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Synthetic Studies for Photo-triggered Release of Bioconjugate Porphyrin Photosensitisers in Photodynamic Therapy

Submitted by

Mohd Bakri Bakar

B.Sc. (Chemistry), M.Sc. (Chemistry), Universiti Teknologi Malaysia

A thesis submitted to the University of Dublin, Trinity College for the degree of Doctor of Philosophy

University of Dublin, Trinity College March 2009
Declaration

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Mohd Bakri Bakar
Summary

The objective of this research was to synthesise porphyrin linked-bioconjugate photosensitisers that can be released upon irradiation with UV light; aiming to improve photodynamic cancer therapy efficiency. This photoreleased-bioconjugate system has potential for use in targeted photosensitiser delivery with a light-triggered control release mechanism. Several approaches were employed towards linking porphyrins to the bioconjugates using thio and o-nitrobenzyl labile linkers.

The classic 1,3-dithiane-2-yl synthon residue is an useful anion which has been used both as a functional and protected formyl group. Based on Umpolung studies, S_NAr reactions via RLi method were carried out to introduce dithianyl residue into porphyrin macrocycle and act as the formyl synthon. The reactivity of related dithio analogues was later investigated to explore their basic chemistry. Subsequent work was focused on constructing labile photocleavable systems using spirobisdithiane and trithiane residues. It has been shown that mono-lithio derivatives of the spirobisdithiane and trithiane can be utilised as nucleophiles for the direct substitution of different porphyrins. However, the possibility to direct cross linking of two to three porphyrins or linking porphyrin to a bioconjugate via di- and tri-lithiated anion species of spirobisdithiane and trithiane was not realised. In most cases, butylation occurred as the competitive reaction. Interestingly, the free base substituted porphyrins exhibit highly photosensitivity towards ambient light and easily converted to formyl porphyrins.

A second labile linker based on o-nitrobenzyl group was utilised in subsequent work. Palladium-catalysed coupling of the Suzuki and Heck reactions followed by hydrolysis reactions were performed to obtain carboxylic acid porphyrins. Subsequent esterification reactions were explored via carbodiimide method to form the model compounds of porphyrin linked-o-nitrobenzyl. The rearrangement products of N-acylisourea-porphyrins were obtained under DCC/DMAP reaction conditions, while targeted compounds were achieved using EDAC carbodiimide activating reagent.

The ultimate construction of porphyrin o-nitrobenzyl-linked bioconjugate was investigated. o-Nitrobenzyl linked-glucose as the example of the carbohydrate ligand was prepared before coupling with carboxylic acid porphyrins was performed. Once the synthesis of the porphyrin linked-glucose compound was achieved, the extent of its photofragmentation was studied and monitored using HPLC. In order to utilise a folic acid moiety as the ligand, different synthetic methods were examined to synthesise hydroxyl-type porphyrin. Its low reactivity currently limits our subsequent studies; however this
precursor provides conveniently naked-eye experimental monitoring due to the colour of porphyrins. A different approach using a palladium catalysed reaction was investigated to prepare o-nitrobenzyl porphyrins with carboxylic acid functionalities. These require further reaction optimisation to pave a way for linking the folic acid ligand. Although the present work contains no preclinical or clinical studies, the basic chemistry and the ‘proof-of-principle’ have been investigated extensively.

Finally, development of new strategies for the synthesis and utilisation of porphyrins containing α,β-unsaturated chains were explored. For comparative studies, different acrylic acid porphyrins were chosen as models which were activated with the subsequent in-situ generation of their corresponding acyl chloride. The activated acrylic porphyrins were then reacted with various nucleophiles to prepare various porphyrinic adducts in good yields. This methodology was employed to construct multifunctional dimeric systems of porphyrins. We have also examined the reactivity of the different porphyrinylacrylic adducts. As an example, yne-ene metathesis of the porphyrinylacrylate propargyl ester and allyl porphyrin gave E/Z bis-porphyrins. Altogether, these synthetic methods can be utilised for the facile transformation of porphyrin bioconjugate building blocks and serve for medicinal applications.
Publications


Conference Abstracts


Mohd Bakri Bakar, Katja Dahms, and Mathias O Senge, 15th European Symposium on Organic Chemistry, University College Dublin, Ireland, July 8-13 2007, 81.


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La tahzan..
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tr>
<td>AlClPc</td>
<td>Aluminium phthalocyanine chloride</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>ARMD</td>
<td>Age-related macular degeneration</td>
</tr>
<tr>
<td>BF$_3$OEt$_2$</td>
<td>Boron trifluoride etherate</td>
</tr>
<tr>
<td>BODIPY</td>
<td>Boron-dipyrromethene</td>
</tr>
<tr>
<td>BPD</td>
<td>Benzoporphyrin derivative</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>CBT</td>
<td>N-Chlorobenzotriazole</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet-doublet</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N'-Dicycloisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DTAD</td>
<td>Di-tert-butyl azodicarboxylate</td>
</tr>
<tr>
<td>EA</td>
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</tr>
<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide</td>
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<td>EDAC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride</td>
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<tr>
<td>eq</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HOBt</td>
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<td>HpD</td>
<td>Hematoporphyrin derivative</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single Quantum Coherence</td>
</tr>
<tr>
<td>ISC</td>
<td>Intersystem crossing</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>$J$</td>
<td>Coupling constant measured in Hertz</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium di(iso-propyl)amide</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass-to-charge ratio</td>
</tr>
<tr>
<td>mAb</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>MEM</td>
<td>Methoxyethoxymethyl</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>MTT</td>
<td>(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium)</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
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</tr>
<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
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<td>Near infrared</td>
</tr>
<tr>
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<tr>
<td>NOE</td>
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<td>PDT</td>
<td>Photodynamic therapy</td>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
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<tr>
<td>PhSeCl</td>
<td>Phenylselenenyl chloride</td>
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<tr>
<td>PS</td>
<td>Photosensitiser</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase-transfer catalysis</td>
</tr>
<tr>
<td>Rᵣ</td>
<td>Retention factor</td>
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<tr>
<td>RLi</td>
<td>Organolithium reagent</td>
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<tr>
<td>ROESY</td>
<td>Rotational nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SCF-MO</td>
<td>Self-Consistent Field Molecular Orbital</td>
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<tr>
<td>SₑAr</td>
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<tr>
<td>t</td>
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<td>TBAF</td>
<td>Tetra-µ-butylammonium fluoride</td>
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<td>TBAH</td>
<td>Tetrabutylammonium hydroxide</td>
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<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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</table>
$p$-THPP 5,10,15,20-Tetrakis(3-hydroxyphenyl)porphyrin
TLC Thin layer chromatography
TPA Two-photon absorption
$p$-TPPS$_4$ 5,10,15,20-Tetrakis(4-sulfonatophenyl)porphyrin
TMEDA $N,N',N''$-Tetramethylethylenediamine
$p$-TsOH Toluene sulfonic acid
UV Ultraviolet
$v/v$ Volume to volume
vis Visible
$\delta$ Chemical shift measured in parts per million (ppm)
$\varepsilon$ Molar absorption coefficient
$\lambda$ Wavelength measured in nanometre (nm)
CHAPTER 1:

Introduction
1.1 Tetrapyrrolic macrocycles

1.1.1 Introduction

Porphyrins are a class of aromatic tetrapyrrolic macromolecules consisting of four pyrrole units connected by methine groups. These compounds possess 22 \( \pi \)-electrons, 18 of which participate in a cyclic delocalised conjugation pathway (Figure 1.1).\(^1\) Porphyrins fulfil the requirements for aromaticity according to Hückel’s rules (4n+2, n=4) with the presence of two active sites known as the meso-position and the \( \beta \)-position.\(^2\)

![Figure 1.1 The 18 \( \pi \)-electron pathway.](image)

Numbering of the porphyrin nucleus runs along the twenty peripheral carbon atoms according to International Union of Applied Chemistry (IUPAC) system.\(^3\) The inner nitrogens are given locants 21-24. In a non-metallated porphyrin (called free-base), the two inner protons are mobile and tautomerise freely among the four nitrogens.\(^4\) The (21, 23-\( H \)) tautomer is energetically preferred compared to the (21, 22-\( H \)) tautomer. Porphyrins have characteristic \(^1\)H-NMR spectra where the inner NH protons are highly shielded (\( \delta = -1 \) to -5 ppm), and the meso-protons on the bridging carbons are strongly deshielded (\( \delta = 8 \) to 11 ppm). Meanwhile, the porphyrin UV–visible spectra are particularly characteristic and have an absorption band in the violet region between 390 - 425 nm known as the Soret band and a number of less intense bands in the visible region, called Q bands, located between 480 - 700 nm.\(^5\)
The pyrrolic double bonds can undergo addition reaction to form chlorin 2 or bacteriochlorin 3 without substantial loss of the macrocyclic aromaticity. Further investigation of porphyrin macrocycles lead to interesting expanded porphyrin analogs such as porphycene 4, N-confused porphyrin 5 and benzoporphyrin 6. Saturation of the meso-position in porphyrin causes an interruption in the macrocyclic conjugation as shown in porphodimethene 7, an intermediate between porphyrinogen and porphyrin 1.

Porphyrsins are the reactive centre of various fundamental biological representatives including hemes, chlorophylls, vitamin B₁₂, and others. Heme proteins (which contain iron porphyrins) are mainly involved in O₂ storage and transport (myoglobin and hemoglobin), electron transport (cytochromes b and c), and O₂ activation and utilisation (cytochrome P450 and cytochrome oxidase). Chlorophylls (which have a central magnesium ion) and
pheophytins (which are metal free) are crucial in the photosynthetic process in plants and bacteria as these capture photons of light. Vitamin B$_{12}$ (which contains a cobalt metallated corrin) is present in bacteria and animals as the prosthetic group for a number of enzymes.

1.1.2 Synthesis of functionalised porphyrins - Condensation reactions

The synthetic challenge in the construction of porphyrins is to control the arrangement of diverse substituents in a specific pattern around the macrocyclic periphery. Porphyrins can be designed based on two families of porphyrins; the $\beta$-substituted porphyrins that resemble naturally occurring porphyrins and the meso-substituted porphyrins. The meso-substituted porphyrins have wide application, even though they have no direct biological counterparts and are only accessible through laboratory synthesis. For example, they have been used in photoactive molecular devices, electro-optic materials and in photodynamic cancer therapy.

It is well-known in porphyrin chemistry that a condensation reaction between aldehyde and pyrrole or pyrrole derivatives represents a facile and straightforward synthetic method, and thus is widely used in various syntheses of porphyrins. For instance, synthetic approaches to alkylated $\beta$-porphyrin such as octaethylporphyrin (OEP) 8 or natural porphyrins related to heme or chlorophyll have been developed from the pyrrolic units. OEP is synthesised via a number of routes based on the condensation of 3,4-dihethylpyrrole and its derivatives. A simple and commonly employed method involved the reduction and cyclisation of 2-ethoxycarbonyl-3,4-dihethylpyrrole 9 (Scheme 1.1).

![Scheme 1.1 Synthesis of octaethylporphyrin 8.](image-url)
Porphyrins may also be synthesised from dipyrrolic precursors such as dipyrromethanes, dipyrromethenes and dipyrroroketones. The MacDonald reaction involved an acid-catalysed condensation of 5,5'-diformyl-dipyrromethane 10 and 5,5-di-unsubstituted dipyrromethanes 11 with toluene sulfonic acid catalyst to give porphyrin 12 (Scheme 1.2). This method was employed by R.B. Woodward for the classical total synthesis of chlorophyll.

Scheme 1.2 The MacDonald synthesis of porphyrin.

Another variation of the MacDonald route is the condensation of 5,5'-diformyl-dipyrroketone 13 and 5,5'-unsubstituted dipyrromethane 14 to give oxophlorin 15. The oxophlorin was then converted to meso-acetoxyporphyrin 16 which upon hydrogenation and re-oxidation gave the meso-unsubstituted porphyrin 17 (Scheme 1.3).

Scheme 1.3 Synthesis of porphyrin from 5,5'-diformyl-dipyrroketone 13.
Meanwhile, synthetic developments of meso-substituted porphyrins have gained more interest as they offer ease of synthesis and amenability towards synthetic elaboration. meso-Tetraarylporphyrins were originally synthesised by heating benzaldehyde and pyrrole in a sealed bomb at 150 °C for 24 hours. Due to severe condition, the aldehyde could not be varied much and the yields were very low too. Adler and Longo modified the Rothemund reaction by allowing pyrrole and benzaldehyde to react for 30 minutes in refluxing propionic acid, open to air. The yields were up to 20% and the milder reaction conditions allowed the use of a wider selection of substituted benzaldehydes. The porphyrins synthesis was later improved by Lindsey with even milder conditions, cleaner reactions for facile purification and increased the batch-to-batch reproducibility. In this modified synthesis, acid-catalysed condensation of pyrrole 18 and benzaldehyde 19 form porphyrinogen 20, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or p-chloranil produces porphyrin 21 in 30-40% yield (Scheme 1.4).

![Scheme 1.4 Synthesis of 5,10,15,20-tetraphenylporphyrin 21.](image)

The Lindsey-type synthesis can accommodate a variety of both alkyl and aryl aldehydes, ranging from p-, o-, and m-substituted benzaldehydes to heterocyclic and organometallic aldehydes with an average yield of 30% for fully symmetrical porphyrins. Figure 1.4 illustrates some examples of aldehydes used in the Lindsey method for the synthesis of symmetrical porphyrins.
Figure 1.4 Various aldehydes used in the synthesis of symmetrical porphyrins. 

Unsymmetrical porphyrins that bear different substituents may be synthesised via the Lindsey method by varying the stoichiometry of differently substituted benzaldehydes, but the yields are reduced due to the statistical formation of a mixture of products. The mixed-condensation also requires intensive chromatographic separation and purification which depends on differences in polarity between the meso-substituents. For example, the reaction of pyrrole with a mixture of two aldehydes (aldehyde A and aldehyde B) will result in the formation a mixture of six different porphyrins: A₄- 22, A₂B₂- 23, 5,10-A₂B₂- 24 and 5,15- A₂B₂- 25, AB₃- 26 and B₄-porphyrins 27 (Figure 1.5).

Figure 1.5 Formation of six different porphyrins from a mixed-aldehyde condensation.
One successful approach to minimise the chromatographic separation is to covalently attach one of the aldehydes to a solid phase.\textsuperscript{[27]} However, this method is limited to the use of aldehydes with functional groups that can be conveniently attached to the solid phase resin.

As porphyrins bearing substituents in the 5,15-position are useful in diverse applications, the separation of 5,10- and 5,15-substituted porphyrins from the mixed condensation are often problematic. Rational synthesis of 5,15-substituted porphyrins have been developed based on 2+2 condensations of a dipyrromethane and an aldehyde.\textsuperscript{[28]} The dipyrromethanes were prepared according to the method that was established for the synthesis of naturally occurring porphyrins. Gunter and Mander established a high yield route to the formation of 5,15-substituted porphyrin 28 by reacting meso-unsubstituted-\(\beta\)-substituted dipyrromethane with an aryl aldehyde in methanol containing \(p\)-toluenesulfonic acid (\(p\)-TsOH) at 20 °C for 6 hours (Scheme 1.5).\textsuperscript{[29]} The resulting porphyrinogen was then isolated by cooling the mixture to 4 °C for 16 hours and then oxidised with DDQ in THF. A small trace of the 5-substituted porphyrin was also formed in the reaction.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{Scheme15.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.5} Rational synthesis of 5,15-disubstituted porphyrin 28.

Osuka further developed the method for the synthesis of porphyrin compounds containing an acid-labile substrate such as an acetal. The condensation reaction was carried out at room temperature in acetonitrile using trifluoroacetic acid as a catalyst and \(p\)-chloranil as oxidant.\textsuperscript{[30]} Lindsey utilised the dipyrromethane-aldehyde condensation in a two-step one-flask room temperature-procedure in dichloromethane with boron trifluoride-diethyl-etherate (\(\text{BF}_3\cdot\text{O(CH}_2\text{CH}_3)_2\)) as catalyst and oxidation with \(p\)-chloranil.\textsuperscript{[31]} These routes have been employed to prepare a variety of 5,15-disubstituted porphyrins through variation of the aldehyde and dipyrromethane.\textsuperscript{[32]} The accessible routes to porphyrins via the MacDonald 2+2 condensation depend on the availability of various types of dipyrromethanes. Wang and Bruce established a one-step procedure to prepare
dipyrromethane 29,[33] while Lindsey developed a method to synthesise dipyrromethane derivatives that enable control of the substituents at the meso- and β-position of porphyrins (Figure 1.6).[34]

a) Wang and Bruce Method

\[
\text{HOAc/ MeOH} \quad \xrightarrow{\text{HOAc/ MeOH}} \quad \text{29}
\]

b) Lindsey method

\[
\text{R} \quad \text{O} \quad \xrightarrow{TFA} \quad \text{R}
\]

**Figure 1.6** Synthesis of dipyrromethane.

Further works were carried out to minimise the scrambling processes that occurred during the condensation reaction. Figure 1.7 illustrates the formation of 5,10-disubstituted porphyrin 30 via scrambling during the condensation reaction of dipyrromethane-A and aldehyde-B.

**Figure 1.7** Formation of 5,10-disubstituted porphyrin 30 via a scrambling mechanism.
Littler et al. have investigated the conditions to synthesise porphyrin 31 that can minimise the scrambling using sterically hindered 5-mesityl dipyrromethane 32 and aldehyde 33 (Scheme 1.6a).\[^{[35]}\] However, the condensation of an aldehyde with a sterically unhindered dipyrromethane such as 5-phenyl dipyrromethanes typically results in low yield and a mixture of porphyrin products derived from acidolytic scrambling. Rao et al. used an alternative approach to the synthesis of porphyrins with unhindered substituents via self-condensation of a dipyrromethanecarbinol 34 to give gram quantities of the desired porphyrin 35 (Scheme 1.6b).\[^{[36]}\]

![Scheme 1.6](image-url)

Scheme 1.6 Synthesis of porphyrin from a) sterically hindered dipyrromethane and b) sterically unhindered dipyrromethane.

Brinas and Brückner have reported the step wise synthesis of less symmetrical 5,10-diphenylporphyrin based on 2+2 methodology (Scheme 1.7a) and 3+1 approaches (Scheme 1.7b).\[^{[37]}\] The key intermediate in 2+2 condensation was identified as the benzoylformyl-dipyrromethane 36, which was reduced to the dicarbinol 37 and condensed in situ with dipyrromethane 29 under low scrambling conditions (CH\(_3\)CN, 25 mM reactant concentrations, 30 mM TFA, 25°C, 10 min.). This method afforded analytically pure disubstituted porphyrin 38 in 10-20% yield. Meanwhile, using a 3+1 method for condensation between tripyrrane 39 (a compound containing three pyrrole groups linked
alpha to the ring nitrogen by two saturated carbons) and hydroxylpyrrole 40 leads to formation of a number of unseparable scrambling products due to the susceptibility of tripyrranes to acid catalysed scrambling.

Scheme 1.7 2+2 and 3+1 condensations to synthesise 5,10-disubstituted porphyrin.

Senge and Hatscher extended this by preparing a range of aryl and aliphatic 5,10-disubstituted porphyrins 41 through variation of the 3+1 condensation procedure from tripyrrane 42 and various aldehydes (Scheme 1.8). This method also gave 5-monosubstituted porphyrin 43 as a second product, especially when sterically demanding groups such as t-butyl were employed.
Scheme 1.8 3+1 Condensation for synthesis 5,10-disubstituted porphyrin.

More unsymmetrical porphyrins of the 5,15-AB2C-type 44 were prepared by Rao et al. via the condensation of an ABA-dipyrromethane dicarbinol 45 and C-dipyrromethane 46 as shown in Scheme 1.9.\(^{[39]}\)

\[
\text{NH} \quad \text{HN-} \\
\text{NH} \quad \text{HN-} \\
\text{OH} \quad \text{HO} \\
\text{45} \\
\text{CH}_2\text{CN, TFA, DDQ} \\
\text{46} \\
\text{44}
\]

Scheme 1.9 Synthesis of A\textsubscript{2}BC-porphyrin.

Meanwhile, the synthesis of a so-called ABCD-porphyrin, which has four different \textit{meso}-substituents has seen significant developments. The first step wise synthesis of this type of unsymmetrical porphyrin was reported by Smith and Wallace in 1990. However, the synthetic route involved two different types of dipyrromethanes and gave a mixture of porphyrin products.\(^{[40]}\) Rao \textit{et al.} designed a rational synthesis towards construction of the ABCD-porphyrin and managed to prepare various ABCD-type porphyrins.\(^{[39, 41]}\) Figure 1.8\(^{[42]}\) shows a general retrosynthetic analysis to synthesise the ABCD-porphyrins; these include the MacDonald 2+2 condensation, condensation of tripyrrane with pyrrole or mixed condensation of four different aldehydes and pyrrole.\(^{[43]}\) In addition, ABCD-porphyrin can also be prepared \textit{via} cyclisation of hydroxymethylbilane or bilane with aldehyde.\(^{[44]}\)
Smith et al.\textsuperscript{[45]} and Ogoshi et al.\textsuperscript{[46, 47]} have described the synthesis of ABCD-porphyrins involving the acid-catalysed condensation of two different dipyrromethanes in refluxing propionic acid. Lindsey et al. further investigated and have developed a rational synthesis to prepare porphyrins bearing four different meso-substituents (Scheme 1.10).\textsuperscript{[39]} An acyl masked of benzoxathiolium tetrafluoroborate 47 is reacted with dipyrromethane 46 to form the first building block of AB-substituents 48. Another treatment with a benzoxathiolium tetrafluoroborate 49 enabled the introduction of the third substituent and afforded the 1,9-dialkylated dipyrromethane 50 in quantitative yield. 1,9-diacyl dipyrromethane 51 was obtained upon hydrolysis and underwent further reduction with LiAlH\textsubscript{4} to biscarbinol 52. The last building block of another substituent was introduced by condensation of 52 with dipyrromethane 53 and gave the ABCD-type porphyrin 54 in 13% yield.
1.1.3 Synthesis of peripherally functionalised porphyrins

As the condensation method offers a path to prepare a range of porphyrins where functionality is introduced during the formation, many other approaches have been developed to introduce various functionalities on preformed porphyrins. There are two different sites where the reactions can occur on the porphyrin macrocycle; the meso-position and the β-position. The meso-carbon has greater electrophilic character relative to β-pyrrolic carbon because the two pyrrolenine units in porphyrins tend to achieve an individual aromatic sextet of electrons; thus withdrawing electron density from the neighbouring meso-carbons. A more general reactivity pattern was established based on theoretical \textit{ab initio} self-consistent field-molecular orbital (SCF-MO) calculations\cite{48} which predict that most reactions on porphyrins macrocycle take place preferentially at the meso-
positions. Steric considerations are also very important since bulky peripheral substituents shield some of the sites on the porphyrin macrocycle. The meso-positions are sterically less accessible, especially when one or two of the adjacent β-positions are substituted. The β-pyrrolic positions are sterically favoured and, as a result, will undergo substitution or addition reactions.

1.1.3.1 Electrophilic aromatic substitution, \( \text{S}_{\text{E}}\text{Ar} \)

Porphyrins readily undergo many electrophilic aromatic substitution reactions, \( \text{S}_{\text{E}}\text{Ar} \) such as formylation, halogenation and nitration. Most electrophilic substitutions are employed on metallated porphyrins since these metallocycles are more stable to electrophilic attack whereas the free base porphyrins are easily protonated under acidic conditions.\(^{[49]}\) Formylation at the meso-position is one of the most common reactions as the aldehyde functionality can offer access to introduce another functional groups via various typical aldehyde reactions such as Wittig, Grignard, McMurry or Knoevenagel. The classical Vilsmeier reaction can be utilised to introduce the formyl group on the corresponding copper or nickel complex of the porphyrins. Inhoffen \textit{et al.} has performed meso-monoformylation of \([2,3,7,8,12,13,17,18\text{-octaalkylporphyrinato}]\text{Ni(II)}\) 55 and reported that the reaction gave reproducibly high yields of the formylated product 56 (Scheme 1.11).\(^{[50]}\) Labile peripheral substituents such as vinyl groups also react under the Vilsmeier reaction conditions affording the corresponding trans-2-formyl derivatives as the main products.\(^{[51]}\) In general, a mixture of dimethylformamide (DMF) and phosphorus oxychloride (POCl\(_3\)) is used to produce the reactive Vilsmeier complex, however using \(N,N\)-diisobutylformamide in place on DMF produced sterically hindered Vilsmeier complex that favoured substitution at the β-pyrrolic positions.\(^{[52]}\)

![Scheme 1.11](image_url)
Porphyrins can also undergo halogenation reactions which can provide an entry to synthetically useful precursors for further porphyrin transformations. N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) have been successfully used for chlorination and bromination reactions on porphyrins. Octachlorination and octabromination of meso-tetraarylporphyrin are usually carried out by refluxing a solution of the metalloporphyrin in methanol, carbon tetrachloride or tetrachloroethane in the presence of excess NCS or NBS.[53] Monohalogenation is achieved with one equivalent of NCS or NBS although dihalogenated products are usually also formed in lower yields. Chlorination of Ni(II) or Cu(II) OEP complex with phenylselenyl chloride gives the mono-, di-, tri-, tetra-meso halogenated porphyrins as shown by van Lier et al.[54] Longo et al. performed a bromination reaction on free base porphin with NBS in CHCl₃ and this reaction gave predominantly meso-brominated product of mixture 5 mono-, 5,15-di- and 5,10,15-tribromo porphyrins.[55] Under similar conditions, 5,15-diphenylporphyrin can be brominated with two equivalents of NBS to afford tetra meso-substituted porphyrin. However, deuteroporphyrin IX dimethylester 57, that contains at least one β-substituent adjacent to meso-position reacts with NBS in CHCl₃ to produce only β-substituted monobromo- 58 and dibromoporphyrin 59 due to steric reason (Scheme 1.12).[56] The site of halogenation is also determined by the size and reactivity of the halogen, thus meso-halogenation is favoured by the smaller and more reactive chlorine. Since bromine is of an intermediate size among halogens, meso-bromination is observed when an excess of brominating reagent is used and favoured by porphyrins bearing unsubstituted adjacent β-positions. meso-Iodination is more difficult due to less reactive and larger steric bulk of iodonium cation, nevertheless Dolphin et al showed that 5,15-diphenyl porphyrin can undergo iodination using bis(trifluoroacetoxy)iodobenzene and iodine with 70% isolated yield.[57] Diido species were also formed in which the second iodine occupies at β-position rather than second available meso-position. Osuka et al. have developed another iodination method using AgPF₆ and iodine which afforded the mono- and disubstituted [5,15-diphenylporphyrinato]Zn(II) complex.[58]
Nitration of OEP using concentrated nitric acid in acetic acid at 0 °C has been employed by Bonnett et al. to give the 5-monomonitrat ed compound, whereas using nitric acid in sulphuric acid afforded meso- di- and trinitro substituted porphyrin products. The latter procedure was used by Longo et al. on porphyrin and afforded meso-mono- and di-nitroporphyrin derivatives while the 5,10-dinitro isomer was reported to be the major product. van Lier et al. used a mixture of phenylselenyl chloride (PhSeCl), and silver nitrite (AgNO₃) for meso-nitration of Ni(II)OEP and the reaction gave the nitrated porphyrin in 75% yield. A nitrating reagent from the mixture of trifluoroacetic acid and sodium nitrite was prepared by Arnold et al. and reacted with 5,15-diarylporphyrin to afford the nitrated products in good yield. Recently, Banfi et al. synthesised a series of nitrosubstituted 5,15-diarylporphyrins where the nitro groups was introduced on the phenyl rings or to the meso-position on the porphyrin periphery.

1.1.3.2 Nucleophilic aromatic substitution, S₆Ar

Application of nucleophilic aromatic substitution (S₆Ar) to the porphyrin macrocycle mostly requires an activated porphyrin core. For example, the activated form of π-cation radical metalloporphyrins reacts with various nucleophiles such as cyanide, nitrite, pyridines, and acetates, affording the corresponding meso- or β-substituted metalloporphyrins. The π-cation radicals are readily obtained from oxidation of the metalloporphyrins with iodine, thalium (III) nitrate, iodine, tris(ρ-bromophenyl) ammonium hexachloroantimonate (TBAH) or N-chlorobenzotriazole (CBT).

Smith et al. treated π-cation radicals of Mg(II), Zn(II) and Cd(II) octa-alkylporphyrins with sodium nitrite affording the corresponding series of meso-nitro substituted porphyrins. Reaction of Mg(II), Zn(II) and Co(II) complexes of OEP in the

![Scheme 1.12 Bromination of deuteroporphyrin IX dimethylester 57.](image-url)
presence of N₂O₄ in dichloromethane also employed and produced the meso-nitro porphyrin derivatives in good yields. Meanwhile, methylation of meso-positions of Cu(II) chlorophyll complex have been accomplished by treatment with chloromethyl methyl sulfide and titanium tetrachloride, followed by Raney-Nickel reduction of the resulting meso-methylthiomethyl derivatives. Nucleophilic attack of organolithium reagents on Rh(III) OEP 60 is also reported, however the reaction occurred both at the chelated metal and meso-position to afford Rh(III) phlorin complex 61, that readily oxidised to give the corresponding meso-substituted porphyrin 62 (Scheme 1.13).

![Scheme 1.13 meso-Substitution reactions of Rh(III) OEP with organolithium reagents.](image)

Seng et al. have successfully developed the SNAr reaction utilising organolithium on unactivated porphyrin core. This method offers a direct introduction of both aryl and alkyl moieties preferentially at meso-positions of porphyrins. Conveniently, the porphyrin anion intermediate which is formed in the SNAr reaction of 5,15-disubstituted porphyrins 63 can be trapped in situ with an organic electrophile to introduce a second, different substituent in the same reaction affording A₂BC-type porphyrins 64 (Scheme 1.14).

![Scheme 1.14 One-pot synthesis of A₂BC-type porphyrins.](image)
1.2 Application in photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a cytotoxic treatment modality based on photoactive substances of photosensitisers such as porphyrins that selectively retain in tumour tissues. Irradiation of the target tissues with appropriate wavelength of light activates the production of highly reactive oxygen and leads to a series of phototoxic reactions that cause selective death of tumor cells. Many investigations have been pursued in the last decades to improve the efficiency of the three PDT basic components namely light, oxygen and photosensitisers (PS), along with understanding the biomedical and biophysical processes. Studies have been conducted on the treatment of a variety of malignant and pre-malignant cancer conditions including head and neck cancer, lung cancer, mesothelioma, Barrett’s esophagus, prostate and brain tumors. PDT is also employed to treat non-cancerous conditions such as psoriasis and age related macular degeneration (ARMD).

1.2.1 Introduction

Photochemotherapy approaches involve the combined action of light and a systemic photosensitiser agent. The recent PDT impetus began in 1960 as the fluorescent properties of hematoporphyrin derivatives (HpD) were utilised in tumour imaging studies. Since then, significant works have been carried out in pre-clinical and clinical studies of the first generation photosensitiser such as hematoporphyrin, resulted in the approval of the photosensitising drug Photofrin® in the US, Canada, Japan and throughout Europe (Figure 1.19). However, it has several limitations as it comprises a complex mixture of porphyrins with various monomeric and oligomeric forms and some of the components are not photoactive. The treatment with Photofrin® also renders the patient photosensitive to strong sunlight because the prolonged accumulation can last up to six weeks. Thus, patients are advised to keep away from direct sunlight. The major drawback is mainly due to the relatively weak electronic absorption band of photosensitisers (630 nm), which does not allow for optimal light penetration.

Second generation photosensitisers were actively developed to improve PDT efficiency, notably by increasing the absorption wavelength and strong absorption band in the red wavelength region (650-800 nm). Ideally, the photosensitisers should be non-toxic, water soluble, exhibit selectivity for the enrichment in tumoured tissue and have pharmacokinetic profiles that show it can be cleared in reasonable times from the body.
The absorption of red light by photosensitisers can be shifted to longer wavelengths by introducing suitable substituents. For example, 5,10,15,20-tetrakis(4-sulfonato phenyl)porphyrin (p-TPPS₄) 67 is substituted porphyrin developed as potential photosensitiser for PDT. p-TPPS₄ also has hydrophilic character, therefore does not require a carrier to avoid self-aggregation during the PDT process. The reduction of a peripheral double bond of a porphyrin macrocycle increases the longest-wavelength absorption band and shifts the λ_max further to the red region as shown for chlorin photosensitisers. Of the purely synthetic chlorins, 5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin (m-THPC) 68 or Foscan® has been approved for use in PDT, where only low drug and light doses are needed to achieve photodynamic responses equivalent to Photofrin®.

As reduced porphyrins are prone to being oxidised, large substituents or an exocyclic ring are often introduced close to the reduced pyrrole ring as observed in benzochlorin structures of tin etiopurin (SnEt₂) 69 or Purlytin® that have an maximum absorption near to 650 nm. Diamagnetic metals such as Sn(IV) are used to increase the singlet oxygen formation of the photosensitisers. Meanwhile, benzoporphyrrin derivatives (BPD) are reported to have absorption around 690 nm and its approved form; verteporfin 70 or Visudyne® is recommended for treatment of neovascularisation on the retina in ARMD.
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Figure 1.10 Second generation of photosensitisers.

Table 1. Porphyrin and chlorin based photosensitisers

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Compound</th>
<th>Treatment</th>
<th>Activation Wavelength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photofrin® 66</td>
<td>HpD</td>
<td>Cervical, oesophageal, bladder and gastric cancer and brain tumour</td>
<td>630 nm</td>
</tr>
<tr>
<td>Foscan® 68</td>
<td>Temoporfin (m-THPC)</td>
<td>Non-melanoma skin cancer of head and neck</td>
<td>652 nm</td>
</tr>
<tr>
<td>Purlytin® 69</td>
<td>Tin ethyl etiopurpurin (SnEt₂)</td>
<td>Cutaneous metastatic breast cancer, basal-cell carcinoma and prostate cancer</td>
<td>664 nm</td>
</tr>
<tr>
<td>Visudyne® 70</td>
<td>Vertiporfin (Benzoporphyrin derivative monoacid A)</td>
<td>Age-related macular degeneration, non-melanoma skin cancer</td>
<td>690 nm</td>
</tr>
</tbody>
</table>
PDT has established itself as the fourth modality for cancer treatment next to surgery, chemo- and radio-therapy because of the advantages of no systemic toxicity with high accumulation and selectivity in tumour tissue. It is a selective, non-invasive treatment that does not destroy healthy tissues, repeated treatments can be given without dose limitation which is common in chemotherapy and usually the treatment can be done as an outpatient procedure. PDT treatment can be combined with surgery to remove microscopic tumours after surgery.\textsuperscript{[85]} It may also be used with chemotherapy or radiation treatment to reduce the size of tumour.

1.2.2 Mechanism of photodynamic therapy

The photochemical processes in PDT are represented by the Jablonski diagram (Figure 1.11).\textsuperscript{[86]} Upon absorption of light with a suitable wavelength, the photosensitisers which have ground electronic singlet state ($P^0$) are excited to the first excited singlet-state ($^1P^*$). The photosensitiser can decay back to the ground state by emitting fluorescence photons enabling identification of tumour tissue. Alternatively, the $^1P^*$ photosensitisers can convert to the first excited triplet state, $^3P^*$ via intersystem crossing (ISC). The $^3P^*$ state is sufficiently long-lived that can be involved in chemical reactions. The $^3P^*$ photosensitisers can also return to the ground state by emitting phosphorescence.

![Jablonski diagram for PDT](Figure 1.11 A simplified Jablonski diagram for PDT.)

There are two types of photodynamic process that promote chemical reactions in a substrate including damage to living tissue; these are referred as type I and type II. Type I photoprocesses involves electron or hydrogen transfer reaction between excited state $^3P^*$ photosensitisers and other molecules. These excited photosensitisers can react directly with
an organic substrate (S) by electron exchange producing an oxidised substrate (S⁺) and a reduced photosensitiser (P'). The reduced photosensitiser (P') can react with oxygen to produce a less reactive superoxide anion (O₂⁻), which can then form the highly reactive hydroxyl radical (·OH). The excited photosensitiser, ³P* also can react with superoxide radicals (O₂⁻) to produce superoxide anions (O₂⁻) which can then form the highly reactive hydroxyl radical (·OH) that is harmful to cells. The type II photoprocess is an electron spin exchange between ³P* photosensitisers and ground state oxygen, ¹O₂. It produces the cytotoxic singlet-state of oxygen, ¹O₂ that reacts with various biomolecules such as triacylglycerols, cholesterol, phospholipids, histidine and nucleic acids. The extent of photodamage and cytotoxicity is dependent on the type of photosensitiser, its localisation, the total dose of administered photosensitiser, total light time exposure, the availability of oxygen and the time between the injection of drug and light exposure.

![Figure 1.12 Type I and II photochemical reactions in PDT.](image-url)
1.2.3 Targeted photosensitisers delivery

Most therapeutic drugs distribute throughout the body resulting in general toxicity that causes negative side effects and poor acceptance of the treatment by the patient. Moreover, to reach the site of action, the drug has to cross many biological barriers and intracellular compartments. As a result, a large drug dose is administered to achieve its required therapeutic concentration. In cancer treatments, targeted chemotherapeutic drug delivery offers an enormous potential to improve its efficiency by selectively localised therapeutically effective drug concentrations at the tumour site. For example, such delivery system can be developed by conjugating the drug to the ligand of specific targets in cell. Furthermore, diseased-associated cells express different pathophysiological features and a thorough understanding of the tumour environment and their growth patterns will allow development of an effective targeted delivery where the therapeutic window can be expanded by increasing the target/non-target tissue ratio. In addition, PDT efficiency is depended on reactive singlet oxygen species that has a short life time ~0.01μs with a range of action of about 0.01-0.02 μm, and thus requires exact localisation of photosensitisers.

Approaches to enhance PDT efficacy and selectivity have been investigated in several strategies. At first, an array of photosensitisers based on different structural, charge and hydrophobicity were designed to analyse their biodistribution properties and cell accumulative capabilities. It can be classified into three categories: a) hydrophilic compounds which are mainly bound to plasma proteins of albumin such as the tetrasulfonated porphyrin derivative b) hydrophobic compounds such as tin-etioptopurpurin that require delivery vehicles and c) amphiphilic compounds that localise at the hydrophilic-hydrophobic interfaces in membranes, such as benzoporphyrin monoacid derivative. Photosensitisers need to have a hydrophilic character in order to facilitate its systemic administration via injection into the bloodstream. However, the increased hydrophilicity will hamper the ability of the photosensitisers to get into cells through lipid membranes. On other hand, hydrophobic properties of photosensitisers can increase unfavourable self-aggregation of the photosensitisers in plasma. Thus, the amphiphilic structure, containing both hydrophilic and hydrophobic parts, will generate better photodynamically active photosensitisers.

A different strategy utilise targeting ligands such as monoclonal antibodies (mAbs) that can bind specifically to the cell surface proteins. An ideal targeting agent should have high affinity and specificity of binding to the cell surface receptors, be compatible for chemical conjugation and able to be produced in sufficient amounts.
first study of a photosensitiser-mAb conjugate utilised hematoporphyrin (Hp) and mAb directed to DBA/2J myosarcoma and the investigation showed inhibition of tumour growth compared with Hp alone.\cite{90} It has also been reported that chlorin e6 conjugates with the mAb OC125 accumulate up to threefold higher compared than free chlorin e6 in murine ovarian tumour,\cite{91} while immunoconjugates of chlorin e6 monoethylene diamine monoamide with the mAb IG12 specific for uveal melanoma cells produce four-fold greater damage than the free chlorin e6 at the same concentration.\cite{92} A modified system has been established with mAb-PS conjugates to include additional components that allow for penetration into the cell by an endocytotic mechanism. For example, the attachment of polylysine to a conjugate containing mAb OC125 directed against ovarian cancer cells can enhance photosensitiser uptake up to 17-fold.\cite{93} Meanwhile, m-tetrahydroxyphenylchlorin attached to internalisable mAb 425, specific for head and neck squamous cell carcinoma, was shown to be more effective than a conjugate with a non-internalisable antibody.\cite{94}

Another strategy that is commonly used is to employ carriers such as polymers, liposomes, microspheres and emulsions to facilitate the photosensitiser delivery. Liposomes have a high loading capacity and are flexible to accommodate photosensitisers of variable physicochemical properties, hence this mode has been extensively used as the photosensitiser delivery vehicle. For instance, Photofrin®, that consists of hydrophobic dimers and oligomers was shown to be more effective against human glioma brain cancer when the photosensitiser was formulated in liposome form.\cite{99} Liposomal verteporfin formulation (Visudyne®) has been approved for clinical application to treat age-related macular degeneration as the verteporfin itself has a very low solubility.\cite{100} The use of other vehicles such as microspheres enables the intracellular delivery of photosensitiser to phagolysosomes. The covalent attachment of the chlorin e6 to 1 μm polystyrene microspheres resulted in its entry into MGH-U1 human transitional cell bladder carcinoma cells via phagocytosis.\cite{101} The photodynamic activity of chlorin e6–microsphere conjugates in MGH-U1 cells has proved to be higher than that of free chlorin e6, although the singlet oxygen-generating capacity of free chlorin e6 is higher than in microspheres. Polymer-bound photosensitisers such as HPMA copolymer-meso chlorin mono ethylenediamine (CMA) also demonstrated a substantial increased tumour accumulation.\cite{102}

Photosensitisers can also be conjugated to specific proteins which are preferentially expressed in or on the cancer cells in comparison to normal cells due to their transformed nature. There are a variety of cell surface receptors for peptides, hormones and essential nutrients like iron and folic acid that are over expressed in many cancer cells, thus
Chapter 1: Introduction

providing opportunity for targeting of photosensitisers to tumor cells. This conjugated system can improve photodynamic therapy targeting by improve its intracellular accumulation via receptor-mediated endocytosis process.\textsuperscript{[103]} For example, the expression of the low density lipoprotein (LDL) receptor is regulated by the cholesterol demand of the cells and is usually higher in fast-growing cells.\textsuperscript{[104]} Thus, hydrophobic photosensitisers of Hematoporphyrin (Hp) was incorporated into LDL and the result exhibited increased uptake in targeted cell.\textsuperscript{[105]} Chlorin e6 was also conjugated to LDL and the cellular uptake of the conjugate was increased as shown in retinoblastoma and fibroblast cells compared with free chlorin e6.\textsuperscript{[106]} Non-proteic ligands such as vitamin B9 of folic acid have also been evaluated as the targeting moieties that can bind selectively the folate receptor. The folate receptor is a highly specific tumor marker frequently over expressed in more than 90% of ovarian carcinoma patients and in many other cancer types (choriocarcinomas, uterine sarcomas, osteocarcinomas).\textsuperscript{[107]} It has been reported that 5,10,15,20-tetraphenylporphyrin conjugated-folic acid shows increasing cellular uptake seven-fold higher against human nasopharyngeal cell line compared to tetraphenylporphyrin.\textsuperscript{[108]} Subsequent reports using tetra(hydroxyl)phenylchlorin shows increasing uptake up to two-fold while the selectivity between tumour and normal tissue was high (5:1).\textsuperscript{[109]} In the meantime, another folate conjugated fluorescent pyropheophorbide-a photosensitiser was designed to improve the efficiency of targeted delivery PDT agents and use for near-infrared (NIR) imaging purposes.\textsuperscript{[110]}

A number of photosensitiser design approaches have been described with particular consideration to enhance targeting to the site of action, increase the selectivity for killing cancer cells, decreases the peripheral/systemic toxicity and to permit dose escalation. As the ideal systems need to both recognise specific targets on cancer cells and have capabilities of efficiently internalizing into the cells, a combination of different targeting approaches may provide immense promise of enhancing the photosensitiser delivery for cancer therapy.

1.2.4 Controlled release of photosensitiser

The development of an ideal photosensitiser delivery system requires channelling of the active photosensitiser solely to the site of action, that is achievable by impose its delivery to a specific receptor. While the targeted photosensitiser delivery capable of attaining site-specific delivery, the major concern that arises is in controlling its release kinetics in a predictable manner. Thus, there are many circumstances in which are need to
sought-after to deliver the photosensitisers to an individual at a predetermined rate and to extend the action over a suitable time span. All controlled release systems are designed to improve the effectiveness of cancer therapy, to ensure safety and improve patient compliance.\textsuperscript{[111]}

One of the methods of releasing photosensitisers in a controlled mode is to utilise coating materials. In general, the photosensitiser is coated with polymers or inorganic materials that can be gradually released upon biodegradation under certain conditions. It has been suggested that pH-sensitivite triggers would be a beneficial approach in order to release the photosensitisers.\textsuperscript{[112]} Change in acidity is a useful environmental stimulus to be exploited as it is reported that the extracellular pH of tumours is slightly more acidic (pH 7.0) than normal tissues (pH 7.4).\textsuperscript{[113]} In addition, it is proposed that micelles are taken up by cells via an endocytosis process while the endocytic pathway begins near the physiological pH of 7.4 and it drops to a lower pH (5.5–6.3) in endosomes and approaches pH 4.6 in lysosomes.\textsuperscript{[114]} Therefore, polymeric micelles that are responsive to these pH gradients can be designed to release the photosensitisers selectively in tumor tissue or within tumor cells. For example, aluminum phthalocyanine chloride (AlClPc) was loaded into a copolymer of pH sensitive N-isopropylacrylamide (NIPA), methacrylic acid (MAA), octadecyl acrylate (ODA) and N-vinyl-2-pyrolidone (VP) to form polymeric micelles and tested on EMT-6 mouse mammary tumor cells.\textsuperscript{[115]} The result indicated that upon light treatment, the micelle formulations induced greater PDT photoactivity due to efficient intracellular localisation. It was shown that the presence of 5 mol\% MAA in the copolymers caused the polymers to precipitate as the pH decreased below 5.7–5.8, hence caused release of the entrapped photosensitiser and improved the intracellular localisation of the photosensitisers.

Meanwhile, polymeric nanoparticles were also employed as control release vehicles for PDT. Early work described in 1991 involved the use of hematoporphyrin adsorbed in polyalkylcyanoacrylate nanoparticles, however the results show rapid photosensitiser release with poor carrier capacity.\textsuperscript{[116]} A series of p-THPP loaded into biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles were studied with the chick embryo chorioallantoic membrane (CAM) model that allows for the comparison of the vascular effects of p-THPP either as a free solution or encapsulated in polymeric nanoparticles.\textsuperscript{[117]} Photosensitisers necessarily remain in blood vessels during light activation for selective destruction of vasculature. The study suggested that the nanoparticles with p-THPP appeared to have a longer residence time inside the vasculature, thus inducing an increased PDT effect; while free p-THPP appeared to leak out before generating an efficient vascular
occlusion. Another photosensitiser of verteporin-loaded PLGA nanoparticle type was investigated with different size of nanoparticles (167 and 370 nm) and tested on EMT-6 mammary tumour cells.\textsuperscript{118} The result indicated that the PDT effect was improved by using small size particle as it had higher intracellular uptake through the endocytosis mechanism. However, smaller-sized particles show higher release rates due to a corresponding increase in the total particle surface area, resulting in a larger fraction exposed to the leaching medium. Thus, it was suggested that an optimal size for a particle diameter is less than 200 nm for the effective blood tumour transfer of nanoparticles and their long retention in tumour tissue.

As the ultimate goal of a controlled release system is to maintain the photosensitiser levels within a desired range, this system are also helpful to control the delivery of complicated photosensitisers such that to slow release of water soluble-photosensitisers and the fast release of low solubility photosensitisers. Further work is necessary to understand site-controlled release capabilities other than pH-induced to improve the photosensitiser delivery system.

\subsection{Light-triggered release systems}

\subsubsection{Introduction}

One area of interest is the development of a drug releasing system that can be triggered by external stimulation such as irradiation.\textsuperscript{118} This photochemically-triggered release of drug is achieved by photocleavage of specific bonds in a prodrug molecular system. It offers more control and specificity as the light beam can be turned on and off (temporal control) and the light can be focussed at particular sites (spatial control). As the photolabile linker is the weakest site of a molecule under irradiation, development of such linker has gained wide consideration. Furthermore, light is used in photodynamic therapy, thus combination of light-medium process for release and activation of the photosensitiser will provide an attractive approach. In addition, tumour necrosis or induced apoptosis that contributes to cell death is affected by the light activation,\textsuperscript{119} therefore utilising photocleavable linkers would be most advantageous.

In general, the photocleavable reaction should be clean, have sufficiently high quantum yield and fast kinetics to ensure that the drug is rapidly released. These linkers should be stable under ambient conditions and be compatible with the necessary synthetic steps. More importantly, they should be cleaved selectively and efficiently with light of an
appropriate energy before the other parts of the compound undergo photoreactions. Upon irradiation, the by-products of the photorelease should be biologically inert and should not absorb light at the associated wavelength of the linkers in order to avoid competitive absorption of the incident light. In this section, several promising photolabile linkages will be discussed in detail albeit most of the linkages are well-established as photoremovable protecting group.

1.3.2 \( \text{o-Nitrobenzyl and derivatives} \)

The most common photolabile linkages are based on photochemically-induced photoisomerisation of aromatic nitro compounds containing a benzylic group in an \( \text{ortho} \) position to the nitro group. The photolytic release mechanism of the \( \text{o}-\text{nitrobenzyl} \) group can be divided into five major steps (Scheme 1.15) and has been investigated both experimentally\(^{[120]} \) and theoretically\(^{[121]} \). It involves an intramolecular hydrogen abstraction by oxygen of the nitro group 71, photoredox activity give the aci-nitro intermediate 72, cyclisation to the benzisoxazole 73, ring opening to the hemiacetal 74 and deprotonation with release of the substrate to form 75.

\[
\begin{align*}
\text{hv} & \quad \text{71} \\
& \rightarrow \quad \text{72} \\
& \rightarrow \quad \text{73} \\
& \rightarrow \quad \text{74} \\
& \rightarrow \quad \text{75}
\end{align*}
\]

Scheme 1.15 Reaction mechanism of the 2-nitrobenzyl group.

Barltrop \textit{et al.} reported the release of benzoic acid from its parent of \( \text{o}-\text{nitrobenzyl} \) ester while irradiated with UV light\(^{[122]} \). Since then, the \( \text{o}-\text{nitrobenzyl} \) group and its derivatives have extensively used, but they also have few disadvantages. A major limitation of the unsubstituted 2-nitrobenzyl linker is that the by-product formation of a reactive \( \text{o}-\text{nitrosobenzaldehyde} \) can be toxic to the cell and may further react to form secondary by product of azobenzene-2,2'-dicarboxylic acid 76 which acts as internal light
filter, thus slowing the desired photoreaction (Scheme 1.16). This side reaction can be eliminated by using α-substituted o-nitrobenzyl compounds that can release less reactive byproduct such as o-nitrosoacetophenone. An alternative method of trapping the nitroso species with pentadienyl group as 77 has been introduced and utilises an intramolecular hetero-Diels-Alder reaction (Scheme 1.17).

![Scheme 1.16 Formation of secondary by product.](image)

![Scheme 1.17 A built-in pentadienyl group to trap nitroso group.](image)

Despite these limitations, the o-nitrobenzyl group is still widely used for a variety of functionalities like alcohols, carboxylic acids, carbonyl, amines, phosphates and thiols. Besides its compatibility with the extensive range of functional groups, the o-nitrobenzyl is prevalent linkage due to ease of synthesis, protection and deprotection, with appropriate light sensitivities and kinetics. Several modifications of the o-nitrobenzyl group have been developed to improve its usability. For example, o-nitrophenylamine 78 and 4,5-dimethoxy-o-nitrophenylamine 79 (Figure 1.13) were used to protect carboxylic acid functional groups. By attaching an oxycarbonyl building blocks 80, this linker was designed to photochemically release alcohols or amines as used in light-directed synthesis of oligonucleotide arrays 81 on glass substrate (Scheme 1.18).
Figure 1.13 Example of 2-nitrobenzyl derivatives.

![Figure 1.13 Example of 2-nitrobenzyl derivatives.](image)

Scheme 1.18 Photolabile o-nitrobenzyloxy carbonyl group for protecting alcohol.

The o-nitrobenzyl linkers have been used in drug studies for photochemical release of the antiproliferative agent of phosphoramide mustard 82 that can treat various types of malignancies such as Hodgkin's disease, leukemia, lymphoma, breast and prostate cancer (Scheme 1.19). This mechanism offers controllable prodrug activation in comparison to other common pathways such as hydrolytic, bioreductive and biooxidative.

Scheme 1.19 UV irradiation to activate phosphoramide mustard agent.

1.3.3 Phenacyl group

The electron delocalisation between a carbonyl group and the phenyl ring makes phenacyl ester photolytically cleavable. The use of the p-methoxy phenacyl (p-MP) group 83 was introduced by Sheehan et al. as a photoremovable protecting group of carboxylic acids that can be photoreleased in a hydrogen donor solvent such as dioxane or ethanol in good yields (Scheme 1.20). Anderson et al. monitored the irradiation of p-methoxy and
hydroxyl phenacyl ester that form phenylacetate derivatives while irradiated in methanol.\textsuperscript{133} The aqueous solubility of the \(p\)-hydroxyphenacyl group (\(p\)-HP) was later investigated by Givens \textit{et al.} as a promising cage for light-activated release of bioactive molecule containing nucleotide and phosphate functionalities.\textsuperscript{134}

\begin{equation}
\text{Scheme 1.20 Photorelease of phenacyl ester.}
\end{equation}

\(p\)-Hydroxyphenacyl groups (\(p\)-HP) have several advantages as a light-triggered molecule such as high quantum yield deprotection and fast releasing rates.\textsuperscript{135} The group can be easily prepared from commercially available \(p\)-hydroxyacetophenone and is soluble in water and stable in aqueous solution. The main by-product from the photorelease process is non-toxic and absorbs at different wavelengths in contrast to its parent. Thus, it will allow for a fully quantitative photochemical conversion of \(p\)-PH. This group has been used to protect different functional groups such as carboxylic acids,\textsuperscript{136} amino acids and peptides,\textsuperscript{137} alcohols and phosphates.\textsuperscript{138} However, it has the disadvantage of having low extinction coefficient at wavelength above 320 nm which require considerable improvements. It was reported that introducing methoxy substituents in phenyl ring will shift the absorption range of \(p\)-HP above 400 nm, but leads to formation of significantly lower quantum yields.\textsuperscript{139} Klan \textit{et al.} have established the use of 2,5-dimethylphenacyl (DMP) for carboxylic acid protection that can undergo self-removable \textit{via} internal hydrogen abstraction without introducing any electron transfer sensitisers\textsuperscript{136} or hydrogen atom donors.\textsuperscript{140}

The photocleavage mechanism of the \(p\)-hydroxyphenacyl group which was proposed by Wirz \textit{et al.} showed the formation of spiro\([2.5]\)octa-4,7,diene-1,6-dione \textbf{84} upon release of the leaving group.\textsuperscript{135} The spiro species is then hydrolysed to yield the \(p\)-hydroxyphenylacetic acid \textbf{85} (Scheme 1.21).
An active drug system was devised by using photocleavable phenacyl ester groups and caging a model drug of biotin with oligonucleotide-based stem-loop type probes \(^8\) (Figure 1.14).\(^{141}\) It was found that 84% yield of biotin is released by photolysis of the photoactive probe upon light irradiation at 312 nm.

The benzoin (Bz) group has several interesting features which offer accessibility to use in photolabile molecular systems. It has high chemical and quantum yields with fast photoreleasing times. In addition, the resulting by-product of benzofuran is biologically-inert whilst its maximum absorbance is rendered at 300 nm, thus allowing an efficient irradiation process. Sheehan \textit{et al.} studied the irradiation of benzoin esters \(^8\) that are able to release the free acid and 2-phenylbenzofuran \(^8\) while further optimisation by introducing methoxy groups gave the best yields (Scheme 1.22).\(^{142}\) The Bz group has been used in caging different functionalities such as carboxylic acids,\(^{142}\) phosphate
Chapter 1: Introduction

esters,[143] amine,[144] oligopeptides,[145] and nucleotides.[146] The Bz group is highly light sensitive and can be released in the presence of ambient light. Moreover, its by-product of benzofuran is inert and does not act as an internal filter. It also has low solubility in aqueous solution which limits its biological application.

Various photo-triggered mechanisms have been proposed based on substituents at the phenyl ring, solvents and the leaving group influence. It was suggested that the 3,5-dimethoxy benzoin group undergoes an intramolecular Paterno-Büchi reaction to form a strained tricyclic intermediate, followed by ring opening and loss of acetate leaving group to give 2-benzofuran.[142] Studies of releasing benzoin diethyl phosphate in different solvents lead to two different pathways.[147] In most solvents, photoreaction will tend to follow path (a) with formation of 2-phenylbenzofuran 89 and diethylphosphoric acid rapidly. Irradiation in fluorinated alcohol (b) resulted in formation of a different major product of alkoxy-susbtituted benzoin 90 (Scheme 1.23). Pirrung et al. proposed the initial heterolytic cleavage and formation of ion pair directly from the singlet state, followed by ring closure and elimination.[148]
McCoy et al. developed the light liberation of a prodrug system based on the 3,5-dimethoxybenzoin (DMB) photoactive group. Three model drugs of acetyl salicylic acid (aspirin) 91, ibuprofen 92 and ketoprofen 93, that contain carboxylic acids functionalities have been studied (Scheme 1.24) and the reaction mixture was monitored by UV-visible spectra throughout the irradiation progress. The photorelease of by-product and drug and the consumption of the precursors were observed, thus enabling details investigation of the drug dosing level delivery.
1.3.5 Coumarinyl derivatives

The 7-methoxycoumarin-4-yl-methyl (MCM) group is the first known photolabile protecting group based on coumarin moiety. It was introduced by Givens et al. who observed the formation of free carboxylic acid 94 and the hydroxymethylcoumarin 95 after irradiation in aqueous media (Scheme 1.25).[150] The coumarinyl groups were later increasingly employed to cage several functional groups such as carboxylic acids,[151] phosphates,[152] nucleotides[153] and amino acids.[154]

\[
\text{MCM} \xrightarrow{\text{hv}} \text{O} \xrightarrow{\text{H}_2\text{O}} \text{R} + \text{OH}
\]

**Scheme 1.25** Photorelease of MCM ester.

The coumarin group has the potential to replace conventional labile groups due to its fast rate of photorelease, good stability in biological systems, and it can be utilised in 2-photon excitation.[154] It also shows high extinction coefficient and the spectral absorption extends to the visible region. Introducing different substituents to its macrocycle can red-shift the absorption spectra and increase the amphiphilicity and its quantum yield.[152] There are a few drawbacks of this protecting group as some of the derivatives have low stability in neutral aqueous media and they have moderate quantum yield.

The mechanism of coumarinyl ester photolysis was investigated by Schade et al. (Scheme 1.26) who demonstrated that higher quantum yield are achievable by using highly polar solvent because of enhancing the solvation of the ion pair.[151]

\[
\text{R} \xrightarrow{\text{hv}} \text{CH}_2\text{X} \xrightarrow{\text{H}_2\text{O}} \text{OH} + \text{HX}
\]

**Scheme 1.27** Reaction mechanism of coumarin derivative.
A polymerisable coumarin dimer system has been developed\cite{155} to investigate the chlorambucil drug release for tumour treatment. Chlorambucil is selected as the model drug because of its sensitivity towards UV light that allowed the monitoring of single and two-photon absorption effects. It was observed that single-photon absorption induced the linker cleavage and decomposed the drug, while no photodegradation of the drug occurred in two-photon absorption.

1.4 Objectives

The objective of this present study was to design a novel approach based on light activation pro-drug/drug system for selective and controlled treatment of cancer by photodynamic therapy (PDT). This research investigated several synthetic methods towards the construction of such system. While porphyrins will act as photosensitisers, the photocleavable synthon will be used to cross-link biologically relevant groups that are able of binding to specific receptors. The incorporation of a range of functional groups into porphyrin macrocycles has been developed previously in our group based on organolithium reactions. Further investigation employed 1,3-dithianyl group as a precursor for masking formyl group based on Umpolung chemistry. In Chapter 2, compounds possessing dithiane and regiochemically substituted dithiane functionalities were explored and their analogue of spirobisdithiane and trithiane as the promising photolabile linkers were prepared.

The main focus of Chapter 3 was the synthesis of photolabile porphyrin based on o-nitrobenzyl linker. A wide variety of reactions have been examined for introducing the linker into the porphyrin macrocycle mainly via esterification reaction from acid porphyrin. In Chapter 4, an investigation of the labile o-nitrobenzyl linkers were further carried out to develop porphyrin linked-bioconjugate system. Several approaches were studied to link potential bioconjugated ligand for targeted receptor such as glucose and folic acid while experimental testing of the photolability of the compound was also investigated. Finally in Chapter 5, a relatively unexplored field of acrylic porphyrins were studied as a building block for synthesis of novel tetrapyrroles. Their reactivity essentially utilised acid porphyrins to generate acyl chloride intermediates which can be converted to a series of multifunctional porphyrins.

These studies will ultimately be the basis for subsequent interdisciplinary studies on the use of photocleavable tetrapyrrrole bioconjugates in medicine; notably, the specific use of the drug chromophore as a photosensitising agent in photodynamic cancer therapy.
and cancer indication. The research is the first stage in long-term efforts to promote the use of improved photosensitisers in the treatment and indication of various diseases.
CHAPTER 2:
Photolabile Thio Porphyrin Derivatives
2.1 Introduction

The photochemistry of dithiane derivatives has been of interest for many years. Numerous progress has been made since McHale et al. discovered the C-C photocleavage of α-hydroxyalkyl-1,3-dithiane. This type of compound was shown to undergo photosynthetic reaction in the presence of benzophenone upon UV irradiation to generate aldehyde or ketone quantitatively (Scheme 2.1). It has been proposed that the process is initiated by a photoinduced electron-transfer involving a single electron transfer from the dithiane moiety to excited benzophenone, followed by benzophenone radical anion assisted O-deprotonation leading to C-C bond cleavage (Scheme 2.2). This method was originally designed to use dithiane as photoremovable protecting group for aldehydes or ketone. Nevertheless it has a potential application as a photolabile linkage to attach various molecular blocks and build photolabile systems that are capable of releasing a guest molecule upon irradiation.

![Scheme 2.1](image1.png)

**Scheme 2.1** Photofragmentation of α-hydroxyalkyl-1,3-dithiane.

![Scheme 2.2](image2.png)

**Scheme 2.2** Mechanism of α-hydroxyalkyl-1,3-dithiane photo-cleavage assisted by a benzophenone sensitiser.

Our group had already established the basic chemical strategies necessary for the synthesis of functionalised porphyrins containing dithianyl residues. A synthon of 1,3-dithian-2-yl has been utilised as a functional and protected formyl group, where its lithio derivative offers the possibility to introduce the latent formyl groups under nucleophilic substitution reaction based on Umpolung chemistry. The dithianyl synthon can also be used in another strategy for the preparation of such porphyrin systems. It can be
converted into the corresponding aldehyde 98, which we have used to prepare porphyrins with two to four dithianyl residues via condensation reactions (Scheme 2.3). Selected dithianylporphyrins could be deprotected to yield the corresponding formylporphyrins, which are important and hitherto often inaccessible for the construction of more complex porphyrin system.

\[
\text{Scheme 2.3 Synthesis of 1,3-dithianylporphyrins via condensation reactions.}
\]

Conditions: (a) n-BuLi, THF, -78 °C, 1 h; then -10 °C, DMF, 2 h; then 0 °C, 16 h; then ice, 85%. (b) CH\textsubscript{2}Cl\textsubscript{2}, dipyrromethane, TFA, 14 h, rt; then DDQ, 10 min, reflux, 16%. (c) CH\textsubscript{2}Cl\textsubscript{2}, pyrrole, BF\textsubscript{3}.OEt\textsubscript{2}, 1 h, rt; then excess DDQ, 1 h, 46%. (d) CH\textsubscript{2}Cl\textsubscript{2}, pyrrole, BF\textsubscript{3}.OEt\textsubscript{2}, 1 h, rt; then NEt\textsubscript{3}, DDQ, 4 min, 15%. (e) CH\textsubscript{2}Cl\textsubscript{2}, tripyrrane, pyrrole, 45 min, rt; then TFA, rt, 16 h; then DDQ; then NEt\textsubscript{3}, 3%.

Kutaledze \textit{et al.} have shown that combining two dithiane groups in a spiro compound results in the formation of potential cross-linking groups that can be cleaved in a photosensitised reaction.\textsuperscript{[160]} These prompted us to envisage this compound as a key intermediate for the ultimate construction of porphyrin spirobisdithianyl-linked bioconjugates. Such systems would have significant potential for drug delivery in photodynamic cancer therapy owing to the cleavable spirobisdithiane linker. Our approach involved the synthesis of these photosensitiser systems which are photochemically inactive.
during transport. However, it could be cleaved in a tumour tissue releasing the active photosensitisers. Thus, this modality involves two prodrug-drug conversion steps. First, cleavage of the photolabile linker to yield the photosensitiser, and then activation of the photosensitiser by light to generate cytotoxic singlet oxygen.

2.2 Synthesis of porphyrin precursor

As mentioned in the previous chapter, the synthesis of simple meso-modified porphyrins can be achieved via condensation of pyrrole or a pyrrolic derivative with various aldehydes. A variety of A₂-type porphyrins (99-103) with two unsubstituted meso-positions available for subsequent functionalisation were synthesised using the dipyrromethane precursor 29 under conditions optimised by Lindsey et al (Scheme 2.4).[31] This starting materials have been previously synthesised and the spectroscopic data are in accordance with those reported in the literature.[33]

Scheme 2.4 Synthesis of 5,15-A₂ porphyrins.

Generally, the synthesis of differently meso-substituted porphyrin via condensation methods depends on the nature of the required substituents. A mixed condensation is usually carried out to produce unsymmetrical porphyrins (Scheme 2.5).
Chapter 2: Photolabile Thio Porphyrin Derivatives

Scheme 2.5 Mixed condensation for meso-substituted porphyrins.

The preparation of AB substituted porphyrins using dipyrromethane and two aldehydes, benzaldehyde and heptaldehyde yielded three products; (A2-type) 5,15-diphenylporphyrin 99, (AB-type) 5-hexyl-15-phenylporphyrin 104, and (B2-type), 5,15-dihexylporphyrin 101, due to the unselective nature of condensation. A mixed condensation was also performed where two dipyrromethane precursors and 5-(1-ethyl)propyldipyrromethane 105 were reacted with a single aldehyde of ethylbutyraldehyde. The synthesis of dipyrromethane 105 was achieved by heating the mixture of an aldehyde and pyrrole catalysed by Lewis acid, followed by purification using Kugel-Rohr distillation. This variation of a mixed condensation reaction afforded 5,15-di-102, 5,10,15-tri-106 and 5,10,15,20-tetrakis(1-ethylpropyl)porphyrin 107 with relatively low yields due to the multiple products formed.

The number of potential products becomes very large while using this mixed condensation reaction for the preparation of unsymmetrical meso-substituted porphyrins bearing three or four different groups. The consequence of this methodology is a complicated purification procedure and ultimately low yields of the desired porphyrins. Although an improvement in the condensation methods has been made involving step-by-step synthesis to produce the unsymmetrical porphyrins, such an approach requires more synthetic steps and currently has only been reported for porphyrins with aryl substituents. Therefore, alternative methods are required to introduce various functionalities on porphyrin periphery and to provide access to the desired unsymmetrical porphyrins.

Senge et al. has extensively studied the incorporation of numerous aryl and alkyl substituents into porphyrin macrocycle via nucleophilic substitution (SNAr) reactions with organolithium reagents. The overall process proceeds via initial reaction of an organic
nucleophile with a meso-carbon yielding an anionic species which is hydrolysed to a hydroporphyrin, followed by oxidation giving meso-substituted porphyrin 108-110 in 67%-81% yield (Scheme 2.6). The reactions of porphyrin 99 and 100 with hexyllithium were performed at -78°C while phenyllithium reacted with porphyrin 99 at 0°C.

\[
\begin{align*}
\text{99} & \xrightarrow{1) \text{R}^2\text{Li}} \text{108} \\
\text{100} & \xrightarrow{2) \text{H}_2\text{O}} \text{109} \\
\text{99} & \xrightarrow{3) \text{DDQ}} \text{110}
\end{align*}
\]

Scheme 2.6 SNAr reaction of porphyrins with an organolithium reagent.

### 2.3 Synthesis of dithianyl porphyrin derivatives

The success of SNAr approach for porphyrin modifications using organolithium reagents prompts us to investigate further applications of this method and use it as a versatile nucleophilic tool. The well known formation of lithio-dithiane offers a convenient strategy to introduce the dithianyl residue as a formyl synthon into the porphyrin macrocycle via formation of a C-C bond.\(^{158}\) 1,3-Dithianes have two polarisable sulfur atoms bonded to the -CH group which causes the H atom to be more acidic with a pK\(_a\) ~32 compared to a pK\(_a\) of ~50 for unactivated C-H bond.\(^{161}\) Thus, 1,3-dithiane can be deprotonated by strong base such as n-butyllithium. The resulted carbanion can be stabilised via electron back-donation effect on vacant sulfur d-orbitals (Scheme 2.7).
This technique can be applied to the free bases and metalloporphyrins due to the mild reaction conditions to produce dithianyl porphyrins in good to excellent yields. For example, 1,3-dithiane was treated with n-butyllithium in THF at -30 °C to generate 2-lithio-1,3-dithiane \textit{in situ}, which then reacted with the porphyrin 99 and 100 leading to the corresponding dithianyl porphyrin 111-112 (Scheme 2.8). The substitution reaction was promoted by tetramethylethylenediamine (TMEDA), quenched with water and oxidised with DDQ. Nevertheless, the reaction of lithio-dithiane with porphyrins is challenging and strongly dependent on porphyrin substituents resulting in inconsistent yields. It was observed that the deprotection of the dithianyl moiety also occurred during chromatography separation processes giving formylporphyrin as the minor product. Occasionally, the n-butyllithium from the reaction mixtures tends to react directly with the porphyrin moiety resulting in the formation of meso-n-butylporphyrin.

The reactivity of organolithium reagents has also been investigated on the \(\beta\)-position of porphyrins to access various chlorins.\cite{162} Therefore, the dithianyl residue presumably can be used in a similar manner. Due to bathochromically shifted absorption
bands (deeper tissue penetration of light), chlorins are of special interest for use in PDT. However, the attempted reactions with meso-tetrasubstituted porphyrins have not been successful due to the inherently lower reactivity of the $\beta$-position. In order to expand the chemistry of the dithio synthon with porphyrins, the reactivity of 1,3-dithiolane was also investigated. Upon generating the lithio-dithiolane nucleophile, the mixture was reacted with free base porphyrin 99 but only starting material was recovered. It is reported that 2-lithio-1,3-dithiolane is an unstable compound which undergoes elimination to form ethylene 113 and dithiocarbinol 114 as shown in Scheme 2.9.\textsuperscript{163}

![Scheme 2.9 Ring opening of 1,3-dithiolane upon RLi treatment.](image)

There are several methods for the hydrolysis of the dithianyl group including photolytic cleavage,\textsuperscript{160} metal coordination,\textsuperscript{164} alkylation\textsuperscript{165} and the use of chemical oxidants.\textsuperscript{166} It was found that the treatment of the dithianylporphyrins 111 with DDQ and BF$_3$.Et$_2$O in CH$_2$Cl$_2$ leads to facile deprotection giving the corresponding formylporphyrins 115 (Scheme 2.10).\textsuperscript{158,167}

![Scheme 2.10 Deprotection of dithianyl porphyrin.](image)

It has been shown that one-pot, two-step disubstitution of free base porphyrins is achievable with both nucleophiles and electrophiles under thermodynamically controlled conditions.\textsuperscript{68} Thus, we also attempt to trap the \textit{in situ} generated dithianylporphyrin anion with electrophiles, akin to the reaction with standard organolithium reagents. Reaction of porphyrin 99 with 1,3-dithian-2-yl lithium and prolonged heating with pentyliodide followed by standard workup yielded the doubly substituted formylporphyrin 116 in low yield (11%). To test the reactivity with more unsymmetrical porphyrins, porphyrin 104 was
Chapter 2: Photolabile Thio Porphyrin Derivatives

treated with 1,3-dithiany-2-yl and propyl iodide. Workup of this reaction yielded a small amount of the deprotected formyl porphyrin 117. Various reactions were further investigated using different electrophile such as n-butyl- and n-hexyl-iodides, and afforded only formyl porphyrins along with starting material. All these reactions already indicated that the stability of the dithian-2-yl residue is limited under the reaction conditions necessary for porphyrin substitution.

![Scheme 2.11 One pot synthesis of disubstituted porphyrin.](image)

A potentially more useful strategy involved utilising the lithio derivative of 2-substituted-1,3-dithiane which should provide an access to acyl porphyrins. However, the reaction of free base porphyrin with sterically more hindered 2-methyl-1,3-dithiane to yield the putative compound of meso-substituted porphyrin 118 was problematic. Spectroscopic evidence indicates the formation of β-adducts in low yields. 1H-NMR shows the presence of seven β-Hs and two free meso-Hs (Figure 2.1). This infers that the substitution reaction occurred at the β-position of porphyrin [MS (ESI): m/z = 595.1990 (M+H)+], which is generally observed for sterically hindered organolithium reagents. Several test reactions were carried out to optimise the reaction conditions which two factors affected the results. First, the conversion to the lithio derivatives should go to completion by the addition of an equal amount of n-butyllithium to the substituted 1,3-dithiane and stirring up to 2 hours at 0 °C. It was found that the yield of the product varied from reaction to
reaction which suggests an inconsistent and difficult formation of the lithio intermediate. An excess of n-buthyl lithium was used to ensure the formation of the lithio-dithiane went to completion. However, n-BuLi reacted with the porphyrin yielding an undesired n-butylporphyrin. In addition, the steric hindrance associated with 2-methyl substituent is believed to reduce the reactivity of the 2-lithio-dithiane considerably.

![Chemical structure](image)

**Figure 2.1** $^1$H-NMR spectrum of β-adduct in CDCl$_3$.

### 2.4 Photolabile spirobisdithianyl- and trithianyl-porphyrin

An assembly of macromolecular hosts equipped with a photolabile latching module based on 2,4,8,10-tetrathiospiro[5.5]undecane, or so-called spirobisdithiane 119, has been developed by Kutateladze et al.\textsuperscript{160} This compound has advantages of being the shortest tether possible in the bis-dithiane family and also is easy to synthesise. The synthetic feasibility is important because it is impractical to recover the latch itself after the photodiassociation step due to partial degradation of the dithiane moiety in the photoprocess.

The spirobisdithiane was synthesised from commercially available pentaerythritol tetrabromide 120. Nucleophilic substitution by potassium thioacetate in DMF yielded the
pentaerythritol thioacetate 121 in 67% yield. The spirobisdithiane was obtained by using hydrochloric acid in the presence of formalin, under acid-catalysed conditions. Both thioacetate hydrolysis and thioacetal formation were performed in one step and afforded the target spiro-bis-dithiane 119 in 72% yield (Scheme 2.12). Excess use of formalin is necessary to enable the complete conversion of the target compound.

![Scheme 2.12 Synthesis of spirobisdithiane.](image)

As described for the 1,3-dithianyl residue, it should also be possible to use the lithio derivatives (both mono- and dilithiated) of the spirobisdithiane as nucleophiles for the direct substitution of porphyrins. In the first stage, a series of mono-substituted spirobisdithiane porphyrins were synthesised. Metallation of porphyrin precursor was achieved by the standard conditions with nickel(II) acetylacetonate in toluene under reflux.[169] Similar to organolithium reactions described earlier, the mechanism involving free base porphyrin 99 comprised the addition of spirobisdithianyl residue into a meso-position of the porphyrin macrocycle and the coordination of two lithium atoms to inner nitrogens resulted in the phlorin-type structure 122. After quenching with water, the hydroporphyrin intermediate 123 is formed and subsequent oxidation with DDQ gave the desired porphyrin 124 in 22% yield (Scheme 2.13).
The reaction mechanism for a metalloporphyrin is slightly different compared to free base porphyrin. The spirobisdithianyl intermediate is added to Ni(II) porphyrin complex 125-127 to form a Meisenheimer-type complex of 128-130. Further hydrolysis with water gave the porphodimethene type molecules 131-133 before undergoing oxidation to give the desired porphyrin 134-136 in 19-33% yield (Scheme 2.14). Due to the steric hindrance of the bulky spirobisdithiane residue, the yields of all spirobisdithianyl porphyrins are comparable to those in iso-propyl or sec-butyl lithium reactions.
Scheme 2.14 Reaction of metalloporphyrin with 2-lithio-spirobisdithiane.

In these reactions, the preparation of the mono-lithiated spirobisdithiane was achieved using 1:1 equivalents of n-butyllithium/spirobisdithiane and underwent completion upon stirring for 2 hours. A large excess of the lithiated spirobisdithiane (22 equivalents) is required to react with porphyrin in situ in the presence of TMEDA giving the respective spirobisdithianyl porphyrins. Notably, the yields for the metallated porphyrins are higher than for the free base porphyrin analogues. This is believed to be due to a stable nickel(II) complex intermediate which exhibits a high degree of nucleophilic reactivity. Most interestingly, 124 was found to undergo photocleavage completely to form a formylporphyrin during column chromatographic purification, highlighting the photosensitivity of these porphyrins. A separation of the adduct mixture was carried out in the dark to minimise splitting of the photolabile spirobisdithiane upon exposing to ambient light. Meanwhile, the metalloporphyrins showed a much greater stability towards light.

In addition, the formation of dilithio species of spirobisdithiane using two equivalents of n-BuLi can be employed for the direct cross-linking of two porphyrins or for the synthesis of porphyrin linked-bioconjugate. Unfortunately, all attempts to use the spirobisdithianyl dianion for the double substitution reactions failed or gave alternative products. For example, the reaction of nickel(II) porphyrin 125 with the dilithio derivative
of spirobisdithiane gave 71% of respective 5-butyl-substituted porphyrin and 6% yield of [10-spirobisdithian-2-yl-5,15-diphenylporphyrinato]nickel(II) 134 respectively. It is reported that the formation of dilithiated spirobisdithiane intermediate is completed by using 3.5 equivalent of n-butylithium,\[160, 170]\ however, the excess of n-BuLi again increases the risk for its direct addition to the porphyrin.

The $^1$H-NMR spectrum for 124 shows the presence of two broad peaks assigned to $\beta$-H neighbouring the spirobisdithiane group (Figure 2.2). These peaks are due to the intramolecular hydrogen bonding between these $\beta$-protons and the sulfur atoms of the spirobisdithiane prevented from free rotation. Similar observations were made under different temperatures of $^1$H-NMR studies for dithianyl porphyrin. $^1$H-NMR resonance of the $\beta$-proton are fused at above the coalescence temperature of 334 K and below this temperature, they resolve into two broad resonances. In contrast with the nickel(II) complex 134, the signals for the $\beta$-proton are split only once (Figure 2.3).

![Figure 2.2 $^1$H-NMR spectrum of porphyrin 124 in CDCl$_3$.](image-url)
Figure 2.3 $^1$H-NMR spectrum of porphyrin 134 in CDCl$_3$.

Potentially, these types of monosubstituted spirobisdithianyl compounds may be coupled with a bioconjugate carrier or with a second porphyrin. Such reactions will require a use of porphyrins where all other meso-positions are substituted by residues in order to prevent self-reaction of the porphyrinyl-lithiospirodithiane resulting in the formation of oligomers or to avoid the meso-substitution of porphyrin in the presence of $n$-BuLi. Thus, the metalloporphyrin 135 was reacted in situ with spirobisdithynyllithium to afford the corresponding porphyrin complex 137. Porphyrin 137 was subsequently treated with $n$-BuLi and reacted with a second porphyrin 125, but yielded the $n$-butyl-meso substituted porphyrin (Scheme 2.15). Another reaction was attempted with porphyrin 135, but gave no formation of the desired porphyrin. As $n$-BuLi has a high tendency to undergo SN$_2$Ar on porphyrin macrocycle, lithium diisopropylamide (LDA) was used as non-nucleophilic base that can also deprotonate weak acidic compounds. Porphyrin 136 was reacted with porphyrin 135 under this condition; however, the reaction recovered only both of the starting materials.
Most of the photocleavable bis-adduct assemblies were synthesised from the formyl derivatives of various macromolecules. The synthetic strategy involved tethering two formylated building blocks with the spirobisdithiane which has one or two photocleavable C-C bonds. Therefore, utilisation of formyl porphyrins as initial precursor provided an alternative method to tether different building blocks. The most common method of porphyrin formylation is the Vilsmeier reaction with an activated metalloporphyrin.\(^{[50]}\) A mixture of phosphorus oxychloride (POCl\(_3\)) and dimethylformamide (DMF) was used to generate the Vilsmeier complex 138 that subsequently reacted with the nickel(II) porphyrin 135 in 1,2-dichloroethane resulting in the desired porphyrin 139 in 48% yield after aqueous workup (Scheme 2.16).
Formyl porphyrin 139 was then reacted with mono-lithiated spirobidithanyl at -78 °C as described by Kutateladze et al.\textsuperscript{[160]} but affording the [5-(hydroxypentyl)-10,20-diphenylporphyrin 140 in 6% yield. Aldehyde functional groups are prone to be attacked by organolithium reagents under nucleophilic addition reaction (Scheme 2.17). A similar reaction was observed in the case of using more simple 1,3-dithianyl residue.

![Scheme 2.16 Vilsmeier formylation of porphyrin.]

![Scheme 2.17 Reaction of formyl porphyrin with lithio-spirobisdithiane.]

The spirobidithiane compound 119 can also be used as a key intermediate in the preparation of bisporphyrin building blocks via the condensation reactions as shown for the
1,3-dithianyl synthon (Scheme 2.3). The diformyl derivative of spirobisdithiane can be transformed into the corresponding dipyrromethane which provides access towards construction of bisporphyrin systems. Preparation of $141$ was carried out using 2:1 equivalents of $n$-butyllithium/spirobisdithiane while workup of the reaction was done using dichloromethane instead of diethylether, as described in the 1,3-dithiane reactions afforded the bisaldehyde in 56% yield (Scheme 2.18).[158] However, the conversion of $141$ to the respective dipyrromethane did not produce the desired compound, most probably due to its low solubility.

![Scheme 2.18](image)

Scheme 2.18 Synthesis of a bisaldehyde spirobisdithiane precursor.

In order to access different labile cross-linking geometries, the trithiane moiety was employed in a synthetic sequence similar to the spirobisdithiane linker giving the corresponding porphyrins $142-145$ in moderate yields (Scheme 2.19).

![Scheme 2.19](image)

Scheme 2.19 Monosubstituted trithianyl porphyrins.

It has been reported that 1,3,5-trithiane can form di- and even trianions when treated with excess $n$-butyllithium.[171] Therefore, successful conversion to these multianion intermediates opens a possibility for the synthesis of photolabile di- and trisubstituted trithianes bearing porphyrins or the targeted bioconjugate systems. However, all attempted reactions usually gave the $n$-butyl porphyrins resulting from $S_N$Ar reactions
of organolithium reagents. As indicated by $^1$H-NMR spectroscopic data for dithianyl- and spirobisthianyl-porphyrins, the $\beta$-H flanking the trithianyl residue exhibits the broad signals in free base and metalloporphyrins, respectively (Figure 2.4 and Figure 2.5).

![Figure 2.4](image1.png) $^1$H-NMR spectrum of porphyrin 142 in CDC13.

![Figure 2.5](image2.png) $^1$H-NMR spectrum of porphyrin 143 in CDC13.
2.5 Conclusions

Starting from the studies on *Umpolung* chemistry of dithianyl synthons, it was shown that this method is useful to introduce formyl group into unactivated or metallated porphyrin macrocycles. An access to acylsubstituted porphyrins via substituted dithiane was difficult due to the low reactivity and steric hindrance of its lithio anion. In addition, it has been shown that the dithianyl nucleophile cannot be fully utilised to prepare stable porphyrin anions that can be trapped by an electrophile.

In employing photolabile spirobisdithiane and trithiane linkers, we have successfully synthesised the porphyrins containing one of these functional groups. Direct di or trisubstitution via SNAr reactions on the porphyrin periphery or addition to formyl functionalities gave a high tendency to form alkyl-functionalised porphyrins. Moreover, the highly photosensitive free base compounds hampered our studies for utilising the labile porphyrins system in PDT.

While the work in this area has shown that we can link the porphyrins with the spirobisdithiane and trithiane at the meso-position, the major aim was to cross-linking the residues with biologically relevant residues. With all the constraints, further investigations require a key intermediate such as dithiane-bismethol residue which contains available groups for the targeted bioconjugations. This precursor can be used in attaching the specific bioconjugates in the initial step before reacted with porphyrins. Nevertheless, we have described an initial paradigm for using such dual-mode system; photoreleased and photoactivated photosensitisers that enable to control the photosensitiser delivery for PDT applications.
CHAPTER 3:

Lead Structures to Photolabile o-Nitrobenzyl Porphyrins
3.1 Introduction

Light-mediated chemical bond cleavage of nitrobenzyl derivatives has provided a simple and efficient method for masking and releasing numerous functional groups. The nitrobenzyl derivatives are by far the most prevalent photolabile groups and they have gained wide acceptance. Of the linkages properties are high stability under ambient light, they can undergo clean cleavage upon exposure to UV irradiation and fast fragmentation reactions upon photoexcitation. Therefore, we extended our studies to incorporating this cleavable unit into porphyrin macrocycle. Since the absorption of the nitrobenzyl group tails out around 400 nm, photolysis is usually carried out with a light of wavelength longer than 320 nm; typically irradiation at 340-350 nm is employed. This feature fits the mode for releasing the photosensitiser in combination with a second irradiation with red light around 650 nm as porphyrins will produce cytotoxic singlet oxygen when irradiated at this wavelength.

The o-nitrobenzyl group has been used previously in designing photo-prodrug systems. In 2005, Zhang et al. proposed a strategy to produce a tumour vascular-targeting photoactivated prodrug of 5-fluorouracil (5-FU) by using a tumour homing peptide CNGRC and photolabile o-nitrobenzyl. Such a tumour vascular-targeting photoactivated prodrug is expected to accumulate and then to be activated selectively by controlled photolysis to release anticancer agent 5-FU within tumour tissues with outstanding spatial and temporal precision. Recently, tegafur, which was formed as 5-FU prodrug, was tethered to a porphyrin system through o-nitrobenzyl linker to prepare light-triggered anticancer prodrug 146 (Figure 3.1). This system increased the tumour affinity of anticancer drug due to its conjugation to highly accumulative porphyrin moieties. An MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium] assay demonstrated that the conjugate shows photoinduced cytotoxicity for MCF-7 mammary cancer cells because of the efficient release of tegafur upon photoirradiation at 350 nm.
Studies of the mode of cell death after photodynamic therapy (PDT) revealed evidence of both necrosis and apoptosis, which are induced under different conditions and differ in morphological and biochemical features. Necrosis is a degenerative cell death resulting from extensive cellular damage whereas apoptosis is a programmed cell death that involves a series of biochemical events leading to a characteristic cell morphology and death. PDT triggers numerous different signalling events that lead to apoptosis such as oxidative stress, alteration of intracellular Ca^{2+} concentration and modulation of gene expression. It has been reported that ultraviolet (UV) light has a role in induced DNA damage that can trigger apoptosis, thus more extensive use of UV light in the photosensitiser activation and cleavable system is advantageous.

In this chapter, we demonstrate the necessary synthetic methodologies for construction of labile systems containing porphyrins photosensitisers based on the cleavable units of o-nitrobenzyl group. While various available approaches for porphyrin functionalisation have been established, an esterification procedure was mainly utilised in our effort to develop such a system.

3.2 Synthesis of carboxylic acid porphyrin precursors

A direct route to obtain carboxylic acid porphyrins is by hydrolysis of ester-type porphyrins whereby these compounds can be prepared using several known methods. One of the methods relies upon Heck or Suzuki reactions with halogenated porphyrin precursors. Both of the reactions give a formation of C-C bonds by using a transition metal catalysed coupling process. Complexes involving palladium such as Pd(PPh_3)_4, PdCl_2(PPh_3)_2 and Pd(OAc)_2 are the most common and widely used catalysts, because they are stable to air and readily reduced to the active Pd(0) complexes with organometallics or phosphine used in the reaction. A general catalytic cycle for the cross-coupling reaction
involves oxidative addition-transmetallation-reductive elimination sequence (Figure 3.2).[177]

Oxidative addition of alkenyl, alkynyl, allyl, benzyl or aryl halides to a Pd(0) complex gives a trans-σ-palladium(II) complex 147 which is prone to react with nucleophiles. The reaction proceeds with complete retention of stereochemistry for alkenyl halides and with inversion for allylic and benzylic halides. The transmetalation step from organopalladium(II) complex is highly dependent on the organometallics or reaction conditions used for the coupling. For instance, an organoboron compound is unlikely to participate in the catalytic cycle of cross-coupling reactions in the absence of base due to its low nucleophilicity. However, the nucleophilicity can be enhanced by quartenisation of the boron with negatively charged bases giving the corresponding active complex. Reductive elimination takes place directly from the cis-complex 148 while the trans-complex isomerise to the cis-complex which can react (Figure 3.3).

![Figure 3.2 A general catalytic cycle for Pd-mediated cross coupling.](image)

![Figure 3.3 Isomerisation of trans- to cis-complex.](image)

The initial step involved preparation of brominated porphyrins from free base porphyrins that are accessible through standard condensation or RLi-alkylation procedures as described in an earlier chapter. In this work, we employed different porphyrins as
scaffolds for further functionalisations. Porphyrin 99 is a commonly used precursor, whereas porphyrin 110 has the advantage of having only one free meso-carbon and this can effectively block any undesired competitive reaction. Porphyrins 103, 108 and 109 incorporated alkyl functionalities and were used to prepare precursors more soluble in common reaction solvents. Porphyrin 109, containing methoxy groups, offers the necessarily deprotection opportunity at a later stage to form hydroxyl-type porphyrin that are suitable in the preparation of water soluble photosensitisers. All the porphyrins were brominated according to standard conditions (NBS in chloroform in the presence of pyridine)\cite{178} to give the corresponding brominated porphyrins 149-153 in high yield (Scheme 3.1). Likewise, the tetrasubstituted porphyrin 154 available from a mixed condensation reaction, was brominated with 1.1 equivalents of NBS according to the literature\cite{178} to yield the \(\beta\)-monobrominated analogue 155 (Scheme 3.2). The bromination of 99 to afford in high yield of monobromo 149 is tedious because the lack of selectivity and difficulty of chromatographic separation of the mono- 149 and dibrominated products 156, while porphyrin 103 was brominated with 2.0 equivalent of NBS to yield disubstituted product 150.

![Scheme 3.1 Bромирование meso-замещенных пурпуринов.](image)

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As porphyrins containing unsaturated side chains or extended π-conjugated substituents are of interest due to potential applications for PDT, the Heck reaction has been utilised to introduce ester functionalities into porphyrin macrocycles. It was reported that palladium catalysed Heck coupling has proved to be a useful method for attaching ethenyl substituents to the β-positions of porphyrins. In a different manner, protoporphyrin was utilised as the vinyl substituent for coupling with arene halide under Heck conditions. Arnold et al. have investigated the reactivity of meso-substituted porphyrin by direct coupling of some Heck-type alkenes and meso-bromoporphyrins in the presence of palladium acetate catalyst Pd(OAc)$_2$, ligand and potassium carbonate K$_2$CO$_3$ under heating condition in a toluene:DMF solvent mixture. Under similar conditions, bromoporphyrins 151 and 152 were reacted with methyl acrylate. These reactions proceeded with complete consumption of starting material in 12 hours to yield α,β-unsaturated porphyrins 157 and 158 in 55% and 60% respectively (Scheme 3.3). These Pd-catalysed couplings required a large excess of methyl acrylate to maximise its concentration in the reaction mixture since it has a low boiling point. The reactions were carried out in a mixture of DMF and toluene (1:1) which conveniently allowed the use of small volumes and high concentration of reactants. This leads to shorter reaction times and avoided solubility problems. It was observed that debromination of the starting material occurred through protolytic cleavage and metallation on porphyrin core with palladium took place to a small extent.
In a second approach, the palladium catalysed Suzuki cross coupling was employed to obtain ester type-porphyrin functionalities in high yield. This reaction provides a versatile methodology for formation of C-C bonds by utilising organoboron compounds and organic electrophiles such as halides or triflates in the presence of a base. This method has the advantages of using mild reaction conditions, being highly stable in water, having high regio- and stereoselectivity and tolerance towards numerous functional groups. Furthermore, the boron-containing by-product from the reaction can be easily separated from the desired product. Suzuki cross-coupling has been widely applied previously in porphyrin chemistry, notably in the synthesis of porphyrin array of \textit{meso,β}-phenylene-linked dimers, \textit{meso}-meso linked dimers and highly substituted porphyrins.

Thus, the Suzuki cross-couplings reactions with bromo porphyrins were carried out under standard conditions as described in the literature. The \textit{meso}-brominated porphyrins 149, 151 and 152 were reacted with methylesterphenylboronic acid in the presence of potassium phosphate, K$_3$PO$_4$ and Pd(PPh$_3$)$_4$ catalyst under reflux conditions in tetrahydrofuran (THF) and gave porphyrins 159-162 in 82% to 98% yield (Scheme 3.4). Dibrominated porphyrins 150 and 156 were also subjected to Suzuki coupling reaction and afforded ester porphyrin 163 and 164 in 94% and 77% yield, respectively (Scheme 3.5).
Scheme 3.4 Suzuki cross-coupling reaction of meso-monosubstituted porphyrins.

Scheme 3.5 Suzuki cross-coupling reaction of meso-disubstituted porphyrins.

Figure 3.4 shows the $^1$H-NMR spectrum for ester porphyrin 163 that contains two ester functional groups at the meso-positions. The overlapping singlet peak at 8.75 ppm which represents H$_4$-proton resonance, is more upfield than other phenyl-H due to
neighbouring carbonyl group. $\text{H}_6$-proton, that is adjacent to $\text{H}_5$- and $\text{H}_7$-protons, appears as triplet while the $\text{H}_5$- and $\text{H}_7$-protons themselves appear as the doublet resonances. The integration ratio between eight $\beta$-protons and phenyl-protons shows the incorporation of two phenyl ester groups into meso-position of the porphyrin core.

![NMR spectrum](image)

**Figure 3.4** $^1$H-NMR spectrum for porphyrin 163 in CDCl$_3$.

Suzuki coupling of the $\beta$-brominated porphyrin 155 was also carried out under similar conditions and afforded the $\beta$-substituted porphyrin 165 in 52% yield (Scheme 3.6). The Suzuki coupling reaction requires the use of a base to enhance the transmetallation step. The role of the base is to form a more electron-rich intermediate with the boronic acid resulting in a more reactive species towards attack of the palladium(II) complex compared to the original boronic acid.

![Scheme 3.6](image)

**Scheme 3.6** Suzuki cross-coupling reaction of $\beta$-substituted porphyrin.
Figure 3.5 shows the $^1$H-NMR spectrum for $\beta$-substituted porphyrin 165. The presence of seven protons in the $\beta$-region indicates that $\beta$-substitution has occurred. One of the significant resonances is the singlet peak at 7.36 ppm which corresponds to the shielded H3-proton resulting from proximate phenyl ring influence. The doublet peak at ~8.15 ppm corresponds to the para-phenyl protons at 5- and 10-meso-position of the porphyrin and are assigned as H$_2$ whereas the para-phenyl protons at 15- and 20-meso-position resonate at ~7.48 ppm.

Another method, that enables the introduction of ester functional groups into the porphyrin macrocycle, is to condense a mixture of pyrrole and the appropriately substituted benzaldehyde. This standard condensation reaction was carried out using one equivalent of 4-carboxymethyl benzaldehyde, 3 equivalents of 3,5-di-tert-butyl-benzaldehyde and 4 equivalents of pyrrole refluxed in propionic acid in the presence of zinc acetate, to give ester porphyrin 166 in 10% yield and meso-tetra substituted compound 167$^{[9c]}$ as a side product in 12% yield. Addition of zinc acetate as a metal template during the condensation process can facilitate the reaction, thus increasing the yield of the condensed products.$^{[187]}$
The corresponding free base ester porphyrins 168 or 169 can be obtained in 8%-9% yields under acidic work-up conditions (Scheme 3.7).

$$\begin{align*}
R^1\text{-CHO} + R^2\text{-CHO} &\rightarrow Zn(OAc) \\
&\text{DDQ, NEt}_3 \\
\end{align*}$$

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,5-di-t-butylPhenyl</td>
<td>4-CO$_2$MePhenyl</td>
<td>9%</td>
<td>168</td>
</tr>
<tr>
<td>Phenyl</td>
<td>4-CO$_2$MePhenyl</td>
<td>8%</td>
<td>169</td>
</tr>
</tbody>
</table>

Scheme 3.7 Entry to ester porphyrin via condensation reaction.

All of the above ester porphyrins were successfully converted to functionalised carboxylic acids porphyrins using base hydrolysis. The ester porphyrin was dissolved in THF before undergoing heating at 110 °C with KOH-EtOH and the reaction was monitored by TLC. Once the reaction was complete, the corresponding carboxylate salt solution was acidified and afforded acid porphyrins 171-182 in 77% to 93% yields (Figure 3.6).
Figure 3.6 Different types of carboxylic acid porphyrins.
Further synthetic work was focused on the construction of porphyrins containing labile o-nitrobenzyl functionalities via esterification between readily prepared carboxylic acid porphyrins and 2-nitrobenzylalcohol as the model linker. Therefore, coupling agents were employed to assist the reaction between carboxylic acid and hydroxyl groups by activating the acid group, making it susceptible to attack by hydroxyl groups. Notably, two common methods for esterification in porphyrin chemistry are acylation and carbodiimide coupling techniques. Carbodiimide coupling offers a more feasible method, as it requires simple and mild conditions. There is a large number of carbodiimide type activating agents, such as \(N,N'-\)dicyclohexylcarbodiimide (DCC), \(N,N'-\)diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). We investigated several preliminary esterification reactions using carbodiimide reagent of \(N,N'-\)dicyclohexylcarbodiimide (DCC) as it has been the coupling reagent of choice for many years.

Carboxylic acid porphyrins 173, 174, 181 and 182 were dissolved in THF and 2 equivalents of DCC and 2-nitrobenzyl alcohol were added in the presence of base, dimethylamino pyridine (DMAP). The reaction was completed after 18 hours under reflux conditions. From a mechanistic point of view, DCC reacts with the carboxyl group first and forms a very reactive intermediate, \(o\)-acylisourea 183. This is the reactive species that can be attacked by the hydroxyl component to give the corresponding ester. Nevertheless, it was observed that the reactions tend to undergo racemisation to form stable \(N\)-acylisourea 184 instead of reactive intermediate of \(o\)-acylisourea and afforded porphyrins 185-188 in 30% to 52% yield (Scheme 3.8).
Both of the \( O \)- and \( N \)-acylisourea compounds have significantly similar \(^1\)H-NMR spectroscopic data except for the differences of the more upfield chemical shift of NH-proton of isourea \( \text{183} \) compared to isourea \( \text{184} \) whereas the \(^{13}\)C NMR data indicate the addition of one C=O resonance in isourea \( \text{183} \) (Figure 3.8). The data from infrared spectroscopy (IR) further support this structure due to the absence of C=N stretch vibration for \( \text{183} \). The substitution pattern was confirmed by X-ray crystallographic analysis of porphyrin \( \text{186} \) (Figure 3.9). In these studies, the structure of this carbodiimide intermediate was determined and supports a similar observation that was mentioned previously in the preparation glycoporphyrins.\(^{193}\)
Figure 3.7 $^1$H-NMR spectrum of porphyrin 185 in CDCl$_3$.

Figure 3.8 $^{13}$C-NMR spectrum of porphyrin 185 in CDCl$_3$. 
Gibson et al. have explained in more detail the transformation of this intermediate in the preparation of cholesteryl esters of crown ether.\cite{Gibson} The rearrangement was suggested to occur via a four-membered transition state due to the presence of an active aza-enamine moiety in the acylisourea intermediate and the formation of the stable carbon-oxygen double bond (Figure 3.10). It was also reported that the presence of the crown ether moiety makes the acylisourea too sterically hindered to react with cholesterol and contributed to the low yield of ester product.

![Figure 3.9 View of the molecular structure of 186 in the crystal. Hydrogen atoms have been omitted for clarity; thermal ellipsoids are drawn for 50% occupancy.](image)

![Figure 3.10 Postulated rearrangement of 184 via four-membered transition state.](image)
As the rearrangement resulted in low yields and contamination of the desired product, further optimisation reactions between carboxylic acid porphyrins and 2-nitrobenzyl alcohol in the presence of DCC/DMAP were carried out. Using 5 equivalents of DCC, 1 equivalent of DMAP and 5 equivalents of 2-nitrobenzylalcohol, we managed to obtain the desired o-nitrobenzyl-porphyrins \(189\) and \(190\) in moderate yields along with the rearrangement products of \(187\) and \(188\) in 43% and 69% yield, respectively (Scheme 3.9). Table 3.1 shows the optimisation condition reactions utilising 1 equivalent of porphyrin \(182\) with different stoichiometry in refluxing THF for 18 h.

Table 3.1 Reaction conditions of DCC carbodiimide coupling.

<table>
<thead>
<tr>
<th>DCC(eq.)</th>
<th>DMAP(eq.)</th>
<th>2-Nitrobenzylalcohol(eq.)</th>
<th>Porphyrin 190</th>
<th>Porphyrin 188</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>52%</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>-</td>
<td>27%</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>13%</td>
<td>31%</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>27%</td>
<td>69%</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>10</td>
<td>13%</td>
<td>52%</td>
</tr>
</tbody>
</table>

To overcome this rearrangement problem, it is necessary to stabilise the intermediate \(\sigma\)-acylisourea using an additive such as \(N\)-hydroxysuccinimide (NHS)\(^{195}\). In the presence of NHS, the intermediate is immediately attacked by the \(N\)-hydroxyl alcohol to give the NHS-type ester, which is reactive towards alcohol, but not prone to racemisation. Besides NHS, 1-hydroxybenzotriazole (HOBt) was proposed as an additive that can suppress the racemisation through formation of active ester intermediate \(191\) (Figure 3.11)\(^{196}\).
Further esterification reactions were investigated using another carbodiimide reagent: 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride (EDAC). It is easier to use due to its high solubility in solvents while the urea produced is water soluble, and thus easily separated from the product. The EDAC-assisted esterification reaction was first carried out using porphyrin 181 with 1 equivalent each of EDAC, DMAP and 2-nitrobenzyl in CH$_2$Cl$_2$ at room temperature for 18 hours, and afforded ester porphyrin 192 in 50% yield. Meanwhile, increasing the reagent amounts to 2 equivalents gave porphyrin 192 in 86% (Scheme 3.10) Therefore, all of the further esterification reactions involving carboxylic acid porphyrins were employed with these general reaction conditions and they afforded a large number of nitrobenzyl ester porphyrins 193-199 (Figure 3.12). Disubstituted o-nitrobenzyl porphyrin 198 is an example of attaching two linkers to porphyrins macrocycle that will allow to potentially doubly increasing the conjugation to targeting receptor.

Scheme 3.10 EDAC coupling of porphyrin and 2-nitrobenzylalcohol.
### Figure 3.12 \(\alpha\)-Nitrobenzyl-linked porphyrins.

The reaction mechanism in using EDAC activating reagent proceeds in similar fashion to other carbodiimide couplings. The O-acylisourea 202 is a highly reactive species that can form the cyclic intermediate 203, and thus prevent unnecessary racemisation. DMAP\(^{[197]}\) is used to liberate the amine salt form of isourea before coupling with a carboxyl group (Scheme 3.11).
Chapter 3. Lead Structures to Photolabile o-Nitrobenzyl Porphyrins

Figure 3.13 shows the $^1$H-NMR spectrum of porphyrin 192 as representative of o-nitrobenzyl type porphyrins. Two peaks appeared as triplets at 7.55 and 7.75 ppm represent the H$_7$- and H$_8$-protons that are located between two neighbouring protons. The doublet resonance at 8.20 ppm refers to H$_9$-proton which is closer to the ester group while the doublet resonance at 7.87 ppm corresponds to H$_6$-proton. Figure 3.14 shows the $^1$H-NMR spectrum of porphyrin 193 as an example of acrylic-type porphyrins. The resonance which appeared as doublets at 6.87 ppm and 10.28 ppm, respectively represent the H$_1$ and H$_2$-protons. The magnitude of the coupling constant, $J$ (15.8 Hz) indicates the E-conformation. Figure 3.15 represents meta-substituted phenyl moiety as shown in porphyrin 200 with the resonance appeared that as triplet at 7.85 ppm belonging to H$_2$-proton, whereas two peaks at 8.41 ppm and 8.49 ppm represent its neighbouring protons H$_1$ and H$_3$. Resonance for H$_4$-proton appeared more downfield as a singlet due to its adjacent carbonyl group.

Scheme 3.11 Mechanism of EDAC carbodiimide coupling.
Figure 3.13 $^1$H-NMR spectrum of porphyrin 192 in CDCl$_3$.

Figure 3.14 $^1$H-NMR spectrum of porphyrin 193 in CDCl$_3$. 
3.4 Conclusions

A number of synthetic methods were investigated with the aim of preparing porphyrins bearing nitrobenzyl functionalities as a model of a labile linker, and the esterification reaction was chosen as the key pathway. We started by utilising transition metal catalysed reactions to introduce simple ester functional groups into porphyrin moieties. Thus, the first step required the synthesis of brominated porphyrins as precursors, followed by palladium catalysed Heck and Suzuki reactions which afforded the ester porphyrins in moderate to good yields. Typical condensation reactions of porphyrins were also employed to introduce the ester functional group. Subsequent base hydrolysis of the porphyrins lead to the formation of carboxylic acid porphyrins.

Esterification reactions towards the preparation of nitrobenzyl-linked porphyrins were carried out via the carbodiimide coupling method which are widely used in peptide syntheses. Numerous types of carboxylic acid porphyrins were esterified with 2-nitrobenzyl alcohol as the model linker. Unfortunately, while employing DCC as the coupling reagent, the major products formed were the result of the rearrangement of the isourea intermediate. Therefore, coupling reagent EDAC was used to obtain the desired

Figure 3.15 $^1$H-NMR spectrum of porphyrin 200 in CDCl$_3$. 
porphyrins in high yields. After we established the use of esterification pathway to incorporate the labile linker, subsequent research was towards the ultimate construction of porphyrin-linker-bioconjugate as discussed in the following chapter.
CHAPTER 4:

Photolabile o-Nitrobenzyl Bioconjugate Porphyrins
4.1 Introduction

The cytotoxic effects of photodynamic therapy (PDT) rely on the photosensitiser localisation and accumulation within the diseased sites, thus requiring the accurate delivery of the photosensitiser agent to specific-PDT susceptible sites of the target cells or tissues. This targeted delivery system will increase the selectivity for destroying cancer cells, minimise the uptake of photosensitisers by normal cells, decrease the systemic toxicity and could permit a dose control. As the limited life-time of the generated reactive oxygen species will also constrain the oxidative damage to a minimal volume of surrounding tissues, construction of such system will be essential. Numerous studies have been investigated to develop delivery strategies that recognise the specific target of receptors on cancer cells and that are capable of efficiently increasing the concentrations of photosensitisers internalised into the cells.

There are a number of cell surface receptors located within the cellular membranes of malignant cells that are overexpressed as compared to normal cells due to their transformed nature.\(^{[103]}\) Therefore, antibodies or ligands that are specific to these membrane receptors can be used to selectively target the photosensitisers to the tumour cells. The choice of targeted receptor should be considered based on two main criteria; high density on the pathological cells but largely absent on normal cells and a heterogeneity factor as its high level of expression on only a small percentage of pathological cells would not allow the drug to enter the diseased tissue evenly.\(^{[103,198]}\)

Our work has examined the feasibility of modifying the labile porphyrin photosensitisers to target specific receptors based on carbohydrates and folic acid ligands. This chapter will discuss further synthetic work to attach porphyrins to the selected ligands through o-nitrobenzyl linker and subsequent photolysis studies. As noted earlier, the labile linker should enable the controlled release of the photosensitisers. Furthermore, addition of the linker to separate the drug and ligands is necessary in drug delivery since drug moieties positioned too close to a low molecular weight ligand can sterically reduce the affinity of the ligand for its receptor.

4.2 Carbohydrate linked-porphyrins

Porphyrins with carbohydrate moieties have been reported as efficient photosensitiser candidates for PDT.\(^{[199]}\) They not only alter the amphiphilicity of the
photosensitisers to facilitate their cellular uptake, but also have specific membrane interactions with glycoprotein receptors, and thus exhibit specific targeting of tumour cells. Many glycoporphyrin conjugates have been synthesised to specifically target the lectin family of receptors which are overexpressed in certain malignant cells. For example, Pandey et al. demonstrated that galactose and lactose-benzochlorin conjugates, which have high affinity for β-galactoside-recognised proteins, produced an enhanced photosensitising ability compared to non-conjugate analogues. Similar studies were also carried out with glycoconjugates of manno-conjugated porphyrins (Figure 4.1) to utilise the expression of sugar receptors on retinoblastoma cells. The amphiphilic glycosylated porphyrins also associate strongly with plasma lipoproteins and can be incorporated into tumour cells through receptor mediated endocytosis of low-density lipoprotein (LDL) due to high level of the LDL receptor in cancer cells. Recently, glycoporphyrin was conjugated to the B-subunit of Shiga toxin (STxB) which has binding affinity for cellular receptor of glycosphingolipid globotriaosylceramide, Gb3 that is expressed on a number of cell malignancies. It was shown that the photosensitising activity of the conjugated glycoporphyrins is 5-fold higher than of the parent porphyrins.

![Figure 4.1 Different types of glycoporphyrins.](image-url)
Synthetic pathways to functionalise porphyrins with glycoconjugates are mainly based on condensation reactions which employ benzaldehydes bearing sugar derivatives. The carbohydrate moieties also can be introduced after formation of porphyrin macrocycle to give porphyrin 205 (Scheme 4.1). Most of the carbohydrates have been conjugated to the phenyl rings of tetraarylporphyrins through an oxygen linkage. A different method has been developed utilising click chemistry from readily available carbohydrate azides and the alkyne porphyrins to prepare porphyrin-carbohydrate conjugates.

![Image of Scheme 4.1 Synthesis of thio-glycosylated porphyrin.](image)

Our approach involved employing carboxylic acid porphyrins as starting materials to react with o-nitrobenzyl-carbohydrate conjugate derivatives. Therefore, the first step required the synthesis of hydroxyl-functionalised conjugates which can be esterified with the acid porphyrins at a later stage. We decided to utilise 5-hydroxyl-2-nitrobenzaldehyde 206 as the precursor which contains hydroxyl group as the active site. It has been reported that the Mitsunobu reaction can be used to convert an alcohol into a variety of functional groups using triphenyl phosphine base and azo ester as shown in formation of aryl ether from a phenolic group. Thus, we intended to explore this reaction in incorporating hemicetal glucose 207 to the precursor. Selective deacetylation at the anomic centre of 1,2,3,4,6-pentaacetyl-D-glucose 208 by treatment with hydrazinium acetate in dimethylformamide at room temperature afforded the hemiacetal 207 in 83% yield with 5:1 ratio of α/β product (Scheme 4.2).
Figure 4.2 Precursor of 5-hydroxyl-2-nitrobenzaldehyde 206.

![Diagram](image_url)

Scheme 4.2 Selective deacetylation of glucose 208.

Subsequent reaction of hemiacetal 207 with benzaldehyde 206 was carried out under typical Mitsunobu conditions. The reagents 206, 207 and triphenyl phosphine were dissolved in tetrahydrofuran (THF) and di-tert-butylazodicarboxylate (DTAD) was added at 0 °C and the reaction was stirred at room temperature for several hours with TLC monitoring. However, this reaction did not proceed as expected. In the second attempt utilising commercially available glucose 209, a different approach was investigated by initial preparation of the preformed betaine 210 by adding the azoester DTAD to triphenylphosphine in tetrahydrofuran (THF) at 0 °C, followed by addition of glucose 209 and hydroxyl benzaldehyde 206. Nevertheless, this method of choice proved to be unsuccessful for preparation of the conjugate (Scheme 4.3). There were several conditions that need to be considered to improve the Mitsunobu reaction. It is necessary to allow the complete formation of oxyphosphonium intermediate by stirring of the betaine 210 longer. Moreover, the basicity of diazo anion can be enhanced using strong electron donating group as piperidine instead of tert-butyl to react with weakly acid phenolic functionality.
Another useful method for glycosylation is the Koenigs-Knorr reaction, which involves the substitution reaction of a glycosyl halide with an alcohol to give glycoside.\[^{209}\]

The attempted preparation of the nitrobenzyl-bioconjugate is shown in Scheme 4.4. The benzaldehyde precursor 206 was reduced with sodium borohydride to give compound 211 in 95%, which was subsequently reacted with acetobromoglucose 212 in the presence of tetra-n-butyl ammonium fluoride (TBAF) catalyst as described in the literature.\[^{210}\] This reaction yielded only starting materials and thus a different approach was employed according to a strategy developed by Thiem and Kruger using phase transfer catalysis (PTC).\[^{211}\]
The PTC technique can accelerate the reaction by facilitating the migration of a reactant in a heterogeneous system between aqueous and organic phases in the presence of a cheap and non-toxic phase-transfer catalyst. The aqueous phase contains bases such as sodium hydroxide (NaOH), whereas the organic phase contains the anion precursor and the electrophile reactant. Typical phase-transfer catalysts are quaternary ammonium salts such as TBAF that are soluble in both the organic and aqueous phase. This catalyst forms a lipophilic ion-pair together with the deprotonated phenolate anion and migrates into the organic phase. In an aprotic nonpolar solvent such as dichloromethane, the ion-pair is not solvated, while the phenolate shows enhanced nucleophilicity (Scheme 4.5).

\[ \text{phenolate ion} + \text{lipophilic cation} \rightarrow \text{lipophilic ion-pair} \]

Scheme 4.5 Phase-transfer catalyst reaction.

As only phenols react under phase transfer catalysis, 5-hydroxy-2-nitrobenzyl alcohol 211 can undergo glycosylation selectively at the phenolic position with acetobromoglucose 212 and afforded a mixture of two aryl β-glycosides, (3-hydroxymethyl-4-nitrophenyl)-2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside 213 and 214 in 10% and 27%, respectively (Scheme 4.6).[212] The acetylated glycoside 214 was obtained due to partial intermolecular acetyl migration, however both of these compounds were easily separated by column chromatography, eluting with ethyl acetate (EtOAc): hexane = 1:10. The glycosylated products formed in lower yield due to good solubility of phenol 211 in water, thus reducing the concentration of the reactive phenolate in organic phase.

The success of the above reaction paved a way to prepare different glycosylated compounds, but required the presence of glycosyl halide. Another synthetic sequence was explored to synthesise the halide due to the limited commercially available glycosyl halide. We choose to employ the glucose 209 due to its susceptibility to undergo deprotection and form water soluble moieties.\[203\] Therefore, 209 was brominated with NBS and triphenylphosphine in chlorobenzene according to the literature,\[213\] to give brominated glucose 215 in 3% yield and the side product of rearrangement 216 in 5% (Scheme 4.7). This rearrangement occurred when employing cyclic acetals containing secondary hydroxyl group where the attack of halogens is significantly hindered.\[214\] A more facile halogenation has been reported by displacement of triflate intermediate of carbohydrates with tetrabutylammonium halides.\[215\]

The lesser yield of 215 limited the reaction scale, however, we managed to perform glycosylation via the PTC method with nitrobenzyl phenol 211 and this afforded the β-glycoside of 217 in 5% yield (Scheme 4.8). Due to tedious chromatography, we were only able to separate (3-hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside 217 from the reaction mixture in low yield.

![Scheme 4.7 Bromination of glucose 209.](image-url)
A model compound of porphyrin-linker-bioconjugate was prepared by reacting carboxylic acid porphyrin 181 with glycoside 213 and this yielded the target compound 218 in 76% yield. However, due to a lower quantity of available nitrobenzyl-linked glucose 217, the similar esterification reaction between porphyrin 174 and glycoside 217 was carried out on small scale and afforded the porphyrin 219 in 72% yield [MS (ESI): m/z= 1060.4479 (M+H)^+] (Scheme 4.9). Nevertheless, this type of precursor was attractive due to facile deprotection of the glucose moieties.

**Scheme 4.8** Preparation of o-nitrobenzyl-linked glucose 217.

**Scheme 4.9** Preparation of porphyrin-linked glucose 218 and 219.
4.3 Folic acid-linked porphyrins

Folic acid 220 is a ligand that can selectively bind the folate receptor (FR), a glycosylphosphatidylinositol-anchored cell surface receptor that is over-expressed in many cancer cells including >90% of ovarian carcinomas. Upon receptor interaction, the folic acid-(FR) complex is taken into cells through folate receptor-mediated endocytosis. The folic acid is taken up by cancer cells preferentially to normal cells, and thus presents an attractive target for cancer selective drug delivery. Folate as a targeting ligand offers many potential advantages over macromolecules such as monoclonal antibodies (mAb) because of its small size, lack of immunogenicity, convenient availability and high tumour specificity.

It was reported that folic acid retains its receptor binding properties when functionalised via its \(\gamma\)-carboxyl group (Figure 4.3). Furthermore, it shows high stability and compatibility with both organic and aqueous solvent and defined conjugation chemistry. Therefore, numerous synthetic procedures has been developed to link folic acid to molecules such as cyclodextrins, radiopharmaceutical imaging agents, polymer nanoparticles, micelles, dendrimers, microgels, along with PDT agents.

Our approach was to couple the hydroxyl functional of nitrobenzyl-porphyrin with the carboxyl site of the folic acid by employing a protecting group synthon. Synthesis of the nitrobenzyl-porphyrin analog containing an active phenolic group started with the protection of the phenolic group of 5-hydroxy-2-nitrobenzaldehyde 206 using the acid-sensitive protecting group of 2-methoxyethoxymethyl (MEM) ether in the presence of Hüning base, \(N,N'\)-disopropylethylamine (DIPEA) and afforded the protected nitrobenzyl benzaldehyde 221 in 89% yield. Reduction of 221 with sodium borohydride at room temperature gave the respective nitrobenzyl alcohol 222 in quantitative yield (Scheme 4.10). It is noted that different protecting groups for phenol functionality such as silyl
derivatives\textsuperscript{222, 223} can also be used, particularly to avoid acidic conditions in the final deprotection step.

![Scheme 4.10 Synthesis of protected nitrobenzyl alcohol.](image)

The next step involved an esterification process of carboxylic acid porphyrin 174 with nitrobenzyl derivative 222 via EDAC carbodiimide coupling and gave hydroxyl-protected nitrobenzylporphyrin 223 in 83\% yield (Scheme 4.11).

![Scheme 4.11 Esterification of porphyrin 223.](image)

Subsequent deprotection of the acetal type of methoxyethoxymethyl (MEM) group was carried out under neutral conditions to avoid adverse reactions from acidic conditions. Heating of porphyrin 223 with ethylene glycol for 5 hours (TLC monitoring) gave hydroxyl porphyrin 224 in 92\% yield. Miyake \textit{et al.} reported that the solvolysis of the ester group is observed to some extent even though in general, the deprotection of the MEM-protected phenyl ester proceeded without destruction of the ester groups.\textsuperscript{224} In our case, the deprotection occurred due to nucleophilic attack from hydroxyl group of ethylene glycol to the prone benzylic carbon.
Nevertheless, porphyrin 224, bearing a hydroxyl group, can be utilised as a precursor to introduce numerous functionalities to produce bioconjugate porphyrins such as porphyrin linked-carbohydrate 202. Moreover, the linkages can be used to construct covalently linked porphyrin dimers that have interesting interaction energy and photoinduced electron transfer process. Notably, different types of porphyrin dimers have been employed in mimicking natural photosynthetic process or for use in electronic devices.\textsuperscript{225} Therefore, the reactivity of porphyrin 224 was examined by esterification reaction with carboxylic acid porphyrin 225 to give dimer porphyrin 226 in 93% yield (Scheme 4.13).
A different neutral MEM-cleavage method was utilised based on bidentate coordination of zinc bromide, ZnBr$_2$ with the methoxyethoxymethyl group. To avoid unnecessary zinc metallation of free base porphyrin due to the presence of ZnBr$_2$, the MEM functionalised porphyrin 223 was metallated with zinc oxide and afforded zinc porphyrin 227 in 94% yield. Consequently, selective deprotection of porphyrin 227 was continued by treatment with ZnBr$_2$ in dichloromethane at room temperature. The initial reaction was set up using 7.0 equivalents of ZnBr$_2$ and stirred in 18 hours, however, only starting material was recovered. While increasing the amount of ZnBr$_2$ to 20 equivalents with similar reaction conditions, mixtures of free base product and starting material were observed but were inseparable due to the close polarity of both compounds (Scheme 4.14). $^1$H-NMR analysis indicated that the product was free base porphyrin 228 as proton signals from methoxyethoxymethyl-group have disappeared. Mass spectrometry also confirmed the composition of the product [MS (ESI): $m/z = 818.3323$ (M+H)$^+$.]
Scheme 4.14 Zinc bromide deprotection of porphyrin 227.

Afterwards, we decided to use trifluoroacetic acid (TFA)\(^{[227]}\) as the MEM removal reagent for metalloporphyrin 227 which could prevent unnecessary porphyrin core protonation under acidic conditions. After treatment of zinc porphyrin 227 with an excess amount of TFA in CH\(_2\)Cl\(_2\) (1:1 eq.), the reaction progressed smoothly to eliminate the MEM-group and undergo demetallation process and afforded porphyrin 228 in 81% yield (Scheme 4.15). Subsequently, we attempted to incorporate folic acid 220 as the targeted bioconjugate via carbodiimide esterification. Folic acid 220 was dissolved in dimethylsulfoxide in the presence of pyridine followed by addition of DCC\(^{[109]}\) The reaction was stirred for 30 min and porphyrin 228 was added to the reaction mixture (Scheme 4.15). Unfortunately, the expected folic conjugate porphyrin 229 was observed only in very low yield and was detected as the polar spot in TLC analysis. Although this approaches is limited due to its low reactivity, porphyrin 228 still has potential to be used to construct various secondary functionalities such as attaching second photosensitiser of boron-dipyrromethene (BODIPY)\(^{[228]}\) or linked with fluorescent marker such as rhodamine B for imaging studies\(^{[229]}\).
Therefore, another pathway was examined to prepare porphyrin precursors that were accessible for linking the folic acid. This method was developed based on reactivity between boronlated porphyrin and its counterpart of halide nitrobenzyl compound via a palladium catalysed cross-coupling reaction. The initial step involved preparation of borolanyl porphyrin from bromo porphyrin according to method described by Therien et al.\textsuperscript{230} Mono bromo porphyrin 152 was coupled with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) 230 as the transmetllating reagent with PdCl\(_2\)(PPh\(_3\))\(_2\) catalyst in 1,2-dichloroethane. The reaction was heated at 90 °C for 20 minutes when the starting material was completely consumed and afforded borolanyl porphyrin 231 in 30% yield and the deprotected porphyrin 109 in 36%. Due to major formation of porphyrin 109, a different reaction system\textsuperscript{231} was employed using bis(pinacolato)diboron 232 in the presence of potassium acetate, KOAc and palladium catalyst Pd(dppf)Cl\(_2\) in toluene/H\(_2\)O to give porphyrin 231 in 65% yield (Scheme 4.16).
Scheme 4.16 Preparation of borolanyl porphyrin 231.

4-Bromomethyl-3-nitrobenzoic acid 233 was chosen as transmetallation reagent due to the existence of carboxylic acid functionality that has been shown to be useful group for attaching folic acid conjugates.\[^{109}\] Porphyrin 231 was then subjected to palladium cross-coupling reaction with bromo nitrobenzoic acid 232 according to the literature\[^{231}\] using Pd(PPh\(_3\))\(_4\) as catalyst and Ba(OH)\(_2\) in toluene/H\(_2\)O (Scheme 4.17). Under unoptimised conditions, the reaction produced only a small amount of desired porphyrin 234 [MS (ESI): \(m/z = 786.3275\) (M+H)\(^+\)] along with unreacted starting material. This problem presents a challenge in achieving our main target, hence requires extensive synthetic investigation.

Scheme 4.17 Palladium catalysed cross-coupling reaction of porphyrin 231.
4.3 Photolysis studies

The photolysis rates of the model porphyrin-linked bioconjugate 218 were measured by photolyzing aliquots of the compound solution for various times followed by determination of the rate of disappearance of the starting material and formation of the cleavage compound. Photolysis measurements were performed using a photochemical reactor (Rayonet Model RMR-600) equipped with 350 nm UV lamp. The light fluency rate was calculated as 16 mW/cm². Times were chosen such that 70% to 80% of the starting material was cleaved in order to derive kinetic parameters, although the cleavage usually showed good linearity over the course of complete cleavage.

The UV spectrum of porphyrin 218 exhibited the anticipated absorption of porphyrin with two electronic transitions of Soret and Q bands. The Soret band has a very large extinction coefficient and is characteristic for the macrocyclic conjugation. At longer wavelengths, four Q bands, with significantly lower intensity than the Soret band, can be detected. The UV spectra of the fragmented o-nitrobenzyl group resulting from the photolysis shows adequate absorption around 350 nm. Consequently, the photolysis progress of the porphyrin 218 could not be detected by UV measurement and required a different analytical measurement such as high performance liquid chromatography (HPLC).

For the photolysis studies, a 50 μM solution of 218 in a Acetone: H₂O (98%:2%) was irradiated with long wavelength UV light (350 ±25 nm) and the photolysis reaction was monitored by HPLC. The compound was photolysed via aci-nitroso mechanism to give o-nitrosobenzaldehyde along with the carboxylic acid porphyrin substrate 178 (Scheme 4.18). The conversion of 218 to 181 was then followed as a function of time.

Scheme 4.18 Photofragmentation of porphyrin 227 upon irradiation.
Figure 4.4. HPLC measurement for different photolysis times of porphyrin 218.

Column: Nucleosile 5µ Si 100A, Size: 250 X 4.00 mm, Eluent: n-hexane: ethylacetate (50:50), Flow rate: 1.5 ml/min, Detection UV: 350 nm

Figure 4.4 shows HPLC analysis of samples upon UV irradiation for 20, 40, 75, 90, 120, and 150 minutes as compared with the starting material of porphyrin 218 and carboxylic acid porphyrin 181 based on the difference of porphyrins retention time. During the irradiation process, the peak represent porphyrin 218 is decreased while the formation of the new peak occurred which is comparable to the retention time of carboxylic acid porphyrin 181. It was observed that upon irradiation for 80 min, approximately 50% of the porphyrin 218 was photolysed (Figure 4.5). The photolysis product was identified as porphyrin 181 [MS (ESI): \( m/z = 995.6233 \) (M+H)⁺]. The mechanism of o-nitrobenzyl alcohol ester cleavage involves photoinduced intramolecular hydrogen abstraction and redox rearrangement to form o-quinonoid intermediate, followed by the released of the carboxylic acid and formation of nitrosobenzaldehyde. o-Nitroso benzaldehyde may further react to form a secondary by-product of azobenzene-2,2'-dicarboxylic acid that can act as internal filter, hence presumably slowing the desired photoreaction. While this technique was unable to quantify the amount of product produced, it did provide an expedient method for determination of relative cleavage kinetics for compounds.
With regards to photolabile linker studies, future work should focus on the investigation of more advanced nitrobenzyl derivatives to improve its modest rates of cleavage. For example, incorporation of two alkoxy groups in the benzene ring and introduction of an additional benzylic methyl group increased the rate of cleavage 5-folds. Moreover, a less damaging release group should be considered because the ubiquitous presence of UV light inducing by one-photon excitation is damaging to cells and absorbed by biological chromophores such as DNA. As most of current caging groups such as o-nitrobenzyl absorb UV light, different approach has been developed to utilise two-photon infrared (IR) excitation as employed in photolabile species of coumarin moieties. Two photon excitation method confines the substrate activation to the focal point. This technique will minimise the phototoxicity to cells and has better tissue penetration than UV. Recently, strategies to enhance two-photon absorption (TPA) of porphyrin photosensitisers have been of great interest to improve the PDT efficiency. The possibility of carrying out PDT by TPA activation in combination with two-photon labile releasing system should make this type of therapy more applicable to deeper tumors in spatial controlled.

**Figure 4.5.** Photolysis conversion of starting material and formation of carboxylic acid porphyrin.
4.4 Conclusions

The results showed our synthetic work for selective targeting and control releasing of the photosensitiser via the porphyrin linked-bioconjugate system. The conjugates can act as a ligand which can covalently link to photosensitisers, aiming to enrich the loading of photosensitiser in the target tissue. Carbohydrate residues have been shown as a candidate to enhance photosensitiser binding to LDL due to glycosyl substituents where the LDL can be incorporated into liposome and uptake in cells by receptor mediated endocytosis mechanism. Therefore, initial studies utilised the carbohydrate ligand as shown in the preparation of porphyrin 218 and 219. While current progress demonstrates that we were able to synthesise a compound containing the required structural motifs, such synthetic sequence need additional improvement as the lower yield of targeted compound gave limitation for our subsequent works in the in vivo and in vitro studies. Nevertheless, we have showed the photolability of this material upon UV-light irradiation, thus providing a novel strategy for future improvement.

In addition, cell membrane folate receptors have been investigated as a molecular target for tumour-selective drug delivery. Thus, folic acid vitamin that target specifically to the folate receptor can be utilised as the ligand. The second target aims to exploit this folic acid residue by employing porphyrin precursor 228. Its low reactivity currently limits subsequent studies; however, this precursor provides conveniently naked-eye experimental monitoring due to colour of porphyrins. A different approach using palladium catalysed reactions were attempted to prepare porphyrin precursor 234, which should pave a way for linking the folic acid. It is noted that the biomolecule consisting double bond character that used as the ligand, potentially quenched the formation of active singlet oxygens from the PDT process, thus incorporating the linker into the system will disconnecting photosensitiser from its bioconjugates.

These studies are the basis for subsequent interdisciplinary studies on the use of photocleavable tetrapyrrole bioconjugates in medicine; notably, the specific use of the drug chromophore as a photosensitising agent in photodynamic cancer therapy and cancer indication. The ultimate target that remains is to find the ideal photosensitiser with a suitable receptor mediated delivery system for each specific pathological condition. Although the present work contains no preclinical or clinical studies, the basic chemistry and the 'proof-of-principle' have been established. This research is the first stage in a long-term effort to promote the use of improved photosensitisers in the treatment and indication of various diseases.
CHAPTER 5:

Reactivity of Porphyrin-Acrylic Acids and Their Homologues
5.1 Introduction

The chemistry of acyl compounds has a long history that can be traced back to the early part of the last centuries. Acyl building blocks are usually derived from carboxylic acids and are some of the best known and valuable synthons that are widely used in fine chemical synthesis. A variety of the synthetic methodologies has been developed to access these highly reactive molecules. The acyl α,β-unsaturated compounds are a subclass of these derivatives and are subunits of numerous natural and synthetic products displaying a wide range of biological activities. These multimodal materials possess two reactive sites consisting of a carbonyl unit as an electrophile and a double bond as a nucleophile. Depending on the conditions and reagents used, these reactive sites can either be activated or deactivated at the same time in a favourable manner. Therefore, their chemistry offers further synthetic prospects based on the different types of the reactions such as Claisen condensation and related acylations, substitutions or additions reactions that can be carried on affording novel materials.

Development of new and more efficient methods have been widely investigated to introduce functional groups into porphyrin macrocycles. At present, the chemistry available for porphyrin modification is generally based on metal-catalysed and organolithium approaches that sometimes require special conditions and are limited by a number of the functionalities to be introduced, thus leaving room for alternative synthetic methodologies.

Thus far, acyl chemistry has not been used much for porphyrin modifications. Several reports described the utilisation of porphyrin-benzoic acids as the building blocks for construction of porphyrin thin films and surface porphyrin monolayers for use as sensor materials, where functionalisation of these compounds mostly involved carbodiimide chemistry that was discussed in an earlier chapter. Only a few reports have been published using porphyrin benzoyl acyl chlorides to leave the chemistry almost untouched. Similarly, while the synthesis of acrylic porphyrins is well-known, their chemistry remains relatively unexplored. In the context of our aim to develop of novel porphyrin bioconjugates suitable for cell targeting, we have systematically studied the reactivity of porphyril acyl acrylates and their homologues. In this chapter, we present the results on the synthesis, transformations and comparative studies of a series of the porphyril acrylic derivatives.
5.2 Reactivity of acyl chloride porphyrins

For initial studies to evaluate the reactivity of acyl chloride porphyrins, compounds 239 and 240, with either one or two acroleinyl groups, were chosen as model compounds. The porphyrins 239 and 240 were synthesised via Heck cross-coupling reactions\(^{[175]}\) from bromoporphyrins 236 and 237 and methyl acrylate in 80% and 95% yield, respectively. Both of the porphyrins were hydrolysed in KOH-EtOH to the acrylic acid porphyrins 225 and 241 in 80% and 95% yields, respectively (Scheme 5.1). The corresponding acyl chlorides 242 and 243 were generated upon treatment of porphyrin 225 and 241 with SOCl\(_2\)-THF *in situ*. Heating at 35 °C is essential to accelerate the formation of these green-purple intermediates. Moreover, acyl chlorides are moisture sensitive and can hydrolyse back to the corresponding acids 225 and 241. Hence, they were used immediately for further transformations. The reactivity of these intermediates 242 and 243 was examined by use of nucleophiles such as alcohol and amine derivatives. These studies have shown that the acyl chloride porphyrins 242 and 243 *in situ* generated can be converted into the novel porphyrin adducts 239, 244-247 in good yields (Scheme 5.2).

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{Phenyl} & \text{Phenyl} & M=H & 153 \\
\text{Phenyl} & \text{Phenyl} & M=\text{Ni} & 236 \\
\text{Phenyl} & \text{Br} & M=\text{Ni} & 237 \\
\hline
\text{R}^1 \quad \text{R}^2 \\
\text{Phenyl} & \text{Phenyl} & M=H & 95\% & 238 \\
\text{Phenyl} & \text{Phenyl} & M=\text{Ni} & 80\% & 239 \\
\text{Phenyl} & \text{CH}=\text{CHCO}_2\text{Me} & M=\text{Ni} & 80\% & 240 \\
\text{Phenyl} & \text{Phenyl} & M=\text{Ni} & 95\% & 225 \\
\text{Phenyl} & \text{CH}=\text{CHCO}_2\text{OH} & M=\text{Ni} & 80\% & 241 \\
\end{array}
\]

Scheme 5.1 Route to the synthesis of carboxylic acid porphyrins 225 and 241.
Scheme 5.2 Generation of the acyl chlorides 242, 243 and synthesis of the porphyrins 239, 244-247.

This methodology can also be applied for the preparation of dimeric porphyrins. For example, the reaction of 242 with 5-(4-hydroxyphenyl)-10,20-bis(3-methoxyphenyl) porphyrin 248 resulted in the formation of dimer porphyrin 249. Noteworthy, the first attempt to carry out this reaction in THF, which was shown to be successful for the synthesis of 239 and 244-247, resulted in a very low yield of 249. However, replacement of THF by dichloromethane provided dimer 249 in 51% yield (Scheme 5.3).

Scheme 5.3. Synthesis of porphyrin dimer 249.

Figure 5.1 shows the $^1$H-NMR spectrum for porphyrin dimer 249. The signals for alkene proton, H$_1$ and H$_2$ appeared as doublets at around 6.73 ppm and 10.28 ppm respectively where H$_1$ which closer to porphyrin core shifted downfield and overlapping with meso-H.
Subsequent work was focused on the reactivity of β-keto ester derivatives. It has been reported that porphyrins bearing keto ester substituents at the β-position of the porphyrin macrocycle can be converted into biologically active phaeoporphyrins via photoinduced cyclisation\textsuperscript{240} While diazo compounds are widely used as precursors in synthetic chemistry\textsuperscript{241} only one strategy was applied for the synthesis of diazo β-keto esters using the acrylic acid halides in the reaction of the latter with mercuryl diazoacetate as reported by Padwa et al.\textsuperscript{242} In our studies, the reaction of acyl chloride 242 with ethyl diazoacetate in the presence of PPh\textsubscript{3} offers an entry into the important and unexplored class of porphyryl β-keto esters. Acyl chloride 242 generated \textit{in situ} was treated with the mixture of ethyl diazoacetate and PPh\textsubscript{3} in dichloromethane at 35 °C for several hours to give phosphazine 250 in 70\%, which was confirmed by \textsuperscript{31}P-NMR spectroscopy (Scheme 5.4). Some structural diversity was observed in solutions of deuterated chloroform (CDCl\textsubscript{3}) where slow conversion of 250 and formation of 251 were detected over the course of 7 days. Compound 251 trapped in CDCl\textsubscript{3} appears to be a product of a partial hydrolysis of the phosphazine 250. However, compound 250 proved to be quite unstable in dichloromethane and autotransformed (24 h) into the stable β-keto ester 252 in 78\% (Scheme 5.4).
Scheme 5.4 Reaction of 242 with ethyl diazoacetate via formation of phosphazine 250 and conversion to 251 and 252.

According to $^1$H-NMR data, porphyrin 252 exists only in the enol-form in a solution of CDCl$_3$ or CD$_2$Cl$_2$. More detailed NMR analysis showed that compound 252 consists of only one stereoisomer. Importantly, no response between either H$_x$ and H$_z$ or in the pair of H$_y$ with H$_z$ were observed in 1D NOE experiments (see experimental part). Strong NOE were detected for the CH$_2$-group of CO$_2$Et and H$_z$, and also between H$_x$, H$_y$ with $\beta$-Hs. These results confirm that 252 has a $2E,4E$-configuration as shown in scheme 5.4. Noteworthy, the synthesis of $\beta$-keto esters generally requires the hydrolysis of the phosphazines formed in the reaction of the nonacrylic acid chlorides with diazoacetate and further elimination of the NNH$_2$ group. In our case, this reaction offers a versatile approach to access porphyrin hydroxydienoates in just one-step.

5.3 Homologues of $\alpha,\beta$-unsaturated porphyrins

The reaction of acyl chlorides bearing $\alpha$-Hs with tertiary amines is an old and common method for the synthesis of ketenes 253 and is used often in cycloadditions and other reactions typical for ketenes. Our investigations were further encouraged by the fact that substituted vinyl ketenes can be formed in situ by dehydrohalogenation of $\alpha,\beta$-unsaturated acyl chlorides 254 and as unstable species; they can be activated and trapped (Scheme 5.5).
Strategically, the series of the next homologues of the acrylates 238-240 bearing CH₂ groups are essential to provide an access for a double bond migration. Therefore, precursor of ally porphyrin 255 and 256 were prepared from brominated porphyrins 153 and 257 with allyboronic acid pinacol ester using Suzuki cross-coupling reaction as described previously (Scheme 5.6).^{[246]}

Subsequent preparation of acrylate ester porphyrins was carried out using an cross-metathesis (CM) approach,^{[246]} followed by ester hydrolysis. It is noted that metathesis conditions have also been utilised for different porphyrin modifications due to their mild reaction conditions and high tolerance towards numerous functional groups.^{[247]} Allyl porphyrins 255, 256 were then reacted with the corresponding acrylate esters in the
presence of second generation Grubbs catalyst; 257. These reactions were performed in dichloromethane and afforded the corresponding esters 258-260 in 78% to 90% yields. Porphyrins 258 and 259 were subjected to Ni-metallation reactions to give porphyrin 261 and 262 before undergoing further transformations (Scheme 5.7).

Scheme 5.7 Synthesis of acrylic ester porphyrins 258-262.

Unexpectedly, the first attempt to hydrolyse the methyl ester 261 in KOH-EtOH resulted in the formation of a very polar compound, which was treated with HCl (1N) yielding 225 in 90% yield. The analytical data obtained were in accordance with the structure of a product prepared through Heck cross-coupling reaction. In order to avoid the basic conditions, an alternative approach for the synthesis of a porphyrin acrylic acid involving allyl porphyrin 255 and the acrylic acid in the presence of Grubbs II catalyst was considered. However, a test reaction gave the acrolein porphyrin 263 in 23% yield. Similar transformations of (allyl porphyrinato)nickel(II) complexes into porphyrinyl acroleins, albeit catalysed by Ni(OAc)2 were previously reported.\textsuperscript{[248]} Finally, the hydrolysis was successfully employed on porphyrin tert-butyl ester 262 in the presence of trifluoroacetic acid in dichloromethane, leading to the free acid porphyrin 265 in 95% (Scheme 5.8).
The corresponding acyl chloride generated from porphyrin 265 by treatment with SOCl$_2$ in THF, reacted with piperidine in the absence of NEt$_3$ to give porphyrin 244 in 41% yield (Scheme 5.9). Reaction of acyl chloride of 265 with MeOH and Hüning base, DIPEA (4 equivalent) led to the formation of porphyrin 239 in almost quantitative yield (95%). Analytical data for the porphyrins 244 and 239 prepared via these routes were in accordance with those derived for the compounds prepared using the alternative approach as shown in Scheme 5.2. The reaction pathway of porphyrin 265 to 239 and 244 seems to be similar to the one for the hydrolytic conversion of 261 into 225, where “elimination” of a CH$_2$ fragment was also observed. Assuming, that a vinylketene might be an intermediate of these transformations; different synthetic approach was made by use of a bulky soft base (DMAP) and the reactive propargyl alcohol. Indeed, the reaction of 265 with propargyl alcohol provided only the esterification product 266 in 57% yield. However, traces of rearrangement product 267 could be detected as well. In order to improve the yield of 267 and to confirm its structure, porphyrin 265 was alternatively treated with the mixture of EDAC/DMAP$^{[190]}$ in dichloromethane followed by addition of propargyl alcohol. Surprisingly, two regioisomeric products 266 and 267 were detected, with regioisomer 267
being the major product. Moreover, porphyrin 267 presented a mixture of stereoisomers in a ratio of 3:1, with an overall yield for the two stereomers of 81% (Scheme 5.9).

Scheme 5.9. Reactivity of porphyrin 265. Condition: a) i: SOCl₂, THF, +35°C
ii: RX, CH₂Cl₂; b) EDAC/DMAP, HC≡CCH₂OH, rt., CH₂Cl₂

¹H-NMR analysis confirmed the differences between 266 and 267 (Figure 5.2 and Figure 5.3). The signal for a double bond hydrogen atom H₃ in 267E was shifted to 8.76 ppm (doublet) compared to 5.83 ppm (doublet) for H₃ in 266. Likewise, the signals for the methylene hydrogen atoms, H₁ (5.48 ppm, doublet) and a double-bond hydrogen atom H₂ (7.92 ppm, doublet of triplets) in 266 were shifted towards higher field compared to 267E (methylen hydrogen atoms, H₁ appeared as doublet at 3.79 ppm and H₂, appeared at 6.17 ppm as doublet of triplet respectively. This confirms compound 267E to be a rearrangement product. An analysis of the ¹H NMR ¹J coupling constants of the CH=CH fragment in the stereomeric mixture 267 (J for E 15.2 Hz and for Z 11.3. Hz) revealed the
stereochemistry of the major product to be \( E \) (Figure 5.3). This major stereoisomer 267E was isolated in 59% yield.

**Figure 5.2** \(^1\)H-NMR spectrum of porphyrin 266 in CDCl\(_3\).

**Figure 5.3** \(^1\)H-NMR spectrum of porphyrin 277E in CDCl\(_3\).
Chapter 5: Reactivity of Acrylic Acid Porphyrins and Their Homologues

The formation of both regioisomers 266 and 267 under different reaction conditions suggests a competition of the two reaction pathways involving substitution and elimination processes. The vinyl ketene is the result of an elimination reaction causing a migration of the double bond and formation of 267. The observation of the \( E/Z \) mixture 267 suggests a pathway via a vinyl ketene intermediate where the original stereochemistry is lost. In contrast, the intermediate of the substitution reaction leading to the esterification product 266 is most likely a zwitterionic dienolate (Scheme 5.10).

![Scheme 5.10 Postulated mechanism for a) porphyrin 266 and b) porphyrin 267.](image)

5.4 C-C Coupling reactions

Enyne metathesis is a unique and interesting transformation involving the reaction between an alkene and an alkyne partner. Therefore, we used the enyne metathesis starting from propargyl ester porphyrin 245 and allyl porphyrins 255 and 278 to prepare synthetically useful 1,3-disubstituted butadiene porphyrin derivatives 279 and 280 (Scheme 5.11). Such compounds offer themselves towards structural elaboration via Diels–Alder and other cycloaddition reactions. We next compared the reactivity and chemoselectivity of both generations of Grubbs catalysts I 281 and II 227. Enyne metathesis of the porphyrin 245 and the allyl porphyrin 255 resulted only in the formation of 279, with \( E/Z = 3:2 \) in a good yield of 76%. Although the selectivity of the reaction of allyl porphyrinonickel 278 and 245 using the same catalyst was slightly improved to give \( E/Z = 2:1 \), compound 280 was isolated in 41% yield. In the case of Grubbs II catalyst, a
competing CM homodimerization of the allyl porphyrin 255 took place, resulting in a mixture of alkene 282 (31%, cis isomer) and the 1,3-disubstituted butadiene derivatives 279 (55%).

Scheme 5.11 Enyne metathesis of porphyrin 245 and allyl porphyrins 255, 278. Synthesis of 1,3-disubstituted butadienes 279 and 280.

The assignment of the stereochemistry of the 1,3-disubstituted butadienes 279 and 280 was based on NMR analyses involving 1D NOE, 2D-ROESY, HSQC, and HMBC experiments (see experimental part). For the major stereomer in the 280E/Z mixture, ROESY experiments showed a reliable correlation between Hx and Hb and between Hy and Hz. A strong response was found for each of the Hx–Hb and Hy–H2 pairs in 1D NOE as well. ROESY analysis of the minor isomer of 280 showed the appropriate correlations between Hx and H2 and between Hy and Hb. The stereochemistry of the minor product in 280 could be assigned as Z and the major one as the E-isomer as illustrated in Figure 5.4.
Similar results were obtained for the porphyrin 279. Thus, based on these analytical data, the major stereomer has $E$ stereochemistry in both mixtures of 279 and 280.

Figure 5.4. Assignments of the stereochemistry for 1,3-disubstituted butadienes 279 and 280.

5.5 Conclusions

Based on acrylic porphyrins and their homologues, a new synthetic approach has been developed for multifunctional porphyrins. Our studies show that the acyl chlorides 242 and 243 generated in situ can be easily converted into the corresponding acyl derivatives using simple nucleophiles. The reaction of 242 with ethyl diazoacetate via the unstable phosphazine 250 represents a convenient entry into the important class of $\beta$-keto esters 252. It was shown that the phosphazine 242 was self-converted into the $\beta$-keto ester, possibly via intermediate 251. Interestingly, compound 252 exists only as the enol form in halogenated solvents, and its stereochemistry was assigned as the $2E,4E$-configuration. The next homologues 265 of the acrylic porphyrins can undergo rearrangement via vinyl ketenes under basic conditions to yield both regioisomers 266 and 267. Variation of the reaction conditions regioselectively provides access to either a rearrangement (267, 81%) or an esterification product (266, 57%). Finally, enyne metathesis of the novel propargyl esters with allyl porphyrins provided an easy access to 1,3-disubstituted butadienes 279 and 280 in up to 76% yield. Porphyrin arrays can be constructed using cycloaddition reactions based on the dimeric porphyrins 279–280, 282 presented. The syntheses described provide access to novel porphyrins and expand the repertoire of porphyrin based reagents to be utilised for the further functionalisation of the porphyrin periphery. They can serve as versatile building blocks for the facile transformation into porphyrin bioconjugates such as amino and hydroxy acid derivatives, especially, for medicinal applications.
EXPERIMENTAL
6.1 Instrumentations and general methods

All chemicals used were of analytical grade and were purchased from Aldrich Co. unless stated otherwise. Dichloromethane was dried over phosphorus pentoxide followed by distillation; THF was dried over sodium followed by distillation. All condensation reactions were performed under an argon atmosphere with the reaction flask shielded from ambient light. Melting points were acquired on Stuart SMP10 melting point apparatus and are uncorrected. Silica gel 60 (Merck or Machery & Nagel) was used for column chromatography. Flash chromatography was carried out using Fluka Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 plates (precoated sheets, 0.2 mm thick, with and without fluorescence indicator F$_{254}$).

NMR spectra were recorded on a Bruker DPX 400 (400.13 MHz for $^1$H NMR and 100.61 MHz for $^{13}$C-NMR) and/or Bruker AV 600 (600.13 MHz for $^1$H-NMR and 150.90 MHz for $^{13}$C-NMR). NOE, ROESY, HMBC and HSQC NMR spectra were recorded using Bruker AV 600. Chemical shifts are reported in ppm referenced to tetramethylsilane set at 0.00 ppm unless stated otherwise. UV–vis measurements were performed on Shimadzu MultiSpec-1501 spectrometer using dichloromethane as solvent. Mass spectra were recorded using a Varian MAT 711 or MAT 112 S mass spectrometer using the EI technique with direct insertion probe and excitation energy of 80 eV. HRMS spectra were measured on Micromass/ Waters Corp. USA LCT time-of-flight spectrometer equipped with ES source and MALDI Q-TOF spectrometer with α-cyano-4-hydroxycinnamic acid (CHCA) as the matrix.
6.2 Synthesis of porphyrin precursors

Dipyrromethane 29 and 105 were prepared as reported in the literature.\(^{[34]}\) Spectroscopic data for meso-disubstituted porphyrins 99, 100, 101, 102 and 103 were in accordance to the literature\(^{[67e,67f,250,251,252]}\) and were prepared using mixed condensation reactions. Porphyrin 107 formed as the second product from mixed condensation reaction was reported previously.\(^{[253]}\) RLi reaction conditions were used to prepare porphyrins 108, 109 and 110 as reported in literature.\(^{[67a,67e]}\) Dithianyl porphyrin 112 was prepared according to method developed by Senge et al.\(^{[158]}\)

5-Hexyl-15-phenylporphyrin (104)

Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane 209 (1.2 g, 8.2 mmol), benzaldehyde (0.46 mL, 4.6 mmol), and heptanal (0.64 mL, 4.6 mmol) were added. The flask was shielded from ambient light and then 140 mL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 hours at room temperature. After this time, 2.77 g (12.2 mmol) of DDQ, suspended in 100 mL of dry dichloromethane were added, and the mixture was stirred for 1 hour. Then, 6 mL of triethylamine were added and the reaction mixture was concentrated in vacuo to about 200 mL. The reaction mixture was filtered through 500 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrins were separated by column chromatography on silica using dichloromethane/hexane (1:1, v/v) as eluent. The first fraction was 5,15-dihexylporphyrin 101 (45 mg, 0.09 mmol, 4%), the second fraction, 5-hexyl-15-phenylporphyrin 104 (189 mg, 0.40 mmol, 14%) and the third fraction, 5,15-diphenylporphyrin 99 (65 mg, 0.14 mmol, 6%). Porphyrin 104 were redissolved/suspended in dichloromethane and then layered with a 2–3-fold excess of methanol. After 24 h, the solution was filtered through D3 frit leaving behind purple crystals. Title compound: mp >310 °C ; Rf=0.86 (SiO2, CH2Cl2/C6H14, 3:1, v/v); \(^1\)H NMR (400 MHz, CDCl3): \(\delta= -3.08\) (s, 2H, N-H), 1.05 (t,
Chapter 6: Experimental

$J=7.6$ Hz, 3H, -$CH_3$), 1.48 (m, 2H, -$CH_2$), 1.51 (m, 2H, -$CH_2$), 1.86 (m, 2H, -$CH_2$), 2.58 (m, 2H, -$CH_2$), 4.96 (s, $J=8.0$ Hz, 2H, -$CH_2$), 7.89 (m, 3H, phenyl-$H$), 8.33 (m, 2H, phenyl-$H$), 9.12 (d, $J=4.5$ Hz, 2H, $\beta$-$H$), 9.38 (d, $J=4.5$ Hz, 4H, $\beta$-$H$), 9.56 (d, $J=7.6$ Hz, 2H, $\beta$-$H$), 10.19 ppm (s, 2H, meso-$H$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta=13.8, 22.4, 29.9, 31.5, 34.3, 38.4, 104.3, 117.9, 126.6, 127.5, 130.3, 131.3, 134.5, 141.0, 144.3, 147.0$ ppm; UV/vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log e) = 408 (4.55), 427 (4.74), 503 (2.90), 539 (3.13), 573 (3.39), 620 nm (3.33); HRMS (ES+) [C$_{32}$H$_{30}$N$_4$]: calcd for [M+H]$^+$ 471.2549, found 471.2553.

5,10,15-Tris(1-ethylpropyl)porphyrin (106)

![Image of 5,10,15-Tris(1-ethylpropyl)porphyrin](image)

The reaction was performed using the same conditions as for the preparation of 104 using dipyrromethane 29 (1.2 g, 8.2 mmol), 5-(1-ethylpropyl)dipyrromethane 105 (1.2 g, 4.1 mmol) and 2-ethylbutyraldehyde (2.02 mL, 16.4 mmol). The first fraction was 5,15-bis(1-ethylpropyl)porphyrin 102 (152 mg, 0.34 mmol, 14%), the second fraction, 5,10,15-tris(1-ethylpropyl)porphyrin 106 (213 mg, 0.41 mmol, 20%) and the third fraction, 5,10,15,20-tetrakis(1-ethylpropyl)porphyrin 107 (97 mg, 0.16 mmol, 8%). Title compound: mp >310 ºC; Rf=0.49 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 1:1, v/v); $^1$H NMR (400 MHz, CDCl$_3$): $\delta=-2.67$ (s, 2H, N-$H$), 0.99 (m, 18H, -CH(CH$_2$CH$_3$)$_2$), 2.84 (m, 12H, -CH(CH$_2$CH$_3$)$_2$), 5.02 (m, 2H, -CH(CH$_2$CH$_3$)$_2$), 5.19 (m, 1H, -CH$_2$(CH$_2$CH$_3$)$_2$), 9.31 (d, $J=4.7$ Hz, 2H, $\beta$-$H$), 9.61 (s, 4H, $\beta$-$H$), 9.70 (s, 2H, $\beta$-$H$), 9.98 ppm (s, 1H, meso-$H$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta=14.0, 34.6, 49.7, 102.5, 127.9, 128.5, 129.2, 130.8$ ppm; UV/vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log e) = 412 (4.77), 433 (4.38), 512 (3.44), 546 (3.18), 588 (3.28), 642 nm (3.29); HRMS (ES+) [C$_{35}$H$_{38}$N$_4$]: calcd for [M+H]$^+$ 521.3644, found 521.3645.
5-Hexyl-10,20-diphenylporphyrin (108)

5,15-Diphenylporphyrin 99 (220 mg, 0.47 mmol) was dissolved in 40 mL of dry THF and cooled to -78 °C. n-Hexyllithium (1.7 mL of a 2.5 M solution in hexane, 3.4 mmol) was subsequently added dropwise under an argon atmosphere. The colour of the mixture changed from deep purple to brown within 30 minutes. The reaction mixture was stirred for 5 hours and monitored by TLC. Water (2 mL) was added for hydrolysis. After stirring of the mixture for 20 minutes, a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 1.6 mmol) was added and the reaction mixture was stirred for another 1 hour at room temperature. The mixture was filtered through silica gel and the organic solvent was removed under vacuum. Final purification was achieved by column chromatography using silica gel and ethyl acetate/n-hexane (1:7, v/v) as eluent; yielding the title compound 108 (175 mg, 0.32 mmol, 67%) as a purple solid, mp >310 °C; Rf=0.61 (SiO2, CH2Cl2/C6H14, 1:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -3.02 (s, 2H, NH), 0.90 (t, J=7.6 Hz, 3H, -CH3), 1.38 (m, 2H, -CH2), 1.54 (m, 2H, -CH2), 1.80 (m, 2H, -CH2), 2.53 (m, 2H, -CH2), 5.06 (t, J=8.2 Hz, 2H, -CH2), 7.78 (m, 6H, phenyl-H), 8.23 (d, J=8.2 Hz, 4H, phenyl-H), 8.95 (m, 4H, β-H), 9.25 (d, J=5.0 Hz, 2H, β-H), 9.54 (d, J=5.0 Hz, 2H, β-H), 10.08 pm (s, 1H, meso-H); 13C NMR (100 MHz, CDCl3): δ= 16.4, 22.4, 28.0, 29.9, 31.5, 39.8, 119.7, 122.1, 127.2, 128.2, 134.2, 151.3 ppm; UV/vis (CH2Cl2): λmax (log ε)= 425 (4.17), 503 (3.74), 526 (3.68), 573 (3.69), 620 nm (3.69); HRMS (ES+) [C36H46N4]: calcd for [M+H]+ 546.2783, found 546.2771.

6.3 Synthesis of dithianyl porphyrins and their derivatives.

General Procedure: A dried out, septum-equipped Schlenk-flask under argon was charged with 1,3-dithiane (1.16, 9.64 mmol). The flask was evacuated for 30 min with an oil pump and 25 mL of freshly distilled THF was added. The solution was cooled to -40 °C and butyllithium (3.84 mL of a 2.5 M solution, 9.6 mmol) was added drop-wise via a syringe through the septum. The reaction mixture was stirred for 2 h at -30 to -40 °C. The solution of the organometallic compound was cooled to -78 °C and mixed with a
Chapter 6: Experimental

suspension (-78 °C) of 0.45 mmol porphyrin in 20 mL of absolute THF. After transfer of the porphyrin suspension, \(N,N,N,N\)-tetramethylethlenediamine (0.25 mL, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 1 min the cold bath was removed and the reaction mixture was stirred for 15 min. Water (6 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 min at room temperature, followed by addition of 10 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF) resulting in a colour change to purple. Stirring was continued for 15 min followed by filtration of the reaction mixture through 200 mL silica, washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and washed with \(n\)-hexane (2 \(\times\) 10 mL). The residue was purified by column chromatography on silica gel in dichloromethane/\(n\)-hexane (3:1, v/v).

5-(1,3-Dithian-2-yl)-10,20-diphenylporphyrin (111)

Prepared from porphyrin 99: Yield: 0.11 g (0.207 mmol, 45%) of purple crystals, mp 295 °C; \(R_f=0.23\) (SiO\(_2\), CH\(_2\)Cl\(_2\)/C\(_6\)H\(_{14}\), 3:1, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta = -3.03\) (s, 2H, NH), 2.53 (m, 2H, -CH\(_2\)), 3.31 (m, 2H, S-CH\(_2\)), 3.63 (m, 2H, S-CH\(_2\)), 7.78 (m, 6H, phenyl-H), 7.87 (s, 1H, -CH), 8.21 (m, 4H, phenyl-H), 8.92 (m, 4H, \(\beta\)-H), 9.25 (d, \(J = 4.6\) Hz, 2H, \(\beta\)-H), 9.71 (s, br., 1H, \(\beta\)-H), 10.12 (s, 1H, meso-H), 10.71 ppm (s, br., 1H, \(\beta\)-H); \(^{13}\)C NMR (600 MHz, CDCl\(_3\)): \(\delta = 26.21, 35.87, 54.51, 105.74, 114.53, 126.74, 127.77, 132.0, 134.60, 141.90\) ppm; UV/vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (log \(\varepsilon\))= 416 (5.49), 512 (4.02), 544 (3.23), 586 (3.45), 640 nm (2.72); MS (EI, 80 eV), \(m/z\) (%): 580 (100) [M\(^+\)], 519 (33) [M\(^+\)-C\(_2\)H\(_2\)S], 506 (62) [M\(^+\)-C\(_3\)H\(_4\)S], 476 (86) [M\(^+\)-C\(_3\)H\(_4\)S\(_2\)], 462 (17) [M\(^+\)-C\(_4\)H\(_6\)S\(_2\)], 290 (8) [M\(^2+\)]; HRMS (ES+) [C\(_36\)H\(_{28}\)N\(_4\)S\(_2\)]: calcd for [M] 580.1755, found 580.1772.

Deprotection of the Dithian-2-ylporphyrins

To a solution of dithian-2-ylporphyrin (0.06 mmol) in dichloromethane (60 mL) DDQ (500 mg, 2.20 mmol) and BF\(_3\)•Et\(_2\)O (0.5 mL, 9.95 mmol) were added and the colour of the red solution changed over yellow to green. After stirring for 45 min the reaction was quenched by the addition of aqueous sodium hydrogen carbonate. The organic phase was washed
several times with a saturated solution of sodium hydrogen carbonate, followed by drying over anhydrous sodium sulfate and evaporation of the solvent in vacuum. After filtration through silica gel and recrystallisation from dichloromethane/methanol the pure product could be obtained.

5-Formyl-10,20-diphenylporphyrin (115)

Prepared from porphyrin 111; Yield: 12 mg (0.03 mmol, 39%) of purple crystals: mp > 310 °C; Rf=0.53 (SiO2, CH2Cl2/C6H14, 2:1, v/v); 1H NMR (600 MHz, CDCl3, TMS): δ= -2.47 (s, 2H, NH), 7.79 (m, 6H, phenyl-H), 8.18 (dd, 4H, J = 6.0 Hz, J = 1.5 Hz, phenyl-H), 8.87 (d, 2H, J = 4.5 Hz, β-H), 9.04 (d, 2H, J = 4.9 Hz, β-H), 9.27 (d, 2H, J = 4.5 Hz, β-H), 10.07 (br. s, 2H, β-H), 10.25 (s, 1H, meso-H), 12.58 ppm (s, 1H, CO); 13C NMR (600 MHz, CDCl3): δ = 108.1, 109.9, 122.1, 124.9, 126.9, 127.8, 128.1, 128.6, 130.2, 131.2, 133.9, 134.4, 141.2, 195.2 ppm; UV/vis (CH2Cl2): λmax (log ε) = 41 (5.49), 508 (3.95), 561 (3.47), 581 (3.56), 647 nm (3.30); MS (80 eV): m/z (%) = 490 (23) [M]+, 462 (6) [M]+-CO, 245 (16) [M]+2; HRMS (ES+) [C33H22N4O]: calcd for [M+H]+ 491.1872, found 491.1885.

5-Formyl-15-pentyl-10,20-diphenylporphyrin (116)

1,3-Dithiane (0.58 g, 4.82 mmol) was placed in a dried, septum-equipped Schlenk flask under argon. The flask was evacuated for 30 minutes, followed by introducing argon and charged with 25 ml of freshly distilled THF. The solution was cooled to -40 °C and n-butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added dropwise via a syringe through the septum. The reaction mixture was stirred for 30-40 minutes at -30 to -40 °C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin 99 (100 mg, 0.22 mmol) in 20 mL of THF.
After transfer of the porphyrin suspension, \(N,N,N',N'\)-tetramethylethylendiamine (0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. The solution was treated with 0.7 mL (0.42 mmol) of \(n\)-pentyl iodide and stirred for 2 days. Water (3 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was allowed to continue for 15 minutes followed by filtration of the mixture through 200 mL silica with washing with dichloromethane. The eluted porphyrins were evaporated to dryness and further purified by column chromatography on silica gel using dichloromethane/\(n\)-hexane (2:1, v/v) as eluent yielding the compound (13.55 mg, 0.02 mmol, 11%) as purple solid: mp >310 °C; \(R_f\) = 0.87 (SiO\(_2\), CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta = -1.81\) (s, 2H, NH), 0.98 (t, 3H, \(J = 7.6\) Hz, -CH\(_3\)), 1.55 (m, 2H, -CH\(_2\)), 1.77 (m, 2H, -CH\(_2\)), 2.50 (m, 2H, -CH\(_2\)), 4.88 (t, \(J = 8.2\) Hz, 2H, -CH\(_2\)), 7.79 (m, 6H, phenyl-H), 8.16 (d, 4H, \(J = 7.0\) Hz, phenyl-H), 8.75 (d, 2H, \(J = 4.7\) Hz, \(\beta\)-H), 8.90 (d, 2H, \(J = 4.7\) Hz, \(\beta\)-H), 9.37 (d, 2H, \(J = 4.7\) Hz, \(\beta\)-H), 9.94 (d, 2H, \(J = 5.2\) Hz, \(\beta\)-H), 12.41 ppm (s, 1H, CHO); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 13.7, 22.3, 29.3, 31.5, 38.0, 126.3, 127.4, 129.8, 133.7, 141.3, 194.0\) ppm; UV/vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (log \(\varepsilon\)) = 422 (4.91), 441 (4.99), 523 (4.12), 563 (4.13), 592 (4.13), 652 nm (4.15); HRMS (ES+) [C\(_{38}\)H\(_{33}\)N\(_4\)O]: calcd for [M+H]\(^+\) 561.2665, found 561.2654.

5-Formyl-10-hexyl-20-phenylporphyrin (117)

1,3-Dithiane (0.58 g, 4.82 mmol) was placed in a dried, septum-equipped Schlenk flask under argon. The flask was evacuated for 30 minutes, followed by introducing argon and charged with 25 ml of freshly distilled THF. The solution was cooled to -40 °C and \(n\)-butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added dropwise via a syringe through the septum. The reaction mixture was stirred for 30-40 minutes at -30 to -40° C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin 99 (100 mg, 0.22 mmol) in 20 mL of THF.
After transfer of the porphyrin suspension, $N,N,N',N'$-tetramethylethylendiamine (0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. The solution was treated with 0.7 mL (0.42 mmol) of $n$-pentyl iodide and stirred for 2 days. Water (3 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was allowed to continue for 15 minutes followed by filtration of the mixture through 200 mL silica with washing with dichloromethane. The eluted porphyrins were evaporated to dryness and further purified by column chromatography on silica gel using dichloromethane/n-hexane (2:1, v/v) as eluent yielding the compound (13.55 mg, 0.02 mmol, 11 %) as purple solid: mp >310 °C; Rf=0.87 (SiO$_2$, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$= -1.81 (s, 2H, NH), 0.98 (t, 3H, $J = 7.6$ Hz, $-CH_3$), 1.55 (m, 2H, $-CH_2$), 1.77 (m, 2H, $-CH_2$), 2.50 (m, 2H, $-CH_2$), 4.88 (t, $J = 8.2$ Hz, 2H, $-CH_2$), 7.79 (m, 6H, phenyl-$H$), 8.16 (d, 4H, $J = 7.0$ Hz, phenyl-$H$), 8.75 (d, 2H, $J = 4.7$ Hz, $\beta$-$H$), 8.90 (d, 2H, $J = 4.7$ Hz, $\beta$-$H$), 9.37 (d, 2H, $J = 4.7$ Hz, $\beta$-$H$), 9.94 (d, 2H, $J = 5.2$ Hz, $\beta$-$H$), 12.41 ppm (s, 1H, CHO); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$= 13.7, 22.3, 29.3, 31.5, 38.0, 126.3, 127.4, 129.8, 133.7, 141.3, 194.0 ppm; UV/vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 422 (4.91), 441 (4.99), 523 (4.12), 563 (4.13), 592 (4.13), 652 nm (4.15); HRMS (ES$^+$) [C$_{38}$H$_{33}$N$_4$O]: calcd for [M+H]$^+$ 561.2665, found 561.2654.

### 6.4 Synthesis of spirobisdithianyl-porphyrins

5,15-Diphenyl-10-(spirobis-1,3-dithian-2-yl)porphyrin (124)

Spirobisdithiane (1.08 g, 4.84 mmol) was dried in vacuo in a septum equipped Schlenk flask for 30 minutes. Dry THF (20 ml) was then added under argon and the suspension cooled to −40 °C. $n$-Butyllithium (1.92 mL of a 2.5 M solution, 4.84 mmol) was added drop-wise via a syringe through the septum and the reaction mixture was stirred for 2 hours.
at −25 °C. The solution of the organometallic compound was cooled to −78 °C and mixed with a suspension (−30 °C) of 5,15-diphenylporphyrin 99 (100 mg, 0.22 mmol) in 20 mL of dry THF. After transfer of the porphyrin suspension, \(N,N,N',N'\)-tetramethylethylendiamine (0.2 mL, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. Upon addition of 3 mL water, the reaction mixture changed its colour to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was continued for a further 15 minutes and the organic solvent was removed under reduced pressure. Final purification was achieved by column chromatography in the dark and eluting with ethyl acetate/hexane (1:20, v/v) to yield the title compound (33 mg, 0.05 mmol, 22%) as a purple solid: mp >310 °C; \(R_f=0.76\) (SiO\(_2\), CH\(_2\)Cl\(_2\)/C\(_6\)H\(_{14}\), 2:1, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta=−3.04\) (s, 2H, NH), 3.38 (d, 2H, \(J=14.7\) Hz, S-CH\(_2\)-S), 3.65 (m, 8H, S-CH\(_2\)), 7.71 (s, 1H, S-C//(−S)), 7.76 (m, 6H, phenyl-H), 8.18 (d, 4H, \(J=6.4\) Hz, phenyl-H), 8.92 (dd, 4H, \(J=4.7\) Hz, \(\beta\)-H), 9.25 (d, 2H, \(J=4.7\) Hz, \(\beta\)-H), 9.53 (s, 1H, \(\beta\)-H), 10.13 (s, 1H, meso-H), 10.55 ppm (s, 1H, \(\beta\)-H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=24.0, 31.8, 35.1, 41.5, 55.0, 105.5, 112.7, 126.3, 127.4, 134.2, 141.4\) ppm; UV/vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (log \(\varepsilon\)) = 415 (4.42), 511 (3.54), 549 (3.39), 586 (3.42), 638 nm (3.34); HRMS (ES+) \([\text{C}_{39}\text{H}_{32}\text{N}_{4}\text{S}_{4}]^+\): calcd for \([\text{M}+\text{H}]^+\) 685.1588, found 685.1578.

\[5,15\text{-Diphenyl-10-(spirobis-1,3-dithian-2-yl)porphyrinato} \text{nickel(II)}\] (134)

The reaction was performed using the same conditions as given for free base 124 using spirobisdithiane (0.89 g, 4.01 mmol), \(n\)-butyllithium (1.59 mL of a 2.5 M solution, 4.0 mmol) and \[5,15\text{-diphenylporphyrinato} \text{nickel(II)}\] 125 (100 mg, 0.18 mmol). The mixture was purified by column chromatography with dichloromethane/hexane (1:1, v/v) as eluent and yielded the title compound (45 mg, 0.06 mmol, 33%) as a red solid: mp >310 °C; \(R_f=0.82\) (SiO\(_2\), CH\(_2\)Cl\(_2\)/C\(_6\)H\(_{14}\), 3:1, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta=3.31\)
(d, 2H, $J = 14.0$ Hz, S-CH$_2$-S), 3.67 (m, 8H, S-CH$_2$), 7.08 (s, 1H, S-CH-S), 7.68 (m, 6H, phenyl-H), 7.95 (d, 4H, $J = 6.4$ Hz, phenyl-H), 8.77 (m, 4H, $J = 4.7$ Hz, $\beta$-H), 9.02 (d, 2H, $J = 4.7$ Hz, $\beta$-H), 9.66 (s, 1H, meso-H), 9.77 ppm (s, 2H, $\beta$-H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ = 22.3, 27.4, 29.3, 36.7, 52.8, 104.8, 126.7, 127.4, 132.1, 132.4, 133.2, 140.0, 141.5, 141.8, 142.2 ppm; UV/vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 413 (5.52), 530 (4.34), 569 nm (3.84).

[5,15-Bis(3-methoxyphenyl)-10-(spirobis-1,3-dithian-2-yl)porphyrinato]nickel(II) (135)

The reaction was performed using the same conditions as given for the free base 124 using spirobisdithiane (0.85 g, 3.81 mmol), n-butyllithium (1.51 mL of a 2.5 M solution, 3.81 mmol) and [5,15-bis(3-methoxyphenyl)porphyrinato]nickel(II) 126 (100 mg, 0.17 mmol). The mixture was purified by column chromatography with dichloromethane/ n-hexane (1:1, v/v) as eluent and yielded the title compound (47 mg, 0.06 mmol, 34 %) as a red solid: mp >310 °C; R$_f$=0.45 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 3:1, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ = 3.33 (d, 2H, $J = 14.0$ Hz, S-CH$_2$-S), 3.74 (m, 8H, S-CH$_2$), 3.92 (s, 6H, -OCH$_3$), 7.09 (s, 1H, S-CH-S), 7.57 (m, 8H, phenyl-H), 8.82 (m, 4H, $\beta$-H), 9.03 (d, 2H, $J = 4.1$ Hz, $\beta$-H), 9.67 (s, 1H, meso-H), 9.77 ppm (s, 2H, $\beta$-H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ = 22.3, 29.3, 31.6, 38.1, 55.0, 104.8, 113.2, 119.1, 126.2, 127.4, 130.5, 132.1, 140.5, 141.3, 141.3, 141.9, 157.7 ppm; UV/vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 414 (4.96), 530 (3.78), 567 nm (3.48).
The reaction was performed using the same conditions as given for free base 124 using spirobisdithiane (0.92 g, 4.11 mmol), n-butyllithium (1.63 mL of a 2.5 M solution, 4.11 mmol) and [5,15-dihexylporphyrinato]nickel(II) 127 (100 mg, 0.19 mmol). The mixture was purified by column chromatography with dichloromethane/n-hexane (1:1, v/v) as eluent and yielded the title compound (28 mg, 0.02 mmol, 19 %) as a red solid: mp >310 °C; Rf=0.67 (SiO2, CH2Cl2/C6H14, 3:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 0.91 (t, 3H, J = 7.0 Hz, -CH3), 1.32 (m, 2H, -CH2), 1.34 (m, 2H, -CH2), 1.58 (m, 2H, -CH2), 2.27 (m, 2H, -CH2), 3.26 (d, 2H, J = 14.0 Hz, S-CH2-S), 4.49 (t, 2H, J = 7.6 Hz, -CH2), 4.80 (m, 8H, S-CH2), 6.95 (s, 1H, S-CH-S), 9.03 (d, 2H, J = 4.7 Hz, β-H), 9.26 (dd, 4H, J = 5.28 Hz, β-H), 9.45 (s, 1H, meso-H), 9.75 ppm (s, 2H, β-H); 13C-NMR (100 MHz, CDCl3): δ= 13.8, 22.3, 23.8, 24.3, 29.7, 31.3, 33.6, 35.1, 37.1, 38.8, 41.5, 43.4, 53.1, 103.8, 117.5, 120.9, 129.4, 129.7, 132.2, 139.3, 140.6, 141.0, 142.0 ppm; UV/vis (CH2Cl2): λmax (log ε) = 416 (4.98), 535 (3.70), 568 nm (3.48).

[5,15-Dihexyl-10-(spirobis-1,3-dithian-2-yl)porphyrinato]nickel(II) (136)


The reaction was performed using the same conditions as given for free base 124 using spirobisdithiane (0.82 g, 3.65 mmol), n-butyllithium (1.45 mL of a 2.5 M solution, 3.65 mmol) and [5-hexyl-10,20-diphenylporphyrinato]nickel(II) 135 (100 mg, 0.17 mmol). The mixture was purified by column chromatography with dichloromethane/n-hexane (2:1, v/v) as eluent and yielded the title compound (54 mg, 0.06 mmol, 40 %) as a red solid: mp
>310 °C; Rf=0.78 (SiO2, CH2Cl2/C6H14, 3:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 0.85 (t, 3H, J = 7.6 Hz, -CH3), 1.36 (m, 2H, -CH2), 1.55 (m, 2H, -CH2), 2.39 (m, 2H, -CH2), 2.61 (m, 2H, -CH2), 3.14 (d, 2H, J = 14.6 Hz, S-CH2-S), 3.59 (m, 8H, S-CH2), 4.46 (t, 2H, J = 7.6 Hz, -CH2), 6.88 (s, 1H, S-CH-S), 7.65 (m, 6H, phenyl-H), 7.91 (d, 4H, J = 6.4 Hz, phenyl-H), 8.67 (dd, 4H, J = 4.7 Hz, β-H), 9.18 (d, 2H, J = 4.7 Hz, β-H), 9.62 ppm (s, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ = 13.7, 22.2, 23.8, 24.3, 29.3, 31.6, 33.6, 37.0, 38.0, 52.9, 109.6, 118.0, 119.6, 126.5, 127.3, 129.6, 132.0, 132.5, 133.1, 139.9, 140.7, 140.8, 141.4, 141.5 ppm; UV/vis (CH2Cl2): λmax (log ε) = 421 (4.95), 539 (4.01), 577 nm (3.79).

[5-(Hydroxypentyl)-10,20-diphenylporphyrinato]Ni(II) (140)

The reaction was performed using the same conditions as given for free base 124 using spirobisdithiane (0.82 g, 3.65 mmol), n-butyllithium (1.45 mL of a 2.5 M solution, 3.65 mmol) and [5-formyl-10,20-diphenylporphyrinato]Ni(II) 139 (100 mg, 0.18 mmol). The mixture was purified by column chromatography with dichloromethane/n-hexane (2:1, v/v) as eluent and yielded the title compound (7 mg, 6%) as a red solid: mp >310 °C; Rf=0.85 (SiO2, CH2Cl2/C6H14, 3:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 1.04 (t, 3H, J = 3.5 Hz, -CH3), 1.41 (s, 1H, -CH-OH), 1.59 (m, 2H, -CH2), 2.31 (m, 2H, -CH2), 3.47 (d, J = 5.2 Hz, 1H, -OH), 4.66 (m, 2H, -CH2), 7.67 (m, 6H, phenyl-H), 8.01 (m, 4H, phenyl-H), 8.44 (d, 1H, J = 4.7 Hz, β-H), 8.81 (d, 3H, J = 4.7 Hz, β-H), 9.05 (d, 2H, J = 5.2 Hz, β-H), 9.35 (m, 2H, β-H), 9.69 ppm (s, 1H, meso-H); 13C NMR (600 MHz, CDCl3): δ = 13.62, 23.01, 29.27, 33.77, 39.28, 103.41, 117.52, 118.80, 126.42, 127.24, 128.95, 131.55, 131.92, 132.11, 133.28, 140.51, 141.59, 142.33 ppm; UV/vis (CH2Cl2): λmax (log ε) = 421 (4.95), 535 (4.00), 567 nm (3.48).
2,8-Diformylspirobisdithiane(141)

Spirobisdithiane 119 (1.00 g, 4.40 mmol) was dried in vacuo in a septum equipped Schlenk flask for 30 minutes. Dry THF (25 ml) was then added under argon and the suspension cooled to -78 °C. n-Butyllithium (9.9 mL of a 2.5 M solution, 15.99 mmol) was added drop-wise via a syringe through the septum and the reaction mixture was stirred for 2 hours at -25 °C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-10 °C) of dimethylformamide (10 mL). The solution was stirred for 2 hours at -10 °C and the colour turned to light yellow. The solution was then stored in freezer for overnight. For work-up, the solution was poured into ice and the aqueous phase was extract with hexane. The aqueous phase was then neutralised with 1M HCL solution before extraction with dichloromethane for the second time. The organic phase was dried over MgSO₄ and the organic solvent was removed under vacuum. The remaining yellow oil was recrystallised from n-hexane:dichloromethane and gave the title compound (0.70 g, 2.49 mmol, 56 %) as a yellow solid; mp 165 °C: ¹H NMR (400 MHz, CDCl₃, TMS) : δ= 2.86 (s, 4H, -S-CH₄), 2.94 (s, 4H, -S-CH₂-), 4.03 (s, 2H, -S-CH₂-S-), 9.39 ppm (s, 2H, -CHO); ¹³C NMR (100 MHz, CDCl₃): δ= 29.7, 31.0, 36.1, 46.6, 186.9 ppm.

6.5 Synthesis of trithianyl-porphyrins

5,15-Diphenyl-10-(1,3,5-trithian-2-yl)porphyrin (142)

n-Butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added under argon atmosphere to a 100 mL Schlenk flask charged with a solution of 1,3,5-trithiane (0.67, 4.84 mmol) in 20 ml dry THF at -40 °C. Then, the reaction mixture was stirred for 2.5 hours at 20°C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin 99 (100 mg, 0.22 mmol) in 20 mL of THF. After transferring the porphyrin suspension, N,N,N',N'-tetramethylethylendiamine
(0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes the cold bath was removed and the reaction mixture was stirred for a further hour at room temperature. Subsequently, water (3 mL) was added for hydrolysis. The mixture was stirred for another 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change to purple. Stirring was continued for another 15 minutes and the organic solvent was removed under vacuum. Final purification was achieved by column chromatography under dark conditions and eluting with ethyl acetate/n-hexane (1:20, v/v) yielded the title compound (24 mg, 0.04 mmol, 18 %) as a purple solid: mp >310 °C; Rf=0.83 (SiO2, CH2Cl2/C6H14, 3:1, v/v); 1H-NMR (400 MHz, CDCl3, TMS): δ= -3.06 (s, 2H, NH), 4.36 (d, 2H, J = 14.6 Hz, S-CH2-S), 5.06 (d, 2H, J = 14.6 Hz, S-CH2), 7.78 (m, 6H, phenyl-H), 7.94 (s, 1H, S-CH-S), 8.18 (d, 4H, J = 7.0 Hz, phenyl-H), 8.91 (d, 4H, J = 15.2 Hz, β-H), 9.25 (s, 2H, β-H), 9.52 (s, 1H, β-H), 10.13 (s, 1H, meso-H), 10.50 ppm (s, 1H, β-H); 13C NMR (100 MHz, CDCl3): δ= 30.5, 40.9, 57.7, 105.6, 113.3, 126.4, 127.4, 134.2, 141.3 ppm; UV/vis (CH2Cl2): λmax (log ε) = 415 (4.25), 512 (3.52), 548 (3.42), 587 (3.43), 640 nm(3.39); HRMS (ES+) [C39H32N4S4]: calcd for [M+H] 599.1398, found 599.1411.

[5,15-Diphenyl-10-(1,3,5-trithian-2-yl)porphyrinato]nickel(II) (143)

The reaction was performed using the same conditions as for free base 142 using 1,3,5-trithiane (0.55 g, 4.01 mmol), n-butyllithium (1.60 mL of a 2.5 M solution, 4.0 mmol) and [5,15-diphenylporphyrinato]nickel(II) 125 (100 mg, 0.18 mmol). Elution with dichloromethane/n-hexane (1:1, v/v) yielded the title compound (46 mg, 0.07 mmol, 38 %) as a purple solid: mp > 310 °C; Rf=0.89 (SiO2, CH2Cl2/C6H14, 2:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 4.27 (d, J = 15.2 Hz, 2H, S-CH2-S), 4.92 (d, 2H, J = 14.6 Hz, S-CH2-S), 7.30 (s, 1H, S-CH-S), 7.68 (m, 6H, phenyl-H), 7.95 (d, 4H, J = 6.4 Hz, phenyl-H), 8.77 (m, 4H, J = 4.7 Hz, β-H), 9.02 (d, 2H, J = 4.7 Hz, β-H), 9.67 (s, 1H, meso-H), 9.72 ppm (s, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ= 35.0, 40.3, 56.0, 102.6, 104.9, 126.5, 127.4, 132.1, 132.2, 133.2, 139.9, 141.6, 141.8, 142.3 ppm; UV/vis (CH2Cl2): λmax (log ε) = 413 (5.73), 530 (4.54), 565 nm(4.11).
5,15-Bis[3-methoxyphenyl-10-(1,3,5-trithian-2-yl)]porphyrinato|nickel(II) (144)

The reaction was performed using the same conditions as for free base 142 using 1,3,5-trithiane (0.53 g, 3.80 mmol), n-butyllithium (1.51 mL of a 2.5 M solution, 3.80 mmol) and [5,15-di(3-methoxyphenyl)porphyrinato|nickel(II) 126 (100 mg, 0.17 mmol). Elution with dichloromethane/n-hexane (1:1, v/v) yielded the title compound as a red solid (42 mg, 0.06 mmol, 34 %): mp > 310 °C; Rf=0.74 (CH2Cl2/C6H14, 3:1, v/v); 1H NMR (400 MHz, CDCl3): δ= 3.92 (s, 6H, -OCH3), 4.29 (d, 2H, J = 15.2 Hz, S-CH2-S), 4.90 (d, 2H, J = 14.6 Hz, S-CH2-S), 7.29 (s, 1H, S-CH-S), 7.50 (s, 2H, phenyl-//), 7.57 (d, 6H, J = 5.3 Hz, phenyl-H), 8.81 (m, 4H, p-//), 9.00 (d, 2H, J=4.6 Hz, β-H), 9.63 (s, 1H, meso-//), 9.74 (s, 2H, β-H); 13C NMR (100 MHz, CDCl3); δ= 26.7, 29.3, 30.6, 40.3, 55.0, 55.9, 61.6, 104.9, 111.4, 113.2, 117.9, 119.2, 123.4, 126.2, 127.4, 132.2, 141.2, 141.9, 157.7 ppm; UV/vis (CH2Cl2): λmax (log ε) = 413 nm (5.05), 531 (4.23), 574 (4.17).

[5,15-Dihexyl-10-(1,3,5-trithian-2-yl)porphyrinato|nickel(II) (145)

The reaction was performed using the same conditions as for free base 142 using 1,3,5-trithiane (0.57 g, 4.11 mmol), n-butyllithium (1.63 mL of a 2.5 M solution, 4.11 mmol) and [5,15-dihexylporphyrinato|nickel(II) 127 (100 mg, 0.19 mmol). Elution with dichloromethane/n-hexane (1:1, v/v) gave the title compound as a red solid (31 mg, 0.05 mmol, 24 %): mp > 310 °C; Rf=0.88 (SiO2, CH2Cl2/ C6H14, 3:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 0.88 (t, J=7.0 Hz, 3H, -CH3), 1.30 (m, 2H, -CH2), 1.51 (m, 2H, -CH2), 2.12 (m, 2H, -CH2), 2.20 (m, 2H, -CH2), 4.38 (t, 2H, J = 14.6 Hz, S-CH2-S), 4.26 (t, 2H, J = 7.6 Hz, -CH2), 4.80 (t, 2H, J = 14.6 Hz, S-CH2-S), 7.10 (s, 1H, S-CH-S), 9.08 (d, 2H, J = 4.7 Hz, β-H), 9.15 (m, 4H, β-H), 9.36 ppm (s, 1H, meso-H), 9.52 (s, 2H, β-H); 13C NMR...
(100 MHz, CDCl₃): δ= 13.7, 19.0, 22.2, 29.6, 31.3, 33.5, 37.0, 40.2, 55.7, 103.8, 108.9, 110.0, 112.9, 117.5, 129.0, 129.3, 132.2, 140.4, 141.1, 142.0 ppm; UV/vis (CH₂Cl₂): λₘₚₓ (log ε) = 418 (5.53), 539 (4.65), 576 nm (4.52).

6.6 Synthesis of bromoporphyrins

Bromoporphyrins 149, 150 and 153 were prepared according to the literature.²⁵⁴, ²⁵⁵ Porphyrin precursor 154 was synthesised from mixed condensation reaction as reported previously.²⁵⁶

5-Bromo-15-hexyl-10,20-diphenylporphyrin (151)

A solution of 5-hexyl-10,20-diphenylporphyrin 108 (0.40 g, 0.73 mmol), 0.3 ml pyridine and N-bromosuccinimide (0.14 g, 0.81 mmol) was dissolved in chloroform (150 ml) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (2:1, v/v) to yield 151 0.46 g (0.29 mmol, 99%) as a purple solid: mp >310 °C; R₇=0.75 (SiO₂, CH₂Cl₂/C₆H₄, 1:1, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -2.72 (s, 2H, NH), 0.92 (t, J=7.0 Hz, 3H, -CH₃), 1.36 (m, 2H, -CH₂), 1.49 (m, 2H, -CH₂), 1.75 (m, 2H, -CH₂), 2.47 (m, 2H, -CH₂), 4.84 (t, J=8.1 Hz, 2H, -CH₂), 7.77 (m, 6H, phenyl-H), 8.16 (d, J=6.4 Hz, 4H, phenyl-H), 8.84 (s, 4H, β-H), 9.37 (d, J=4.7 Hz, 2H, β-H), 9.58 ppm (d, J=4.7 Hz, 2H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ= 13.7, 22.3, 29.8, 31.4, 35.1, 38.4, 101.5, 119.8, 121.3, 126.4, 127.4, 130.5, 131.5, 141.6 ppm; UV-vis (CH₂Cl₂): λₘₚₓ (log ε)= 420 (5.21), 520 (3.90), 554 (2.64), 598 (3.48), 654 nm (3.62); HRMS (ES+) [C₃₈H₃₃N₄Br]: calcd for [M+H]⁺ 625.1953, found 625.1967.
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5-Bromo-15-hexyl-10,20-bis(3-methoxyphenyl) porphyrin (152)

A solution of 5-hexyl-10,20-bis(3-methoxyphenyl) porphyrin 109 (0.50 g, 0.82 mmol), 0.3 ml pyridine and N-bromosuccinimide (0.16 g, 0.91 mmol) was dissolved in chloroform (150 ml) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) to yield 0.54 g of 152 (0.37 mmol, 95%) as a purple solid: mp = 225 °C; Rf=0.36 (SiO2, CH2Cl2/C6H14, 1:1, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.71 (s, 2H, NH), 0.91 (t, J=7.4 Hz, 3H, -CH3), 1.37 (m, 2H, -CH2), 1.48 (m, 2H, -CH2), 1.76 (m, 2H, -CH2), 2.48 (m, 2H, -CH2), 3.99 (s, 6H, -OCH3), 4.87 (t, J=7.7 Hz, 2H, -CH2), 7.34 (dd, J1=1.8 Hz, J2=1.8 Hz, 2H, phenyl-H), 7.64 (t, J=8.1 Hz, 2H, phenyl-H), 7.76 (m, 4H, phenyl-H), 8.89 (d, J=4.4 Hz, 4H, β-H), 9.37 (d, J=4.8 Hz, 2H, β-H), 9.58 ppm (d, J=4.8 Hz, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ= 22.7, 29.8, 30.3, 31.9, 35.5, 38.8, 55.5, 101.9, 113.6, 119.9, 120.5, 121.7, 127.5, 129.6, 143.4, 158.0 ppm; UV-vis (CH2Cl2): λmax (log ε)= 421 (5.50), 520 (4.25), 554 (4.00), 598 (3.78), 654 nm (3.70); HRMS (ES+) [C40H37N402Br]: calcd for [M+H]+ 685.2178, found 685.2166.

2-Bromo-5,10,15,20-tetrakis(3,5-di-tert-butyl-phenyl)porphyrin (155)

A solution of 5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin 154 (0.20 g, 0.19 mmol), 0.5 ml pyridine and N-bromosuccinimide (0.04 g, 0.21 mmol) was dissolved in chloroform (100 ml) and stirred for 1 hour. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) to yield 155 (0.21 g, 0.24 mmol, 96%) as a purple solid: mp > 310 °C; Rf=0.75 (SiO2, CH2Cl2/C6H14, 1:1, v/v);
v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta = -2.79\) (s, 2H, NH), 1.50 (s, 18H, -C(CH\(_3\))\(_3\)), 1.52 (s, 54H, C(CH\(_3\))\(_3\)), 7.78 (t, \(J=1.8\) Hz, 3H, phenyl-H), 7.80 (t, \(J=1.8\) Hz, 1H, phenyl-H), 7.92 (d, \(J=1.8\) Hz, 1H, phenyl-H), 7.93 (d, \(J=1.8\) Hz, 1H, phenyl-H), 8.03 (t, \(J=1.8\) Hz, 1H, phenyl-H), 8.04 (d, \(J=1.8\) Hz, 1H, phenyl-H), 8.06 (t, \(J=1.8\) Hz, 3H, phenyl-H), 8.09 (d, \(J=1.8\) Hz, 1H, phenyl-H), 8.82 (d, \(J=1.8\) Hz, 1H, \(\beta\)-H), 8.90 (m, 5H, \(\beta\)-H), 8.94 ppm (d, \(J=4.8\) Hz, 1H, \(\beta\)-H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 29.7, 32.0, 35.1, 120.9, 121.4, 129.1, 129.7, 141.0, 141.4, 148.7, 148.9\) ppm; UV-vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (log \(e\)) = 423 (5.10), 520 (3.64), 554 (2.64), 598 (3.48), 654 nm (3.62); HRMS (ES+) [C\(_{76}\)H\(_{94}\)N\(_4\)Br\(_2\)]: calcd for [M+H]\(^+\) 1141.6662, found. 1141.6544.

6.7 Synthesis of ester porphyrins

Method A: Heck coupling approach

Bromoporphyrin (1 eq.), palladium acetate (0.2 eq.) di-tert-butylbiphenylphosphine (0.5 eq.) and K\(_2\)CO\(_3\) (1.2 eq.) were added to a Schlenk tube and dried under vacuum. The vessel was filled with argon, followed by addition of dry DMF, dry toluene, and the vinyl reagent (50-fold excess). The mixture was then degassed via three freeze-pump-thaw cycles before the vessel was purged with argon again to ensure the reaction mixture was free of oxygen. The Schlenk flask was sealed and heated to 105 °C and the mixture was stirred for 15 hours. The progress of reaction was monitored by TLC and, upon completion, the mixture was diluted with toluene and washed with water. The organic layer was separated, dried over MgSO\(_4\) and the residue was purified by column chromatography.

5-Hexyl-15-(2-methoxycarbonyl ethenyl)-10,20-diphenylporphyrin (157)

Methyl acrylate (0.72 mL, 7.97 mmol) was added to the solution of 5-bromo-15-hexyl-10,20-diphenylporphyrin 151 (0.10 g, 0.16 mmol), palladium acetate (7.22 mg, 0.03 mmol), di-tert-butylbiphenylphosphine (24.59 mg, 0.08 mmol) and K\(_2\)CO\(_3\) (27.33 mg, 0.20
mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 hours. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:2, v/v) and yielded 0.06 g (0.04 mmol, 60%) of 157 as a purple solid: mp >310 °C; Rf = 0.61 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ = -2.44 (s, 2H, N=), 0.90 (t, J=7.4 Hz, 3H, -CH3), 1.36 (m, 2H, -CH2), 1.49 (m, 2H, -CH2), 1.77 (m, 2H, -CH2), 2.49 (m, 2H, -CH2), 4.04 (s, 3H, -OCH3), 4.91 (t, J=7.7 Hz, 2H, -CH2), 6.79 (d, J=15.8 Hz, 1H, -CH=), 7.78 (m, 6H, phenyl-H), 8.16 (d, J=6.2 Hz, 4H, phenyl-H), 8.83 (dd, J1=4.8 Hz, J2=4.8 Hz, 4H, β-H), 9.40 (t, J=4.4 Hz, 4H, β-H), 10.20 ppm (d, J=15.8 Hz, 1H, =CH); 13C NMR (100 MHz, CDCl3): δ = 14.2, 22.7, 30.3, 31.9, 35.5, 38.8, 52.1, 111.2, 120.6, 122.7, 130.3, 142.2, 146.0, 166.9 ppm; UV-vis (CH2Cl2): λmax (log ε) = 426 (5.11), 526 (3.97), 565 (3.96), 600 (3.79), 654 nm (3.79); HRMS (ES+) [C42H38N4O2]: calcd for [M+H]+ 631.3073, found 631.3062.

5-Hexyl-15-(2-methoxycarbonyl)ethenyl)-10,20-bis(3-methoxyphenyl)porphyrin (158)

Methyl acrylate (0.66 mL, 7.26 mmol) was added to a solution of 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin 152 (0.10 g, 0.15 mmol), palladium acetate (6.59 mg, 0.03 mmol), di-tert-butylbiphenylphosphine (22.42 mg, 0.08 mmol) and K2CO3 (24.85 mg, 0.18 mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 hours (see 4.38). The mixture was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:4, v/v) and yielded 0.06 g (0.04 mmol, 55%) of 158 as a purple solid: mp =275 °C; Rf = 0.65 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ = -2.43 (s, 2H, NH), 0.96 (t, J=7.6 Hz, 3H, -CH3), 1.36 (m, 2H, -CH2), 1.49 (m, 2H, -CH2), 1.77 (m, 2H, -CH2), 2.48 (m, 2H, -CH2), 3.99 (s, 6H, -OCH3), 4.04 (s, 3H, -OCH3), 4.90 (t, J=7.6 Hz, 2H, -CH2), 6.80 (d, J=15.8 Hz, 1H, -CH=), 7.34 (dd, J1=2.3 Hz, J2=2.3 Hz, 2H, phenyl-H), 7.65 (t, J=8.2 Hz, 2H, phenyl-H), 7.77 (t, J=7.6 Hz, 4H, phenyl-H), 8.89 (dd, J1=4.7 Hz, J2=4.7 Hz, 4H, β-H), 9.39 (q, J=4.7 Hz, 4H, β-H), 10.21 ppm (d, J=15.8 Hz, 1H, =CH); 13C NMR (100 MHz, CDCl3): δ =13.7, 22.3, 29.8, 31.5, 35.0, 38.4, 51.6, 55.1, 110.8, 113.2, 119.8, 120.0, 122.3, 129.9, 131.9, 143.0, 145.5, 157.5, 166.4 ppm;
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UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 427 (5.23), 526 (4.01), 566 (4.00), 5.99 (3.79), 657 nm (3.81); HRMS (ES+) [C$_{44}$H$_{29}$N$_4$O$_2$]: calcld for [M+H]$^+$ 691.3284, found 691.3293.

**Method B: Suzuki cross coupling approach**

To a stirred slurry of K$_3$PO$_4$ (40 eq.) in anhydrous THF were added bromoporphyrin (1 eq.), boronic acid (20 eq.), and Pd(PPh$_3$)$_4$ (0.2 eq.). The reaction was heated to reflux at 85 °C for 18 hours and shielded from light. The solvent was evaporated after completion and the residue was dissolved in CH$_2$Cl$_2$. This mixture was washed with saturated NaHCO$_3$, H$_2$O, and brine followed by drying over Na$_2$SO$_4$. The organic solvent was evaporated and the crude product was purified by column chromatography.

5-(4-Methoxycarbonylphenyl)-10,20-diphenylporphyrin (159)

![Chemical Structure](image)

K$_3$PO$_4$ (1.57g, 7.38 mmol), 5-bromo-10,20-diphenylporphyrin 149 (0.20 g, 0.37 mmol), 4-methoxy carbonylphenyl boronic acid (0.66 g, 3.69 mmol) and Pd(PPh$_3$)$_4$ (0.04 g, 0.04 mmol) were reacted in anhydrous THF (70 ml) according to method A. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:2, v/v) and yielded 0.22 g of 159 (0.13 mmol, 98%) as a purple solid: mp $>$310 °C; R$_f$=0.42 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 2:1, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ = -3.02 (s, 2H, NH), 4.11 (s, 3H, -OCH$_3$), 7.79 (m, 6H, phenyl-H), 8.24 (dd, $J_1$=2.3 Hz, $J_2$=1.8 Hz, 4H, phenyl-H), 8.31 (d, $J$=8.2 Hz, 2H, phenyl-H), 8.42 (d, $J$=4.7 Hz, 2H, phenyl-H), 8.42 (d, $J$=4.7 Hz, 2H, β-H), 9.03 (d, $J$=4.7 Hz, 2H, β-H), 9.32 (d, $J$=4.7 Hz, 2H, β-H), 10.20 ppm (s, 1H, meso-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.9, 52.0, 65.5, 104.8, 118.5, 119.4, 126.4, 127.4, 129.1, 130.6, 134.3, 141.2, 147.0, 166.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 413 (5.57), 509 (4.04), 542 (3.60), 584 (3.64) 638 nm (3.30); HRMS (ES+) [C$_{40}$H$_{29}$N$_4$O$_2$]: calcld for [M+H]$^+$ 597.2291, found 597.2285.
5-Hexyl-15-(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin (160)

K$_3$PO$_4$ (1.36 g, 6.39 mmol), 5-bromo-15-hexyl-10,20-diphenylporphyrin 151 (0.2 g, 0.32 mmol), 4-methoxy carbonylphenylboronic acid (0.58 g, 3.20 mmol) and Pd(PPh$_3$)$_4$ (0.04 g, 0.03 mmol) were reacted in anhydrous THF (70 ml) following method A. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) and yielded 160 (0.29 g, 0.20 mmol, 82%) as a purple solid: mp $>$ 310 °C; R$_f$=0.60 (SiO$_2$, EtOAc/n-hexane, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= -2.67 (s, 2H, NH), 0.96 (t, J=7.0 Hz, 3H, -CH$_3$), 1.39 (m, 2H, -CH$_2$), 1.50 (m, 2H, -CH$_2$), 1.78 (m, 2H, -CH$_2$), 2.53 (m, 2H, -CH$_2$), 4.13 (s, 3H, -OCH$_3$), 4.91 (t, J=8.2 Hz, 2H, -CH$_2$), 7.79 (m, 6H, phenyl-H), 8.23 (d, J=7.6 Hz, 4H, phenyl-H), 8.32 (d, J=7.6 Hz, 2H, phenyl-H), 8.45 (d, J=7.6 Hz, 4H, phenyl-H), 8.79 (d, J=4.7 Hz, 2H, $\beta$-H), 8.85 (d, J=4.7 Hz, 2H, $\beta$-H), 8.93 (d, J=4.7 Hz, 2H, $\beta$-H), 9.44 ppm (d, J=4.7 Hz, 2H, $\beta$-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$= 13.8, 22.3, 29.8, 31.5, 35.1, 38.5, 52.0, 117.3, 119.4, 120.8, 127.3, 127.6, 129.1, 134.2, 141.9, 146.6, 167.0 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$)= 419 (5.52), 517 (3.20), 551 (3.91), 593 (3.76), 649 nm (3.83); HRMS (ES$^+$) [C$_{46}$H$_{41}$N$_4$O$_2$]: calcd for [M+H]$^+$ 681.3230, found 681.3256.

5-Hexyl-15-(4-methoxycarbonylphenyl)-10,20-bis(3-methoxyphenyl)porphyrin (161)

K$_3$PO$_4$ (3.10, 14.59 mmol), 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin 152 (0.50 g, 0.73 mmol), 4-methoxycarbonylphenylboronic acid (1.31 g, 7.29 mmol) and
Pd(PPh₃)₄ (0.08 g, 0.07 mmol) were reacted in anhydrous THF (80 ml) following method A. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:2, v/v) and yielded 161 (0.41 g, 0.30 mmol, 63%) as a purple solid: mp = 210 °C; Rf = 0.36 (SiO₂, EtOAc/n-hexane, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ = -2.73 (s, 2H, NH), 0.92 (t, J= 7.4 Hz, 3H, -CH₃), 1.38 (m, 2H, -CH₂), 1.52 (m, 2H, -CH₂), 1.80 (m, 2H, -CH₂), 2.54 (m, 2H, -CH₂), 3.99 (s, 6H, -OCH₃), 4.10 (s, 3H, -OCH₃), 4.98 (t, J= 7.8 Hz, 2H, -CH₂), 7.37 (dd, J₁= 2.4 Hz, J₂= 2.0 Hz, 2H, phenyl-H), 7.64 (t, J= 8.3 Hz, 2H, phenyl-H), 7.79 (t, J= 7.8 Hz, 4H, phenyl-H), 8.27 (d, J= 7.8 Hz, 2H, phenyl-H), 8.42 (d, J= 8.3 Hz, 2H, phenyl-H), 8.73 (d, J= 4.8 Hz, 2H, β-H), 8.86 (d, J= 4.9 Hz, 2H, β-H), 8.96 (d, J= 4.4 Hz, 2H, β-H), 9.46 ppm (d, J= 4.9 Hz, 2H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 22.8, 30.3, 31.9, 35.6, 38.9, 52.5, 55.5, 113.6, 117.8, 119.5, 120.5, 121.3, 127.5, 127.6, 128.0, 129.5, 134.6, 143.6, 147.0, 157.9, 167.4 ppm; UV-vis (CH₂Cl₂): λmax (log ε) = 419 (5.34), 516 (4.26), 551 (4.06), 593 (3.98), 650 nm (3.94); HRMS (ES⁺) [C₄₈H₄₄N₄O₄]: calcd for [M+H]⁺ 741.3441, found 741.3441.

5-Hexyl-15-(3-methoxycarbonylphenyl)-10,20-diphenylporphyrin (162)

K₃PO₄ (1.36 g, 6.39 mmol), 5-hexyl-15-bromo-10,20-diphenylporphyrin 151 (0.20 g, 0.32 mmol), 3-methoxycarbonylphenylboronic acid (0.58 g, 3.20 mmol), and Pd(PPh₃)₄ (0.03 g, 0.03 mmol) were reacted in anhydrous THF (70 ml) according to method A. The title compound was isolated by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) to give 0.18 g of 162 (0.12 mmol, 84%) as a purple solid: mp > 310 °C; Rf = 0.77 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ = -2.71 (s, 2H, NH), 0.93 (t, J= 7.3 Hz, 3H, -CH₃), 1.38 (m, 2H, -CH₂), 1.52 (m, 2H, -CH₂), 1.80 (m, 2H, -CH₂), 2.54 (m, 2H, -CH₂), 3.98 (s, 3H, -OCH₃), 4.98 (t, J= 8.0 Hz, 2H, -CH₂), 7.77 (m, 6H, phenyl-H), 7.82 (t, J= 7.7 Hz, 1H, phenyl-H), 8.21 (d, J= 6.2 Hz, 4H, phenyl-H), 8.37 (d, J= 7.7 Hz, 1H, phenyl-H), 8.46 (d, J= 7.7 Hz, 1H, phenyl-H), 8.73 (d, J= 4.8 Hz, 2H, β-H), 8.82 (d, J= 4.4 Hz, 2H, β-H), 8.89 (s, 1H, phenyl-H), 8.92 (d, J= 4.8 Hz, 2H, β-H), 9.47 ppm (d, J= 4.8 Hz, 2H, β-H); ¹³C NMR (100 MHz, CDCl₃):
δ = 14.2, 22.8, 30.3, 31.9, 35.6, 38.9, 52.4, 117.8, 119.8, 121.1, 126.7, 126.9, 127.7, 128.9, 129.0, 134.5, 134.9, 138.5, 142.4, 142.5, 167.4 ppm; UV-vis (CH₂Cl₂): λ\text{max} (log ε) = 418 (5.14), 516 (4.08), 551 (3.93), 593 (3.88), 651 nm (3.89); HRMS (ES⁺) [C₄₆H₄₀N₄O₂]: calcd for [M+H]⁺ 681.3230, found 681.3238.

5,15-Bis(3,5-di-tert-butyphenyl)-10,20-bis(3-methoxycarbonylphenyl)porphyrin (163)

K₂PO₄ (1.01 g, 4.74 mmol), 5,15-dibromo-10,20-bis(3,5-di-tert-butyphenyl)-porphyrin 150 (0.10 g, 0.12 mmol), 3-methoxycarbonylphenylboronic acid (0.43 g, 2.47 mmol) and Pd(PPh₃)₄ (0.03 g, 0.02 mmol) were heated to reflux in anhydrous THF (50 ml) following method A. The title compound was isolated by column chromatography on silica gel with n-hexane/dichloromethane (1:2, v/v) to yield 0.09 g of 163 (0.09 mmol, 77 %) as a purple solid: mp = 260 °C; Rf = 0.56 (SiO₂, CH₂Cl₂/C₆H₄, 1:1, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ = -2.76 (s, 2H, NH), 1.51 (s, 36H, -(CH₂)₃), 3.96 (s, 6H, -OCH₃), 7.79 (d, J = 8.8 Hz, 2H, phenyl-H), 7.83 (d, J = 7.6 Hz, 2H, phenyl-H), 8.06 (d, J = 1.8 Hz, 4H, phenyl-H), 8.39 (d, J = 7.6 Hz, 2H, phenyl-H), 8.45 (d, J = 7.6 Hz, 2H, phenyl-H), 8.75 (d, J = 4.7 Hz, 4H, β-H), 8.89 ppm (d, J = 4.6 Hz, 6H, phenyl-H and β-H); ¹³C NMR (100 MHz, CDCl₃): δ = 13.7, 22.3, 29.3, 31.4, 34.6, 51.9, 118.1, 120.7, 121.4, 126.4, 128.3, 128.6, 129.5, 134.3, 137.9, 140.5, 142.3, 148.4, 166.9 ppm; UV-vis (CH₂Cl₂): λ\text{max} (log ε) = 421 (5.20), 517 (3.86), 553 (3.68), 595 (3.64), 654 nm (3.90); HRMS (ES⁺) [C₆₄H₆₆N₄O₄]: calcd for [M+H]⁺ 955.5162, found 955.5205.
**5,15-Bis(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin (164)**

K$_3$PO$_4$ (2.74 g, 12.90 mmol), 5,15-dibromo-10,20-diphenylporphyrin 156 (0.20 g, 0.32 mmol), 4-methoxycarbonylphenylboronic acid (1.16 g, 6.44 mmol) and Pd(PPh$_3$)$_4$ (0.07 g, 0.06 mmol) were reacted in anhydrous THF (70 ml) following procedure A. The crude mixture was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) and yielded 164 (0.24 g, 94%) as a purple solid: mp >310 °C; R$_f$=0.38 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 1:1 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ=-2.80 (s, 2H, NH), 4.10 (s, 6H, -OCH$_3$), 7.64 (d, J=8.2 Hz, 6H, phenyl-H), 7.76 (m, 4H, phenyl-H), 8.09 (d, J=8.8 Hz, 2H, phenyl-H), 8.18 (d, J=7.6 Hz, 2H, phenyl-H), 8.31 (d, J=8.2 Hz, 2H, phenyl-H), 8.42 (d, J=7.6 Hz, 2H, phenyl-H), 8.80 (d, J=4.7 Hz, 4H, β-H), 8.86 ppm (d, J=4.7 Hz, 4H, β-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ= 51.8, 118.5, 120.2, 126.3, 126.8, 127.5, 129.8, 134.1, 141.5, 143.9, 146.5, 166.4, 166.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log ε) = 419 (5.43), 515 (4.04), 550 (3.62), 592 (3.45), 648 nm (3.45); HRMS (ES+) [C$_{48}$H$_{34}$N$_4$O$_4$]; calcd for [M+H]$^+$ 731.2658, found 731.2620.

**2-(4-Methoxycarbonylphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (165)**

K$_3$PO$_4$ (0.37 g, 1.75 mmol), 2-bromo-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin 155 (0.10 g, 0.09 mmol), 4-methoxycarbonylphenylboronic acid (0.16 g, 0.88 mmol) and Pd(PPh$_3$)$_4$ (0.01 g, 0.01 mmol) were reacted in anhydrous THF (50 ml) according to method A. The product was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1, v/v) to yield 0.04 g of 165 (0.05 mmol, 52 %) as a purple
solid: mp >310 °C; Rf=0.57 (SiO₂, EtOAc/C₆H₁₄, 1:5 v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -2.54 (s, 2H, NH), 1.35 (s, 18H, -C(C₃H₃)₃), 1.53 (s, 54H, -C(CH₃)₃), 3.94 (s, 3H, -OCH₃), 7.24 (s, 1H, phenyl-H), 7.47 (d, J= 8.0 Hz, 2H, phenyl-H), 7.81 (m, 7H, phenyl-H), 8.08 (dd, J₁= 1.8 Hz , J₂= 1.4 Hz, 4H, phenyl-H), 8.15 (d, J= 1.4 Hz, 2H, phenyl-H), 8.74 (m, 2H, β-H), 8.87 ppm (m, 5H, p-H); ¹³C NMR (100 MHz, CDCl₃): δ= 29.7, 31.9, 35.1, 52.0, 53.4, 121.0, 121.3, 122.2, 127.0, 128.6, 129.8, 130.7, 140.2, 141.4, 141.6, 148.6, 148.7, 167.2 ppm; UV-vis (CH₂Cl₂): λ<sub>max</sub> (log ε)= 426 (5.43), 5.22 (4.00), 559 (3.56), 598 (3.08), 655 nm (3.51); HRMS (ES+) [C₈₄H₁₀₀N₄O₂]: calcld for [M+H]<sup>+</sup> 1197.7930, found. 1197.7880.

Method C: Condensation approach

Ester porphyrin 168 and 169 were synthesised using condensation reaction as reported previously.¹⁸⁸,²⁵⁶

General procedure: To a mixture of aldehyde (4 eq.) and Zn(OAc)<sub>2</sub> (1 eq.) in propionic acid, pyrrole (4 eq.) was added at 100 °C over the course of 1 hours under vigorous stirring. The resulting dark solution was refluxed for further 4h and then cooled to room temperature. The solvent was evaporated and the solid residue was filtered through silica gel and all product containing fractions were collected. The volume was reduced to 100 ml and pyridine and excess DDQ were added. The resulting mixture was refluxed for 1 hour. The solution was cooled to room temperature and evaporated to give a black-purple crude product followed by column chromatography on silica gel.

[5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-methoxycarbonylphenyl)porphyrinato] zinc(II)) (166)

4-Carboxylmethylbenzaldehyde (0.25 g, 1.53 mmol), 3,5-di-tert-butylbenzaldehyde (1.00 g, 4.58 mmol), Zn(OAc)<sub>2</sub> (0.34 g, 1.53 mmol) and pyrrole (0.42 mL, 6.12 mmol) were reacted in propionic acid (30 mL) following method C. The solution volume was reduced
to 100 ml and pyridine (0.5 mL) and DDQ (0.5 g) were added. The title compound was purified by column chromatography on silica gel with n-hexane/dichloromethane (1:1 v/v) gave a red solid of 166 as the second fraction (0.16 g, 0.17 mmol, 10%): mp >310 °C; Rf=0.44 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ=1.53 (s, 54H, -C-(CH3)3), 4.03 (s, 3H, -OCH3), 7.80 (d, J= 1.76 Hz, 3H, phenyl-H), 8.10 (s, 6H, phenyl-H), 8.31 (d, J=8.2 Hz, 2H, phenyl-H), 8.36 (d, J=8.2 Hz, 2H, phenyl-H), 8.89 (d, J=4.7 Hz, 2H, β-H), 9.02 ppm (d, J=5.3 Hz, 6H, β-H); 13C NMR (100 MHz, CDCl3): δ=31.34, 34.62, 51.91, 118.69, 120.42, 122.22, 127.29, 128.71, 129.25, 130.83, 131.83, 131.98, 141.30, 147.59, 148.14, 149.03, 149.96, 150.16, 166.99 ppm; UV-vis (CH2Cl2): λmax (log ε)= 423 (5.34), 549 (4.87), 589 nm (4.77); HRMS (ES+) [C70H78O2N4Zn]: calcd for [M] 1070.5416, found 1070.5425. The first fraction contained [5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrinato]zinc(II) 167 (0.198 g, 0.22 mmol, 12%) as a red solid. mp >310 °C; Rf=0.73 (SiO2, EtOAc/C6H14, 1:3 v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 1.63 (s, 72H, -C-(CH3)3), 7.89 (s, 4H, phenyl-H), 8.22 (s, 8H, phenyl-H), 9.13 ppm (s, 8H, β-H); 13C NMR (100 MHz, CDCl3): δ= 31.5, 34.7, 120.4, 122.0, 129.3, 131.8, 141.6, 148.1, 150.0 ppm; UV-vis (CH2Cl2): λmax (log ε)= 422 (5.12), 549 (4.87), 654 nm (4.84); HRMS [C70H77N4O2Zn]: calcd for [M+H+] 1070.5416, found 1070.5428.

6.8 Synthesis of carboxylic acid porphyrins

Carboxylic acid porphyrins 177, 178, 181 and 182 were prepared as reported previously using base hydrolysis.188, 256

General method: A solution of porphyrin in THF, was mixed with ethanol and 2N NaOH and the suspension was heated to reflux (TLC monitoring) before cooled to room temperature. The mixture was acidified with aqueous HCl (1N) and extracted with chloroform. The organic extract was washed with saturated sodium bicarbonate aqueous solution and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure and undergo purification.
5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin (171)

5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-diphenylporphyrin 157 (0.03 g, 0.02 mmol) was heated in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 3 hours. Filtration through a plug of silica gel eluting with (CH$_2$Cl$_2$: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of 171 (0.03 g, 0.02 mmol, 93%): mp >310 °C; R$_f$=0.19 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= -2.40 (s, 2H, N $\equiv$), 0.93 (t, $J$=7.4 Hz, 3H, -CH$_3$), 1.39 (m, 2H, -CH$_2$), 1.43 (m, 2H, -CH$_2$), 1.74 (m, 2H, -CH$_2$), 2.25 (m, 2H, -CH$_2$), 5.09 (t, $J$=7.7 Hz, 2H, -CH$_2$), 6.83 (d, $J$=15.8 Hz, 1H, -CH=), 7.92 (m, 6H, phenyl-CH), 8.26 (d, $J$=6.2 Hz, 4H, phenyl-CH), 8.80 (d, $J$=4.7 Hz, 4H, $\beta$-CH), 8.96 (d, $J$=5.3 Hz, 2H, $\beta$-CH), 9.71 (t, $J$=4.4 Hz, 2H, $\beta$-CH), 10.16 ppm (d, $J$=15.8 Hz, 1H, =CH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=13.7, 22.2, 24.2, 29.2, 29.7, 31.3, 38.3, 55.0, 94.3, 106.6, 126.3, 127.6, 128.0, 128.6, 133.7, 141.3 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 426 (5.26), 527 (3.78), 569 (3.86), 601 (3.30), 654 nm (3.48); HRMS (ES$^+$) [C$_{41}$H$_{36}$N$_4$O$_2$]: calcd for [M+H]$^+$ 617.2917, found. 617.2901

5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (172)

5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-bis(3-methoxyphenyl)porphyrin 158 (0.06 g, 0.08 mmol) was heated in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 3 hours. Filtration through a plug of silica gel eluting with (CH$_2$Cl$_2$: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of 172 (0.05 g, 0.03 mmol, 88%): mp =197 °C; R$_f$=0.19 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$=...
−2.43 (s, 2H, NH), 0.98 (t, J=7.6 Hz, 3H, -CH₃), 1.30 (m, 2H, -CH₂), 1.58 (m, 2H, -CH₂), 1.86 (m, 2H, -CH₂), 2.58 (m, 2H, -CH₂), 4.06 (s, 6H, -OCH₃), 5.12 (t, J=7.6 Hz, 2H, -CH₂), 6.85 (d, J=15.8 Hz, 1H, -CH=), 7.48 (d, J=8.2 Hz, 2H, phenyl-H), 7.75 (t, J=8.2 Hz, 2H, phenyl-H), 7.84 (t, J=7.6 Hz, 4H, phenyl-H), 8.94 (d, J=13.4 Hz, 4H, β-H), 9.72 (d, J=4.7 Hz, 2H, β-H), 9.91 (d, J=4.7 Hz, 2H, β-H), 10.20 ppm (d, J=15.8 Hz, 1H, =CH); ^13C NMR (100 MHz, CDCl₃): δ=14.2, 21.3, 22.7, 25.6, 29.5, 31.8, 34.3, 38.7, 54.4, 55.6, 68.0, 112.3, 118.9, 119.8, 120.5, 126.8, 128.3, 135.8, 142.6, 143.3, 151.6, 156.8 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε)= 427 (5.33), 525 (4.32), 571 (4.32), 599 (4.18), 654 nm (4.15); HRMS (ES+) [C₄₃H₄₀N₄O₄]: calcd for [M+H]^+ 677.3128, found. 677.3121.

5-(4-Carboxyphenyl)-10,20-diphenylporphyrin (173)

5-(4-Methoxycarbonylphenyl)-10,20-diphenylporphyrin 159 (0.15 g, 0.09 mmol) was heated to reflux in THF, ethanol (40mL) and 2N NaOH (95 ml) for 11 hours. Filtration through a plug of silica gel eluting with (CH₂Cl₂: EtOAc = 5:1) and evaporation of the solvent followed by recrystallization from MeOH/H₂O gave a purple solid of 173 (0.11 g, 0.06 mmol, 77%): mp >310 °C; Rf=0.29 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ^1H NMR (400 MHz, CDCl₃, TMS): δ= −3.30 (s, 2H, NH), 7.60 (m, 6H, phenyl-H), 8.03 (m, 6H, phenyl-H), 8.17 (d, J=7.5 Hz, 2H, phenyl-H), 8.68 (d, J=14.0 Hz, 4H, β-H), 8.82 (s, 2H, β-H), 9.17 (s, 2H, β-H), 10.05 ppm (s, 1H, meso-H); ^13C NMR (100 MHz, CDCl₃): δ= 30.7, 31.4, 32.0, 97.0, 107.4, 109.5, 113.2, 118.7, 120.9, 122.2, 122.4, 129.9, 130.2, 133.9, 136.6, 144.0, 147.5, 176.0 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε)= 413 (5.27), 509 (4.23), 542 (4.04), 582 (4.04), 636 nm (3.95); HRMS (ES+) [C₃₅H₂₇N₄O₂]: calcd for [M+H]^+ 583.2134, found. 583.2134.
5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenyl porphyrin (174)

5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenyl-porphyrin 160 (0.10 g, 0.15 mmol) was heated in THF (20 mL), ethanol (25 mL) and 2N NaOH (50 mL) for 2 hours. Filtration through a plug of silica gel eluting with (CH₂Cl₂: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of 174 (0.09 g, 0.06 mmol, 93%): mp >310 °C; Rₐ=0.24 (SiO₂, EtOAc/C₆H₄, 1:3, v/v); ^1H NMR (400 MHz, CDCl₃, TMS): δ= -2.67 (s, 2H, NH), 0.96 (t, J=7.0 Hz, 3H, -CH₃), 1.21 (m, 2H, -CH₂), 1.58 (m, 2H, -CH₂), 1.76 (m, 2H, -CH₂), 2.53 (m, 2H, -CH₂), 5.17 (t, J=8.2 Hz, 2H, -CH₂), 7.90 (m, 6H, phenyl-H), 8.08 (d, J=7.6 Hz, 4H, phenyl-H), 8.28 (d, J=7.6 Hz, 2H, phenyl-H), 8.40 (d, J=7.6 Hz, 4H, phenyl-H), 8.52 (d, J=4.7 Hz, 2H, β-H), 8.87 (d, J=4.7 Hz, 2H, β-H), 8.96 (d, J=4.7 Hz, 2H, β-H), 9.21 ppm (d, J=4.7 Hz, 2H, β-H); ^13C NMR (100 MHz, CDCl₃): δ=13.7, 22.3, 27.8, 29.0, 29.8, 31.5, 34.0, 34.9, 38.3, 99.9, 118.4, 119.7, 122.8, 125.1, 126.1, 127.3, 128.4, 130.9, 134.1, 135.1, 141.0, 143.9, 149.0 ppm; UV-vis (CH₂Cl₂): λmax (log ε) = 419 (5.26), 518 (4.60), 552 (4.54), 594 (4.49), 647 nm (4.47); HRMS (ES+) [C₄₅H₃₉N₄O₂]: calcd for [M+H]^+ 667.3073, found. 667.3068.

5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (175)

5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-bis(3-methoxy-phenyl)porphyrin 161 (0.18 g, 0.24 mmol) was heated in THF (15 mL), ethanol (30 mL) and 2N NaOH (30 mL) for 5
hours. Filtration through a plug of silica gel eluting with \((\text{CH}_2\text{Cl}_2: \text{EtOAc} = 5:1 \text{ v/v})\) and evaporation of the solvent gave a purple solid of 175 (0.16 g, 0.11 mmol, 93%): mp >310 °C; \(R_f=0.13\) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta= -3.07\) (s, 2H, N\(\equiv\)), 0.95 (t, \(J=7.4\) Hz, 3H, -CH\(_3\)), 1.36 (m, 2H, -CH\(_2\)), 1.45 (m, 2H, -CH\(_2\)), 1.71 (m, 2H, -CH\(_2\)), 2.40 (m, 2H, -CH\(_2\)), 3.98 (s, 6H, -OCH\(_3\)), 5.00 (t, \(J=7.8\) Hz, 2H, -CH\(_2\)), 7.37 (d, \(J=7.8\) Hz, 2H, phenyl-\(H\)), 7.72 (t, \(J=8.2\) Hz, 2H, phenyl-\(H\)), 7.85 (t, \(J=7.8\) Hz, 4H, phenyl-\(H\)), 8.14 (d, \(J=7.8\) Hz, 2H, phenyl-\(H\)), 8.47 (d, \(J=8.3\) Hz, 2H, phenyl-\(H\)), 8.73 (d, \(J=4.8\) Hz, 2H, \(\beta\)-\(H\)), 8.86 (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)), 9.12 ppm (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=13.7, 20.7, 22.2, 27.7, 31.4, 33.8, 35.1, 38.4, 65.9, 67.5, 117.9, 119.2, 120.4, 124.4, 125.0, 126.1, 127.2, 128.7, 134.0, 135.0, 137.6, 143.9, 144.3, 151.1, 168.9

5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin (176)

5-(3-Methoxycarbonylphenyl)phenyl)-15-hexyl-10,20-diphenylporphyrin 162 (0.14 g, 0.21 mmol) was heated in THF (20 mL), ethanol (30 mL) and 2N NaOH (30 mL) for 2 hours. Filtration through a plug of silica gel eluting with \((\text{CH}_2\text{Cl}_2: \text{EtOAc} = 5:1 \text{ v/v})\) followed by evaporation of the solvent gave a purple solid of 176 (0.13 g, 0.09 mmol, 94%): mp >310 °C; \(R_f=0.24\) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta= -2.78\) (s, 2H, NH\(_2\)), 0.88 (t, \(J=7.3\) Hz, 3H, -CH\(_3\)), 1.32 (m, 2H, -CH\(_2\)), 1.44 (m, 2H, -CH\(_2\)), 1.77 (m, 2H, -CH\(_2\)), 2.49 (m, 2H, -CH\(_2\)), 4.96 (t, \(J=7.8\) Hz, 2H, -CH\(_2\)), 7.70 (m, 6H, phenyl-\(H\)), 7.76 (t, \(J=7.7\) Hz, 1H, phenyl-\(H\)), 8.13 (d, \(J=6.8\) Hz, 4H, phenyl-\(H\)), 8.27 (d, \(J=6.8\) Hz, 1H, phenyl-\(H\)), 8.49 (d, \(J=7.8\) Hz, 1H, phenyl-\(H\)), 8.72 (d, \(J=4.9\) Hz, 4H, \(\beta\)-\(H\)), 8.85 (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)), 8.93 (s, 1H, phenyl-\(H\)), 9.43 ppm (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=13.7, 20.7, 22.2, 27.7, 31.4, 33.8, 35.1, 38.4, 65.9, 67.5, 117.9, 119.2, 120.4, 124.4, 125.0, 126.1, 127.2, 128.7, 134.0, 135.0, 137.6, 143.9, 144.3, 151.1, 168.9
ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 418 (5.31), 517 (4.30), 550 (4.18), 595 (4.00), 651 nm (4.00); HRMS (ES+) [C$_{45}$H$_{38}$N$_4$O$_2$]: calcd for [M+H]$^+$ 667.3073, found 667.3072.

5,15-Bis(3-carboxyphenyl)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (178)

5,15-Bis(3-methoxycarbonylphenyl)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin 163 (0.02 g, 0.02 mmol) was heated in THF (10 mL), ethanol (20 mL) and 2N NaOH (20 mL) for 5 hours. Filtration through a plug of silica gel eluting with (CH$_2$Cl$_2$): EtOAc = 5:1 v/v) followed by evaporation of the solvent gave a purple solid of 178 (16.5 mg, 0.02 mmol, 89%): mp > 310 °C; R$_f$=0.23 (SiO$_2$, EtOAc/C$_6$H$_5$, 1:3, v/v); $^1$H NMR (400 MHz, CDC$_3$, TMS): $\delta$ = -2.83 (s, 2H, N-H), 1.50 (s, 36H, -(CH$_3$)$_3$), 7.29 (s, 2H, phenyl-N), 7.92 (m, 6H, phenyl-H), 8.04 (t, $J$=4.0 Hz, 2H, phenyl-H), 8.44 (dd, $J_1$=1.5 Hz, $J_2$=3.4 Hz, 4H, phenyl-H), 9.07 (d, $J$=4.7 Hz, 4H, $\beta$-H), 9.37 ppm (d, $J$=4.6 Hz, 4H, $\beta$-H); $^{13}$C NMR (100 MHz, CDC$_3$): $\delta$ = 31.3, 32.1, 44.7, 119.2, 123.7, 124.4, 126.7, 127.6, 128.4, 129.6, 132.2, 140.7, 142.2, 149.5, 165.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) = 408 (5.11), 503 (4.61), 573 (4.58), 598 (4.54), 652 nm (4.54); HRMS (ES+) [C$_{62}$H$_{63}$N$_4$O$_4$]: calcd for [M+H]$^+$ 927.4849, found 927.4872.

2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (179)

2-(4-Methoxycarbonylphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (0.03 g, 0.03 mmol) 165 was heated to reflux in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 5 hours. Filtration through a plug of silica gel eluting with CH$_2$Cl$_2$ followed by
evaporation of the solvent gave a purple solid of 179 (0.03 g, 0.03 mmol, 82%): mp >310 °C; \( R_f = 0.28 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:5, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \( \delta = -2.77 \) (s, 2H, phenyl-\( H \)), 1.22 (s, 48H, -C(CH\(_3\))\(_i\)), 7.52 (s, 2H, phenyl-\( H \)), 7.79 (s, 1H, phenyl-\( H \)), 7.89 (s, 5H, phenyl-\( H \)), 8.06 (s, 2H, phenyl-\( H \)), 8.42 (br. s, 2H, phenyl-\( H \)), 8.73 (d, \( J = 1.8 \) Hz, 2H, phenyl-\( H \)), 8.81 (d, \( J = 1.8 \) Hz, 2H, phenyl-\( H \)), 8.85 (d, \( J = 4.8 \) Hz, 5H, \( \beta \)-\( H \)), 8.95 ppm (s, 2H, \( \beta \)-\( H \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 29.7, 31.9, 35.1, 52.0, 53.5, 121.0, 121.5, 122.2, 127.0, 128.6, 129.8, 130.7, 141.6, 148.7, 167.2 \) ppm; UV-vis (CH\(_2\)Cl\(_2\)): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 426 (5.25), 523 (4.20), 560 (4.04), 598 (3.90), 653 nm (3.95); HRMS (ES+) \([\text{C}_{83}\text{H}_{98}\text{N}_4\text{O}_2]\): calcd for [M+H]\(^+\) 1183.7768, found. 1183.7727.

\[ \text{[5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-\( \beta \)-butylphenyl)porphyrinato]zinc(II)} \] (180)

\[ \text{[5,10,15-Tris(3,5-di-\( \beta \)-butylphenyl)-20(4-methoxycarbonylphenyl)porphyrinato]zinc(II)} \] (166) (0.12 g, 0.13 mmol) was heated to reflux in THF (5 mL), ethanol (20 mL) and 2N NaOH (20 mL) for 5 hours. Filtration through a plug of silica gel eluting with CH\(_2\)Cl\(_2\) followed by evaporation of the solvent yielded a purple solid of 180 (0.10 g, 0.10 mmol, 82%): mp >310 °C; \( R_f = 0.32 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \( \delta = 1.40 \) (s, 36H, -C(CH\(_3\))\(_i\)), 1.52 (s, 18H, -C(CH\(_3\))\(_3\)), 7.68 (s, 1H, phenyl-\( H \)), 7.78 (s, 2H, phenyl-\( H \)), 8.01 (s, 4H, phenyl-\( H \)), 8.08 (s, 2H, phenyl-\( H \)), 8.44 (s, 2H, phenyl-\( H \)), 8.97 (s, 2H, phenyl-\( H \)), 8.97 ppm (s, 8H, \( \beta \)-\( H \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 31.2, 34.5, 120.2, 122.1, 128.1, 129.2, 131.1, 131.7, 134.1, 141.3, 148.0, 149.2, 149.9, 149.9 \) ppm; UV-vis (CH\(_2\)Cl\(_2\)): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 423 (5.11), 551 (4.86), 589 nm (4.78); HRMS (ES+) \([\text{C}_{69}\text{H}_{76}\text{N}_4\text{O}_2\text{Zn}]\): calcd for [M+H]\(^+\) 1056.526, found. 1056.530.
6.9 Synthesis of o-nitrobenzyl porphyrins

Method A: DCC carbodiimide reagent approach

To a solution of porphyrin, N,N-dicyclohexylcarbodiimide (DCC), and dimethylamino-pyridine (DMAP) in dry THF, a solution of 2-nitrobenzylalcohol in THF was added at room temperature. The mixture was heated to reflux for 18 hours and diluted with THF before being extracted with a solution of aq. NH₄Cl. The organic solvent was washed with brine and dried over Na₂SO₄ followed by evaporation of the solvent under reduced pressure and purification by column chromatography.

5-(4-Di-cyclohexylurea-carbonylphenyl)-10,20-diphenylporphyrin (185)

5-(4-Carboxyphenyl)-10,20-diphenylporphyrin 173 (0.05 g, 0.09 mmol), DCC (17.7 mg, 0.09 mmol), DMAP (9.25 mg, 0.09 mmol) and 2-nitrobenzylalcohol (65.6 mg, 0.43 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 185 as a purple solid (26.4 mg, 0.02 mmol, 39%): mp >310 °C; Rf=0.32 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -3.01 (s, 2H, NH), 0.89 (m, 2H, -CH₂), 1.18 (m, 2H, -CH₂), 1.42 (m, 4H, -CH₂), 1.63 (m, 2H, -CH₂), 1.74 (m, 2H, -CH₂), 1.92 (m, 4H, -CH₂), 2.05 (m, 2H, -CH₂), 2.19 (m, 2H, -CH₂), 3.73 (m, 1H, -N-CH), 4.42 (m, 1H, -CON-CH), 6.33 (d, J= 7.0 Hz, 1H, -NH), 7.79 (t, J= 7.6 Hz, 6H, phenyl-H), 7.97 (d, J= 7.6 Hz, 2H, phenyl-H), 8.24 (d, 4H, J=6.4 Hz, phenyl-H), 8.28 (d, J=7.6 Hz, 2H, phenyl-H), 8.82 (d, J=4.7 Hz, 2H, β-H), 8.92 (d, J=4.7Hz, 2H, β-H), 9.02 (d, J=4.7 Hz, 2H, β-H), 9.31 (d, J=4.7 Hz, 2H, β-H), 10.19 ppm (s, 1H, meso-H); ¹³C NMR (100 MHz, CDCl₃): δ=24.5, 26.0, 29.3, 30.5, 32.3, 57.1, 104.8, 118.5, 119.5, 124.8, 126.5, 127.4, 134.3, 135.9, 141.2, 144.9, 154.1, 167.4, 170.8 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε)= 413 (5.29), 509 (3.87), 542 (3.04), 586 (3.11), 654 nm (2.90); HRMS (ES+) [C₅₂H₄₀N₆O₂]: calcd for [M+H]^+ 789.3917 found 789.3934.
5-(4-Di-cyclohexylurea-carbonylphenyl)-15-hexyl-10,20-diphenylporphyrin (186)

5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin 174 (0.03 g, 0.04 mmol), DCC (9.3 mg, 0.04 mmol), DMAP (4.84 mg, 0.04 mmol) and 2-nitrobenzylalcohol (34.4 mg, 0.03 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 186 as a purple solid (11.7 mg, 0.01 mmol, 30%): mp >310 °C; Rf=0.37 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= −2.71 (s, 2H, NH), 0.89 (m, 2H, -CH2), 0.96 (t, J= 14.6 Hz, 3H, -CH3), 1.17 (m, 2H, -CH2), 1.42 (m, 4H, -CH2), 1.53 (m, 2H, -CH2), 1.61 (m, 2H, -CH2), 1.67 (m, 4H, -CH2), 1.75 (t, J=15.2 Hz, 2H, -CH2), 1.91 (m, 4H, -CH2), 2.01 (m, 2H, -CH2), 2.19 (m, 2H, -CH2), 2.58 (m, 2H, -CH2), 3.74 (m, 1H, -N-C), 4.41 (m, 1H, -CON-CH), 5.04 (t, J= 8.2 Hz, 2H, -CH2), 6.31 (d, J=7.0 Hz, 1H, -NH), 7.81 (t, J= 7.6 Hz, 6H, phenyl-H), 7.98 (d, J= 7.6 Hz, 2H, phenyl-H), 8.24 (d, J=6.4 Hz, phenyl-H), 8.28 (d, J=7.6 Hz, 2H, phenyl-H), 8.76 (d, J=4.7 Hz, 2H, β-H), 8.84 (d, J=4.7 Hz, 2H, β-H), 8.95 (d, J=4.7 Hz, 2H, β-H), 9.52 ppm (d, J=4.7 Hz, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ=13.7, 22.3, 24.2, 26.0, 30.5, 31.5, 35.2, 38.5, 49.5, 57.1, 62.1, 119.4, 120.8, 124.9, 126.2, 127.3, 134.0, 141.9, 144.4, 154.1 ppm; UV-vis (CH2Cl2): λ_{max} (log ε)= 419 (5.31), 517 (3.94), 551 (3.64), 594 (4.51), 653 nm (3.75); HRMS (ES+) [C58H61N6O2]: calcd for [M+H]^+ 873.4856 found 873.4874.
Chapter 6: Experimental

5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-(o-nitrobenzyl-carboxy)phenyl)porphyrin (189)

5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-tert-butylphenyl)porphyrin 181 (0.02 g, 0.02 mmol), DCC (23.25 mg, 0.10 mmol), DMAP (12.10 mg, 0.10 mmol) and 2-nitrobenzylalcohol (0.11 g, 0.10 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. The crude product was purified on silica gel (n-hexane/dichloromethane = 2:1, v/v) and the first fraction corresponded to the title compound 189 as purple solid (8.6 mg, 0.01 mmol 38%): mp >310 °C; Rf=0.48 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.71 (s, 2H, N\textsubscript{4}), 1.52 (s, 54H, -C\textsubscript{6}H\textsubscript{5}), 5.96 (s, 2H, -OC\textsubscript{6}H\textsubscript{5}), 7.55 (t, J= 7.6 Hz, 1H, phenyl-H\textsubscript{1}), 7.73 (d, J=8.1 Hz, 1H, phenyl-H\textsubscript{2}), 7.76 (s, 3H, phenyl-H\textsubscript{3}), 7.86 (d, J=7.9 Hz, 1H, phenyl-H\textsubscript{4}), 8.08 (t, J=7.9 Hz, 6H, phenyl-H\textsubscript{5}), 8.20 (d, J=8.1 Hz, 1H, phenyl-H\textsubscript{6}), 8.35 (d, J=8.2 Hz, 2H, phenyl-H\textsubscript{7}), 8.48 (d, J=8.2 Hz, 2H, phenyl-H\textsubscript{8}), 8.79 (d, J=4.7 Hz, 2H, β-H\textsubscript{A}), 8.91 ppm (s, 6H, β-H\textsubscript{B}); 13C NMR (100 MHz, CDCl\textsubscript{3}): δ=13.7, 22.3, 29.3, 31.3, 34.6, 63.2, 120.6, 121.2, 127.6, 128.7, 129.4, 134.3, 140.7, 148.3, 165.8 ppm; UV-vis (CH\textsubscript{2}Cl\textsubscript{2}): λ\textsubscript{max} (log ε)= 422 (5.16), 518 (4.66), 571 (4.65), 599 (4.61), 651 nm (4.65); HRMS (ES+) [C\textsubscript{76}H\textsubscript{83}N\textsubscript{5}O\textsubscript{4}]: calcd for [M+H]\textsuperscript{+} 1130.6523, found 1130.6526.

Alternatively compound 189 was prepared via method B. 5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-tert-butylphenyl)porphyrin 181 (0.02 g, 0.02 mmol), EDAC (7.66 mg, 0.04 mmol), DMAP (4.88 mg, 0.04 mmol) and 2-nitrobenzylalcohol (12.4 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL). Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 189 as a purple solid (19.5 mg, 0.02 mmol, 86%).
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5-(4-Di-cyclohexylurea-carbonylphenyl)-10,15,20-tris(3,5-di-tert-butylphenyl) porphyrin (187)

The second fraction from the synthesis of porphyrin 189 via method A corresponded to 5-(4-di-cyclohexylurea-carbonyl phenyl)-10,15,20-tris(3,5-di-tert-butylphenyl)porphyrin 187 as a purple solid (10.3 mg, 0.01 mmol, 43%): mp >310 °C; Rf=0.46 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.69 (s, 2H, NH), 0.89 (m, 2H, -CH2), 1.18 (m, 2H, -CH2), 1.43 (m, 4H, -CH2), 1.52 (s, 54H, -C(CH3)3), 1.80 (m, 2H, -CH2), 1.96 (m, 4H, -CH2), 2.06 (m, 2H, -CH2), 2.20 (m, 2H, -CH2), 2.56 (m, 2H, -CH2), 3.74 (d, J=7.6 Hz, 1H, -NCH), 4.45 (t, J=11.7 Hz, 1H, CON-CH), 6.23 (d, J=6.4 Hz, 1H, -NH), 7.85 (d, J=1.8 Hz, 3H, phenyl-H), 8.00 (d, J=7.0 Hz, 2H, phenyl-H), 8.12 (dd, J1=1.8 Hz, J2=1.8 Hz, 6H, phenyl-H), 8.34 (d, J=7.0 Hz, 2H, phenyl-H), 8.82 (d, 2H, β-H), 8.95 ppm (s, 6H, β-H); 13C NMR (100 MHz, CDCl3): δ=24.3, 26.0, 29.3, 31.3, 32.3, 34.6, 62.1, 117.4, 120.6, 121.2, 124.6, 128.0, 129.5, 133.7, 136.3, 140.7, 148.3, 154.1, 165.7 ppm; UV-vis (CH2Cl2): λmax (log ε)= 421 (5.33), 518 (3.64), 554 (3.20), 596 (2.60), 655 nm (3.64); HRMS (ES+) [C82H60N6O2]: calcd for [M+H]+ 1201.799 found 1201.804.

5-(4-β-Nitrobenzylcarboxyphenyl)-10,15,20-triphenylporphyrin (190)

5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin 182 (0.02 g, 0.03 mmol), DCC (34.88 mg, 0.15 mmol), DMAP (18.15 mg, 0.15 mmol) and 2-nitrobenzylalcohol (0.17 g, 0.15
mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. The crude product was purified on silica gel (n-hexane/dichloromethane = 2:1, v/v) and the first fraction corresponded to the title compound of 5-(4-((o-nitrobenzyl carboxy)phenyl)-10,15,20-triphenylporphyrin 190 as a purple solid (6.6 mg, 0.01 mmol, 27%). >310 °C; \( R_f \approx 0.69 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \( \delta \approx -2.80 \) (s, 2H, NH), 5.95 (s, 2H, -OCH\(_2\)), 7.55 (t, \( J = 8.2 \) Hz, 1H, phenyl-H), 7.72 (d, \( J = 2.8 \) Hz, 1H, phenyl-H), 7.76 (t, \( J = 7.3 \) Hz, 9H, phenyl-H), 7.86 (d, \( J = 7.0 \) Hz, 1H, phenyl-H), 8.18 (s, 1H, phenyl-H), 8.20 (m, 6H, phenyl-H), 8.32 (d, \( J = 8.2 \) Hz, 2H, phenyl-H), 8.47 (d, \( J = 8.2 \) Hz, 2H, phenyl-H), 8.79 (d, \( J = 4.7 \) Hz, 2H, \( \beta \)-H), 8.84 ppm (t, \( J = 5.2 \) Hz, 6H, \( \beta \)-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 13.70, 22.27, 29.27, 31.49, 63.25, 117.84, 119.97, 124.79, 126.29, 127.67, 131.93, 133.49, 134.11, 141.57, 147.17, 147.28, 165.73 ppm; UV-vis (CH\(_2\)Cl\(_2\)): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 419 (5.15), 516 (4.59), 551 (4.51), 597 (4.48), 649 nm (4.54); HRMS (ES\(^+\)) [C\(_{52}\)H\(_{36}\)N\(_5\)O\(_4\)]: calcd for [M+H]\(^+\) 794.2767, found 794.2781.

Alternatively compound 190 was prepared via method B. 5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin 182 (0.02 g, 0.03 mmol), EDAC (5.83 mg, 0.03 mmol), DMAP (3.71 mg, 0.03 mmol) and 2-nitrobenzylalcohol (4.66 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) at rt. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 190 as a purple solid (17.6 mg, 0.01 mmol, 73%).

5-(4-Di-cyclohexylurea-carbonylphenyl)-10,15,20-triphenylporphyrin (188)

The second fraction from the synthesis of porphyrin 190 via method A corresponded to 5-(4-dicyclohexylurea-carbonylphenyl)-10,15,20-triphenylporphyrin 188 as a purple solid (13.7 mg, 0.12 mmol, 52%); mp >310 °C; \( R_f = 0.52 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \( \delta = -2.83 \) (s, 2H, NH), 0.86 (m, 2H, -CH\(_2\)), 1.16 (m, 2H, -CH\(_2\)), 1.38 (m, 4H, -CH\(_2\)), 1.61 (m, 2H, -CH\(_2\)), 1.71 (m, 2H, -CH\(_2\)), 1.89 (m, 4H, -CH\(_2\)), 2.02 (m, 2H, -CH\(_2\)), 2.14 (m, 2H, -CH\(_2\)), 3.73 (m, 1H, -N-CH\(_2\)), 4.37 (m, 1H, CON-CH\(_2\)),...
6.30 (d, 1H, -NH), 7.75 (d, J= 6.4 Hz, 9H, phenyl-\(H\)), 7.95 (d, J= 7.0 Hz, 2H, phenyl-\(H\)), 8.20 (d, 6H, J=7.0 Hz, phenyl-\(H\)), 8.26 (d, J=7.0 Hz, 2H, phenyl-\(H\)), 8.77 (s, 2H, \(\beta\)-\(H\)), 8.83 ppm (s, 6H, \(\beta\)-\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)=29.3, 32.2, 62.1, 124.6, 126.3, 127.4, 128.0, 129.5, 133.7, 134.1, 141.6, 167.5 ppm; UV-vis (CH\(_2\)Cl\(_2\)): \(\lambda_{max}\) (log e)= 418 (5.16), 515 (3.95), 550 (3.75), 597 (3.64), 649 nm (3.72); HRMS (ES+) [C\(_{58}\)H\(_{53}\)N\(_6\)O\(_2\)]: calcd for [M+H]\(^+\) 865.423, found 865.4211.

**Method B: EDAC carbodiimide reagent approach**

To a solution of porphyrin (1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (2 eq.) and dimethylaminopyridine, (DMAP) (2 eq.) in dry DCM, a solution of 2-nitrobenzylalcohol (4 eq.) in DCM was added at rt. The mixture was stirred at rt for 18 hours. Upon completion, the solution was diluted with DCM and extracted with a solution of aqueous NH\(_4\)Cl. The mixture was washed with brine and dried over Na\(_2\)SO\(_4\), followed by evaporation of the solvent to give the crude product and purification by column chromatography.

**5-Hexyl-15-(2-o-nitrobenzyl-carboxyethenyl)-10,20-diphenylporphyrin (193)**

5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin 171 (0.01 g, 0.02 mmol), EDAC (6.21 mg, 0.03 mmol), DMAP (3.95 mg, 0.03 mmol) and 2-nitrobenzylalcohol (10.05 mg, 0.06 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (\(n\)-hexane/dichloromethane = 1:2, v/v) yielded 193 as a purple solid (9.88 mg, 0.01 mmol, 81%): mp >310 °C; Rf=0.53 (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta\)= -2.39 (s, 2H, NH\(_3\)), 0.88 (t, J=7.3 Hz, 3H, -CH\(_2\)), 1.36 (m, 2H, -CH\(_2\)), 1.47 (m, 2H, -CH\(_2\)), 1.77 (m, 2H, -CH\(_2\)), 2.49 (m, 2H, -CH\(_2\)), 4.93 (t, J=7.6 Hz, 2H, -CH\(_2\)), 5.88 (s, 2H, -OCH\(_3\)), 6.86 (d, J=15.8 Hz, 1H, -CH\(_2\)=), 7.53 (t, J=8.2 Hz, 2H, phenyl-\(H\)), 7.70 (d, J=7.6 Hz, 1H, phenyl-\(H\)), 7.77 (m, 6H, phenyl-\(H\)), 7.83 (d, J=7.6 Hz, 1H, phenyl-\(H\)).
phenyl-$H$), 8.16 (dd, $J_1$=7.6 Hz, $J_2$=7.0 Hz, 4H, phenyl-$H$), 8.84 (dd, $J_1$=4.7 Hz, $J_2$=4.7 Hz, 4H, $\beta$-$H$), 9.41 (t, $J$=4.7 Hz, 4H, $\beta$-$H$), 10.27 ppm (d, $J$= 15.8 Hz, 1H, =C$\equiv$H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=13.7, 22.3, 29.3, 29.8, 31.4, 35.1, 38.4, 62.1, 62.9, 120.3, 122.6, 124.6, 126.3, 127.5, 128.0, 128.7, 129.5, 134.0, 136.3, 141.7, 146.7 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 427 (5.46), 526 (4.62), 572 (4.66), 599 (4.56), 653 nm (4.56); HRMS (ES+) [C$_{49}$H$_{41}$N$_5$O$_4$]: calcd for [M+H]$^+$ 752.3231, found 752.3237.

5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(2-o-nitro-benzylcarboxyethenyl)porphyrin (194)

5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin 172 (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.05 mmol), DMAP (6.71 mg, 0.05 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.10 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 194 as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; R$_f$=0.36 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= -2.41 (s, 2H, NH), 0.90 (t, $J$=7.3 Hz, 3H, -CH$_3$), 1.37 (m, 2H, -CH$_2$), 1.48 (m, 2H, -CH$_2$), 1.78 (m, 2H, -CH$_2$), 2.49 (m, 2H, -CH$_2$), 4.13 (t, $J$=7.6 Hz, 2H, -CH$_2$), 4.94 (s, 6H, -OCH$_3$), 5.89 (s, 2H, -OCH$_2$), 6.86 (d, $J$=15.8 Hz, 1H, -CH=), 7.33 (d, $J$=8.4 Hz, 2H, phenyl-$H$), 7.45 (t, $J$=8.0 Hz, 2H, phenyl-$H$), 7.53 (t, $J$=7.7 Hz, 1H, phenyl-$H$), 7.64 (t, $J$=7.7 Hz, 4H, phenyl-$H$), 7.83 (d, $J$=7.7 Hz, 1H, phenyl-$H$), 8.07 (d, $J$=8.1 Hz, 1H, phenyl-$H$), 8.17 (d, $J$=8.0 Hz, 1H, phenyl-$H$), 8.88 (dd, $J_1$=4.4 Hz, $J_2$=4.4 Hz, 4H, $\beta$-$H$), 9.41 (s, 4H, $\beta$-$H$), 10.26 ppm (d, $J$=15.8 Hz, 1H, =C$\equiv$H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=14.2, 22.7, 28.2, 31.9, 35.5, 38.9, 55.5, 62.6, 110.6, 117.9, 120.4, 126.3, 128.9, 134.2, 143.4, 144.6, 148.0, 165.6, 169.7 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 426 (5.26), 527 (3.72), 575 (4.79), 600 (4.75), 652 nm (4.75); HRMS (ES+) [C$_{50}$H$_{45}$N$_5$O$_4$]: calcd for [M+H]$^+$ 812.3455, found 812.3448.
5-Hexyl-15-(4-(o-nitrobenzylcarboxy)phenyl)-10,20-diphenylporphyrin (195)

5-Hexyl-15-(4-carboxyphenyl)-10,20-diphenylporphyrin 174 (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 195 as a purple solid (13.0 mg, 0.01 mmol, 81%): mp >310 °C; Rf=0.75 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.75 (s, 2H, NH), 0.92 (t, J=7.3 Hz, 3H, -CH3), 1.40 (m, 2H, -CH2), 1.46 (m, 2H, -CH2), 1.76 (m, 2H, -CH2), 2.54 (m, 2H, -CH2), 5.01 (t, J=8.0 Hz, 2H, -CH2), 5.95 (s, 2H, -OCH2), 7.50 (t, J=8.2 Hz, 1H, phenyl-H), 7.56 (d, J=2.8 Hz, 1H, phenyl-H), 7.74 (m, J=7.3 Hz, 6H, phenyl-H), 7.86 (d, J=7.0 Hz, 1H, phenyl-H), 8.18 (dd, J1=1.8 Hz, J2=1.1 Hz, 4H, phenyl-H), 8.24 (s, 1H, phenyl-H), 8.29 (d, J=8.4 Hz, 2H, phenyl-H), 8.45 (d, J=8.4 Hz, 2H, phenyl-H), 8.72 (d, J=4.8 Hz, 2H, β-H), 8.79 (d, J=4.8 Hz, 2H, β-H), 8.89 (d, J=4.8 Hz, 2H, β-H), 9.48 ppm (d, J=4.8 Hz, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ=14.1, 22.7, 29.4, 30.1, 30.3, 31.5, 32.0, 35.0, 63.7, 124.2, 124.4, 125.3, 126.7, 127.8, 128.0, 128.9, 128.9, 129.2, 130.9, 133.9, 134.7, 142.3, 151.2, 151.9 ppm; UV-vis (CH2Cl2): λmax (log ε)= 419 (5.48), 516 (4.48), 551 (4.37), 592 (4.33), 651 nm (4.29); HRMS (ES+) [C52H44N5O4]: calcd for [M+H]+ 802.3393, found 802.3401.
5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(4-(o-nitrobenzylcarboxy)phenyl)-porphyrin (196)

5-(3-carboxyphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin 175 (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.06 mmol), DMAP (6.71 mg, 0.06 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.11 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:1, v/v) yielded 196 as a purple solid (19.6 mg, 0.02 mmol, 83%): mp = 227 °C; Rf=0.38 (SiO2, EtOAc/C6H14, 1:3, v/v); ¹H NMR (400 MHz, CDCl3, TMS): δ= -2.84 (s, 2H, NH), 0.92 (t, J=7.3 Hz, 3H, -CH₃), 1.38 (m, 2H, -CH₂), 1.51 (m, 2H, -CH₂), 1.60 (m, 2H, -CH₂), 1.82 (m, 2H, -CH₂), 3.98 (s, 6H, -OCH₃), 4.99 (t, J=7.7 Hz, 2H, -CH₂), 5.93 (s, 2H, -OCH₂), 7.33 (d, J=8.1 Hz, 2H, phenyl-H), 7.53 (t, J=7.7 Hz, 1H, phenyl-H), 7.58 (t, J=8.0 Hz, 2H, phenyl-H), 7.72 (t, J=7.36 Hz, 1H, phenyl-H), 7.78 (t, J=7.7 Hz, 4H, phenyl-H), 7.83 (d, J=7.7 Hz, 1H, phenyl-H), 8.17 (d, J= 8.1 Hz, 1H, phenyl-H), 8.29 (d, J=8.4 Hz, 2H, phenyl-H), 8.46 (d, J=8.4 Hz, 2H, phenyl-H), 8.73 (d, J=4.8 Hz, 2H, β-H), 8.85 (d, J=4.8 Hz, 2H, β-H), 8.95 (d, J=4.8 Hz, 2H, β-H), 9.46 ppm (d, J=4.8 Hz, 2H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ=14.2, 22.7, 29.7, 30.3, 31.9, 35.6, 39.0, 55.6, 62.4, 63.7, 113.6, 117.5, 119.6, 120.5, 121.4, 125.0, 127.5, 128.4, 128.9, 129.8, 132.4, 133.9, 134.8, 136.8, 143.5, 147.5, 157.9, 166.2 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε)= 419 (5.31), 514 (4.26), 550 (4.15), 578 (4.30), 654 nm (4.45); HRMS (ES⁺) [C₅₄H₄₇N₅O₆]: calcd for [M+H]⁺ 862.3605, found 862.3610.
5,15-Bis(3,5-di-tert-butylphenyl)-10,20-bis(3-(o-nitrobenzylcarboxy)phenyl)porphyrin (198)

5,15-Bis(3,5-di-tert-butylphenyl)-10,20-bis(3-carboxyphenyl)-porphyrin 178 (0.01 g, 0.01 mmol), EDAC (10.91 mg, 0.11 mmol), DMAP (6.94 mg, 0.11 mmol) and 2-nitrobenzylalcohol (17.63 mg, 0.23 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:1, v/v) yielded the title compound 198 as a purple solid (8.30 mg, 0.01 mmol, 58%): mp >310 °C; Rf=0.48 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ^1H NMR (400 MHz, CDCl₃, TMS): δ= −2.76 (s, 2H, NH), 1.51 (s, 36H, -C(CH₃)₃), 5.85 (s, 4H, -OCH₂), 7.42 (t, J=7.3 Hz, 2H, phenyl-H), 7.57 (t, J=7.7 Hz, 2H, phenyl-H), 7.69 (d, J=7.7 Hz, 2H, phenyl-H), 7.79 (s, 2H, phenyl-H), 7.87 (t, J=7.7 Hz, 2H, phenyl-H), 8.08 (d, J=9.6 Hz, 6H, phenyl-H), 8.44 (d, J=8.1 Hz, 2H, phenyl-H), 8.51 (d, J=8.51 Hz, 2H, phenyl-H), 8.77 (s, 2H, phenyl-H), 8.78 (s, 2H, β-H), 8.90 (d, J=4.76 Hz, 4H, β-H), 8.94 ppm (s, 2H, β-H); ^13C NMR (100 MHz, CDCl₃): δ=27.9, 29.7, 31.7, 35.1, 36.2, 52.3, 59.4, 63.6, 118.4, 121.2, 122.0, 125.1, 126.6, 128.4, 129.6, 132.3, 133.9, 137.6, 138.8, 140.9, 142.9, 147.5, 148.9, 151.6, 166.2, 171.0 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε) = 420 (5.30), 514 (4.53), 545 (4.48), 577 (4.53), 652 nm (4.51); HRMS (ES⁺) [C₇₆H₇₂N₆O₈]: calcd for [M+H]^⁺ 1197.5490, found 1197.5450.

5,10,15,20-Tetrakis(3,5-di-tert-butylphenyl)-2-(4-(o-nitrobenzylcarboxy)phenyl) porphyrin (199)

2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butyl-phenyl)porphyrin 179 (0.01 g, 0.01 mmol), EDAC (3.24 mg, 0.02 mmol), DMAP (2.06 mg, 0.02 mmol) and 2-
nitrobenzylalcohol (5.24 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:1, v/v) yielded 199 as a purple solid (7.57 mg, 0.01 mmol, 68%): mp >310 °C; Rf=0.82 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.56 (s, 2H, -N//), 1.50 (s, 72H, -C(CH3)3), 5.81 (s, 2H, -OCH2), 7.34 (t, J=1.8 Hz, 1H, phenyl-H), 7.50 (d, J=8.0 Hz, 1H, phenyl-H), 7.69 (m, 4H, phenyl-H), 7.77 (m, 4H, phenyl-H), 7.82 (d, J=1.8 Hz, 2H, phenyl-H), 7.85 (d, J=8.4 Hz, 1H, phenyl-H), 8.06 (dd, J1=1.8 Hz, J2=1.8 Hz, 4H, phenyl-H), 8.12 (d, J=1.8 Hz, 2H, phenyl-H), 8.18 (d, J=8.1 Hz, 1H, phenyl-H), 8.71 (d, J=4.8 Hz, 1H, β-H), 8.74 (s, 1H, β-H), 8.82 (m, 1H, β-H), 8.85 (d, J=3.6 Hz, 2H, β-H), 8.90 ppm (m, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ=14.2, 23.9, 29.4, 30.1, 32.8, 34.9, 37.1, 121.0, 128.7, 129.6, 130.0, 130.7, 133.8, 140.0, 148.0, 148.6, 148.8, 165.9 ppm; UV-vis (CH2Cl2): λmax (log ε)= 426 (5.23), 525 (4.23), 576 (4.30), 601 (4.28), 653 nm (4.33); HRMS (ES+) [C90H103N3O4]: calcd for [M+H]+ 1318.8090, found 1318.8030.

5-Hexyl-15-(3'-o-nitrobenzylcarboxy)phenyl-10,20-diphenylporphyrin (200)

5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin 176 (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (n-hexane/dichloromethane = 1:1, v/v) yielded 200 as a purple solid (16.8 mg, 0.01 mmol, 70%): mp >310 °C; Rf=0.60 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.74 (s, 2H, NH), 0.92 (t, J=7.3 Hz, 3H, -CH3), 1.36 (m, 2H, -CH2), 1.50 (m, 2H, -CH2), 1.80 (m, 2H, -CH2), 2.54 (m, 2H, -CH2), 5.00 (t, J=8.0 Hz, 2H, -CH2), 5.83 (s, 2H, -OCH2), 7.38 (t, J=8.4 Hz, 1H, phenyl-H), 7.52 (t, J=7.7 Hz, 1H, phenyl-H), 7.65 (d, J=7.7 Hz, 1H, phenyl-H), 7.76 (m, 6H, phenyl-H), 7.85 (t, J=7.7 Hz, 1H, phenyl-H), 8.06 (d, J=8.4 Hz, 1H, phenyl-H), 8.19 (d, J=6.2 Hz, 4H, phenyl-H), 8.41 (d, J=7.7 Hz, 1H, phenyl-H), 8.49 (d, J=7.7 Hz, 1H, phenyl-H), 8.72 (d, J=4.8 Hz, 2H, β-H), 8.80 (d, J=4.8 Hz, 2H, β-H), 8.91 (t, J=2.2 Hz, 3H, β-H and phenyl-H), 9.48 ppm (d, J=4.8 Hz, 2H, β-H); 13C NMR (100 MHz, CDCl3): δ=14.2, 22.7, 29.5, 29.7, 30.3, 31.9,
35.6, 39.0, 63.6, 117.5, 119.8, 121.2, 125.1, 126.7, 127.1, 127.8, 128.3, 129.2, 133.8, 134.9, 142.3, 147.4, 166.2 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$)= 418 (5.48), 516 (4.47), 551 (4.36), 594 (4.32), 650 nm (4.33); HRMS (ES$^+$) [C$_{52}$H$_{44}$N$_5$O$_4$]: calcd for [M+H]$^+$ 802.3393, found 802.3380.

[5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-(o-nitrobenzylcarboxy)phenyl)porphyrinato]zinc(II) (201)

[5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-tert-butyl-phenyl)porphyrinato]zinc(II) (0.02 g, 0.02 mmol), EDAC (7.21 mg, 0.04 mmol), DMAP (4.59 mg, 0.04 mmol) and 2-nitrobenzylalcohol (11.5 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded 201 as a purple solid (19.4 mg, 0.02 mmol, 81%): mp >310 °C; $R_f$=0.65 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$=1.52 (s, 54H, -C(CH$_3$)$_3$), 5.91 (s, 2H, -OCH$_2$), 7.52 (t, $J$=8.4 Hz, 1H, phenyl-H), 7.73 (t, $J$=8.4 Hz, 1H, phenyl-H), 7.79 (m, 3H, phenyl-H), 7.83 (d, $J$=8.0 Hz, 1H, phenyl-H), 8.08 (m, 6H, phenyl-H), 8.18 (dd, $J_1$=1.8 Hz, $J_2$=1.8 Hz, 1H, phenyl-H), 8.35 (d, $J$=8.2 Hz, 2H, phenyl-H), 8.48 (d, $J$=8.2 Hz, 2H, phenyl-H), 8.89 (d, $J$=4.7 Hz, 2H, $\beta$-H), 8.91 ppm (s, 6H, $\beta$-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=22.7, 29.7, 31.8, 35.1, 63.6, 118.9, 120.9, 122.7, 125.2, 127.9, 128.9, 129.6, 132.4, 133.9, 134.6, 141.7, 148.6, 149.4, 150.4, 166.3 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$)= 423 (5.29), 549 (4.65), 650 nm (4.54); HRMS (ES$^+$) [C$_{76}$H$_{81}$$\text{N}_5$$\text{O}_4$$\text{Zn}$]: calcd for [M] 1191.5580, found 1191.5614.

6.10 Synthesis of porphyrin linked-bioconjugates

1-Hydroxyl-2,3,4,6-pentaacetyl-D-glucose 207, 5-hydroxy-2-nitrobenzylalcohol 211, (3-hydroxymethyl-4-nitrophenyl)-2,3,4,6-tetra-O-acetyl-$\beta$-$D$-galactopyranoside 213, 3-bromo-1,2:5,6-di-$O$-isopropylidene-$\alpha$-$D$-glucofuranoside 215 and 5-
(methoxyethoxymethyl)-2-nitrobenzaldehyde \textsuperscript{221} were prepared according to literature procedure and their spectroscopic data were in accordance with the references.

\textbf{(3-Hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-\(O\)-isopropylidene-\(\alpha\)-D-glucofuranoside (217)}

3-Bromo-1,2:5,6-di-\(O\)-isopropylidene-\(\alpha\)-D-glucofuranoside \textsuperscript{215} (1.80 g, 5.80 mmol) was dissolved in \(\text{CH}_2\text{Cl}_2\) (15 mL) together with 1 equivalent of tetrabutylammonium fluoride (1.50 g, 5.80 mmol) and 3 equivalents of 5-hydroxy-2-nitrobenzyl alcohol \textsuperscript{211} (2.95 g, 17.40 mmol). 1M NaOH solution (15 mL) was added and the reaction mixture was stirred vigorously at 35 °C in h. After dilution with EtOAc, the organic phase was washed three times with a 1M NaOH solution, twice with water and finally with brine. The organic phase was dried with magnesium sulphate and then the solvent removed under diminished pressure. Purification was carried out by chromatography (SiO\(_2\), EtOAc/C\(_6\)H\(_4\)= 20:1, v/v) and yielded \textsuperscript{217} as a white solid (0.12 g, 0.15 mmol, 5\%): mp = 145 °C; MALDI-TOF MS (ES\(^+\)): calcd for [M+Na\(^+\)-C\(_4\)H\(_7\)NO\(_2\)] 333.0950, found 333.0945.
5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4′-(o-nitro-p-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranoside)benzyl)carboxy)phenyl)porphyrin (218)

5-(Carboxyphenyl)-10,15,20-tris(3,5-di-tert-butylphenyl)porphyrin 181 (0.08 g, 0.08 mmol), EDAC (30.8 mg, 0.16 mmol), DMAP (19.6 mg, 0.16 mmol) and 5-((aceto-glucose)-2-nitrophenyl)methanol (0.16 g, 0.32 mmol) were stirred for 18 h in DCM (15 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH₄Cl. The mixture was washed with brine and dried over Na₂SO₄, followed by evaporation of the solvent to give the crude product. Purification on silica gel (n-hexane/dichloromethane=1:1, v/v) yielded 218 as a purple solid (90.3 mg, 0.02 mmol, 76%): mp >310 °C; Rf=0.32 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -2.71 (s, 2H, NH), 1.52 (s, 54H, -CH₃(CH)₃), 1.83 (s, 3H, -COCH₃), 1.99 (s, 3H, -COCH₃), 2.06 (s, 6H, -COCH₂), 3.91 (m, 1H, -CH), 4.16 (d, J=10.5 Hz, 1H, -CH), 4.28 (dd, J₁=5.0 Hz, J₂=5.0 Hz, 1H, -CH), 5.18 (m, 1H, -CH), 5.31 (m, 3H, -CH and -CH₂CO), 5.97 (s, 2H, -OCH₂), 7.10 (dd, J₁=2.2 Hz, J₂=2.2 Hz, 1H, phenyl-H), 7.42 (d, J=2.28 Hz, 1H, phenyl-H), 7.79 (s, 3H, phenyl-H), 8.07 (s, 6H, phenyl-H), 8.27 (d, J=9.0 Hz, 1H, phenyl-H), 8.38 (d, J=8.0 Hz, 2H, phenyl-H), 8.49 (d, J=8.0 Hz, 2H, phenyl-H), 8.79 (d, J=4.5 Hz, 2H, β-H), 8.91 ppm (s, 6H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ=31.8, 35.1, 61.7, 63.7, 67.8, 70.9, 72.4, 98.1, 115.7, 116.8, 117.6, 121.1, 121.7, 122.1, 128.1, 128.6, 129.8, 134.8, 135.7, 141.1, 142.4, 148.3, 160.5, 169.2, 170.1, 170.4 ppm; UV-vis (CH₂Cl₂): λmax (log ε)= 421 (5.18), 518 (3.81), 553 (3.60), 593 (3.41), 667 nm (3.75); HRMS (ES+) [C₉₀H₁₀₁N₅O₁₄]: calcd for [M+H]+ 1476.7420, found 1476.7410.
Chapter 6: Experimental

5-Hexyl-15-(4'-o-nitro-m-(1,2:5,6-di-O-isopropyldene-α-D-glucosanoside)benzyl-carboxy)phenyl)-10,20-diphenylporphyrin (219)

5-Hexyl-15-(4-carboxyphenyl)-10,20-diphenylporphyrin 174 (10 mg, 0.06 mmol), EDAC (18.2 mg, 0.12 mmol), DMAP (14.6 mg, 0.12 mmol) and (3-hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-O-isopropyldene-α-D-glucosanoside 217 (98 mg, 0.24 mmol) were stirred for 18 h in DCM (10 mL). Purification (SiO₂, n-hexane/dichloromethane= 1:1 v/v) yielded 219 as a purple solid (46 mg, 0.02 mmol, 72%): mp >310°C; R₉=0.30 (SiO₂, EtOAc/C₆H₁₄, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -2.76 (s, 2H, NH), 0.97 (t, J=7.0 Hz, 3H, -CH₃), 1.21 (m, 2H, -CH₂), 1.51 (s, 12H, -C(CH₃)₂), 1.68 (m, 2H, -CH₂), 1.93 (m, 2H, -CH₂), 2.67 (m, 2H, -CH₂), 4.00 (m, 1H, C-C=O), 4.04 (m, 1H, C-C=O), 4.27 (m, 1H, -CCH₂), 4.31 (d, J= 3.0 Hz, 1H, O-CH₂), 4.38 (m, 1H, O-CH₂), 4.44 (m, 1H, OCH₂-C), 5.04 (s, 2H, -OCH₂), 7.49 (dd, J= 2.8 Hz, 2.8Hz, 1H, phenyl-H), 7.84 (d, J= 2.5 Hz, 1H, phenyl-H), 7.98 (m, 6H, phenyl-H), 8.19 (d, J= 6.3 Hz, 1H, phenyl-H), 8.53 (m, 6H, phenyl-H), 8.59 (d, J= 3.8 Hz, 2H, phenyl-H), 8.77 (m, 4H, β-H), 8.91 (d, J= 4.8 Hz, 1H, β-H), 9.10 (d, J= 4.0 Hz, 4H, β-H), 9.49 ppm (d, J= 4.8 Hz, 1H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ= 24.6, 25.3, 25.6, 26.3, 26.5, 26.6, 26.8, 27.5, 38.4, 65.6, 66.0, 68.0, 73.0, 74.6, 75.6, 79.8, 80.5, 84.1, 105.0, 106.4, 108.5, 110.1, 110.9, 111.8, 114.2, 121.4, 122.4, 122.7, 125.0, 126.7, 127.1, 127.5, 128.5, 130.2, 130.4, 134.5, 138.8, 139.0, 145.1, 145.2, 145.9, 146.2, 155.2, 164.2 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε)= 419 (5.25), 514 (3.90), 551(3.56), 593 (3.45), 667 nm (3.51); HRMS (ES⁺) [C₆₄H₆₁N₅O₁₀]: caled for [M+H]⁺ 1060.4497, found 1060.4479.
5-(Methoxyethoxymethyl)-2-nitrophenylmethanol (222)

5-(Methoxyethoxymethyl)-2-nitrobenzaldehyde 221 (0.62 g, 2.44 mmol) was dissolved in THF and the solution was cooled to 0 °C. Sodium borohydride (92 mg, 2.44 mmol) was added and the mixture was stirred for 2 hours. The mixture was filtered through silica gel and the solvent was evaporated in vacuo to yield the title compound 222 as a yellow solid (0.62 g, 0.16 mmol, 98%): mp 98-101 °C; Rf=0.29 (SiO2, EtOAc/C6H14, 1:3, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 3.22 (s, 3H, -OC(CH3)), 3.45 (m, 2H, -CH(OH)), 3.72 (m, 2H, -OCH2), 4.11 (br.s, 1H, -OH), 4.84 (s, 2H, -CH2OH), 5.24 (s, 2H, -OCH2O), 6.88 (dd, J1=2.4 Hz, J2=2.3 Hz, 1H, phenyl-H), 7.30 (s, 1H, phenyl-H), 7.95 (d, J=9.36 Hz, 1H, phenyl-H), 13C NMR (100 MHz, CDCl3): δ= 58.3, 61.3, 67.6, 70.9, 92.6, 113.8, 114.6, 127.0, 139.8, 140.7, 161.2 ppm; HRMS (ES+) [C11H14N2O4]: calcd for [M+Na]+ 280.0797, found 280.0800.

5-Hexyl-15-(4-(o-nitro-p-methoxyethoxymethylbenzylcarboxy)phenyl)-10,20-diphenylporphyrin (223)

5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin 174 (0.05 g, 0.08 mmol), EDAC (28.8 mg, 0.15 mmol), DMAP (18.3 mg, 0.15 mmol) and 5-(methoxyethoxymethyl)-2-nitrophenylmethanol 222 (77.2 mg, 0.30 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH4Cl. The mixture was washed with brine and dried over Na2SO4, followed by evaporation of the
solvent to give the crude product. Purification on silica gel \(n\)-hexane/dichloromethane = 1:2, v/v) yielded 223 as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; \(R_f=0.36\) (SiO\(_2\), EtOAc/C\(_6\)\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta=-2.72\) (s, 2H, NH), 0.93 (t, \(J=6.8\) Hz, 3H, -CH\(_3\)), 1.38 (m, 2H, -CH\(_2\)), 1.50 (m, 2H, -CH\(_2\)), 1.80 (m, 2H, -CH\(_2\)), 2.52 (m, 2H, -CH\(_2\)), 3.31 (s, 3H, -OCH\(_3\)), 3.53 (t, \(J=3.9\) Hz, 2H, -OCH\(_2\)), 3.82 (t, \(J=3.9\) Hz, 2H, -CH\(_2\)O), 7.09 (dd, \(J_1=2.0\) Hz, \(J_2=2.0\) Hz, 1H, phenyl-\(H\)), 7.43 (d, \(J=1.96\) Hz, 1H, phenyl-\(H\)), 7.76 (m, 6H, phenyl-\(H\)), 8.20 (s, 1H, phenyl-\(H\)), 8.22 (d, \(J=5.8\) Hz, 4H, phenyl-\(H\)), 8.33 (d, \(J=7.8\) Hz, 2H, phenyl-\(H\)), 8.49 (d, \(J=7.8\) Hz, 2H, phenyl-\(H\)), 8.77 (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)), 8.84 (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)), 8.92 (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)), 9.46 ppm (d, \(J=4.9\) Hz, 2H, \(\beta\)-\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta=13.7, 22.3, 29.3, 29.8, 31.5, 35.2, 38.5, 58.6, 62.1, 62.7, 63.4, 67.9, 71.0, 93.0, 114.4, 115.7, 117.1, 119.4, 120.9, 126.2, 127.3, 127.7, 128.45, 134.0, 140.7, 141.8, 147.1, 159.7, 161.2, 165.7, 169.9 ppm; UV-vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (log \(\varepsilon\))= 418 (5.16), 516 (3.90), 551 (3.65), 594 (3.58), 653 nm (3.78); HRMS (ES\(^+\)) [C\(_{56}\)H\(_{51}\)N\(_5\)O\(_7\)]: calcd for [M+H]\(^+\) 906.3867, found 906.3899.

5-Hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin (224)

![](image)

5-Hexyl-15-(4-(o-nitro-p-(methoxyethoxymethyl)benzylcarboxy)phenyl)-10,20-di-phenyl porphyrin 223 (0.05 g, 0.06 mmol) was dissolved in a small amount of THF. Ethylene glycol (10 mL) was added to the solution and was heated at 140 °C for 5 hours (TLC monitoring). The reaction was cooled to room temperature and was washed with saturated aqueous sodium bicarbonate and brine. The solution was dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to yield 224 as a purple solid (64.7 mg, 0.05 mmol, 92%): mp >310 °C; \(R_f=0.44\) (SiO\(_2\), EtOAc/C\(_6\)\(_{14}\), 1:3, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta=-2.75\) (s, 2H, NH), 0.91 (t, \(J=7.0\) Hz, 3H, -CH\(_3\)), 1.37 (m, 2H, -CH\(_2\)), 1.50 (m, 2H, -CH\(_2\)), 1.80 (m, 2H, -CH\(_2\)), 2.52 (m, 2H, -CH\(_2\)), 4.09 (s, 2H,
-OCH$_2$), 4.64 (t, $J$=4.0 Hz, 2H, -CH$_2$OH), 5.00 (t, $J$=8.2 Hz, 2H, -CH$_2$), 7.74 (m, 6H, phenyl-H), 8.18 (d, $J$=6.4 Hz, 4H, phenyl-H), 8.27 (d, $J$=8.2 Hz, 2H, phenyl-H), 8.43 (d, $J$=8.2 Hz, 2H, phenyl-H), 8.71 (d, $J$=5.3 Hz, 2H, β-H), 8.79 (d, $J$=4.7 Hz, 2H, β-H), 8.90 (d, $J$=5.2 Hz, 2H, β-H), 9.47 ppm (d, $J$=4.7 Hz, 2H, β-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ=14.2, 22.7, 30.3, 31.9, 35.6, 39.0, 61.6, 67.0, 93.5, 114.9, 116.5, 117.6, 119.8, 121.3, 127.9, 128.9, 134.8, 142.3, 147.3, 167.2 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log ε)= 418 (5.17), 517 (2.30), 551 (3.45), 594 (3.28), 650 nm (3.38); HRMS (ES+) [C$_{47}$H$_{42}$N$_4$O$_3$]: calcd for [M+H]$^+$ 711.3335, found 711.3354.


5-(2-Carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) 225 (0.01 g, 0.02 mmol), EDAC (2.88 mg, 0.03 mmol), DMAP (1.83 mg, 0.03 mmol) and 5-hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin 224 (11 mg, 0.02 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH$_4$Cl. The mixture was washed with brine and dried over Na$_2$SO$_4$, followed by evaporation of the solvent to give the crude product. Purification on silica gel (n-hexane/dichloromethane = 1:2, v/v) yielded the title compound as a purple solid (19.0 mg, 0.03 mmol, 93%): mp >310 °C; R$_f$=0.15 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ= -2.78 (s, 2H, NH), 0.97 (t, $J$=7.3 Hz, 3H, -CH$_3$), 1.64 (m, 2H, -CH$_2$), 1.77 (m, 2H, -CH$_2$), 1.96 (m, 2H, -CH$_2$), 2.53 (m, 2H, -CH$_2$), 4.54 (m, 4H, -CH$_2$), 5.00 (m, $J$=7.6 Hz, 2H, -CH$_2$), 6.41 (d, $J$=15.2 Hz, 1H,-CH=C), 7.51 (m, 6H, phenyl-H),
7.69 (m, 9H, phenyl-H), 7.86 (d, J=7.0 Hz, 4H, phenyl-H), 7.91 (d, J=8.2 Hz, 2H, phenyl-H), 8.13 (d, J=6.44 Hz, 4H, phenyl-H), 8.25 (d, J=8.2 Hz, 2H, phenyl-H), 8.48 (d, J=8.2 Hz, 2H, phenyl-H), 8.57 (d, J=4.7 Hz, 2H, β-H), 8.63 (d, J=4.7 Hz, 2H, β-H), 8.66 (d, J=4.7 Hz, 2H, β-H), 8.69 (d, J=4.7 Hz, 2H, β-H), 8.77 (d, J=5.2 Hz, 2H, β-H), 8.87 (d, J=4.7 Hz, 2H, β-H), 9.39 (d, J=4.7 Hz, 2H, β-H), 9.46 (d, J=4.7 Hz, 2H, β-H), 9.98 ppm (d, J=15.8 Hz, 1H, =CH CO); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$=14.2, 20.8, 22.7, 23.4, 23.8, 25.0, 25.6, 29.1, 29.5, 29.7, 30.3, 31.9, 35.6, 38.9, 62.8, 63.2, 68.0, 73.6, 91.2, 109.3, 117.6, 119.5, 119.8, 120.5, 121.3, 126.6, 127.0, 127.0, 129.2, 130.7, 131.4, 132.3, 132.8, 133.5, 133.5, 134.5, 134.7, 140.2, 141.5, 142.2, 142.8, 144.8, 147.3, 166.2, 166.8 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 420 (5.11), 523 (4.41), 546 (4.41), 597 (4.40), 653 nm (4.45); HRMS (ES$^+$) [C$_{88}$H$_{66}$NiN$_8$O$_4$]: calcld for [M+H]$^+$ 1357.4639, found 1357.4669.


5-Hexyl-15-(4-(o-nitro-p-(methoxyethoxy-methyl)benzylcarboxyphenyl)-10,20-di-phenylporphyrin 223 (0.10 g, 0.11 mmol) was dissolved in CHCl$_3$. Two drops of TFA were added, followed by zinc(II)oxide (26.9 mg, 0.33 mmol). The solution was stirred for 18 hours and filtered. The solvent was evaporated and subjected to column chromatography (SiO$_2$, n-hexane/dichloromethane = 1:2, v/v) and gave the 227 as a purple solid (100.24 mg, 0.10 mmol, 94%): mp >310 °C; R$_f$=0.32 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$=0.93 (t, J=7.0 Hz, 3H, -CH$_3$), 1.40 (m, 2H, -CH$_2$), 1.50 (m, 2H, -CH$_2$), 1.84 (m, 2H, -CH$_2$), 2.55 (m, 2H, -CH$_2$), 3.15 (s, 3H, -OCH$_3$), 3.35 (t, J=4.1 Hz, 2H, -OCH$_2$), 3.39 (t, J=4.1 Hz, 2H, -CH$_2$OCH$_3$), 4.97 (t, J=8.2 Hz, 2H, -CH$_2$), 5.24 (s, 2H, -OCH$_2$), 5.85 (s, 2H, -OCH$_2$O), 7.03 (d, J=2.9 Hz, 1H, phenyl-H), 7.36 (d, J=2.4 Hz, 1H, phenyl-H), 7.74 (m, 6H, phenyl-H), 8.16 (s, 1H, phenyl-H), 8.18 (d, J=5.8 Hz, 4H, phenyl-
5-Hexyl-15-(4'-(o-nitro-p-hydroxybenzyl-carboxy)-phenyl)-10,20-diphenylporphyrin (228)

A solution of [5-hexyl-15-(3-o-nitro-p-(methoxyethoxymethyl)benzyl carboxyphenyl)-10,20-diphenylporphyrinato]zinc(II) 227 (0.06 g, 0.06 mmol) in CH₂Cl₂ (3.30 ml) was treated with trifluoroacetic acid (3.30 ml), stirred at rt for 7 hours and concentrated. The solution was neutralized with aqueous-KOH and extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to yield the title compound 228 as a purple solid (34.8 mg, 0.03 mmol, 71%): mp >310 °C; Rf=0.28 (SiO₂, EtOAc/C₆H₄, 1:3, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= -2.62 (s, 2H, NH), 0.93 (t, J=7.0 Hz, 3H, -CH₃), 1.38 (m, 2H, -CH₂), 1.49 (m, 2H, -CH₂), 1.79 (m, 2H, -CH₂), 2.53 (m, 2H, -CH₂), 4.98 (t, J=7.6 Hz, 2H, -CH₂), 5.86 (s, 2H, -OCH₂), 6.63 (dd, J₁=2.8 Hz, J₂=2.5 Hz, 1H, phenyl-H), 7.03 (s, 1H, phenyl-H), 7.73 (m, 6H, phenyl-H), 8.10 (dd, J₁=2.0 Hz, J₂=1.8 Hz, 1H, phenyl-H), 8.18 (m, 4H, phenyl-H), 8.26 (d, J=8.2 Hz, 2H, phenyl-H), 8.42 (d, J=7.6 Hz, 2H, phenyl-H), 8.71(d, J=4.6 Hz, 2H, β-H), 8.79 (d, J=4.7 Hz, 2H, β-H), 8.90 (d, J=4.7 Hz, 2H, β-H), 9.46 ppm (d, J=4.7 Hz, 2H, β-H); ¹³C NMR (100 MHz, CDCl₃): δ=14.2, 20.8, 22.7, 29.4, 32.0, 35.7, 39.0, 62.6, 114.9, 121.1, 126.7, 127.8, 128.2, 128.4, 129.7, 134.8, 142.3, 148.7, 161.3, 169.5 ppm; UV-vis (CH₂Cl₂): λ_max (log ε)= 419 (5.45), 517 (4.06), 551 (3.69), 594 (3.56), 650 nm (3.68); HRMS (ES+) [C₅₂H₄₃N₅O₃Zn]: calcd for [M+H]^+ 818.3342, found 818.3313.
5-Hexyl-15-(4',4',5',5'-tetramethyl(1',3',2')dioxaborolan-2'-yl)-10,20-bis(3-methoxyphenyl)porphyrin (231)

A Schlenk flask was charged with 5-bromo-15-hexyl-10,20-di(3'-methoxyphenyl)porphyrin 152 (0.5 g, 0.73 mmol), pinacolborane (0.18 mL, 1.22 mmol), triethylamine (0.26 mL, 1.90 mmol), trans-dichlorobis(triphenylphosphine)palladium(II) (4.38 mg, 0.004 mmol) and 1,2-dichloroethane (15 mL) under argon. The mixture was stirred at 90 °C for 30 min, at which point TLC showed that the 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin 152 was completely consumed. The reaction was quenched with aq. KCl (10 mL), washed with water and dried over MgSO4. The solvent was evaporated and the residue was taken up in CH2Cl2 and subjected to column chromatography (SiO2, n-hexane/dichloromethane= 1:2 v/v). The first isolate band corresponded to 5-hexyl-10,20-bis(3-methoxyphenyl)porphyrin 109 (0.16 g, 0.10 mmol, 36%), while the second band contained the title compound 231 as purple solid (0.16 g, 0.12 mmol, 30%).

Alternatively, a suspension of 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin 152 (0.2 g, 0.29 mmol), KOAc (0.29 g, 3.0 mmol) and bis(pinacolato)diboron (0.29 g, 1.16 mmol) in toluene (10 mL) and de-ionised water (20 ml) was degassed with nitrogen for 10 min, Pd(dppf)Cl2 (47.6 mg, 0.06 mmol) was added and the reaction mixture heated to 110 °C for 3.5 h with vigorous stirring. After addition of water and CH2Cl2 to the reaction mixture, the separated aqueous phase was extracted with CH2Cl2 and the combined organic layers then dried over MgSO4. Removal of the solvent in vacuo and purification by column chromatography (SiO2, n-hexane/dichloromethane= 1:2 v/v) yielded 231 as a purple solid (0.14 g, 0.10 mmol, 65 %). mp >310 °C; Rf=0.42 (SiO2, EtOAc/C6H14, 1:5, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= -2.54 (s, 2H, NH), 1.01 (t, J=7.0 Hz, 3H, -CH3), 1.45 (m, 2H, -CH2), 1.57 (m, 2H, -CH2), 1.84 (m, 2H, -CH2), 1.89 (s, 12H, -CH3), 2.59 (m, 2H, -CH2), 4.01 (s, 6H, -OCH3), 5.02 (t, J=7.6 Hz, 2H, -CH2), 7.42 (dd, J= 2.3 Hz, J= 2.4 Hz, 2H, phenyl-H), 7.23 (t, J= 8.2 Hz, 2H, phenyl-H), 7.90 (t, J= 7.04 Hz, phenyl-H), 9.01 (d, J=4.7 Hz, 2H, β-H), 9.07 (d, J=4.7 Hz, 2H, β-H), 9.13 (d, J=4.7 Hz,
2H, β-H), 9.21 (d, J=4.6 Hz, 2H, β-H), 9.99 ppm (d, J=4.7 Hz, 2H, β-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ= 22.3, 24.9, 29.9, 31.5, 35.1, 38.5, 55.1, 84.7, 105.9, 113.2, 118.9, 119.9, 122.3, 127.0, 127.2, 130.7, 131.4, 143.6, 157.5 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log ε)= 414 (5.08), 511 (3.83), 545 (3.41), 585 (3.48), 641 nm (3.30); HRMS (ES+) \([\text{C}_{46}\text{H}_{49}\text{BN}_4\text{O}_4]\): calcd for [M+H]$^+$ 733.3925, found 733.3911.

5-(3-Benzyl-4' -nitrobenzoic acid)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (233)

A Schlenk flask filled with 4-bromomethyl-3-nitrobenzoic acid (0.02 g, 0.07 mmol), boronic ester porphyrin 231 (0.05 g, 0.07 mmol), and Ba(OH)$_2$·8H$_2$O (0.22 g, 0.68 mol) was evacuated and flushed with argon. Toluene (10 mL) and de-ionised water (2 mL) were added and the solution was degassed with argon for 10 min. Then, Pd(PPh$_3$)$_4$ (15.8 mg, 13.6 μmol) was added and the reaction mixture heated to 110 °C for 14 h with vigorous stirring. After addition of water and CH$_2$Cl$_2$, the organic phase was separated, the aqueous layer extracted three times with CH$_2$Cl$_2$, and the combined organic layers dried over MgSO$_4$. Concentration of the filtrate and purification of the resulting residue by column chromatography (SiO$_2$, EtOAc/C$_6$H$_{14}$= 1:10 v/v) afforded 233 as purple solid (5.34 mg, 4.19 μmol, 10%). mp >310 °C; R$_f$=0.28 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ= -2.21 (s, 2H, NH), 0.94 (t, J=7.0 Hz, 3H, -CH$_3$), 1.45 (m, 2H, -CH$_2$), 1.53 (m, 2H, -CH$_2$), 1.74 (m, 2H, -CH$_2$), 1.84 (s, 12H, -CH$_3$), 2.58 (m, 2H, -CH$_2$), 3.90 (s, 6H, -OCH$_3$), 4.01 (d, J= 5.8 Hz, 2H, -CH$_2$), 5.10 (t, J=7.6 Hz, 2H, -CH$_2$), 7.21 (s, 1H, phenyl-H), 7.34 (t, J= 8.8 Hz, 1H, phenyl-H), 7.54 (t, J= 7.6 Hz, phenyl-H), 7.77 (m, 6H, phenyl-H), 8.00 (d, J=4.7 Hz, 2H, β-H), 8.55 (d, J=3.5 Hz, 2H, β-H), 8.99 (d, J=4.7 Hz, 2H, β-H), 9.55 (d, J=4.7 Hz, 2H, β-H); UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log ε)= 416 (5.09), 523 (4.29), 558 (3.72), 595 (3.76), 652 nm (3.41); HRMS (ES+) \([\text{C}_{48}\text{H}_{44}\text{N}_4\text{O}_6]\): calcd for [M+H]$^+$ 786.3292, found 786.3275.
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6.11 Photolysis experiment

A solution of 50 μM 5,10,15-tris(3,5-di-tert-butylphenyl)-20-(4’-(o-nitro-p-(2’,3’,4’,6’-tetera-O-acetyl-β-D-galactopyranoside)benzyl)carboxy)phenyl)porphyrin \( \text{218} \) in 2% water/98% acetone was placed in a quartz cuvette. Photolysis was performed using a photochemical reactor (Rayonet Model RMR-600) with 350 ±25 nm UV lamps. Aliquots of 20 μL were removed at different time intervals of photolysis and analyzed by analytical HPLC (detection UV: 350 nm) using a nucleosile 5u Silica (250 X 4.00 mm) column and eluting with a mixture of n-hexane: ethyl acetate (50:50) at a flow rate of 1.5 ml/min.

6.12 Reactivity of acyl chloride porphyrins

Bromoporphyrin precursor \( \text{236, 237, 238} \); and hydroxyl porphyrin \( \text{248} \) were prepared according to procedure as previously reported.\(^{[246,67e]}\)

\[
[5,15-\text{Bis(2-methoxycarbonylethenyl)-10,20-diphenylporphyrinato} \text{ni} \text{c} \text{kel(II) (240)}
\]

A heterogeneous solution of (5,15-dibromo-10,20-diphenylporphyrinato)nickel(II) \( \text{237} \) (200 mg, 0.32 mmol), methyl acrylate (0.58 mL, 6.4 mmol), PPh\(_3\) (420 mg, 1.6 mmol), \( \text{Pd(OAc)}_2 \) (14.4 mg, 0.064 mmol), and \( \text{K}_2\text{CO}_3 \) (885 mg, 6.4 mmol) in toluene (120 mL) was heated under argon at 110 °C for 72 h (TLC control). The reaction mixture was filtered through a plug of silica and washed with ethyl acetate. After removal of the solvents under reduced pressure, the residue was recrystallised from \( \text{CH}_2\text{Cl}_2/\text{MeOH} \) to give \( \text{240} \) (200 mg, 91%) as a green-violet solid: mp >310 °C; \( R_f < 0.7 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:2 v/v); \(^1\text{H NMR (400 MHz, CDCl}_3\):} \( \delta = 3.97 \) (s, 6H, -OCH\(_2\)), 6.28 (d, \( J = 15.6 \) Hz, 2H, =CH-), 7.71 (m, 6H, phenyl-\( H \)), 7.95 (m, 4H, phenyl-\( H \)), 8.75 (d, \( J = 4.9 \) Hz, 4H, β-\( H \)), 9.31 (d, \( J = 4.9 \) Hz, 4H, β-\( H \)), 9.81 ppm (d, \( J = 15.6 \) Hz, 2H, -CH=); \(^{13}\text{C NMR (100.6 MHz, CDCl}_3\):} \( \delta = 51.6, 110.5, 119.5, 126.7, 127.6, 131.3, 131.5, 133.0, 133.2, 139.3, 140.6, \)
141.3, 143.0, 166.2 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log ε)= 438 (5.3), 568 (4.2), 610 nm (4.3); TOF MS LD+ (C$_{40}$H$_{26}$N$_4$NiO$_4$): calcd for [M + Na] 709.1362, found 709.1369.

**General procedure for the synthesis of 225 and 241 via hydrolysis with EtOH–KOH**

To porphyrins 239 and 240 (0.3 mmol) in EtOH (30 mL) was added an aqueous solution (2 mL) of KOH (400 mg). The reaction was heated at 70 °C for 24–72 h (TLC control) resulting in complete dissolution of the porphyrin. Ethanol was removed under reduced pressure, and the violet solid left was treated with HCl (1 N). The crystals formed were filtered off and washed with HCl (1 N) (10 mL) and distilled H$_2$O (20 mL). The free acid was dried in vacuo to yield the products 225 and 241 (91–95%).


Purple solid (189 mg, 95%); mp >310 °C; Rf=0.2 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:2 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta= 6.39$ (d, $J= 15.4$ Hz, 1H, $=\text{CH}$-), 7.72 (m, 9H, phenyl-$H$), 8.00 (m, 6H, phenyl-$H$), 8.69 (m, 4H, β-$H$), 8.87 (d, $J= 4.8$ Hz, 2H, β-$H$), 9.42 (d, $J= 4.8$ Hz, 2H, β-$H$), 10.03 ppm (d, $J= 15.4$ Hz, 1H, -CH=); $^{13}$C NMR (150.9 MHz, CDCl$_3$): $\delta= 108.4, 119.6, 120.7, 126.8, 126.9, 127.8, 129.0, 131.0, 132.2, 132.7, 133.3, 133.4, 133.8, 140.0, 141.4, 142.1, 142.9, 146.7, 159.4, 169.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log ε)= 429 (5.3), 546 (4.3), 585 (4.2) nm; TOF MS LD+ (C$_{41}$H$_{26}$N$_4$NiO$_2$): calcd for [M] 664.14, found 664.11.
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Violet solid (180 mg, 91%); mp >310 °C; Rf=0.1 (SiO₂, EtOAc/C₆H₁₄, 1:2 v/v); ᵃ¹H NMR (400 MHz, THF-d₈): δ= 6.24 (d, J =15.8 Hz, 2H, =CH-), 7.71 (m, 6H, phenyl-H), 7.97 (m, 4H, phenyl-H), 8.72 (d, J = 4.7 Hz, 4H, β-H), 9.40 (d, J = 4.7 Hz, 4H, β-H), 9.80 (d, J = 15.8 Hz, 2H, -CH-), 11.28 ppm (br, 2H, -CO₂H); ᵃ¹³C NMR (100.6 MHz, THF-d₈): δ 112.6, 120.6, 128.2, 129.1, 133.0, 134.2, 134.4, 134.5, 141.2, 142.3, 142.9, 143.5, 167.0 ppm; UV-vis (CH₂Cl₂): λ max (log ε)= 435 (4.2), 561 (3.2), 607 nm (3.2); TOF MS LD+ (C₃₈H₂₄N₄NiO₄): calcd for [M] 658.1151, found 658.1132.

General procedure for synthesis of 244–247: generation of acyl chloride 242 and 243 and its reactions with nucleophiles

To a solution of acid 225 (30 mg, 0.045 mmol) in anhydrous THF (4 mL) was added SOCl₂ (0.025 mL, 0.225 mmol) in 1 mL of THF and DMF (2–3 drops) under argon. The mixture was warmed to 35 °C and stirred for 60 min (color change from red to green). The volatiles were removed under reduced pressure, and the remaining acyl chloride 242 (purple-greenish solid) was dissolved in anhydrous CH₂Cl₂ (ca. 5 mL). The respective nucleophile (0.09–0.225 mmol) dissolved in CH₂Cl₂ (ca. 2–5 mL) followed by NEt₃ (0.013 mL, 0.09 mmol) in CH₂Cl₂ (0.5 mL) were added, and the reaction was stirred for several hours (TLC control) at 35 °C under argon. The reaction mixture was filtered through a plug of silica and washed with CH₂Cl₂, and the solvents were removed in vacuo. The crude products were purified by flash chromatography on silica with CH₂Cl₂/hexane or ethyl acetate/hexane to give the corresponding porphyrins 244–246 (68–95%).
[5-(2-(Piperidiny-1-yl)carbonyl ethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (244)

To a solution of the acyl chloride 242 generated from 225 (30 mg, 0.045 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) were added piperidine (0.015 mL, 0.15 mmol) in CH$_2$Cl$_2$ (1 mL) and NEt$_3$ (0.008 mL, 0.06 mmol) in CH$_2$Cl$_2$ (0.5 mL). The reaction was stirred for 1 h (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by column chromatography on silica (hexane/CH$_2$Cl$_2$, 2:1 v/v) to give 244 (18.2 mg, 83%) as a violet solid.

244 via 265: To a solution of acid 265 (30 mg, 0.044 mmol) in anhydrous THF (5 mL) were added SOCl$_2$ (0.016 mL, 0.22 mmol) in 1 mL of THF and DMF (2-3 drops) under argon. The mixture was stirred at 35 °C for 1 h. The volatiles were removed under reduced pressure, and the remained acyl chloride was dissolved in anhydrous CH$_2$Cl$_2$ (5 mL). Piperidine (0.031 mL, 0.309 mmol) in CH$_2$Cl$_2$ (1 mL) was added to the reaction mixture, which was stirred for 18 h (TLC control) at 35 °C under argon. The reaction mixture was filtered through a plug of silica and washed with CH$_2$Cl$_2$, and the solvents were removed in vacuo. The crude products were purified by flash chromatography on silica (hexane/CH$_2$Cl$_2$, 1:1 v/v) to give 244 (13.8 mg, 42%) as a violet solid: mp >310 °C; R$_f$=0.5 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= 1.68 (m, 6H, -CH$_2$), 3.50 (m, 2H, -CH$_2$N), 3.77 (m, 2H, -CH$_2$N), 6.79 (d, $J$= 15.8 Hz, 1H, -CH=), 7.66 (m, 9H, phenyl-H), 7.93 (m, 6H, phenyl-H), 8.60 (m, 4H, β-H), 8.79 (d, 2H, $J$ = 4.4 Hz, β-H), 9.33 (d, 2H, $J$ = 4.4 Hz, β-H), 9.82 ppm (d, $J$ = 15.8 Hz, 1H, -CH=); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$= 24.5, 25.7, 26.5, 29.7, 42.6, 47.3, 108.3, 109.7, 114.3, 120.1, 121.4, 127.1, 128.1, 131.2, 132.4, 133.0, 133.5, 134.2, 136.5, 140.0, 141.5, 141.8, 142.2, 143.2, 147.0, 165.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$)= 423 (4.3), 538 nm (3.1); TOF MS LD+ (C$_{46}$H$_{35}$N$_3$ONi): calcd for [M] 731.2195, found 731.2225.
To a solution of acyl chloride 242 generated from 225 (30 mg, 0.045 mmol) in anhydrous CH₂Cl₂ (5 mL) were added propargyl alcohol (0.013 mL, 0.225 mmol) in CH₂Cl₂ (1 mL) and NEt₃ (0.013 mL, 0.09 mmol) in CH₂Cl₂ (0.5 mL). The reaction was stirred for several hours (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by flash chromatography on silica (CH₂Cl₂/hexane = 1/1) to give 245 (31.7 mg, 73%) as a purple solid: mp 143–158 °C dec; Rₚ=0.6 (SiO₂, CH₂Cl₂/C₆H₁₄ = 1/1, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= 2.62 (br, 1H, =CH), 5.01 (br, 2H, -C//=), 6.37 (d, J = 15.8 Hz, 1H, =CH-), 7.71 (m, 9H, phenyl-H), 7.99 (m, 6H, phenyl-H), 8.68 (dd, J = 4.7, 4.7 Hz, 4H, β-H), 8.85 (d, J = 4.7 Hz, 2H, β-H), 9.39 (d, J = 4.7, 2H, β-H), 9.97 ppm (d, J = 15.8 Hz, 1H, =CH=); ¹³C NMR (100.6 MHz, CDCl₃): δ= 51.9, 74.7, 108.6, 119.1, 120.1, 126.5, 126.6, 127.47, 127.5, 129.5, 130.9, 131.9, 132.4, 133.06, 133.1, 133.2, 133.3, 139.7, 141.0, 141.1, 141.7, 142.4, 144.7, 165.0 ppm; UV-vis (CH₂Cl₂): λ_max (log ε) = 429 (5.4), 547 (4.3), 587 nm (4.2); TOF MS LD+ (C₄₄H₉₈N₄NiO₂): calcld for [M] 702.1566, found 702.1531.
To a solution of acyl chloride 242 generated from 225 (30 mg, 0.045 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) were added 4-bromophenol (15.6 mg, 0.09 mmol) in CH$_2$Cl$_2$ (1 mL) and NEt$_3$ (0.013 mL, 0.09 mmol) in CH$_2$Cl$_2$ (0.5 mL). The reaction was stirred for several hours (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by flash chromatography on silica (CH$_2$Cl$_2$/hexane, 1:1 v/v) to give 246 (25.1 mg, 68%) as a violet solid: mp 173 °C; R$_f$=0.25 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$ = 1/1, v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= 6.50 (d, $J$ = 15.2 Hz, 1H, =CH-), 7.24 (d, $J$ = 8.8 Hz, 2H, phenyl-H), 7.61 (d, $J$ = 8.8 Hz, 2H, phenyl-H), 7.71 (m, 9H, phenyl-H), 7.99 (m, 6H, phenyl-H), 8.66 (d, $J$ = 5.2 Hz, 2H, $\beta$-H), 8.70 (d, $J$ = 5.2 Hz, 2H, $\beta$-H), 8.87 (d, $J$ = 5.2 Hz, 2H, $\beta$-H), 9.44 (d, $J$ = 5.2 Hz, 2H, $\beta$-H), 10.08 ppm (d, $J$ = 15.2 Hz, 1H, -CH=); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$= 108.3, 118.5, 119.3, 120.4, 123.1, 123.6, 125.1, 126.5, 126.6, 127.5, 127.6, 129.2, 130.8, 132.0, 132.1, 132.2, 132.5, 132.6, 133.0, 133.1, 133.5, 139.7, 141.1, 141.8, 142.5, 145.7, 149.5, 163.9 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$)= 430 (5.3), 547 (4.3), 592 nm (4.3); TOF MS LD+ (C$_{47}$H$_{29}$BrN$_4$NiO$_2$): calcd for [M] 818.0827, found 818.0826.
To a solution of acid 241 (30 mg, 0.045 mmol) in anhydrous THF (5 mL) were added SOCl₂ (0.013 mL, 0.18 mmol) in 1 mL of THF and DMF (2–3 drops) under argon, and the mixture was stirred for 2 h. The volatiles were removed under reduced pressure, and the remaining purple-greenish acyl chloride 243 was dissolved in anhydrous THF (5 mL). NEt₃ (0.013 mL, 0.09 mmol) in THF (1 mL) was added, and stirring was continued for 15 min. Piperidine (0.09–0.225 mmol) dissolved in THF (1 mL) was added, and the reaction was stirred for 30 min (TLC control) at rt under argon. The mixture was filtered through a plug of silica and washed with ethyl acetate, followed by removal of the solvents in vacuo. The residue was purified by flash chromatography on silica with ethyl acetate/hexane = 1:2 v/v to give 247 (16 mg, 44%) as a green-purple solid: mp 282 °C; Rₓ=0.15 (SiO₂, EtOAc/C₆H₁₄ = 1/2, v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ= 1.67 (m, 12H, -CH₂), 3.54 (m, 4H, -CH₂N), 3.82 (m, 4H, -CH₂N), 6.67 (d, J= 15.2 Hz, 2H, =CH-), 7.70 (m, 6H, phenyl-H), 7.96 (m, 4H, phenyl-H), 8.74 (d, J= 4.7 Hz, 4H, β-H), 9.32 (d, J = 4.7 Hz, 4H, β-H), 9.80 ppm (d, J = 15.2 Hz, 2H, -CH=); ¹³C NMR (100.6 MHz, CDCl₃): δ= 24.2, 25.2, 26.3, 43.1, 46.6, 112.1, 119.0, 126.7, 127.6, 131.5, 132.7, 132.9, 133.0, 139.5, 140.6, 141.1, 164.0 ppm; UV-vis (CH₂Cl₂): λₓₘₐₓ (log ε)= 436 (5.5), 557 (4.6), 604 nm (4.6); TOF MS LD⁺ (C₄₈H₄₂N₆NiO₂): calcd for [M] 792.2723, found 792.2720.

To a solution of acyl chloride 242 generated from 225 (30 mg, 0.045 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) were added 5-(4-hydroxyphenyl)-10,20-bis(3-methoxyphenyl)porphyrin 248 (26.3 mg, 0.43 mmol) in CH$_2$Cl$_2$ (1 mL) and NEt$_3$ (0.013 mL, 0.09 mmol) in CH$_2$Cl$_2$ (0.5 mL). The reaction was stirred for 24 h (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. Purification by flash chromatography on silica (ethyl acetate/hexane, 1:2 v/v) afforded 249 (27.6 mg, 51%) as a purple solid: mp 247 °C; R$_f$=0.8 (SiO$_2$; EtOAc/C$_6$H$_4$, 1:2 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= -2.97 (s, 2H, -NH), 4.05 (s, 6H, -OCH$_3$), 6.73 (d, $J$= 15.8 Hz, 1H, =CH-), 7.40 (m, 2H, phenyl-H), 7.74 (m, 13H, phenyl-H), 7.89 (m, 4H, phenyl-H), 8.04 (m, 6H, phenyl-H), 8.35 (m, 2H, phenyl-H), 8.72 (dd, $J$= 4.7, 4.7 Hz, 4H, $\beta$-H), 8.94 (d, $J$= 4.7 Hz, 2H, $\beta$-H), 9.02 (dd, $J$= 4.7, 4.7 Hz, 4H, $\beta$-H), 9.12 (d, $J$= 4.7 Hz, 2H, $\beta$-H), 9.37 (d, $J$= 4.7 Hz, 2H, $\beta$-H), 9.58 (d, $J$= 4.7 Hz, 2H, $\beta$-H), 10.28 ppm (m, 2H, -C//=); $^1$C NMR (100.6 MHz, CDCl$_3$): $\delta$= 55.1, 104.5, 108.3, 113.1, 119.0, 119.3, 119.5, 120.2, 120.3, 126.6, 126.7, 127.3, 127.4, 127.5, 127.6, 129.8, 130.5, 131.0, 131.1 (br), 132.0, 132.5, 133.1, 133.2, 133.5, 134.9, 139.7, 139.8, 141.2, 141.8, 142.5, 142.6, 145.6, 146.2 (br), 150.4, 157.6, 164.4 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$)= 413 (5.5), 432 (5.2), 508 (4.4), 543 (4.3), 585 (4.3), 635 nm (4.0); TOF MS LD+ (C$_8$H$_{34}$N$_8$NiO$_4$): calcd for [M + H] 1261.3700, found 1261.366.
Reaction of 242 with ethyl diazoacetate. synthesis of 250–252


Ethyl diazoacetate (20.6 mg, 0.18 mmol) in CH$_2$Cl$_2$ (1 mL), PPh$_3$ (47.3 mg, 0.18 mmol), and NEt$_3$ (0.013 mL, 0.09 mmol) in CH$_2$Cl$_2$ (0.5 mL) were added to a solution of acyl chloride 242 generated from 225 (30 mg, 0.045 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL). The reaction was stirred for 2 h (TLC control) at 35 °C under argon, and the resulting mixture was diluted with hexane and quickly filtered through a short column of silica. The volatiles were removed in vacuo, and the solid residue was washed with hexane (3 × 5 mL) and dried under vacuum to give 250 (32.2 mg, 70%) as a pale purple solid: Rf=0.4 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_4$, 1:1 v/v); $^1$H NMR (400 MHz, CD$_2$Cl$_2$); δ= 1.45 (t, J= 7.0 Hz, 3H, -CH$_3$), 4.44 (q, J= 7.0 Hz, 2H, -CH$_2$), 6.84 (d, J= 15.4 Hz, 1H, =CH-), 7.54 (m, 9H, phenyl-H), 7.74 (m, 15H, phenyl-H), 8.00 (m, 6H, phenyl-H), 8.68 (dd, J= 5.0 Hz, 5.0 Hz, 4H, β-H), 8.83 (d, J= 5.0 Hz, 2H, β-H), 9.38 (d, J= 5.0 Hz, 2H, β-H), 9.80 ppm (d, J= 15.4 Hz, 1H, -CH=); $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$): 44.26 ppm; $^{13}$C NMR (150.9 MHz, CD$_2$Cl$_2$): δ= 14.2, 62.5, 110.2, 120.0, 120.8, 127.2, 127.3, 128.2, 128.7, 128.8, 131.2, 131.8, 131.9, 132.4, 132.5 (m), 132.9, 133.1, 133.6, 133.7, 133.8, 133.9, 136.0, 140.4, 140.5, 141.6, 141.7, 141.9, 142.6, 143.2, 145.8, 148.6, 162.6 ppm; TOF MS LD+ (C$_{63}$H$_{45}$N$_6$NiO$_3$P): calcd for [M + 2H - O] 1008.2852, found 1008.2845; calcd for [M - H$_2$O - PPh$_3$] 745.1862, found 745.1868.

Yield 12 mg (35%); Rf=0.6 (SiO2, EtOAc/C6H14, 2:1 v/v); 1H NMR (400 MHz, CDCl3, TMS): δ= 1.38 (t, J= 7.0 Hz, 3H, -CH3), 4.32 (q, J = 7.0 Hz, 2H, -CH2), 6.75 (br, 1H, -NH), 7.35 (d, J = 15.8 Hz, 1H, =CH-), 7.71 (m, 9H, phenyl-), 7.99 (m, 6H, phenyl-), 8.67 (dd, J = 5.3 Hz, 5.0 Hz, 4H, p-), 8.85 (d, J = 5.3 Hz, 2H, p-), 9.44 (d, J = 5.3, 2H, p-), 10.06 (d, J = 15.8 Hz, 1H, -CH=), 12.46 ppm (br, 1H, -OH); UV-vis (CH2Cl2): λmax (log ε)= 433 (1.0), 547 (0.1), 592 nm (0.09); TOF MS LD+ (C45H32N6Ni03); calcd for [M + Na] 785.1787, found 785.1779.


Phosphazine 250 (32 mg, 0.31 mmol) was dissolved in dichloromethane and allowed to stand for 24 h. The solvent was removed under reduced pressure, and the residue was recrystallised from CH2Cl2/MeOH to give 252 (18 mg, 78%) as a violet solid: mp >310 °C; 1H NMR (600 MHz, CDCl3, TMS): δ= 1.46 (t, J = 7.0 Hz, 3H, -CH3), 4.47 (q, J = 7.0 Hz, 2H, -CH2), 6.84 (d, J = 15.2 Hz, 1H, =CH-), 7.59 (s, 1H, =CH), 7.71 (m, 9H, phenyl-), 7.99 (m, 6H, phenyl-), 8.67 (dd, J = 4.7, 4.7 Hz, 4H, β-), 8.85 (d, J = 5.2 Hz, 2H, β-), 9.37 (d, J = 5.2, 2H, β-), 9.79 ppm (d, J = 15.2 Hz, 1H, -CH=); 13C NMR (150.9 MHz,
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CDCl₃: δ = 14.2, 62.2, 109.7, 119.7, 120.6, 126.9, 127.0, 127.9, 128.0, 131.1, 132.4, 132.8, 133.5, 133.6, 133.7, 135.7, 140.2, 141.4, 141.6, 142.3, 142.9, 145.6, 147.8, 162.5 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε) = 435 (5.8), 547 (4.8), 597 nm (4.8); TOF MS LD⁺ (C₄₅H₃₂N₄NiO₃): calcd for [M + 2H + 2Na] 782.1780, found 782.1621.

6.13 Synthesis of α,β-unsaturated porphyrins

Ally porphyrin precursors 255 and 256 were prepared according to procedure as previously reported.²⁴⁶

General Procedure: synthesis of 258–260 via cross-metathesis

A mixture of allyl porphyrin (0.3 mmol), acrylate (1.5–3.0 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) in dry CH₂Cl₂ (25 mL) was stirred at 35 °C under argon for 12 h (TLC control). The solution was filtered through a plug of silica and washed with CH₂Cl₂. The solvent was removed under reduced pressure followed by recrystallization of the solid residue from CH₂Cl₂/MeOH to give 258–260 (78–90%).

5-(Methylbut-2-enoate)-10,15,20-triphenylporphyrin (258)

![Porphyrin 258](image)

Porphyrin 255 (174 mg, 0.3 mmol), methyl acrylate (129 mg, 1.5 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave 258 (153 mg, 80%) as a violet solid: mp >310 °C; Rᵣ=0.45 (SiO₂, EtOAc/C₆H₁₄, 1:5 v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ = -2.74 (s, 2H, -N₂), 3.55 (s, 3H, -OCH₃), 5.72 (d, J = 15.8 Hz, 1H, =C⁻H⁻), 5.87 (d, J = 5.9 Hz, 2H, -CH₂), 7.76 (m, 9H, phenyl-H), 7.94 (m, 1H, -CH⁻), 7.99 (m, 6H, phenyl-H), 8.81 (br, 4H, β-H), 8.91 (d, J = 4.8 Hz, 2H, β-H), 9.34 ppm (d, J = 4.8 Hz, 2H, β-H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 37.4, 51.4, 113.2, 120.0, 120.3, 123.0, 126.6, 127.8, 134.5, 142.0, 142.6, 150.7, 166.9 ppm; UV-vis (CH₂Cl₂): λₘₐₓ (log ε) = 419 (4.3), 517 (3.1), 553 (2.8), 657 nm (2.8); HRMS (ES⁺) [C₄₅H₃₂N₄O₂]: calcd for [M + H] 637.2604, found 637.2596.
5-(tert-Butyl but-2-enoate)-10,15,20-triphenylporphyrin (259)

Porphyрин 255 (174 mg, 0.3 mmol), tert-butyl acrylate (192 mg, 1.5 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave 259 (159 mg, 78%) as a violet solid: mp >310 °C; Rf=0.4 (SiO2, EtOAc/C6H14=1/5, v/v); 1H NMR (400 MHz, CDCl3, TMS): δ=−2.70 (s, 2H, -NH), 1.34 (s, 9H, -CH3), 5.66 (d, J = 15.8 Hz, 1H, =CH-), 5.91 (d, J = 5.8 Hz, 2H, -CH2), 7.80 (m, 9H, phenyl-H), 7.90 (dt, J = 15.8, 5.8 Hz, 1H, -CH=), 8.25 (m, 6H, phenyl-H), 8.36 (br, 4H, β-H), 8.97 (d, J = 4.7 Hz, 2H, β-H), 9.42 ppm (d, J = 4.7 Hz, 2H, β-H); 13C NMR (100.6 MHz, CDCl3): δ= 27.5, 36.8, 79.8, 113.2, 119.5, 119.8, 124.8, 126.2, 126.3, 127.3, 127.6 (br), 130.6 (br), 134.1, 141.5, 141.7, 148.8, 165.5 ppm; UV-vis (CH2Cl2): λmax (log ε)= 418 (4.0), 444 (3.6), 516 (2.6), 550 (2.3), 594 (2.3), 654 nm (2.7); HRMS (ES+) [C46H38N4O2]: calcd for [M + H] 679.3073, found 679.3085.

5,15-Bis(methylbut-2-enoate)-10, 20-ditolylporphyrin (260)

Porphyрин 256 (171 mg, 0.3 mmol), methyl acrylate (258 mg, 3.0 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave 260 (186 mg, 90%) as a violet solid: mp >310 °C; Rf=0.4 (SiO2, EtOAc/C6H14, 1:2 v/v); 1H NMR (400 MHz, CDCl3, TMS): δ=−2.68 (s, 2H, -NH), 2.75 (s, 6H, -CH3), 3.60 (s, 6H, -OCH3), 5.74 (d, J = 15.8 Hz, 2H, =CH-), 5.91 (d, J = 5.3 Hz, 4H, -CH2), 7.59 (m, 4H, phenyl-H), 7.96 (dt, J = 15.8, 5.3 Hz, 1H, -CH=), 8.09 (m, 4H, phenyl-H), 8.93 (d, J = 4.7 Hz, 4H, β-H), 9.35 ppm (d, J = 4.7 Hz, 4H, β-H); 13C NMR (100.6 MHz, CDCl3): δ= 22.3, 36.8, 51.0, 112.7, 119.5, 122.5, 127.0, 134.0, 137.0,
138.7, 150.3, 166.5 ppm; UV-vis \((\text{CH}_2\text{Cl}_2)\): \(\lambda_{\text{max}}(\log \varepsilon)\) = 516 (4.1), 552 (4.0), 592 nm (3.0); HRMS (ES+) \([\text{C}_{44}\text{H}_{38}\text{N}_4\text{O}_4]\) calcd for [M + H]: 687.2971, found 687.2972.


A mixture of porphyrin 258 (191 mg, 0.3 mmol) and Ni(II)(acac)\(_2\) (308 mg, 1.2 mmol) in toluene (100 mL) was stirred at 110 °C for 2 h (TLC control). The reaction mixture was filtered through a plug of silica and washed with CH\(_2\)Cl\(_2\). The solvents were removed under reduced pressure, and the residue was recrystallized from CH\(_2\)Cl\(_2\)/MeOH to give 261 (204 mg, 98%) as a purple solid: mp >310 °C; R\(_f\)=0.33 (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:5 v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\), TMS): \(\delta\) = 3.60 (s, 3H, -O CH\(_3\)), 5.36 (d, \(J = 4.4\) Hz, 2H, -CH\(_2\)), 5.81 (d, \(J = 15.6\) Hz, 1H, =CH\(_2\)), 7.67 (m, 9H, phenyl-H), 7.82 (m, 1H, -CH=), 7.98 (m, 6H, phenyl-H), 8.71 (br, 4H, \(\beta\)-H), 8.77 (d, \(J = 4.8\) Hz, 2H, \(\beta\)-H), 9.13 ppm (d, \(J = 4.4\) Hz, 2H, \(\beta\)-H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)):\(\delta\) = 36.5, 51.5, 111.9, 118.8, 122.8, 126.9, 127.8, 129.2, 132.4, 133.1, 133.7, 140.7, 142.2, 142.3, 142.5, 142.7, 150.3, 166.9 ppm; UV-vis \((\text{CH}_2\text{Cl}_2)\): \(\lambda_{\text{max}}(\log \varepsilon)\) = 416 (4.3), 530 (3.0) nm; TOF MS LD+ \([\text{C}_{43}\text{H}_{30}\text{N}_4\text{O}_2\text{Ni}]\) calcd for [M + Na]: 715.1620, found 715.1596.
Compound 262 was prepared from 259 (203 mg, 0.3 mmol) using the same procedure as for the synthesis of 261. Recrystallisation from CH$_2$Cl$_2$/MeOH gave 264 (210 mg, 95%) as a purple solid: mp >310 °C; R$_f$=0.75 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:5 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ = 1.40 (s, 9H, -C$_3$), 5.26 (d, J = 4.9 Hz, 2H, -CH$_2$), 5.73 (d, J = 15.6 Hz, 2H, -CH), 7.70 (m, 10H, -CH=, phenyl-H), 8.03 (m, 6H, phenyl-H), 8.78 (br, 4H, $\beta$-H), 8.81 (d, J = 4.9 Hz, 2H, $\beta$-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 28.1, 36.3, 80.4, 112.3, 118.8, 119.0, 124.9, 127.0, 127.9, 129.4, 132.4, 133.1, 133.8, 140.8, 142.2, 142.4, 142.5, 142.8, 148.8, 166.0 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log e) = 416 (4.4), 530 nm (3.2); TOF MS LD+ [C$_{46}$H$_{36}$N$_4$O$_2$Ni]: calcd for [M] 734.2219, found 734.2192.

5-Acroleinyl-10,15,20-triphenylporphyrin (263)

Grubbs II catalyst (8.5 mg, 0.01 mmol) and acrylic acid (0.03 mL, 0.43 mmol) were added to a solution of porphyrin 255 (51 mg, 0.09 mmol) in dry CH$_2$Cl$_2$ (20 mL). The mixture was stirred for 18 h and then filtered through a plug of silica eluting with CH$_2$Cl$_2$. Purification by column chromatography (hexane/CH$_2$Cl$_2$, 2:1 v/v) gave 263 (12 mg, 0.02 mmol, 23%) as a purple solid: mp >310 °C; R$_f$=0.48 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ = -2.40 (s, 2H, -NH), 7.16 (d, J = 7.8 Hz, 15.6 Hz, 1H, =CH-), 7.76 (m, 9H, phenyl-H), 8.17 (m, 6H, phenyl-H), 8.77 (dd, J = 4.8, 4.8 Hz, 4H, $\beta$-H), 8.91 (d, J = 4.8 Hz, 2H, $\beta$-H), 9.39 (d, J = 4.8 Hz, 2H, $\beta$-H), 10.02 (d, J = 15.6 Hz, 1H,
-CH=), 10.23 ppm (d, J = 7.8 Hz, 1H, -CHO); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 29.7, 32.0, 110.8, 121.7, 122.7, 126.8, 128.0, 134.4, 141.2, 141.8, 154.0, 192.4\) ppm; UV-vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}} \text{ (log } \varepsilon) = 429 (4.3), 523 (2.9), 570 (3.0), 660 (2.7), 666\) nm (2.6); HRMS (ES\(+\)) [C\(_{41}\)H\(_{28}\)N\(_4\)O]: calcd for [M + H] 593.2341, found 593.2357.

\[\text{[5-(But-2-enoic acid)-10,15,20-triphenylporphyrinato]nickel(II) (265)}\]

A solution of porphyrin 262 (100 mg, 0.136 mmol) and TFA (0.85 mL) in CH\(_2\)Cl\(_2\) (20 mL) was stirred at 35 °C for 12 h (TLC control). The solvent was removed under reduced pressure, and the solid residue was dried in vacuo to give 265 (88 mg, 95%) as red solid: mp >310 °C; R\(_f\) = 0.1 (SiO\(_2\), CH\(_2\)Cl\(_2\)/C\(_6\)H\(_{14}\), 2:1 v/v); \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\), TMS): \(\delta = 5.40\) (d, \(J = 4.8\) Hz, 2H, -CH\(_2\)), \(5.80\) (d, \(J = 15.6\) Hz, 1H, =CH-), \(7.66\) (m, 9H, phenyl-\(H\)), \(7.95\) (m, 7H, phenyl-\(H\), -CH=), \(8.69\) (br, 4H, \(\beta-\text{H}\)), \(8.77\) (d, \(J = 5.0\) Hz, 2H, \(\beta-\text{H}\)), \(9.10\) ppm (d, \(J = 5.0\) Hz, 2H, \(\beta-\text{H}\)); \(^{13}\text{C}\) NMR (100.6 MHz, CDCl\(_3\)): \(\delta = 25.1, 31.0, 36.6, 111.9, 118.9, 119.2, 126.9, 127.8, 129.0, 132.4, 132.4, 133.2, 133.8, 140.7, 142.2, 142.5, 142.8, 154.0\) ppm; UV-vis (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}} \text{ (log } \varepsilon) = 415 (5.3), 529\) nm (4.2); TOF MS LD\(+\) (C\(_{42}\)H\(_{28}\)N\(_4\)NiO\(_2\)): calcd for [M] 678.1566, found 678.1564.

\[\text{[5-(Propargyl-but-2-enoate)-10,15,20-triphenylporphyrinato]nickel(II) (266)}\]

DMAP (15 mg, 0.124 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added to a solution of the acyl chloride generated from 265 (42 mg, 0.062 mmol) in anhydrous CH\(_2\)Cl\(_2\) (5 mL). The reaction mixture was stirred for 10 min, and propargyl alcohol (0.036 mL, 0.62 mmol) in
CH$_2$Cl$_2$ (0.5 mL) was added. Stirring was continued for 1 h (TLC control) at 35 °C under argon. The resulting mixture was filtered through a plug of silica and washed with CH$_2$Cl$_2$. Purification using silica TLC plates (CH$_2$Cl$_2$/hexane, 1:2 v/v) afforded 266 (25 mg, 57%) as a purple solid: mp $>310$ °C; R$_f$=0.4 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 1:1 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ = 2.35 (t, $J = 2.3$ Hz, 1H, $=CH$), 4.61 (d, $J = 2.3$ Hz, 2H, -CH$_2$), 5.48 (d, $J = 5.8$ Hz, 2H, -CH$_2$), 5.83 (d, $J = 15.6$ Hz, 1H, $=CH-$), 6.78 (m, 9H, phenyl-$H$), 7.92 (dt, $J = 5.8$ Hz, 15.6 Hz, 1H, -CH=$-), 7.98 (m, 6H, phenyl-$H$), 8.70 (s, 4H, $\beta$-$H$), 8.79 (d, $J = 5.0$ Hz, 2H, $\beta$-$H$), 9.18 ppm (d, $J = 5.0$ Hz, 2H, $\beta$-$H$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 36.6, 51.9, 74.8, 111.5, 118.8, 119.1, 122.3, 126.9, 127.78, 127.8, 129.2, 132.4, 133.2, 133.7, 140.7, 142.2, 142.3, 142.5, 142.7, 151.6, 165.6 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$) = 415 (4.7), 530 nm (3.7); TOF MS (C$_{45}$H$_{30}$N$_4$NiO$_2$) calcd for [M - H] 717.1598, found 717.1612.

5-(Propargyl but-3-enoate)-10,15,20-triphenylporphyrinato|nickel(II) (267E)

N-Ethyl-$N'$-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.7 mg, 0.124 mmol) and propargyl alcohol (0.036 mL, 0.62 mmol) were added to a solution of 265 (42 mg, 0.062 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) and DMAP (15 mg, 0.124 mmol). The reaction mixture was stirred for 12 h (TLC control) at rt. The resulting mixture was filtered through a plug of silica and washed with CH$_2$Cl$_2$. Purification by column chromatography (CH$_2$Cl$_2$/hexane, 1:2 v/v) afforded 267-E/Z (ratio E/Z = 3:1, 36 mg, 81%) as a purple solid. Additional purification on silica TLC plates (ethyl acetate/hexane = 1:10 v/v) gave 267E (26.2 mg, 59%); mp $>300$ °C; R$_f$=0.45 (SiO$_2$, CH$_2$Cl$_2$/C$_6$H$_{14}$, 1:1 v/v); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.57 (t, $J = 2.0$ Hz, 1H, $=CH$), 3.79 (d, $J = 7.8$ Hz, 2H, -CH$_2$), 4.88 (d, $J = 2.0$ Hz, 2H, -CH$_2$), 6.17 (dt, $J = 7.8$ Hz, 15.2 Hz, 1H, $=CH-$), 7.71 (m, 9H, phenyl-$H$), 8.00 (m, 6H, phenyl-$H$), 8.71 (dd, $J = 4.9$ Hz, 4.9 Hz, 4H, $\beta$-$H$), 8.76 (d, $J = 15.2$ Hz, 1H, -CH=$-), 8.82 (d, $J = 4.9$ Hz, 2H, $\beta$-$H$), 9.38 ppm (d, $J = 4.9$ Hz, 2H, $\beta$-$H$); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 38.7, 52.1, 74.8, 113.4, 118.3, 118.5, 126.5, 127.3, 131.1, 131.76, 131.8, 132.2, 133.17, 133.2, 135.0, 140.2, 141.0, 141.4, 141.86, 141.9, 170.3 ppm; UV-vis (CH$_2$Cl$_2$):
\( \lambda_{\text{max}} \ (\log \epsilon) = 419 (5.2), \ 534 \ \text{nm} (4.1); \ \text{TOF MS LD}^+ (C_{45}H_{30}N_4NiO_2) \): calcd for [M] 716.1722, found 716.1746.

2-Methylene-5-[(5,10,15-triphenyIporphyrin-20-yl)pent-3-enyl-3-[(5,10,15-Triphenylporphyrinato-20-yl)nickel(II)]acrylate (279)

The allyl porphyrin 255 (8.2 mg, 0.014 mmol) in dry CH\(_2\)Cl\(_2\) (10 mL) was added dropwise under argon to a solution of porphyrin propargyl ester 245 (10 mg, 0.014 mmol) and Grubbs I catalyst (2.34 mg, 0.003 mmol) in dry CH\(_2\)Cl\(_2\) (10 mL). The reaction mixture was stirred for 18 h at 35 °C and then filtered through a plug of silica and washed with CH\(_2\)Cl\(_2\). The volatiles were removed in vacuo, and the remaining solid was purified by flash chromatography on silica (hexane/CH\(_2\)Cl\(_2\), 1:1 v/v) to yield 279 (13.9 mg, 76%, E/Z 3:2) as a purple solid: mp >310 °C; \( R_f = 0.3 \) (SiO\(_2\), EtOAc/C\(_6\)H\(_{14}\), 1:5 v/v); UV-vis (CH\(_2\)Cl\(_2\)) \( \lambda_{\text{max}} \ (\log s) = 420 (4.0), \ 519 (3.0), \ 550 (3.0), \ 596 (3.0), \ 656 \ \text{nm} (3.2); \ \text{TOF MS LD}^+ (C_{85}H_{58}N_8O_2Ni): \) calcd for [M] 1280.4036, found 1280.4056; NMR key data (279E) \(^1\)H NMR (600 MHz, CDCl\(_3\), TMS): \( \delta = 5.01 \) (m, 3H, -CH\(_2\)OCO, -CCHH), 5.24 (s, 1H, -CCHH), 5.93 (d, \( J = 5.6 \) Hz, 2H, -CH\(_2\)CH), 6.29 (d, \( J = 15.8 \) Hz, 1H, -CHCHCH\(_2\)) 6.30 (d, \( J = 15.4 \) Hz, 1H, -CHCHCO), 6.93 (dt, \( J = 5.6 \) Hz, 15.8 Hz, 1H, -CHCHCH\(_2\)), 9.83 ppm (d, \( J = 15.4 \) Hz, 1H, -CHCHCO); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)): \( \delta = 38.0 \) (CH\(_2\)CH), 64.2 (CH\(_2\)OCO), 116.8 (CCH\(_2\)), 130.9 (CHCHCO), 134.2 (CHCHCH\(_2\)), 133.9 (CHCHCH\(_2\)), 144.2 (CHCHCO), 165.3 ppm (CO\(_2\)); (279Z) \(^1\)H NMR (600 MHz, CDCl\(_3\), TMS): \( \delta = 5.30 \) (s, 2H, -CH\(_2\)OCO), 5.97 (s, 1H, -CCHH), 6.04 (s, 1H, -CCHH), 6.16 (m, 3H, -CH\(_2\)CH, -CHCHCH\(_2\)), 6.48 (d, \( J = 15.4 \) Hz, 1H, -CHCHCO), 6.83 (dt, \( J = 6.8 \) Hz, 11.3 Hz, 1H, -CHCHCH\(_2\)), 10.03 ppm (d, \( J = 15.4 \) Hz, 1H, -CHCHCO); \(^1^3\)C NMR (150
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75 MHz, CDCl\textsubscript{3}): \(\delta = 35.1\) (CH\textsubscript{2}CH), 68.0 (CH\textsubscript{2}OCO), 118.2 (CCH\textsubscript{2}), 124.2 (CHCHCH\textsubscript{2}), 130.9 (CHCHCO), 137.5 (CHCHCH\textsubscript{2}), 144.5 (CHCHCO), 165.6 ppm (CO\textsubscript{2}).

2-Methylene-5-[(5,10,15-triphenylporphyrinato-20-yl)nickel(II)]pent-3-enyl-[(5,10,15-Triphenylporphyrinato-20-yl)nickel(II)]acrylate (280)

The synthesis of 280 was carried out as described above for 279 using the porphyrin propargyl ester 245 (10 mg, 0.014 mmol), Grubbs I catalyst (2.34 mg, 0.003 mmol), and allyl porphyrin 278 (9.0 mg, 0.014 mmol). The mixture of 280 (7.8 mg, 41%, E/Z 2:1) was obtained as a purple solid: mp >310 °C; R\textsubscript{f} 0.49 (SiO\textsubscript{2}, ethyl acetate/hexane, 1:5 v/v); UV-vis (CH\textsubscript{2}Cl\textsubscript{2}): \(\lambda_{\text{max}}\) (log \(\varepsilon\)) = 418 (4.0), 533 (2.9), 590 nm (2.0); TOF MS LD+ (C\textsubscript{85}H\textsubscript{56}N\textsubscript{8}O\textsubscript{2}Ni\textsubscript{2}) calcld for [M + H] 1337.3311, found 1337.3322; NMR selected data

(280\textsuperscript{E}) \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 5.02\) (s, 2H, -CH\textsubscript{2}OCO), 5.16 (s, 1H, -CCH\textsubscript{2}H), 5.31 (s, 1H, -CCH\textsubscript{2}H), 5.46 (d, \(J = 5.6\) Hz, 2H, -CH\textsubscript{2}CH), 6.29 (d, \(J = 15.8\) Hz, 1H, -CCH\textsubscript{2}HCO), 6.43 (d, \(J = 16.2\) Hz, 1H, -CHCHCH\textsubscript{2}), 6.84 (dt, \(J = 5.6\) Hz, 16.2 Hz, 1H, -CHCHCH\textsubscript{2}), 9.82 ppm (d, \(J = 15.8\) Hz, 1H, CHCHCO); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): \(\delta = 36.8\) (CH\textsubscript{2}CH), 64.0 (CH\textsubscript{2}OCO), 117.0 (CCH\textsubscript{2}), 130.4 (CHCHCH\textsubscript{2}), 130.9 (CHCHCO), 133.7 (CHCHCH\textsubscript{2}), 144.0 (CHCHCO), 165.3 ppm (CO\textsubscript{2}); (280\textsuperscript{OZ}) \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 5.24\) (s, 2H, -CH\textsubscript{2}OCO), 5.68 (d, \(J = 6.4\) Hz, 2H, -CH\textsubscript{2}CH), 5.83 (s, 1H, -CCH\textsubscript{2}H), 5.94 (s, 1H, -CCH\textsubscript{2}H), 6.18 (d, \(J = 11.7\) Hz, 1H, -CHCHCH\textsubscript{2}), 6.44 (d, \(J = 15.4\) Hz, 1H, -CHCHCO), 6.77 (dt, \(J = 6.4\) Hz, 11.7 Hz, 1H, -CHCHCH\textsubscript{2}), 10.01 (d, \(J = 15.4\) Hz, 1H, -CHCHCO); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 33.7\) (CH\textsubscript{2}CH), 67.4 (CH\textsubscript{2}OCO), 118.0 (CCH\textsubscript{2}), 124.7 (CHCHCH\textsubscript{2}), 130.8 (CHCHCO), 136.9 (CHCHCH\textsubscript{2}), 144.4 (CHCHCO), 165.4 ppm (CO\textsubscript{2}).
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Synthesis of 279 and 280 using Grubbs II catalyst

The allyl porphyrin 255 (8.2 mg, 0.014 mmol in 10 mL dry CH$_2$Cl$_2$) was added dropwise under argon to a solution of the porphyrin propargyl ester 245 (10 mg, 0.014 mmol) and Grubbs II catalyst (2.41 mg, 0.003 mmol) in dry CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred for 18 h at 35 °C and then filtered through a plug of silica. Flash column chromatography on silica (hexane/CH$_2$Cl$_2$, 1:1 v/v) gave 279 (10 mg, 55%, $E/Z$ 3:2) as the first fraction and 282 (18.2 mg, 31%) as the second fraction.

1,4-Bis[5,10,15-triphenylporphyrin-20-yl]but-2-ene (282)

Yield 18.2 mg (31%); mp 310 °C; R$_f$=0.54 (SiO$_2$, EtOAc/C$_6$H$_{14}$, 1:3 v/v); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$= -2.73 (s, 4H, -N=), 5.70 (br, 4H, -CH$_2$), 6.67 (br, 2H, -CH=), 7.75 (m, 20H. phenyl-H), 8.19 (m, 12H, phenyl-H), 8.81 (br, 12H, $\beta$-H), 9.40 ppm (d, 4H, J = 5.2 Hz, $\beta$-H); $^1$C NMR (100.6 MHz, CDCl$_3$): $\delta$= 29.3, 116.3, 119.2, 126.1, 126.3, 127.2, 128.4, 134.0, 134.1, 135.1, 141.8 ppm; UV-vis (CH$_2$Cl$_2$): $\lambda_{max}$ (log $\varepsilon$)= 420 (4.2), 517 (3.0), 551 (2.6), 593 (2.5), 650 nm (2.5); HRMS (ES+) [C$_{41}$H$_{28}$N$_4$O]: calcd for [M + H] 1129.4710, found 1129.4679.
Chapter 6: Experimental

279 (key data)

### 279E

$^1$H NMR (600 MHz, CDCl$_3$) δ 5.01 (m, 3H, CH$_2$OCO, C=CHH), 5.24 (s, 1H, C=CHH), 5.93 (d, J = 5.6 Hz, 2H, CH$_2$CH=), 6.29 (d, J = 15.8 Hz, 1H, CH=CHCH$_2$) 6.30 (d, J = 15.4 Hz, 1H, CH=CHCO), 6.95 (dt, J = 5.6 Hz, 15.8 Hz, 1H, CH=CHCH$_2$), 9.83 (d, J = 15.4 Hz, 1H, CH=CHCO); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 38.0 (CH$_2$CH=), 64.2 (CH$_2$OCO), 116.8 (C=CH$_2$), 130.9 (CH=CHCO), 134.2 (CH=CHCH$_2$), 133.9 (CH=CHCH$_2$), 144.2 (CH=CHCO), 165.3 (CO$_2$);

### 279Z

$^1$H NMR (600 MHz, CDCl$_3$) δ 5.30 (s, 2H, CH$_2$OCO), 5.97 (s, 1H, C=CHH), 6.04 (s, 1H, C=CHH), 6.16 (m, 3H, CH$_2$CH=, CH=CHCH$_2$), 6.48 (d, J = 15.4 Hz, 1H, CH=CHCO), 6.83 (dt, J = 6.8 Hz, 11.3 Hz, 1H, CH=CHCH$_2$), 10.03 (d, J = 15.4 Hz, 1H, CH=CHCO); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 35.1 (CH$_2$CH=), 68.0 (CH$_2$OCO), 118.2 (C=CH$_2$), 124.2 (CH=CHCH$_2$), 130.9 (CH=CHCO), 137.5 (CH=CHCH$_2$), 144.5 (CH=CHCO), 165.6 (CO$_2$);

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Figure 6.1 HH COSY spectrum of porphyrin 279.
Figure 6.2 ROESY spectrum of porphyrin 279.
Figure 6.3 HSQC spectrum of porphyrin 279.
Figure 6.4 HMBC spectrum of porphyrin 279.
280 (key data)

**280E**: $^1$H NMR (600 MHz, CDCl$_3$) δ 5.02 (s, 2H, CH$_2$OCO), 5.16 (s, 1H, C=CHH), 5.31 (s, 1H, C=CHH), 5.46 (d, $J$ = 5.6 Hz, 2H, CH$_2$CH=), 6.29 (d, $J$ = 15.8 Hz, 1H, CH=CHCO), 6.43 (d, $J$ = 16.2 Hz, 1H, CH=CHCH$_2$), 6.84 (dt, $J$ = 5.6 Hz, 16.2 Hz, 1H, CH=CHCH$_2$), 9.82 (d, $J$ = 15.8 Hz, 1H, CH=CHCO); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 36.8 (CH$_2$CH=), 64.0 (CH$_2$OCO), 117 (C=CH$_2$), 130.9 (CH=CHCO), 130.4 (CH=CHCH$_2$), 133.7 (CH=CHCH$_2$), 144.0 (CH=CHCO), 165.3 (CO$_2$);

**280Z**: $^1$H NMR (600 MHz, CDCl$_3$) δ 5.24 (s, 2H, CH$_2$OCO), 5.68 (d, $J$ = 6.4 Hz, 2H, CH$_2$CH=), 5.83 (s, 1H, C=CHH), 5.94 (s, 1H, C=CHH), 6.18 (d, $J$ = 11.7 Hz, 1H, CH=CHCH$_2$), 6.44 (d, $J$ = 15.4 Hz, 1H, CH=CHCO), 6.77 (dt, $J$ = 6.4 Hz, 11.7 Hz, 1H, CH=CHCH$_2$), 10.01 (d, $J$ = 15.4 Hz, 1H, CH=CHCO); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 67.4 (CH$_2$OCO), 33.7 (CH$_2$CH=), 118 (C=CH$_2$), 124.7 (CH=CHCH$_2$), 130.8 (CH=CHCO), 136.9 (CH=CHCH$_2$), 144.4 (CH=CHCO), 165.4 (CO$_2$);

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Figure 6.5 HH COSY spectrum of porphyrin 280.
Figure 6.6 ROESY spectrum of porphyrin 280.
Figure 6.7 NOE spectrum of porphyrin 280E.

Figure 6.8 NOE spectrum of porphyrin 280Z.
Figure 6.9 HSQC spectrum of porphyrin 280.
Figure 6.10 HMBC spectrum of porphyrin 280.
Figure 6.11 $^1$H-NMR and NOE spectrum of porphyrin 282.
REFERENCES


