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REVIEW ARTICLE

Synthesis and properties of photo-activable phthalocyanines: a brief overview

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Abstract Phthalocyanines (Pcs) can very well satisfy the different demands of photosensitizer in photodynamic therapy (PDT) such as absorption, amphiphilicity and most importantly, high photochemical reactivity, depending on the subtle interplay of structure–function relationships. They have been shown to be phototoxic against a number of tumor cells. Certain criteria of ideal photosensitizers for PDT were described. A brief summary of the synthesis and some properties of photo-activable Pcs have been presented and an outlook for future photocytotoxic Pcs given. These Pcs are classified into three groups: (1) Pcs with different peripheral and/or non-peripheral substitution; (2) Pcs with different axial substitution; (3) Pcs with different metal center.

Keywords Phthalocyanine · Photodynamic therapy · Photodynamic activity · Synthesis · Photosensitizer

Introduction

First discovered about 103 years ago, phthalocyanine (Pc) has attracted considerable attention, and presents an important and active research frontier involving electrophotography, photovoltaic and solar cells, molecular electronics, Langmuir–Blodgett films, photosensitizers, electrochromic display devices, gas sensors, liquid crystals, low-dimensional conductors and optical disks [1–10]. This is because such material possesses interesting biological, electronic, optical, catalytic and structural properties [1, 8]. Currently, numerous studies have been carried out to modify this macrocyclic compound with the goal of moderating its properties and optimizing its performance. In fact, remarkable progress has been made in recent years in the use of Pc derivatives as photosensitizers for photodynamic therapy (PDT) of cancer due to their outstanding advantage that they can selectivity destroy tumor cells without harming the normal tissue [11].

Certainly, an immediate practical application for most of these compounds is not obvious and there rarely is for any truly class of compounds [12], most of our discussions will focus on synthesis and the photodynamic properties of Pcs, since this is where most of the current progress is occurring. A brief introduction to the certain criteria of ideal photosensitizers for PDT will precede the overview of various photocytotoxic Pcs and their corresponding photophysicochemical properties. The emphasis is on recent progress, but for convenience for the reader, old literature is also cited when appropriate.

Certain criteria of ideal photosensitizers for PDT

As we known, photosensitizer is a key factor in PDT which can accumulate in malignant tumors resulting in a desired biological effect and minimize damage to surrounding issues [13, 14]. Porphyrins, hematopotfyrins, chlorins, pyropheophorbides and hypocrellins are

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traditional photosensitizers. These photosensitizers, however, generally induce sustained skin photosensitivity, are a mixture of various mostly unidentified compounds, and absorb light at relatively short wavelengths that can not penetrate deeply into the issue, making them far from ideal for the use in PDT [15]. Pcs, because of the stronger absorption in the red visible region, higher efficiency at generating singlet oxygen and extraordinary stability, have emerged as a promising class of photosensitizers for PDT [16, 17]. Ideal photosensitizers for PDT must meet certain criteria described in the following sections.

Excellent amphiphilicity (hydrophilic and hydrophobic)

Excellent amphiphilicity, particularly water-solubility, is an important aspect of ideal photosensitizer, allowing direct intravenous administration and transport to the intended diseased tissue [14, 18, 19]. Falling this, it may prevent many potentially good therapeutic agents from reaching clinics. Unsubstituted Pcs and metal Pcs are slightly soluble in most common organic solvents. Generally, the low solubility circumstance in various organic solvents and water is a major problem for their practical application in PDT. But their solubility can be greatly improved by placing substituents on the Pc ring at the peripheral and/or non-peripheral benzo-sites. The substituents reduce intermolecular attractions and encourage dissolution in a solvent.

High chemically pure and constant composition

The photosensitizers should be single, well-characterised compounds and maintain a constant composition in the process of PDT with minimal photobleaching [20]. It is highly possible to obtain the chemically pure Pc or its derivatives according to the modern synthetic and purify method. As such, obtaining a pure sample is more apparent. The purification of photosensitizers is important for the healing efficacy of PDT. But most of traditional photosensitizers exist as a mixture of various, mostly unidentified compounds [18]. During the process of PDT, the relation of dose and healing effect is already highly complicated, it is more possible to induce some additional changes, i.e. absorption wavelength, physiological activity, and toxicity, due to the complex mixture of photosensitizers. Photosensitizers also need to have favorable photothermal stability, otherwise it is of no use, and even to lead to the patient is sensitive to sunlight. Some MPcs are important organic dyes, which have favorable photo-thermal stability and constant composition [16].

Appropriate absorb wavelength and high extinction coefficient

The sensitizers should have strong absorptions in the body's therapeutic windows (600–850 nm) with a high extinction coefficient [14]. Generally, the effective penetration depth of the PDT treatment is based on the wavelength of the light and the optical properties of the tissue. In fact, the selected wavelength usually coincides with the absorption of the photosensitizer. Traditional photosensitizers have two very significant disadvantages [11]. On the one hand, these compounds have a number of absorption peaks between 400 and 650 nm that not belong to the body's therapeutic window. On the other hand, they have a lower extinction coefficient that goes against the generation of the excited-state singlet oxygen $^1O_2$. These disadvantages limit their practical applications in PDT. But Pcs differ from the traditional photosensitizers by having nitrogen atoms link the individual pyrrole units and high extinction coefficient. The highly conjugated π system in Pc, afforded by the peripheral benzene rings, strengthens its absorption in the red visible region and overlaps the region of maximum light penetration in tissue, thus making them ideal candidates for PDT [21].

Favorable physiology activity, minimal dark toxicity and lower systemic toxicity

There is a great demand for biodistribution of photosensitizers in PDT [22, 23]. It must have a favorable selectivity toward malignant tissues resulting in only negligible toxicity to surrounding healthy biological matter [24]. Pcs, generally having this desirable characteristic, are promising photosensitizers, which have received considerable attention [25]. Traditional photosensitizers are readily taken up and retained in the skin for up to several weeks, leading to the complication of pronged cutaneous photosensitivity. This is an obvious disadvantage for patients that require them to avoid bright sunlight [17, 18, 26]. Substituted Pcs, belonging to the new generation of substances for PDT, have minimal dark toxicity and lower systemic toxicity. The kinetics of Pcs is much more rapid than traditional photosensitizers, with high tumor to tissue ratio (8:1) which reached after 1–3 h. After an interval of 24–72 h, Pcs are eliminated much more rapidly, almost without fluorescence seen in the tumor [16].

High photochemical reactivity

During the process of medical diagnosis, we usually pay attention to the triplet lifetime of photosensitizers in PDT. The lifetime of triplet state is an important criterion to judge the healing effect of photosensitizers. The time of

reacting with oxygen will be reduced resulting in the shorter lifetime of triplet state, which will not produce enough the singlet oxygen. The energy of triplet state must be higher than the singlet oxygen, or else the photosensitizers will not transfer energy to the ground-state oxygen and finally may not generate singlet oxygen [27]. Modified Pcs with pertinent substituents, generally having these desirable characteristics, are promising second-generation photosensitizers, and be able to effectively produce singlet oxygen and other reactive oxygen species [28].

As described above, Pcs have many advantages compared to traditional photosensitizers. However, aggregation (especially in aqueous media) is a very common phenomenon in this family of compounds due to their large π-conjugated systems, which reduces their photosensitizing efficiency [29, 30]. Thus, no photosensitizer can be expected to fulfill all of these parameters. There should be a lot of work to do in order to overcome the shortcomings of Pcs and to take advantage of their more ideal properties.

General study: structural characteristics and photophysicochemical properties

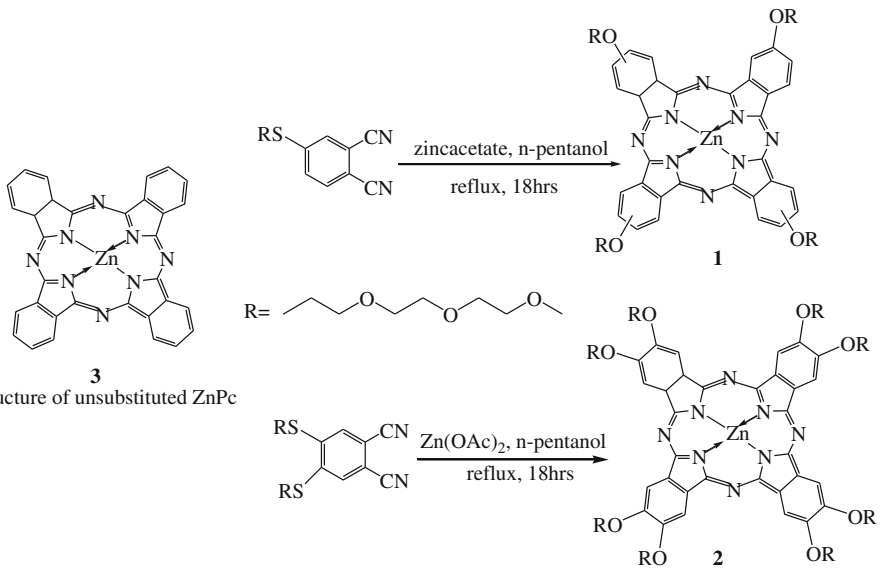
Phthalocyanines with different peripheral and/or non-peripheral substitution

Zinc phthalocyanines with different substitution

The chemical structure of a photosensitizer plays a key role in the success of the compound as a PDT agent. In the year 2007, Atilla et al. reported the synthesis and photodynamic activities of water soluble zinc phthalocyanines (**1**, **2**) bearing tetra- or octa-triethyleneoxysulfonyl groups [31]. Treatment of 4-(4,7,10-trioxaundecan-1-sulfonyl)phthalonitrile with $Zn(O_2CMe)_2$ in the presence of 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) in dried 1-hexanol resulted in the green product **1** in the yield of 33%. Similarly, Pc **2** was also prepared following the same procedure but starting with 4,5-bis(4,7,10-trioxaundecan-1-sulfonyl)phthalonitrile (Scheme 1). The Q-bands of both compounds were observed at 693 and 709 nm for Pcs **1** and **2** in chloroform, respectively. Due to the effect of thia-substitution, a shift to higher wavelengths was observed for both compounds when compared to unsubstituted ZnPc **3**. The fluorescence quantum yields of Pcs **1** and **2** were determined to be 0.20 and 0.13, respectively. This different fluorescence quantum yields indicated that the larger number of substituents in Pc **2** resulting in the increased quenching of this compound. According to the laser scanning microscope of both compounds in cell nucleus, the authors observed that the fluorescence of Pc **1** was increased during scanning due to the higher fluorescence quantum yield of Pc **1** compared to Pc **2**. Both compounds did not show any dark toxicity at Pc concentrations from 0 to 100 μM, it was also observed that the human breast cancer cells survival was decreased after irradiation. However, the photobiological activity of Pc **1** was higher compare to Pc **2**. This was assigned to several factors involving cell uptake, photochemical properties and cell killing ability.

A new series of amphiphilic metal Pcs containing amino units **4**–**9** were reported for PDT [32]. Starting from the 4,5-dichlorophthalonitrile and 2-(dimethylamino)ethanethiol hydrochloride, the precursors **4a** and **7a** were obtained in dimethylsulfoxide (DMSO) at 50 and 80 °C, respectively. Compound **4** was then prepared through, what we term, an "statistical condensation method" in the presence

Scheme 1 Synthesis of compounds **1**–**2** and structure of compound **3**



3
Structure of unsubstituted ZnPc

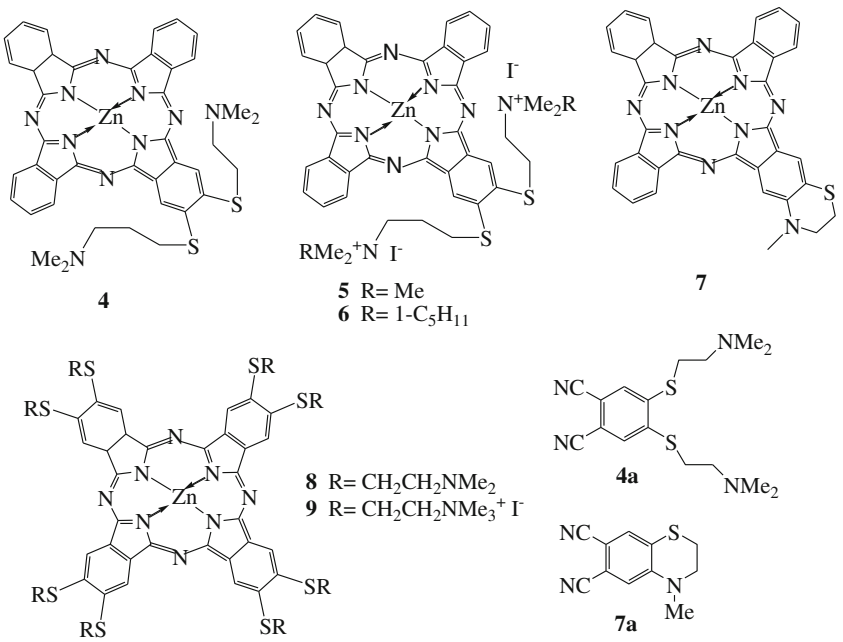


Fig. 1 Structures of phthalocyanines **4–9**

of phthalonitrile **4a**, 3 equiv of the unsubstituted phthalonitrile, $Zn(OAc)_2{\cdot}2H_2O$ and DBU. The dicationic compounds **5** and **6** were obtained through methylation and pentylation of compound **4** using iodomethane and 1-iodopentane. Similarly, Pc **7** was synthesized using precursor **7a** instead of **4a**. For comparison, the compound **8–9** were also prepared with the similar procedures (Fig. 1). According to the steady-state method, all these compounds (except **7**) could generate singlet oxygen with 1,3-diphenylisobenzofuran (DPBF) as the scavenger. The singlet oxygen quantum yield of peripheral disubstituted Pc **4** was determined to be 0.50 that was 2-fold higher than other compounds. Pc **7** containing the non-ionic amino substituent could not generate singlet oxygen. This was assigned to the excited state of Pc **7** which was quenched by the amino substituent. The results of photodynamic activity of Pcs **4–7** and **9** in Cremophor EL emulsions against three different cell lines showed that Pc **4–6** were significantly efficient with IC_{50} value in the range of 0.08–0.29 μM (compared with 0.82–0.93 μM for **7**). The ionic amino octa-substituted Pc **9** was not favorable for PDT due to the IC_{90} value could not be determined. The photodynamic activity of the non-ionic amino octa-substituted Pc **8** was not studied because of its insolubility. According to the fluorescence microscopy, a strong intracellular fluorescence could be observed for the HT29 human colon adenocarcinoma cells after incubation with Pcs **5** and **6** upon excitation at 630 nm. These results suggested that Pcs **5–7** were promising photosensitizers for PDT.

Some new unsymmetrical substituted Pcs **10–16** have been presented for therapeutic applications by Cosimelli et al. [27]. The starting precursors were prepared based on the literature [33]. Being similar to Pcs **4** and **7**, Pcs **10–16** were also prepared through the statistical condensation approach (Fig. 2). The antimicrobial activity of Pcs **10–16** were carried out with Candida albicans as a model. The authors found that Pcs **12**, **14**, **15** and **16** could be considered as inactive, but the mono-substituted Pc **13** displayed some activities. These results suggested that the photoinhibitory activity of mono-substituted Pcs should be related to their amphiphilic property. This behavior has been previously found during a structure activity relationship study on Pc quaternary ammonium salt derivatives.

The design, synthesis and photodynamic activity of a panel of eight Zn–Pcs with different substituted on the benzo units were reported by Banfi et al. [28]. Starting from the desired phthalonitrile, Pcs **17** and **18** were obtained by direct cyclictetramerization (Scheme 2). Pcs **19** and **20** were prepared via the reaction of zinc (II)–tetrasulphonylchloride Pc with 2-(2-aminoethoxy)ethanol and 4-aminobenzonitrile in 27 and 38% yields, respectively. The non-symmetric Pcs **21–24** were obtained by reacting the chloromethyl Pc derivative with different nucleophiles. The results of photodynamic activities of the Pcs **17–24** against human colon adenocarcinoma cells showed that only the dicationic Pc **21** was significantly more phototoxic than porfimer sodium. Although another cationic Pc **22** only differed in the position of OH group with Pc **21**, it showed a contrary effect. However, the other Pcs **17–20**, **23** and **24** did not have phototoxicity. These results indicated that the Pcs with different number and position of benzo-substitution resulted in a different phototoxicity.

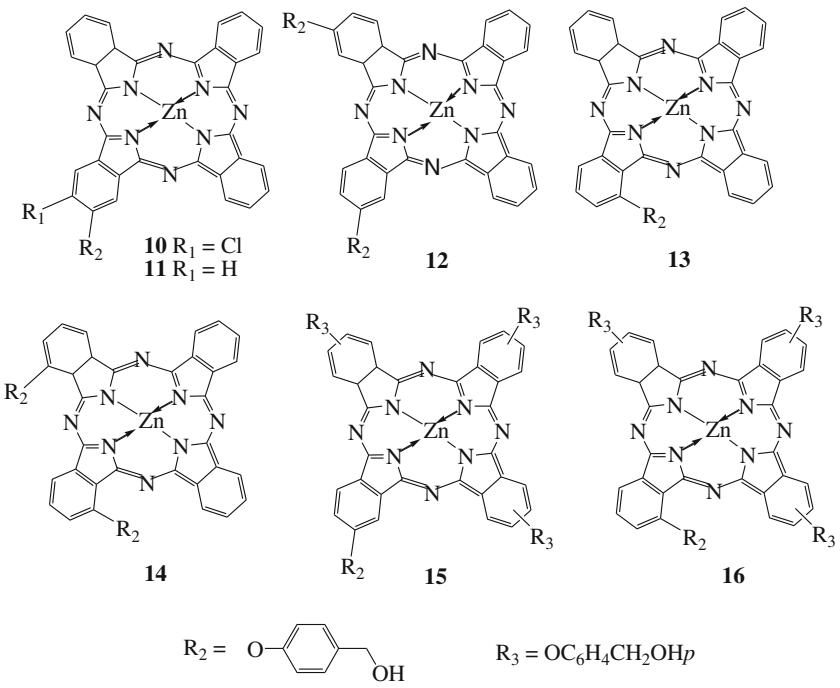
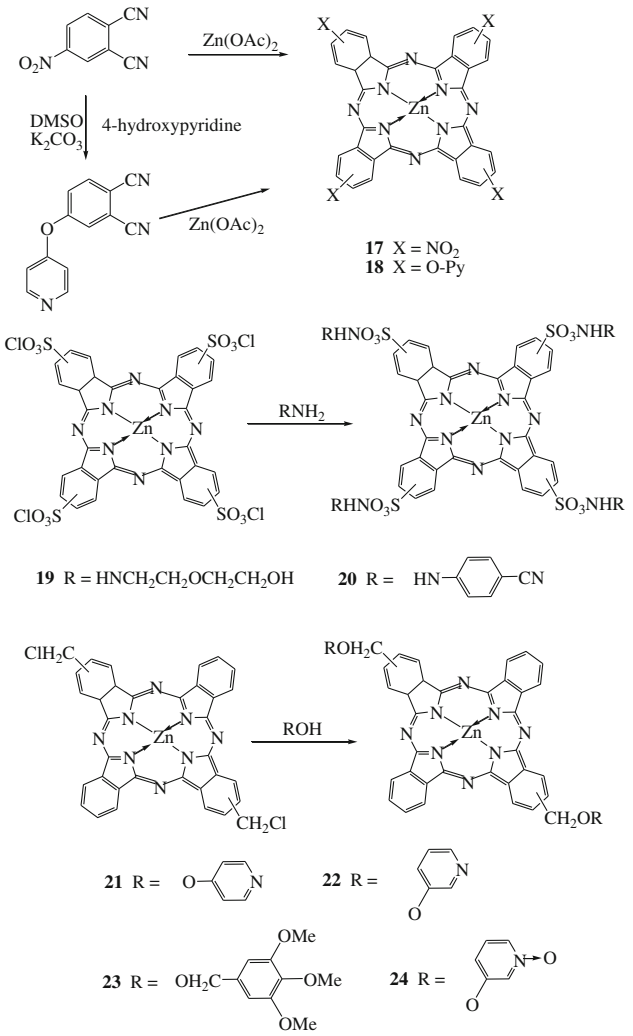


Fig. 2 Structures of phthalocyanines **10**–**16**

Ogunsipe et al. described the effects of different solvents on the singlet oxygen, photobleaching, fluorescence quantum yields and ground state spectra for Pcs **25** and **26**, depicted in Fig. 3 [34]. Pcs **25** and **26** were prepared as described in the literature via total synthesis [35]. When DMSO was used as solvent, the broadening of Q-band and the appearance of a new band centered at 629 nm were observed for Pc **25**. But in other solvents, the changes were not found. This suggested that there were monomeric and aggregated species in DMSO. Pc **26** displayed an extra band centered at 698 nm in tetrahydrofuran (THF). This was ascribed to the more flexible property of the phenoxy rings. For Pc **25**, the singlet oxygen quantum yield ranged from 0.43 (DMSO) to 0.64 in Pyridine, and for Pc **26**, ranged from 0.45 (toluene) to 0.60 in DMSO. The lower singlet oxygen quantum yield of Pc **25** was attributed to its highly aggregated nature that resulted in the dissipation of energy in DMSO. Comparing the photobleaching quantum yields in different solvents, the highest photobleaching was observed for Pc **25** in DMSO. When THF and *n*-butylamine were used as solvents, the lowest photobleaching quantum yields were observed for Pcs **25** and **26**. Comparing the same solvent, there was very little variation in the fluorescence quantum yield for Pcs **25** and **26**. This indicated that the property of the peripheral substituents did not significantly influence the fluorescence of Pc.

Wei et al. designed a novel amphiphilic zinc Pc **27** containing the naphthoxy substituents for use in PDT [36]. The starting phthalonitrile, 4-(5-sulfo-1-naphthoxy) phthalonitrile, was obtained from 4-nitrophthalonitrile [37, 38]. The 4-(5-sulfo-1-naphthoxy) phthalonitrile was then tetracyclized to produce Pc **27**, in 51.8% yield (Scheme 3). The introduction of sulfonated naphthoxy substituents enhanced the amphiphilic and nonaggregated character of Pc **27** that was important for the study of photodynamic activity. When water was used as solvent, zinc phthalocyanine tetrasulfonate ($ZnPcS_4$) only displayed the aggregate band centered at 634 nm, however, Pc **27** showed the enhanced monomer absorption at 677 nm and the decreased aggregate band at 635. This difference was ascribed to the steric hindrance of the peripheral naphthoxy substituents in Pc **27**, which enlarged the distance between two neighbouring macrocycles. When DMSO or ethanol was used as solvent, Pc **27** displayed only the monomer absorption band at 678 nm. These results suggested that Pc **27** was not significantly aggregated in ethanol or DMSO and displayed a lower tendency to form stacked aggregates when compared to $ZnPcS_4$ in water. The quantum yield of singlet oxygen of Pc **27** was determined to be 1.26 using hematoporphyrin as a reference in DMSO. This value was higher when compared to $ZnPcS_4$. This suggested that Pc **27** was a promising photosensitizer for PDT. The photoinduced damage to CT DNA was also tested in air-saturated buffer solution. The 33.70% damaged rate of Pc **27** was much higher than hematoporphyrin (20.91%).

Erdoğmuş and Nyokong recently utilized three novel fluorinated Pcs **28**–**30** as potential photosensitizers for photodynamic activity research [39]. Pc **28** was prepared by the template cyclotetramerization of the precursor 4-[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylthio)phenooxy]-phthalonitrile catalyzed by DBU in the presence of 1-pentanol in 10% yield (Fig. 4). The synthesis



Scheme 2 Synthesis of phthalocyanines **17**–**24**

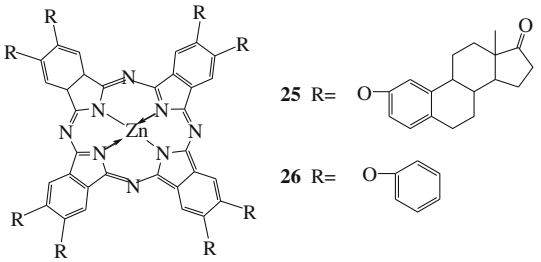


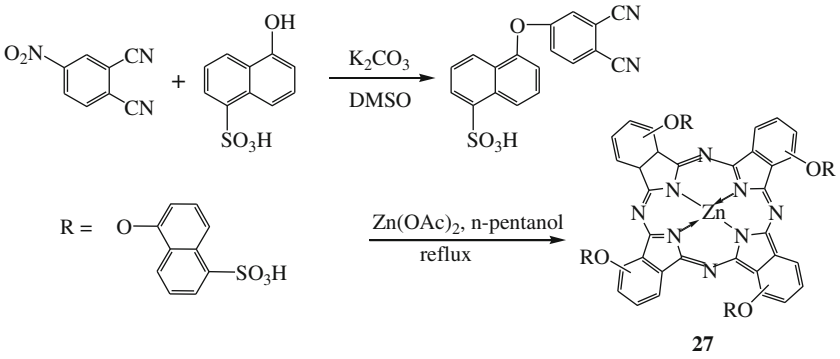
Fig. 3 Molecular structures of phthalocyanines **25** and **26**

of Pc **29** and **30** was similar to that of Pc **29** except 4-[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl thio)phenooxy]-phthalonitrile instead of 4-[4-(trifluoromethyl)pyrimidine-2-thiol]-phthalonitrile and 4-[7-(trifluoromethyl)quinoline-4-thiol]-phthalonitrile was employed in 12 and 7% yields, respectively. The fluorescence quantum yield was determined to be 0.041, 0.035 and 0.021 for Pcs **28**, **29** and **30** in toluene, respectively. The lower values of fluorescence quantum yield of Pcs **28**–**30** (**28**: 0.041, **29**: 0.035 and **30**: 0.021) compared to ZnPc (0.07) in toluene was ascribed to the heavy atom effect of halogen. The triplet life time for Pc **28** (110 μs), **29** (90 μs) and **30** (100 μs) were much lower than unsubstituted ZnPc (330 μs) in toluene. This indicated that the triplet state was quenched by the fluoro substituents. However, the triplet quantum yields for Pcs **29** and **30** (0.69, and 0.71, respectively) were higher than ZnPc (0.65). This suggested that there was more efficient intersystem crossing for Pcs **29** and **30**. According to the photodegradation quantum yields for Pcs **28** (8.11×10^{-6}), **29** (1.39×10^{-6}) and **30** (4.22×10^{-6}), the order of the photobleaching stabilities among the three Pcs was **29** > **30** > **28** in toluene.

Huang et al. studied the photodynamic activities of a series of sulfonated phthalimidomethyl zinc Pcs [40]. In vitro evaluation of the photodynamic activities of the five separating parts of $ZnPcS_nP_m$ series to kill the leukaemia HL60 cells (here, S and P represent suffocates and phthalimidomethyl group, respectively, depicted in Fig. 5) suggested that $ZnPcS_2P_2$, $ZnPcS_1P_3$ and $ZnPcS_{2.5}P_{1.5}$ could kill all the cancer cells. A comparison of the data led to the following order in photodynamic activity: $ZnPcS_2P_2$ > $ZnPcS_1P_3$ > $ZnPcS_{2.5}P_{1.5}$ > $ZnPcS_{2.9}P_{1.1}$ > $ZnPcS_{3.6}P_{0.4}$, i.e. the activity of $ZnPcS_2P_2$ is the biggest one. This could be explained by the following two factors: (1) the amphiphilic structure of $ZnPcS_2P_2$, with the ratio of the number of S group and P group is 2:2, increased the selective uptake of sensitizer by tumor cells; (2) the little steric hindrance of benzene ring and the hydrogen effects of the oxygen atom of P group benefited $ZnPcS_2P_2$ to enrich in tumor tissue. Siejak et al. also synthesized some similar Pcs and studied their photodynamic activities [41]. The author found that the population of the triplet state relied on both the kind of Pc and the number of sulfo group and the mesomeric effect which dominated over the inductive effect in the Pc with two sulfo groups, while the Pc with three or four sulfo groups the inductive effect was essential.

Liu et al. reported the effects of the number (1, 2 or 4) and position (α or β) of substituents on the photodynamic activities of glucosylated zinc (II) Pcs **31**–**36** (Fig. 6) in order to gain insight about the structure–activity–property relations [42]. In his study, these glucosylated compounds exhibited a great influence on their phototoxicities, which followed the order: di-α-substituted (**34** and **35**) > di-β-substituted (**36**) > mono-β-substituted (**33**) > tetra-β-substituted (**31** and **32**) derivatives. As we known, the molecular aggregation provides an efficient non-radiative relaxation pathway for the singlet excited state of Pcs, the fluorescence intensity as well as efficiency at generating singlet oxygen will be reduced as the aggregation tendency increase [31]. Thus, this could explain the order of phototoxicity, because the extent of aggregation of the Pcs

Scheme 3 Synthesis and structure of phthalocyanine **27**



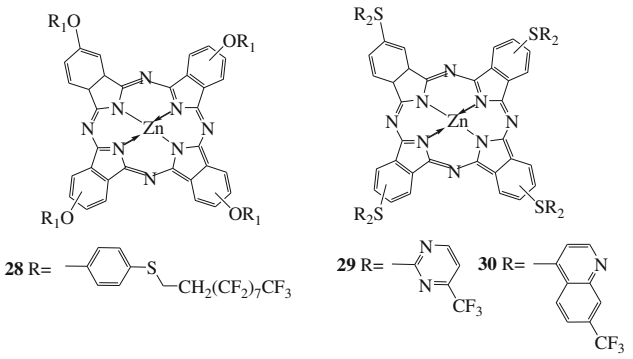


Fig. 4 Molecular structures of phthalocyanines **28–30**

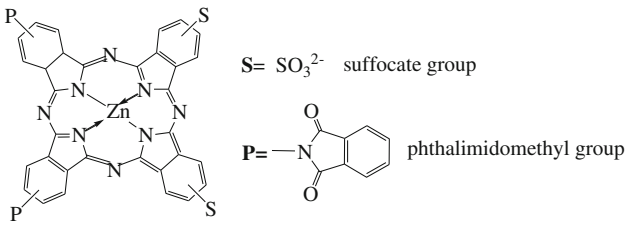


Fig. 5 The structure of $ZnPcS_2P_2$

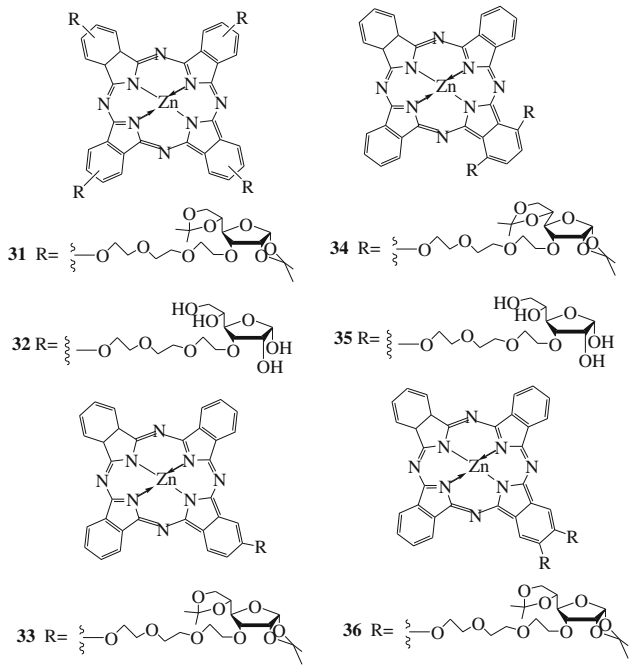


Fig. 6 Chemical structure of phthalocyanine **31–36**

followed the order: di-α > di-β > mono-β > tetra-β-substituted derivatives.

Liu et al. also designed a new series of 1,4-dipegylated Pcs **37–42** for studying the effects of the chain length on the photodynamic activities [43]. Scheme 5 showed the synthesis of di-α-substituted Pcs **37–40** containing diethylene glycol to polyethylene glycol methyl ether chains. The three starting precursors were prepared via the nucleophilic substitution reaction. Then, Pcs **37–40** were obtained through the statistical condensation method in *n*-pentanol with DBU as the base catalyst (Scheme 4). Pcs **41** and **42** were prepared from the reaction of **41** with the tosylates in the presence of NaH in 53 and 51% yields, respectively. These compounds displayed a sharp Q-band centered at 689 nm, a Soret band centered at 340 nm and a vibronic band at 621–622 nm. The fluorescence quantum yield of Pc **37–42** was measured to be 0.18–0.19 in dimethylformamide (DMF) that was lower than ZnPc (0.28). This was ascribed to the lower energy of the Q-band that decreased the HOMO-LUMO gap. All these compounds were highly efficient singlet oxygen generators with a quantum yield of 0.81–0.83 in DMF using DPBF as the scavenger. According to the fluorescence microscopic images of HT29 human colorectal carcinoma, the fluorescence intensity decreased as the length of the substituent increased, i.e. **37** > **38** > **41** > **42** > **39**. Due to the strong dipole–dipole interactions among the side chains, Pcs tend to aggregate in the culture media when the oxyethylene units are larger than 6.

Tetra-trifluoroethoxyl Pc **43** was prepared as a potential photosensitizer for use in PDT of cancer [44]. A mixture of 4-trifluoroethyloxyl phthalic anhydride, urea, zinc acetate and ammonium molybdate was heated at 200–210 °C for 4 h. The crude product was then purified by flash column

chromatography to afford Pc **43** (Fig. 7). Pc **43** displayed maximum absorption band centered at 668, which was suitable for PDT. It has no photobioactivity without irradiation. But under the irradiation of light, it showed very obvious photocytotoxicity on Chinese hamster ovary cells and myeloma cells. The introduction of trifluoro-substituents decreased the photodynamic activity compared to ZnPc, but improved solubility of Pc **43**. This makes this Pc more favorable for PDT.

The synthesis and photochemical properties of novel octa- and tetra-substituted Pcs **44–50** containing fluorinated and nonfluorinated *n*-propanol were reported by Gürol et al. [45]. Fluorophthalonitriles were starting materials for the synthesis of Pcs that were obtained through the nucleophilic substitution of the nitro group (Scheme 5). The zinc Pcs **44–50** were obtained in the presence of starting phthalonitriles, anhydrous zinc acetate and DBU as base in anhydrous *n*-amyl alcohol according to the reported methods. The Q-band positions of these compounds were red-shifted compared to unsubstituted ZnPc. The Q bands of Pcs **45**, **47** and **50** were also red-shifted relative to the corresponding nonfluorinated Pcs **44**, **45**, **48** and **49** in DMSO. This was ascribed to the electron-withdrawing abilities of the fluorine atoms. The fluorescence quantum yields of all these compounds were obtained as 0.13 for **44**, 0.10 for **45**, 0.31 for **46**, 0.26 for **47**, 0.32 for **48**, 0.20 for **49** and 0.27 for **50** in DMSO, respectively. Thus, the fluorescence quantum yields of fluorinated Pcs **44** and **46** were higher than those of the nonfluorinated Pcs **45** and **47**. A decrease of the fluorescence quantum yield in Pcs containing aromatic fluoro groups was also observed compared to Pcs with fluoro-aliphatic groups. The singlet oxygen

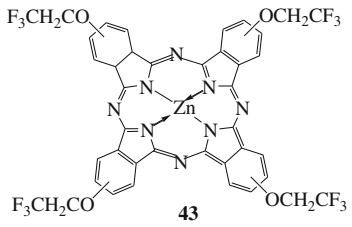
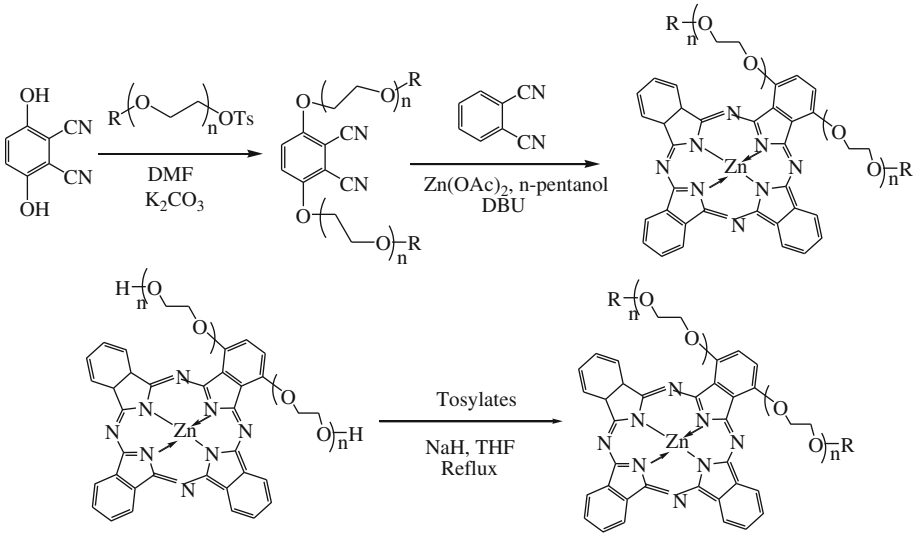


Fig. 7 Chemical structure of phthalocyanine **43**

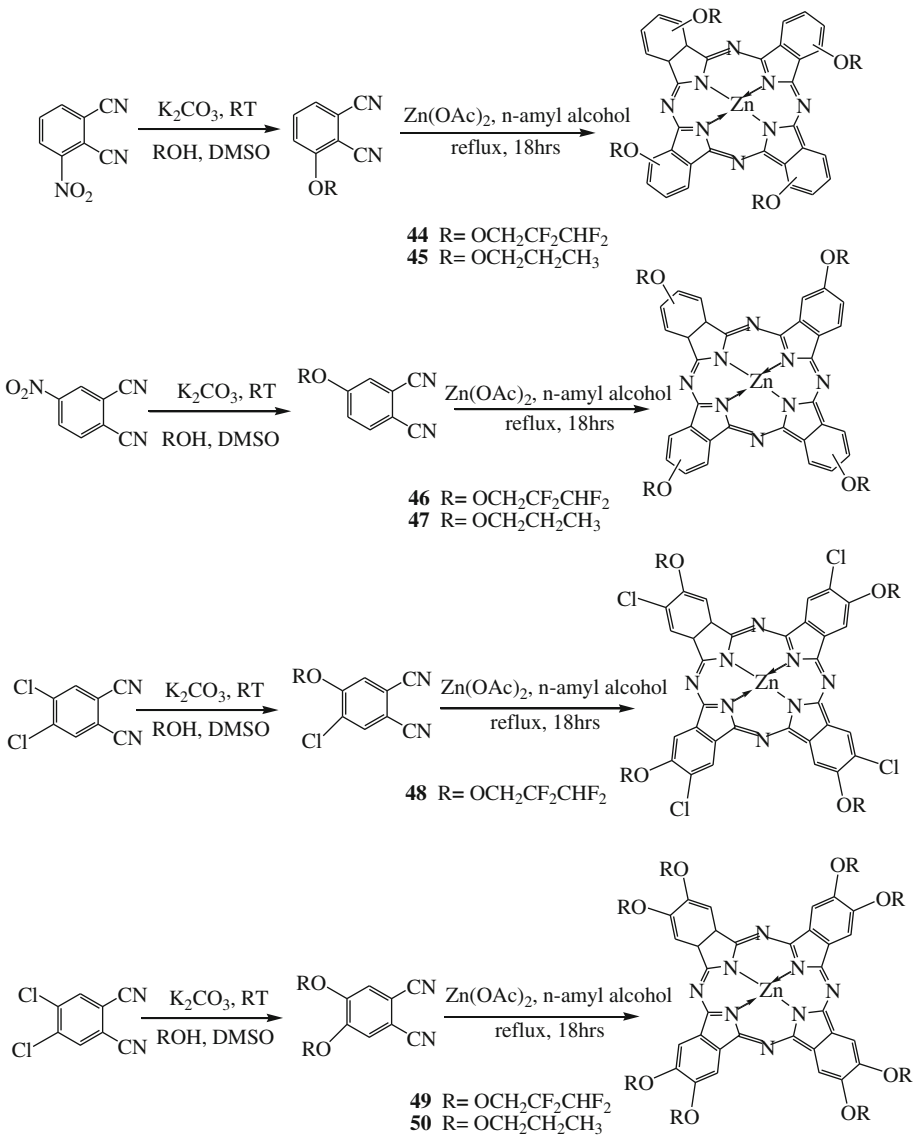
quantum yields of Pc **46** and **48** were lower, and those of the other Pcs **44**, **45**, **47**, **48** and **50** were higher compared to unsubstituted ZnPc in DMSO. The singlet oxygen quantum yields among these compounds decreased as follows: **45** > **44** > **49** > **50** > **47** > ZnPc > **48** > **46**. The singlet oxygen quantum yields ranged from 0.53 to 0.88 suggested that these Pcs were promising photosensitizers for PDT.

Two novel ZnPc derivatives containing 3,5-di-tert-butyl-4-hydroxy-phenyl **51** and 3,5-dimethylphenoxy **52** (Fig. 8) have been prepared for the research of photodynamic activities of these neutral Pcs [46]. The starting phthalonitriles, 4-(3,5-di-butyl-4-hydroxyphenyl)phthalonitrile and 4-(3,5-dimethylphenoxy)phthalo-nitrile, were prepared from 2,6-di-tert-butylphenol and 3,5-di-methylphenol in DMF, respectively. Compounds **51** and **52** were obtained through the tetramerization of these starting materials in the presence of acetate dihydrate in DMF. The singlet oxygen generation abilities of Pcs **51** and **52** were studied in DMSO. The DPBF was employed as a selective singlet oxygen trap. Under the same experimental conditions, the absorption band of DPBF centered at 416 nm

Scheme 4 Synthetic routes of compounds **37–42**



37 n = 2 R = CH_3 **38** n = 4 R = CH_3
39 n = 12 R = CH_3 **40** n = 4 R = H
41 n = 6 R = CH_3 **42** n = 8 R =CH_3



Scheme 5 Chemical pathway used to synthesis the tetra- (**44**, **45**, **46**, and **47**) and octasubstituted (**48**, **49 and 50**) phthalocyanine derivatives

varied slowly in the absence of Pcs. However, the absorbance of solution of Pcs decreased greatly. The degradation of 1,3-dipheny-iso-benzofuran was completely finished within 30 min. This suggested that the two Pcs **51** and **52** have singlet oxygen generation ability. According to the results of photodynamic activity research, Pc **51** could be used as potential photosensitizer against bacterial cells, whereas Pc **52** due to its poor affinity have suggested that the lack of this activity.

Perfluoroisopropyl-substituted zinc Pcs **53**–**56** (Fig. 9) conjugated with deoxyribonucleosides were prepared as potential photosensitizers for PDT [47]. All these unsymmetrical A_3B-type Pcs were synthesized through standard statistical conditions. They all showed two sharp absorption bands centered at 385 and 705 nm for Soret and Q-band, respectively. The fluorescence quantum yields of Pcs **53**, **54**, **55** and **56** were measured to be 0.13, 0.17, 0.14 and 0.16 in EtOH, respectively. This indicated that they were essentially free from aggregation. The in vitro photodynamic activities of these compounds against HT-1080 human fibrosarcoma cell lines were also carried out. The authors found that Pcs **53**, **54** and **55** were promising photosensitizers for PDT due to the fact that they could effectively kill most of the cancer cells.

Two novel Pcs containing methoxy **57** and trifluoromethylbenzyloxy **58** were prepared via a two-step route starting from 4-nitrophthalonitrile in the presence of zinc (II) acetate and DBU in *n*-pentanol (Scheme 6) [48]. The fluorescence quantum yields of Pcs **57** and **58** were determined to be 0.26 and 0.25 in THF, respectively. The singlet oxygen quantum yields of the two Pcs were similar to unsubstituted ZnPc with the value of 0.56. In Hep-2 cellular cultures, no toxicity was observed for Pcs **57** and **58** in the dark. The authors found that the photodynamic

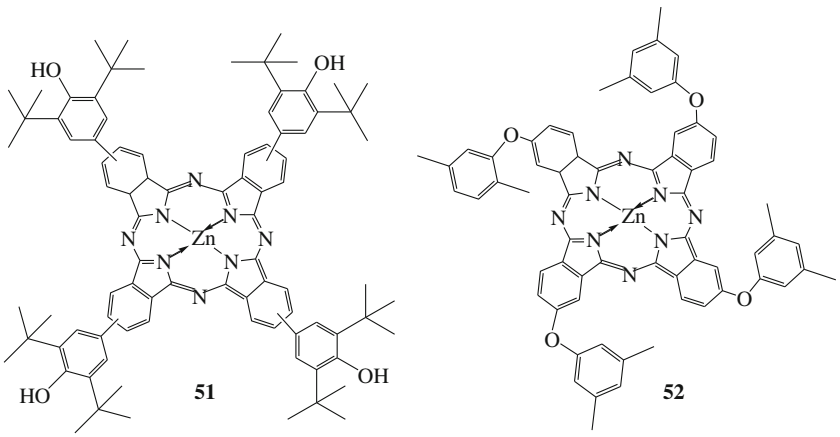


Fig. 8 Chemical structures of phthalocyanines containing 3,5-di-tert-butyl-4-hydroxy-phenyl **51** and 3,5-dimethylphenoxy **52**

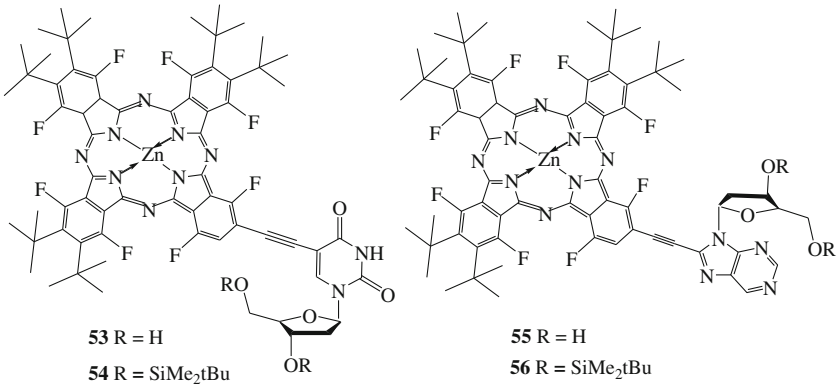
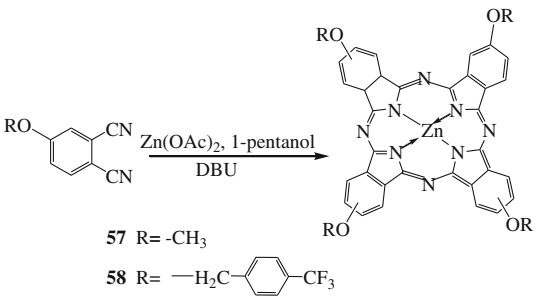


Fig. 9 Structures of perfluoroisopropyl-Pc-deoxyribonucleoside conjugates **53–56**



Scheme 6 Synthesis of phthalocyanine derivatives **57** and **58**

efficiency of Pc **57** was higher compared to Pc **58** under the same conditions. This was ascribed to formation of aggregate in biological medium.

Photodynamic activities of three novel Pcs **59–61** (Fig. 10) containing glycerol and galactose groups were presented by Zorlu et al. [49]. Pc **59** was obtained by the cyclotetramerisation of the starting phthalonitrile that was prepared following Ziegler–Hanack's glycosylation approach. Pcs **60** and **61** were prepared through the click chemistry. Pcs **59** and **60** displayed one shorter wavelength Q band around 634 nm in water. But the Q band of Pc **61** was red-shifted to 694 nm. The in vitro photodynamic activities of the three Pcs were investigated against HT-29 human cells. The LD90 value of Pc **59** and **61** could not be obtained even at the highest concentrations (100 μM). The LD90 value of Pc **61**, however, was determined to be 35 μM that was high when compared to tetra(propyl)hydroxyl ZnPc (0.65 μM). No fluorescence was observed for Pcs **59** and **60** after incubated with HT-29 cells, whereas a clearly fluorescence was found for Pc **61**. This indicated that Pc **61** was a promising new photodynamic sensitizer for PDT.

Saydan et al. described the preparation and photodynamic activity of water soluble Pcs **62** and **63**, with the aim to be used as potential photosensitizers for PDT [50]. Pc **62** was obtained in the presence of substituted phthalonitrile and anhydrous zinc(II)acetate catalyzed by DBU in *n*-hexanol (Scheme 7). Quaternization of Pc **63** was afforded by reacting Pc **62** and excess dimethylsulphate in DMF resulting in water solubility. The two compounds displayed a Q-band centered at 685 nm in DMSO. The B bands were found at 319 and 366 nm for Pc **63** and **62** in DMSO, respectively. The fluorescence quantum yields of Pc **62** and **63** were determined to be 0.03 and 0.02 in DMSO, respectively. The values were much lower when compared to unsubstituted ZnPc. This was assigned to the quenching of the singlet state. The singlet oxygen yields were 0.86 and 0.82 in DMSO for Pc **62** and **63**,

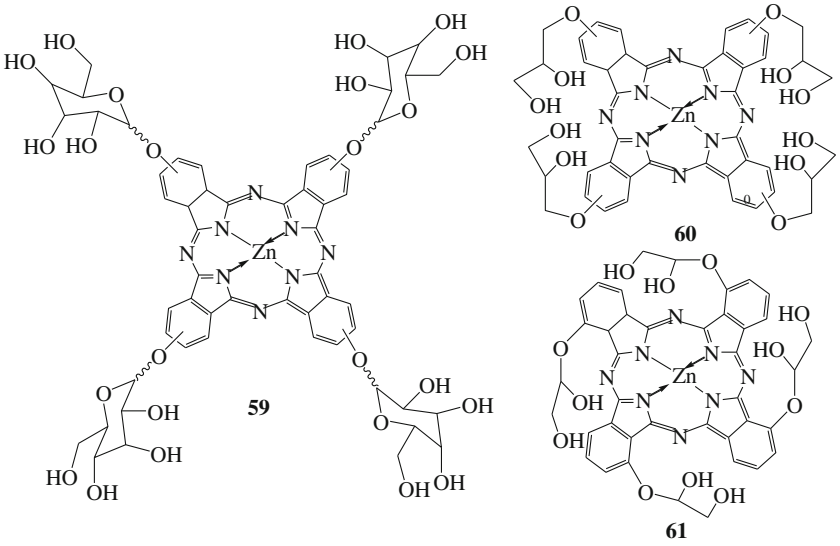


Fig. 10 Structures of galactose (**59**) and glycerol (**60**, **61**) substituted zinc phthalocyanines

respectively. But the value of Pc **63** was decreased to be 0.45 in water suggesting that it was affected partly by aggregation. Pc **63** did not show any dark toxicity at Pc concentration of 0.8, it was also observed that the mesothelioma cell survival was decreased after irradiation.

As expected, the two compounds **64** and **65** (Fig. 11) were well water-soluble and presented the monomer formation in aqua media [51]. The Q-band and fluorescence maximum were observed at 675 and 690 nm for Pcs, respectively. Photocytotoxicity against the fungi Candida albicans, the gram-negative *Pseudomonas aeruginosa* and the gram-positive Staphylococcus aureus was investigated and the results suggested that the two compounds are proposed photosensitizers for clinical PDT and they exhibited no dark toxicity at the used Pc concentration of 0.5.

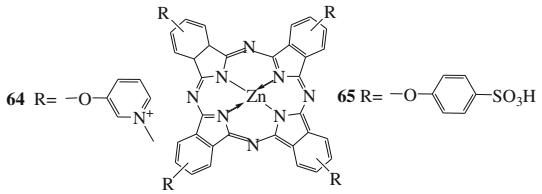
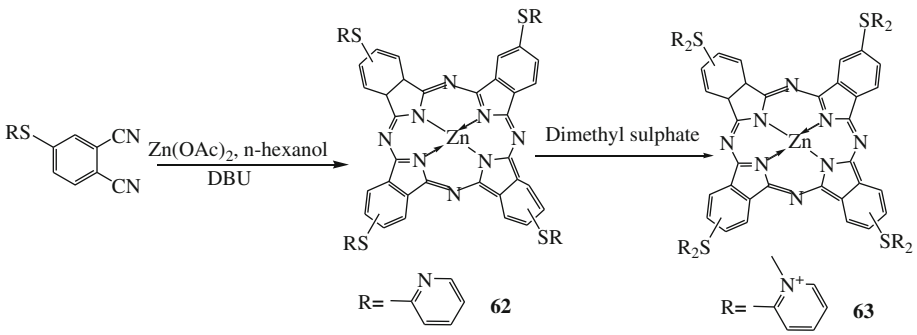


Fig. 11 Molecular structures of substituted phthalocyanines **64** and **65**

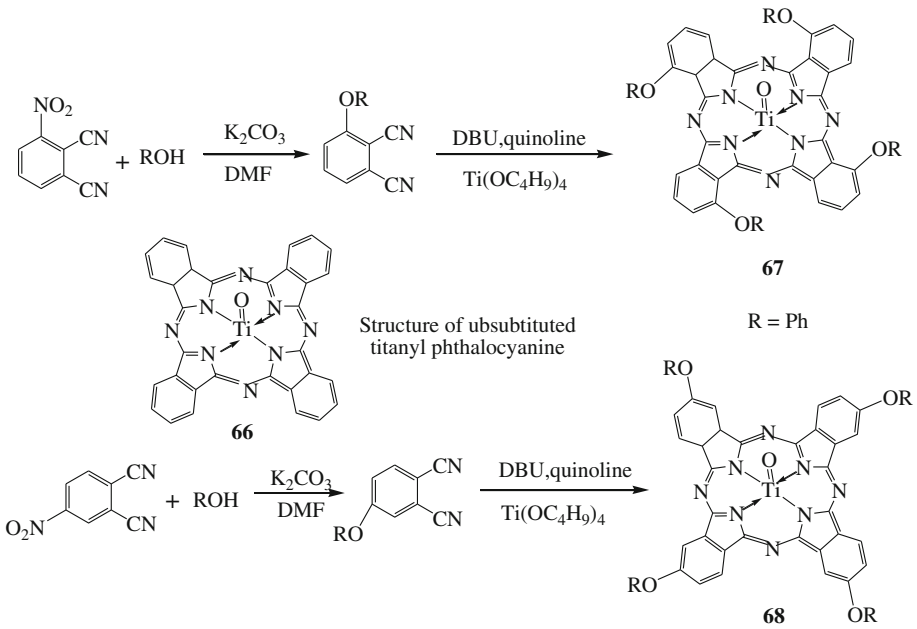
Titanyl phthalocyanines with different substitution

In the year 2010, Zhang et al. reported the results of a study on unsubstituted titanyl Pc **66** and phenoxy substituted titanyl Pcs **67** and **68** [5]. Titanyl Pc **66** was a product of Aldrich. Pcs **67** and **68** containing phenoxy substitutions were obtained from the corresponding precursors 4-phenoxyphthalonitrile and 3-phenoxyphthalonitrile, respectively (Scheme 8). The author found that when *n*-pentanol was employed as the solvent, the yield was very low. This indicated that the complex was difficult to form between titanium and Pc due to the presence of metal free Pcs. The problem could be solved by raising reaction temperature. The three Pcs all displayed a B-band near 350 nm and a narrow Q-band centered around 700 nm. However, a larger red shift was observer for Pc **67** containing α substitution (compared to Pc **30** with β substitution). This was also assigned to the variation of energy gap between the HOMO



Scheme 7 Synthetic routes of phthalocyanine **62** and its quaternized derivative **63**

Scheme 8 Synthesis of phenoxy substituted phthalocyanines **67** and **68** and structure of titanyl phthalocyanine **66**



and LUMO. The singlet oxygen quantum yields were measured to be 0.79, 0.76 and 0.86 in DMSO using DPBF as a chemical quencher for Pcs **66**, **67** and **68**, respectively. These values were all very higher compared to other Pcs.

Photophysical properties and photodynamic activity of Pcs (Fig. 12) containing pyridiniomethyl **69** and cholinyl groups **70** were investigated by Kuznetsova et al. [52]. The two compounds were soluble in water and polar organic solvent. They showed a strong Q-band near 700 nm and one B band around 350 nm. One broad band was also found between 370 and 450 nm that was ascribed to charge transfer electronic transitions between axial oxygen and titanium. The singlet oxygen quantum yields of Pc **69** were 0.17, 0.06 and 0.03 in water, methanol and ethanol, respectively. However, the values of Pc **70** (water: 0.19, methanol: 0.17, ethanol: 0.14) were higher than Pc **69**. No dark toxicity was observed for the two Pcs at applied concentration of 2.5 μM. But after irradiation with visible light, the toxicity was increased strongly.

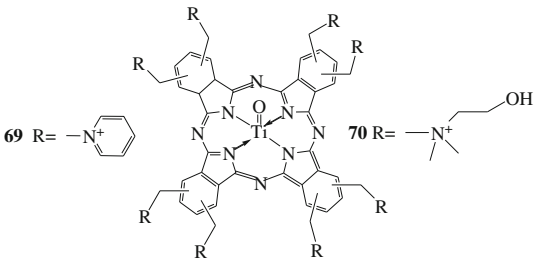


Fig. 12 Structures of phthalocyanines **69** and **70**

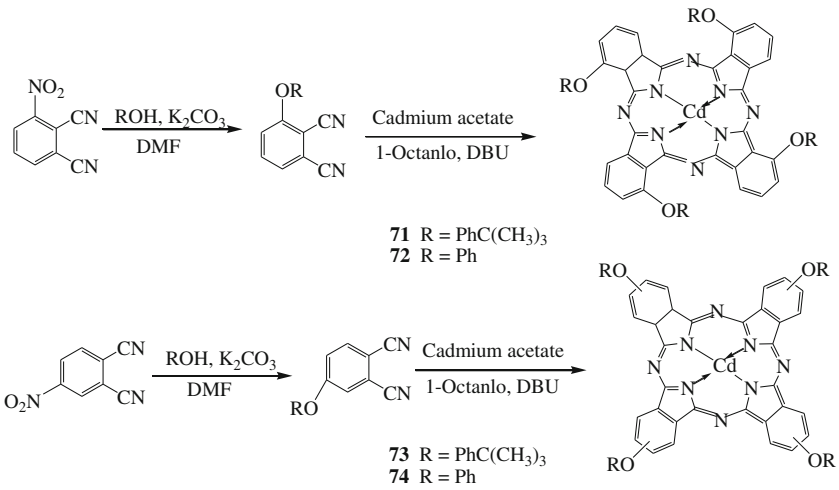
Cadmium phthalocyanines with different substitution

Chidawanyika et al. recently reported the synthesis and photophysicochemical properties of phenoxy Pcs **71–74** [53]. The starting substituted phthalonitrile and phenoxy derivatives were prepared as reported before [54]. Then, Pcs **71–74** were obtained by self-cyclization of the substituted phthalonitrile derivatives in the presence of cadmium acetate in 1-octanol in the yields varying between 15 and 40% (Scheme 9). The four Pcs all showed a sharp and intense Q-band around 700 nm. However, a large red shift (14–19 nm) was observed for Pcs **71** and **72** containing α substitution compared to Pcs **73** and **74** with β substitution. All these compounds displayed a small band between 740 and 750 nm. This was assigned to the flexible σ attachment of phenoxy units at the α-positions resulting in a slight loss in symmetry, hence splitting the Q-band. The singlet oxygen quantum yields of Pcs **71** and **72** were much higher than Pcs **73** and **74**. This suggested that the position of substitution related to the photodynamic activity of Pcs. When toluene was employed as solvent, the triplet quantum yield of α-substituted derivatives **72** and **72** were found to be lower than β-substituted derivatives **73** and **74**. However, in DMF and DMSO, the triplet quantum yield of Pcs **71** and **72** were higher compared to Pcs **73** and **74**.

Phthalocyanines with different metal center

Pc macrocycle can engage most metal ions in its cavity; hence scores of different metal phthalocyanine (MPc) complexes have been prepared. Although most metals can

Scheme 9 Synthesis of cadmium complexes **71–74**

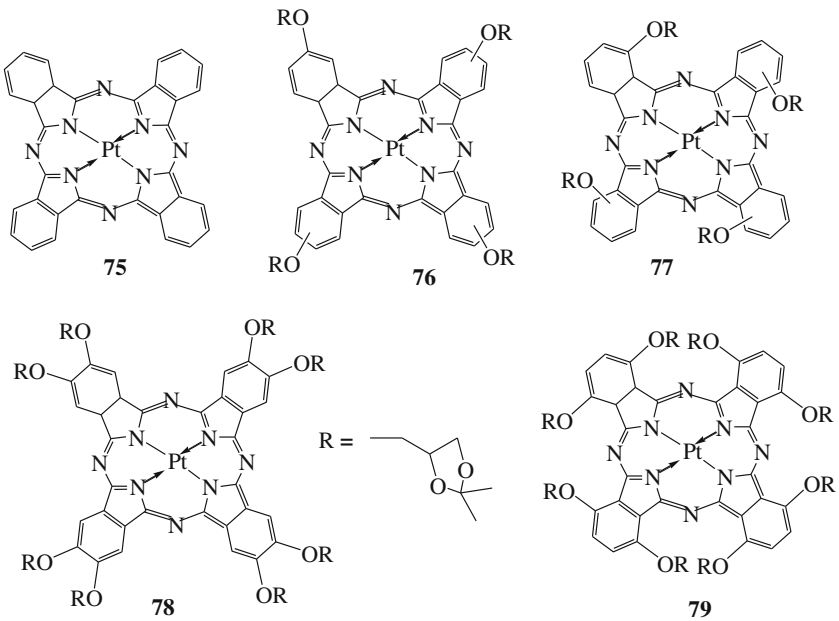


coordinate to Pc ligands, only a few of them can form highly photoactive complexes with both high triplet yields and long lifetimes due to the closed shell nature of the electronic configuration.

Small ring-substituted phthalocyanines with different metal center

Comparative studies of photochemical and photophysical properties of Pcs **75–79** and ZnPcs were presented by Zorlu et al. with the aim of evaluating the contribution of metal platinum to the photosensitizing properties [55]. All these compounds were obtained based on the reported procedures [49, 56]. The chemical structures of platinum Pcs were shown in Fig. 13. Fluorescence studies were carried out in DMF due to the best average solubility for all these compounds. Pcs **79**-Zn and **79**-Pt displayed feeble fluorescence emission compared to the other compounds. The Stokes shifts for **76**-Zn, **77**-Zn, **78**-Zn and **79**-Zn are of 13, 14, 10 and 17 nm, respectively, and for **76**-Pt, **77**-Pt and **78**-Pt are of 22, 24 and 28 nm, respectively. The fluorescence quantum yields and lifetime of PtPcs were lower than those of ZnPcs due to the heavy metal effect of platinum. The singlet quantum yields were determined to be 0.56, 0.50, 0.57, 0.54 and 0.48, for **75**-Zn, **76**-Zn, **77**-Zn, **78**-Zn and **79**-Zn, respectively, and 0.35, 0.63, 0.65 and 0.35, for **76**-Pt, **77**-Pt, **78**-Pt and **79**-Pt, respectively. This indicated that the singlet quantum yields of **77**-Pt and **78**-Pt were higher than the other Pcs. This difference was assigned to the different property of zinc and platinum. These results suggested that **77**-Pt and **78**-Pt are promising agents for photodynamic therapy.

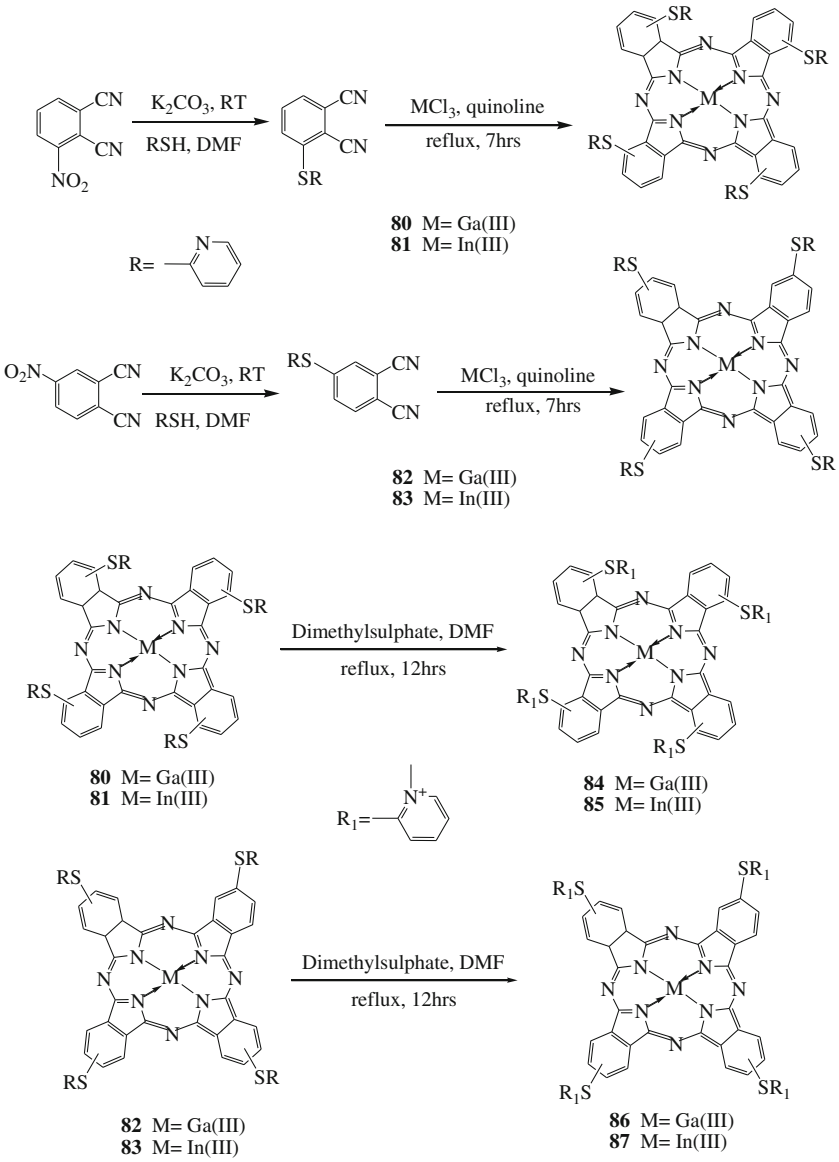
Fig. 13 Representation of the platinum phthalocyanines **75–79**



Phthalocyanines containing quaternized nitrogen atom in the side chain

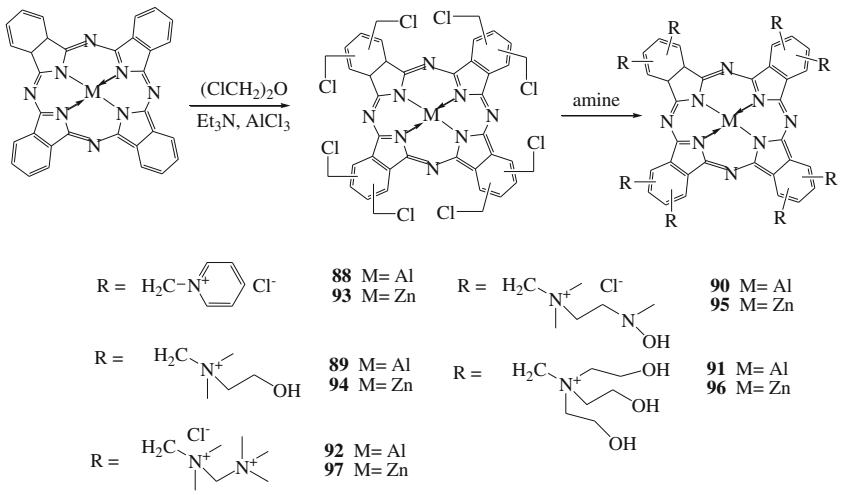
Several new gallium (III) and indium (III) Pcs containing 2-mercaptopyridine groups **80–83** and their quaternized derivatives **84–87** were prepared and characterized for photodynamic therapy [57]. The quaternized Pcs **84–87** were soluble in water that made them promising photosensitizer for PDT. The synthesis of all these compounds was presented in Scheme 10. Pcs **84–87** were prepared from Pcs **80–83** through the click chemistry. The fluorescence quantum yields for Pcs **80–83** in DMSO and for Pcs **84–87** in both DMSO and water were studied. The authors found that the fluorescence quantum yields and fluorescence lifetimes of Pcs **80**, **82**, **84**, and **86** were higher than Pcs **81**, **83**, **85** and **87** due to the heavy metal effect. But all these compounds (particular Pcs **84–87**) have good singlet oxygen quantum yields in DMSO. Thus, these Pcs showed potential as photosensitizers for PDT of cancer.

A series of Zn(II) and Al(III) Pcs **88–97** containing cationic substituents of different structure have been reported by Makarov et al. for photosensitizing properties research [58]. The synthetic routes of these compounds were shown in Scheme 11. At the first step, the chloromethyl substituted MPcs were prepared from unsubstituted ClAlPc and ZnPc, respectively. At the next step, these complexes containing cationic ammonium substituents were obtained in the presence of chloromethyl substituted MPcs and excess tertiary. The photosensitizing efficiency of these compounds was carried out against tryptophan. A red shift (2–3 nm) was observed for Pcs **93–95** and **97** upon addition of tryptophan due to the tryptophan axial



Scheme 10 Synthesis of tetra-2-mercaptopyridine substituted gallium (III) and indium (III) phthalocyanine complexes and their quaternized derivatives

Scheme 11 Synthetic routes of cationic Zn and Al phthalocyanines



coordination on the metal zinc atom. For Pc **96**, only a slight disaggregation was found in the presence of tryptophan. However, the spectra of Pcs **88–92** were not changed upon addition of tryptophan. The authors also found that Pcs **91** and **96** containing hydroxyl groups were unable to sensitize the formation of singlet oxygen. This may be ascribed to the intermolecular interactions through hydrogen bonding.

Sulfonated phthalocyanines with different metal center

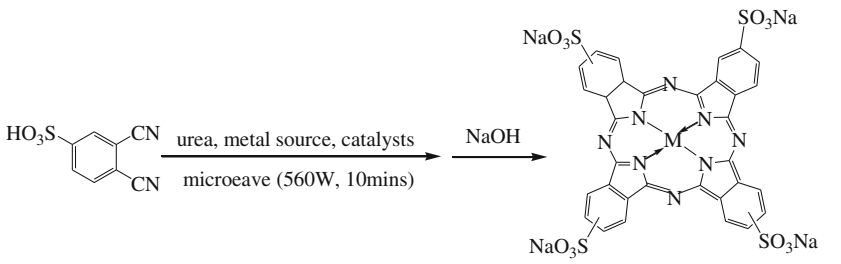
The photodynamic applications of water-soluble sodium salt of sulfonated Pcs **98–101** have been reported as photosensitizers [59]. Pc **98** was prepared from 4-sulfophthalic acid, urea and zinc chloride catalyzed by ammonium molybdate and ammonium chloride (Scheme 12). The same procedure was carried out in the presence of sulfonated copper, chloroaluminum and cobalt, respectively, with appropriate catalysts to prepare Pcs **98–101**. The introduction of four hydrophilic sulfonated groups increased the solubility of these Pcs. All these compounds displayed Q-band around 600–800 nm and B-band near 300–400 nm in water. However, when ethanol was used as solvent, the absorption bands were blue-shifted due to the aggregation. The guanine was oxidized to be parabanic acid in the presence of Pcs **98–101** suggesting that the singlet oxygen was generated. Thus, Pcs **98–101** could be used as photosensitizers for PDT. However, the killing effect of **99** was higher than **98** due to the absence of aggregation.

Water soluble mixed sulfonated Pcs complexes **102–105** were designed for the research of photodynamic activity against human oesophageal carcinoma cells (SNO) [60]. All these compounds were prepared through the click chemistry from the starting materials H_2Pc, $(OH)_2SiPc$, $(OH)_2GePc$ and $(OH)_2SnPc$, respectively (Fig. 14). The triplet quantum yield of these Pcs was determined to be 0.33, 0.45, 0.67 and 0.58, for **102**, **103**, **104** and **105**, respectively. All these compounds displayed absorption band centered at 670 nm in cell culture medium. However, Pc **105** has a lower absorbance at 670 nm compared to Pc **103**, yet both have the same killing ability against the SNO. Pc **104** resulted in a significantly increase in inflammation compare to **102**, **103** and **105**. Thus, Pc **104** was a more promising as a photosensitizer.

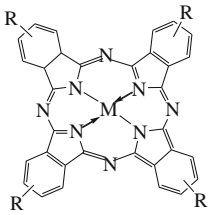
Aromatic ring-substituted phthalocyanines

The effects of metal on photochemical and photophysical activities of Pcs containing aryloxo **106–108** and alkylthio

Scheme 12 Experiment details of the prepared phthalocyanines **98–101**

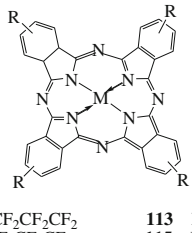


98 M= Zn, **99** M= Cu, **100** M=ClAl, **101** M= Co



102 M= H_2 R=SO_3H **103** M= Si R=SO_3H
104 M= Ge R=SO_3H **105** M= Sn R=SO_3H

Fig. 14 Molecular structures of $MPcS_{mix}$, M = H_2, Si, Ge or Sn



112 M= Co R= $CF_3CF_2CF_2CF_2$ **113** M= Cu R= $CF_3CF_2CF_2CF_2$
114 M= Zn R=$CF_3CF_2CF_2CF_2$ **115** M= Fe R=$CF_3CF_2CF_2CF_2$
116 M= Co R=$CF_3CF_2CF_2CF_2CF_2CF_2$ **117** M= Cu R=$CF_3CF_2CF_2CF_2CF_2CF_2$
118 M= Zn R=$CF_3CF_2CF_2CF_2CF_2CF_2$ **119** M= Fe R=$CF_3CF_2CF_2CF_2CF_2CF_2$

Fig. 15 Structures of perfluoroalkyl metal phthalocyanines **112–119**

groups **109–111** were investigated by Ogunbayo and Nyokong [61]. All these compounds were obtained by cyclotetramerization of 4,5-diphenoxyphthalonitriles and 4,5-bis-(benzyloxyphenoxy)phthalonitrile, respectively (Scheme 13). The Q-bands of these compounds were observed arranged from 658 to 709 nm in 1-chloronaphthalene. A clear red shift was observed for Pcs **106** and **109** compared to **107** and **110**. This indicated that the destabilization of the HOMO of Pcs **106** and **109** was larger than Pcs **107** and **108**. The triplet quantum yield of Pcs **107**, **108**, **110** and **111** was determined to be 0.51, 0.62, 0.65 and 0.73, respectively. But Pcs **106** and **109** did not display any triplet absorption band indicating that an extremely short triplet quantum yield or lifetime. The open-shell nature was reflected by the triplet lifetimes of these Pcs (**107**: 23 μs, **108**: 17 μs, **110**:20 μs, **111**:13 μs,). The trend of the singlet oxygen quantum yield was as follows: Pd (**107** and **110**) > Pt (**108** and **111**) > Ni (**106** and **109**). This indicated that Pcs **108** and **111** was less efficient in generating singlet oxygen compared to Pcs **107** and **110**.

Long perfluoroalkyl chain-substituted phthalocyanines

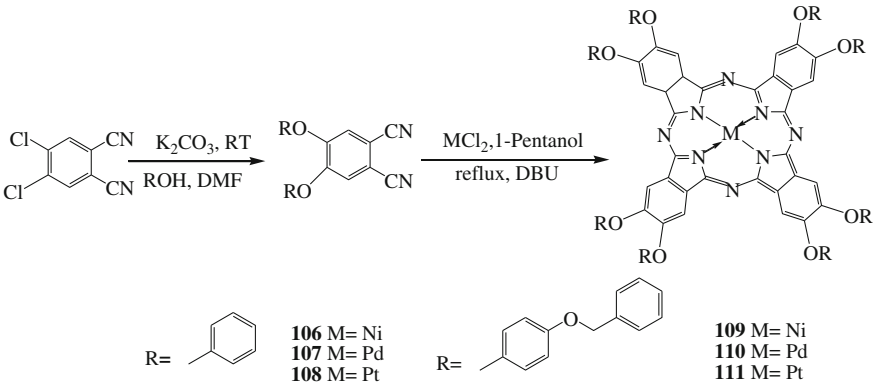
Novel perfluoroalkyl metal Pcs (Fig. 15) bearing perfluorobutyl **112–115** and perfluorohexyl groups **116–119** were prepared by reacting 4-iodophthalonitrile [62]. All these compounds were soluble in methanol, ethanol, THF and ethyl acetate. The photodynamic activity of compounds **114** and **118** were investigated only because of the high fluorescence quantum yields. Pc **114** and **118** showed an intense Q-band centered at 665 and 666 nm with the fluorescence quantum yields of 0.11 and 0.38, respectively. Photocytotoxic activity of compounds **114** and **118** were measured toward Hl-60 leukemic cell and A375 melanotic cancer cell. They displayed no toxicity after incubation in the dark. Surprisingly, Pc **118** presented the higher photocytotoxicity when compared to Pc **114**.

Phthalocyanines with different axial substitution

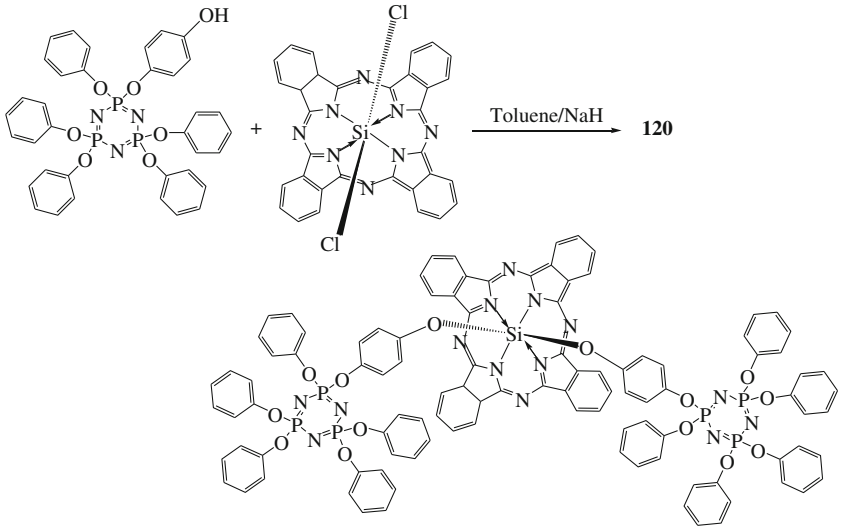
Axial substituted phthalocyanines with cyclotriphosphazenyl group

An axially-disubstituted SiPc **120** bearing cyclotriphosphazenyl group was prepared by Çoşut et al. [63]. Pc **120** was obtained in the presence of hydroxyl substituted hexa-(phenoxy)cyclotriphosphazen and $SiPc(Cl)_2$ catalyzed by sodium hydride through the nucleophilic displacement reaction (Scheme 14). The fluorescence quantum yield of Pc **120** (0.17) was slightly lower compared to unsubstituted ZnPc (0.20) in DMSO. The fluorescence lifetime (3.11 ns) and natural radiative lifetime (18.29 ns) of Pc **120** was also longer than unsubstituted ZnPc (1.21 and 6.80 ns). The singlet oxygen quantum yield was determined to be 0.22 in DMSO that was also lower compared to ZnPc (0.67).

Scheme 13 Synthetic routes for oxy-derivatised phthalocyanines



Scheme 14 Chemical structure and synthetic pathway of **120**

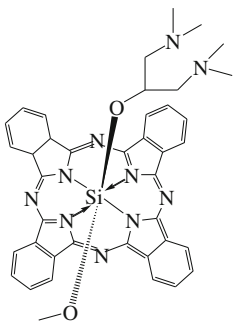


Axial substituted phthalocyanines containing nitrogen atom in the side chain

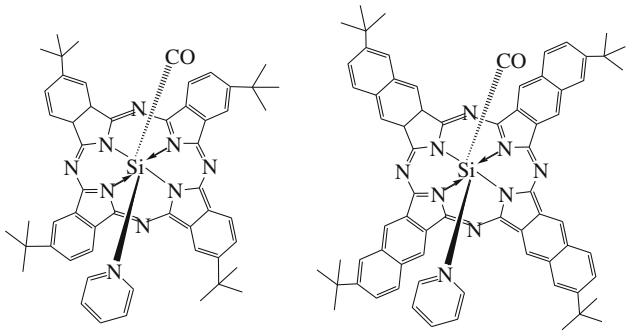
The photodynamic activity of unsymmetrical bisamino Pc **121** (Fig. 16) was studied as a continuous search for more potent photosensitizers [64]. This compound displayed high phototoxicity against cancer cells in in vitro cell culture. Pc **121** showed a high uptake in liver and most could be cleared within 24 h. Thus, it was better when compared to AlClPc that was completely removed within 1 week. Although the amount of Pc **121** was lower than AlPc-PVA, it was still enough to cause significant tumour cell death. These results suggested that Pc **121** could be used as a potential photosensitizer in clinical PDT. Photodynamic activity of this Pc was also investigated against *Candida albicans* [65]. This compound displayed no toxicity at concentrations below 0.08 μM in the absence of light. The authors observed an IC_{50} value (0.013 μM) for Pc **121** 1923 times lower than the cationic porphyrin Trip. The results of the tests performed against *Candida albicans* provided a much more efficient tumor growth inhibition for Pc **121**. The application of confocal laser scanning microscopy had revealed the effective cellular uptake of this Pc. The authors also found that the 5–15 min incubation period was enough for this Pc to exert its photocytotoxic effect against *Candida albicans*, and further increased in incubation time did not increase its activity.

Ishii et al. investigated the photodynamic effects and photochemical properties of Pc **122** and naphthalocyanine (Nc) **123** (Fig. 17) [66]. Pc **122** showed two intense Q-bands centered at 675 and 699 nm. Pc **123** also displayed two intense Q-bands at 745 and 728.5 nm. However, Pc **123** RuNc(CO) (Py) exhibited a red shift compared to RuNc $(Py)_2$. In order to examine the phototoxic origin quantitatively, singlet oxygen yield of the two Pcs was also measured. The singlet oxygen yields were determined to be 0.48 and 0.35, for Pc **122** and Nc **123**, respectively. This high singlet oxygen yield indicated that they were promising candidates for PDT. According to the results of phototoxicity against HeLa Cells, the photodynamic effect of Pc **122** was higher compared to Nc **123**. This was assigned to the higher ability to generate singlet oxygen.

Fig. 16 Chemical structure of phthalocyanine **121**



121



122 **123**

Fig. 17 Chemical structures of phthalocyanines **122** and **123**

Pc **124** bearing methylpyridiniumoxy group has been prepared and investigated for its photocytotoxicity against J774 and HepG2 cancer cells [67]. The starting Pc was obtained from silicon Pc dichloride and 4-hydroxypyridine in the presence of pyridine in toluene. Then, Pc **124** was prepared through click chemistry from the starting Pc (Scheme 15). This Pc showed a sharp Q-band centered at 695 nm and one Soret band centered at 349 nm concurrent with two vibronic bands centered at 624 and 662 nm. The fluorescence quantum yield (0.15) of Pc **124** in water was lower when compared to unsubstituted ZnPc (0.28) in DMF. This was assigned to the strong hydrophobic interactions of this compound in aqueous media resulting in the formation of non-fluorescent aggregates. Pc **124** showed no dark toxicity; however, it exhibited photocytotoxicity at high concentration. The author also found that the photodynamic activity of Pc **124** was greatly increased by conjugation with bovine serum albumin (BSA). This study demonstrated the high potential of Pc **124**-BSA compared to PC **124** for use in PDT.

Zhu et al. reported the photodynamic activities of Pcs (Fig. 18) containing 2-morpholine ethoxy group **125** or its *N*-methylated derivative **126**, with the aim to enhance the water solubility and inhibit the self-aggregation of these compounds [68]. Pc **125** had good solubility in water, whereas Pc **126** was soluble in mixed solvents of water and 0.1% DMF. The fluorescence quantum yields were 0.03 and 0.45 for Pcs **125** and **126** in DMF, respectively. However, Pc **126** displayed a strong fluorescence emission at 690 nm with a fluorescence quantum yield of 0.26 and a fluorescence lifetime of 5.38 ns in water. This suggested that Pc **126** remained essentially non-aggregated in water. The singlet oxygen quantum yield of Pc **126** was ten times higher than that of Pc **125**. This was attributed to the singlet excited state was quenched effectively by the amino group in Pc **125**. Both compounds exhibited a high photodynamic activity toward B16 melanoma tumour cells, which could be ascribed to their efficiency to generate singlet oxygen.

Two novel axially substituted Pcs **127** and **128** (Fig. 19) have been prepared by Jiang et al. for PDT application

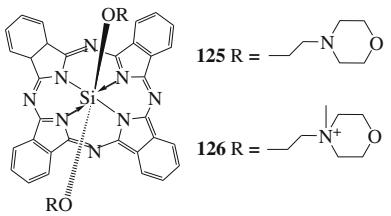


Fig. 18 Chemical structures of morpholine-substituted phthalocyanines **125** and **126**

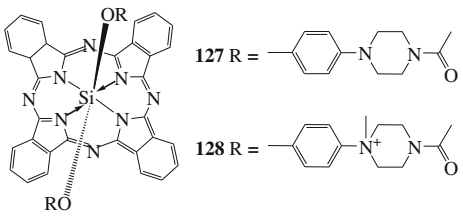
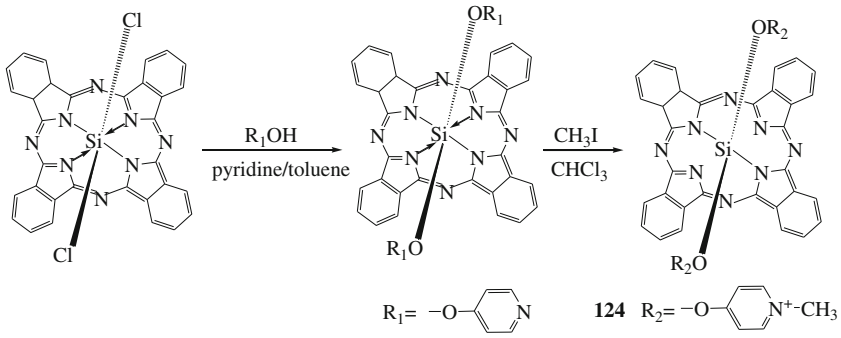


Fig. 19 Chemical structures of axially-substituted phthalocyanines **127** and **128**

[69]. Pc **127** displayed a broad band centered at 710 nm in water suggesting that it was significantly aggregated in this system. However, Pc **128** showed a strong and sharp band centered at 690 nm in water. This indicated that it remained non-aggregation in this system. The fluorescence quantum yield of Pc **127** was three times when compared to Pc **128**. With the aim to enhance the selectivity, Pcs **127** and **128** were complexed with BSA. Both conjugates had good solubility in water. Pc **128** was not cytotoxic in the absence of light, but exhibited a high photodynamic activity toward B16 melanoma cell line at concentration of 0.1 μM. However, Pc **127** did not show any photocytotoxicity against this cancer cell. This might be attributed to the lower efficiency to generate singlet oxygen.

A new series of silicon Pcs **129–131** (Fig. 20) have been synthesized via nucleophilic substitution or alkoxy exchange reactions. Interestingly, Pcs **132–134** were also obtained in the process of preparing Pcs **130** and **131**. Two dicationic Pc **135** and tetracationic Pc **136** were also

Scheme 15 Synthetic routes of dicationic silicon (IV) phthalocyanine **124**



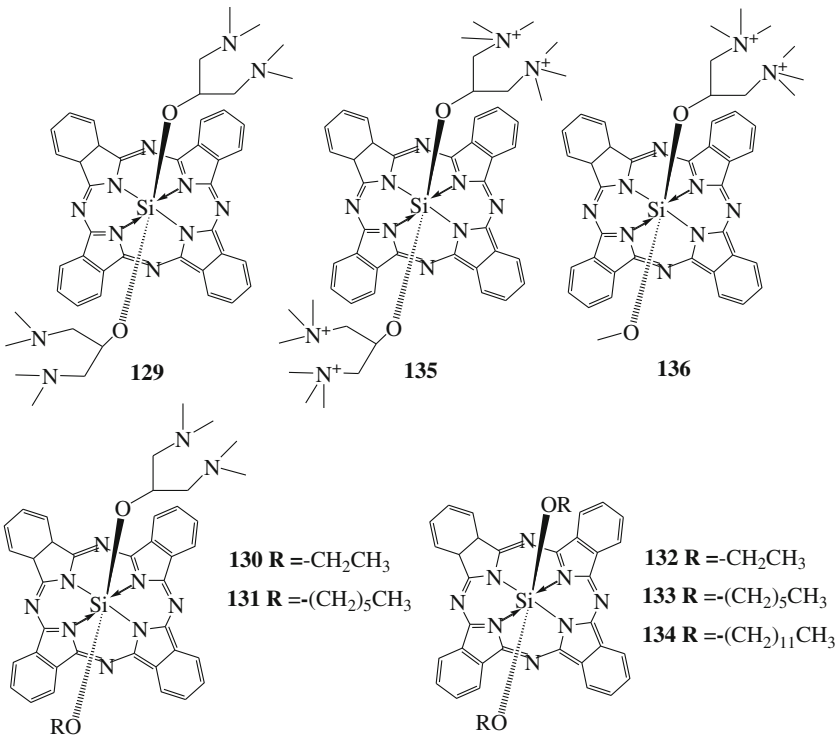
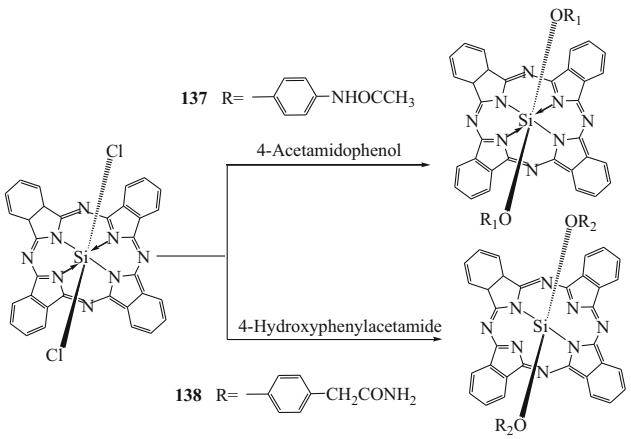


Fig. 20 Structures of phthalocyanines **129–134**

prepared through the click chemistry of Pcs **121** and **129** in the presence of iodomethane, respectively. Pcs **129–134** remained non-aggregated in most common organic solvents and exhibited a weaker fluorescence emission, whereas Pcs **135** and **136** also existed essentially in non-aggregated form in aqueous media and showed a strong fluorescence emission. All these compounds, particular Pc **133**, **134**, **135** and **136**, displayed a highly photocytotoxic toward J774 mouse macrophage and HepG2 human hepatocarcinoma cell lines with the lower IC_{50} value of 0.02 μM, which could be assigned to the high cellular uptake and efficiency to produce singlet oxygen [70]. The interactions between serum albumins and incorporated Pcs (**121**, **129**, **135** and **136)** have been also studied by fluorescence spectroscopy [71]. In order to enhance this incorporation, these Pcs were covalently bound to the serum albumins. The fluorescence emission of the serum albumins was effectively quenched by Pcs (**121**, **129**, **135** and **136)** in a similar manner. However, the interactions between the unsymmetrically Pcs (**121** and **135**) and the serum albumins were much stronger than that between the symmetrically Pcs (**129** and **136**) and the serum albumins. The photodynamic activity of these conjugates was measured toward HepG2 human hepatocarcinoma cells. Fortunately, the photocytotoxicity of conjugates **129** and **135** was enhanced by up to eight times when compare to free Pcs **129** and **135**, respectively. But the bioconjugation induced negligible effect on Pcs **121** and **136**.

Axial substituted phthalocyanines with aromatic ring

Huang et al. described the synthesis and photobiological activity of silicon (IV) Pcs conjugated to paracetamol **137** or 4-hydroxyphenylacetamide **138**, with the aim to increase the hydrophilicity and inhibit the self-aggregation of these Pcs, but also, as previously reported, to enhance the photodynamic activities [72]. These two Pcs were obtained from silicon Pc with 4-acetamidophenol or 4-hydroxyphenyl through nucleophilic substitution in the presence of NaH in toluene (Scheme 16). Both compounds displayed a Soret band around at 355 nm and an intense Q-band around



Scheme 16 Synthesis of silicon (IV) phthalocyanines **137** and **138**

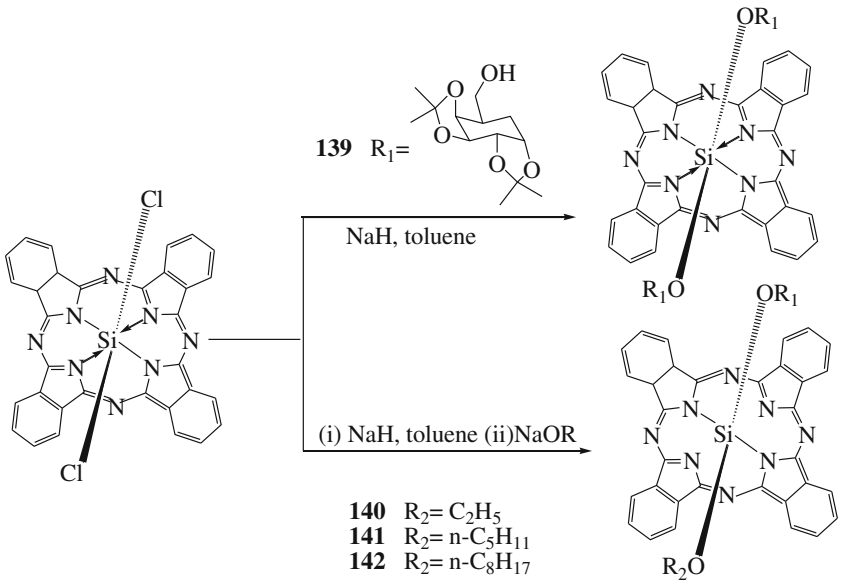
at 680 nm in DMF. The fluorescence quantum yield of Pc **137** (0.01) was much lower compared to Pc **138** (0.1). However, the singlet oxygen quantum yield of Pc **138** was 0.18 that was much higher than that of Pc **137**. This was attributed to the quenched singlet-excited state of Pc ring. Pc **138** exhibited a high photodynamic activity toward the HT29 cells compared to Pc **137**, which could be ascribed to the higher efficiency to generate singlet oxygen.

Axial substituted phthalocyanines with small ring

Lee et al. presented the preparation and photodynamic activity of Pcs **139–142** bearing galactose groups at α position (s) [73]. Pc **139** was prepared by typical substitution reaction in the presence of silicon (IV) Pc dichloride and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose catalyzed by NaH in toluene (Scheme 17). With the aim to increase the amphiphilicity of photosensitizers Pcs, the unsymmetrical Pcs **140–142** were also synthesized by mixed substitution. Treatment of silicon (IV) Pc dichloride with 0.8 equiv of deprotonated 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of NaH resulted in the mono-galactose-substituted Pc, which was converted into the desired unsymmetrical analogous **140–142** by reacting with the corresponding 0.8 equiv of NaOR. All these compounds showed the Q band around 671–673 nm, the Soret band around 352–356 nm concurrent with two vibronic bands around 604–606 and 641–644 nm. The singlet oxygen quantum yields were determined to be 0.94, 0.79, 0.82 and 0.88, for Pcs **139**, **140**, **141** and **142**, respectively. Pc **139** showed no dark toxicity at concentrations lower than 8 μM, but they exhibited a high photodynamic activity with an IC_{50} value of 0.10 μM. Pcs **130–132** displayed the similar photocytotoxicity with an IC_{50} value of 0.10, 0.48 and 0.79 respectively. These values indicated that the photodynamic activity decreased with increasing length of the alcohols chain.

The in vitro uptake and photocytotoxicity of free Pc **143** (Fig. 21) and its loaded micelles were investigated against B16F10 and 14C cancer cells [74]. The Q-band of Pc **143** centered at 674 nm was red-shifted to 689 nm when compared to **143**-loaded micelles. The Soret band was also shift from 350 to 359 nm. This indicated that **143**-loaded micelles existed mainly in non-aggregated form in DMF. Both compounds presented a high photocytotoxicity toward B16F10 and 14C cancer cells, especially after 6 h incubation in medium with 10% serum ($IC_{50} = 5$ and 3 nM, respectively). Unexpectedly, the photocytotoxicity of both compounds decreased with increasing foetal bovine serum concentration. The cellular uptake of **143**-loaded micelles was about 60 times lower than Pc **143** in the absence of serum. This was attributed to the minimal leakage of the photosensitizer **143** from the interior of the micelles into the serum medium. The results suggested that **143**-loaded micelles were hardly taken up by the serum cells.

Two novel Pcs **144** and **145** (Fig. 22) were prepared and investigated for their photophysical and photodynamic properties [75]. Both compounds were soluble in most common organic solvents and exhibited highly solubility in water. Pc **145** exhibited a weaker fluorescence emission at 679 nm with the fluorescence quantum yield of 0.24 and higher efficiency to produce singlet oxygen with the singlet quantum yield of 0.41 when compared to Pc **144** due to the heavy atom effect of chlorine. Both compounds showed essentially no dark toxicity, whereas exhibited a very high



Scheme 17 Preparation of galactose-containing silicon (IV) phthalocyanines **139–142**

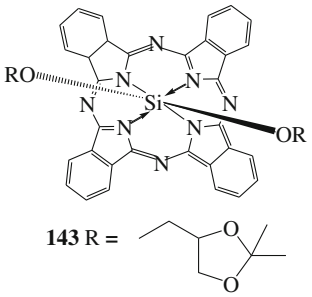


Fig. 21 Chemical structure of the axially solketal-substituted silicon phthalocyanine **143**

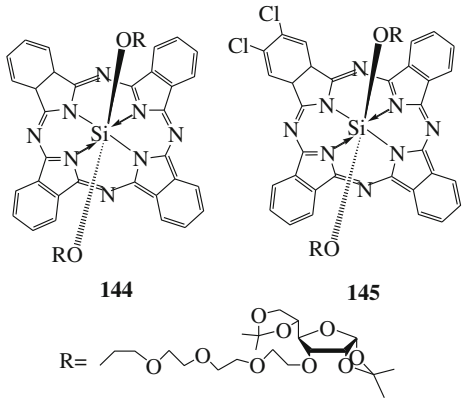


Fig. 22 Chemical structures of glucoconjugated phthalocyanine **144** and **145**

photocytotoxicity toward HepG2 human hepatocarcinoma and HT29 human colorectal carcinoma cell lines, particularly, Pc **144** with the lower IC_{50} value of 6 nM. The lower photodynamic activity of Pc **145** could be ascribed to the higher aggregation in the media resulting in a lower efficiency to produce reactive oxygen inside the cancer cells. These results indicated that Pc **144** was a highly promising photosensitizer for PDT.

Conclusions and perspectives

This paper has focused on the recent developments in the field of photo-activable Pcs. Pcs have been grouped into three classifications: (a) Pcs with different peripheral and/or non-peripheral substitution; (b) Pcs with different axial substitution; (c) Pcs with different metal center, and their synthesis and representative photophysicochemical properties summarized. The examples described in this review illustrate the potential of them in the rapidly growing field of photocytotoxic Pcs as photosensitizers in PDT. Beyond the scope of this review, the chemistry of Pcs continues as their properties are influenced by three changeable structure factors: (non)peripheral substitution, central metal ion, and axial substitution. By comprehensive investigation of the photochemical and photophysical activities of Pcs with different central metals, it's concluded that Pcs with heavier central metals may have higher triplet yields and longer lifetimes owing to the enhanced spin–orbit coupling by heavy atom effect.[1] The peripheral substitutions and axial ligands can not only improve the solubility, but also weaken the molecular aggregation. This is favorable for PDT. However, an immediate practical application in PDT for most of these Pcs is not obvious and there rarely is for any truly class of compounds. Thus, it is critical important to further explore and establish the comprehensive relationships between Pc structure and photodynamic activities for guiding the future rational design and development of new Pc compounds for PDT. With rational molecular design and chemical synthesis, investigators could consequently tailor the photodynamic properties of Pcs to specific applications in broadband. Such molecular engineering will pave the way to final applications of these functional phthalocyanine-based materials in practical photosensitizers in the near future.

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Glossary

Pc	Phthalocyanine
Nc	Naphthalocyanine
PDT	Photodynamic therapy is a binary therapy involving the combination of light and a chemical substance (a photosensitizer), which results in cell damage or death [14]
Φ_F	Fluorescence quantum yields are the ratio of photons absorbed to photons emitted through fluorescence. They could be determined by the comparative method (Eq. 1): $\Phi_F = \Phi_F$ (Std) $\cdot$ $FA_{Std}\eta^2/F_{Std}A\eta^2_{Std}$, where F and F_{Std} are the areas under the fluorescence emission curves of the samples and the reference, respectively; A and A_{Std} are the respective absorbance of the sample and standard at the excitation wavelengths, respectively; η and η_{Std} are the refractive indices of solvents used for

[1] Heavy atom effect enhances the rate of a spin-forbidden process by the presence of an atom of high atomic number, which is either pert of, or external to, the excited molecular entity. Mechanistically, it responds to a spin–orbit coupling enhancement produced by a heavy atom [14].

	the sample and standard, respectively [63]. The sample and the standard should be excited at the same relevant wavelength
τ_F	Fluorescence lifetimes refer to the average time that a molecule remains in its excited state before returning to its ground state. They were evaluated using Eq. 2: $\Phi_F = \tau_F/\tau_0$, where τ_F is the fluorescence lifetime. The τ_0 is the natural radiative life time which can be determined using PhotochemCAD program using the Strickler–Berg equation [57]
Φ_T	Triplet quantum yields usually were determined using the comparative method based on the triplet decay, using Eq. 3: $\Phi_T^{Sample} = \Phi_T^{Std} \cdot \Delta A_T^{Sample} \cdot \varepsilon^{Std}/\Delta A_T^{Std} \cdot \varepsilon^{Sample}$, where ΔA_T^{Sample} and ΔA_T^{Std} are the changes in the triplet state absorbance of metal Pcs and the standard, respectively. ε^{Sample} and ε^{Std} are the triplet state extinction coefficients for the metal Pcs and the standard, respectively. Φ_T^{Std} is the triplet state quantum yield for the standard [16]. Triplet lifetimes (τ_T) were determined by exponential fitting of the kinetic curves using OriginPro 7.5 software [53]
Φ_Δ	Singlet oxygen quantum yield is a key property of a photosensitizer. It was defined as the number of molecules of $^1O_2$ molecules generated for each photon absorbed by a photosensitizer. Equation 4 was used for the calculations of the singlet oxygen yield: $\Phi_\Delta = \Phi_\Delta^{Std} \cdot R \cdot I_{abs}^{Std}/R^{Std} \cdot I_{abs}$, where Φ_Δ^{Std} is the singlet oxygen quantum yield for the standard. R and R^{Std} are the trap photobleaching rates in the presence of studied samples and references, respectively. I_{abs} and I_{abs}^{Std} are the intensities of light absorption by the studied samples and the standards, respectively [58]
DBU	1,8-Diazabicyclo-[5,4,0]undec-7-ene
IC_{50}	Half maximal inhibitory concentration, which is defined as the dye concentration required to kill 50% of the cells
DMSO	Dimethylsulfoxide
THF	Tetrahydrofuran
DMF	Dimethylformamide
DPBF	1,3-Diphenylisobenzofuran
HOMO, LUMO	Highest occupied molecular orbital and the lowest unoccupied molecular orbital, respectively. The energy difference between the HOMO and LUMO is termed as the band gap
LD90	Lethal dose 90%. The estimated dose at which 90% of the cells is expected to die
SNO	Human oesophageal carcinoma cells
BSA	Bovine serum albumin

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