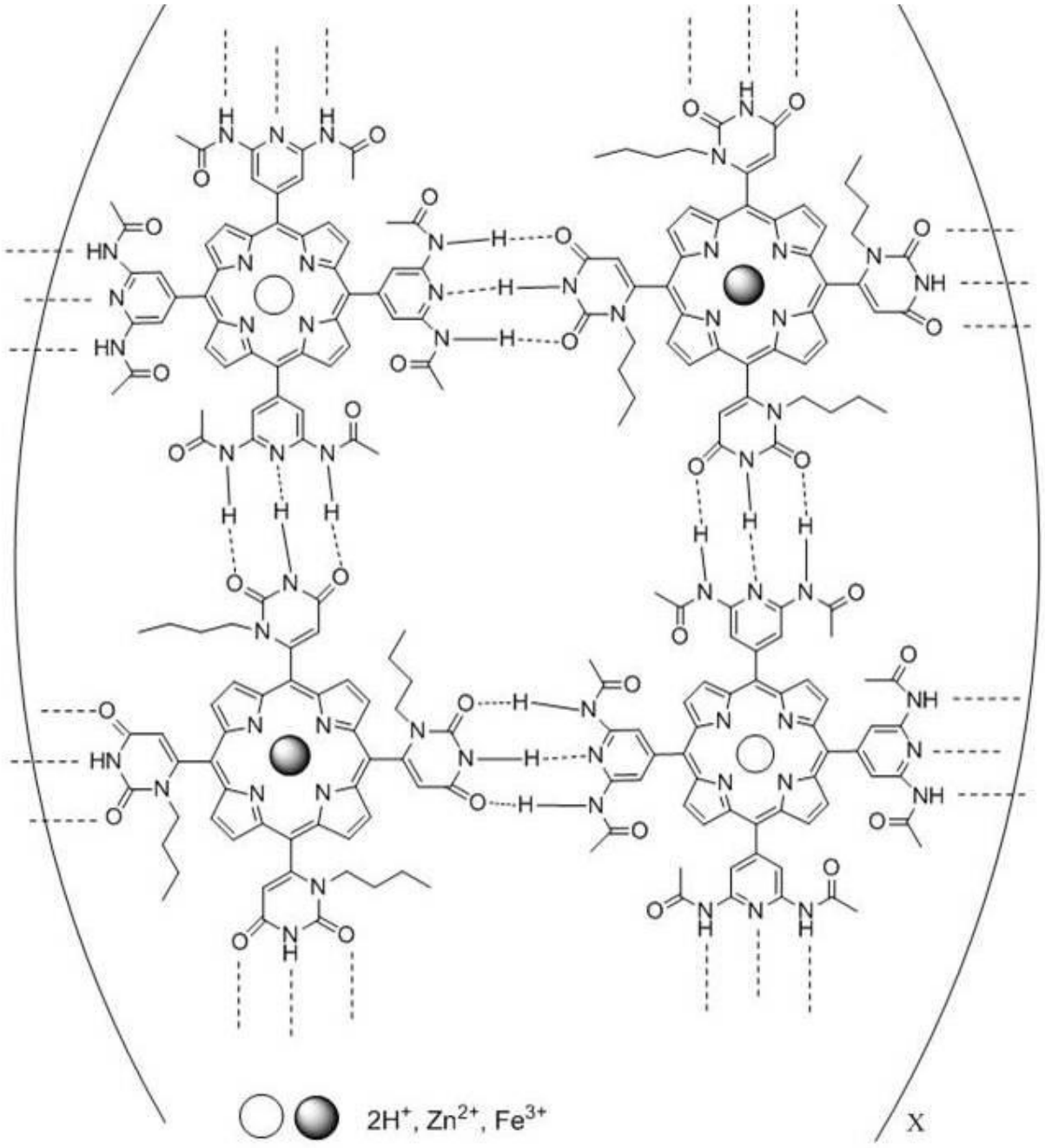
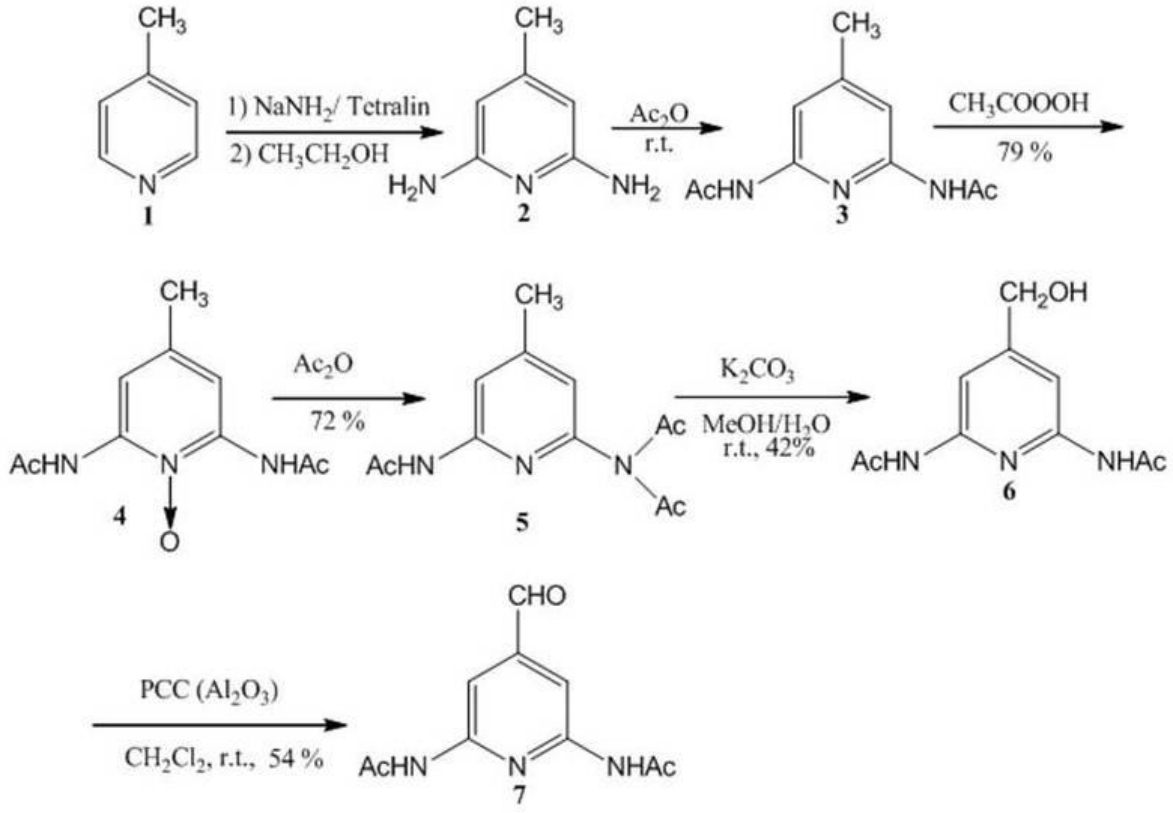
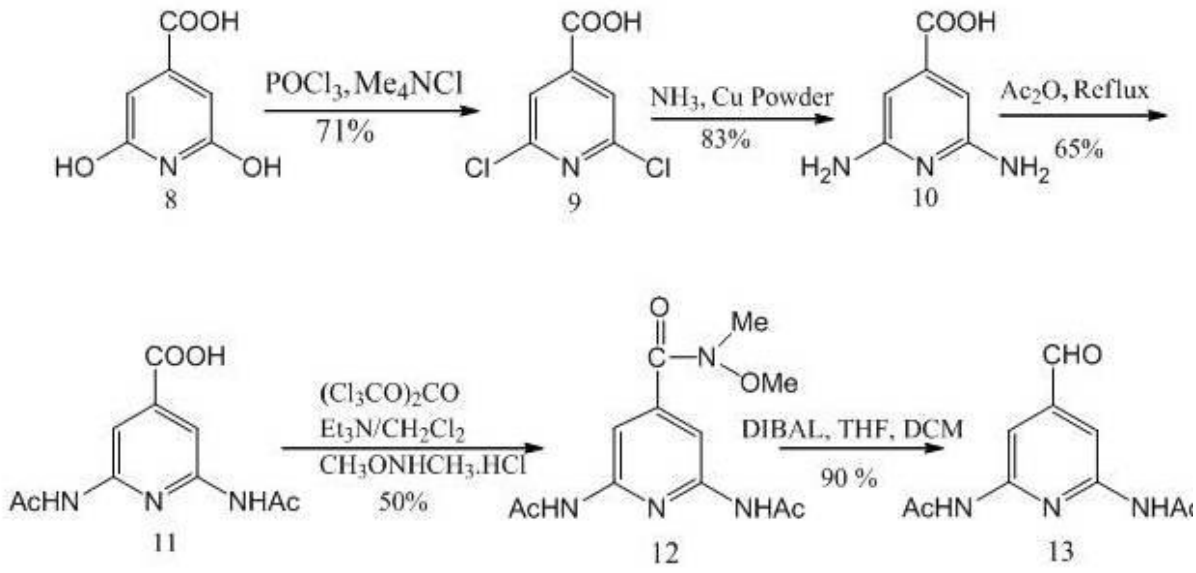


Figure 5.4. 5, 10, 15, 20-tetrakis(3, 5-diacetamido-4-pyridyl) porphyrin and 5, 10, 15, 20-tetrakis(1'-butyl-6'-uracyl) porphyrin (Zn) mixed in different organic solvents in ratio 1:1 can result in the formation of arrays of various sizes.

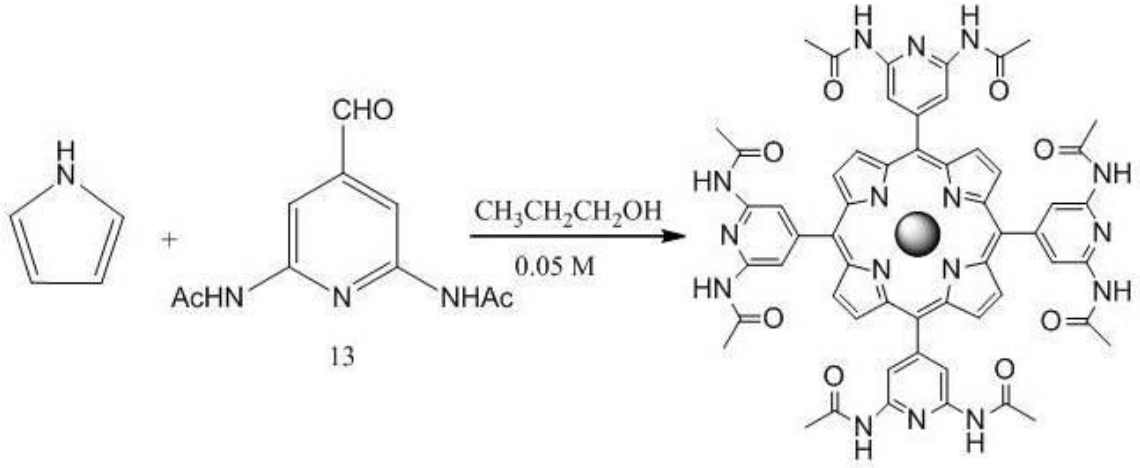
However, the synthesis of the diacetamidopyridyl porphyrin is challenging because of the difficulty in preparing the precursor aldehyde. Herein, we report a new method for the synthesis of 2,6-diacetamido-4-formylpyridine (scheme 5.2). The aldehyde can be produced by fewer steps and higher yield than what is previously reported(*7*) by our group. (Scheme 5.1).



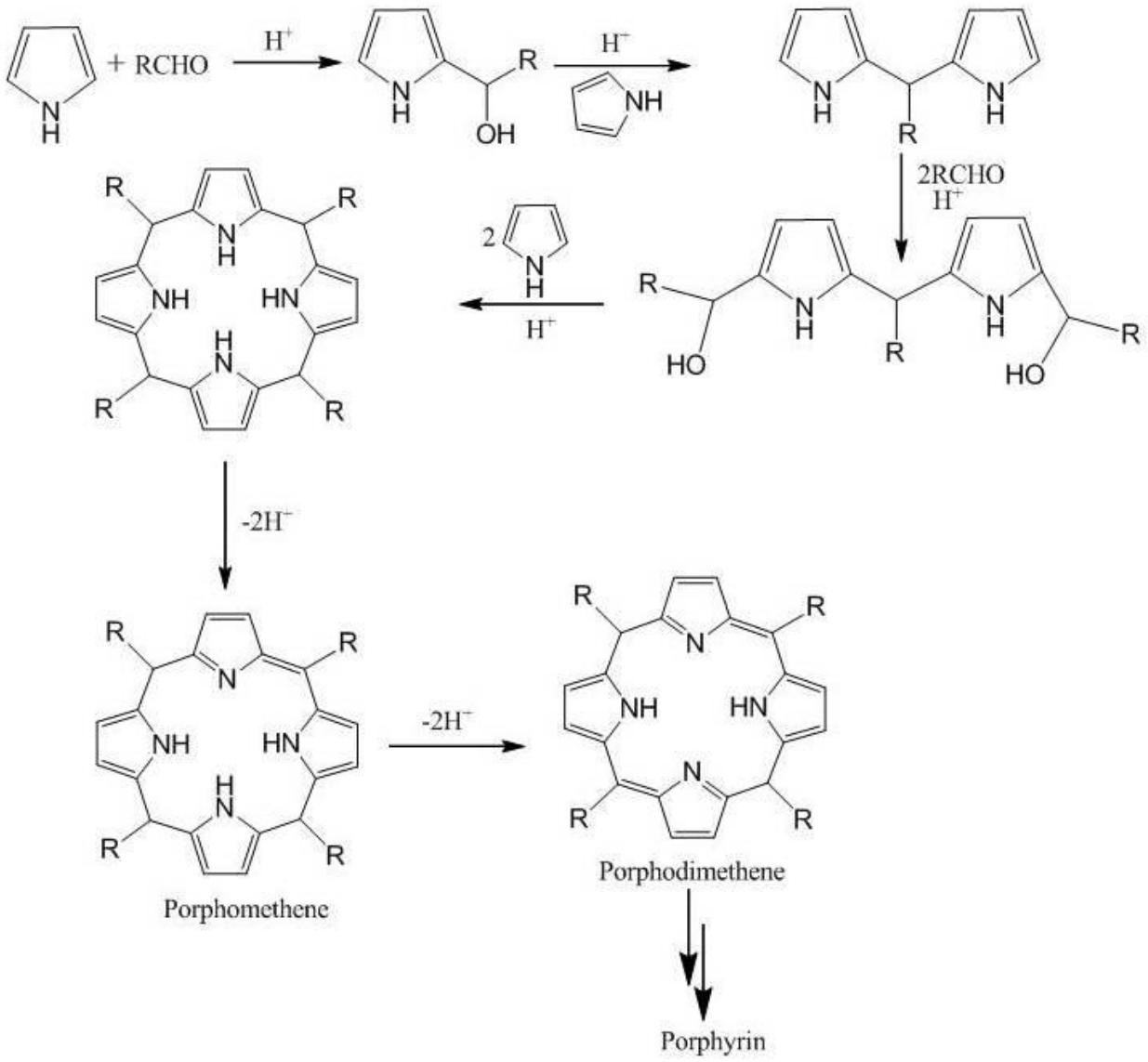
Scheme. 5.1. Synthesis of 2,6-diacetamido-4-formylpyridine by our previous method (*7*)**.**



Scheme 5.2. Improved synthesis of 2,6-diacetamido-4-formylpyridine.



Scheme 5.3. Synthesis of 5, 10, 15, 20-tetrakis(3, 5-diacetamido-4-pyridyl) porphyrin (I).



Scheme 5.4. Mechanism of porphyrin synthesis**.**

5.2 Experimental Procedure

Materials and Instrumentation

^{1}H and ^{13}C Spectra were recorded in a Brüker Avance 500 MHz spectrometer. Mass spectrometry analyses were performed at the CUNY Mass Spectrometry Facility at Hunter College by electrospray ionization on an Agilent Technologies G6520 Q-TOF instrument and Agilent 1200 HPLC system. The electrospray ionization was done in methanol, with 0.1% formic acid. UV-visible spectra were recorded on a Varian Bio3 spectrophotometer. All reagents were obtained from commercial sources and used without purification. Flash column chromatography was performed using silica gel-60, and the analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick) both from Sorbent Technologies.

Synthesis of 5,10,15,20-tetrakis(3, 5-diacetamido-4-pyridyl) porphyrin

Compound **8** was purchased from Aldrich. Compounds **9** (2,6-dichloro-4-pyridinecarboxylic acid) and **10** (2,6-diamino-4-pyridinecarboxylic acid) were synthesized by previously described procedures.(*8-10*)

2,6-Diacetamido-4-pyridinecarboxylic acid (11)

10.0 mL of acetic anhydride was added to 2.0 g (13.0 mmol) of the diamine **3**. The resultant solution was stirred for 4 h at refluxing conditions and 2.02 g (65%) of a brown solid **11** was collected by filtration, washed with water. ^{1}H NMR (DMSO-d_6) δ 13.53 (s, 1H), 10.28 (s, 2H), 8.21 (s, 2H), 2.13 (s, 6H); ^{13}C NMR (DMSO-d_6) δ170.03, 166.64, 151.57, 142.50, 108.77, 24.53; HRMS (ESI, m/z): Calcd for $C_{10}H_{12}N_3O_4$, 238.0828 $(M+H)^+$, observed, 238.0825.

2,6-Diacetamido-4-pyridine-N-methoxy-N-methyl amide (12)

To a stirred solution of the carboxylic acid (**11**) 0.5 g (2 mmol) in CH_2Cl_2 (10 mL) at 0^oC were added triphosgene 0.3 g (1 mmol) and triethylamine 0.15 mL (10 mmol). The N,O-

dimethylhydroxylamine hydrochloride 0.2 g (2 mmol) was added to the solution and the ice bath was removed. The reaction mixture was stirred at room temperature and monitored by TLC. After completion, the triethylamine hydrochloride was removed by suction filtration. The filtrate was collected and the solvent was removed under reduced pressure and the solid was subjected to column chromatography on flash silica gel and eluted with dichloromethane/methanol 9:1 and the 0.58 g product was obtained in 50 % yield. ^{1}H NMR (MeOD-d_4) δ 7.93 (s, 2H), 3.65 (s, 3H), 3.31 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (MeOD-d_4) δ 170.64, 150.39, 146.17, 106.91, 60.59, 56.07, 22.65; HRMS (ESI, m/z): Calcd for $C_{12}H_{16}N_4O_4$, 280.1176 (M^+), observed 280.1172.

2,6-Diacetamido-4-formylpyridine (13)

To a solution of compound 5 (0.5 g, 1.78 mmol) in CH_2Cl_2 (65 mL) was added DIBAL-H (1M in THF, 14 ml, 14 mmol) at -78^{o}C, and the mixture was stirred at the same temperature for 2 h. After addition of methanol (to quench the DIBAL-H), the resulting mixture was partitioned between $CHCl_3$ and 1 N HCl and the organic layer was washed with brine, dried with Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, ethylacetate/ethanol (9:1) to give 370 mg, 90 % of the aldehyde. ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 2H), 9.96 (s,1H), 8.11 (s, 2H), 2.10 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 194.1, 170.7, 152.6, 146.5, 108.9, 25.3; HRMS (ESI, m/z): Calcd for $C_{10}H_{12}N_3O_3$, 222.0879 $(M+H)^+$, observed, 222.0876.

5, 10, 15, 20-Tetrakis(3,5-diacetamido-4-pyridyl)porphyrin (I)

Pyrrole (69.5 µL, 1.0 mmol) and 2, 6-diacetamido-4-formylpyridine **13** (221 mg, 1.0 mmol) were added to boiling propionic acid (10.0 mL). The reaction mixture was refluxed for 2 h and then taken to dryness under vacuum. The resulting solid was purified by chromatography on silica gel eluting with ethanol/ethylacetate (1:1) to yield 70 mg (25%) of porphyrin. ^{1}H NMR

(DMSO-d_6) δ 10.52 (s, 8H), 8.99 (s, 8H), 8.60 (s, 8H), 2.16 (s, 24H), -3.10 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 170.25, 152.67, 149.50, 130.12, 118.82, 115.80, 24.53. HRMS (ESI, m/z): Calcd. for $C_{56}H_{50}N_{16}O_8$, 1075.4076 $(M+H)^+$, observed, 1075.4043; UV/visible (DMSO) λ_{max} (€) = 422.6, 514.8, 549.0, 587.2 and 642.3 nm

5.3 Results and Discussion

The method (Scheme 5.2) has certain advantages over previously reported method for several reasons: (A) This method avoids the first step (Scheme 5.1) to convert 4-methylpyridine **1** to 2,6-diamino-4-methylpyridine **2** which is a difficult step. The reagents such as sodamide and tetralin should be very anhydrous, since slight moisture can drastically lower the yield of the reaction. (B) This method avoids the use of the strong oxidant peracetic acid at elevated temperatures. (C) This method has fewer steps and gives better overall yield of the aldehyde.

This new method (Scheme 5.2) involves conversion of commercially available citrazinic acid (**8**) to the 2,6-dichloroisonicotinic acid **9** in 71 % yield by treatment with phosphorous oxychloride and tetramethylammonium chloride.(*8, 11*) Compound **9** was reacted with ammonia with a copper catalyst, at high temperature ~180^{o}C and at high pressure, 20 bar. The copper was filtered from the solution and compound was precipitated from the filtrate by treatment with acid to pH 5 with overall yield of the free acid of about 80 %.(*10*) The compound **10** was treated with acetic anhydride at refluxing conditions to give compound **11** which was filtered and washed with water several times, to yield 65% of 2,6-diacetamido-4-pyridinecarboxylic acid **11**. Compound **11** was treated with triphosgene to form an acid chloride, followed by addition of *N,O*-dimethylhydroxylamine to yield the desired Weinreb amide in 50% yield **12**.(*12*) This is a versatile method for direct conversion of carboxylic acids to the corresponding Weinreb amides.

The direct conversion relies on *in situ* activation of carboxylic acids to attack of *N,O*-dimethylhydroxylamine.(*13-15*) Reduction of Weinreb amide **12** to the aldehyde was done by treatment with DIBAL-H and the corresponding aldehyde was obtained in 90% yield in this step. (*16*) The porphyrin was synthesized from 2,6-diacetamido-4-formylpyridine using Adler conditions using propionic acid.(*17*)

This porphyrin can form a second type of supramolecular assembly with naphthalene diimide (NDI) (Figure 5.5). In this system, the porphyrin can act as an donor and NDI as an acceptor. Having NDI motif directly attached to the meso position of a diacetamido porphyrin can reduce both the conformational freedom of the assembly as well as provide a suitable through-bond pathway for energy transfer.(*18*) Naphthalene diimides can act as ideal candidates in the design of conducting materials because of their electron deficient nature and unique photophysical, electronic properties and enhanced solubility properties.(*19, 20*)

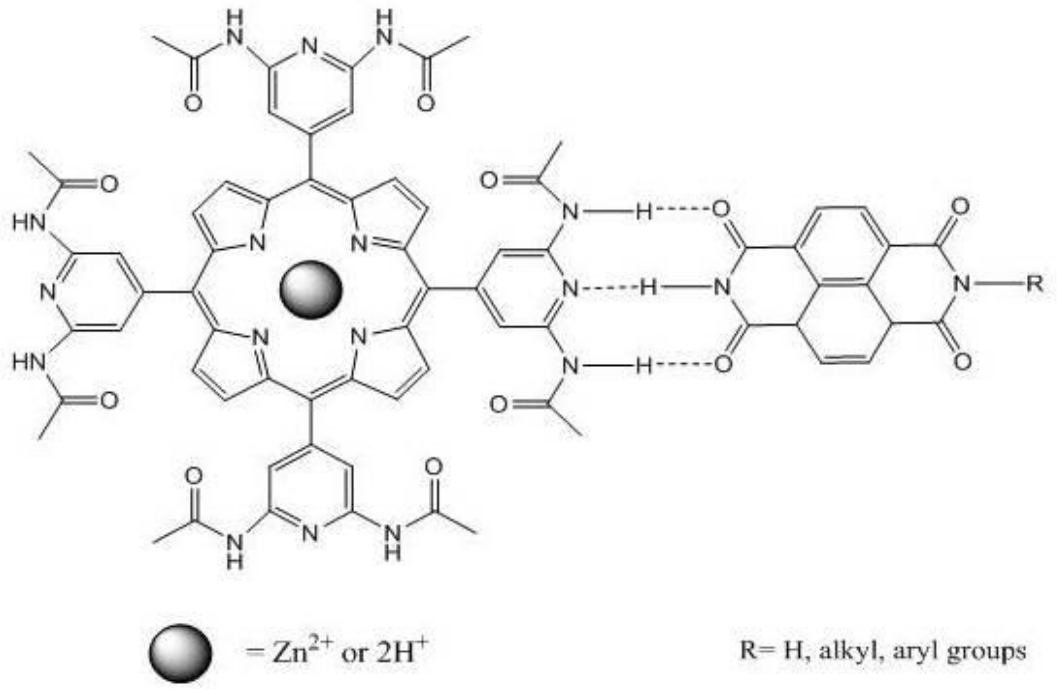


Figure 5.5. The rigid coplanar dyad, assembled by three-point hydrogen bonding which may mediate energy transfer processes, can be formed by mixing 5,10,15,20-tetrakis(3,5-diacetamido-4-pyridyl) porphyrin (**I**) and NDI in different aprotic solvents.

Substitution on diimide nitrogens produces analogues whose absorption and emission are variable and are often used as electron acceptors. For example, substitution of diimide nitrogens by alkyl groups produces the white-blue fluorescent compounds while if these nitrogens are substituted by aromatic functional groups, non-fluorescent or weakly fluorescent compounds are produced(*21*, *22*).

5.4 Conclusions

We have developed a simple, synthesis for an important aldehyde, 2,6-diacetamido-4-formylpyridine, that is key to forming a porphyrin bearing rigid H-bond moieties on the meso positions This protocol provides a practical alternative to the existing method available for the synthesis of this aldehyde. The meso-substituted pyridyl porphyrin can be used for constructing supramolecular structures with NDI through hetero-complementary assembly where porphyrin can act as a donor and NDI as an acceptor. These supramolecular materials are expected to have unique optical and physical properties e.g. redox properties and can contribute to major effort in basic research on optoelectric nanomaterials.

5.5 References

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5.6 Appendix

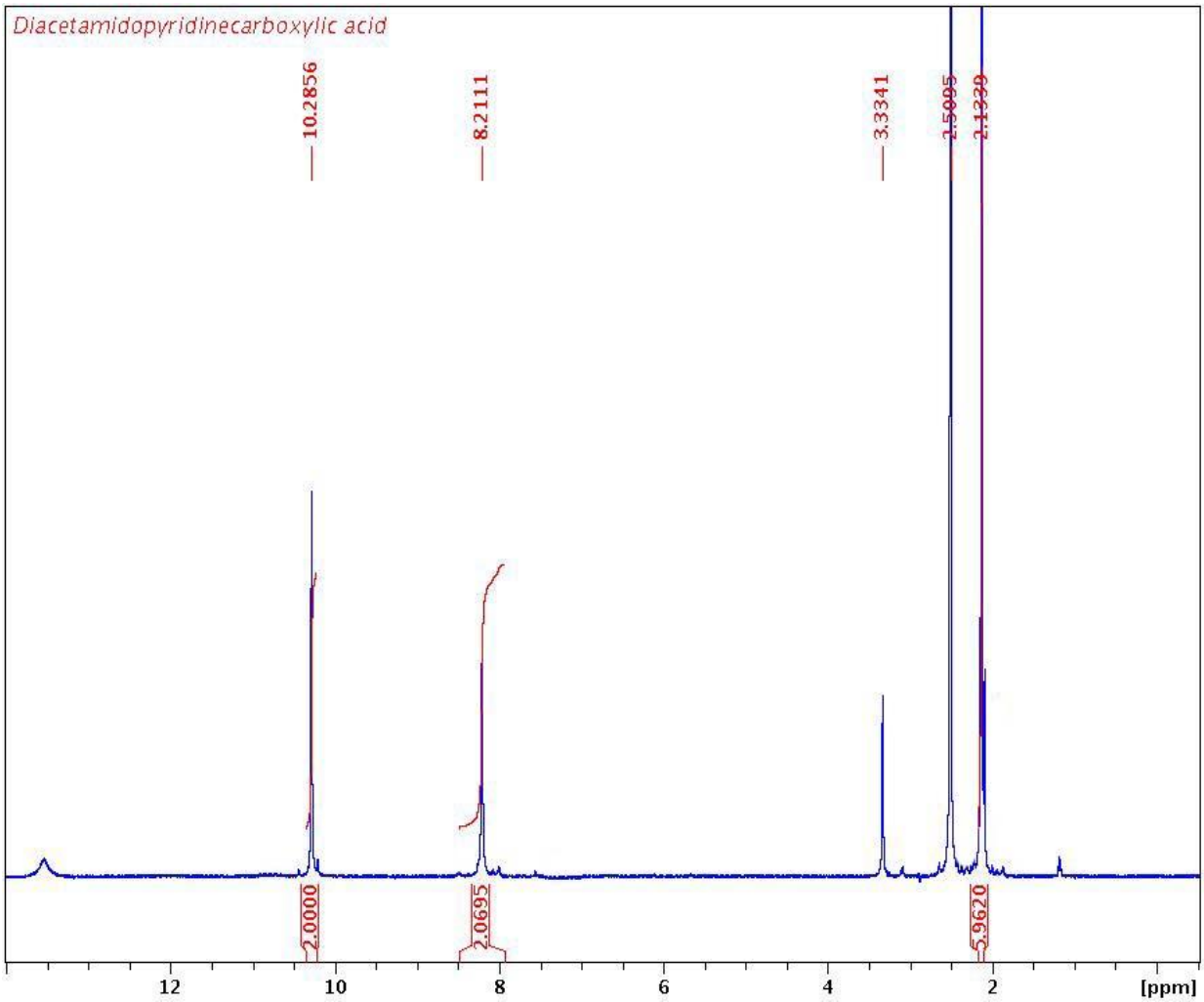


Figure A5.1: ^{1}H NMR of compound **11** in (DMSO-d_6 2.5 ppm, water 3.31 ppm).

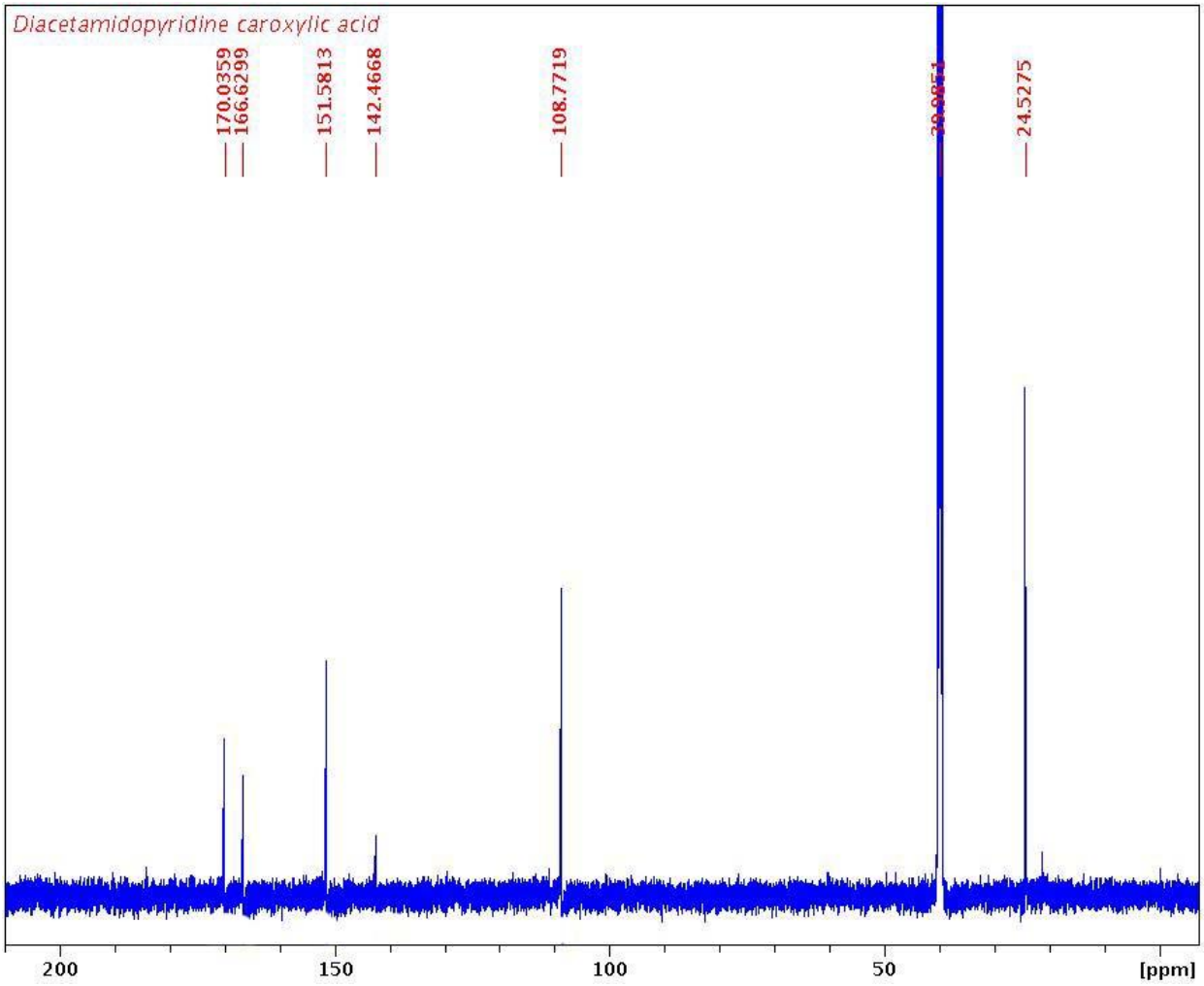


Figure A5.2: ^{13}C NMR of compound **11** (DMSO-d_6 40 ppm).

Data File	HCMDSS39A.d	**Sample Name**	2,6-diaceatimidoacid
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	4/21/2010 5:06:45 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=237.0750 M=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Name	Formula	Tgt Mass	Diff (ppm)
Cpd 2: C10H11N3O4	0.23	237.0752	17267		C10H11N3O4	237.075	0.93

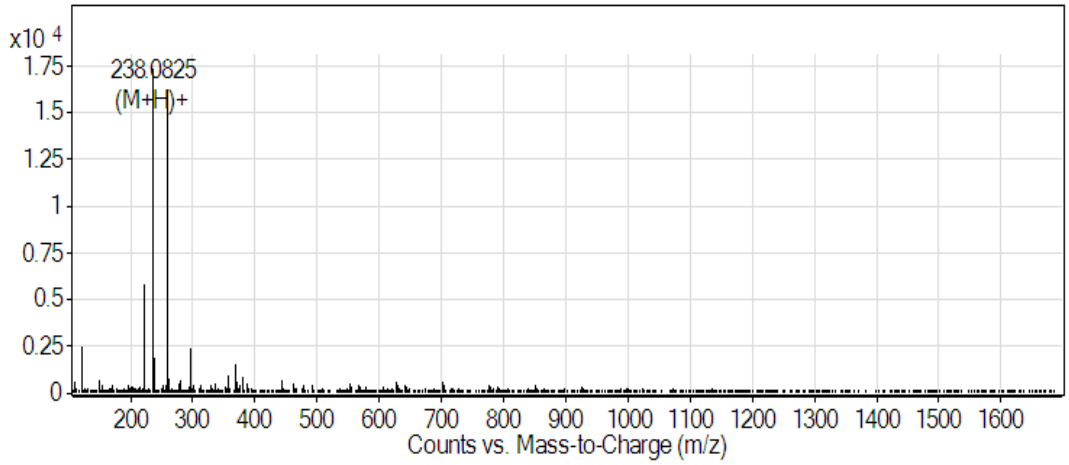


Figure A5.3: Mass spectrum of compound **11**.

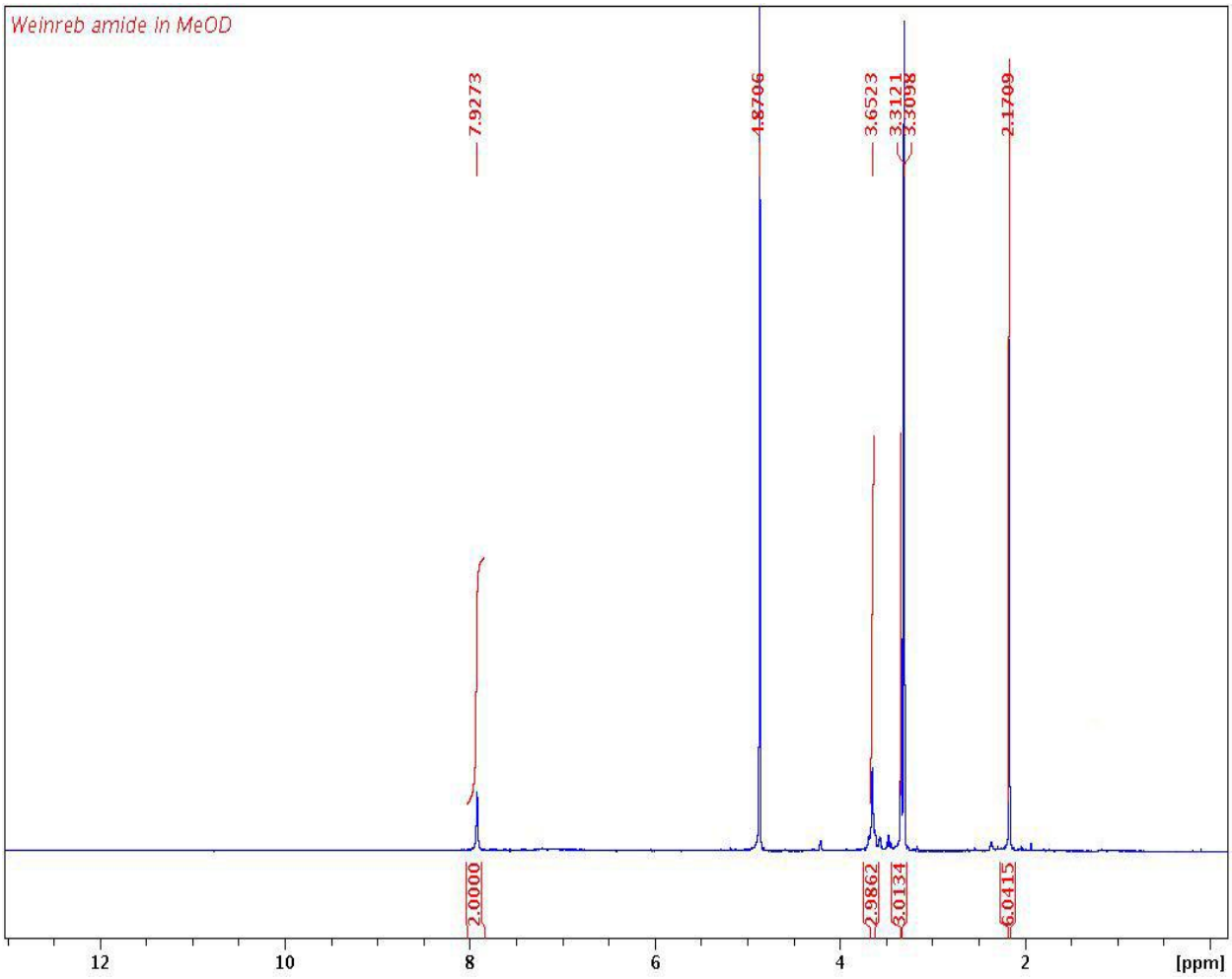


Figure A5.4: ^{1}H NMR of compound **12** (MeOD-d_4 4.87 and 3.31 ppm, water 4.9 ppm).

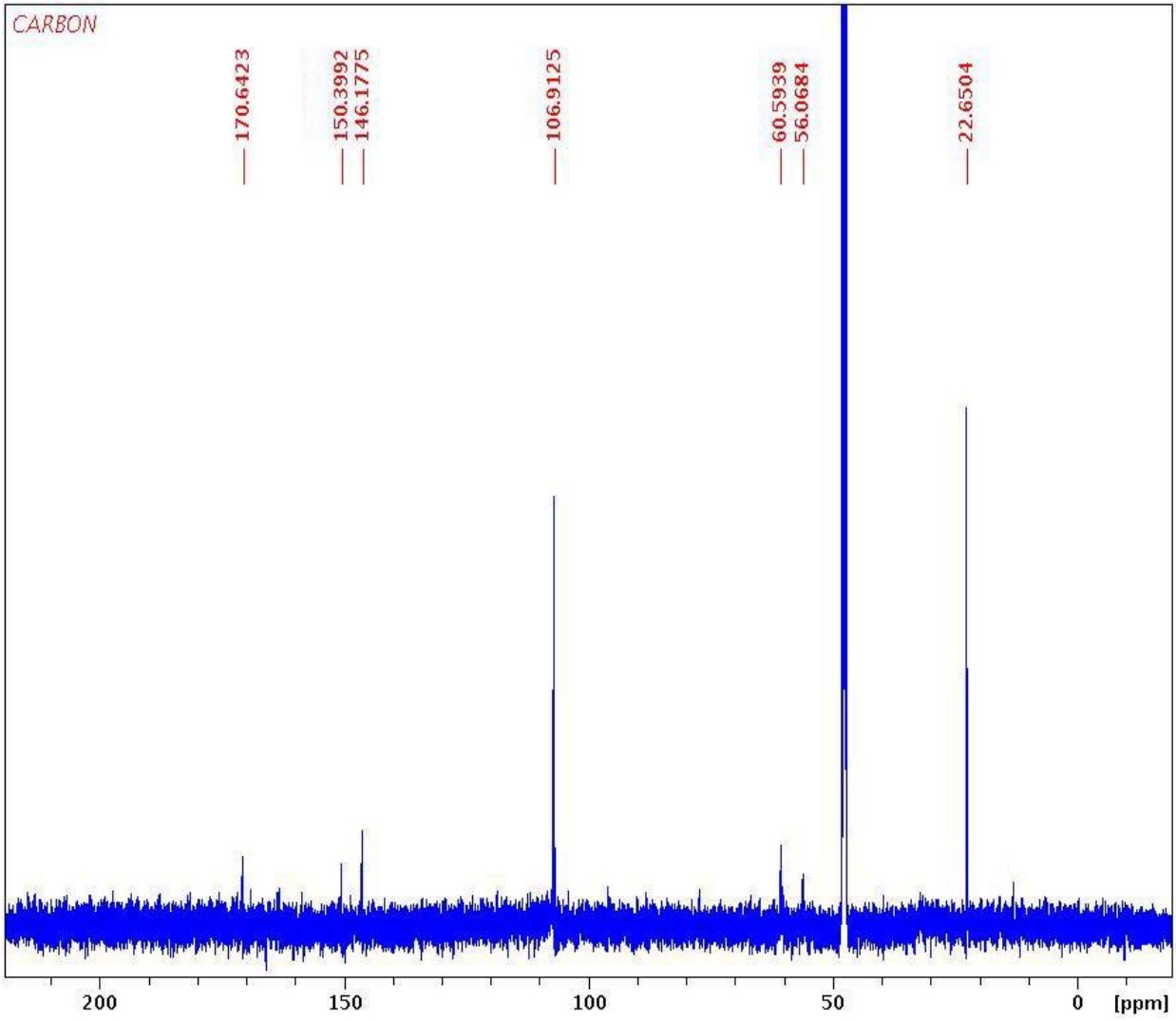


Figure A5.5: ^{13}C NMR of compound **12** (MeOD-d_4 49.15 ppm).

Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	4/30/2010 5:17:11 PM
IRM Calibration Status	Some Ions Missed	**DA Method**	HCEmpirical1.m
Comment	EM=280.1172 M=HC APPII Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C12H16N4O4	0.094	280.1176	7421	C12H16N4O4	280.1172	1.48

Compound Label	RT	Algorithm	Mass
Cpd 1: C12H16N4O4	0.094	Find By Formula	280.1176

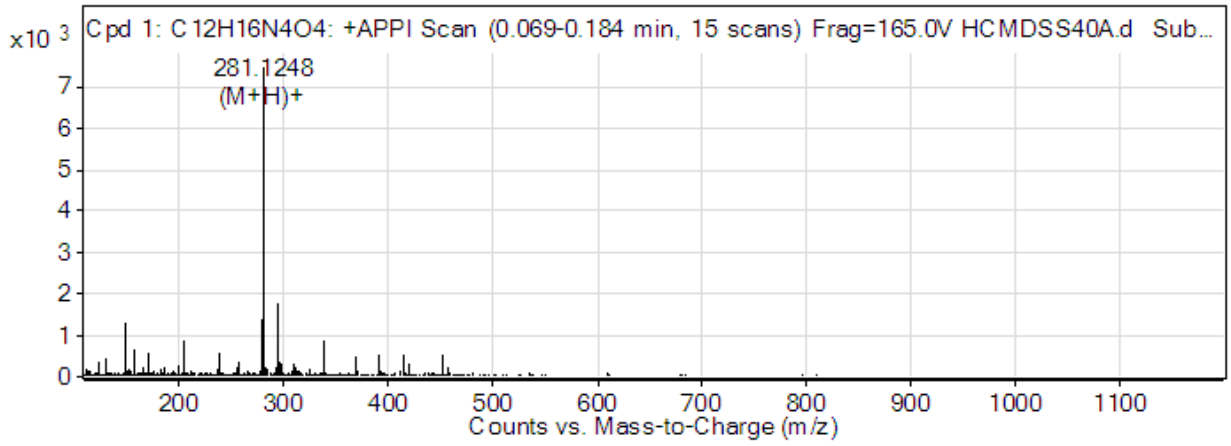


Figure A5.6: Mass spectrum of compound **12**.

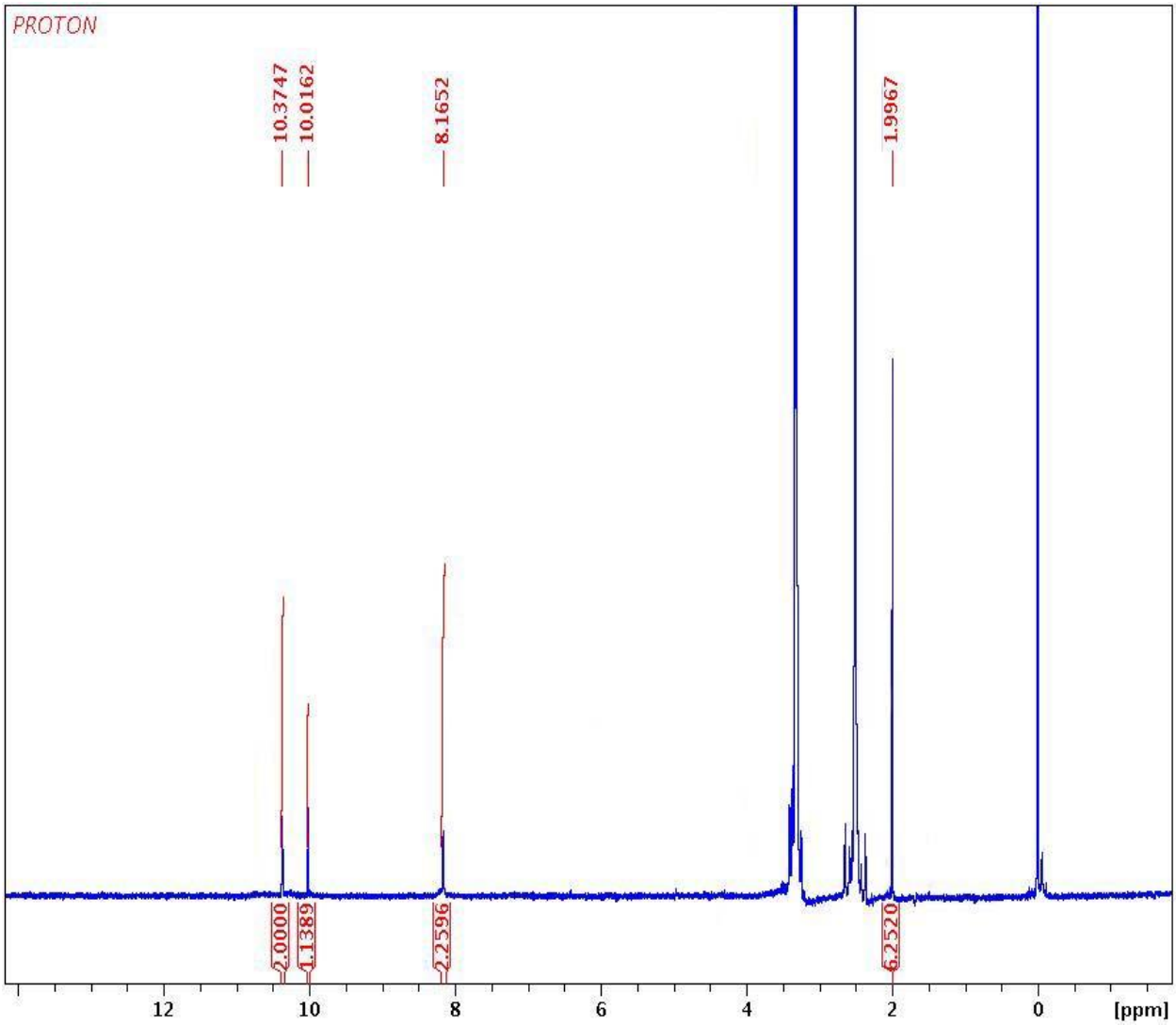


Figure A5.7: ^{1}H NMR of compound **13** (DMSO-d_6 2.5ppm, water 3.34 ppm).

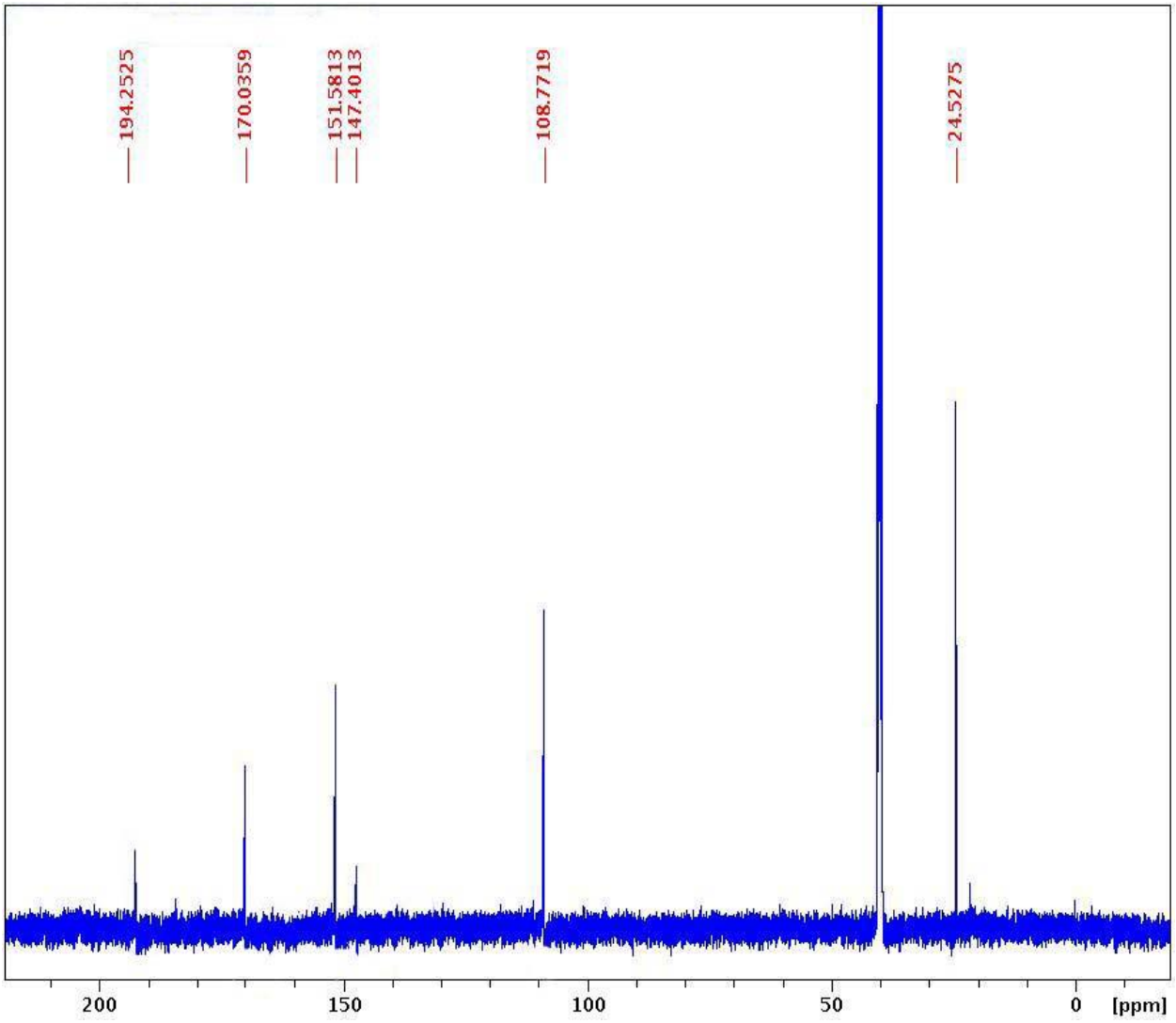


Figure A5.8: ^{13}C NMR of compound **13** (DMSO-d_6, 40 ppm).

Data File	HCMDSS42A.d	**Sample Name**	Pyrido Aldehyde
Sample Type	Sample	**Position**	P1-A3
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	5/26/2010 12:41:24 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=221.0800 M=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C10H11N3O3	0.223	221.08	14059	C10H11N3O3	221.08	-0.26

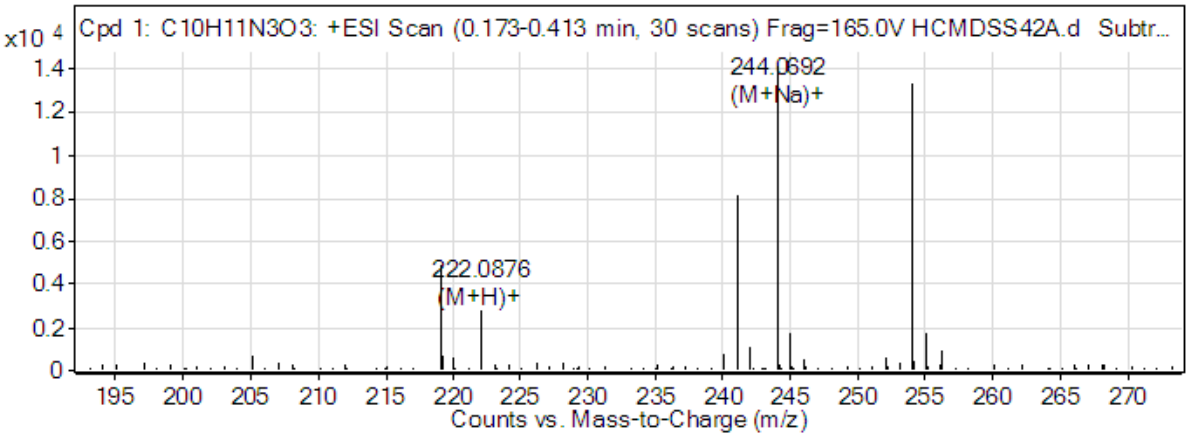


Figure A5.9: Mass spectrum of compound **13.**

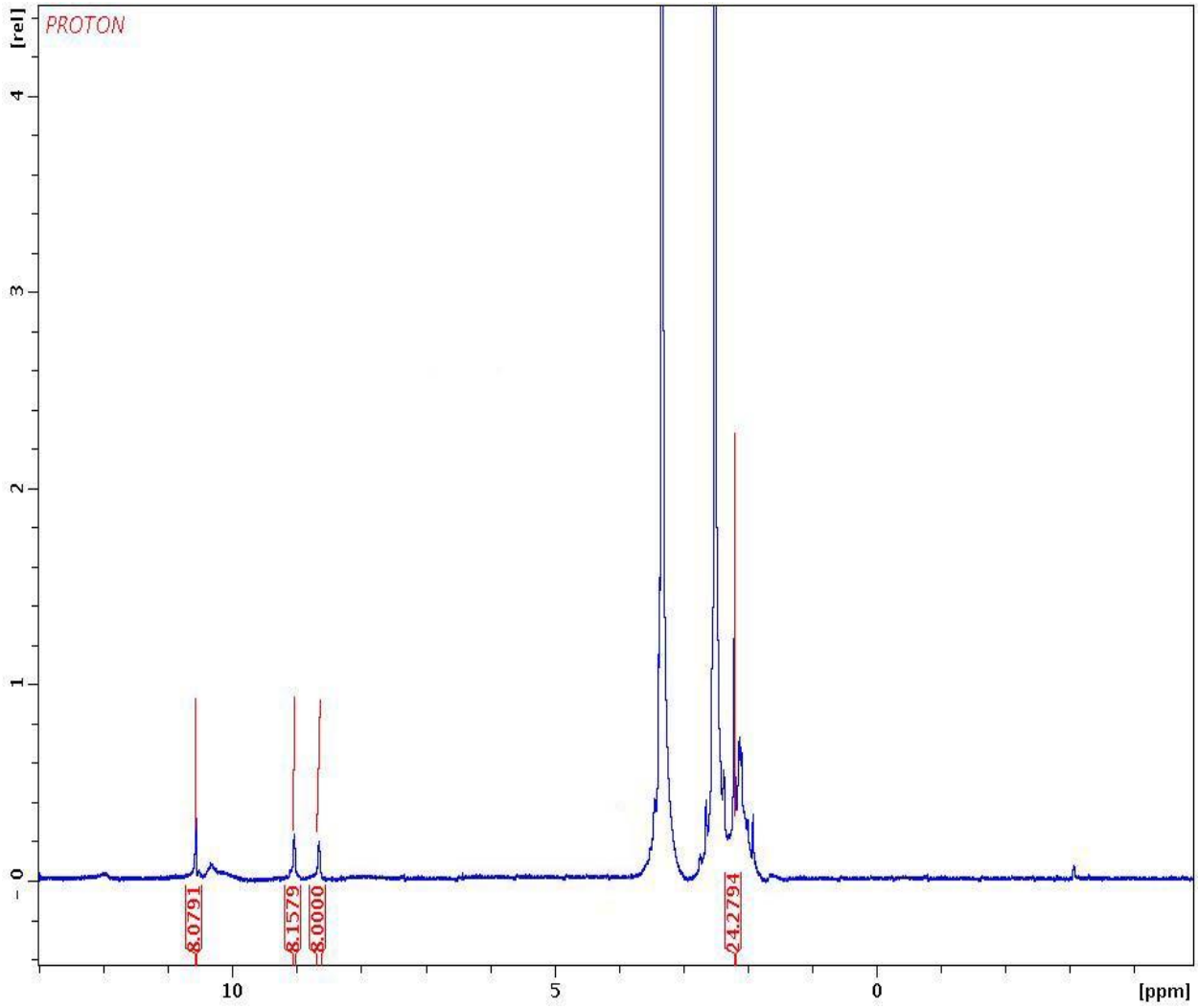


Figure A5.10: ^{1}H NMR of porphyrin I (DMSO-d_6 2.5ppm, water 3.34 ppm).

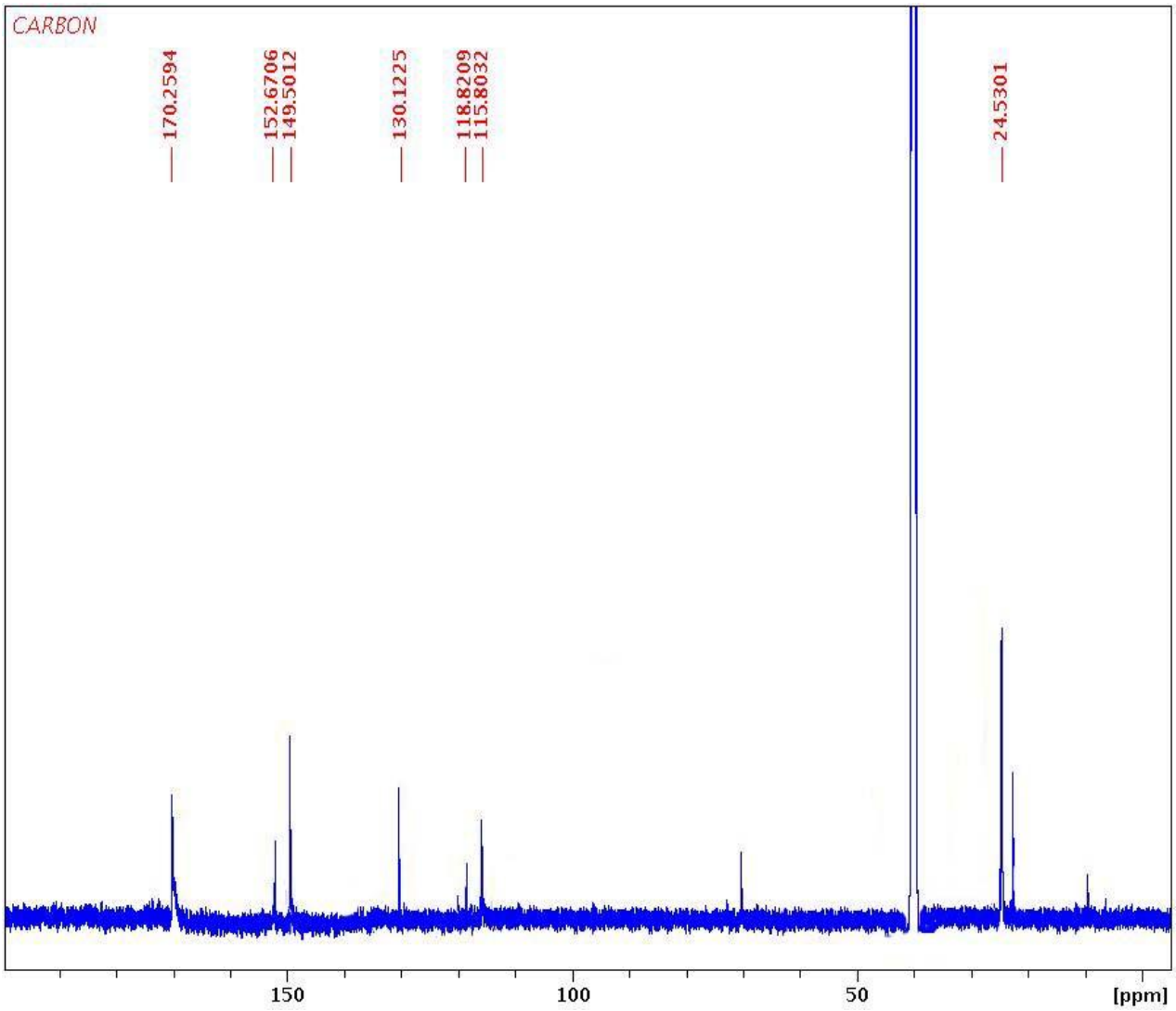


Figure A5.11: ^{13}C NMR of porphyrin I (DMSO-$d_6$40 ppm).

Data File	HCMDSS52A.d	**Sample Name**	Pyridylporphyrin
Sample Type	Sample	**Position**	P1-A2
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	8/9/2010 3:31:10 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=1074.3994 M=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C56H50N16O8	0.27	1074.3985	33196	C56H50N16O8	1074.3998	-1.14

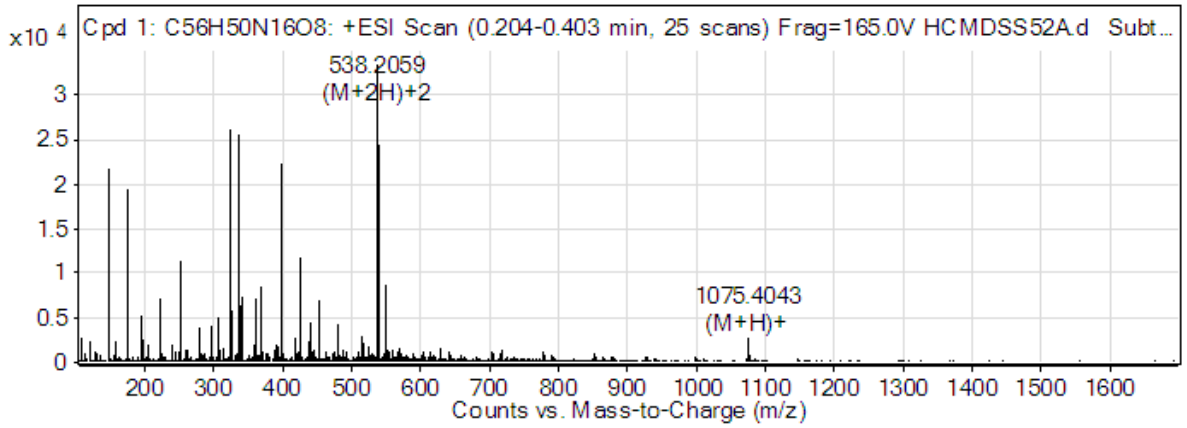


Figure A5.12: Mass spectrum of Porphyrin I

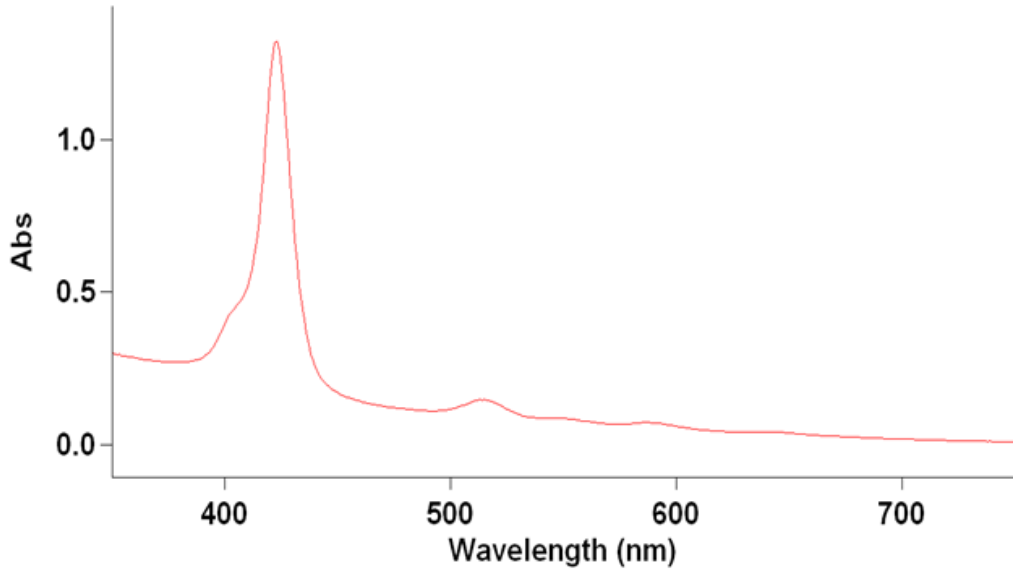


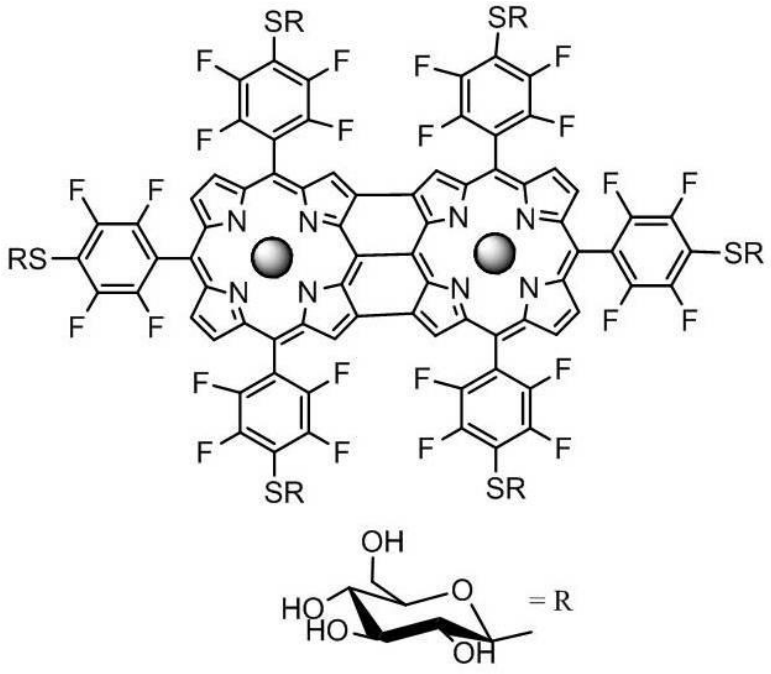
Figure A5.13: UV-visible spectrum of porphyrin I in DMSO.

CHAPTER 6

SYNTHESIS OF TRIPLY BRIDGED DIPORPHYRINS APPENDED WITH THIOGLUCOSE

Abstract

The synthesis of a triply bridged diporphyrin appended with six thioglucose units is reported. The electronic spectrum of this triply bridged porphyrin has enhanced intensity at low-energy wavelengths that reaches the near infrared region. The goal of this project is to create tumor targeting dyes that can be activated with red wavelengths of light that penetrate deeper into tissues. This new compound is amphiphilic in nature, chemically and photochemically stable, expected to have unusual photophysical and electrochemical properties, and can potentially be used as a photosensitizer in photodynamic therapy.



Triply Linked Diporphyrin Glucose Conjugate

6.1 Introduction

Photodynamic therapy (PDT) is a non-invasive treatment for cancer that involves the interaction of light, a photosensitizer, and oxygen that results in generation of the highly reactive singlet oxygen and other cytotoxic reactive oxygen species (ROS). In turn, the ROS oxidatively damages cells and causes localized cell death and ultimately apoptosis or tissue necrosis.(*1*) PDT has several advantages over conventional cancer therapies because the selective irradiation of light, noninvasive, repeatable, lower costs, and minimum side effects.(*2*)

Porphyrin and phthalocyanines derivatives are the most common and efficient photosensitizers used in PDT due to their long lived triplet excited state and are non-toxic under dark condition.(*3, 4*) Photofrin is the first and is only drug approved by the Food and Drug Administration (FDA) in the USA for PDT treatment of various forms of cancers such as lung, bladder, gastric and cervical cancer. With the exception of Photofrin, the only other PDT compound currently approved for cancer treatment is Foscan (m-THPC, meta-tetra(hydroxyphenyl)chlorin). Foscan is approved in Europe since 2001 for the treatment of head and neck cancers.(*5*) Both of these photosensitizers have one-photon absorption peaks in the visible region of optical spectra. The chlorin macrocycle of Foscan was developed to improve light absorption in the red region of the UV-visible spectrum near 630 nm compared to Photofrin. However, the significant absorption at wavelengths less than about 650 nm by biological tissues significantly diminished the effectiveness of these photosensitizers for treatment of cancers deeper into tissues.(*6*) To reduce this limitation, it is important to design a PS which has absorption bands in the near-infrared or infrared region, i.e. between 700-1100 nm, as the absorption and diffusion these wavelengths in tissues are much less. This range is also known as the window of biological tissues.(*7*)

Covalently linked multiporphyrin arrays have attracted considerable attention because of their remarkable photophysical properties such as high polarizability and high nonlinear optical (NLO) behavior.(*8-12*) These directly fused porphyrin arrays have strong communication between neighboring porphyrins. Among these arrays, *meso-meso, β-β, β-β*, triply bridged porphyrins have low energy absorption bands that reach into the infrared region because of extensive conjugation due to a coplanar geometry of these fused porphyrins. These porphyrins have absorption spectra featuring three major bands (I, II, III). Absorption bands I are typically between 408-420 nm, which is similar to those of the Soret band of porphyrin monomers. Bands II are observed at 550-565 nm, which are much more intense than the Q bands of porphyrin monomers, and bands III are exceedingly red-shifted in the 850-1075 nm region. Triply bridged porphyrins exhibit exceptionally large two-photon absorption (TPA) cross sections (σ), where two lower energy photons are *simultaneously* absorbed by the dye to leave it in the excited state, where upon it undergoes the normal excited state decay processes. In this case the wavelength ranging from 800-1100 nm.(*13, 14*)

The enhanced intensity of the low-energy absorption and lowest energy absorption bands that reach the infrared region of these triply bridged porphyrins allows more efficient use of wavelengths of light that penetrate deeper into tissues and hence these compounds may be potential photosensitizers for photodynamic therapeutic (PDT) applications.(*15, 16*) Sugar moieties appended on these compounds can increase the selective uptake of these compounds by cancer cells. The number, type, and position of the sugar moieties have long been known to effect cell uptake and photochemical properties.(*17, 18*) However, most reported glucose appended compounds have O-glyco linkages where hydrolysis may diminish in vivo effectiveness compared to corresponding nonhydrolyzable derivatives.

The objective of this work is to synthesize a triply bridged diporphyrin appended with perfluorophenyl groups which can act as a platform for biochemical applications because the para fluoro atom can be substituted with a variety of nucleophiles to form bioconjugates and biocompatible compounds.(*19-21*)

The synthesis of these directly fused porphyrin relies on oxidative coupling procedures reported by Osuka's group using oxidants such as tris(4-bromophenyl)aminium hexachloroantimonate (BAHA), DDQ-$Sc(OTf)_3$, and $AuCl_3$-AgOTf.(*8, 22-24*) However, the presence of electron withdrawing groups on the starting porphyrins inhibits or disturbs the oxidative coupling reactions due to lowering of the oxidation potential. Recently, hypervalent iodine(III) reagents, such as phenyliodinediacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA) have been recognized as powerful oxidative coupling agents; specially PIFA which has a highly electrophilic iodine center.(*25*) The nature of the metal present in the porphyrin also affects the reactivity by altering electron density on different parts of the macrocycle, thereby enhancing some sites to oxidative coupling reactions. We now report the synthesis of perfluorphenyl substituted triply bridged diporphyrins appended with thioglucose.

6.2 Experimental Procedure

Materials and Methods. *General.* ^{1}H and ^{13}C NMR spectra were recorded in a Brüker Avance 500 MHz spectrometer and the ^{19}F spectra in a JEOL 400 MHz spectrometer. Electrospray ionization mass spectrometric analyses were performed at the CUNY Mass Spectrometry Facility at Hunter College using an Agilent Technologies HP-1100 LC/MSD instrument. The electrospray ionization was run in methanol, with 0.1% formic acid. UV-visible spectra were recorded on a Varian Bio3 spectrophotometer. All reagents were obtained from commercial sources and used without further purification. Flash column chromatography was performed using silica gel-60, and the analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick), both from Sorbent Technologies. The porphyrin ZnP2-F_{15} was prepared according to reported procedures and results were consistent with previous work(*26, 27*). The iodine(III) reagent PIFA was purchased from Aldrich.

Meso-Meso Singly Bridged Zn^{II}-Diporphyrin (6).

A sample of 5,10,15-tris(pentafluorophenyl)porphyrinatozinc(II) (ZnP2-F_{15}) (43 mg, 0.05 mmol) in 15 mL of CH_2Cl_2 was cooled to -78^{o}C and then PIFA (22 mg, 0.05 mmol) was added. Then, the cooling bath was removed and the mixture was stirred at room temperature for about 2 h. The resulting yellow-brown mixture was then washed with water several times, the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/hexane = 1:1) to give **6** (18 mg, 40% yield). ^{19}F NMR (CD_2Cl_2-d_2): δ -138.40 to -138.23 (m, 8F, Ar-o-F), -153.95 to -153.80 (m, 4F, Ar-p-F), -163.42 to -163.19 (m, 8F, Ar-m-F). ^{1}H NMR (CD_2Cl_2-d_2): δ 8.23-8.24 ppm (d, 2H, Por-β) 8.74-8.75 ppm (d, 2H, Por-β), 9.15-9.17 ppm (2d, 4H, Por-β) ^{13}C NMR (CD_2Cl_2-d_2): δ

103.59, 104.74, 116.33, 116.35, 121.02, 130.74, 131.92, 135.85, 136-146 (C_6F_4), 149.81, 150.38, 155.31. HRMS Calcd for $C_{76}H_{16}F_{30}N_8Zn_2$ (M) $^{+\cdot}$: 1737.9602 found 1737.9618.

Meso-Meso *β-β β-β* Triply Bridged Zn^{II} Diporphyrin (7).

A sample of 5,10,15-tris(pentafluorophenyl)porphyrinatozinc(II) (ZnP2-F_{15}) (43 mg, 0.05 mmol) in 15 mL of CH_2Cl_2 was cooled to -78^{o}C and then PIFA (50 mg, 0.125 mmol) was added. Then, the cooling bath was removed, and the mixture was stirred at room temperature for about 2 h. The resulting yellow-brown mixture was then washed with water several times, the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/hexane = 1:1) to give **7** (10 mg, 22% yield). ^{19}F NMR (CD_2Cl_2-d_2): δ -138.36 to -138.00 (m, 8F, Ar-*o*-F), -153.31 to -153.23 (m, 4F, Ar-p-F), -162.28 to -162.05 (m, 8F, Ar-m-F). ^{1}H NMR (CD_2Cl_2-d_2): δ 7.28-7.30 ppm (d, 2H, Por-β) 7.15-7.17 ppm (d, 2H, Por-β), 7.14 ppm (s, 4H, Por-β) ^{13}C NMR (CD_2Cl_2-d_2): δ 107.35, 120.36, 126.33, 127.94, 128.81, 130.95, 137.49, 140-146 (C_6F_4), 148.98, 152.89, 155.20. HRMS Calcd for $C_{76}H_{12}F_{30}N_8Zn_2$ (M) $^{+\cdot}$: 1733.9289 found 1733.9301.

Synthesis of $FBGlc_3$ (4a)

To a solution of FBF_{15} **4** (10 mg, 12.3μmol) and 2,3,4,6-tetra-*O*-acetyl-glucosylthioacetate (18 mg, 36.9 μmol, 3.0 equiv) in DMF (1.0 mL), diethyl amine (0.2 mL) was added. The reaction mixture was stirred at room temperature for 4h. The reaction mixture was precipitated with methanol/H_2O and the solid filtered through a short column of Celite and washed with water. The crude mixture was recovered in CH_2Cl_2 and purified by flash chromatography (silica gel) using a mixture of ethyl acetate/hexanes (3:1) as eluent. $FBGlc_3$ **4a** (19 mg, 86%) was obtained after crystallization in CH_2Cl_2/hexanes, as a pink powder. ^{19}F NMR ($CDCl_3$): δ -154.0 to -153.6 (m, 6F, Ar-m-F), -158.0 to -157.6 (m, 6F, Ar-*o*-F). ^{1}H NMR

($CDCl_3$): δ 10.42 (s, 1H, meso-H), 9.50-9.51 (d, 2H, pyrrolic β-H), 9.03-9.05 (m, 6H, pyrrolic β-H), 5.19-5.28 (m, 12H, Glc-H), 4.30 (m, 6H, Glc-H), 3.90-3.92 (m, 3H, Glc-H), 2.06-2.23 (m, 36H, acetyl-H), -3.05 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 20.68 (CH_3CO_2), 61.93, 68.13, 70.68, 73.95, 76.46, 84.70 (Glc), 103.16, 107.69, 111.69, 122.23, 130.35, 131.02-131.16, 133.43-133.50, 145.36-147.35 (C_6F_4), 169.44, 169.52, 170.23 and 170.70 (CH_3CO_2). HRMS calcd for $C_{80}H_{68}F_{12}N_4O_{27}S_3$ $(M)^{+\cdot}$ 1840.3041 found 1840.3003.

Synthesis of $ZnGlc_3$ (5a).

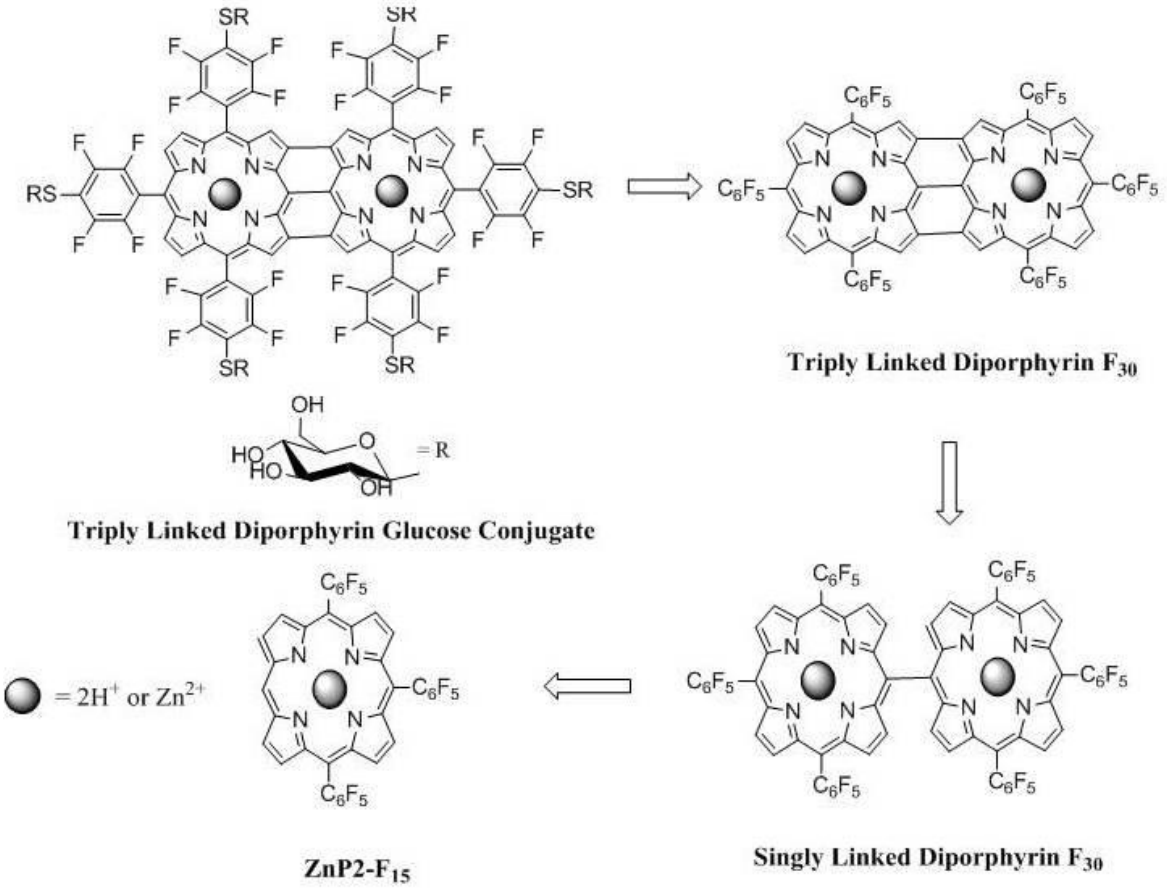
A solution of porphyrin **4a** (15 mg, 8 μmol) in a mixture of $CHCl_3$/methanol (3:1, 9 mL: 3 mL) was treated with $Zn(OAc)_2.2H_2O$ (0.130 g, 0.6 mmol). The reaction mixture was stirred overnight at room temperature after which it was concentrated to dryness. The crude product was dissolved in CH_2Cl_2 (50 mL), washed with water and brine, dried over Na_2SO_4 and concentrated to dryness. $ZnGlc_3$ **5a** (14 mg, 95%) was obtained after crystallization in CH_2Cl_2/hexanes, as a pink powder. ^{19}F NMR ($CDCl_3$): δ -154.0 to -153.5 (m, 6F, Ar-m-F), -158.0 to -157.4 (m, 6F, Ar-*o*-F). ^{1}H NMR ($CDCl_3$): 10.42 (s, 1H, meso-H), 9.54-9.55 (d, 2H, pyrrolic β-H), 9.07-9.13 (m, 6H, pyrrolic β-H), 5.18-5.35 (m, 21H, Glc-H), 4.30 (m, 6H, Glc-H), 3.90-3.92 (m, 3H, Glc-H), 2.06-2.23 (m, 36H, acetyl-H). ^{13}C NMR ($CDCl_3$): δ 20.58 (CH_3CO_2), 61.95, 68.11, 70.67, 73.92, 76.39, 84.87 (Glc), 103.16, 107.69, 111.69, 122.23, 130.35, 131.25-131.82, 133.43-133.50, 145.36-147.35 (C_6F_4), 150.55, 169.42, 169.49, 170.22 and 170.71 (CH_3CO_2). HRMS calcd for $C_{80}H_{66}F_{12}N_4O_{27}S_3Zn$ $(M)^{+\cdot}$ 1902.2176 found 1902.2176.

Synthesis of Zn_2Glc_6 (9a)

A sample of porphyrin **5a** (20 mg, 0.0105 mmol) in 15 mL of CH_2Cl_2 was cooled to -78^{o}C and then PIFA (12 mg, 0.026 mmol) was added. Then, the cooling bath was removed, and the mixture was stirred at room temperature for about 2 h. The resulting ink-blue mixture was

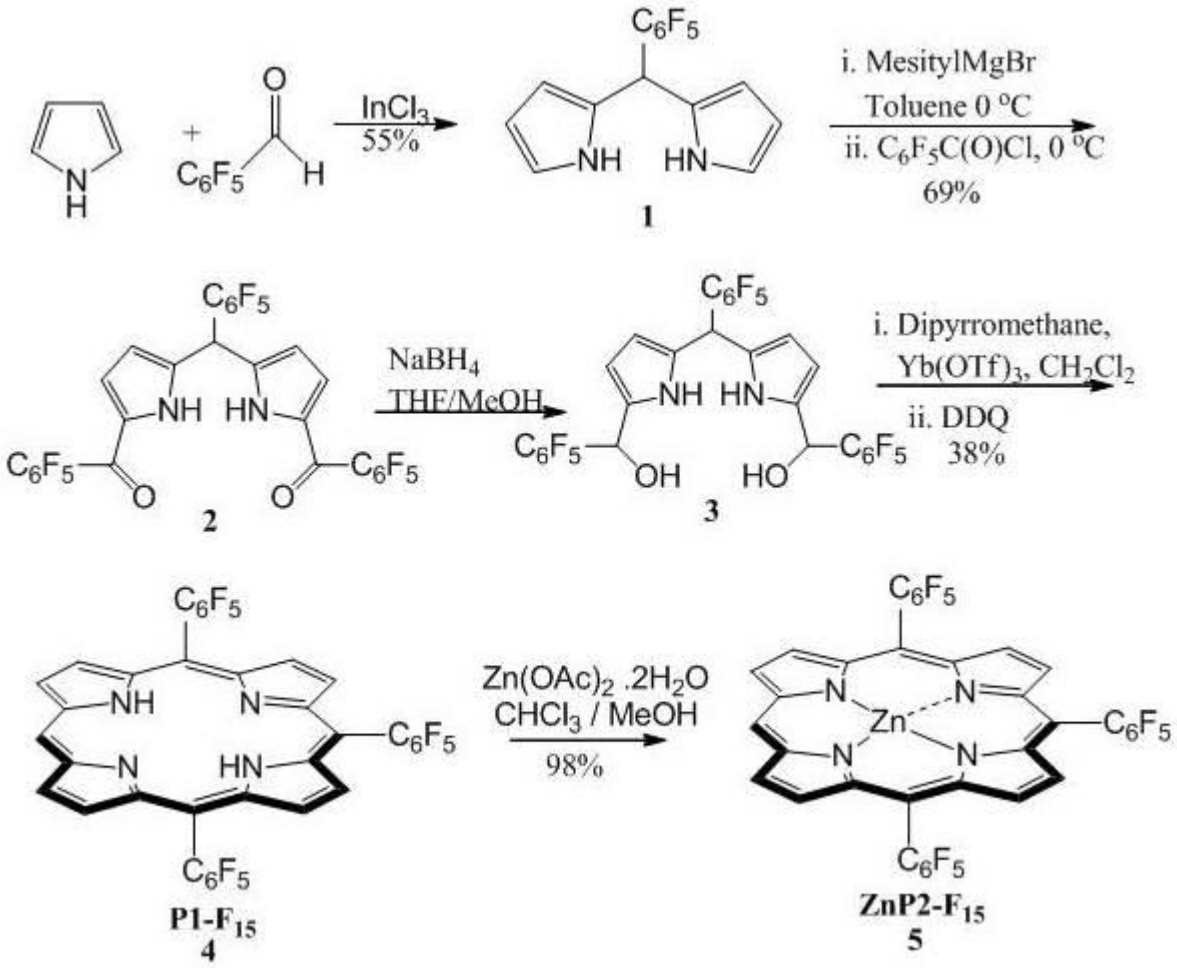
then washed with water several times, the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vaccum. The residue was purified by flash column chromatography (silica gel, ethylacetate/hexane = 3:2) to give **9a** (8 mg, 40% yield). ^{19}F NMR (THF-d_8): δ -133.48 to -133.18 (m, 12F, Ar-m-F), -140.39 to -139.51 (m, 12F, Ar-*o*-F). ^{1}H NMR (DMSO-d_6): 7.93-7.94 (d, 4H, pyrrolic β-H), 7.85-7.86 (d, 4H, pyrrolic β-H), 7.35 (s, 4H, pyrrolic β-H), 5.36-5.51 (m, 10H, Glc-H), 5.01-5.05 (m, 13H, Glc-H), 4.05-4.16 (m, 19H, Glc-H), 2.03-2.13 (m, 72H, acetyl-H). ^{13}C NMR (DMSO-d_6): δ 20.78 (CH_3CO_2), 62.25, 68.41, 70.80, 73.55, 76.39, 84.92 (Glc), 107.83, 131.72, 131.81, 146.42-148.53 (C_6F_4), 152.77, 155.01, 169.71, 169.80, 170.08 (CH_3CO_2). MALDI $C_{160}H_{126}F_{24}N_8O_{54}S_6Zn_2$ $(M+H)^+$ 3804.96, found 3804.587.

6.3 Results and Discussion



Scheme 6.1. Retrosynthesis of Triply Bridged diporphyrin appended with glucose.

5,10,15-Tris(pentafluorophenyl)porphyrinatozinc(II) (ZnP2-F_{15}) is the key parent molecule for the synthesis of singly and triply bridged diporphyrins. This porphyrin was synthesized using reported procedure by the Nocera group(*26*) as shown in Scheme 6.2. 5-Pentafluorophenyl dipyrromethane **1** and 1,9-diacyldipyrromethane **2** were synthesized according to reported procedures.(*27-29*) Reduction of **2** gave the dipyrromethane dicarbinol (2-OH), which upon condensation with dipyrromethane **3** gave the corresponding free base porphyrin P1-F_{15} in 38% yield. This porphyrin was then metalated using $Zn(OAc)_2$ affording ZnP2-F_{15} porphyrin in 98% yield.(*30*)



Scheme 6.2. Synthesis of ZnP2-F_{15} (5) porphyrin

The one electron oxidation of porphyrin **5** bearing a sterically uncongested meso position with different equivalents of PIFA results in the formation of *meso-meso* linked diporphyrin **6** and *meso-meso, β-β, β-β* triply bridged diporphyrins **7** as shown in Scheme 6.3.(*31-35*) The mechanism of reaction involves the loss of a single electron by metalloporphyrin followed by nucleophilic attack by a neutral metalloporphyrin. If the porphyrin is oxidized to the radical cation, one of the orbitals A_{1u} or A_{2u} becomes the magnetic orbital.(*36, 37*) Closed shell metals such as Mg^{II} and Zn^{II} metalloporphyrins favor the A_{2u} HOMO orbitals where there is significant

electron density at the *meso* position; therefore, the *meso,meso* porphyrin dimers are produced. Conversely, open shell metal such as Cu^{II}, Pd^{II} and Ni^{II} metalloporphyrins favor A_{1u} cation radicals, where there is large electron density at the *β*-position, which leads to the formation of *meso,β* porphyrin dimers, as is shown in Figure 6.1.(*8*) Thus, we used the Zn(II) complex.

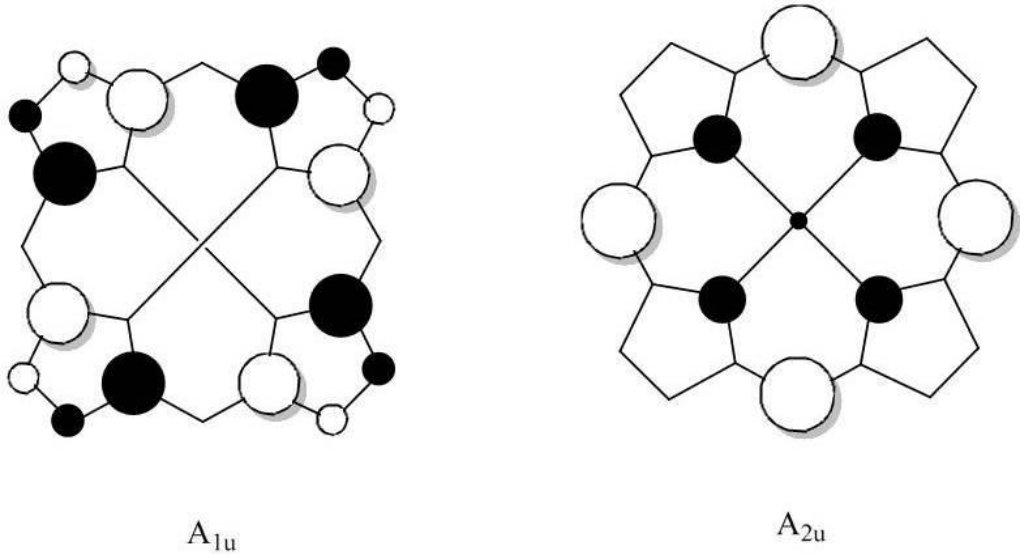
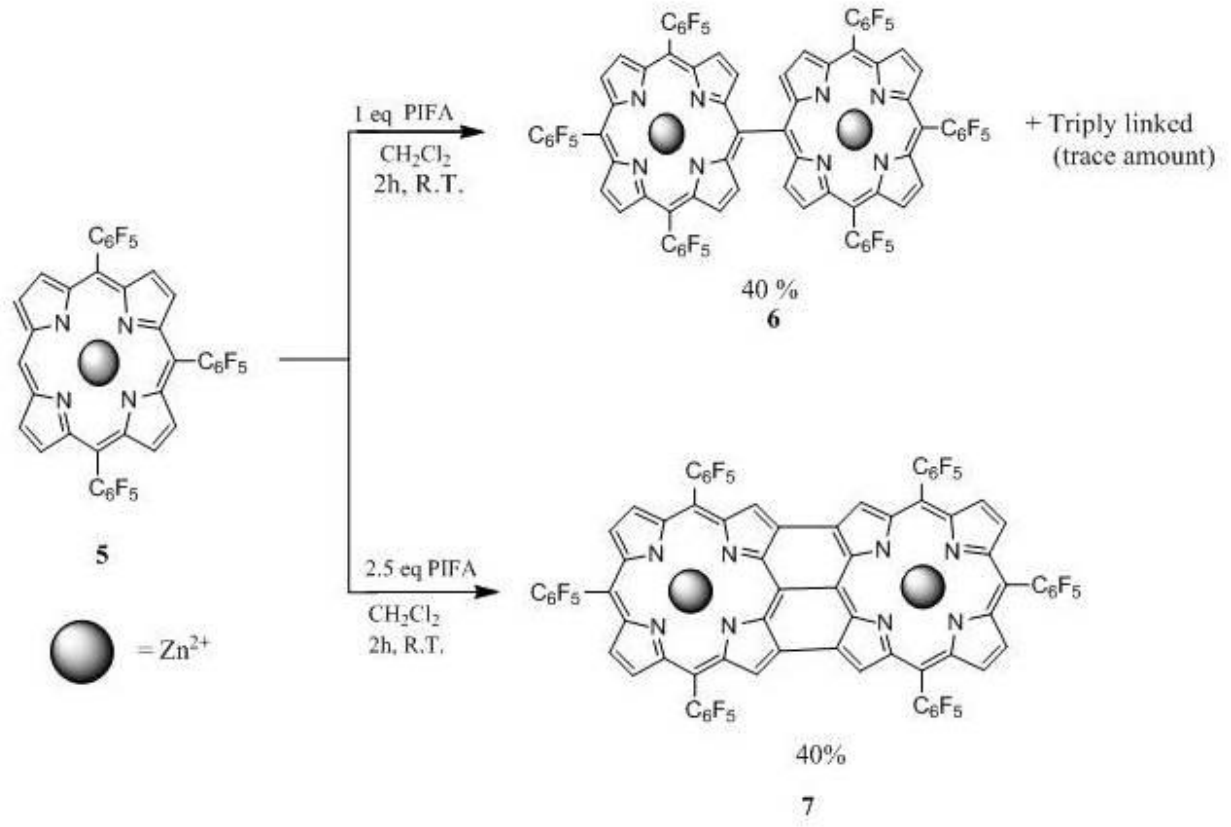


Figure 6.1. Schematic representation of the two HOMO orbitals of the D_{4h} porphyrin ring.

To a solution of **ZnP2-F$_{15}$** in dry CH_2Cl_2 at -78^{o}C was added PIFA, and the resulting mixture was stirred at room temperature for 1-2 h. The reaction was monitored by TLC using hexane/CH_2Cl_2 as an eluent. The amount of PIFA added and the concentration of solution had significant influence on reaction rate and product distribution. The PIFA was added at -78^{o}C to avoid polymerization byproducts.(*25*)



Scheme 6.3. Synthesis of Singly and Triply Bridged Diporphyrin

The structure of the dimeric Zn(II) porphyrins (**6** and **7**) were determined by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, as well as high resolution electrospray ionization mass spectrometry and UV-visible spectroscopy. During the reaction, the *meso* proton signal of ZnP2-F_{15} (δ = 10.51 ppm) disappeared. The chemical shifts of the peripheral β-protons provide important information on the structure and aromaticity of the porphyrins. For singly linked diporphyrins the inner β protons H_a and H_b are significantly shifted up field to 8.24 and 8.74 ppm, respectively, while the outer β protons (H_c and H_d) remain near the 9.1 ppm chemical shifts found for the monomer (Fig. 6.2). The inner β-protons are shifted up field indicating that they are perturbed by the ring current of the perpendicularly arranged counterpart porphyrin. In the triply bridged diporphyrin, the outer β-protons (H_c and H_d) are also shifted upfield which may be related to the decreased

aromatic ring current associated with enhanced conjugation over the array.(*8*) Figure 6.2 shows chemical shifts of porphyrin **5**, **6** and **7**.

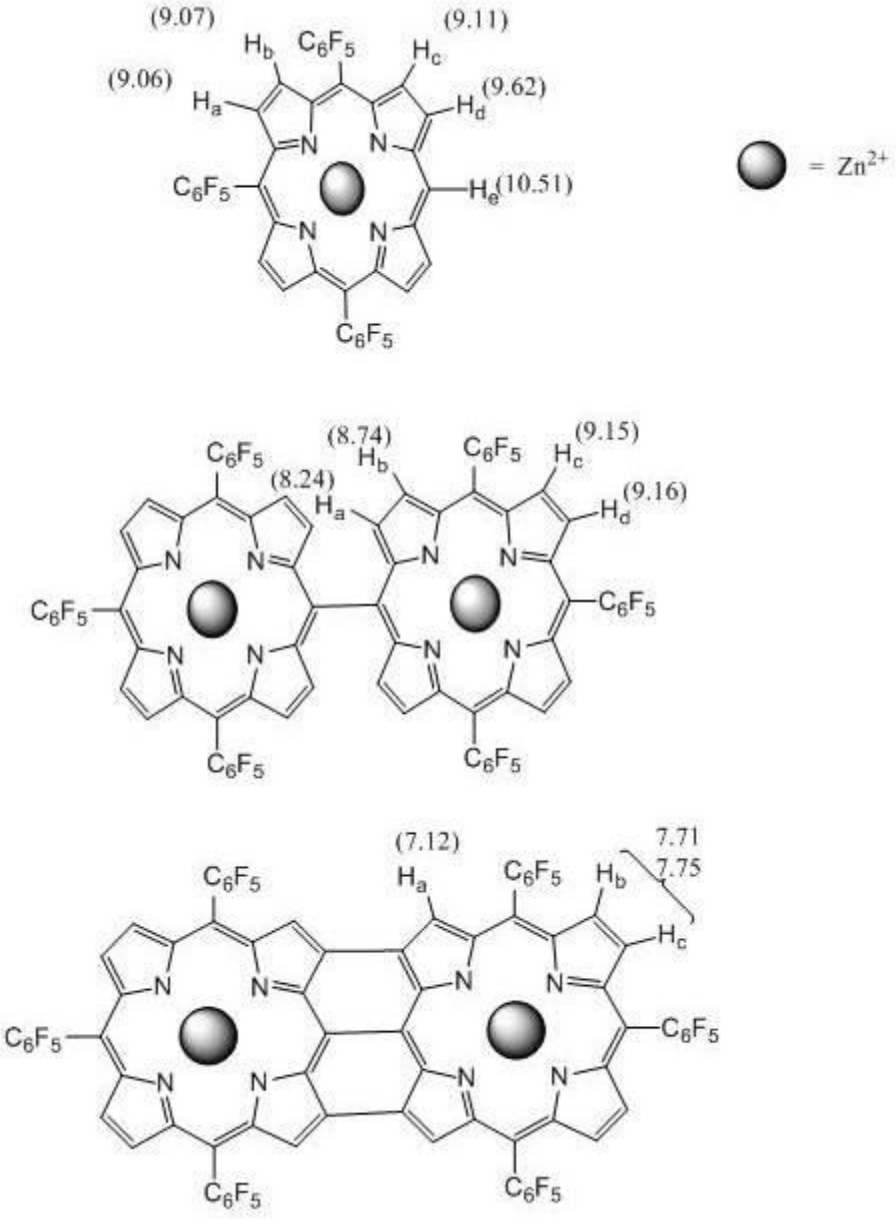


Figure 6.2. ^{1}H NMR chemical shifts of ZnP2-F_{15}, **6** (singly linked) and **7** (triply linked) porphyrins.

The HRMS spectrum of diporphyrins gave M^+ for **6** = 1737.9618 (calculated = 1737.9602) and for **7** M^+ = 1733.9301 (calculated = 1733.9289); in addition, a cluster of peaks with the same pattern as one calculated based upon the isotopic distribution of the formula was observed. Additional evidence of the structure of the compounds **6** and **7** were obtained from UV-visible spectrum that shows a split Soret band for compound **6** at 412 nm and 448 nm of nearly equal intensity, and this pattern is typical for *meso-meso* singly linked diporphyrins.(*36, 38-40*) For diporphyrin **7**, the Soret band is observed as a broad peak at 415 nm with a shoulder at 455 nm, and the Q-bands are observed between 557 and 1068 nm. UV-visible spectra of compounds **5**, **6** and **7** are shown in Figure 6.3

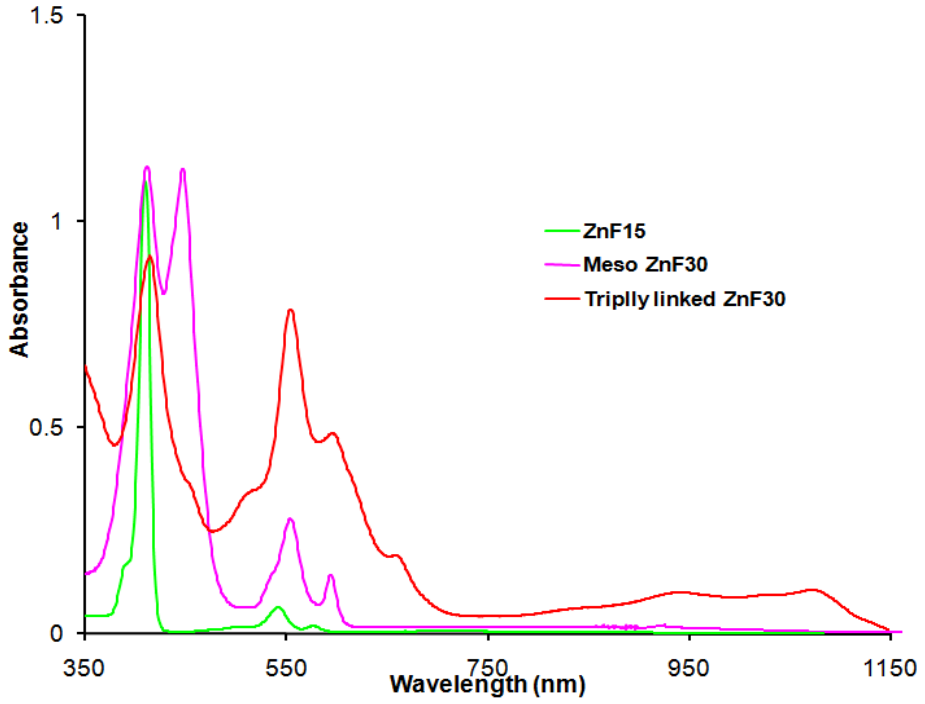
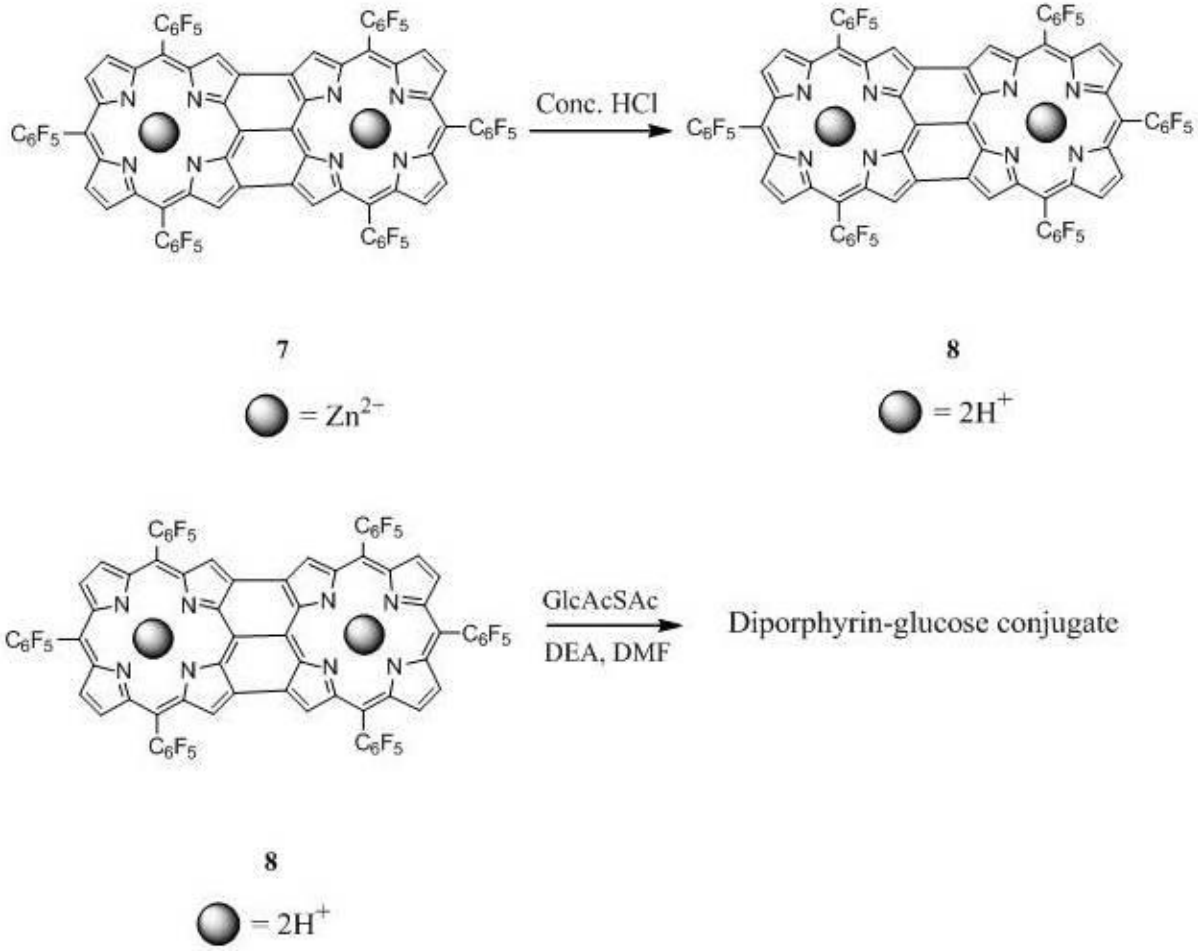
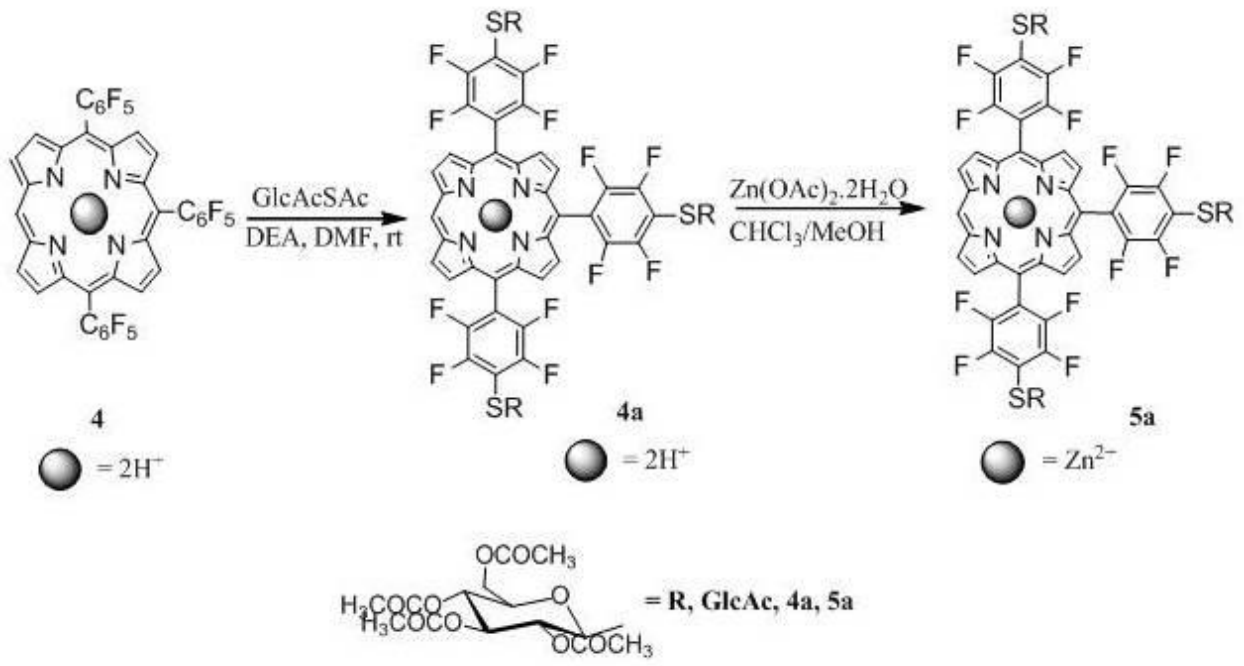


Figure 6.3. UV-visible spectra of compounds **5**, **6** and **7**.



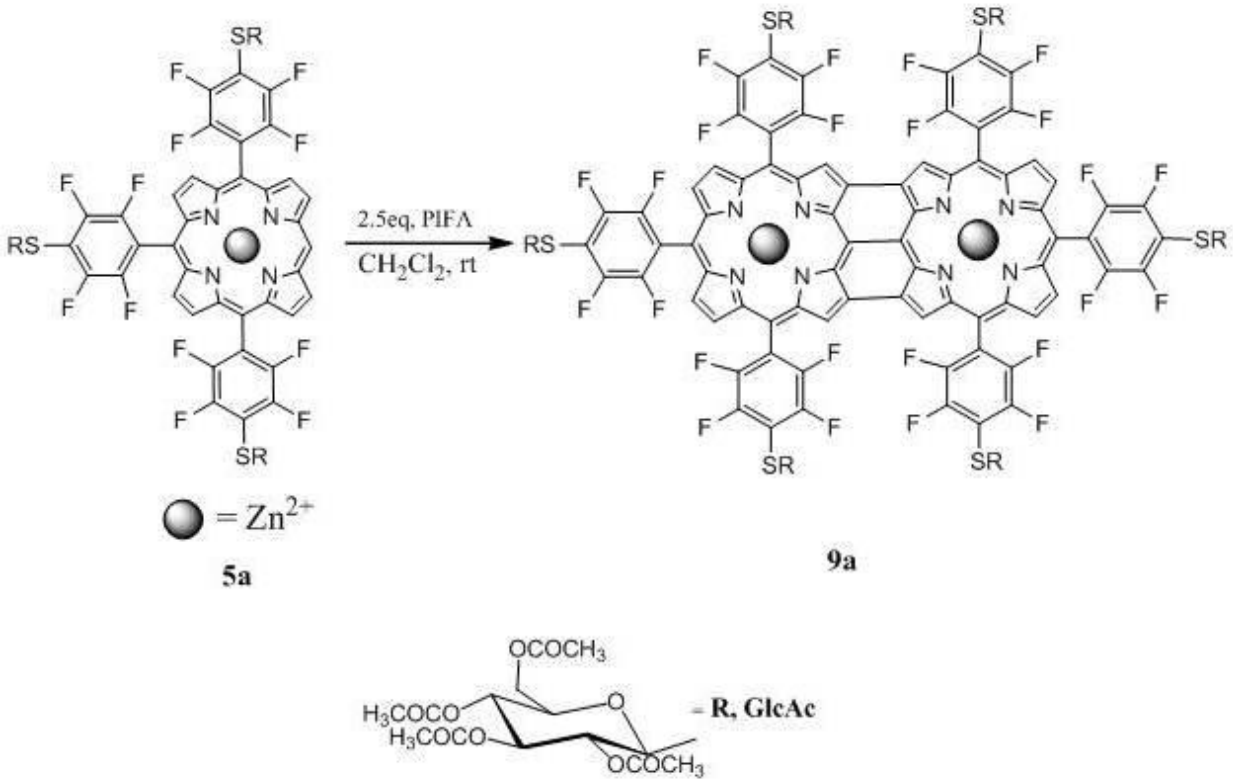
Scheme 6.4. Synthesis of the free base fused diporphyrin-glucose conjugate followed by glycosylation.

We focused on diporphyrin **7** because it has absorption in the far infrared region and can act as a potential photosensitizer. To increase the selectivity, compound 7 was demetallated and was treated with 6.5 equivalents of thioglucose in the presence of diethylamine as a base as shown in scheme 6.4. This substitution reaction gave a mixture of 4, 5, 6, 7 and 8 substituted isomers with very close polarity, thus are difficult to separate as shown in MALDI-TOF spectrum (**Figure A6.23**). So to avoid the isomer problem, we followed a different route to synthesize the desired glucose substituted triply bridged diporphyrin as shown in scheme 6.5 and 6.6.



Scheme 6.5. Synthesis of $ZnGlc_3$ from 5,10,15-Tris(pentafluorophenyl)porphyrin (**4**)

Here, porphyrin **4** was treated with 3.5 equivalents of thioglucose and then Zn(II) was inserted (**5a**). Compound **5a** was treated with PIFA to give the triply bridged compound (**9a**) in 40% yield as shown in scheme 6.6. This compound was characterized by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, UV-visible and MALDI-TOF spectra.



Scheme 6.6. Synthesis of *meso-meso, β-β, β-β* triply bridged Zn^{II} diporphyrin appended with six thioglucose units.

The structures of all porphyrinoids were confirmed by NMR, UV-visible, and MALDI-TOF spectra. The ^{1}H NMR spectra of **9a** show the porphyrinoid core pyrrole *β* protons as one singlet at 7.35 ppm and two doublets at 7.85 and 7.93 ppm peaks. The ^{1}H NMR spectra of this compound show resonances at 2.03 and 2.16 ppm, due to the acetyl protons, and the resonances of the other protons of the carbohydrate unit appear between 4 and 6 ppm. The resonances of the anomeric protons appear as doublets at 5.36 ppm to 5.50 ppm. The ^{19}F NMR spectra confirm the substitution of the para-fluorine atom by the sugar unit, showing the disappearance of the resonances due to the para-fluorine atoms in **7** at -150 ppm. An important diagnostic is the signal due to the meta-fluorine atom shift from -160 ppm in **7** to -140 ppm for **9a**. The ortho-fluorine atom resonances remain near -134 ppm.

The electronic spectra of **7** and the glycosylated derivative (**9a**) are very similar with a broad peak at 413 nm and the Q-bands are observed between 557 and 1088 nm as shown in Figure 6.4

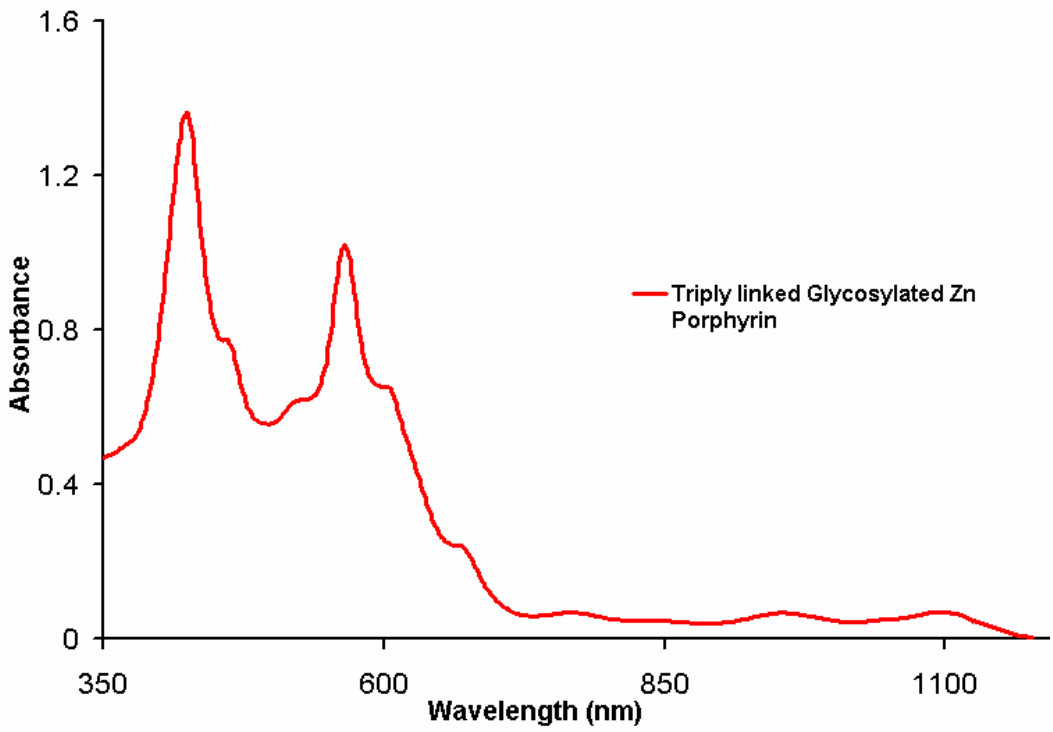
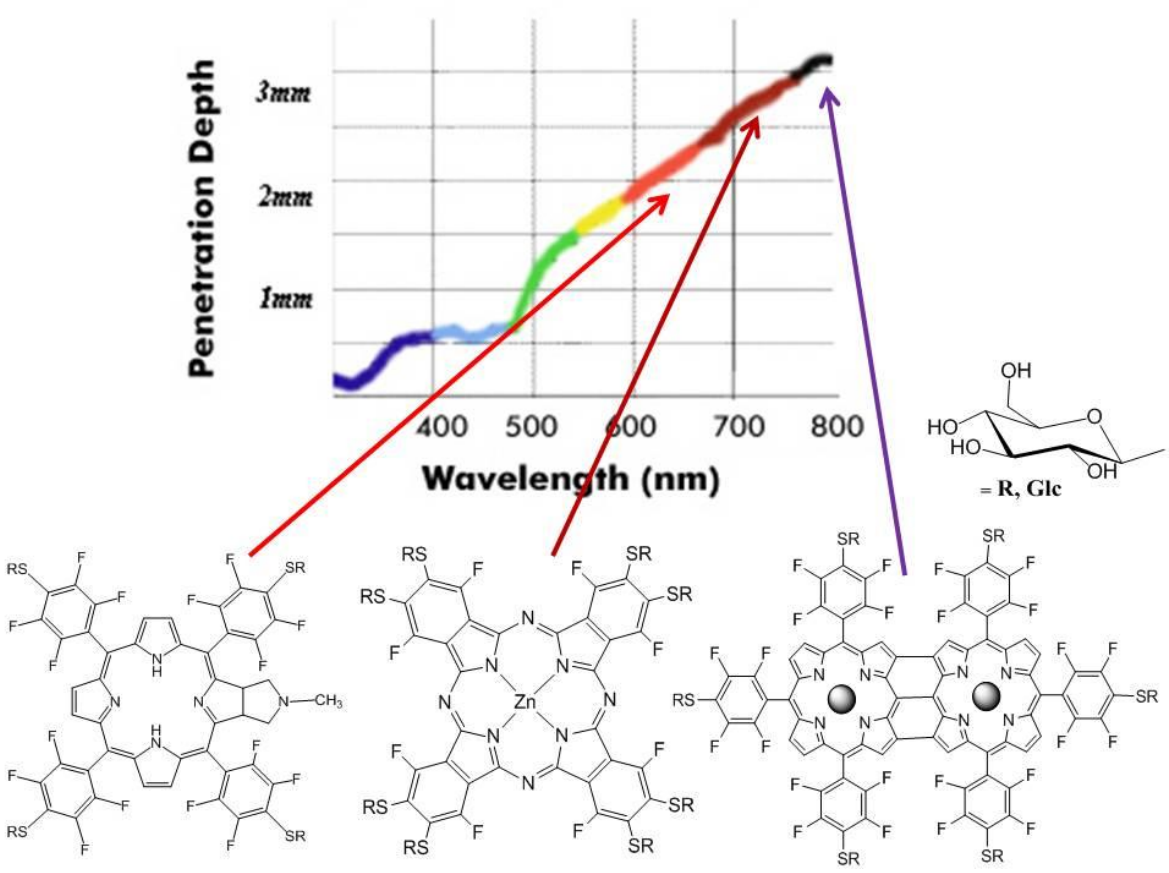


Figure 6.4: UV-visible spectra of compound **9a**.

6.4 Conclusions

The remarkable chemical and photophysical properties include: very low HOMO-LUMO (highest occupied/lowest unoccupied molecular orbital) gaps, low one-electron oxidation potentials, and rigidity, and large molecular size (about 4 nm from glucose to glucose on the long axis), and the triply bridged arrays are stable in air. Further investigation of this promising new photodynamic sensitizer is currently underway.

Overall summary of PDT project



6 different dyes with a range of photophysical properties were made and evaluated in several cancer cell lines.

6.5 References

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6.6 Appendix

Data File	HCMDSS49A.d	**Sample Name**	FBF15
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Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 2: C38H11F15N4	0.275	808.0747	46509	C38H11F15N4	808.0744	0.4
Cpd 1: C18H35NO	0.275	281.2721	27995	C18H35NO	281.2719	0.75

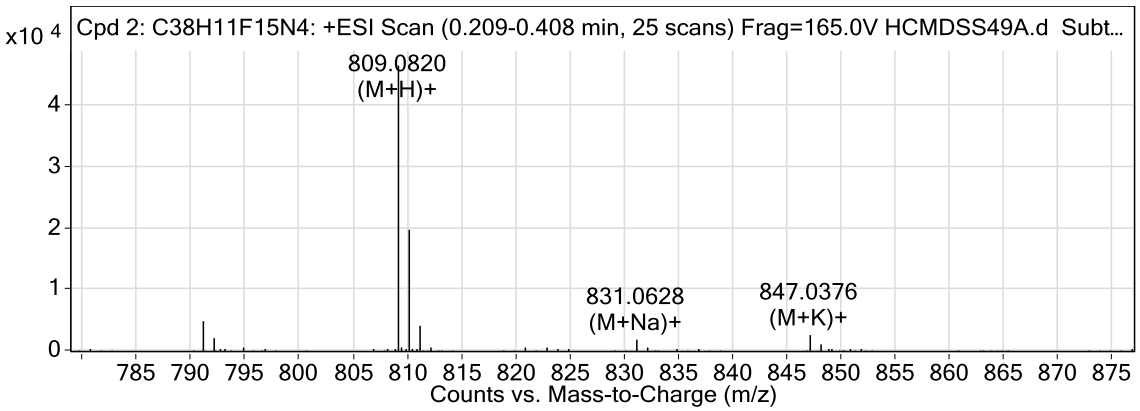

Figure A6.1: Porphyrin P1-F_{15} (**4**) HRMS.

Data File	HCMDSS53A.d	**Sample Name**	ZnF15
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
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IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=869.9879 M=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
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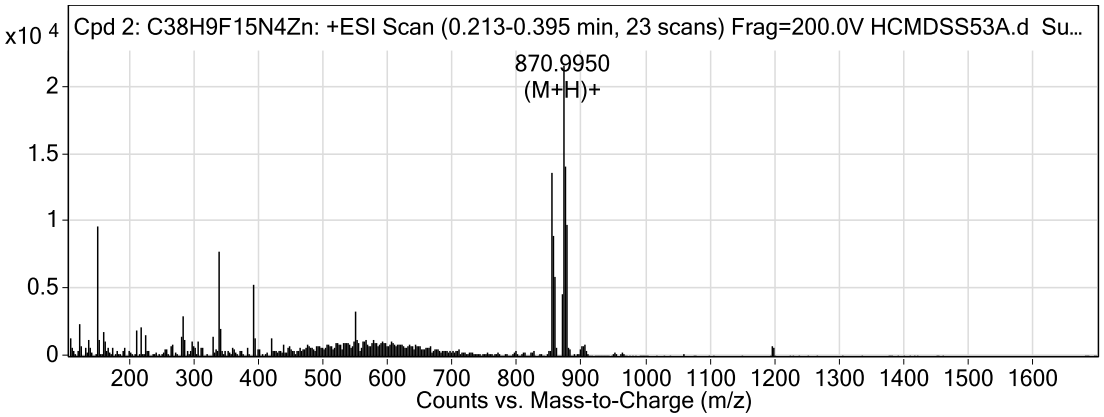

Figure A6.2: Porphyrin ZnP2-F_{15} (**5**) HRMS.

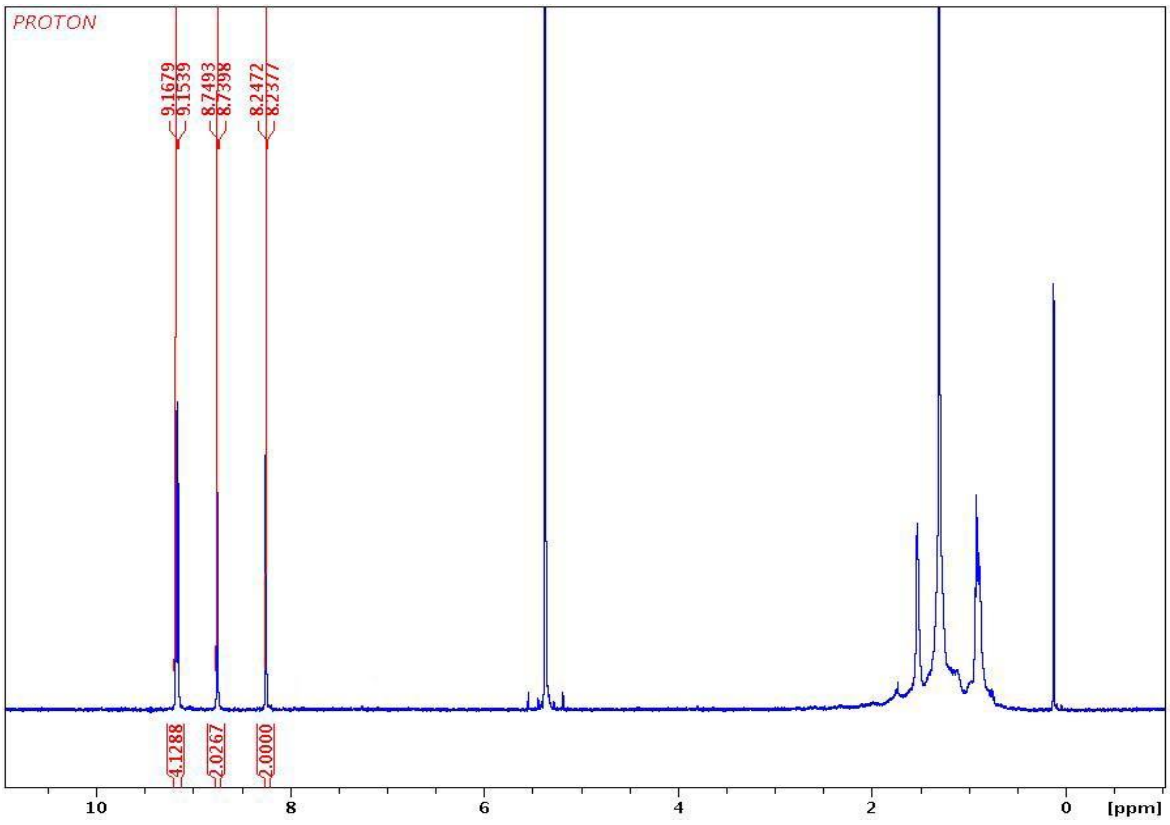

Figure A6.3: *Meso-Meso* singly linked Zn^{II}-Diporphyrin **(6)** ^1H NMR CD_2Cl_2(5.32 ppm, water 1.5 ppm)

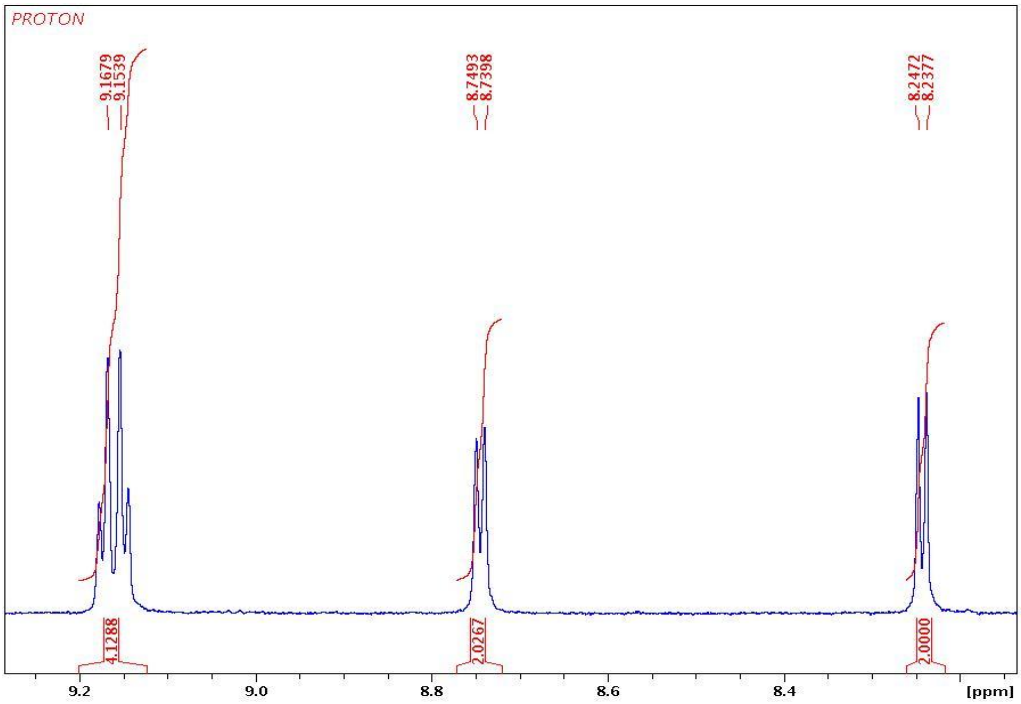

Figure A6.4: Expanded ^1H NMR spectrum of compound **6.**

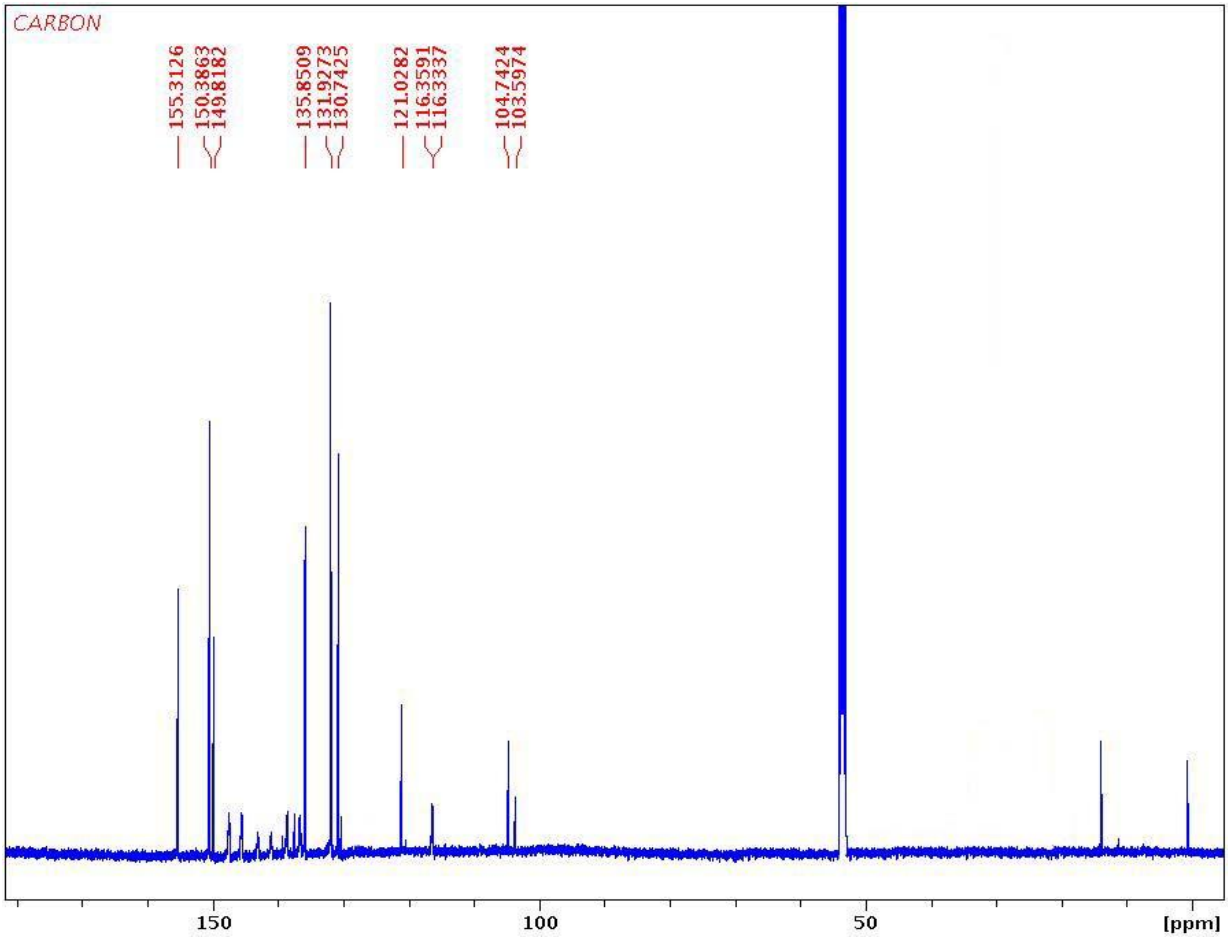

Figure A6.5: *meso-meso* singly linked Zn^{II}-Diporphyrin **(6)** ^{13}C NMR (CD_2Cl_2).

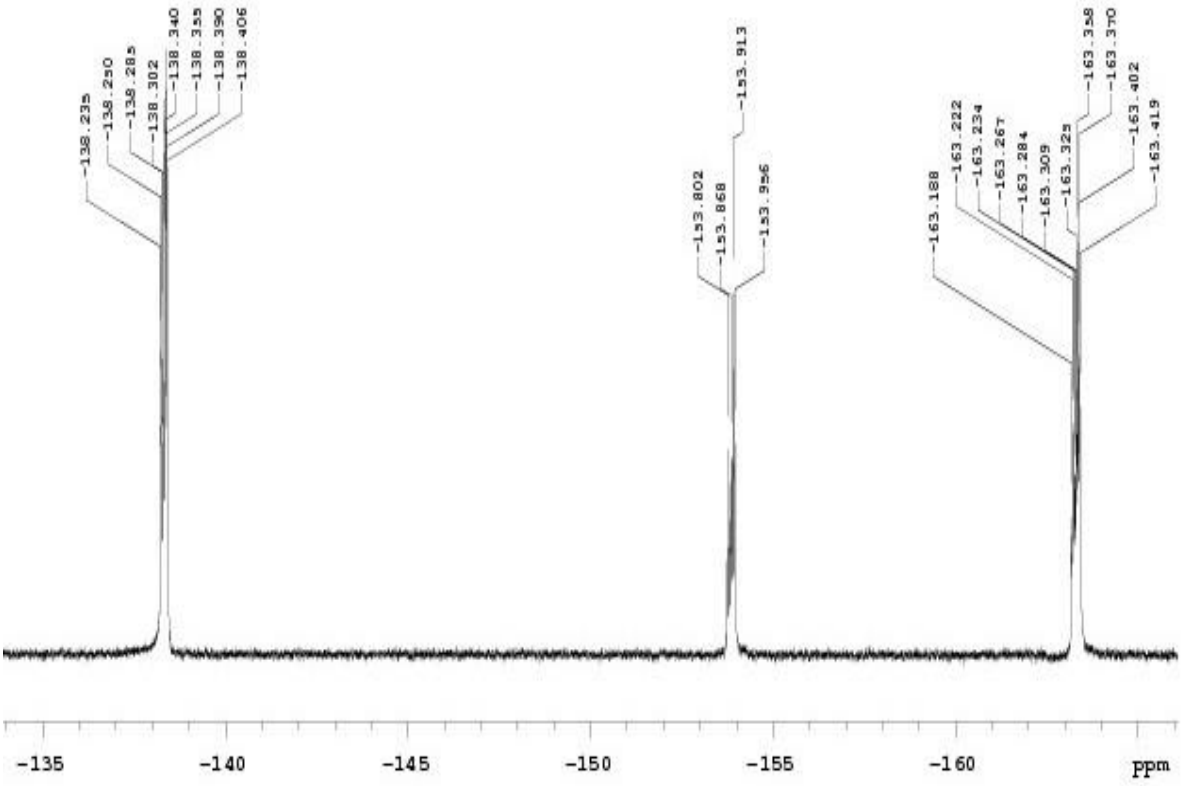

Figure A6.6: *meso-meso* singly linked Zn^{II}-Diporphyrin **(6)** ^{19}F NMR (CD_2Cl_2).

Data File	HCMDSS60E.d	**Sample Name**	Zndiporphyrin-2
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IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=1737.9602 EM=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
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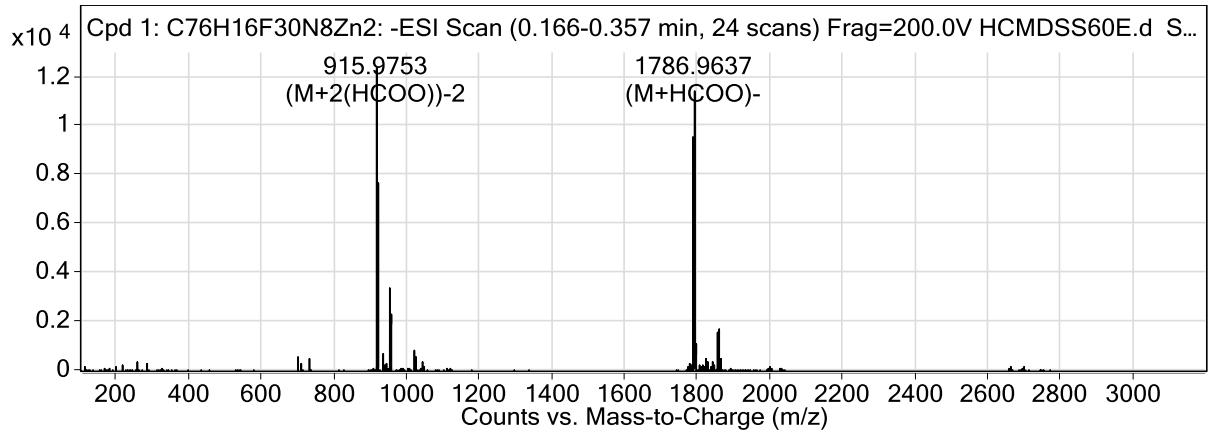

Figure A6.7: *meso-meso* singly linked Zn^{II}-Diporphyrin **(6)** HRMS.

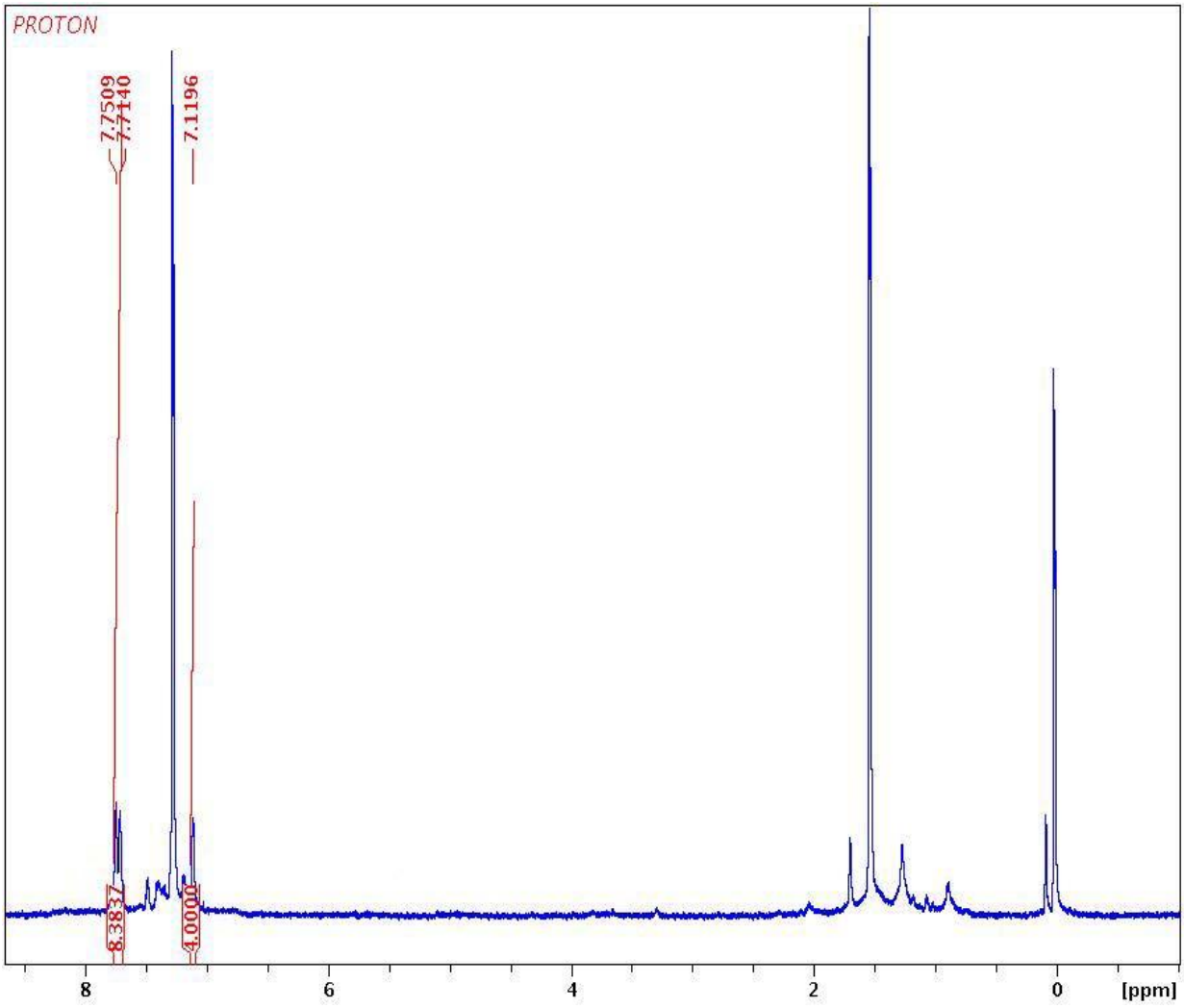

Figure A6.8: *meso-meso β-β β-β* triply linked Zn^{II} diporphyrin **(7)** ^{1}H NMR $CDCl_3$(7.28 ppm, water 1.5 ppm)

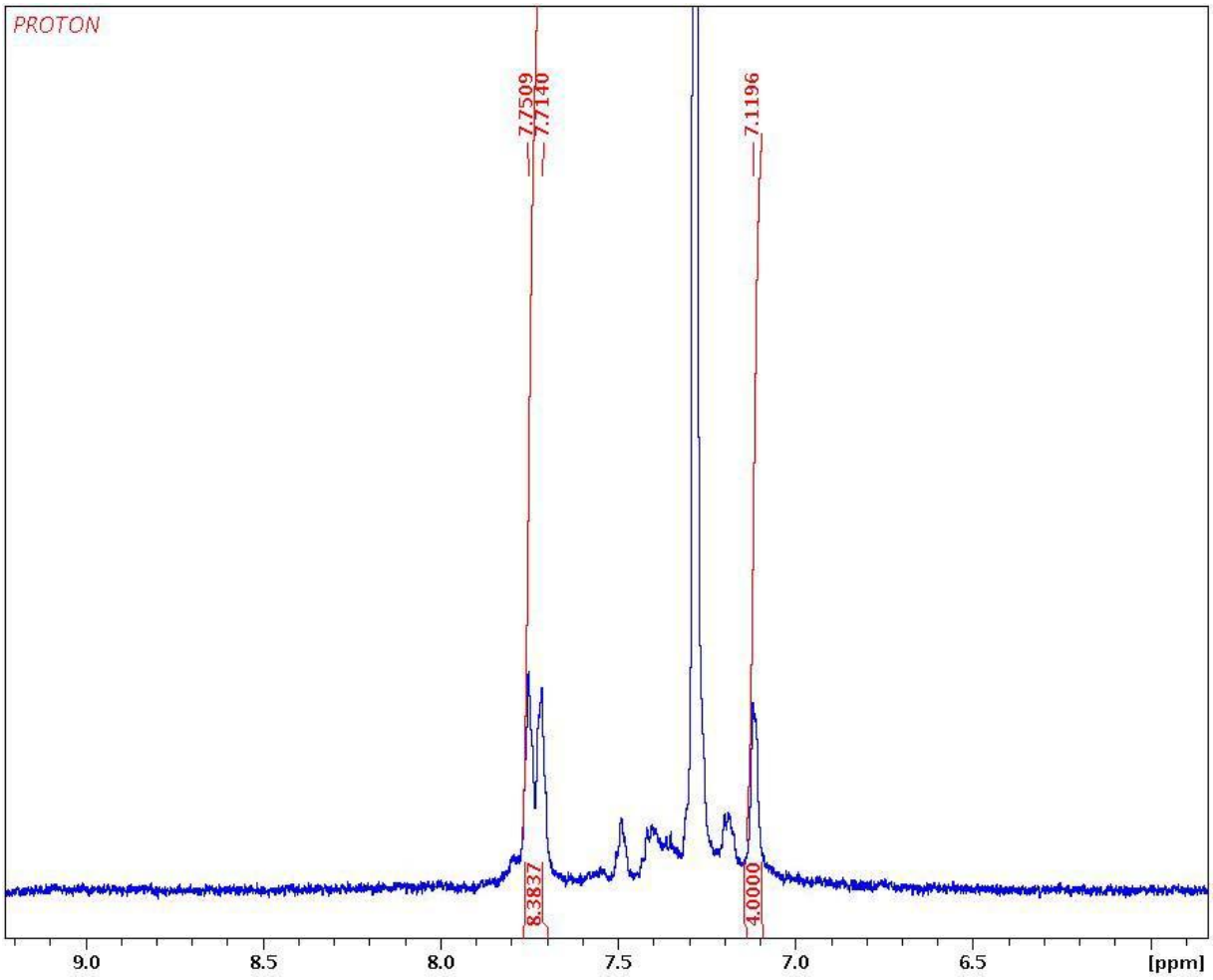

Figure A6.9: Expanded spectrum ^{1}H NMR *meso-meso β-β β-β* triply linked Zn^{II} diporphyrin **(7)**

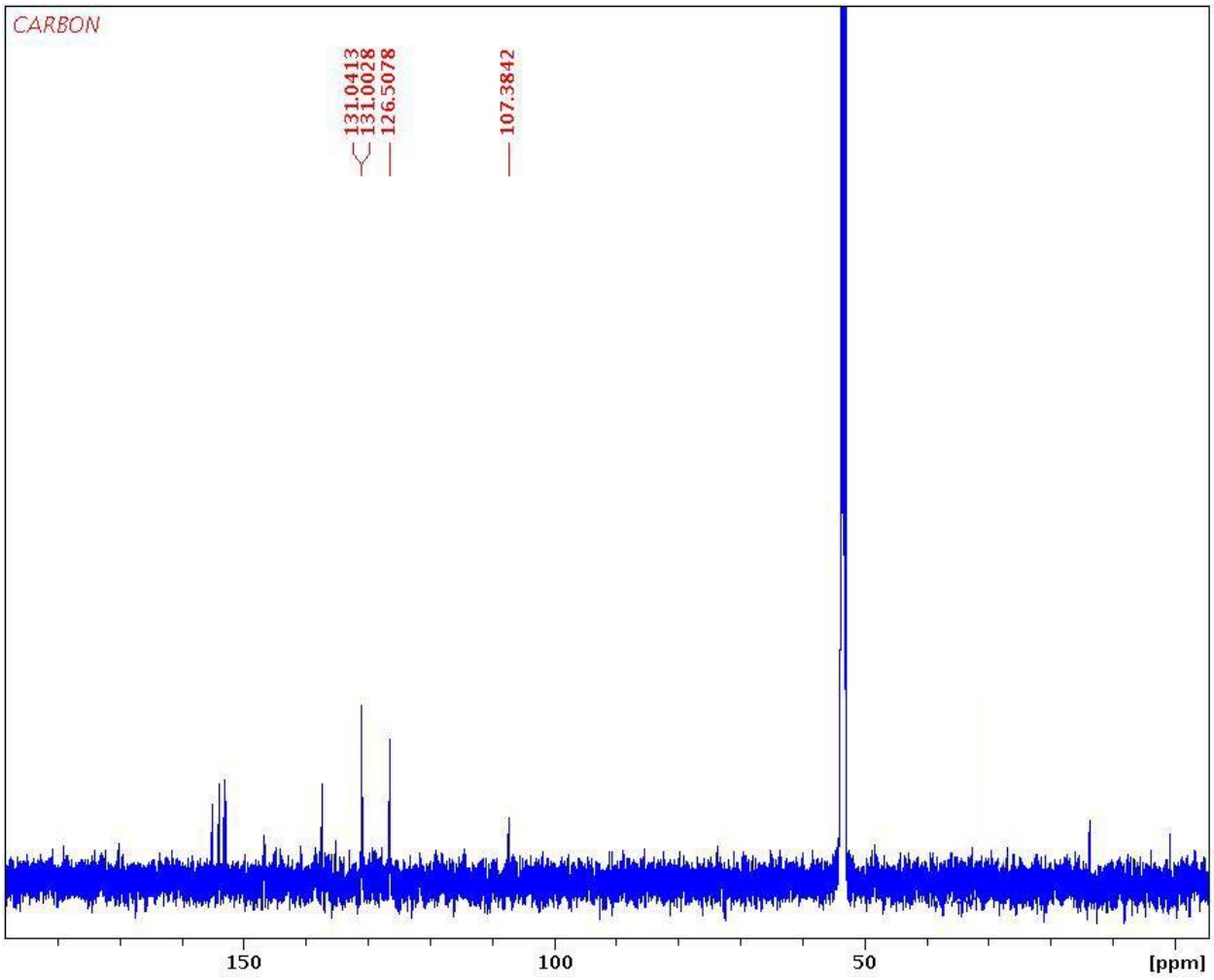

Figure A6.10: *meso-meso β-β β-β* triply linked Zn^{II} diporphyrin **(7)** ^{13}C NMR CD_2Cl_2.

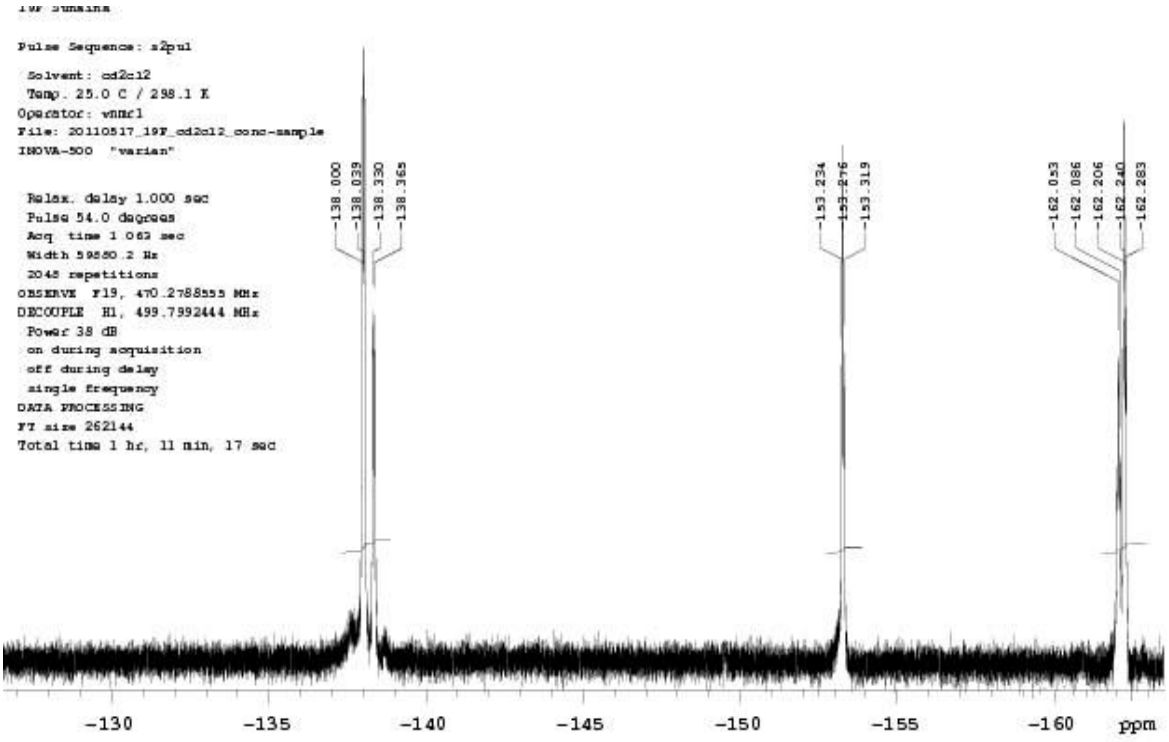

Figure A6.11: *meso-meso β-β β-β* triply linked Zn^{II} diporphyrin **(7)** ^{19}F NMR (CD_2Cl_2)

Data File	HCMDSS61A.d	**Sample Name**	Zndiporphyrin-1
Sample Type	Sample	**Position**	P1-A2
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Acq Method		**Acquired Time**	12/29/2010 4:51:03 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=1733.9289 EM=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
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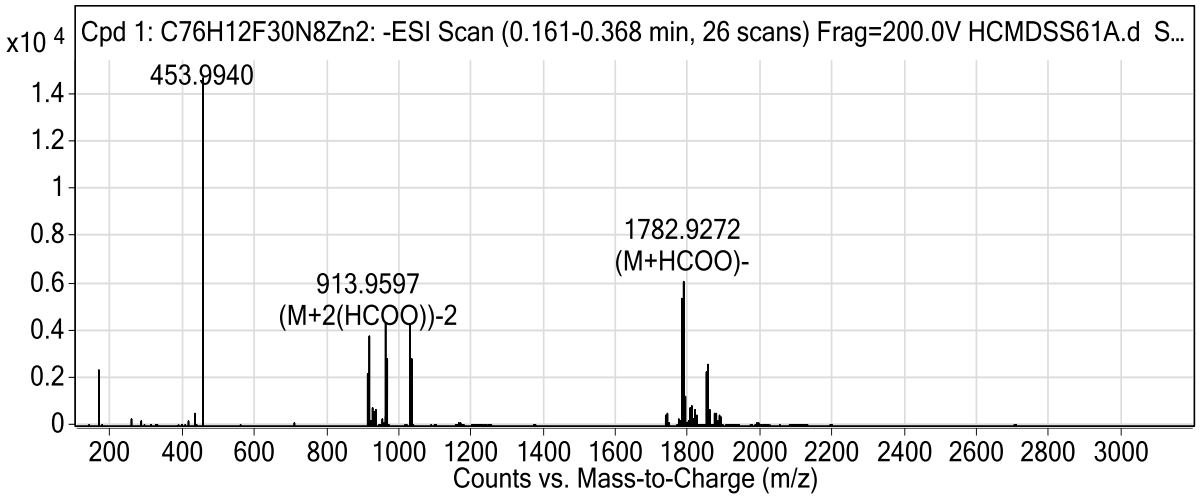

Figure A6.12: *meso-meso β-β β-β* triply linked Zn^{II} diporphyrin **(7)** HRMS.

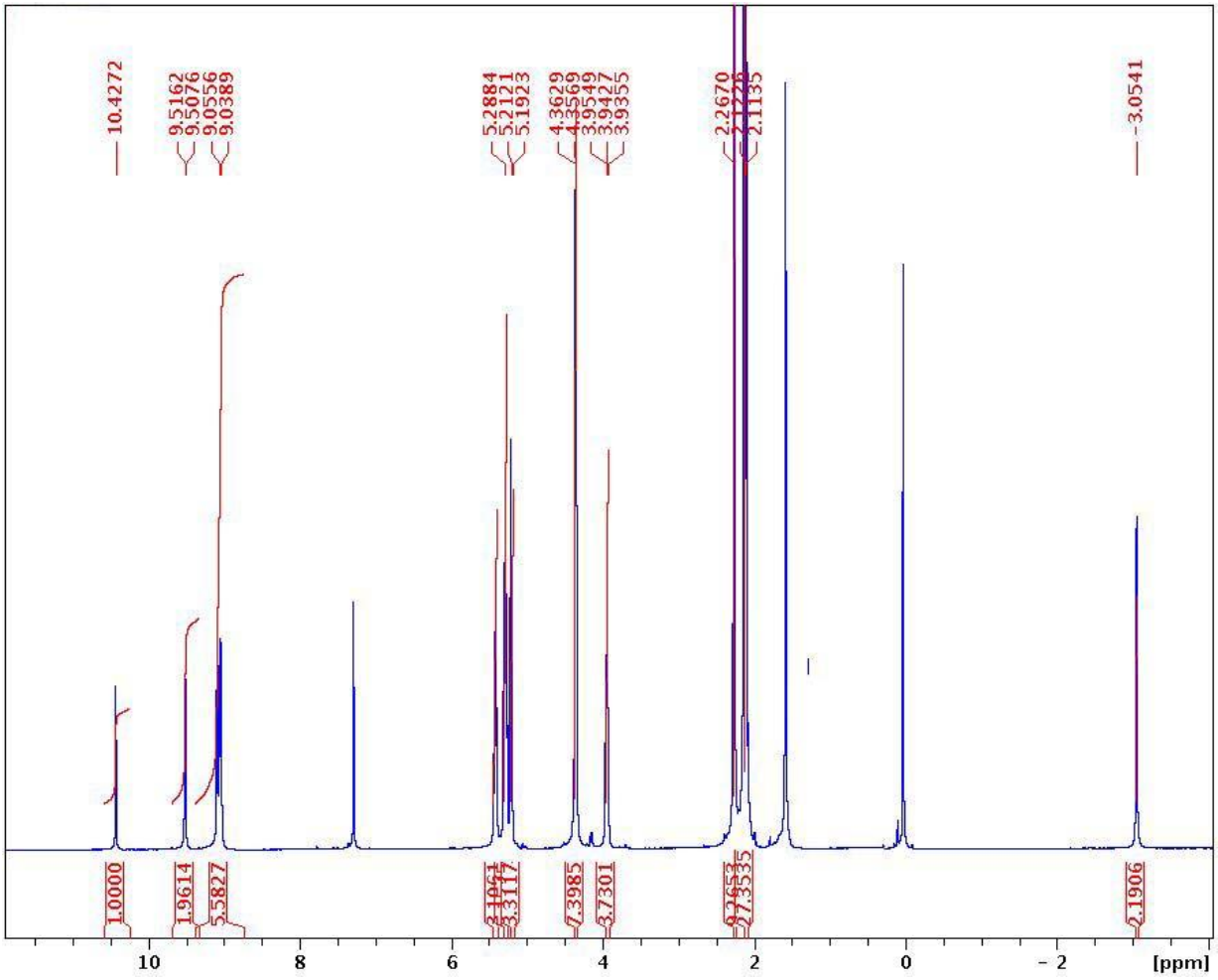

Figure A6.13: $FBGlc_3$ **(4a)** ^1H NMR $CDCl_3$ (7.28 ppm, water 1.6 ppm)

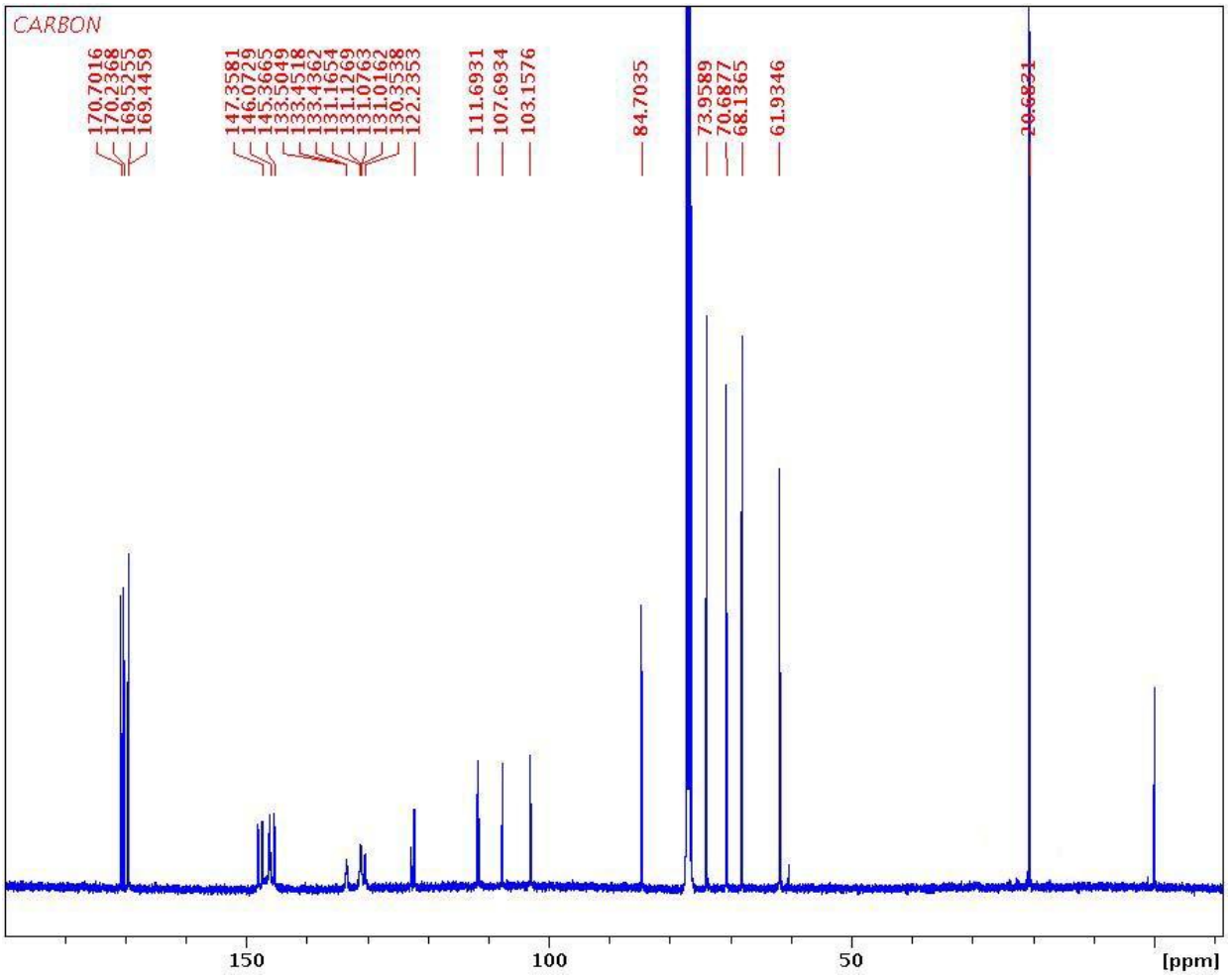

Figure A6.14: $FBGlc_3$ **(4a)** ^{13}C NMR ($CDCl_3$).

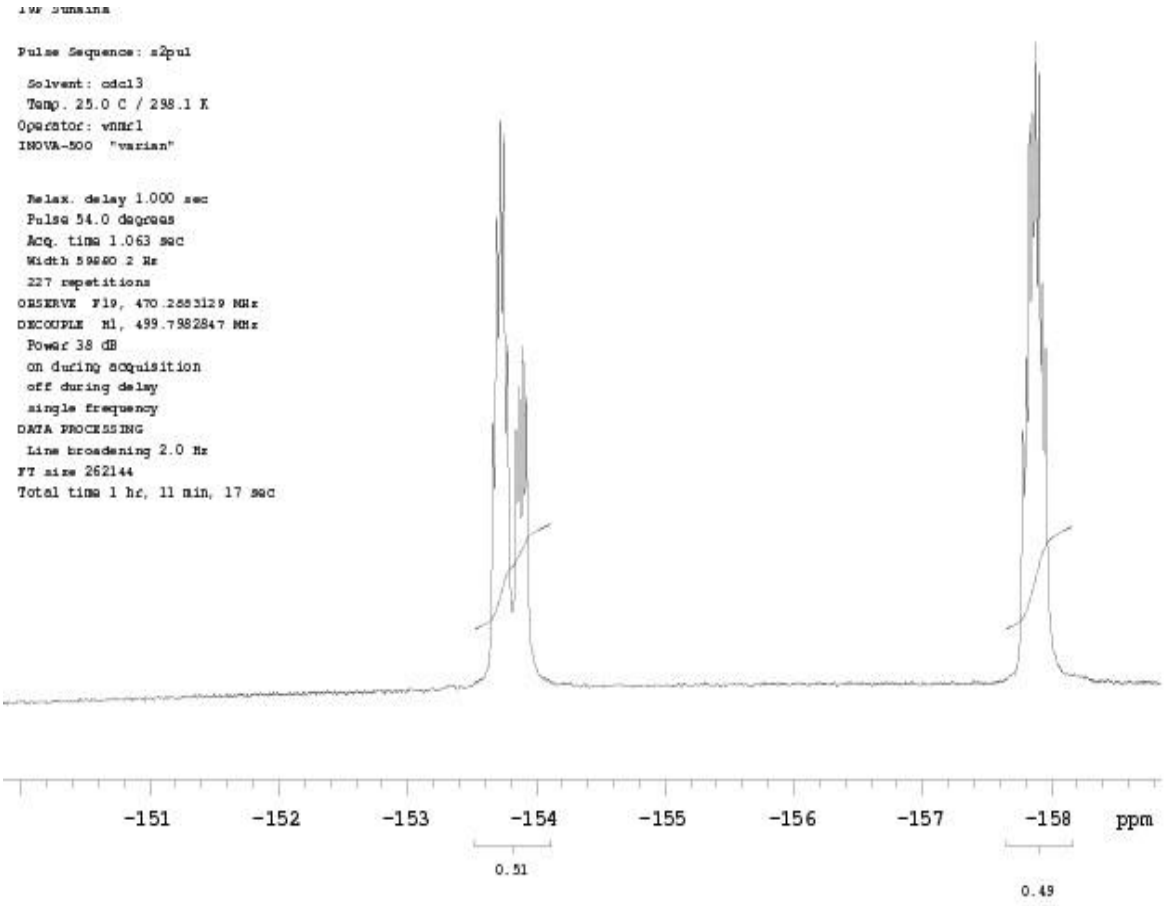

Figure A6.15: $FBGlc_3$ **(4a)** ^{19}F NMR ($CDCl_3$)

Data File	HCMDSS56B.d	**Sample Name**	FBGlu3
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	9/27/2010 6:11:40 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=1840.3041 EM=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C80H68F12N4O27S3	0.239	1840.3056	1605	C80H68F12N4O27S3	1840.3041	0.81
Cpd 2: C80H71F12N5O27S3	0.288	1857.331	19655	C80H71F12N5O27S3	1857.3307	0.14

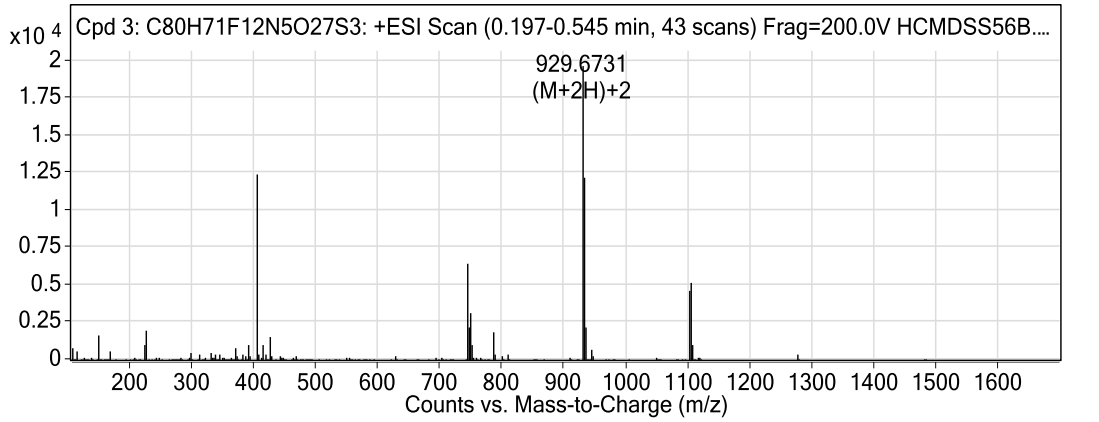

Figure A6.16: $FBGlc_3$ **(4a)** HRMS

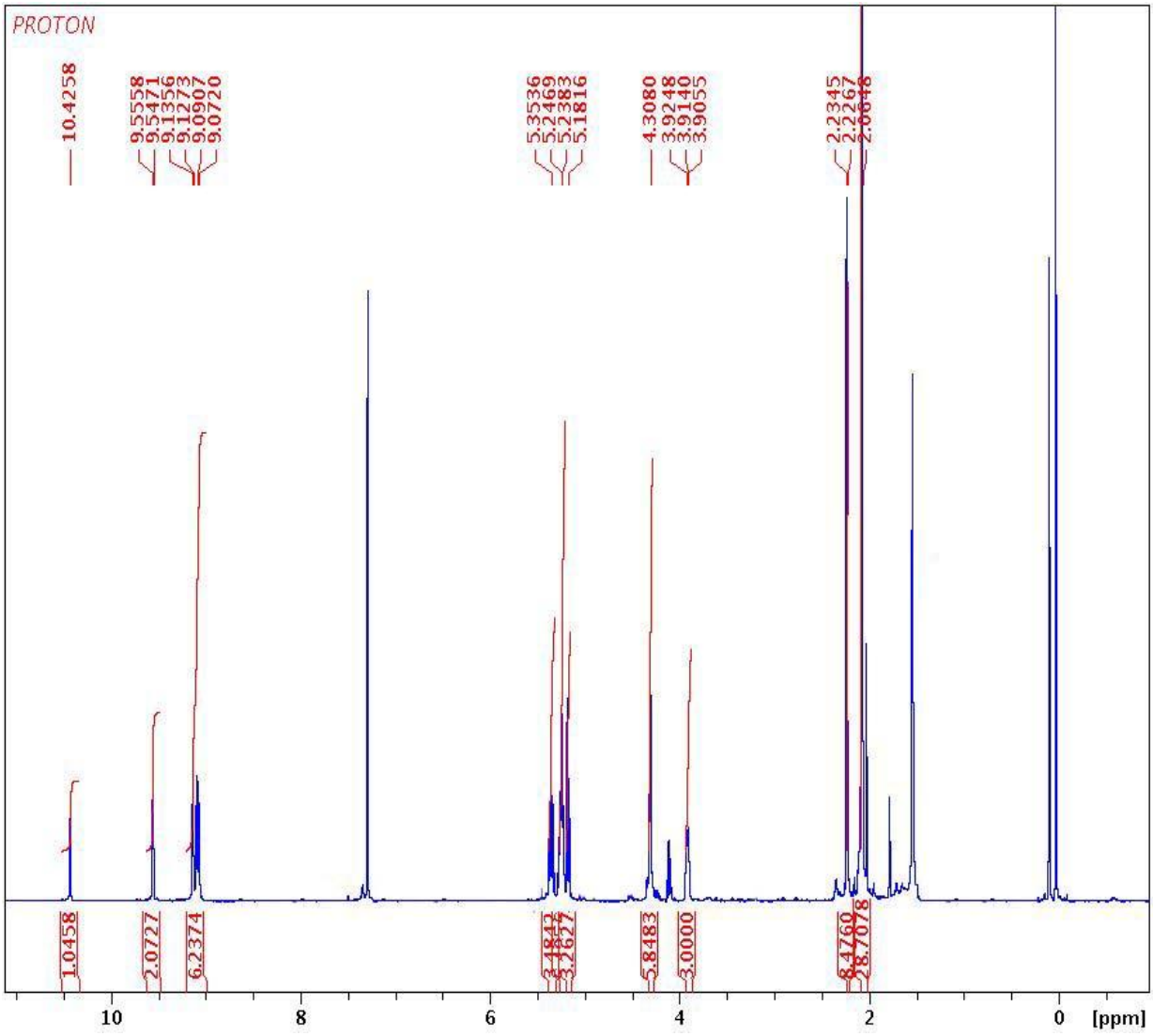

Figure A6.17: $ZnGlc_3$ **(5a)** ^1H NMR $CDCl_3$ (7.28 ppm, water 1.6 ppm)

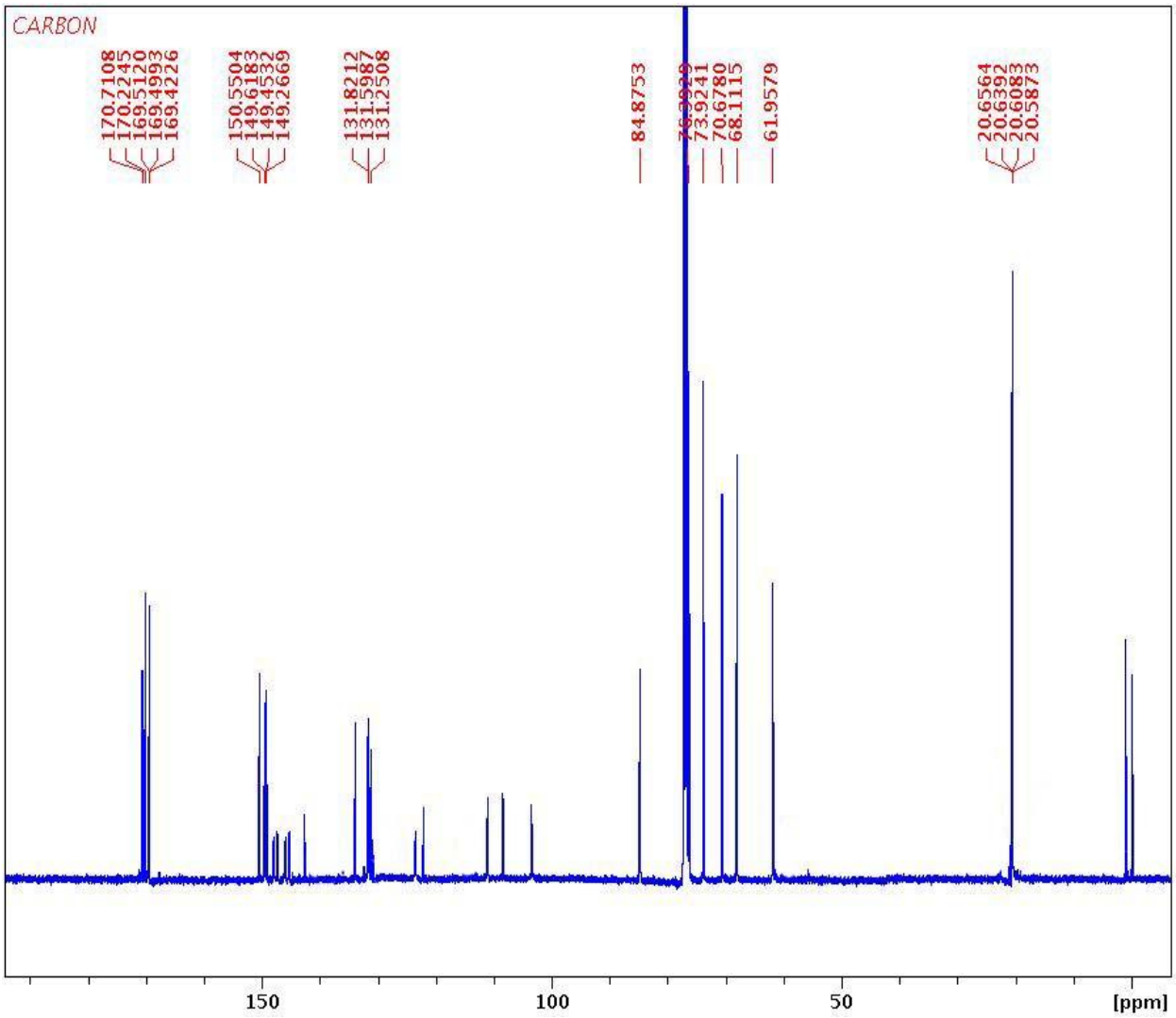

Figure A6.18: $ZnGlc_3$ **(5a)** ^{13}C NMR $CDCl_3$

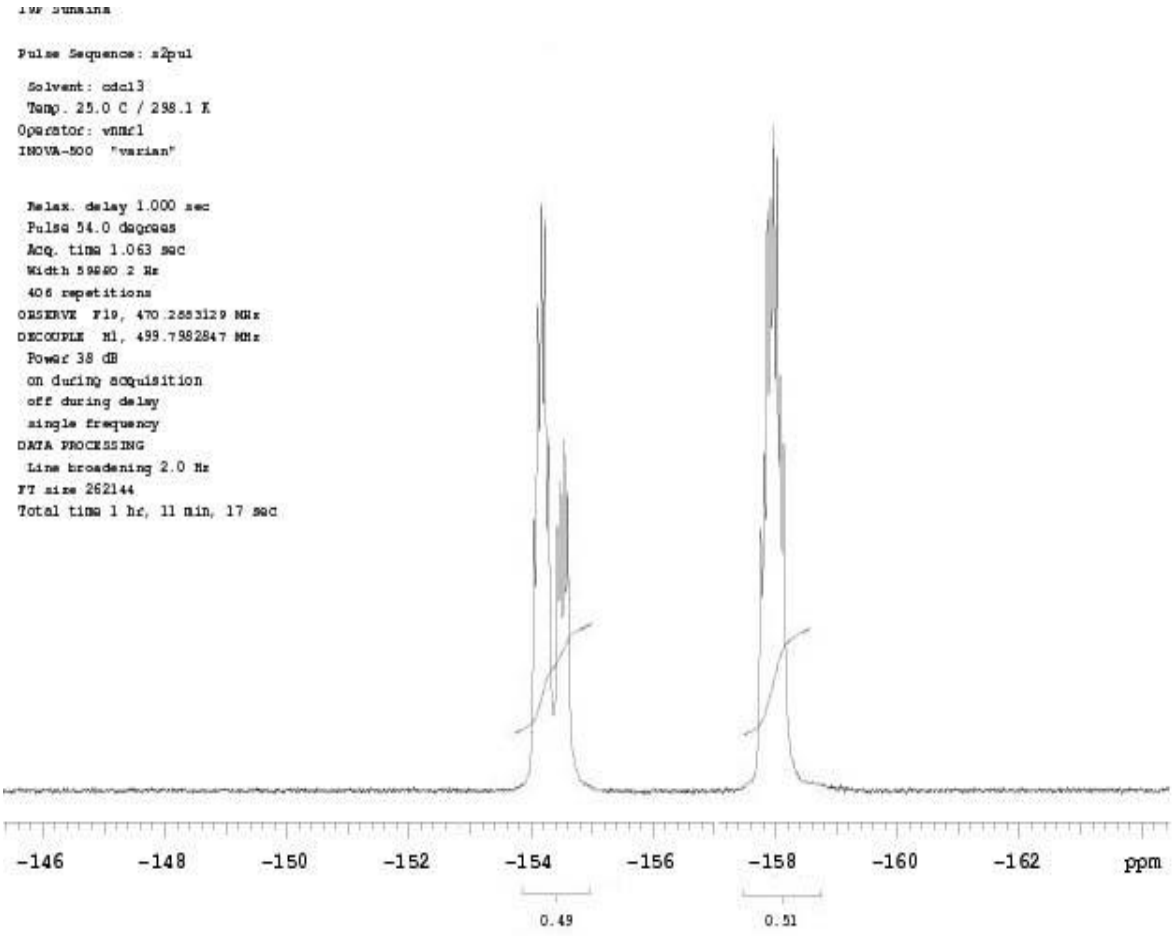

Figure A6.19: $ZnGlc_3$ **(5a)** ^{19}F NMR $CDCl_3$

Dat File	HCMDSS57A.d	**Sample Name**	ZnGlu3
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	9/29/2010 6:21:31 PM
IRM Calibration Status	Success	**DA Method**	HCEmpirical1.m
Comment	EM=1902.2176 EM=HC ESI Pos Small Molecule No HPLC.m		

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C80H66F12N4O27S3Zn	0.261	1902.2176	23190	C80H66F12N4O27S3Zn	1902.2176	-0.03

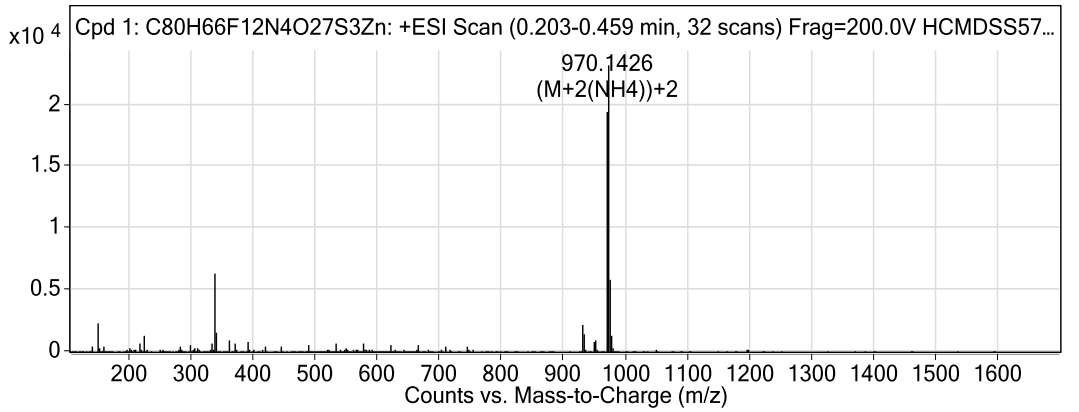

Figure A6.20: $ZnGlc_3$ **(5a)** HRMS

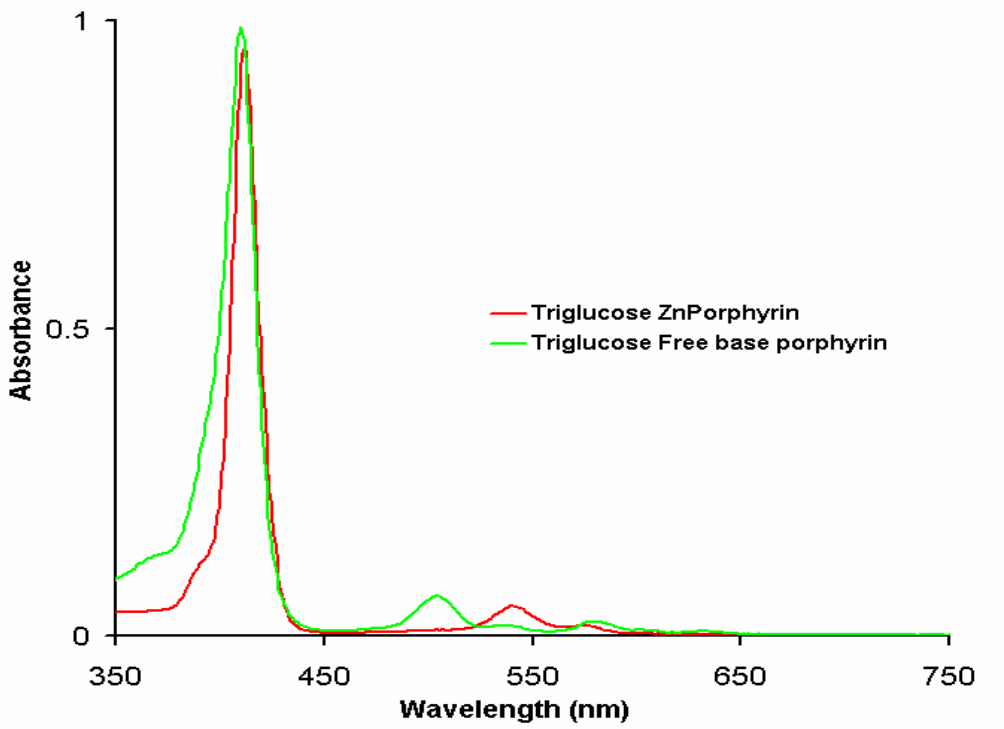

Figure A6.21: UV-visible spectra of porphyrin **4a** and **5a.**

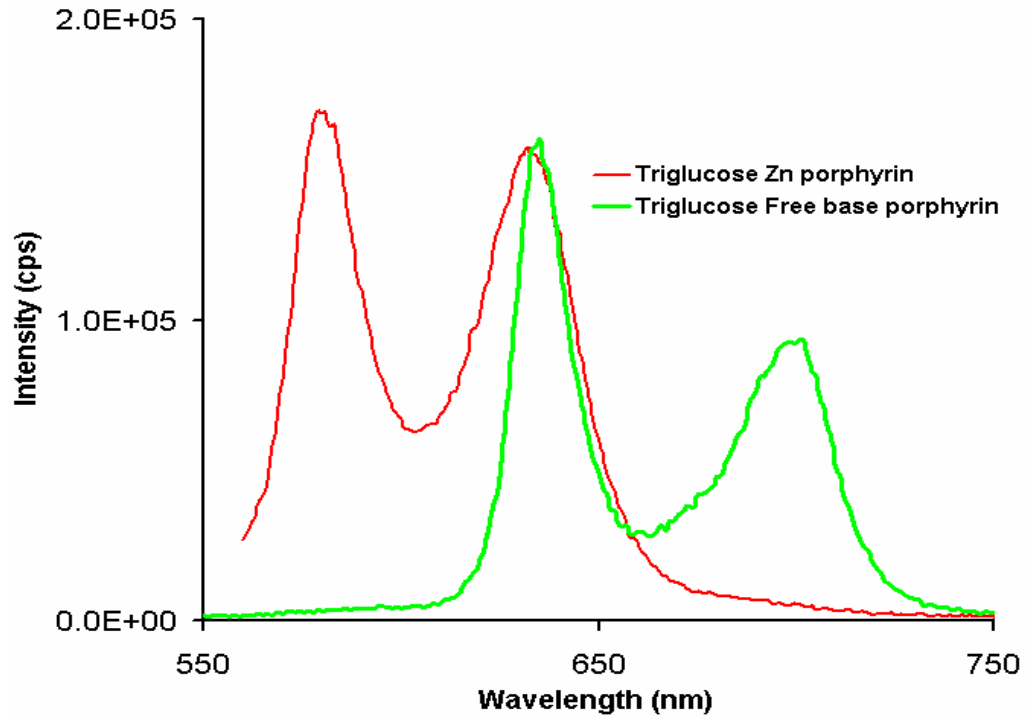

Figure A6.22: Emission spectra of porphyrin **4a** and **5a**.

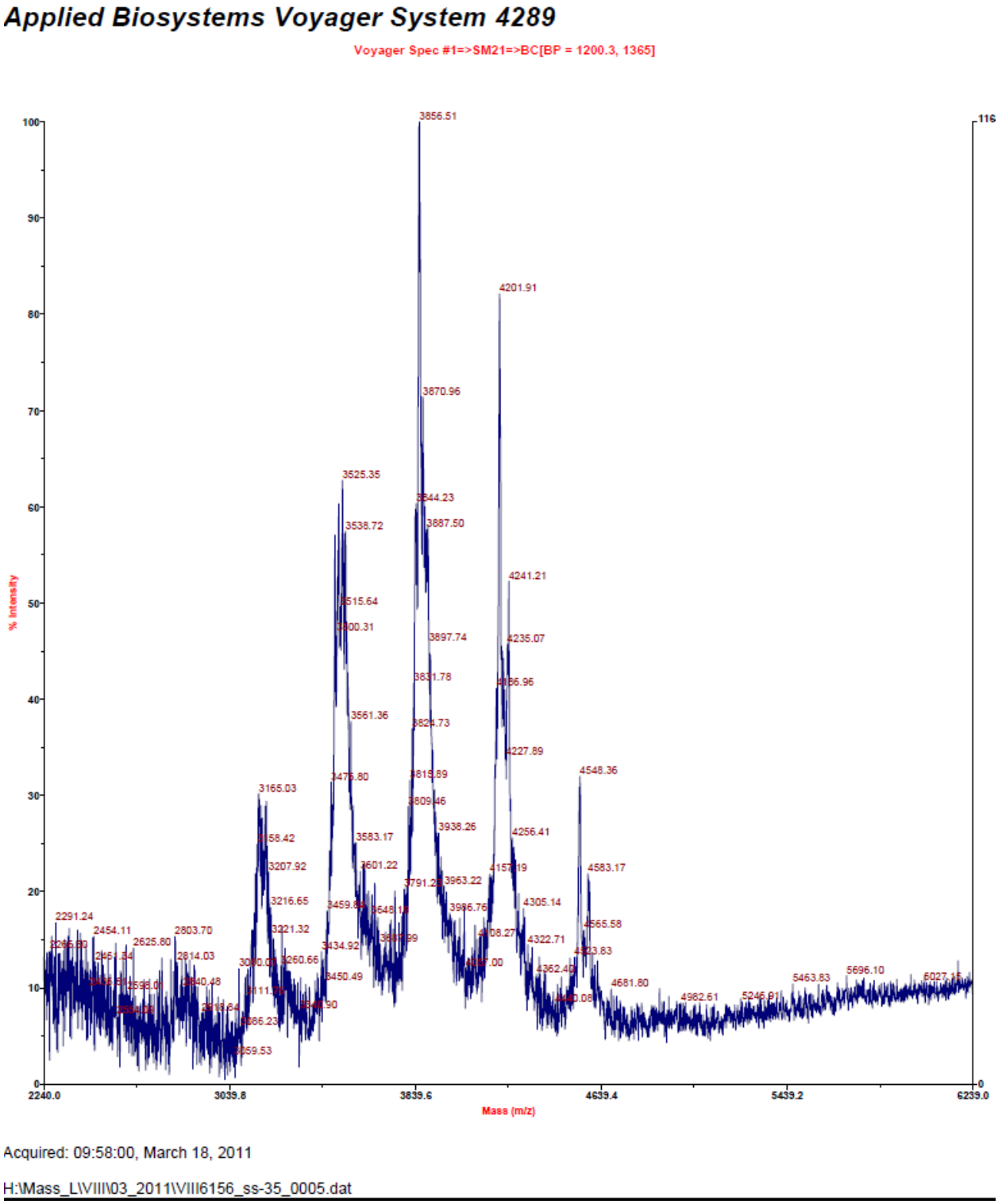

Figure A6.23: MALDI-TOF spectrum of mixture of 4,5,6,7 and 8 substituted isomers.

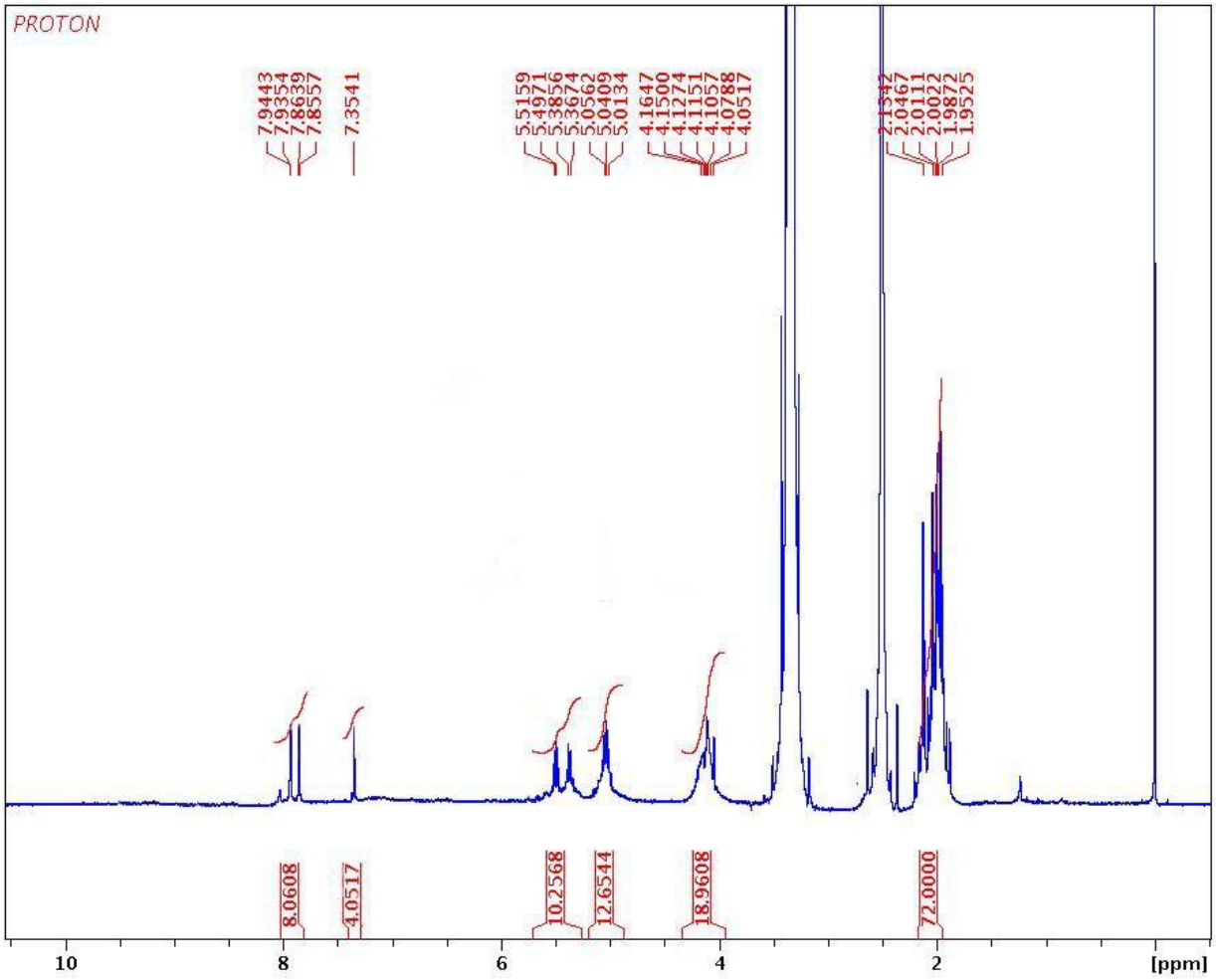

Figure A6.24: Zn_2Glc_6 **(9a)** ^{1}H NMR DMSO-d_6 (2.5 ppm, water 3.34 ppm)

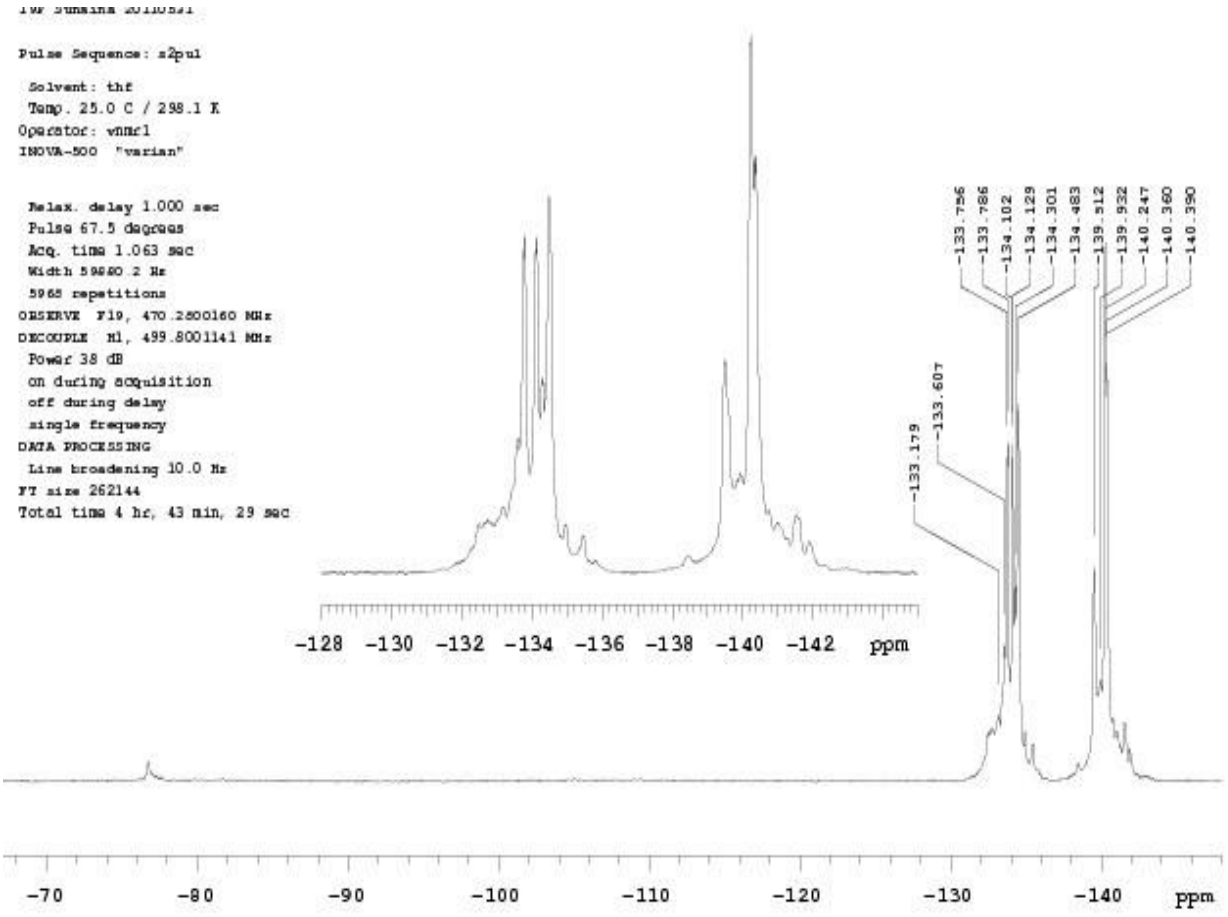

Figure A6.25: Zn_2Glc_6 **(9a)** ^{19}F NMR (THF-d_8)

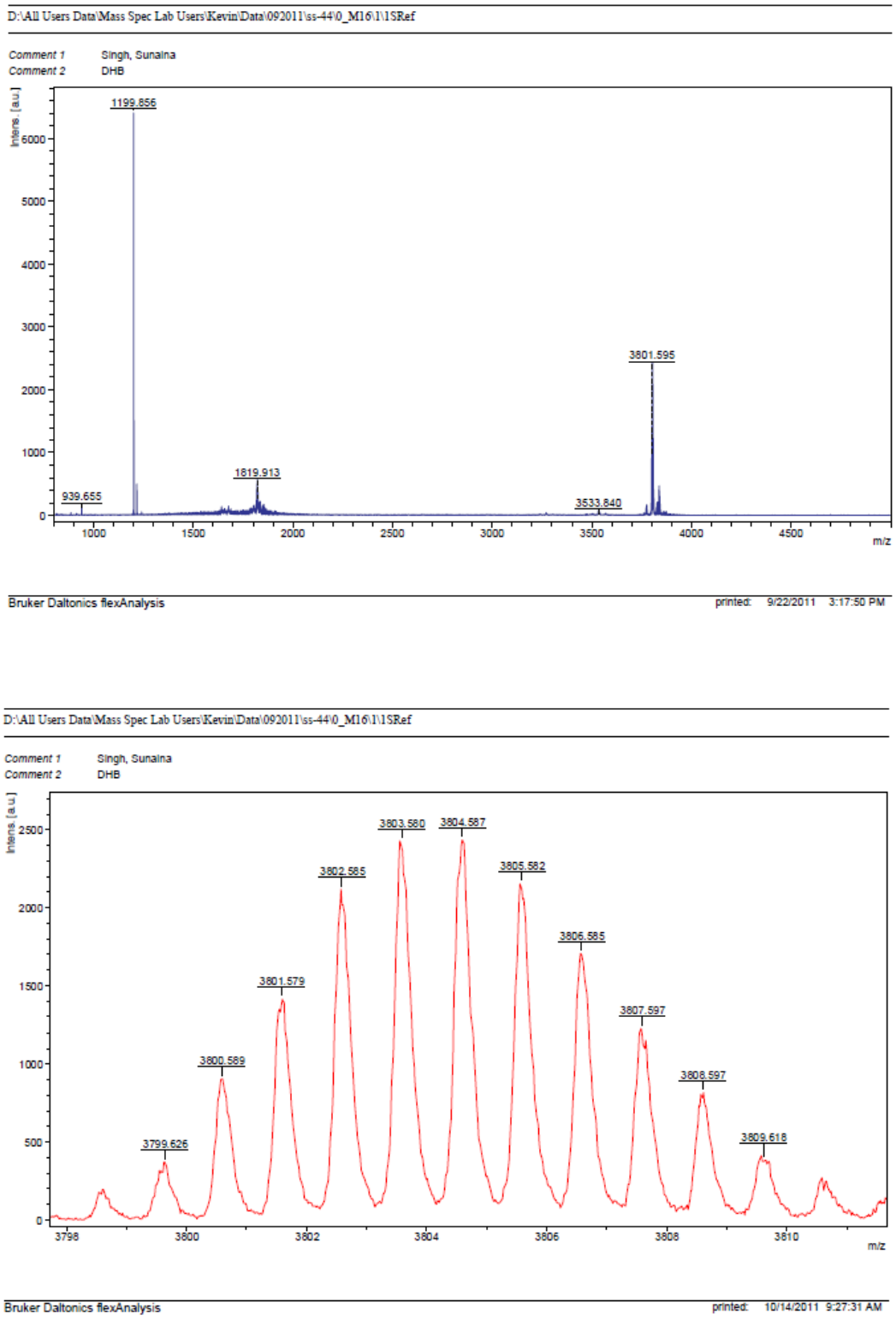

Figure A6.26: Zn_2Glc_6 **(9a)** MALDI-TOF spectrum.

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Chapter 1

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Chapter 2

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