Synthesis of new glycosylated zinc phthalocyanines and naphthalocyanines

Synthese neuer glycosylierter Zink Phthalocyanine und Naphthalocyanine

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Für meine Eltern, Familie, Son Fraz und Tochter Mishal

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1 Introduction

Phthalocyanines (Pc's) are macrocyclic compounds with wide applications in various fields. Metal (PcM) and metal free phthalocyanines (PcH_2) are used as dyes and pigments in textile and dyeing industries. More recently phthalocyanines find a large number of applications in various fields of materials science. This will be discussed later on page 9.

1.1 Historical background

The compound that was later named as phthalocyanine was first observed in 1907 as highly dark colored insoluble byproduct during the preparation of 2-cyanobenzamide.[1] In laboratory for the first time a copper phthalocyanine was prepared in 23 % yield by reacting 1,2-dibromobenzene with copper (I) cyanide in pyridine.[2] However these new compounds did not find much significance until 1928 when accidental appearance of a blue-green material was observed at the Grangemouth plant of Scottish dyes. During the synthesis of phthalimide from phthalic anhydride, the glass lined steel vessel had cracked resulting in the formation of a blue-green material.[3,4] Preliminary studies at Scottish Dyes revealed that the iron-containing by-product may acquire potential applications as pigments because it is exceptionally stable and insoluble in common organic solvents. Later on Scottish Dyes were acquired by ICI in 1928. Due to the business interests ICI started investigations about the preparation and structural evaluation of these novel blue colored compounds. The structure of this newly formed substance was extensively investigated by Linstead at Imperial College London, who later published a series of papers on the synthesis and structural investigations.[5-10] He was the first one who used the name phthalocyanine, deriving the name from the Greek words naphtha (rock oil) and cyanine (blue). In the subsequent years he developed procedures for the synthesis of metal and metal free Pc's.

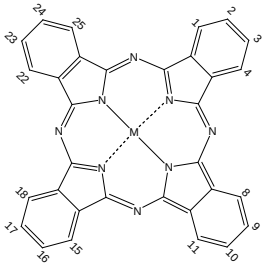


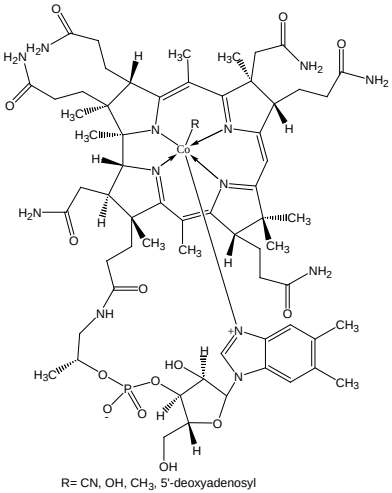
Figure 1: Structure of PcM.

Structure of a typical metal phthalocyanine (PcM) with IUPAC nomenclature is shown in figure 1. The positions 1, 4, 8, 11, 15, 18, 22 and 25 are usually referred as α-positions whereas, 2, 3, 9, 10, 16, 17, 23, and 24 are called as β-positions. The substituents located at α-positions are named as α-substituents, while those located at β-positions are regarded as β-substituents.

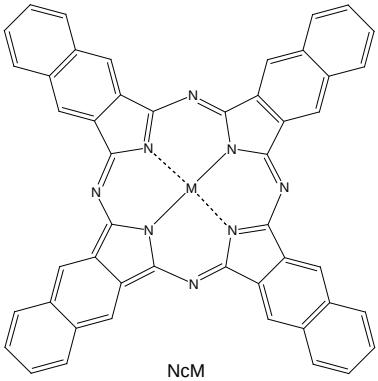
Nowadays Pc's are most familiar organic compounds with a vast variety of applications. A square planar phthalocyanine ring has coordination number of four, can tightly bind almost all metals. Metals having coordination number higher than four can bond with a variety of axial ligands which enables the Pc ring to be used in the extension and formation of polymers.

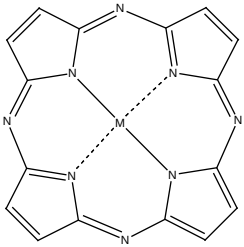
1.2 Phthalocyanines and related macrocycles

Phthalocyanines although not found in nature have resemblance with some naturally occurring substances such as haemoglobin, vitamin B_{12} and chlorophyll. Porphyrins (P) and porphyrazines (Pz) are among the other substances which are structurally related with phthalocyanines (see figure 2).

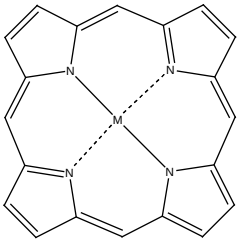


Vitamin B_{12}


NcM



PzM



Porphyrin (PM)

Figure 2: Structures of vitamin B_{12}, naphthalocyanine (NcM), porphyrazine (PzM) and porphyrin (PM).

Phthalocyanines are further modified on the periphery to form naphthalocyanines (Nc's), anthracenocyanines (Ac's) as well as mixed structures containing phthalocyanine and naphthalocyanine subunits.

1.3 Phthalocyanine and naphthalocyanine precursors

Various 1,2-disubstituted benzene precursors, e.g. phthalic anhydride, phthalimide, phthalamide, *o*-cyanobenzamide and phthalonitrile, are used to synthesize metal free and metal phthalocyanines as shown in figure 3. Among them phthalonitriles are the most widely used starting materials for the synthesis of metal and metal free phthalocyanines. However these precursors are not discrete as one type of precursor is often an intermediate in the cyclotetramerization reaction of other. For example phthalonitrile is formed as an intermediate during cyclotetramerization of 1,2-dibromobenzene with copper (I) cyanide. Similarly diiminoisoindoline is formed during tetramerization of phthalonitrile induced by ammonia under more forcing conditions. Phthalonitriles can be synthesized from other phthalic acid derivatives by a step wise progression from the dicarboxylic acid through to the anhydride , imide and diamide and finally to the desired phthalonitrile.[13] An excellent example of this was employed in the synthesis of 4,5-dichlorophthalonitrile from the inexpensive commercially available 1,2-dichloro-3,4-benzenedicarboxylic acid (figure 4).[14]

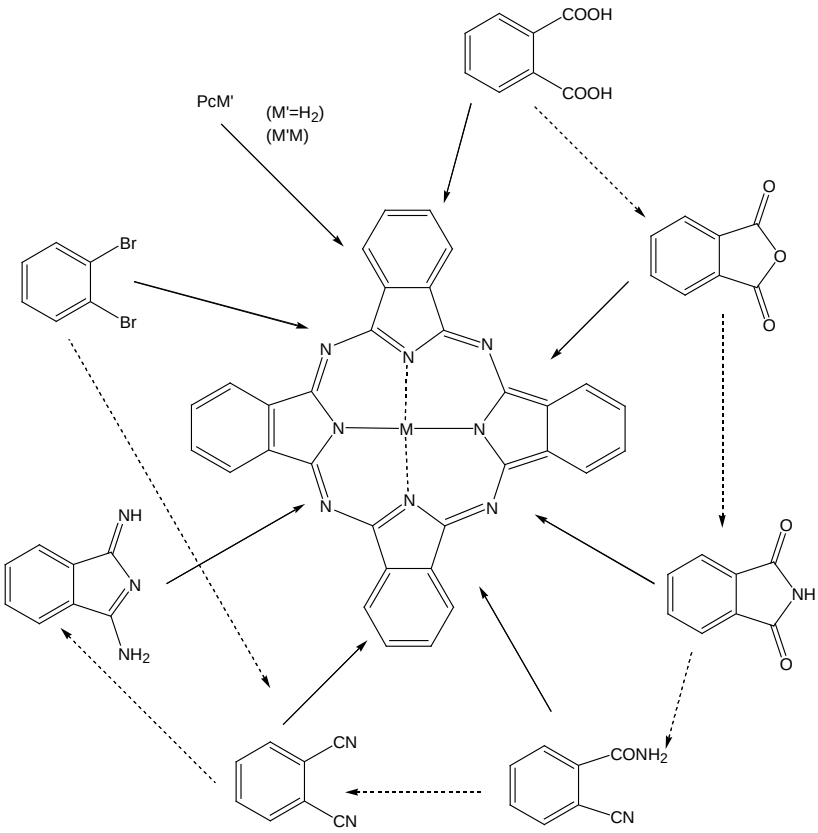


Figure 3: General methods for the synthesis of metal phthalocyanine (PcM).

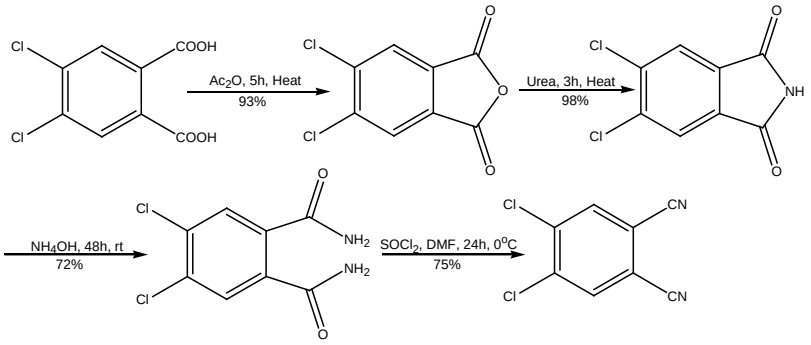


Figure 4: Synthesis of 4,5-dichlorophthalonitrile.

A highly popular method of synthesizing phthalonitriles is by a cyano-dehalogenation reaction known as the Rosenmund-von Braun reaction.[15] In this method aryl halides are converted into the corresponding aryl nitriles using cuprous cyanide in refluxing DMF. Although it is known that aryl iodides react 40-100 times[16] more readily than aryl bromides, phthalonitrile synthesis is usually accomplished using the corresponding aryl bromides. This is due to the ready availability of brominated precursors (see figure 5).

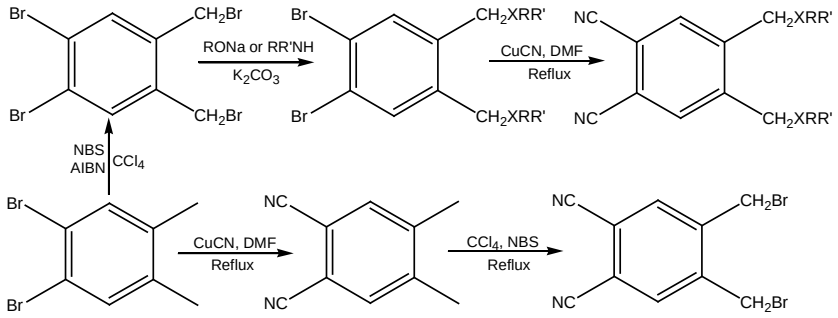


Figure 5: General synthesis of 4,5-disubstituted phthalonitriles (X = O or N).

Another more simple approach for the preparation of mono or disubstituted phthalonitriles, is the modification of preexisting phthalonitrile molecules.[13] A number of substituted phthalonitriles bearing chemically versatile functional groups such as NO_2, OH and halides etc., are commercially available. Others can be easily synthesized from inexpensive commercially available starting materials using one of the classic methods discussed above.

Phthalocyanines and metal phthalocyanines may also be synthesized by the modification of already formed metal free or metal phthalocyanines. This involves the reactions of substituents present on the peripheral ring of already formed phthalocyanines.[13]

Peripherally substituted Pc's are generally synthesized by corresponding substituted phthalonitriles as starting material. In contrast to octasubstituted systems tetrasubstituted Pc's are obtained as a mixture of four constitutional isomers, by tetramerization of monosubstituted phthalonitriles or their derivatives.

Attempts to separate these constitutional isomers were carried out with tetra-*tert*-butyl substituted 1,2-naphthalocyanine [1,2-NcFe($C_6H_{11}NC)_2$.].[17] But only the C_{4h}-isomer could be separated from the three other ones.

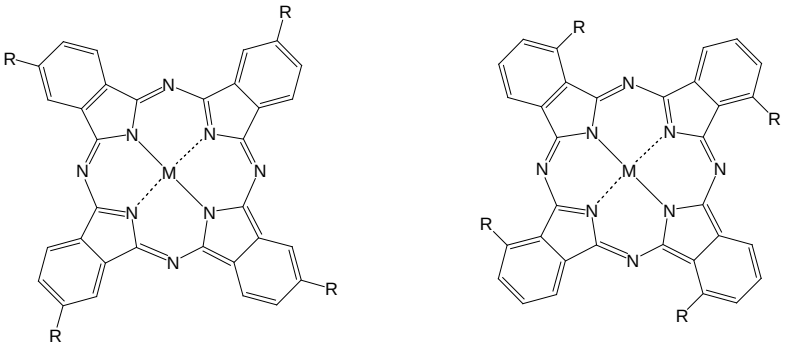


Figure 6: Tetrasubstituted metal phthalocyanines.

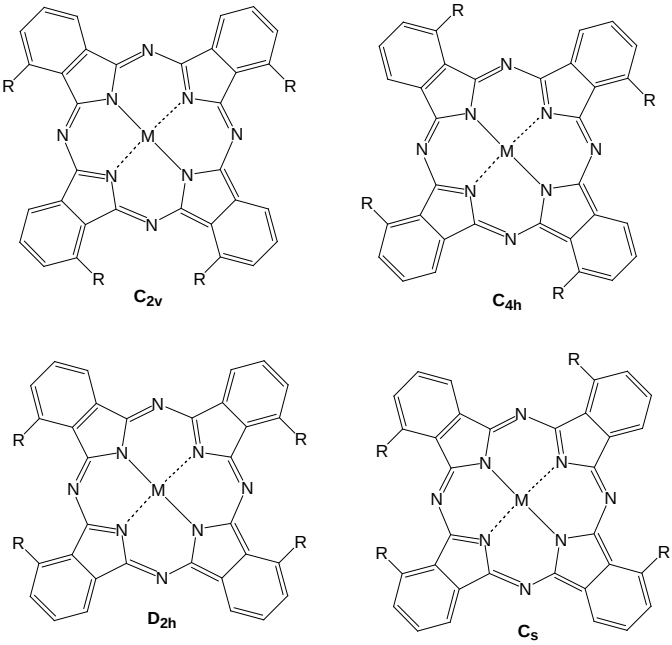


Figure 7: Constitutional isomers of tetrasubstituted metal phthalocyanines.

Complete separation of a 1,4-tetrasubstituted Pc- the 1,4-tetrakis(2-ethylhexyloxy)phthalocyaninatonickel(II) [1,4-(2-Et-$C_6H_{12}O$)PcNi], was first achieved by Hanack and coworkers using high performance liquid chromatography (HPLC).[18] The four isomers were also isolated in a preparative scale with medium pressure liquid chromatography (MPLC). The four isomers of 2,3-tetra-*tert*-butylphthalocyaninatonickel [2,3-(*t*-Bu)$_4$PcNi] were separated with MPLC on a silica gel column with toluene and n-hexane.[19] Attempts failed to separate 2,3-tetrasubstituted alkoxyphthalocyanine with nickel or hydrogen as the central atoms, on silica gel or using nitrophenyl phase. Using newly developed nitrophenylquinoline phase 1,4-tetrasubstituted Pc's can be completely separated.[20] From all 2,3-substituted alkoxyphthalocyanines with more than 6 C-atoms in the side chains or ring systems of the periphery the C_{4h}- and D_{2h}-isomers can be easily separated.[20]

For the synthesis of naphthalocyanines, naphthalonitriles are the most commonly used precursors, due to their reactivity, ease of synthesis and possibility of numerous substituents at different positions of naphthalene ring. Likewise already formed naphthalocyanines may also be modified by the reactions of reactive substituents on the naphthalocyanine ring with other functional groups to form a diverse range of new naphthalocyanines.[21]

1.4 Absorption spectra of phthalocyanines

Purity and intensity of phthalocyanine's color arises from an isolated and intense band (Q-band) at the red end of the visible spectrum of light, between 650 and 720 nm approximately. A second band (B-band) appears between 300 and 400 nm, being generally less intense (figure 8). In the spectra of metal phthalocyanine solutions, the intense Q-band arises from doubly degenerate π-π* transition between the A_{1g} (a^2_{1u}) ground state to the first excited singlet state, which has E_u ($a^1_{1u}e^1_g$) symmetry. The second allowed π-π* transition (B-band) is caused by a transition between either an a_{2u} or a b_{2u} orbital to the e_g orbital (LUMO).[22]

In the case of metal free phthalocyanines all states are non-degerated, due to the reduced D_{2h} molecular symmetry. The Q-band is polarized in either the x or y direction and is therefore splitted in two bands. [23]

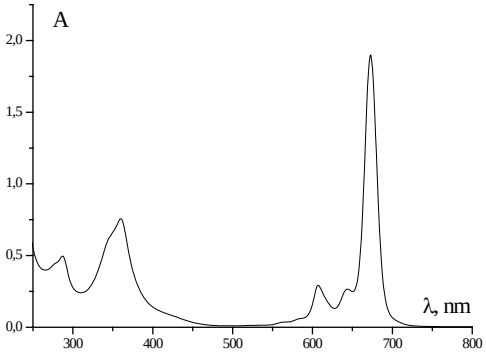


Figure 8: UV/vis spectrum of a typical phthalocyanine.

Additional bands, which appear in the spectra of certain molecules can be assigned to metal-ligand or ligand-metal charge transfer or even to exciton coupling between the π-systems of dimeric complexes.[11]

1.5 Solubility of phthalocyanines

The solubility of phthalocyanines in common organic solvents can be increased by introduction of bulky or long chain substituents in the periphery of macrocycle (peripheral substitution) and/or, in case of possibility, by coordination of the central metal with additional axial ligands (axial substitution).[24] Substituents enable phthalocyanine solvation because they increase the distance between the stacked molecules.[11,25] The peripherally substituted phthalocyanines studied in more detail are the tetra and octasubstituted ones.[25] Generally, the solubility of tetrasubstituted phthalocyanines is higher than the octasubstituted analogues, mainly due to the fact that the tetrasubstituted phthalocyanines are prepared as a mixture of isomers and therefore, leading to a lower degree of order in the solid state, when compared to the symmetrically octasubstituted phthalocyanines (figure 9).

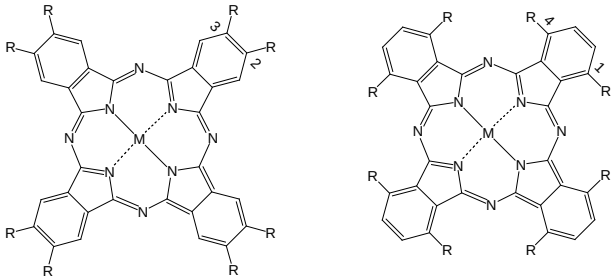


Figure 9: 1,4- and 2,3-octasubstituted phthalocyanines.

1.6 Applications of phthalocyanines

Phthalocyanines (Pc's) have traditionally found use as dyes and pigments, however, now have been employed in a variety of high-tech fields, including semiconductor devices[26], photovoltaic solar cells[27], electrophotography[28], rectifying devices[29], molecular electronics[30], Langmuir-Blodgett films[31], electrochromism in display devices[32], low-dimentional metals[33], gas sensors[34], liquid crystals[35], nonlinear optics[36], photodynamic reagents for cancer therapy and other medical applications[37]. A few of the important applications of Pc's will be discussed in detail.

1.6.1 Phthalocyanine pigments and dyes

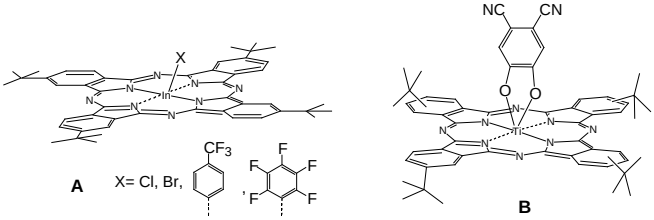
Pthalocyanines found their first application as pigments, with the industrial discovery of phthalocyanines at Scottish Dyes Ltd. (see page 1) in 1928.[38] Copper phthalocyanine was first manufactured by Imperial Chemical Industries (ICI) in 1935 under trade name *Monastral Blue*.[39] Later on in 1936, IG Farbenindutrie began production of PcCu in Germany under trade name *Heliogene Blue* followed by Du Pont in 1937 in the United States. Todays phthalocyanines are predominantly (ca. 90%) used as pigments. These pigments are almost copper phthalocyanines, including the chloro and bromo derivatives.[40] Modification of nearly insoluble phthalocyanines by introduction of various substitutions at peripheral positions of Pc ring has led to the solublization of these

pigments leading to their use as dyes. The first phthalocyanine dye was sulfonated phthalocyanine. Since 1930 many other derivatives such as sulfonamides, aminomethyl, sulfur and azo dyes, and vinylsulfone and triazine reactive dyes have been patented. The colors of these dyes range from brilliant blue through turquoise to green. Phthalocyanine dyes are therefore used as direct, solvent and reactive dyes in dyeing of textiles, paper and leather and for the manufacture of high quality ink.[40]

Recently Kodak has put new ink jet inks on the market in which the Aluminium phthalocyanine is employed as cyan colorant. This new cyan ink exhibits a very clean yellowish shade of blue.[41] Many phthalocyanines with different central metal atoms, which have been theoretically investigated, may become active members in this field of application in future.

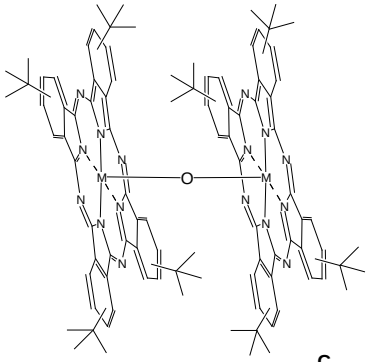
1.6.2 Phthalocyanines in nonlinear optics

Another important application of Pc's and Nc's is the use of these compounds as optical limiters. Optical limiters are devices designed to have high transmittance for low level inputs (such as in images) while blocking the transmittance for high intensity laser beams. Among the phthalocyanine based nonlinear absorbers that have been used as optical limiting (OL) materials and approach the necessary characteristics for a practical device are (*tert*-butyl)$_4$PcInX **(A)**[42] and (*tert*-butyl)$_4$PcTi[$O_2C_6H_2(CN)_2$] **(B)**[43].



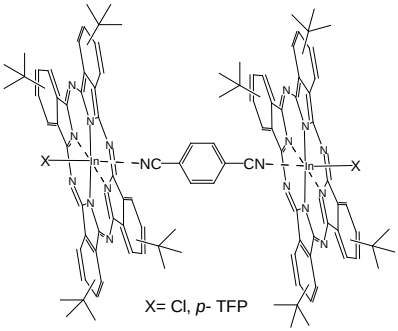
As far as dimeric Pc's are concerned, the non linear optical (NLO) properties of μ-oxo bridged Pc dimers with the general structure Pc(X)M-O-M(X)Pc [M = Fe, Ga and In **(C)**, diisocyanobenzene (dib) **(D)** and 2,3,5,6 tetrafluorophenylene (TFP) **(E)**, X= Cl and TFP][44], have been studied mostly by Hanack and coworkers. The

larger OL effect generated by the dimers PcInX-dib-XInPc as bridging ligand with respect to the bridged dimers PcIn-TFP-InPc.



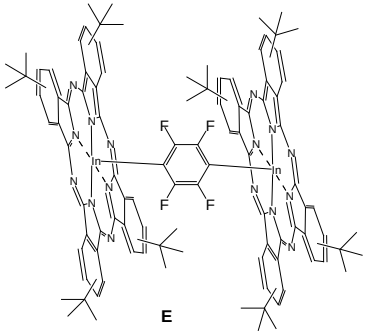
M = Fe, Ga, In

C



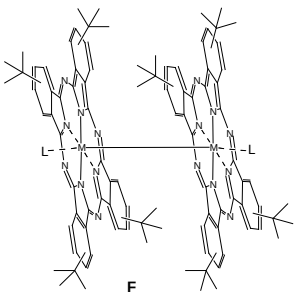
X= Cl, *p*- TFP

D

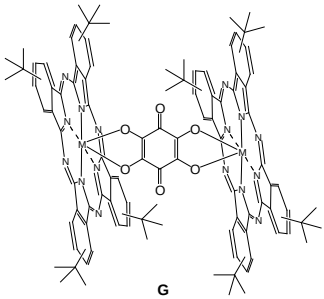


E

A newly synthesized dimer with a direct M-M bond [*t*-Bu_4PcM]$_2$ 2L, with M= In and L= tmed (tmed= N, N, N', N'-tetramethylethylenediamine) **(F)** display OL properties with improved features with respect to the single Pc ring coordinated by one single metal atom.[45] Similarly, the Pc dimer with central Ti atoms bridged by tetrahydroxy-*p*-benzoquinone **(G)** also displays an OL effect with improved characteristics if compared with the parent monomer.[46]



F

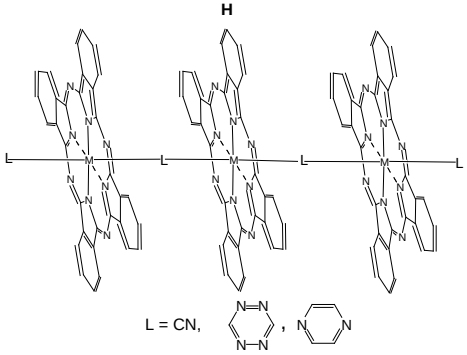


G

1.6.3 Phthalocyanine semiconducting properties

Hanack and his group has studied very much in detail the properties of phthalocyanines as semiconductors especially transition metal Pc's with compounds of polymeric structures.[47] Formula **H** shows a typical example for a Pc transition metal polymer in which L (ligand) is an organic molecule e.g. pyrazine (pyz), cyano (CN) or tetrazine (tz). Compounds of this type exhibit semiconducting properties with out external doping. [47]

H



It is evident from table 1[25] that the polymerization of Pc through cyano and tetrazine bridging is particularly effective for the rising of conductivity in neutral Pc's. The chemical nature of ligand L in stacked bridged polyphthalocyanines plays a significant role on the conductivity of the resulting bridged complexes $[PcM(L)]_n$[47]. This is especially true when tz is the bridging ligand and possess an

electronically conjugated path. The reason for that has to be ascribed to the energy difference between the lowest unoccupied molecular orbital (LUMO) of the bridging ligand acting as an acceptor and the highest occupied molecular orbital (HOMO) of the metal-macrocycle complex acting as a donor. [48]

Table 1: Conductivity values of undoped polymeric stacked phthalocyanines at room temperature.[25]

Compound	σ/S cm^{-1}
$[2,3NcFe(tz)]_n$	3.0 x 10^{-1}
$[2,3NcCo(CN)]_n$	1.0 x 10^{-1}
$[PcFe(tz)]_n$	2.0 x 10^{-2}
$[PcRu(tz)]_n$	2.0 x 10^{-2}
$[(CH_3)_8PcFe(tz)]_n$	1.0 x 10^{-2}
$[PcRu(tz)]_n$	1.0 x 10^{-2}
$[PcFe(CN)]_n$	6.0 x 10^{-3}
$[PcFe(pyz)]_n$	1.0 x 10^{-6}
$[PcRu(pyz)]_n$	1.0 x 10^{-7}

The conductivity of stacked polymeric phthalocyanines can be further improved through doping processes[49], which lead to the increase of the charge carrier number as a consequence of the partial oxidation or reduction of the molecular entities constituting the polymeric complex.

1.7 Naphthalocyanines

Naphthalocyanines are analogs of phthalocyanines. Two types of naphthalocyanines are known to date. If 2,3-dicyanonaphthalene or its derivatives are used as starting materials, they are named as 2,3-naphthalocyanines (2,3-Ncs) or simply Ncs. If 1,2-dicyanonaphthalene and its analogs are condensed, the resultant Ncs are termed as 1,2-Ncs (figure 10).

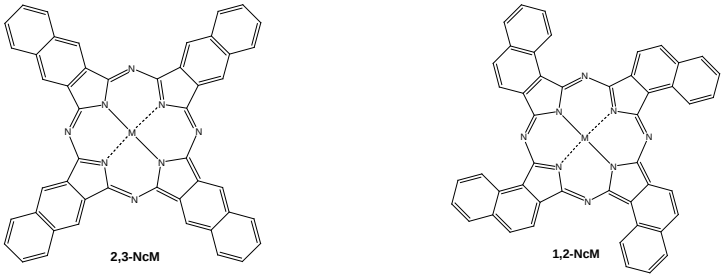


Figure 10: Types of metal naphthalocyanines (NcM's).

Concerning the π-systems, there is no isomer for 2,3-Nc, while there are four types of isomers (C_{4h}, C_s, D_{2h} and C_{2v}) in the case of 1,2-Ncs (figure 11). In 1936 Bradbrook and Linstead[50] first prepared 1,2-Ncs due to the inaccessibility of 2,3-dicyanonaphthalene. Because of the presence of several isomers of 1,2-Ncs, the solubility is higher than for the unsubstituted phthalocyanines.

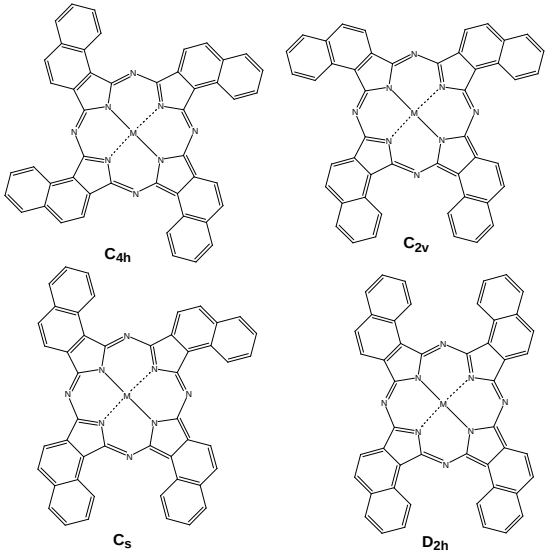


Figure 11: Constitutional isomers of 1,2-metal naphthalocyanines (1,2-NcM's).

In 1988, pentacarbonyliron was reacted with 1,2-dicyanonaphthalene in chloronaphthalene at 260 ^{o}C under nitrogen to produce black-green air stable

Fe(1,2-Nc) isomer.[51] When the mixture was left at room temperature or slightly warmed in chloroform, with isocyanides, it formed bis-isocyanide complexes.[52]

The most simpler nonmetalated 2,3-Nc, was obtained by boiling 2,3-dicyanonaphthalene and sodium isoamylate in amylalcohol, and subsequent replacement of two sodiums by two protons in 26% yield, and is insoluble in majority of solvents.[53] Mg and Fe (2,3-Ncs) were obtained by fusing the nitrile and the appropriate metal salt or metal dust with or without solvent. However when metal chlorides were used as templates with out any solvent, partial chlorination of Nc occurred.[53]

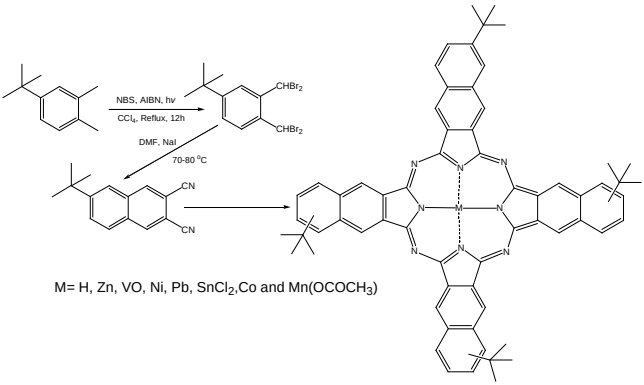


Figure 12: Synthesis of 6-*tert*-butyl-2,3-dicyanonaphthalene.

6-*tert*-butyl-2,3-dicyanonaphthalene was synthesized (figure 12) from 4-*tert*-butyl-*o*-xylene[54] via 1,2-*bis*(dibromomethyl)-4-*tert*-butylbenzene in usual manner. Because of the *tert*-butyl group, these compounds are soluble in many solvents, and accordingly could be purified using columns.[55]

1.8 Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a technique for the treatment of cancer cells. PDT uses drugs, called *photosensitizers*, visible light and oxygen. The photosensitizer is administered systemically in to the body or put on the skin in case of skin cancer. Over a certain interval of time the photosensitizer is preferentially absorbed by the cancer cells and reaches a favorable tumor/normal tissue ratio.

Red light (~640 nm) is applied to the area to be treated with fiber optics. The light activates the drug to react with oxygen, which forms reactive singlet oxygen species that kill the cancer cells (figure 13).[56]

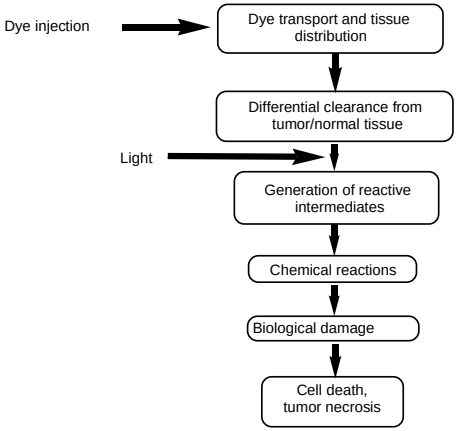


Figure 13: Schematic representation of photodynamic treatment.

The interval of time between the application of photosensitizer and its activation by the light is called drug-to-light interval. It may range from a couple of hours to a couple of days and depends on the drug used.[57]

1.8.1 History of PDT

In 1900, Oscar Raab discovered that a combination of light and acridine dyes could kill a living organism (Paramecium). This is commonly considered as the start of PDT.[58] The first clinical trial of photodynamic therapy on skin tumors was carried out by von Tappeiner and Jesionek in 1903. These two researchers introduced the term photodynamic action in 1907.[58] However studies of PDT were not very successful until the mid century because of the use of inefficient photosensitizers. In 1955 Samuel Schwartz isolated a tumor localizing byproduct, a hematoporphyrin derivative (HpD) from hematoporphyrin isolated from blood. This product was used by Richaard Lipson in detecting tumor tissues by observing

the fluorescence of the HpD. His experiments opened the possibility of using HpD as a photosensitizer to treat cancer.[59]

A major breakthrough was made in the 1970s by Thomas Dougherty, who showed that Schwartz's HpD could be used as a photosensitizer in PDT. HpD had some advantages over previously used compounds, e.g., a relatively high $^1O_2$ quantum yield, an absorption maximum in the red region and selectivity for tumor tissues. A purified product from HpD, Photofrin (figure 14), was produced in the mid 1970s.[58] In 1993, Photofrin was approved for the treatment of bladder cancer in Canada.[60] Now it has been approved in more than 40 countries for various cancers and nearly 10,000 patients in the United States, Canada, Japan and European Union have been treated using Photofrin.[58]

1.8.2 Second–Generation photosensitizers

Porfimer sodium (Photofrin, figure 14) was the first photosensitizer which was licensed to treat the oesophagus, lung, stomach, cervix and bladder carcinomas and is refered as first generation photosensitizer. It is only moderately active in tissue because the wavelength of light needed for activation (630 nm) penetrates tissue only slightly and the absorption band at this wavelength is weak.[61]

Considerable work has been carried out on second generation photosensitizers, and now three more drugs have been approved in various countries. Verteporfin (Visudyne, p. 19), and 5-aminolevolinic acid (**ALA**, Levulan, p. 18) were approved in 1999 whereas Foscan was approved in 2001.[62]

1.8.3 Pros and cons of PDT

PDT works well in treating various kinds of cancers and pre-cancers. It has certain advantages over the other therapeutic techniques, such as: It has no long-term side effects when used properly. It is less invasive than surgery. It can be targeted very precisely. It can be repeated many times at the same site if needed.

On the other hand PDT has some limitations e.g. it can only treat the body parts where light can reach, so it is mainly used to treat skin cancers and tumors

present in the lining of internal organs. It can not be used to treat the cancers which have been spread over many organs. PDT can not be used in people who have a blood disease called *acute intermittent porphyria* or people who are allergic to porphyrins.[63]

1.8.4 Approved drugs for PDT: *Porfimer sodium (Photofrin)*

Porfimer sodium is the most widely used and studied photosensitizer. It is activated by red light from a laser to treat patients with cancer of the esophagus. It is also used for Bowen's disease, basal cell carcinoma and some tumors of the vagina, vulva and cervix that can be reached by the activating light.[64]

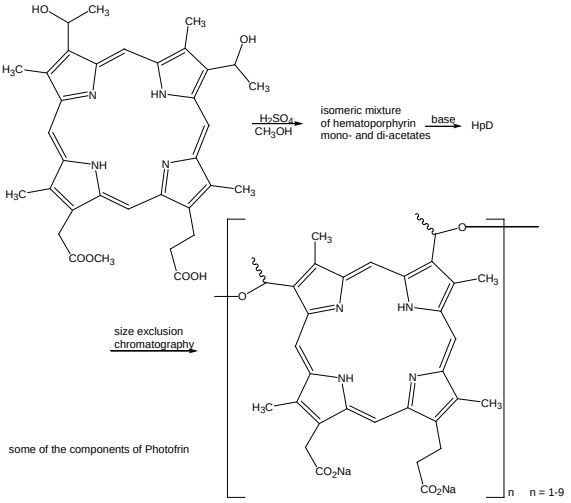
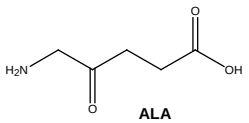


Figure 14: Synthesis of Photofrin.

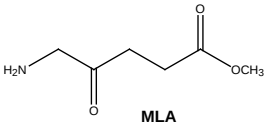
5-Aminolevulinic acid (ALA or Levulan)



ALA

5-Aminolevulinic acid (ALA) is applied directly on the skin. It is used to treat actinic keratosis, a skin condition that can become cancer, Bowen's disease, superficial basal cell and squamous cell carcinoma. It is approved for use only on the face or scalp. A special blue light, rather than laser light, is used to activate this drug.

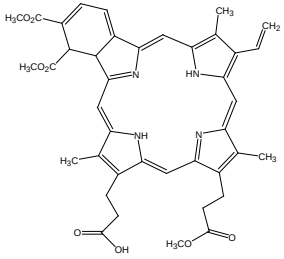
Methyl ester of 5-aminolevulinic acid (MLA) was approved by the FDA in July 2004 for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp.[65]



MLA

Verteporfin (Visudyne)

Verteporfin (VP) has been developed and used to treat age-related macular degeneration, a progressive eye problem that leads to blindness.[66]

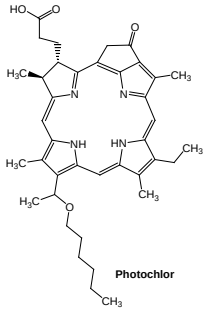


VP

1.8.5 The future of photodynamic therapy

Photodynamic therapy may be used to treat other cancers and diseases in the future. Current studies are testing the use of PDT for several types of cancer and pre-cancerous conditions, including cancers of the, skin, cervix, bladder, prostate, bile duct, pancreas, stomach, brain, head and neck.[59-62]

1.8.6 Desired properties of photosensitizers for PDT



Photochlor

Based on the extensive biological work done on photosensitizers, an ideal photosensitizer should posses the following properties: It should be chemically pure and maintain a constant composition during the treatment. Its photobleaching and dark toxicity should be minimal. It should have a high quantum yield of long lived triplet states and a strong absorption peak in the region of 600-800 nm.It should be able to treat tumors under the skin or in body tissues. Its tumor selectivity should be high. It should accumulate in the cancer cells more quickly and it should be removed from the body more quickly.[67]

A number of second generation photosensitizeers such as tetra(meta-hydroxyphenyl)chlorin, Photochlor and mono-L-aspartyl chlorin e_6, are currently being evaluated in PDT clinical trials.[68]

Photochlor is under clinical trials for the treatment of tumors of esophagus, lungs, skin, mouth and throat. So far, studies have shown that the photosensitivity lasts for much shorter time because the drug is removed from the body much faster than Photofrin.[69]

1.9 Phthalocyanines, cellular uptake and biodistribution

The interest for phthalocyanines in PDT dates back to 1985 following the demonstration that some Pc's can photosensitize inactivation of mammalian cells, by Ben-Hur and coworkers.[70] The ability of some Pc's to act as second generation photosensitizers is due to a long wavelength band with large extinction coefficient. Presence of diamagnetic metals e.g. Zn, Al, Ga etc. in Pc core enhance the photo activity due to long lived triplet state, leading to the generation of higher concentration of singlet oxygen ($^1O_2$), with quantum yield of 0.18-0.62.[71] Moreover Pc's show generally low dark toxicity and are easily obtainable in pure form.[56]

It is noted that the aggregation of phthalocyanine molecules in aqueous medium leads to decrease in excited singlet state by internal conversion. This results in the reduction of triplet quantum yield and consequent decrease in the photosensitizing efficiency.[56] To date mono-, di-, tri-, or tetra-sulfonated derivatives (Pc'S_n) of zinc and chloro aluminium phthalocyanines have been most commonly studied photosensitizers, but increasing attention is given to an axially substituted silicon phthalocyanine called as Pc 4 (p. 23).[72]

Intracellular localization of photosensitizer is affected by non lethal light doses. Thus $PcAlS_3$ and $PcAlS_4$ (where S = OSO_2H) localized initially in extracellular organelles of cells, were translocated from lysosomes to the whole cytoplasm with a small fraction localizing into the cell's nuclei, with irradiation of small doses of light. At low concentration of sensitizer no dye translocation occurred.[73] Similarly

in V79 cells, $PcAlS_2$ or $PcAlS_4$ initially stain the lysosomes but following the exposure to harmless doses of light a similar redistribution in the cells occurred.[74]

The association of photosensitizer with blood serum components is critical to the degree of uptake and cellular distribution. The effect of human serum on photodynamic activity of PcZn was observed on V79 Chinese Hamster cells. High density lipoproteins present in the serum increase the uptake of PcZn by 23%, when compared to the incubation of PcZn with the same cells in serum free medium, whereas low density lipoproteins and globulins decrease the dye uptake.[75]

Analysis of tumor growth indicates that malignancies have a high demand for cholesterol. Thus PcGe bearing two axially ligated cholesterol moieties, injected into mice bearing an intramuscularly implanted MS-2 fibrosarcoma, is quantitatively transferred and localized in the tumor tissue with good efficiency.[76]

Pharmacokinetic studies have pointed out that the hydrophobic Pc's become largely associated with serum lipoproteins and can be administered in association with liposome as delivery system. In liposomal formulation it is important that PcZn should be in monomeric and not in aggregated form.[77]

A different approach to tumor affinity is the covalent binding of the sensitizer to monoclonal antibodies directed against antigens present at the surface of malignant cells. This selective phototoxicity has been achieved *in vitro* by targeting $PcAlS_n$ with monoclonal antibodies directed against a human bladder carcinoma cell line [78]

The details of chemical structure 'in and around' the phthalocyanine macrocycle, are determinants of biodistribution. Thus differences in tissue localization were observed in a series of Pc's chelated with either Al or Zn and sulfonated to different degrees, as studied *in vivo* in rats. Al dyes showed highest fluorescence signal and seemed superior tumor localizers over Zn dyes. Increasing peripheral sulfonate groups favor tumor localization. Overall the ratios tumor/normal tissue distribution decrease in the following order: $PcAlS_4 \geq PcAlS_2 > PcZnS_4 > PcZnS_2 > PcAlS_1 > PcZnS_1$.[79]

In addition to the chemical structure of the sensitizer, the biodistribution and cellular uptake depends on the specifics of the biological tissue. The comparative

distribution of $PcAlS_4$ and $PcAlS_2$ administered in rat was higher in colon and colon wall structures, in murine fibrosarcoma, in bladder and bladder carcinoma. The duodenal concentration of $PcAlS_2$ was much higher than stomach and pancreas observed after 24 h administration in Chinese Hamster.[80]

1.10 Photodynamic activity

Once localized in the biological tissues and activated by light, the sensitizer initiates a cytotoxic chain of events whose details are not yet completely clear. The presence of molecular oxygen is determinant in photo toxicity of Pc's and the photosensitized oxidation is the accepted basis for photodynamic action.[81]

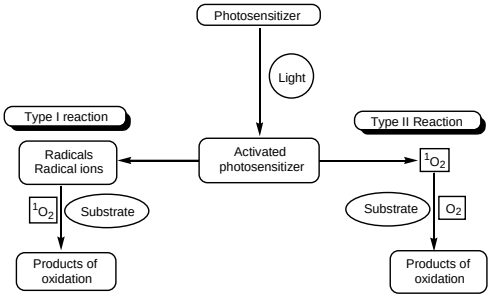


Figure 15: Type I and Type II reaction in photodynamic therapy.

It is widely accepted that the PDT process goes through two pathways. Both begin with the absorption of light. The light excites the photosensitizer from its ground state to its excited singlet state. The excited photosensitizer decays back to its ground state in many ways. If it decays directly to the ground state, the absorbed energy is released in the form of light resulting into fluorescence. Photosensitizer may undergo intersystem crossing (ISC) to its excited triplet state. Two types of reactions may occur when photosensitizer releases energy while going back from excited triplet state to the ground state. Type I reaction may occur, if excited photosednsitizer reacts with the oxygen in the cells to form hydroxyl ($^{\cdot}OH$) or superoxide ($^{\cdot}O_2^-$) radicals which damage or destroy the cells. Type II reaction occurs when it transfers its energy to nearby oxygen to produce singlet oxygen ($^1O_2$) which is the most toxic among the reactive oxygen species. Type I reactions

generally predominate at low oxygen concentrations and high photosensitizer concentrations, while Type II reactions predominate at high oxygen concentrations. Biological studies have shown that Type II reactions are dominant in normal PDT conditions.[81]

1.11 Phthalocyanines/naphthalocyanines and PDT

A silicon phthalocyanine, **Pc 4**, shown in figure 16 has attracted considerable interest as a PDT agent since it was reported for this use in 1993.[82] Biological studies have shown that **Pc 4** has good phototoxicity against V79 Chinese Hamster cells, MCF-7v cells and MCF-7c3 cells,[83] human erythrocyte ghosts and liver microsomes *in vitro* and mouse tumors *in vivo*[84]. This photosensitizer contains an aminosiloxy and a hydroxyl ligand on axial positions of the silicon central metal. It has strong absorption in red (~670 nm), minimum tendency to produce cutaneous photosensitivity after PDT treatment.[85]

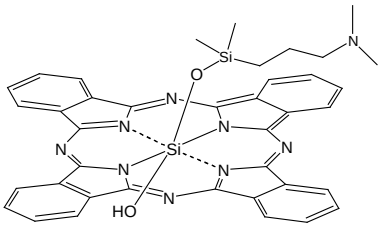


Figure 16: Structure of Pc 4.

In addition to porphyrins and Pc's also naphthalocyanines (Nc's) have been used as photosensitizers in PDT. Nc's are of particular interest due to their absorption maxima in the range of 750 to 800 nm, where light penetration through skin and tissues is approximately twice for that of Pc's at 630 nm.[86] This would allow treatment of larger and more deeply lying tumors.[87] Several peripherally substituted metal naphthalocyanines have been synthesized and studied for their use in PDT by various research groups.[88]

A silicon naphthalocyanine bearing two methoxyethylenglycol axial ligands (**NcSi1**) to the centrally coordinated metal ion (figure 17) was assayed for the phototherapeutic activity against Lewis lung carcinoma or B16 pigmented melanoma in mice. Photodynamic therapy after 24 h of **NcSi1** injection causes an efficient tumour response for Lewis lung carcinoma while the pigmented melanoma shows only a minor response regarding the rate of tumour growth. The

pharmacokinetic behavior and phototherapeutic effectiveness of bis(di-isobutyloctadecylsiloxy)silicon naphthalocyanine (**NcSi2**, figure 17) incorporated into liposome have been studied in Balb/c mice bearing an MS-2 fibrosarcoma, shows that it is a highly effective photosensitizer for PDT of tumors.[89]

Bis(*tert*-butyldimethylsiloxy, **NcSi3**), bis(dimethylhexylsiloxy, **NcSi4**), bis(tri-n-hexylsiloxy, **NcSi5**), and bis(dimethyloctadecylsioxy, **NcSi6**)silicon naphthalocyanines (figure 17) were prepared via substitution of the bis(hydroxy) precursor with the corresponding chlorosilane ligands. They were evaluated as potential photosensitizers for the photodynamic therapy (PDT) of cancer *in vitro* against V-79 cells and *in vivo* against the EMT-6 tumor in Balb/c mice. *In vitro* all four dyes showed limited phototoxicity combined with substantial dark toxicity. Surprisingly, *in vivo* all dyes induced tumor regression in at least 50% of mice whereas **NcSi4** gave a complete tumor response in 80% of mice without apparent systemic toxicity at doses as high as 10 pm/kg.[90]

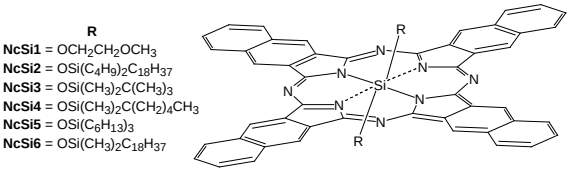


Figure 17: Bis axially substituted silicon naphthalocyanines.

Four zinc naphthalocyanines, unsubstituted (**NcZn1**), tetraacetylamido substituted (**NcZn2**) tetraamino substituted (**NcZn3**) and tetramethoxy substituted (**NcZn4**), as shown in figure 18, incorporated into liposome have been injected to male C57/Black mice bearing a transplanted Lewis lung carcinoma. The pharmacokinetic investigations show that three of the four NcZn's, are good tumor localizers in Lewis lung carcinoma except tetramino substituted **NcZn3**. The lowest tumor concentration as well as the lowest phototherapeutic effect was also established with tetraamino substituted **NcZn3**. PDT of rhabdomyosarcoma was

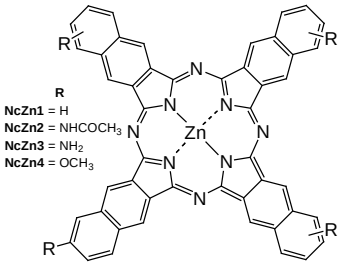


Figure 18: Tetrasubstituted zinc naphthalocyanines.

carried out using liposome-delivered NcZn's. The best effect was found after PDT with tetraacetylamido substituted **NcZn2** where 50% of the treated animals were cured.[91]

1.12 Glycosylation

The preparation of complex carbohydrates has emerged as a major focus in synthetic organic chemistry due to many important roles of this class of molecules in biology.[92] The most important reaction in the chemical synthesis of carbohydrates is the formation of glycosidic bond which is primary means of controlled assembly of comlex oligosaccharides and glycoconjugates from monosaccharide precursors. A general description of glycosidic bond formation is given in the figure 19.[93] The process starts with a carbohydrate coupling partner which is subjected to initial derivatization whereby the anomeric substituent is transformed into a good leaving group (LG). The resulting intermediate is isolated and anomeric leaving group is activated with an appropriate glycosylation promoter or catalyst. This process usually takes place in the presence of a nucleophilic glycosyl donor (aglycon), which undergoes displacement of leaving group to form the anomeric bond in the product glycoside.[93]

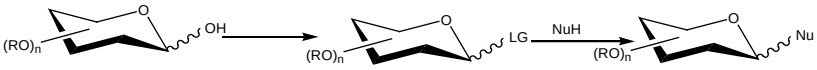


Figure 19: General description of glycosidic bond formation.

The first synthesis of glycosidic linkage was the coupling of peracetylated glucosyl chloride to potassium phenolate in ethanol, which was reported by Michael in 1879.[94] Since then, carbohydrate synthesis has evolved into a thriving field with an abundance of methods for the formation of the glycosidic linkage. The most common donors and their interconversions are summarized in figure 20.[95]

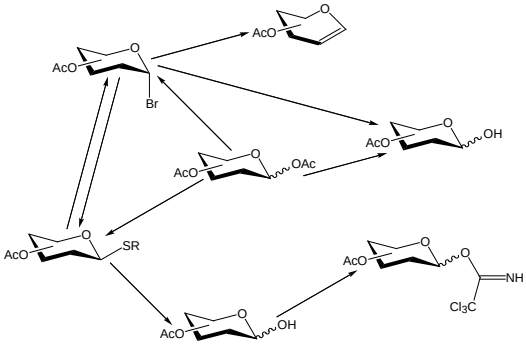


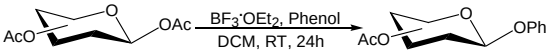
Figure 20: Examples of donor interconversions.

Glycosidic bonds can be formed either through an S_N2 type mechanism, usually under basic conditions with glycosyl halides, or through an S_N1 type mechanism under acidic conditions. The stereochemical outcome of Lewis acid-promoted glycosylations is influenced by several factors. The anomeric effect generally directs the aglycon to the thermodynamically preferred axial orientation. However, participating groups (e.g., esters) at C2 can interact with the intermediate oxacarbenium ion to form a cyclic dioxolenium ion. The dioxolenium ion is subsequently opened by the acceptor in an S_N2 manner, which results in a 1,2-trans-glycosidic bond.[96]

1.12.1 Use of glycosyl acetates

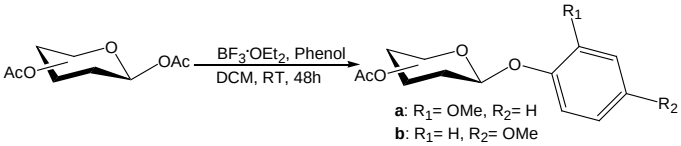
Glycosyl acetates can be activated by Lewis as well as Brønsted acids (Helferich conditions) and used as donors in aromatic O-glycosylations (scheme 1). The strength of glycosyl acetates as donors in glycoside synthesis lies in their simplicity, i.e. the peracetylated compounds are inexpensive and either commercially available or easily synthesized in one step from the corresponding free sugars. The yields of aromatic O-glycosylation using anomeric acetates are usually lower compared to trichloroacetimidates. One reason is the anomerization of both the starting material and the product. For example, in a few hours using 3 equiv of $BF_3{\cdot}Et_2O$ peracetylated β-glucose pentaacetate anomerized to α-glucose pentaacetate, which was shown to be inert.[97]

Typical aromatic β-glycosylations are performed in dichloromethane as solvent with equimolar amounts of $BF_3{\cdot}Et_2O$ and reactants for 1–24 h at room temperature (scheme 1). $SnCl_4$, *p*-toluenesulfonic acid and other Lewis acids have also been used, but most often with substantially lower yields.[98]



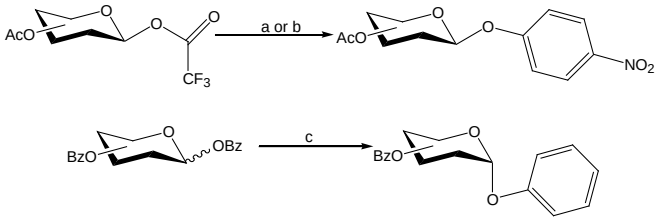
Scheme 1: General $BF_3{\cdot}Et_2O$ catalyzed aromatic O-glycosylation.

The yields and reaction rates are clearly dependent on the nucleophilicity of the phenol; electron donating groups (e.g., alkoxy) usually give better yields. Generally, substituents in the ortho-position tend to give lower yields irrespective of the electronic properties (scheme 2).[99]



Scheme 2: Examples of $BF_3{\cdot}Et_2O$ catalyzed aromatic O-glycosylation.

Anomeric trifluoroacetates have been used for the synthesis of a number of aromatic glycosides.[100] The trifluoroacetate was activated either by $BF_3{\cdot}Et_2O$ or trimethylsilyltriflate (TMSOTf) and gave good yields (85–90%) using activated aromatic aglycons. Deactivated aromatic acceptors gave lower yields using $BF_3{\cdot}Et_2O$, but the yields could be improved using TMSOTf (scheme 3). The drawback of this method is the multi-step synthesis of donor. Perbenzoylated glucose has also been used as donor and gave an excellent yield of α-glucoside upon prolonged reaction times (scheme 3).[101] There are also examples of the use of other anomeric benzoates.[102]



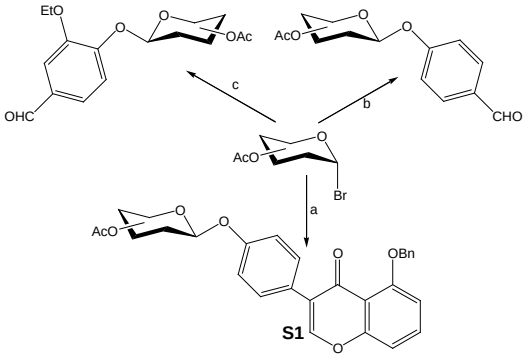
Scheme 3: Reagents and conditions: (a) *p*-nitrophenol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -20 °C, 50 min, 62% (b) *p*-nitrophenol, TMSOTf, CH_2Cl_2, 20 °C, 50 min, 80% (c) phenol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 50 °C, 48 h.

1.12.2 Use of glycosyl halides

Glycosyl halides are by far the most used carbohydrate donors for aromatic O-glycosylation. Of these, the vast majority are glycosyl bromides. Glycosyl bromides are generally more reactive compared to glycosyl chlorides, yet not as unstable as the corresponding iodides. There are very few examples of aromatic O-glycosylations using glycosyl iodides.[103]

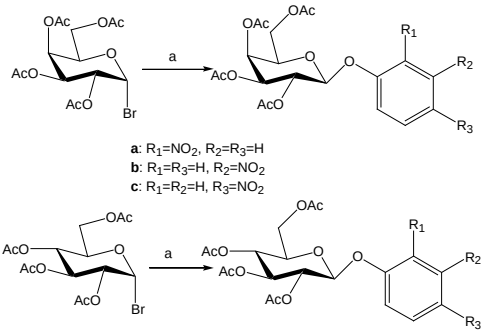
Generally, the glycosyl halides give less than 60% yield of the product but their strength lies in their simplicity and well-known procedures; they are especially useful for glycosylation under basic conditions. Glycosyl bromides are usually isolated as the thermodynamically favored α-anomer and glycosylation generally results in the inversion of stereochemistry.

In these reactions, the glycosyl bromide is dissolved in dichloromethane or chloroform and a water/methanol solution of the base (NaOH, K_2CO_3 or LiOH) is added together with a suitable phase transfer catalyst (PTC) such as tetrabutylammonium salts or crown ethers. A few typical examples are shown in Scheme 4. The synthetically challenging compound **S1** was prepared using the corresponding protected glucosyl bromide under PTC conditions, which gave better results compared to both acetate and trichloroacetimidate donors.[104]



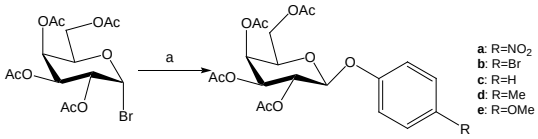
Scheme 4: Reagents and conditions: (a) appropriate phenol, K_2CO_3, $CHCl_3$, $BnEt_3NCl$, rt, 2 d (b) appropriate phenol, n-Bu_4NBr, $CHCl_3$, NaOH 60 °C, 6 h (c) appropriate phenol, n-Bu_4NBr, CH_2Cl_2, NaOH rt, 45 min.

An anionic exchange resin was used for the formation of nitrophenoxides and subsequent glycosylation, which provided the products in yields from 40% up to 98% as shown in scheme 5.[105] The use of DMF as a solvent resulted in increased formation of 2-substituted glycols, which are produced by elimination. Apparently, due to less β-elimination, galactose generally seems to give better yields compared to glucose as illustrated in schemes 5.[106]



Scheme 5: Reagents and conditions: (a) appropriate phenol bound to Amberlyst A-26, 2-propanol, rt, 8 h.

Another general observation is that aromatic residues with electron-withdrawing groups tend to give better yields, possibly due to easier deprotonation and subsequent phase transfer. A few examples are given in scheme 6.[107]

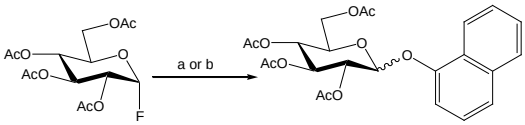


Scheme 6: Reagents and conditions: (a) appropriate phenol, NaOH, $CHCl_3$, $BnEt_3NBr$, 60 ^oC, 3 h.

PTC conditions have also been used in a solid phase approach.[108] Apart from Michael type reactions, glycosyl halides can be activated using the Koenigs–Knorr procedure, i.e., the use of silver salts (e.g., Ag_2CO_3,[109] AgOTf[104] or Ag_2O[110]) or mercury salts.[104] Typical solvents are CH_2Cl_2,[104] quinoline[110] and pyridine.[110]

Glycosyl fluorides are relatively stable (both α and β), which facilitates synthesis and purification but hampers their use as donors in glycosylation reactions. For aromatic O-glycosylations, the use of $BF_3{\cdot}Et_2O$ is most common and typical reaction conditions are given in scheme 7.

The addition of a hindered base (1,1,3,3 tetramethylguanidine) resulted in excellent β-selectivity,[111] and also lowered the amount of C-glycosides formed.[112] Another promoter system that gives good yield is $Cp_2HfCl_2/AgClO_4$.[113] Finally, glycosyl fluorides have been used in Michael type reactions using sodium phenolate in ethanol–CH_2Cl_2.[114]



Scheme 7: Reagents and conditions: (a) 1-naphthol, $BF_3{\cdot}Et_2O$, CH_3CN, rt, 3 h (b) 1-naphthol, $BF_3{\cdot}OEt_2$, 1,1,3,3-tetramethylguanidine, CH_3CN, rt, 3 h.

1.12.3 Use of glycosyl trichloroacetimidates

Anomerically pure trichloroacetimidates can be synthesized from the corresponding hemiacetal by treatment with trichloroacetonitrile in CH_2Cl_2 and a suitable base (K_2CO_3 for β-imidate, NaH for α imidate or DBU for an anomeric mixture).[104,115]

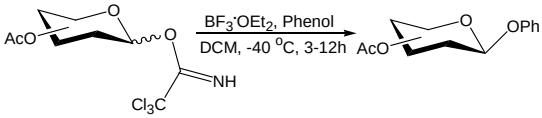


Figure 21: General trichloroacetimidate reaction.

Typical aromatic β-glycosylations using trichloroacetimidates are performed in CH_2Cl_2 as solvent, using a sub-stoichiometric amount of the promoter, usually $BF_3{\cdot}Et_2O$. There are also examples of reactions run in dichloroethane,[116] acetonitrile[117] or diethylether.[118] $BF_3{\cdot}Et_2O$ is the far most common promoter (>90%) but there are examples of other promoters such as TMSOTf,[117,119] AgOTf[120] and even $LiClO_4$ (which was used as a nearly neutral system).[117] Normal temperatures are between - 40 °C up to room temperature but there are examples of reactions run at -78 °C[121] and in CH_2Cl_2 at reflux.[122] Even if the reaction is likely complete in a few minutes, typical reaction times are 3-12 h. Some examples of compounds synthesized using the trichloroacetimidate methodology is shown in figure 22.[123] Among other imidates used for glycoside synthesis was an *N*-methylacetimidate[124] used for aromatic O-glycosylation. Another example is the use of an N-phenyltrifluoroacetimidate for the synthesis of flavonoid 7-*O*-glucosides.[125]

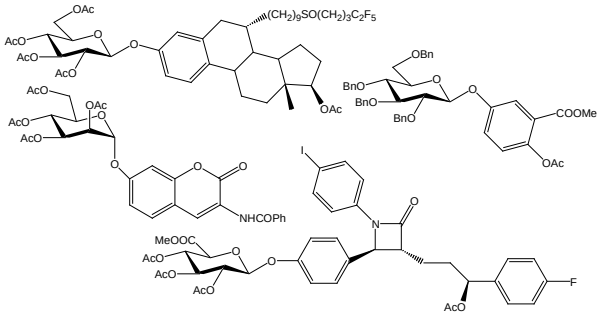


Figure 22: Examples of compounds synthesized using the trichloroacetimidate methodology.

1.12.4 Use of thioglycosides and related compounds

Thioglycosides are relatively stable carbohydrate derivatives that can be activated by thiophilic reagents, usually iodonium species generated from, for example, N-

iodosuccinimide and triflic acid (NIS/TfOH, figure 23). There are also anomeric sulfoxides as well as a few examples of glycosylselenides and -tellurides used for aromatic O-glycosylation. Generally, the thioglycosides give lower yields compared to other donors.

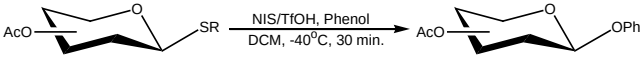
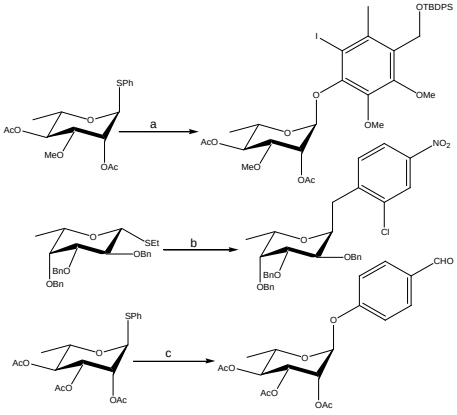


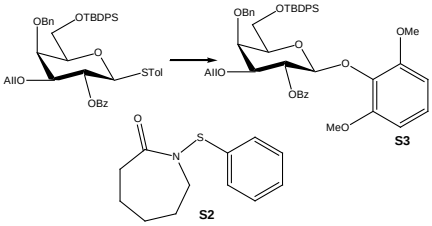
Figure 23: General thioglycoside reaction.

Despite the fact that thioglycosides are the most popular donors in carbohydrate synthesis (approx 50% of all donors used in carbohydrate synthesis in the year 2000 were thioglycosides),[126] they are not frequently used for aromatic O-glycosylation. The major reason is probably incompatibilities between the promoter systems used for thioglycoside activation and the aromatic residues. In particular, activated aromatic compounds are prone to react with iodonium ions, an observation that has been used for the synthesis of iodoarenes.[127] The aromatic residues that have been glycosylated using thioglycosides are usually relatively simple phenols and the yields are moderate to good. A few examples are given in scheme 8.



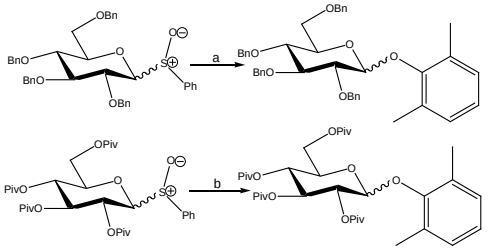
Scheme 8: Reagents and conditions: (a) appropriate phenol, NIS, TMSOTf, CH_2Cl_2, 4A° MS, 0 °C, 2 h (b) appropriate phenol, NIS, TMSOTf, CH_2Cl_2, - 42 °C, 30 min (c) appropriate phenol, NIS, TfOH, CH_2Cl_2.

The difficulties using thioglycosides for aromatic O-glycosylation stimulated the development of a new promoter system, that is, N-(phenylthio)-ε-caprolactam **S2**, which was used to synthesize compound **S3** in 85% yield (Scheme 9).[128]



Scheme 9: Appropriate phenol, 60, MS AW-300, Tf_2O, CH_2Cl_2, - 45 °C to rt, 1 h.

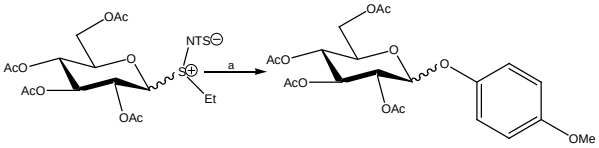
Glycosyl sulfoxides were introduced for glycosylation of unreactive substrates, such as phenols, in 1989.[129] Thioglycosides can easily be oxidized to sulfoxides, which can be used as donors by activation with triflic anhydride (Tf_2O). Interestingly, the α/β-ratios can be controlled by careful choice of protecting groups and solvent as shown in scheme 10.



Scheme 10: Reagents and conditions: (a) appropriate phenol, Tf_2O, 2,6-di-t-butyl-4-methylpyridine, toluene, - 78 °C (b) appropriate phenol, Tf_2O, 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2, - 78 °C.

Subsequently, the methodology was used for glycosylation of 2,6-dimethoxyphenol, activated as the tributyltin derivative, in an excellent 92% yield.[130] One problem associated with the use of Tf_2O for activation was interference with amides, but this could be suppressed by pretreatment with $BF_3 \cdot OEt_2$.[131] The analogous sulfimides, formed from the thioglycoside by reaction with chloramines T, can also be used for glycosylation, upon activation with

$Cu(OTf)_2/CuO$.[132] Sulfimides have been used for glycosylation of *p*-methoxyphenol in excellent yields (scheme 11).



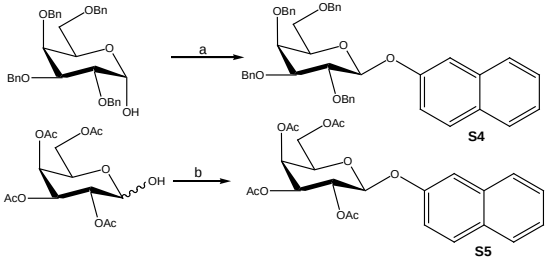
Scheme 11: Reagents and conditions: (a) *p*-methoxyphenol, $Cu(OTf)_2$, CuO, 4A˚ MS, CH_2Cl_2, rt, 2.5 h.

1.12.5 Other methods for aromatic O-glycosylation

Carbohydrate derivatives unsubstituted at the anomeric centre can be used directly, either by in situ activation or by using the carbohydrate as the nucleophile. Other possibilities are glycals and anomeric phosphates; Fischer glycosylation is usually not viable.

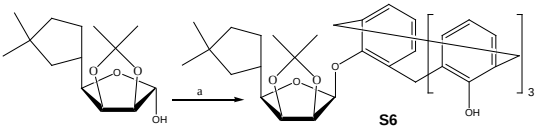
1.12.5.1 Mitsunobu reaction

Carbohydrate hemiacetals can be activated in situ by using Mitsunobu conditions. The sugar hemiacetal and a suitable phenol are stirred with triphenylphosphine and diethyl azadicarboxylate (DEAD) to give aromatic glycosides. Perbenzylated 2-naphthyl glucoside **S4**[133] and α-L-arabinopyranoside **S5**[134] were thus synthesized according to scheme 12.



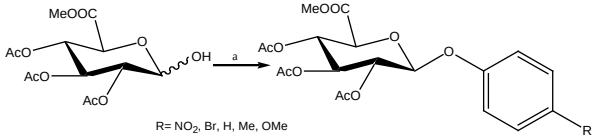
Scheme 12: Reagents and conditions: (a) 2-naphthol, PPh_3, DEAD, THF, 0 °C to rt, 12 h (b) 2-naphthol, PPh_3, DEAD, toluene, 0 °C, 2.75 h.

Mitsunobu conditions were also used for glycosylation of calixarenes in toluene.[135] The reaction of calix[4]-arene with 1.1 equivalent of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose using 1.5 equivalent of DEAD and PPh_3 in toluene gave monoglycosylated compound **S6** in 71% yield (scheme 13). Bisglycosylation using tetraacetyl α/β-D-glucopyranose (2.2 equiv) gave 50% yield of a mixture of the α, α - and α, β -diglucopyranosides.



Scheme 13. Reagents and conditions: (a) calix[4]arene, PPh_3, DEAD, toluene, 70 ^oC, 30 min.

Finally, Mitsunobu glycosylation was evaluated using several different phenols, where the acidity of the phenols was varied using electron donating or withdrawing substituents in the para-position (scheme 14).[136] The yields were clearly dependent on the acidity of the phenols, that is, the least acidic compounds gave low yields.



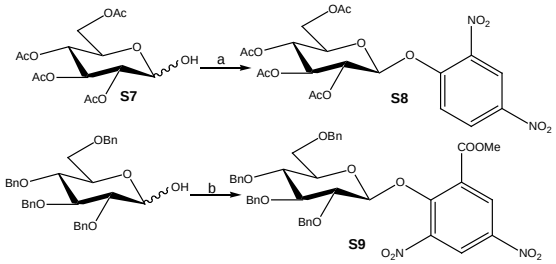
Scheme 14: Reagents and conditions: (a) appropriate phenol, PPh_3, DEAD, THF, rt, 24 h.

1.12.5.2 Nucleophilic aromatic substitution

Carbohydrate hemiacetals can also be used as the nucleophile in aromatic substitutions using activated fluoroarenes. Unprotected glucose and nine other unprotected mono and disaccharides were reacted with 1-fluoro-2,4-dinitrobenzene in saturated aqueous $NaHCO_3$ solution to give the corresponding β-glycosides in 15–30% yield.[137] The low yields can be explained by the formation of both α - and β -pyranosides as well as furanosides, but the simplicity makes the method valuable. Reaction with acetylated compound **S7**, using 1,4-

diazabicyclo- [2,2,2]octane (DABCO) as base, gave 80% yield of **S8** which could be converted to the α-anomer with K_2CO_3 in DMF.[138]

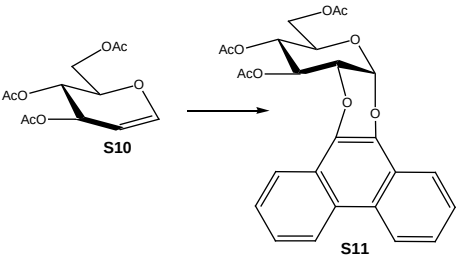
Glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate (DISAL, e.g., compound **S9**) are used for glycosylation under neutral or mildly basic conditions. These glycosides are synthesized from methyl 2-fluoro-3,5-dinitrobenzoate under basic conditions as exemplified by compound **S9** (scheme 15).[139] The anomeric ratio of the product was directed by the anomeric ratio of the starting material, that is, the pure α -hemiacetal gave an 8.4:1 α:β ratio.



Scheme 15: Reagents and conditions: (a) 1-fluoro-2,4-dinitrobenzene, DABCO, DMF, rt, 90 min (b) methyl 2-fluoro-3,5-dinitrobenzoate, Li_2CO_3, DMAP, CH_2Cl_2, rt, 0.5 h.

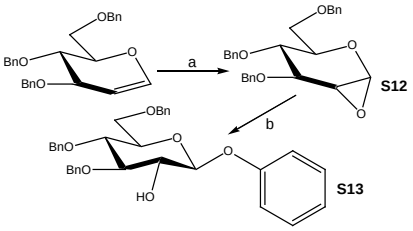
1.12.5.3 Use of glycals

An unusual aromatic O-glycosylation was performed by Helferich et al. where glucal **S10** was reacted with 9,10- phenanthrenequinone in a UV-promoted [4+2] cycloaddition to give compound **S11** in 50% yield (scheme 16).[140] **S11** was then subsequently opened by ozonolysis to remove the aromatic moiety.



Scheme 16: Reagents and conditions: (a) 9,10-phenanthrenequinone, hv, benzene.

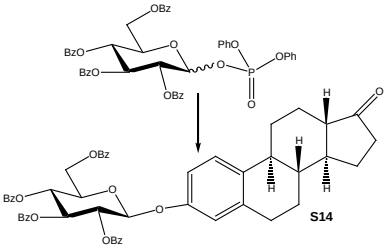
Glucals can also be oxidized to the corresponding α-1,2-anhydroglucoside by treatment with 3,3-dimethyldioxirane. The anhydrosugar can then react with nucleophiles such as phenols (scheme 17).[141] Danishefskyet al. noted that anhydroglucoside **S12** reacted slowly with phenol under Lewis acidic conditions ($ZnCl_2$) to give a 1.8:1 ratio of α- and β-phenylglucoside **S13**. However, reaction with potassium phenolate gave a clean conversion to the β -glucoside without any trace of the α-anomer.[141] Glycal derivatives with good leaving groups at the allylic position are readily converted into aryl 2,3-unsaturated aldosides by heating with phenols.[142]



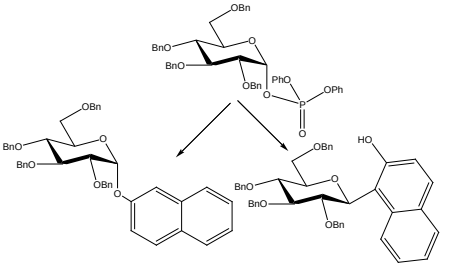
Scheme 17: Reagents and conditions: (a) 3,3-dimethyldioxirane, acetone, CH_2Cl_2, 0 ^oC, 10 min (b) phenol, K_2CO_3, 18-crown-6, acetone, reflux, 4 h.

1.12.5.4 Use of glycosyl phosphates

Anomeric phosphates were introduced as synthetic carbohydrate donors by Ikegami and co-workers,[143] and compound **S14** was synthesized in an excellent 92% yield (scheme 18). It was later shown that O-glycosides were formed in good yields (79%) in 15 min but then rearranged to C-glycosides on prolonged reaction times (3 h, scheme 19).[144] Anomeric dimethylphosphinothioates gave aromatic glycosides in moderate yields (79%, α:β 65:35 for *p*-methoxyphenol) upon activation by silver perchlorate.[145]



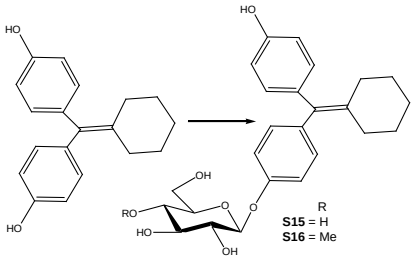
Scheme 18: Reagents and conditions: Phenol, TMSOTf, 1,1,3,3-tetramethylurea, CH_2Cl_2, rt, 1h.



Scheme 19: Reagents and conditions: 2-naphthol, TMSOTf, CH_2Cl_2, 0 ^{o}C.

1.12.5.5 Glycosylation by biotransformation

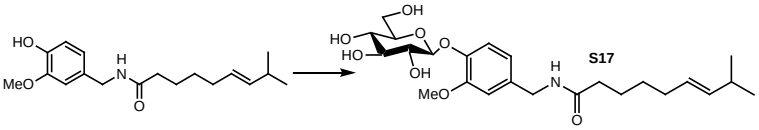
Despite the natural abundance of aromatic glycosides, there are few examples of biotransformations for glycosylation of phenolic compounds. Kieslich et al. published glucosylations of a number of aromatic compounds, exemplified by the reaction with *Sporotrichum sulfurescens*, which gave 4-O-methylated glucoside **S15**, and *Rhizopus colinii*, which gave **S16** (scheme 20).[146]



Scheme 20: Reagents and conditions: (a) *Sporotrichum sulfurescens*, 60 h (b) *Rhizopus colinii*, 90 h. The medium contained 3% glucose.

Recently, capsaicin was glucosylated to give compound **S17** in 50% yield by *Phytolacca americana* (scheme 21).[147] There are several examples of glycosylations using UDP activated glucose[148] or glucuronic acid.[149] A wide range of phenols were tested for UDP-glucose dependent glycosylation by *Rauvolfia* arbutin synthase and gave yields from 0.8% up to 100%.[148] Other sugars (e.g., L-noviose) can also be used by specific enzymes (e.g., L-noviosyl

transferase).[150] Recently, use of nucleotide diphosphosugars (NDP-sugars) was presented for glycorandomization using a large set of carbohydrates and four aromatic aglycons,[151] and a similar approach was used for randomization of vancomycin.[152]



Scheme 21: Reagents and conditions: (a) *Phytolacca americana*, 25 ^{o}C, 3 days. The medium contained 3% sucrose.

1.13 Glycosylated phthalonitriles and naphthalonitriles

Phthalocyanines can be synthesized from a variety of starting materials such as treatment of o-dibromoarenes and its derivatives with CuCN in boiling DMF furnishes CuPc, whereas phthalic acid, phthalic anhydride, phthalimide, phthalamide and cyanobenzamide and their derivatives can be converted to metal and metal free phthalocyanies using several possibilities (p. 3,4).[13-15,153] Each individual precursor however possesses certain limit of advantages and disadvantages associated with it. Among all the known phthalocyanine precursors phthalonitriles are the most widely used starting materials for the synthesis of metal as well as metal free Pc's. Owing to their high reactivity and possibility in the ease of modification and substitution on the aromatic ring which results into the formation of many derivative of phthalonitriles, these precursors furnish corresponding phthalocyanines in relatively high yield.[13]

Selective glycosidic bond formation in order to gain chemically well defined oligosaccharides and glycoconjugates is probably the most significant challenge of carbohydrate chemistry today. Although great achievements in the development of versatile and efficient glycosylation and building block strategies have been made during the last years, there is still need for more efficient procedures to prepare glycoconjugates.

Glycosylated phthalonitriles are not very common in literature. The first example of glycosylated phthalonitriles comes from Hanack-Ziegler and coworkers.[154] These

phthalonitriles (figure 24) were synthesized by nitrite substitution in 4-nitrophthalonitrile when it was reacted with anomerically deprotected glucose in DMF or DMSO, while NaH or K_2CO_3 was used as base. S_NAr displacement of nitro group in 4-nitrophthalonitrile proved to be an efficient method leading to monoglycosylated phthalonitrile product in high yield at ambient reaction conditions. The reaction was further studied with different glycons protected with benzyl (Bn), benzoyl (Bz) or acetyl (Ac) groups while anomeric carbon was attached with OH or SH groups as shown in figure 24.[155] All sugar substrates were successfully conjugated to form glycosylated phthalonitriles in good to excellent yields.

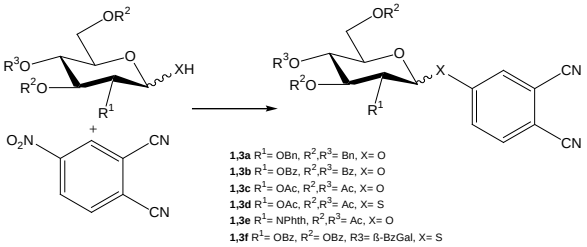
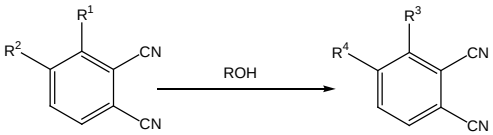


Figure 24: Synthesis of glycosylated phthalonitriles.

The above described method has been successfully used by other research groups to synthesize glycophthalonitriles by using 3- or 4-nitrophthalonitriles. Substitutions of nitrite in these phthalonitriles with a number of glycons containing OH groups at different positions of sugar moiety leads to satisfactory yields of corresponding substituted products. From experimental data it is known that the yields in case of reacting the same substrate with 3-nitrophthalonitrile is lesser than that of 4-nitrophthalonitrile. A number of glycosylated phthalonitriles synthesized so far have been shown in figure 25.[156]



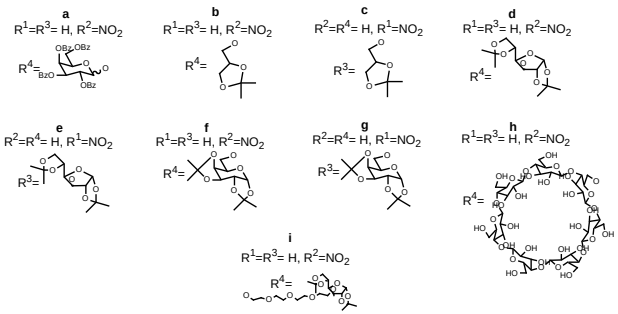


Figure 25: 3- or 4-glycosylated phthalonitriles synthesized from 3- or 4-nitrophthalonitrile.

In contrast to the monoglycosylated phthalonitriles, the diglycosylated phthalonitriles are not very common in literature. An example of 3,6-diglucosylated phthalonitrile linked through polyethylene glycol, has been synthesized by nucleophilic substitution of tosylated polyethyleneglycol substituted glucose with 3,6-dihydroxyphthalonitrile as shown in figure 26.[156]

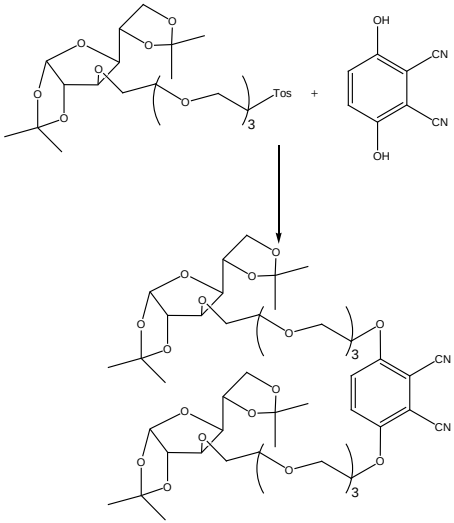


Figure 26: Synthesis of 3,6-diglycosylated phthalonitrile.

3,4,5,6-Tetrafluorophthalonitrile (figure 27), a commercially available reagent, has been used to synthesize a tetragalactose phthalonitrile which was subsequently

cyclized in mixed condensation with phthalonitrile to form an asymmetrical zinc (II) phthalocyanine.[157]

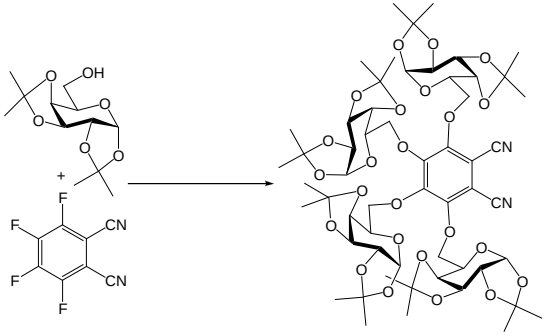


Figure 27: Synthesis of 3,4,5,6-tetragalactosephthalonitrile.

1.14 Glycosylated phthalocyanines, synthesis and photodynamic studies.

Pthalocyanines have emerged as a promising class of second generation photosensitizers for PDT, owing to their strong and long wavelength absorptions, high efficiency at generating reactive oxygen species (ROS) and ease of chemical modification.[158] Over the last decade, a substantial number of phthalocyanine based photosensitizers have been prepared and evaluated for their photodynamic activity, with the focus on silicon, zinc and aluminium analogues. To date, several phthalocyanine systems such as the silicon(IV) phthalocyanine PC4 (see p. 23) and a liposomal preparation of zinc(II) phthalocyanine have been in clinical trials. Photosense, which is a mixture of sulfonated aluminium(III) phthalocyanines, is clinically used in Russia for the treatment of a number of cancers.[158]

One of the major challengers in PDT is to develop selective photsensitizers which can preferentially accumulate in malignant tissues relative to normal tissues. Various approaches have been explored to enhance the photosensitizer concentrations in target tissues, which include encapsulation of sensitizer in colloidal carriers such as liposomes and polymeric micelles[159], and conjugation to tumor specific carrier molecules such as antibodies, synthetic peptides, epidermal growth factor and adenoviruses.[160]

Carbohydrates are also promising candidates for bioconjugation to photosensitizers to achieve targeted PDT. It has been known that cancer cells have increased level of glucose uptake and glycolysis in order to provide sufficient metabolic energy to sustain their proliferation.[161] By taking advantage of this, glycoconjugation of various sensitizers such as porphyrins,[162] chlorines,[163] pyropheophorbides[164] and hypocrillins[165] have been carried out with a view to enhance their PDT efficacy.

In contrast to carbohydrate-porphyrin conjugates, glycoconjugated phthalocyanines are extremely rare despite their great potential in PDT. First example of anomerically glucosylated zinc(II) phthalocyanine was synthesized in our group by cyclotetramerization of 4-(2,3,4,6-tetra-*o*-acetyl-α/β-D-glucose)phthalonitrile in boiling n-butanol/DMAE (2:1) containing zinc acetate and subsequent deacetylation of glucose moities under Zemplen's conditions.[154]

A series of tetraglycosylated zinc(II) phthalocyanines containing galactose, thioglucose, lactose, thiolactose and cellobiose as carbohydrate moieties, were further synthesized by using the same method.[166] Later on several other researchers synthesized a number of glycoconjugated silicon(IV)[167] and zinc(II)[156,157] phthalocyanines and studied their effectiveness in PDT.

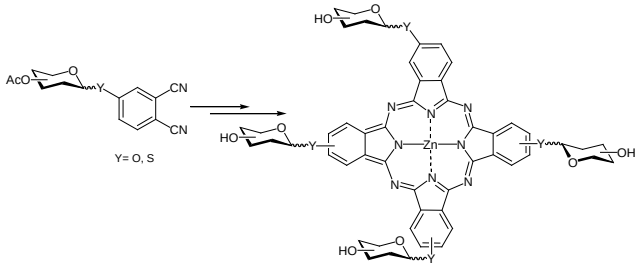


Figure 28: First example of glycosylated zinc(II) phthalocyanine.

Symmetrically as well as asymmetrically substituted zinc(II) phthalocyanines containing a variety of sugar moieties on the periphery of Pc ring have been prepared and a few of them have been examined for their *in vitro* phototoxicity using different cancer cell lines. A water soluble asymmetrical phthalocyanine starting from condensation of tetrakis(1,2:3,4-di-*O*-isopropylidene-α-D-

galactopyranos-6-yl)phthalonitrile with phthalonitrile in refluxing dimethylaminoethanol (DMAE) for 12h yielded 30% zinc(II) phthalocyanine followed by deprotection of isopropylidene groups with trifluoroacetic acid (TFA) in H_2O was synthesized and characterized (figure 29).[157]

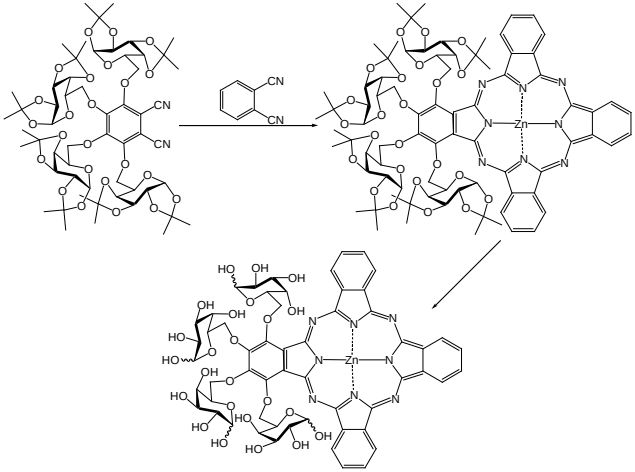


Figure 29: A water soluble asymmetrical zinc(II) phthalocyanine.

Similarly asymmetrical zinc(II) phthalocyanines-β-cyclodextrin dyads were prepared via a cross condensation of a 4-(β-cyclodextrin)phthalonitrile with phthalonitrile and 4,5-dibutoxyphthalonitrile as shown in figure 30.[156]

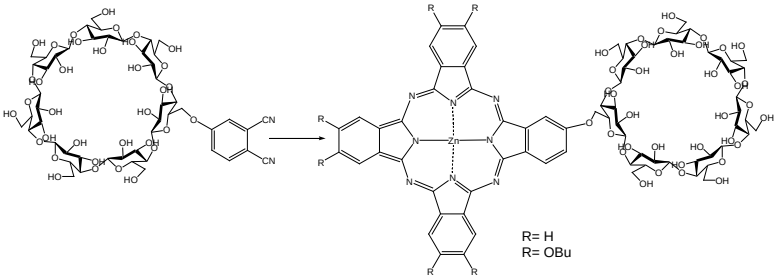


Figure 30: Asymmetrical zinc(II)phthalocyanines-β-cyclodextrin dyads.

A number of tetraglycosylated zinc(II) phthalocyanines substituted with glucose, galactose or glycerol subunits (figure 31) at peripheral positions of Pc ring have been synthesized by other authors and studied for their PDT applications.

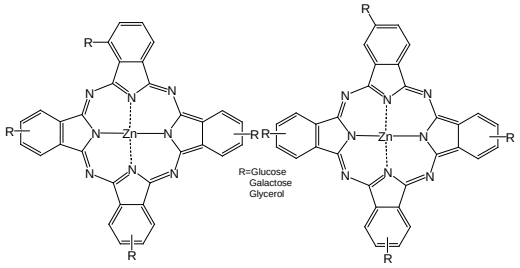


Figure 31: Tetraglycosylated zinc(II) phthalocyanines substituted at α or β position.

Photocytotoxicity of these PcZn's against HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cell lines revealed the effect of the position of substituents on the Pc ring. Monoglycosylated PcZn's substituted at either α- or β-position of Pc ring were found to be more cytotoxic in nature as compared to the tetra-α-glycosylated PcZn's. Whereas tetra-β-substituted analogues were found to be inactive, indicating their negligible cellular uptake due to high aggregation tendency of these Pcs in the cellular medium. Galactose substituted PcZn's were more effeicient in the generation of reactive oxygen species in comparison with tetraglucosylated zinc phthalocyanines.[156]

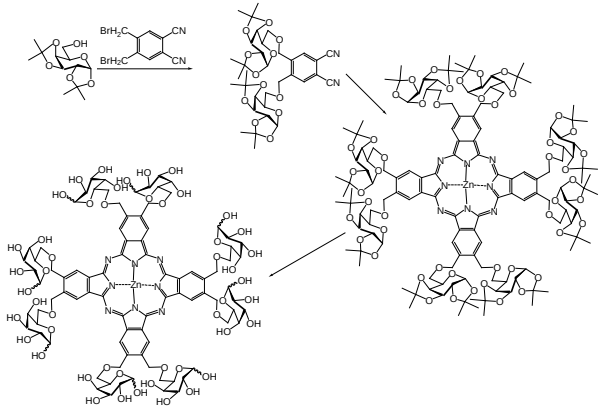


Figure 32: Synthesis of octasubstituted galactose zinc(II) phthalocyanine.

Comparison of aggregation behavior of tetra-α-glycerol zinc phthalocyanine with its β-analogue resulted in higher aggregation tendency of later in water rendering it

ineffective against HT29 human adenocarcinoma cells even at higher concentrations of 100 μM. Terta-α-glycerol substituted zinc phthalocyanine however was being less aggregated attained LD_{90} value of 35 μM.Only one example of octasubstituted galactose zinc(II) phthalocyanine has been found so far in literature, which is prepared according to the figure 32.[156]

Photodynamic activities of a series of silicon(IV) phthalocyanines with different axial substituents including the 1,3-bis(dimethlamino)-2-propoxy group, isopropylidene protected galactose (figure 33) and glucose and polyethylene glycol have been investigated against HT29 and T84 human colon adenocarcinoma cells. While these compounds are not cytotoxic in the absence of light, they exhibit high photocytotoxicities wit IC_{50} values as low as 17 nM. The most potent compound having a 1,3-bis(dimethylamino)-2-propoxy group and a methoxy (figure 33) as the axial substituents, has high and selective affinity to the mitochondria of HT29 cells, as revealed by fluorescence microscopy.[167]

Effect of peripheral chloro substitution on the photophysical properties of axially substituted glucose and galactose silicon(IV) phthalocyanines have been studied. The non, mono, and dichlorinated phthalocyanines (figure 33) formulated with Cremophor EL are all photodynamically active against HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cells with IC_{50} values ranging from 0.03 to 0.1.05 μM. The photocytotoxicity as well as the efficiency to generate interacellular reactive oxygen species decrease along this series because of the increase in aggregation tendency upon chloro substitution.[167]

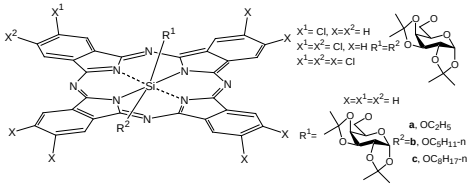
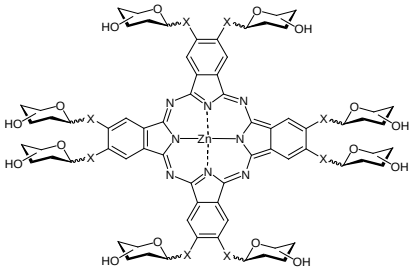
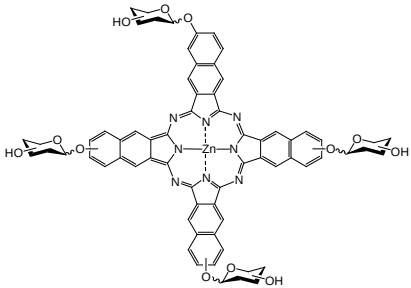


Figure 33: Silicon(IV) phthalocyanines with different axial substituents.

2 Aim of the work

Aim of the present work is to synthesize glycosylated zinc(II) phthalocyanines and naphthalocyanines for PDT investigations. Since there are several structural varieties which can be explored in case of sugar substituted phthalocyanines and naphthalocyanines, until a very effective structure could be found for PDT applications. Therefore we planned to go through the systematic study for the synthesis of sugar substituted PcZn's and NcZn's. To start with simple structures we initially planned to synthesize tetrasubstituted PcZn's in which sugar moieties such as glucose, galactose, maltose, thioglucose and thiogalactose, are attached at 1 position of the Pc macrocycle, in order to achieve the structural modification of already described tetraglycosylated PcZn's containing sugar susbtituents at 2 position of phthalocyanine ring. We further aimed to develop the methods for the synthesis of octaglycosylated zinc(II) phthalocyanines and tetraglucosylated zinc(II) naphthalocyanines targeted to the following structures.





In case of PcZn's several acetyl protected sugar moieties (X = O, S) e.g. glucose, galactose, lactose, cellobiose and maltose were chosen to synthesize corresponding acetyl protected octaglycosylated PcZn's. Deprotection of the acetyl groups in these Pc's should lead to water soluble systems.

An essential part was to find a new method to prepare substituted phthalonitriles which are the most important starting materials for the preparation of substituted Pc's.

3 Results and Discussion

3.1 A new method for the preparation of phthalonitriles

Phthalonitriles are the most important starting materials for preparation of metal-free and metal phthalocyanines.[11,12,25] A common pathway for the preparation of phthalonitriles proceeds by the cyano-dehalogenation process known as Rosenmund–von Braun reaction.[153] Starting from 1,2-dibromobenzenes and reacting them with cuprous cyanide, in refluxing DM .F, this reaction often proceeds unsatisfactorily concerning the yields. The harsh reaction conditions and subsequent oxidation of nitrile–cuprous halide, for example, with NH_4OH/air or O_2, $FeCl_3$ and HCl, prohibit the presence of many functional groups.[153,168] The use of cuprous cyanide also generally leads to the formation of the corresponding copper phthalocyanine as a byproduct.

Earlier, Hanack and coworkers proposed an easier method to prepare substituted phthalonitriles from substituted catechols via their corresponding aryl bistriflates. The displacement of the triflate groups in catechol triflates by cyanide ions proceeded in high yields using zinc cyanide and tris(dibenzylideneacetone)dipalladium $[Pd_2(dba)_3]$ and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) as catalyst.[169] The mild conditions tolerate numerous functional groups and represent an improvement to the Rosenmund–von Braun reaction for the synthesis of phthalonitriles.

Transition metal catalyzed cyanation of halobenzenes is an alternate to Rosenmund–von Braun reaction for the preparation of substituted benzonitriles. Most common catalysts for exchange of halobenzenes or triflates with cyanide are transition metal complexes of the platinum group, especially palladium or nickel complexes.[170] In general the cyanation of bromo- and iodobenzenes has been performed in the presence of an excess of cyanide sources like sodium, potassium, or zinc cyanide and potassium hexacyanoferrate(II) in dipolar aprotic solvents like DMF, DMAC, or NMP at 100-160 °C. Various sources for palladium such as $PdCl_2$, Pd/C, $Pd(OAc)_2$ and $Pd_2(dba)_3$ have been employed successfully to convert the halobenzenes into the corresponding benzonitriles.[171]

As an other alternative to Rosenmund–von Braun reaction and our earlier triflate method for the preparation of substituted phthalonitriles we now introduce palladium-catalyzed cyanation of mono- and disubstituted *o*-dibromobenzenes with $Pd_2(dba)_3$ and DPPF as the catalyst system (figure 34) in dimethylacetamide (DMAC) as solvent with $Zn(CN)_2$ as cyanating agent at a temperature of 100-120 °C (Table 1).

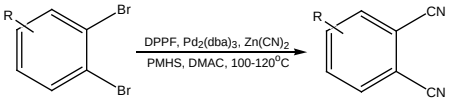
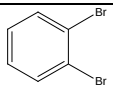
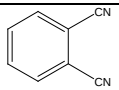
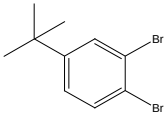
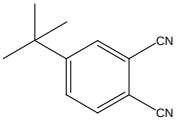
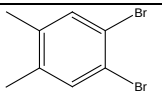
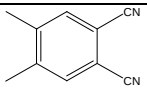
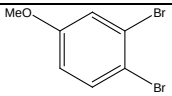
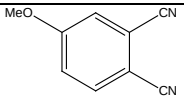
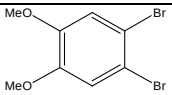
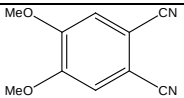
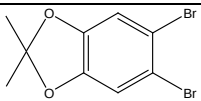
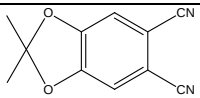
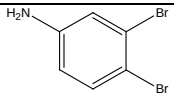
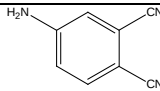
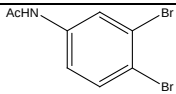
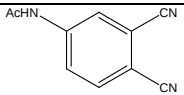
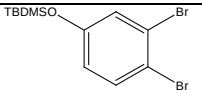
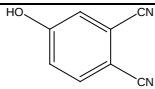
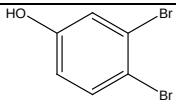
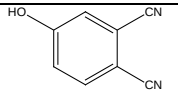


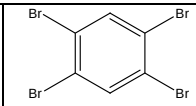
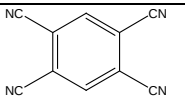
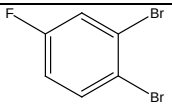
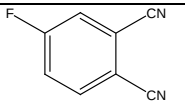
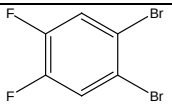
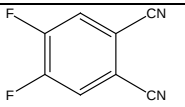
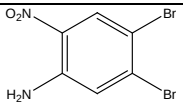
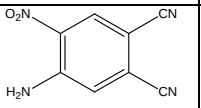
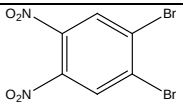
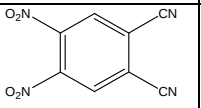
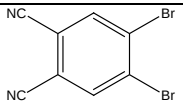
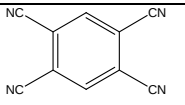
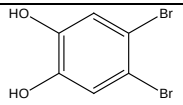
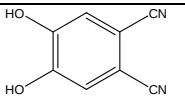
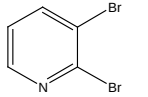
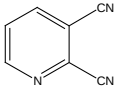
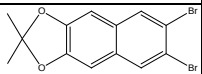
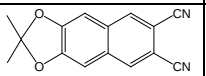
Figure 34: Synthesis of phthalonitriles using a palladium catalyst.

The reaction can be performed without an inert atmosphere, which is otherwise a necessary condition for other palladium-catalyzed reactions. The use of inert gas was avoided by using a small amount of polymethylhydrosiloxane (PMHS).[172] Moreover, we did not find any traces of corresponding phthalocyanine byproduct. The reaction also is easier to perform as our earlier described route via catecholtriflates. Tris(dibenzylideneacetone) dipalladium, DPPF and $Zn(CN)_2$ was used earlier with some iodo- and bromobenzenes as well as aryltriflates which react with formation of the corresponding benzonitriles.[173] To the best of our knowledge, however, this catalyst system has not been applied for the synthesis of phthalonitriles starting with *o*-dibromobenzenes.

The exchange of the bromo atoms in *o*-dibromobenzenes against CN groups depends upon the substituents in the *para* position of the bromo atoms in the benzene ring: *o*-dibromobenzene **(1a)** itself and the dibromobenzenes **2a**– **6a**[174] with electron-donating substituents in these positions in comparatively short reaction times are converted into the corresponding phthalonitriles **1b**–**6b** in yields between 80 and 96% (Table 2). This is also true for 3,4-dibromoaniline **(7a)** and 3,4-dibromoacetanilide **(8a)**. As expected, 3,4-dibromophenol **(10a)** is also easily converted into the corresponding phthalonitrile **9b**; the same applies to the protected *tert*-butyl(3,4-dibromophenoxy)dimethylsilane **(9a)** leading to 4-hydroxyphthalonitrile **(9b)**. The latter is probably formed after an initial deprotection of **9a** to form **10a**, which is subsequently converted into 4-hydroxyphthalonitrile **(9b)**.

Table 2: Palladium-catalyzed cyanation of various *o*-dibromobenzenes.

Substrate		Product		Temp (^{o}C)	Time (h)	Yield (%)
1a		**1b**		100	3	86
2a		**2b**		120	2	80
3a		**3b**		110	2	96
4a		**4b**		110	1.5	95
5a		**5b**		120	2.5	90
6a		**6b**		120	2	80
7a		**7b**		110	2	91
8a		**8b**		100	1.5	97
9a		**9b**		100	2	90
10a		**10b**		110	1.5	89

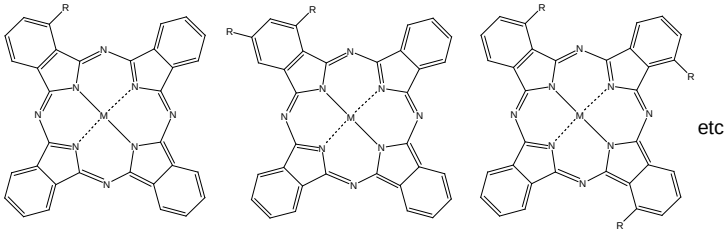
Substrate		Product		Temp (°C)	Time (h)	Yield (%)
11a		**11b**		100	8	72
12a		**12b**		100	2	87
13a		**13b**		100	3	92
14a		**14b**		120	6	62
15a		**15b**		100-120	3-5	-
16a		**16b**		100	4	73
17a		**17b**		100-120	3-5	-
18a		**18b**		100	4	78
19a		**19b**		110	1	93

Also bromine and fluorine in *para* position to the reacting bromide as in 1,2,4,5-tetrabromobenzene **(11a)**, 1,2-dibromo-4-fluorobenzene **(12a)**, and 1,2-dibromo-4,5-difluorobenzene **(13a)** allow an easy exchange of the bromine atoms against CN groups. Fluoro atoms are stable against an exchange reaction with the

catalyst system. The specific influence of the *para* substituents on the reactivity of the bromo atoms can be seen especially clearly with 4,5-dibromo-2-nitroaniline **(14a)**:[175] only the bromo atom in the *para* position to the electron-donating NH_2 group is exchanged against the CN group, the strong electron- attracting NO_2 group ($\sigma_{p\text{-}NO2}$ = 0.778) in *para* position to the second bromo atom prevents its exchange. This is supported by the results with 1,2-dibromo-4,5-dinitrobenzene **(15a)**[176] which does not react with formation of the corresponding dinitrophthalonitrile **15b**.

Contrary to 1,2-dibromo-4,5-dinitrobenzene **(15a)**, 4,5-dibromophthalonitrile **(16a)**[177] also with two but lesser electron-attracting CN groups ($\sigma_{p\text{-}CN}$ = 0.628) in *para* position to the bromine atoms reacts with formation of 1,2,4,5-tetracyanobenzene **(11b)** although in somewhat lower yields. In spite of the fact that 3,4-dibromophenol **(10a)** was converted in high yields into the 4-hydroxyphthalonitrile **(9b)**, 4,5-dibromocatechol **(17a)** even after a longer reaction time could not be reacted to form 4,5-dihydroxyphthalonitrile **(17b)**. This is probably due to a partial decomposition of the catalyst because of its reaction with catechol **17a**. 2,3-Dibromopyridine **(18a)** also reacts under the applied conditions with formation of 2,3-dicyanopyridine **(18b)** in good yield. Only one dibromonaphthalene was investigated: 6,7-dibromo-2,2-dimethylnaphtho[2,3-*d*][1,3]dioxole **(19a)** was converted in a yield of 93% into the corresponding naphthalonitrile **19b** within one hour at 110 °C.

A structural variety of metal phthalocyanines is essential for their applications in PDT. Tetra substituted sugar Pc's at positions 1(α) or 2(β) of Pc ring are possible. Similarly sugar moieties can be substituted at 1(α) and 1'(α') or 2(β) and 2'(β') positions of the Pc macrocycle to get the octasubstituted sugar phthalocyanines. Tetraglycosylated Pc's at positions 2(β) of phthalocyanine ring substituted with different sugar moieties have already been synthesized by Hanack-Ziegler and coworkers. Now we have planned to synthesize tetra- and octasubstituted sugar Pc's containing sugar moieties at positions 1(α) resulting in tetraglycosylated Pc's and 2(β) and 2'(β') for the formation of octaglycosylated phthalocyanines. Other structural modifications in sugar substituted Pc's are also possible e.g.



R = Sugar molecule

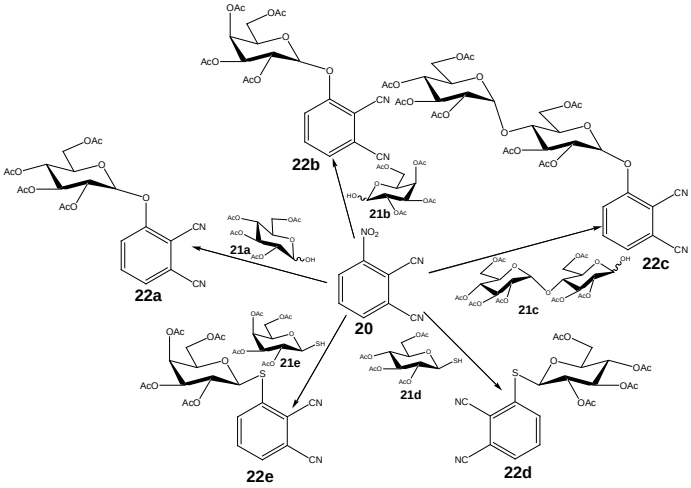
Concerning central metal atoms, Zn, Al and In etc. are important and have been investigated for their singlet oxygen generation abilities. To start with we have chosen Zn as metal ion because of its relatively low toxicity and known singlet oxygen generation efficiency. As sugar substituents glucose, galactose, maltose, cellobiose and lactose containing O or S atom at anomeric position have been selected.

3.2 Synthesis and characterization of 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines

3.2.1 Synthesis of tetraglycosylated phthalonitriles 22a-22e

The syntheses of the anomerically glycosylated phthalonitriles **22a-22e** (scheme 22) were carried out by our previously described method[155], through nitrite displacement in 3-nitrophthalonitrile **(20)** with anomerically deprotected glycoses

21a-21e. The phthalonitriles **22a-22e** with sugar substituents such as glucose **(22a)**, galactose **(22b)**, maltose **(22c)**, thioglucose **(22d)** and thiogalactose **(22e)**, were purified by column chromatography using toluene and acetone as eluent to furnish white solid in 77-97% yield. Characterization of the glycosylated phthalonitriles **22a-22e** was carried out with NMR, HRMS(FT-ICR) and elemental analysis.



Scheme 22: Synthesis of 3-glycosylated phthalonitriles. Reagents and conditions K_2CO_3, DMF, rt, 24h.

^{1}H NMR spectra of these compounds **22a-22e** show two distinct regions of signals associated with aromatic region of phthalonitriles as well as the signals originating from sugar substituents. A representative spectrum of phthalonitrile **22b** is shown in figure 35. Phthalonitriles **22a-22c** containing oxygen atom at anomeric position has been assigned α-configuration due to the doublets at 5.83 ppm (*J*= 3.8Hz) and 5.88 ppm (*J*= 3.8Hz) for **22a** and **22b** respectively, indicative of the presence of αH-1 and multiplet at 5.74-5.69 ppm assigned to αH-1 and αH-1' for compound **22c**. It is further confirmed by ^{13}C NMR spectra of compounds of **22a-22c**, which show signals at 96.6, 97.6 and 96.0 ppm respectively, assigned to αC-1 of the sugar moities of these phthalonitriles. However phthalonitriles **22d** and **22e,** like their respective sugar precursors **21d** and **21e**, are β-anomers which is obvious

from their ^{13}C NMR spectra containing signals at 84.8 and 85.7 which is typical signal for βC-1 of the sugar molecules.

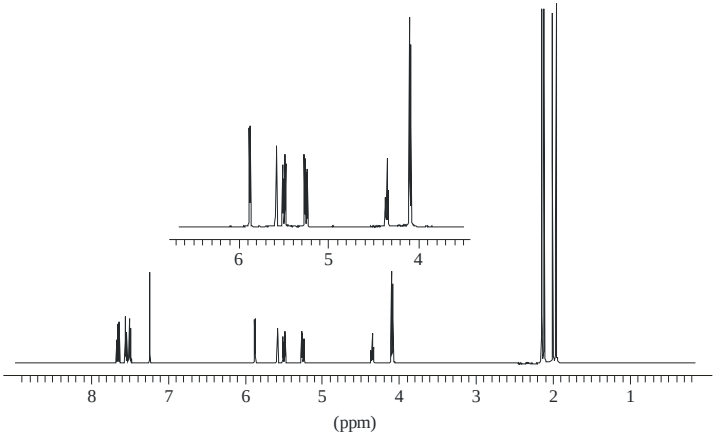


Figure 35: ^{1}H NMR spectrum of phthalonitrile **22b** measured in $CDCl_3$.

3.2.2 Synthesis of 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines (scheme 23)

Syntheses of PcZn's **23a-23e** turned out to be difficult. Many conventional methods were tried until we found a successful route for the syntheses of Pc's **23a-23e**. First of all phthalonitrile **22a** was subjected to acetyl deprotection in sugar part by Zemplen's method [178]. The deprotected phthalonitrile **22a** was now treated with $Zn(OAc)_2$ $2H_2O$ in DMAE at various temperatures ranging from 110-135 ^{o}C, which resulted only in tarry material from decomposition of the starting material. Changing solvent from DMAE to DMF did not improve the method.

Now instead of **22a**, the thioglucosylated phthalonitrile **22d** was used assuming a higher reactivity for tetramerization. Deprotection of the acetyl groups in **22d** under Zemplen's conditions [178] followed by evaporation of the solvent, the obtained compound was heated at 110 ^{o}C in DMF. After sometime the solution turned green, zinc acetate was added and the mixture was further heated at the same temperature for 12 h. The cooled solution was poured in small amount of water and recrystallized from excess acetone to afford PcZn **23d** in 27% yield. However

this method only worked for the phthalonitriles containing the thiosugars **22d** and **22e**.

Recently, hexamethyldisilazane (HMDS) is found to be an excellent reagent for use in the formation of PcM's from phthalonitriles or phthalimides.HMDS in combination with other promoters such as ammonium sulphate or *p*-toluenesulfonic acid activates the cyano group of phthalonitrile for intramolecular cyclization to give the diiminoisoindoline derivative. This activated HMDS also promotes further intermolecular reactions.[179] The possible mechanism is shown in figure 36.

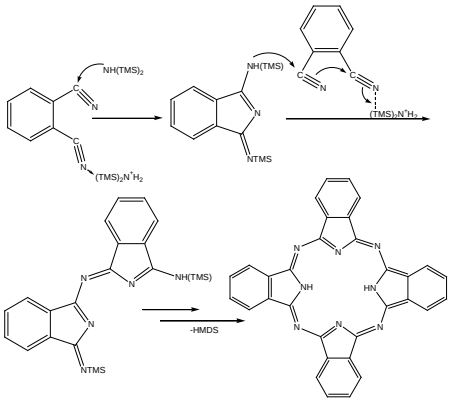
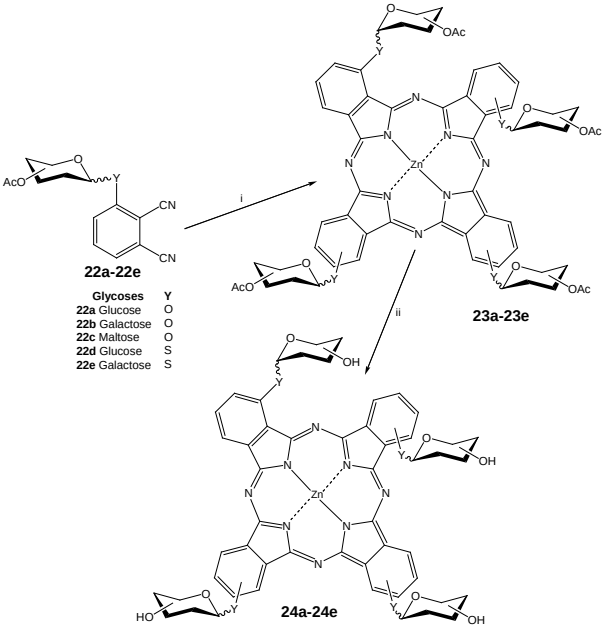


Figure 36: Mechanism for the formation of phthalocyanine catalyzed by HMDS.

In next attempt phthalonitrile **22a** was treated with HMDS, *p*-toluenesulfonic acid (*p*-TsOH) and $Zn(OAc)_2$ $2H_2O$ in DMF at 110-115 ^oC overnight, leading to the conversion of the phthalonitrile **22a** into the coresspoing PcZn **23a**, however the yield was low.



Scheme 23: Synthesis of 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines. Reagents and conditions: (i) TMSOTf, HMDS, DMF, $Zn(OAc)_2.2H_2O$, 115-120 ^oC, 15h (ii) MeOH, DMSO, NaOMe, rt, 15h.

In order to improve the yield *p*-TsOH was replaced by trimethylsilyltriflate (TMSOTf), which proved to be successful. Finally all the individual phthalonitriles **22a-22e** were heated with HMDS, TMSOTf, $Zn(OAc)_2$ $2H_2O$ and DMF sealed in a glass tube, at 115-120 ^oC to form the corresponding PcZn's **4a-4e** in good yield. Purification of the formed Pc's **23a-23e** was carried out by column chromatography to obtain the Pc's **23a-23e** which were further recrystallized from DCM and hexane.

Phthalocyanines **23a-23e** were characterized by UV/vis, NMR and MALDI-TOF data. UV/vis spectra of PcZn's **23a-23e** measured in dichloromethane, show intense Q-bands and B-bands which are typical for phthalocyanines. Q-bands of Pc's **23d** and **23e** are red shifted at 727 nm as compared to anomerically oxygen containing Pc's **23a-23c** showing Q-bands at 691, 689 and 693 nm respectively. ^1H NMR signals for compounds **23a-23e** although, are broad and not clearly

defined, however contain signals from sugar as well aromatic phthalocyanine ring, in the regions comparable to the parent phthalonitriles **22a-22e**.

Deprotection of acetyl groups in Pc's **23a-23e** was accomplished by catalytic amount of NaOMe in methanol/DMSO mixture at room temperature to form the PcZn's **24a-24e** in good yields. Pc's **24a-24e** were purified by repeated recrystallization from water and acetone and further purified by reverse phase HPLC. Pc's **24a-24e** are completely water soluble. For the characterization deprotected systems **24a-24e,** UV/vis, NMR and MALDI-TOF were used. Red shift of 10-15 nm was observed in Q-bands of unprotected Pc's **24a-24c**, at wavelengths 702, 704 and 703 respectively, as compared to the acetyl protected systems **23a-23c**. Whereas in case of sulfur containing phthalocyanines **24d** and **24e**, the Q-bands appeared at 710 and 712 nm respectively, showing a blue shift of ~15 nm compared to the coressponding acetyl protected PcZn's **23d** and **23e**. ^{1}H NMR spectrum of an unprotected PcZn **24b** is shown in figure 37. whereas a representative MALDI-TOF spectrum of compound **24d** is shown in figure 38.

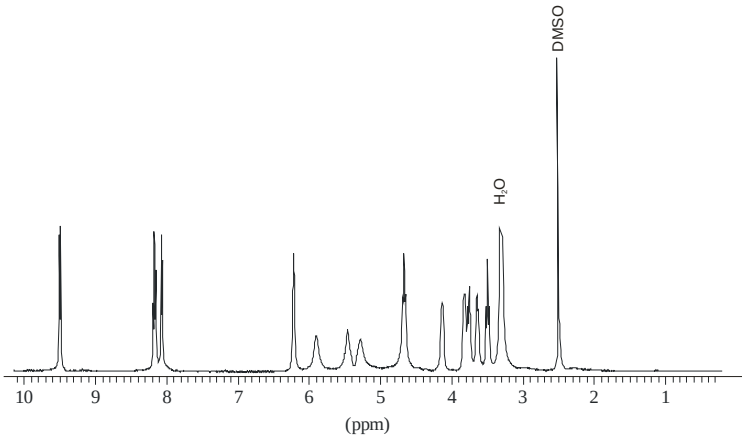


Figure 37: ^{1}H NMR spectrum of PcZn **24b**.

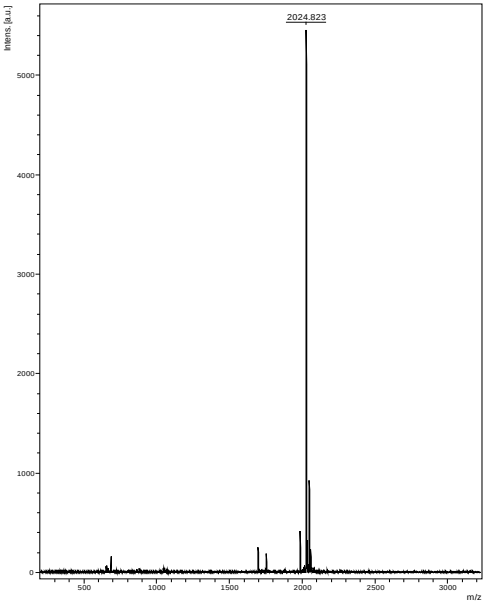


Figure 38: MALDI-TOF spectrum of compound **24d**.

3.3 Synthesis of 2,3,9,10,16,17,23,24-octaglycosylated phthalocyanines

Two types of octaglycosylated PcZn's have been synthesized and characterized.
1. Octagalactose PcZn in which the sugar part is attached to the Pc macrocycle through its position 6 (scheme 25, p. 63).
2. The octaglycosylated zinc(II) phthalocyanines in which different sugar substituents such as glucose, galactose, maltose, lactose and cellobiose are attached with Pc macrocycle through anomeric position (scheme 27, p.69).

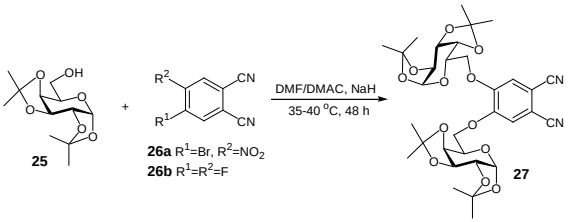
3.3.1 Synthesis of 2,3,9,10,16,17,23,24-octagalactose zinc(II) phthalocyanines

For the synthesis of 2,3,9,10,16,17,23,24-octagalactose zinc(II) phthalocyanines we chose 1,2:3,4-di-*O*-isopropylidene-α-D-glalactopyranose **(25)** which is easily available from galactose,[180] and which was planned to be attached to the

macrocycle via its position 6. In our earlier reported tetraglycosylated Pc's, the sugar moieties were anomerically attached to the Pc macrocycle (see p. 46). Here, however, we changed the attachment mode of the galactose residue from the anomeric position to position 6 because we anticipated that a better recognition by the cancer cells in PDT can be achieved this way.

3.3.1.1 Synthesis of 4,5-di(1,2:3,4-di-O-isopropylidene-α-D-glalactopyranosyl)-phthalonitrile (27)

As starting material for the synthesis of octaglactose PcZn, coressponding phthalonitrile i.e 4,5-di(1,2:3,4-di-*O*-isopropylidene-α-D-glalactopyranosyl)-phthalonitrile **(27)** was needed (scheme 24). Previously, glycosylated phthalonitriles were prepared from 4-nitrophthalonitrile by nucleophilic displacement of nitrite with a partially protected glycopyranose.[154,155] However, attempts to synthesize 4,5-dinitrophthalonitrile starting from 1,2-dibromo-4,5-dinitrobenzene under Rosenmund-von-Braun reaction conditions were unsuccessful. 4-Bromo-5-nitrophthalonitrile (**26a**) which was previously used for the preparation of 4,5-disubstituted phthalonitriles also could not be efficiently disubstituted with **25**.[181] Reaction of **25** with **26a** using K_2CO_3 or NaH in DMF predominately resulted in the substitution of bromo group. The disubstituted product **27** was only formed in a small amount (scheme 24). Therefore, diacetone galactose **25** was instead reacted with 4,5-difluorophthalonitrile **(2a)**.[182] Under optimized conditions (dimethyl acetamide or DMF, NaH, 35-40 °C, 48 h), the S_NAr reaction proceeded smoothly and gave the bis-galactosylated phthalonitrile **27** in a virtually quantitative yield.



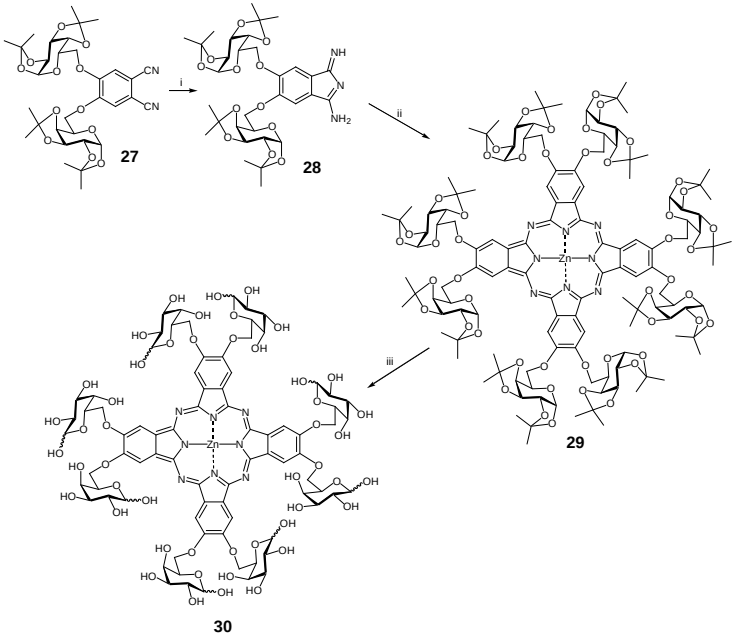
Scheme 24: Synthesis of 4,5-di(1,2:3,4-di-*O*-isopropylidene-α-D-glalactopyranosyl)-phthalonitrile **(27)**.

3.3.1.2 Synthesis of [2,3,9,10,16,17,23,24-octakis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-yl)phthalocyaninato]zinc(II) (29)

Next, attempts to cyclize compound **27** under various conditions which had been previously found suitable[154] failed. Heating **27** in various solvents in the presence of $Zn(OAc)_2$ or $ZnCl_2$ did not alter the starting material. Therefore, phthalonitrile **27** was first converted into the isoindoline **28** by bubbling gaseous NH_3 through a refluxing solution of **27** in THF/MeOH (1:1). Thus obtained crude isoindoline **28** (95%) was pure enough for the subsequent cyclization step. Refluxing a solution of **28** and $Zn(AcO)_2.2H_2O$ in DMAE for 24 h and purification of the obtained product by chromatography afforded Pc **29** in 29% yield as a green amorphous solid (Method A, experimental section). Alternatively, heating **28** and $Zn(AcO)_2.2H_2O$ without a solvent in a sealed glass tube for 15 h also yielded **29** in 30% yield (Method B, experimental section). Since compound **29** is sensitive to light, all experimental manipulations were performed in the dark. The NMR spectra of **29** showed only one doublet for H-1 of the 8 galactose moieties. This indicates that the galactoses in **28** are not sterically hindered and can freely rotate at room temperature.

3.3.1.3 Synthesis of [2,3,9,10,16,17,24,25-octakis(α/ß-D-galactopyranos-6-yl)phthalocyaninato]zinc(II) (30)

Deprotection of the 16 isopropylidene groups was achieved by treating **29** with aqueous trifluoroacetic acid (TFA). Final purification by reverse phase HPLC afforded the fully deprotected octasubstituted Pc **30** in 81% yield. The obtained Pc **30** is highly soluble in water, DMSO and DMF and is insoluble in common organic solvents such as DCM, ethyleacetate and acetone.



Scheme 25: Synthesis of octasubstituted galactose zinc(II) phthalocyanines, **29** and **30**. Reagents and conditions: (i) THF/MeOH, NH_3, $NaOCH_3$, 0°C-rt, 1h, reflux, 1h, 95% (ii) DMAE, $Zn(AcO)_2.2H_2O$, 24h, reflux, 29% (iii) TFA/H_2O, rt, 4h, 81% **30**.

PcZn **30** was characterized by NMR, UV/vis and MALDI-TOF spectroscopic data. ^{1}H NMR spectrum of compound **30** measured in DMSO is shown in figure 37. The spectrum shows a singlet at 8.99 ppm for aromatic Pc macrocycle while deprotection of all isopropylidene groups is evident from the absence of methyl signals at 2.00 ppm. Signals from galactose moieties are broad and can not be clearly defined. MALDI-TOF spectrum was in agreement with the structure of compound **30**.

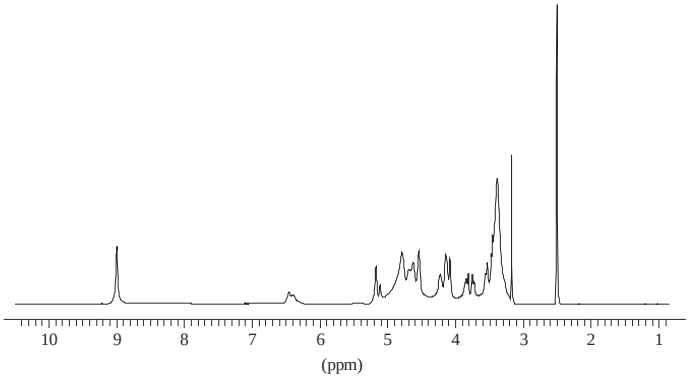


Figure 37: ^{1}H NMR spectrum of octasubstituted PcZn **30** measured in DMSO-d6.

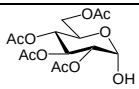
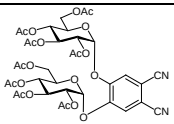
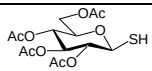
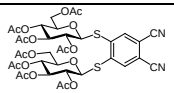
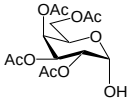
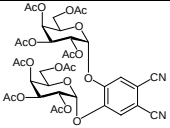
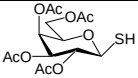
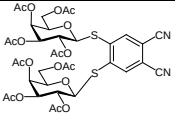
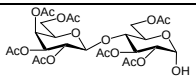
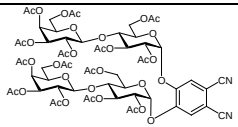
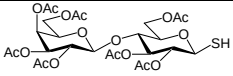
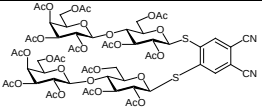
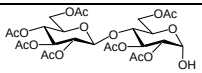
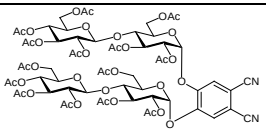
3.3.2 Syntheses of 4,5-diglycosylated phthalonitriles 32a-32i (table 3)

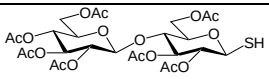
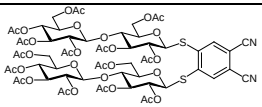
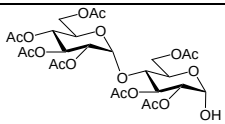
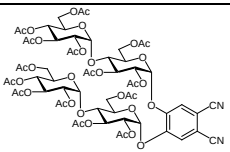
For the syntheses of the octaglycosylated phthalocyanines **33a–33i** and **34a–34i**, in which sugar molecules are anomerically attached with Pc macrocycle, we needed 4,5-diglycosylated phthalonitriles **32a-32i**.

As the first step for the synthesis of the 4,5-diglycosylated phthalonitriles, 4-bromo-5-nitrophthalonitrile **(26a)** was reacted with anomerically deprotected glucose **31a** (scheme 26). Mostly the monoglucosylated product was formed in poor yield, only traces of diglucosylated phthalonitrile **32a** could be found. In the monoglucosylated product only Br was replaced by the sugar molecule in **26a** while the NO_2 group remained intact. Therefore 4,5-difluorophthalonitrile **(26b)** instead was reacted with the sugar molecules, assuming that F would be easier to exchange by the nucleophilic anomeric OH of the sugar than Br or NO_2 respectively in the bromo-nitrophthalonitrile **26a**.

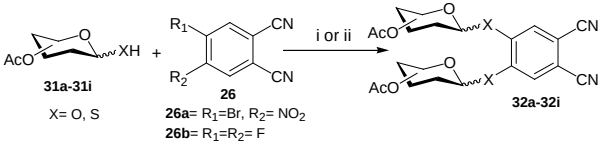
Reaction of 4,5-difluorophthalonitrile **(26b)** with anomerically deprotected glucose **31a** (see table 3) in dimethylacetamide (DMAC) with NaH at room temperature even after long reaction time lead to diglucosylated phthalonitrile **32a** only in poor yield. The major product again was the monoglucosylated phthalonitrile. The use of other solvents like DMF or DMSO did not improve the yield of **32a**. Increasing the temperature to 40 ^{o}C with DMAC as solvent decreased the reaction time but led to the same product ratio between mono- and diglucosylated phthalonitriles.

Table 3: 4,5-Diglycosylated phthalonitriles and corresponding zinc(II) phthalocyanines.

Sugar	4,5-Diglycosylated phthalonitrile	Yield (%)		
		32	**33**	**34**
 31a	 32a	64	75	94
 31b	 32b	65	-	19
 31c	 32c	72	70	91
 31d	 32d	80	70	89
 31e	 32e	56	62	93
 31f	 32f	55	70	87
 31g	 32g	74	55	90

Sugar	4,5-Diglycosylated phthalonitrile	Yield (%)		
		32	**33**	**34**
 31h	 32h	71	64	91
 31i	 32i	62	68	85

Finally in DMAC, K_2CO_3 was used as the base at 35-40 ^oC under which conditions the diglucosylated phthalonitrile **32a** was formed in good yield (table 3), exclusively as the α-linked product (figure 38) beside small amounts of the monoglucosylated phthalonitrile. Purification of **32a** was done by column chromatography (scheme 26).



Scheme 26: Synthesis of octaglycosylated zinc(II) phhthalocyanines. Reagents and conditions: (i) K_2CO_3, DMAC, 35-40 ^oC, 48h (ii) TBAH, DCM, rt, 48h.

For the reaction of 4,5-difluorophthalonitrile **(26b)** with anomerically deprotected thioglucose **31b** in presence of K_2CO_3 at 35-40 ^oC in DMAC the results were quite different. As the major product the monosubstituted phthalonitrile was formed. Replacing K_2CO_3 with NaH, using a variety of different solvents like DMF or DMSO also did not change the product composition. Only the use of tetrabutylammoniumhydroxide (TBAH) in dichloromethane at room temperature proved to be a successful route to obtain the diglucosylated phthalonitrile **32b** in good yield (table 3). **31b** was obtained as the β-anomer (figure 39).

After establishing the optimized reaction conditions also the sugar molecules **31c**, **31e**, **31g** and **31i** containing an anomerically deprotected OH group were reacted as described above with 4,5-difluorophthalonitril **(26b)** using K_2CO_3 as base at 35-40 ^oC in DMAC as solvent. The 4,5-diglycosylated phthalonitriles **32c**, **32e**, **32g** and **32i** respectively were obtained in moderate to good yields (table 1). The sugars **31d**, **31f**, and **31h** respectively containing SH groups were reacted with 4,5-difluorophthalonitrile **(26b)** under the described conditions for **32b** using tetrabutylammonium hydroxide in dichloromethane to give the 4,5-diglycosylated phthalonitriles **32d**, **32f**, and **32h** respectively (scheme 26). All phthalonitriles were purified by column chromatography.

The O-glycosides **32a**, **32c**, **32e**, **32g** and **32i** respectively were obtained as α-glycosides (figure 39) whereas the S-glycosides **32b**, **32d**, **32f** and **32h** were formed as β-anomers (figure 40). This was clearly evident from the NMR spectra of glycosides **32** which showed vicinal coupling constants $J_{1,2}$ of 3.3-3.8 Hz for the α-linked glycosides and 10.2 Hz for the β-linked compounds.

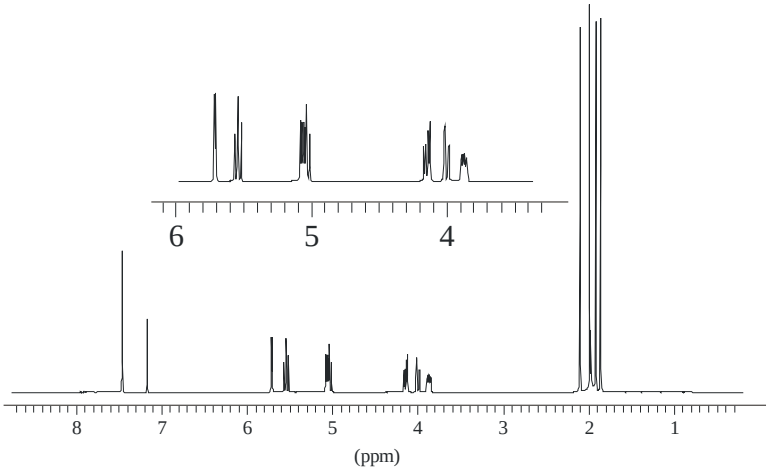


Figure 39: ^1H NMR spectrum of 4,5-diglycosylated phthalonitrile **32a**.

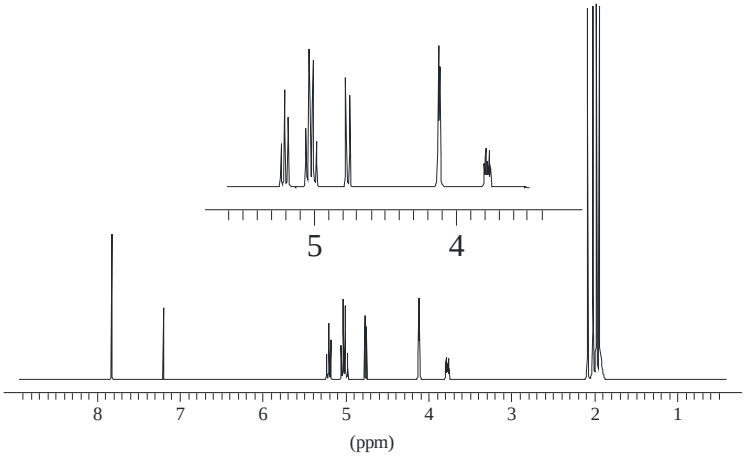
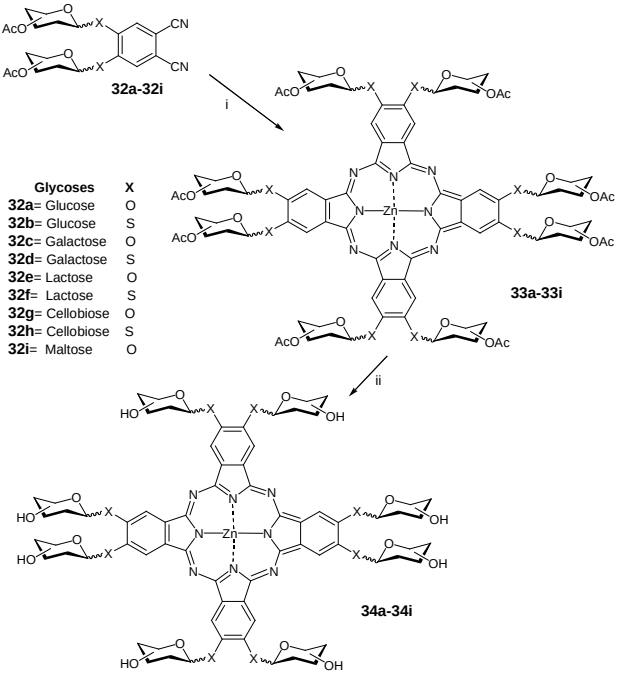


Figure 40: ^{1}H NMR spectrum of 4,5-diglycosylated phthalonitrile **32b**.

3.3.3 Syntheses of the protected octaglycosylated phthalocyanines 33a–33i and the deprotected octaglycosylated phthalocyanines 34a–34i

The syntheses of the octaglycosylated phthalocyanines **33a–33i** and **34a–34i** respectively turned out to be rather difficult; quite a few methods had to be applied before a successful route could be found.

First the protected 4,5-diglucosylated phthalonitrile **32a** was taken as starting material which was heated for 12h in a mixture of DMAE/n-butanol and $Zn(OAc)_2.2H_2O$. No indication for the formation of phthalocyanine was found only a black jelly tar was formed. In the next attempt phthalonitrile **32a** was deprotected with MeONa/MeOH using our previously described method[154] and then subjected to the same reaction condition as described before to convert it into the corresponding octaglucosylated zinc phthalocyanine **34a**. However also this reaction was unsuccessful, no phthalocyanine was formed.



Scheme 27: Synthesis of octaglycosylated zinc(II) phthalocyanines. Reagents and conditions: (i) *p*-TsOH, HMDS, DMF, $Zn(OAc)_2.2H_2O$, 125-130 ^oC, 15h (ii) MeONa, DMSO, rt, 15h.

To increase the reactivity of phthalonitrile **32a** it was converted first into its corresponding isoindoline in MeONa/MeOH while passing gaseous NH_3 through the solution. This process leads to deprotection of the acetyl groups in the sugar part of the phthalonitrile **32a**. The isoindoline was heated with $ZnCl_2$ or $Zn(OAc)_2.2H_2O$ in various solvents like DMAE, DMF, pentanol, butanol, hexanol as well as in mixtures of these solvents with DMAE. In all cases the isoindoline could not be converted into the zinc phthalocyanine **34a**.

Now instead of phthalonitrile **32a** phthalonitrile **32b** in which the glucose parts are connected via sulfur to the aromatic ring was taken considering its higher reactivity as compared with phthalonitrile **32a**. Also **32b** did not react with formation of the phthalocyanine **33b** using similar reaction conditions as described above in a variety of experiments. It forms phthalocyanine **34b** in 19% yield when **32b** was

refluxed in MeOH/THF (1:1) containing traces of conc. HCl while Zn dust was used as metal source. Advantage of this method was that it led to deprotection of the acetyl groups in sugar in one step reaction however the yield obtained was poor. When this method was applied on phthalonitrile **32a**, it failed to indicate any formation of phthalocyanine **34a**.

Finally the following route for the syntheses of the phthalocyanines was successful using phthalonitrile **32a** for the first trial: **32a** was heated in DMF with 30 mol% hexamethyldisilazane (HMDS)[179], *p*-toluenesulfonic acid and $Zn(OAc)_2.2H_2O$ at 125-130 °C overnight (p. 57). Using this procedure the protected octaglucosylated phthalocyanine **33a** was formed in 75 % yield. As shown by MALDI-TOF the acetyl groups were not affected. The octaglycosylated phthalocyanines **33c-33i** were obtained in yields between 55 and 78% (table 1). The phthalocyanines were purified by column chromatography.

For deprotection of the acetyl groups phthalocyanine **33a** was treated with MeONa in methanol at room temperature. As shown by Maldi TOF only partial deprotection took place, at least eight acetyl groups were still intact. The only partial deprotection of the acetyl groups might have been due to the low solubility of the deprotected phthalocycanine **34a** in methanol. To overcome this problem DMSO was used as cosolvent together with methanol and a catalytic amount of Na metal. By applying this procedure all acetyl groups in phthalocyanines **33a–33i** could be removed with formation of the phthalocyanines **34a–34i**.

The purity of the deprotected phthalocyanines **34a-34i** was shown by reverse phase HPLC and for all the Pc's **33a-33i** and **34a-34i** by MALDI-TOF (figure 42) which showed the calculated compositions.

^{1}H NMR spectra of the acetyl protected Pc's **33a-33i** in $CDCl_3$ due to rather higher concentration lead to partial aggregation and thereby to broad peaks. This is also due for the deprotected systems **34a-34i** measured in DMSO-d_6. As an example ^{1}H NMR spectrum of PcZn **34c** is shown in figure 41.

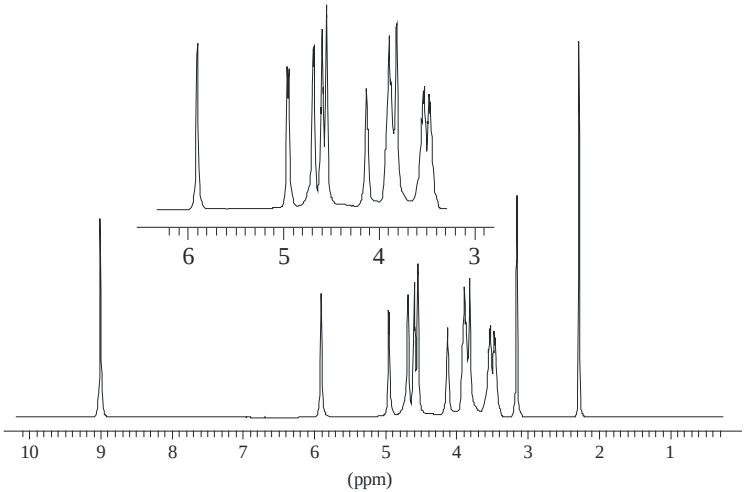


Figure 41: ^{1}H NMR spectrum of PcZn **34c** measured in DMSO-d6.

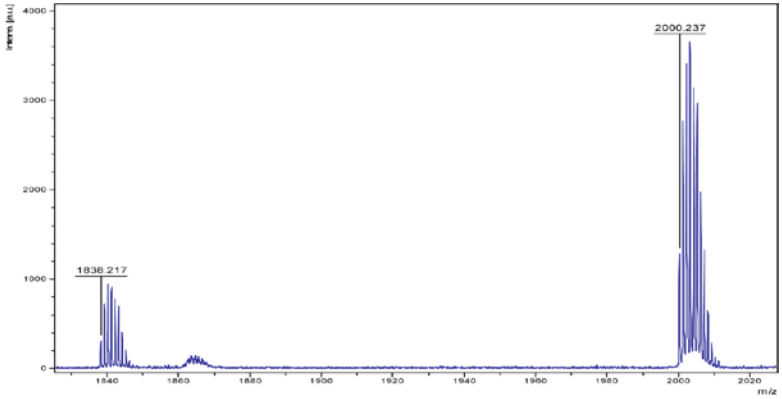


Figure 42: MALDI-TOF spectrum of PcZn **34c**.

3.4 Aggregation behavior of acetyl protected phthalocyanines 33a-33i

The aggregation behaviour of the acetyl protected **33a-33i** and deprotected octaglycosylated PcZn's **34a-34i** was investigated by their UV/Vis spectra in different solvents.

The data of the acetyl protected octaglycosylated PcZn's dissolved in DCM are given in table 4. The PcZn's **33a-33i** show almost no aggregation, as an example

UV/Vis spectrum of **33a** is given in figure 43. This is in contrast to the aggregation behaviour of acetyl protected tetraglucosylated naphthalocyaninato zinc **46**: Its UV/Vis spectrum in DCM shows a strong broad Q_2-band with the maximum at 696 nm typical for strong aggregation. The Q_1-band only appears as shoulder at 769 nm. Traces of pyridine added to the DCM solution lead to an interruption of the aggregation shown in the UV/Vis spectrum by a now strong narrow Q_1-band with the maximum at 763 nm and a broad Q_2-band of low intensity at 704 nm.

All data given in table 4 have been measured in concentration range of 0.35×10^{-5} M – 0.86×10^{-5} M for acetyl protected PcZn's **33a-33i**.

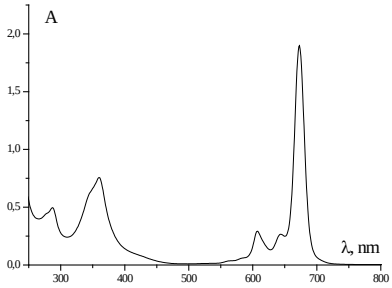


Figure 43: UV/Vis spectrum of PcZn **33a** in DCM ($c = 0.60 \times 10^{-5}$ M).

Table 4: UV/Vis data of acetyl PcZn's **33a-33i** in DCM.

Pc	Q_1-band, λ(logε)	Pc	Q_1-band, λ(logε)
33a	673 (5.50)	33d	700 (5.63)
33c	673 (5.38)	33f	700 (5.11)
33e	674 (5.29)	33h	700 (5.30)
33g	673 (5.59)		
33i	673 (5.49)		

3.5 Aggregation behavior of deprotected phthalocyanines 34a-34i

In DMSO as solvent the deprotected glycosylated PcZn's **34a-34i** show almost no aggregation as demonstrated by the strong narrow Q_1-bands between 678-710 nm (table 5) and bands of low intensity between 612-635 nm indicating very little aggregation. As can be seen from table 5 the anomerically oxygen bound sugar Pc's dissolved in DMSO show the Q_1-band at 678-680 nm, whereas a red shift of Q_1-band is observed for the corresponding S-bound sugar Pc's to 708-710 nm.

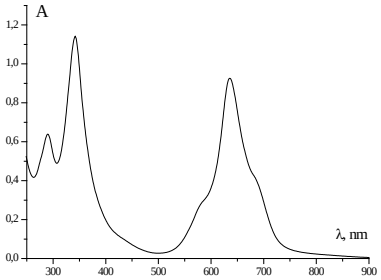


Figure 44: UV/Vis spectrum of **34a** in H_2O ($c = 1.25 \times 10^{-5}$ M).

Table 5: UV/Vis data of PcZn's **34a-34i** in DMSO.

Pc	Q_1-band, λ(logε)	Pc	Q_1-band, λ(logε)
34a	678 (4.89)	34b	710 (5.38)
34c	680 (5.34)	34d	708 (5.06)
34e	679 (4.99)	34f	708 (5.01)
34g	679 (5.31)	34h	709 (5.32)
34i	679 (4.68)		

In water as the solvent all deprotected PcZn's **34a-34i** are highly aggregated as shown with one example (glucose) in figure 44. The UV/Vis spectrum of **34a** shows a broad Q_2-band with the maximum at 635 nm, the Q_1-band only appears as a small shoulder at ~ 670 nm. Addition of pyridine did not interrupt the strong aggregation of Pc's **34a-34i** in water.

Figure 45 shows the UV/Vis spectrum of the deprotected octaglucosylated PcZn **34a** in pure DMSO and the UV/Vis spectra of **34a** in different DMSO/water mixtures with an increasing amount of water. It can be seen that increasing the amount of water leads to an increase of the aggregation band Q_2 at 612 nm and a decrease of the Q_1-band at 678 nm. In mixtures of DMSO/water (2:1) the Q_1-band as in case of pure water almost vanished and the main absorption occurs at 637 nm indicating strong aggregation.

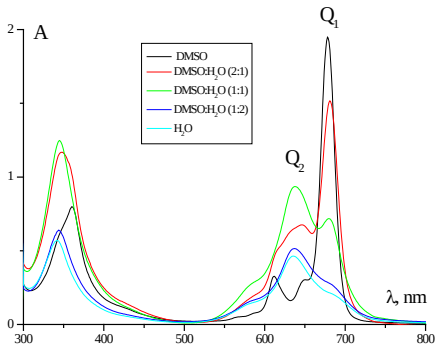


Figure 45: UV/Vis spectrum of octaglucosylated PcZn **34a** in DMSO with different amounts of H_2O.

The ratios of the two Q-bands, Q_1 (nonaggregated) and Q_2 (aggregated) for **34a-34i** in a DMSO/water mixture of 1:1 (volume) are given in table 6. Figure 46 shows the UV/Vis spectra of the deprotected systems **34c**, **34e**, **34g**, **34h** and **34i**. From table 6 and figurte 46 it is evident that in DMSO/water 1:1 the anomerically oxygen bound octaglycosylated PcZn's **34a**, **34c**, **34g** and **34i** are less aggregated than the anomerically sulphur bound systems **34b**, **34d**, **34f** and **34h**.

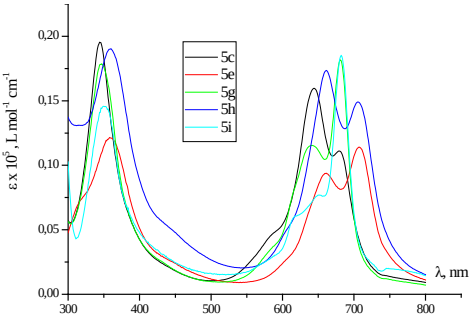


Figure 46: UV/Vis spectra of PcZn's **34a-34i** in DMSO:H_2O (1:1) mixture.

Table 6: Absorption and A_{Q1}/A_{Q2} band ratios of PcZn's **34a-34i** in DMSO:H_2O mixture (1:1).

Pcs	A_{Q1}	A_{Q2}	A_{Q1}/A_{Q2}
34a	0.38	0.49	0.78
34b	0.34	0.38	0.89
34c	0.28	0.40	0.70
34d	0.27	0.20	1.35
34e	0.37	0.23	1.61
34f	0.15	0.12	1.25
34g	0.36	0.23	1.57
34h	0.28	0.33	0.85
34i	0.12	0.00	∝

The Q_1-band of the oxygen bound octaglycosylated PcZn's appear at 678 nm, whereas the Q_1-band of sulphur bound PcZn's appears somewhat higher at ~ 710 nm indicating a red shift ~ 30 nm for the sulphur bound systems.

Aggregation of Pc's **34a-34i** in DMSO/H_2O mixture (1:1) as solvent, also depends upon the size of sugar substituents. Pc's **34e-34i** with bulky sugar substituents are less aggregated in comparison with those containing less bulky sugar substituents, i.e. Pc's **34a-34d**. Pc's with sulfur atoms at anomeric position show more aggregation as compared to the Pc's with oxygen atoms at anomeric position of sugar part, while Pc **34i** with maltose as sugar part is almost non aggregated in this mixture of solvents. All data given in table 5 and 6 have been measured for the deprotected PcZn's **34a-34i** in the concentration ranges from 0.70×10^{-5} M to 1.29×10^{-5} M.

3.6 Synthesis of tetraglucosylated zinc(II) naphthalocyanines 45 and 46 (scheme 28)

Our synthesis of the tetraglucose NcZn's **45** and **46** (scheme 29) in high yield via template reaction of the glucosylated naphthalonitrile **39** (scheme 28) is based on the possibility to obtain glucosyloxyphthalonitriles, in high yields by nucleophilic substitution of 4-nitrophthalonitrile with protected glycopyranoses.[155]

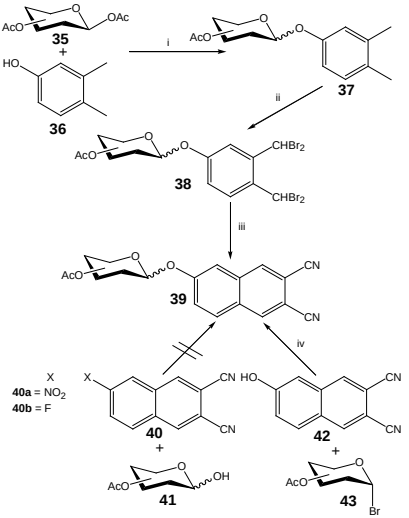
To synthesize the glucosylated naphthalodinitrile **39** (scheme 28) the same S_NAr displacement of nitrite in 6-nitronaphthalodinitrile **40a** by anomerically deprotected glucose **41** in various polar aprotic solvents such as DMF, DMSO and HMPA at room temperature, with NaH and K_2CO_3 as bases was followed. In spite of different conditions which were applied, no sugar nitrite exchange was observed. Increasing the temperature mostly led to the degradation of the sugar part. To increase the reactivity of the leaving group X in the naphthalodinitrile **40**, instead of the nitro- the corresponding fluoronaphthalodinitrile **40b** was reacted with sugar **41**. However also the fluoronaphthalodinitrile **40b** using different conditions did not react with sugar **41** to form the expected substitution product **39**.

A more detailed investigation concerning the reactivity of both the 6-nitro and the 6-fluoronaphthalodinitriles **40a,b** not only with sugar **41** but e.g. with n-hexanol as the alcohol part in solvents like DMF, DMSO and HMPA respectively and K_2CO_3 or NaH as bases gave no indication for a substitution reaction at room temperature or slightly elevated temperatures. At higher temperatures (80-100^oC) only degradation products were found.

Nucleophilic substitution of **40a** has only been reported with sterically hindered phenols.[183] Even in these cases the yields of substitution products are low and side products of unknown structure are formed. These and our own experiments also demonstrate that the nuleophilic reactivity of the nitro and fluoro substituted naphthalonnitriles **40** are much lower and less clear than the well investigated reactivity of the 4-substituted phthalonitriles.

Therefore the synthesis of glucosylated naphthalodinitrile **39** was carried out using the well known route for the preparation of substituted naphthalonitriles[184] (scheme 28): first the glucose part was introduced by a Koenigs-Knorr type

glycosidation reaction of 3,4-dimethylphenol **36** with penta-*O*-acetyl-β-D-glucose **35** under activation with BF_3:etherate leading to compound **37**.[185]

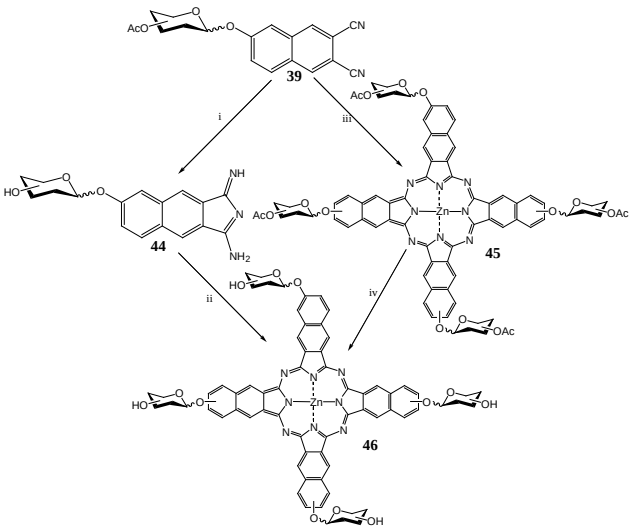


Scheme 28: Synthesis of glucosylated naphthalonitrile **39**. Reagents and conditions: (i) BF_3:etherate, benzene, rt, 48 h, 94% (ii) NBS, benzoyl peroxide, CCl_4, reflux, 48h, 91% (iii) fumaronitrile, NaI, DMF, 75-80°C, 24 h, 65% (iv) Ag_2O, CH_3CN, 50°C, 24h, 71%.

37 could be brominated with NBS in CCl_4 to form tetrabromide **38** in good yield which was reacted with fumaronitrile and NaI in DMF in a Diels-Alder process to obtain the glucosylated naphthalonitrile **39** (scheme 28). Naphthalonitrile **39** was also obtained by reacting 6-hydroxy naphthalonitrile[186] (**42**) with the acetylated bromoglucose **43**.

The sugar part of naphthalonitrile **39** was deprotected with Na in methanol while passing gaseous NH_3 through the solution to form the corresponding diiminoisoindoline **44** which was subsequently reacted with $Zn(OAc)_2.2H_2O$ in DMAE as the solvent, after which the tetraglucosylated NcZn **46** was obtained as a mixture of structural isomers.

Naphthalocycanine **45** was formed by direct tetramerisation of naphthalonitrile **39** with hexamethyldisilazan, *p*-toluensulfonic acid (*p*-TsOH) and $Zn(OAc)_2$ $2H_2O$ in refluxing DMF.[179] Treating **45** with CH_3ONa in a DMSO/methanol mixture (2:1) the acetyl groups were removed and the deprotected NcZn **46** was formed.



Scheme 29: Synthesis of tetraglucosylated zinc(II) naphthalocyanines **45** and **46**. Reagents and conditions: (i) Na, NH_3, methanol, rt-reflux, 2h, 99% (ii) $Zn(OAc)_2.2H_2O$,DBU, DMAE, reflux, 24h, 29% (iii) $Zn(OAc)_2.2H_2O$, HMDS, *p*-TsOH, DMF, reflux, 15h, 45% (iv) CH_3ONa, MeOH, DMSO, rt, 12h, 93%.

Contrary to the completely water soluble tetraglucose substituted PcZn[155] the corresponding NcZn **46** is much less soluble in water at room temperature, but soluble in DMF, DMSO and hot water. The lower solubility of **46** in water is a result of the larger hydrophobic Nc macrocycle for which the four hydrophilic substituents are not sufficient enough to allow water solubility. NcZn **45** is soluble in organic solvents like $CHCl_3$, THF etc.

The ^1H NMR spectra of **45** and **46** were recorded in Methanol-d_4 and DMSO-d_6 respectively. Both NMR spectra were very much depending upon the temperature of the solution which for both compounds have been increased from 20–100 ^oC. Only at higher temperatures clear very well resolved spectra were obtained indicating a strong aggregation of **45** and **46** even in coordinating solvents like DMSO-d_6 and Methanol-d_4. In non-coordinating solvents, e.g. $CDCl_3$, the spectra especially in the aromatic region were of very low intensity. Even the addition of pyridine-d_5 did not change the spectra very much at ambient temperature.

3.7 Aggregation behavior of zinc(II) naphthalocyanines 45 and 46

In solution both Nc's **45** and **46** depending upon the solvent are aggregated. This was directly demonstrated through the UV/Vis spectra of the acetyl protected tetraglucosylated NcZn **45**: Its UV/Vis spectrum in DCM shows a strong broad band with the maximum at 696 nm typical for a strong aggregation. The Q-band of **45** only appears as shoulder at 769 nm. Traces of pyridine added to the DCM solution of **45** lead to an interruption of the aggregation shown in the UV/Vis spectrum by a now strong narrow Q-band with the maximum 763 nm and a broad band of low intensity at 704 nm. In DMSO as the solvent **45** and **46** show less aggregation as shown by strong Q-bands at 769 and 773 nm respectively.

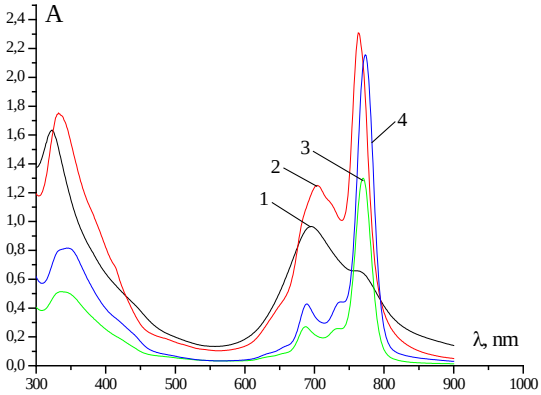


Figure 47: UV/Vis spectra of NcZn's **45** and **46**. (1) NcZn **45** in DCM (c = 0.16x10^{-7} M) (2) NcZn **45** in DCM with traces of. Pyridine (3) NcZn **45** in DMSO (c = 0.14x10^{-7} M) (4) NcZn **46** in DMSO (c = 0.6x10^{-7} M).

3.8 Glycosylated zinc phthalo/naphthalocyanines and PDT studies

Samples of tetra-**(24a-24e)** and octaglycosylated **(30,34a-34i)** PcZn's as well as tetraglucosylated NcZn **46** have been sent to various research groups for PDT investigations. Studies for the efficiency of these compounds for the generation of singlet oxygen molecules is also underway and the results will be published in due course of time.

4 Experimental section

4.1 General informations

All commercially available reagents were purchased and used as acquired. Solvents were dried according to standard methods. The following equipment, methods and materials were used for the analysis and characterization of the compounds.

NMR spectroscopy

^{1}H NMR spectra were measured with either Bruker ARX 250 (250 MHz) or Bruker Avance 400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured by using either Bruker ARX 250 (62 MHz) or Bruker Avance 400 (100 MHz) spectrometer. The deuterated solvent was used as internal standard and the chemical shift values (δ) are given in parts per million (ppm) units in relation with known values of internal standards.

Mass spectroscopy

EI: Finnigen MAT TSQ 70 with direct inlet, temperature of ion source 200 ^{o}C and electron energy 70 ev.
FT-ICR: Bruker Daltronic APEX 2 specrtometer with electron spray ionization (ESI) mode of ionization technique.
MALDI-TOF: Buker Autoflex, 2,5-dihydroxybenzoic acid or α-cyano-4-hydroxycinnamic acid was used as matrix.

IR spectroscopy

Bruker Tensor 27 spectrometer was used. Solid substances were grounded with KBr and pressed to pelltets whereas liquid compounds were measured directly in the instrument.

UV/Vis spectroscopy

The absorption spectra of the compounds were recorded as solutions in CH_2Cl_2 (otherwise stated) contained in quartz cuvett of 1 cm path length, by using Perkin Elmer lamda25 spectrometer.

Elemental analysis

Euro EA 3000 instrument from HEKAtech GmbH.

Optical rotation

Perkin-Elmer 341 polarimeter. The measurements were recorded as $CHCl_3$ solutions of the compounds taken in 10 cm glass cell at 20 ^{o}C.

Preparative chromatography

Preparative RP-HPLC was performed on an aqueous system using a GROM SIL 120 ODS-4HE;10 mm; 250 × 20 mm (C-18 column). The eluents used were H_2O and acetonitrile. Silica gel 60 (particle size 0.040–0.063 mm) from Macherey-Nagel, was used for column chromatography.

Analytical chromatography

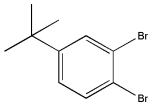
Thin layer chromatography (TLC) was performed on Macherey-Nagel Polygram SIL G/UV_{254} plastic plates, precoated with 0.2 mm thickness of silica gel containing fluorescent indicator. Detection of spots on TLC was carried out by UV light whereas sugar containing compounds were visualized by spraying the TLC with 5% H_2SO_4 solution in EtOH and heating the plate.

Melting points

Melting points were taken on a Büchi B-540 and are uncorrected.

4.2 Synthesis of substituted phthalonitrile precursors

4.2.1 1,2-Dibromo-4-*tert*-butylbenzene (2a)

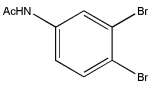


To a solution of 1-bromo-4-*tert*-butylbenzene (8 g, 0.04 mol) in CCl_4 (5 ml) in the presence of a small amount of iron powder was added a solution of bromine (9.5 g, 0.12 mol) in CCl_4 (4 ml) at 5 °C over 10 min. The mixture was stirred at 15 °C for 2h. Solvent was evaporated and product was purified by column chromatography using CH_2Cl_2/hexane (1:1) as eluent; yield 11 g (92%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.59 (d, ^4J = 2.3 Hz, 1 H), 7.50 (d, ^3J = 8.4 Hz, 1 H), 7.16 (dd, ^3J = 8.4 Hz, ^4J = 2.3 Hz, 1 H), 1.27 (s, 9 H).

MS (EI): *m/z* (%) = 291.8 (45) $[M]^+$, 276.8 (100).

4.2.2 1,2-Dibromo-4-acetanilide (8a)

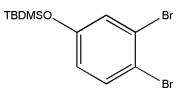


To a solution of 3-bromoacetanilide (2.10 g, 10 mmol) and NBS (1.95 g, 11mmol) in acetone (20 ml), 100 µl of 1 M HCl was added at room temperature. The resulting yellow solution was stirred until the solution became colorless .The acetone was removed in vacuo and 5 ml of hexanes were added. After cooling the mixture in an ice bath, the succinimide was removed by filtration. Removal of the hexanes in vacuo yielded the crude product. After purification by column chromatography with silica gel eluted by CH_2Cl_2, the compound **8a** was obtained as white solid. Yield 2.63 g (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.50 (d, ^3J = 8.8 Hz, 1 H), 7.38 (br s, 1 H), 7.30 (d, ^3J = 8.8 Hz, 1 H), 2.15 (s, 3 H).

MS (EI): *m/z* (%) = 293.0 (100) $[M]^+$.

4.2.3 *tert*-Butyl-(3,4-dibromophenoxy)dimethylsilane (9a)

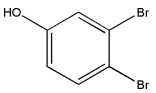


tert-Butyldimethylsilyl chloride (1.5 g, 10 mmol) and imidazole (0.68 g, 10 mmol) were dissolved in 30 ml of CH_2Cl_2 under N_2. 3-Bromophenol (1.72 g, 10 mmol) was added, and the solution stirred overnight. The solution was diluted with H_2O and washed twice with 1 N HCl, followed by saturated aqueous $NaHCO_3$. The organic layer was collected, dried, filtered, and condensed by rotatory evaporation. Chromatography through a short column using CH_2Cl_2/hexanes (1:1), afforded *tert*-butyl(3-bromophenoxy)dimethylsilane quantitatively as a slightly golden oil. *tert*-Butyl(3-bromophenoxy)dimethylsilane was then brominated following the procedure described for compound **8a** to afford **9a** as white solid. Yield 2.85g (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, ^3J = 7.5 Hz, 1 H), 7.10 (d, ^4J = 2.5 Hz, 1 H), 6.64 (dd, ^3J = 7.5 Hz, ^4J = 2.5 Hz, 1 H), 0.95 (s, 9 H), 0.18 (s, 6 H).

MS (EI): *m/z* (%) = 365.9 (40) $[M]^+$, 308.9 (100).

4.2.4 3,4-Dibromophenol (10a)

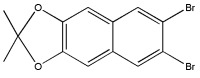


The *tert*-butyldimethylsilyl protected compound **9a** (1.83 g, 5 mmol) was taken in THF (20ml) and cooled to -78 °C. TBAF (5 ml, 5 mmol 1.0 M in THF) was added via syringe in two portions. Three quarters of the TBAF were added and the reaction was stirred for 3 h at -78 °C, then the remaining TBAF was added followed by stirring for 1 h at -78 °C. The reaction was quenched with 3 ml of 10% AcOH/THF. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was collected, dried, filtered, and concentrated in vacuo. Column chromatography using CH_2Cl_2 as the eluent afforded **10a** as white solid. Yield 1.6 g (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, ^3J = 8.6 Hz, 1 H), 7.02 (s, 1 H), 6.55 (d, ^3J = 8.6 Hz, 1 H).

MS (EI): *m/z* (%) = 252.0 (100) [M]+.

4.2.5 6,7-Dibromo-2,2-dimethylnaphtho[2,3-*d*][1,3]dioxole (19a)

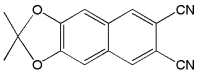


To 5.6 g (17.6 mmol) of 2,3-dibromo-6,7-dihydroxynaphthalene dissolved in toluene (40 ml) and anhydrous acetone (5 ml) was added P_2O_5 in three portions during 48 h while the reaction mixture was heated at 50 °C. The solution was diluted with toluene (50 ml), washed with H_2O, 10% NaOH solution, H_2O and brine. Combined organic phase was concentrated with a rotary evaporator. Purification of the crude product was carried out by column chromatography using dichloromethane as eluent. Yield 3.42 g (57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 2 H), 6.87 (s, 2 H), 1.71 (s, 6 H).

MS (EI): *m/z* (%) = 357.9 (60) $[M]^+$, 342.8 (100).

4.3 General procedure for the synthesis of phthalonitriles



A 25 ml two-neck round-bottom flask was charged with 1 mmol of *o*-dibromobenzene in DMAC (2 ml) and PMHS (20 mg) was added at r.t. The reaction mixture was heated to the required temperature (Table 2) and Pd_2 $(dba)_3$ (20 mg, 2 mol%) and DPPF (15 mg, 2.7 mol%) were added. Afterwards, $Zn(CN)_2$ (117 mg, 1 mmol) was added in 4–5 portions during the time mentioned in Table 2 till TLC indicated completion of the reaction. The reaction mixture was cooled, diluted with EtOAc and filtered. Filtrate was washed with H_2O, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography using CH_2Cl_2 as eluent.

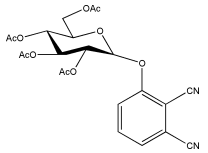
Compound **19b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 2 H), 7.10 (s, 2 H), 1.77 (s, 6 H).

MS (EI): *m/z* (%) = 250.0 (40) $[M]^+$, 235.0 (100), 210.0 (50).

4.4 Syntheses of 1,8(11),15(18),22(25)-tetraglycosylated phthalocyaninato zinc (II) 24a-24e

4.4.1 Synthesis of 3-glycosylated phthalonitriles 22a-22e

4.4.1.1 3-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)-phthalonitrile (22a)



K_2CO_3 (5.80g, 42 mmol) was added to a mixture of 3-nitrophthalonitrile **(20)** (1.0 g, 5.78 mmol) and 2,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranose **(21a)** (2.44 g, 7 mmol) in dimethylformamide (DMF) (50ml). The reaction mixture was stirred at room temperature for 12h. After completion the reaction mixture was poured into water. Precipitates formed were filtered washed with water, dried and purified by column chromatography on silica gel using toluene acetone (5:1) as eluent to afford 2.10 g of **22a** in 77% yield.

Mp: 142-144 °C. $[\alpha]_D^{20}$ = +13.9 (*c* 0.5, $CHCl_3$).

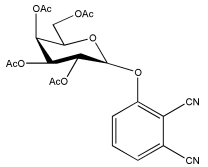
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.63 (m, 1H, H^{Ar}), 7.53-7.48 (m, 2H, H^{Ar}), 5.83 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1), 5.66 (t, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1H, H-3), 5.17 (t, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz,1H, H-4), 5.03 (dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 9.8Hz, 1H, H-2), 4.23 (dd, $J_{5,6a}$ = 4.6 Hz, $J_{6a,6b}$ = 12.2Hz, 1H, H-6a), 4.16-4.12 (m, 1H, H-5), 4.10 (dd, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 12.2Hz, 1H, H-6b), 2.09 (s, 3H, CH_3), 2.02 (s, 9H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.5, 170.0, 169.7 (4C,C=O), 159.1 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.3 (1C, H-C^{Ar}), 121.2 (1C, H-C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.2 (1C, CN), 112.4 (1C, NC-C^{Ar}), 107.6 (1C, NC-C^{Ar}), 96.9 (1C, C-1), 70.5 (1C, C-2), 69.9 (1C, C-3), 69.6 (1C, C-5), 68.2 (1C, C-4), 61.7 (1C, C-6), 21.1, 21.0, 21.0, 20.9 (4C, CH_3).

HRMS (FT-ICR): *m/z* calcd for $[M+Na]^+$ 497.1166, found 497.1169.

Anal. calcd. for $C_{22}H_{22}N_2O_{10}$: C 55.70, H 4.67, N 5.90. Found: C 55.34, H 4.94, N 5.80.

4.4.1.2 3-(2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl)-phthalonitrile (22b)



Prepared from 2,3,4,6-tetra-*O*-acetyl-α/β -D-galactopyranose (**21b**, 2.44 g, 7 mmol) and 3-nitrophthalonitrile (**20**, 1 g, 5.78 mmol.) as described for compound **22a**. Purification was carried out by column chromatography using toluene

acetone mixture (5:1) as eluent to afford 2.29 g product as white solid. Yield (84%).

Mp: 192-194 °C. $[\alpha]_D^{20}$ = +14.7 (*c* 0.3, $CHCl_3$).

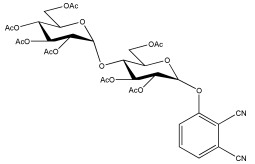
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 1H, H^{Ar}), 7.55-7.48 (m, 2H, H^{Ar}), 5.88 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1), 5.58 (d, $J_{4,5}$ = 2.8 Hz, 1H, H-4), 5.51 (dd, $J_{3,4}$ = 3.3Hz, $J_{3,2}$ = 10.9 Hz,1H, H-3), 5.27 (dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 10.9 Hz, 1H, H-2), 4.37 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5), 4.10 (d, $J_{6,5}$ = 6.6 Hz, 2H, H-6), 2.15, 2,12, 2.01, 1.96 (4s, 4x3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 170.3, 170.2, 169.9 (4C,C=O), 159.4 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.2 (1C, H-C^{Ar}), 121.3 (1C, H-C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.3 (1C, CN), 112.5 (1C, NC-C^{Ar}), 107.6 (1C, NC-C^{Ar}), 97.6 (1C, C-1), 70.7 (2C, C-2,3), 67.7 (2C, C-4,5), 61.7 (1C, C-6), 21.2, 21.0 (4C, CH_3).

HRMS(FT-ICR): *m/z* calcd for $[M+Na]^+$ 497.1166, found 497.1170.

Anal. calcd. for $C_{22}H_{22}N_2O_{10}$: C 55.70, H 4.67, N 5.90. Found: C 55.98, H 5.04, N 5.74.

4.4.1.3 3-(2,3,6,2',3',4',6'-Hepta-O-acetyl-α-D-maltose)-phthalonitrile (22c)



Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α/β-D-maltose (**21c**, 4.45 g, 7 mmol) and 3-nitrophthalonitrile (**20**, 1 g, 5.78 mmol.) as described for compound **22a**. Purification was carried out by column chromatography using toluenen acetone (4:1) mixture to form 3.80 g white solid. Yield (86%).

Mp: 188-190 °C. $[\alpha]_D^{20}$ = +12.2 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.63 (m, 1H, H^{Ar}), 7.53-7.49 (m, 2H, H^{Ar}), 5.74-5.69 (m, 2H, H-1,1'), 5.42 (d, *J* = 4.1, 1H, H-2'), 5.35-5.26 (m, 1H, H-5'), 5.03 (t, $J_{3,2}$ = $J_{3,4}$ = 9.9 Hz, 1H, H-3), 4.92 (dd, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 3.8 Hz, 1H, H-2), 4.85 (dd, *J* = 10.4Hz, 1H, H-3'), 4.48 (dd, *J* = 2.6 Hz, *J* = 12.4Hz, 1H, H-6b), 4.22 (dd, *J* = 3.6 Hz, *J* = 12.4Hz, 2H, H-6a',b'), 4.14-3.94 (m, 4H, H6a, H-4, H-5) 2.08, 2.07, 2.06, 2.03, 2.01, 1.98, 1.97 (7s, 7 x 3H, CH_3).

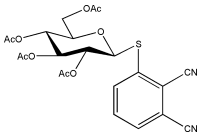
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 171.0, 170.9, 170.5, 170.2, 169.8, 169.7 (7C,C=O), 159.1 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.6 (1C, H-C^{Ar}), 121.6 (1C, H-

C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.3 (1C, CN), 112.4 (1C, NC-C^{Ar}), 107.9 (1C, NC-C^{Ar}), 96.9 (1C, C-1'), 96.0 (1C, C-1), 72.7 (1C, C-3), 71.9 (1C, C-5), 71.5 (1C, C-4), 70.6 (1C, C-2), 70.3 (1C, C-2'), 69.6 (1C, C-3'), 69.0 (1C, C-5), 68.4 (1C, C-4'), 62.6 (1C, C-6), 61.9 (1C, C-6'), 21.8, 21.2, 21.2, 21.1, 21.0, 21.0, 20.9 (7C, CH_3).

HRMS(FT-ICR): *m/z* calcd for $[M+Na]^+$ 785.2011, found 785.2007.

Anal. calcd. for $C_{34}H_{38}N_2O_{18}$: C 53.54, H 5.02, N 3.67. Found: C 53.48, H 5.14, N 3.75.

4.4.1.4 3-(2,3,4,6-Tetra-O-acetyl-1-thio-β-D-glucopyranosyl)-phthalonitrile (22d)



Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**21d**, 2.54 g, 7 mmol) and 3-nitrophthalonitrile (**1**, 1 g, 5.78 mmol) as described for compound **3a**. Column chromatography was carried out by using toluene acetone mixture (5:1) to afford 2.27g of white solid. Yield (80%).

Mp: 137-139 °C. $[\alpha]_D^{20}$ = -3.0 (*c* 0.25, $CHCl_3$).

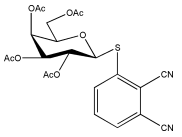
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 1.0Hz, *J* = 8.1Hz, 1H, H^{Ar}), 7.78 (dd, *J* = 1.0Hz, *J* = 7.9Hz, 1H, H^{Ar}), 7.68 (t, *J* = 1.0 Hz, *J* = 7.9Hz, 1H, H^{Ar}), 5.22 (t, $J_{3,4}$ = $J_{3,2}$ = 9.4 Hz, 1H, H-3), 4.99 (t, $J_{4,3}$ = $J_{4,5}$ = 9.4 Hz, 1H, H-4), 4.87 (t, $J_{2,1}$ = 9.9 Hz, 1H, H-2), 4.786 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.25 (dd, $J_{6a,5}$ = 5.1 Hz, $J_{6a,6b}$ = 12.5Hz, 1H, H-6a), 4.16 (dd, $J_{6b,5}$ = 2.3 Hz, $J_{6b,6a}$ = 12.5 Hz, 1H, H-6b), 3.78-3.72 (m, 1H, H-5), 2.11, 2.07, 2.00, 1.96 (4s, 4 x 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.3, 169.7, 169.9, 169.8 (4C,C=O), 139.0 (1C, O-C^{Ar}), 138.1 (1C, H-C^{Ar}), 133.5 (1C, H-C^{Ar}), 133.1 (1C, H-C^{Ar}), 121.1 (1C, H-C^{Ar}), 117.9 (2C, CN), 115.3 (1C, NC-C^{Ar}), 114.1 (1C, NC-C^{Ar}), 84.8 (1C, C-1), 76.7 (1C, C-2), 73.9 (1C, C-3), 69.6 (1C, C-4), 68.2 (1C, C-5), 62.2 (1C, C-6), 21.1 21.1, 20.9 (4C, CH_3).

HRMS(FT-ICR): *m/z* calcd for $[M+Na]^+$ 513.0938, found 513.0943.

Anal. calcd. for $C_{22}H_{22}N_2O_9S$: C 53.87, H 4.52, N 5.71, S 6.54. Found: C 53.83, H 4.65, N 5.69, S 6.47.

4.4.1.5 3-(2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosyl)-phthalonitrile (22e)



Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose (**21e**, 2.54 g, 7 mmol) and 3-nitrophthalonitrile (**20**, 1 g, 5.78 mmol.) as described for compound **22a**. Purification was carried out by column chromatography using toluene acetone (5:1) to produce 2.74 g of white solid. Yield (97%).

Mp: 139-141 °C. $[\alpha]_D^{20}$ = -0.23 (*c* 0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 1.0Hz, *J* = 7.9Hz, 1H, H^{Ar}), 7.75 (dd, *J* = 1.0Hz, *J* = 7.9Hz, 1H, H^{Ar}), 7.66 (t, *J* = 1.0 Hz, *J* = 7.9Hz, 1H, H^{Ar}), 5.42 (d, $J_{4,5}$ = 2.8 Hz, 1H, H-4), 5.15 (t, $J_{2,1}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.05 (dd, $J_{3,4}$ = 3.3 Hz, $J_{3,2}$ = 9.9Hz, 1H, H-3), 4.78 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.17 (dd, $J_{6a,5}$ = 6.9 Hz, $J_{6a,6b}$ = 11.4Hz, 1H, H-6a), 4.10 (dd, $J_{6b,5}$ = 6.1 Hz, $J_{6b,6a}$ = 11.4 Hz, 1H, H-6b), 3.96 (t, $J_{5,6a}$ = 6.9, 1H, H-5), 2.11, 2.10, 2.02, 1.94 (4s, 4 x 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ =170.8, 170.3, 170.2, 170.0, (4C,C=O), 139.4 (1C, O-C^{Ar}), 138.1 (1C, H-C^{Ar}), 133.2 (1C, H-C^{Ar}), 132.9 (1C, H-C^{Ar}), 120.2 (1C, H-C^{Ar}), 117.8 (2C, CN), 115.4 (1C, NC-C^{Ar}), 114.1 (1C, NC-C^{Ar}), 85.7 (1C, C-1), 75.4 (1C, C-5), 72.0 (1C, C-3), 67.4 (1C, C-2), 66.7 (1C, C-4), 61.8 (1C, C-6), 21.1 21.1, 21.0, 20.9 (4C, CH_3).

HRMS(FT-ICR): *m/z* calcd for $[M+Na]^+$ 513.0938, found 513.0941.

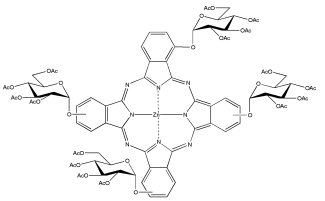
Anal. calcd. for $C_{22}H_{22}N_2O_9S$: C 53.87, H 4.52, N 5.71, S 6.54. Found: C 53.74, H 4.69, N 5.63, S 6.37.

4.4.2 Syntheses of acetyl protected phthalocyanines 23a-23e: General Procedure

A mixture of phthalonitrile (2 mmol), $Zn(OAc)_2.2H_2O$ (440 mg, 2 mmol), DMF (1.5 ml), hexamethyldisilazane (HMDS) (65 mg, 0.40 mmol) and TMSOTf (77 mg, 0.35 mmol) in a sealed glass tube was stirred and heated at 115-120 ^oC overnight. The

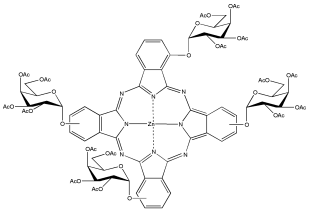
semisolid obtained was cooled and precipitated with methanol water (1:2) mixture. The precipitates obtained were dried and purified with column chromatography using ethylacetate containing 0-3% methanol.

4.4.2.1 1,8(11),15(18),22(25)-Tetra(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)phthalocyaninato zinc (II) 23a



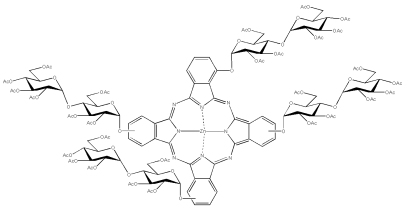
Prepared from 3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)phthalonitrile (**22a**, 2.0 g, 4.2 mmol.) to afford green solid. Yield 1.34 g (65%).
^{1}H NMR (400MHz, $CDCl_3$): δ = 8.08-7.91 (m, 4H, H^{Ar}), 7.67-7.48 (m, 8H, H^{Ar}), 5.84 (d, *J* = 3.8Hz, 4H, H-1), 5.65 (t, *J* =9.6, 4H), 5.42-5.37 (m, 8H), 5.18-5.00 (m, 4H), 4.26-4.00 (m, 8H), 2.10-2.00 (m, 48H, CH_3).
UV/Vis (DCM): λ_{max} (log ε) = 691 (5.11), 623 (4.40), 362 (4.50).
HRMS (MALDI–TOF): *m/z* calcd for $C_{88}H_{88}N_8O_{40}Zn$ 1960.4389; found, 1960.436 $[M]^+$.

4.4.2.2 1,8(11),15(18),22(25)-Tetra(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)phthalocyaninato zinc (II) 23b



Prepared from 3-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)phthalonitrile (**22b**, 2.0 g, 4.2 mmol.) to afford green solid. Yield 0.96 g (47%).
^{1}H NMR (400MHz, $CDCl_3$): δ = 8.32-8.03 (m, 4H, H^{Ar}), 7.83-7.40 (m, 8H, H^{Ar}), 5.98-5.85 (m, 4H, H-1), 5.68-5.23 (m, 8H), 5.15-4.97 (m, 2H), 4.59-4.49 (m, 2H), 4.40-4.26 (m, 2H), 4.20-3.99 (m, 8H), 2.32-1.74 (m, 48H, CH_3).
UV/Vis (DCM): λ_{max} (log ε) = 689 (4.90), 622 (4.24), 362 (4.33).
HRMS (MALDI–TOF): *m/z* calcd for $C_{88}H_{88}N_8O_{40}Zn$ 1960.4389; found, 1960.441 $[M]^+$.

4.4.2.3 1,8(11),15(18),22(25)-Tetra(2,3,6,2',3',4',6'-hepta-O-acetyl-α-D-maltose)phthalocyaninato zinc (II) 23c



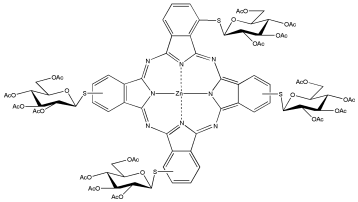
Prepared from 3-(2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-D-maltose)-phthalonitrile **(22c**, 3.0 g, 4. mmol.) to afford green solid. Yield 0.90 g (29%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.33-8.15 (m, 4H, H^{Ar}), 8.09-7.93 (m, 4H, H^{Ar}), 7.70-7.42 (m, 4H, H^{Ar}), 6.72-6.49 (m, 4H), 5.61-5.19 (m, 6H), 5.11-4.75 (m, 6H), 4.36-3.79 (m, 12H), 2.22-1.86 (m, 48H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 693 (4.92), 625 (4.14), 356 (4.27).

HRMS (MALDI–TOF): *m/z* calcd for $C_{136}H_{155}N_8O_{72}Zn$ $[M+3H]^+$, 3115.8004; found, 3115.808.

4.4.2.4 1,8(11),15(18),22(25)-Tetra(2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosyl)phthalocyaninato zinc (II) 23d



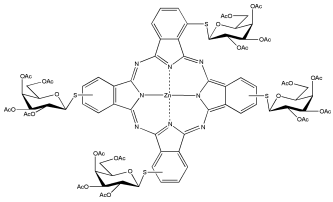
Prepared from 3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)phthalonitrile (**22d**, 2.5 g, 4.2 mmol.) to afford green solid. Yield 0.84 g (39%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.35-9.05 (m, 4H, H^{Ar}), 8.09-7.96 (m, 8H), 5.70-5.18 (m, 12H), 4.49-4.27 (m, 8H), 4.21- 4.01 (m, 8H), 2.21-1.83 (m, 48H, CH_3).

UV/Vis (DCM). λ_{max} (log ε) = 727 (4.73), 693 (5.09), 626 (4.47), 333 (4.65).

HRMS (MALDI–TOF): *m/z* calcd for $C_{88}H_{88}N_8O_{36}S_4Zn$ $[M]^+$, 2024.3476; found, 2024.348.

4.4.2.5 1,8(11),15(18),22(25)-Tetra(2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosyl)phthalocyaninato zinc (II) 23e



Prepared from 3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)phthalonitrile (**22e**, 2.5 g, 4.2 mmol.) to afford green solid. Yield 0.67 g (32%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.55-9.33 (m, 4H, H^{Ar}),8.32-8.03 (m, 4H, H^{Ar}), 7.79-7.51 (m, 4H, H^{Ar}), 5.75-5.50 (m, 8H), 5.30-4.96 (m, 6H), 4.47-4.20 (m, 12H), 4.09-4.00 (m, 2H), 2.22-1.91 (m, 48H, CH_3).

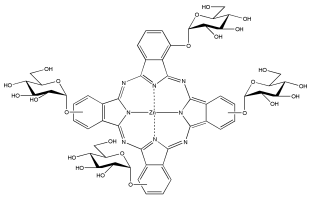
UV/Vis (DCM): λ_{max} (log ε) = 727 (4.97), 695 (5.17), 333 (4.67).

HRMS (MALDI–TOF): *m/z* calcd for $C_{88}H_{88}N_8O_{36}S_4Zn$ $[M]^+$, 2024.3476; found, 2024.348.

4.4.3 Syntheses of deprotected phthalocyanines 24a-24e: General procedure

Acetylated phthalocyanines **23a-23e** (400 mg) were dissolved in 2:1 mixture of DMSO/MeOH (15 ml). Catalytic amount of MeONa was added and the reaction mixture was stirred at room temperature overnight. Precipitation of the unprotected phthalocyanine was carried out by adding access of acetone. Precipitates formed were filtered and extensively washed with acetone to remove all of DMSO. The crude product was dissolved in small amount of water and repeatedly recrystallized with acetone.

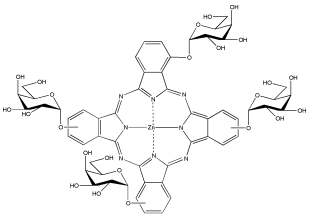
4.4.3.1 1,8(11),15(18),22(25)-Tetra-α-D-glucosephthalocyaninato zinc (II) 24a



Prepared from phthalocyanine **23a**
(1.0 g, 0.5 mmol.) to afford bluish green solid. Yield 630 mg (96%).

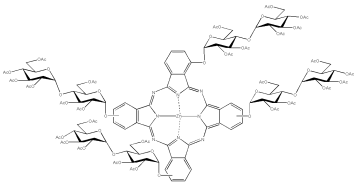
^{1}H NMR (400MHz, DMSO-d_6): δ = 9.51-9.48 (m, 4H, H^{Ar}), 8.19-8.06 (m, 8H, H^{Ar}), 6.22 (bs, 4H, H1), 5.90 (bs, 4H), 5.47 (bs, 4H), 5.28 (bs, 4H), 4.69-4.64 (m, 8H), 4.13 (bs, 4H), 3.82-3.74 (m, 8H), 3.64 (bs, 4H), 3.51-3.47 (m, 4H).
UV/Vis (DMSO): λ_{max} (log ε) = 702 (5.09), 633 (4.42), 352 (4.47).
HRMS (MALDI–TOF): *m/z* calcd for $C_{56}H_{57}N_8O_{24}Zn$ $[M+H]^+$, 1289.2777; found, 1289.287.

4.4.3.2 1,8(11),15(18),22(25)-Tetra-α-D-galactosephthalocyaninato zinc (II) 24b



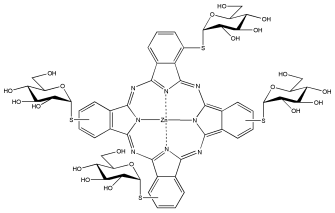
Synthesized from phthalocyanine **23b**
(800 mg, 0.4 mmol.) to afford bluish green solid. Yield 500 mg (95%).
^{1}H NMR (400MHz, DMSO-d_6): δ = 9.44-9.42 (m, 4H, H^{Ar}), 8.17-8.08 (m, 8H, H^{Ar}), 6.27 (bs, 4H, H1), 5.04-4.74 (m, 12H), 4.50-4.35 (m, 6H), 4.28-4.09 (m, 10H), 3.81-3.54 (m, 16H).
UV/Vis (DMSO): λ_{max} (log ε) = 704 (5.17), 633 (4.48), 333 (4.55).
HRMS (MALDI–TOF): *m/z* calcd for $C_{56}H_{57}N_8O_{24}Zn$ $[M+H]^+$, 1289.2777; found, 1289.267.

4.4.3.3 1,8(11),15(18),22(25)-Tetra-α-D-maltosephthalocyaninato zinc (II) 24c



Prepared from phthalocyanine **23c**
(800 mg, 0.25 mmol.) to afford bluish green solid. Yield 440 mg (91%).
^{1}H NMR (400MHz, DMSO-d_6): δ = 9.51-9.25 (m, 4H, H^{Ar}), 8.18-8.03 (m, 8H, H^{Ar}), 6.28 (bs, 4H, H1), 5.26 (bs, 4H), 5.10-4.87 (m, 12H), 4.23 (bs, 8H), 3.93-3.71 (m, 16H).
UV/Vis (DMSO): λ_{max} (log ε) = 703 (5.03), 633 (4.29), 329 (4.41).
HRMS (MALDI–TOF): *m/z* calcd for $C_{80}H_{97}N_8O_{44}Zn$ $[M+H]^+$, 1937.4890; found, 1937.482.

4.4.3.4 1,8(11),15(18),22(25)-Tetra(1-thio-β-D-glucose)phthalocyaninato zinc (II) 24d



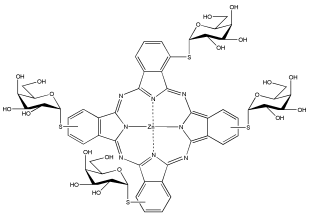
Prepared from phthalocyanine **23d** (600 mg, 0.3 mmol.) to afford green solid. Yield 381 mg (94%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.33-9.27 (m, 4H, H^{Ar}), 8.27-8.12 (m, 8H, H^{Ar}), 5.47 (d, *J* = 10.2 Hz, 4H), 5.32 (bs, 4H), 5.15 (bs, 4H), 4.69 (bs, 4H), 3.85-3.74 (m, 6H), 3.70-3.61 (m, 6H), 3.52-3.40 (m, 16H).

UV/Vis (DMSO): λ_{max} (log ε) = 710 (5.16), 639 (4.46), 336 (4.66), 260 (4.72).

HRMS (MALDI–TOF): *m/z* calcd for $C_{56}H_{56}N_8O_{20}S_4Zn$ $[M+H]^+$, 1353.1863; found, 1353.181.

4.4.3.5 1,8(11),15(18),22(25)-Tetra(1-thio-β-D-galactose)phthalocyaninato zinc (II) 24e



Prepared from phthalocyanine **23e** (500 mg, 0.35 mmol.) to afford green solid. Yield 328 mg (94%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.33-9.26 (m, 4H, H^{Ar}), 8.33-8.07 (m, 8H, H^{Ar}), 5.41 (d, *J* = 9.7 Hz, 4H), 5.27 (bs, 4H), 5.10 (bs, 4H), 4.80 (bs, 4H), 4.16-4.02 (m, 6H), 3.94-3.77 (m, 6H), 3.70-3.52 (m, 16H).

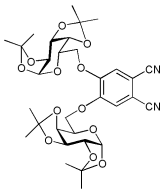
UV/Vis (DMSO): λ_{max} (log ε) = 712 (5.15), 639 (4.42), 336 (4.63), 261 (4.72).

HRMS (MALDI–TOF): *m/z* calcd for $C_{56}H_{56}N_8O_{20}S_4Zn$ $[M+H]^+$, 1353.1863; found, 1353.187.

4.5 Synthesis of 2,3,9,10,16,17,23,24-octa(α/ß-D-galactopyranos-6-yl)phthalocyaninato zinc(II) 30

4.5.1 4,5-Di(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)phthalonitrile (27)

NaH (800 mg, 20 mmol) was added to a mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**25**, 5.2 g, 20 mmol) and 4,5-difluorophthalonitrile (**26b**, 1.64 g, 10 mmol) in 50 ml DMAC or DMF. The reaction mixture was heated at 35-40°C for 2 days. After completion, the reaction mixture was cooled and poured in excess of water. Precipitates formed were collected by filtration and dried in vacuo. Purification of the crude product was carried out by column chromatography using toluene: acetone (5:1) mixture to yield 6.2 g of white solid: yield 96%.

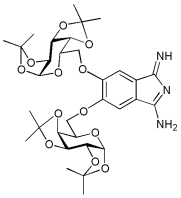


^{1}H NMR (400MHz, $CDCl_3$): δ = 7.16 (s, 2H, H^{Ar}), 5.5 (d, *J* = 5Hz, 2H, H-1 anomeric), 4.61 (dd, *J* = 2.5Hz, *J* = 7.88Hz 2H, H-4), 4.36 (d, *J* = 7.88Hz 2H, H-3), 4.32 (dd, *J* = 2.5Hz, *J* = 5.1Hz 6H, H-2), 4.20-4.12 (m, 6 H, H-5, H-6a,b), 1.49 (s, 6H,CH_3), 1.42 (s, 6H, CH_3), 1.32 (s, 12H, CH_3).

IR (KBr): 2987, 2933, 2231, 1590, 1519, 1370, 1212, 1115, 1003, 920, 536 cm^{-1}.

HRMS(FT-ICR): *m/z* calcd for $[M+Na]^+$ 644.2581; found, 644.249.

4.5.2 4,5-Di(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)isoindoline (28)

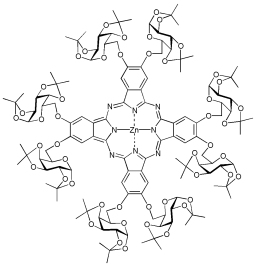


(502 mg, 9.3 mmol) $NaOCH_3$ was added to 40 ml 1:1 mixture of dry THF and methanol at room temperature. The mixture was cooled to 0°C while passing gaseous NH_3 through it. Phthalonitrile **27** (6g, 9.3 mmol) was added and the mixture was bubbled with NH_3 for next half an hour. Afterwards the reaction mixture was allowed to stir at room temperature for

1 hour followed by reflux for more 1 hour while passing gaseous NH_3 through it. After the completion flow of gas was stopped and the reaction mixture was allowed to cool. Poured into water, precipitates formed filtered, washed with water, small portion of MeOH and DCM and dried in vacuo: yield 5.9 g (95%).

LC-MS: $(M+Na)^+$ 684.

4.5.3 2,3,9,10,16,17,23,24-octa(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)phthalocyaninato zinc(II) (29)



Method A: Isoindoline **28** (661 mg, 1 mmol) and $Zn(AcO)_2.2H_2O$ (110mg, 0.5 mmol) were refluxed in 1 ml DMAE for 24 hr. Reaction mixture was cooled, poured in methanol water (1:1) mixture. Precipitates formed were filtered, dried and chromatographed first with n-hexan and ethylacetate (1:1) mixture to remove side products and then with ethylacetate. Yield 196 mg (29%).

Method B: Isoindoline **28** (661 mg, 1 mmol) and $Zn(AcO)_2.2H_2O$ (220mg, 1 mmol) were mixed well and taken in sealed tube. The tube was heated at 140-145 °C overnight. The solid material was then cooled and subjected to column chromatography as described in method A. Yield 198 mg (30%)

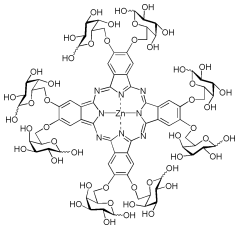
^{1}H NMR (400MHz, $CDCl_3$): δ =7.16 (br. s, 8H, H^{Ar}), 5.6 (d, *J* = 4.84Hz, 8H, H-1 anomeric), 4.76-4.43 (m,48H, H-Gal.), 1.53-1.36 (m, 96H, CH_3).

IR (KBr): 2987, 2936, 1609, 1492, 1456, 1383, 1281, 1211, 1070, 1005, 891, 748, 511 cm^{-1}.

HRMS (MALDI–TOF): *m/z* calcd for $C_{128}H_{160}N_8O_{48}Zn$, $[M]^+$,2644.0551; found, 2644.053.

UV/Vis (DMSO): λ_{max} (log ε) = 669 (4.95), 604 (4.48), 352 (4.91), 289 (4.67).

4.5.4 2,3,9,10,16,17,24,25-Octakis(α/ß-D-galactopyranos-6-yl)phthalocyaninato zinc(II) (30)



Phthalocyanine **29** (100 mg) was stirred in 10 ml 9:1 mixture of trifluoroacetic acid (TFA) and water, for 4 hours at room temperature. The acid was neutralized by slow addition of aqueous Na_2CO_3. Resulting solution was concentrated in vacuo and crude product was purified by reverse phase HPLC using acetonitrile/H_2O as eluent. Yield 60 mg (81%).

^{1}H NMR (400MHz, DMSO-d_6): δ =8.99 (br. s, 8H, H^{Ar}), 5.16-3.71 (3m, 56H, H-Gal).

IR (KBr): 3428, 2925, 1716, 1637, 1495, 1399, 1256, 1074, 744, 616, 580 cm^{-1}.

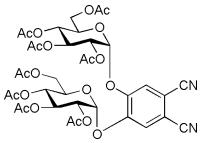
HRMS (MALDI–TOF): *m/z* calcd for $C_{80}H_{96}N_8O_{48}Zn$, $[M]^+$,2000.4609; found, 2000.899.

UV/Vis (DMSO): λ_{max} (log ε) = 679 (4.67), 613 (3.90), 360 (4.34), 291 (4.12).

4.6 Synthesis of 2,3,9,10,16,17,23,24-octaglycosylated zinc(II) phthalocyanines

4.6.1 Synthesis of 4,5-diglycosylated phthalonitrile precursors 32a-32i

4.6.1.1 4,5-Di(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)phthalonitrile (32a)



K_2CO_3 (16.56 g, 120 mmol) was added to a mixture of 4,5-difluorophthalonitrile **(26b)** (1.64 g, 10 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose **(31a)** (6.96 g, 20 mmol) in dimethylacetamide (DMAC, 50ml). The reaction mixture was heated at 35-40 ^oC for 48 hours. After completion the reaction mixture was cooled and poured into water. Precipitates formed were filtered washed with water, dried and purified by column chromatography on silica gel using toluene acetone (5:1) as solvent to afford 5.25 g of **32a** in 64% yield.

Mp: 145-150 °C. $[\alpha]_D^{20}$ = +171 (*c* 0.5, $CHCl_3$).

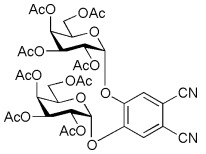
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 2H, H^{Ar}), 5.78 (d, $J_{1,2}$ = 3.3 Hz, 2H, H-1), 5.61 (t, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 2H, H-3), 5.13 (dd, 2H, H-2), 5.10 (t, $J_{4,5}$ = 9.8 Hz, 2H, H-4), 4.21 (dd, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 12.4 Hz, 2H, H-6a),4.07 (dd, $J_{5,6b}$ = 2.0 Hz, 2H, H-6b), 3.96-3.92 (m, 2H, H-5), 2.17, 2.06, 2.00, 1.93 (4s, 4 x 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.7, 169.9, 169.6 (8C, C=O), 149.5 (2C, O-C^{Ar}), 119.7 (2C, H-C^{Ar}), 115.2 (2C, CN), 111.3 (2C, NC-C^{Ar}), 95.9 (2C, C-1), 70.8 (2C, C-2), 69.9 (4C, C-3,5), 68.5 (2C, C-4), 61.9 (2C, C-6), 21.1, 21.0, 20.9, 20.8 (8C, CH_3).

HRMS (FT-ICR): *m/z* 843.19498 $[M+Na]^+$.

Anal. calcd. for $C_{36}H_{40}N_2O_{20}$: C 52.68, H 4.91, N 3.41. Found: C 52.60, H 4.83, N 3.43.

4.6.1.2 4,5-Di(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)phthalonitrile (32c)



Prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**31c**, 2 mmol) as described for compound **32a**. Purification was carried out by column chromatography using toluene acetone mixture (5:1) to afford the product as white solid. Yield (72%).

Mp: 113-115 °C. $[\alpha]_D^{20}$ = +238 (*c* 0.5, $CHCl_3$).

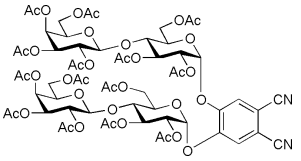
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 2H, H^{Ar}), 6.24 (d, $J_{1,2}$ = 3.3 Hz, 2H, H-1), 5.47 (d, $J_{4,3}$ = 3.0 Hz, 2H, H-4), 5.42 (dd, $J_{3,2}$ = 10.7, $J_{3,4}$ = 3.0 Hz, 2H, H-3), 5.30 (dd, $J_{2,3}$ = 10.76 Hz, $J_{2,1}$ = 3.3 Hz, 2H, H-2), 4.21 (t, $J_{5,6a}$ = 6.4 Hz, 2H, H-5),4.04 (d, *J* = 6.4 Hz, 4H, H-6a,b), 2.15, 2.06, 1.93, 1.86 (4s, 4 x 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9, 167.8, 167.7, 167.4 (8C, C=O), 146.7 (2C, O-C^{Ar}), 118.7 (2C, H-C^{Ar}), 113.7 (2C, CN), 107.0 (2C, NC-C^{Ar}), 92.4 (2C, C-1), 66.0 (2C, C-2), 65.5 (2C, C-3), 65.2 (2C, C-4), 64.2 (2C, C-5), 59.3 (2C, C-6), 19.1, 18.4, 18.3, 18.2 (8C, CH_3).

HRMS (FT-ICR): *m/z* 843.20553 $[M+Na]^+$.

Anal. calcd. for $C_{36}H_{40}N_2O_{20}$: C 52.68, H 4.91, N 3.41. Found: C 52.76, H 4.38, N 3.38.

4.6.1.3 4,5-Di(2,3,6,2',3',4',6'-hepta-O-acetyl-α-D-lactose)phthalonitrile (32e)

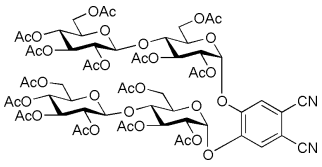


Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-D-lactose (**31e**, 2 mmol) as described for compound **32a**. Purification was carried out by column chromatography using toluene acetone mixture (4:1) to afford the product as white solid. Yield (56%).

Mp: 138-140 °C. $[\alpha]_D^{20}$ = +102.4 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 2H, H^{Ar}), 5.68 (d, $J_{1,2}$ = 3.6 Hz, 2H, H-1), 5.53 (t, $J_{3,2}$ = $J_{3,4}$ = 9.9 Hz, 2H, H-3), 5.28 (d, $J_{4',5'}$ = 2.8 Hz, 2H, H-4'), 4.99 (dd, $J_{2,3}$ = 9.9, $J_{2,1}$ = 3.6 Hz, 2H, H-2), 4.89 (dd, $J_{2',1'}$ = 7.6, $J_{2',3'}$ = 3.0 Hz, 2H, H-2'), 4.35 (br, $J_{1',2'}$ = 7.6 Hz, 4H, H-6b, H-1'), 4.06-4.03 (m, 8H, H-6a, H-6a',b', H-3'), 3.85-3.72 (m, 6H, H-4, H-5, H-5'), 2.09, 2.08, 2.04, 2.01, 1.98, 1.90, 1.87 (7s, 7 x 6H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.7, 170.3, 169.9, 169.4, 169.1, 168.9 (14C, C=O), 150.1 (2C, O-C^{Ar}), 119.9 (2C, H-C^{Ar}), 115.3 (2C, CN), 111.0 (2C, NC-C^{Ar}), 101.5 (2C, C-1'), 95.9 (2C, C-1), 76.4 (2C, C-5), 71.2 (2C, C-4), 71.1 (2C, C-3), 70.8 (2C, C-5'), 69.9 (2C, C-3'), 69.4 (2C, C-2), 69.3 (2C, C-2'), 69.2 (2C, C-4'), 67.0 (2C, C-6), 61.2 (2C, C-6'), 21.2, 21.1, 21.0, 20.9, 20.8, 20.8, 20.7 (14C, CH_3).
HRMS (FT-ICR): *m/z* 1419.37678 $[M+Na]^+$.
Anal. calcd. for $C_{60}H_{72}N_2O_{36}$: C 51.58, H 5.19, N 2.00. Found: C 51.62, H 5.10, N 1.95.

4.6.1.4 4,5-Di(2,3,6,2',3',4',6'-hepta-O-acetyl-α-D-cellobiose)phthalonitrile (32g)

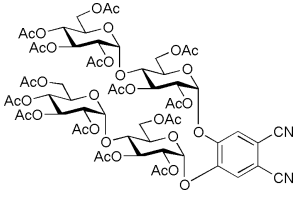


Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-D-cellobiose (**31g**, 2 mmol) as described for compound **32a**. Purification was carried out by column chromatography using hexane ethylacetate mixture (2:5) to afford the product as white solid. Yield (74%).
Mp: 150-155 °C. $[\alpha]_D^{20}$ = +97.6 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 2H, H^{Ar}), 5.65 (d, $J_{1,2}$ = 3.3 Hz, 2H, H-1), 5.51 (t, $J_{3,2}$ = $J_{3,4}$ = 10.2 Hz, 2H, H-3), 5.07 (t, $J_{3',2'}$ = 9.2, 4H, H-4', H-3'), 4.98 (dd, $J_{2,3}$ = 10.2, $J_{2,1}$ = 3.3 Hz, 2H, H-2), 4.77 (t, $J_{4,5}$ = 9.2 Hz, 2H, H-4), 4.39(bd, $J_{1',2'}$ = 8.1 Hz, 2H, H-1'), 4.36-4.32 (m, 4H, H-2', H6b'), 4.08-3.97 (m, 4H, H-6a, H-6a'), 3.72-3.60 (m, 6H, H-6b, H-5, H-5'), 2.10, 2.06, 2.04, 1.96, 1.95, 1.90, 1.89 (7s, 7 x 6H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 170.7, 170.5, 169.9, 169.7, 169.4, 169.0 (14C, C=O), 150.4 (2C, O-C^{Ar}), 119.4 (2C, H-C^{Ar}), 115.3 (2C, CN), 111.0 (2C, NC-C^{Ar}), 101.2 (2C, C-1'), 95.9 (2C, C-1), 73.2 (2C, C-4), 72.3 (2C, C-5), 71.7 (2C, C-

3'), 70.9 (2C, C-3), 70.6 (2C, C-5'), 69.7 (2C, C-2'), 68.9 (2C, C-2), 68.1 (2C, C-4'), 62.0 (2C, C-6), 61.8 (2C, C-6'), 21.2, 21.1, 21.0, 20.9, 20.8, 20.8, 20.7 (14C, CH_3). HRMS (FT-ICR): *m/z* 1419.42746 $[M+Na]^+$.

Anal. calcd. for $C_{60}H_{72}N_2O_{36}$: C 51.58, H 5.19, N 2.00. Found: C 51.46, H 5.29, N 1.89.

4.6.1.5 4,5-Di(2,3,6,2',3',4',6'-hepta-O-acetyl-α-D-maltose)phthalonitrile (32i)



Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-D-maltose (**31i**, 2 mmol) as described for compound **32a**. Purification was carried out by column chromatography using hexane ethyl acetate mixture (2:5) to afford the product as white solid. Yield (62%).

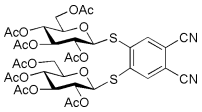
Mp: 128-131 °C. $[\alpha]_D^{20}$ = +213.8 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (s, 2H, H^{Ar}), 5.79 (d, $J_{1,2}$ = 3.8 Hz, 2H, H-1), 5.61 (t, $J_{3',4'}$ = 9.9 Hz, 2H, H-3'), 5.32 (d, $J_{1',2'}$ = 4.0 Hz, 2H, H-1'), 5.26 (t, $J_{3,2}$ = $J_{3,4}$ = 10.2 Hz, 2H, H-3), 5.05-5.01 (m, 4H, H-2', H-4'), 4.86 (dd, $J_{2,3}$ = 10.2 Hz, $J_{2,1}$ = 3.8 Hz, 2H, H-2), 4.43 (bd, *J* = 10.7, 2H, H-6a), 4.23-4.19 (m, 4H, H-5', H-6b), 4.05-3.94 (m, 8H, H-4, H-5, H-6a',6b'), 2.11, 2.08, 2.07, 2.04, 2.01, 1.98, 1.96 (7s, 7 x 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.7, 170.3, 169.9, 169.4, 169.1, 168.9 (14C, C=O), 150.1 (2C, O-C^{Ar}), 119.9 (2C, H-C^{Ar}), 115.3 (2C, CN), 111.0 (2C, NC-C^{Ar}), 96.8 (2C, C-1'), 95.9 (2C, C-1), 77.1 (2C, C-3), 74.1 (2C, C-5), 71.9 (2C, C-4), 70.4 (2C, C-2), 70.3 (2C, C-2'), 69.4 (2C, C-3'), 69.1 (2C, C-5), 68.3 (2C, C-4'), 63.0 (2C, C-6), 61.8 (2C, C-6'), 21.2, 21.1, 21.0, 21.0, 21.0, 20.9, 20.8 (14C, CH_3). HRMS (FT-ICR): *m/z* 1419.37527 $[M+Na]^+$.

Anal. calcd. for $C_{60}H_{72}N_2O_{36}$: C 51.58, H 5.19, N 2.00. Found: C 51.73, H 5.01, N 2.04.

4.6.1.6 4,5-Di(2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosyl)phthalonitrile (32b)



Tetrabutylammonium hydroxide (14 ml, 20 mmol) was added to a mixture of 4,5-difluorophthalonitrile **(26b)** (1.64 g, 10 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **(31b)** (7.29 g, 20 mmol) in DCM (20ml). The reaction mixture was stirred at room temperature for 48 hours, diluted with water and extracted with DCM. Organic phase was washed with water, dried with $MgSO_4$ and concentrated in vacuo. The obtained syrup purified by column chromatography over silica gel using toluene acetone (5:1) mixture as solvent to afford white solid in 65% yield.

Mp: 226-230 °C. $[\alpha]_D^{20}$ = -79.2 (*c* 0.5, $CHCl_3$).

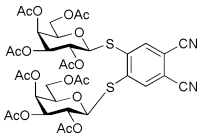
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 2H, H^{Ar}), 5.24 (t, $J_{4,3} = J_{4,5}$ 9.9 Hz, 2H, H-4), 5.07 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 9.9 Hz, 4H, H-2, H-3), 4.81 (d, $J_{1,2}$ = 10.2 Hz 2H, H-1), 4.16 (d, *J* = 4.3 Hz, 4H, H-6a,b), 3.84-3.79 (m, 2H, H-5), 2.13, 2.06, 2.02, 1.98 (4s, 4 x 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.3, 169.7, 169.6 (8C, C=O), 142.9 (2C, O-C^{Ar}), 134.4 (2C, H-C^{Ar}), 115.3 (2C, CN), 114.6 (2C, NC-C^{Ar}), 84.1 (2C, C-1), 76.7 (2C, C-5), 73.7 (2C, C-3), 69.7 (2C, C-2), 68.2 (2C, C-4), 62.5 (2C, C-6), 21.2, 21.0, 20.9, 20.9 (8C, CH_3).

HRMS (FT-ICR): *m/z* 875.16136 $[M+Na]^+$.

Anal. calcd. for $C_{36}H_{40}N_2O_{18}S_2$: C 50.70, H 4.73, N 3.28. Found: C 50.75, H 4.69, N 3.41.

4.6.1.7 4,5-Di(2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranosyl)phthalonitrile (32d)



Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose (**31d**, 2 mmol) as described for compound **32b**. Column chromatography was carried out by using hexane ethylacetate mixture (1:1) to afford the product as white solid. Yield (80%).

Mp: 108-112 °C. $[\alpha]_D^{20}$ = -18.8 (*c* 0.5, $CHCl_3$).

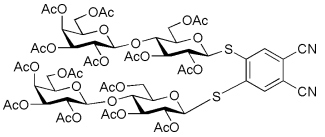
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 2H, H^{Ar}), 5.46 (d, $J_{4,3}$ = 3.1 Hz, 2H, H-4), 5.29 (t, $J_{2,1}$ = $J_{2,3}$ = 9.9 Hz, 2H, H-2), 5.08 (dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 3.1 Hz, 2H, H-3), 4.78 (d, $J_{1,2}$ = 9.9 Hz, 2H, H-1), 4.17-4.00 (m, 6H, H-5, H6a,b), 2.19, 2.08, 2.06, 1.96 (4s, 4 x 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.4, 170.2, 169.8 (8C, C=O), 142.8 (2C, O-C^{Ar}), 134.5 (2C, H-C^{Ar}), 115.5 (2C, CN), 114.2 (2C, NC-C^{Ar}), 84.5 (2C, C-1), 75.8 (2C, C-5), 71.9 (2C, C-3), 67.5 (2C, C-4), 66.6 (2C, C-2), 62.5 (2C, C-6), 21.4, 21.1, 21.0, 20.9 (8C, CH_3).

HRMS (FT-ICR): *m/z* 875.16055 $[M+Na]^+$.

Anal. calcd. for $C_{36}H_{40}N_2O_{18}S_2$: C 50.70, H 4.73, N 3.28. Found: C 50.43, H 4.47, N 3.13.

4.6.1.8 4,5-Di(2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-D-lactose)phthalonitrile (32f)



Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-1-thio-β-D-lactose (**31f**, 2 mmol) as described for compound **32b**. Purification was carried out by column chromatography using hexane ethyl acetate mixture (1:2) to afford the product as white solid. Yield (55%).

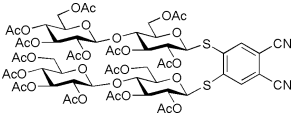
Mp: 140-145 °C. $[\alpha]_D^{20}$ = -47.2 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 2H, H^{Ar}), 5.33 (d, $J_{4',3'}$ = 3.6 Hz, 2H, H-4'), 5.21 (t, $J_{3,2}$ = $J_{3,4}$ = 8.9 Hz, 2H, H-3), 5.07 (dd, $J_{2,1}$ = 10.2, $J_{2,3}$ = 8.9 Hz 2H, H-2), 4.92 (m, 4H, H-2', H-3'), 4.75 (d, $J_{1,2}$ = 10.2, Hz, 2H, H-1), 4.50 (bd, $J_{6b,6a}$ = 11.9 Hz, 2H, H-6b), 4.47 (d, $J_{1',2'}$ = 7.9 Hz, 2H, H-1'), 4.09-4.05 (m, 6H, H-6a, H-6a',b'), 3.86 (t, $J_{5',6a'}$ = 6.6 Hz, 2H, H-5'), 3.78-3.71 (m, 4H, H-4, H-5), 2.15, 2.11, 2.04, 2.03, 2.01, 1.93 (6s, 42H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.7, 170.4, 170.4, 169.9, 169.8, 169.4 (14C, C=O), 142.8 (2C, O-C^{Ar}), 134.4 (2C, H-C^{Ar}), 115.3 (2C, CN), 114.5 (2C, NC-C^{Ar}), 101.5 (2C, C-1'), 83.9 (2C, C-1), 77.1 (2C, C-5), 76.1 (2C, C-4), 73.6 (2C, C-

3), 71.3 (2C, C-5'), 71.2 (2C, C-3'), 70.8 (2C, C-2), 69.9 (2C, C-2'), 69.4 (2C, C-4'), 62.5 (2C, C-6), 61.2 (2C, C-6'), 21.2, 21.1, 21.0, 21.0, 20.9, 20.9, 20.8 (14C, CH_3).
HRMS (FT-ICR): *m/z* 1451.32976 $[M+Na]^+$.
Anal. calcd. for $C_{60}H_{72}N_2O_{34}S_2$: C 50.42, H 5.08, N 1.96. Found: C 50.41, H 5.12, N 1.85.

4.6.1.9 4,5-Di(2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-D-cellobiose)phthalonitrile (32h)

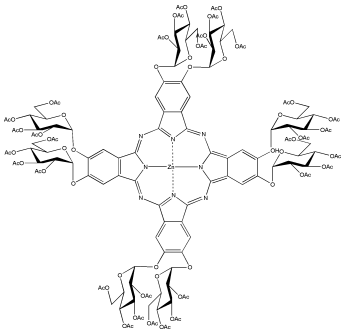


Prepared from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-1-thio-β-D-cellobiose (**31h**, 2 mmol) as described for compound **32b**. Purification was carried out by column chromatography using hexane ethylacetate mixture (1:3) to afford the product as white solid. Yield (71%).
Mp: 275-280 °C. $[\alpha]_D^{20}$ = -58.6 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 2H, H^{Ar}), 5.19 (t, $J_{4',3'}$ = 5.1 Hz, 2H, H-4'), 5.12 (t, $J_{2,1}$ = 10.2 Hz, 2H, H-2), 5.10-4.96 (m, 4H, H-2', H-3), 4.89 (t, $J_{3',4'}$ = 5.1 Hz, 2H, H-3'), 4.75 (d, $J_{1,2}$ = 10.2, Hz, 2H, H-1), 4.52 (bd, $J_{6b,6a}$ = 8.9 Hz, 2H, H-6b), 4.48 (d, $J_{1',2'}$ = 6.4 Hz, 2H, H-1'), 4.36 (dd, $J_{6b',6a'}$ = 12.5 Hz, $J_{6b',5}$ = 4.1 Hz, 2H, H-6b'), 4.07-4.01 (m, 4H, H-6a, H-6a'), 3.74-3.67 (m, 4H, H-4, H-5), 3.65-3.63 (m, 2H, H-5'), 2.15, 2.05, 2.03, 1.99, 1.97, 1.94 (6s, 42H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.7, 170.5, 169.9, 169.8, 169.6, 169.4 (14C, C=O), 142.8 (2C, O-C^{Ar}), 134.5 (2C, H-C^{Ar}), 115.3 (2C, CN), 114.5 (2C, NC-C^{Ar}), 101.2 (2C, C-1'), 83.9 (2C, C-1), 77.1 (2C, C-5), 76.3 (2C, C-4), 73.3 (2C, C-3), 73.2 (2C, C-4'), 72.4 (2C, C-5'), 71.9 (2C, C-2'), 69.8 (2C, C-2), 68.0 (2C, C-3'), 62.4 (2C, C-6), 61.8 (2C, C-6'), 21.3, 21.1, 20.9, 20.8 (14C, CH_3).
HRMS (FT-ICR): *m/z* 1451.33138 $[M+Na]^+$.
Anal. calcd. for $C_{60}H_{72}N_2O_{34}S_2$: C 50.42, H 5.08, N 1.96. Found: C 50.16, H 5.07, N 1.91.

4.6.2 Synthesis of acetyl protected octaglycosylated zinc(II) phthalocyanines 33a-33i: General Procedure

A mixture of phthalonitrile (1 mmol), *p*-toluenesulfonic acid monohydrate (0.1 mmol), hexamethyldisilazane (HMDS) (0.3 mmol), DMF (0.5 ml) and $Zn(OAc)_2.2H_2O$ (0.5 mmol) in a sealed glass tube was stirred and heated at 125-130 ^oC overnight. The semisolid obtained was cooled and precipitated with methanol water (1:2) mixture. The precipitates obtained were dried and column chromatographed with ethylacetate containing 0-5% methanol.

4.6.2.1 2,3,9,10,16,17,23,24-Octa(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-phthalocyaninato zinc(II) 33a



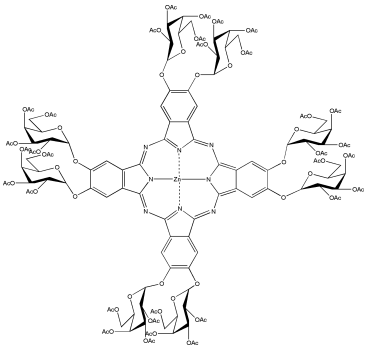
Prepared from phthalonitrile **32a** (5 g, 6.1 mmol), using general procedure to furnish green solid. Yield: 3.8 g (75%).

^1H NMR (400MHz, $CDCl_3$): δ = 9.16 (bs, 8H, H^{Ar}), 6.47 (bs, 8H, H-1), 5.92-5.88 (m, 8 H), 5.41-5.25 (m, 16H), 4.35-4.18 (m, 24H), 2.28-1.96 (m, 96 H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 673 (5.50), 607 (4.68), 360 (5.10), 288 (4.76).

HRMS (MALDI–TOF): *m/z* calcd for $C_{144}H_{161}N_8O_{80}Zn$, $[M+H]^+$, 3345.8068; found, 3345.942, calcd for $[M+H-C_2H_2O]^+$,3303.7962; found 3303.941, calcd. for $[M+H-2(C_2H_2O)]^+$,3261.7856; found 3261.852. HRMS (FT-ICR): m/z calcd for $[M+2Na]^{2+}$, 1760.7989; found, 1760.7967.

4.6.2.2 2,3,9,10,16,17,23,24-Octa(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-phthalocyaninato zinc(II) 33c



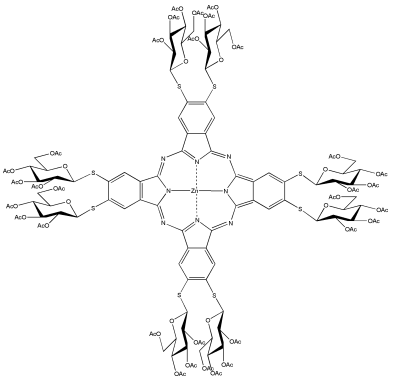
Prepared from phthalonitrile **32c** (5 g, 6.1 mmol), using general procedure to furnish green solid. Yield: 3.56 g (70%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.15 (bs, 8H, H^{Ar}), 6.67 (bs, 8H, H-1), 5.74- 5.58 (m, 20H), 4.60-3.99 (m, 28H), 2.29-1.96 (m, 96H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 673 (5.38), 607 (4.56), 359 (4.96), 288 (4.76).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{144}H_{160}N_8O_{80}Zn$, $[M+H]^+$, 3345.8068; found, 3345.848, calcd. for $[M+H\text{-}C_2H_2O]^+$, 3303.7962; found 3303.869, calcd. for $[M+H\text{-}2(C_2H_2O)]^+$,3261.7850;found 3261.816.

4.6.2.3 2,3,9,10,16,17,23,24-Octa(2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranosyl)-phthalocyaninato zinc(II) 33d



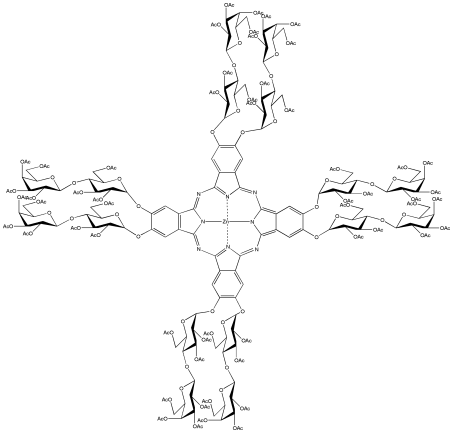
Synthesized from phthalonitrile **32d** (2.56 g, 3 mmol), using general procedure to furnish green solid. Yield: 2.0 g (78%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.35 (bs, 8H, H^{Ar}), 5.54 (bs, 8H, H1), 5.40-5.09 (m, 24H), 4.42 (bs, 8H), 4.06-3.99 (m, 16H), 1.96-1.74 (m, 96H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 700 (5.63), 629 (4.90), 369 (5.24), 302 (4.84).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{144}H_{160}N_8O_{72}S_8Zn$, $[M+H]^+$, 3473.6240; found, 3473.619, calcd. for $[M+H\text{-}C_2H_2O]^+$, 3431.6212; found 3431.504.

4.6.2.4 2,3,9,10,16,17,23,24-Octa(2,2',3,3',4',6,6'-hepta-O-acetyl-α-D-lactose)-phthalocyaninato zinc(II) 33e



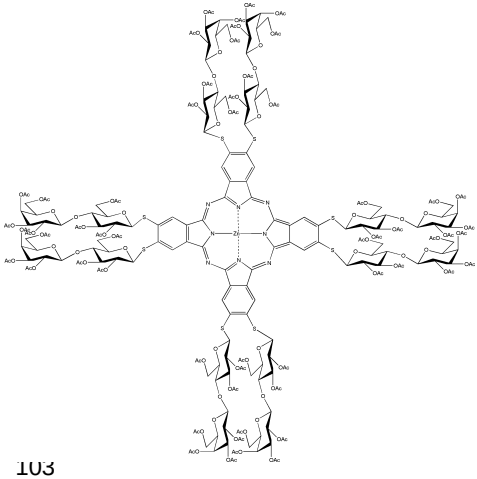
Prepared from phthalonitrile **32e** (4 g, 2.87 mmol), using general procedure to afford green solid. Yield: 2.5 g (62%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.17 (bs, 8H, H^{Ar}), 5.28-5.14 (m, 22H), 4.89-4.71 (m, 22H), 4.31-3.95 (m, 68H), 2.10-1.88 (m, 168H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 674 (5.29), 611 (4.24), 359 (5.00).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{240}H_{288}N_8O_{144}Zn$, $[M]^+$, 5654.2122; found, 5654.067, calcd. for $[M\text{-}2(C_2H_2O)]^+$, 5570.1389; found 5570.553,calcd. for $[M\text{-}3(C_2H_2O)]^+$,5529.1104; found 5529.569,calcd. for $[M\text{-}4(C_2H_2O)]^+$, 5487.655; found 5487.782, calcd. for $[M\text{-}6(C_2H_2O)]^+$, 5403.5922; found 5403.651.

4.6.2.5 2,3,9,10,16,17,23,24-Octa(2,2',3,3',4',6,6'-hepta-O-acetyl-1-thio-β-D-lactose)-phthalocyaninato zinc(II) 33f



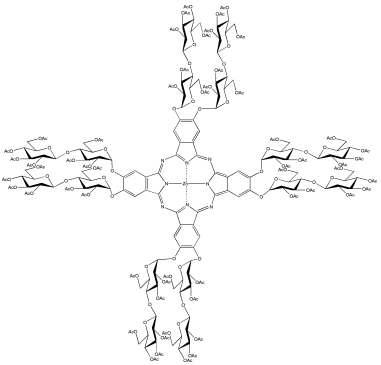
Prepared from phthalonitrile **32f** (4.3 g, 3 mmol), using general procedure to furnish green solid. Yield: 3.0 g (70%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.17 (bs, 8H, H^{Ar}), 6.40 (bs, 8H, H1), 5.80-5.65 (m, 8H), 5.37- 5.21 (m, 24H), 4.97-4.93 (m, 16H), 4.36-3.99 (m, 56H), 2.10-1.91 (m, 168H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 700 (5.11), 628 (4.91), 364 (4.80).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{240}H_{288}N_8O_{136}S_8Zn$, $[M+H]^+$, 5783.7530; found, 5783.981, calcd. for $[M+H-2(C_2H_2O)]^+$,5700.1401; found 5700.190, calcd. for $[M+H-8(C_2H_2O)]^+$,5447.4595; found 5447.484.

4.6.2.6 2,3,9,10,16,17,23,24-Octa(2,2',3,3',4',6,6'-hepta-O-acetyl-α-D-cellobiose)-phthalocyaninato zinc(II) 33g



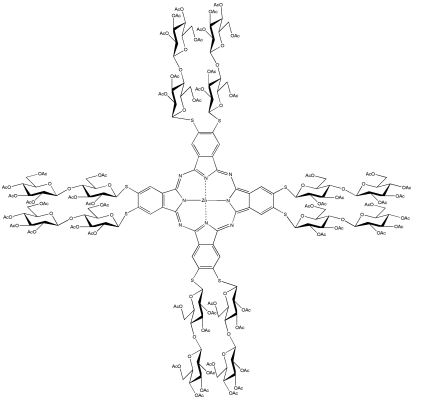
Prepared from phthalonitrile **32g** (4.2 g, 3 mmol), using general procedure to furnish green solid. Yield: 2.3 g (55%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.07 (bs, 8H, H^{Ar}), 6.31 (bs, 8H, H1), 5.71 (bs, 8H), 5.26-5.21 (m, 22H), 4.87-4.74 (m, 22H), 4.29-3.86 (m, 52H), 2.05-1.86 (m, 168 H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 673 (5.59), 612 (4.42), 360 (4.84), 288 (4.70).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{240}H_{288}N_8O_{144}Zn$, $[M+H]^+$, 5655.22; found, 5655.085, calcd. for $[M+H-C_2H_2O]^+$, 5613.1914; found 5613.067, calcd. for $[M+H-2(C_2H_2O)]^+$, 5571.1548; found 5571.093, calcd. for $[M+H-3(C_2H_2O)]^+$, 5529.1181; found 5529.081, calcd. for $[M+H-4(C_2H_2O)]^+$, 5487.0814; found 5486.953.

4.6.2.7 2,3,9,10,16,17,23,24-Octa(2,2',3,3',4',6,6'-hepta-O-acetyl-1-thio-β-D-cellobiose)-phthalocyaninato zinc(II) 33h



Prepared from phthalonitrile **32f** (4.3 g, 3 mmol), using general procedure to furnish green solid. Yield: 2.7 g (64%).

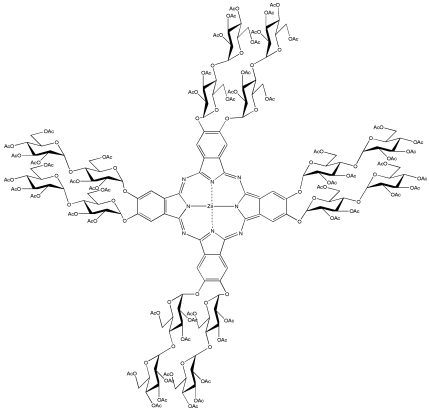
^{1}H NMR (400MHz, $CDCl_3$): δ = 9.35 (bs,

8H, H^{Ar}), 5.50 (bs, 8H, H1), 5.17-4.99 (m, 8H), 4.76-4.64 (m, 24H), 4.08-3.68 (m, 72H), 1.75-1.64 (m, 168H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 700 (5.30), 629 (4.61), 370 (4.96).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{240}H_{288}N_8O_{136}S_8Zn$, $[M+H]^+$, 5783.7530; found, 5783.823, calcd. for $[M+H-C_2H_2O]^+$,5741.7242; found 5741.948, calcd. for $[M+H-2(C_2H_2O)]^+$, 5699.6876; found 5699.947, calcd. for $[M+H-3(C_2H_2O)]^+$, 5657.6509; found 5657.670, calcd. for $[M+H-4(C_2H_2O)]^+$, 5615.6142; found 5615.502, calcd. for $[M+H-5(C_2H_2O)]^+$, 5573.5775; found 5573.653.

4.6.2.8 2,3,9,10,16,17,23,24-Octa(2,2',3,3',4',6,6'-hepta-O-acetyl-α-D-maltose)-phthalocyaninato zinc(II) 33i



Prepared from phthalonitrile **32i** (4.2 g, 3 mmol), using general procedure to afford green solid. Yield: 2.8 g (68%).

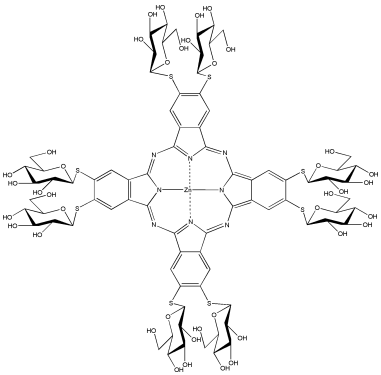
^{1}H NMR (400MHz, $CDCl_3$): δ = 9.17 (bs, 8H, H^{Ar}), 6.40 (bs, 8H, H1), 5.80-5.65 (m, 8H), 5.37-5.21 (m, 24H), 4.97-4.93 (m, 16H), 4.36-3.99 (m, 56H), 2.10-1.91 (m, 168 H, CH_3).

UV/Vis (DCM): λ_{max} (log ε) = 673 (5.49), 608 (4.69), 359 (5.06), 288 (4.84).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{240}H_{288}N_8O_{144}Zn$, $[M+H]^+$, 5655.2202; found 5655.261, calcd. for $[M+H- C_2H_2O]^+$, 5613.1835; found 5613.593, calcd. for $[M+H-2(C_2H_2O)]^+$, 5571.1468; found 5571.489, calcd. for $[M+H-7(C_2H_2O)]^+$, 5360.9634; found 5360.961.

4.6.3 Synthesis of octaglycosylated zinc(II) phthalocyanines 34a-34i

4.6.3.1 2,3,9,10,16,17,23,24-Octa-α-D-glucopyranosyl phthalocyaninato zinc(II) 34b



Zn dust (33 mg, 0.5 mmol) was added to phthalonitrile **33b** (852 mg, 1 mmol) dissolved in THF/MeOH mixture (1:1) in a glass tube. Catalytic amount of conc. HCl was then added. The tube was sealed and the reaction mixture was refluxed overnight. The reaction mixture was diluted with small amount of water and filtered to remove unreacted metal. The filtrate was concentrated to obtain crude phthalocyanine, which was purified by reverse phase HPLC with water/acetonitrile as solvent; Yield: 100 mg (19%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 7.79 (bs, 8H, H^{Ar}), 5.60 (bs, 8H, H1), 5.39-4.95 (m, 32H), 3.51-3.19 (m, 48H).

UV/Vis (DMSO): λ_{max} (log ε) = 710 (5.38), 636 (4.66), 371 (4.99).

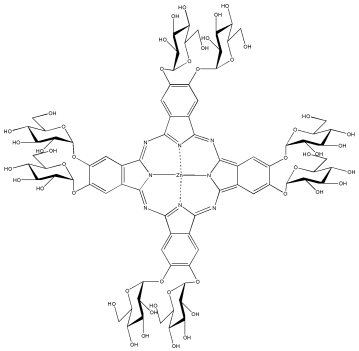
HRMS (MALDI–TOF): *m/z* calcd. for $C_{80}H_{96}N_8O_{40}S_8Zn$, $[M]^+$, 2128.2781; found, 2128.258, calcd. for $[M\text{-}C_6H_{10}O_5]^+$, 1966.2253; found 1966.232. HRMS (FT-ICR): *m/z* calcd. for $[M+2Na]^{2+}$, 1089.1278; found, 1089.1282.

4.6.4 Deprotection of acetyl groups: General procedure

Phthalocyanine (400 mg) was dissolved in 2:1 mixture of DMSO/MeOH (15 ml). Catalytic amount of Na metal was added and the reaction mixture was stirred at room temperature overnight. Ion exchange resin amberlite IR-120H was added to neutralize the solution. The solution was filtered to remove the resins. Precipitation of the product was carried out by excess of acetone. Precipitates formed were filtered and dissolved in small amount of water and reprecipitated with acetone.

The crude product was dried and purified with reverse phase HPLC using water acetonitrile as eluent.

4.6.4.1 2,3,9,10,16,17,23,24-Octa-α-D-glucopyranosyl phthalocyaninato zinc(II) 34a



Prepared from phthalocyanine **33a**, using general procedure to afford bluish green solid. Yield: 225 mg (94%).

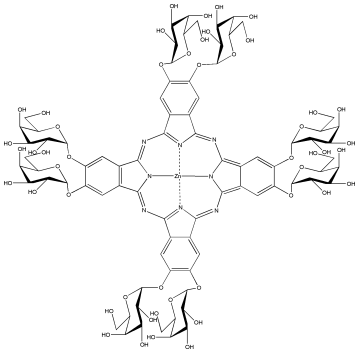
^{1}H NMR (400MHz, DMSO-d_6): δ = 9.24 (bs, 8H, H^{Ar}), 6.21 (bs, 8H, H1), 6.18-6.02 (m, 8H), 5.46 (bs, 8H), 4.42-4.28 (m, 8H), 4.04-3.70 (m, 56H).

UV/Vis (DMSO): λ_{max} (log ε) = 678 (4.89), 612 (4.12), 360 (4.51), 288 (4.23).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{80}H_{96}N_8O_{48}Zn$, $[M^+]$, 2000.4608; found, 2000.380, calcd. for $[M\text{-}C_6H_{10}O_5]^+$, 1838.4080; found 1838.319.

HRMS (FT-ICR): *m/z* calcd. for $[M+2Na]^{2+}$, 1023.7212; found, 1023.7214.

4.6.4.2 2,3,9,10,16,17,23,24-Octa-α-D-galactopyranosyl phthalocyaninato zinc(II) 34c



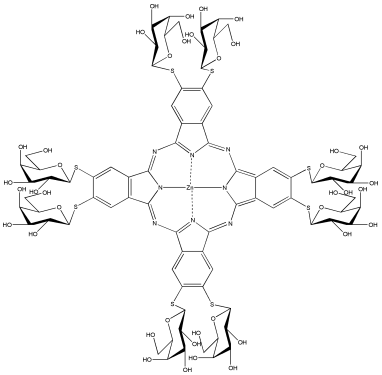
Prepared from phthalocyanine **33c**, using general procedure to afford bluish green solid. Yield: 218 mg (91%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.26 (bs, 8H, H^{Ar}), 6.16 (bs, 8H, H1), 5.21 (d, *J* = 6.32, 8H), 4.94 (d, *J* = 4.6, 8H), 4.86-4.79 (m, 16H), 4.38 (bs, 8H) 4.14-4.07 (m, 24H), 3.79-3.71 (m, 18H).

UV/Vis (DMSO): λ_{max} (log ε) = 680 (5.34), 613 (4.58), 360 (4.97), 290 (4.67).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{80}H_{96}N_8O_{48}Zn$, $[M^+]$, 2000.4608; found, 2000.237,calcd. for $[M\text{-}C_6H_{10}O_5]^+$, 1838.4080; found 1838.217.

4.6.4.3 2,3,9,10,16,17,23,24-Octa-1-thio-β-D-galactopyranosylphthalocyaninato zinc(II) 34d



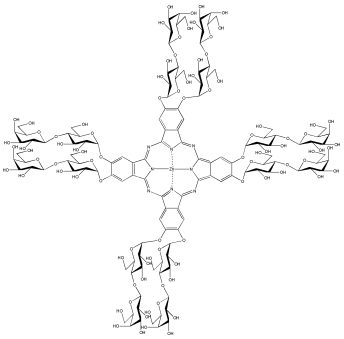
Prepared from phthalocyanine **33d**, using general procedure to afford green solid. Yield: 218 mg (89%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.49 (bs, 8H, H^{Ar}), 5.52 (bs, 8H, H1), 5.37 (bs, 8H), 5.06-4.70 (m, 24H), 3.95-3.63 (m, 48H).

UV/Vis (DMSO): λ_{max} (log ε) = 708 (5.06), 635 (4.33), 371 (4.66), 314 (4.41).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{80}H_{95}N_8O_{40}S_8Zn$, $[M+H^+]$, 2129.2859; found, 2129.283, calcd. for $[M+H\text{-}C_6H_{10}O_5]^+$, 1967.2331; found 1967.225.

4.6.4.4 2,3,9,10,16,17,23,24-Octa-α-D-lactosephthalocyaninato zinc(II) 34e



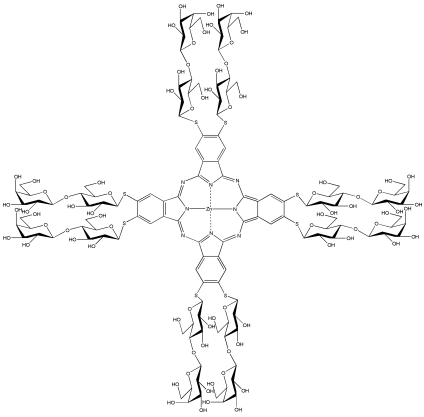
Synthesized from phthalocyanine **33e**, using general procedure to afford bluish green solid. Yield: 217 mg (93%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.18 (bs, 8H, H^{Ar}), 6.12 (bs, 8H, H1), 5.21 (bs, 16H), 4.82-4.11 (m, 56H), 3.87-3.68 (m, 88H).

UV/Vis (DMSO): λ_{max} (log ε) = 680 (4.99), 358 (4.14).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{128}H_{177}N_8O_{88}Zn$, $[M+H]^+$, 3297.8912; found, 3297.478, calcd. for $[M+H\text{-}2(C_6H_{10}O_5)]^+$, 2973.7856; found 2973.426, calcd. for $[M+H\text{-}3(C_6H_{10}O_5)]^+$, 2811.7328; found 2811.266.

4.6.4.5 2,3,9,10,16,17,23,24-Octa-1-thio-β-D-lactose phthalocyaninato zinc(II) 34f



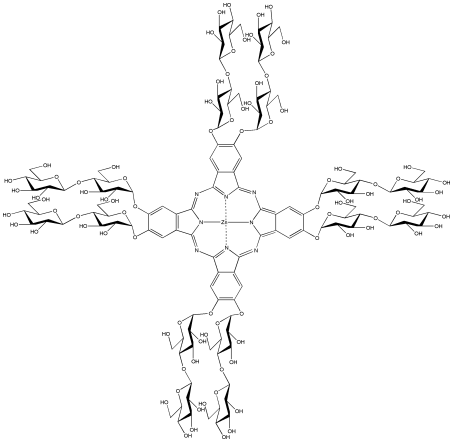
Prepared from phthalocyanine **33f**, using general procedure to furnish green solid. Yield: 206 mg (87%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.41 (bs, 8H, H^{Ar}), 5.11 (bs, 8H, H1), 4.78-4.65 (m, 56H), 3.84-3.32 (m, 112H).

UV/Vis (DMSO): λ_{max} (log ε) = 708 (5.01), 370 (4.76).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{128}H_{176}N_8O_{80}S_8Zn$, $[M]^+$, 3424.7007; found, 3424.352, calcd. for $[M\text{-}2(C_6H_{10}O_5)]^+$, 3100.5951; found 3100.124.

4.6.4.6 2,3,9,10,16,17,23,24-Octa-α-D-cellobiose phthalocyaninato zinc(II) 34g



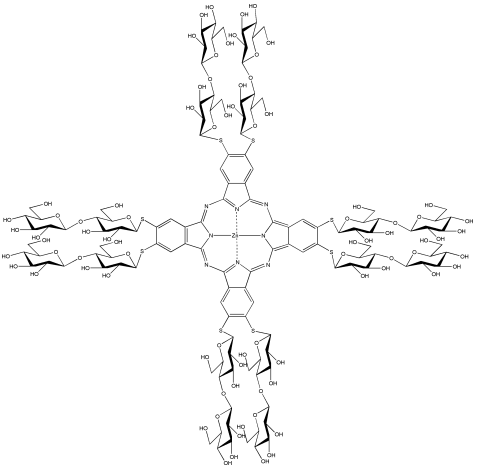
Synthesized from phthalocyanine **33g**, using general procedure to afford bluish green solid. Yield: 210 mg (90%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.16 (bs, 8H, H^{Ar}), 6.13 (bs, 8H, H1), 5.39-5.25 (m, 8H), 5.01 (bs, 16H), 4.76-4.22 (m, 48H), 3.83-3.12 (m, 80H).

UV/Vis (DMSO): λ_{max} (log ε) = 679 (5.31), 612 (4.54), 361 (4.94), 289 (4.73).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{128}H_{176}N_8O_{88}Zn$, $[M]^+$, 3296.88; found, 3297.023,calcd. for $[M\text{-}C_6H_{10}O_5]^+$, 3134.8306; found 3134.858, calcd. for $[M\text{-}2(C_6H_{10}O_5)]^+$, 2972.7778; found 2972.752.

4.6.4.7 2,3,9,10,16,17,23,24-Octa-1-thio-β-D-cellobiose phthalocyaninato zinc(II) 34h



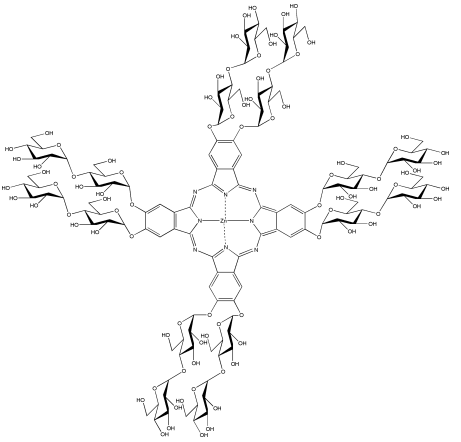
Prepared from phthalocyanine **33h**, using general procedure to afford green solid. Yield: 216 mg (81%).

^{1}H NMR (400MHz, DMSO-d_6): δ = 9.46 (bs, 8H, H^{Ar}), 6.29 (bs, 8H, H1), 5.39-5.31 (m, 16H), 5.01 (bs, 16H), 4.80-4.41 (m, 48H), 3.97-3.17 (m, 80H).

UV/Vis (DMSO): λ_{max} (log ε) = 709 (5.32), 636 (4.60), 372 (4.95).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{128}H_{176}N_8O_{80}S_8Zn$, $[M]^+$, 3424.7007; found, 3424.646, calcd. for $[M+H\text{-}2(C_6H_{10}O_5)]^+$, 3101.6029; found 3101.486.

4.6.4.8 2,3,9,10,16,17,23,24-Octa-α-D-maltose phthalocyaninato zinc(II) 34i



Synthesized from phthalocyanine **33i**, using general procedure to furnish bluish green solid. Yield: 198 mg (85%).

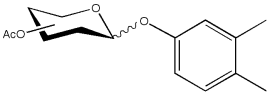
^{1}H NMR (400MHz, DMSO-d_6): δ = 9.23 (bs, 8H, H^{Ar}), 6.03 (bs, 8H, H1), 5.50-5.03 (m, 48H), 4.19 (bs, 12H), 3.91-3.11 (m, 92H).

UV/Vis (DMSO): λ_{max} (log ε) = 679 (4.68), 611 (4.43), 361 (4.35).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{128}H_{176}N_8O_{88}Zn$, $[M]^+$, 3296.8834; found, 3296.746, calcd. for $[M\text{-}C_6H_{10}O_5]^+$, 3134.8306; found 3134.762, calcd. for $[M\text{-}2(C_6H_{10}O_5)]^+$, 2972.7778; found 2972.718, calcd. for $[M\text{-}3(C_6H_{10}O_5)]^+$, 2810.725; found 2810.607, calcd. for $[M\text{-}4(C_6H_{10}O_5)]^+$, 2648.6722; found 2648.515.

4.7 Synthesis of tetraglucosylated zinc(II) naphthalocyanines 45 and 46

4.7.1 3,4-Dimethylphenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (37)



To a solution of penta-*O*-acetyl-β-D-glucopyranose **(35)** (11.71 g, 30 mmol.) and 3,4-dimethylphenol **(36)** (4g, 33 mmol) in dry benzene (100 ml) was added boron trifluorideetherate (0.4 ml). The reaction mixture was stirred at room temperature for 48 hours. After completion, the reaction was terminated by dilution with of benzene (100 ml). The benzene solution was washed with water, sodium hydroxide (1N) and water to neutral washings, dried with sodium sulphate and evaporated in vacuo to obtain syrup like product which was recrystallised from hot ethanol to get white solid. Yield 12.76 g (94%).

Mp: 113-115 °C. $[\alpha]_D^{20}$ = -7.1 (*c* 1, $CHCl_3$).

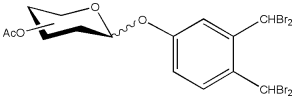
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, ^3J = 8.1 Hz, 1H, H-5'), 6.76 (d, J = 2.3 Hz, 1H, H-2'), 6.70 (dd, ^3J = 8.1 Hz, J = 2.3 Hz, 1H, H-6'), 5.28 – 5.19 (m, 2H, H-1, H-3), 5.12 (t, 1H, H-2), 5.01 (d, ^3J = 7.4 Hz, 1H, H-4), 4.27 (dd, $J_{6a,6b}$ = 12.4, $J_{6a,5}$ = 5.4, 1H, H-6a), 4.15 (dd, $J_{6b,6a}$ = 12.4, $J_{5,6b}$ = 2.5, 1H, H-6b), 3.84 –3.78 (m, 1H, H-5), 2.20, 2.17 (2s, 6H, H-CH_3), 2.06, 2.03, 2.01, 2.00 (4s, 12H, H(Ac)).

^{13}C NMR (100 MHz, $CDCl_3$): δ =171.0, 170.6, 169.8, 169.7 (4C,C=O), 155.4 (1C, C1'), 138.3 (1C, C-2'), 131.9 (1C, C-6'), 130.7 (1C, *C*-5'), 118.9 (1C, C-3'), 114.4 (1C, C-4'), 99.8 (1C, C-1), 73.1 (1C, C-2), 72.3 (1C, C-3), 71.6 (1C, C-5), 68.7 (1C, C-4), 62.4 (1C, C-6), 21.2, 21.0, 20.9, 20.8, 20.3, 10.3 (6C, CH_3).

HRMS (FT-ICR): *m/z* 475.15747 $[M+Na]^+$.

IR (KBr): 2957, 1755, 1607,1503, 1429, 1368, 1213, 1169, 1095, 1077, 1045, 908, 817, 600 cm^{-1}.

4.7.2 3,4-Bis(dibromomethyl)phenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (38)



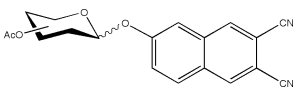
3,4-Dimethylphenyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside **(37)** (9 g, 20 mmol) , NBS (14.24 g, 80 mmol) and benzoyl peroxide (0.15 g) were stirred in dry CCl_4 (100 ml) at reflux for 48 h, while illuminating the mixture with 250W tungsten lamp. The warm solution was filtered and the precipitate was washed with warm CCl_4 (50 ml). After removal of bromine traces with $NaHSO_3$, the filtrate was dried and concentrated to yield a white solid. Crude product was purified by column chromatography using n-hexane: ethylacetate (3:1) mixture. Yield 14 g (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, ^3J = 8.1 Hz, 1H, H-5'), 7.05 (d, J = 2.3 Hz, 1H, H-2'), 6.93 (dd, ^3J = 8.1 Hz, J = 2.3 Hz, 1H, H-6'), 6.90 (s, 1H, H-$CHBr_2$), 6.88 (s, 1H, H-$CHBr_2$), 5.31 – 5.01 (m, 2H, H-1, H-3), 4.54 (s, 1H, H-2), 4.40-4.29 (m, 2H, H-4, H-6a), 4.05-3.80 (m, 2H, H-5, H-6b), 2.09-1.83 (m, 12H, H-CH_3).

IR (KBr): 3050, 2960, 1759, 1606, 1576, 1498, 1429, 1368, 1240, 1042, 907, 702, 639, 599 cm^{-1}.

HRMS (FT-ICR): *m*/*z*: 788.794 $[M + Na]^+$, 802.773 $[M + K]^+$.

4.7.3 6-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)naphthalodinitrile 39



Method A: Compound **38** (7.68 g, 10 mmol) was stirred with fumaronitrile (780 mg, 10 mmol) and NaI (10 g) in dry DMF (100 ml) at 75-80 °C for 24 h. Afterwards additional fumaronitrile (780 mg, 10 mmol) was added, the reaction mixture was stirred for another 24 h. The cold solution was poured into a solution of $NaHSO_3$ in water. Precipitates formed were filtered, dried and purified by column chromatography with acetonitrile: DCM (1:9). Yield 3.4 g (65%).

Method B: 6-Hydroxynaphthalonitrile **(42)** (1.36 g, 7 mmol) and acetobromoglucose **43** (7 mmol) were suspended in acetonitrile (100 ml). Silver(I) oxide (2.32 g, 10 mmol) was added and the reaction mixture was heated at 50 ^{o}C for 24 h. The reaction mixture was cooled and filtered to remove inorganic salts

and solvent was evaporated by rotary evaporator. The solid obtained was purified by column chromatography using toluene aceton (4:1) mixture as solvent. Yield 2.53 g (69%).

Mp: 190-192 °C. $[\alpha]_D^{20}$ = -19 (*c* 0.8, $CHCl_3$).

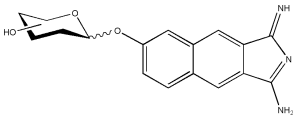
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.68 (s, 1H, H-1'), 8.59 (s, 1H, H-4'), 8.23 (d, *J* = 9.2 Hz, 1H, H-8'), 7.84 (d, *J* = 2.3, 1H, H-5'), 7.64 (dd, *J* = 9.2 Hz, *J* = 2.3 Hz, 1H, H-7'), 5.79 (d, *J* = 7.9 Hz, 1H, H-1), 5.46 (t, *J* = 9.6 Hz, 1H, H-3), 5.31 (t, *J* = 7.9 Hz, 1H, H-2), 5.21 (t, *J* = 9.6, 1H, H-4), 4.37-4.25 (m, 3H, H-5, H-6a,b), 2.03 – 2.01 (m, 12H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ =170.1, 170.7, 170.4, 170.1 (4C,C=O), 159.3 (1C, C6'), 137.3 (1C, C-7'), 137.2 (1C, C-5'), 135.6 (1C, C-8'), 131.0 (1C, C-4'), 124.4 (1C, C-1'), 117.4 (1C, C-2'), 117.3 (1C, C-3'), 113.1 (1C, C-CN),111.6 (1C, C-CN), 99.1 (1C, C-1), 73.6 (1C, C-2), 73.3 (1C, C-3), 72.6 (1C, C-5), 72.0 (1C, C-4), 68.9 (1C, C-6), 21.1, 21.0, 20.9, 20.8, 20.3 (4C, CH_3).

IR (KBr): 2958, 2234 (CN), 1755, 1623, 1597, 1500, 1465, 1369, 1233, 1040, 908, 822, 700 cm^{-1}.

HRMS (FT-ICR): *m/z*: 547.132 $[M + Na]^+$, 563.106 $[M + K]^+$.

4.7.4 6-Glucosyloxyisoindoline 44



Naphthalonitrile **39** (1.0 g, 1.9 mmol) was suspended in dry methanol (10 ml), cooled in ice bath while bubbling the gaseous ammonia through the suspension. At 0°C Na metal (46 mg, 2 mmol) was added.

After some time the solid dissolved in methanol indicating the deprotection of acetyl groups of sugar part. The reaction mixture now warmed slowly to room temperature during 2 h while bubbling the gaseous ammonia through the solution. After completion of the reaction, the solution was cooled, ammonia gas removed and mixture was bubbled with air to remove access of ammonia. Precipitates formed were separated and dried to get the crude product, which was used without further purification for the next step. Yield: 1.2 g (99%).

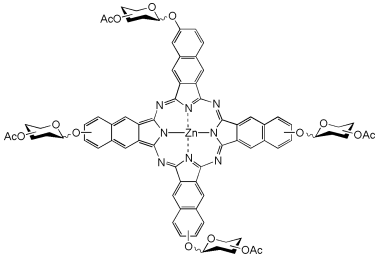
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.28 (s, 1H, H-1'), 8.23 (s, 1H, H-4'), 8.02 (d, *J* = 9.2 Hz, 1H, H-8'), 7.61 (s, 1H, H-5'), 7.40 (dd, *J* = 9.2 Hz, *J* = 2.3 Hz, 1H, H-7'), 5.10 (d, *J* = 7.1 Hz, 1H, H-1), 3.80-3.72 (m, 2H), 3.55-3.41 (m, 4H), 3.37-3.28 (m, 4H), 3.24-3.18 (m, 2H, H-5), 1.22 (s, 1H), 0.89-0.75 (m, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.9 (1C, C6'), 135.5 (1C, C-7'), 131.9 (1C, C-5'), 131.2 (1C, C-8'), 129.7 (1C, C-4'), 121.1 (1C, C-1'), 120.4 (1C, C-NH_2), 112.6 (1C, C-NH), 100.7 (1C, C-1), 77.5 (1C, C-2), 76.9 (1C, C-3), 73.6 (1C, C-5), 70.0 (1C, C-4), 61.0 (1C, C-6).

IR (KBr): 3381 (N-H, O-H), 2957, 1614, 1549, 1517, 1398, 1290, 1079, 1049 cm^{-1}.

HRMS (FT-ICR): *m*/*z*: 374.13466 $[M + Na]^+$.

4.7.5 3,12(13),21(22),30(31)-Tetra(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)naphthalocyaninato zinc(II) 45



A mixture of naphthalonitrile **39** (1.57 g, 3 mmol), *p*-toluenesulfonic acid monohydrate (57 mg, 0.3 mmol), hexamethyldisilazane (HMDS) (0.21 ml, 1 mmol), DMF (2 ml) and $Zn(OAc)_2.2H_2O$ (330 mg, 1.5 mmol) in a sealed glass tube was stirred and heated at 150 ^{o}C overnight. The semisolid obtained was cooled and precipitated with methanol water (1:2) mixture. The precipitates obtained were dried and chromatographed first with ethylacetate to remove unreacted naphthalodinitrile **39** and side products then with ethylacetate containing 2-5% methanol. Yield 730 mg (45%).

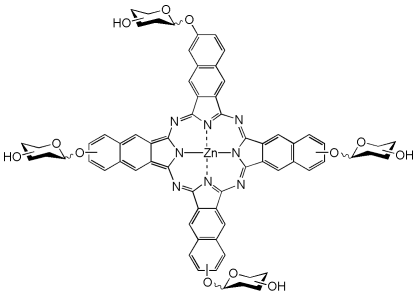
^{1}H NMR (250MHz, CD_3OD-d_4): δ =9.38 (bs, 8H), 8.38 (bs, 4H), 8.11 (bs, 4H), 7.45 (bs, 4H), 5.91-5.68 (m, 4H), 5.39-5.29 (m, 4H), 5.23-5.06 (m, 12H), 4.85-4.48 (m, 8H), 2.25-2.06 (m, 48H).

UV/Vis (DMSO): λ_{max} (log ε) = 769 (5.46), 336 (5.05).

HRMS (MALDI–TOF): *m*/*z* calcd. for $C_{104}H_{96}N_8O_{40}Zn$, $[M]^+$, 2160.5281; found 2160.475 [M]+.

4.7.6 3,12(13),21(22),30(31)-Tetra-D-glucosenaphthalocyaninato zinc(II) 46

Method A: Isoindoline **44** (373 mg, 1 mmol) and DBU 2-3 drops were refluxed in DMAE (1 ml) for 24 h. Reaction mixture was cooled to room temperature and washed with methanol. Precipitates formed were separated by centrifugation. Crude product was extracted with methanol in Soxhlet apparatus. Yield 108 mg (29%).



Method B: Naphthalocyanine **45** (400 mg) was dissolved in 2:1 mixture of DMSO/MeOH (15 ml). Catalytic amount of CH_3ONa was added and the reaction mixture was stirred at room temperature overnight. Ion exchange resin amberlite IR-120H was added to neutralize the solution. The solution was filtered to remove the resins. Precipitation of the product was carried out by excess of acetone. Precipitates formed were filtered and dissolved in small amount of water and reprecipitated with acetone. The crude product was dried and purified with reverse phase HPLC using water acetonitrile as eluent. Yield 257 mg (93%).

^{1}H NMR (250MHz, DMSO-d_6): δ =9.75 (s, 4H), 8.70 (s, 4H), 8.61 (d, *J* = 9.2, 4H), 8.24 (s, 4H), 7.68 (d, *J* = 9.2, 4H), 5.38 (s, 4H), 3.98-3.94 (m, 12H), 3.77-3.42 (m, 28H).

UV/Vis (DMSO): λ_{max} (log ε) = 773 (7.55), 688 (6.85), 344 (7.13).

HRMS (MALDI–TOF): *m/z* calcd. for $C_{72}H_{64}N_8O_{24}Zn$, $[M]^+$, 1488.3241; found 1488.325 $[M]^+$.

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6 Summary

Glycosylated phthalocyanines (Pc's) despite their great potential for the generation of reactive oxygen species (singlet oxygen), are less common in literature. Reactive oxygen species are potent oxidant and are used for the destruction of cancer cells in a therapeutic technique called as photodynamic therapy (PDT). Objective of this work was to synthesize a structural variety of glycosylated zinc(II) phthalocyanines for PDT applications. We chose to prepare phthalocyanines, tetra- and octaglycosylated with different sugar moieties such as glucose, galactose, cellobiose, lactose and maltose. In tetraglycosylated zinc(II) phthalocyanines sugar moieties e.g. glucose, galactose and maltose were linked at 1,8(11),15(18),22(25) positions of the Pc macrocycle through anomeric oxygen or sulphur atoms (pages 55,86). Synthesis of these Pcs started from 3-nitrophthalonitrile, in which NO_2 group was substituted with anomerically deprotected sugar moieties through S_NAr mechanism. Hence appropriate acetyl protected sugar molecules were reacted with 3-nitrophthalonitrile to furnish 3-glycosylated phthalonitriles in good yields (page 53). Synthesis of acetylated sugar substituted phthalocyanines was accomplished when 3-glycosylated phthalonitriles were reacted with hexamethyledisilazane (HMDS) in DMF contaning trimethylsilyltriflate (TMSOTf) and zinc acetate, at 130 ^oC (pages 55,86). Deprotection of acetyl groups in sugar molecules was achieved by reacting the phthalocyanines with MeONa in DMSO/MeOH mixture to afford water soluble 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines in excellent yields (pages 55,89).

For the synthesis of 2,3,9,10,16,17,23,24-octaglycosylated zinc(II) phthalocyanines, corresponding 4,5-diglycosylated phthalonitriles were synthesized from 4,5-difluorophthalonitrile. Therefore 4,5-difluorophthalonitrile was reacted with acetyl protected sugar moieties such as glucose, galactose, lactose, cellobiose and maltose, containing OH or SH groups at anomeric positions (pages 63,94). 4,5-Diglycosylated phthalonitriles were converted into their corresponding acetyl protected PcZn's. Removel of the protecting groups of sugar molecules

afforded water soluble octaglycosylated phthalocyanine systems in good yields (pages 67,101).

2,3,9,10,16,17,23,24-Octagalactosylated PcZn in which Pc macrocycle is attached via position 6 of galactose, was synthesized and characterized. Thus 1,2:3,4-diisopropylidene-α-D-galactopyranose was reacted with 4,5-difluorophthalonitrile to obtain 4,5-(1,2:3,4-diisopropylidene-α-D-galactopyranosyl)phthalonitrile in good yield (pages 59,91). It was further converted to diisopropylidene protected octagalactosylated PcZn. Removal of isopropylidene groups in galactose units furnished water soluble octagalactosylated PcZn in good yield (pages 60,92).

Aggregation behavior of tetra- and octaglycosylated PcZn's was studied by UV/Vis spectroscopy (page 70). In DCM acetyl protected PcZn's show almost no aggregation. In DMSO as solvent deacetylated Pc's also exhibit no aggregation whereas in water these PcZn's are highly aggregated. The aggregation of these Pc's also depends on the size of the sugar substituents e.g. Pc's with bulky sugar substituents in DMSO are less aggregated in comparison to Pc's containing lower analogs. Comparing aggregation behaviour of these Pc's it is evident that the PcZn's in which sugar moieties are linked to the Pc macrocycle through anomeric sulphur atoms show higher aggregation tendency as compared to the Pc's linked via anomeric oxygen atoms, in DMSO solutions.

Naphthalocyanines (Nc's) being higher analogs of Pc macrocycles are also promising candidates for PDT applications. A tetraglucosylated NcZn was synthesized and characterized during this study (page 74). For the synthesis of 6-glucosylated naphthalonitrile two different approaches were adopted. In one methodology glucose pentaacetate was reacted with 3,4-dimethylphenol to furnish glucosylated-o-xylene, which was brominated to give tetrabrominated product. Conversion of tetrabrominated product with fumaronitrile in Diels-Alder process resulted into glucosylated naphthalonitrile (page 75). Alternatively 6-hydroxynaphthalonitrile was converted in to 6-glucosyalted naphthalonitrile by its reaction with acetobromoglucose in the presence of Ag_2O. Naphthalonitrile was tetramerized to form acetyl protected tetraglucosylated NcZn, which was further subjected to deacetylation process to yield tetraglucosylated zinc naphthalocyanine (pages 76,115).

The formed naphthalocyanine was soluble in DMF, DMSO and hot water but almost insoluble in cold water. Acetyl protected NcZn is aggregated in DCM solution as shown by UV/Vis spectroscopic data (page 77). Addition of traces of pyridine in DCM solution of acetyl protected Nc, however diminish this effect, which appears as an increase in the intensity of Q-band. Deacetyalted NcZn does not show any aggregation in DMSO solution as shown by intense Q-band in UV/Vis spectrum.

One major objective of this work was to find a more productive and efficient method for the synthesis of substituted phthalonitriles, considering the importance of phthalonitriles as starting materials for phthalocyanines. In our new method substituted o-dibromobenzenes can be converted in to their corresponding phthalonitriles in good to excellent yields, using Pd(0) catalyst under moderate reaction conditions (pages 48,82).

6 Zusammenfassung

Glycosylierte Phtalocyanine (Pc) sind trotz ihres großen Potentials für die Generierung von reaktiven Sauerstoffspezies (Singulett-Sauerstoff) selten in der Literatur zu finden. Reaktive Sauerstoffspezies sind starke Oxidationsmittel und werden in einer Behandlungsmethode, die als „Photodynamische Therapie (PDT)“ bekannt ist, zur Zerstörung von Krebszellen eingesetzt. Ziel dieser Arbeit war die Synthese von verschiedenen glycosylierten Zink(II) – Phtalocyanine für den Einsatz in der PDT. Wir entschieden uns dazu, tetra- und oktaglycosylierte Phtalocyanine mit verschiedenen Zuckerresten wie Glucose, Galactose, Cellobiose, Lactose und Maltose herzustellen. An tetraglycosylierten Zink(II) – Phtalocyanine wurden Zuckerreste wie z.B. Glucose, Galactose und Maltose an die Positionen 1,8(11), 15(18), 22(25) des Pc-Heterocyclus durch anomeren Sauerstoff oder Schwefel (Seiten 55, 86) gebunden.

Die Synthese dieser Pcs begann mit 3-Nitrophtalonitril, an dem die Nitrogruppe mit anomer ungeschützten Zuckerresten in einer S_NAr-Reaktion ersetzt wurden. So war es möglich, passend acetylgeschützte Kohlenhydrate mit 3-Nitrophtalonitril in guter Ausbeute zu 3-glycosylierten Phtalonitrilen umzusetzen (Seite 53). Die Synthese von Phtalocyanine, die mit acetylierten Kohlenhydraten substituiert sind, geschah durch Reaktion von 3-glycosylierten Phtalonitrilen, die mit Hexamethyldisilazan (HMDS) in DMF mit Trimethylsilyltriflat (TMSOTf) und Zinkacetat bei 130° C (Seiten 55, 86). Das Entfernen der Acetylschutzgruppen an den Kohlenhydratresten wurde durch Reaktion der Phtalocyanine mit NaOMe in DMSO und MeOH durchgeführt und ergab wasserlösliche 1,8(11), 15(18), 22(25)tetraglycosylierte Zink(II) – Phtalocyanine in hoher Ausbeute (Seiten 55, 89). Für die Synthese von 2,3,9,10,16,17,23,24-oktaglycosylierte Zink(II)-Phtalocyanine wurden entsprechende 4,5-diglycosylierte Phtalonitrile aus 4,5-Difluorphtalonitril hergestellt. Dazu wurde 4,5-Difluorphtalonitril mit Acetylgeschützen Kohlenhydraten wie z.B. Glucose, Lactose, Cellobiose und Maltose mit Hydroxyl- bzw. Thiogruppen am anomeren Zentrum umgesetzt (Seiten 63, 94). Die 4,5-digylcosylierten Phtalonitrile wurden zu den korrespondierenden acetylgeschützten PcZns umgesetzt. Das Entfernen der

Acetylschutzgruppen der Kohlenhydratreste ergab wasserlösliche oktaglycosylierte Phtalocyninsysteme in hoher Ausbeute (Seiten 67, 101).

2,3,9,10,16,17,23,24-Oktagalactosylierte PcZn, in denen der Pc-Makrozyklus an der Position 6 der Galactose angebunden ist, wurden hergestellt und charakterisiert. Dafür wurde 1,2:3,4-diisopropyliden-α-D-Galactopyranose mit 4,5-Difluorphtalonitril umgesetzt, um 4,5-(1,2:3,4-Diisopropyliden- α-D-galactopyranosyl)Phtalonitril in hoher Ausbeute zu erhalten (Seiten 59, 91). Es wurde weiterhin zum diisopropylidengeschützten oktaglycosylierten PcZn verarbeitet. Das Entfernen der Isopropylidengruppen an den Galactoseeinheiten führte zu wasserlöslichem oktaglycosylierten PcZn in guter Ausbeute (Seiten 60, 92).

Das Aggationsverhalten von tetra- und oktaglycosylierten PcZns wurde mit UV/Vis-Spektroskopie untersucht (Seite 70). In DCM zeigen acetylgeschützte PcZns fast keine Aggregation. In DMSO als Lösemittel weisen deacetylierte Pcs ebenfalls keine Aggregation auf, währen PcZns in Wasser stark aggregieren. Das Maß der Aggregation hängt auch von den Zuckersubstituenten ab, z.B. aggregieren Pcs mit sperrigen Zuckerrresten in DMSO weniger als Pcs mit kleineren Zuckerresten. Ein Vergleich des Aggregationsverhaltens dieser Pcs zeigt, dass die PcZns, in denen die Zuckerreste über eine Thiobrücke am anomeren Zentrum an den Pc-Makrozyklus gebunden sind, in DMSO eher zur Aggregation tendieren als Systeme, in denen Zuckerrest und Makrozyklus durch eine Sauerstoffbrücke verbunden sind.

Napththalocyanine (Ncs), die höhere Analoge der Pc-Makrozyklen sind, sind ebenfalls vielversprechende Kandidaten für die Anwendung in der PDT. Ein tetraglycosyliertes NcZn wurde hergestellt und charakterisiert (Seite 74). Für die Darstellung von 6-glycosyliertem Napththalonitril wurden zwei verschiedene Syntheserouten gewählt. In einem Weg wurde Pentaacetylglucose mit 3,4-dimethylphenol umgesetzt, um glycosyliertes o-Xylen zu ergeben, das durch Bromierung zum tetrabromierten Produkt umgesetzt wurde. Eine Diels-Alder-Reaktion mit der tetrabromierten Verbindung und Fumaronitril ergab glycosyliertes Napththalonitril (Seite 75). Im zweiten Syntheseweg wurde 6-glycosylierten Naphthalonitril durch Reaktion von 6-Hydroxynapththalonitril mit

Acetobromglucose in Gegenwart von Ag_2O dargestellt. Naphthalonitril wurde tetramerisiert, um acetylgeschütztes tetraglycosyliertes NcZn zu ergeben, das durch Verseifung tetraglycosylierte Zink(II)-Naphthalocyanine zu ergeben (Seiten 76, 115).

Das entstandene Napththalocyanine war löslich in DMF, DMSO und heißem Wasser, jedoch in kaltem Wasser beinahe unlöslich. Wie mit UV/Vis-Spektroskopie beobachtet werden kann, aggregiert acetylgeschütztes NcZn in DCM (Seite 77). In einer Lösung aus acetylgeschütztem NcZn in DCM kann dieser Effekt durch die Zugabe von Spuren von Pyridin verringert werden, dies zeigt sich durch eine Intensitätssteigerung der Q-Banden. Deacetyliertes NcZn seigt in DMSO keinerlei Aggregation, wie aus der hohen Intensität der Q-Banden im UV/Vis-Spektrum ersichtlich ist.

Ein Hauptziel der vorliegenden Arbeit war, in Anbetracht der Bedeutung von Phthalonitrilen als Ausgangsverbindungen für Phtalocyanine eine effizientere Methode zur Synthese von substituierten Phthalonitrilen zu finden. In unsere neuen Strategie können substituierte o-Dibrombenzole in ihre entsprechenden Phtalonitrile in hohen bis sehr hohen Ausbeuten umgesetzt werden, indem Pd(0)-Katalysator unter milden Bedingungen eigesetzt wird (Seiten 48, 82).

Abbreviations

δ	chemical shift	**UV/vis**	Ultra-violet/Visible
λ	wavelength	**m**	multiplet
J	coupling constant	**d**	doublet
ε	Extinction coefficient	**dd**	doublet of doublet
		DMSO	Dimethylsulfoxide
c	concentration	**EtOH**	Ethanol
br	broad	**h**	hour
cm	centimeter	**M**	Molar
^{o}C	Degree Celsius	**m/z**	Mass/Charge
DCM	dichloromethane	**ml**	millilitre
DBU	1,8diazabicyclo[5.4.0]-undec-7-ene	**mmol**	millimol
		nm	nanometer
DMAE	Dimethylaminoethanol	**s**	Singlet
DMF	*N,N'*-dimethylformamide	**NBS**	N-Bromosuccinimide
		HPLC	High Performance Liquid Chromatography
EI	Electron Ionization		
FAB	Fast Atom Bombardement	**MPLC**	Medium Pressure Liquid Chromatography
HOMO	Highest Occupied Molecular Orbital	**OL**	Optical Limiting
		PDT	Photodynamic Thereapy
HRMS	High Resolution Mass Spectroscopy	**TMSOTf**	Trimethylsilyltriflate
FT	Fourier Transform	**rt**	Room temperature
ICR	Ion Cyclotron Resonance	**NIS**	*N*-Iodosuccinimide
		TfOH	Triflic acid
LUMO	Lowest Unoccupied Molecular Orbital	**A˚**	Angstrom
		Tf_2O	Triflic anhydride
IR	Infra Red	**PPh_3**	Triphenylphosphene
MALDI	Matrix Assisted Laser Desorption Ionization	**LD**	Lethal Dose
		μ	micro
TOF	Time of Flight	**M**	Molar

MS	Mass Spectroscopy	**NMP**	N-methylpyrrolidinone
MeOH	methanol	**S_NAr**	Substitution
NMR	Nuclear Magnetic Resonance		Nucleophilic Aromatic
		HMPA	Hexamethylphosphortriamide
ppm	parts per million	**MHz**	Megahertz
THF	Tetrahydrofuran	**TBAF**	Tetrabutylammonium fluoride
TLC	Thin Layer Chromatography	**AcOH**	Acetic acid

Erklärung

Ich versichere, das ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollsg angegeben und die Stellen der Arbeit –einschließlich Tabellen und Abbildungen-, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfallals Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie -abgesehen von den unten angegebenen Teilpublikationen- noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluß des Promotionsverfahrens nicht vornehmen werde.

Die Bestimmungen dieser Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von **Prof. Dr. Dr. h. c. Michael Hanack** betreut worden.

Publications

1. Alexey Lyubimtsev, Zafar Iqbal, Michael Hanack. *Aust. J. Chem.* **2008**, *61*, 273-278.
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