CHEMICAL REVIEWS

Review

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# Glycosylated Porphyrins, Phthalocyanines, and Other Porphyrinoids for Diagnostics and Therapeutics

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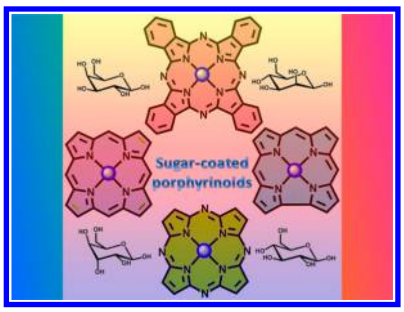
Supporting Information

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## 1. INTRODUCTION

As deaths from preventable diseases abate, cancer is becoming one of the leading causes of death in the world. Photodynamic therapy (PDT) is a noninvasive treatment for cancer involving the interactions of light with suitable frequency, a photosensitizer (PS), and molecular oxygen that results in generation of highly reactive oxygen species (ROS) such as singlet oxygen, hydroxyl radicals, the superoxide anion, and hydrogen peroxide.[1−3] These ROS react with diffusion limited kinetics with a range of biochemical structures in cells such as lipids, aromatic amino acids, the heterocyclic bases, the backbone of nucleic acids, and flavonoids to induce oxidative damage to the cell, thereby causing cell death via apoptosis or necrosis.[4,5] It was proposed that multiple sites of cellular damage may enable more efficient PDT effects.[6−9] Selectivity arises from the high reactivity and short lifetime of the ROS, so the cytotoxic

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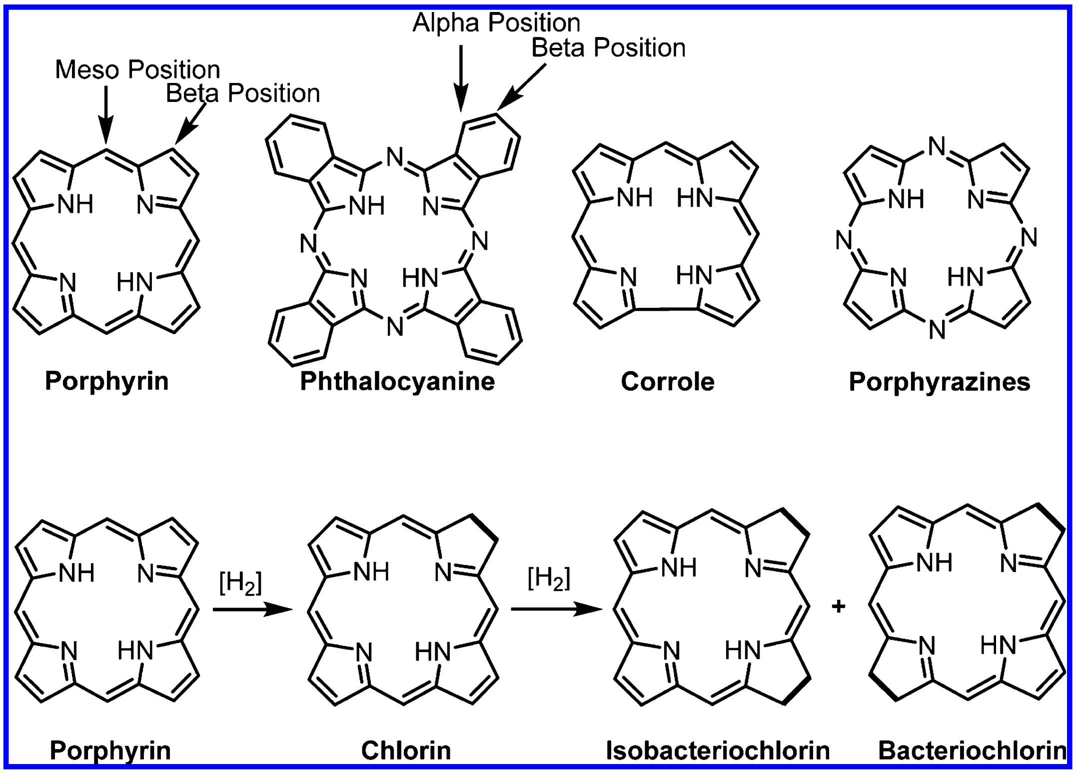


**Figure 1.** Structures of common porphyrinoid macrocycles (top). Structures of reduced porphyrins, such as chlorin, isobacteriochlorin, and bacteriochlorin (bottom).

response is limited to the irradiated area containing the PS dye.[10−12] Because the diffusion distance of singlet oxygen is approximately 2 $\mu$m, it reacts at the intracellular level because the diameter of eukaryotic cells is in the range of 10−30 $\mu$m. The localization of the PS in the cell influences the mechanism of cell death and is a determinant of biological efficacy.[13,14]

PDT has been used as a treatment for a variety of cancers including bladder, brain, breast, skin, lung, esophagus, and bronchial cancer.[15,16] It also has nononcological applications, such as treatment for age-related macular degeneration, hair growth, acne, and psoriasis.[17−23] PDT has several advantages over conventional therapies because this treatment is selective via the selective irradiation of light, PDT is noninvasive for tumors that can be irradiated, it is repeatable, of low cost, and has minimal side effects.[24] Because of these properties, applications of PDT can enhance both the quality of life and lengthen survival rate for patients with advanced diseases. Current limitations of PDT are that this treatment may cause skin photosensitivity, and is generally limited to treating tumors that are on or just under the skin because the light that is used to activate the PS cannot pass through more than few millimeters of tissue. Because the irradiation of the whole body with appropriate doses of light is not possible, PDT cannot be used for treating advanced disseminated diseases.[25]

Porphyrins and phthalocyanines (Pc's) are the most common and efficient photosensitizers (PSs) used in PDT because of their absorption in the visible range of the electromagnetic spectrum, long-lived triplet excited state, and efficient phototoxicity toward cancer cells.[26,27] Porphyrinoid-based PSs have several disadvantages such as poor water solubility, poor light absorption, poor selectivity, and light sensitivity after treatment because they do not efficiently target cancer cells. Current research addresses these pitfalls to make a next-generation PDT agent: (1) synthesis of pure PS in high yields, (2) improve water solubility, (3) fine-tune photophysical properties to efficiently make reactive oxygen species, (4) PSs that selectively target tumors, (5) strong light absorption in the red 650−750 nm for PDT deeper in tissues and for cancer imaging, and (6) minimize dark toxicity and skin sensitivity.

Numerous derivatives can be prepared from porphyrins and phthalocyanines because of the stability of the core macrocycle (Figure 1). In recent years, new methods were developed to synthesize dihydroporphyrins (chlorins) and tetrahydroporphyrins (isobacteriochlorins and bacteriochlorins) (Figure 1).[28−30] Chlorins and bacteriochlorins have absorptions bands at longer wavelength than porphyrins (for the lowest energy Q bands, $\lambda_{max}$ = 650−670 nm for chlorins and $\lambda_{max}$ = 730−800 nm for bacteriochlorins), yet still have high singlet oxygen quantum yields. Chlorin compounds are in various stages of evaluation for PDT. Pandey and co-workers, Hasan and co-workers, and Senge and co-workers recently reviewed the role of porphyrin derivatives in tumor imaging and PDT,[15,31,32] and there are more reviews on PDT.[33] Older reviews shed light on the development of the field over the last 20 years.[28,34−37] Boron-dipyrromethene, BODIPY (Figure 2), is a related class of

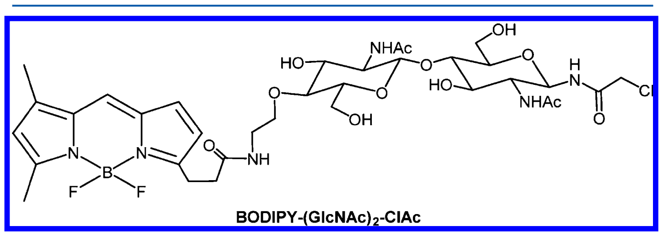


**Figure 2.** A representative example of a BODIPY conjugated to a simplified chloroacetamidyl chitobiose derivative.[41]


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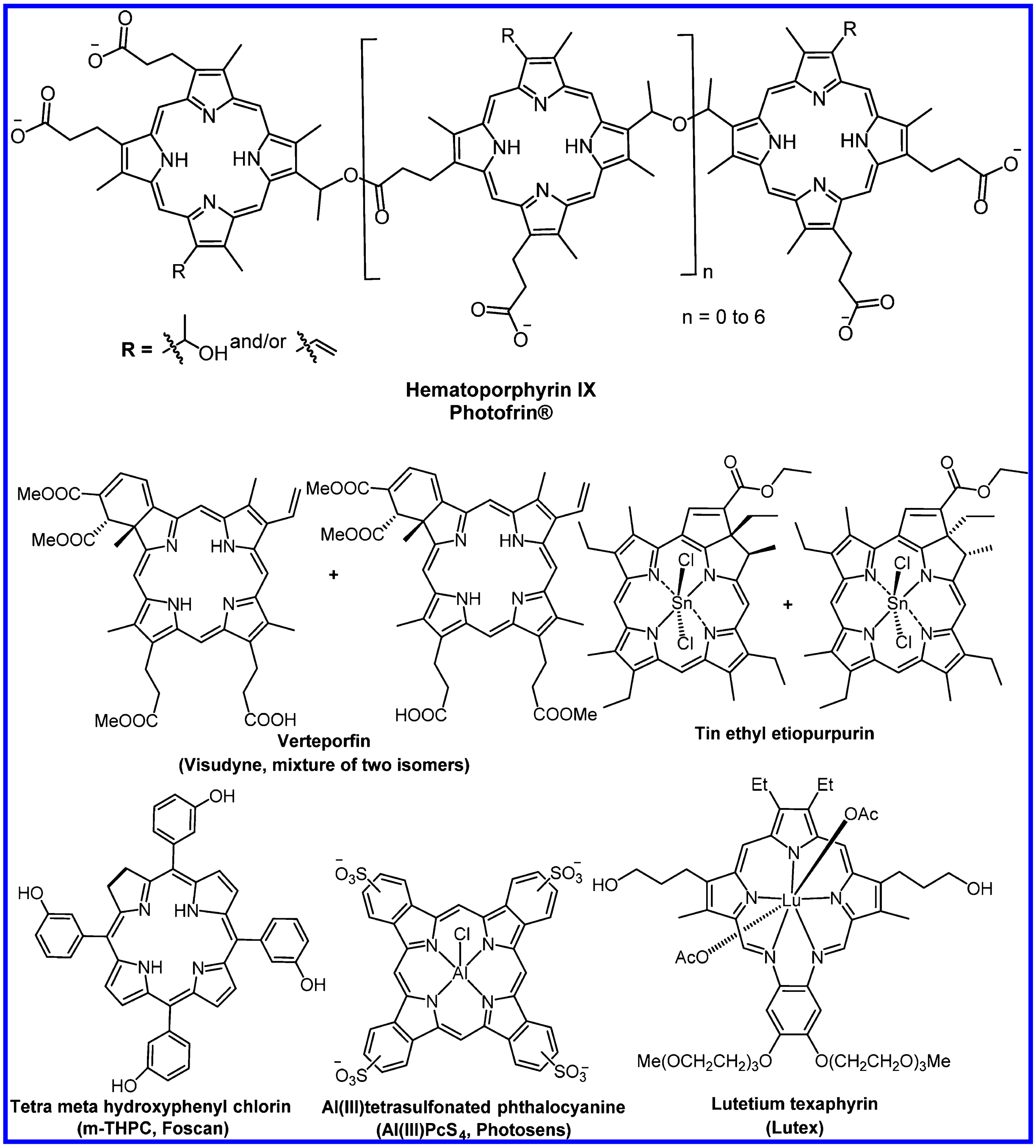


**Figure 3.** Structures of photosensitizers in clinical or preclinical trials for PDT.

fluorescent dyes that are under investigation for PDT[38] but is not included in this Review. Recently, the corrole macrocycle, a cognate molecule to the porphyrin, has also been studied as a PS.[39,40]

Porfimer sodium (Photofrin), a complex mixture of hematoporphyrin derivatives, was the first drug approved by the United States Food and Drug Administration (FDA) for PDT treatment of various forms of cancers such as lung, bladder, gastric, and cervical cancer (Figure 3). In addition to Photofrin, another PDT compound currently approved for cancer treatment in Europe is Foscan (*m*-THPC, *meta*-tetra(hydroxyphenyl)chlorin), which is a mixture of four atropisomers that have somewhat different solubility and aggregation properties in aqueous environments. Foscan was approved in Europe in 2001 for the treatment of head and neck cancers (Table 1).[42] Other PSs currently approved for clinical applications or in human trials include (Figure 3): 5-ALA (5-aminolevulinic acid), which is a porphyrin precursor, Metvix (5-aminolevulinic acid methyl ester), which can be used for warts, acne, and fungal infections,[8] Lu-Tex (lutetium texaphyrin), and Purlytin (tin ethyl etiopurpurin).[43−47] Lutex combines the advantage of water solubility and selective localization, and is capable of being activated by deeply penetrating far-red light.[48,49] Light fluences of 50−500 J/cm$^2$ of red light are needed in clinical PDT with Photofrin, whereas chlorins such as *m*-THPC that have larger extinction coefficients in the red fluences of 10 J/cm$^2$ are typically used.[16] White light, white light with red band-pass filters, pulsed and continuous lasers, and photodiodes are all viable light sources. The physics, biophysics, and technology of PDT are well reviewed.[24] The


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**Table 1. Photophysical Properties of Some Approved PDT Agents or Those in Clinical Trials**

| dye photosensitizer | $\lambda_{max}$ abs (nm) | $\varepsilon$ ($M^{-1}$ $cm^{-1}$) | $^1O_2$ quantum yield ($\Phi_\Delta$)[a] | year approved by FDA/EMEA/clinical trials |
|---|---|---|---|---|
| hematoporphyrin | 630 | 1170 | 0.25−0.89 | (FDA) 1990s[38,50] |
| protoporphyrin IX | 635 | 5000 | 0.22−0.54 | (FDA) 2000[15,38] |
| m-THPC | 650 | 39 000 | 0.22−0.50 | (EMEA) 2001[51] |
| verteporfin | 689 | 31 200 | 0.79 | (FDA) 2000[15] |
| chlorin e6 | 654 | 50 000 | 0.75 | clinical trials (Phase I/II)[38] |
| ethyl etiopurpurin Sn(IV) | 666 | 33 900 | 0.70 | clinical trials (Phase I/II)[15,52] |
| Al(III) tetrasulfonated phthalocyanine | 675, also two-photon | 100 000 | 0.36 | −[53−56] |

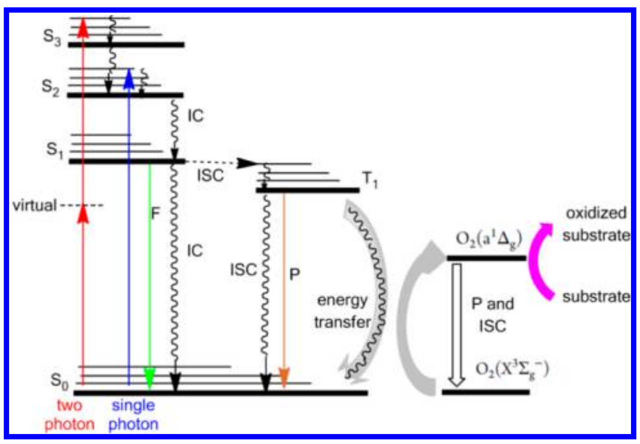
[a] $\Phi_\Delta$ is less in aqueous, polar, or protic solvents versus organic solvents or in surfactants.

light dosimetry depends on the optical cross section of the dye at a given wavelength, the absorption and scattering of light by tissues, the light intensity and duration, and that light can be applied multiple times.

The benzoporphyrin derivative verteporfin (Visudyne) is approved by the FDA for the treatment of age-related macular degeneration, subfoveal choroidal, neovascularization, and glocoma.[57−59] An aluminum phthalocyanine (Al(III)$PcS_4$) drug under clinical trial for age-related macular degeneration is (Photosens),[55] and a silicon phthalocyanine (Si(IV)$PcS_4$) is under clinical trial for cutaneous skin cell lesions and sterilization of blood products. The broad success of Photofrin is tempered by several factors including that it is a mixture of porphyrin oligomers, is poorly soluble in water, and has low selectivity toward tumor cells. Additionally, the molecular absorption coefficient of Photofrin is low ($\varepsilon$ = 1170 $M^{-1}$ $cm^{-1}$) at the clinically used wavelength of 630 nm,[19] so this PS cannot be used to treat deep cancers.[6] The photophysics of PS are reviewed,[24,60] and there are photoactivatable porphyrin designs.[61]

In terms of molecular design, there are several important considerations that are germane to the photophysics of the porphyrinoids (Scheme 1). When the eight $\alpha$ positions bear hydrocarbon substituents, the phthalocyanine (Pc) macrocycle becomes distorted because of steric crowding. Similarly, when both the $\beta$ pyrrole and the *meso* positions of porphyrins have hydrocarbon substituents, the porphyrin becomes distorted. Distortions in the otherwise planar macrocycles realign the molecular orbitals and reduce the HOMO−LUMO energy gap as observed by substantial red shifts and broadening of the bands in the electronic spectra. These distortions also lower the barrier to out-of-plane macrocycle vibrational dynamics, thereby increasing the amount of excited-state energy dissipated by internal conversion and concomitantly reducing fluorescence and inter system crossing to the triplet manifold.[62] Thus, the all $\alpha$-substituted Pc, and the dodeca-substituted porphyrins may be good for photothermal applications but not well suited to PDT and luminescent sensors. Closed-shell metal ions, most notably Zn(II), enhance intersystem crossing to the triplet state by the heavy atom effect, as do Pt(II) and Pd(II). Most open-shell first row transition metals, for example, Ni(II) complexes of porphyrinoids, are minimally or non luminescent because the excited-state energy rapidly goes to low energy d,d states.[64−66]

**Scheme 1. Jablonski Diagram Adapted from Pimenta et al.[63a]**




[a] S is the singlet manifold and T is the triplet manifold, IC is internal conversion by heat loss, F is fluorescence, P is phosphorescence, ISC is intersystem crossing from one manifold to another, and collision of the dye in the triple state with ground-state triplet oxygen photosensitizes the formation of singlet oxygen. Singlet oxygen and hydroxyl radicals react with cell constituents such as double bonds in lipids, flavins, heterocycles, sugar−phosphate backbones of nucleic acids, as well as systems to mitigate oxidative stress like super oxide dismutase.

The major drawback of Photofrin is that it leaves the skin photosensitive for a prolonged period of time. Pharmacokinetics studies in patients have shown that the active oligomeric component in Photofrin has a biological half-life time of about 19 days. This leads to the patient with prolonged skin photosensitivity after treatment, due to accumulation and retention of the drug in skin tissues.[67] To overcome the limitations associated with Photofrin, much research has been devoted to develop PSs with improved photophysical properties and fewer side effects. Next-generation PS should meet certain requirements for use in PDT.[19,29,68,69] (i) The PS should possess significant absorption in the near-infrared or infrared region between 700 and 1100 nm because biological tissues have low absorption in this region, thus enabling treatment of deeper cancers.[70,71] (ii) The PS should minimally aggregate intracellularly, or disaggregate upon entering the cell, thereby maximizing the singlet oxygen quantum yield. (iii) The PS should have high selectivity toward tumor cells and favor intracellular localization[68,72,73] such as in mitochondrial membranes and the endoplasmic reticulum to achieve maximum cellular damage within the small diffusion radius of singlet oxygen. (iv) The PS should be chemically stable and be stable to photobleaching.[74] (v) It should have a high triplet quantum yield to maximize PDT, or a balance between intersystem crossing to the triplet manifold and fluorescence for dual function imaging and therapy agents.

In 1999, Redmond et al.[75] compiled singlet oxygen ($^1O_2$) quantum yields ($\Phi_\Delta$) of several biological molecules and PSs that include: solvent used, intersystem quantum yield ($\Phi_{isc}$), fraction of oxygen quenching reactions that leads to $O_2(S_\Delta)$, values of the rate constant ($k_q$), excitation wavelengths ($\lambda_{ex}$) of PS, and methods or techniques used to measure $^1O_2$ quantum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yield. Four techniques used to calculate $^1O_2$ quantum yields described by Wilkinson et al.[76] follow: (1) time-resolved luminescence upon relaxation of singlet oxygen, (2) steady-state direct detection of the luminescence produced on relaxation of singlet oxygen, (3) photoacoustic calorimetry, and (4) time-resolved thermal lensing calorimetric techniques calculated on the basis of oxygen uptake or loss of absorbance or fluorescence. These organized data serve as a reference for the $^1O_2$ quantum yield calculations of many dye molecules to date.

In a classic paper in 1956, Warburg outlined the metabolic differences displayed by cancer cells, and what we now term the "Warburg effect" in terms of glycolysis, and the strategy of adding saccharides to drugs as a means to target cancer is reviewed.[77−82] In the late 1980s, it was recognized that the coupling of sugar molecules to hydrophobic porphyrin dyes can make them amphiphilic, thereby improving their solubility in physiological fluids, and promoting cellular recognition via specific carbohydrate protein interactions on cell surfaces.[83−89] The hypothesis was that this strategy would increase PDT efficiency by increasing targeted uptake and subcellular localization into critical areas such as mitochondria and the endoplasmic reticulum. However, the hydrolysis of the sugars diminished the effectiveness of the approach, vide infra. Herein, we will focus on saccharide conjugates of porphyrinoids (porphyrins, Pc's, corroles, tetrabenzoporphyrins) made to address the tumor targeting and photophysical requirements of PDT. The saccharide(s) can be appended via a direct coupling to the dye or via intervening linkers/spacers. Correlation of chemical structure with targeting, biological activity, and aggregation properties will be a particular focus. Indeed, the cellular uptake of these dyes can be improved through glycoconjugation because various types of sugar transporters, specific for different monosaccharides, are overexpressed in cancer cells.[90−92] Also, the presence of chiral functionalities, for example, the sugar moieties, on these macrocycles imparts interesting stereochemical properties in terms of chiral recognition, self-recognition, and aggregation. The biological evaluation of these conjugates reveals that they can be both efficient PSs for PDT[93−97] and efficient antibiotic and antiviral agents.[98,99]

PDT can also be used as an alternative treatment for microbial infections and is shown to be effective in killing pathogenic microorganisms. The mechanism of destruction of microorganisms is similar to the PDT of cancer in that light activation of certain PSs leads to generating singlet oxygen, which then compromises the bacterial membranes. Several porphyrin and Pc-based PSs are reported to be effective for the photodynamic inactivation (PDI) of bacteria and viruses.[99−106] The work reported so far is promising for the deployment of novel glycosylated porphyrinoids to obtain therapies with a large spectrum of antibacterial activity.

The charge and charge distribution on the macrocycle play an important role in cell uptake as well, where it is generally observed that cationic compounds more strongly interact with the negatively charged membrane, but there are some conflicting conclusions in that there are reports that two charges on the same side of the porphyrinoid are better than opposite sides and vice versa.[6,107] Our observations using MDA-MB-231, HeLa, and other cell lines are that one cationic *N*-methylpyridinium is likely optimal with the sugar or other solubilizing groups, and that two cationic groups on the same side are better than on opposite sides of the macrocycle. These observations are consistent with the notion that the amphipathic character of the macrocycle is as important and that the hydrophobic part of the molecule confined to one end or side imparts lipid-like properties. Second, while tetracationic porphyrins certainly bind to cells, they are not actively or passively taken up because of the high energetic costs of traversing the membrane arising from both the +40−60 mV barrier in the center of the membrane arising from the orientation of ions and dipoles of the head groups (electrostatic repulsion of cationic molecules from the membrane core),[108] and the hydrophobic membrane core does not accommodate hydrophilic ionic compounds. Cationic compounds that are more hydrophobic, for example, *N*-alkylpyridinium (where the alkyl group is a long chain) or with lipophilic counterions mitigate the solvation issue, but the large positive potential in the membrane core remains a barrier. An intriguing experiment might be to assess preformed nanoaggregates of cationic and anionic porphyrinoids because lipophilic cations and anions of porphyrins are known to form ionic chain assemblies in lipid bilayers.[109]

Porphyrinoids offer unique platforms to construct diagnostic and therapeutic agents because of the tunable photophysical properties and the diverse array of methods to append multiple copies of targeting agents, or combinations of targeting and biocompatibility moieties, to result in multifunctional systems. For instance, multifunctional systems that serve as diagnostics and concomitantly as therapeutics, the portmanteau theranostics used hereafter, have many advantages over using one system to diagnose and another to treat disease because the same compound is used, thereby obviating the differences in localization and uptake of a diagnostic agent and a separate therapeutic agent.[110−112]

## 2. GLYCOSYLATED PORPHYRINS

### 2.1. Sugars Appended to *meso*-Tetraphenylporphyrins

The synthetic strategies to form *meso*-substituted porphyrin−carbohydrate conjugates include the synthesis of the dye precursors bearing the sugar, for example, aldehydes for *meso*-substituted porphyrins. Appending the sugar, for example, on *meso* substituents, to the preformed macrocycle has the distinct advantage of minimizing losses of sometimes precious saccharides, and has been accomplished using substituion, click chemistry, and other approaches.[7,113] The sugar units can be covalently linked to the porphyrin macrocycle, or to a tether, via several heteroatom functional groups: N-,[114] S-,[7,86,115,116] C-,[89,117,118] and O-,[84,99,119−127] as well as by a 1,2,3-triazole.[128,129] In addition to phenyl spacer derivatives on *meso*-arylporphyrins, glycosides can also serve as spacers[88,130−133] (Figure 4).

Two general synthetic strategies are currently used to obtain glycosylated porphyrins. (1) The first is cyclization of glycosylated benzaldehydes with pyrroles into the corresponding porphyrins either by the Lindsey or by the Adler method.[89,124,134−138] By changing the structure of the benzaldehyde, *meso*-substituted porphyrins can be prepared with different numbers, types, and positions of sugar units, and may also incorporate other substituents. This method gives low yields in the cyclization step that may be exasperated by the steric hindrance caused by the sugar or other moieties on the 2- and/or 6-position on the aldehyde (Figure 5a). However, this is a versatile synthetic approach that affords a rich array of *meso*-aryl porphyrin compounds to evaluate photosensitizing efficacy


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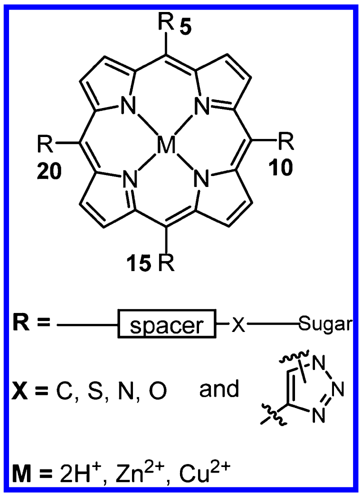


**Figure 4.** Generalized structure representation of *meso*-5,10,15,20-substituted porphyrin–carbohydrate conjugates. Spacers vary widely and include phenyl, phenylalkyl, and polyethylene glycol (PEG). Many reports examine the role of the substitution pattern on biochemical properties, for example, the six possible compounds using two different *meso* substituents.[7]

and can be easily adapted to yield specific substitution patterns.[119,139,140] (2) Benzaldehydes bearing amine, hydroxy-, carboxy-, halo-, haloalkyl-, or other functional groups enable glycosylation of premade *meso*-arylporphyrins using appropriate reactions with spacers or carbohydrates to yield the conjugates. Similarly, the six possible compounds with two functionalized aldehydes can be made statistically (Table 2) or by design, to yield small libraries of compounds to assess the role of the number and position of the carbohydrate on uptake and efficacy.[7] The second method is free from the problems associated with the porphyrin forming cyclization step, but the efficiency of the coupling chemistry must significantly increase with the number of carbohydrates to be appended to avoid separation of the complex statistical mixtures resulting from low yield reactions (Figure 5b).[119,141,142] In general, to develop useful PSs for PDT that can be translated into clinical use, it is important that the carbohydrate units should be introduced onto the porphyrin systems using straightforward and nearly quantitative reactions.

**2.1.1. Direct Linkage of Sugars on *meso*-Tetraphenylporphyrins without Spacer.** Glycoporphyrins without spacers are mostly synthesized via substitution of sugars onto preformed porphyrins to achieve better yields, and very few are synthesized with the Lindsey or Alder methods using glycobenzaldehydes and pyrroles. Direct linkage of glucose on porphyrin with O, S, N, C and 1,2,3-triazole without spacer is discussed below.

*2.1.1.1. Ether and Ester Linkages.* Heretofore, much of the research effort was devoted to appending sugar moieties on the *meso*-aryl groups of the tetraarylporphyrins via ether or *O*-glycoside linkages.[6,99,119,122−127,138,143] Recently, a simple and highly efficient method for the preparation of glycoporphyrins using trichloroacetimidates as glycosyl donors (Figure 6) was developed by Aicher et al.[144] They reported that the presence of Zn(II) in the macrocycle and use of well-matched Lewis acids were necessary for this procedure. This method has advantages as compared to prior methods[84,119,120,145−147] because one or more sugar units can be append onto the porphyrin with short reaction times, high yields, and with high purities. This may be a potential method to append other monoglycosylated to polyglycosylated conjugates on porphyrin macrocycle.

Several *meso*-substituted glycoporphyrin conjugates, where glucose is attached to tetraphenylporphyrin via an ester bond without any spacer, were also reported.[114,148−150] One typical example is discussed here. The commercially available cationic water-soluble tetra cationic porphyrins such as 5,10,15,20-tetrakis(*N*-methyl-4-pyridinum)porphyrin and 5,10,15,20-tetrakis[4-(trimethylamonium)-phenyl]porpyrin are active PSs.[151,152] Cationic porphyrins and their derivatives can bind with the negatively charged cell membrane and with DNA through intercalation and electrostatic interactions.

Depending on the molecular structure, cationic dyes often times are retained preferentially in cancer cells as compared to normal cells,[151,153] thereby enhancing light-induced damage to mitochondria and other cell components and causing cell death.[154] Because many cationic porphyrins have significant dark toxicity, there continues to be significant interest in developing porphyrins with low dark toxicity bearing both sugars and cationic groups.[6]

Molecular design of porphyrins that focuses on increased water solubility and membrane permeability also needs to consider selectivity to make them better PSs.[155−157] Studies demonstrated that cationic porphyrins and glycoconjugated porphyrins can both be efficient PSs in PDT and exhibit strong antiviral and antibacterial activity after photoactivation.[158] To explore this further, Tome et al.[148] reported the synthesis of neutral and cationic tripyridylporphyrin-D-galactose (Figure 7) and their antiviral activity against herpes simplex virus type 1 (HSV-1). The in vitro studies of these compounds showed that the porphyrins were significantly active under noncytotoxic dark concentrations, but photoactivation revealed potential antiherpetic activity.[148]

*2.1.1.2. Thioether Linkage.* Thioglycosides were first reported by Fischer et al. in 1909,[159] and many are readily synthesized as glycosylating agents and for polysaccharide formation.[160,161] Replacement of the oxygen atom with a sulfur atom at the anomeric position yields reagents that can be used to efficiently make thioglycosylated porphyrins. The *S*-glycosylated porphyrins are important because these are resistant to endogenous hydrolysis catalyzed by glycosidases, and exhibit greater stability in both acidic and basic media as compared to the corresponding *O*-glyco analogues,[6,137,162] and so are stable under physiological conditions including the reduced pH around cancer cells.

The core 5,10,15,20-tetrakis(2,3,4,5,6-pentafluorophenyl)-porphyrin ($TPPF_{20}$, Figure 8) chromophore has proven to be a remarkably versatile platform on which a wide variety of biotargeting, biocompatibility, and functional motifs can be rapidly appended in excellent yields; therefore, it has been adopted by many laboratories for evaluation of different molecular design concepts with diverse functionalities.[7,163−166] The facile nucleophilic aromatic substitution of the 4-fluorine group by primary S, N, and O groups enables rapid synthesis of dyes appended with diverse substituents including small polylysine peptides, boron clusters, PEGs, and polyamines.[7,167−170] This approach can also afford combinatorial libraries of porphyrins wherein the statistical mixture is obtained when the substituents all have the same nucleophile.[7,163] Increasing temperatures are needed as the nucleophile becomes harder. This is an improvement over the synthesis of combinatorial libraries from a mixture of


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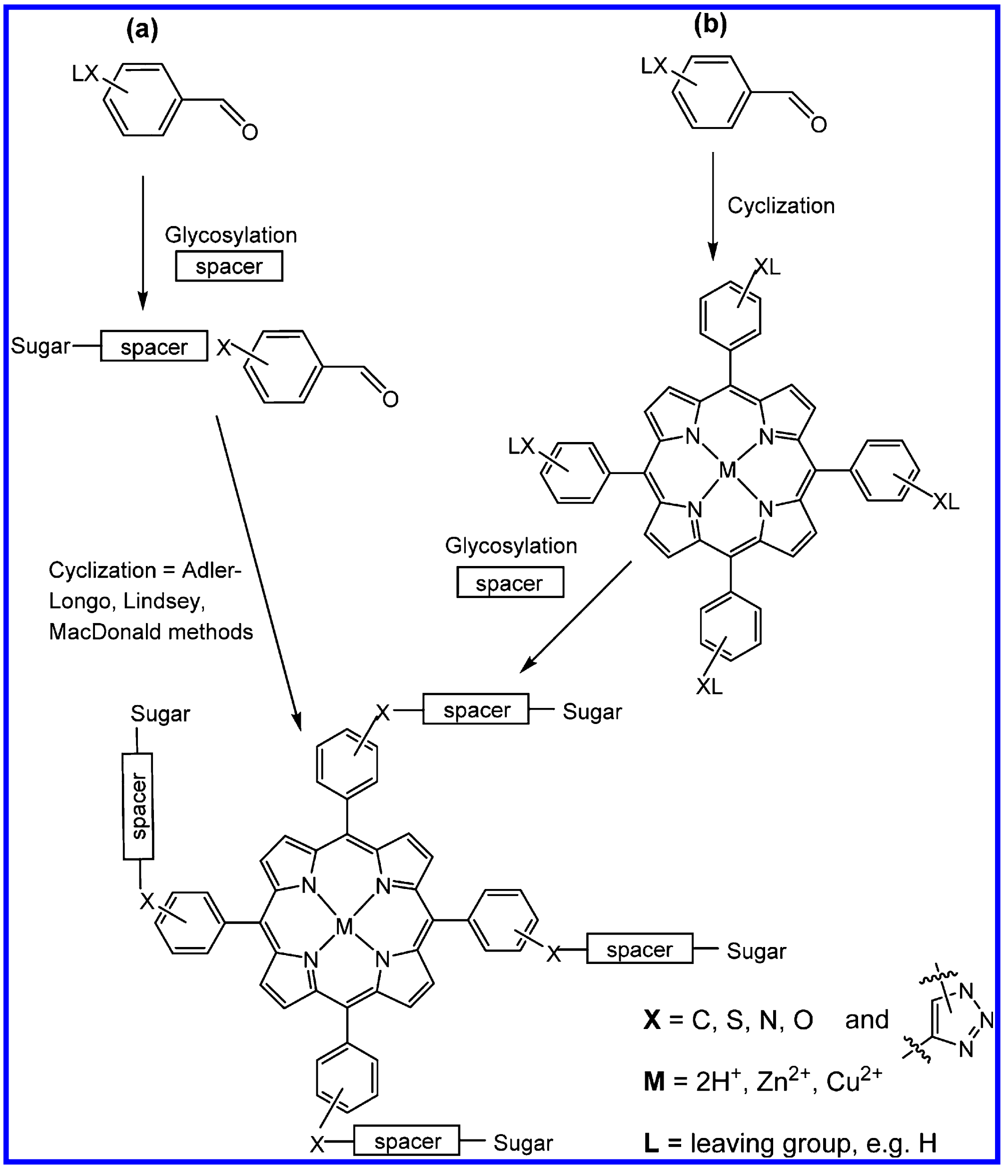


**Figure 5.** General scheme of the two major synthetic routes toward multiglycosylated porphyrins: (a) cyclization of glycosylated benzaldehydes by the Lindsey, Adler-Longo, or MacDonald methods;[119,139,140,176] (b) glycosylation of porphyrins by reactions with functional groups on the *meso*-aryl groups.[141,142] The spacers may or may not be used.

aldehydes and pyrroles because of the variable reactivity of the aldehydes, the low yield of the porphyrin, and the purification.[151]

In 2001, our group reported a facile method to append nonhydrolyzable thioglucose and thiogalactose units on $TPPF_{20}$ to yield $PGlc_4$ and $PGal_4$ (Figure 8) in high yield using this click-type chemistry.[89] These compounds were shown to be selectively taken up by several cancer cell lines[86] and exert PDT effects by damaging multiple cellular components, especially the endoplasmic reticulum.[171] These studies demonstrated the differences in selectivity and uptake resulting from glucose versus galactose targeting moieties, and that uptake of a particular porphyrin−carbohydrate conjugate is proportional to the expression of carbohydrate receptors on the cell. They also demonstrated selectivity for cancerous cell versus the corresponding normal cells. For example, human breast cancer cells (MDA-MB-231) take up $PGlc_4$ conjugate over the corresponding $PGal_4$ conjugate, and $PGlc_4$ predominantly accumulates in the endoplasmic reticulum.

Furthermore, $PGlc_4$ and $PGal_4$ are effective PDT agents as they induce cell death by necrosis and/or apoptosis, depending on the concentration of the conjugate and on the light exposure.[86,171] Tanihara and co-workers[172] synthesized the mono-, 5,10 and 5,15 di-, and tri- thio-glycosylated porphyrins along with $PGlc_4$, and cell uptake and phototoxicity on HeLa cells were conducted. The *cis* 5,15-dithio-glycosylated $TPPF_{20}$ displayed the greatest cellular uptake and phototoxicity among the series. This is in contrast to previous results showing that the 5,10-dithio-glycosylated compounds bearing either phenyl or 4-*N*-methylpyridinium on the 15,20 positions were taken up and more active than the *cis* compounds using MDA-MB-231 cells.[6,115] The differences may be due to the cell lines, the hydrophobicity, and the substituents.

Recently, Vicente and co-workers reported the synthesis of an asymmetric porphyrin containing three *p*-carborane and a glucose unit substituted on the *para*-phenyl position using the same chemistry (Figure 9).[173] This compound showed continuous uptake over 24 h by T98G human glioma cells,


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**Table 2. Six-Member Libraries**[a]

| 5 | 10 | 15 | 20 |
|---|---|---|---|
| A | A | A | A |
| A | A | A | B |
| A | A | B | B |
| A | B | A | B |
| A | B | B | B |
| B | B | B | B |

[a]Six compounds result when two different aldehydes, A and B, are used to synthesize *meso* porphyrins, and similarly there are six compounds that result from the mixed condensation reactions of phthalocyanines, for example, with two different phthalonitriles A and B. These can be separated by chromatography. Many porphyrin and phthalocyanine cores are constructed using this approach. Note that the *meso* aryl group on porphyrins is nominally orthogonal to the dye so that substitutions on any of the 2′ or 3′ positions that result in an aryl group that is not symmetric result in a set of four atropisomers; see Foscan, Figure 3. Because of the symmetry of phthalocyanines, isoindoles with one substituent are made as a mixture of four positional isomers; see Photosens, Figure 3.

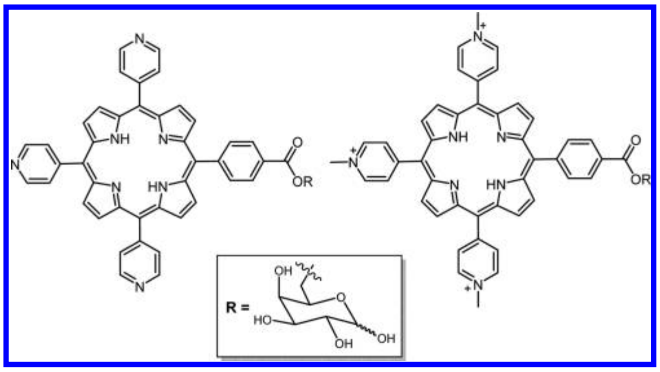


**Figure 7.** Structure of neutral and cationic tripyridyl porphyrin appended with D-galactose.[148]

with low darktoxicity and low phototoxicity, which makes it a good boron neutron capture therapy (BNCT) agent but not a good PS for PDT. In vitro blood brain barrier (BBB) studies on hCMEC/D3 human brain capillary endothelial cell of this compound were also carried out, where a moderate permeability was observed.

Boyle and co-workers reported a mild method for the synthesis of water-soluble porphyrins appended with three thioglycosyl units and pyridyl substituent (Figure 10).[115] The dark toxicity observed for these compounds was less as compared to cationic porphyrins with no sugar residues, indicating that the sugars play an important role in moderating dark toxicity. A new series of cationic and neutral water-soluble dimers of glycosylated porphyrins linked at the *meso*-position via a flexible hydrocarbon spacer were developed by Krausz and co-workers to understand the nature and organization of substituents around the porphyrin macrocycle.[136] Here, six glycosylated porphyrin dimers were synthesized differing in the nature, number, and position of the glycosyl units on macrocycle. The preliminary, in vitro biological data suggest that the number of glycosyl units on the porphyrin macrocycle modulates the hydrophilic/lipophilic balance and hence are essential features for an efficient photodynamic activity.[99,115,116]

*2.1.1.3. Amide Linkage.* The number of sugars and the position on the macrocycle are determinants of photobiological activity.[130] In this study, glycosamide porphyrins and the corresponding chlorins were synthesized by DiStasio et al. (Figure 11).[137] The effects of structural modifications, influenced by symmetric or asymmetric position of the

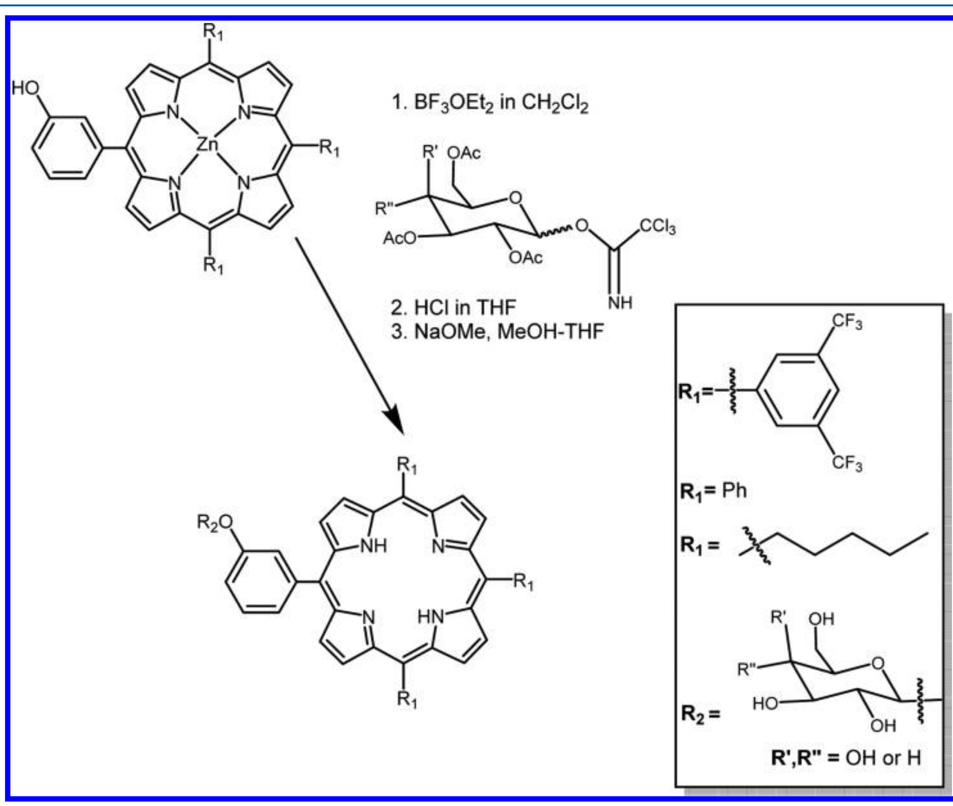


**Figure 6.** Glycosylated derivatives of hydroxyphenylporphyrin using trichloroacetimidate reagents reported by Aicher et al.[144]


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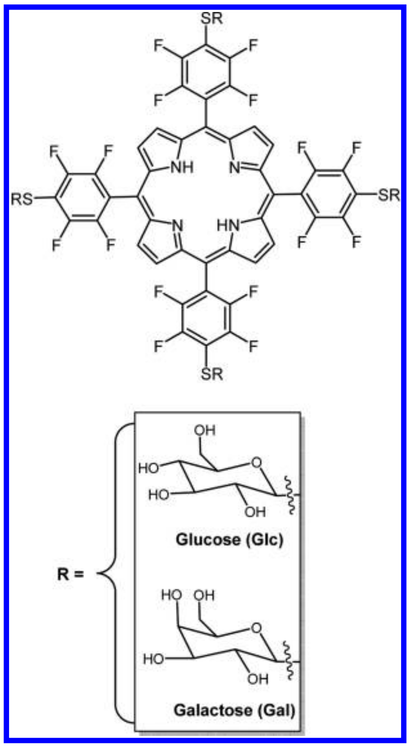


**Figure 8.** Nearly any primary thiol and unencumbered secondary thiol can substitute for the 4-fluoro group of the commercially available $TPPF_{20}$ in high yields under mild conditions in this click-type reaction.[163] Here, the tetra glycosyl- and tetra galactosyl- conjugates are shown, $PGlc_4$ and $PGal_4$, respectively, reported by Drain and co-workers.[86,89]

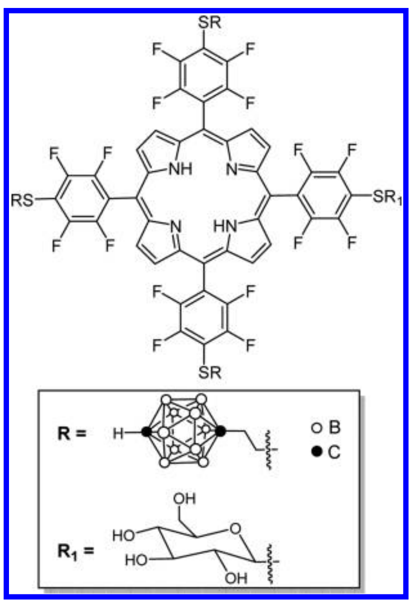


**Figure 9.** Glucose carboranylporphyrin conjugate reported by Vicente and co-workers made by first appending the thiol carborane and then the thiol glucose.[173]

glycoconjugation, in these compounds were correlated with the photophysical and photosensitizing properties. As expected, higher photodynamic efficacy was achieved for these compounds as compared to tetraphenylporphyrin (TPP), when incubated with HT29 human adenocarcinoma cells. These cells were found to be more sensitive to asymmetric, monoglycosylated conjugates during survival measurements using photocytotoxicity assays.

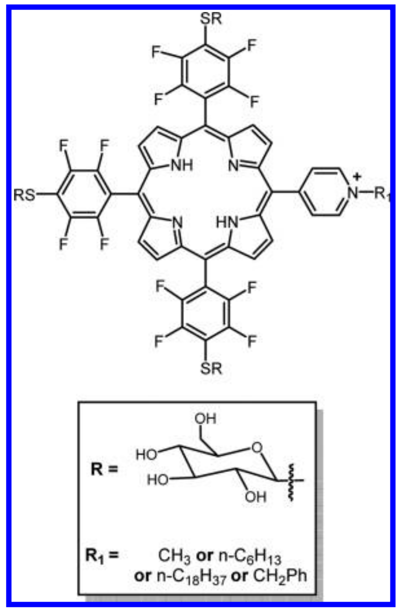


**Figure 10.** Porphyrin substituted by three glycosyl units and one pyridinium substituent reported by Boyle and co-workers probed lipophilic balance and synergy between glycosylation and cationic moieties.[115] The core porphyrin was made from a mixed aldehyde reaction using the Adler and Longo method, and the compounds separated.

*2.1.1.4. C-Linkage.* A novel class of glycoporphyrins use *C*-glycoside linkages to append the sugar moieties to *meso*-aryl groups on porphyrin macrocycles, as demonstrated by Franck and co-workers in 2001,[89] and later by others.[174] These chemically and metabolically robust carbon−carbon bonds retain much of the bond angles and conformations found in the *O*-glycoside linkages. The approaches to synthesize *C*-linked (versus *O*- and *S*-linked) porphyrin−carbohydrate conjugates remain a challenge and often result in low yields of the target compounds. *C*-Glycosylated porphyrins conjugated with xylofuranose, glucofuranose, and galactopyranose were also reported by Maillard et al.[175] Another example of the synthesis of *meso*-*C*-glycoconjugated porphyrins was reported by Casiraghi et al.[117] where the porphyrins were prepared by the Lindsey method[176] in 6−16% yield, through condensation of suitable dipyrrylglycosides with aryl aldehydes in the presence of Lewis acids such as trifluoroacetic acid or $BF_3$.

A second class of porphyrin−sugar conjugate with carbon−carbon linkages via methylene bridges was reported by Stepanek et al.[118] Porphyrin derivatives containing "*C*-glycoside" units, either in the 5,10,15,20-*meso* positions resulting from the direct cyclization of sugar aldehydes with pyrrole (Figure 12, type A), or in 5,15-*meso*-positions, resulting from the sequential construction of the dyes from the dipyrromethane precursors (Figure 12, type B), were synthesized. The presence of the sugar moieties on these porphyrin macrocycles imparts amphiphilic properties and enables self-organization into chiral suprastructures upon solvent-driven self-aggregation in different aqueous−organic solvent mixtures. The latter property of these compounds was further studied for potential use as building blocks for more elaborate and functional architectures in development of supramolecular chemistry.[118,177] Although these types of conjugates have not yet


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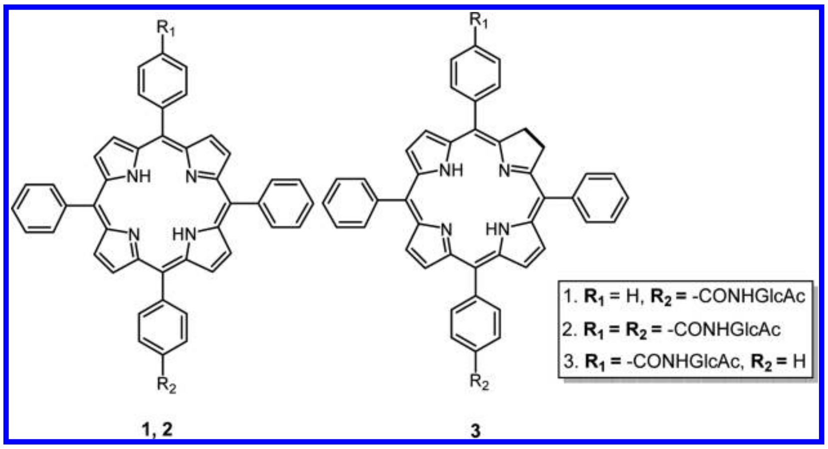


**Figure 11.** Glycosamide porphyrins and the corresponding chlorins studied reported by DiStasio et al.[137] The mono carboxylic acid porphyrins were synthesized via mixed aldehyde condensation using the Adler and Longo method, and the compounds separated. The carboxylic acid chlorin was obtained by diimide reduction of corresponding porphyrin. Amino sugars were conjugated to carboxylic porphyrin and chlorin using a typical amide coupling reaction. *trans*-Bis-glucose porphyrin was obtained using the [2+2] Mcdonald condensation method starting with *O*-acetylated glucosamine benzaldehyde.

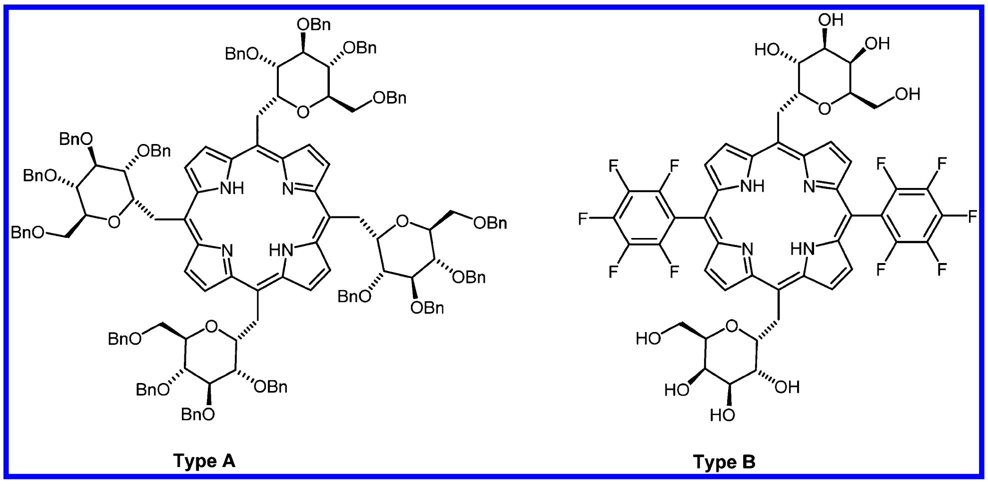


**Figure 12.** *meso*-*C*-Glycosylated porphyrins reported by Drasar and co-workers.[118,177]

been studied for PDT, they are expected to have important applications as PSs for PDT as well as for other therapeutics and diagnostics.

*2.1.1.5. 1,3-Cyclo Addition Reaction.* Sharpless and co-workers[178] proposed an effective 1,3-dipolar cycloaddition of azides and alkynes (click reaction) to give a stable 1,2,3-triazole cross-link between two molecules. Because of the ease of the reaction and high yields, this chemistry was employed to conjugate several carbohydrates to porphyrins, chlorins, and Pc's. Vicente and co-workers reported the expeditious preparation of tetraphenylporphyrin (TPP) (Figure 13) and tetraphenylbenzoporphyrin (TBP) (see Figure 41) appended with lactose or galactose moieties in high yield from readily available sugar azides using Cu(I)-catalyzed azide−alkyne 1,3-dipolar cycloaddition click chemistry.[129] The four galactose moieties were linked via triazole units to a *meso*-phenyl group of a TPP and TBP macrocycles. The time-dependent uptake and subcellular distribution of these conjugates were evaluated in human carcinoma HEp2 cells. These assays indicated that the TPP conjugates localized mainly in the ER and endosomes, but the TBP−galactose conjugate was taken up by the HEp2 cells ca. 5-fold more than the TPP conjugates, and localized preferentially within the cell lysosomes. The methodology developed here is highly regioselective and uses milder reaction conditions that are compatible with a large number of functional groups and allows the synthesis of highly water-soluble carbohydrate-substituted TBPs.

Scanlan and co-workers[128] successfully optimized the synthesis of glycoporphyrins without any spacer using 1,3-cyclo addition reaction under microwave (MW) conditions. They could obtain the desired glucose and mannose-substituted tetraphenylporphyrins in quantitative yields within 20 min as opposed to 3 days of conventional heating.

**2.1.2. Sugars Linked to *meso*-Tetraphenylporphyrins with Spacer.** The synthesis of glycoporphyrins with different length spacers was achieved, which reduces the steric interactions between the sugars and the macrocycle and improves the carbohydrate recognition when tested in vitro and in vivo. Using PEG spacers would have an added advantage of solubility and stability of the glycoporphyrin drugs. Here, we discuss the glycoporphyrins with spacers that were synthesized by reacting sugars to preformed porphyrins.

*2.1.2.1. Ether Linkage.* In the 1990s, Krausz and co-workers[135,179] reported glycoporphyrin conjugates with a propyl spacer, where the sugar moiety is attached to porphyrin via an ether linkage. Recently, Blais and co-workers[88] reported


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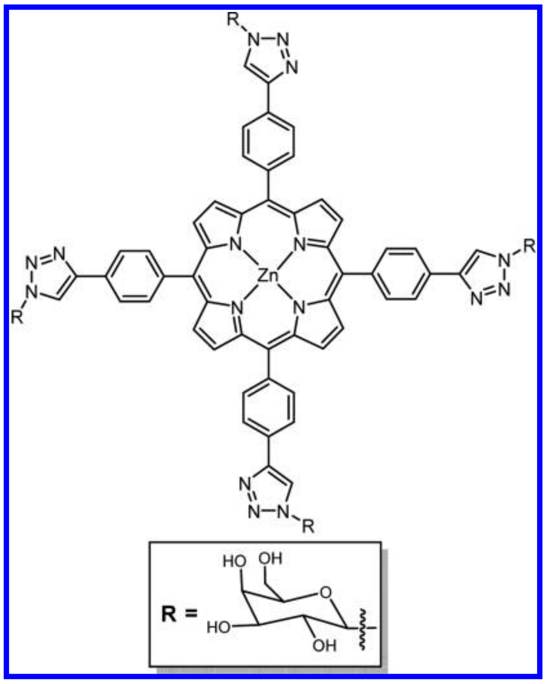


**Figure 13.** Structure of TPP−galactose conjugate linked via triazole unit.[129]

*O*-glycoporphyrin conjugates with diethylene glycol (DEG) spacers. Human retinoblastoma cells are known to express sugar receptors that have preferential affinity for galactose and mannose residues.[180,181] Exploiting this property, Blais and co-workers synthesized a series of glycoconjugate porphyrin-based PSs for a potential PDT treatment of retinoblastoma.[88] The glycoconjugated porphyrins include TPP(*p*-DEG-*O*-α-GalOH)$_3$, TPP(*p*-DEG-*O*-β-GalOH)$_3$, TPP(*p*-DEG-*O*-α-ManOH)$_3$ (Figure 14), and their *S*-analogues in which the sugar motif and porphyrin core were linked by a DEG spacer. The biological and photobiological properties of these DEG-linked *O*- and *S*-galacto/mannoconjugated *meso*-tetraphenyl porphyrins (TPPs) were tested in vitro on a human retinoblastoma cell line (Y79). The photo induced toxicity of these glycosylated derivatives was compared to those of the parent unconjugated DEG porphyrin, TPP(*p*-DEG−OH)$_3$, and the corresponding monoethylene glycol (MEG)-linked mannose appended porphyrin, TPP(*p*-MEG-*O*-α-ManOH)$_3$. The photobiological activities of these glycosylated porphyrin conjugates depend on the nature and length of the spacer and anomeric configuration of the sugar unit. The increase in the length of the spacer linking the porphyrin with the sugar moiety resulted in higher cellular uptake of these glycosylated porphyrin conjugates relative to that of nonglycoconjugated compounds.[88,182]

*2.1.2.2. Thioether Linkage.* *S*-Glycosyl bonds were found to be stable to enzymatic hydrolysis by glycosidase enzymes in vitro and in vivo. Thiosugars linked to symmetrical tetra-substituted porphyrin with DEG spacer was reported by Blais and co-workers.[88] Krausz and co-workers[116] reported the synthesis of thioglycoporphyrins with propyl linkage/spacer. Three of such derivatives containing glucose, galactose, and mannose were reported (Figure 15). In vitro phototoxicity studies of these conjugates against K562 human chronic myelogenous leukemia cell line were carried out. Cells that had taken up the compounds were irradiated with white light for 0−2 h. An increase in cell death was observed with increased

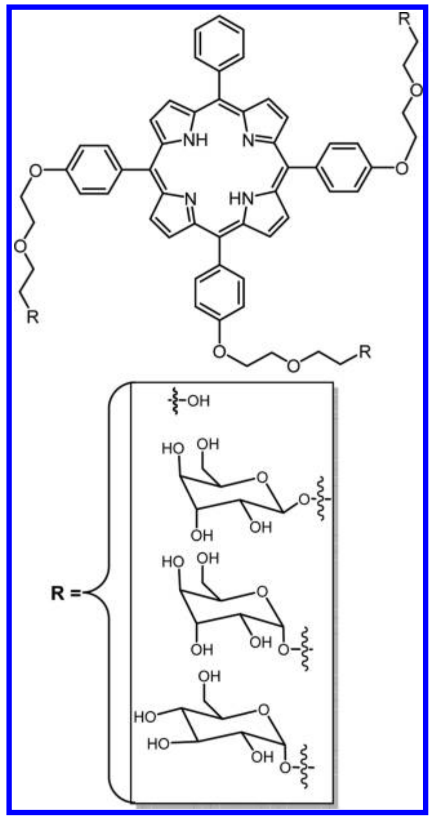


**Figure 14.** Structures of the parent unconjugated DEG porphyrin and corresponding sugar conjugate; the latter binds to human retinoblastoma cells.[88] The porphyrin core was synthesized via mixed aldehyde condensation using the Adler and Longo method. The DEG with or without sugars was substituted onto the porphyrin core via a Williamson type reaction.

irradiation time, and subsequent incubation of cells in dark resulted in continued death of the cells presumably by apoptosis. Among the series, all of the *ortho*-isomers were found to be more photoactive.

*2.1.2.3. Amide Linkage.* Another approach for the synthesis of derivatives of tetraphenylporphyrin substituted by eight galactose or glucose units with amide linkages containing ethyl spacer was developed by Fujimoto et al.[87] These porphyrin glycoconjugates were remarkably water-soluble and fluorescent. Consistent with other reports, the cell uptake studies of these compounds indicate that appending different sugar moieties on porphyrin macrocycle may direct the chromophore toward different cell types and play a significant part in the photosensitizing properties.[6]

Krausz and co-workers[136,183,184] reported the synthesis of tetraphenylporphyrins appended with both amino acids and *O*-glycosyl, as well as two different glucose porphyrin (*para* and *ortho*-substituted) conjugates connected via an amide bond. A propyl group was used as a spacer between the glucose and tetraphenylporphyrin core (Figure 16).[183,184] Phototoxicity studies of these compounds were tested on K562 human chronic myelogenous leukemia cells, and the *ortho*-substituted glycoporphyrin was more PDT active as compared to the *para*-substituted derivative.

Asayama and co-workers[185] reported Mn(II) porphyrin−lactose conjugates linked by an amine with propyl spacer. Human hepatoma HepG2 cells were used to test this compound for its superoxide dismutase (SOD) activity, dark


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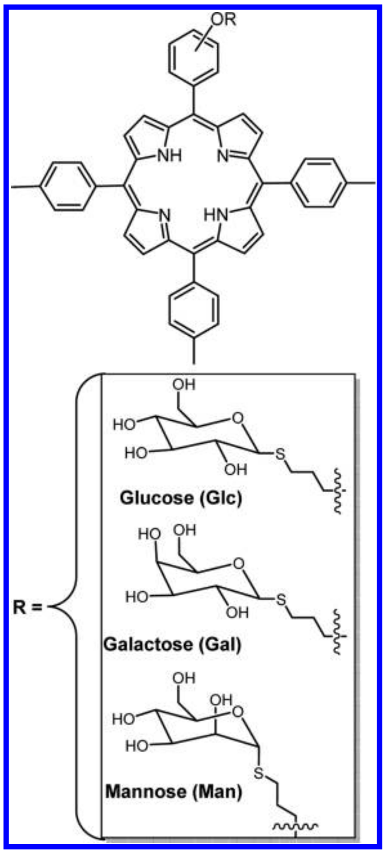


**Figure 15.** Thioglycosylated *meso*-porphyrins reported by Krausz and co-workers synthesized via condensation of 1-thioacetylated sugars with monobromotritolyl-porphyrins followed by deprotection of acetate groups using NaOMe.[116]

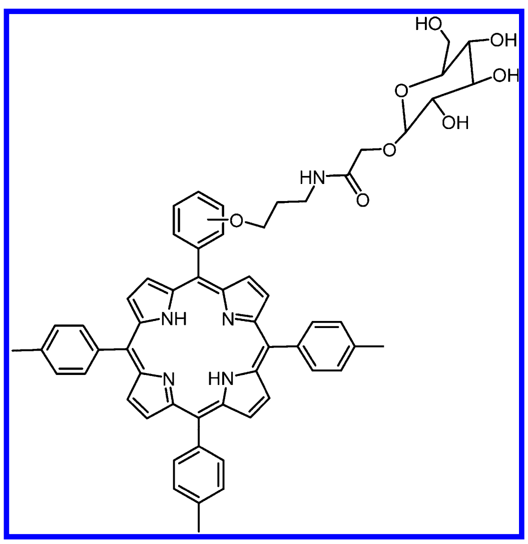


**Figure 16.** Glycosylated porphyrin reported by Krausz and co-workers starts by using a mixed aldehyde condensation to yield the monohydroxyphenyltritolylporphyrin.[183,184]

toxicity, and cellular recognition. Results showed a very good SOD activity, low dark toxicity, and significant cellular recognition.

*2.1.2.4. 1,3-Cyclo Addition Reaction.* Large numbers of sugar units were appended onto the porphyrin via 1,3-cyclo addition click chemistry with different spacers.[121,128,129,186−189] One embodiment of click chemistry takes the advantage of Cu(I)-catalyzed chemoselective coupling between organic azides and terminal alkynes in a simple, convenient, and quantitative method.[190,191] Although this is a good method to append multiple sugar units on porphyrin macrocycle, simultaneous insertion of Cu(II) ions into the porphyrin core is disadvantageous for PDT, because Cu(II) porphyrins have poor singlet oxygen quantum yield and therefore serve as poor PSs (Figure 17).[142]

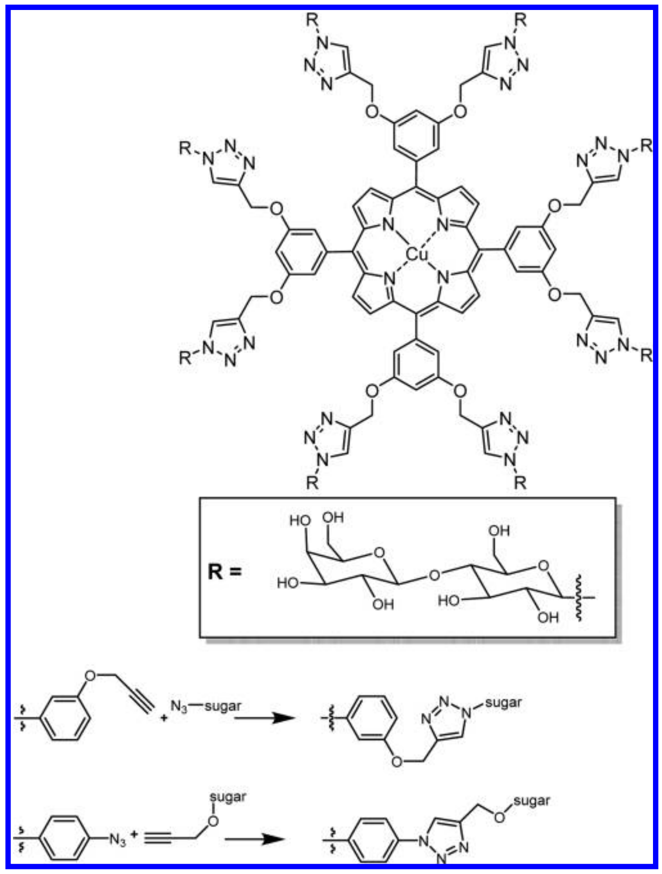


**Figure 17.** Top: Octa-$\beta$-lactoglycosylated porphyrinatocopper (PorCu-Lac$_8$) prepared by click chemistry.[142] Bottom: Two general routes to azide click chemistry to append sugars onto *meso*-arylporphyrins.[190,191]

Garcia et al. reported the synthesis, biological, and photobiological studies of a series of glycosylated porphyrins linked by triazole spacer to target the tumor cells over-expressing lectin type membrane receptors.[189] The triazole spacer group is relatively stable toward metabolic degradation and does not pose toxicity problems.[192] These porphyrins were prepared by click chemistry under microwave heating and were found to have good singlet oxygen quantum yield. Various factors were investigated such as the nature of the sugar moieties, length of the spacer, and position and orientation of the triazole group to assess the photocytotoxicity of these chromophores. The photocytotoxicity was tested on two different cell lines, HT29 (colorectal adenocarcinoma cell line) and Y79 (human retinoblastoma cell line). Some of these compounds exhibited a good activity in particular against the Y79 cell line and are reported to have less photocytotoxicity as compared to molecules bearing diethylene glycol spacers, for example, those reported by Blais and co-workers (Figure 14).[88] *meso*-Arylporphyrins can be grafted onto cotton fabric via


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cellulose azidation followed by a click reaction with an acetylenic porphyrin to yield a material with antibacterial activity against representative strains of *Escherichia coli* and *Staphylococcus aureus*.[128,193]

Mukosera et al. recently used Cu(II)-catalyzed 1,3-dipolar cycloaddition reaction for the synthesis of per-*O*-acetylated glucose, galactose, lactose, and glucosamine conjugates appended directly to 5,15-[*p*-(ethynyl)diphenyl]porphyrinato zinc(II) and 5,10,15,20-[*p*-(ethynyl)-diphenyl]porphyrinato zinc(II) compounds.[194]

Scanlan and co-workers reported the synthesis of a library of glycosylated porphyrin conjugates by using Cu(I)-catalyzed 1,3-dipolar click methodology.[121] Here, the ligation reactions are between *meso* 4-azidophenyl moieties on the porphyrin and the propargylic carbohydrate. In this case, using the Zn(II) metalloporphyrin diminished metalation by the copper catalyst. The reaction conditions were optimized to allow the efficient coupling of porphyrins with biologically active fully protected or deprotected carbohydrates. Synthetic sugars such as an amido derivative of lactose (*N*-acetylated lactosamine) and the histo blood-group antigen trisaccharide, Lewis$^x$, were ligated to the porphyrin macrocycle for the first time. The PDT activities of these compounds were tested against human esophageal cancer cells.[121] A Cu(I)-catalyzed click reaction was used in the synthesis of other triazole-linked mono-, di-, tri-, and tetra-modified glycoporphyrins under microwave-heating conditions,[128] wherein a sequential "double-click" reaction sequence yielded bis-modified 5,10-diglycoporphyrins appended with different sugars (Figure 18).

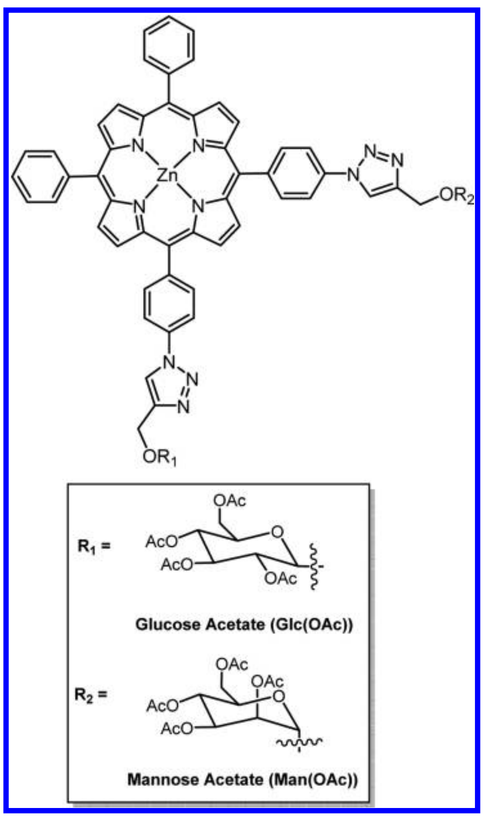


**Figure 18.** 5,10-Bis-glycoporphyrin synthesized via a microwave heated sequential double click reaction. Core 5,10-bis-azido porphyrin was obtained first by synthesizing 5,10-bis-nitroporphyrin using the Adler and Longo method followed by reduction of nitro groups.[128]

### 2.1.3. Glycodendrimeric Porphyrins.

Appending sugars on a porphyrin core modifies the amphiphilicity of the macrocycle and makes them specific for binding with lectin-type receptors that are overexpressed in many types of cancer cells.[83,195,196] Because the glycoconjugates of the dye are too large for sugar transporters, cell uptake must go by other mechanisms, and these likely depend strongly on the specific molecule under investigation. Passive diffusion of lipophilic species, endocytosis, and other mechanisms may all play a part in uptake to different degrees, again depending on the specific molecular structure. The identification of the transport mechanisms through the biological membranes is challenging, yet is important for optimization of the PSs targeted toward the malignant cells.[88,197] For example, the $PGlc_4$ species in Figure 9 has been shown to enter cells both by diffusive and by endocytotic processes.[198]

The use of glycodendrimers as recognition motifs is a promising avenue toward understanding uptake.[199] Carbohydrate–protein interactions play an important role in a large number of biological processes, because not only sugar moieties but also proteins are also active components in cell recognition.[131,200−202] Stoddart and co-workers reported the synthesis of two symmetric tetrasubstituted porphyrin glycoconjugated dendrimers with four and 12 $\beta$-D-glucopyranosyl residues present on the periphery of the tetrapyrrolic macrocycle (Figure 19).[203]

Rosilio and co-workers reported a family of glycoconjugated PS with only one glycodendrimer moiety on the para position of one *meso*-phenyl group attached to the porphyrin.[204,205] Here, the mannose sugar unit is attached to the macrocycle with variable length spacers (Figure 20) to create a lipid-like structure where the dye is the hydrophobic end. The interactions of these glycodendrimeric porphyrins with phospholipids were studied at the air–water interface and in liposome bilayers. These studies found that the conjugate with the longer spacer interacted well with the lipid bilayer with the sugar moieties protruding into the surrounding aqueous phase, which aggregated with Concanavalin A (Con A), a mannose-specific lectin.[206] This work highlights the role of complex interactions between the lipid molecules, the sugar moieties, and the hydrophobic porphyrin cores in the passive diffusion of glycoconjugates across cancer cell membranes. The dendrimeric structure was reported to show high binding affinity to plasma proteins and phototoxicity against retinoblastoma cells Y79.[207] From another perspective, these and similar glycoporphyrin constructs may constitute efficient targeting carriers for other drugs in addition to PDT. Other porphyrin-based glycoconjugates made by azide–alkyne click chemistry were used in sensors for specific binding of two bacterial lectins that present different carbohydrate preference such as Concanavalin A.[208]

Kushwaha and Tiwari reported the synthesis of a series of azide-functionalized glycodendrimer porphyrins having 8, 12, 16, and 24 $\beta$-glucopyranose units at the peripheral position using azide click chemistry; the structure of 24 $\beta$-glucopyranose porphyrin is shown here (Figure 21).[209]

Other examples of glycodendritic conjugates of porphyrins and Pc's were reported by Silva et al., bearing 8 and 16 D-galactopyranose units, respectively (Figures 22 and 53).[132] Both of these conjugates were reported to have high singlet oxygen production, suggesting the potential to be used as PDT agents.


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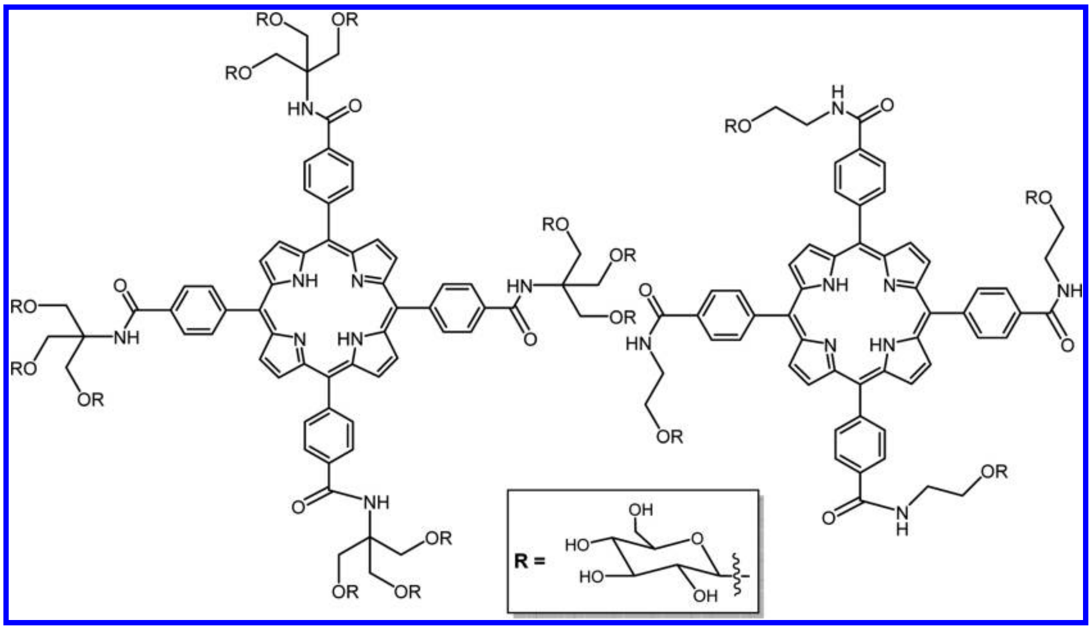


**Figure 19.** Glycoconjugated dendrimers symmetrically appended to a porphyrin core with 4 and 12 $\beta$-D-glucopyranosyl residues reported by Stoddart and co-workers.[203]

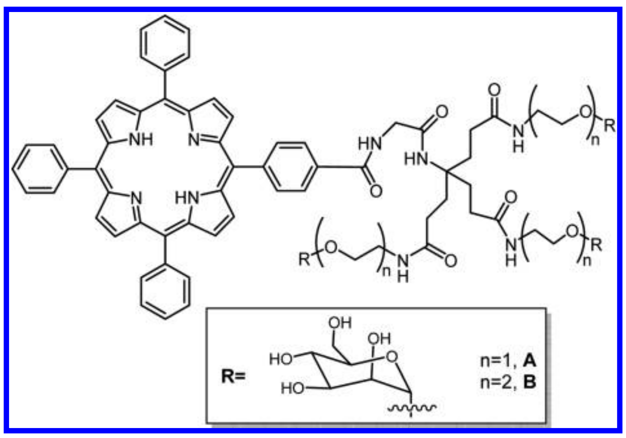


**Figure 20.** Structures of glycodendrimeric porphyrins reported by Rosilio and co-workers,[204] where the porphyrin core was made by mixed aldehyde condensations using the Adler and Longo method.

**2.1.4. Polysaccharide Porphyrin Conjugates.** Although several porphyrin carbohydrate conjugates are reported to have good in vitro PDT efficacy, many of these compounds show lack of selectivity and the moderate solubility in water leads to aggregation (see section 9), thus complicating in vivo testing and analysis. In this section, strategies to overcome aggregation via appending polysaccharides to the porphyrin core are discussed. Cyclodextrins (CDs) are a family of natural compounds widely used in the pharmaceutical and cosmetic industries as insipients, the more hydrophobic interior allows CD to host small molecules, and as covalently attached carriers. Porphyrin−CD conjugates as supramolecular systems were reviewed.[210] Supramolecular chemistry is chemistry beyond the covalent bond; therefore, supramolecular systems result from the spontaneous association of molecules driven by intermolecular interactions. The covalent attachment of molecules into macromolecules does not result in supramolecular systems a priori. Self-assembly refers to the formation of discrete systems, for example, porphyrin arrays,[211,212] whereas self-organization refers to formation of open or nondiscrete systems,[213,214] and the supramolecular porphyrinoid materials are reviewed.[215−217] Many of the porphyrin−CD supramolecular systems are designed to examine electron and energy transfer or as potentially catalytic systems, but herein we focus on the conjugates designed for therapeutic applications. For example, *meso*-tetrakis(4-sulfonatophenyl)porphyrin spontaneously assembles with CDs in aqueous solutions.[218]

Kral and co-workers[219,220] reported several porphyrin−CD conjugates as a potential PDT agent as well as a drug delivery system for cancer therapy (Figure 23). Binding studies of several chemotherapy drugs on porphyrin−CD conjugates showed that doxorubicin had good binding affinity toward porphyrin $\gamma$-CD **3** and paclitaxel had good binding affinity toward porphyrin $\beta$-CD conjugates **1**, **2**, and **4**. In vitro studies using mouse mammary carcinoma 4T1 cells and human chronic myelogenous leukemia K562 cells, and in vivo studies using BALB/c mice transplanted with 4T1 cells on the supramolecular carrier−chemotherapy drug complexes were tested. These studies showed that this system works as an efficient combination therapy (PDT and chemotherapy) to treat cancer.

Kun and co-workers[221,222] reported acetyl chondroitin sulfate chlorin e6 and acetyl hyaluronic acid porphyrin derivatives as nanodrugs for PDT. The triplet quantum yield of nanogels of pullulan/folate-pheophorbide-a conjugates was suppressed in PBS due to self-quenching of the PS, but when the nanogel was coincubated with esterase in the presence of HeLa cancer cells, the PDT activity was restored.[223] In vitro studies of acetyl chondroitin sulfate porphyrin drug were conducted on HeLa cells.[222] Continuous uptake of the compound was observed when monitored by confocal microscopy, and a moderate phototoxicity was observed. In vitro cell uptake and phototoxicity studies of acetyl hyaluronic acid porphyrin conjugates (Figure 24)[221] were also tested on HeLa cells. A rapid uptake of the compound was observed, suggesting an internalization of compound via endocytosis. Low phototoxicity was also observed with this compound. Low phototoxicity of both


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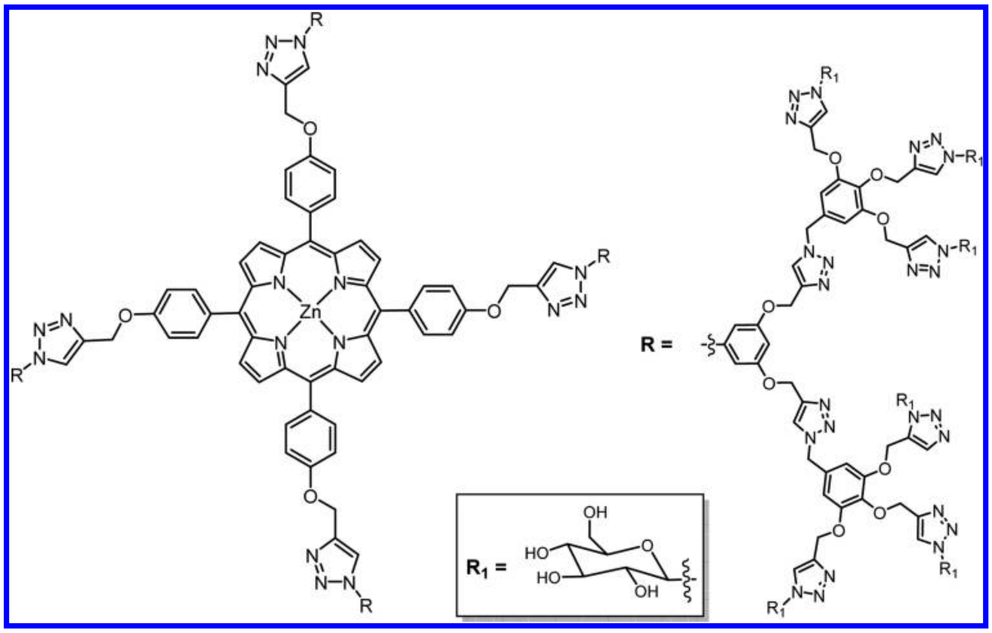

**Figure 21.** Structure of azide-functionalized glycodendrimers of porphyrin having 24 $\beta$-glucopyranose units.[209]

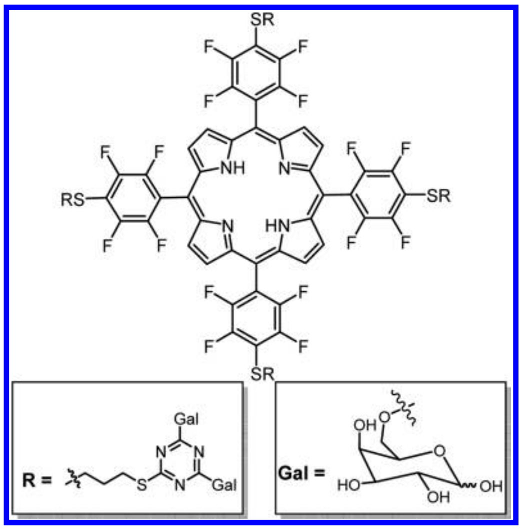

**Figure 22.** Structure of porphyrin glycodendritic conjugate with eight galactopyranose units.[132]

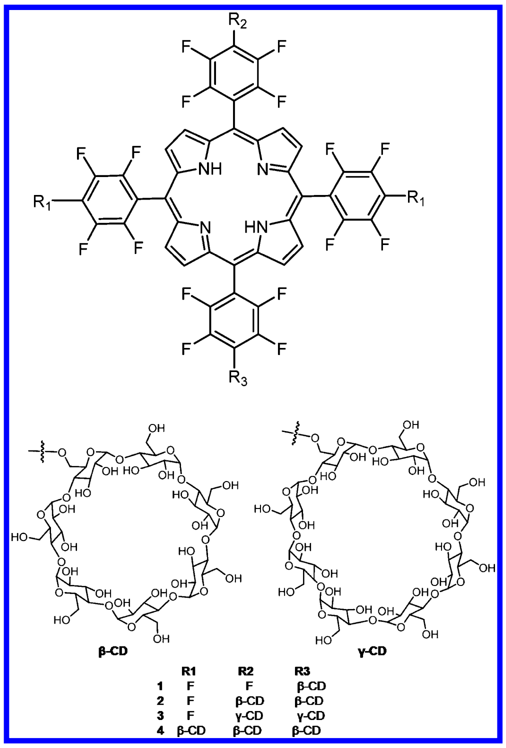

**Figure 23.** Porphyrin−CD conjugates used as carrier−drug complex for therapy.[219,220] Other porphyrin−CD conjugates formed using click chemistry and amide linkers are reported, and there are various strategies that self-assemble CD with porphyrins into supramolecular materials.[210]

conjugates revealed self-quenching due to proximity of the dyes on the hyaluronic acid and chondroitin sulfate backbones.

Mikata et al. reported the synthesis of a series of free base and Zn(II) derivatives of porphyrin bearing 1−4 maltohexoses units at the *meso* positions. The maltohexoses unit on the porphyrin macrocycle is reported to increase the solubility of the PS. Out of all of the conjugates, only the mono-substituted maltohexaosylated glycoconjugate was reported to be efficient PS using HeLa cells.[224] This is another example of how the exocyclic motifs are only part of the story and that amphipathicity, as measured by octanol/water partition coefficients, is a key parameter in designing PDT agents.

## 2.2. $\beta$-Pyrrole-Substituted Porphyrin Sugars

Kupriyanov and co-workers[225] first reported the synthesis of porphyrin sugar derivatives substituted at the $\beta$-pyrrolic position in 1978 using ester bonds, and the first example of a *C*-glycosylated porphyrin in which four sugar molecules were attached to the $\beta$-pyrrole positions of the porphyrin macrocycle was reported by Maruyama and co-workers in 1992.[96] Following these reports, several *meso*-substituted glycoporphyrins were studied along with a few more $\beta$-pyrrolic-substituted sugar porphyrin conjugates.[113] Among these, the sugars were substituted on porphyrin via sulfur,[116] nitrogen,[114] and carbon groups.[226] One such example was recently reported by Cavaleiro and co-workers shown in Figure 25.[226] Five different allyl sugars were conjugated to zinc(II)protoporphyrin-IX


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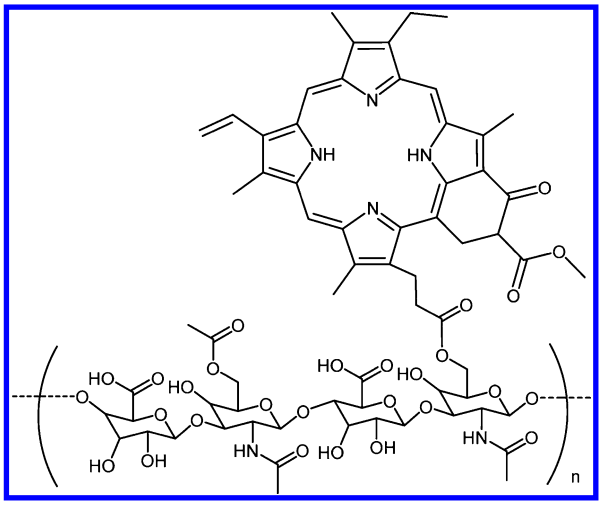

**Figure 24.** Hyaluronic acid porphyrin conjugate as a PDT agent.[221]

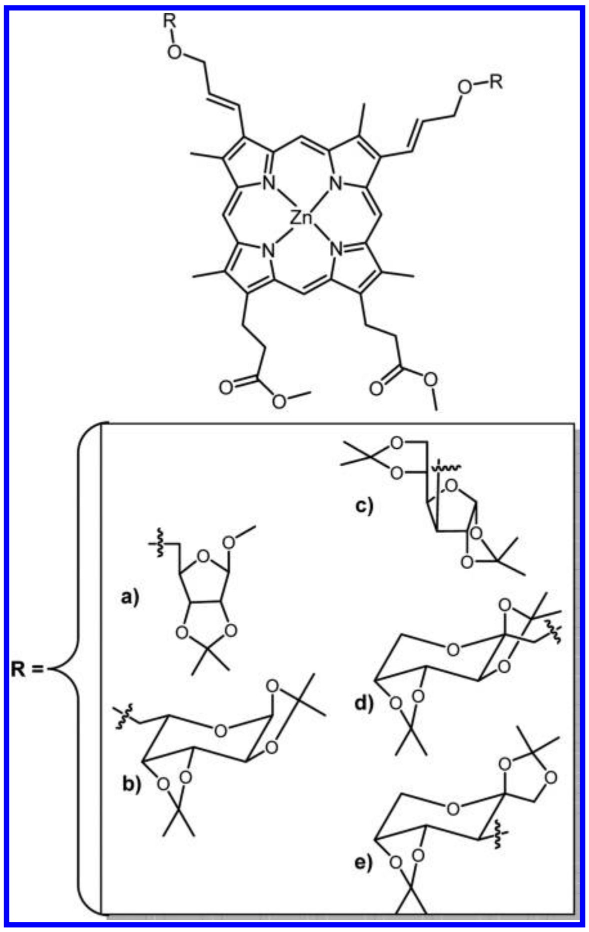

**Figure 25.** Recently reported *β*-substituted porphyrin sugar by Cavaleiro and co-workers.[226]

dimethyl ester via cross-metathesis using Grubbs catalyst resulting in two carbohydrate units appended to the core metalloporphyrin.

## 3. GLYCOSYLATED CHLORINS, ISOBACTERIOCHLORINS, AND BACTERIOCHLORINS

Hydroporphyrin-type derivatives, such as chlorins, isobacteriochlorins, and bacteriochlorins, have considerably stronger absorptions in the red and/or near-infrared (NIR) region of the electromagnetic spectrum. The near IR absorption and tunable optical properties make hydroporphyrins promising for the next generation PS for PDT and NIR bioimaging agents. While *m*-THPC is in clinical use, there remain issues of selectivity; see section 1. Over the past few years, new synthetic methods were developed to obtain novel hydroporphyrin derivatives such as Diels–Alder reaction,[227,228] 1,3-dipolar cycloadditions,[30,229,230] electrocyclizations,[231,232] and cyclopropanation[233] reactions.

### 3.1. Sugars Substituted on *meso*-Phenyl Groups

**3.1.1. Thioether Linkage.** Recently, Drain and co-workers reported the facile synthesis, photophysical properties, and in vitro studies of three nonhydrolyzable, tetrathioglycosylated porphyrinoids: chlorin ($CGlc_4$), isobacteriochlorin ($IGlc_4$), and bacteriochlorin ($BGlc_4$) (Figure 26).[234] By tuning the photophysical properties relative to $TPPF_{20}$ and glycosylated conjugates $PGal_4$ and $PGlc_4$,[86,235] this work expands the toolbox of core platforms that can be used for therapeutics, theragnostics, diagnostics, and tracker dyes. The conjugation of biotargeting motifs, for example, appending thio-sugars, on all four platforms is facile; therefore, this allows most laboratories to rapidly synthesize and evaluate new conjugate dyes for a wide array of applications.

$TPPF_{20}$ can be used as a starting material because it is readily available and can serve as a platform to append a host of biomolecules by substitution of the para fluoro group with a variety of nucleophiles to form bioconjugates (the reactivity is dictated by the nucleophile: S > N > O, primary > secondary).[86,163,168,236] The photophysical properties of this macrocycle can be fine-tuned by adjusting the number of double bonds. The perfluorophenylchlorin ($CF_{20}$), perfluorophenylisobacteriochlorin ($IF_{20}$), and perfluorophenylbacteriochlorin ($BF_{20}$) were prepared by 1,3-dipolar cycloaddition reaction.[30] As compared to the parent glycosylated porphyrin conjugate, $CGlc_4$ and $IGlc_4$ have stronger red absorption bands, and the fluorescence quantum yield increases by 6- and 12-fold, respectively, in phosphate buffered saline (PBS). On the other hand, the fluorescence quantum yield of the $BGlc_4$ conjugate is ca. 5% and similar to $PGlc_4$, but has the lowest energy Q-band is considerably red-shifted to near 730 nm with nearly 50-fold greater absorbance. The singlet oxygen quantum yield for $PGlc_4$, $CGlc_4$, $IGlc_4$, and $BGlc_4$ was found to be 0.85, 0.32, 0.59, and 0.28, respectively, in methanol-$d_1$ solvent.[234] The uptake of these glycosylated conjugates into cells such as human breast cancer cells MDA-MB-231 and mouse embryonic fibroblast cells K:Molv NIH 3T3 can be observed at nanomolar concentrations and is reported to be selectively taken up by cancer cells over the normal cells (Figures 27 and 28). These platforms will enable the development of new multifunctional imaging, sensing, and therapeutic agents for specific targets.[237] Following this work, Pd(II) complexes of thioglycosylated porphyrin and chlorin were prepared by Hirohara and co-workers to study the heavy atom effect on in vitro photocytotoxicity.[238] As expected from numerous prior studies,[239,240] the presence of the heavy atom enhanced the singlet oxygen quantum yield of the Pd(II) complexes. Somewhat surprisingly, insertion of Pd(II) did not improve the in vitro photocytotoxity as compared to the corresponding free base porphyrin and chlorin thioglucose conjugates, perhaps due to differences in octanol/water partition coefficients or axial binding to an endogenous ligand.



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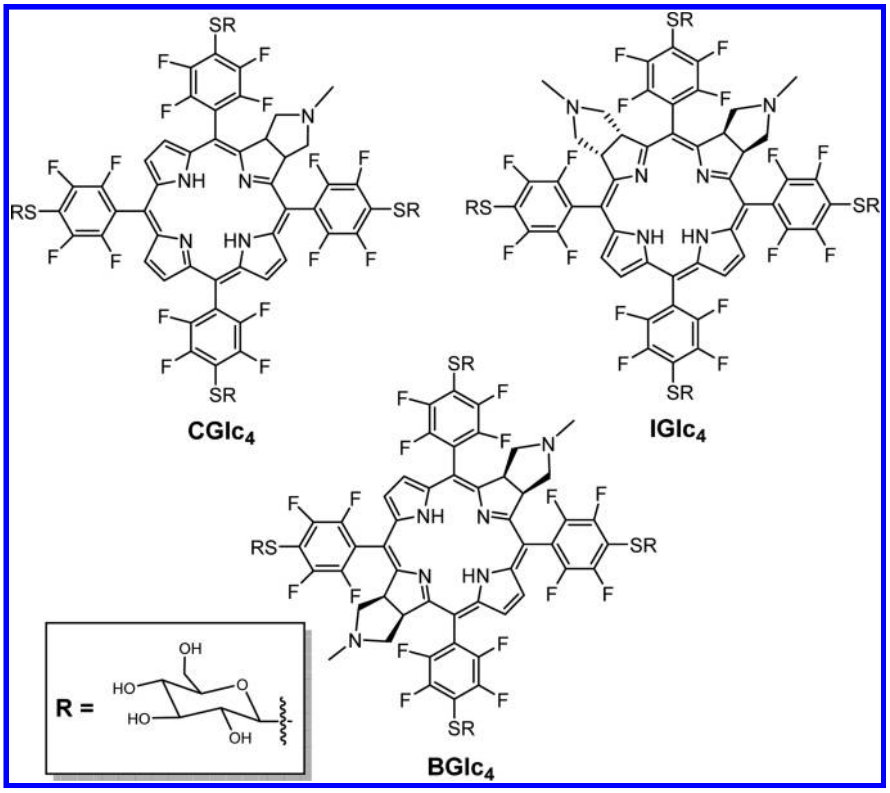


**Figure 26.** Structures of thioglycosylated chlorin ($CGlc_4$), isobacteriochlorin ($IGlc_4$), and bacteriochlorin ($BGlc_4$) appended with four thioglucose units reported by Singh et al.[234]

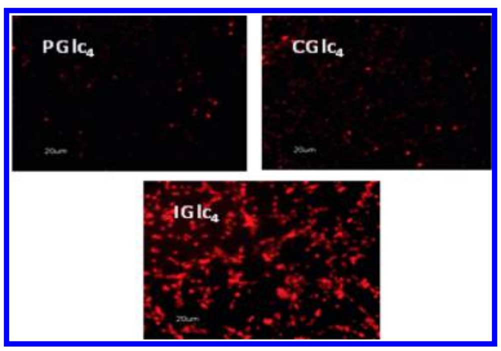


**Figure 27.** Fluorescence microscopy of K:Molv NIH 3T3 cells treated with 2.5 $\mu$M $PGlc_4$, $CGlc_4$, and $IGlc_4$. K:Molv NIH 3T3 cells were incubated for 20 h with porphyrinoids, followed by removal of unbound dye from the cell culture by repeated rinsing with PBS, and the cells were imaged under identical microscope settings and not enhanced; magnification 10×. Reproduced with permission from ref 234. Copyright 2010 American Chemical Society.

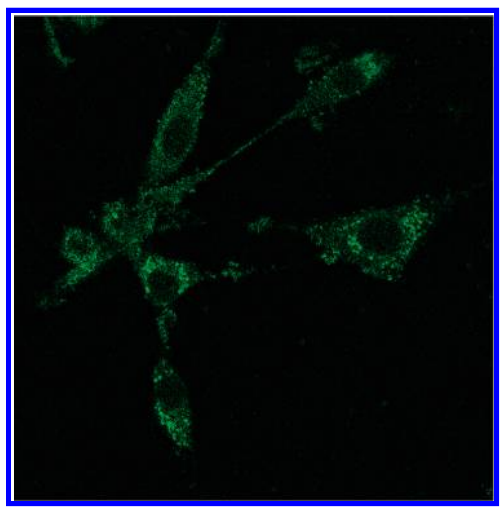

**Figure 28.** K:Molv NIH 3T3 cells were incubated with 10 $\mu$M $BGlc_4$ for 24 h, rinsed three times with PBS buffer, and fixed with 4% paraformaldehyde solution. Confocal microscope excitation at 514 nm, emission monitored with a 710−750 band-pass filter. Under similar conditions using the $IGlc_4$, $CGlc_4$, or $PGlc_4$, no fluorescence images are observed using a 610−650 nm emission band-pass filter. The image is not enhanced; magnification is 60×. Reproduced with permission from ref 234. Copyright 2010 American Chemical Society.

Sakuma et al. have shown that the thioglycosylated chlorins (e.g., $CGlc_4$) have more photodynamic efficacy over the nonglycosylated conjugate (H2TFPC) and aspartyl chlorin (NPe6) using several different human cancer cell lines.[241] This reports that in a xenograft tumor model, H2TFPC-SGlc-mediated PDT suppresses tumor growth and shows no adverse effect on the surrounding tissues.[242]

All of the tetraglycosylated porphyrins reported by Drain and co-workers, and likely most of the others reported, aggregate to some extent in aqueous solutions such as PBS buffers when concentrations are greater than a few $\mu$M (Table 3).[234] This is evidenced by broadening of the UV−visible spectral bands, fluorescence quenching, and dynamic light scattering (DLS). Aggregation and the consequences of aggregation are discussed in section 9.

Tang et al.[243] reported another class of glycoconjugate of a chlorin in which the $\beta-\beta'$ pyrrole double bond is substituted by an electron-withdrawing lactone unit, which is known to decrease the lipophilicity of the conjugate (Figure 29). This glucose conjugated porpholactone was shown to have high


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**Table 3. Aggregation of Selected Glycosylated Dyes in Figure 26 in PBS Buffer Measured by DLS**

| | conc. | | | |
|---|---|---|---|---|
| | 4.53 $\mu$M, nm | 1.18 $\mu$M, nm | Soret $\lambda_{max}$, nm | octanol/water partition coefficient |
| $IGlc_4$ | 47 ± 8 | 4 ± 2 | 385 | 9.1 ± 1 |
| $BGlc_4$ | | | 357 | 12.7 ± 1 |
| $CGlc_4$ | 48 ± 6 | 10 ± 3 | 409 | 28.5 ± 3 |
| $PGlc_4$ | 49 ± 4 | 20 ± 6 | 410 | 43.9 ± 5 |

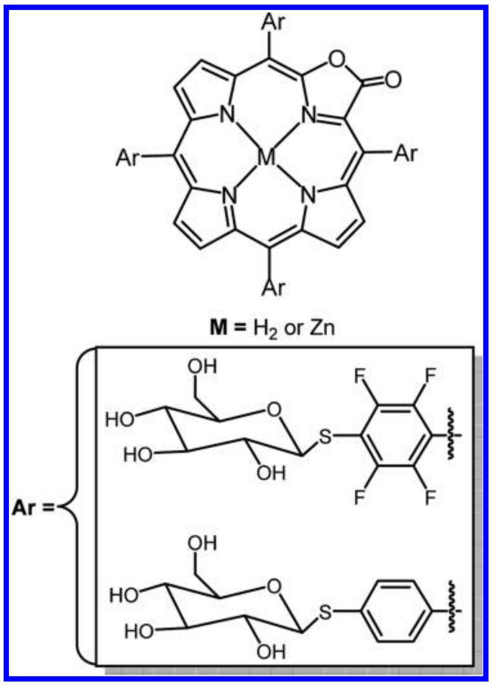


**Figure 29.** Structure of gluco-conjugate of porpholactone.[243]

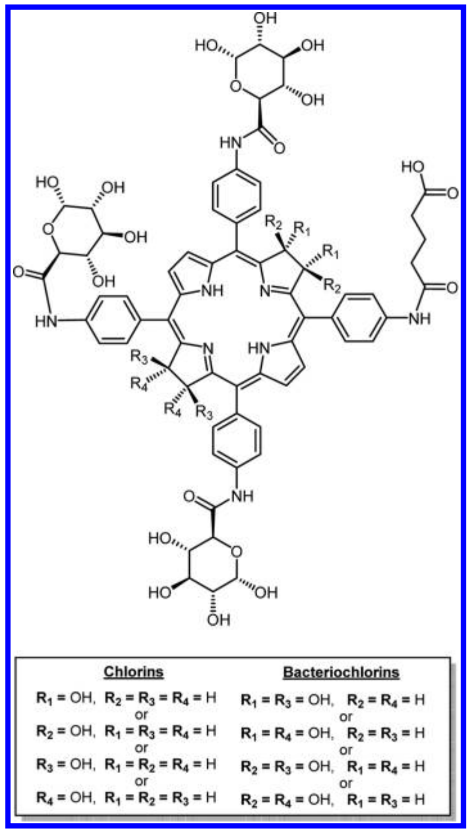


**Figure 30.** Glycosylated chlorins and bacteriochlorins synthesized from 5,10,15-tris(4-1′,2′,3′,4′-*O*-acetyl-glucopyranuron-*N*-phenylamide)-20-[4-(5′methoxy-1′,5′-dioxopentyl) aminophenyl]porphyrin, reported by McCarthy et al.,[244] use $OsO_4$ to make the chlorin and bacteriochlorin.

binding affinity with low density lipoprotein (LDL), which enhances the cellular uptake efficacy and localization within the lysosomes. The lactone moiety on the glycoconjugated porpholactone was reported to increase the singlet oxygen quantum yield associated with increasing intracellular ROS levels, and thus this is a new approach for PSs for PDT.[243]

**3.1.2. Amide Linkage.** Recently, McCarthy et al. reported glucose-modified chlorin and isobacteriochlorins-based PS intended for PDT.[244] These glucose-substituted conjugates were synthesized in high yields from *meso*-tetra(*p*-aminophenyl)porphyrin and resulted in the formation of neutral, hydrophilic chromophores (Figure 30). The presence of sugar groups on these conjugates increases their polarity, and the carboxylic acid-functionalized linker allows facile conjugation of the PS to the biomolecules. The presence of sugar moieties on the macrocycle increases the number of dyes that can be conjugated or cross-linked to dextran-coated nanoparticles and maintains the stability of the suspension. These glycosylated conjugates have potential to be useful in the development of a number of the next generation of targeted nanotherapeutic systems.

## 3.2. $\beta$-Pyrrole Conjugation

**3.2.1. Ester Linkage.** Cavaleiro and co-workers reported the synthesis of new glyco−hydroporphyrin conjugates by reaction of sugar-substituted $\alpha$-diazoacetates with zinc(II) *meso*-tetrakis(pentafluorophenyl)porphyrin in the presence of a catalytic amount of CuCl.[245] The major products of these reactions are chlorins, which, when acidified, afford the corresponding free bases with deprotected sugar units (Figure 31). These chlorin derivatives are reported to be better singlet oxygen producers than methylene blue (MB). This new synthetic methodology can lead to new glycoporphyrin derivatives with the location of the sugars on the pyrroles rather than *meso* aryl moieties.

**3.2.2. Amide Linkage.** Zhang et al.[246] reported the synthesis of an amide linked glycosylated porphyrin, pyropheophorbide 2-deoxyglucosamide (pyro-2DG, Figure 32), that can serve as both a targeted PDT agent and a NIR fluorescence imaging agent. The intravenous administration of the pyro-2DG theragnostic into a 9L glioma rat model selectively accumulates the compound into the tumor area as indicated by fluorescence imaging studies. Photo illumination of the pyro-2DG accumulated in the tumor area causes selective mitochondrial damage to the tumor region, without affecting nearby areas lacking the PDT agent or in tissues treated with the dye but not irradiated with light. The pyro-2DG theragnostic is tumor selective for tumor-targeted NIR fluorescence imaging and as a good PDT agent.[246]

**3.2.3. 1,3-Cyclo Addition Reaction.** "Click chemistry" exploits one or more high yield reactions to generate a library of organic compounds for creating therapeutics, imaging agents, and other biochemically active molecules. Click chemistry has significantly increased the rate of development of new biologically active compounds.[167,247,248] Key features include that the starting compounds are readily accessible, mild


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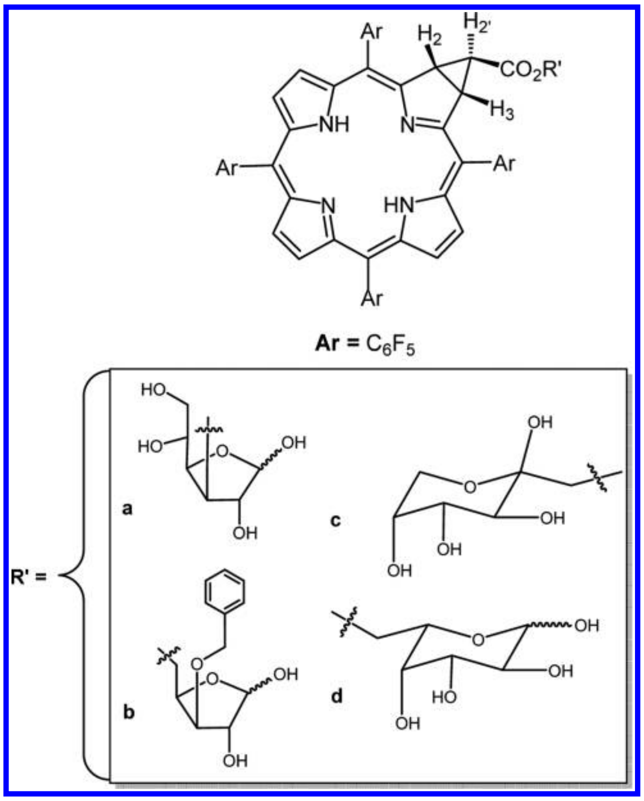


**Figure 31.** Cavaleiro and co-workers[245] made chlorins by reactions of *meso*-tetrakis(pentafluorophenyl) porphyrinatozinc(II) with $\alpha$-diazoacetates derived from diacetonides of the glucofuranose (a), monoacetonide of xylofuranose (b), fructopyranose (c), and galactopyranose (d).

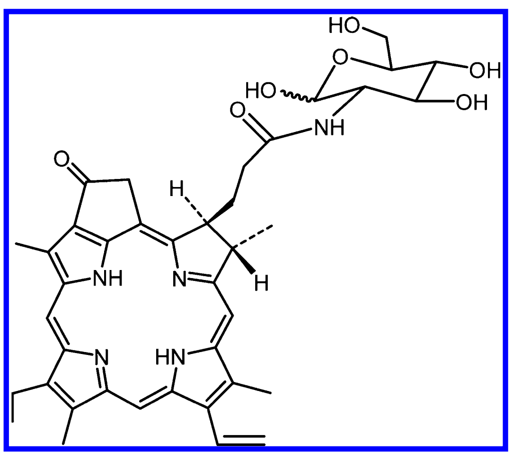

**Figure 32.** Structure of pyropheophorbide 2-deoxyglucosamide (Pyro-2DG) theragnostic reported by Zhang et al.[246]

reaction conditions, high yields, and minimal side products.[7] The core porphyrin platforms for many click reactions (e.g., the tetra-4-X-phenylporphyrins where X = carboxy, amino, fluoro) are easily made or commercially available. Following the combinatorial approach, Mironov and co-workers used the "click chemistry" methodology to synthesize chlorin $e_6$-based PS appended with $\beta$-lactose.[248,249] 1,3-Dipolar cyclo addition reaction of a sugar azide was carried out on a propargyl derivative of chlorin $e_6$[249,250] (Figure 33). The lactose conjugates display a high singlet oxygen quantum yield ($\varphi$ $^1O_2 \approx 0.75$) and enhanced selectivity toward cancer cells, and so may serve as a PDT photosensitizer.

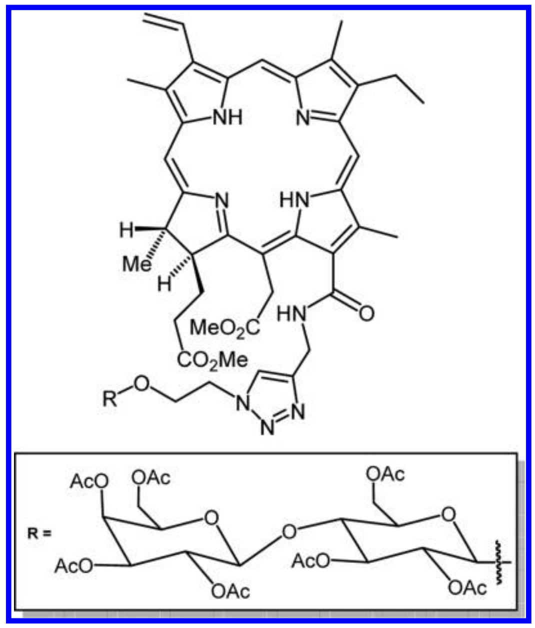

**Figure 33.** Structure of the chlorin $e_6$−carbohydrate conjugate reported by Grin et al.[250]

## 4. GLYCOSYLATED CORROLES

Corroles are a tetrapyrrolic macrocycle with 18-$\pi$ conjugated electrons. Like porphyrins, corroles are tetradentate ligands that chelate to a large variety of metal ions, and because they are trianionic ligands they stabilize +3 oxidation states better than the porphyrins.[251] The corrole macrocycle has been extensively studied as a new generation PS for applications in PDT.[39,40] The absorption spectrum of the corroles is similar to that of the porphyrins with a Soret band around 420 nm and several Q absorption bands, which are much stronger than that of porphyrins between 450 and 650 nm. Thus, corroles have larger optical cross sections in the red regoin as compared to porphyrins. Preliminary studies reveal that many corroles are metabolized faster in vivo[252,253] and can have high singlet oxygen generation quantum efficacy, and so can act as good cancer therapeutic agents.[254] Ventura et al. reported the photophysical properties of a series of *meso*-substituted corroles in toluene. They were reported to be quite thermally and photochemically stable and have high singlet oxygen quantum yields, 0.51−0.77.[252] Agadjanian et al. have shown that pyrrole-substituted sulfonated corroles form stable complexes with protein carriers by a noncovalent assembly and can pass into breast cancer cells and induce toxicity.[255]

To date, only a few examples of sugar conjugates of corroles are reported (Figure 34) wherein the thioglucose was appended using the substitution chemistry on the perfluorophenyl group,[7,163] and an *O*-glycosyl derivative.[256] In vitro uptake and phototoxicity studies of a galactose appended corrole were carried out on human acute T cell leukemia (Jurkat cells). The results showed an increase in cell uptake of the compound but a low PDT efficacy. The low PDT effect was attributed to less efficient singlet oxygen production of the compound. In the future, other glycocorroles with better triplet quantum yields will be needed that can have good cellular uptake, exhibit



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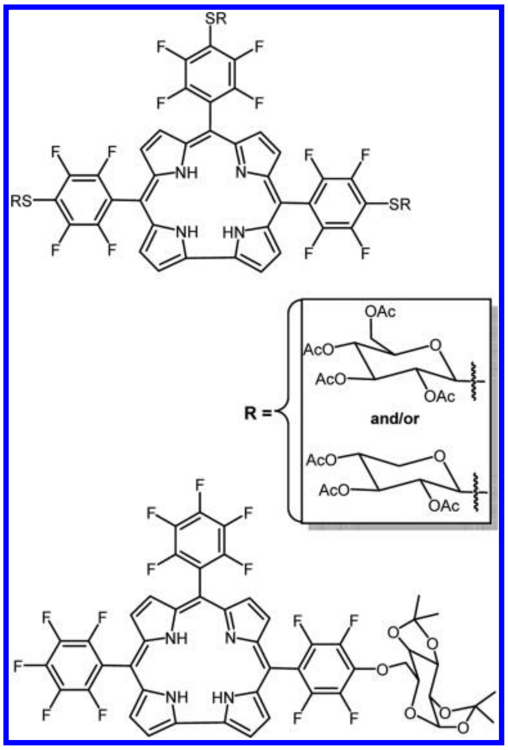


**Figure 34.** Top: Three thioglucose or three thioxyloses appended to corroles reported by Samaroo et al.,[163] made by substitution of the para fluoro group. Note that the para fluoro groups on opposite perfluorophenyls substitute somewhat faster than the central. The bottom pentafluorophenylcorrole-D-galactose conjugate was reported by Röder and co-workers.[256]

strong absorption in the red region of the optical spectra, and can be good sensitizers for singlet oxygen generation, making them promising PDT agents.

## 5. PORPHYRIN–CARBOHYDRATE CONJUGATES WITH TWO-PHOTON ABSORPTION PROPERTIES

The currently approved PSs have one-photon absorption peaks in the visible region of the optical spectra. The chlorin macrocycle of Foscan, for example, was developed to improve light absorption in the red region of the UV–visible spectrum near 630 nm as compared to Photofrin. Other chlorins, bacteriochlorins, isobacteriochlorins, phthalocyanines, and porphyrin dimers were prepared because of the stronger absorption cross section in the red to NIR region.[234,257,258] However, the significant absorption at wavelengths less than about 650 nm by biological tissues substantially diminishes the effectiveness of PSs for treatment of cancers deeper into tissues.[71] To surmount this limitation, several groups embarked on the design of PS with absorption bands in the near-infrared or infrared region, between 700 and 1100 nm, where the absorption and scattering of these wavelengths in tissues are much less than higher energy photons. This range is also known as "the window of biological tissues".[259] Bacteriochlorins and Pc's are dyes that have significant absorption in this region, but another strategy is to design dyes with good two-photon cross sections. In two-photon absorption (TPA), the dye simultaneously absorbs two lower energy photons to arrive at the same excited state as single photon absorptions. TPA is a nonlinear optical process where the combined energy of two low energy photons is sufficient to produce the excited state, and afterward the normal photophysics occurs. The advantage of TPA is that the molecule can be excited in the NIR region, facilitating deeper light penetration into tissues, but the disadvantages include the high light flux needed to excite the molecule and the small excitation areas of ca. 1 $mm^2$.[260−263]

Recently, in vivo experiments demonstrated that PDT performed with PS with high TPA enables the treatment of deep and large sized tumors by conventional one-photon excitation.[264,265] Covalently linked multiporphyrin arrays, especially those connected with acetylene linkers[266,267] or that are fused together,[268,269] have attracted considerable attention because of their remarkable photophysical properties such as high polarizability and high nonlinear optical (NLO) properties such as TPA. Several types of multiporphyrin compounds are reported,[270−274] some having sugars appended to the chromophores (Figure 35).[267]

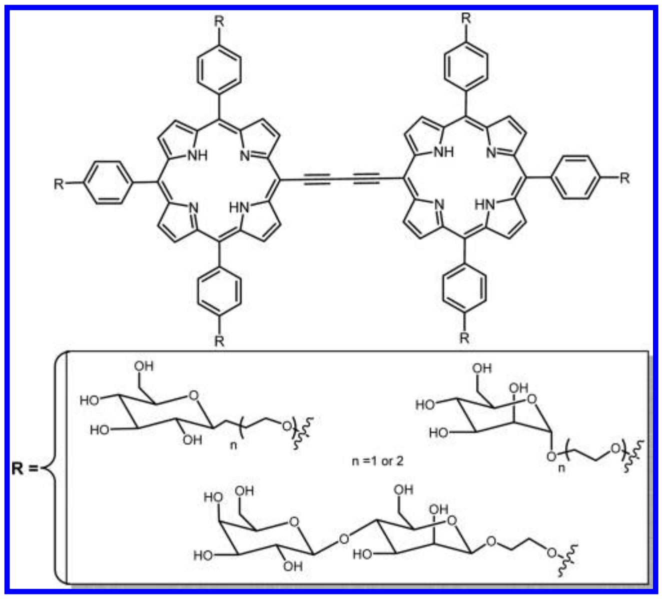


**Figure 35.** Porphyrin dimers conjugated to carbohydrates were evaluated for potential applications in one-photon and two-photon PDT by Maillard and co-workers.[267]

Achelle et al. reported the synthesis of series of zinc porphyrin oligomers appended with $\alpha$-mannose that have good TPA cross sections and high singlet oxygen quantum yields (Figure 36).[71] To obtain the conjugated oligomers, porphyrin monomers were linked with bridges that do not twist out of plane with the porphyrin macrocycle. For this reason, sterically hindered neutral $\pi$-conjugated cores, ethynyl, butadiyne, diethynylbenzene, and electron-donor triphenyl amine were incorporated between the porphyrin monomers because ethynyl bridges are one of the most effective ways of making strong electronic connections to the *meso* position of the porphyrin.[274−277]

Singh et al.[169] recently reported the synthesis and phototoxicity of NIR dye hexathioglucose triply bridged fused porphyrin (Figure 37). The singlet oxygen quantum yield of this compound in DMSO was found to be 0.78 ± 0.03. In vitro darktoxicity and phototoxicity studies were carried using the MDA-MB-231 breast cancer cell line. No dark toxicity was observed, while the phototoxicity results were in agreement with the singlet oxygen quantum yield. Significant cell death


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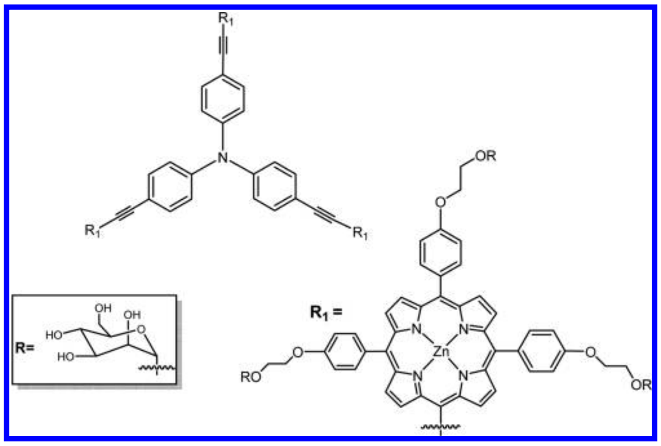

Figure 36. Structure of conjugated zinc porphyrin oligomer reported by Achelle et al. with good two-photon cross sections.[71]

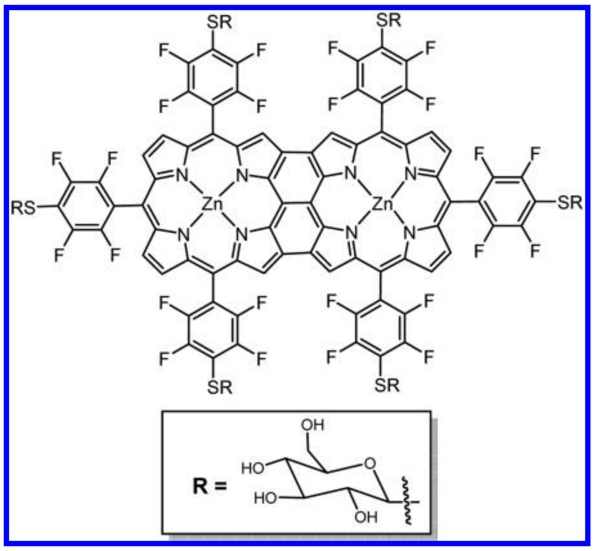

Figure 37. Triply bridged hexaglycosylated fused porphyrin dye with large two-photon cross section reported by Singh et al.[169]

($IC_{50}$ = 13 $\mu$M) was observed with light exposure for 20 min, and after 24 h 75% of cells were necrotic.

Maillard and co-workers reported the synthesis, spectroscopic, and biological properties of carbohydrate-vectorized porphyrin−triphenylamine hybrids, which may have potential to be two-photon PSs (Figure 38).[278] The scaffold of these compounds is based on the electronic conjugation of a porphyrin core and a triphenylamine group via an alkyne spacer and shows high singlet oxygen quantum yields as well as good two-photon cross sections. These compounds are inactive against the HT29 cancer cell line as well as retinoblastoma cells Y79 using one-photon phototoxicity assays, which was attributed to aggregation of these compounds in biological media due to their hydrophobicity. Further efforts are being made to overcome this problem by attaching hydrophilic groups on the triphenylamime part of the conjugates.[278]

Recently, Drain and Coworkers[279] studied $CGlc_4$, $IGlc_4$, and $BGlc_4$ (Figure 26)[234] for two-photon fluorescence imaging on Chinese hamster ovary cells and found that $IGlc_4$ has a good TPA between 760−880 nm, and the cross section is 24.5 GM at 860 nm. Figure 39 shows two-photon microscopy of a 5:1 mixture of $IGlc_4$ and $BGlc_4$ on Chinese hamster ovary cells excited at 860 nm.

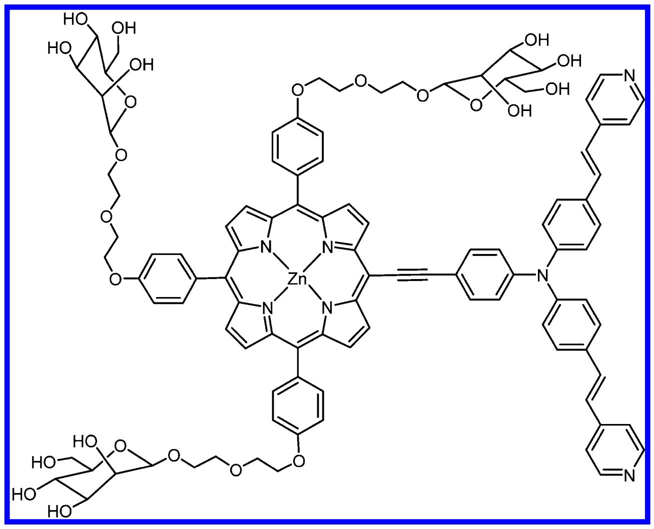

Figure 38. Structure of triphenylamine porphyrin bearing three $\alpha$-mannose groups attached via DEG tether for two-photon activity reported by Millard and co-workers.[278]

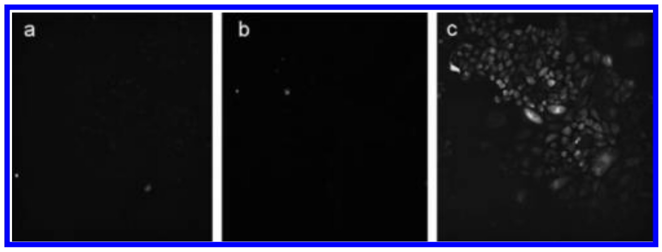


Figure 39. Two-photon microscope images of (a) $PGlc_4$, (b) $CGlc_4$, and (c) $IGlc_4$:$BGlc_4$ (5:1) on Chinese hamster ovary cells excited at 860 nm.[279] Reproduced with permission from ref 279. Copyright 2014 John Wiley and Sons, Inc.

## 6. GLYCOSYLATED TETRABENZOPORPHYRINS

Tetrabenzoporphyrins (TBP) comprise four benzene rings fused to the pyrroles on a porphyrin, with no phenyl rings on *meso* positions.[280,281] These compounds may be promising candidates for PDT because they have strong absorption in the red region of the optical spectra.[282] TBPs are chemically stable due to the extended $\pi$-conjugated systems. As compared to porphyrins, TBP compounds are poorly soluble due to increased conjugation and $\pi$-stacking;[281,283,284] however, the solubility of *meso*-substituted tetraaryltetrabenzoporphyrin ($Ar_4$TBP) in water can be increased by appending sulfonic acid, carboxylic acid, or nido-carborane functional groups.[166,285,286] Taking into account the data, TBP bearing glucosyl or polyamine units on *meso* positions to improve the targeting of cancer cells were synthesized and characterized by Krausz and co-workers (Figure 40).[280] The synthesis of these glycosylated tetrabenzoporphyrins was done by condensation of tetrahydroisoindole with aromatic aldehyde followed by oxidation with DDQ.[287,288]

Two *meso*-tetraglycosylaryltetrabenzoporphyrins were synthesized by appending glucose units directly on the macrocycle or attached by a tetraethylene glycol spacer (Figure 40). These two compounds were prepared by different methods: compound **A** was prepared by condensation of glucosylated aldehydic precursors with tetrahydroisoindole, and compound **B** was prepared by amidation followed by glycosylation of synthetic tetrabenzoporphyrin. The first approach opens

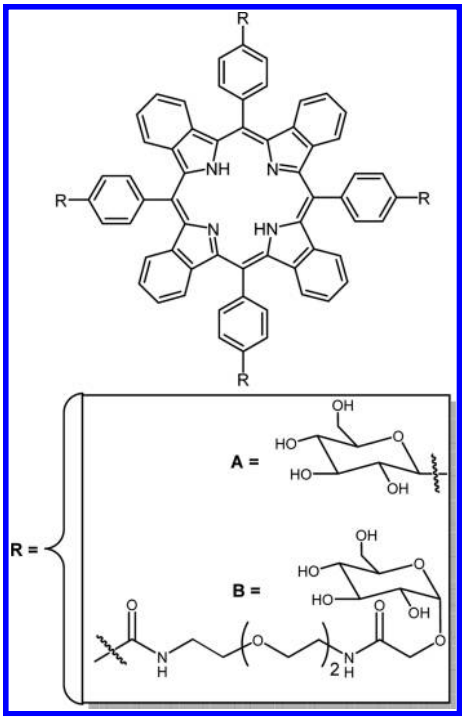


**Figure 40.** Structures of the glycosylated tetrabenzoporphyrins reported by Krausz and co-workers.[280]

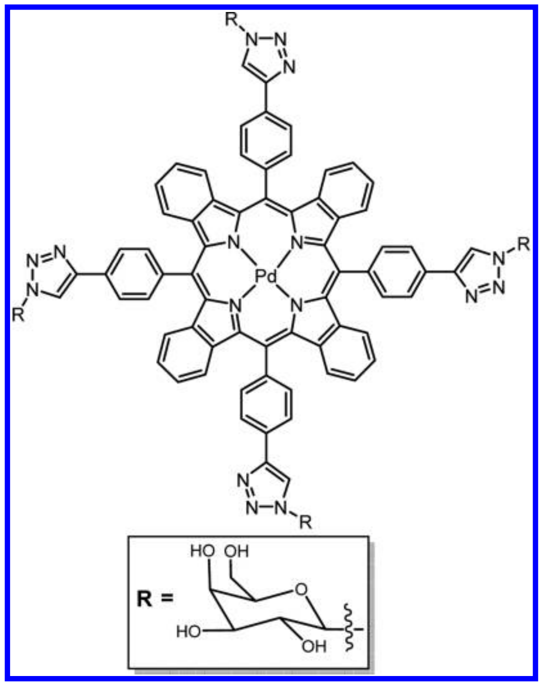


**Figure 41.** Structure of tetraphenylbenzoporphyrin (TBP)−galactose conjugate linked via triazole unit.[129] In these and similar compounds, the rotational barriers between the phenyl and triazole units are likely low enough that interconversion between atropisomers is facile at room temperature, such that they cannot be isolated.

interesting prospects for the synthesis of new functionalized asymmetric benzoporphyrins. A strong absorption band was obtained for both of these compounds around 700 nm, and both were capable of producing singlet oxygen, but due to the hydrophilic nature of the core dye they have propensity to aggregate in methanol and water as observed from UV−vis and fluorescence. Compound **B** with its tetraethylene glycol spacer is more hydrophilic and therefore less efficient as a PDT agent because it lacks the amphiphilic character required for an efficient cell uptake.[289] Cell incubation studies using two different human cancer cell lines, MCF-7 and HaCaT, were also done for these compounds, and preliminary results show that these compounds have very low photocytotoxicity and are even weaker than Photofrin II, which was used as a reference.[280] TBP−galactose conjugate formed using click chemistry (Figure 41) was reported by Vicente and co-workers,[129] and the chemistry is outlined in previous sections.

## 7. GLYCOSYLATED PHTHALOCYANINES

Pc's are promising second generation PSs. Since their discovery in 1907 by Brown and Tcheriac,[290] numerous work has been done on their synthesis and functionalization to tune their photochemical and photophysical properties.[291] Pc's are well suited as PSs for PDT and for bioimaging agents because of the tunable photophysical properties, and they can be more efficient in generating reactive oxygen species than porphyrins.[53,292,293] Pc's often exhibit low dark toxicity, are chemically stable, and have a strong absorption peak in the red region of the optical spectra ($\lambda_{max} \approx 670$ nm, $\varepsilon \approx 10^5$ L mol$^{-1}$ cm$^{-1}$) where light penetrates deeper into tissues relative to the weaker absorption of porphyrins ($\lambda_{max} \approx 610$ nm, $\varepsilon \approx 5 \times 10^3$ L mol$^{-1}$ cm$^{-1}$). This absorption can be fine-tuned both by the coordination chemistry and redox properties of the metal present in the central cavity and by the number and type of substituents on the periphery of the macrocycle.[25,294] To date, fewer Pc-based PS were tested in vivo for PDT studies than porphyrin-based PS, due in part to the complex purification of the compounds with one moiety per isoindole, or the statistical mixture of four isomers can be used.[295] Second, Pc's have a strong tendency to aggregate in buffers and physiological fluids even with eight substituents on the periphery. Thus, numerous new pathways for the synthesis of Pc's are under investigation to solve the problems of purification and make them more water-soluble and less prone to aggregation. Significant research aimed at improving the selectivity of the Pc's toward cancerous cells has resulted in limited success because these compounds show aggregation in physiological fluids and have unfavorable intracellular localization.[296]

Pc's that may act as potential PS for PDT include derivatives of zinc(II)phthalocyanine (Zn(II)Pc),[297−300] silicon(IV)-phthalocyanine (Si(IV)Pc),[301−303] and aluminum(III)-phthalocyanine (Al(III)Pc).[304,305] An advantage of the latter two is an increased solubility brought on by a decrease in aggregation where the +4 or +3 oxidation state of the metal ion weakens intermolecular interaction via electrostatic repulsion and the axial ligation of alkoxide counterions prevents H aggregation and mitigates J aggregation. While substitution of these compounds at the peripheral position by bulky or charged groups prevents the stacking of the hydrophobic Pc core and aggregation,[306,307] this may also inhibit cell uptake. The conjugation of Pc's with carbohydrate units increases water solubility, avoids the use of a delivery system to tumor cells, and provides better tumor specificity.[85,301,308−311] Herein, Pc carbohydrates are discussed in two sections: one where the carbohydrate units are attached at the axial position of metallophthalocyanines and the other where the carbohydrate units are attached at the $\alpha$ and $\beta$ positions.


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### 7.1. Axial Phthalocyanine−Carbohydrate Conjugates

To improve the steric shielding of the Pc core, alkoxide axial ligands can be strongly coordinated to tri- or tetravalent chelated oxophilic metal ions, such as Al(III), Ga(III), or Si(IV), which can improve solubility in the aqueous media.[301,312,313] Lee et al. reported the preparation and in vitro photodynamic activity of Si(IV)Pc with one or two axial acetal-protected galactose substituents (Figure 42).[301] The galactose groups were introduced by substitution reactions with the goal of improving the hydrophilic properties and inhibiting the self-aggregation of these compounds. These axially coordinated sugar Si(IV)Pc's display a good photodynamic activity against HepG2 human hepatocellular carcinoma, which may be due to high cellular uptake and high singlet oxygen production ($^1O_2$,$\Phi_\Delta$ = 0.94).[301] Ng and co-worker reported the photodynamic efficacy of two glycosylated Si(IV)Pc in which the D-glucofuranose unit binds axially to the Si center through the tetraethylene glycol spacer (Figure 43).[314] The compounds were reported to be highly phototoxic against HT29 human colorectal carcinoma and HepG2 human hepatocarcinoma cells.[314]

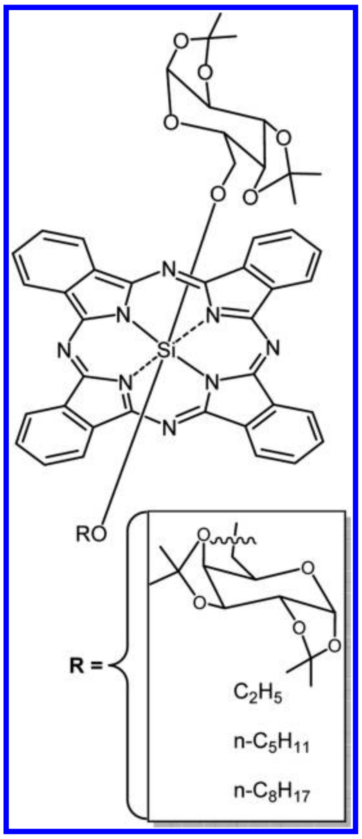


**Figure 42.** Galactose-containing Si(IV)Pc reported by Lee et al.[301]

### 7.2. Sugar Substitution on $\alpha$ and $\beta$ Positions of Phthalocyanine

Several glycophthalocyanine conjugates were reported where the carbohydrate was substituted on the $\alpha$ and $\beta$ positions of Pc. Substitution of carbohydrates was achieved with S-, O-, N-heteroatoms and 1,2,3-triazole moiety.[293] These are discussed in the following sections where sugars are attached to Pc with and without spacers. Synthetic approaches to glycophthalocyanines are reviewed.[293]

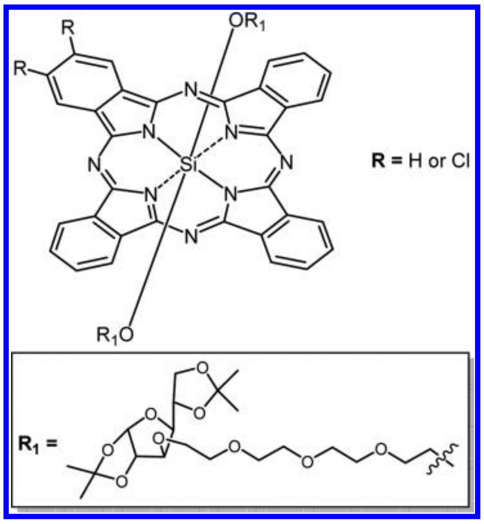


**Figure 43.** Structure of glycosylated Si(IV)Pc from a mixed condensation reaction in which the D-glucofuranose unit binds axially to the Si(IV) center through the tetraethylene glycol spacer.[314]

**7.2.1. Direct Sugar Substitution.** The crucial step in the development of peripheral, directly linked glycosylated Pc's is the efficient synthesis of their precursors, that is, glycosylated phthalonitriles prepared via $S_NAr$ reaction of nitro-phthalonitriles or halo-phthalonitriles with anomerically unprotected glycopyranoses and 1-thio-glycopyranoses.[315] Thus, a series of peripherally substituted mono-, di-, tri-, tetra-, and octa-glycosylated Pc's can be synthesized with carbohydrates such as D-glucopyranose, $\beta$-D-galactopyranose, 1-thio-$\beta$-D-glucopyranose, D-mannose, $\beta$-D-cellulose, $\beta$-D-lactobiose, 1-thio-$\beta$-D-cello-, and lactobiose.[85,293,310,316−321] In vitro studies using human amniotic epithelial WISH cells showed that tetraglycosylated PC's can be good lead compounds for PDT.[320]

*7.2.1.1. Ether Linkage.* Choi et al.[319] and Iqbal et al.[322] reported several water-soluble asymmetrical tetra *O*-glycosylated Pc isomers. One such example is shown in Figure 44A[322] where glucose was substituted at the peripheral ($\alpha$ and/or $\beta$) positions via the anomeric carbon and the classical Pc template reactions with unprotected phthalonitriles were applied.[320]

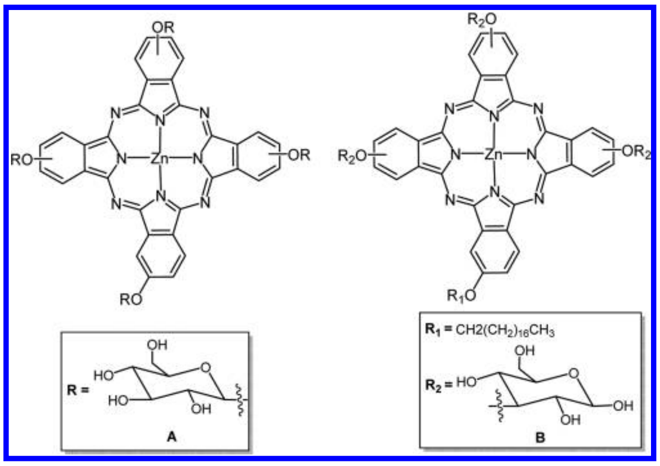


**Figure 44.** (A) Asymmetric anomeric glycoconjugated Zn(II)Pc reported by Iqbal et al.[322] (B) Asymmetric Zn(II)Pc bearing octadecyloxy and glucosyl groups by Zhang et al.[298] The way of representing the peripheral-OR groups indicates that a mixture of positional isomers was used, including $\alpha$ or $\beta$.


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Similarly, an asymmetrical Zn(II)Pc bearing three hydrophilic glucosyl groups and a lipophilic octadecyloxy group was synthesized by Zhang et al. (Figure 44B).[298]

Kimani et al. reported an isopropylidene protected tetra-$\beta$-glycosylated Zn(II)Pc that has 100-fold better cellular uptake than the tetra-$\beta$-glycosylated Zn(II)Pc and a 10-fold increase in uptake as compared to second generation PS Al(III)Pc$S_4$ (Figure 3) using MCF-7 cancer cells, and this compound has better PDT efficacy than both the corresponding deprotected conjugate (Figure 45) and the Al(III)Pc$S_4$.[323] The low biological efficacy of tetra-$\beta$-glycosylated Zn(II)Pc as compared to protected conjugate was attributed to the aggregation caused by the hydrophobic stacking between the aromatic rings of Pc and H-bonding between the free OH groups on glucose.

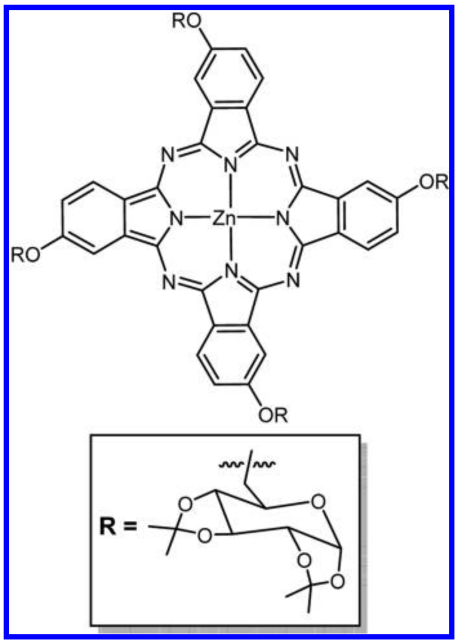


**Figure 45.** Structure of isopropylidene-protected tetra-$\beta$-glycosylated Zn(II)Pc (one isomer shown).[323]

Tetra-substituted Pc such as Al(III)Pc$S_4$ and the tetra glucose conjugates have significant potential to be used as a PS for PDT, but the structural characterization can be difficult because these are obtained as mixtures of positional isomers that are difficult to separate. Mixtures of compounds and/or isomers may have advantages in terms of PDT, because each may partition or localize in different parts of cell or tissue resulting in oxidative damage at multiple sites. Thus, the small physical and chemical differences, for example, the octanol/water partition coefficients and photophysics, of the four isomers with one substituent on each isoindole or the four atropisomers on Foscan, may result in synergistic PDT activities. For Pc's, derivatives with 0, 8 $\alpha$, 8 $\beta$, and 16 substituents can be pure compounds without isomers. Therefore, to avoid the formation of isomers upon tetramerization of monoglycosylated phthalonitriles, Iqbal et al. reported the preparation of octa-glycosylated Pc's synthesized from 4,5-diglycosylated phthalonitriles, which is one of the first examples of a Pc symmetrically octasubstituted with D-galactose residues (Figure 46B).[317] In vitro studies using human amniotic epithelial WISH cells showed that tetragalactophthalocyanines can be good lead compounds for PDT. Later, they reported several symmetrically pure octaglycophthalocyanines.[320] Cavaleiro and co-workers prepared asymmetrically pure tetra-substituted glyco conjugated Pc's bearing four galactose units (Figure 46A).[310] Choi et al.[319] recently observed that mono-substituted, isomerically pure *O*-glucose and *O*-galactose Pc's had better in vitro PDT efficacy as compared to isomeric mixtures of tetra *O*-glucose and *O*-galactose Pc's, when tested on HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cells.

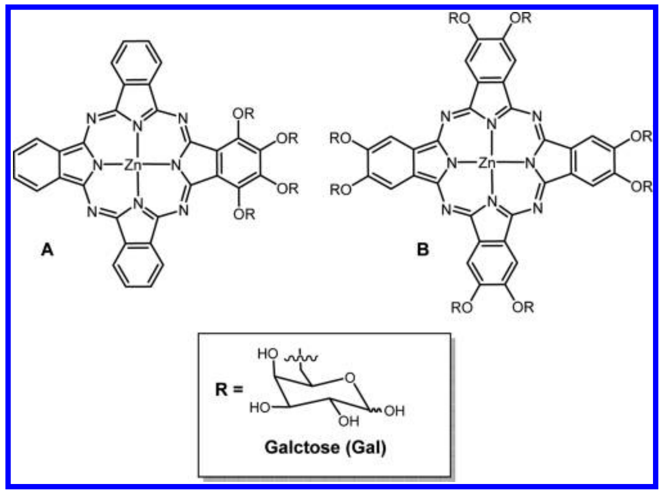


**Figure 46.** Structure of pure glycophthalocyanine appended with (A) four galactose units from a mixed condensation reaction,[310] and (B) eight galactose units made from the phthalonitrile[317] in 21% overall yield.

*7.2.1.2. Thioether Linkage.* Hanack and co-workers[320] reported several tetra-substituted *S*-glycosylphthalocyanine derivatives obtained by cyclization of the *S*-glycosylated phthalonitrile. All of these compounds were obtained as their isomeric forms, which are difficult to purify.

Recently, Drain and co-workers reported the facile synthesis, photophysical, and cell uptake studies of a Zn(II)Pc appended with eight nonhydrolysable thioglucose units, ZnPcGlc$_8$ (Figure 47).[257] This work is the first example of base-promoted

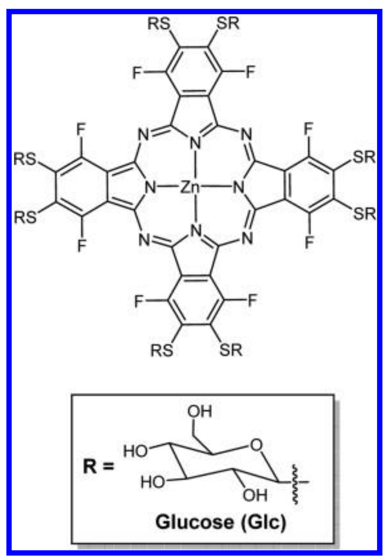


**Figure 47.** Symmetrical octa-substituted Zn(II)Pc's with thioglucose units derived from a core perfluorophthalocyanine platform made in ca. 70% yield in two steps.[257] Similar conjugates are also reported using different linkers, for example, Figure 46.[320,325,326]


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substitution of Pc with thioglucose units using the commercially available $ZnPcF_{16}$ and takes advantage of the leaving group character of fluoride and different reactivities of the F atoms present on the $\alpha$ versus $\beta$ positions. Zn(II)Pc's are of great interest to develop Pc-based new generation PS for PDT because of the high triplet quantum yield and long triplet lifetimes.[324,325] The longer lifetimes of the PS are advantageous as they promote the diffusional encounter between the excited triplet state of the PS and endogeneous molecular oxygen.

$ZnPcGlc_8$ is amphiphilic in nature and was found to be chemically stable. In dry DMSO the compound is highly soluble, but was found to aggregate in water, PBS, or in DMSO−water mixtures as indicated by the significantly quenched fluorescent signal. The low fluorescence quantum yield ($\Phi_f$ = 0.06 in DMSO) for $ZnPcGlc_8$ and correspondingly high singlet oxygen generation quantum yield ($^1O_2$, $\Phi_\Delta$ = 0.41 in DMSO) indicate the potential for this compound to be a good PS for PDT. Even though this PS aggregates in aqueous solutions, the small, diffuse spots initially observed by fluorescence microscopy indicate that $ZnPcGlc_8$ is taken up by MDA-MB-231 breast cancer cells mostly as poorly fluorescent nanoaggregates (Figure 48). After 4 days, the slides

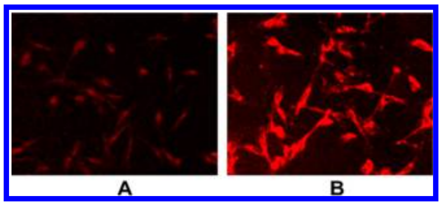


**Figure 48.** MDA-MB-231 cells were incubated with 50 nM $ZnPcGlc_8$ for 24 h, rinsed three times with PBS buffer to remove unbound dye, and fixed with 4% paraformaldehyde solution. Fluorescence images were captured by exciting at 540−580 nm, magnification 20× under identical conditions. (A) Just after preparation of the fixed cells slide, and (B) 4 days after later. The contrast of each was enhanced by 40% for publication.[257] Reproduced with permission from ref 257. Copyright 2011 Elsevier, Inc.

of the same fixed cells show a significant increase in the fluorescence because of the disaggregation of PS nanoparticles; however, the cell morphology remains the same. These observations clearly indicated uptake of the chromophore into these cells, and the role of nanoaggregated PS is discussed in section 9 in terms of uptake, disaggregation in cancer cells, and the implications for viable strategies for new PDT agents.

### 7.2.2. Sugars Linked to Phthalocyanines with Spacers.

Glycosyl−phthalocyanine conjugates with short and long spacers between sugar and Pc linked using O-,[71,316,327−330] N-[331] heteroatoms, and 1,2,3-triazole link[330−333] are reported. As noted above, several studies suggest that the presence of appropriate spacers can improve the biological efficacy of the drug, but the reasons for this are not clear.

*7.2.2.1. Ether Linkage.* Two series of water-soluble Pc−carbohydrate conjugates with tetraethylene glycol spacers, linked via an O-, were reported by Lafont et al. and Ermeydan et al.[329,330] Both of these series of compounds have only one sugar moiety appended to the dye and were synthesized by appending sugar moieties on preformed Pc by direct glycosylation of a terminal hydroxyl unit. One glycosyl-phthalocyanine containing glycerol on three $\alpha$-positions reported by Lafont et al. is shown in Figure 49A. Asymmetric amphiphilic glycosyl-phthalocyanines containing thiol-hexane groups on the six $\beta$ positions of Pc, which is a single isomer as shown in Figure 49B, were reported by Ermeydan et al.[330] The biological efficacies of these compounds are discussed in section 7.2.2.3. Other isomeric mixtures of tetra glycosylated pure asymmetric substituted *O*-glycosyl Pc with different ethylene glycol spacers were reported by Álvarez-Micó et al.[316] and Liu et al.[328] In vitro PDT efficacy studies on a series of mono-, di-, and tetra-substituted *O*-glycosyl Pc conjugates were reported by Liu et al. (Figure 50),[328] to study the effect of the number and position of the substituents. HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cells were used in this study, and the results revealed that isomerically pure disubstituted *O*-glycosylated Pc's, in particular the di-$\alpha$-substituted O-glycosylated Pc's, had the best PDT efficacy, followed by pure mono-substituted conjugate, as compared to the isomeric mixture of tetra substituted *O*-glycosylated Pc's. These results contrast with other studies involving mixtures of isomers, wherein the mixtures of glycosylated Pc perform better than the individual components; this may also reflect differences in octanol/water partition coefficients. A single isomer of an octaglycophthalocyanine with methylene linker was reported by Soares et al. (Figure 51).[327] The glycophthalonitrile precursor was prepared by nucleophilic substitution of 4,5-bis(bromomethyl) phthalonitrile followed by the condensation reaction and is reported to have sufficient hydrophilicity and specificity toward tumors, potentially increasing the PDT efficacy.

*7.2.2.2. Carbamoylation Reaction.* Glycoconjugated Pc's (Figure 52A) were reported by Schotten and co-workers.[331] Substitution of the preformed Zn(II)Pc with sugars was achieved by carbamoylation and 1,3-dipolar cycloaddition reactions. The approach of appending targeting moieties to preformed Pc can diminish isomer and purification problems as long as high-yield reactions are used on symmetrically substituted Pc, and, as applied here, can lead to the formation of diverse Pc's bearing different biomolecules such as amino acids, peptides, proteins, nucleic acids, and steroids. These bioconjugated Pc's can be useful in generating structure−activity relationships (SAR) for the development of new PSs for PDT, but can provide key starting materials toward the incorporation of Pc cores into functional supramolecular biological matrixes.[331]

*7.2.2.3. 1,3-Cyclo Addition Reaction.* After Berthold et al.[331] reported the substitution of glycosyl groups on preformed Pc's using a 1,3-cycloaddition reaction (Figure 52B), Lafont and co-workers[329,330,332] reported two different series of monoglycosylated Pc's linked by 1,2,3-triazole with triethylene glycol spacers and *O*-glycosylphthalocyanine (Figure 53) to assess the role of the click unit along with two series of Pc−carbohydrate conjugates with tetraethylene glycol spacers, linked via an O- (Figure 49). Two sets of water-soluble monoglycosyl phthalocyanines (Figures 49A and 53A) were investigated for their PDT activity using HT29 human colon adenocarcinoma cells.[329] The most active compounds were the *O*-mannose and *O*-galactose sugars appended on the terminal hydroxyl unit on preformed Pc with tetraethylene glycol spacer shown in Figure 49A. Thus, the triazole link may play a role in diminishing the effectiveness when compared to the *O*-linkage sugars, perhaps because of the increased molecular size of the triazole of the conjugates.

The physical and photophysical properties of Pc's depend upon the central metal ion, the nature of the substituents, and the number and position of these substituents. These distorted


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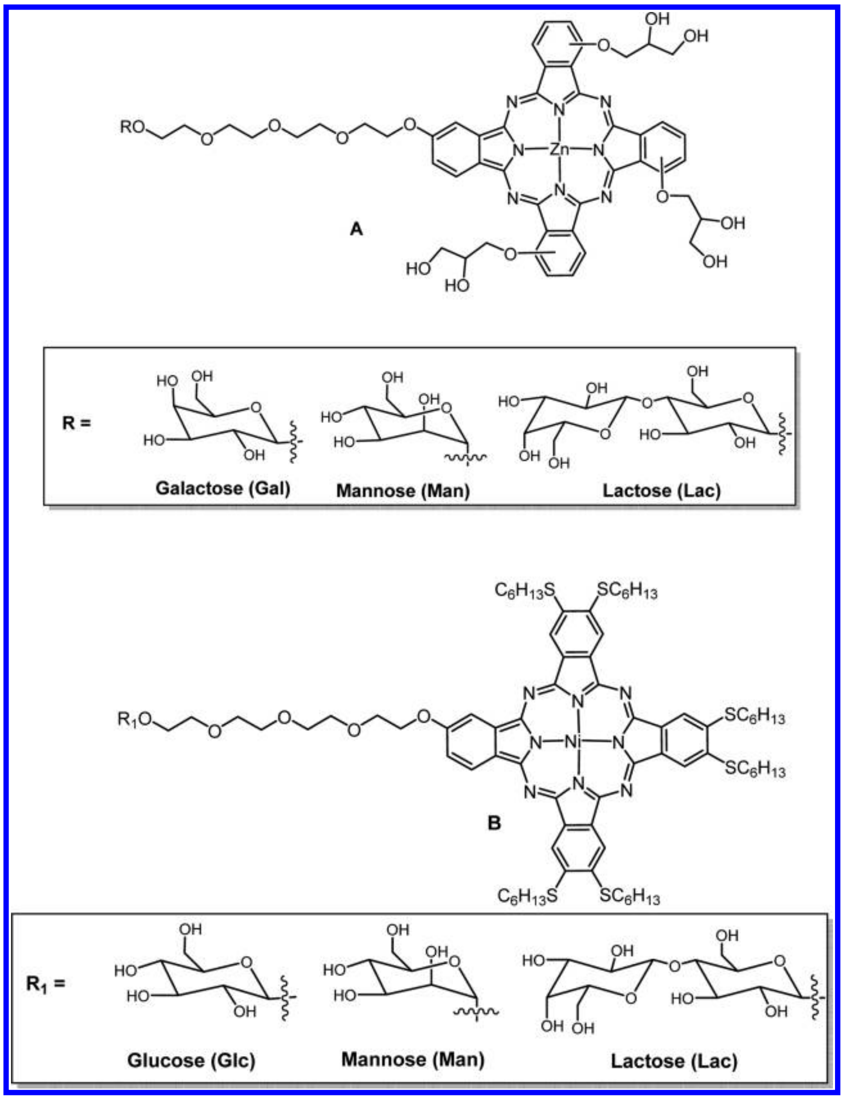


**Figure 49.** Structures of glycosylated glycerol-Zn-phthalocyanine (A) with an intervening tetraethylene glycol spacer, and glycosylated thiol-hexane-Ni-phthalocyanine[329] (B) with an intervening tetraethylene glycol spacer; the core Pc was made by a mixed condensation reaction. Ni(II)Pc generally have unfavorable photophysical properties for PDT because of a low-lying d,d state.[330]

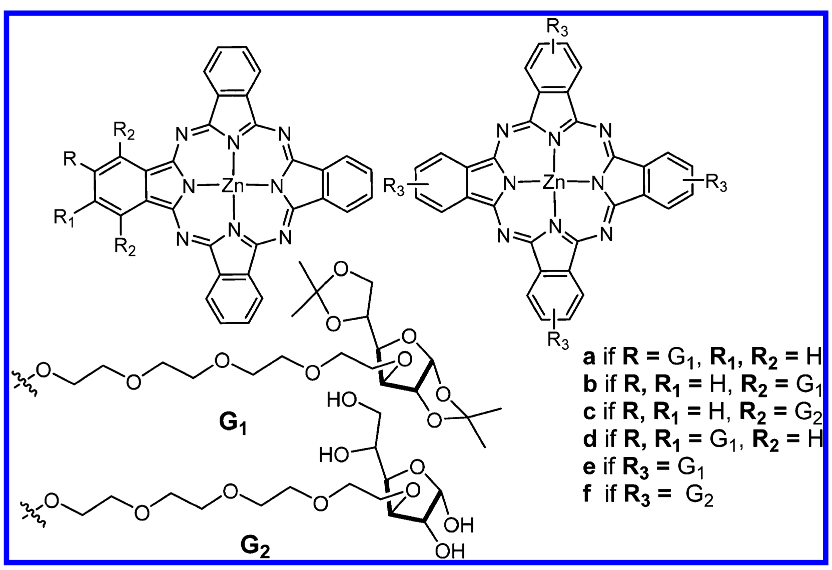


**Figure 50.** Mono-, di-, and tetra-*O*-glycosyl-substituted Pc containing tetraethylene glycol spacer synthesized via condensation of glycosyl phthalonitrile reported by Liu et al.[328]



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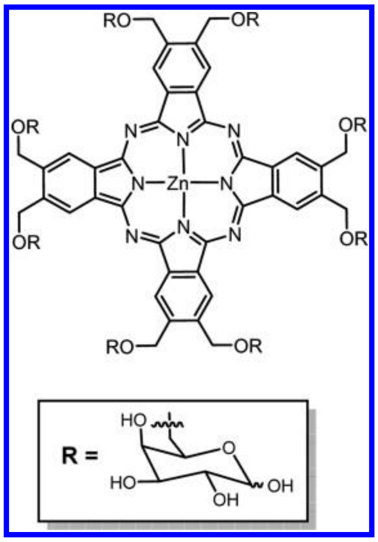


**Figure 51.** Pc's bearing eight D-galactose units on the periphery synthesized via condensation of 4,5-(di-D-galactose) phthalonitrile.[327]

Pc's likely do not have optimal photophysical properties for PDT because of the increased internal conversion. To achieve good solubility and limit the aggregation of Pc's in most solvents, one strategy is to incorporate branched or bulky substituents or those on the $\alpha$ positions to inhibit $\pi$-stacking. Kanat and Dincer prepared the $\alpha$-substituted tetra terminal alkynyl-substituted Pc's by the tetramerization of the corresponding precursor having a terminal alkyne function at the C-3 position in the presence of Zn and Co metal salts and/or DBU without protection/deprotection (Figure 54).[334] The glycoconjugation of alkyne-functionalized ZnPc prepared was easily achieved via the click reaction between the Pc and azido functional glucopyranosyl in high yield. The glucose units promote water solubility of this ZnPc, and its applications as a PS are currently under investigation.[334]

**7.2.3. Phthalocyanine Dendrimers.** Tome and co-workers[132,196] reported the synthesis of hexadeca-galacto Pc dendrimer (Figure 55), and recently in vitro studies of this compound were carried on two different human bladder cancer cell lines UM-UC-3 and HT-1376 for their PDT efficacy.[196,335] This compound was found to be nontoxic in dark but showed good uptake and has high phototoxicity in both cell lines. Good cell uptake and PDT efficacy of the compound were attributed to the presence of galectin-1 and GLUT1 receptors on the two aforementioned bladder cell lines.

**7.2.4. Phthalocyanine–CD Conjugates.** Liu and co-workers reported the synthesis of a glucopyranose conjugated Zn(II)Pc for application as a NIR fluorescent imaging agent.[261] The compound was tested as an optical probe on liver tumor bearing nude mice using in vivo fluorescence imaging. The water solubility, stability to photo bleaching, and good emission quantum yield of the compound in the NIR region show that this glucopyranose conjugate of Zn(II)Pc has potential in cancer diagnosis as a NIR optical probe or possibly fluorescence guided surgery.[261,321,333,336] Torres and co-workers proposed a new method to obtain water-soluble Pc's using a covalent linkage to the $\beta$-CD, a cyclic glucose heptameric polysaccharide.[337] Here, CD provides good amphiphilic character to these compounds because the hydrophilic properties of the CD combined with the hydrophobic cavity in the center of the macrocycle allow these sugar conjugated Pc's to be soluble in water.[338,339] These compounds were prepared via a statistical cross condensation of a 4-($\beta$-CD)phthalonitrile with an excess of phthalonitriles or 4,5-dibutoxypthalonitrile and were characterized by MALDI-TOF-MS (Figure 56).[337] The same group also reported a methodology to synthesize asymmetrical sugar appended water-soluble Pc's by statistical cross condensation of galactosyl-phthalonitrile with phthalonitrile. These CD conjugates have good properties as PSs, and may be useful for constructing supramolecular systems for molecular recognition, with potential applications in optical sensing,[340] and in the construction of Pc-based nanostructured materials.[210,341,342]

CD can also be attached axially to the metallophthalocyanines. Soft, 5- or 6-coordinate metal ions in Pc can axially bind

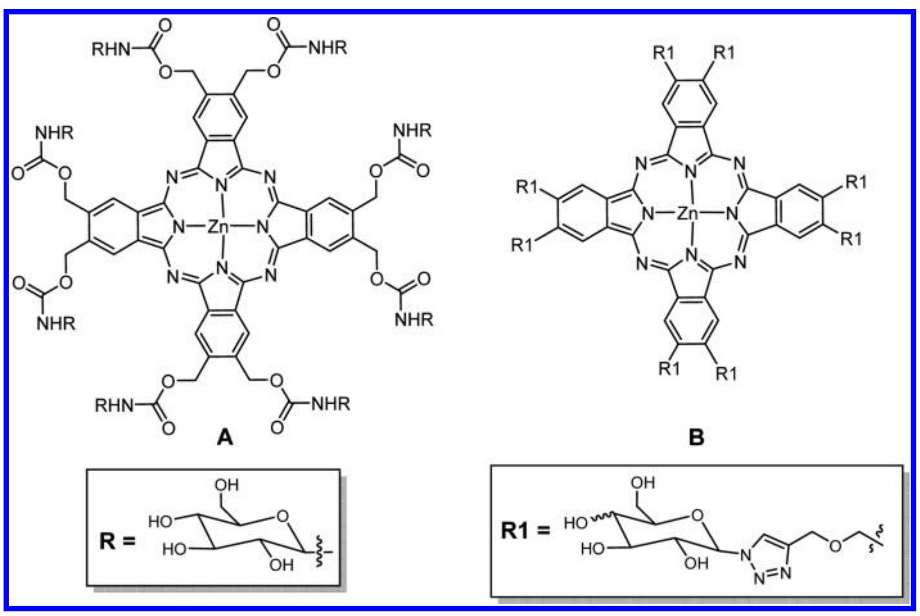


**Figure 52.** (A) Structure of octacarbamoyl glycosylated-substituted Zn(II)Pc made from the isocyanate and the hydroxymethylphthalocyanine, and (B) click chemistry to prepare the octaglycosylated Pc starting with the Zn(II)Pc-octa-$\beta$-$CH_2OCH_2C{\equiv}CH$.[331]


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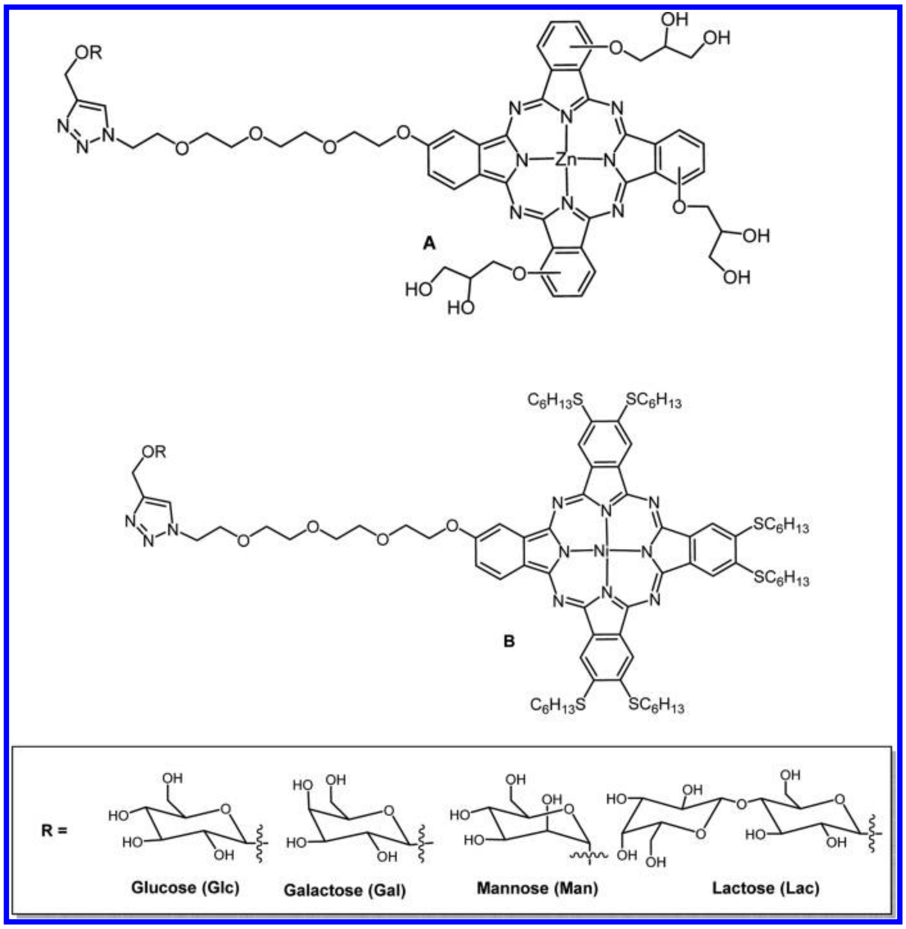


**Figure 53.** Structures of glycosylated glycerol-Zn-phthalocyanine (A) with an intervening triethylene glycol spacer and glycosylated thiol-hexane-Ni-phthalocyanine[329,332] and (B) with an intervening triethylene glycol spacer prepared via 1,3-dipolar cycloaddition reported by Lafont and co-workers,[330] wherein the core Pc was made from a mixed condensation reaction or from a core hydroxyl Pc.

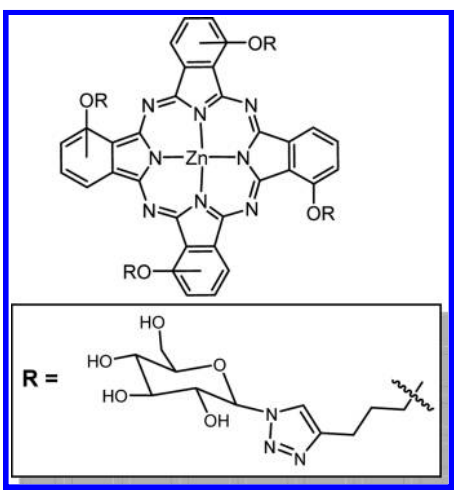


**Figure 54.** Structure of tetra glycosyl-substituted Zn(II)Pc on the $\alpha$ position.[334] The core Pc was obtained by cyclotetramerization of 3-pent-4-ynyloxy phthalonitrile.

amines on sugars, albeit with relatively weak binding constants. Conceivably, Pc with both exocyclic and axial sugars can be used to administer the drug, and the axial ligands can exchange with amines on albumin or other biological molecules in vivo, which then can carry the drug to the disease site. Alternatively, Pc coordinating oxophilic metal ions, especially Sn(IV) and Si(IV), can robustly bind oxygen ligands as counterions in a

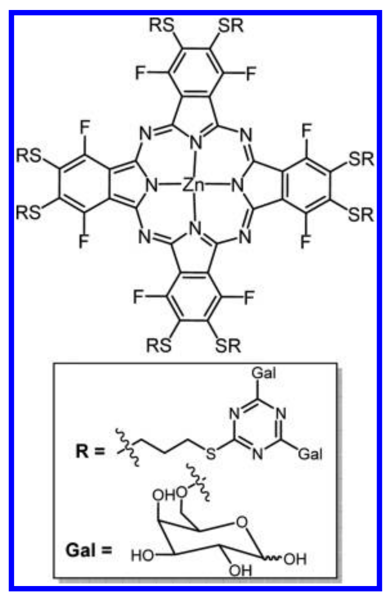


**Figure 55.** Structure of Zn(II)Pc glycodendritic conjugate with 16 galactopyranose units.[132]

strategy used to self-assemble multichromophore arrays of these dyes.[343] Examples of the latter were reported by Ng and co-workers where two CD units attached axially to form a symmetric analogue via an oxomethylene bridge to Si(IV) Pc's,


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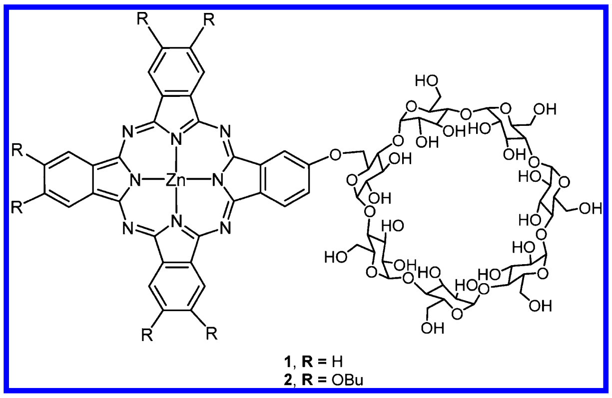


**Figure 56.** A Zn(II)Pc functionalized with $\beta$-CD from a mixed condensation reaction.[337]

and unsymmetrical analogues with CD on one side and sugar units on the other side (Figure 57).[303] The in vitro

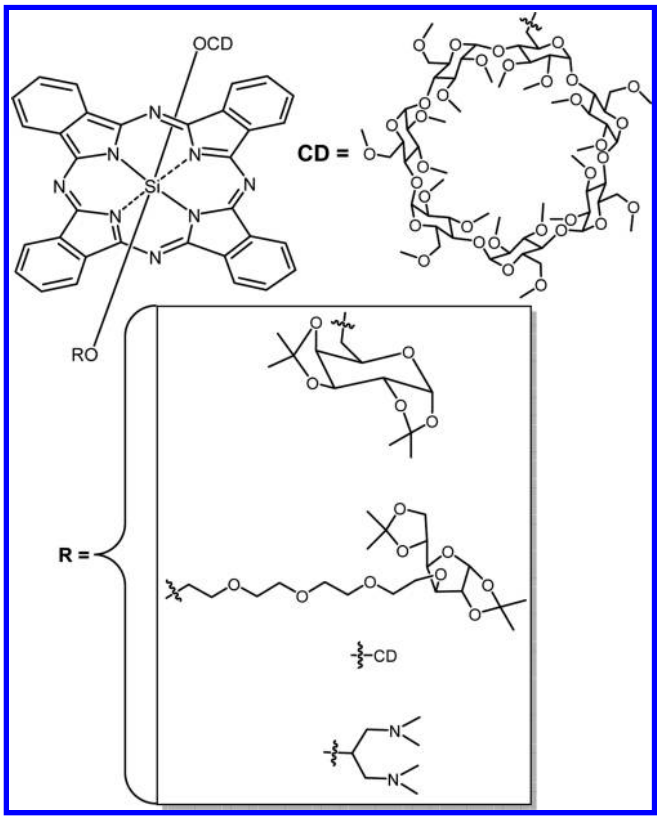


**Figure 57.** Structure of a series of symmetrical and unsymmetrical Si(IV)Pc with a permethylated $\beta$-CD unit and a sugar as axial substituents.[303]

photodynamic activities of these symmetrical and unsymmetrical analogues were tested against HT29 human colorectal carcinoma and HepG2 human hepatocarcinoma cells. Because the unsymmetrical analogue is more efficient in generating intracellular ROS, it is thus reported to exhibit greater photocytotoxicity than the symmetrical analogue.[303]

Recently, Tome and co-workers reported three hydrophilic phthalocyanine−CD conjugates, Pc-$\alpha$-CD, Pc-$\beta$-CD, and Pc-$\gamma$-CD, via nucleophilic substitution of oxygen atoms of cyclo-maltohexaose ($\alpha$-CD), cyclo-maltoheptaose ($\beta$-CD), and cyclo-maltooctaose ($\gamma$-CD) on two fluorine atoms of PcF16.[344] The UM-UC-3 bladder cancer cell line was used to study the phototoxicity of these conjugates. Among these conjugates, Pc-$\alpha$-CD and Pc-$\gamma$-CD exhibited higher phototoxicity as compared to Pc-$\beta$-CD.

Similar strategies can be used to append other biocompatible motifs such as amino acids, polylysine, peptides, etc., to increase the Pc's selectivity and targeting for specific cells and tissues.[345] For example, palladium-catalyzed Sonogashira cross-coupling reactions afford mono iodotriglycerol-substituted Zn(II)Pc's.[247]

## 8. GLYCOSYLATED PORPHYRAZINES

Porphyrazines (*tetra*-azaporphyrins, Pz's) meet all of the requirements to be a good PDT agent, but they are notoriously insoluble in most common solvents. Peripheral-carbohydrate functionalization and core-metal ion complexes can enhance the solubility of the Pz and thus can increase the cellular uptake and phototoxicity. Novel free-base and metallo-Zn(II) or Ni(II) carbohydrate-functionalized Pz (Pz-galactopyranose/ribose derivatives) derivatives were reported by Horne et al.[346] and Williams et al.[347] for potential use in the administration of PDT (Figure 58). These conjugates proved insoluble in most of the

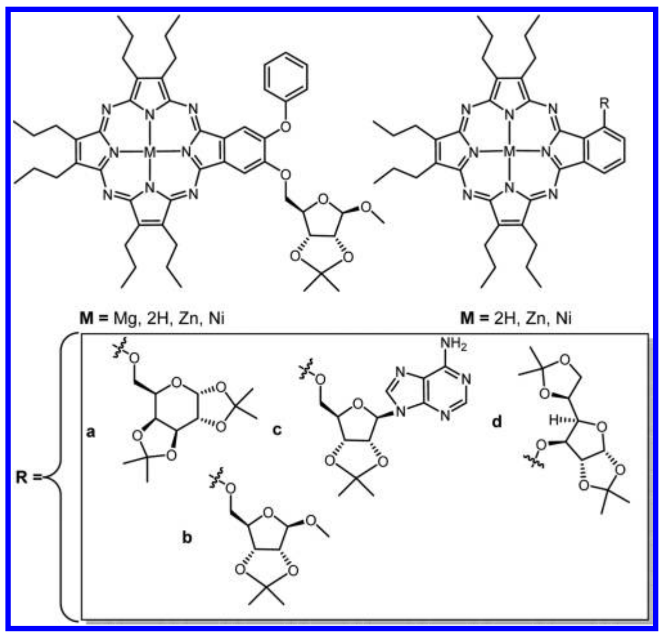


**Figure 58.** Structure of Pz's substituted with (a) galactopyranose and (b−d) ribose derivatives.[346,347]

conventional organic solvents except dichloromethane (DCM) and tetrahydrofuran (THF). Pz-galactopyranose/ribose derivatives were solubilized using DCM-based PEG-DSPE$_{5000}$-PBS encapsulation for biological studies. Only Zn(II) Pz showed sufficient aqueous solubility and low toxicity usig MCF-7 cancer cells, while the free base and Ni(II) derivatives showed persistent aggregation. Further studies are being done on Zn(II)Pz for possible induction of cell death and cell type specificity.[346]

## 9. NANOAGGREGATES OF SUGAR-SUBSTITUTED PORPHYRINOIDS AND RELATED MACROCYCLE

The supramolecular chemistry of porphyrinoids is well reviewed,[216,343] and the explosive growth of reports on porphyrinoid materials in the last three decades is driven by the facile formation and diverse applications of new photonic


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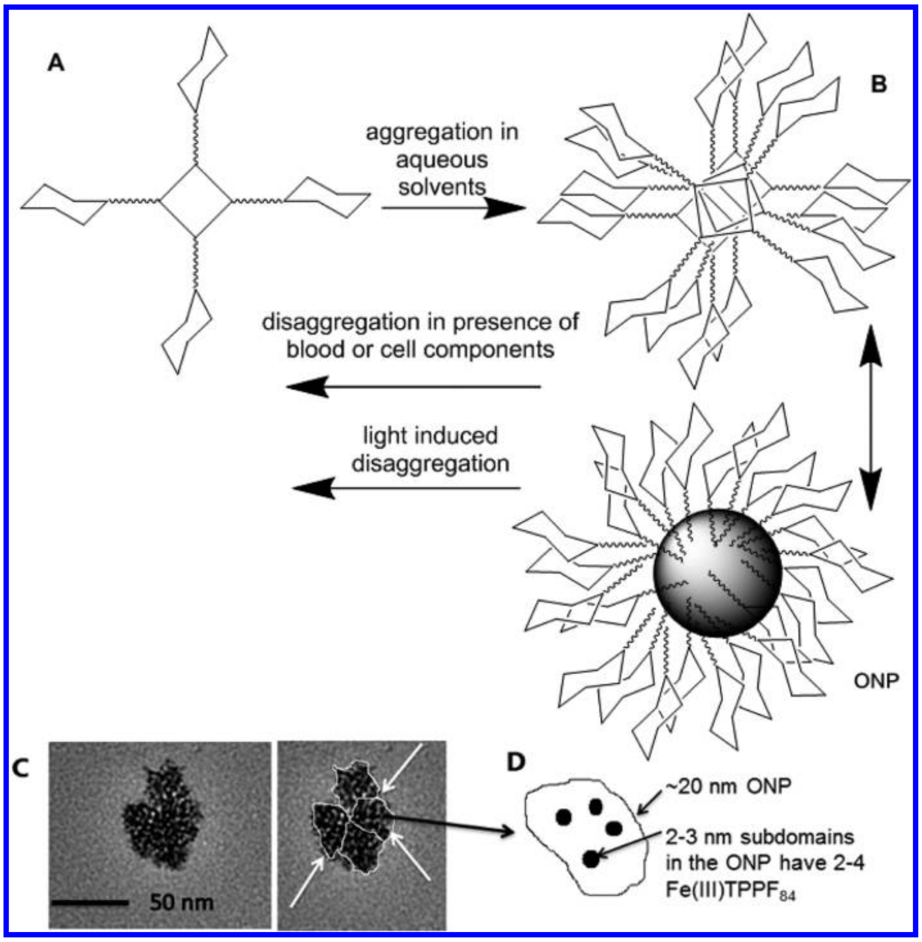


**Figure 59.** Hydrophobic core of porphyrinoid dyes (A) often drives aggregation in aqueous media into small $\pi$-stacked aggregates (B), which can further aggregate into larger organic nanoparticles (ONP). The nanoaggregates can be driven to disassemble by interaction with cellular components such as lipid head groups and protein and/or photothermal processes. While the free bases do not have sufficient contrast in transmission electron microscope studies, the Fe(III) complexes of a fluorous porphyrin do, and reveal the presence of small domains within a larger ONP (C and D).[353] Reproduced with permission from ref 353. Copyright 2012 John Wiley and Sons, Inc. If <ca. 50 nm, the aggregate can be taken up by the cell, for example, by endocytosis, where it can disaggregate because of interactions with cellular components, photothermally by internal conversion, and PDT damage to the endosome. Also, the loosely bound subdomains may be induced to break out of the ONP by the same processes and be taken up by the cells. Polysaccharide possessing in the cell will also contribute to the dye distributions, and is a key factor in why nonhydrolyzable bioconjugates can be more effective therapeutics.

and catalytic materials for modern technologies. These technologies include sensors in optical devices, catalysts, drug delivery systems, therapeutics for treatment of variety of diseases, and PSs for photodynamic therapeutic treatment of a variety of diseases such as cancers. To improve the amphiphilicity of the macrocycle, significant effort continues to be invested in appending a variety of biocompatible motifs to the PS, such as sugars, peptides, polylysine, PEGs, and amino acid groups wherein these motifs are also designed to target cancer or bacteria.[7,101,348−352] Despite being appended with sugars, the large size and the hydrophobic nature of porphyrinoid cores often cause a rapid aggregation in aqueous media (Figure 59). The size and stability of the aggregate depend on a variety of factors, including number and position of the sugars, the core macrocycle (e.g., $\pi-\pi$ interactions between porphyrin, Pc, corrole), other substituents, and whether the compound is the free base or metalated. If the metalloporphyrinoid is used, the charge on the metal ion influences electrostatic interactions, and axial ligands also contribute to the degree of aggregation by inhibiting $\pi-\pi$ interactions.[213,353−356] The specific intermolecular interactions and size of the nanoaggregates dictate to a large extent cellular uptake and subcellular localization wherein <50 nm diameter nanoaggregates can be endocytosed by cells. The hierarchical structure of the dyes within the nanoaggregates also dictates the photosensitizing properties of the porphyrinoid, wherein the quantum yield of singlet oxygen generation and fluorescence are usually quenched relative to the individual dyes.

Because aggregates of porphyrinoids can be quite stable[356,357] and intermolecular interactions affect the photophysical properties of the chromophore, the study of PS aggregates is key to deployment as photonic materials. The degree of aggregation is indicated by the shift, broadening, or the appearance of shoulders on one or both sides of the optical bands, typically focusing on the Soret band. Blue shifts or shoulders indicate face-to-face H- aggregates, and red shifts or shoulders indicate edge-to-edge J-aggregates. Often in porphyrinoid aggregates, one observes both red and blue features, indicating diversity in the intermolecular interactions. In addition to shading effects in aggregates that reduce the relative optical cross sections, aggregates of isoenergetic dyes facilitate excited-state energy transfer, and the resulting branching kinetics significantly diminishes the fluorescence and triplet quantum yields. Thus, aggregates can have limited use as luminescent biochemical tags and PS for PDT. It is difficult to predict the aggregation behavior of these molecules in terms of size and stability because of the aforementioned factors.[356] Herein, we focused only on the aggregates of the sugar conjugates of the porphyrinoids and related macrocycles.

Because the porphyrinoid nanoaggregates are self-organized[358] by supramolecular interactions,[215] they can be induced to disaggregate by a combination of factors. Many of the sugar-coated porphyrins and Pc's spontaneously aggregate into 10−50 nm aggregates in PBS and other biological buffer systems commonly employed in in vitro and in vivo (Figure 59) studies. These particle sizes can, for example, be endocytosed by cancer cells. Disaggregation can be induced by interactions with proteins in the blood such as albumin, high density lipoproteins (HDL), low density lipoproteins (LDL), and by interactions with a variety of cellular components inside the cell such as proteins, polar head groups of membranes, etc. We have postulated that the sugars on the outside of the aggregates induce the cell to take up the aggregates and then decompartmentalize and disassemble the aggregate to allow the distribution of the dyes in the cell by mechanisms similar for large polysaccharides.[171] Because the strength of the supramolecular interactions within an aggregate depends on the specific dye under investigation, the rate of disaggregation is highly dependent on molecular structure and specific interactions with cellular components. Typically, the Pc's, Pz's, and benzoporphyrins form more robust aggregates than *meso*-arylporphyrins and corroles.

Individual porphyrinoids, especially those that have flat molecular architectures, for example, when the sugars are appended to the *para* positions of *meso*-arylporphyrins versus the *ortho* or *meta* positions, can passively diffuse through the membrane driven by concentration gradients and amphipathic properties. Conversely, passive diffusion is much less likely with bulky molecules and aggregates that have a hydrophobic shell (sugars) around a hydrophilic core (dye). At low concentrations of sugar-appended porphyrins and Pc's, the dyes can be largely nonaggregated. However, as these dyes collect around the target cells driven by the receptors expressed on the membrane exterior, the local dye concentration substantially increases in the cell micro environment, and this can result in the self-organization of nanometer scale aggregates that are near the cell or attached via the receptor(s) (Figure 60). Thus, there are two possible mechanisms for dye aggregation, and they are not mutually exclusive.

When dyes are aggregated, the excitation energy is largely dissipated by internal conversion (vibrations as heat), which then can reduce the strength of the intermolecular interaction in the nanoaggregates. Photoinduced heating to initiate disaggregation of the dyes may also cause release from endosomes and similar structures, and some photothermal stress to the cell similar to other nanoparticles used in photothermal therapy (PTT).[359] Although reduced, the singlet oxygen that is formed in the nanoaggregates can damage the vesicle and cause the dyes to be released. The extent of each of these factors will depend on the specific system under investigation. Both in vitro and in vivo studies have shown that a short light irradiation followed by an induction period and then the therapeutic light treatment significantly increases the PDT efficacy of a variety of dyes.[5,171,360] PDT is postulated to have a role in overcoming drug resistance by cancer.[361]

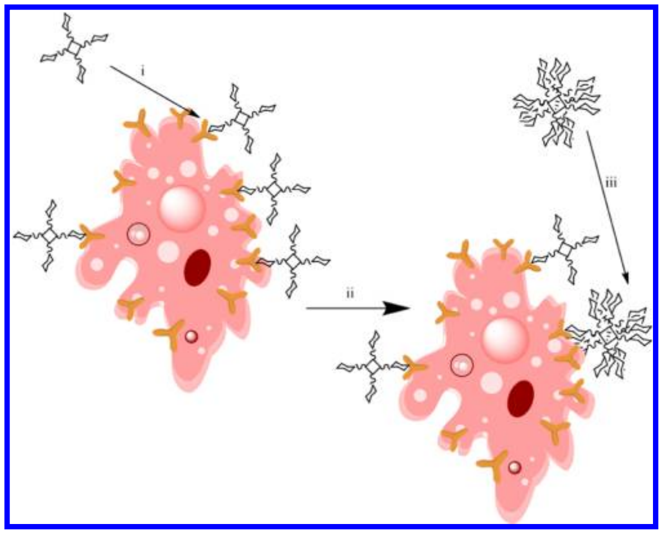


**Figure 60.** (i) At low concentrations, the porphyrinoid dyes are solvated and not aggregated. (ii) Upon binding to the target cell, the local concentration increases and the dyes then aggregate. (iii) Nanoaggregates in aqueous media have sugar-coated shells around the dye core, which then can bind to cell receptors. Either or both processes can be present depending on the specific dye and cell types and media.

## 9.1. Sugar Porphyrin Aggregates

Self-aggregation of porphyrinoids in aqueous media or in mixed solvent systems is common and is mainly driven by $\pi-\pi$ interactions between the macrocycles and is a complex process that may involve the formation of dimers, trimers, oligomers, and/or large-scale aggregates. The particle size distribution also varies with both dye and environment.

Sugar appended porphyrinoids, in which the sugar group is attached through C-, S-, and O- atom to the macrocycle, are known to form aggregates in buffer, polar and nonpolar organic solvents, and in mixed solvent systems.[118,142,147,157] The size and structural organization of organic nanoparticles of sugar porphyrinoids depend on a variety of factors including concentration, solvent, mixing technique, number of appended sugar groups, and the architecture of the component molecule, for example, relative orientation of the sugars and structure of tethers. Formation of aggregates of sugar porphyrinoid conjugates in aqueous solvents such as PBS or buffers with serum albumin quenches the fluorescence and thereby decreases the singlet oxygen generation efficiency. Singh et al. have investigated the aggregation of tetra-thioglycosylated porphyrin conjugates ($PGlc_4$), the chlorin ($CGlc_4$), and isobacteriochlorin ($IGlc_4$) in PBS.[234] The aggregates of these chromophores were characterized by UV−visible spectroscopy, and the sizes were measured by dynamic light scattering. These conjugates aggregate to a different extent to form various sizes range particles. However, all of these are taken up by cancer cells as shown by fluorescence microscopy (see Figures 27 and 28).

Hirohara et al. reported the aggregation behavior in PBS of a series of sugar conjugates on the *meta* position of tetraarylchlorins (Figure 61) including 5,10,15,20-tetrakis[3-(*β*-D-glucopyranosyloxy)phenyl]chlorin, 5,10,15,20-tetrakis[3-(*β*-D-galactopyranosyloxy)phenyl]chlorin, 5,10,15,20-tetrakis-[3-(*β*-D-xylopyranosyloxy)phenyl]chlorin, and 5,10,15,20-tetrakis[3-(*β*-D-arabinopyranosyloxy)phenyl]chlorin. Their data suggest that the mode of aggregation, H-aggregate versus

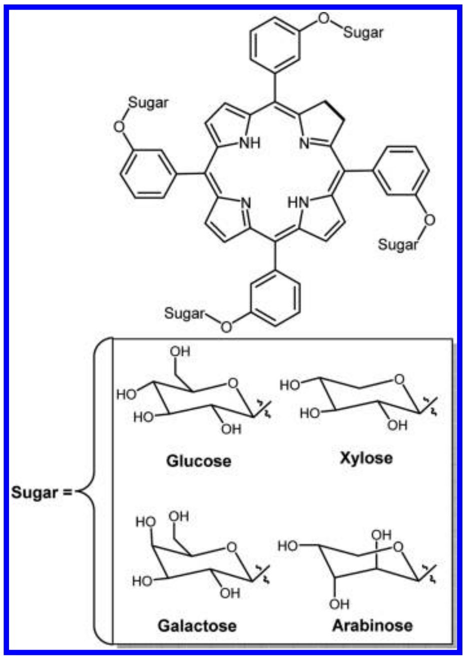


**Figure 61.** Aggregation properties were correlated with the 5- and 6-carbon sugars, where the former is reported to have a propensity to form H-aggregates and the latter J-aggregates.[147]

J-aggregate, depends on the number of carbon atoms in the sugar units. Hexose conjugates of chlorin such as glucose and galactose predominantly formed H-aggregates, while sugar conjugates of chlorin with five carbon atoms such as xylose and arabinose form J-aggregates.[147] The steric bulk and orientation of these sugars are roughly equivalent, so it may be that cooperative H-bonding interactions give rise to the differences in aggregation.

Mikata et al. reported the aggregation behavior of a series of tris(maltohexoses) linked to tetraarylporphyrins with an alkyl chain of varying number of C atoms. Tris(maltohexoses) porphyrins without the alkyl group undergo H-aggregation predominantly where the porphyrin macrocycles are rotated relative to each other (see Figure 59), while the compounds with 2, 4, 6, 10, and 16 C atoms in the alkyl chain predominantly show J-aggregation where the porphyrin macrocycles are further away from each other.[362]

Song et al. studied the size-controlled aggregates of tetrakis(4-carboxyphenyl)porphyrin−pullulan conjugate and 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin−pullulan conjugate in PBS buffer. They observed a smaller aggregate (~100 nm) for tetrakis(4-carboxyphenyl)porphyrin-pullulan conjugate as compared to the other conjugate (~320 nm). This was attributed due to the core tetrakis(4-carboxyphenyl)-porphyrin molecule, which is more hydrophilic with three extra carboxylic groups as compared to 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin.[363]

Drasar and co-workers reported the aggregation of a series of glycosylated porphyrins with glycosylated groups directly attached to the *meso* position via a C atom linkage, and 5,15-diglycosylated compounds with 10,20-*meso*-perfluorophenyl groups in mixed solvent systems such as DMF−water, DMSO−water, and $CH_3CN$−water.[118,177]

These studies indicate that the self-aggregation of sugar porphyrins also depends on the position of sugar moiety attached. These chromophores show good solubility in that they stay in the monomeric form in polar solvents such as DMSO, DMF, MeCN, $CH_3OH$ but form H-type aggregates in mixed solvent system with water, such as $CH_3CN$−$H_2O$ and $CH_3OH$−$H_2O$. The degree of aggregation also depends on the % composition of water in the solvent mixture. The critical aggregation solvent composition is ≥~45% water for tetra *meso*-*C*-D-glucose porpphyrin, ≥45% for di *meso*-*C*-D-glucose porphyrin, ≥50% for tetra *meso*-*C*-D-galacto poprhyrin, and ≥60% for di *meso*-*C*-D-galacto porphyrin. The formation of aggregates in solvent mixture containing water is due to hydrophobic effects, for example, $\pi-\pi$ interactions and dispersion forces, as well as specific carbohydrate−$\pi$ interactions. Ibrahim et al. reported the tetra *para* glycosylated derivative of TPP aggregates rapidly in aqueous media as compared to the corresponding tetra *meta* glycosylated derivative of TPP, and the mono glycosylated compounds insert into liposomes and albumin.[364] This makes sense because the *ortho* and *meta* positions direct the sugars to one face or the other, and in both cases the compounds exist as statistical mixtures of four atropisomers.

## 9.2. Sugar Phthalocyanine Nanoaggregates

Drain and co-workers recently reported that octa thioglycosylated Zn(II)phthalocyanine, $ZnPcGlc_8$ does not aggregate in pure DMSO solvent,[257] but forms different sized aggregates in other organic solvents such as ethyl acetate, toluene, ethanol, PBS, and also in mixed solvent systems such as DMSO:$H_2O$. About 250 nm diameter aggregates were observed without sonication, and after sonication of this solution for ca. 15 min these large sized aggregates reorganized to form ca. 65 nm sized aggregates in mixed solvent system such as DMSO−water, and in PBS. For Pc's, the lowest energy Q-band is blue-shifted upon aggregation, indicative of the formation of H-aggregates.[4,257] Lyubimtsev et al.[365] reported the aggregation of both tetra- and octa-glycosylated Pc bearing the sugars at the $\alpha$ and $\beta$ positions through O- and S- atoms in aqueous solutions and mixed DMSO−water solvent system. These authors concluded that the degree of aggregation of *O*-glycosylated ZnPc is greater than that of the *S*-glycosylated compound because of electronic effects. The degree of aggregation of sugar Pc's also depends on the nature and number of sugar moieties attached. Choi et al.[319] reported that the tetra 1,2:5,6-di-*O*-isopropylidene-$\alpha$-D-glucofuranose or 1,2:3,4-di-*O*-isopropylidene-$\alpha$-D-galactopyranose-substituted Zn(II)Pc's made from the glycosubstituted phthalonitriles were less active than the corresponding monosubstituted derivatives against HepG2 human hepatocarcinoma and HT29 human colon adenocarcinoma cells because of decreased cell uptake. Somewhat counterintuitively, the tetra glycosylated derivatives significantly aggregate in aqueous solution as compared to the mono substituted; however, it may be that the mono glyco-Pc forms small aggregates suspended in water that were not detected.

The biomedical application of aggregates of glycosylated porphyrinoids such as porphyrins and Pc's is complicated by the delivery of the chromophore to target tissues and into target cells. Where aggregates bind to cells and how, or if, they disaggregate is dependent on the specific molecular component. The octanol/water partition coefficient is representative of the lipophilicity of the glycosylated macrocycle but does not reveal the nature of the aggregation in either solvent. Because <50 nm nanoaggregates can be endocytosized into cells, we found that the nanoaggregates of $ZnPcGlc_8$ (Figure 47) can go into MDA-MB-231 human breast cancer cells, but exhibit poor fluorescent


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signaling evidenced by the mapping of the emission energy between the various chromophoric units in the nanoaggregates. However, $ZnPcGlc_8$ disaggregates with time, and as a result the fluorescence signals significantly increase in confocal microscopy. The uptake of aggregates of sugar conjugated porphyrins and Pc's into cancer cells, the subsequent disaggregation, and concomitant increase in PDT and fluorescence activities indicate that these compounds may be viable PDT agents.

Corroles and corrolazines are the cognates of the porphyrinoid compounds. Amphiphilic corroles appended with phenyl carboxylic acid moieties at the *meso* position are reported to aggregate in mixed water ethanol solvent system.[366] Miao et al. reported the formation of self-aggregates of corroles dimers on surfaces such as highly ordered pyrolytic graphite (HOPG), mica, and Au.[367,368] Hameren et al. reported the self-aggregation of corroles trimers in *n*-hexane solution.[369,370] To date, characterization of the aggregates of sugar-coated corroles or sugar-coated corrolazines is not reported. However, we speculate that sugar conjugates of corroles and corrolazines will exhibit aggregation behavior similar to that of the sugar porphyrin and Pc compounds. Because of the missing *meso* position, corroles with sugars have polar and nonpolar regions, and so presumably aggregate in water.[256]

## 10. CONCLUSIONS

Despite vigorous research efforts, the optimal PSs for PDT and a fluorophore for bioimaging that fulfills the entire set of requirements for in vivo applications have not been created. For theranostics, a balance between fluorescence for optical imaging and singlet oxygen quantum yield for PDT is needed, and the chlorins seem to be the best candidates. However, the optical cross section between 650 and 750 nm of the Pc's is much larger than for the chlorins, but the fluorescence is significantly less than chlorins. Both chlorins and Pc's are stable to photo bleaching, but there are few if any quantitative studies on the fate of the sugars during and after PDT, which are likely oxidized and hydrolyzed. In this regard, the C- and S- glycoside bonds likely enhance the activity of the sugar–porphyrinoid conjugate.

One promising aspect of recent research is that there are now a variety of organic synthetic strategies that are easy, straightforward, and of high yield. Efficient syntheses are needed for the construction of porphyrinoid conjugates to any biomolecular species or biocompatible motif to rapidly assess the role of the targeting moiety rather than spending time on the synthesis of the dye. Second, straightforward syntheses facilitate scaling up the synthesis for trials and afford commercial viability. In this regard, the fluorine substitution chemistry can be done on an array of porphyrinoids.[7] The presence of fluorine on a PS, for example, derivatives of perfluorophenylporphyrin $TPPF_{20}$, perfluorophenyl corrole ($CorF_{15}$), and perfluorophthalocyanine ($PcF_{16}$) platforms, imparts several properties and opens several new functionalities. Fluorine groups are known to modulate pharmacokinetics, increase photostability to bleaching, enhance singlet oxygen formation, and alter lipophilicity.[371,372] The 16 remaining fluoro groups on the porphyrin or chlorin or bacteriochlorin, 12 remaining on the corrole, and eight remaining on the Pc may be suitable for $^{19}F$ NMR imaging, which can be correlated with fluorescence imaging. Reactions of the above fluorous dyes with $K^{18}F$ and the $K^+$ chelator kryptofix at elevated temperatures may allow F-18 labeling and enable positron emission tomography (PET) without altering the photophysics for fluorescence imaging or PDT.

Over the last three decades, four PS drugs for PDT were approved in the U.S. and Europe. There are more PS under clinical trials for treating different kinds of diseases. One of the most important aspects that needs to be addressed is to increase the efficacy of the PS while decreasing the side effects. So, different targeting and delivery systems have been employed, either on the PS or on vesicles or nanoparticles to effectively deliver it to the targeted site.[373] These involve silicon nanoparticle,[374,375] hyaluronic acid-PS nanoparticle,[376] gold nanoconjugates,[377] micelle nanoparticle,[378] liposomes,[379,380] peptides,[381,382] and sugars to improve the water solubility, stability, targeting efficiency, and improve the pharmacokinetics or prolonged release of the PS.[383,384] In combination with other therapies such as BNCT, PDT is particularly attractive for the treatment of cancers because it targets different mechanisms of cancer cell destruction and increases the overall therapeutic effect. Recently, age related macular degeneration has been treated using combination of anti-VGFR and PDT.[385] Also reported recently is PDT combined with the intravitreal ranibizumab (IVR) technique for the treatment of eye related polypoidal choroidal vasculopathy (macular degeneration) disease resulting in visual and anatomical improvements.[386]

Because the porphyrinoids cores are poorly soluble or insoluble in physiological conditions of cells/tissues, they aggregate quickly into highly stable precipitates. In addition to targeting, appending biocompatible moieties to the macrocycles increases solubility in aqueous environments, and therefore diminishes aggregation and destabilizes the intermolecular interactions. Clearly, aggregation needs to be considered, but can be exploited because the aggregates are less photo active, which might reduce unwanted side effects such as light sensitivity. The sugar moieties can be attached to the macrocycle either covalently at the peripheral positions or coordinately, axially to the central metal ion, especially to oxophilic metal ion centers. In comparison with *O*-glycosylated PSs, CONH-glycosyl, thio-glycosyl, and *C*-glycosyl bonds should resist endogenous hydrolysis catalyzed by glycosidases and lower pH.[137] Appending cyclodextrin moieties on these macrocycles may be a potential strategy to make new generation PS for PDT and has proven capacity as a vehicle for the drug delivery. Because of the new chemistries allowing rapid synthesis, many targeting motifs can be assayed.

The fact that Photofrin is a complex mixture may be the single best reason that it remains the gold standard for PDT because different components can partition into different cellular and tumor environments. Given that mixtures of different PS may have synergistic effects for PDT, one can envision designed mixtures using the same platform dye but with different groups that target quite different cellular structures or that are activated in different parts of the cell. This designed mixture would then synergistically and simultaneously disrupt or destroy essential cellular functions and structures to affect tumor necrosis or antiviral or antibacterial activities.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.chemrev.5b00244.


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Appendix with references (PDF)

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### Author Contributions

∥A.A. and S.S. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

### Biographies

Sunaina Singh received her Masters in Chemistry (Honors School) from Punjab University, Chandigarh, India, in 2002. She received her Ph.D. in 2011 from Hunter College of the City University of New York under the supervision of Prof. Charles Michael Drain, laboratory of Supramolecular Photonics. She then pursued her postdoctoral research work from 2011−2013 with Dr. Ronald Koder at The City College of New York, CUNY. In August 2013, she joined as a faculty member at the department of Natural Sciences, LaGuardia Community College, where her research focuses on the synthesis of porphyrin-based photosensitizers for photodynamic therapy and imaging.

Amit Aggarwal received his M.Sc. in Chemistry from D. A. V. College, Jalandhar, India, in 2000. He then joined the Department of Chemistry, Lyallpur Khalsa College as a lecturer and worked there from 2002−2005. In 2006 he joined Hunter College of The City University of New York for his graduate studies and received his Ph.D. in 2011 under the supervision of Prof. Charles Michael Drain. His doctoral research focused on the study of catalytic properties and photophysics of porphyrinoid-based materials. He conducted his Postdoctoral Research in the Department of Biochemistry at Weill Cornell Medical College, New York, from 2011−2013. Currently, he is an Assistant Professor in the department of Natural Sciences at LaGuardia Community College of The City University of New York. His research focuses on the preparation of porphyrinoid-based nanomaterials for their catalytic properties and also to develop new porphyrin-based photosensitizer for both imaging and photodynamic therapeutic treatment of cancers.

N. V. S. Dinesh K. Bhupathiraju was born in Andhrapradesh, India. He obtained his Bachelor's degree in chemistry (2005) and Master's degree in physical organic chemistry (2008) from Osmania University, Hyderabad, India. In 2013 he obtained his Ph.D. in organic chemistry from Louisiana State University, LA, under the guidance of Prof. Maria Graça H. Vicente. Presently, he is working as a postdoctoral associate at Hunter College of the City University of New York in Prof. Charles Michael Drain's laboratory of Supramolecular Photonics and also as a visiting lecturer in the Department of Chemistry and Biochemistry, Hunter College of the City University of New York. His research projects in Prof. Drain's laboratory involve theranostic nanomedicines for cancer and the development of new dyes for solar energy harvesting materials for coating on windows in urban applications.

Gianluca Arianna began research under the supervision of Dr. Charles Michael Drain in 2008, during his junior year of high school. His research project focused on the dynamic aggregation and cellular uptake of three novel porphyrinoid therapeutics designed for clinical photodynamic therapy and as cancer killing agents. He presented his research in 2009 at NYSCEF, reaching the semifinals, and was awarded the Ezra Levy Award for research in clinical chemistry for his work. From 2009−2013 Mr. Arianna attended CUNY Hunter College, where he worked to complete the ACS certification major and continued his research in the application of porphyrins for cancer treatment, studying their phototoxicity in cancer cell lines. In 2014, after completing his ACS requirements, he received his Bachelor of



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Arts, graduating magna cum laude. Currently, he is an Adjunct Lecturer in the chemistry department at Hunter College and a volunteer at Bellevue Hospital. He is also conducting research at Weill Cornell Medical College in the Department of Biochemistry and at Memorial Sloan Kettering Cancer Center. His research at Cornell focuses on the elucidation of neuronal protein pathways that regulate synaptic transmission using the *C. elegans* genetic model, while his research at MSKCC focuses on developing computer models for simulating growth of gold nanocrystals for use in cancer imaging.

Kirran Tiwari was born in Oklahoma City, OK, and was raised in Floral Park, NY. He is currently a junior at the Macaulay Honors College at Hunter College and is pursuing a Biochemistry major. In 2014, he joined Charles Michael Drain's lab where he is developing a mild extraction method to improve the extraction of pigments from avian eggshells to understand how eggshell pigmentation chemistry is exploited by avian in different ecological contexts. Previously, he studied the antimicrobial properties and the relative toxicity of various medicinal herbs in the West Indies.

Charles Michael Drain is Professor of Chemistry at Hunter College of the City University of New York and adjunct faculty at Rockefeller University. He started his career in chemistry at the University of Missouri in St. Louis. He received his Ph.D. from Tufts University in the laboratory of Barry B. Corden where he worked on porphyrin synthesis. Afterwards, he did postdoctoral work in the laboratory of David Mauzerall at The Rockefeller University where he examined self-organizing systems composed of porphyrins and lipid bilayers and developed one of the first examples of a purely organic, synthetic phototransistor. He also examined the interactions between chiral ion channels helices and chiral centers in lipids with R. Bruce Merrifield. The following two years he was a guest researcher in the laboratory of Jean-Marie Lehn at the University Louis Pasteur in Strasbourg, France, where he developed methodologies to self-assemble porphyrins. Afterward, he spent two years as a research fellow in the Dewey Holten Chris Kirmaier laboratory at Washington University studying the complex dynamics of nickel porphyrins. Since joining Hunter College, 1996, his research continues to focus on the design, synthesis, and characterization of self-assembled and self-organized photonic systems.

## ACKNOWLEDGMENTS

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## DEDICATION

This work is dedicated to the memory of Dr. Clifford E. Soll, all around excellent chemist and colleague.

## ABBREVIATIONS

| | |
|---|---|
| PDT | photodynamic therapy |
| PS | photosensitizer |
| ROS | reactive oxygen species |
| BODIPY | boron-dipyrromethene |
| FDA | Food and Drug Administration |
| EMEA | European Medicines Evaluation Agency |
| 5-ALA | 5-aminolevulinic acid |
| Metvix | 5-aminolevulinic acid methyl ester |
| Lu-Tex | lutetium texaphyrin |
| Glc | glucose |
| Gal | galactose |
| Man | mannose |
| TPP | tetraphenylporphyrin |
| $TPPF_{20}$ | 5,10,15,20-tetrakis(2,3,4,5,6-pentafluorophenyl)-porphyrin |
| $CF_{20}$ | perfluorophenylchlorin |
| $IF_{20}$ | perfluorophenylisobacteriochlorin |
| $BF_{20}$ | perfluorophenylbacteriochlorin |
| $PGlc_4$ | thioglycosylated porphyrin |
| $CGlc_4$ | thioglycosylated chlorin |
| $IGlc_4$ | thioglycosylated isobacteriochlorin |
| $BGlc_4$ | thioglycosylated bacteriochlorin |
| $PGal_4$ | thiogalactosylated porphyrin |
| *m*-THPC | *meta*-tetra(hydroxyphenyl)chlorin |
| $PorCu\text{-}Lac_8$ | octa-$\beta$-lactoglycosylated porphyrinato copper |
| Pc | phthalocyanine |
| $PcF_{16}$ | perfluorophthalocyanine |
| Zn(II)Pc | zinc(II) phthalocyanine |
| Si(IV)Pc | silicon(IV) phthalocyanine |
| Al(III)Pc | aluminum(III) phthalocyanine |
| $ZnPcGlc_8$ | octa thioglycosylated zinc(II) phthalocyanine |
| TBP | tetraphenylbenzoporphyrin |
| Ar4TBP | tetraaryltetrabenzoporphyrin |
| $CorF_{15}$ | perfluorophenyl corrole |
| Pz | porphyrazines |
| MEG | monoethylene glycol |
| DEG | diethylene glycol |
| PEG | polyethylene glycol |
| CD | cyclodextrin |
| MB | Methylene blue |
| pyro-2DG | pyropheophorbide-2-deoxyglucosamide |


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| | |
|---|---|
| DMSO | dimethyl sulfoxide |
| DCM | dichloromethane |
| PBS | phosphate buffered saline |
| HOPG | highly ordered pyrolytic graphite |
| ONP | organic nanoparticles |
| $^1O_2$ | singlet oxygen |
| $\Phi\Delta$ | quantum yield |
| $\Phi_{isc}$ | intersystem quantum yield |
| HSV-1 | Herpes simplex virus type 1 |
| IC | internal conversion |
| ISC | intersystem crossing |
| MW | microwave |
| SOD | superoxide dismutase |
| Con A | Concanavalin A |
| NIR | near infrared |
| DLS | dynamic light scattering |
| LDL | low density lipoproteins |
| HDL | high density lipoproteins |
| TPA | two-photon absorption |
| NLO | non linear optical |
| BNCT | boron neutron capture therapy |
| BBB | blood brain barrier |
| PTT | photothermal therapy |

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