Synthesis and Functionalization of Fluorinated Tetrapyrroles, Dipyrromethanes and Borondipyrrins

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The work of this dissertation has resulted so far in the following four publications, a US patent and as well as three poster presentations at international conferences and symposiums.

1. Hartwig R. A. Golf, Hans-Ulrich Reissig, Arno Wiehe, "The Regioselective Nucleophilic Aromatic Substitution Reaction of *meso*-Pentafluorophenyl-Substituted Porphyrinoids with Alcohols", *European Journal of Organic Chemistry* **2015**, 1548–1568.
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2. Hartwig R. A. Golf, Hans-Ulrich Reissig, Arno Wiehe, "Nucleophlic Substitution on (Pentafluorophenyl)dipyrromethane - A New Route to Building Blocks for Functionalized BODIPYs and Tetrapyrroles", *Organic Letters* **2015**, *17*, 982–985.
   DOI: 10.1021/acs.orglett.5b00082

3. Hartwig R. A. Golf, Hans-Ulrich Reissig, Arno Wiehe, "Synthesis of SF_5-Substituted Metalloporphyrins, BODIPYs and their Dipyrrane Precursors", *The Journal of Organic Chemistry* **2015**, *80*, 5133–5143.
   DOI: 10.1021/acs.joc.5b00528

4. Hartwig R. A. Golf, Anna M. Oltmanns, Duc H. Trieu, Hans-Ulrich Reissig, Arno Wiehe, "Synthesis of Functionalized BODIPYs, BODIPY-Corrole and BODIPY-Porphyrin Arrays with 1,2,3-Triazole Linkers Using the 4-Azido(tetrafluorophenyl)-BODIPY Building Block", *European Journal of Organic Chemistry* **2015**, *In press*.
   DOI: 10.1002/ejoc.201500413

5. Hartwig R. A. Golf, Arno Wiehe, Susanna Graefe, Volker Albrecht, Hans-Ulrich Reissig, "Specifically *meso*-Substituted Porphyrins and Chlorins for Photodynamic Therapy", US Patent Application Nr. 62057353.

National and international conferences and symposiums:

1. ORCHEM 2012, **Weimar**, Germany.
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In loving memory

for my grandmother

Abbreviations

The numbers of compounds described in the text are given in bold font. The following abbreviations are used throughout the whole thesis. If not otherwise stated, indexing for the tetrapyrrole type, e.g. A_4 or AB_3 refers to the substituents in *meso*-position. Except for systems with SF_5-groups, "A" refers to the pentafluorophenyl substituent and "B" to the other aryl moiety, e.g. 3-acetoxyphenyl.

BOC	*tert*-butoxycarbonyl
BODIPY	difluoroboraindacene or borondipyrrin
br s	broad singlet
d	doublet
δ	chemical shift
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPM	dipyrromethane
EA	elemental analysis
ESI-TOF	electrospray ionization time-of-flight
eq	equivalents
FR	folate receptor
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
IR	infrared
m	multiplet

m_c	centered multiplet
ns	nanosecond
ν	wavenumber
PDT	photodynamic therapy
PFBA	pentafluorobenzaldehyde
PFP	pentafluorophenyl
p-TSA	*para*-toluenesulfonic acid
PS	photosensitizer
quin	quintet
r.t.	room temperature
s	singlet
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TpFPP	tetrakis(pentafluorophenyl)porphyrin
TpFPC	tetrakis(pentafluorophenyl)corrole
TMS	trimethylsilyl
2D-NMR	two dimensional nuclear magnetic resonance
UV-Vis	ultraviolet-visible

Abstract

This thesis comprises four separate investigations on the synthesis and functionalization of novel porphyrins, corroles, borodipyrrins (BODIPYs) and their dipyrromethane (DPM) precursors which are described in the following:

The S_NAr-reaction of pentafluorophenyl(PFP)-substituted porphyrinoids with alcohols under variation of bases and reaction conditions was extensively investigated, resulting in the development of an optimized and generally applicable method for tetrapyrrole functionalization. Utilizing a variety of alcohols or sodium azide, it was demonstrated that a broad spectrum of key functional groups can be introduced into the tetrapyrrole periphery. Furthermore, several examples of amphiphilic porphyrins with a mixed lipophilic-hydrophilic substitution pattern were realized and their suitability as photosensitizers for photodynamic therapy (PDT) was studied with promising results. This project provides a convenient access to a broad variety of functionalized tetrapyrroles and their Zn(II)-metal complexes with a high potential for further transformations as exemplified by a copper(I)-catalyzed azide-alkyne cycloaddition.

The second project was focused on the functionalization of PFP-DPM with a broad variety of in-situ generated alkoxides by the S_NAr protocol. The alkoxy-substituted DPMs were further utilized for tetrapyrrole and BODIPY synthesis. Access to *trans*-A_2B_2-porphyrins was given by condensation with aryl-aldehydes. Oxidation and complexation with $BF_3{\cdot}OEt_2$ led to *meso*-functionalized BODIPYs. Moreover, the S_NAr protocol applied on PFP-BODIPY with sodium azide allowed a nearly quantitative direct azidation. This approach offers a flexible and efficient entry to pre-functionalized DPMs.

The adoption of the SF_5group on tetrapyrrole and BODIPY dyes by classic condensation was demonstrated in the third project. Optimization of the A_4-type porphyrin synthesis was carried out under variation of the acid catalyst. SF_5-substituted DPMs allowed access to porphyrins and corroles with a mixed *meso*-substitution pattern. Additionally, the S_NAr protocol with alcohols was applied on several A_2B_2-type porphyrins, AB_2- and A_2B-type corroles. The unique properties of the SF_5 group offer new possibilities in regard to tetrapyrrole fine-tuning and design of amphiphilic systems. Moreover, one example for a BODIPY-Cu(III)-corrole conjugate was presented, opening the way towards more complex multichromophoric dyes.

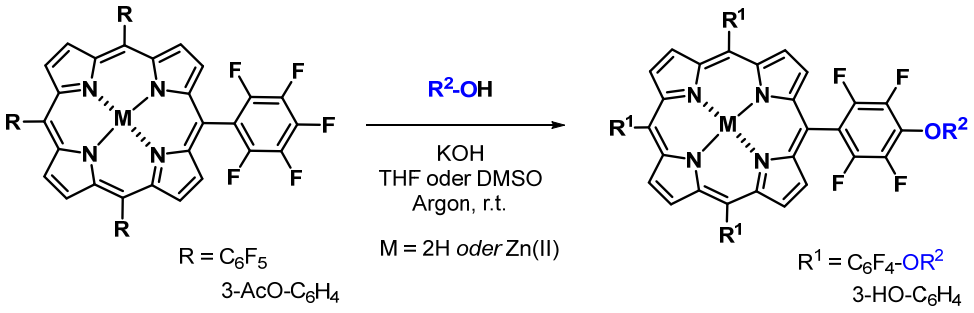
A stepwise synthesis of *meso*-functionalized BODIPYs, BODIPY-Cu(III)-corrole and BODIPY-Zn(II)-porphyrin arrays was investigated in the fourth project, utilizing terminal alkynes as well as alkyne-substituted tetrapyrroles and an azido-BODIPY within the copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition. The use of the 4-azido(tetrafluorophenyl)-BODIPY building block resulted in several *meso*-, di- and trivalent BODIPYs. This approach demonstrates a new pathway with a convenient access to highly functionalized *meso*-BODIPY systems and multi-chromophoric arrays, offering the possibility to connect the azido-BODIPY macrocycle to other systems, e.g. bioactive materials, serving as a fluorescent marker.

Zusammenfassung

Die vorliegende Dissertation umfasst vier Forschungsvorhaben zur Synthese und Funktionalisierung verschiedenartiger Porphyrine, Chlorine, Boro-dipyrrine bzw. Boro-dipyrromethene (BODIPYs) und deren Dipyrromethan (DPM)-Vorstufen, die im Folgenden zusammengefasst werden:

1. Synthese alkoxy-substituierter Tetrapyrrole

Im Rahmen dieses Projektes wurde die nukleophile aromatische Substitution (S_NAr) von pentafluorphenyl(PFP)-substituierten Porphyrinen, deren Zn(II)-Komplexen sowie Corrolen mit verschiedenen Alkoholen unter der Variation der Reaktionsbedingungen (z.B. Basen, Lösungsmittel) eingehend untersucht. Daraus resultierend wurde eine für verschiedene Systeme anwendbare Methode entwickelt. Es konnte gezeigt werden, dass unter Verwendung von alkyl-substituierten, fluorierten und perfluorierten bis hin zu funktionelle Gruppen tragenden Alkoholen sowie Natriumazid, ein breites Spektrum an Substituenten mit hoher Effizienz in die Peripherie der Makrocyclen eingeführt werden kann.

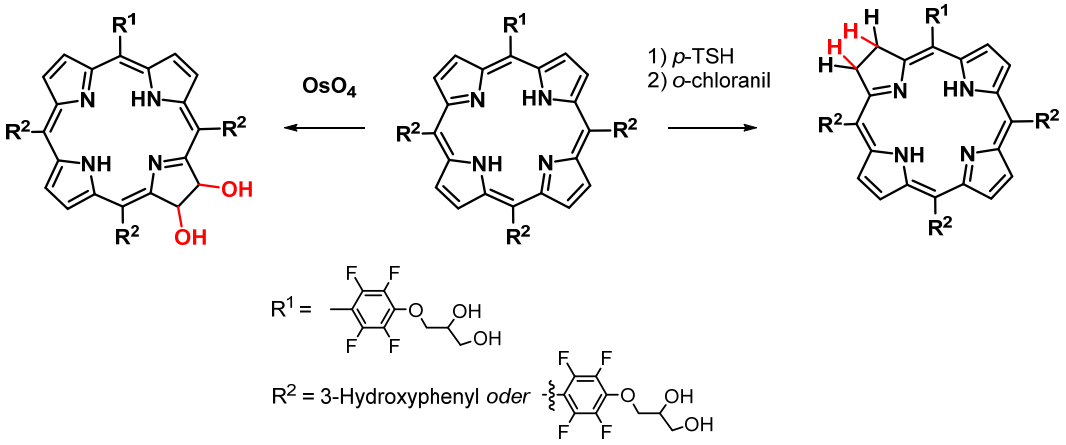


Weiterhin gelang die Darstellung diverser amphiphiler Systeme mit einem gemischten Substitutionsmuster durch gezielte Einführung lipophiler Gruppen an Porphyrinen mit hydrophilen 3-Hydroxyphenyl-Substituenten in den anderen *meso*-Positionen. Die große Bandbreite an modifizierten Tetrapyrrolen und deren Zink(II)-Komplexen ermöglicht aufgrund der terminalen, funktionellen Gruppen in der Peripherie des Tetrapyrrols weitere Umsetzungen. Beispielhaft wurde dies anhand der 1,3-dipolaren Azid-Alkin Cycloaddition zwischen zwei AB_3-Porphyrinen gezeigt.

2. Darstellung alkoxy-substituierter Chlorine

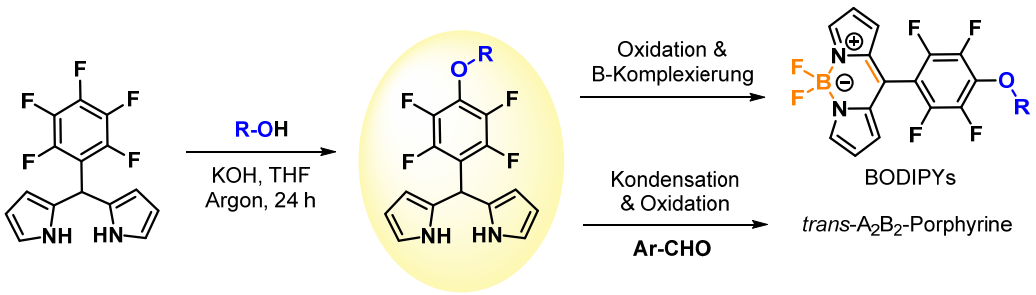
Für die potentielle Verwendung in der Photodynamischen Therapie(PDT) wurde das S_NAr Reaktionsprinzip zudem auf die Synthese amphiphiler Porphyrine und Chlorine übertragen. Diese Porphyrine zeigten in *in vitro* Zelltests verschiedener Zelllinien eine hohe Phototoxizität bei Bestrahlung und geringe Dunkeltoxizität. Insbesondere traf dies für Verbindungen mit endständigen Hydroxyl-Gruppen zu.

Darauf aufbauend wurden drei Glycerol-substituierte Porphyrine mit A_4-, *trans*-A_2B_2- sowie AB_3-Substitutionsmuster mit *para*-Tosylhydrazin (PTSH) zu den entsprechenden Dihydrochlorinen umgesetzt. Analog erfolgte die Synthese Glycerol-substituierter Dihydroxychlorine durch Umsetzung mit Osmium(IV)tetroxid. Die erhaltenen Chlorinsysteme erwiesen sich in *in vitro* Tests als geeignete Photosensibilisatoren aufgrund ihrer hohen Phototoxizität. Besonders positive Resultate wurden mit Dihydroxychlorinen erzielt, da diese selbst in hohen Konzentrationen der jeweiligen Tetrapyrrole nahezu keine Dunkeltoxizität und eine gute Löslichkeit im alkoholischen Medium vorwiesen.



3. Synthese *meso*-funktionalisierter Dipyrromethane

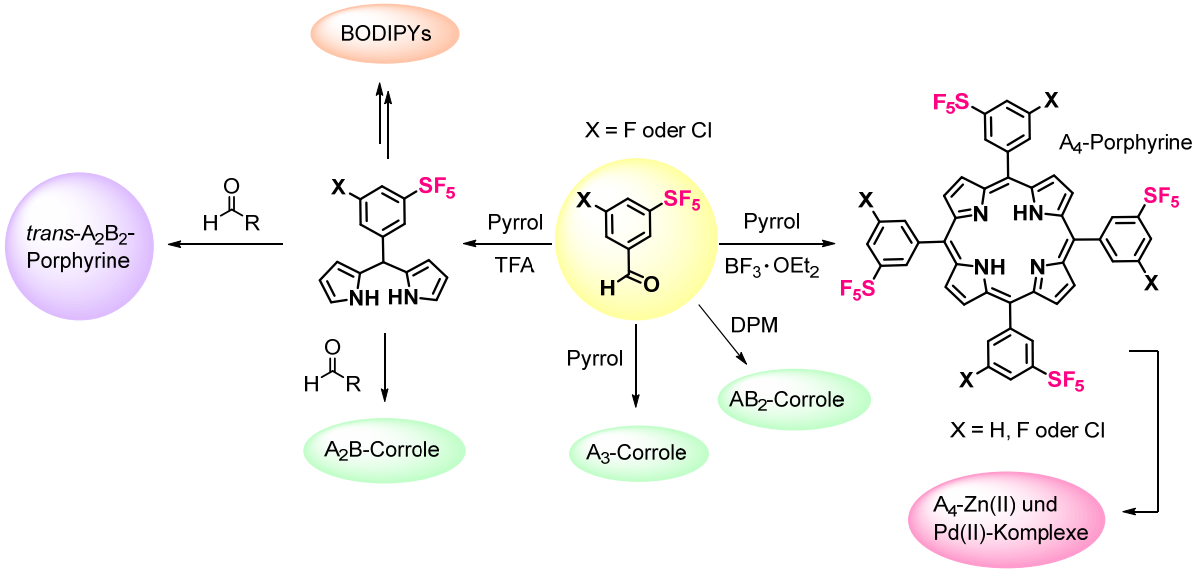
In diesem Projekt wurde die Funktionalisierung von PFP-DPM mit *in-situ* dargestellten Alkoxiden über den selektiven Austausch des *para*-Fluoratoms am PFP-Substituenten untersucht. Als Beispiel möglicher, weiterführender Reaktionen wurden die modifizierten DPM-Bausteine zur Synthese von Tetrapyrrolen und BODIPYs eingesetzt. Die klassische Kondensationsreaktion mit einem weiteren Arylaldehyd ermöglichte so den Zugang zu *trans*-substituierten A_2B_2-Porphyrinen, wobei u.a. Pentafluorbenzaldehyd verwendet wurde. Die daraus resultierenden *trans*-Porphyrine bieten die Möglichkeit weiterer PFP-Substitutionen zur Darstellung von tetrasubstituierten *trans*-Porphyrinen mit definiertem *meso*-Substitutionsmuster.



Die Oxidation *meso*-funktionalisierter DPM-Bausteine und die anschließende Komplexierung mit $BF_3{\cdot}OEt_2$ ermöglichte die Synthese von *meso*-substituierten BODIPYs. Des Weiteren gelang durch S_NAr Reaktion mit Natriumazid am PFP-BODIPY – in Form einer direkten Azidierung – die nahezu quantitative Umsetzung zum entsprechenden Azido-BODIPY. Als 1,3-Dipol eignet sich diese Verbindung besonders zur Verknüpfung mit terminalen Alkinen über die 1,3-dipolare Cycloaddition, um in Kombination mit dem BODIPY Grundgerüst Konjugate zu realisieren. Die gezeigten Reaktionen erlauben einen flexiblen und effizienten Zugang zu vor-funktionalisierten Dipyrromethanen, welche als vielseitige Bausteine für weitere Synthesen, u.a. von *trans*-substituierten Tetrapyrrolen oder von BODIPYs, eingesetzt werden können.

4. Synthese von Tetrapyrrolen und BODIPYs mit Pentafluorothio-Substituenten

Dieses Projekt beschreibt die erste Adaption der SF_5-Funktionalität an Tetrapyrrole und BODIPYs durch Kondensationsreaktionen von Pyrrol mit SF_5-substituierten Aryl-aldehyden. Dazu erfolgte zu Beginn eine Optimierung der Reaktionsbedingungen zur Synthese von A_4-Porphyrinen unter Variation des eingesetzten Säurekatalysators – Trifluoressigsäure und $BF_3{\cdot}OEt_2$ – sowie dessen eingesetzter Menge. Durch Komplexierung mit Zn(II)acetat bzw. Pd(II)acetat wurden die entsprechenden Metalloporphyrine erhalten. Die Darstellung von Porphyrinen und Corrolen mit gemischtem *meso*-Substitutionsmuster wurde ebenfalls untersucht, wobei diese aus den entsprechenden SF_5-substituierten DPM-Bausteinen durch Kondensation mit Pentafluorbenzaldehyd erhalten wurden. Das zuvor beschriebene Prinzip der S_NAr Reaktion mit Alkoholen ermöglichte auch hier die selektive Darstellung Alkoxy-substituierter A_2B_2-Porphyrine, AB_2- und A_2B-Corrole. Die Alkoxy-Substitution gemischt-substituierter Systeme mit PFP- und SF_5-Substituenten erfolgte hierbei unter den gewählten Reaktionsbedingungen mit sehr hoher Präferenz für den PFP-Substituenten.

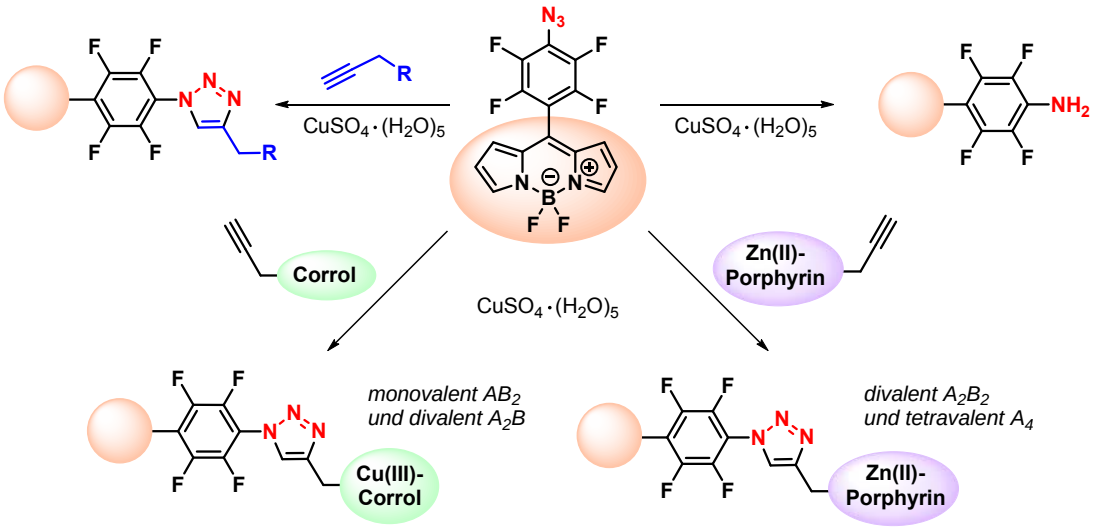


Besondere Eigenschaften wie die hohe Lipophilie und die chemische Resistenz der SF_5-Gruppe eröffnen neue Möglichkeiten, Tetrapyrrole gezielt für die entsprechenden Anwendungen – z.B. die Synthese von amphiphilen Verbindungen oder Katalysatoren mit stark elektronenziehenden Substituenten - darzustellen. Zudem wurde erstmals ein BODIPY-Cu(III)-Corrol-Konjugat synthetisiert, als ein Beispiel einer Kupfer(I)-katalysierten 1,3-dipolaren Cycloaddition zum Aufbau komplexer multichromophorer Systeme.

5. Synthese von Triazol-verknüpften BODIPYs und BODIPY-Tetrapyrrol-Arrays

Dieses Projekt befasste sich mit der umfassenden Untersuchung von 4-Azido(tetrafluorphenyl)-BODIPY und dessen Reaktionen. Hierbei konnten verschiedenartige funktionalisierte *meso*-substituierte BODIPYs, sowie di- und trivalente BODIPY-Systeme dargestellt werden. Weiterhin gelang die Synthese von 1,2,3-Triazol-verknüpften BODIPY-Tetrapyrrol-Arrays mit ein bis vier BODIPY-Einheiten. Dazu wurden SF_5- und Hydroxy-funktionalisierte, monovalente AB_2- und divalente A_2B-Corrole mit entgegengesetzter Polarität sowie ein divalentes A_2B_2- und ein A_4-Porphyrin mit tetravalenter Verknüpfung gewählt. Interessanterweise wurde bei Ausschluss eines terminalen Alkins als Reaktionspartner eine nahezu quantitative Reduktion der Azidgruppe zur Aminogruppe beobachtet.

Die dargestellte Methode erlaubt einen effizienten und einfachen Zugang zu *meso*-funktionalisierten BODIPY-Systemen sowie zu multi-chromophoren Arrays mit unterschiedlichen Porphyrinoiden als Bausteinen. Weiterhin besteht die Möglichkeit, das 4-Azido-BODIPY über 1,3-dipolare Cycloadditionen an bioaktive Substanzen zu binden, um die Fluoreszenzeigenschaften des Bora-indacens nutzen zu können.



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A Perspective on the Synthesis of Tetrapyrroles, DPMs and BODIPYs

1.1 *Introduction*

1.1.1 *Porphyrins and their Chlorin Analogs*

Tetrapyrroles are a remarkable class of macrocycles whose skeleton is comprising four pyrrole units in a cyclic interconnection perfected by Nature as multifunctional dyes. The conjugation type between the single pyrroles can be either by carbon bridges as spacer (sp^3 methylene- or sp^2 methine-bridges) or by a direct pyrrole-pyrrole connection. This "bridge" is defined as the *meso*-position. The amount of existent bridges and their hybridization type divides tetrapyrroles into subclasses, e.g. porphyrins, corroles, calixpyrroles or corrins (Figure 1). Tetrapyrroles play a crucial role in many biochemical processes of living organisms due to their characteristic features to act as ligands for metal complexation or light absorption due to a conjugated π-electron system described in detail as follows. Hemoglobin and myoglobin are examples of naturally occurring iron(II) porphyrins which act as oxygen transport proteins. Chlorophylls are magnesium complexes of chlorins and function as essential components for natural photosynthesis and light harvesting sequences in plants and several cyanobacteria.

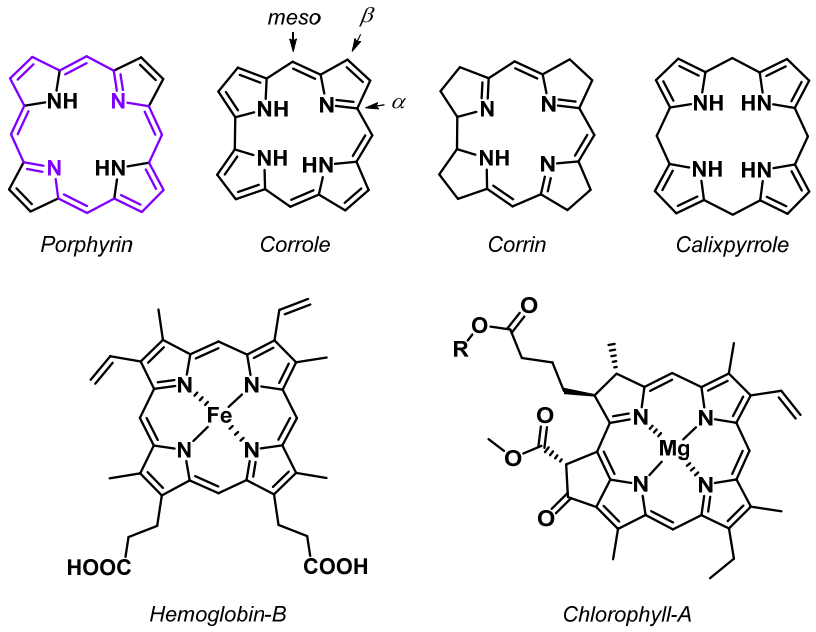


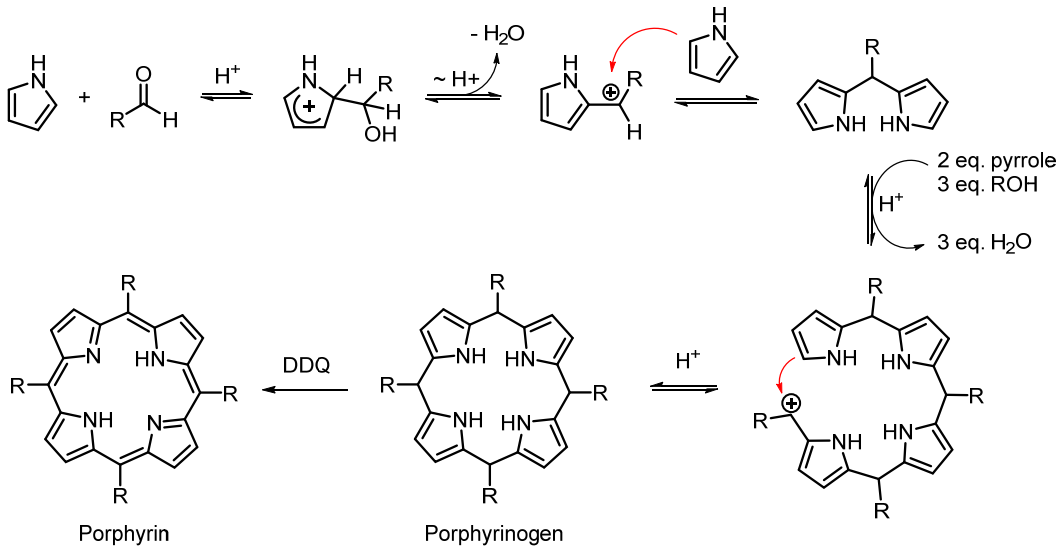
Figure 1. Structural comparison of several tetrapyrroles and their naturally occurring derivatives.

The most common tetrapyrrole classes are further diversified in dependence on their structural characteristics: arrangement of the pyrrole units, the position of pyrrole-pyrrole linkage and type of carbon-bridge, etc. For example, mixed *meso*-positions of sp^2 and sp^3 centers in one macrocycle are typical characteristics for *calixphyrins*, while a "reversed" pyrrole unit is an attribute of *N-inverted porphyrinoids*. This thesis is fundamentally based on chemistry with the *porphyrin* and *corrole* macrocycle subclass described as follows.

Pioneering reports on **porphyrins** date back to 1912 by KÜSTER.[1] These heterocyclic macrocycles comprise of four pyrrole subunits linked by their *α*-position over methylene bridges in a highly stable, planar cyclic arrangement with D_{2h} symmetry and two inner *N*-pyrrolic positions. HÜCKEL aromaticity is given by 18 of overall 22 conjugated π-electrons (see Figure 1) and their chemistry is comparable with basic aromatic systems. The remaining 4 π-electrons – characterized by two C-C double bonds in two pyrrole units – exhibit an olefin-type character and allow typical addition, reduction or cyclo-addition reactions.[2] Though these two peripheral double bonds are involved in the overall π-electron distribution, they are not sustainable for aromaticity and a displacement of one or both leads to chlorins or bacteriochlorins, respectively. After full deprotonation of the two inner NH-positions, porphyrins act as tetradentate dianionic ligands with the ability to coordinate many transition metal ions.

Porphyrins - as well as other tetrapyrroles - absorb light in specific regions of the visible electromagnetic spectrum as a consequence of the extended π-system, resulting in several shades of purple color. Free-base porphyrins exhibit absorption in the blue and red region characterized by a strong SORET-band around 400 nm and four weaker Q-bands of higher wavelength between 450 to 700 nm. Protonation of the inner cavity or complexation with metals on the other hand, significantly influences the absorption behavior. For example, metalloporphyrins exhibit a strong SORET and one or two Q-bands in the same region as their free base pendants.

Historically, the first synthesis of a simple porphyrin was carried out 1936 by ROTHEMUND through condensation of pyrrole and formaldehyde.[3] In 1967 ADLER and LONGO were able to improve the yield up to 20%, however with the restriction to simple tetraphenylporphyrins as the harsh reaction conditions used (boiling propionic acid) did not allow other functionalized aldehydes.[4] LINDSEY and co-workers developed a different protocol and achieved the first breakthrough in porphyrin synthesis 1987 by use of mild reaction conditions and room temperature.[5] The acid-catalyzed condensation of pyrrole and aldehydes in high dilution afforded a broad variety of *meso*-substituted porphyrins with yields up to 40%. Their applied strategy is based on the formation of porphyrinogen through several condensation steps catalyzed by TFA or $BF_3{\cdot}OEt_2$ and followed by a subsequent DDQ-oxidation (Scheme 1).



Scheme 1. Mechanism of the porphyrin synthesis according to LINDSEY.[5]

The described method is very sensitive to even minor deviations in catalyst loading or degree of dilution with a high impact on the overall yield. Nevertheless, it allows in particular the synthesis of A_4-porphyrins as well as *trans*-A_2B_2 and AB_3-systems in a mixed condensation with several aldehydes, resulting in a statistical distribution of several products.

This is exemplified in Figure 2 by condensation of two aldehydes with similar reactivity in a 1:1 ratio with pyrrole. The statistical distribution is susceptible to the reactivity of the utilized aldehyde and can be tuned by use of a different substrate ratio and acid catalysts. For example, a 1:3 (A:B) ratio affords mainly AB_3-type porphyrins.

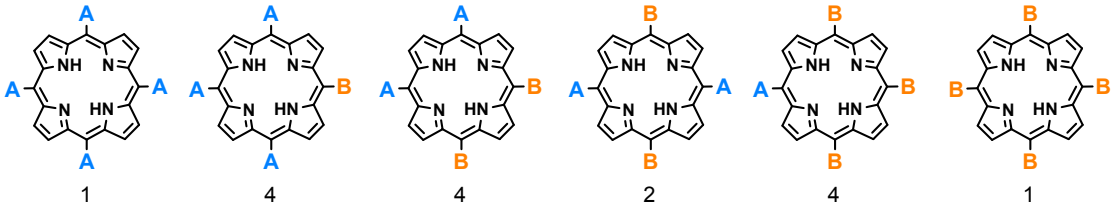
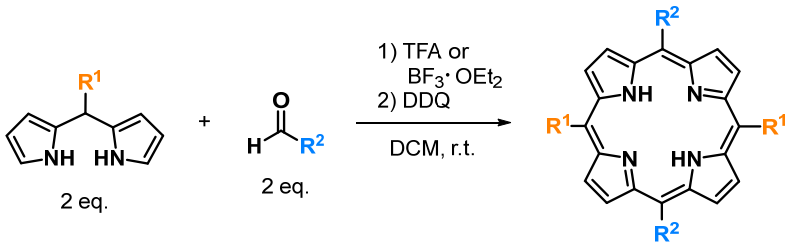


Figure 2. Statistical distribution of a mixed condensation with two similar aldehydes in a 1:1 ratio.

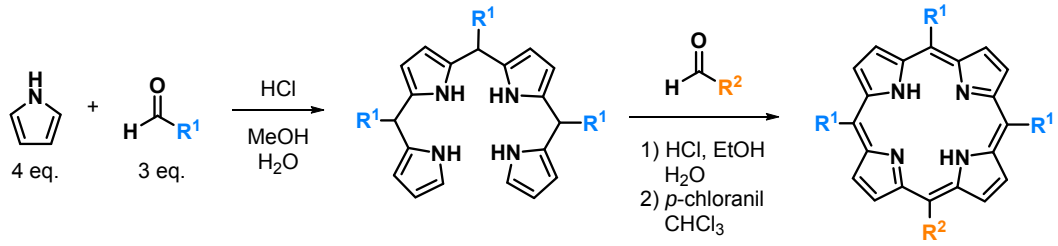
A rational strategy is demonstrated by use of dipyrromethanes (DPMs) as these allow a straightforward synthesis of specifically *trans*-A_2B_2-porphyrins.[6] Depending on the steric hindrance and reactivity of the aldehyde, this building-block approach offers for some cases a selective synthesis of porphyrins without significant side product formation by statistical distribution or scrambling (Scheme 2). A general obstacle in acid-catalyzed porphyrin syntheses under complete reversibility is the rearrangement of the substituents known as "scrambling".[7]

Hence, the condensation of a DPM with an aldehyde would result in an identical distribution of products similar to the corresponding mixed condensation of aldehydes. Sterically hindered DPMs or DPMs with electron-withdrawing substituents, e.g. 5-mesityl- or pentafluorophenyl-dipyrromethane, are less prone to undergo acid catalyzed scrambling, whereas aldehydes with less or no hindrance, e.g. 5-phenyldipyrromethane, are more susceptible. Detailed investigations on the origin of scrambling were reported by LINDSEY and co-workers.[7]



Scheme 2. Approach towards *trans*-A_2B_2 porphyrins by condensation of a DPM with an aldehyde.

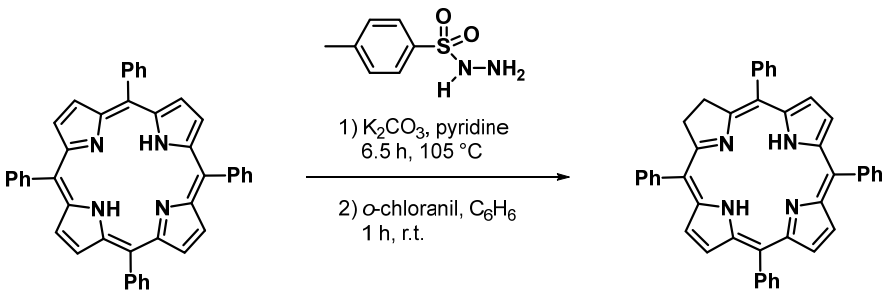
A second milestone towards green chemistry in porphyrin synthesis was achieved by GRYKO and co-workers very recently.[8] The condensation of DPMs with aldehydes in a water/methanol or water/ethanol mixture under HCl-catalysis and subsequent oxidation afforded a broad variety of *trans*-A_2B_2- and AB_3-porphyrins with a mixed *meso*-substitution pattern (Scheme 3). While the preparation of *trans*-porphyrins proceed similar to LINDSEY's method by direct condensation of a DPM with an aldehyde, AB_3-porphyrins were realized through a bilane intermediate, followed by reaction with another aldehyde and subsequent oxidation with *p*-chloranil. This bilane approach was previously investigated by the same group for the straightforward corrole synthesis in aqueous media.[9]



Scheme 3. Access to AB_3-type porphyrins through a bilane intermediate according to GRYKO.[8]

Regarding the porphyrin skeleton and its two peripheral *β*-*β* double bonds with an olefinic character, the reduction with hydrogen or oxidation by hydroxylation of one or both to the pyrroline unit results in **chlorins** or **bacteriochlorins**, respectively. This change of the π-electron distribution has a substantial impact on the properties of the macrocycle such as the redox potential and photo physical attributes. Chlorins are naturally occurring as chlorophylls and are used in photosynthesis as electron donors and acceptors as well as in multiporphyrin arrays for photoinduced electron transfer.

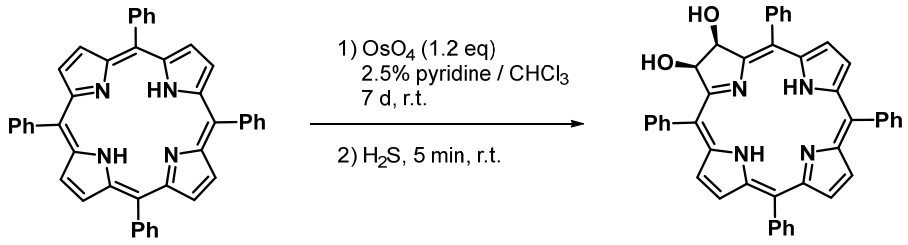
The first report of a porphyrin reduction to its corresponding dihydrochlorin dates back to 1929 by FISCHER and co-workers.[10] This procedure was further improved roughly 20 years later by a palladium-catalyzed dihydrogenation in the presence of elemental hydrogen.[11] A different and nowadays most common strategy - also for the synthesis of Temoporfin and its analogs[12] - was described by WHITLOCK 1969 on tetraphenylporphyrin (TPP), utilizing *p*-toluenesulfonyl hydrazine (PTSH) and the *in situ* generation of a reactive diimine.[13] This method is not selective and results also in the formation of bacteriochlorins, which can be re-oxidized subsequently under mild reaction conditions with *p*-chloranil to dihydrochlorins (Scheme 4).



Scheme 4. Reduction of TPP to a dihydrochlorin according to WHITLOCK.[13]

Dihydrochlorins are lacking in stability and tend to undergo several types of re-oxidations to porphyrins or hydroxychlorins in the presence of oxygen or silica gel in combination with visible light. Additionally, the reduction of unsymmetrical porphyrins affords regioisomeric compound mixtures, non-separable by standard column chromatography as the polarity difference of the isomers is too small to achieve a clean separation. Referring to this, LIU reported a convenient procedure for chlorin synthesis by the regioselective oxidation of bacteriochlorins with an unsymmetrical *meso*-substitution pattern.[14]

The very first report of an osmium(VIII)tetroxide application towards a dihydroxychlorin was described by FISCHER 1940.[15] BRÜCKNER and co-workers reported 1995 the osmium-mediated dihydroxylation of a *meso*-substituted porphyrin.[2b,16] Regarding the mechanism, the *syn*-cycloaddition of OsO_4 with an olefinic tetrapyrrole *β*-*β* bond leads to the formation of an osmate(IV) ester by a cyclic transition state. A subsequent reductive cleavage with hydrogen sulfide liberates the dihydroxylated tetrapyrrole (Scheme 5).



Scheme 5. Preparation of a dihydroxychlorin from TPP according to BRÜCKNER.[16]

The use of OsO_4 has become established and led to several reports on dihydroxylation of porphyrins and also porphyrin-*N*-oxides with a broad variety of *meso*-substituents.[12b,16,17] In contrast to dihydrochlorins, their dihydroxy-analogs possess a higher stability at the oxidized *β*-pyrrole positions. However, a pinakol-pinakolon type rearrangement may still occur under strong acidic reaction conditions, leading to ketochlorins[18] which hold a solvent-dependent equilibrium with their hydroxy-porphyrin tautomers[19].

1.1.2 *Corroles*

Corroles are an important class of tetrapyrrolic macrocycles closely related to porphyrins, both of which are characterized by 18 π-electrons in conjugation with the main exception of a contracted skeleton by a direct pyrrole-pyrrole bond, three *meso*-bridging carbons and three *N*-pyrrolic protons. In contrast to porphyrins, corroles are characterized by C_{2v} symmetry with a nonplanar skeleton (Figure 3). The inner NH-protons exhibit a higher acidity due to steric hindrance which leads to an orientation slightly out of the plane. Regarding their photophysical properties, corroles possess a characteristic absorbance with a sharp SORET band around 400 nm and Q-bands in the range between 500 to 600 nm.

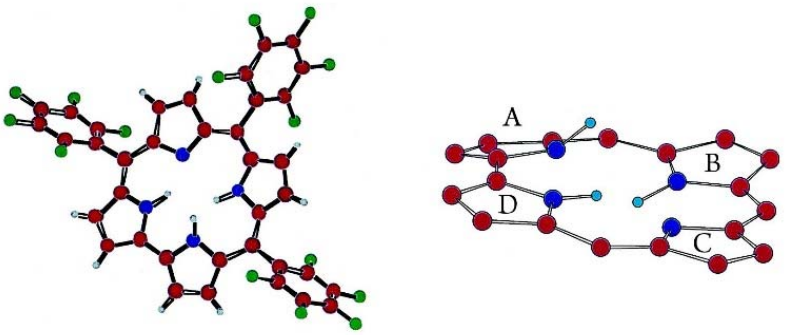


Figure 3. Crystallographic structure of triphenylcorrole (TpFPC-H_3) by GROSS.[20]

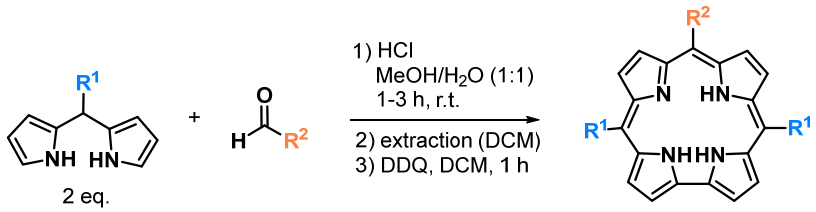
The chemistry and first report of these "unusual" macrocycles dates back to the early 1960's with first attempts towards artificial vitamin B_{12} analogs.[21] Regarding their coordination chemistry, corroles act after full deprotonation as tetradentate trianionic ligands, allowing the stabilization of metal anions in high oxidation states such as iron(IV), cobalt(IV) and cobalt(V).[22] The coordination is not restricted to transition metals as several examples with main group elements[23] and lanthanides[24] as well as actinides[25] were reported. The conformational contraction by the direct pyrrole-pyrrole linkage results also in a narrower inner cavity and coordination of several metals partly out of the plane.

While corroles as well as porphyrins share similar electronic properties, they diverge in regard to the peripheral reactivity even in straightforward functionalization reactions and stability, e.g. the *meso*-positions which are more prone to undergo oxidation due to the higher electron density of the macrocycle.[20,26] Strong electron withdrawing substituents, e.g. pentafluorophenyl groups, can stabilize the electron density with the overall result of a more stable macrocycle. For example, tris(pentafluorophenyl)corrole is one of the most stable functionalized corroles known, which hardly undergoes degradation. Detailed investigations on the formation of decomposition products and their nature were reported by several groups.[27] Furthermore, corroles often exhibit line broadening in NMR spectroscopy which makes a characterization almost impossible.[28] This is often depending on the *meso*-substituents and their steric hindrance as well as the central metal ion. For example, in the case of copper-complexes, difficulties for NMR characterization arise from a copper-based redox equilibrium between the diamagnetic Cu(III)-corrole complex and its Cu(II) cation radical, depending on temperature and solvent.[29]

Historically, it can be seen from the very limited number of reports on corrole applications that the preparation is more difficult compared to porphyrins, due to severe synthetic obstacles and lack of efficient preparation procedures. JOHNSON and KAY were the first who reported the synthesis of a corrole in 1965 by cyclization of a biladiene.[30]

First approaches to corrole syntheses with a broad variety of substituents were carried out under heterogeneous solid state reactions on silica gel or aluminum oxide[26a,31] and a variation of the ADLER conditions[32] (boiling propionic acid) which also resulted in formation of the corresponding porphyrin. Further improvements, in particular towards *trans*-substituted A_2B-corroles were achieved through the building block approach by use of DPMs and an aldehyde under acid catalysis or 1,9-dicarbinol substituted DPMs and 2,2'-bipyrrol by [2+2]-cycloaddition reactions.[33] Since 1999 several leading groups in tetrapyrrole chemistry e.g. GROSS,[20,26a] PAOLESSE,[28d] and GRYKO[9,34] redraw the attention to corroles by numerous publications on their synthesis, leading to utilization as oxidation[35] and reduction[36] catalysts, sensors[37] and medicinal applications.[38]

A milestone in corrole synthesis was reached by GRYKO and co-workers with the development of a straightforward and convenient method (Scheme 6).[9] Halogenated solvents usually utilized for the condensation reactions were exchanged by a methanol/water (1:1) mixture and the condensation step of an aldehyde with pyrrole or a DPM with an aldehyde was carried out under HCl-catalysis. This approach allowed the preparation of several A_3 and *trans*-AB_2-corroles with key functional groups in the *meso*-periphery with good yield.



Scheme 6. Synthesis of corroles in a water/methanol mixture according to GRYKO and co-workers.[9]

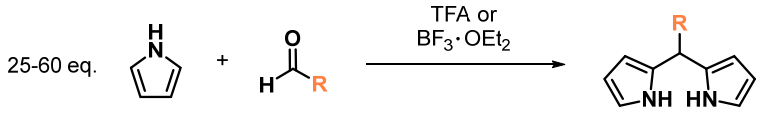
1.1.3 *Dipyrromethanes*

The dipyrromethane compound class is characterized by two pyrrole units with a 1,1-methylene bridging connection and possesses a significant importance in tetrapyrrole chemistry. These bipyrroles are being mostly utilized for a straightforward and selective synthesis of porphyrinoids with a defined *meso*-substitution pattern, e.g. *trans*-A_2B_2-porphyrins, A_2B-corroles, hexaphyrins or calixpyrroles.[39] DPMs are sensitive to light, air and acid exposure and may decompose more or less quickly depending on the nature of the *meso*-substituent. Strong electron-withdrawing groups, e.g. pentafluorophenyl, lead to more stable DPMs as the tendency to undergo an oxidation is reduced at the *meso*-position. Moreover, DPMs carrying an electron-withdrawing substituent in the *meso*-position are more resistant to acid exposure. DPM-research expanded within the last years onto synthesis of BODIPY dyes and other applications in fields such as photonic organic-based materials, optical anion sensors and biological systems.[40]

From a retrosynthetic view, 5'-*meso*-substituted DPMs are accessible by condensation of an aldehyde or ketone with pyrrole under acid catalysis, similar to the preparation of porphyrins. This protocol is often aligned with severe drawbacks due to the competitive formation of side products, such as tripyrranes, *N*-confused dipyrromethanes and higher oligomers.[41] The first synthesis was reported 1974 by ASHLEY through condensation of pyrrole with 4-pyridin-carboxaldehyde.[42] CASIRAGHI described 1992 the preparation of several sugar-derived DPMs by use of an *in situ* generated pyrrole-magnesium salt in the presence of $TiCl_4$.[43] This initiated detailed investigations on the condensation of aldehydes and pyrrole by use of diverse catalysts, e.g. TFA, $BF_3{\cdot}OEt_2$, $SnCl_4$, $InCl_3$ or *p*-TsOH.[39]

Scheme 7. First attempts towards 5'-*meso*-substituted DPMs.[42,43]

A significant step forward for DPM syntheses was achieved by LINDSEY et al. by use of 40 equivalents excess pyrrole to aldehyde without additional solvents (Scheme 8).[44] The condensation of several aromatic and aliphatic aldehydes under TFA acid catalysis afforded 5'-*meso*-DPMs efficiently in yields between 47% and 86% with a minimal formation of oligomers. Since then, several approaches with diverse LEWIS or BRØNSTED acid catalysts, e.g. trifluoroacetic acid,[45] $BF_3{\cdot}OEt_2$[46] or $InCl_3$[47] and variation of the pyrrole to aldehyde ratio were reported, allowing the synthesis of DPMs in gram scale. Other pathways involve a stepwise approach from α-acylpyrroles which enable the synthesis of unsymmetrical DPMs[48] or, addition of pyrrole to terminal alkynes under $In(OTf)_3$[49] catalysis. The mentioned approaches are also suitable for the synthesis of polysubstituted DPMs with functional groups in *α*- and/or *β*-position towards functionalized systems.[50]



Scheme 8. Synthesis of 5'-*meso*-substituted DPMs according to LINDSEY.[44]

1.1.4 *Boron-dipyrrins – or simply BODIPYs*

Boron-dipyrrins are a class of chromophores that absorb light in the visible electromagnetic spectrum and are mostly known by their abbreviation "BODIPYs", derived from the name **bo**ron **dipy**rrin for the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene core. Consisting of two methine bridged pyrrole units with coordination to a boron-difluoride centre, these systems follow the numbering rule in analogy to the tricyclic *s*-indacene which differs from the DPM or dipyrrin skeleton. Similar to porphyrins, the 8-methin bridge – and 5-position of DPMs – is denoted as the *meso*-position (Figure 4).

The rigid framework can also be considered as a monomethine cyanine structure with lacking flexibility, responsible for most of its unique chemical and in particular photophysical properties such as high fluorescence quantum yields, high molar absorption coefficients, low intersystem crossing rates, long lifetime after excitation and high photostability. Their favorable properties resulted in a variety of applications in fields like organic based photonics,[9] biological labelling,[10] OLED-technology,[11] fluorescent probes for cell imaging[12] and artificial photosynthetic systems.[13]

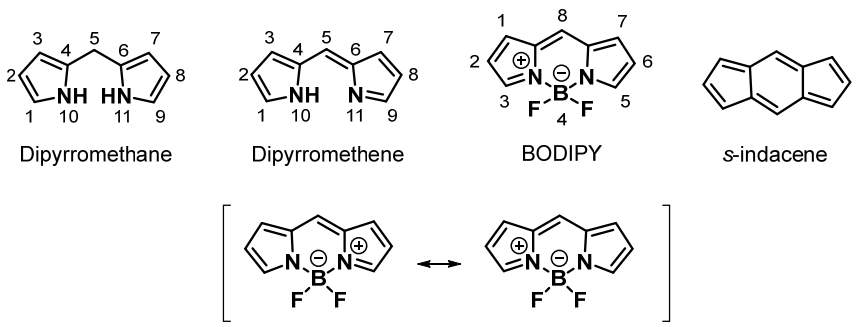
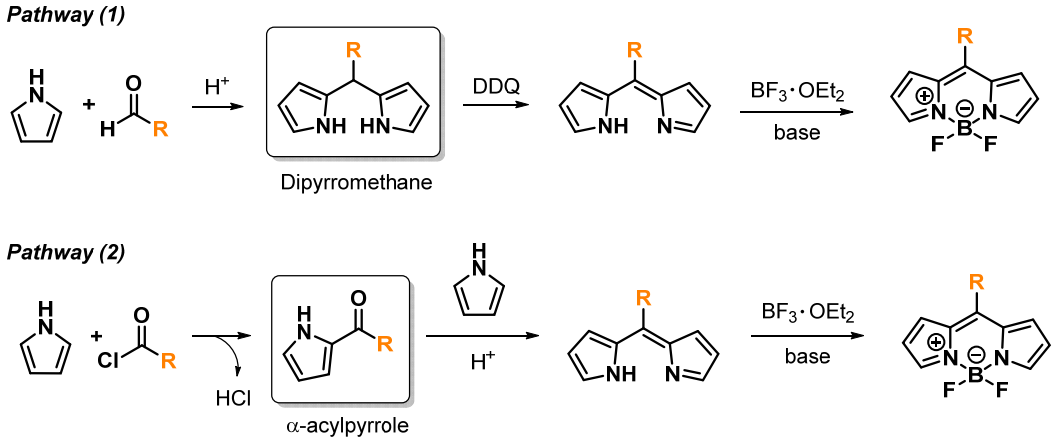


Figure 4. Resonance structures and IUPAC numbering of the BODIPY and DPM framework.

The first report on a BODIPY system dates back to 1968 when TREIBS and KREUZER obtained it during an acylation reaction of 2,4-dimethylpyrrole with acetic anhydride and borontrifluoride catalysis.[8] Generally, an access to BODIPYs can be gained by two pathways: 1) Starting with the preparation of DPM precursors from pyrrole and an aldehyde – as originally developed for the synthesis of tetrapyrroles described above – followed by a subsequent three-step protocol involving oxidation, e.g. with DDQ, to the corresponding dipyrrin and complexation with $BF_3{\cdot}OEt_2$ in the presence of an amine-base;[51] 2) A different route in particular for asymmetric systems is described through preparation of acylpyrroles by condensation of pyrrole with an acid chloride,[52] anhydride[53] or an orthoester[54] which can be condensed further with another pyrrole unit to obtain dipyrrins, followed by subsequent $BF_3{\cdot}OEt$ complexation in the presence of a suitable base (Scheme 9).



Scheme 9. Two different approaches for the synthesis of BODIPY dyes via DPMs (1) or acylpyrroles (2).

Simple BODIPYs without peripheral substituents exhibit sharp, slightly STOKES-shifted absorption and emission bands in the visible light spectrum around 500 nm. Structural modifications at the reactive *a*-pyrrole positions by extension of the delocalized π-electron system results in an absorbance shift to far-red or near-IR regions, which allows a fine-tuning of the optical and electronic properties for desired applications. Several approaches towards such "extended" systems were reported by introduction of vinyl, phenyl or thiophene substituents.[55] Further modifications can be carried out at the *meso*-position: This route bears the advantage of a broad variety of readily available aryl aldehydes which upon condensation with pyrrole result in functional fluorophores and allow post-modifications without an impact on the spectroscopic properties of the BODIPY core. This approach is not restricted to the condensation protocol with aldehydes, as properly functionalized acylpyrroles can also result in *meso*-substituents.[56]

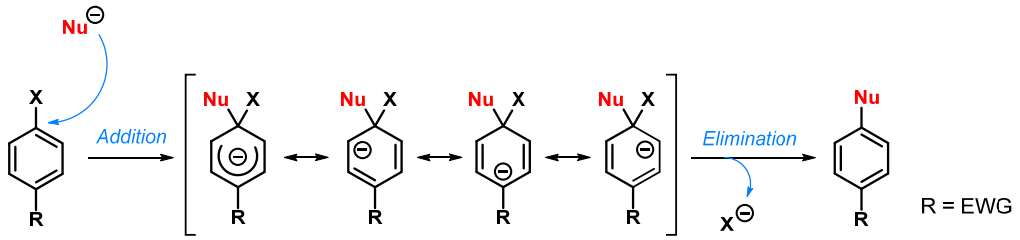
Resent publications were dedicated to modifications of the boron center with hard nucleophiles such as oxygen under LEWIS acidic or basic reaction conditions, e.g. with sodium methoxide in methanol, to afford alkoxylated dyes.[57] ZIESSEL and co-workers investigated the fluorine exchange with carbon nucleophiles extensively by use of GRIGNARD and organolithium reagents to obtain both, aryl- and alkynyl-bora indacenes.[58] Combining such systems with other chromophores, e.g. another indacene, allows the synthesis of donor-acceptor interacting conjugates.

1.1.5 *The Nucleophilic Aromatic Substitution*

Aryl systems are known to undergo diverse transformations depending on their substituents, which determine their reactivity to a high extent. Substitution reactions with electrophiles (S_EAr) are well-established due to the electronic nature of the aryl core with a general high electron density, allowing the attack of electron-deficient species by the two-stage *addition-elimination* mechanism.[59] The efficiency becomes higher and the reaction kinetics faster as the electron donating properties of the substituents, the overall electron density of the aryl system and the electrophilicity of the reaction partner increase.

Therefore, nucleophilic substitutions (S_NAr) are in contrast to S_EAr reactions less common and require highly electron-deficient systems which allow the attack of nucleophiles. This electron deficient state can be achieved by functional groups with a negative inductive effect (-I), e.g. halogen atoms, or a negative mesomeric effect (-M), e.g. nitro, cyano or sulfonyl. Most of these substituents exhibit both effects in combination with a preponderance for the M-effect.

Another requirement for a successful substitution is that the additional electrons resulting from the *addition* step are able to be "taken up" by anion stabilizing groups, e.g. nitro-substituents (simplified as R in Scheme 10). Typical nucleophiles utilized for S_NAr reactions can be cyanide, oxygen or nitrogen centered nucleophiles while good leaving groups are halogen atoms, in particular fluorine.



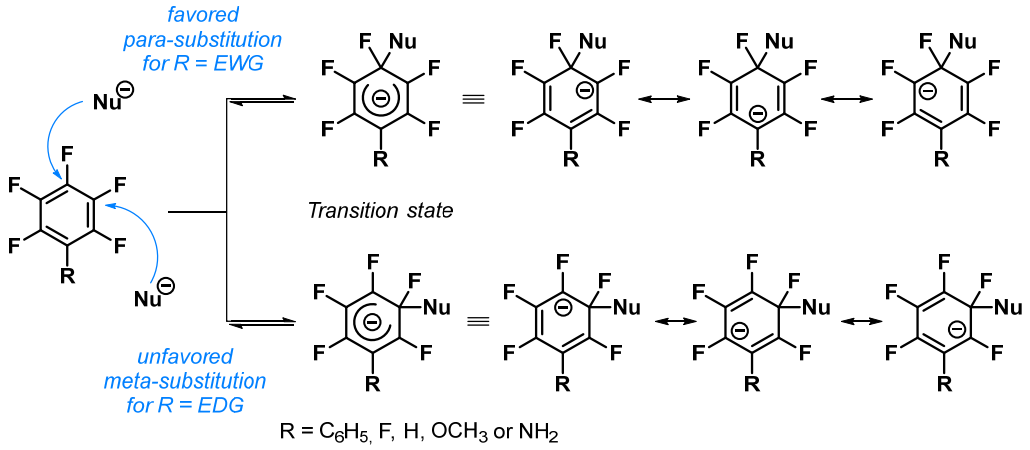
Scheme 10. The generally established reaction mechanism for a nucleophilic aromatic substitution.

S_NAr reactions involving fluorine generally proceed faster, although fluorine itself is a bad leaving group due to the very strong C-F bond. The rate determining step for the overall reaction is the *addition* in which fluorine accelerates this step by its strong inductive effect. This acceleration is observed dramatically on aryl systems with several fluorine atoms, in which case the usually necessary anion stabilizing group becomes dispensable.

The pentafluorophenyl group stands apart from common electron-rich aromatics and is one example for a highly electron-deficient aryl system with a high susceptibility for nucleophilic substitution reactions. Due to this electron deficiency it is impossible to carry out conventional electrophilic substitution reactions. It is assumed, that the electron distribution of the aryl moiety is highly disturbed due to interaction of the p-orbital electrons of the five fluorine atoms with the π-system, leading to an untypical behavior for aromatic systems.[60] The carbon-fluorine bond is characterized by a high polarization due to the strongly diverging electronegativity of the two elements, with a partially negatively charged fluorine and partially positive carbon center.

Since the lack of additional nodal planes in the orbital geometry of the fluorine atoms, no anti-bonding interactions towards the carbon atom occur, in contrast to other halogen atoms e.g. chlorine or bromine. This results in a parallel alignment of the fluorine and its adjacent carbon p-orbitals which can interact perfectly with each other. As result of the strong dipolar state the fluorine atom behaves as an σ-electronegative and as well as a π-electropositive element, due to partial charge transfer from the p-orbitals towards the π-system. This work uses the nucleophilic aromatic substitution reaction on pentafluorophenyl-substituted porphyrinoids. However, it should be mentioned that the free *meso*-positions in the basic porphyrin chromophore (which is usually considered as an electron-rich aromatic system) are also susceptible to nucleophilic aromatic substitution reactions with organolithium reagents, as reported by SENGE and co-workers.[61] K. M. KADISH and co-workers were presumably the first to report on the nucleophilic substitution of pentafluorophenyl-substituted porphyrins with amines, leading to further detailed investigations by diverse groups utilizing thiols[62] or amines[63] and scattered reports with alcohols[64] as nucleophiles. In most cases the fluorine exchange proceeds with a high regioselectivity in the *para*-position.

Recent mechanistic studies based on DFT calculations by PALETA et al. with pentafluorobiphenyl and monosubstituted PFP-moieties explained the strong regioselectivity and suggested a tetrahedral S_N2-type mechanism in contrast to the generally accepted two-stage *addition-elimination* sequence by the MEISENHEIMER-complex (Scheme 11).[65] Regarding the substituent effects of functional groups attached at the pentafluoroaryl, electron-withdrawing groups (EWG), e.g. fluorine, allow a charge stabilization and favor the substitution in *ortho*- and *para*-position with respect to "R". In contrast, electron-donating groups (EDG), e.g. amines, facilitate substitution in *meta*-position. The tetrapyrrole and BODIPY scaffold can be regarded as such an electron-stabilizing group what would explain the regioselective *para*-fluorine exchange described by numerous reports with thiols, amines and alcohols.



Scheme 11. Studied regioselectivity of the S_NAr protocol of PFP-substituted systems by PALETA.[65]

The studies within this thesis demonstrate that porphyrins and corroles can undergo a regioselective *para*-fluorine exchange with alcohols and sodium azide at the PFP-moiety. However, after deprotonation of the inner *N*-pyrrolic positions in consequence to the basic reaction conditions, porphyrins result in a di-anionic and corroles in a tri-anionic intermediate. This reflects also in their reactivity, as the PFP-substitution reactions described in the following proceed slightly better with porphyrin and metalloporphyrins than with corroles.

1.1.6 *Photodynamic Therapy*

Treatment of diseases by phototherapy has been applied since centuries.[66] However, a major breakthrough was reached by the combination of light and drug administration, as used in the photodynamic therapy (PDT). PDT is a mild method towards cancer treatment and other (non-malignant) diseases, the principle being discovered the first time 1899 by RAAB.[67] PDT involves the administration of a photosensitizer (PS), e.g. a porphyrin-based dye, and subsequent exposure of the affected tissue to non-thermal light of the visible light spectrum in the range of 400-750 nm. Many naturally occurring and synthetic PS have been evaluated within the last decades, tetrapyrrole-based dyes, e.g. porphyrins and chlorins, probably being the most intensely studied systems among them.[68]

Photodynamic reactions are divided into two categories. Type I photosensitization processes involve charge transfers (to oxygen or other substrates), whereas type II reactions are based on an energy transfer from the dye onto triplet oxygen.[69] The light exposure induces an excitation of the PS, followed by a transformation of the excited singlet state of the PS into a long-lived triplet state – which is the case for tetrapyrroles – which interacts with the triplet oxygen present in all cells eventually resulting in excitation of this intercellular oxygen into the reactive singlet state or in charge transfer reactions to triplet oxygen or other substrates (Figure 5). These highly reactive species exhibit short lifetimes around 250 ns and are responsible for the eventual cell death induced by apoptosis, with minimal destruction of the healthy surrounding tissue.[70]

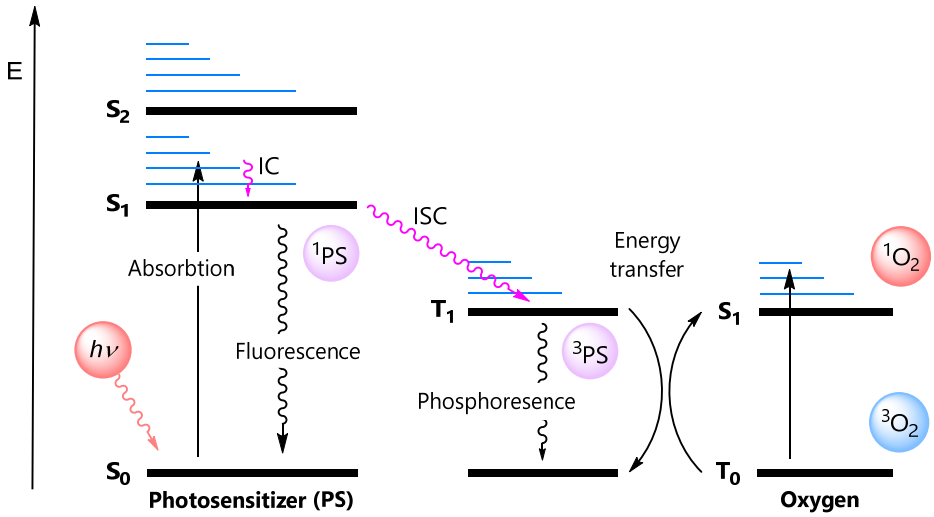


Figure 5. JABLONSKI diagram of the PDT (IC = Internal conversion, ISC = Inter System Crossing).

A simplified mechanism of the occurring type II sensitization process can be described as follows: The photosensitizer is excited from the S_0 ground state into the singlet state S_1 by a linear light absorption followed by subsequent decay, which can take place by either fluorescence emission back into the S_0 ground state or intersystem crossing, a spontaneous electron spin inversion to its T_1 triplet state. Further relaxation from the long-lived T_1 state results in either phosphorescence (back to S_0) or in an energy transfer (Type II reaction) onto oxygen in its T_0 triplet ground state. Singlet oxygen is formed by excitation from T_0 to S_1 triplet state.

In addition, the T_1 triplet state can induce type I reactions resulting in charged, either anionic or cationic radical species. The relative contribution of both, type I and type II processes highly depends on the local oxygen concentration around the PS,[69-71] while its cellular distribution and consequently, its efficiency is determined by the lipophilic and hydrophilic characteristics of the PS.

The efficiency of applied photosensitizers depends on several properties. In order to reach deeper tissue regions and to treat more expanded tumors, a strong absorption in wavelength region around 650-700 nm is desirable. Unfortunately, most of the currently applied porphyrin-based photosensitizers lack efficiency as their absorbance maximum (the absorption band with the highest extinction coefficient) lies around 450-500 nm far from the desired red region of the visible light spectrum. In contrast to porphyrins, chlorins and even more bacteriochlorins possess a more intense absorption in the red to near-infrared region of the electromagnetic spectrum, what predestines these compound classes for photodynamic applications. Additional prerequisites for an optimal photosensitizer in PDT are a good solubility in polar media, a high toxicity in combination with light excitation (but a low dark toxicity), a high quantum yield for singlet oxygen generation and probably most importantly a high selectivity in the (passive) targeting of cancer tissue.

Since the first generation of photosensitizers, most prominent among them an oligomeric mixture of haematoporphyrin, merchandised since 1993 as "Photofrin", remarkable improvements have been achieved. The second generation of photosensitizers comprises well-defined structures. One of these second generation photosensitizers is Temoporfin commercially known as Foscan® depicted in Figure 6. This second generation PS is based on the chlorin macrocycle scaffold and possesses the desirable properties of more intense red light absorption at 650 nm, increased solubility in polar solvents and a four- to six-fold higher efficiency compared to Photofrin.[72]

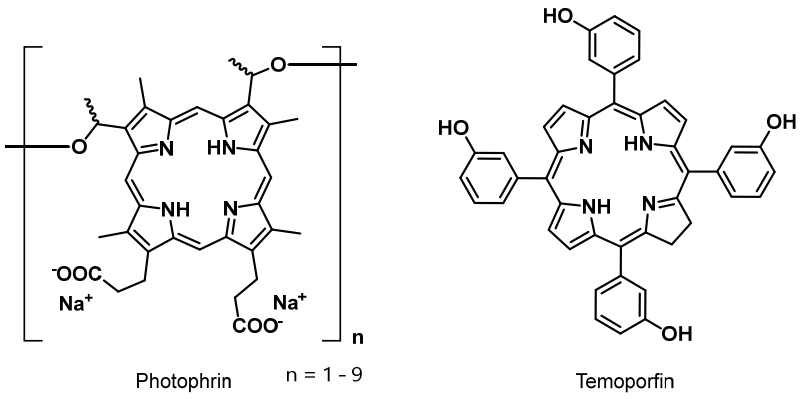


Figure 6. Structures of Photofrin and Temoporfin.

In the current research focus are also porphyrins with the AB_3-type *meso*-substitution pattern. This approach allows the synthesis of amphiphilic systems by functionalization of only one reactive site for example, while keeping the residual macrocyclic periphery fixed. Such AB_3-systems can subsequently be transformed into their chlorin analogs, sometimes without the formation of isomers (see below), which is an important factor in regarding industrial scale synthesis and cost efficiency.

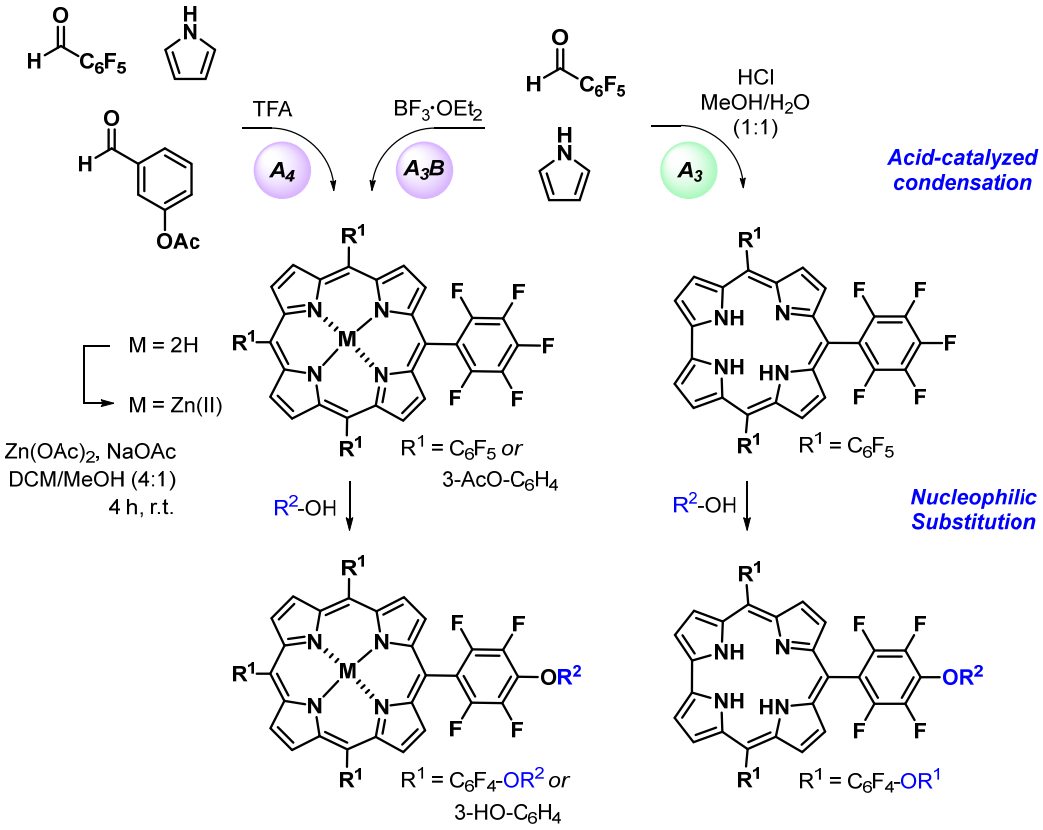
The lack of selective tumor targeting is an obstacle all accredited photosensitizers share in common. Selectivity plays an important role to prevent side-effects which come along with photodynamic treatments, photosensitivity for example, which is caused by the undesired distribution of applied photosensitizers in healthy skin. Several approaches with promising results towards higher selectivity and tumor to normal cell differentiation for cancer tissue are under development, e.g. synthesis and evaluation of glyco-porphyrins[12b,73] or conjugates between porphyrins and cyclodextrins[64e,74] (oligosaccharides in cyclic arrangement). As tumors usually exhibit an increased metabolism, the utilization of carbohydrates as carrier molecules can significantly enrich the PS at the target site and increase the effectiveness of PDT.

Further advances were achieved with multicomponent photosensitizers such as PPF – a conjugate composed of a multifunctional porphyrin, folate moiety and a peptide linker in-between – which allow the selective targeting of folate receptors (FR).[75] While healthy tissue has a small expression of FR, several human cancer types, e.g. breast, colon, brain or lung cancer, exhibit an FR overexpression. Another benefit for small molecules like folate, is their ability to bypass the immune response. The development of PS with antibody fragments attached for targeting had striking drawbacks in this regard.[76] To achieve a minimum level of side effects future developments will be directed towards photosensitizers with high efficiency, high selectivity and reduced dark toxicity.

1.2 *Aim of the Work*

Since fluoro-substituted porphyrinoids are gaining growing interest in diverse fields e.g. biomedical applications, material science or artificial light harvesting, their synthesis and functionalization experiences rising importance. The pentafluorophenyl (PFP) group is one example, whose peripheral introduction into porphyrinoids and their substructural DPM building blocks can be carried out by classic condensation chemistry starting with pentafluorobenzaldehyde (PFBA) and pyrrole under acid catalysis. Due to the highly electron deficient aryl system, the PFP substituent is prone to undergo nucleophilic substitution reactions (S_NAr) which in addition proceed highly regioselective. This approach underwent diverse explorations involving mainly thiols and amines but more recently has also been expanded to alcohols in combination with suitable bases. Moreover, only few examples of PFP-functionalization with alcohols are known, often involving harsh reaction conditions unsuitable for sensitive functional groups, while the reported protocols lack detailed investigations and a general applicability to diverse systems.

Therefore one of the main objectives of this thesis was the development of an optimized and convenient synthetic approach towards alkoxy-functionalized porphyrins, their Zn(II)-metal complexes and corroles by the S_NAr protocol. Interesting key functional groups can be introduced by suitable alcohols and additionally, sodium azide into the *meso*-periphery for advanced modifications and lead to novel applications. As model substrates A_4- and AB_3-porphyrins as well as PFP-corrole with A_3-substitution pattern were chosen.

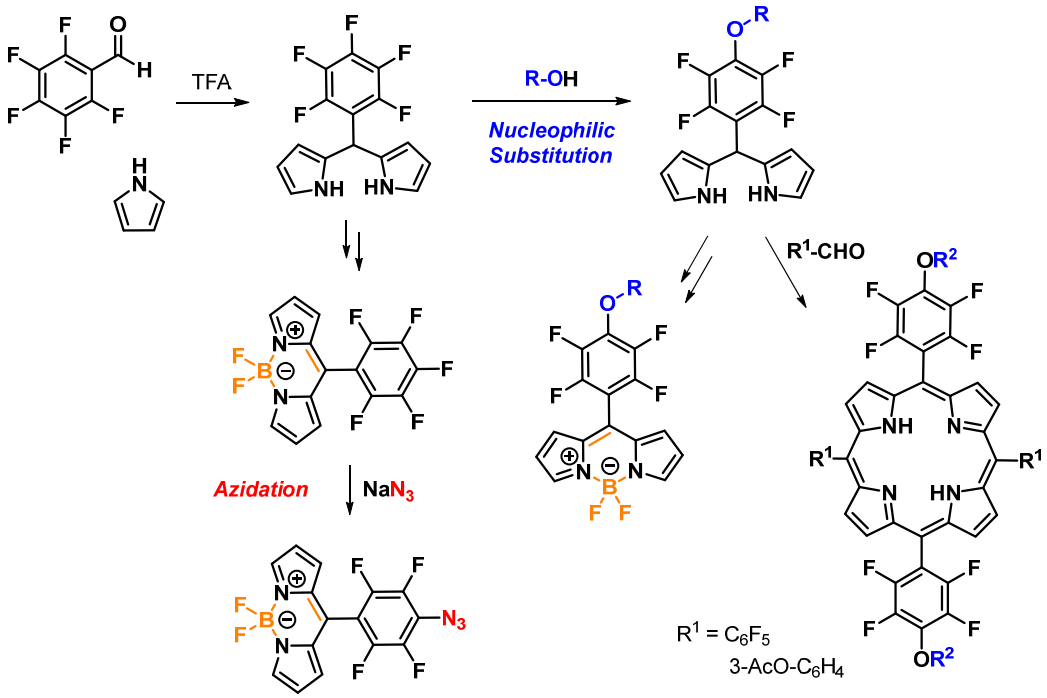


Scheme 12. Synthesis of PFP-substituted tetrapyrroles and functionalization with alcohols by S_NAr.

Photodynamic therapy (PDT) is one of the leading fields regarding medical application of tetrapyrroles. The photosensitizers applied in this method of cancer treatment require several properties, hydrophilicity being one important requirement among them. Hence, one subproject of this thesis was dedicated to the rational design of porphyrins with an AB_3 *meso*-substitution pattern and a structural resemblance to Temoporfin – a PS applied in clinical PDT – with several functionalized alcohols to obtain amphiphilic and hydrophilic porphyrins. Furthermore, selected examples were transformed by selective reduction or oxidation of the macrocycle into the analogous chlorins and dihydroxychlorins, respectively. The suitability of these porphyrins and chlorins for PDT was explored by standardized tests against several cancer cell lines.

The preparation of functionalized DPMs is another objective of the present work, in particular regarding the construction of porphyrinoids with a strongly defined *meso*-substitution pattern. This building-block approach utilizing DPMs, pre-determines the position of the *meso*-substituents and allows a selective synthesis of *trans*-substituted systems.

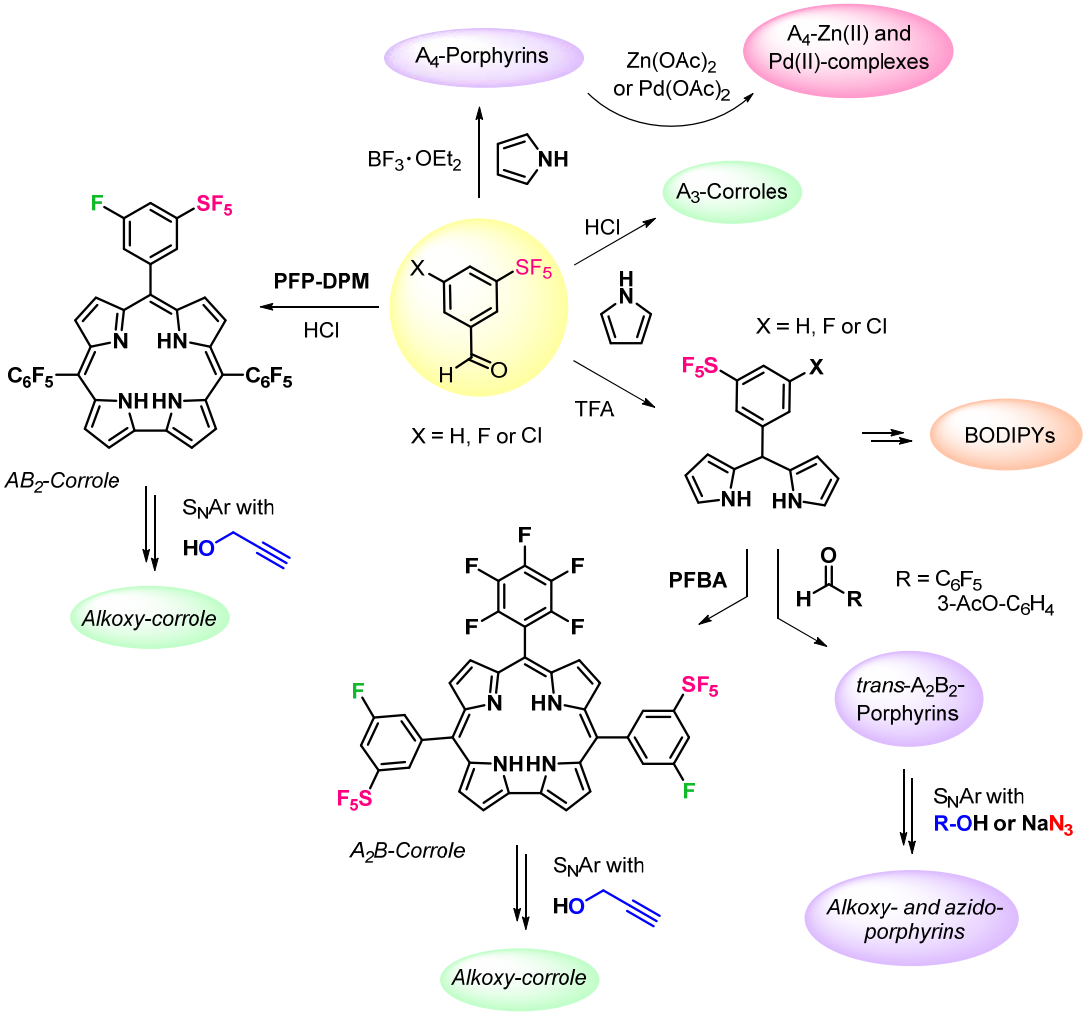
Though a functionalization of PFP-substituted tetrapyrroles can be carried out directly with the macrocycles, attached sensitive groups at other positions may undergo decomposition or cleavage – in case of protecting groups – under the basic reaction conditions applied. Furthermore, the selective functionalization of a single PFP-substituent in a multiply-substituted macrocycle is challenging and mostly results in product mixtures or low yields. Therefore, the S_NAr protocol should be expanded onto pentafluorophenyl-dipyrromethane (PFP-DPM) and the ability towards functionalization be explored systematically, as a pre-modification of PFP-DPM offers high potential towards a selective and stepwise approach to highly functionalized tetrapyrroles.



Scheme 13. Entry to functionalized DPMs, BODIPYs and *trans*-A_2B_2-porphyrins by S_NAr on PFP-DPM.

Another objective involves the exploration of novel porphyrinoids, BODIPYs and their DPM precursors with SF_5 groups, as this remarkable substituent provides unique features e.g. high lipophilicity, chemical resistance and bulkiness, interesting for the construction of highly lipophilic or amphiphilic tetrapyrroles. Readily available SF_5-substituted aryl-aldehydes allow a straightforward approach using classic condensation reactions with pyrrole – to obtain DPMs, A_4-porphyrins and A_3-corroles – or a DPM to obtain AB_2-coroles (For this project "A" equals to the SF_5-aryl moiety).

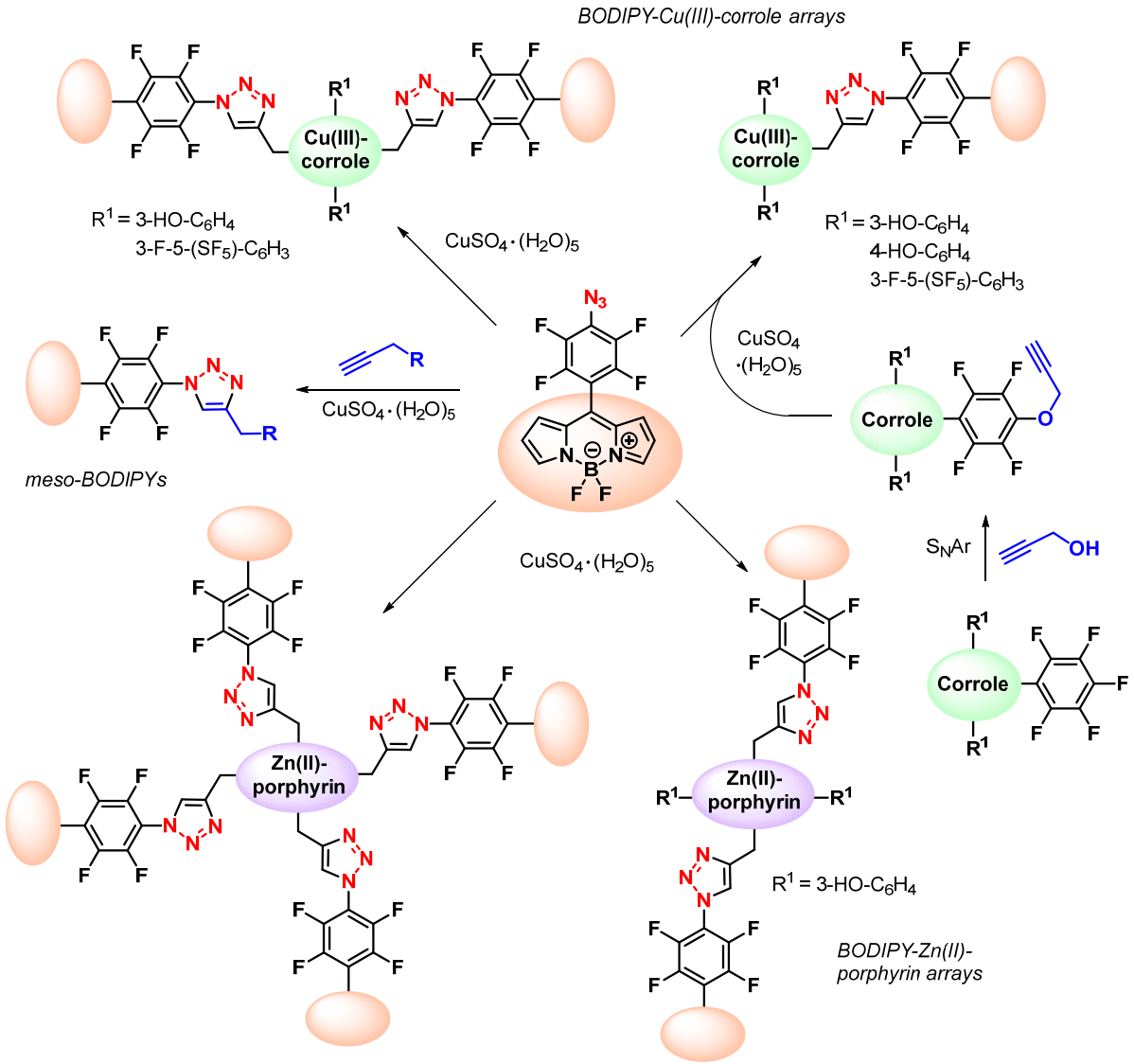
As this type of substituent in combination with tetrapyrrole chemistry is unknown to date, a systematic analysis under variation of the acid catalyst is essential. To open the door for new metallo-porphyrin catalysts, the synthesized macrocycles can undergo a metal-insertion e.g. with palladium(II)- and zinc(II)acetate. Furthermore, the corresponding DPM precursors can be utilized in two pathways: Condensation reactions with aryl aldehydes for the selective construction of *trans*-substituted porphyrins or A_2B-corroles with the possibility of advanced modifications and a direct oxidation of the DPM scaffold to BODIPYs. Systems with a mixed substitution pattern involving PFP-groups are prone to undergo nucleophilic substitution reactions. These should be explored by several selected examples with alcohols and sodium azide to evaluate the S_NAr protocol for these systems.



Scheme 14. Approach towards synthesis and modification of SF_5-substituted porphyrinoid systems.

The last objective of this thesis involves investigations on copper(I)-catalyzed 1,3-dipolar cycloaddition reactions for further transformations of functionalized porphyrins, corroles and BODIPYs as a rational approach to novel multichromophore-based BODIPY-tetrapyrrole arrays. Beside the modification of PFP-substituted systems with alcohols, a direct azidation of the PFP group with sodium azide results in azido-functionalized tetrapyrroles and in addition, the analogous azido-BODIPY, serving as the 1,3-dipole counterpart for azide-alkyne click reactions.

The aim was to investigate the behavior of this azido-BODIPY in copper(I)-catalyzed reactions first by conjugation with functionalized alkynes and then extending the scope to alkynyl-substituted tetrapyrroles obtained by the methods given in the first three objectives of this thesis. Such porphyrins and corroles with a mixed substitution pattern can be obtained by the S_NAr protocol with propargyl alcohol and undergo a subsequent coupling reaction with the azido-functionalized BODIPY to construct 1,2,3-triazole-linked arrays with peripheral lipophilic and hydrophilic substituents at the tetrapyrrole for e.g. artificial light harvesting compounds or catalytic applications.



Scheme 15. Entry to 1,2,3-triazole-linked *meso*-BODIPYs and BODIPY-tetrapyrrole arrays.

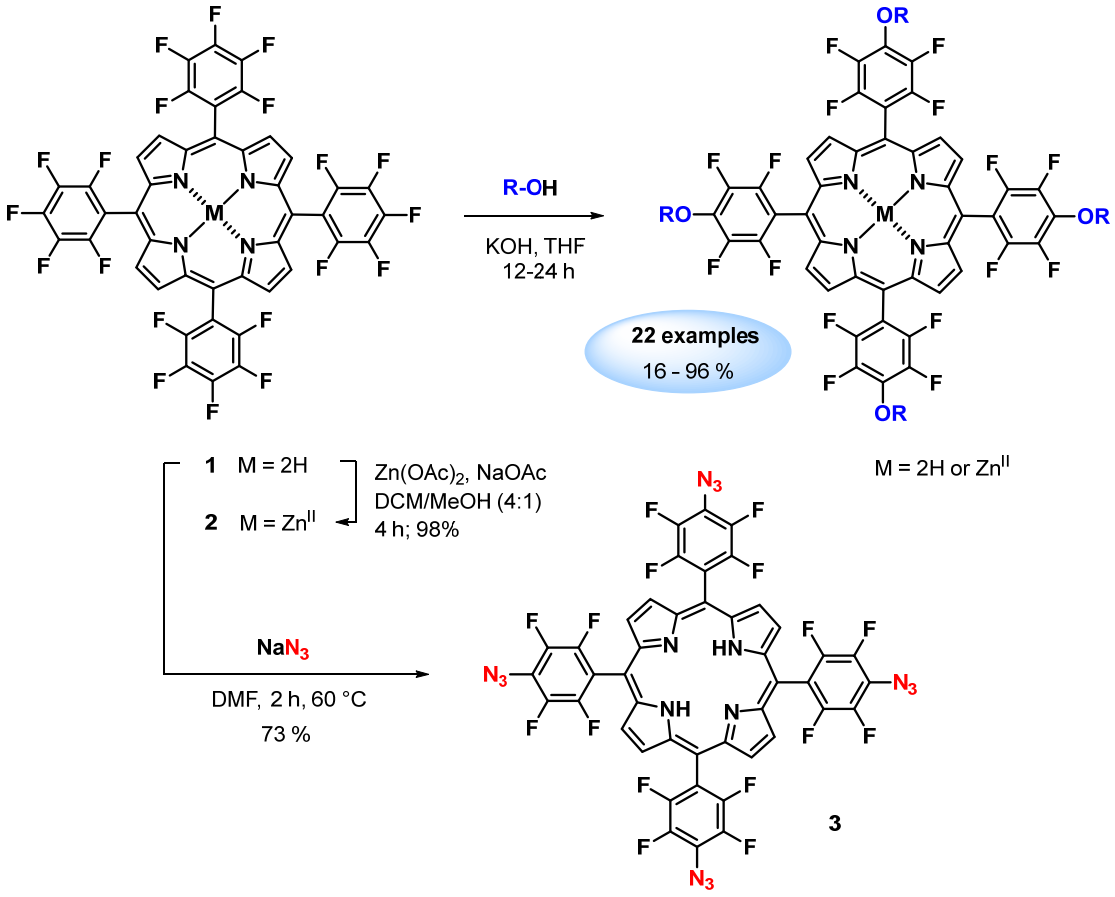
1.3 *Summary of Publications*

1.3.1 *Synthesis of Alkoxy-Functionalized Porphyrins*

The functionalization of tetrapyrrolic macrocycles is one of the main requirements for their utilization, since every field of application needs a minimum of one specific key functional group. Through the classic condensation reaction between pyrrole or DPMs with aldehydes, such functional groups can in principle be introduced during the tetrapyrrole synthesis. The presence of sensitive groups on any of the deployed substrates may result in its decomposition or side reactions due to the acidic reaction medium which is necessary for the macrocycle formation. Hence, generally applicable methods towards the introduction of a broad variety of functional groups are highly desirable. In this regard, the pentafluorophenyl (PFP) group was extensively investigated because of its particular property to undergo a highly regioselective nucleophilic aromatic substitution reaction if treated with appropriate nucleophiles, e.g. thiols, amines or alcohols. While the field of PFP-substituted tetrapyrroles and their peripheral functionalization has already been explored within the last decades, only few scattered reports describe the use of alcohols as nucleophilic precursors with a lack of systematic studies. Therefore, with the intention to expand the diversity of functionalization of the PFP moiety, a method was developed, which allows the convenient introduction of versatile functional groups onto the PFP peripheral moiety of several porphyrins, their Zn(II)-metal complexes and corroles, utilizing in-situ generated alkoxides under basic reaction conditions.

The first project initiated with an optimization study, utilizing tetrakis(pentafluorophenyl)porphyrin (TpFPP) towards an efficient tetra-*meso*-alkoxy functionalization. TpFPP was obtained via the typical condensation of pentafluorobenzaldehyde (PFBA) with pyrrole and reacted with a selected set of simple alcohols e.g. methanol and 2-propanol, under basic reaction conditions under variation of the base. Optimal reaction conditions were established with KOH in THF or DMSO leading to high yields of the corresponding products without a significant side-product formation, e.g. an OH-attack or over-reaction at the PFP-substituent as observed with extended reaction times, demonstrating the efficiency and regioselectivity of the S_NAr protocol.

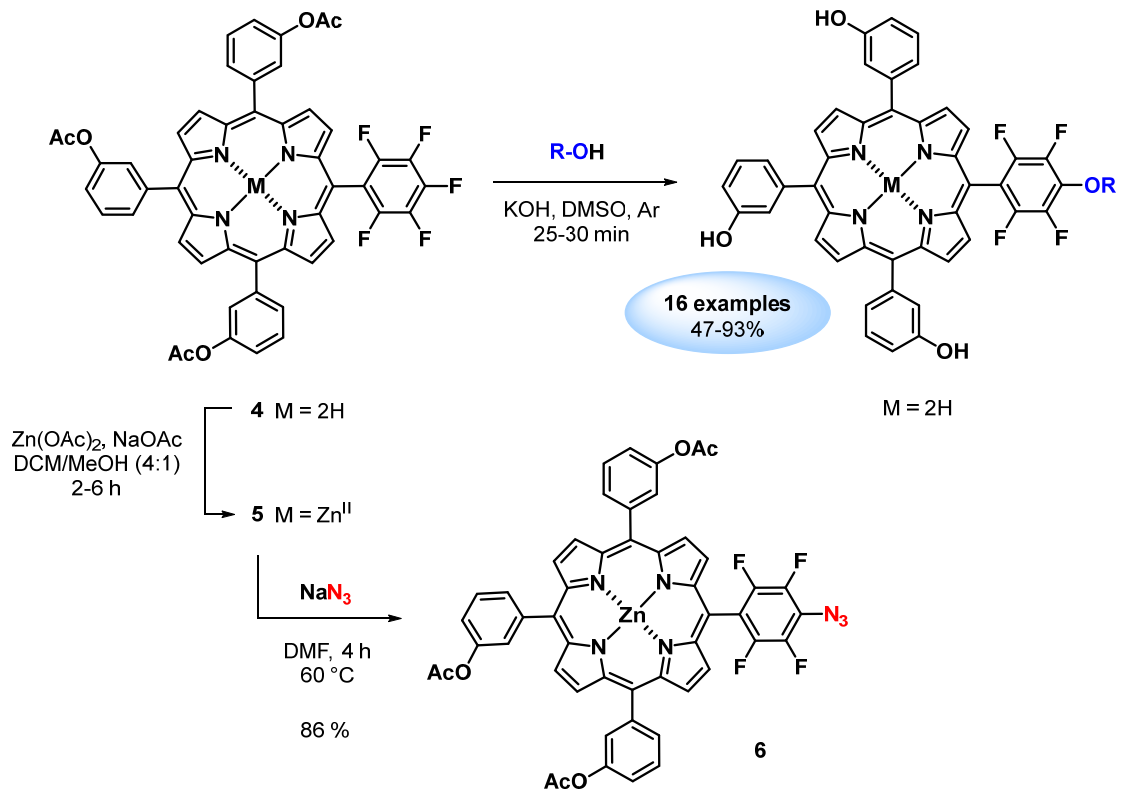
A broad variety of simple alcohols as well as alcohols with additional functional groups, e.g. a terminal alkyne, an alkene, free OH groups or steroids could be employed to construct *meso*-substituted A_4-porphyrins. In an additional set of experiments the S_NAr reaction between TpFPP-Zn(II) and corroles with alkoxides was examined, whereby transformations with the zinc(II)-complex afforded shorter reaction times and higher product yields in comparison with the free base porphyrin (Scheme 16).



Scheme 16. S_NAr reaction of TpFPP **1** or TpFPP-Zn(II) complex **2** with various alcohols.

To expand the diversity of the developed method, A_3B porphyrins with suitable protective groups were investigated to obtain multi-functionalized polar systems with a substitution pattern similar to Temoporfin, a chlorin based photosensitizer applied for PDT. In this subproject the use of DMSO for the nucleophilic substitution of 3-acetoxy-substituted porphyrin **4** proved to be beneficial with respect to product yield and in particular, reaction time which was drastically reduced down to 25–30 minutes for a full conversion in comparison to 24–48 hours in THF, mainly used for the functionalization of A_4-porphyrins.

The substitution reaction with diols offered a selective transformation to the desired monomeric species, although the second free hydroxyl group may have reacted in a side reaction with another PFP-porphyrin to form a dimer. This formation was, however, intentionally achieved with one of the substrates by selective reaction of the alkoxy-functionalized porphyrin with its non-functionalized PFP-substrate giving access to an ether-linked porphyrin dimer.



Scheme 17. Synthetic approach to polar, functionalized AB_3-porphyrins via a two-step-one-pot procedure with alcohols and synthesis of an azido-substituted derivative **6** with NaN_3.

A direct azidation of the two selected PFP-porphyrins **1** and **5** with sodium azide afforded in a clean transformation the azido-porphyrins **3** and **6**, respectively, expanding the scope for further functionalizations (Scheme 16 and 17). The exploration of such follow-up transformations at the already introduced functional sites allowed the synthesis of a 1,2,3-triazole-linked porphyrin dimer through copper(I)-mediated cycloaddition between a terminal alkynyl- and an azido-functionalized AB_3-porphyrin system.

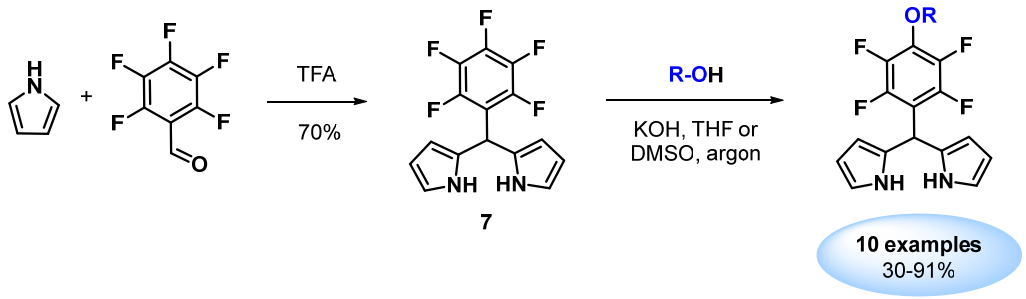
In summary, this project presents the development of a systematic investigation of various alcohols and bases in two different solvents (DMSO and THF) towards the functionalization of tetrapyrroles leading to optimized reaction conditions. This investigation afforded the synthesis of over 50 new *meso*-alkoxy- and azido-functionalized A_4- and AB_3-porphyrins, selected zinc(II)-metal complexes and several corroles with a broad variety of substituents in moderate to high yields via the regioselective substitution reaction of the *para*-fluorine atom. The extensively investigated S_NAr reaction applied on several PFP-substituted tetrapyrroles outlines the high value of this protocol through a convenient procedure with general applicability. Beside the option of diverse additional transformations via the introduced functional groups in the *meso*-position, these compounds have potential applications in e.g. photomedicine, fluorous-phase synthesis or material sciences. An example for this is our patent application on new photosensitizer structures which also resulted from these investigations (see publication list).

1.3.2 *Synthesis of Alkoxy-Functionalized Dipyrromethanes*

Since the investigated S_NAr protocol with alkoxides worked well and with high yields on different PFP-porphyrins and corroles, leading to a broad variety of functionalized tetrapyrroles, we intended to explore this reaction type on PFP-dipyrromethane, aiming the preparation of pre-functionalized DPM building blocks for applications in porphyrinoid design.

In general, DPMs are of high interest particularly for porphyrinoid chemistry, as they are being used in building blocks approaches towards the selective synthesis of mixed *meso*-substituted systems, e.g. A_2B_2-porphyrin, AB_2-corrole, A_3B_3-hexaphyrin or calixpyrrole macrocycles. DPM modifications have been described for the *α*- or *β*-pyrrole position, however, substituents in the *meso*-position are nearly exclusively introduced during the formation of DPMs from the respective aldehyde and pyrrole, whereas its *meso*-functionalization having remained mostly unexplored.

In this regard, the functionalization of PFP-DPM **7** with suitable functional groups seems beneficial, as the resulting compounds allow the subsequent synthesis of specific macrocycles. The TFA-mediated condensation of pyrrole and PFBA afforded PFP-DPM **7** on a gram scale. With sufficient starting material in hand, the S_NAr protocol was applied with a variety of alcohols resulting in various alkoxy-functionalized DPMs, demonstrating the first modification of PFP-DPM via this route (Scheme 18).



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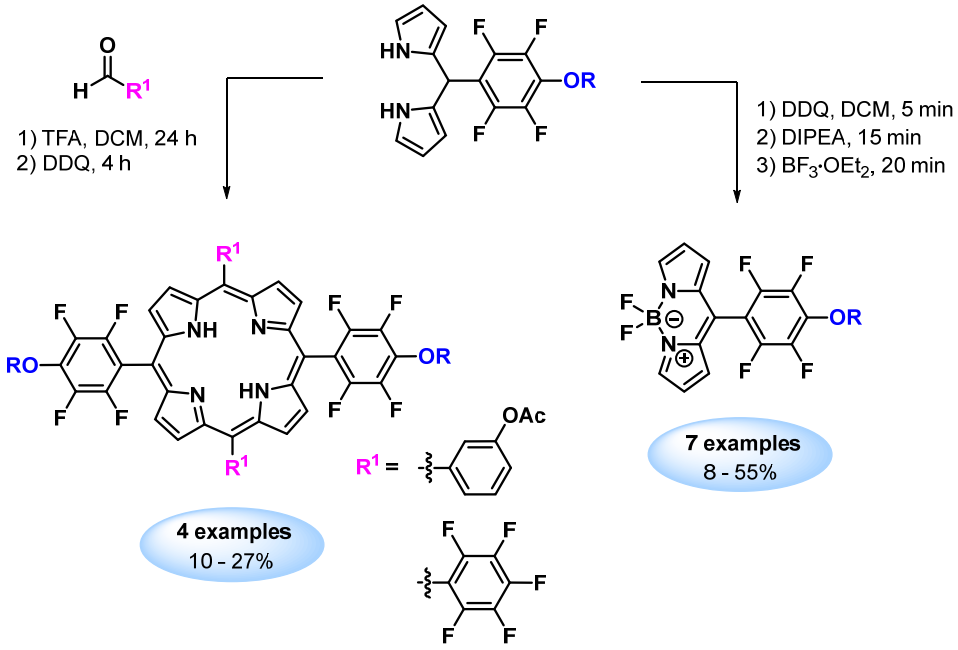
Scheme 18. Preparation of PFP-DPM **7** and subsequent modification via S_NAr reaction with alcohols.

It is noteworthy to mention that for some alcohols (e.g. with allyl alcohol) the reaction progress for the functionalization is difficult to monitor via TLC as product and substrate share very similar solubility and adsorption behavior. In general, the transformations were carried out with KOH and mostly in THF overnight, as these reaction conditions resulted in the highest yields. In contrast, the reaction with 2-butyne-1,4-diol possess one exception with better results in DMSO, probably due to a higher solubility of the alkoxide.

The intention was then to explore subsequent modifications with the obtained alkoxy-functionalized DPMs. Only one leap away from the DPM scaffold are BODIPY dyes, which hold remarkable chemical and optical properties, their research having attracted a lot of attention within the last decades, allowing their preparation in a three-step one pot procedure (see chapter 1.1.4) starting with DPM building blocks.

Following this procedure seven new *meso*-substituted BODIPYs were successfully synthesized. Due to the strong Lewis acidity of $BF_3{\cdot}OEt_2$ (used for the boron complexation step), one example with an attached 1,3-dioxolane scaffold underwent a simultaneous deprotection under formation of a free diol group (Scheme 19).

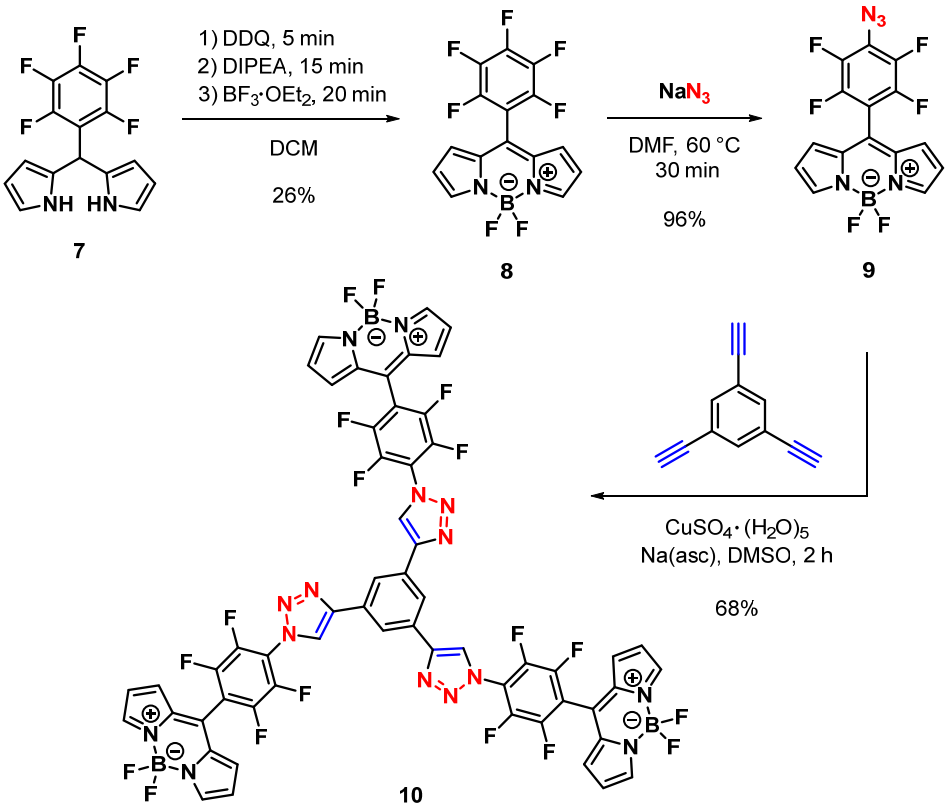
In order to prepare more complex tetrapyrroles with a mixed *meso*-substitution pattern, several alkoxy-functionalized DPMs were selected as key building blocks, since these pre-define the orientation of the *meso*-substituents in the tetrapyrrole, promoting regiospecifically pure products. The acid-catalyzed condensation with PFBA or 3-acetoxybenzaldehyde as model substrates, afforded *trans*-A_2B_2-porphyrins in typical yields (Scheme 19).



Scheme 19. Transformation of alkoxy-functionalized DPMs into BODIPYs and *trans*-A_2B_2-porphyrins via condensation with aryl aldehydes.

In addition, a direct azidation of the PFP-substituent in accordance with previously described porphyrins in the first project in chapter 1.3.1 was aimed with the intention to increase the diversity of functional sites. The test reaction to introduce the azido-group into PFP-DPM **7** employing the reaction conditions used for porphyrin azidation failed unexpectedly, leaving the unreacted substrate behind. We than applied this method to PFP-BODIPY **8**, resulting in a nearly quantitative transformation to azido-BODIPY **9** (Scheme 20), which can serve as a building block for e.g. 1,3-dipolar cycloaddition reactions with terminal alkynes to afford either functionalized BODIPYs with 1,2,3-triazole linkers or conjugates of the bora-indacene dye with other compounds.

One follow-up transformation was exemplified with the copper(I)-mediated 1,3-dipolar cycloaddition of **9** with tri(ethynyl)benzene, resulting in a trimeric BODIPY chromophore after 2 hours, illustrating the potential for the synthesis of dye conjugates (Scheme 20).



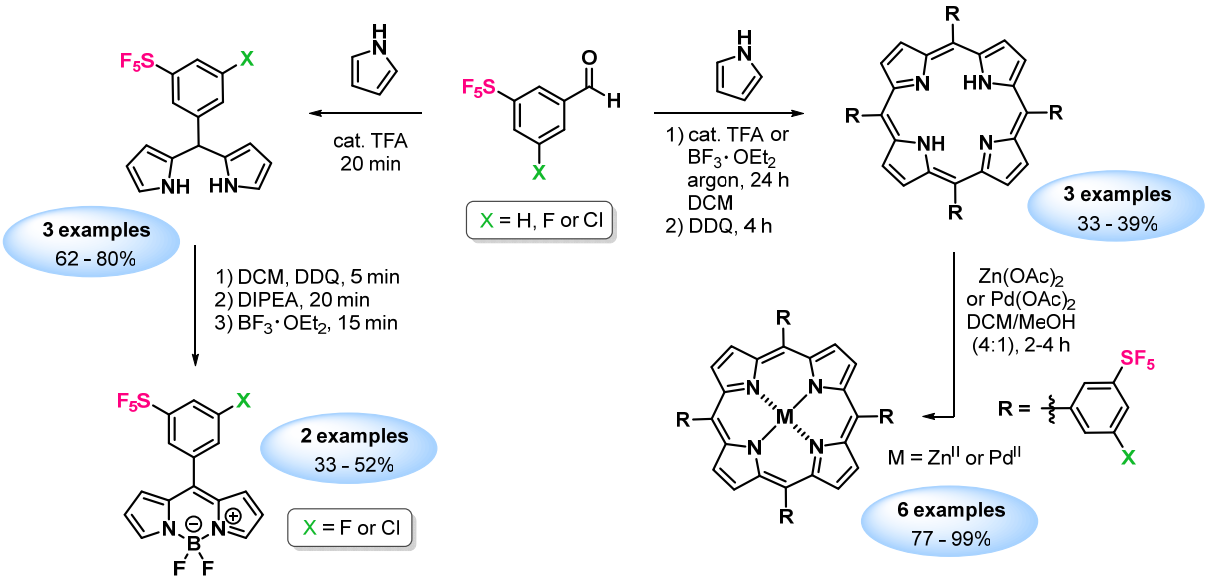
Scheme 20. Preparation of PFP-BODIPY **8**, its direct azidation with NaN_3 to azido-BODIPY **9** and the triple azide-alkyne 1,3-dipolar cycloaddition with BODIPY **10**.

In summary, this project represents the first modification of the PFP-DPM **7** building block with alcohols via the nucleophilic substitution reaction towards a selective early-stage functionalization of tetrapyrroles and BODIPYs. The obtained alkoxy-substituted DPMs were applied for two subsequent transformation reactions: DDQ-oxidation followed by boron-complexation affording *meso*-substituted BODIPYs and acid-catalyzed condensations with aromatic aldehydes, affording porphyrins with a strongly defined *trans*-A_2B_2-substitution pattern. This approach renders these alkoxy-substituted DPMs as valuable building blocks for the synthesis of diverse porphyrinoids.

1.3.3 *Synthesis of SF_5-Substituted Dipyrromethanes and Tetrapyrroles*

The pentafluorothio or simply SF_5 group is a remarkable motif with unique properties first explored by SHEPPARD in 1962.[77] Research in SF_5 chemistry expanded within the last decades leading to many aromatic SF_5-substituted compounds and several applications, e.g. in agricultural or biochemical fields. The highly lipophilic nature, chemical resistance and strong electron-withdrawing effect of the SF_5 group are also of interest for tetrapyrrole chemistry regarding the synthesis of lipophilic or amphiphilic tetrapyrroles. Based on this the synthesis of SF_5-substituted porphyrins, corroles, their DPM building block precursors and SF_5-substituted BODIPYs is presented. Moreover, the combination of SF_5- and PFP-substituents in mixed *trans*-A_2B_2-porphyrins and AB_2- or A_2B-corroles allowed additional modifications by the above-described S_NAr protocol with alcohols. As an example for a follow-up transformation the synthesis of a multichromophoric BODIPY-Cu(III)corrole conjugate via copper(I)-mediated 1,3-dipolar cycloaddition is outlined.

For the synthesis of A_4-porphyrins three SF_5-substituted aryl aldehydes, two of them with an additional halogen atom, were chosen as model substrates and condensed with pyrrole under acid catalysis. In addition, the effect of acid catalyst (TFA and $BF_3{\cdot}OEt_2$) was examined under the variation of the catalyst loading, affording SF_5-substituted A_4-porphyrins after optimization in yields of up to 39%. The metal coordination of all three A_4-porphyrins was studied by complexation with two typical metal salts for tetrapyrrole complexation. $Zn(OAc)_2$ and $Pd(OAc)_2$ were selected in a methanol/DCM solvent mixture under the aid of sodium acetate as buffer system affording in all cases the desired metal complexes in good yields (Scheme 21).



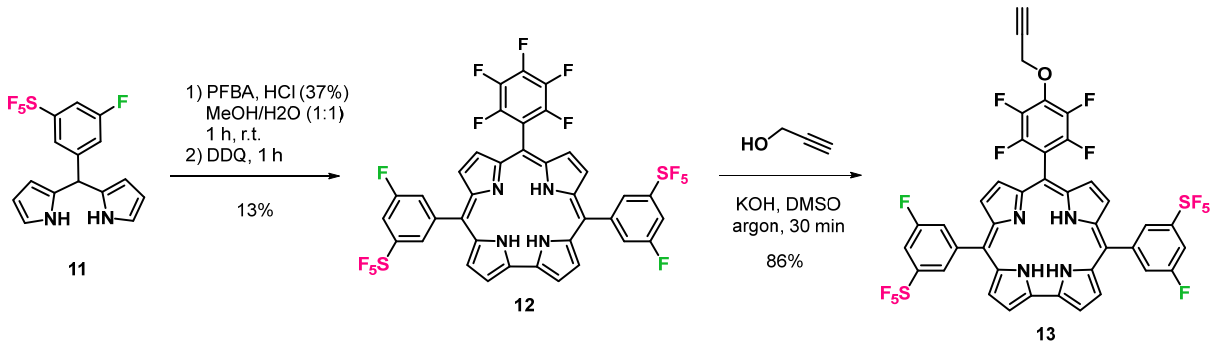
Scheme 21. Synthesis of SF_5-substituted A_4-porphyrins, DPMs and BODIPYs.

In the second part, a TFA-catalyzed condensation of the aryl aldehydes with excess pyrrole gave SF_5-substituted DPMs with a strong resistance towards scrambling due to the electron deficiency induced by the SF_5 group and the additional halogen substituent (Scheme 21). These compounds were used as substrates to synthesize *meso*-BODIPYs, *trans*-A_2B_2-porphyrins and A_2B-corroles, giving access to macrocycles suitable for further modifications via the S_NAr protocol.

For this purpose a model reaction of 3-fluoro-5-(pentafluorothio)-substituted A_4-porphyrin was investigated with propargyl alcohol under reaction conditions usually applied in the S_NAr protocol. The additional halogen atom, in this case fluorine, attached in 3-position may undergo a nucleophilic displacement if treated with alkoxides due to the strong electron-withdrawing effect of the SF_5 group. The model study showed that such a 3-fluorine exchange occurs only partly and only with heating above 60 °C, affording a mixture of 3-propargyloxy-substituted porphyrins. In contrast, the PFP-substitution reaction with alkoxides usually proceeds at room temperature. This allows a selective nucleophilic functionalization of mixed systems bearing PFP and SF_5/X substituents with a strict preference for the PFP group (X equals to F or Cl).

PFBA and 3-acetoxybenzaldehyde were selected as aldehydes and condensed with SF_5-substituted DPMs under TFA catalysis to yield the corresponding *trans*-porphyrins. Then, the nucleophilic substitution reaction was carried out with two alcohols and sodium azide, affording the *meso*-functionalized porphyrins.

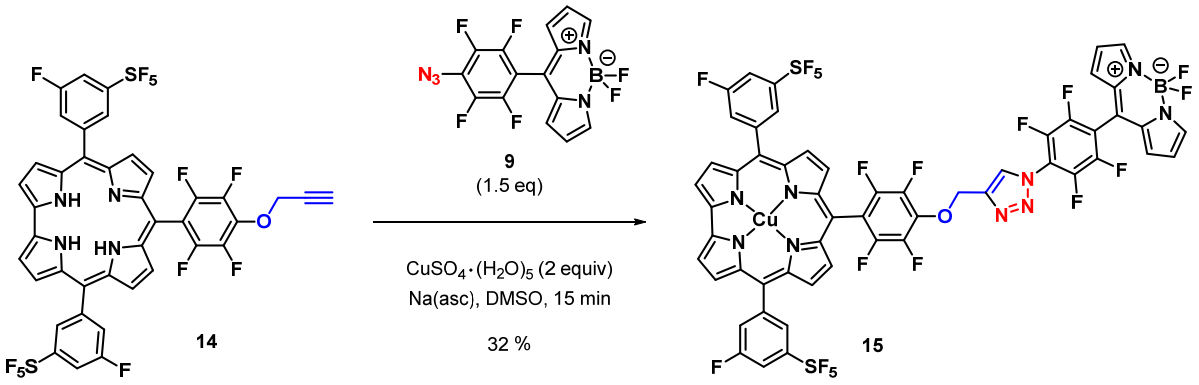
A brief exploration of corroles with the A_2B substitution pattern was carried out by condensation of two SF_5-substituted DPMs with PFBA, while the synthesis for the AB_2 corrole system was realized with 3-fluoro-5-(pentafluorothio)benzaldehyde and PFP-DPM **7**. In addition, one example for an A_3-corrole was prepared by condensation of an SF_5-substituted aldehyde with pyrrole. For prospective azide-alkyne 1,3-dipolar cycloaddition reactions, the nucleophilic fluorine exchange (exemplified on A_2B-corrole **12**) with both, 3-fluoro-5-(pentafluorothio)-substituted A_2B- and AB_2-corroles was demonstrated utilizing propargyl alcohol, affording the two alkynyl-functionalized corroles in high yields (Scheme 22).



Scheme 22. Synthesis and functionalization of an A_2B-corrole with propargyl alcohol.

The mentioned copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition was exemplified by the reaction between alkynyl-derived porphyrin **12** and azido-BODIPY **9** as substrates (Scheme 23). In general, reactions of free-base tetrapyrroles involving copper-catalysts result in the formation of their corresponding copper(II) or (III) complexes. Because of its paramagnetism the structural determination of Cu(II)-porphyrin systems by means of NMR-spectrometry is difficult. In contrast, corroles act as tridentate ligands where the copper-coordination results in a diamagnetic Cu(III)-complex.

This is the case for conjugate **15** that was synthesized under catalysis of $CuSO_4 \cdot 5\ H_2O$ and sodium ascorbate in DMSO with an acceptable yield. This conjugate describes one of the first examples of BODIPY-corrole conjugates, creating a basis for further explorations towards multichromophoric dyes, e.g. for light harvesting applications.



Scheme 23. Synthesis of a BODIPY-Cu(III)-corrole array by 1,3-dipolar cycloaddition.

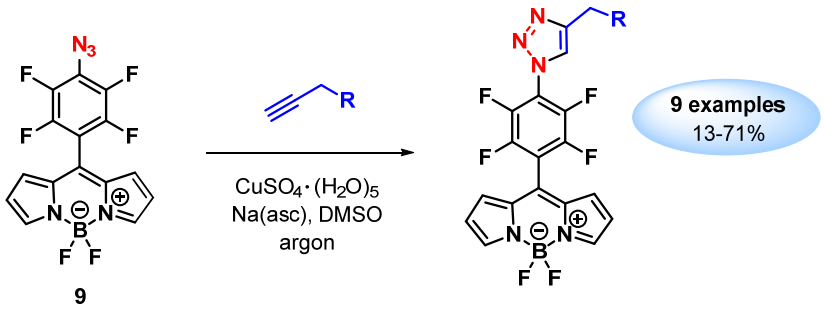
In conclusion, this report demonstrates the first adoption of the SF_5 group to tetrapyrrole chemistry, giving examples of A_4- and A_2B_2-substituted (metallo-)porphyrins, A_3- and A_2B-substituted corroles, BODIPYs and their DPM precursors by utilizing classic condensation chemistry and the nucleophilic substitution methodology. The SF_5 substituent withstands decomposition in TFA or HCl acid-catalyzed transformations, even treatment with strong bases gave no evidence for decomposition or side reactions, opening the way to explore further modifications as exemplified with a BODIPY-Cu(III)-corrole conjugate.

1.3.4 *Synthesis of Triazole-linked BODIPYs and BODIPY-Tetrapyrrole Arrays*

The imitation of naturally occurring photosynthetic processes by chromophore-based energy transfer arrays is a significant topic in current chemistry. Such systems often contain porphyrinoid units to mimic light harvesting and charge separation, due to the structural resemblance of porphyrins to chlorophyll-based systems in nature. As porphyrins possess limitations in their range for light absorption conjugation to other chromophores, e.g. BODIPYs is beneficial, as such array systems complement their absorption ranges and increase the efficiency for enhanced light harvesting throughout a broad range in the visible light spectrum. Beside numerous reports on BODIPY-porphyrin conjugates, less is known about their BODIPY-corrole analogs.

In continuation of the previous projects, the intention of this study was to explore the chemistry of azido-BODIPY **9**, its functionalization with selected alkynes and the conjugation to tetrapyrroles by 1,3-dipolar cycloadditions to gain access to multi-chromophoric systems.

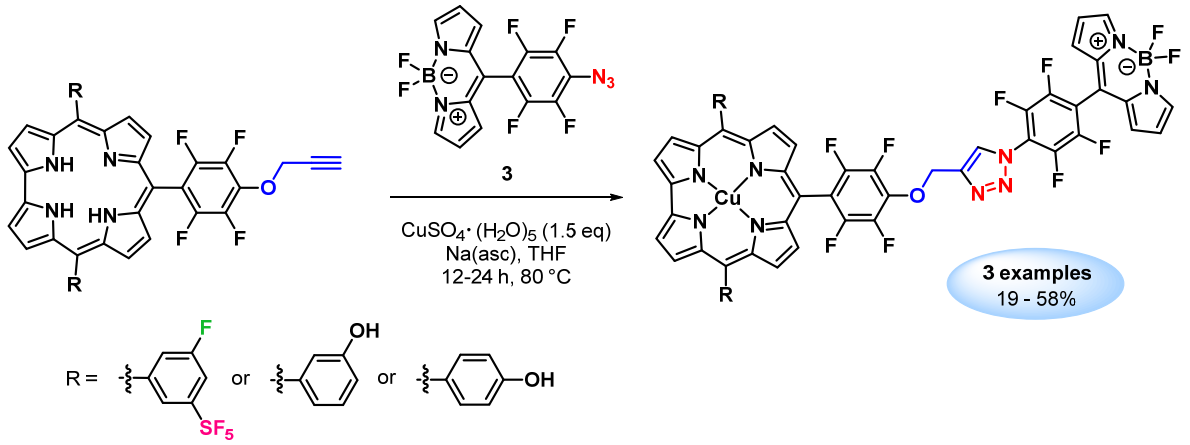
To investigate the scope of functionalization with the 1,3-dipole **9**, several copper(I)-catalyzed coupling reactions with terminal alkynes in DMSO were carried out. This protocol provided a variety of 1,2,3-triazole-linked *meso*-BODIPYs with e.g. lipophilic alkyl- and hydrophilic carbohydrate-derived sidechains. As outlined in chapter 1.3.2 with alkoxy-functionalized systems, modifications at the 4-azido group of the tetrafluorophenyl-substituent preserve the optoelectical properties of the BODIPYs. In addition, di- and trivalent alkynes afforded multivalent BODIPYs in analogy to trimer **10** shown in the second project.



Scheme 24. Copper(I)-catalyzed 1,3-dipolar cycloaddition of azido-BODIPY **9** with terminal alkynes.

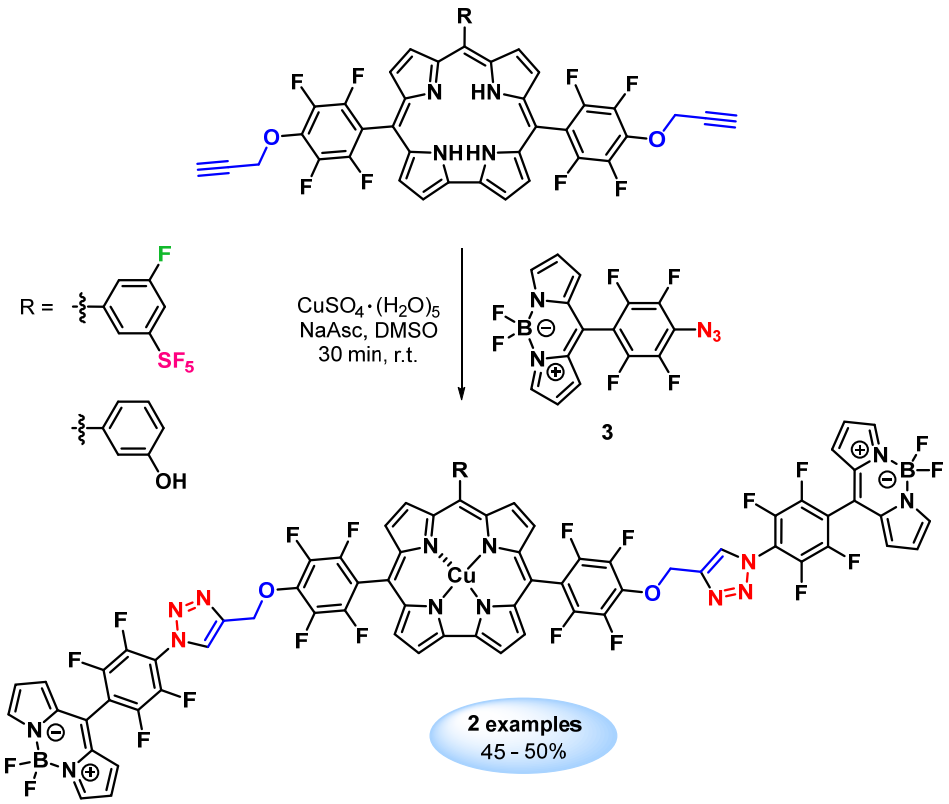
In order to build up more complex array systems appropriate AB_2- and A_2B-corroles with a mixed *meso*-substitution pattern were synthesized involving hydrophilic hydroxyl- and lipophilic SF_5-substituted aryl moieties, respectively. For two corroles of the AB_2 type, 3- and 4-acetoxy-DPM was condensed first with PFBA. Both macrocycles were selectively functionalized at the PFP-substituent with propargyl alcohol to introduce the terminal alkyne moiety.

The follow-up modification was carried out by copper(I)-mediated 1,3-dipolar cycloadditions with azido-BODIPY **9**, providing the triazole-linked BODIPY-Cu(III)corrole conjugates in moderate yields (Scheme 25).



Scheme 25. Copper(I)-catalyzed 1,3-dipolar cycloadditions of AB_2-corroles with azido-BODIPY **9**.

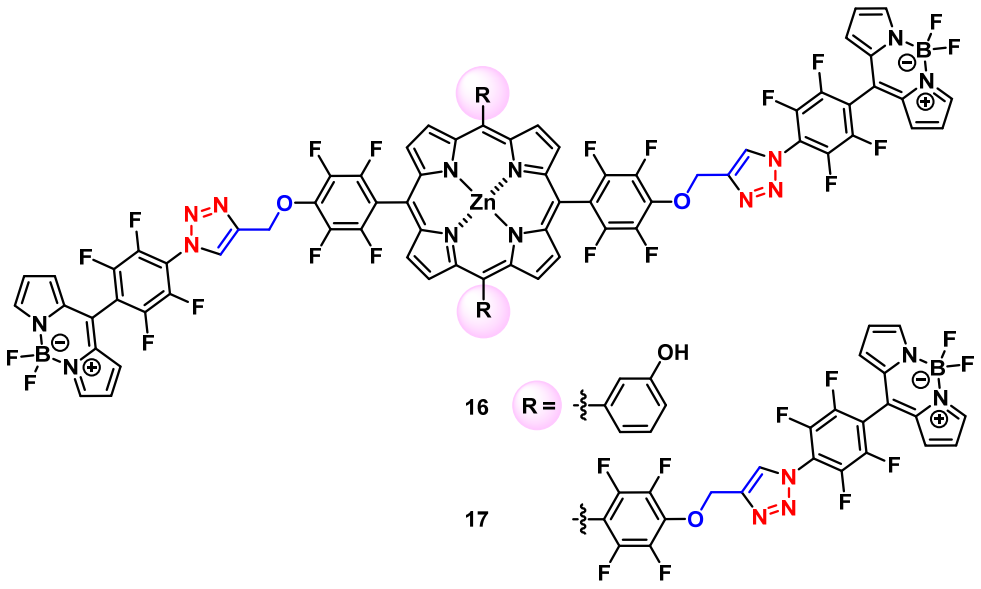
In an analogous procedure, two A_2B-type corroles were obtained by condensation of PFP-DPM **7** with 3-acetoxybenzaldehyde and 3-fluoro-5-(pentafluorothio)-DPM **11**, respectively, and further functionalized to the dialkynyl-substituted systems according to the S_NAr protocol. The subsequent copper(I)-mediated cycloaddition with azido-BODIPY **3** resulted in two divalent BODIPY-Cu(III)corrole arrays (Scheme 26). The reaction differs from the synthesis of monovalent BODIPY-corrole conjugates by use of DMSO at room temperature instead of THF and heating (Scheme 10), as this promotes a faster reaction with overall better yields.



Scheme 26. Copper(I)-catalyzed 1,3-dipolar cycloadditions of A_2B-corroles with azido-BODIPY **9**.

Based on the promising results for BODIPY-corrole conjugates, the generality of the copper(I)-mediated cycloaddition with azido-BODIPY **9** was tested on selected porphyrins. In contrast to corroles, porphyrins coordinate the copper ions in a lower oxidation state, resulting in paramagnetic copper(II)-complexes which would make structural determination by NMR spectroscopy difficult. Hence, to avoid an undesired copper insertion the inner cavity of the porphyrin was protected by complexation with another metal, e.g. zinc(II). The resulting zinc-complexes can undergo a subsequent acid-mediated demetallation, whereas the copper(II) displacement would require much harsher reaction conditions.

Thus, two porphyrins were synthesized by condensation of PFBA with pyrrole for the A_4-system, and of PFP-DPM **7** with 3-acetoxybenzaldehyde for the *trans*-A_2B_2-system, respectively, followed by subsequent metalation with zinc acetate and functionalization with propargyl alcohol via S_NAr reaction. The alkynyl-substituted porphyrins underwent a coupling reaction with azido-BODIPY **9**, providing the corresponding triazole-linked BODIPY-Zn(II)-porphyrins with yields of 69% (A_2B_2-array **16**) and 60% (A_4-array **17**), respectively (Scheme 27).



Scheme 27. Triazole-linked BODIPY-Zn(II)porphyrin arrays obtained by 1,3-dipoar cycloaddition.

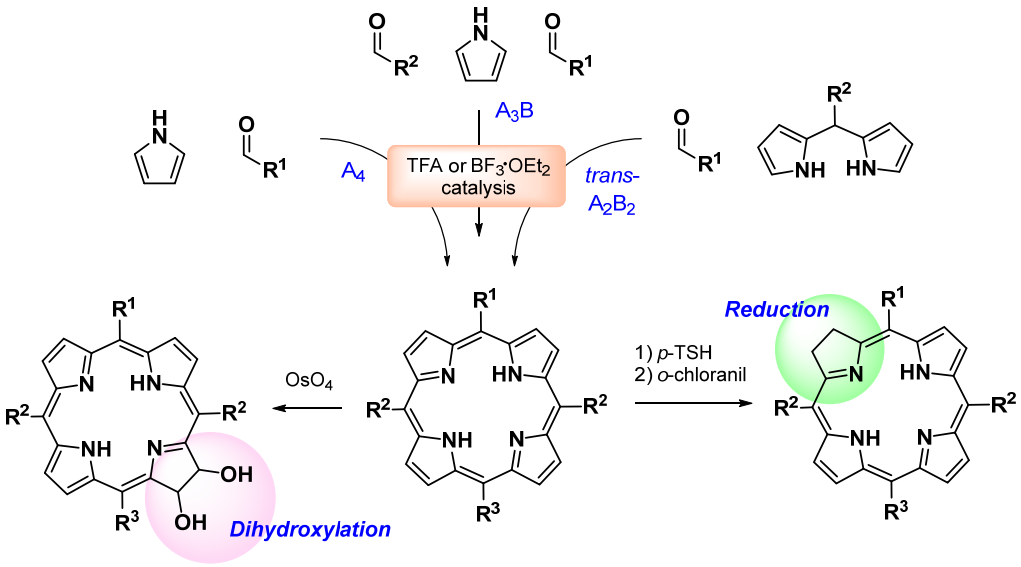
In summary, the fourth project demonstrates an in-depth investigation on the copper(I)-catalyzed 1,3-dipolar cycloaddition between azido-BODIPY **9** and several terminal alkynes, as model substrates towards functionalized, triazole-linked *meso*-BODIPYs. Several examples with polar and unpolar peripheral residues were obtained and the scope of reactivity explored by the synthesis of multivalent BODIPYs utilizing di- and trivalent alkyne linkers. The synthesis of several BODIPY-corrole conjugates was achieved by copper(I)-mediated cycloaddition reactions, offering novel systems for potential application in light harvesting chemistry and catalysis.

1.4 Unpublished Results

Within the first project towards synthesis and functionalization of tetrapyrroles as potential PS for the PDT, the transformation of selected porphyrins to their corresponding chlorin and dihydroxychlorin analogs was explored. The principles of PDT and the requirements for photosensitizers are described in more detail in chapter 1.1.6 – *Photodynamic therapy*.

The chlorin and bacteriochlorin scaffold is usually accessible by derivatization of naturally occurring chlorophylls or bacteriochlorophylls from phototropic bacteria, plants and algae. Unfortunately this approach requires vast resources while the chemical sensitivity of the reduced macrocycles hampers their transformations. Alternatively, a total synthesis of such compounds seems reasonable starting with the preparation of porphyrins, as these precursors can be synthesized conveniently by condensation of aldehydes with pyrrole or aldehydes with DPMs. Condensation of an aldehyde with pyrrole leads to A_4-systems, whereas two aldehydes in 3:1 ratio afford A_3B-porphyrins (in such a case $R^2 = R^3$ in Scheme 28). The *trans*-systems are accessible by condensation of an aldehyde with a DPM ($R^1 = R^3$ in Scheme 28).

Several approaches are known where the porphyrin is subsequently converted into the chlorin or bacteriochlorin derivative e.g. by reduction with an *in-situ* generated diimine[13] or by *cis*-dihydroxylation with osmium(VIII) tetroxide.[2b,15-17] A discussion on chlorins and bacteriochlorins and their synthesis can be found in chapter 1.1.1 – *Porphyrins and their analogs*.



Scheme 28 – General approaches towards the total synthesis of chlorins and dihydroxychlorins.

The first approach towards systems with structural resemblance to Temoporfin analogs was realized by the introduction of hydroxyl groups by nucleophilic fluorine exchange of PFP-substituted A_4- and AB_3-type porphyrins with diols, to increase the overall polarity and solubility of the corresponding macrocycles. These porphyrins were tested within cell tests against several cancer cell lines to explore potential suitability as PS with promising results, exemplified for porphyrin **18** in Figure 7.

Even with low concentrations of 2 µM of the PS a moderate to high toxicity in respect to the applied cell cultures was observed after irradiation at 652 nm. Dark toxicity (DT) increased with higher concentrations of the diol-functionalized PS.

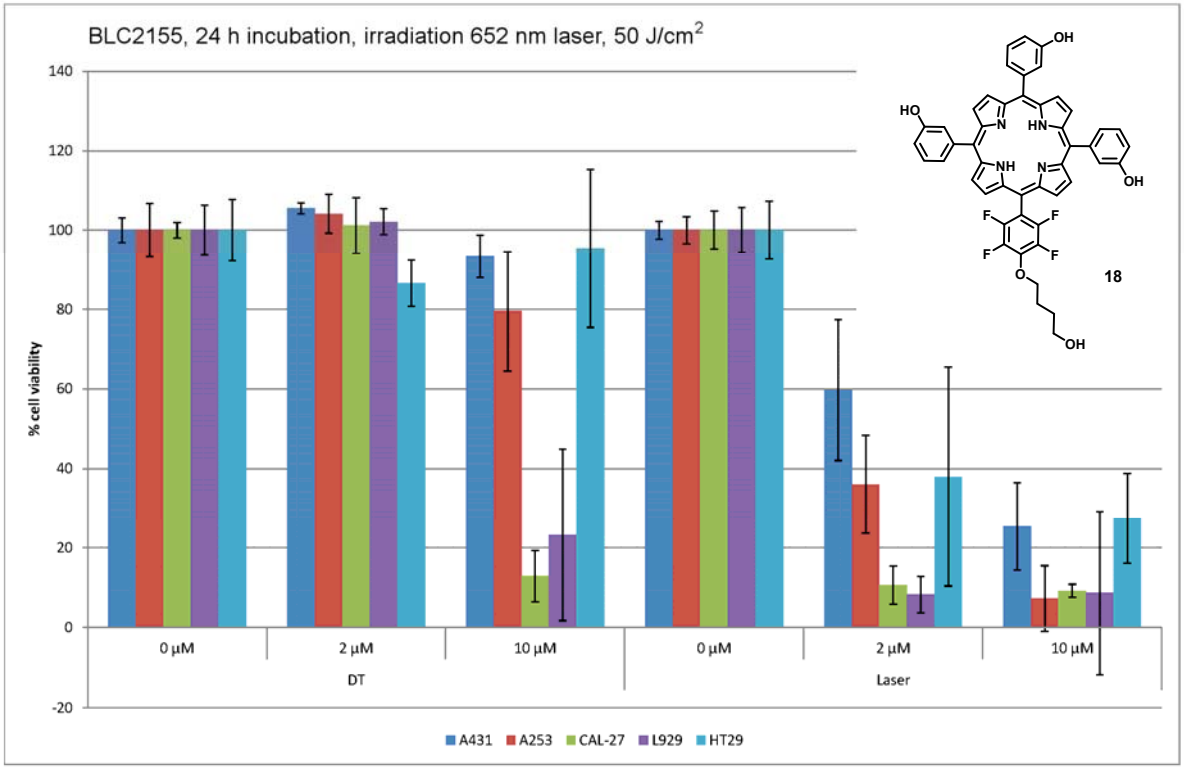
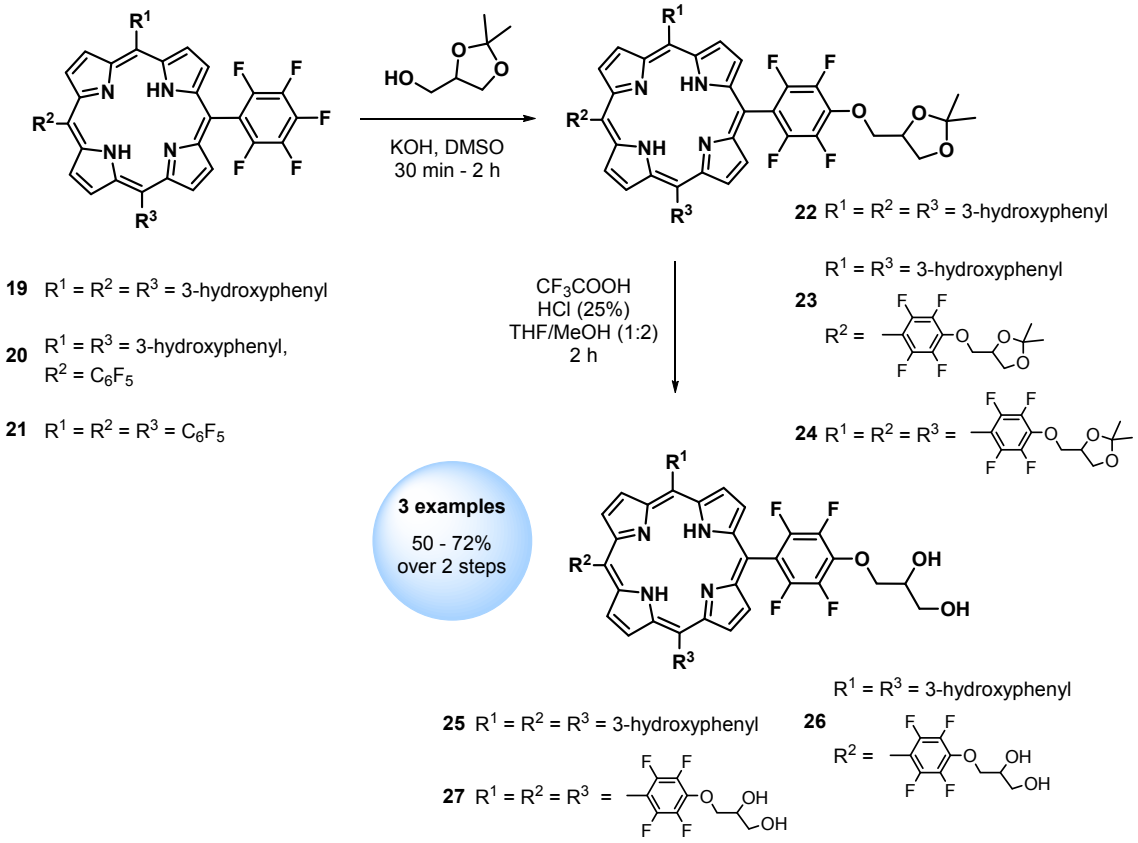


Figure 7. Cell test result of the diol-functionalized AB_3-porphyrin **18** (DT = dark toxicity).

Furthermore, tetrapyrroles functionalized with the 1,3-dioxolane motif can undergo a subsequent acid catalyzed deprotection, affording two additional hydroxyl groups per one *meso*-substituent in the periphery to increase the solubility in polar media. This approach allowed the synthesis of highly polar porphyrins with a potential suitability for PDT (Scheme 29). Test results against several cancer cell lines confirmed this: A lower dark toxicity even at high PS concentrations compared to the diol-substituted systems and higher efficiency after irradiation at high and low PS concentrations of 10 and 2 µM, respectively. Thus these compounds provided promising characteristics for further investigations. The cell test result for the glycerol-substituted porphyrin **26** is demonstrated as one example in Figure 8.



Scheme 29. Synthesis and acid-mediated deprotection of 1,3-dioxolane-substituted porphyrins **19**-**27**.

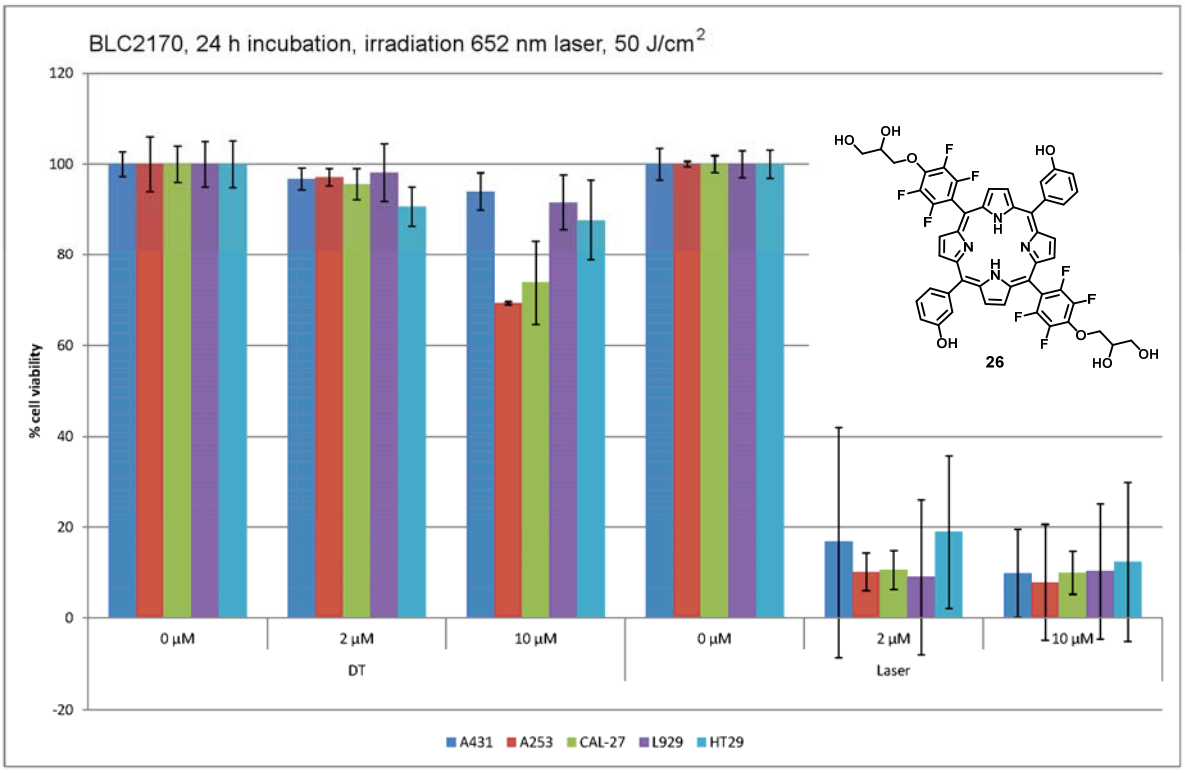
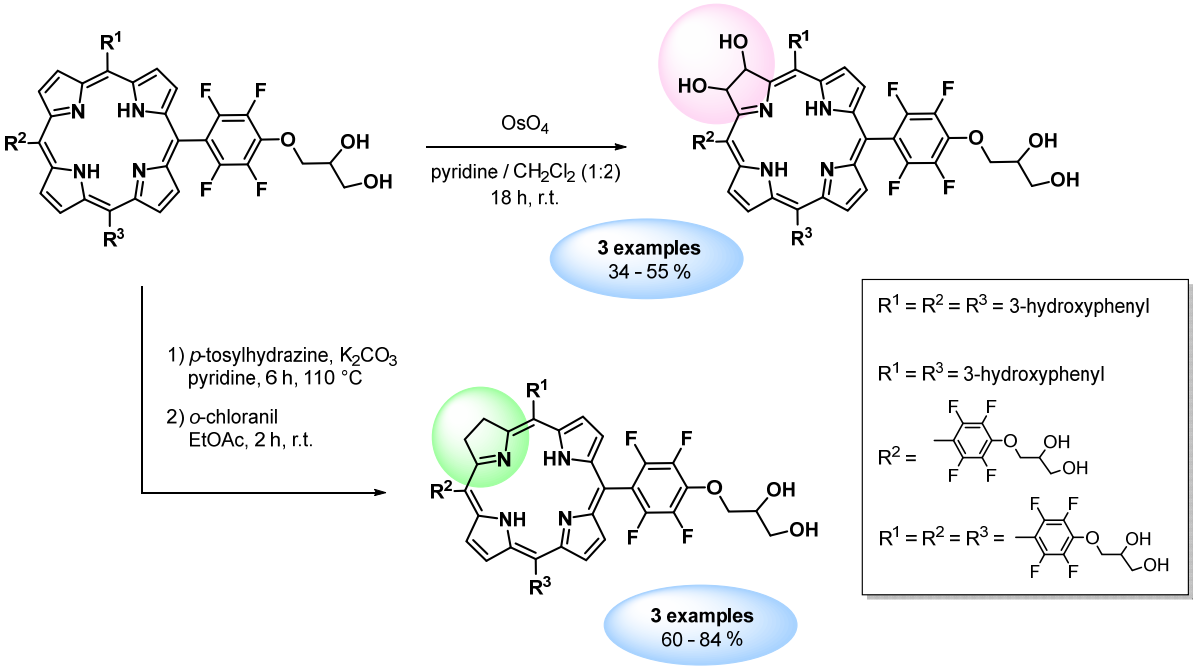


Figure 8. Cell test result of the functionalized A_2B_2-porphyrin **26**.

Besides a high solubility in polar media, a strong absorbance in the region around 650 to 750 nm is another beneficial factor for PDT and an essential property for photosensitizers. Light in the range of such wavelengths can reach deeper regions of the skin and increase the efficiency towards cancer treatment. Free-base porphyrins exhibit absorption bands in the blue and red region around 400 to 800 nm characterized by a strong SORET and four Q-bands. A bathochromic shift of light absorbance towards higher wavelengths, with an increase of the extinction coefficient can be achieved through reduction of the porphyrin core.

Chlorins and bacteriochlorins are porphyrinoids with a structural resemblance to the porphyrin skeleton while exhibiting the desirable property of a strong red shifted absorbance and an increased absorbance at higher wavelength, respectively. As outlined at the beginning of this chapter, this approach was explored in a subproject with three selected porphyrins using two pathways to obtain their hydrochlorin and dihydroxychlorin analogs.

According to the protocol developed by WHITLOCK (Chapter 1.1.1), the reduction of the glycerol-functionalized porphyrins with *p*-tosylhydrazine and potassium carbonate afforded a mixture of the corresponding chlorins and bacteriochlorins within six hours in pyridine. The bacteriochlorins were subsequently re-oxidized in the second step by treatment with *o*-chloranil to obtain the chlorins with good yields up to 84%. Alternatively, a dihydroxylation of porphyrins with osmium(VIII) tetroxide achieves both described benefits within one reaction step: An increased polarity through introduction of two hydroxyl groups and an increased absorbance at higher wavelengths by selective oxidation of two adjacent carbons of the porphyrin skeleton. Hence, osmium-mediated dihydroxylations of all three glycerol-functionalized systems afforded the dihydroxychlorins after 18 hours at room temperature with moderate yields up to 55% (Scheme 30).



Scheme 30. Dihydroxylation and reduction of glycerol-substituted porphyrins to chlorins.

Looking at further transformations and applications, the dihydroxylated chlorins feature a higher stability towards decomposition compared to 'normal' dihydrochlorins. The application of osmium(VIII) tetroxide for the synthesis of dihydroxychlorins is questionable first in regard to economic aspects, as its utilization requires equimolar amounts of the very expensive metal oxide. Second, the high toxicity hampers the use of OsO_4 in syntheses for medical purposes. In this respect it is important that recently an alternative osmium-free pathway to dihydroxychlorins has been published.[78]

The dihydroxychlorins were further tested against cancer cell cultures and also revealed a high potential as PS for PDT. All examples exhibit an extremely low dark toxicity and high toxicity after irradiation at 652 nm which virtually led to a total cell death at high and low PS concentrations as outlined with dihydroxychlorin **28** in Figure 9. Cell test results for all other analyzed compounds can be found in chapter 1.7.4.

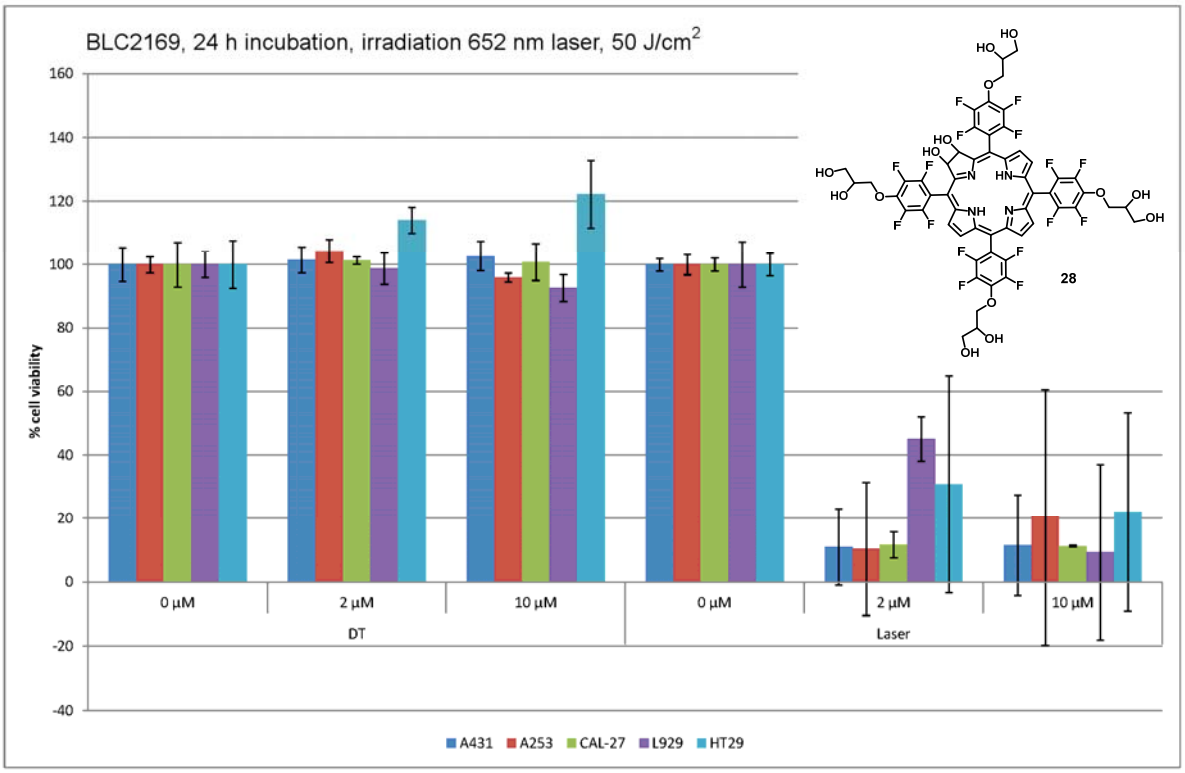
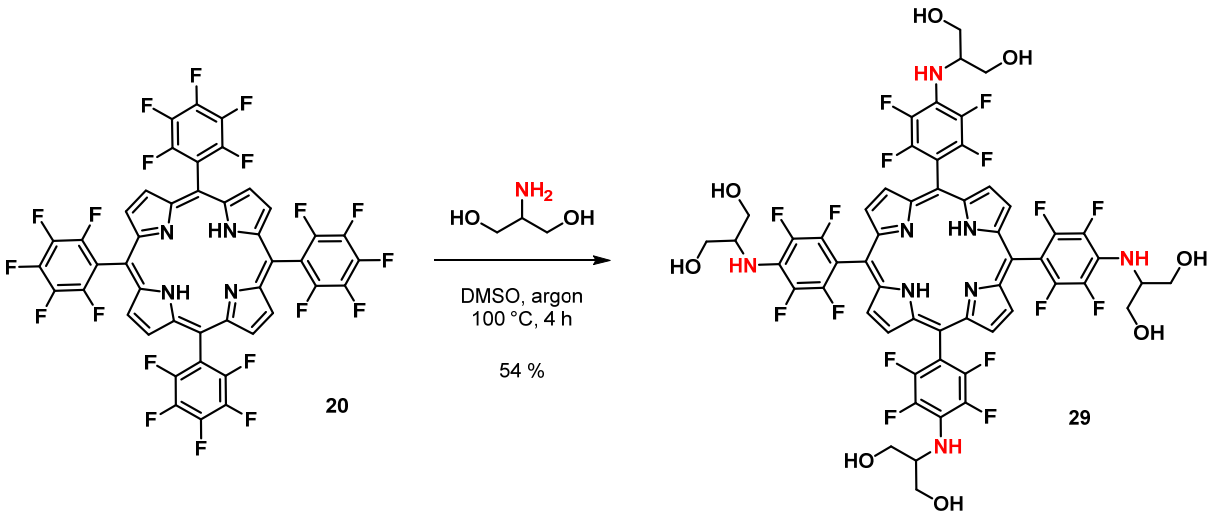


Figure 9. Cell test result of functionalized A_4-dihydroxychlorin **28**.

The selective *para*-fluorine exchange of PFP-porphyrins with amines is known and well described in the literature by numerous reports.[63,79] In structural similarity to glycerol-substituted A_4-porphyrin **26**, the synthesis of an amine analog was explored and for this purpose 1,3-dihydroxy-2-amino-propane was chosen as model substrate to afford porphyrin **29** by selective substitution. The reaction proceeded exclusively by an attack of the nucleophilic amino group as no additional base is necessary in contrast to alcohols (Scheme 31). This example illustrates the possibility to conduct the S_NAr reaction selectively with certain nucleophiles under appropriate reaction conditions without side reactions.

The nucleophilicity of alcohols is significantly lower compared to amines, that it why only the amino-group acts as the reactive species. Nevertheless, substitution reactions with amines require often high temperatures which may prove unsuitable for PFP-tetrapyrrole modification with sensitive key functional groups.

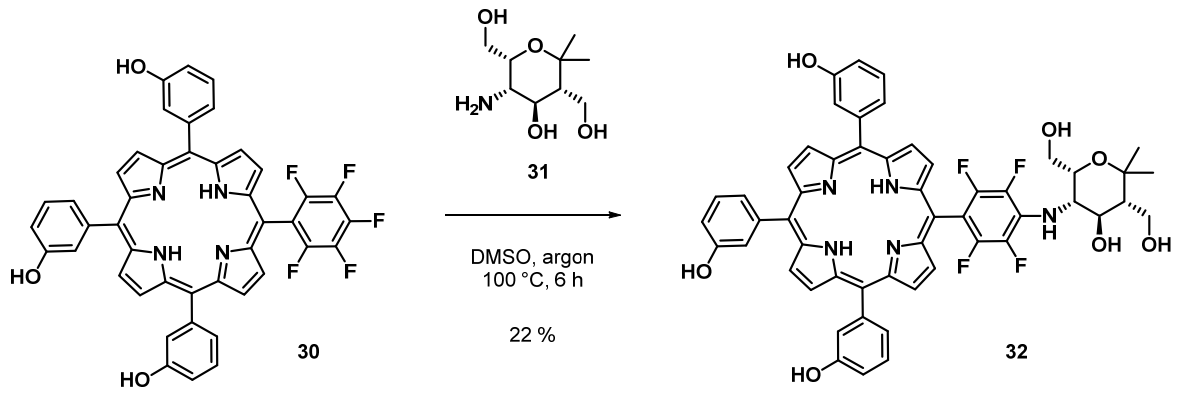


Scheme 31. Synthesis of amino-substituted porphyrin **29** by S_NAr-reaction.

As mentioned in chapter 1.1.6 – *Photodynamic therapy* a selective targeting of cancer cells and tumors is essential for an optimal photosensitizer. Carbohydrates are naturally occurring small molecules and belong to the most important classes of biomolecules with a wide range of applications and crucial roles in living organisms such as energy source for metabolic processes or cell-cell recognition in form of gyco-lipids or glyco-proteins.[80] Therefore, these molecules can be referred as "bioinformation" carriers with a structural diversity and a high density of functional groups. The use of carbohydrates for drug targeting is aligned with severe drawbacks such as metabolic instability and poor hydrophobicity and oral bioavailability.[81] Carbohydrate mimetics are by definition synthetic molecules with structural resemblance to naturally occurring carbohydrates with improved properties such as higher selectivity for specific receptors or better bioavailability for drug design and targeting.[82] The interaction of carbohydrate mimetics with e.g. targeted receptors are fundamentally based on hydrogen bonds, hydrophobic or ionic interactions.

In this regard, the conjugation of a carbohydrate mimetic with a hydrophilic porphyrin **30** was explored in cooperation with J. SALTA.[81] The amino-carbohydrate mimetic **31** was designed through a five step protocol developed by REISSIG and co-workers. According to the synthesis of amino-porphyrin **29** (Scheme 29) – which can be recognized as a model study for more complex structures by S_NAr with amines – porphyrin **30** was reacted with aminopyran **31** under argon atmosphere in DMSO (Scheme 32). A prolonged reaction time was necessary to obtain conjugate **32** with 22% yield after purification. Substitution reactions with amines as demonstrated by OSUKA and co-workers, usually require the reacting amine in excess amounts (50 to 100 equivalents)[63d] which in this case cannot be provided as the synthesis of aminopyran **31** is not affordable in a large scale.

Nevertheless, sufficient amounts of the carbohydrate-porphyrin conjugate could be isolated for a full characterization. The lacking efficiency of S_NAr reactions involving highly substituted and sterically hindered amines requires the use of different strategies to obtain structurally similar systems. This may be achieved by the efficient copper(I)-mediated 1,3-dipolar cycloaddition reaction between alkynyl-substituted tetrapyrroles – as described in the chapters above – and azido-sugars, as the amine-function can be further converted to the corresponding azide.[81]



Scheme 32. Synthesis of aminopyran-porphyrin conjugate **32** by S_NAr-reaction.

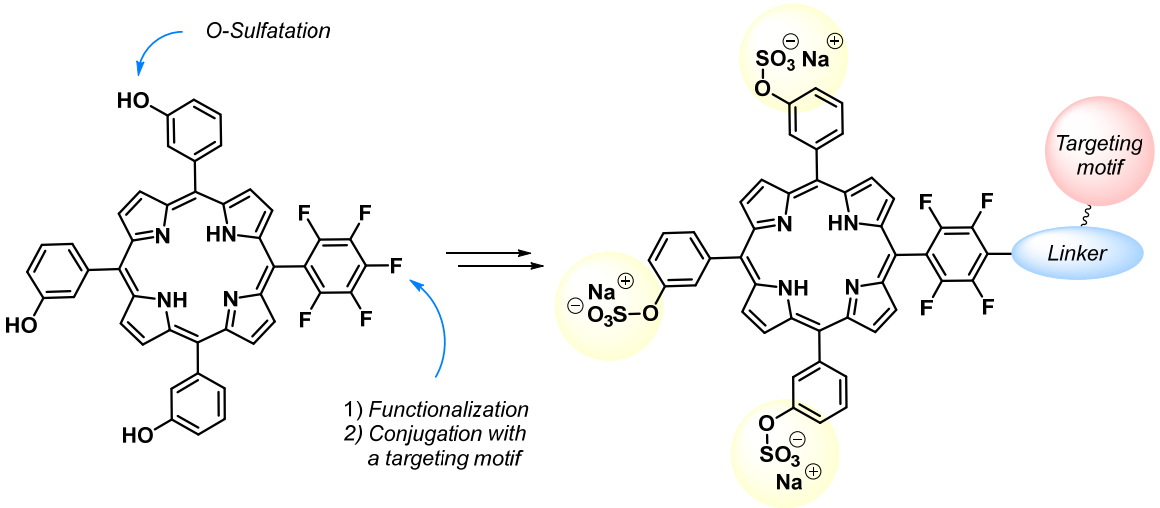
1.5 Outlook

The work presented in this thesis is focused mainly on the synthesis and functionalization of novel tetrapyrroles and their DPM precursors. These may prove as suitable substrates for further research projects and interesting applications. Several topics and future trends for the S_NAr reaction are shortly discussed in the following.

1.5.1 Design of Photosensitizers and Selective Targeting for PDT

Cancer targeting has been widely investigated in therapeutical photodynamic therapy by use of passive and active mechanisms with tumor surface markers, e.g. growth factor receptors, low-density lipoprotein (LDL) receptors or folic acid receptors among others.[83] Glycerol-functionalized porphyrins and their chlorin analogs described within this thesis showed distinguished results regarding their activity against several cancer cell lines. In order to apply these for clinical trials and later use as pharmaceutical agents, further testing phases involving, e.g. living tissues, are necessary. The investigated S_NAr method for a selective conjugation of tetrapyrroles with functionalized alcohols may allow the introduction of appropriately designed substrates within the periphery of tetrapyrroles.

In this regard, two plausible pathways are possible: i) Introduction of functional groups, e.g. alkyne, alkene, azide or amine by S_NAr reaction at a PFP-substituent followed by conjugation with a specific active targeting moiety, e.g. folate or cyclodextrin by 1,3-dipolar cycloaddition, HECK- or amidation reaction among other methods; ii) Conjugation of a PFP-tetrapyrrole with a targeting motif directly by S_NAr reaction. However, high amounts of the desired "targeter" are required for the nucleophilic substitution. Combining both, active targeting sites and highly polar residues, e.g. by *O*-sulfatation of the 3-hydroxy aryl groups – to obtain ionic systems – or introduction of glycerol or higher branched polyglycerols, could afford photosensitizers with an increased solubility in water and alcoholic media with specific abilities for PDT. Regarding amphiphilic systems, *meso*-SF_5-substituted or polyfluorinated *trans*-porphyrins could be functionalized in a similar fashion, resulting in systems with a lipophilic core and highly polar or active side chains.



1.5.2 *Supramolecular Assemblies*

A broad variety of porphyrinoids are found in the complex multifunctional systems involved in naturally light-harvesting or oxygen- and electron-transfer processes.[84] The research on synthetically prepared assemblies to mimic their properties for desired applications is gaining growing interest. For example, the design of self-assembled supramolecular systems by non-covalent interactions, π-π stacking or hydrogen bonding is one of the main topics regarding surface pattering of bulk materials with potential application in fields like optoelectronics,[85] catalysis,[86] chemical sensors[87] and solar cells.[88] The corroles, porphyrins and their metal complexes presented in this thesis could be interesting substrates for the construction of such supramolecular assemblies and the investigation of their properties due to the diverse peripheral functional groups. These allow simple and straightforward transformations, e.g. click chemistry or metal-catalyzed coupling reactions.

1.5.3 *Artificial Photosynthesis and Light Harvesting*

Porphyrinoid-based light harvesting ensembles play a crucial role in naturally occurring energy- and oxygen-transfer processes. The artificial reproduction of light-harvesting complexes and their properties is an important research field, as the applied porphyrinoidal scaffolds can be obtained synthetically straightforward and share similar characteristic features such as electron transfer properties or excitation energies.[89] The efficiency of light harvesting complexes depends highly on the absorption behavior of its functional "antennas" which transfer harvested energy to a central acceptor unit, e.g. a porphyrin or metalloporphyrin core. As a single chromophore possesses limitations to specific wavelength ranges, the conjugation with additional chromophores of different absorption behavior – either by covalent or non-covalent interactions – results in a broader band of light absorption.

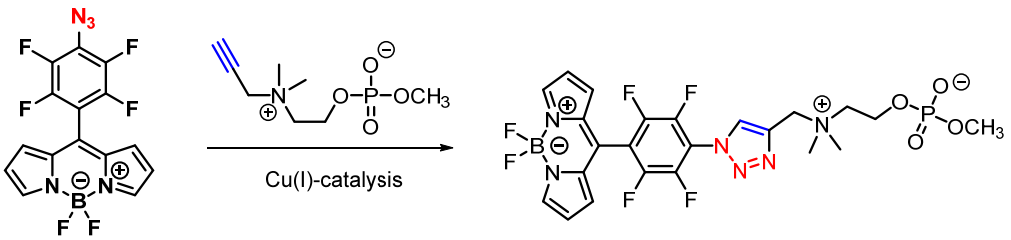
The synthesis of fluorinated multi-chromophore arrays through a multistep reaction profile demonstrated in this thesis bears high potential for further analyses. It would be interesting to explore the electron- or energy-transfer processes in these compounds in more detail, particularly those of the BODIPY-Cu(III)-corrole-based systems. Free-base corroles undergo a copper metal insertion during the coupling reaction. These metallocorroles exhibit highly different spectroscopic properties and therefore, a protection with an easy to remove metal prior to coupling with azido-BODIPYs may allow the study of free-base BODIPY-corrole arrays. Although no conjugation of the π-system between the single chromophores is necessary for an energy transfer, it would be interesting to study the behavior of multi-chromophoric BODIPY-tetrapyrrole arrays with full conjugation.

1.5.4 Catalysis

Metal complexes of corroles and porphyrins have become established within the last decades in the field of catalyzed transformations: Iridium, cobalt, manganese and iron are only a few transition metals which coordinate to the porphyrin scaffold affording catalytic systems for transformations such as oxygen transfer,[90] oxygen generation by water oxidation[91], aerobic oxidation,[92] or olefin cyclopropanation[93] whereas metal complexes of corroles with iron[94] and manganese[95] and cobalt,[96] have also been described with applications such as hydrogen generation. However, these metals can be stabilized in higher oxidation states due to the trianionic inner cavity of corroles. The tetrapyrroles synthesized in this thesis are suitable candidates for metal complexation studies. Through the extensively investigated S_NAr protocol it is possible to tune the desired macrocyclic periphery efficiently, followed by a metal coordination. Zinc(II) porphyrins and copper(III) corroles were explored. Other transition metals, their coordination chemistry and catalytic activity could be investigated. Furthermore, SF_5-substituted tetrapyrroles are highly interesting substrates for potential use as fluorous phase catalysts with the possibility for further modifications through the PFP-substituent. To increase the overall solubility in fluorous media and decrease it in organic solvents, perfluorinated alkylchains could be introduced by S_NAr into present PFP-substituents, e.g. *trans*-porphyrins. Moreover, these metalloporphyrins with fluorine substitution exhibit an oxidation potential favorable for oxidation reactions.

1.5.5 Tetrapyrrole and BODIPY Fluorescence Markers

The hydrophilic phosphatidyl choline (PC) headgroup is a significant motif of phospholipids found in cell membranes of living organisms. In recent investigations on biomembrane binding it was shown that using the inverse choline phosphate (CP) structure, several membranes and liposomes containing the PC motif can be bound electrostatically.[97] The binding strength was highly depending on the density of CP groups attached to the studied macromolecules. The prepared choline phosphates were designed with a terminal alkyne function and coupled by 1,3-dipolar cycloaddition to hypervalent polyglycerols. Such choline phosphates could also be combined with azido-functionalized macromolecules presented in this thesis, in particular 4-azido-BODIPY to obtain functional adhesive dyes for e.g. fluorescence imaging. The zwitterionic nature of the CP scaffold could also be useful as a highly polar functional group – attached to e.g. porphyrins – to increase the solubility in aqueous media and study the resulting conjugates as potential photosensitizers for PDT.

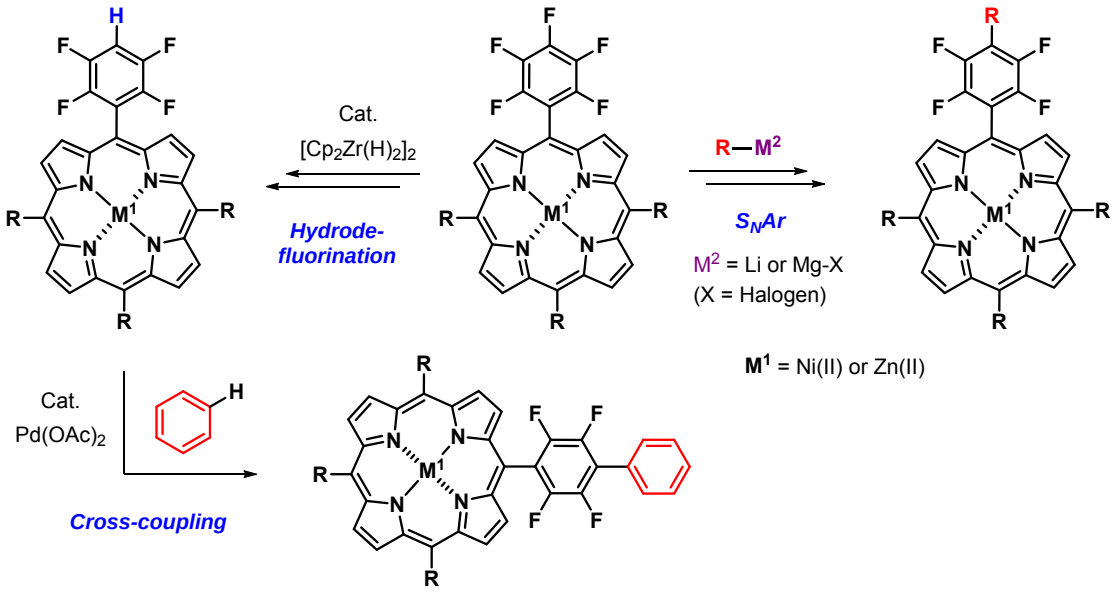


1.5.6 Future Trends for the Functionalization of PFP-Systems

The variety of alcohols investigated for the preparation of alkoxy-functionalized porphyrins, corroles and dipyrromethanes within this thesis revealed the high modification potential of the pentafluorophenyl moiety. Without significant limitations, literally any primary, secondary or tertiary alcohol with base-stable residual functional groups may be utilized in the *para*-fluorine exchange reaction to obtain functional dyes in moderate to high yields. The reaction efficiency and atom economy could also be improved further, as the alcohols were applied in an excess compared with substrate. This would allow a functionalization with various substrates without a significant waste.

Despite the fact that the nucleophilic substitution on PFP-substituted tetrapyrroles has been studied extensively with sulfur, nitrogen and oxygen centered nucleophiles, this principle could also work for other nucleophilic species such as organometallic reagents. Although the first nucleophilic substitutions on tetrapyrroles were described by SENGE and co-workers[98] through functionalization of the macrocyclic core by the use of such carbon nucleophiles, PFP-groups may as well be prone to undergo an attack by several organometallic reagents.[98b] Such an approach may lead to a regioselective carbon-carbon bond formation and increase the variety of functional tetrapyrroles, e. g. the construction of extended π-systems for further functionalization.

Recent advances in fluorine chemistry reported the synthesis of fluorinated building blocks by transition metal-mediated hydrodefluorination.[99] Suitable zircocene hydrido or cerium hydrido complexes allow a selective fluorine/hydrogen exchange of perfluorinated arenes e.g. pentafluoro-benzene or pentafluoropyridine. This protocol could be investigated within tetrapyrrole chemistry for the selective preparation of 4-*H*-2,3,5,6-tetrafluorophenyl substituted systems. These may undergo further functionalization by substitution with several nucleophiles to afford a *meta*-fluorine exchange or cross-coupling reactions[100] with arenes under palladium-catalysis.



1.6 Publications

1.6.1 *Synthesis of Alkoxy-Functionalized Porphyrins*

"The Regioselective Nucleophilic Aromatic Substitution Reaction of *meso*-Pentafluorophenyl-Substituted Porphyrinoids with Alcohols"

This chapter has been published in:

Hartwig R. A. Golf, Hans-Ulrich Reissig and Arno Wiehe, *European Journal of Organic Chemistry* **2015**, 1548–1568. DOI: 10.1002/ejoc.201403503

All the experiments, spectral data interpretations as well as writing the draft of this publication have been done by Hartwig R. A. Golf under the supervision of Dr. A. Wiehe and Prof. Dr. H.-U. Reissig.

The original article is available *via* the following web-links:

http://onlinelibrary.wiley.com/doi/10.1002/ejoc.201403503/abstract

http://onlinelibrary.wiley.com/doi/10.1002/ejoc.201403503/suppinfo

1.6.2 *Synthesis of Alkoxy-Functionalized Dipyrromethanes*

"Nucleophilic Substitution on (Pentafluorophenyl)dipyrromethane - A New Route to Building Blocks for Functionalized BODIPYs and Tetrapyrroles"

This chapter has been published in:

Hartwig R. A. Golf, Hans-Ulrich Reissig, Arno Wiehe, *Organic Letters* **2015**, *17*, 982–985. DOI: 10.1021/acs.orglett.5b00082

All the experiments, spectral data interpretations as well as writing the draft of this publication have been done by Hartwig R. A. Golf under the supervision of Dr. A. Wiehe and Prof. Dr. H.-U. Reissig.

The original article is available *via* the following web-links:

http://pubs.acs.org/doi/abs/10.1021/acs.orglett.5b00082

http://pubs.acs.org/doi/suppl/10.1021/acs.orglett.5b00082

1.6.3 *Synthesis of SF_5-Substituted Dipyrromethanes and Tetrapyrroles*

"Synthesis of SF_5-Substituted Metalloporphyrins, BODIPYs and their Dipyrrane Precursors"

This chapter has been published in:

Hartwig R. A. Golf, Hans-Ulrich Reissig, Arno Wiehe, *The Journal of Organic Chemistry* **2015**, *80*, 5133–5143. DOI: 10.1021/acs.joc.5b00528

All the experiments, spectral data interpretations as well as writing the draft of this publication have been done by Hartwig R. A. Golf under the supervision of Dr. A. Wiehe and Prof. Dr. H.-U. Reissig.

The original article is available *via* the following web-links:

http://pubs.acs.org/doi/abs/10.1021/acs.joc.5b00528

http://pubs.acs.org/doi/suppl/10.1021/acs.joc.5b00528

1.6.4 *Synthesis of Triazole linked BODIPYs and BODIPY-Tetrapyrrole Arrays*

"Synthesis of Functionalized BODIPYs, BODIPY-Corrole and BODIPY-Porphyrin Arrays with 1,2,3-Triazole Linkers Using the 4-Azido(tetrafluorophenyl)-BODIPY Building Block"

This chapter has been accepted for publication in:

Hartwig R. A. Golf, Anna M. Oltmanns, Duc. H. Trieu, Hans-Ulrich Reissig, Arno Wiehe, *European Journal of Organic Chemistry* **2015**, *In press*.

The experiments and spectral data interpretations were carried out by Hartwig R. A. Golf, Anna M. Oltmanns (Synthesis and characterization of BODIPY-Cu(III)corrole arrays **8a** and **8b**) and Duc H. Trieu (Synthesis of *meso*-BODIPYs **4a**-**h** and Cu(III)-corrole array **13**). Writing the draft of this publication was done by Hartwig R. A. Golf under the supervision of Dr. A. Wiehe and Prof. Dr. H.-U. Reissig.

The original article is available *via* the following web-links:

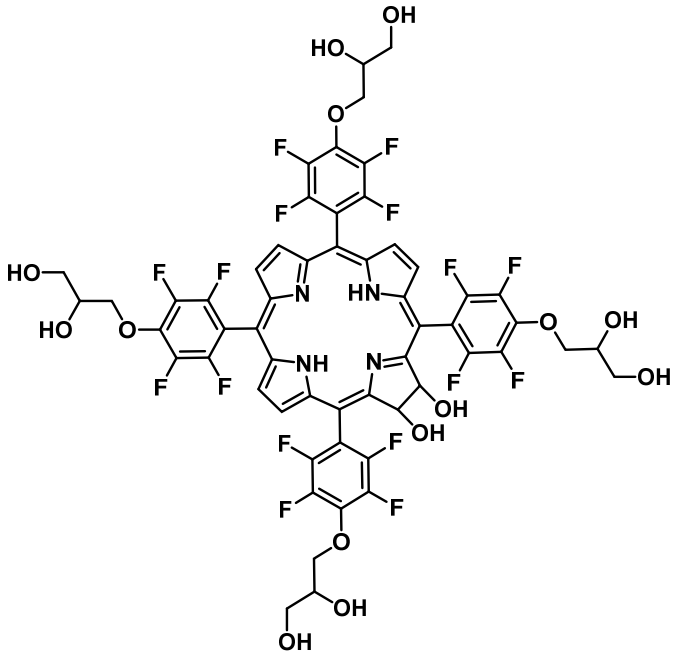
http://onlinelibrary.wiley.com/doi/10.1002/ejoc.201500413/abstract

http://onlinelibrary.wiley.com/doi/10.1002/ejoc.201500413/suppinfo

1.7 Synthesis and Characterization Data of Compounds so far Unpublished

1.7.1 *Dihydroxylation with Osmium(IV)tetroxide*

5,10,15,20-[2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl]-7,8-dihydroxychlorin (28)



All reaction steps were performed under argon atmosphere. In a 250 mL three-necked flask with two gas-inlet valves 5,10,15,20-tetrakis[2,3,5,6-tetrafluor-4-(2,3-dihydroxypropyloxy)phenyl]porphyrin (413 mg, 0.237 mmol) was dissolved in 15.0 mL pyridine, OsO_4 (100 mg, 0.393 mmol) added and the mixture stirred for 18 hours at RT. Then, Na_2SO_3 (1.0 g in a saturated solution of H_2O/MeOH = 1:1, v/v) was added and the mixture stirred again over night at room temperature. The mixture was then poured over celite, washed off with methanol, evaporated to dryness, dissolved in ethyl acetate and washed three times with water. The product was purified by column chromatography (ethyl acetate/MeOH = 17:3, v/v) and recrystallization (acetone/*n*-hexane) to obtain the product as a purple solid. Yield: 142 mg (34%); m.p.: > 300 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -1.96 (s, 2H, NH), 3.77-3.85 (m, 8H, C*H*$_2$OH), 3.97-4.02 (m, 4H, CH_2-O*H*), 4.14-4.24 (m, 4H, OCH_2C*H*), 4.37 (t, *J* = 5.6 Hz, 4H, CHO*H*), 4.54 (dd, *J* = 10.2, 6.2 Hz, 2H, Ar_F-OCH_2), 4.59 (dd, *J* = 10.2, 6.2 Hz, 2H, Ar_F-OCH_2), 4.65 (dd, *J* = 10.1, 4.4 Hz, 2H, Ar_F-OCH_2), 4.70 (dd, *J* = 10.1, 4.4 Hz, 2H, Ar_F-OCH_2), 5.41 (dd, *J* = 5.2, 1.9 Hz, 2H, 2,3-*β*-$H_{Pyrrole}$), 6.35-6.39 (m, 2H, 2,3-*β*-OH), 8.80 (s, 2H, 12,13-*β*-$H_{Pyrrole}$), 8.88 (d, *J* = 5.0 Hz, 2H, 7,18-*β*-$H_{Pyrrole}$), 9.10 (d, *J* = 5.0 Hz, 2H, 8,17-*β*-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 63.0 (CH_2OH), 71.2 (OCH_2CH), 71.3 (OCH_2CH), 73.4 (2,3-*β*-$H_{Pyrrole}$), 76.7 (Ar_F-OCH_2), 99.4 (5,20-Ar_F-C_{meso}), 106.7 (10,15,-Ar_F-C_{meso}), 113.3 (t, $^2J_{C\text{-}F}$ = 19.8 Hz, 10,15-Ar_F-C_{ipso}), 113.6 (t, $^2J_{C\text{-}F}$ = 20.3 Hz, 5,20-Ar_F-C_{ipso}), 124.9 (7,18-*β*-$C_{Pyrrole}$), 128.6 (8,17-*β*-

$C_{Pyrrole}$), 133.0 (12,13-β-$H_{Pyrrole}$), 135.8 (9,16-α-$C_{Pyrrole}$), 138.8 (Ar_F-C_{para}), 139.3 (Ar_F-C_{para}), 140.6 (6,19-α-$C_{Pyrrole}$), 141.4 (d, J = 246.4 Hz, Ar_F-C_{meta}), 146.1 (d, J = 244.3, Ar_F-C_{ortho}), 146.7 (d, J = 241.7 Hz, Ar_F-C_{ortho}), 147.4 (d, J = 242.6 Hz, Ar_F-C_{ortho}), 153.3 (11,14-α-$C_{Pyrrole}$), 165.6 (1,4-α-$C_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -138.54 to -138.72 (m, 2F, Ar-F_{ortho}), -142.15 (dd, J = 23.7, 8.3 Hz, 2F, Ar-F_{ortho}), -142.25 (dd, J = 23.7, 8.2 Hz, 2F, Ar-F_{ortho}), -143.75 (dd, J = 23.3, 8.1 Hz, 2F, Ar-F_{ortho}), -158.61 to -158.87 (m, 4F, Ar-F_{meta}), -159.30 to -159.63 (m, 4F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): m/z calc. for $C_{56}H_{41}F_{16}N_4O_{14}$ $[M + H]^+$: 1297.2364; found: 1297.2345.

UV-VIS (MeOH), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 400 (5.15), 503 (4.22), 527.5 (3.87), 594 (3.78), 646 (4.51).

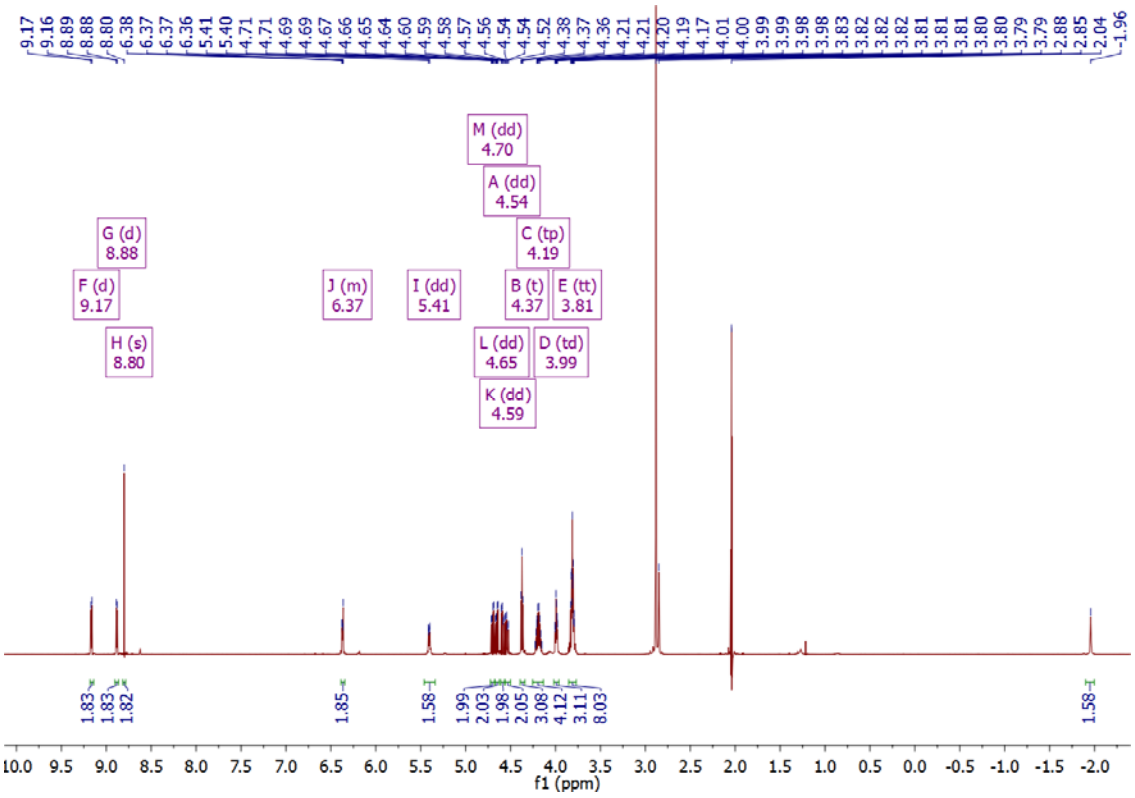


Figure 10. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of dihydroxychlorin **28**.

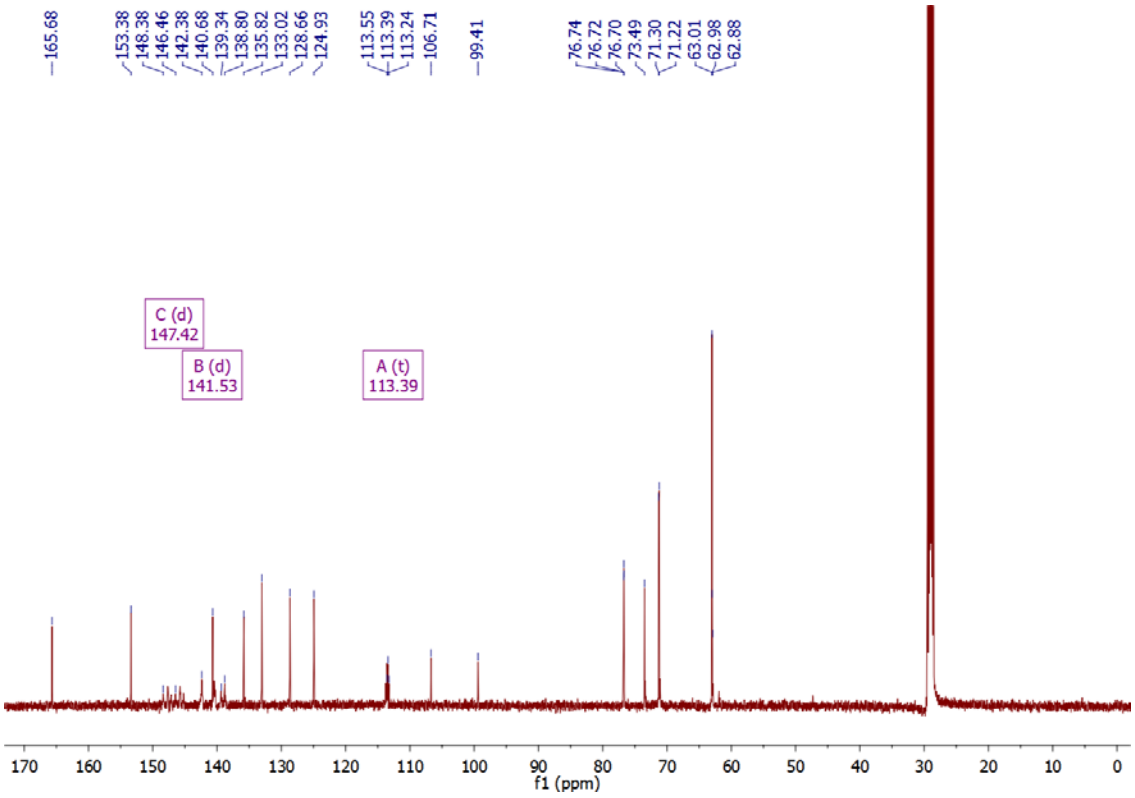


Figure 11. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydroxychlorin **28**.

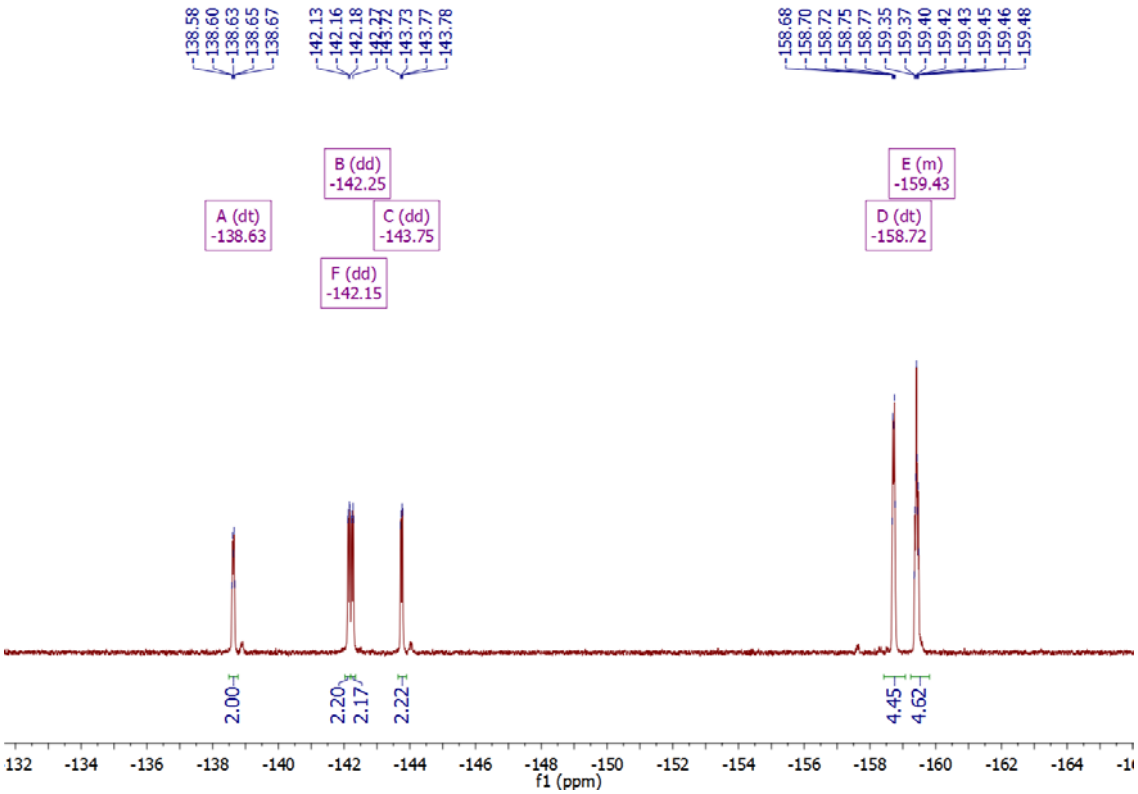


Figure 12. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of dihydroxychlorin **28**.

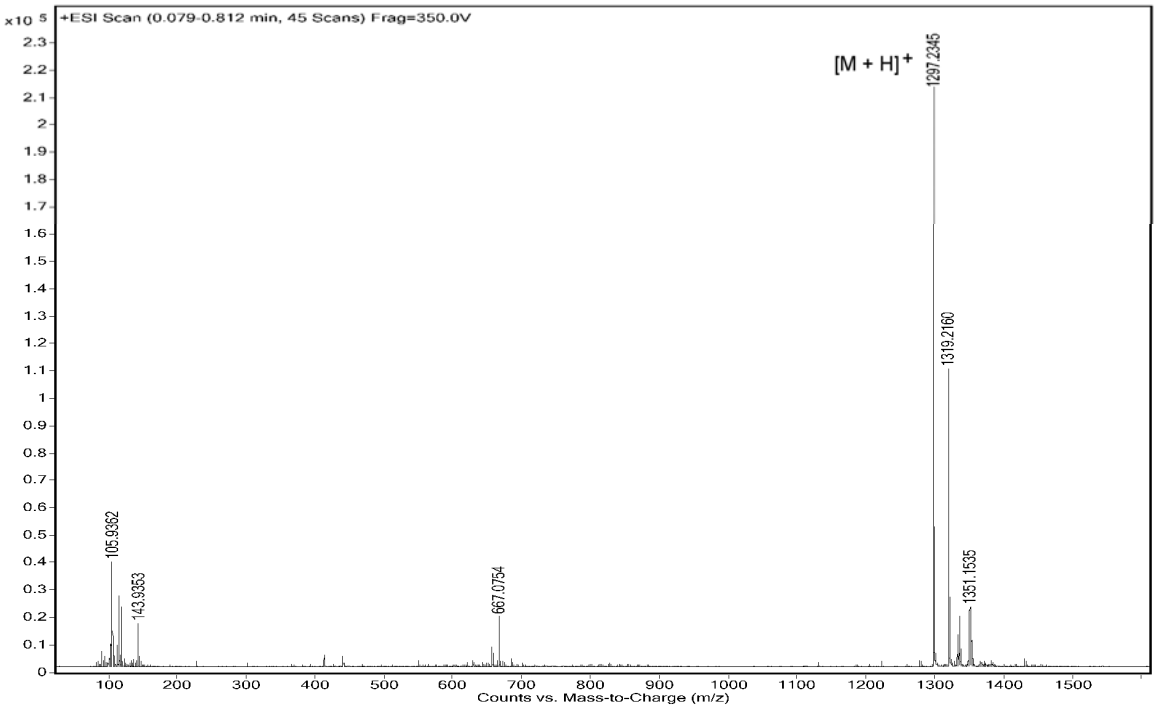
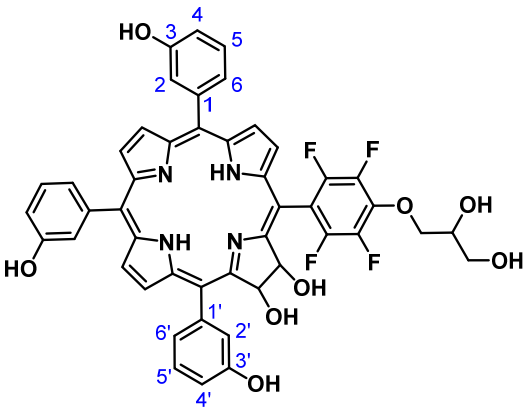


Figure 13. HRMS spectrum of dihydroxychlorin **28**.

5-[2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl]-7,8-dihydroxy-10,15,20-(3-hydroxyphenyl)chlorin (33)



All reaction steps were performed under argon atmosphere. In a 250 mL three-necked flask with two gas-inlet valves 5,10,15-tris(3-hydroxyphenyl)-20-[2,3,5,6-tetrafluor-4-(2,3-dihydroxypropyloxy) phenyl]porphyrin (490 mg, 0.594 mmol) was dissolved in 15.0 mL pyridine, OsO_4 (250 mg, 0.393 mmol) added and the mixture stirred for 18 hours at RT. Then, Na_2SO_3 (1.0 g in a saturated solution of H_2O/MeOH = 1:1) was added and the mixture stirred again over night at room temperature. The mixture was then poured over celite, washed off with methanol, evaporated to dryness, dissolved in ethyl acetate and washed three times with water. The product was purified by column chromatography (ethyl acetate/MeOH = 17:3, v/v) and recrystallization (acetone/*n*-hexane) to obtain the product as a purple solid. Yield: 278 mg (54%); m.p.: 285 °C.

^{1}H-NMR (400 MHz, D_6-acetone): δ = -1.67 (s, 1H, NH), -1.60 (s, 1H, NH), 3.76-3.85 (m, 2H, C*H*$_2$OH), 4.04 (br s, 1H, CH$_2$O*H*), 4.12-4.22 (m, 1H, OCH$_2$C*H*), 4.35-4.45 (br s, 1H, CH-O*H*), 4.52 (dd, *J* = 10.1, 6.1 Hz, 1H, Ar$_F$-OCH$_2$), 4.63 (dd, *J* = 10.1, 4.5 Hz, 1H, Ar$_F$-OCH$_2$), 4.90 (br s, 1H, 2,3-*β*-OH), 5.04 (br s, 1H, 2,3-*β*-OH), 6.18-6.28 (m, 1H, 2,3- *β*-H$_{Pyrrole}$), 6.34-6.40 (m, 1H, 2,3- *β*-H$_{Pyrrole}$), 7.15-7.20 (m, 1H, Ar-H-6′), 7.24-7.29 (m, 2H, Ar-H-6), 7.46-7.71 (m, 9H, Ar-H), 8.42 (d, *J* = 4.9 Hz, 1H, *β*-H$_{Pyrrole}$), 8.52 (s, 2H, *β*-H$_{Pyrrole}$), 8.66 (d, *J* = 5.0 Hz, 1H, 7-*β*-H$_{Pyrrole}$), 8.73 (br s, 1H, Ar-OH), 8.76 (d, *J* = 4.9 Hz, 1H, *β*-H$_{Pyrrole}$), 8.78 (br s, 1H, Ar-OH), 8.82 (d, *J* = 4.9 Hz, 1H, 8-*β*-H$_{Pyrrole}$) 8.86-8.96 (m, 1H, Ar-OH) ppm.

^{13}C-NMR (126 MHz, D_6-acetone): δ = 63.0 (CH$_2$OH), 71.2 (OCH$_2$CH), 72.3 (2,3-*β*-C$_{Pyrrole}$), 75.5 (2,3-*β*-C$_{Pyrrole}$), 76.6 (Ar$_F$-OCH$_2$), 96.7 (5-Ar$_F$-C$_{meso}$), 114.3 (20-Ar-C$_{meso}$), 114.5 (Ar$_F$-C$_{ipso}$), 114.6 (Ar-C-6′), 115.1 (Ar-C-6), 120.0 (Ar-C), 121.3 (Ar-C), 121.4 (Ar-C), 121.7 (Ar-C), 122.7 (7-*β*-C$_{Pyrrole}$), 123.3 (Ar-C$_{meso}$), 123.8 (Ar-C$_{meso}$), 124.2 (Ar-C), 124.7 (*β*-C$_{Pyrrole}$), 125.6 (Ar-C), 125.7 (Ar-C), 126.0 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 128.2 (Ar-C), 128.4 (*β*-C$_{Pyrrole}$), 128.9 (*β*-C$_{Pyrrole}$), 132.5 (*β*-C$_{Pyrrole}$), 132.7 (*β*-C$_{Pyrrole}$), 135.3 (*α*-C$_{Pyrrole}$), 135.4 (*α*-C$_{Pyrrole}$), 138.2 (Ar$_F$-C$_{para}$), 140.0 (*α*-C$_{Pyrrole}$), 141.2 (*α*-C$_{Pyrrole}$), 141.4 (d, $^1J_{C\text{-}F}$ = 245.5 Hz, Ar$_F$-C$_{meta}$), 142.5 (Ar-C-1′), 142.6 (Ar-C-1′), 142.8 (Ar-C-1), 142.9 (Ar-C-1), 146.31 (d, *J* = 241.9 Hz, Ar$_F$-C$_{ortho}$), 147.20 (d, *J* = 241.2 Hz, Ar$_F$-C$_{ortho}$), 153.0 (*α*-C$_{Pyrrole}$), 153.1 (*α*-C$_{Pyrrole}$), 156.1 (Ar-C-3′), 156.3 (Ar-C-3), 156.5 (Ar-C-3), 163.3 (*α*-C$_{Pyrrole}$), 164.4 (1,4-*α*-C$_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-acetone): δ = -138.45 to -138.63 (m, 2F, Ar-F_{ortho}), -144.57 to -144.85 (m, 2F, Ar-F_{ortho}), -159.83 to -160.13 (m, 2F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): *m/z* calc. for $C_{47}H_{35}F_4N_4O_8$ $[M + H]^+$: 859.2351, found: 859.2837.

UV-VIS (MeOH), λ_{max} [log ε (L · mol^{-1} · cm^{-1})]: 405 (5.19), 511.5 (4.37), 538.5 (4.07), 592 (3.72), 644.5 (4.40).

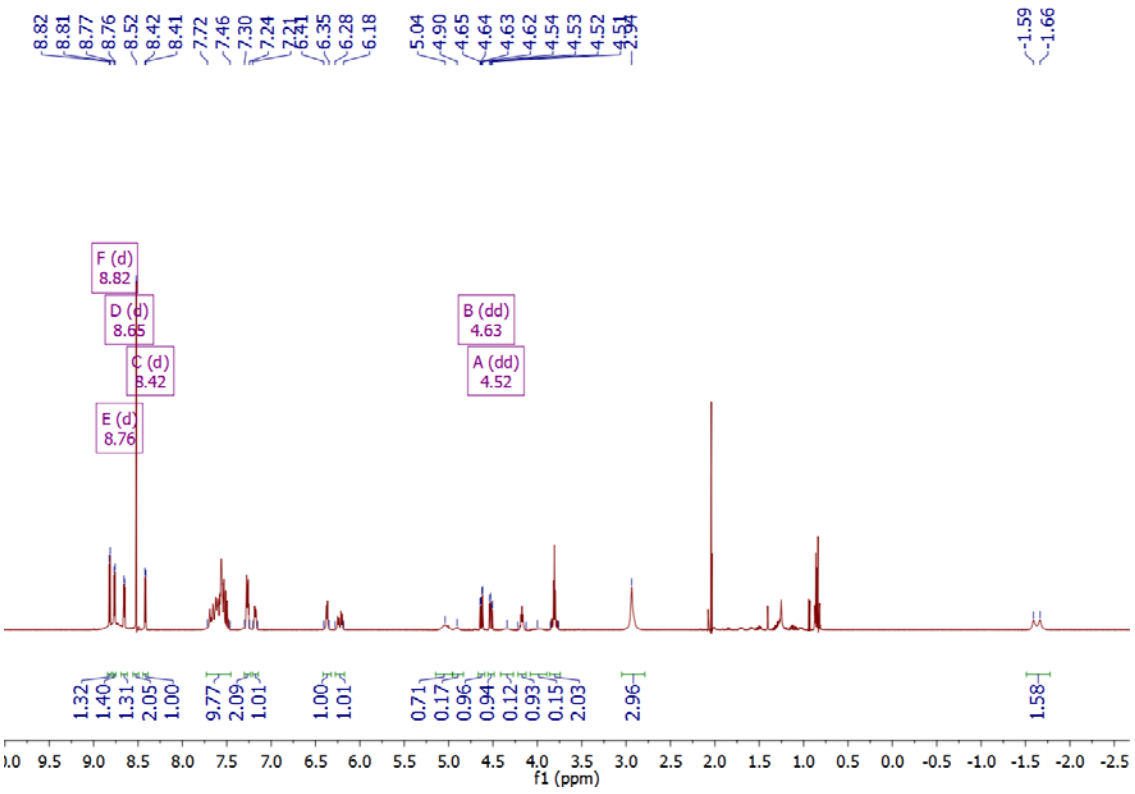


Figure 14. ^{1}H-NMR (400 MHz, D_6-acetone) spectrum of dihydroxychlorin **33**.

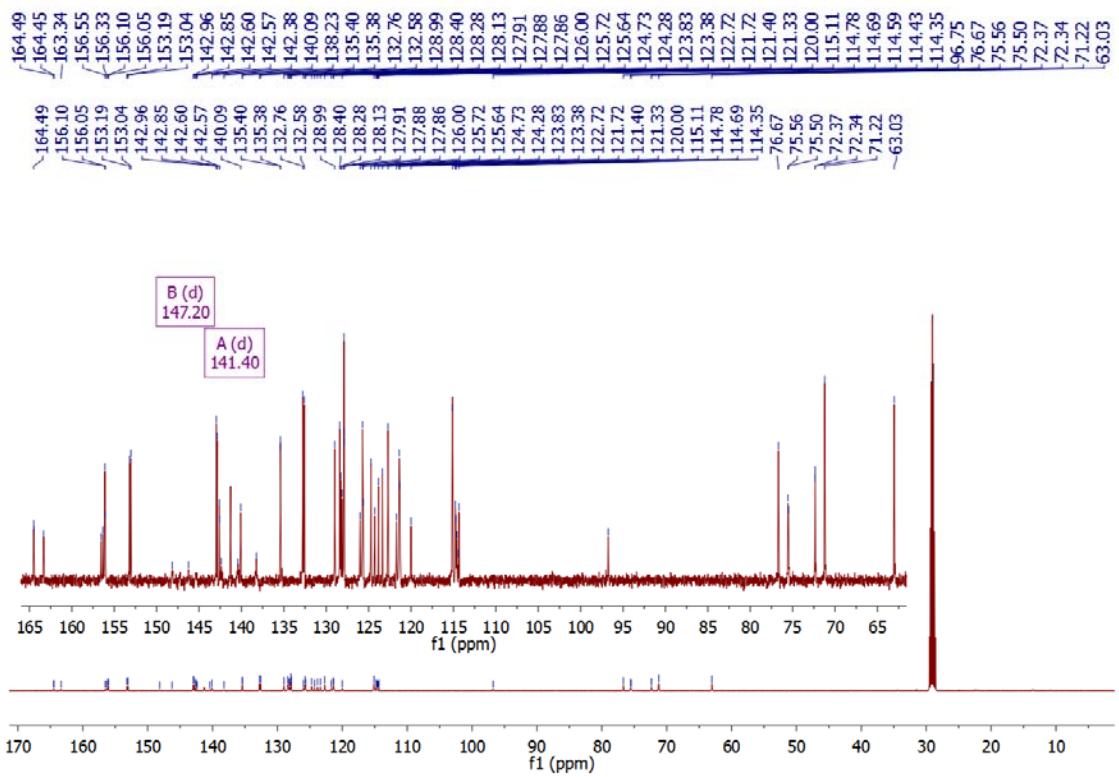


Figure 15. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydroxychlorin **33**.

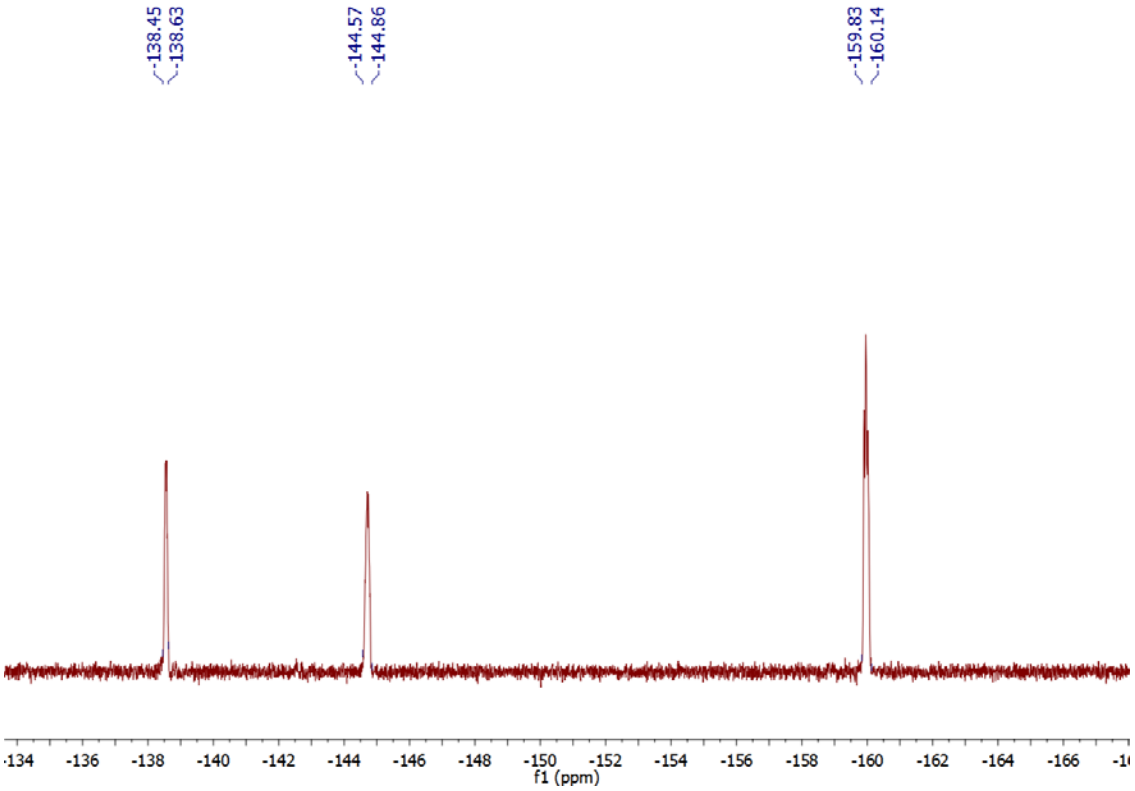


Figure 16. ^{19}F-NMR (400 MHz, D_6-acetone) spectrum of dihydroxychlorin **33**.

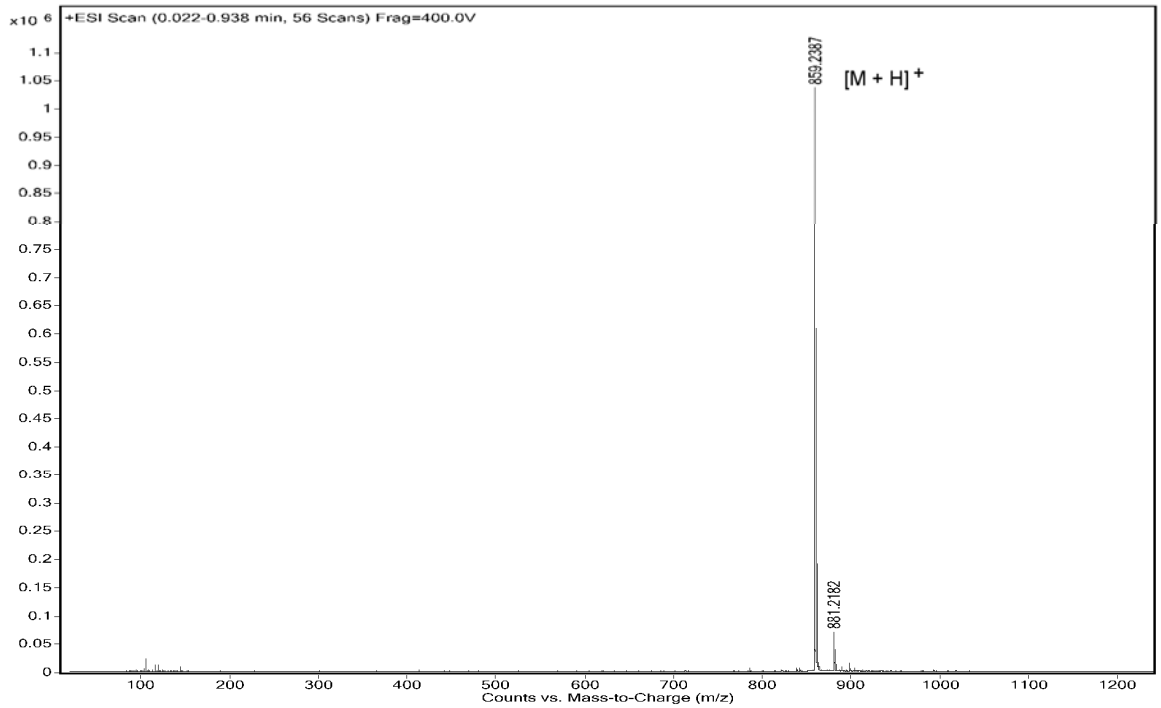
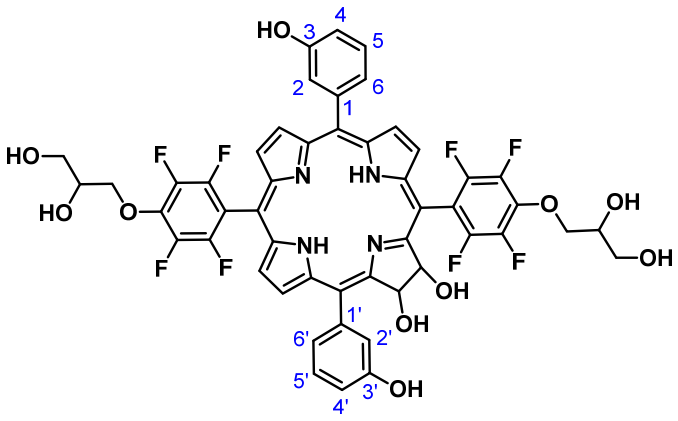


Figure 17. HRMS spectrum of dihydroxychlorin **33**.

5,15-[2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl]-7,8-dihydroxy-10,20-(3-hydroxyphenyl)chlorin (34)



All reaction steps were performed under argon atmosphere. In a 250 mL three-necked flask with two gas-inlet valves 5,15-bis(3-hydroxyphenyl)-10,20-bis[2,3,5,6-tetrafluoro-4-(2,3-dihydroxypropyloxy) phenyl]porphyrin (185 mg, 0.190 mmol) was dissolved in 15.0 mL pyridine, OsO_4 (50 mg, 0.196 mmol) added and the mixture stirred for 18 hours at RT. Then, Na_2SO_3 (1.0 g in a saturated solution of H_2O/MeOH = 1:1, v/v) was added and the mixture stirred again over night at room temperature. The mixture was then poured over celite, washed off with methanol, evaporated to dryness, dissolved in ethyl acetate and washed three times with water. The product was purified by reversed phase column chromatography (MeOH/H_2O = 9:1, v/v) and recrystallization (acetone/*n*-hexane and washed with DCM) to obtain the product as a purple solid. Yield: 72 mg (38%); m.p.: > 300 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -1.90 (s, 1H, NH), -1.79 (s, 1H, NH), 3.75-3.85 (m, 4H, C*H*$_2$OH), 3.96 (d, J = 6.3 Hz, 2H, CH-O*H*), 4.13-4.25 (m, 2H, OCH$_2$C*H*), 4.28-4.40 (m, 2H, CH$_2$O*H*), 4.52 (dd, *J* = 10.1, 6.2 Hz, 2H, Ar$_F$-OCH$_2$), 4.58 (dd, *J* = 10.1, 4.5 Hz, 2H, Ar$_F$-OCH$_2$), 4.63 (dd, *J* = 10.1, 4.5 Hz, 2H, Ar$_F$-OCH$_2$), 4.69 (dd, *J* = 10.2, 4.4 Hz, 2H, Ar$_F$-OCH$_2$), 4.93-4.98 (m, 2,3-*β*-OH), 5.02-5.12 (m, 2,3-*β*-OH), 6.23-6.33 (m, 1H, 2,3-*β*-H$_{Pyrrole}$), 6.37-6.43 (m, 2,3-*β*-H$_{Pyrrole}$), 7.17-7.22 (m, 1H, Ar-H-6′), 7.27-7.31 (m, 1H, Ar-H-6), 7.49-7.68 (m, 6H, Ar-H), 8.61 (d, *J* = 5.0 Hz, 1H, *β*-H$_{Pyrrole}$), 8.66 (d, *J* = 4.6 Hz, 1H, *β*-H$_{Pyrrole}$), 8.69 (br s, 1H, Ar-OH), 8.72 (d, *J* = 5.0 Hz, *β*-H$_{Pyrrole}$), 8.82 (br s, 1H, Ar-OH), 8.87 (d, *J* = 4.6 Hz, 1H, *β*-H$_{Pyrrole}$), 8.98 (d, *J* = 5.0 Hz, 1H, *β*-H$_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 63.0 (CH$_2$OH), 71.2 (OCH$_2$CH), 71.3 (OCH$_2$CH), 72.4 (2,3-*β*-C$_{Pyrrole}$), 75.3 (2,3-*β*-C$_{Pyrrole}$), 76.7 (Ar$_F$-OCH$_2$), 76.7 (Ar$_F$-OCH$_2$), 98.1 (5-Ar$_F$-C$_{meso}$), 105.2 (15-Ar$_F$-C$_{meso}$), 113.4 (20-Ar-C$_{meso}$), 114.0 (m, 15-Ar$_F$-C$_{ipso}$), 114.4 (m, 5-Ar$_F$-C$_{ipso}$), 114.8 (Ar-C-6′), 114.9 (Ar-C-6′), 115.0 (Ar-C-6), 115.2 (Ar-C-6), 120.0 (Ar-C), 121.4 (Ar-C), 121.7 (Ar-C), 123.1 (*β*-C$_{Pyrrole}$), 123.7 (10-Ar-C$_{meso}$), 124.3 (Ar-C), 125.8 (Ar-C), 126.0 (*β*-C$_{Pyrrole}$), 127.1 (*β*-C$_{Pyrrole}$), 127.9 (Ar-C), 127.9 (Ar-C), 128.1 (Ar-C), 128.3 (Ar-C), 129.1 (*β*-C$_{Pyrrole}$), 130.5 (*α*-C$_{Pyrrole}$), 131.3 (*β*-C$_{Pyrrole}$), 132.9 (*α*-C$_{Pyrrole}$), 133.9 (*β*-C$_{Pyrrole}$), 135.4 (*α*-C$_{Pyrrole}$), 135.7 (*α*-C$_{Pyrrole}$), 138.3 (Ar$_F$-C$_{para}$), 139.8 (*α*-C$_{Pyrrole}$), 141.1-141.4 (m, Ar$_F$-C$_{meta}$), 141.4 (*α*-C$_{Pyrrole}$), 142.2 (Ar-C-1′), 142.2 (Ar-C-1), 142.5 (*α*-C$_{Pyrrole}$), 145.7 (Ar$_F$-C$_{ortho}$), 147.6 (Ar$_F$-C$_{ortho}$), 152.6 (*α*-C$_{Pyrrole}$), 153.4 (*α*-C$_{Pyrrole}$), 156.0 (Ar-C-3′), 156.3 (Ar-C-3), 164.33-164.61 (m, 1,4-*α*-C$_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -138.57 (dd, *J* = 22.7, 10.1 Hz, 1F, Ar-F_{ortho}), -142.18 (d, *J* = 23.3 Hz, 1F, Ar-F_{ortho}), -142.35 (d, *J* = 23.1 Hz, 1F, Ar-F_{ortho}), -144.63 to -144.84 (m, 1F, Ar-F_{ortho}), -158.80 to -159.05 (m, 2F, Ar-F_{meta}), -159.78 to -160.04 (m, 2F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): *m/z* calc. for $C_{50}H_{37}F_8N_4O_{10}$ $[M + H]^+$: 1005.2382, found: 1005.2372.

UV-VIS (MeOH), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 409 (5.35), 509 (4.33), 537 (4.20), 594 (3.90), 648 (4.61).

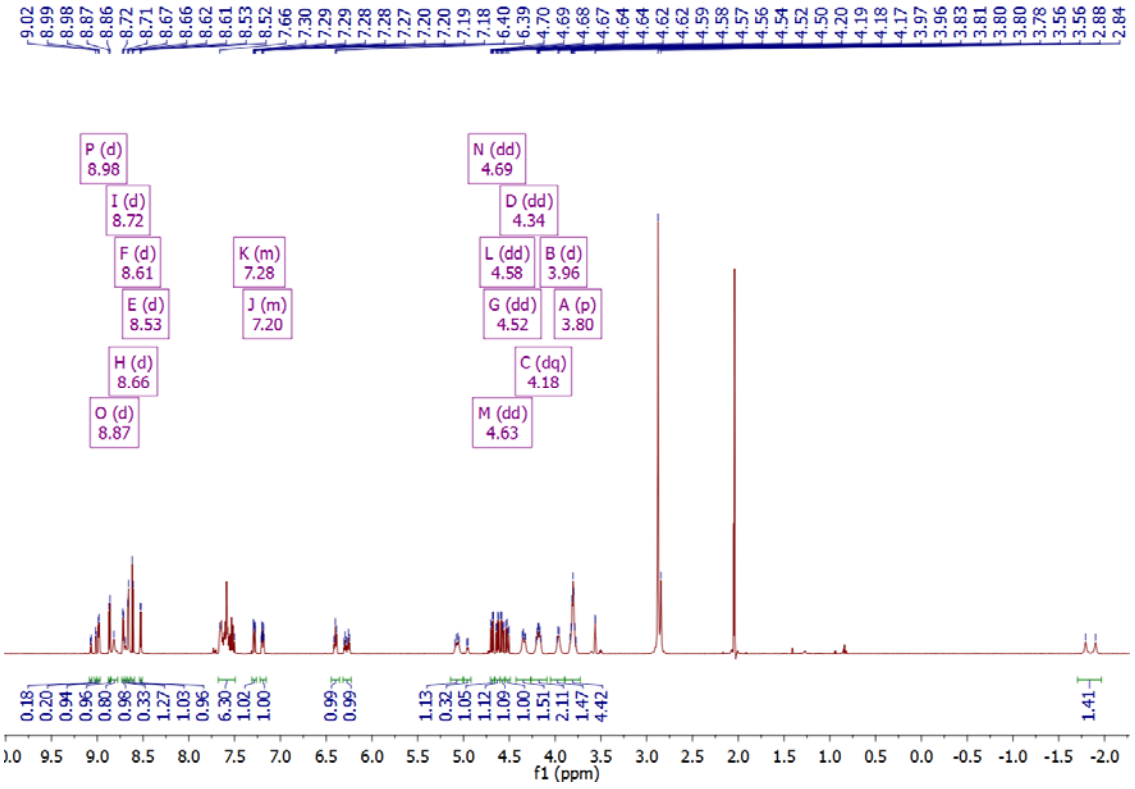


Figure 18. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of dihydroxychlorin **34**.

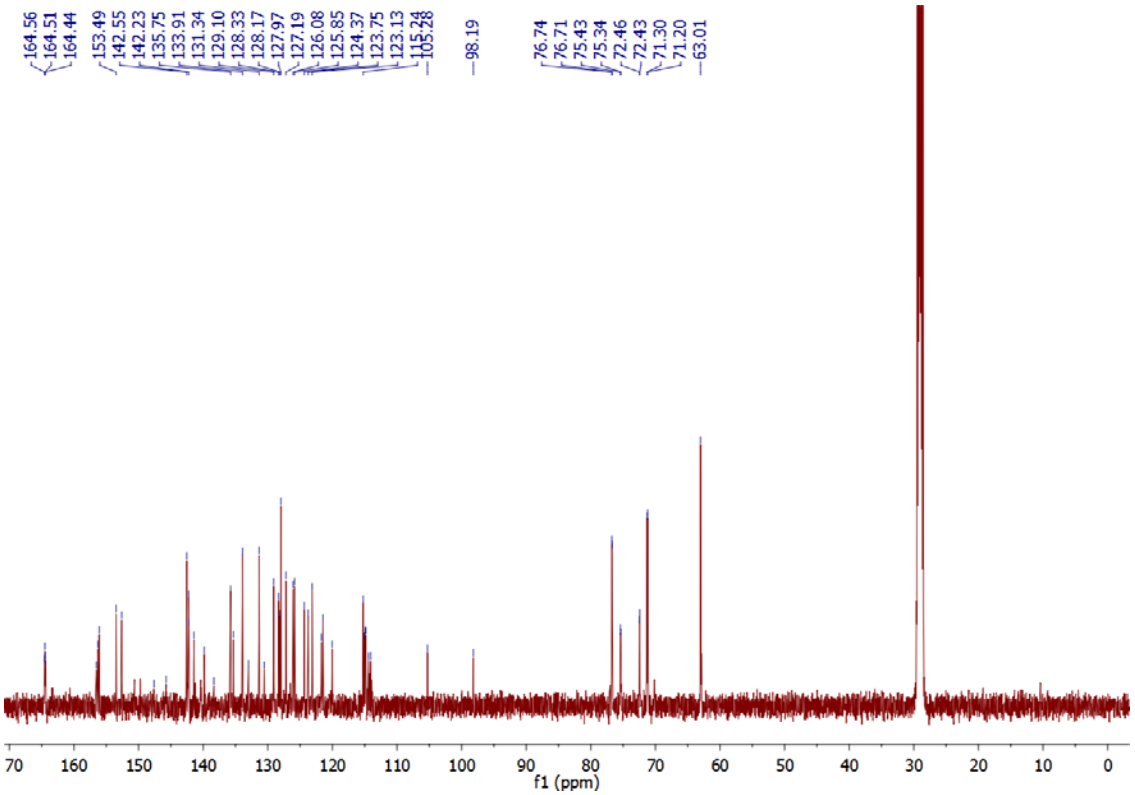


Figure 19. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydroxychlorin **34**.

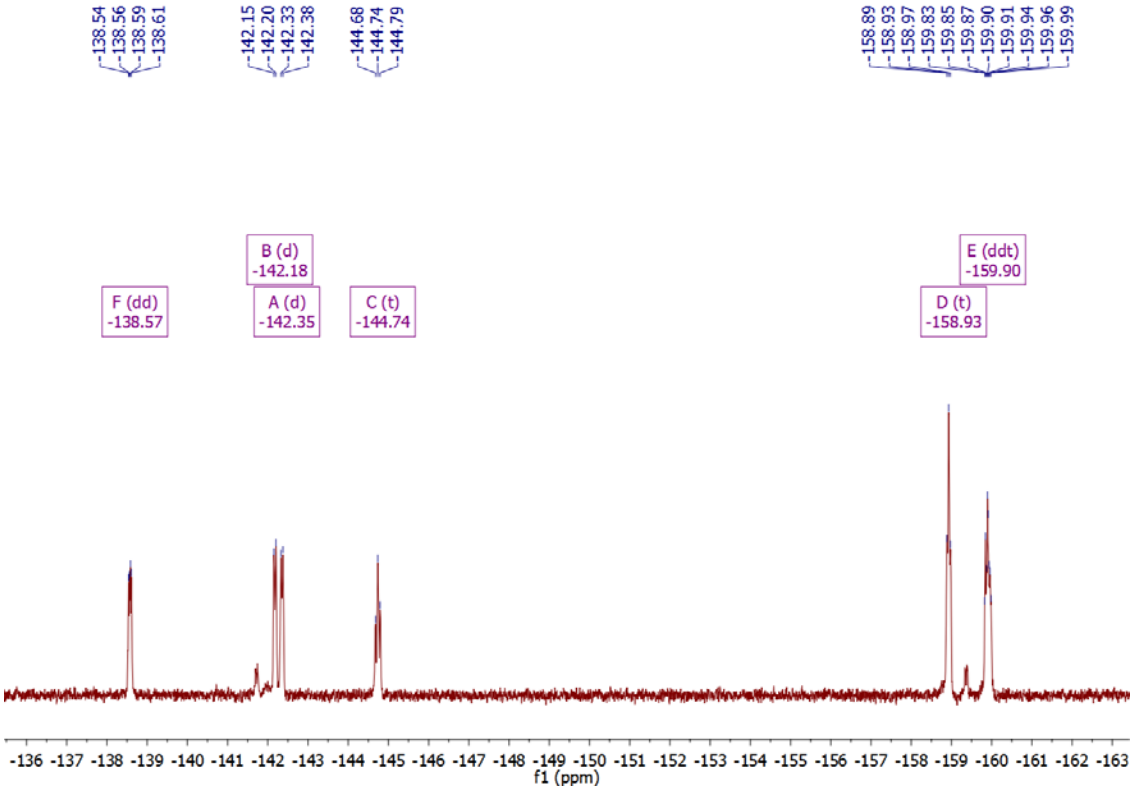


Figure 20. ^{19}F-NMR spectrum (376 MHz, D_6-acetone) of dihydroxychlorin **34**.

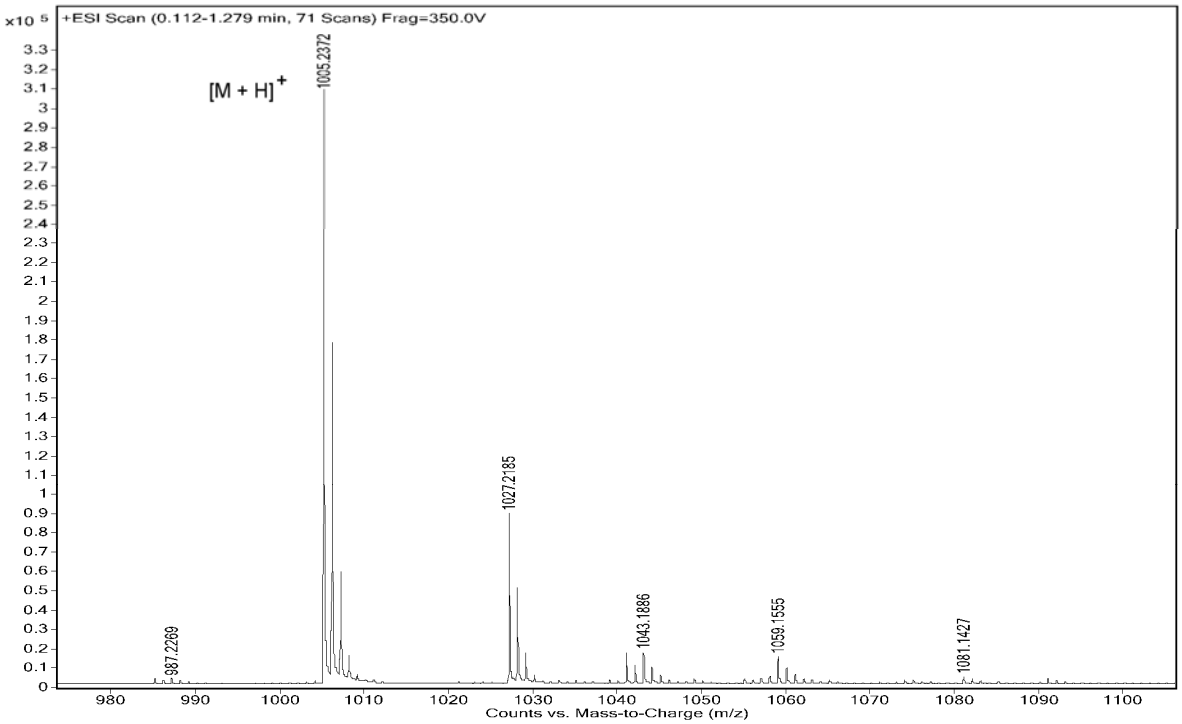
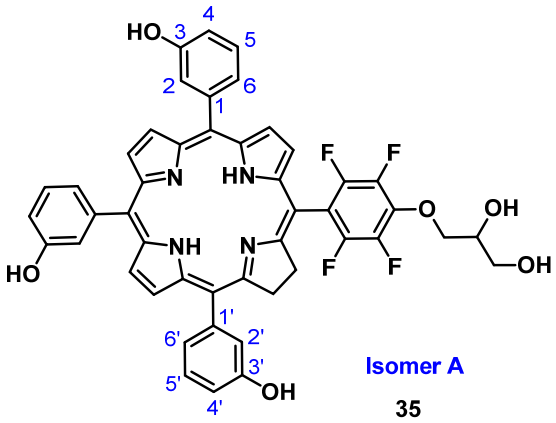


Figure 21. HRMS spectrum of dihydroxychlorin **34**.

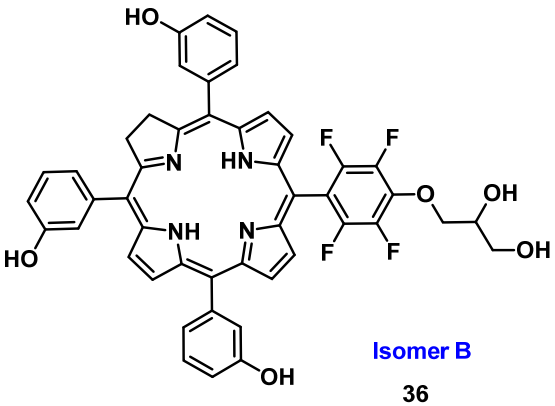
1.7.2 *Reduction to Chlorins*

5-(2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl)-7,8-dihydro-10,15,20-(3-hydroxyphenyl)chlorin (35) and (36)



Isomer A

35



Isomer B

36

All steps were performed under argon atmosphere. In a 250 mL three-necked flask *p*-toluenesulfonyl hydrazide (359.0 mg, 0.482 mmol), 5,10,15-tris(3-hydroxyphenyl)-20-[2,3,5,6-tetrafluor-4-(2,3-dihydroxypropyloxy)phenyl]porphyrin (400 mg, 2.89 mmol) and K_2CO_3 (400 mg, 2.89 mmol) were dissolved in 25.0 mL pyridine and stirred for 20 min at RT. Afterwards the reaction mixture was heated to 105 °C. Additional *p*-toluenesulfonyl hydrazide (359 mg, 1.93 mmol) in 1.0 mL pyridine was added after 2 and 4 h. After 6.5 h heating 168 mL ethyl acetate and 84 mL H_2O were added and the reaction mixture was refluxed for 1 h at 100 °C. The organic layer was washed with 168 mL 2 M HCl, 168 mL H_2O and 168 mL saturated $NaHCO_3$-solution, afterwards dried over Na_2SO_4 and evaporated to dryness. Then, the solid was dissolved in ethyl acetate (100 mL) and tetrachloro-*o*-benzoquinone (in a total of 288 mg, 1.17 mmol) was added in small portions (20 mg) every 15 min at RT to the stirring solution until the band at 735 nm in the UV/Vis spectrum just disappeared. The organic layer was washed twice with 168 mL 5% NaHSO3, once with 224 mL 0.01 M NaOH and once with 180 mL saturated $NaHCO_3$-solution and afterwards dried over Na_2SO_4. The product was evaporated to dryness and purified by reversed phase column chromatography (acetone/*n*-hexane = 3:2, v/v) to obtain the isomeric mixture as purple crystals. Yield: 243 mg (60%); m.p.: 290 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -1.69 (s, 1H, NH), -1.65 (s, 1H, NH), -1.33 (s, 1H, NH), -1.20 (s, 1H, NH), 3.75-3.85 (m, 2H, CH_2OH), 4.13-4.21 (m, 1H, OCH$_2$C*H*), 4.23-4.32 (m, 4H, 2,3-*β*-$H_{Pyrrole}$ + 12,13-*β*-$H_{Pyrrole}$), 4.51-4.60 (m, 1H, Ar_F-OCH$_2$), 4.62-4.71 (m, 1H, Ar_F-OCH$_2$), 7.17-7.19 (m, 1H, Ar-H-6′), 7.19-7.21 (m, 1H, Ar-H-6′), 7.23-7.25 (m, 1H, Ar-H-6), 7.25-7.29 (m, 1H, Ar-H-6), 7.36-7.45 (m, 4H, Ar-H-2′ + Ar-H-4′), 7.52-7.64 (m, 8H, Ar-H), 8.30 (d, *J* = 4.9 Hz, 1H, *β*-$H_{Pyrrole}$), 8.35 (d, *J* = 4.9 Hz, 1H, *β*-$H_{Pyrrole}$), 8.40 (d, *J* = 5.0 Hz, 1H, *β*-$H_{Pyrrole}$), 8.42-8.45 (m, 2H, *β*-$H_{Pyrrole}$), 8.48 (d, *J* = 4.9 Hz, 1H, *β*-$H_{Pyrrole}$), 8.54 (d, *J* = 4.5 Hz, 1H, *β*-$H_{Pyrrole}$), 8.57 (d, *J* = 4.5 Hz, 1H, *β*-$H_{Pyrrole}$), 8.69 (d, *J* = 4.9 Hz, 1H, *β*-$H_{Pyrrole}$), 8.73 (d, *J* = 4.8 Hz, 1H, *β*-$H_{Pyrrole}$), 8.83 (br s, 3H, Ar-OH), 8.88 (d, *J* = 4.9 Hz, 1H, *β*-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 34.7 (β-$C_{Pyrrole}$), 35.3 (β-$C_{Pyrrole}$), 35.4 (β-$C_{Pyrrole}$), 35.6 (β-$C_{Pyrrole}$), 62.9 (CH_2OH), 71.2 (OCH_2CH), 76.7 (Ar_F-OCH_2), 112.5 (Ar-C_{meso}), 113.2 (Ar-C_{meso}), 113.5 (Ar-C_{meso}), 114.6 (Ar_F-C_{ipso}), 114.7-115.1 (m, Ar-C-6′ + Ar-C-6), 119.4 (Ar-C-2′), 121.2 (Ar-C-2), 121.7 (β-$C_{Pyrrole}$), 122.8 (Ar-C), 123.4 (Ar-C_{meso}), 123.5-123.9 (m, β-$C_{Pyrrole}$ + Ar-C-4′), 124.8 (β-$C_{Pyrrole}$), 125.5 (Ar-C-4), 125.6 (Ar-C), 126.6 (β-$C_{Pyrrole}$), 127.8 (Ar-C-5′), 128.0 (β-$C_{Pyrrole}$), 128.7 (β-$C_{Pyrrole}$), 128.8 (β-$C_{Pyrrole}$), 129.2 (Ar-C-5), 130.3 (β-$C_{Pyrrole}$), 132.0 (β-$C_{Pyrrole}$), 132.2 (β-$C_{Pyrrole}$), 133.1 (β-$C_{Pyrrole}$), 134.8 (α-$C_{Pyrrole}$), 134.8 (α-$C_{Pyrrole}$), 135.1 (α-$C_{Pyrrole}$), 135.2 (α-$C_{Pyrrole}$), 139.6 (α-$C_{Pyrrole}$), 141.3 (α-$C_{Pyrrole}$), 140.3 (α-$C_{Pyrrole}$), 140.4 (α-$C_{Pyrrole}$), 141.3 (α-$C_{Pyrrole}$), 142.9 (Ar-C-1′), 143.0 (Ar-C-1′), 143.0 (Ar-C-1), 143.8 (Ar-C-1), 143.8 (Ar-C), 144.1 (α-$C_{Pyrrole}$), 151.8 (α-$C_{Pyrrole}$), 152.4 (α-$C_{Pyrrole}$), 152.5 (α-$C_{Pyrrole}$), 152.8 (α-$C_{Pyrrole}$), 156.0 (Ar-C-3′), 157.2 (Ar-C-3), 167.6 (α-$C_{Pyrrole}$), 167.8 (α-$C_{Pyrrole}$), 168.8 (α-$C_{Pyrrole}$), 168.9 (α-$C_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -142.14 to -142.34 (m, 2F, Ar-F_{ortho}), -142.71 to -142.94 (m, 2F, Ar-F_{ortho}), -158.15 to -158.36 (m, 2F, Ar-F_{meta}), -159.07 (d, J = 20.6 Hz, 2F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): m/z calc. for $C_{47}H_{35}F_4N_4O_6$ $[M + H]^+$: 827.2493; found: 827.2484.

UV-VIS (Acetone), λ_{max} [log ε (L · mol^{-1} · cm^{-1})]: 416.5 (5.11), 515 (4.27), 542 (4.02), 599 (3.84), 652.5 (4.52) nm.

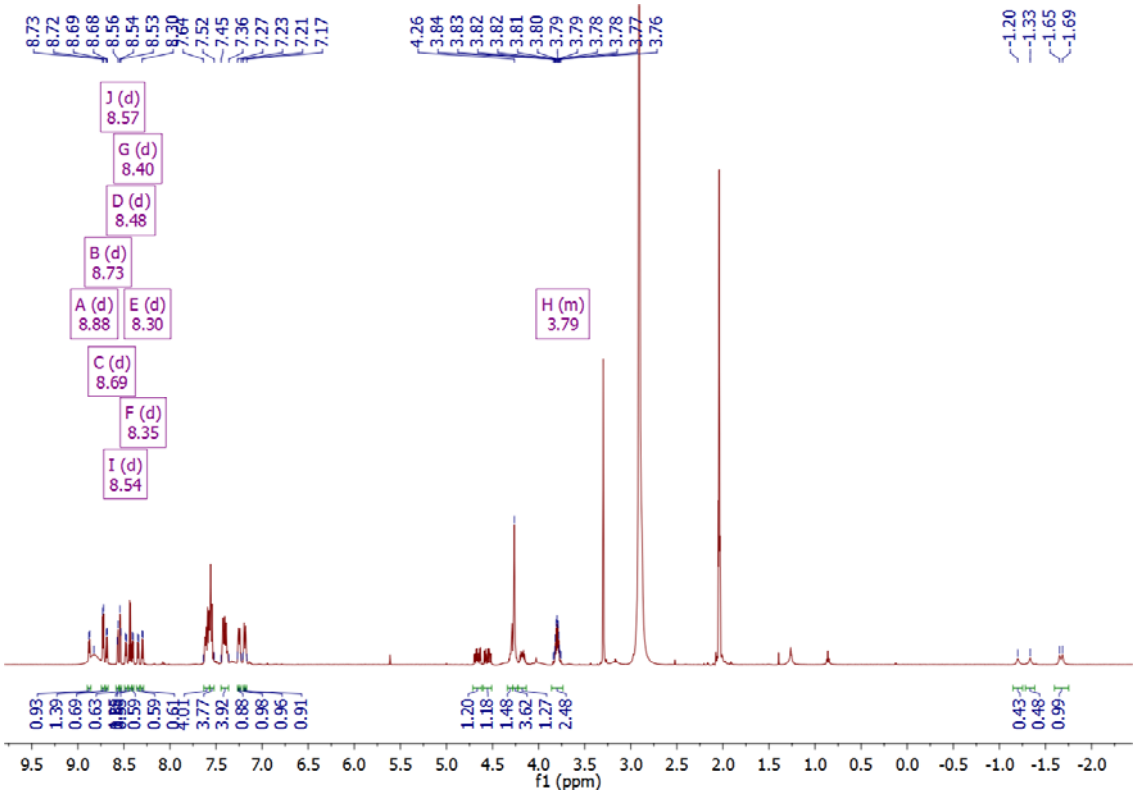


Figure 22. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of dihydrochlorin **35** and **36**.

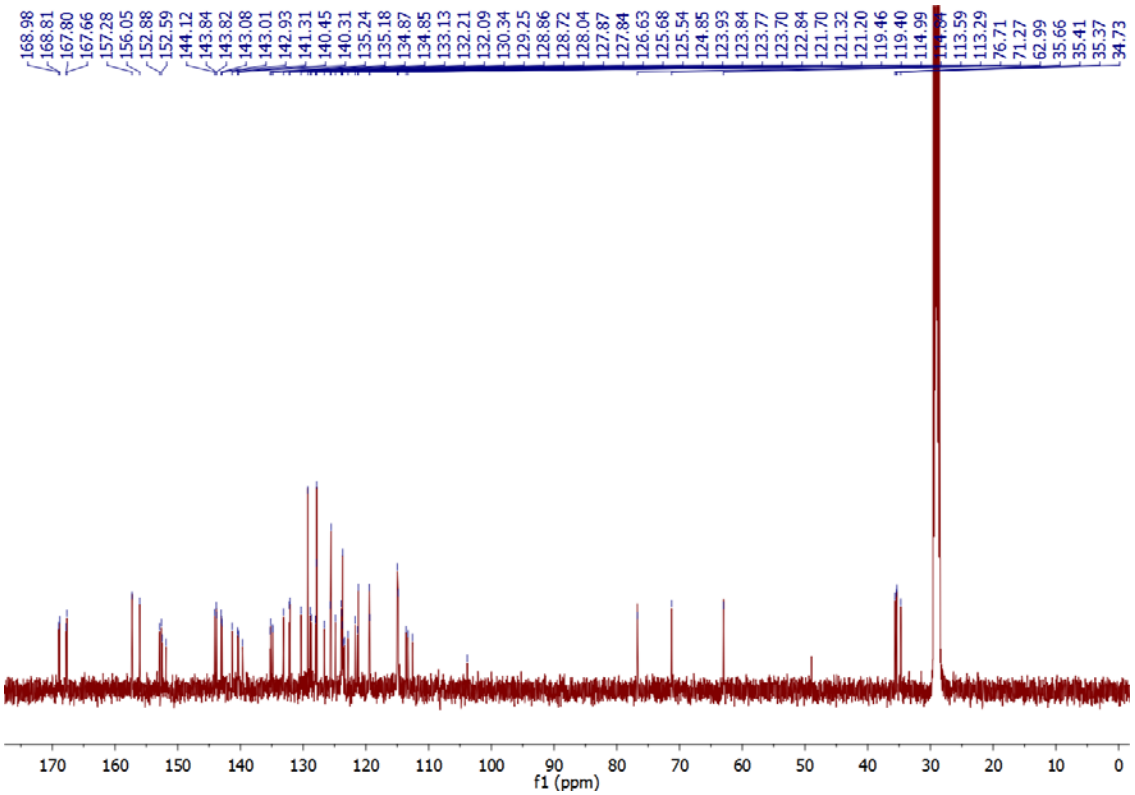


Figure 23. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydrochlorin **35** and **36**.

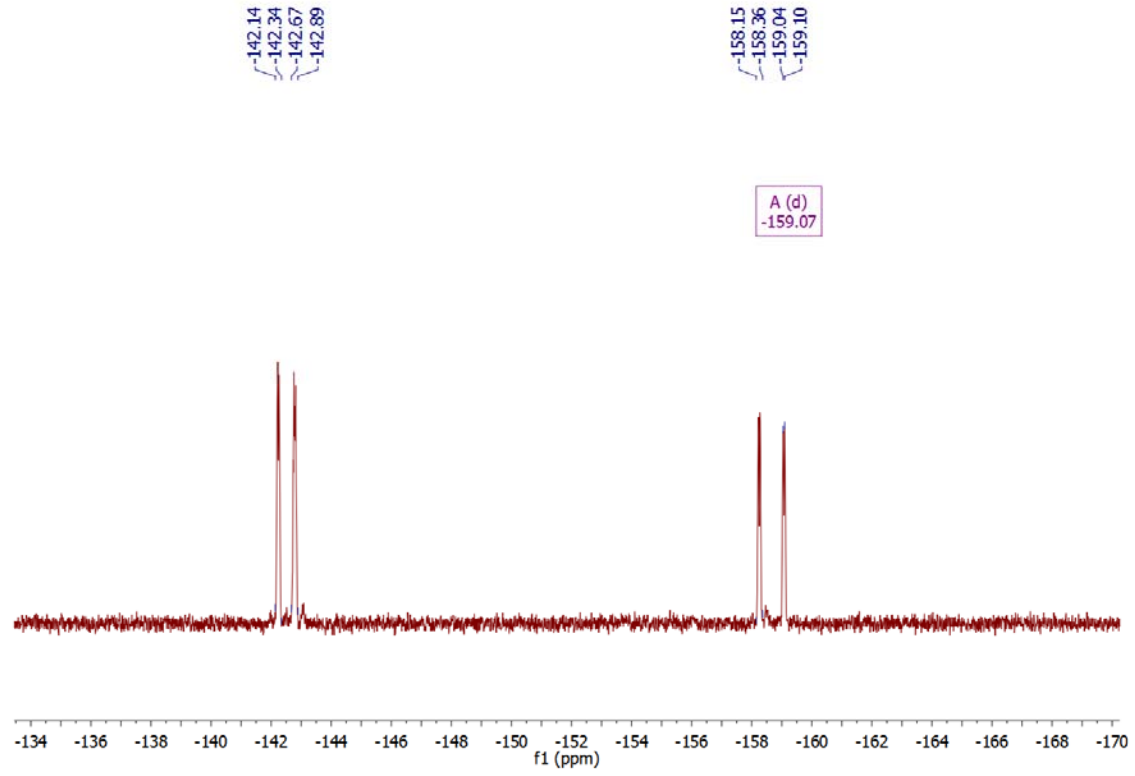


Figure 24. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of dihydrochlorin **35** and **36**.

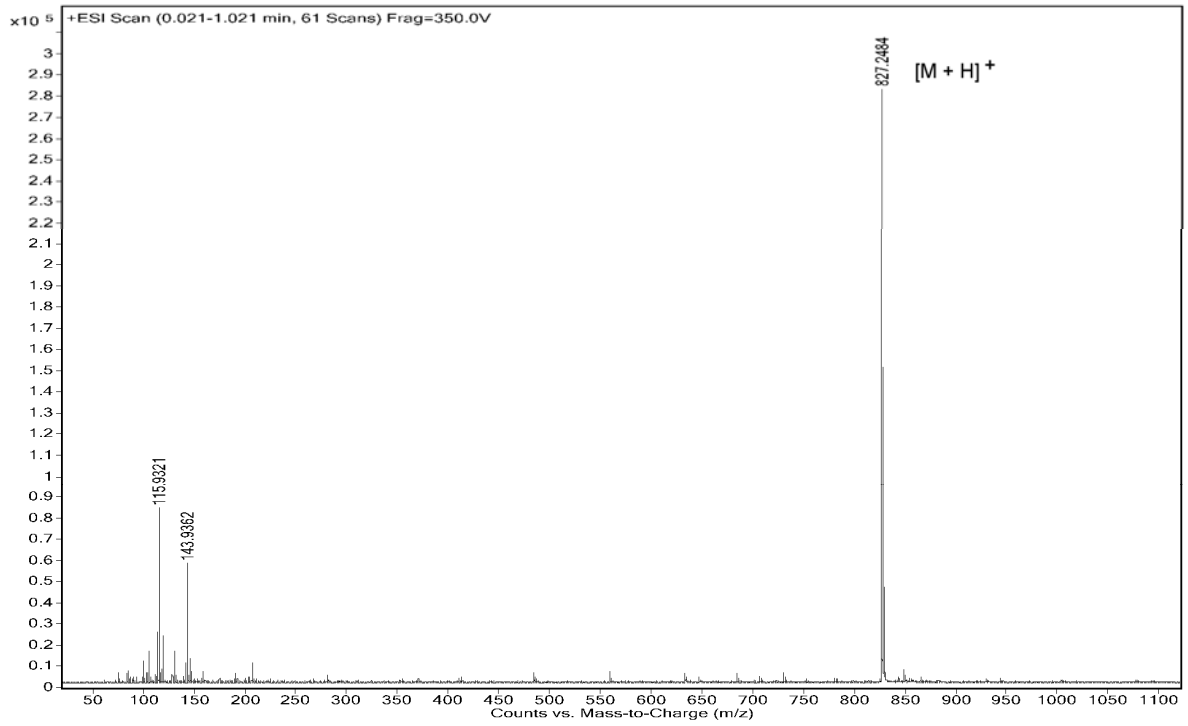
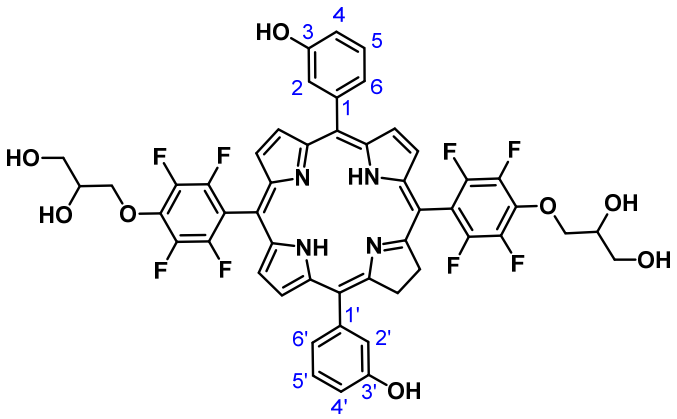


Figure 25. HRMS spectrum of dihydrochlorin **35** and **36**.

5,15-[2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl]-7,8-dihydro-10,20-(3-hydroxyphenyl)chlorin (37)



All steps were performed under argon atmosphere. In a 250 mL three-necked flask *p*-toluenesulfonyl hydrazide (150.0 mg, 0.80 mmol), 5,15-bis(3-hydroxyphenyl)-10,20-bis[2,3,5,6-tetrafluoro-4-(2,3-dihydroxypropyloxy)phenyl]porphyrin (234 mg, 0.185 mmol) and K_2CO_3 (400 mg, 2.89 mmol) were dissolved in 25.0 mL pyridine and stirred for 20 min at RT. Afterwards the reaction mixture was heated to 105 °C. Additional *p*-toluenesulfonyl hydrazide (150.0 mg, 0.80 mmol) in 1.0 mL pyridine was added after 2 and 4 h. After 6.5 h heating 168 mL ethyl acetate and 84 mL H_2O were added and the reaction mixture was refluxed for 1 h at 100 °C. The organic layer was washed with 168 mL 2 M HCl, 168 mL H_2O and 168 mL saturated $NaHCO_3$-solution, afterwards dried over Na_2SO_4 and evaporated to dryness. Then, the solid was dissolved in ethyl acetate (100 mL) and tetrachloro-*o*-benzoquinone (in a total of 167 mg, 0.68 mmol) was added in small portions (20 mg) every 15 min at RT to the stirring solution until the band at 735 nm in the UV/Vis spectrum just disappeared. The organic layer was washed twice with 168 mL 5% $NaHSO_3$, once with 224 mL 0.01 M NaOH and once with 180 mL saturated $NaHCO_3$-solution and afterwards dried over Na_2SO_4. The product was evaporated to dryness and purified by reversed phase column chromatography ($MeOH/H_2O$ = 9:1, v/v) to obtain the product as purple crystals. Yield: 240 mg (74%); m.p.: >300 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -1.51 (s, 1H, NH), -1.35 (s, 1H, NH), 3.75-3.86 (m, 4H, C*H*$_2$OH), 3.93-4.11 (m, 2H, CH-O*H*), 4.14-4.23 (m, 2H, OCH$_2$C*H*), 4.27-4.33 (m, 2H, 3-*β*-$H_{Pyrrole}$), 4.34-4.44 (m, 4H, 2-*β*-$H_{Pyrrole}$ + CH$_2$O*H*), 4.52-4.61 (m, 2H, Ar_F-OCH$_2$), 4.63-4.71 (m, 2H, Ar_F-OCH$_2$), 7.19-7.22 (m, 1H, Ar-H-6′), 7.25-7.29 (m, 1H, Ar-H-6), 7.41-7.44 (m, 1H, Ar-H-4′), 7.45-7.47 (m, 1H, Ar-H-2′), 7.55-7.60 (m, 2H, Ar-H-5 + Ar-H-5′), 7.60-7.62 (m, 1H, Ar-H-4), 7.63-7.65 (m, 1H, Ar-H-2), 8.42 (d, *J* = 5.0 Hz, 1H, *β*-$H_{Pyrrole}$), 8.53-8.58 (m, 3H, *β*-$H_{Pyrrole}$), 8.78 (d, *J* = 4.9 Hz, *β*-$H_{Pyrrole}$), 8.85 (br s, 1H, Ar-OH), 8.89 (br s, 1H, Ar-OH), 8.91 (d, *J* = 5.1 Hz, 1H, *β*-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 34.7 (3-*β*-$C_{Pyrrole}$), 35.7 (2-*β*-$C_{Pyrrole}$), 62.9 (CH$_2$OH), 63.0 (CH$_2$OH), 71.2 (OCH$_2$CH), 71.3 (OCH$_2$CH), 76.7 (Ar_F-OCH$_2$), 76.7 (Ar_F-OCH$_2$), 96.5 (5-Ar_F-C_{meso}), 104.9 (15-Ar_F-C_{meso}), 113.4 (20-Ar-C_{meso}), 114.2 (t, $^2J_{C\text{-}F}$ = 20.0 Hz, 15-Ar_F-C_{ipso}), 114.6 (t, $^2J_{C\text{-}F}$ = 20.4 Hz, 5-Ar_F-C_{ipso}), 115.0 (Ar-C-6′), 115.1 (Ar-C-6), 119.4 (Ar-C-2′), 121.2 (Ar-C-2), 122.0 (*β*-$C_{Pyrrole}$), 123.7 (Ar-C-4′), 124.2 (10-Ar-C_{meso}), 125.3 (*β*-$C_{Pyrrole}$), 125.6 (Ar-C-4), 127.5 (*β*-$C_{Pyrrole}$),

127.9 (Ar-C-5′), 129.0 (β-$C_{Pyrrole}$), 129.3 (Ar-C-5), 130.6 (β-$C_{Pyrrole}$), 133.5 (β-$C_{Pyrrole}$), 135.1 (α-$C_{Pyrrole}$), 135.3 (α-$C_{Pyrrole}$), 138.6-139.1 (m, 5-Ar_F-C_{para} + 15-Ar_F-C_{para}), 139.4 (α-$C_{Pyrrole}$), 141.26 (dd, $^{1,2}J_{C\text{-}F}$ = 246.7, 15.7 Hz, Ar_F-C_{meta}), 141.3 (α-$C_{Pyrrole}$), 141.8 (dd, $^{1,2}J_{C\text{-}F}$ = 246.6, 15.1 Hz, Ar_F-C_{meta}), 142.6 (Ar-C-1′), 143.4 (Ar-C-1), 146.17 (d, $^{1}J_{C\text{-}F}$ = 238.6 Hz, Ar_F-C_{ortho}), 146.68 (d, $^{1}J_{C\text{-}F}$ = 242.3 Hz, Ar_F-C_{ortho}), 152.3 (α-$C_{Pyrrole}$), 152.7 (α-$C_{Pyrrole}$), 156.1 (Ar-C-3′), 157.3 (Ar-C-3), 167.8 (4-α-$C_{Pyrrole}$), 170.3 (1-α-$C_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -142.28 (d, *J* = 22.0 Hz, 2F, Ar-F_{ortho}), -142.71 to -142.94 (m, 2F, Ar-F_{ortho}), -158.14 (dd, *J* = 23.7, 8.4 Hz, 2F, Ar-F_{meta}), -158.95 (d, *J* = 22.1 Hz, 2F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): *m/z* calc. for $C_{50}H_{37}F_8N_4O_8$ $[M + H]^+$: 973.2484; found: 973.2490.

UV-VIS (Acetone), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 411.5 (5.25), 510.5 (4.30), 537.5 (3.97), 599 (3.85), 653 (4.56) nm.

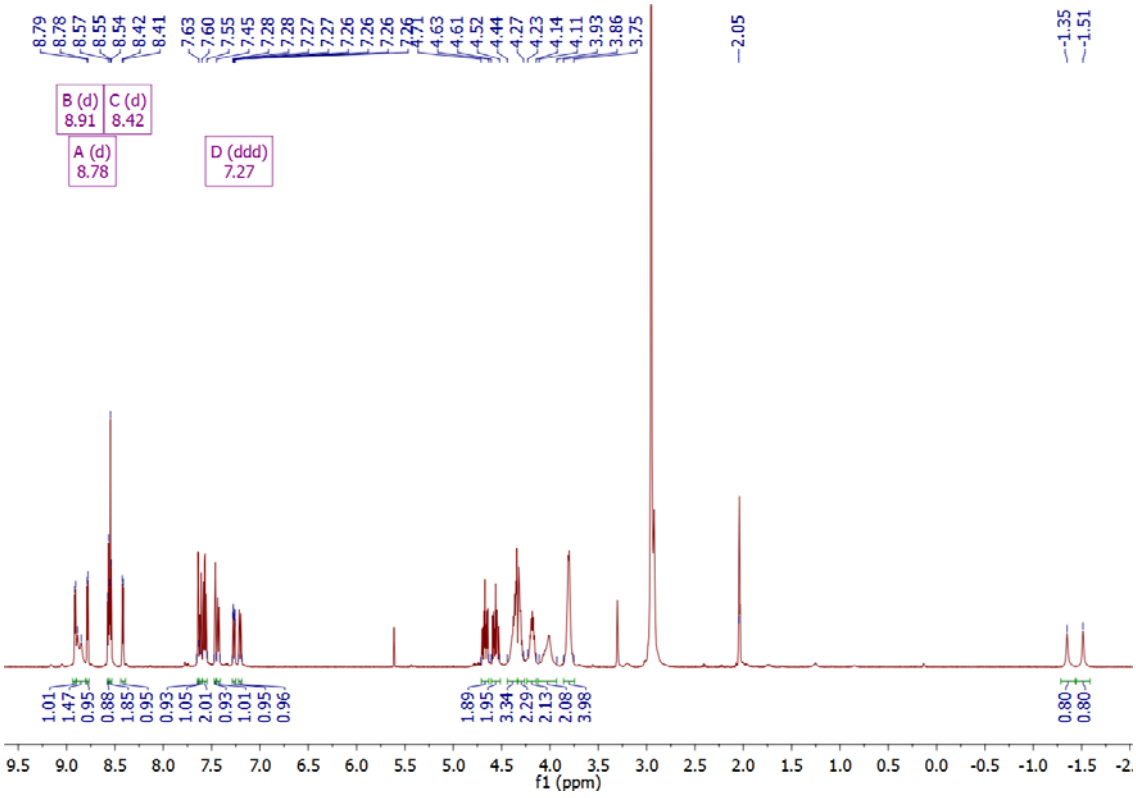


Figure 26. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of dihydrochlorin **37**.

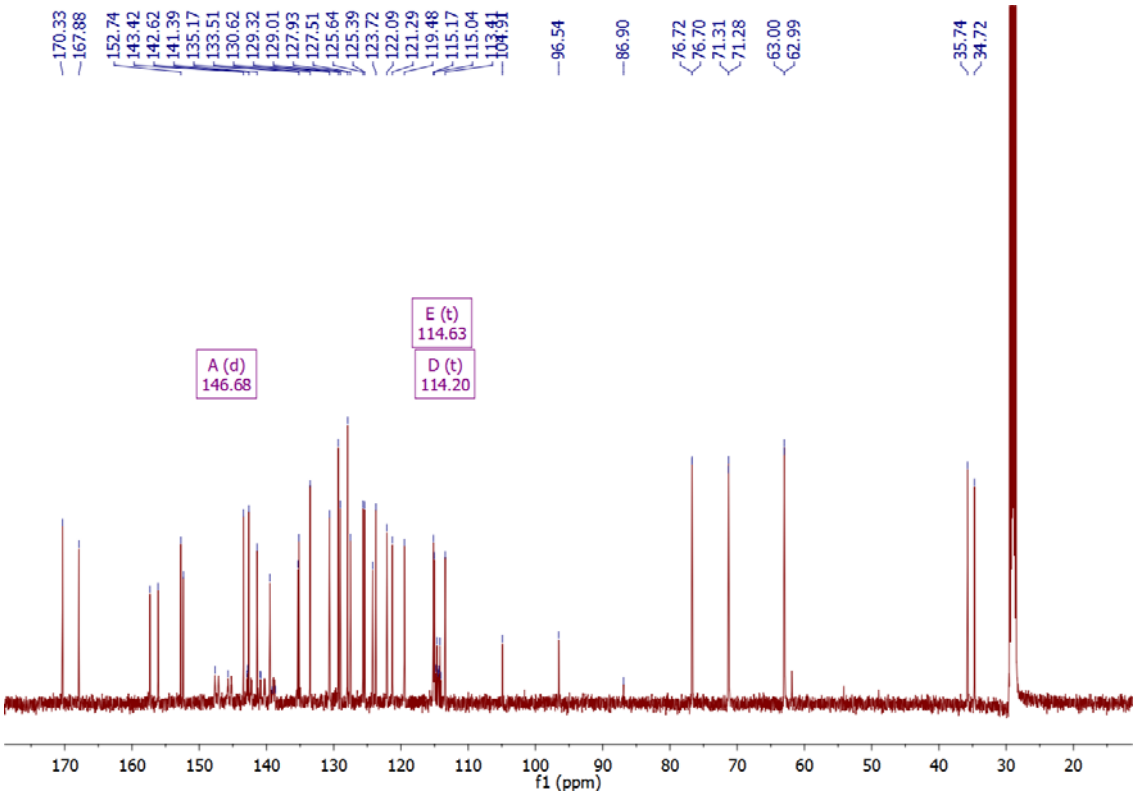


Figure 27. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydrochlorin **37**.

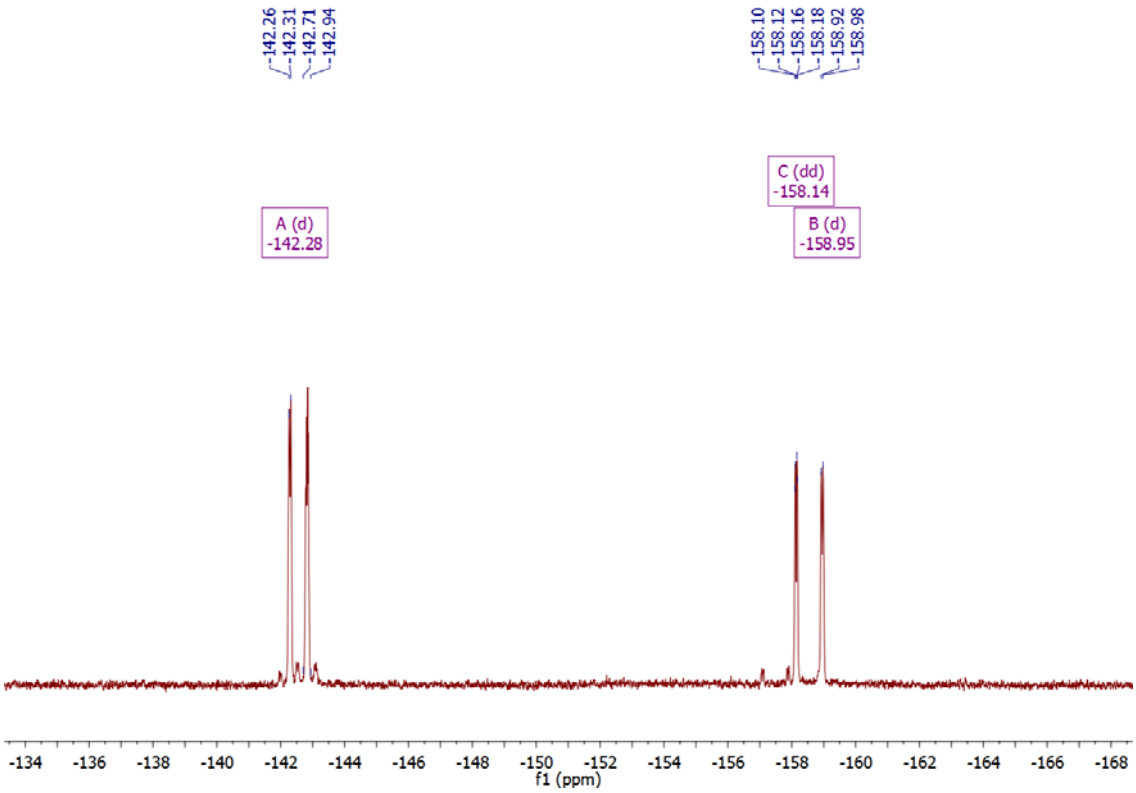


Figure 28. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of dihydrochlorin **37**.

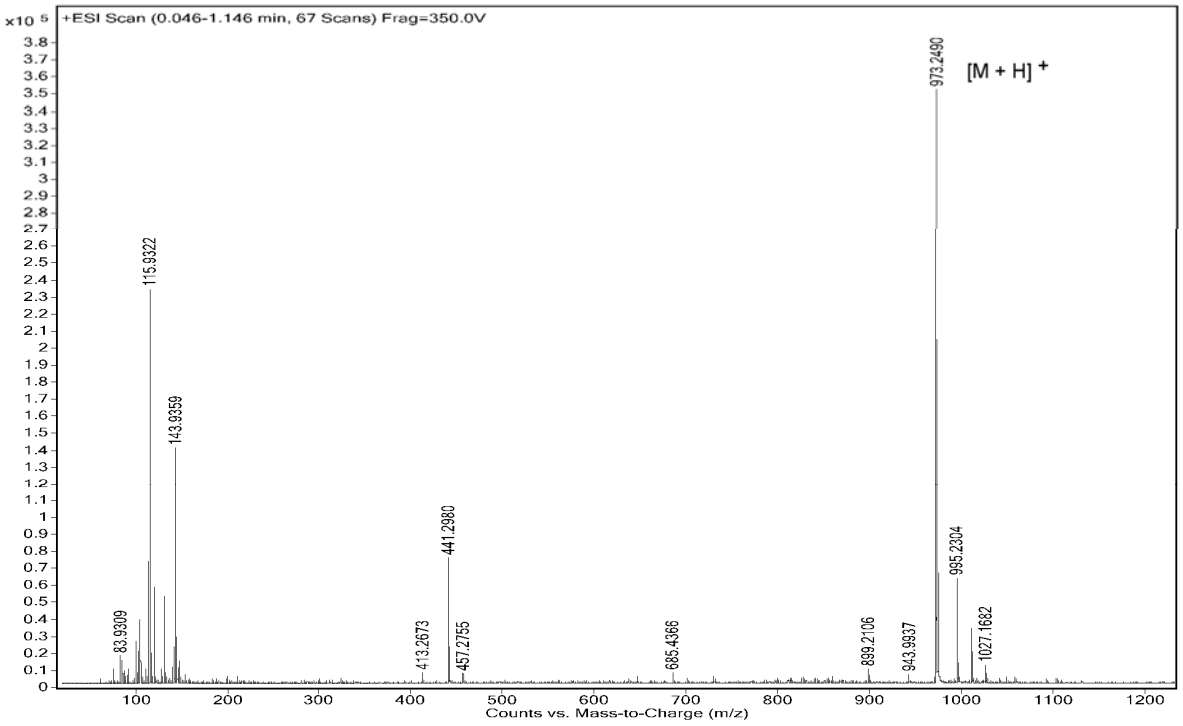
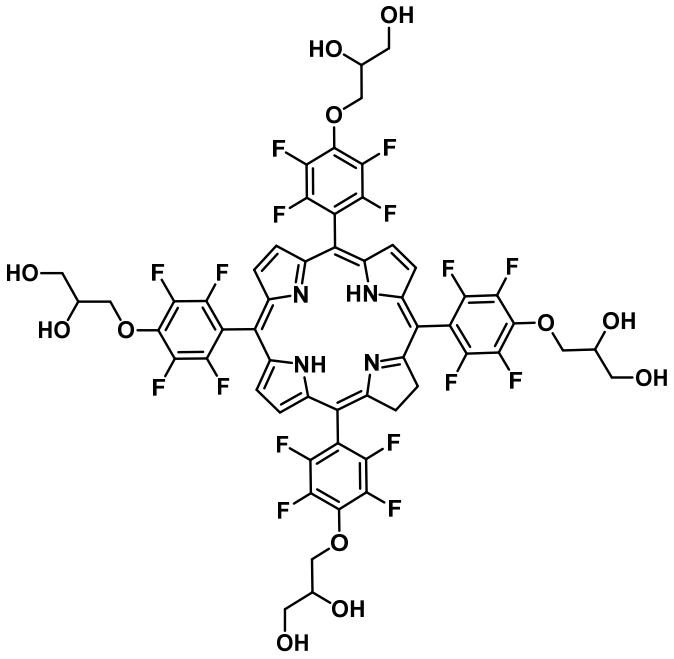


Figure 29. HRMS spectrum of dihydrochlorin **37**.

5,10,15,20-[2,3,5,6-Tetrafluoro-4-(2,3-dihydroxy-propyloxy)phenyl]-7,8-dihydrochlorin (38)



All steps were performed under argon atmosphere. In a 250 mL three-necked flask *p*-toluenesulfonyl hydrazide (70.0 mg, 0.37 mmol), 5,10,15,20-tetrakis[2,3,5,6-tetrafluor-4-(2,3-dihydroxypropyloxy) phenyl]porphyrin (234 mg, 0.185 mmol) and K_2CO_3 (230 mg, 1.66 mmol) were dissolved in 25.0 mL pyridine and stirred for 20 min at RT. Afterwards the reaction mixture was heated to 105 °C. Additional *p*-toluenesulfonyl hydrazide (70.0 mg, 0.37 mmol) in 1.0 mL pyridine was added after 2 and 4 h. After 6.5 h heating 168 mL ethyl acetate and 84 mL H_2O were added and the reaction mixture was refluxed for 1 h at 100 °C. The organic layer was washed with 168 mL 2M HCl, 168 mL H_2O and 168 mL saturated $NaHCO_3$-solution, afterwards dried over Na_2SO_4 and evaporated to dryness. Then, the solid was dissolved in ethyl acetate (100 mL) and tetrachloro-*o*-benzoquinone (in a total of 147 mg, 0.59 mmol) was added in small portions (20 mg) every 15 min. at RT to the stirring solution until the band at 735 nm in the UV/Vis spectrum just disappeared. The organic layer was washed twice with 168 mL 5% $NaHSO_3$, once with 224 mL 0.01 M NaOH and once with 180 mL saturated $NaHCO_3$-solution and afterwards dried over Na_2SO_4. The product was evaporated to dryness and purified by column chromatography (DCM/ethyl acetate = 98:2, v/v) and recrystallization (acetone/*n*-hexane) to obtain the product as dark green-purple crystals. Yield: 198 mg (84%); m.p.: > 300 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -1.39 (s, 2H, NH), 3.79-3.94 (m, 8H, C*H*$_2$OH), 4.00-4.17 (m, 4H, CH-O*H*), 4.18-4.32 (m, 4H, OCH$_2$C*H*), 4.44 (br s, 4H, CH$_2$O*H*), 4.50 (s, 4H, 2,3-*β*-$H_{Pyrrole}$), 4.56-4.66 (m, 4H, Ar_F-OCH$_2$), 4.67-4.82 (m, 4H, Ar_F-OCH$_2$), 8.73 (s, 2H, 12,13-*β*-$H_{Pyrrole}$), 8.76 (d, *J* = 5.1 Hz, 2H, 7,18-*β*-$H_{Pyrrole}$), 9.10 (d, *J* = 5.0 Hz, 2H, 8,17-*β*-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 35.0 (2,3-*β*-$C_{Pyrrole}$), 62.9 (CH_2OH), 71.2 (OCH$_2$CH), 76.7 (Ar_F-OCH$_2$), 97.4 (5,20-Ar_F-C_{meso}), 106.8 (10,15-Ar_F-C_{meso}), 113.3 (t, $^2J_{C\text{-}F}$ = 20.0 Hz, 10,15-Ar_F-C_{ipso}),

113.81 (t, $^{2}J_{C\text{-}F}$ = 20.0 Hz, 5,20-Ar_F-C_{ipso}), 124.0 (7,18-β-$C_{Pyrrole}$), 128.7 (8,17-β-$C_{Pyrrole}$), 132.3 (12,13-β-$H_{Pyrrole}$), 135.4 (9,16-α-$C_{Pyrrole}$), 139.1 (Ar_F-C_{para}), 140.6 (6,19-α-$C_{Pyrrole}$), 141.22 (d, J = 243.3 Hz, Ar_F-C_{meta}), 141.82 (dd, J = 247.0, 15.1 Hz, Ar_F-C_{meta}), 146.1 (d, J = 242.1 Hz, Ar_F-C_{ortho}), 146.5 (d, J = 243.7 Hz, Ar_F-C_{ortho}), 152.8 (11,14-α-$C_{Pyrrole}$), 170.2 (1,4-α-$C_{Pyrrole}$) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -142.21 (dd, J = 23.8, 8.2 Hz, 4F, Ar-F_{ortho}), -142.61 (dd, J = 21.7, 6.7 Hz, 4F, Ar-F_{ortho}), -157.86 (dd, J = 22.6, 8.8 Hz, 4F, Ar-F_{meta}), -158.66 (dd, J = 25.2, 9.2 Hz, 4F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): m/z calc. for $C_{56}H_{41}F_{16}N_4O_{12}$ $[M + H]^+$: 1265.2465; found: 1265.2490.

UV-VIS (Acetone), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 408.5 (5.12), 504 (4.13), 600 (3.61), 653 (4.56) nm.

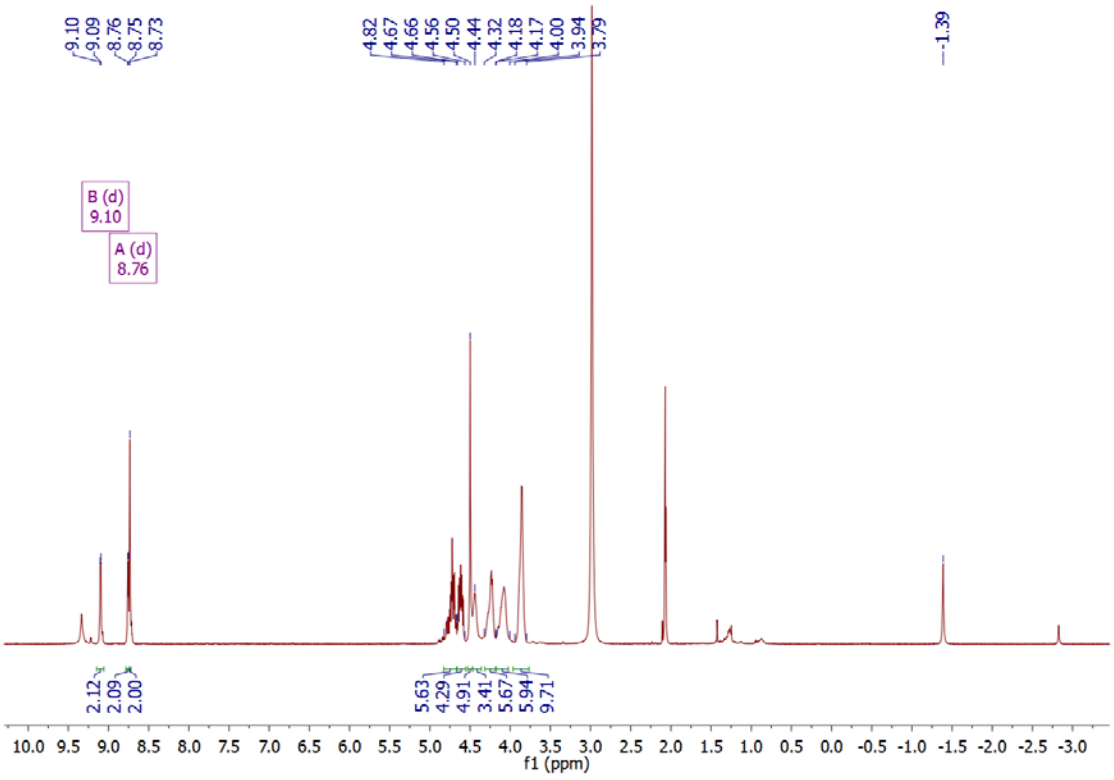


Figure 30. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of dihydrochlorin **38**.

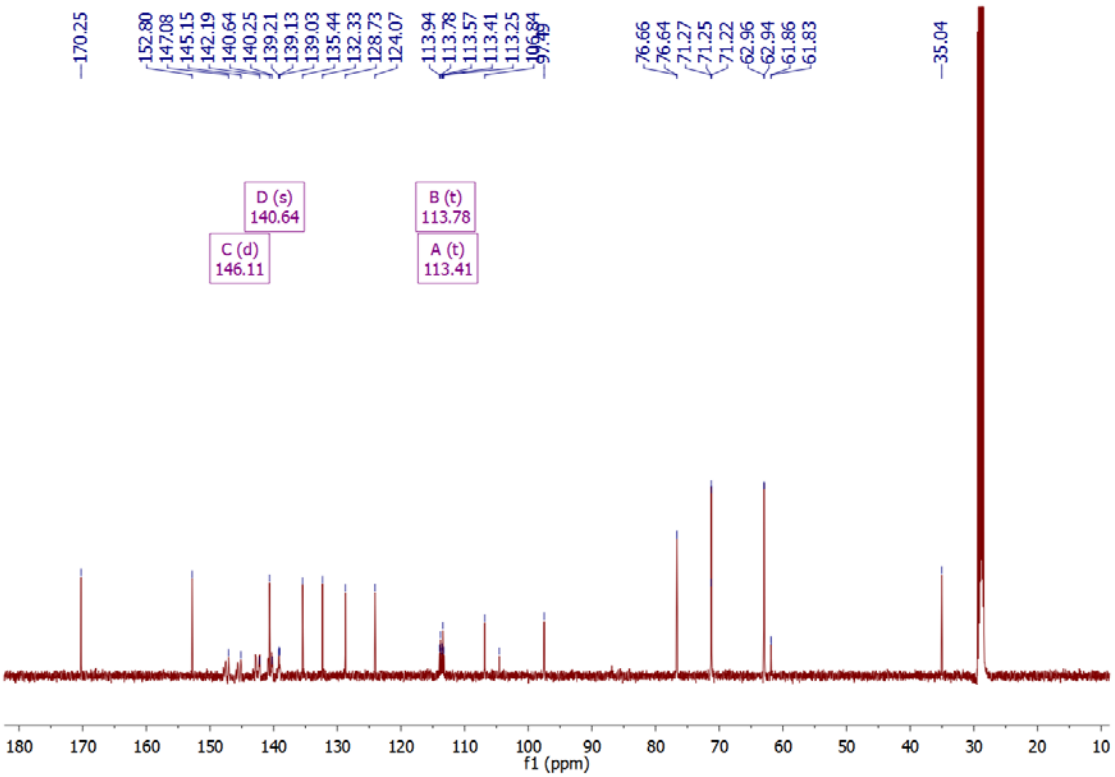


Figure 31. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of dihydrochlorin **38**.

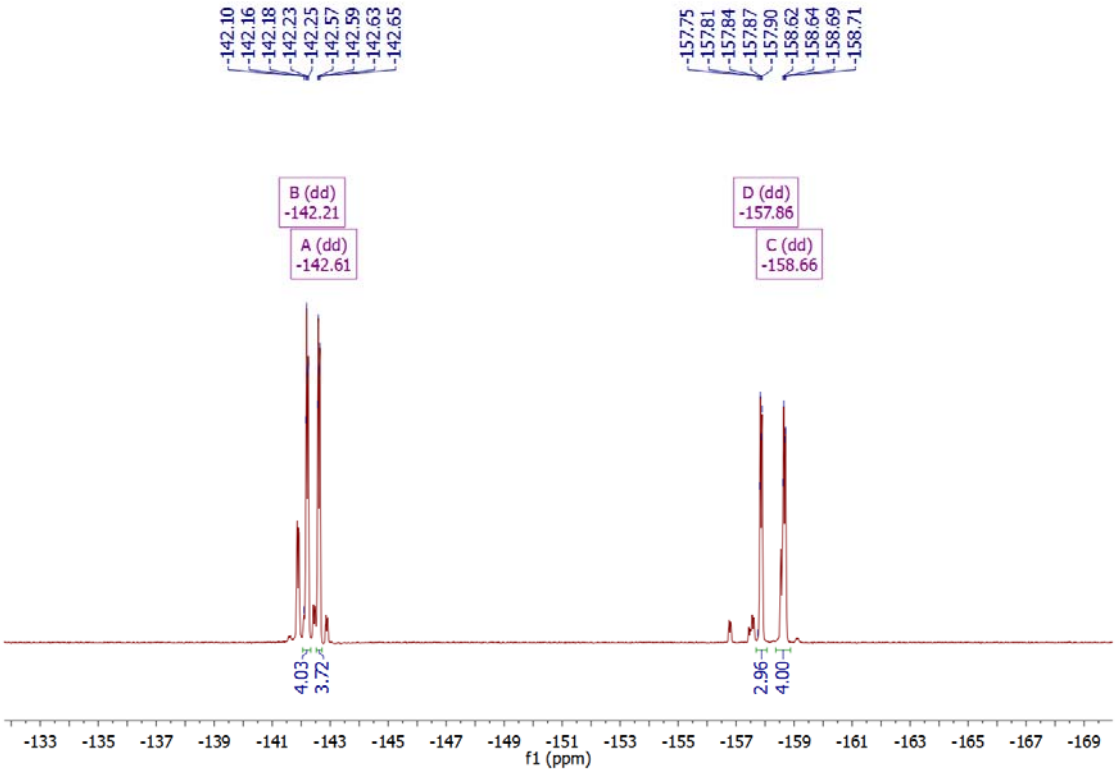


Figure 32. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of dihydrochlorin **38**.

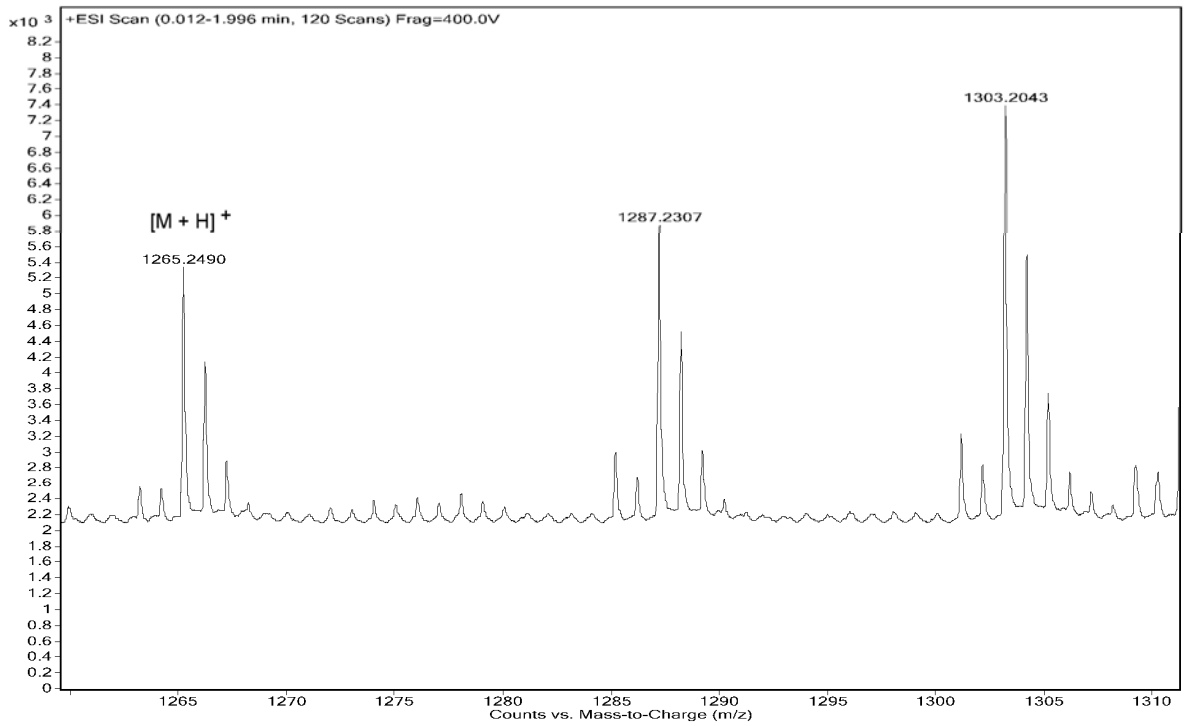
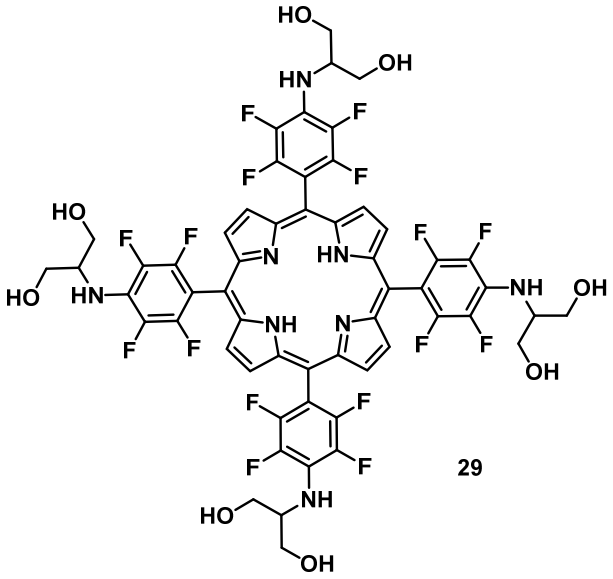


***Figure* 33**. HRMS spectrum of dihydrochlorin **38**.

1.7.3 *Functionalization with Amines*

5, 10,15,20-Tetrakis-[2,3,5,6-tetrafluoro-4-(1,3-dihydroxy-2-aminopropyl)phenyl]porphyrin (29)



29

5,10,15,20-Tetrakis(pentafluorophenyl)porphyrin (107 mg, 0.109 mmol) was dissolved in a two-necked round bottle flask with dry DMSO (2.0 mL), 2-Amino-1,3-dihydroxy-propane (260 mg, 2.85 mmol) was added and the reaction mixture stirred at 100 °C for 4 hours. After aqueous workup, extraction with ethyl acetate and drying over sodium sulfate, the crude product was purified by reversed phase column chromatography ($MeOH/H_2O$ = 85:15, v/v) and recrystallized ($MeOH/H_2O$) to obtain a purple solid. Yield: 77 mg (54%); m.p.: 210 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -2.82 (s, 2H, NH), 3.94-4.08 (m, 16H, OCH_2), 4.17 (d quin, *J* = 9.9, 5.1 Hz, 4H, NHC*H*), 4.25 (t, *J* = 5.5 Hz, 8H, OH), 5.30 (dt, $^3J_{H\text{-}H}$ = 9.8, $^4J_{H\text{-}F}$ = 3.0 Hz, 4H, NH), 9.25 (s, 8H, β-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 58.8 (NH-CH), 62.7 (OCH_2), 62.8 (OCH_2), 106.0 (Ar_F-C_{meso}), 107.2 (t, $^2J_{C\text{-}F}$ = 20.1 Hz, Ar_F-C_{ipso}), 130.5 (t, *J* = 11.5 Hz, Ar_F-C_{para}), 132.7 (β-$C_{Pyrrole}$), 138.3 (dd, $^{1,2}J_{C\text{-}F}$ = 238.8, 16.0 Hz, Ar_F-C_{meta}), 147.8 (d, $^1J_{C\text{-}F}$ = 238.8 Hz, Ar_F-C_{ortho}) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -143.38 (d, *J* = 16.1 Hz, 4F, Ar-F_{ortho}), -161.29 (d, *J* = 19.3 Hz, 4F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): *m/z* calc. for $C_{56}H_{43}F_{16}N_8O_8$ $[M + H]^+$: 1259.2948; found: 1259.3045.

UV-VIS (DCM), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 417 (5.42), 509 (4.38), 544 (3.82), 586 (3.88), 648 (3.07) nm.

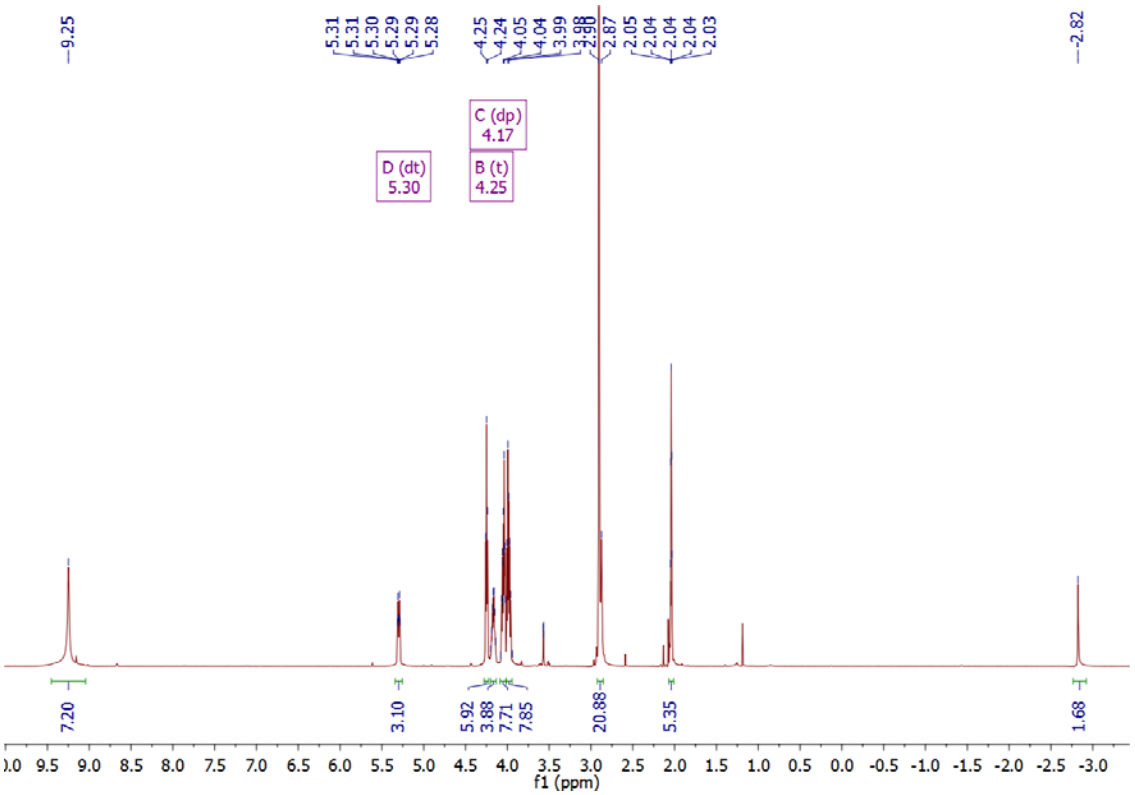


Figure 34. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of amino-porphyrin **29**.

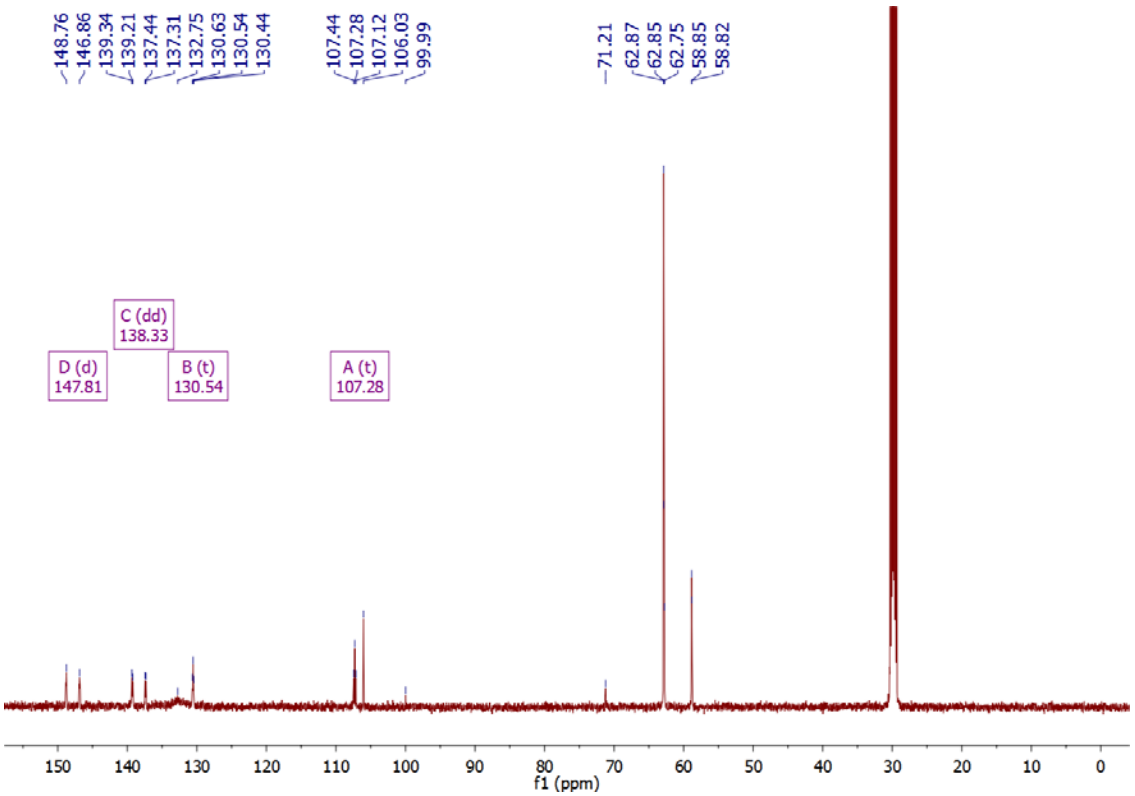


Figure 35. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of amino-porphyrin **29**.

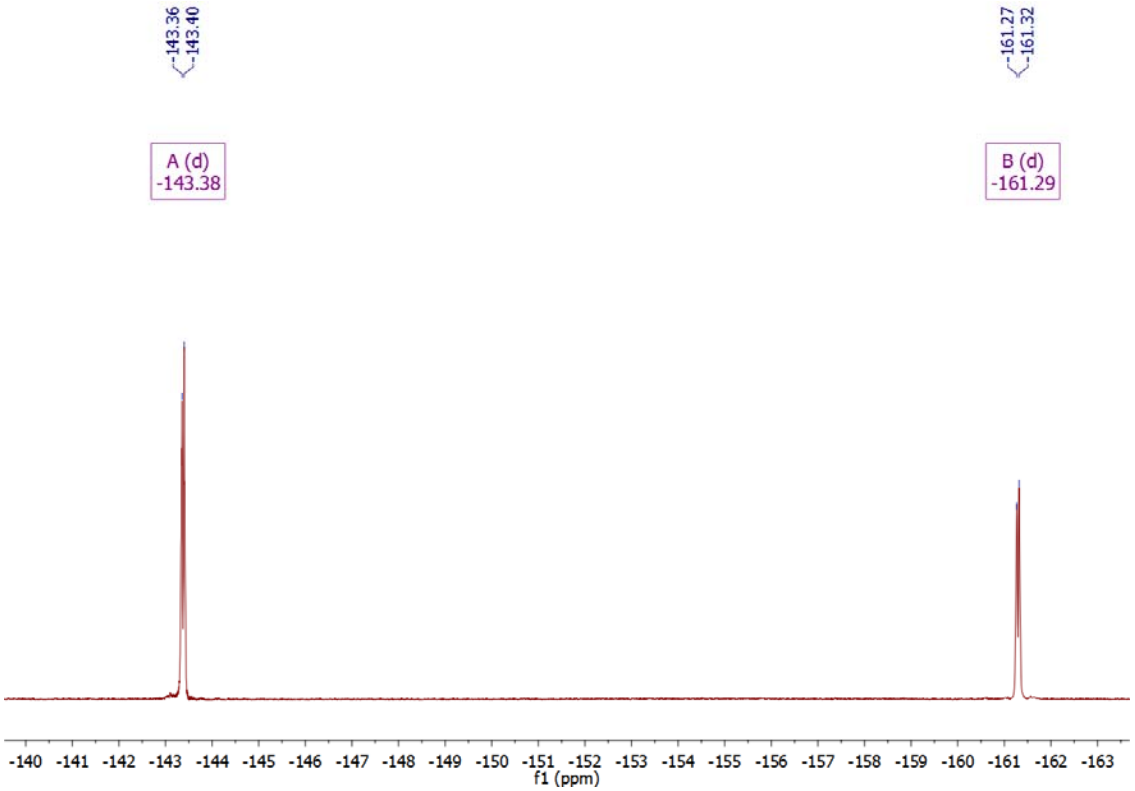


Figure 36. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of amino-porphyrin **29**.

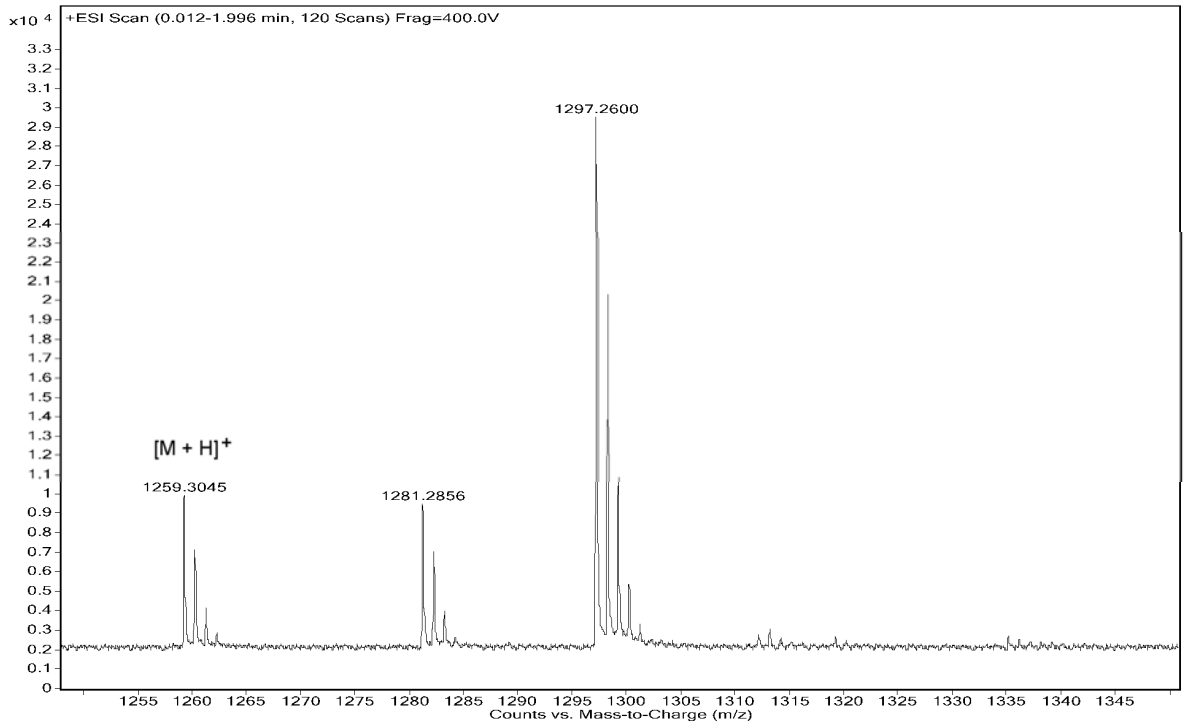
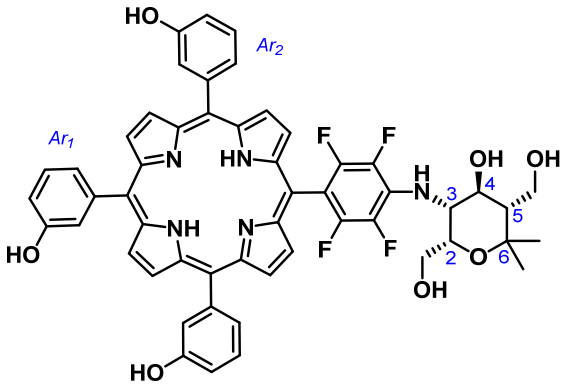


Figure 37. HRMS spectrum of amino-porphyrin **29**.

5,10,15-Tris(3-hydroxyphenyl)-20-{2,3,5,6-tetrafluoro-4-[*N*-((2*S*,3*R*,4*S*,5*S*)-2,5-bis(hydroxyphenyl)-6,6-dimethyl-4-hydroxy-tetrahydro-2*H*-pyran)-3-aminyl]phenyl}-porphyrin (32)



5,10,15-Tris(3-hydroxyphenyl)-20-(pentafluorophenyl)porphyrin (50 mg, 66.4 µmol) was dissolved in a two-necked round bottle flask with dry DMSO (1.0 mL), [(2*S*,3*R*,4*S*,5*S*)-3-amino-4-hydroxy-6,6-dimethyltetrahydro-2*H*-pyran-2,5-diyl]dimethanol (50 mg, 242 µmol) was added and the reaction mixture stirred at 100 °C for 6 hours. After aqueous workup, extraction with ethyl acetate and drying over sodium sulfate, the crude product was purified by reversed phase column chromatography ($MeOH/H_2O$ = 95:5, v/v) and recrystallized ($MeOH/H_2O$) to obtain a purple solid. Yield: 14 mg (22%); m.p.: 165 °C.

^{1}H-NMR (500 MHz, D_6-Acetone): δ = -2.78 (s, 2H, NH), 1.30 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.96 (td, *J* = 6.6, 5.3 Hz, 1H, H-5), 3.81-3.96 (m, 4H, C*H*$_2$-OH), 4.12 (t, *J* = 4.7 Hz, H-2), 4.22 (t, *J* = 3.8 Hz, H-3), 4.24 (t, *J* = 4.1 Hz, CH_2-O*H*), 4.37-4.44 (m, 2H, H-4 + H-2), 4.82 (d, *J* = 4.1 Hz, 4-OH), 5.55-5.60 (m, 1H, 3-NH), 7.30-7.34 (m, 3H, Ar-H-6), 7.60-7.65 (m, 3H, Ar-H-5), 7.69-7.76 (m, 6H, Ar-H-2 + Ar-H-4), 8.82-9.16 (m, 8H, *β*-$H_{Pyrrole}$) ppm.

^{13}C-NMR (126 MHz, D_6-Acetone): δ = 25.4 (CH_3), 26.8 (CH_3), 48.9 (C-5), 62.1 (C-3), 70.2 (2-CH_2), 74.4 (5-CH_2), 77.9 (C-2), 78.2 (C-6), 78.4 (C-4), 115.0 (20-C_{ipso}), 115.1 (5,10,15-C_{ipso}), 120.5 (Ar-C_{meso}), 121.9 (Ar_1-C-2), 122.0 (Ar_2-C-2), 126.3 (Ar_1-C-4), 126.4 (Ar_2-C-4), 127.8 (Ar_1-C-5), 127.9 (Ar_2-C-5), 143.0 (Ar_2-C-1), 143.1 (Ar_1-C-1), 155.9 (Ar_1-C-3), 156.0 (Ar_2-C-3) ppm.

^{19}F-NMR (376 MHz, D_6-Acetone): δ = -143.53 (d, *J* = 20.8 Hz, 4F, Ar-F_{ortho}), -161.00 (d, *J* = 18.3 Hz, 4F, Ar-F_{meta}) ppm.

HRMS (ESI-TOF): *m/z* calc. for $C_{53}H_{43}F_4N_5O_7$ $[M + H]^+$: 938.3177; found: 938.3154.

UV-VIS (Acetone), λ_{max} [log ε ($L \cdot mol^{-1} \cdot cm^{-1}$)]: 414 (5.21), 507 (4.15), 543.5 (3.76), 585 (3.62), 647 (2.96) nm.

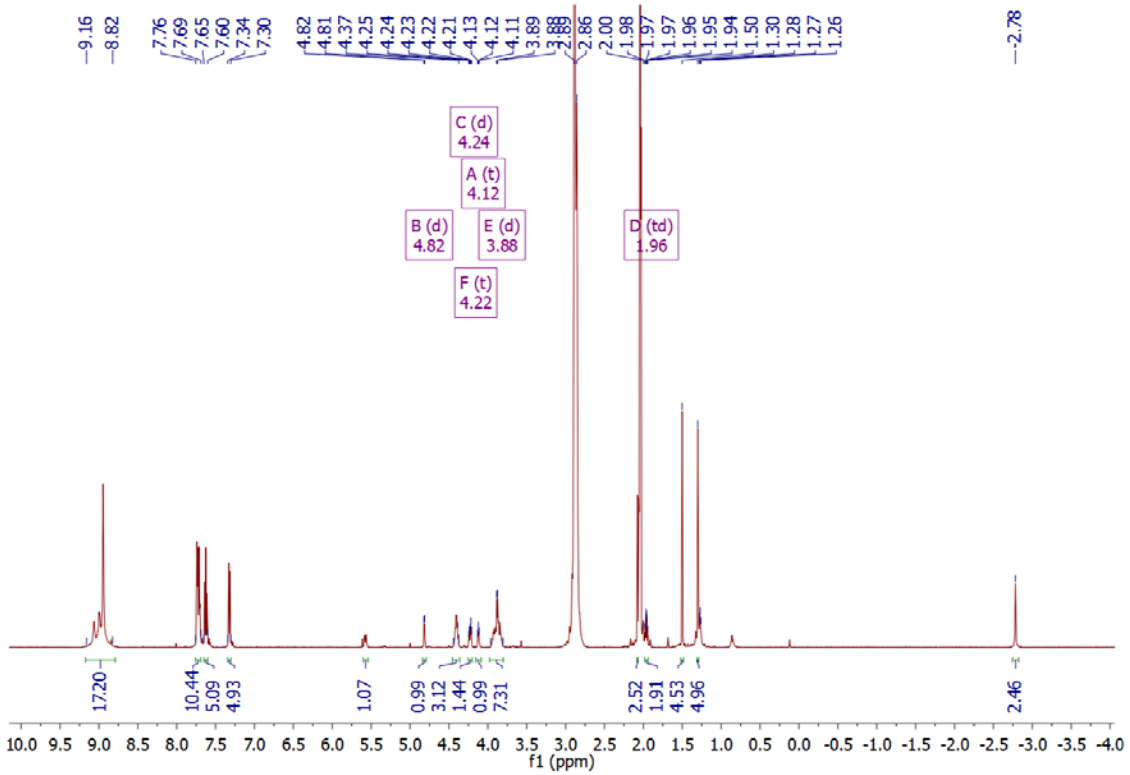


Figure 38. ^{1}H-NMR (500 MHz, D_6-acetone) spectrum of amino-porphyrin **32**.

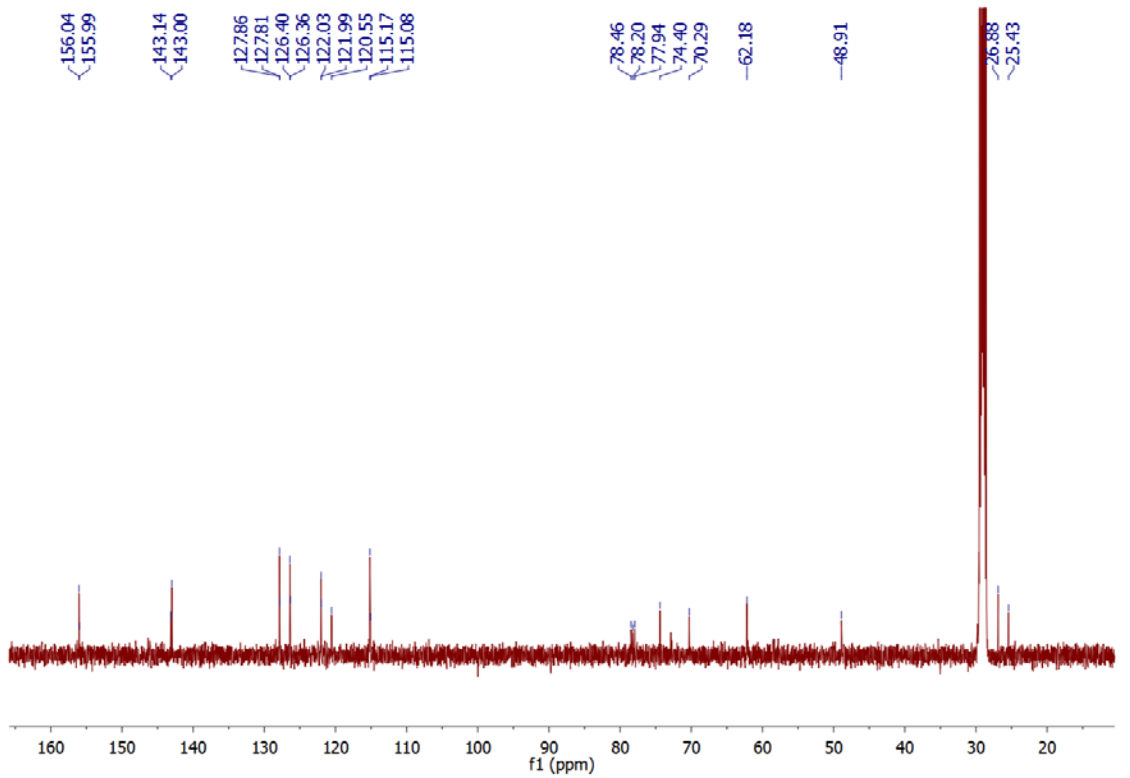


Figure 39. ^{13}C-NMR (126 MHz, D_6-acetone) spectrum of amino-porphyrin **32**.

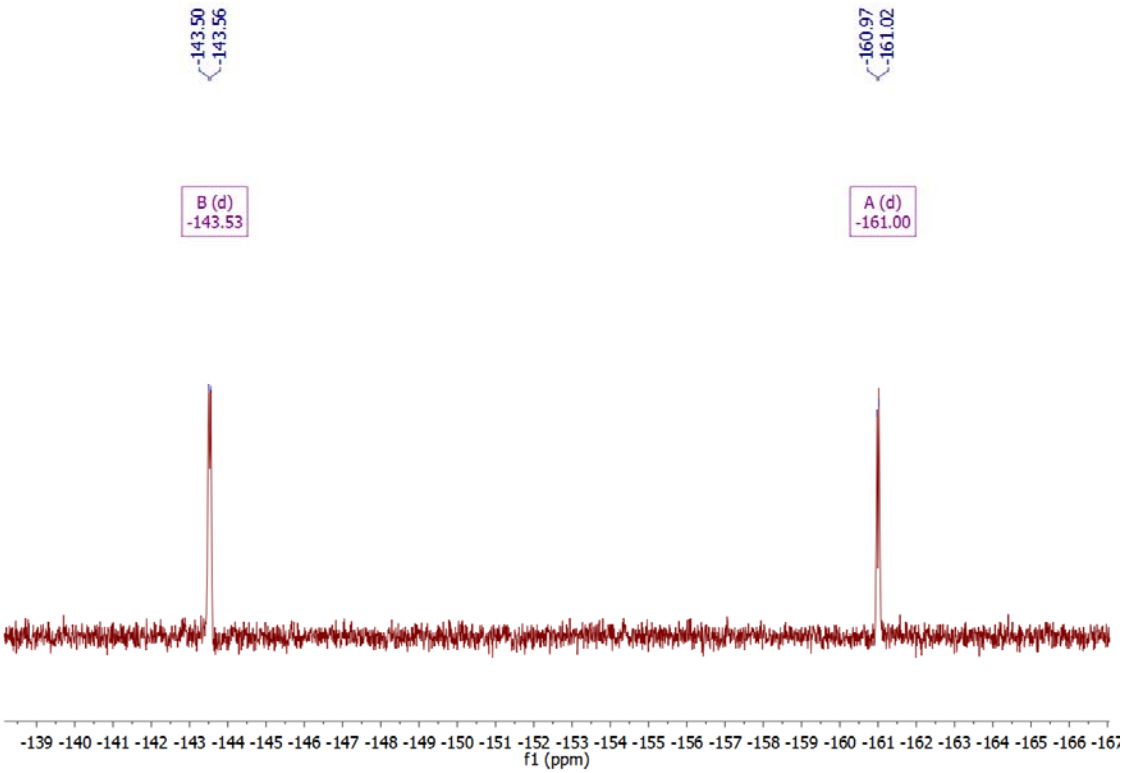


Figure 40. ^{19}F-NMR (376 MHz, D_6-acetone) spectrum of amino-porphyrin **32**.

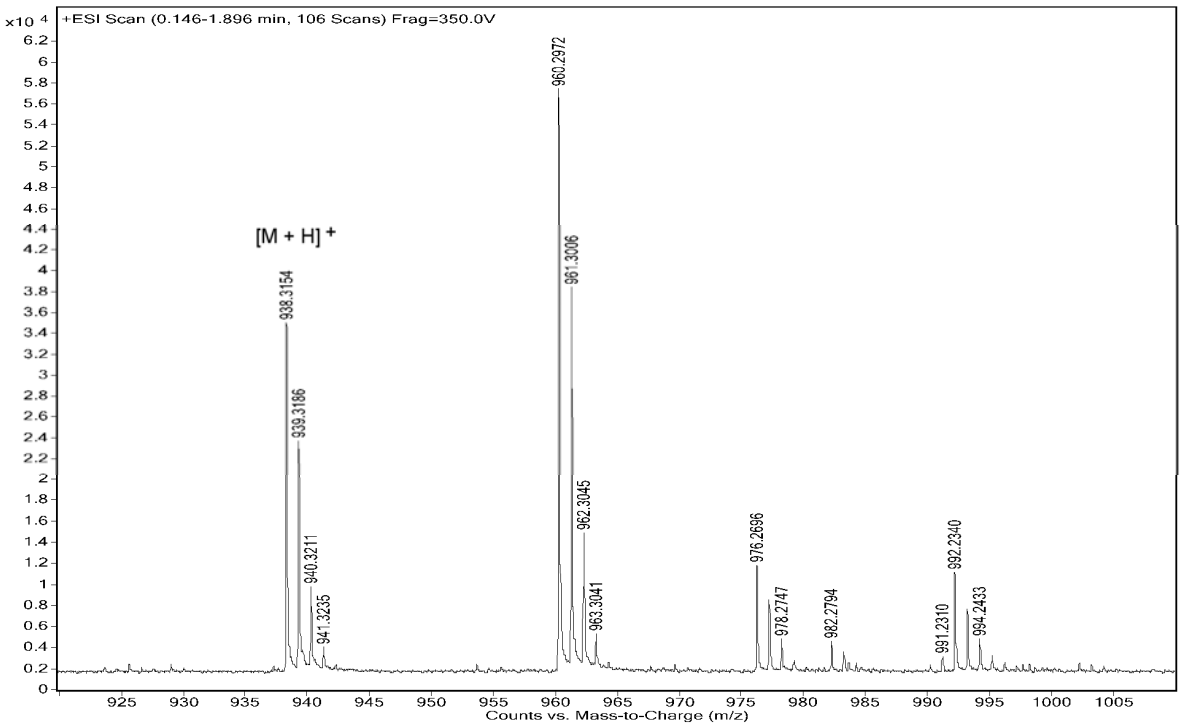


Figure 41. HRMS spectrum of amino-porphyrin **32**.

1.7.4 *Cell Test Results*

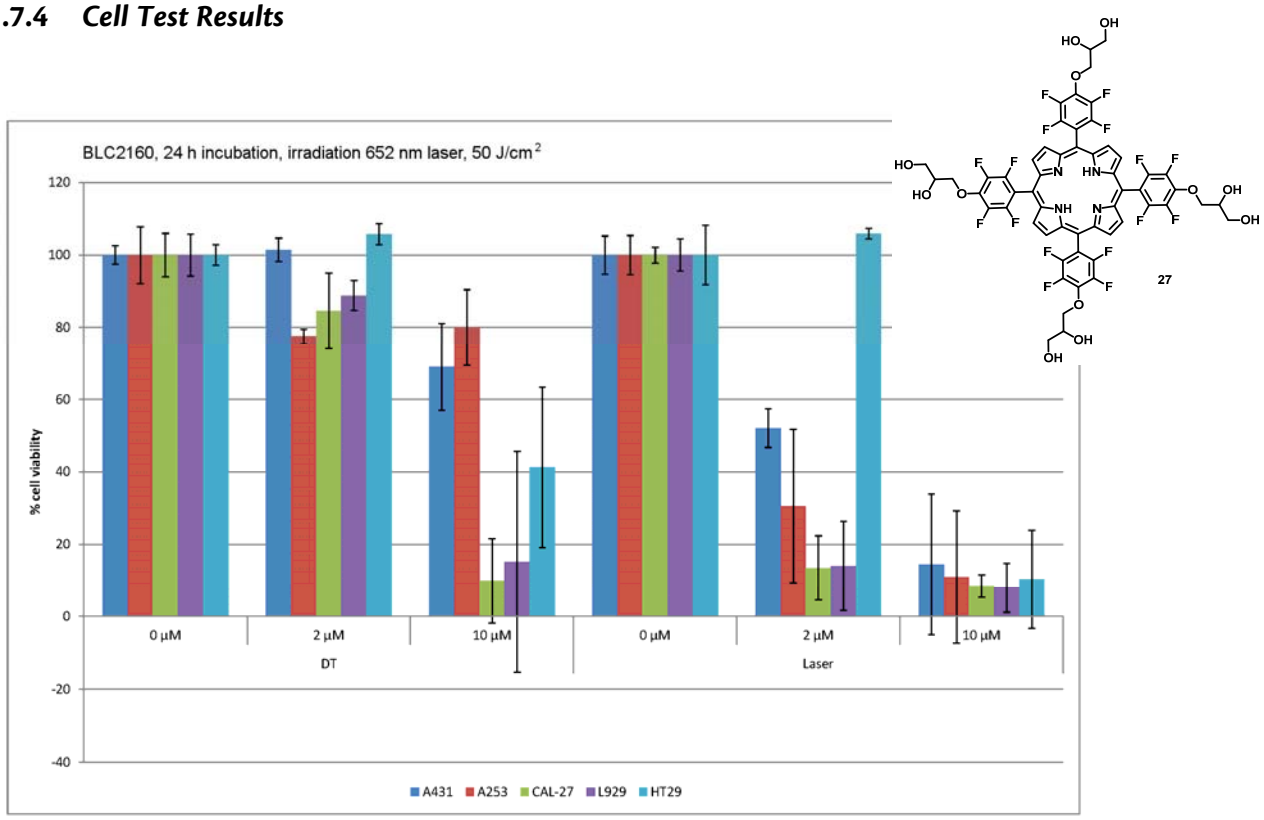


Figure 42. Cell test result for porphyrin **27**.

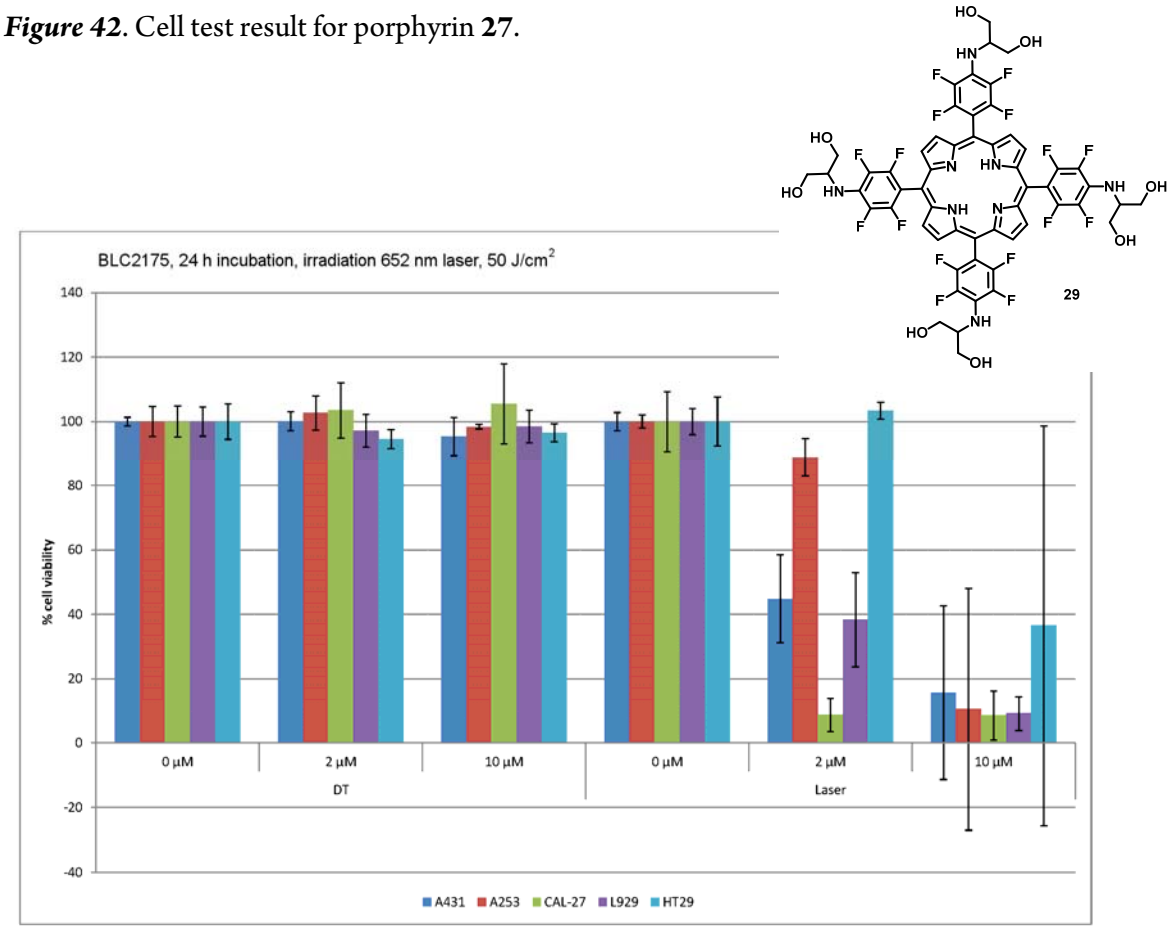


Figure 43. Cell test result for porphyrin **29**.

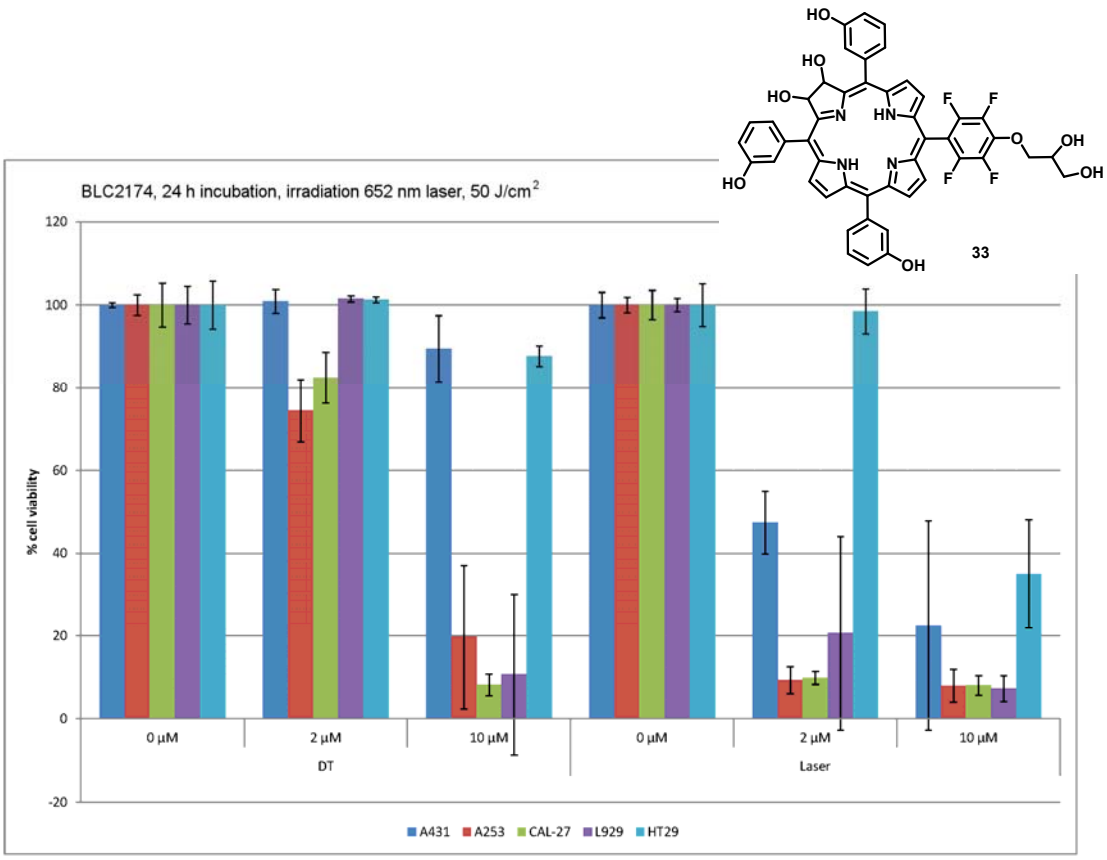


Figure 44. Cell test result for porphyrin **33**.

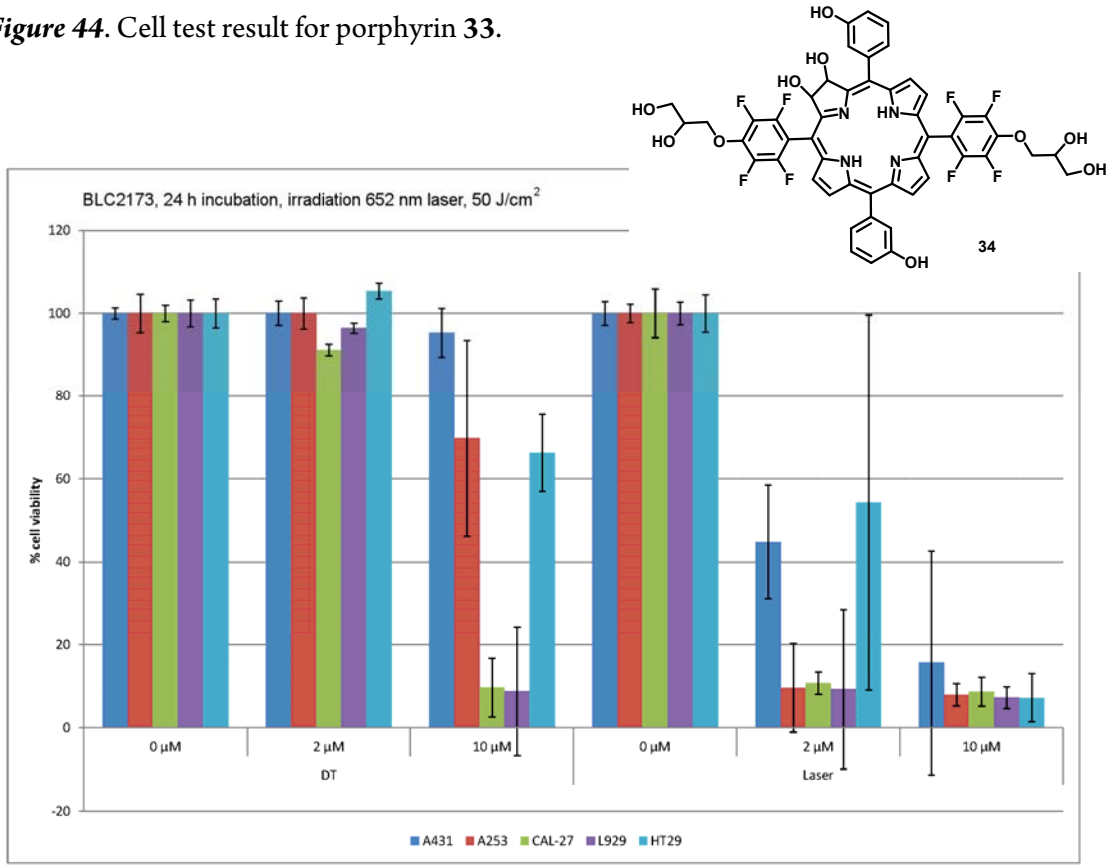


Figure 45. Cell test result for porphyrin **34**.

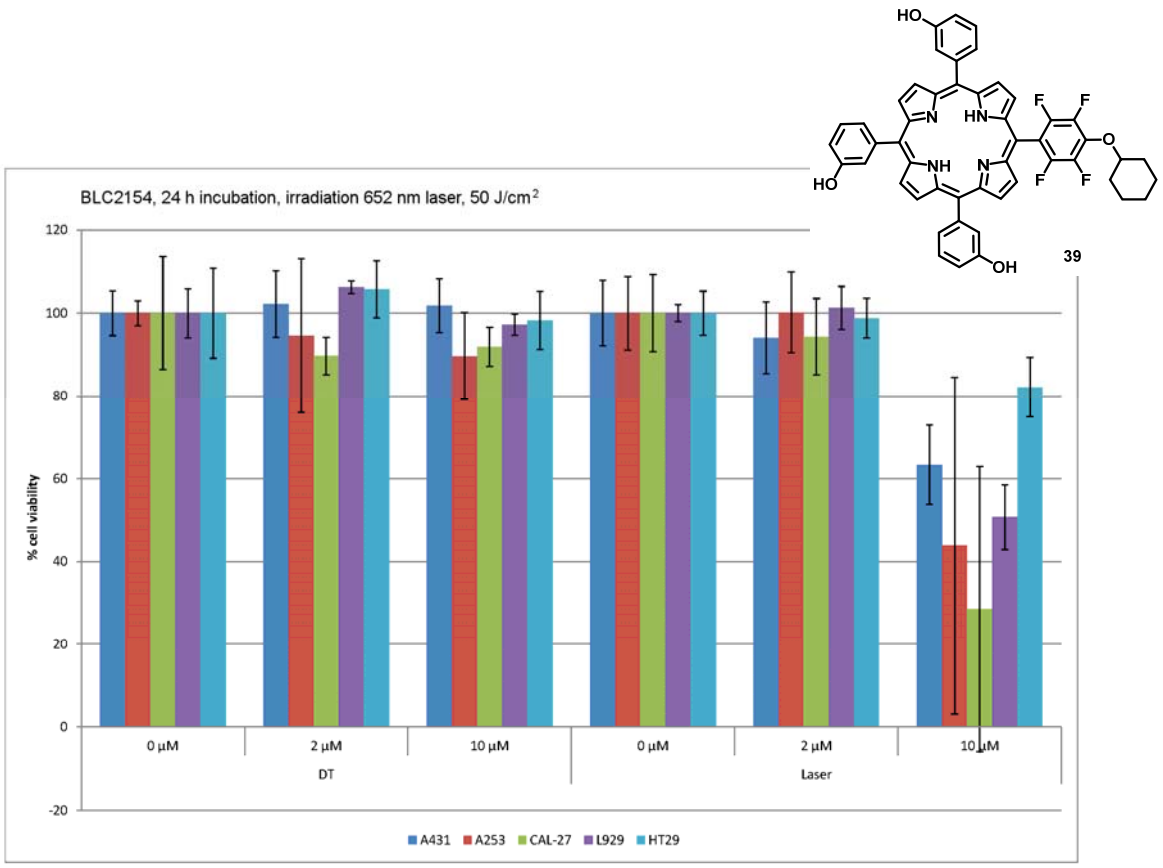


Figure 46. Cell test result for porphyrin **39**.

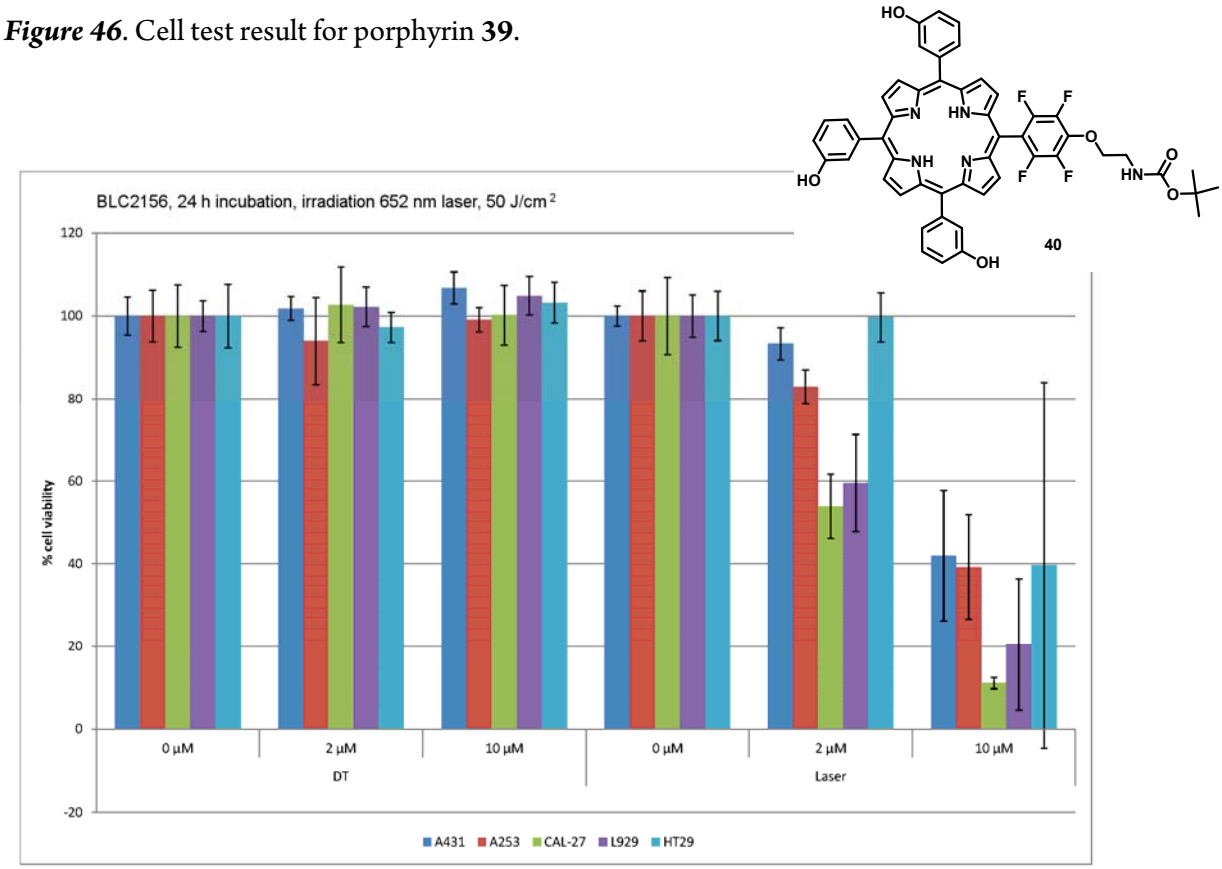


Figure 47. Cell test result for porphyrin **40**.

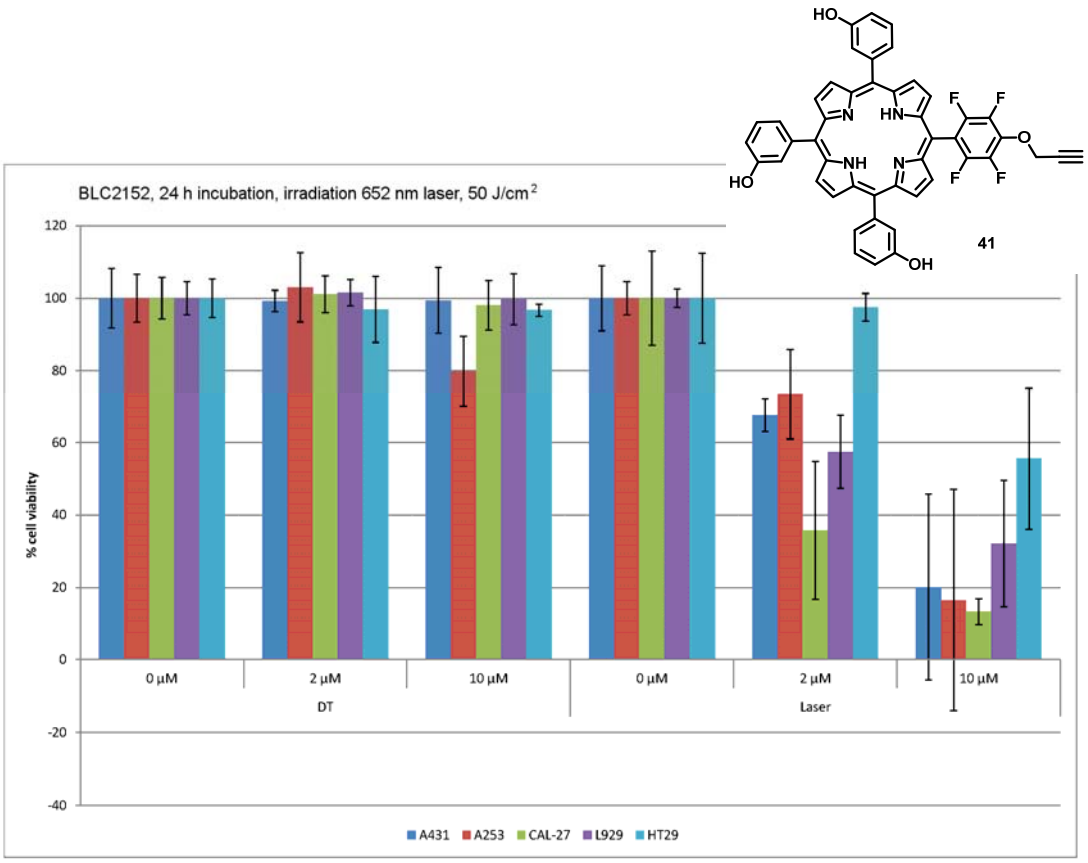


Figure 48 Cell test result for porphyrin **41**.

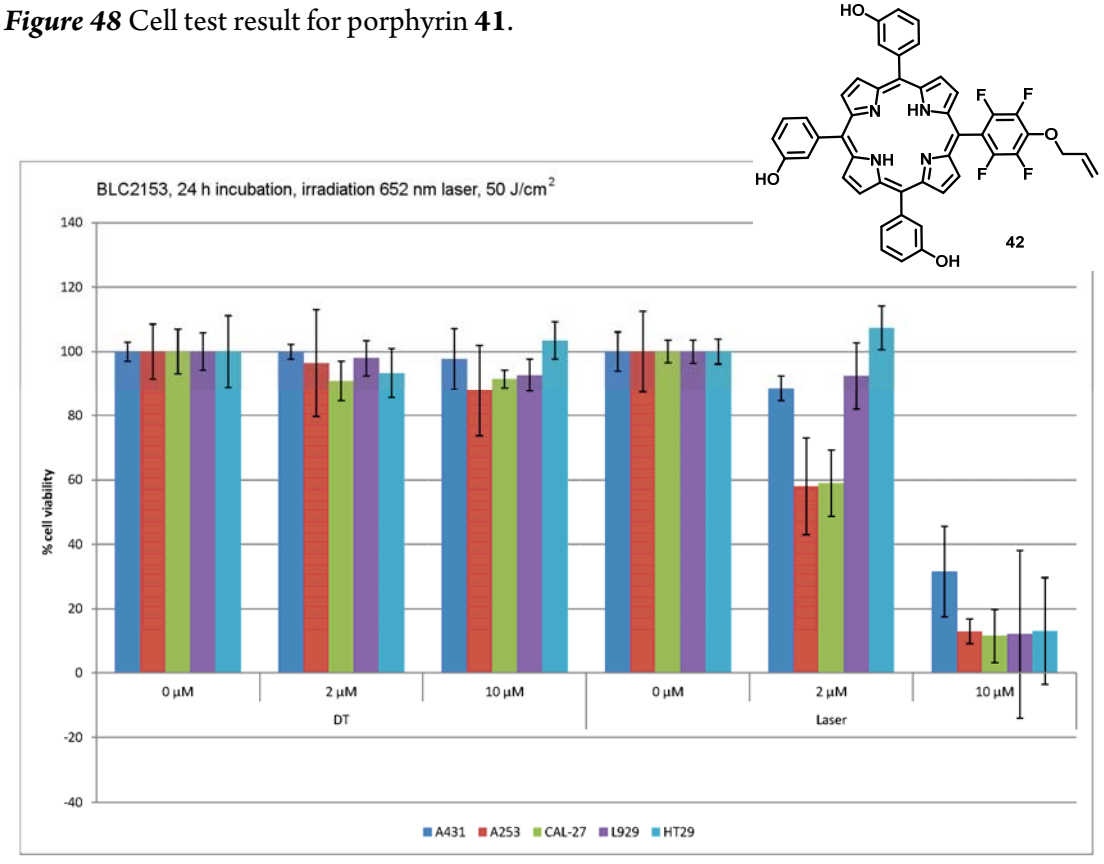


Figure 49. Cell test result for porphyrin **42**.

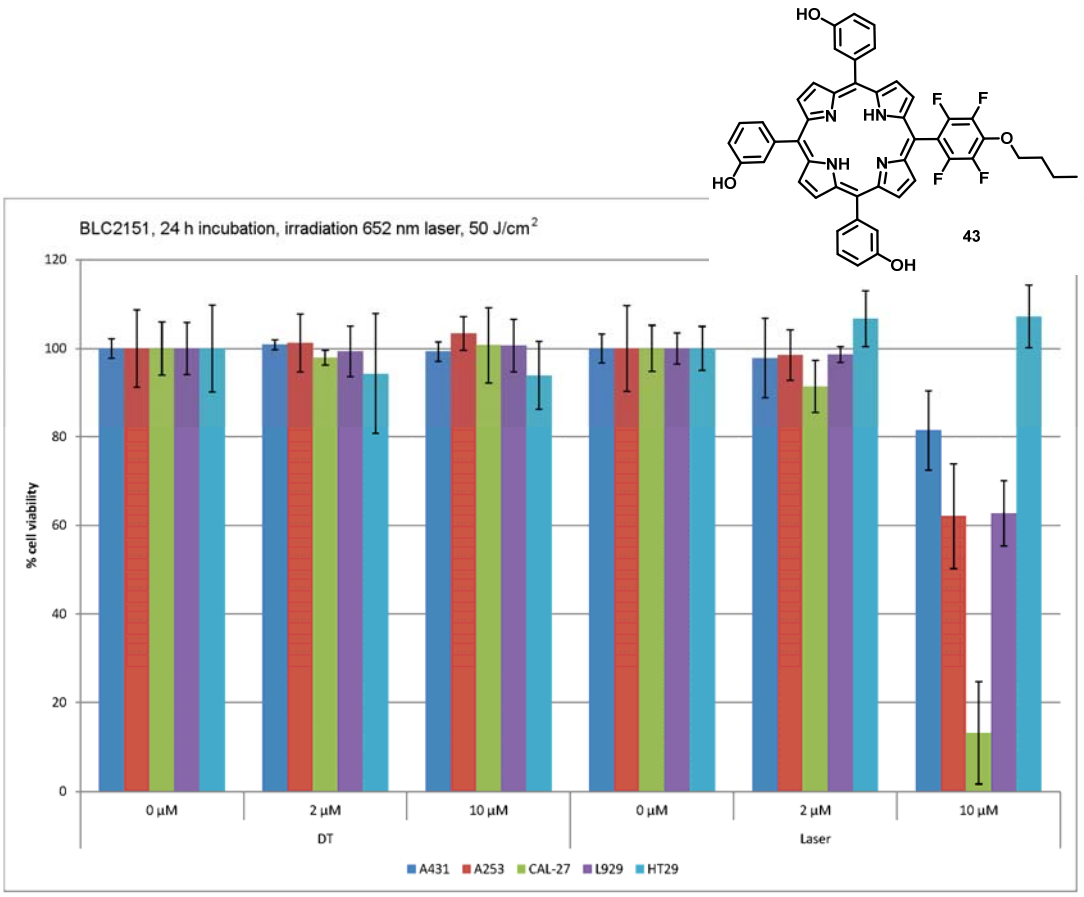


Figure 50. Cell test result for porphyrin **43**.

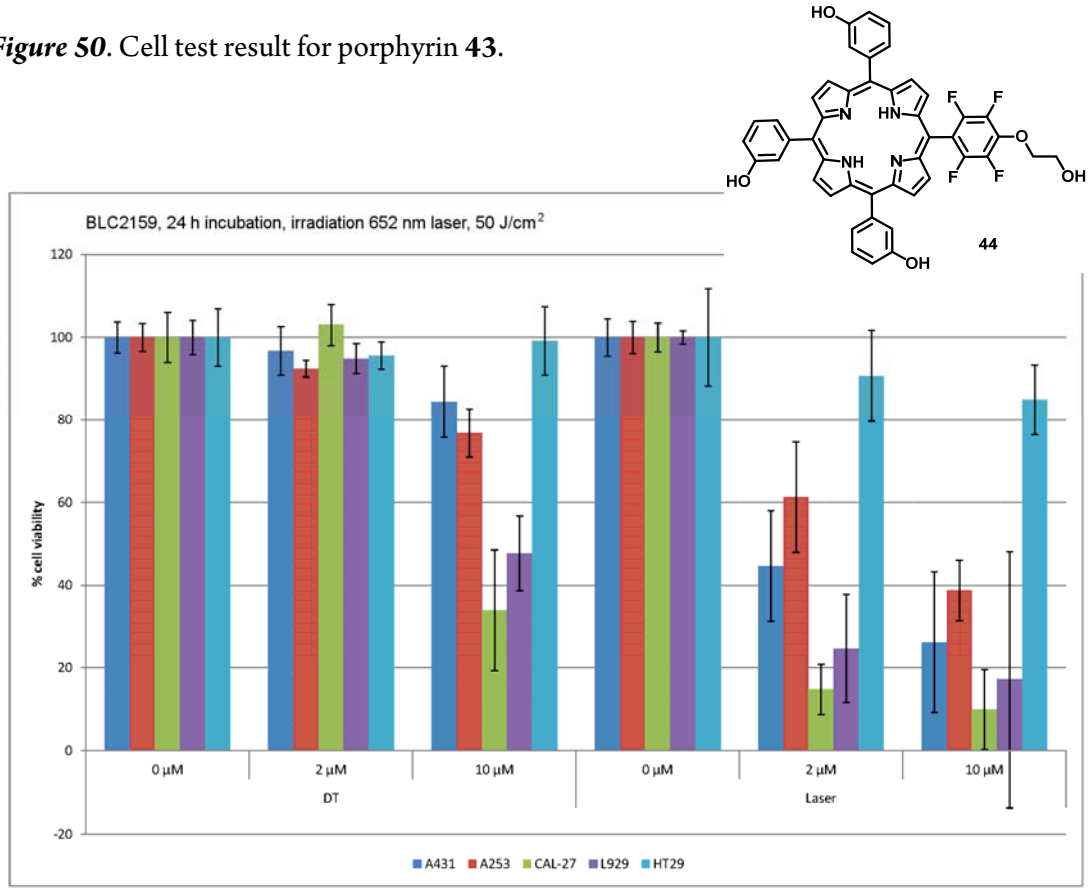


Figure 51. Cell test result for porphyrin **44**.

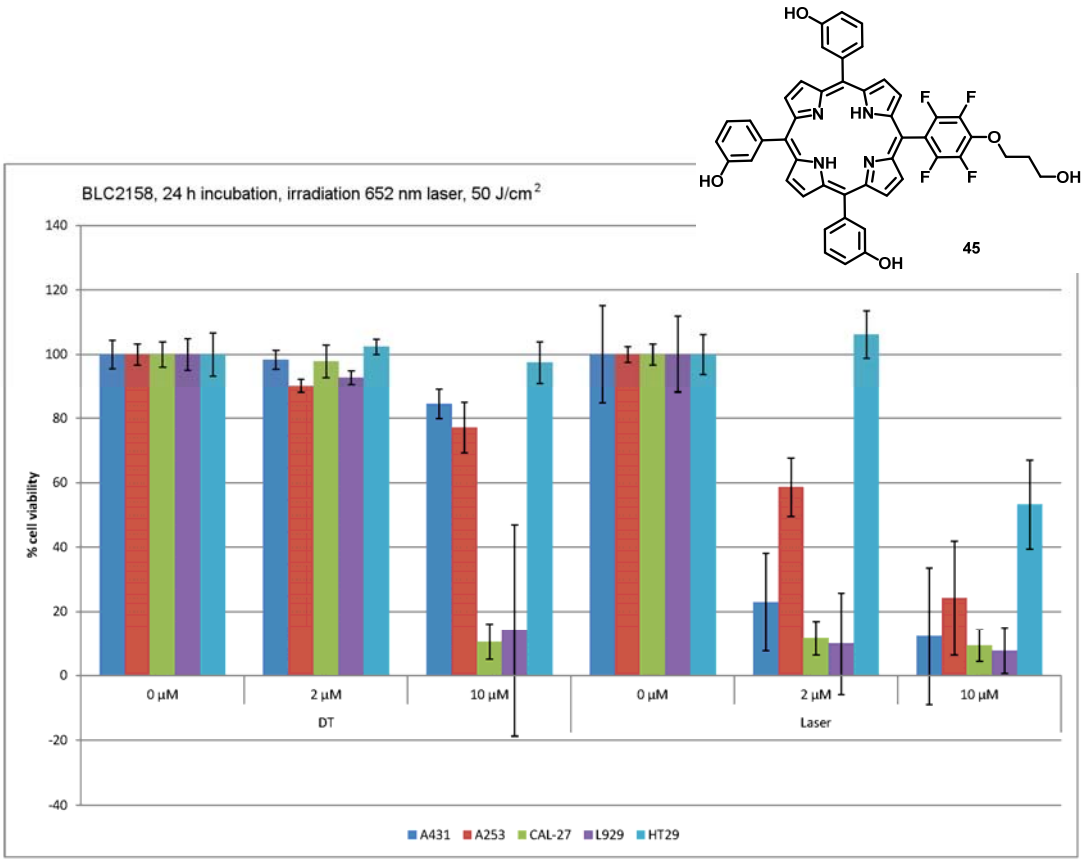


Figure 52. Cell test result for porphyrin **45**.

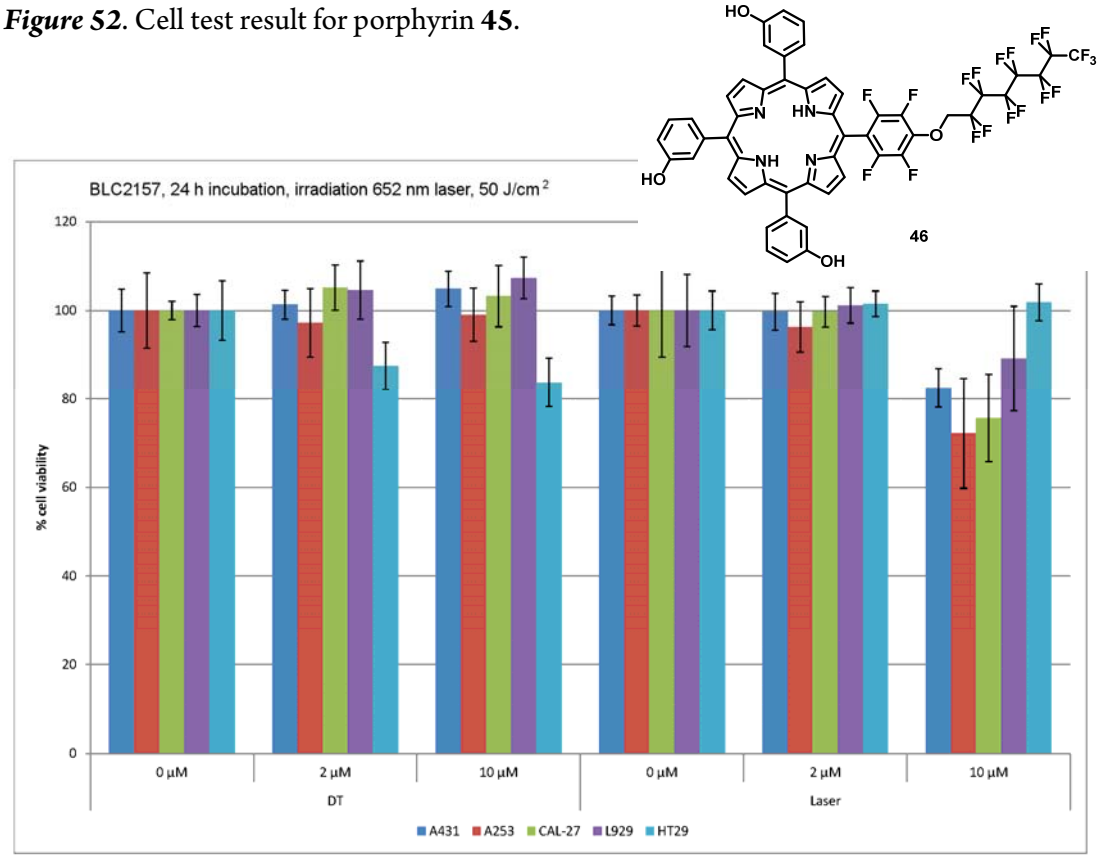


Figure 53. Cell test result for porphyrin **46**.

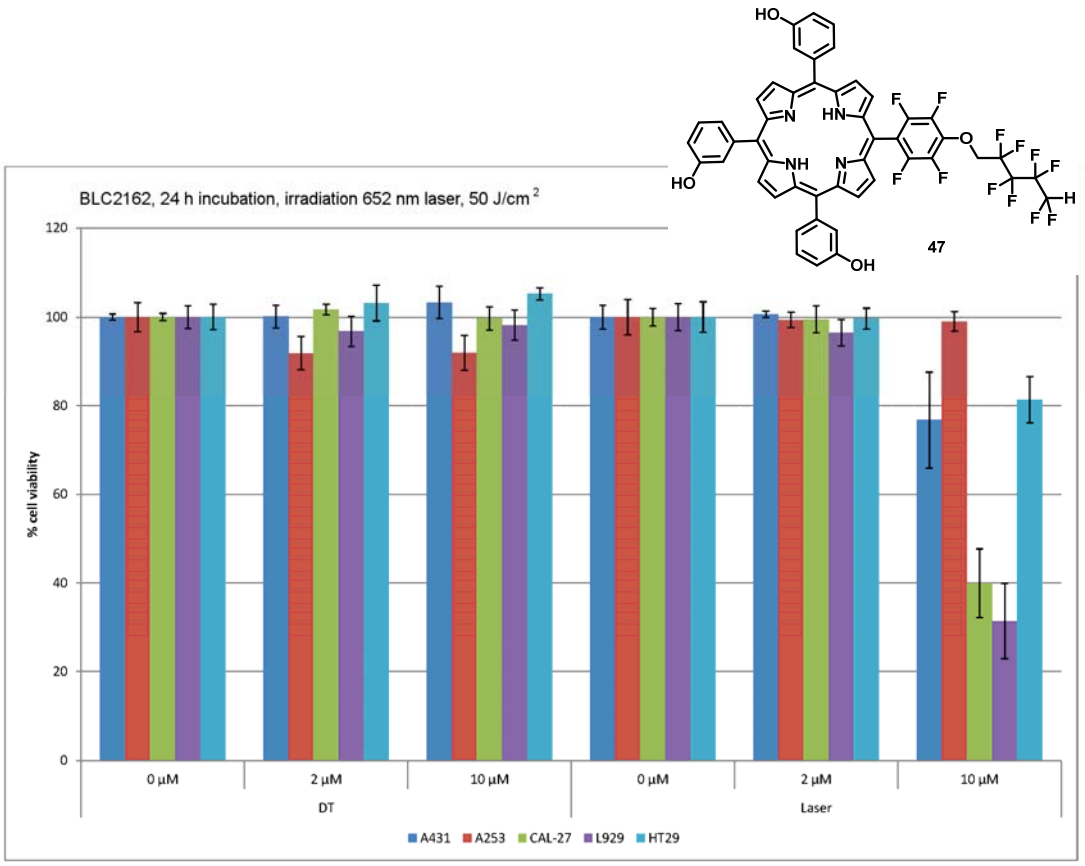


Figure 54. Cell test result for porphyrin **47**.

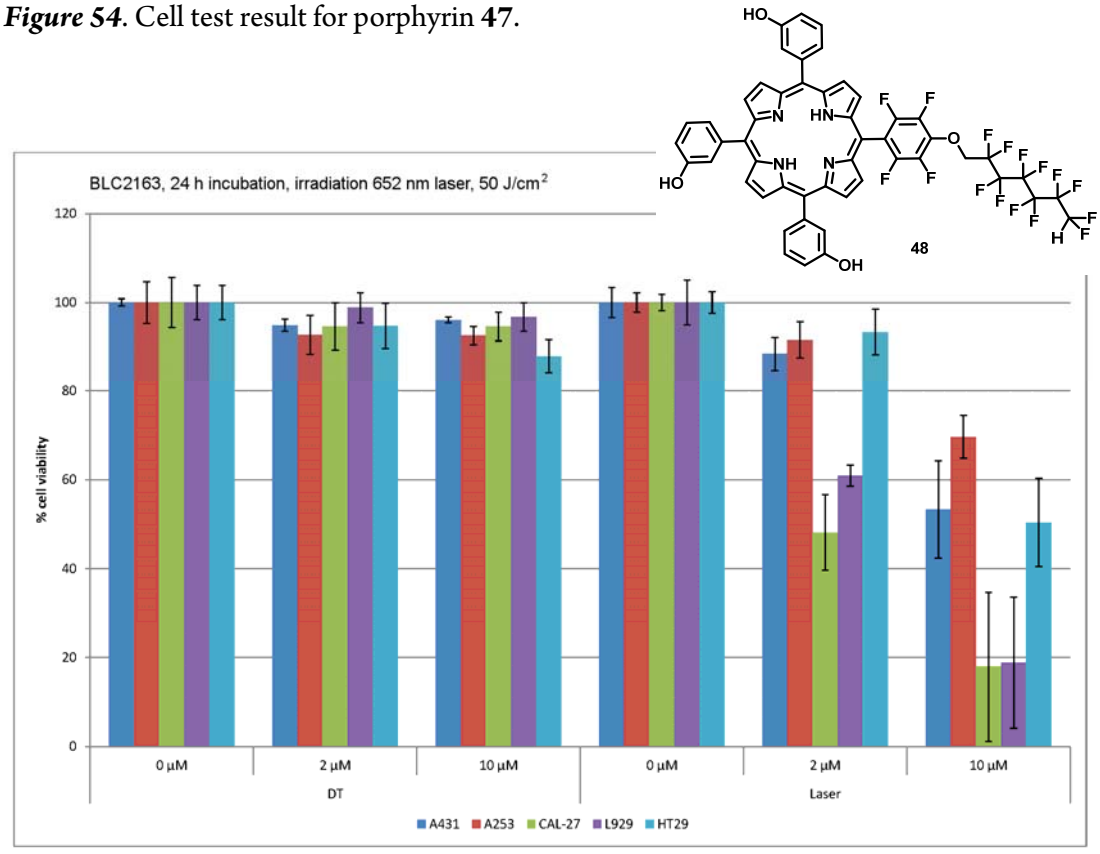


Figure 55. Cell test result for porphyrin **48**.

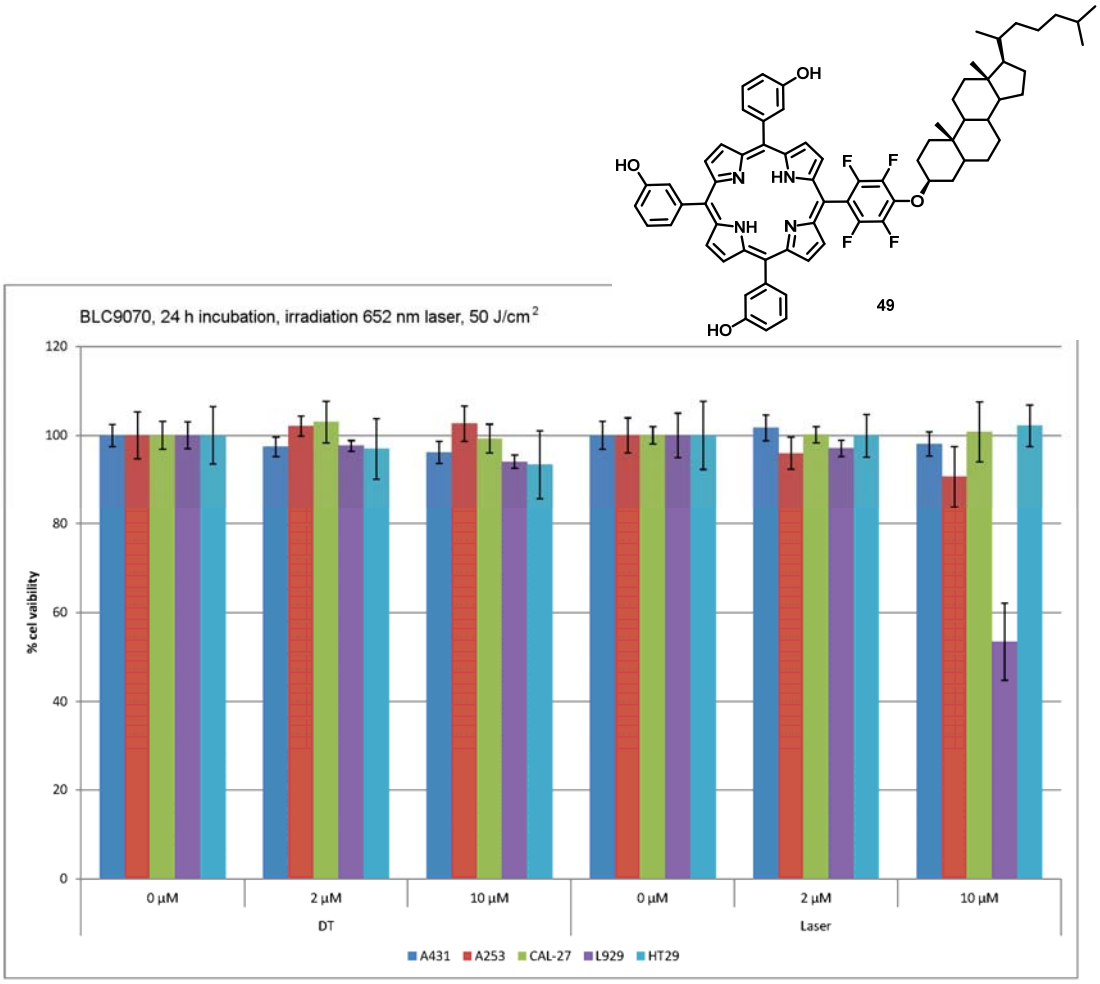


Figure 56. Cell test result for porphyrin **49**.

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