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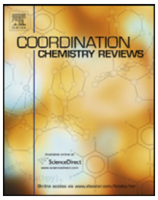

Review

Synthetic pathways to water-soluble phthalocyanines and close analogs

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ABSTRACT

The different types of water-soluble phthalocyanines are presented and their synthesis is reviewed.

Ac	acetate
ALA	5-aminolevulinic acid
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Boc	tert-butyloxycarbonyl
CD	cyclodextrin
Chol	choline
DBN	1,5-diazabicyclo(4.3.0)non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAE	dimethylaminoethanol
DMF	dimethylformamide
DMS	dimethylsulfate
DMSO	dimethylsulfoxide
DOPA	3,4-dihydroxyphenylalanine
Et_2N	*N*-*N*′-diethylamine
Et_3N	triethylamine
EtO	ethoxide
Glc	glycol
Gal	galactose
HPLC	high pressure liquid chromatography
Me	methyl
MeOH	methanol
NBS	*N*-bromosuccinimide
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PEG	polyethylene glycol
PDT	photodynamic therapy
Ph	phenyl
tBu	tert-butyl
TBA	tetrabutylammonium
TCPC	tetracarboxylic acid substituted phthalocyanines
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THPO	tetrahydropyranyloxy
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Tos	tosylate
TPPS	triphenylphosphine monosulfonate
TPPTS	triphenylphosphine-3,3,3-trisulfonate

1. Introduction

Since the discovery of the phthalocyanines, the main focus of the chemists has been on tailoring of their properties to produce molecular materials for previously targeted medical or technological applications [1–13]. Thus many efforts are geared towards the synthetic strategies in order to increase the range of possible molecules [14–17].

The intense blue-green color of phthalocyanines is due to the electronic delocalization of their 18 π electrons. This made them to be initially utilized industrially as dyes and pigments in various fields [18–23].

Since then, their outstanding and tailorable properties such as liquid crystallinity [24–26], generation of singlet oxygen [27–30] and redox properties [31,32] have enhanced their use as efficient agents in several high technology applications including: photodynamic therapy, a technique for which phthalocyanines are currently the most promising class of compounds [33–43], for photodynamic antimicrobial chemotherapy [44–47], as sensors [48–51] including biosensors [52,53], for non-linear optical applications [54–59], dye sensitised photovoltaic production [60–63], semiconductor materials [64,65], oxidation or reduction catalysts and photocatalysts [66–68] among others. Their combination with nanomaterials (quantum dots, nanotubes, liposomes, dendrimers) [69–74] may efficiently enhance the desired properties.

The intrinsic structure of these compounds makes them, when unsubstituted, insoluble in nearly all the solvents. However appropriate substitution pattern helps to overcome this problem. Indeed, the flexible points for a chemist aiming at synthesizing soluble phthalocyanines are the substitution pattern (macrocyclic and/or axial) as well as the choice of the metal (Fig. 1). The introduction of one or two nitrogen atoms on the isoindole subunits (the corresponding tetrapyridinoporphyrazine and pyrazinoporphyrazine derivatives being commonly designated as azaphthalocyanines [75]) is another point allowing for the tailoring of properties.

Water-solubility is a quest for many chemists in various fields, as several of the current applications of phthalocyanines are of biological interest and/or require environment friendliness, necessitating water-solubility in various concentration, pH, etc. ranges. This is the case of biological and medical applications such as photodynamic therapy. Another very important application of water-soluble phthalocyanines is the catalysis of reactions in aqueous media, the main one being the degradation of pollutants. Catalysis of reactions in aqueous media is currently becoming of major interest [76]. Thus, when designing a phthalocyanine on demand for a specific application, or to get a precisely targeted property, its water-solubility may be a requirement.

A first historical approach for using phthalocyanine in aqueous media was to formulate insoluble phthalocyanines mainly with the preparation of emulsion [77] or incorporation in water-soluble polymers, covalently [78], by weaker interactions [79] or by dialysis procedure [70,80]. Conferring intrinsic water-solubility to phthalocyanines is based on two main strategies: ionic substituents or strongly hydrophilic ones, commonly carbohydrates or polyethylene glycol. Water-soluble phthalocyanines are not systematically used in aqueous solutions. Some phthalocyanines that are not water-soluble may become so after bonding to some polymers [81,82]. In order to limit the scope of this review, and as the

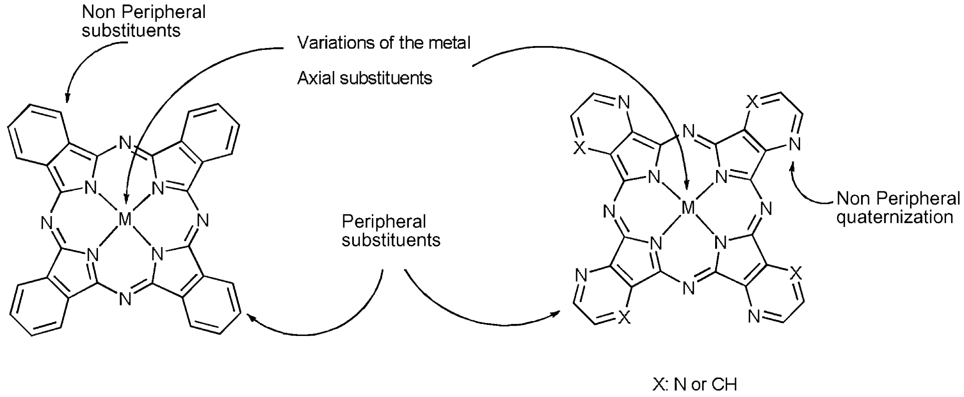


Fig. 1. Modulable points of phthalocyanines.

water-solubility is not an intrinsic property of the phthalocyanines, they will not be mentioned here.

In this review, we will overview the synthesis of the reported water-soluble phthalocyanines: anionic, cationic or non-charged.

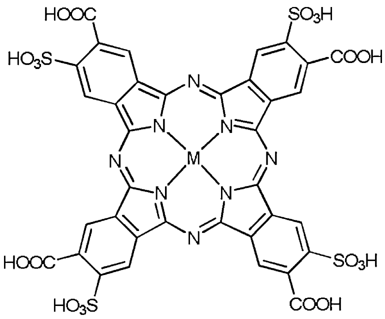
It is important at this point to define the water-solubility we are speaking about. Many of the applications said to require water-soluble phthalocyanines will in fact occur in aqueous medium, for example buffered solutions. Such media are considered to belong to our topic. The phthalocyanine macrocycle is a hydrophobic system: to make it water-soluble, hydrophilic moieties must be added, and the resulting system will be more or less amphiphilic. Its water-solubility depends on its overall amphiphilic balance, and as well on other parameters such as aggregation, the "nature" of the aqueous medium in terms of pH [83], ionic strength, presence of a cosolvent [84] among others.

2. Anionic water-soluble phthalocyanines

Anionic substituents commonly utilized to confer water-solubility to phthalocyanines are sulfonate, carboxylate, phosphorus-based functions, attached directly on the macrocycle or borne by various spacers.

Their water-solubility is strongly pH-dependent, the conjugated acid forms of these groups being not necessarily water-soluble. The reported phthalocyanines bear usually only one type of these functions, with the notable exception of **1** (Fig. 2) which bears concomitantly two of the most common functions: sulfonic and carboxylic acids [85].

Some metallated unsubstituted phthalocyanines can axially complex cyanide ions [86–88]. This allows the solubilization of these unsubstituted phthalocyanines (when metalated by metals such as Fe, Ru and Os) in aqueous KCN or NaCN solutions, as a result of the formation of water-soluble complexes bearing axial cyanide [89–91].



1

M: Cu, Co, Zn, Fe(OH)

Fig. 2. Phthalocyanine **1** substituted by carboxylic and sulfonic acids [85].

2.1. Sulfonated phthalocyanines

Most of the anionic phthalocyanines bear sulfonate or sulfonic acid groups. Their synthesis can follow different pathways, by using sulfonated phthalocyanine's precursors or by introducing the sulfonate function on preformed phthalocyanine, either by sulfonation of the macrocycle or substitution in axial position. Sulfonated naphthalocyanines have also been reported [92–94]. van Lier and his group have extensively studied sulfonated phthalocyanines and have developed synthetic pathways to obtain asymmetric sulfonated substitution patterns.

The synthetic pathways are unfortunately not always described, as in the case of **2** (TX-101A), **3** (TX-105-A) and **4** (TX-106A) prepared by Nippon Shokubai Co. Ltd., (Osaka, Japan) (Fig. 3) [95].

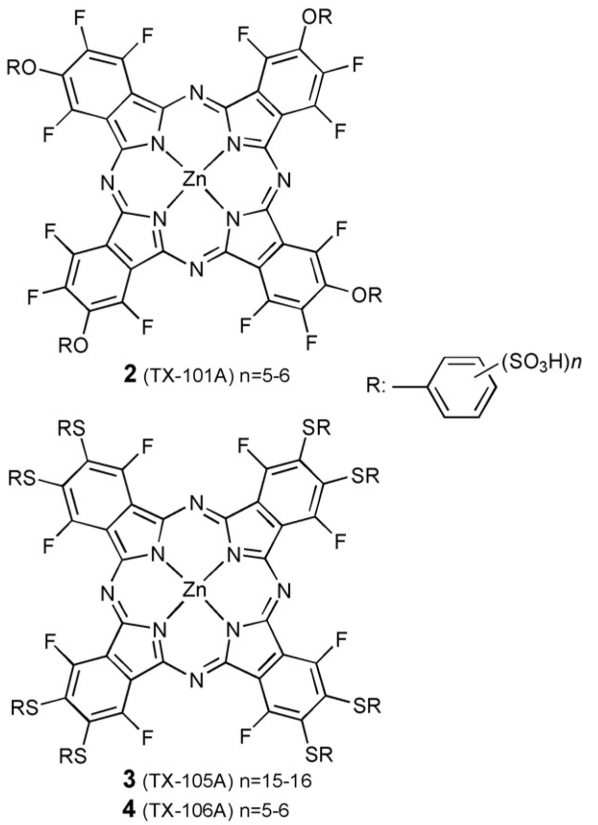
2.1.1. Symmetrically sulfonated phthalocyanines

Two strategies are reported: achieving the synthesis from sulfonated precursors or by sulfonating the phthalocyanine itself.

2.1.1.1. From sulfonated precursors. Synthetic precursors of directly tetrasulfonated phthalocyanines **6** are sulfonated phthalic acid and its corresponding sulfonated phthalic anhydride. The precursor can be the sulfonic acid or the sodium salt. The first descriptions of sulfonated phthalocyanines date from the 50's, by Baumann [96] and Fukada [97]. The method was then modified by Weber and Busch [98] to limit the metallic impurities. The starting product is the monosodium salt of 4-sulfo phthalic acid **5**, mixed with urea, ammonium molybdate, ammonium chloride and the appropriate metal salt and heated in nitrobenzene at 180 °C (Scheme 1). The yield is strongly related to the introduction rate of the reagents to nitrobenzene, indeed increased when this addition is slow, over 1 hour [99].

After removal of nitrobenzene by methanol, metallic residues are removed by an acidic washing (1N hydrochloric acid saturated by sodium chloride). Sulfonic acid is recovered by a 0.1N sodium hydroxide treatment. Yield is around 80%. Sulfophthalic acid can be used as well as a starting compound for this method [100]. This template assisted synthesis has been used to prepare a wide range of metallated phthalocyanines, using various metal salts: metal sulfate, metal chloride, etc. This method was then modified to be solvent-free [101,102]. An advantage of this method is the possibility to prepare nitrogen-labeled derivatives by using ^{15}N-urea [103].

The known enhancing effect of microwaves [104] in phthalocyanines synthesis [105] was successfully applied as well on the



2 (TX-101A) n=5-6

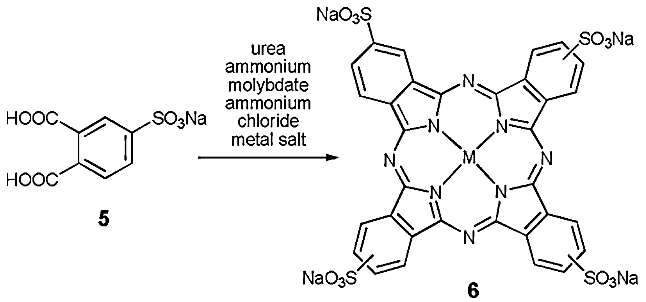
3 (TX-105A) n=15-16
4 (TX-106A) n=5-6

Fig. 3. Fluorinated and sulfonated phthalocyanines TX-101A (**2**), TX-105A (**3**) and TX-106A (**4**) [95].

synthesis of sulfonated phthalocyanines. Same precursors irradiated by microwaves lead, in the presence of the suitable metal salt, to 2H, Zn, Cu, Co, AlCl, Mg, Ga(OH) [106], Sn [107], Ni, Pd, Pt [108] phthalocyanines in excellent yields [109,110]. The metal can be inserted as well on free-base sulfonated phthalocyanines, this is the case of radioactive isotope of gallium (^{67}Ga) [111] and copper (^{64}Cu) [112].

The amphiphilicity of tetrasulfonated phthalocyanines has been modulated by exchanging the sodium counter ion with various tetraammonium cations, leading to **7** and **8**, which are soluble in a wide range of solvents, **8** being soluble in dichloromethane and in water (Fig. 4) [113].

Other sulfonated phthalocyanine precursors have been reported such as substituted phthalonitriles in which the sulfonic acid function is borne by aromatic rings (**9**, **10** and **11**, Fig. 5). They are prepared by the condensation of 4-nitrophthalonitrile with 4-hydroxybenzene sulfonic acid [114,115], monosulfonated naphthol (1-naphthol-4-sulfonic acid) sodium salt [116] and its isomer: 5-hydroxy-1-naphthalene sulfonic acid [117].



5

6

Scheme 1. Weber and Busch's synthesis of tetrasulfonated phthalocyanines [98].

The cyclotetramerisation of **9** was initiated in pentanol, then metalated in situ [118,119]. Phthalonitrile **10** was cyclotetramerised into the corresponding metal free phthalocyanine in hexanol/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and later on its metalation lead to CuPc [120], ZnPc [121] or CoPc [122] in moderate yields. Phthalonitrile **11** was directly converted into the corresponding Zn phthalocyanine (pentanol, DBU, $ZnCl_2$).

Heterocyclic aromatic sulfonamide substituted phthalonitriles such as **15**, despite a more complex synthesis, are a versatile protected form of sulfophthalonitriles [123]. They are prepared by the chlorosulfonation of 1,2-dibromobenzene **12** and subsequent reaction with pyrrole (and related aromatic structures such as 2-ethylpyrrole, 3,5-dimethylpyrazole, imidazole, indole), the sulfonate being protected by a heterocyclic amide function before undergoing the Rosenmund–von Braun dinitrilation (Scheme 2: example of the protection by pyrrole). The sulfonate function was similarly successfully protected by a diphenylamine, but this protection results in the inconvenience of resistance to final deprotection steps. After formation of the phthalocyanine, the protecting groups are removed by lithium methoxide in methanol, methanol/THF or lithium 2-*N*,*N*′-dimethylaminoethoxide in DMAE, yielding **16**.

The strongly activated 4-chlorosulfonylphthalonitrile **17** [114], another sulfonated precursor, was used as the starting compound for sulfonated subphthalocyanines formation. Thanks to the activating effect of the chlorosulfonyl function, 1-chlorobenzene could be used as the solvent, the trimerization occurring at a temperature as low as 40 °C, when similar reactions commonly require the 1-chloronaphthalene's boiling point. Sulfosubphthalocyanine **18** was obtained in high yields (around 60%) and immediately used for the following steps. It was converted into the sulfonated pyridinium salt **19** prior to undergoing the Kobayashi's ring expansion [124,125]. **19** is an intermediate for the formation of asymmetric phthalocyanines (Scheme 3).

Finally, some original octasubstituted sulfonated phthalocyanines are described. The disulfonated precursor **21**, obtained in three steps from dipotassium 2-hydroxynaphthalene-6,8-disulfonate **20** (Scheme 4), is cyclotetramerised into an isomeric mixture of octa sulfonated phthalocyanines [126].

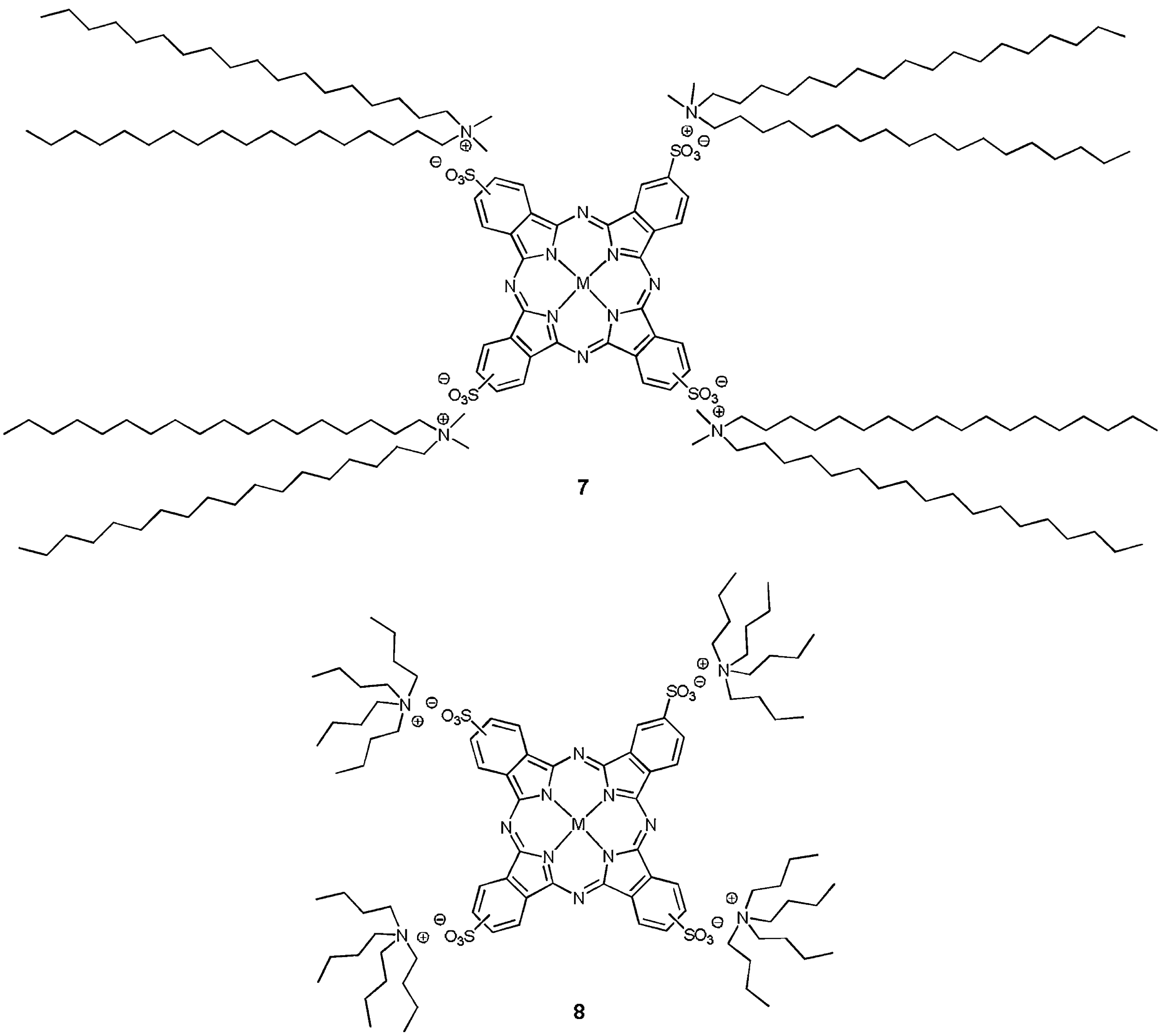
Isomeric mixture of tetrasulfonated and tetrabrominated phthalocyanines **23** is obtained in six-step synthesis from 4-bromo phthalic acid **22** (Scheme 5) [127].

2.1.1.2. Sulfonation of phthalocyanines. The second widely utilized method to prepare sulfonated phthalocyanines is the sulfonation of the macrocycle itself.

Metal free or metallated unsubstituted phthalocyanines are sulfonated when treated by concentrated sulfuric acid (H_2SO_4, 35% SO_3 free) at 80–100 °C. A mixture of mono-, di-, tri- and tetrasulfonated phthalocyanines (**24**–**28**) is obtained (Fig. 6), the sulfonation degree being determinable by high performance liquid chromatography (HPLC). The stability of the metallation is proved by UV–vis measurements. A subsequent basic treatment easily leads to the corresponding sodium sulfonated Al, Ce or 2H phthalocyanines [100,128]. Only one sulfo unit is introduced on the 4-position of each isoindole sub-unit, as established by Linstead in 1950, "although it may not be the only position attacked" [129] as observed for halogenation [130], thus contradicting previous observations [131].

This method was then extended to other metallated phthalocyanines [132,133] (AlPcSmix, SiPcSmix, GePcSmix, SnPcSmix, and ZnPcSmix) following referenced procedures [134].

Attempts to control the sulfonation process and ratio remain tedious despite attempts to play on the temperature and fuming acid's concentrations [135]. Tetrachlorosulfonation in meta posi-



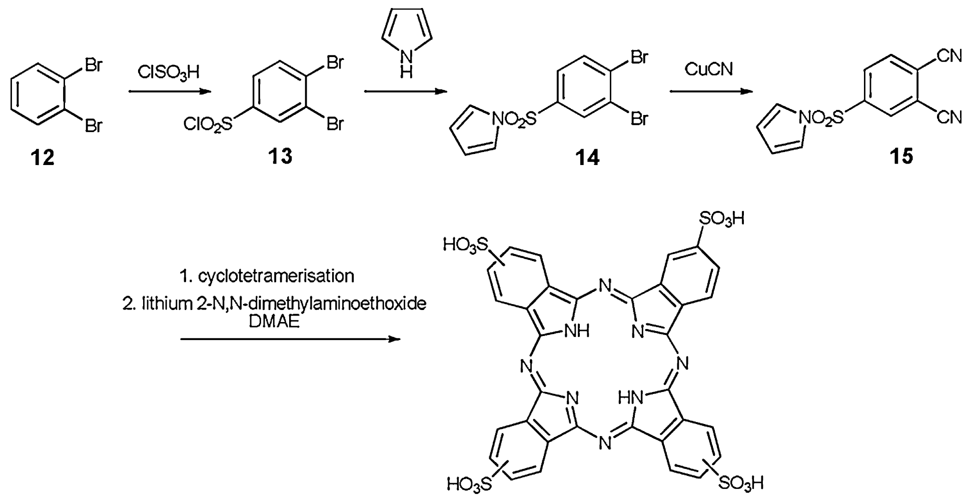
7

8

Fig. 4. Introduction of tetraalkylammonium counter ions on tetrasulfonate substituted phthalocyanines. M: Ni(II), Co(II), Fe(III)Cl, Cr(III)Cl [113].

tion of a cobalt phthalocyanine in quite soft conditions is reported, with no proof of the sulfonation positions [136]. Attempts to quaternize the macrocyclic nitrogen of bis-(2,3)pyridinoporphyrazine **29** by common quaternizing agents (diethyl or dimethyl sulfate) resulted surprisingly in the sulfonation of the pyridine rings, yielding **30** (Scheme 6) [137–139].

Metallated octaphenyltetrapyrazinoporphyrazines **31** (M: Fe^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}) [140,141] undergo selectively the sulfonation of



Scheme 2. Synthesis of sulfonated phthalocyanine via pyrrole protected intermediates [123].

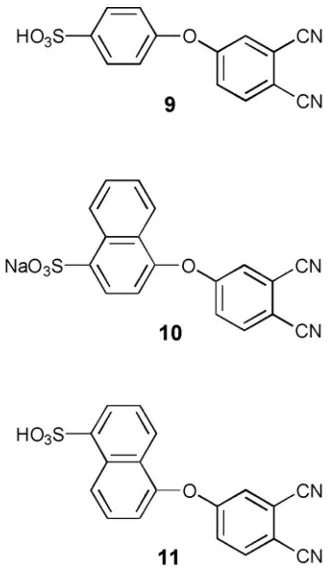


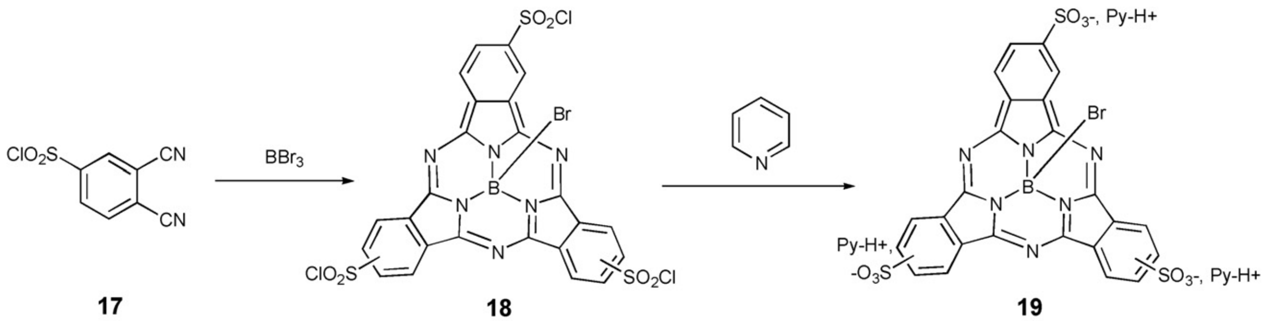
Fig. 5. Aryl sulfonated phthalonitriles **9**, **10** and **11** [114–117].

the para position of each of the eight phenyl groups (Scheme 7), leading to the water-soluble derivative **32** [142].

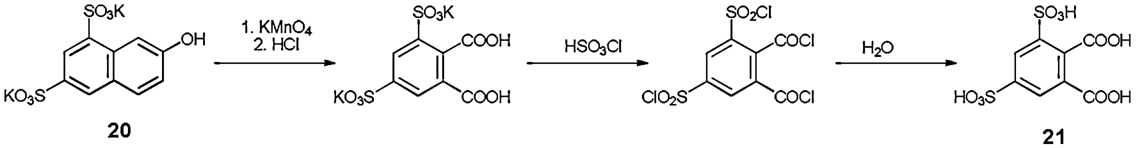
Aiming at obtaining species likely to coordinate alkali or transition metal ions, the pentanuclear crown ether substituted phthalocyanine **38** has been designed and synthetized [143]. 1,1′-Oxybis(ethyleneoxy)-bis(2-toluene-p-sulfonylaminobenzene) **33** was first condensed on **34**, and the resulting dibrominated **35** was either directly converted into **37**-**Cu** or underwent a dinitrilation leading to **36** before being converted into **37**. Attempts to remove tosyle protecting groups required strong acidic medium, and the use of concentrated sulfuric acid lead to the tetrasulfonation, **38** being obtained as a mixture of isomers (Scheme 8). **38** was highly satisfactorily soluble in water even if the presence of sulfonate groups is not suitable to extract alkali metal by coordination.

The other way to introduce sulfonate groups on a preformed phthalocyanine is the coupling of tetraiodinated **39** and **40** (M = Zn, AlOH or GaOH) with vinylsulfo groups, using Heck coupling in water. Sodium vinyl sulfonate provided the vinylsulfo moieties in the presence of trisodium triphenylphosphine-3,3,3-trisulfonate (TPPTS) (Scheme 9) [144], following previously tested aqueous coupling on porphyrins [145–147]. Overall yields in **41** and **42** are around 30–40% for this tetrasubstitution.

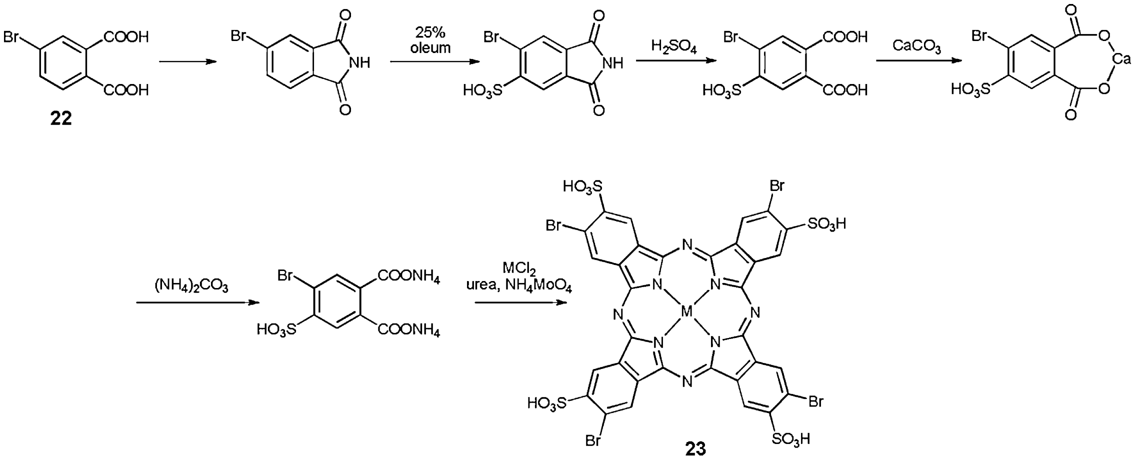
2.1.1.3. Axial sulfonation of phthalocyanines. Reports on anionic substitution in the axial position of metallated phthalocyanines



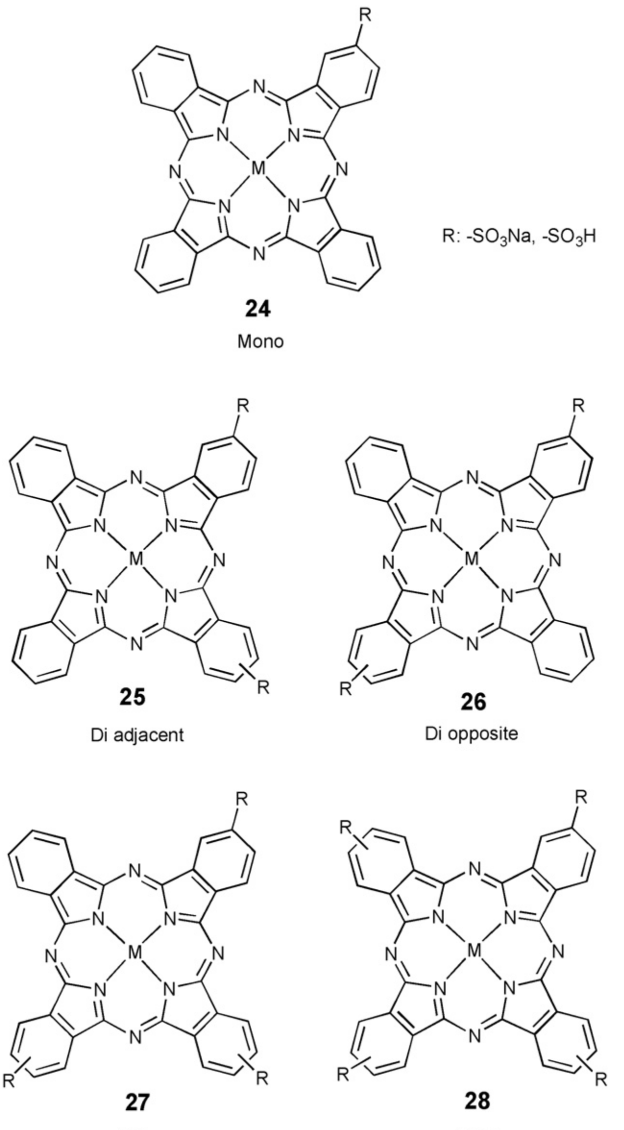
Scheme 3. Synthesis of trisulfonate substituted subphthalocyanine **19** [124–125].



Scheme 4. Preparation of disulfonated phthalic acid **21** [126].



Scheme 5. Synthesis of tetrahalogenated tetrasulfonated phthalocyanines **23** [127].



24 Mono

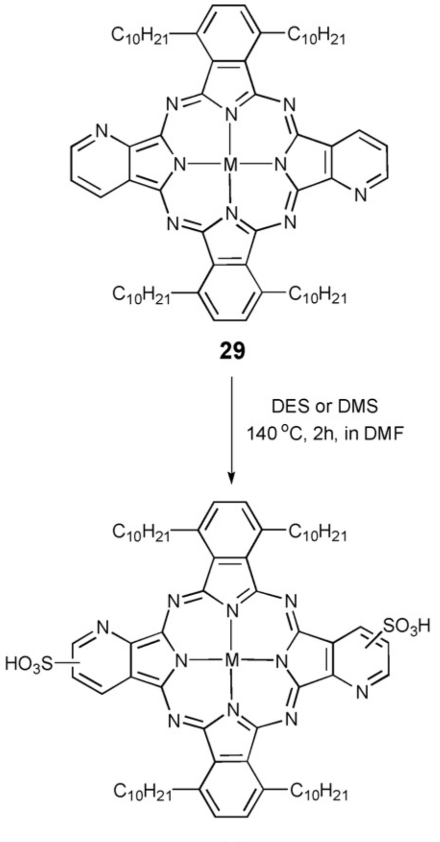
25 Di adjacent

26 Di opposite

27 Tri

28 Tetra

Fig. 6. Mixture of sulfonated phthalocyanines obtained by treatment of unsubstituted phthalocyanine.

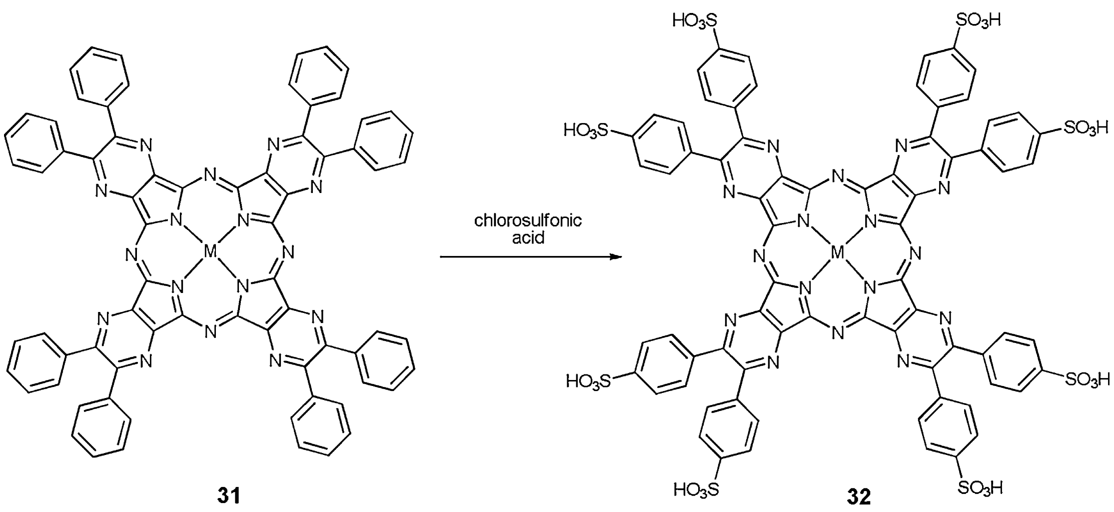


29

30

Scheme 6. Unexpected sulfonation of bis (2,3)-pyridinoporphyrazines [137–139].

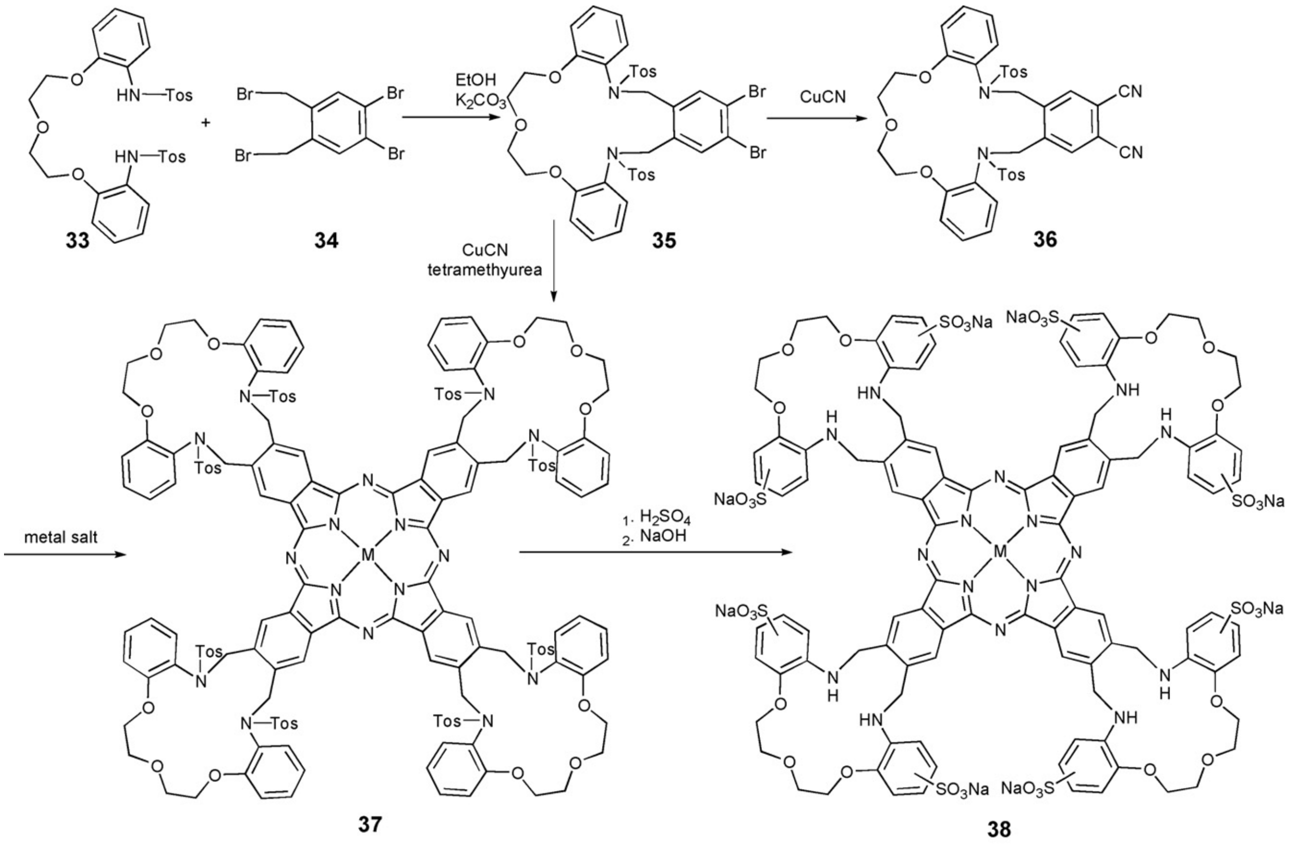
are very few and include zirconium and hafnium phthalocyanines [148], and the interesting synthesis of axially substituted (Pc)RuL$_2$, where L can be sulfonate or amino groups [149,150]. The reported optimized method overcomes many problems routinely encountered in ruthenium phthalocyanines synthesis [151–153] and is based on the preliminary formation of an insoluble (Ru)Pc(NH$_3$)$_2$ complex (**44**) from an original ruthenium complexing species (**43**), **44** being easily converted into the soluble (Ru)Pc(PhCN)$_2$ (**45**) that can undergo further ligand exchange with tetrabutylammonium triphenylphosphine monosulfonate (TBA(TPPS)) leading to **46** in high yields (Scheme 10).



31

32

Scheme 7. Sulfonation of **31** [142].

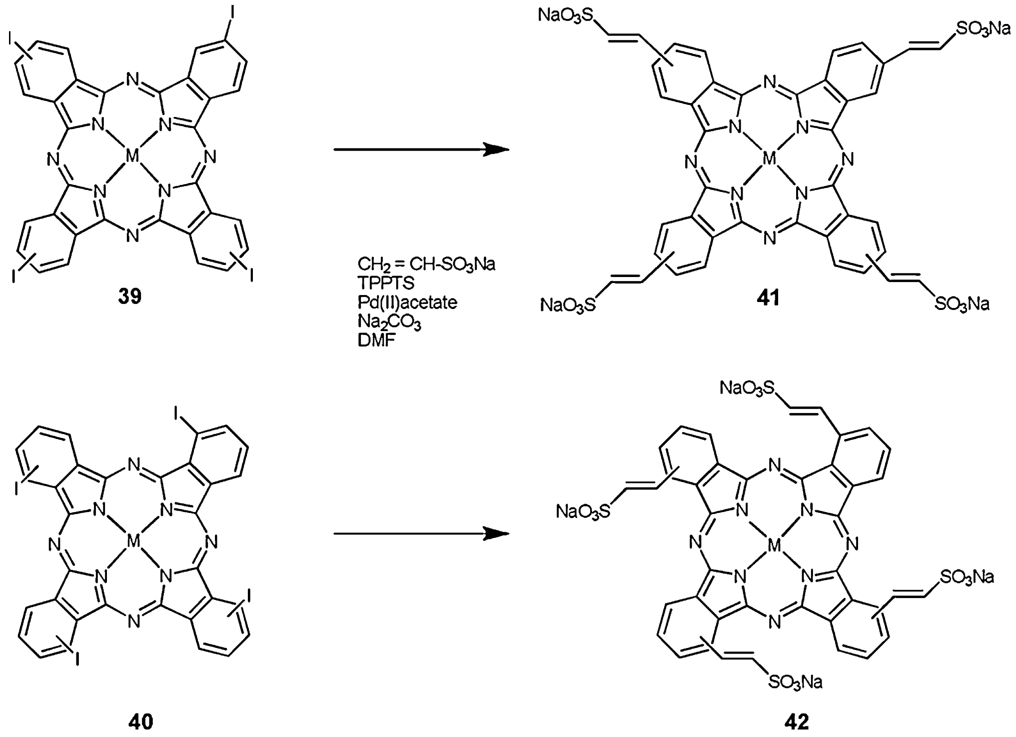


Scheme 8. Synthesis of sulfonated crown ether substituted phthalocyanine **38** [143].

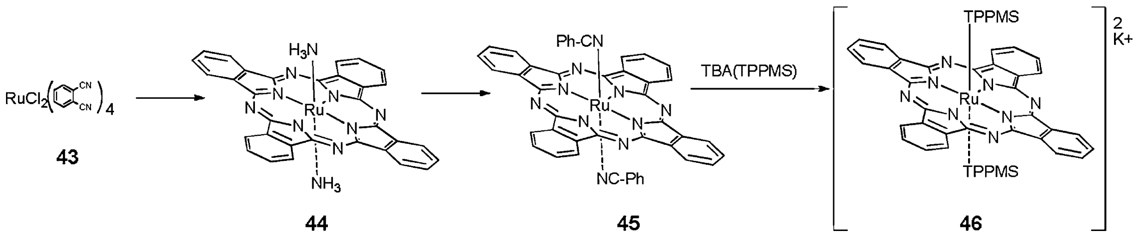
2.1.2. Asymmetrically sulfonated phthalocyanines

Asymmetrically substituted sulfonated phthalocyanines are obtained either by reaction on previously formed phthalocyanines, by the selective formation of phthalocyanines using the Kobayashi subphthalocyanine ring expansion method, or by the cyclotetramerisation of a mixture of two precursors (of same or different type).

Obtaining asymmetric phthalocyanines is useful in that they can combine desired properties such as water-solubility and functionalization for targeted applications, such as when there are



Scheme 9. Preparation of sodium vinyl sulfonate substituted phthalocyanines **41** and **42** [144].



TPPMS: $Ph_2P(3\text{-}C_6H_4SO_3^-)$

Scheme 10. Preparation of axially sulfonate substituted phthalocyanine **46** [149,150].

three sulfonate units and one different substituent (the presence of only one or two sulfonates [115] may not be enough to confer water-solubility but can enhance other interesting properties from a spectral absorption point of view). The other interest of asymmetric phthalocyanines is the modulation of the amphiphilicity of the molecule, hence of its biological interactions and activities, one of the main application fields of water-soluble phthalocyanines.

2.1.2.1. Reactions on phthalocyanines. The direct sulfonation of the macrocyclic leads to phthalocyanines with different degrees of sulfonation, which were studied for their biological activities [154].

Only one case of asymmetric functionalization of a formed phthalocyanine is reported, using modified sulfonation conditions to introduce at the same time phthalimidomethyl and sulfonate groups on unsubstituted Zn phthalocyanine, leading to the asymmetric phthalocyanine **47** (Fig. 7). The unsubstituted phthalocyanine is firstly stirred in sulfuric acid, then phthalimide, paraformaldehyde and oleum are added and refluxed for several hours. Separation of the different isomers previously purified by several washing and precipitating steps was achieved by reverse phase HPLC [155].

The monoamidification of tetraclorosulfonyl aluminium phthalocyanine **48** by stoichiometric reaction with *n*-alkylamines is described (Scheme 11) [156]. The resulting **49** is highly amphiphilic.

2.1.2.2. Ring enlargement of subphthalocyanines. The symmetric sulfosubphthalocyanine **18**, prior to undergoing ring enlargement, was converted into **19** to prevent likely reaction between the highly reactive chlorosulfonyl moieties and diiminoisoindoline. **19** was condensed with chosen iminoisoindolines in DMSO, leading to asymmetric phthalocyanines in elevated yields (up to 30%) under mild conditions. This is explained by the electron-withdrawing effect of sulfonyl substituents [124,125]. A series of amphiphilic water-soluble phthalocyanines **50a**–**c** was obtained, using diiminoindoline **51**, diiminoazaisoindoline **52**, or the naphthadiiminoisoindoline **53**, the sulfonated functions being regenerated by an acidic work-up (Scheme 12). Zn is inserted at the last step of the synthesis.

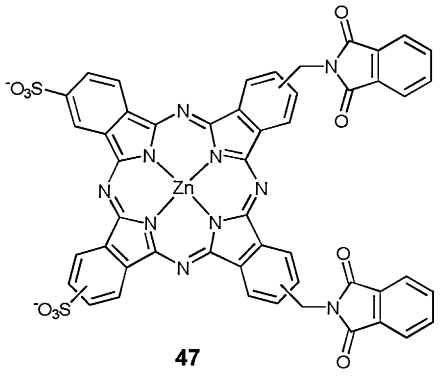
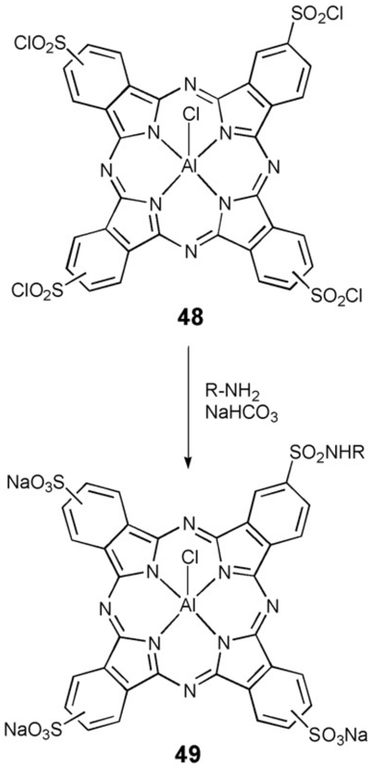


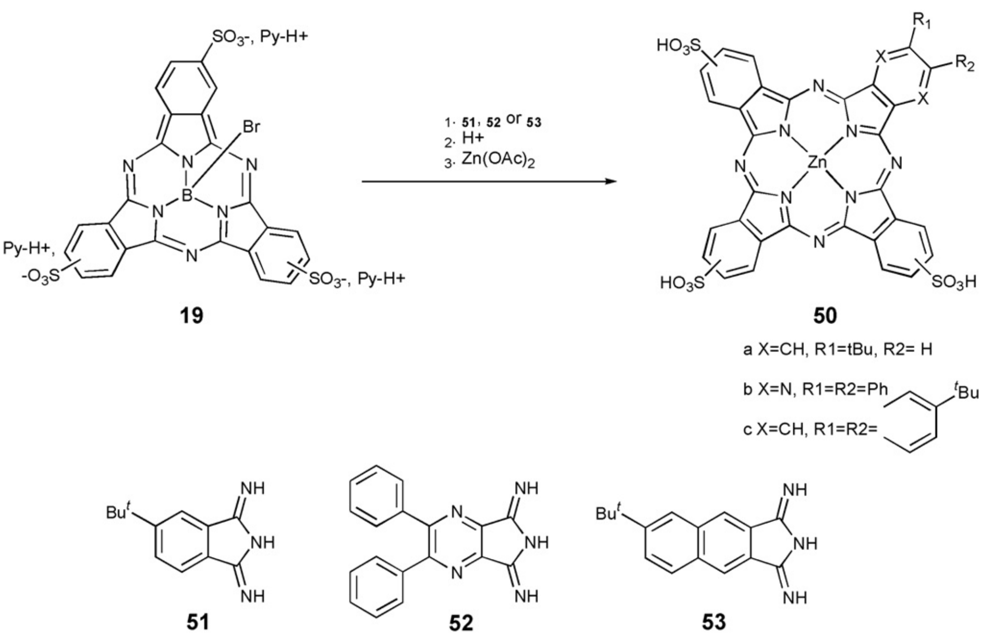
Fig. 7. Amphiphilic sulfonated phthalocyanine **47** [155].

2.1.2.3. Mixed statistical condensations. Mixed statistical condensation of two different precursors is another method used to obtain asymmetrically substituted phthalocyanines. Following Weber and Busch's method, mixed cyclotetramerisation of phthalic and sulfophthalic acids can be used to obtain asymmetric phthalocyanines. The resulting mixtures are separated and characterized as the mixtures resulting from sulfonation of the phthalocyanine itself.

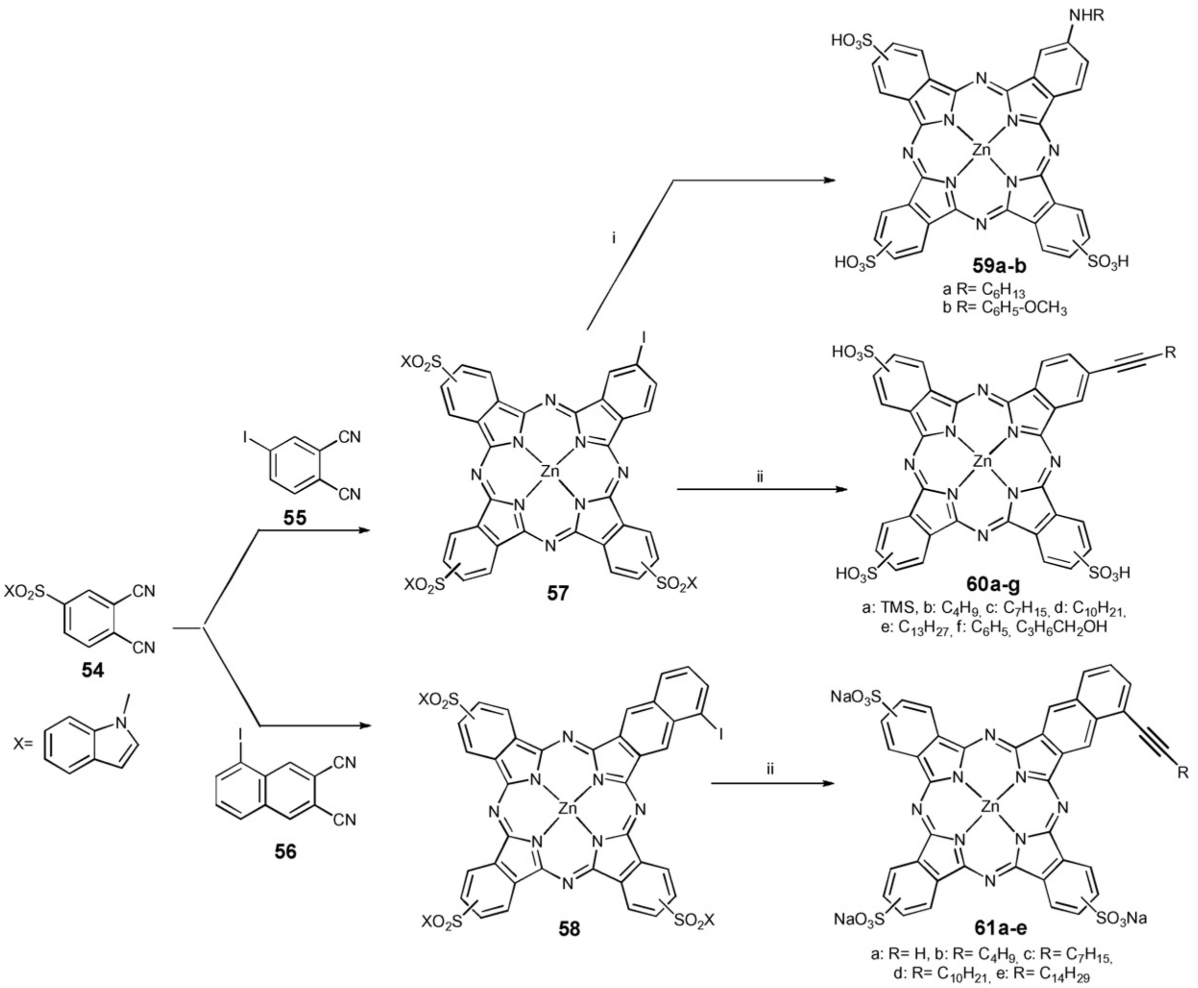
Indole-protected sulfophthalonitrile **54** [123] was engaged in a statistical cyclotetramerisation with the iodophthalonitrile **55** [157,158] or 5-iodo-2,3-dicyanonaphthalene **56** [159] in the presence of Zn salts. Thanks to the protecting group's stability in weakly basic media, the resulting asymmetric phthalocyanines bearing three indolylsulfonate and one iodide (**57** and **58**) can undergo versatile coupling reactions with various alkynes. The indolyl group is then easily removed by lithium methylate in refluxing methanol-THF. A series of three types of amphiphilic phthalocyanines (**59a**–**b**, **60a**–**g** and **61a**–**e**) are obtained after respectively Buchwald's palladium-catalyzed amination and palladium-catalyzed Sonogashira coupling (Scheme 13).



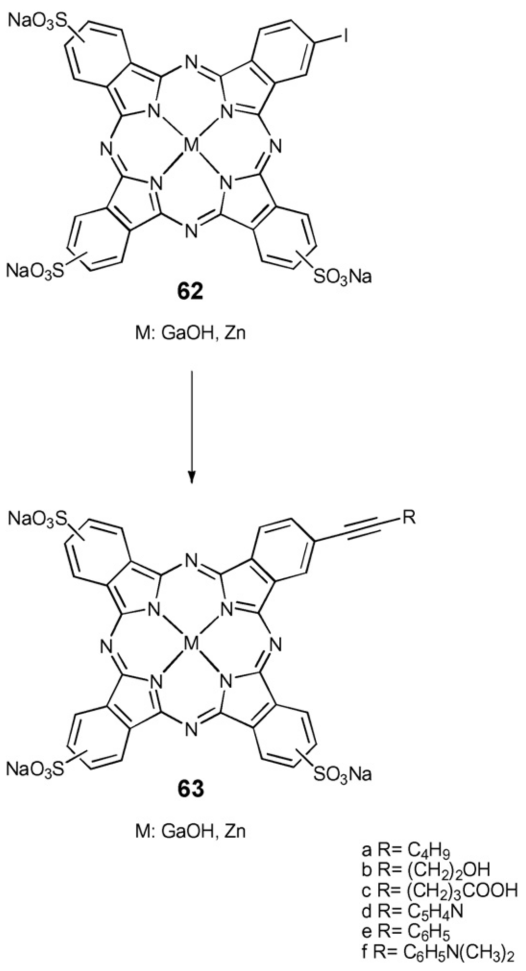
Scheme 11. Monoamidification of **48**. R: –C_4H_9, –C_8H_{17}, –$C_{12}H_{25}$ and –$C_{16}H_{33}$ [156].



Scheme 12. Expansion of subphthalocyanine **19** by different diiminoisoindolines [124–125].



Scheme 13. (i): $Pd_2(dba)_3$/(S)-BINAP, Cs_2CO_3, and (ii): alkyne, $PdCl_2(Ph_3P)_2$, CuI, THF, Et_3N [157–159].



Scheme 14. Coupling on phthalocyanine **62** [146].

Avoiding protection steps of the sulfo function, the phthalic acid **5** reacts with 4-iodophthalonitrile **55** (molar ratio 5:1) in presence of ammonium chloride, ammonium molybdate, urea and gallium chloride, leading directly to the water-soluble asymmetric phthalocyanine **62** which easily undergoes palladium-catalyzed cross-coupling reactions: Heck, Suzuki and Sonogashira, leading to the amphiphilic water-soluble phthalocyanines **63a**–**f** (Scheme 14) [146].

AB3 type asymmetric phthalocyanines bearing three sulfonate groups and one tert-butyl have been prepared following the same way, from 4-sulfophthalic acid and tert-butyl phthalic acid [160].

2.2. Phosphorus-based substituted phthalocyanines

Only a few water-soluble phthalocyanines bearing phosphorus-based substituents are reported. Either phosphate, phosphonate or phosphinate functions are described.

The synthesis of phosphonate substituted phthalocyanines is particularly useful for comparison of their properties with those of their homologous derivatives: sulfonated phthalocyanines. This was the purpose of the first phosphonated phthalocyanine **66**: its interest lay on the modulation of its pKa values compared to analogous sulfonated phthalocyanines, leading to adjustment of some properties associated with water-solubility for further biological applications. From a synthetic strategy point of view, the phosphate group is introduced on the bromomethylphthalonitrile **64**, obtained by the NBS alkylbromination of 4-methylphthalonitrile. **64** reacts with triethylphosphite. Subsequent elimination of ethyl bromide by Arbuzov's rearrangement leads to the diethyl 3,4-dicyanobenzylphosphonate phthalonitrile **65** [161]. Phosphonate substituted zinc phthalocyanine **66** was obtained by the cyclotetramerisation of **65** in presence of zinc salts, one ethyl group being finally removed by basic hydrolysis (Scheme 15).

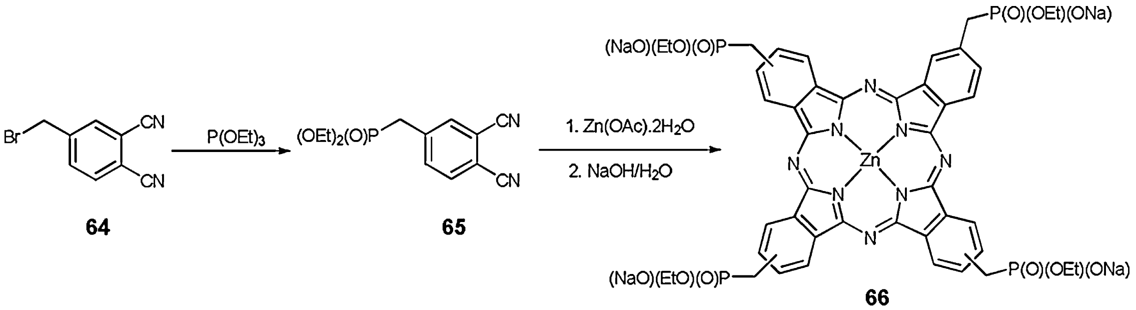
The phthalocyanine **69** bears four esterified phosphate groups and was prepared in four steps from 4-iodophthalonitrile **55** [162]. Its Heck coupling with but-3-yn-1-ol led to the hydroxylated phthalonitrile **67** later on esterified by diethylchlorophosphate (Scheme 16).

The two previously described phosphonate-containing phthalocyanines **66** and **69** included an alkyl space between the phosphorus-based groups and the phthalocyanine macrocycle. The hereafter reported phthalocyanines **72** and **73** bear phosphonate functions directly on the macrocycle.

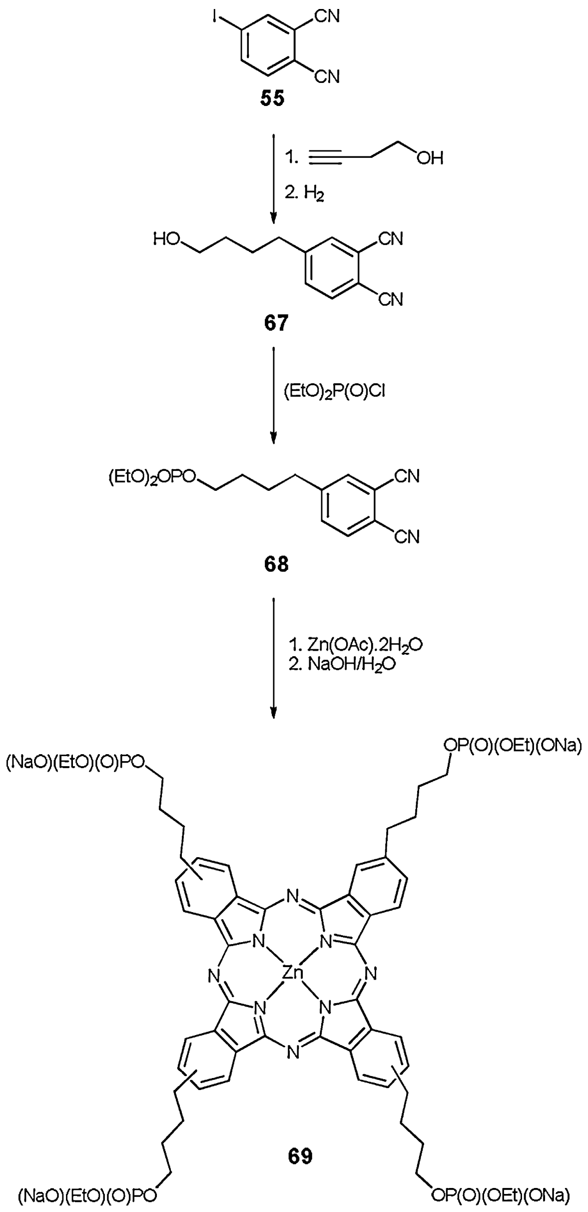
The direct phosphorylation of 4-iodophthalonitrile **55** into 4-diethoxyphosphinyl phthalonitrile **71**, its subsequent cyclotetramerisation into **72** followed by acidic deprotection lead to **73** (Scheme 17) [163]. Solvent-free cyclotetramerisation was attempted, as well as the use of high boiling solvent, but basic solvents were also appropriate (yields between 30 and 60%). Removal of ethyl groups is achieved in quite harsh conditions (HCl 6N, 20 h refluxing), leading to phosphonate-containing phthalocyanines proving to have a highly pH-dependent aggregation behavior. In another team's studies [164], **72** was obtained from bromophthalonitrile **70** (itself synthesized in two steps from bromophthalimide [165]) and used to produce the free-base derivative, in addition to the Cu and Zn ones. Final hydrolysis was achieved in basic conditions.

2.3. Carboxyles and carboxylates substituted phthalocyanines

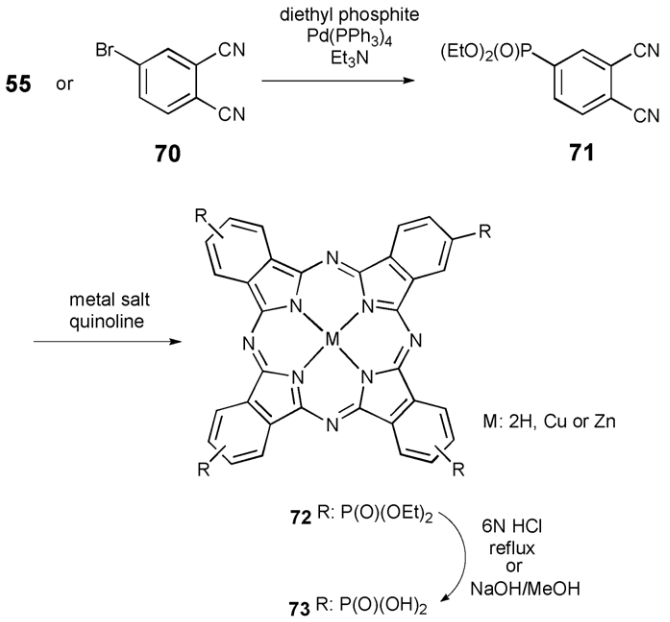
Polycarboxylated phthalocyanines are soluble in alkaline aqueous media in which they are unprotonated. They can also be soluble in neutral or acidic solutions but less systematically, the



Scheme 15. Synthesis of phosphonate substituted phthalocyanine **66** [161].



Scheme 16. Preparation of esterified phosphate substituted phthalocyanine **69** [162].



Scheme 17. Preparation of phosphonate substituted phthalocyanines **73** [163].

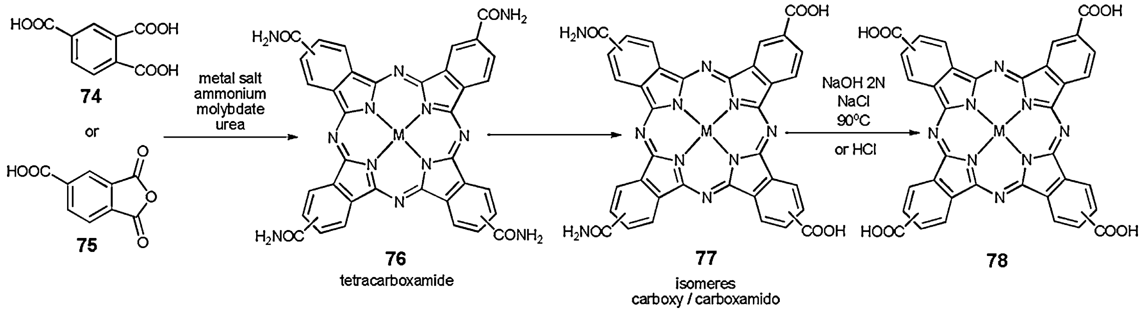
water-solubility being dependent on their metallic and substitution pattern [166]. The characterization of carboxylated phthalocyanines by mass spectroscopy was extensively studied and proved to be complex [167]. Carboxylated phthalocyanines can be divided into several types: the case of tetra and octa macrocyclic carboxylation, and the case of molecules substituted by carboxyl groups separated from the macrocycle by various spacers.

2.3.1. Carboxylic functions borne directly by the macrocycle

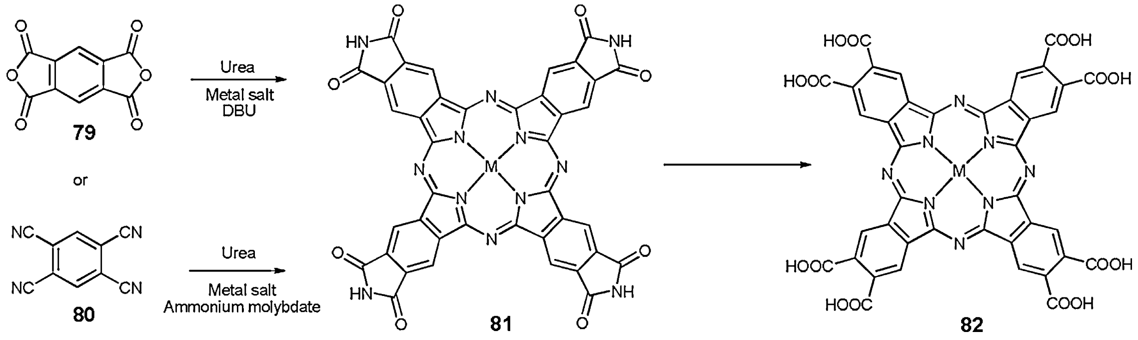
2.3.1.1. Tetrasubstitution. The first syntheses of tetracarboxylic acid substituted phthalocyanines (TCPc) **78** were described by Achar et al. [168,169] and Shirai et al. [170] and their coworkers and are directly inspired from Weber and Bush's methods. The precursor metillic acid **74** [171] or trimetillic anhydride **75** [101,166,172–177] is condensed in the absence or presence of metals salts (e.g. $CuSO_4$, $CoCl_2$, $Co(Ac)_2$, $AlCl_3$ or $ZnCl_2$), and in the presence of urea, ammonium chloride and ammonium molybdate (Scheme 18). This leads to tetraamido derivatives **76** whose further hydrolytic conversion into the desired tetracarboxy derivatives remained unsuccessful despite several attempts and different methods. Complete hydrolysis could not be observed, the main product being a diamido dicarboxy derivative **77** [173,178]. The carboxylic function is nevertheless said to be obtained by harsh alkaline or acidic hydrolysis [175,179].

Non-peripheral derivatives were prepared by the same method from benzene-1,2,3-tricarboxylic acid [171].

2.3.1.2. Octasubstitution. Tetraphthalimide phthalocyanine **81**, obtained from pyromellitic anhydride **79** can be hydrolyzed into the octacarboxy phthalocyanine **82** in quite harsh acidic conditions (20% refluxing sulfuric acid, over 3 days) [106,180].



Scheme 18. Preparation of TCPc **78** from trimetillic acid **74** or anhydride **75** [168–177].



Scheme 19. Synthesis of octacarboxylic acid substituted phthalocyanine **82** [171].

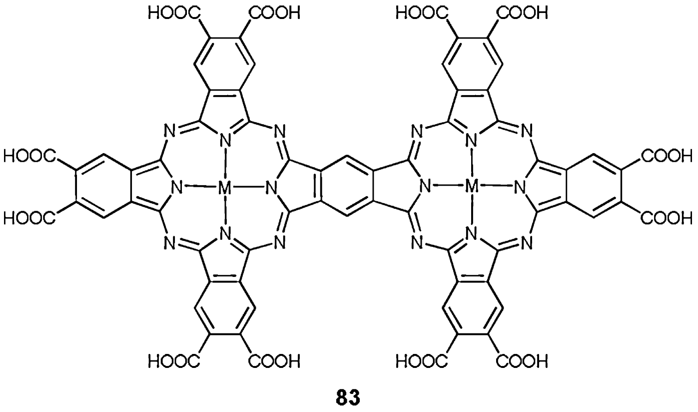
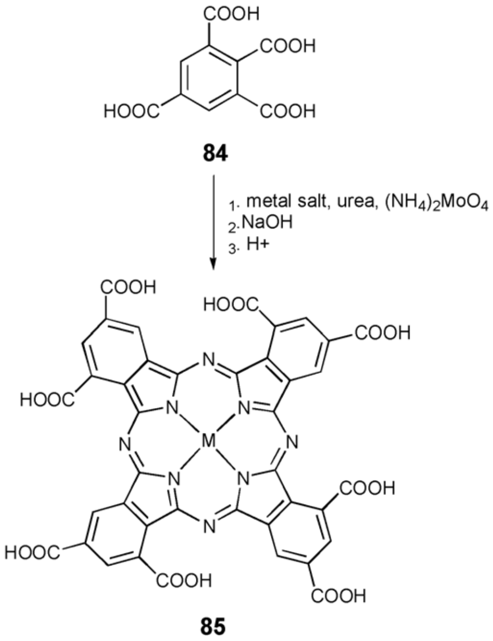


Fig. 8. Dodecacarboxylated phthalocyanine **83** [181].



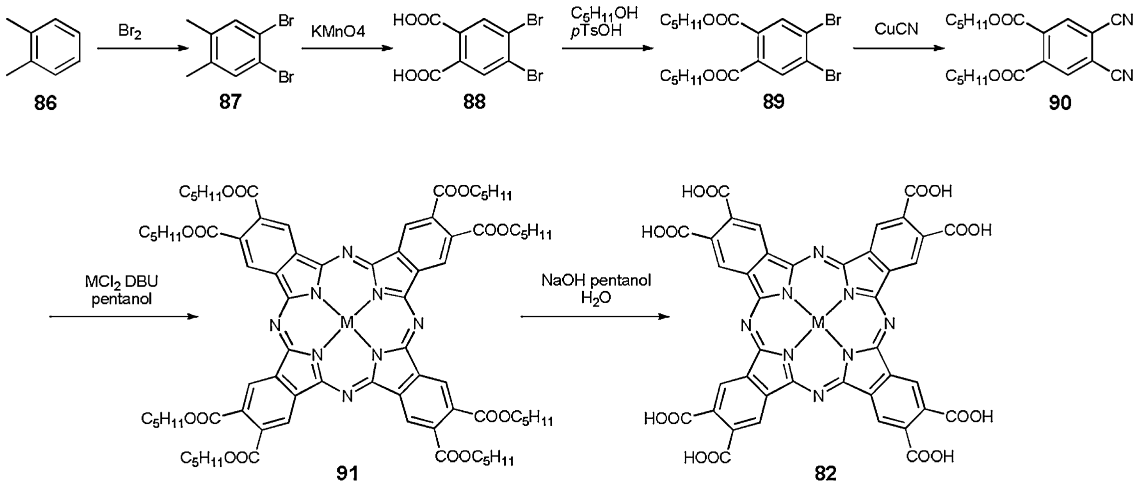
Scheme 20. Synthesis of octacarboxylated phthalocyanine **85** [171].

The use of tetracyanobenzene **80** in the presence of ammonium molybdate, urea and metal salts also leads to octaamido phthalocyanine which can be hydrolyzed into the desired octacarboxylated derivatives by alkaline alcoholic hydrolysis (Scheme 19) [171].

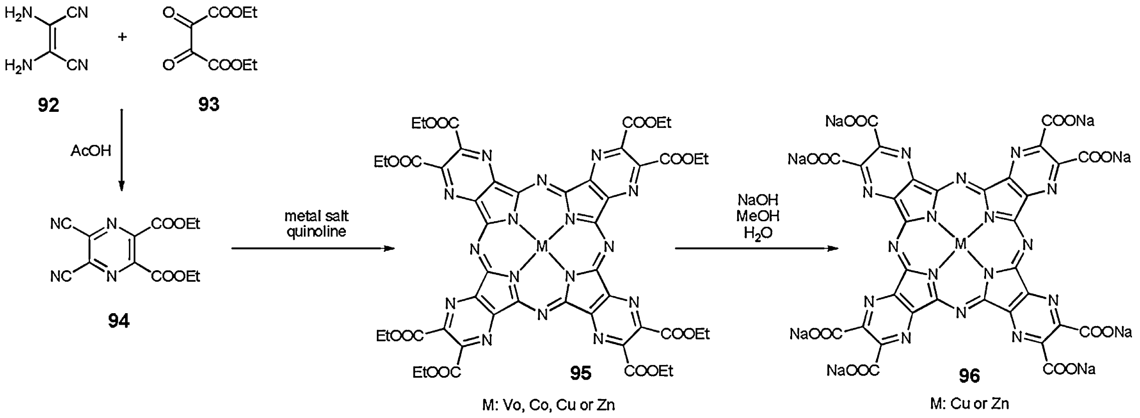
79 was used to prepare the Fe(II)$_2$ and Co(II)$_2$ fused dimeric phthalocyanines **83** (Fig. 8) in respectively 19 and 24% yields [181].

The use of benzene-1,2,3,5-tetracarboxylic acid **84** (urea, ammonium molybdate, metal salt followed by hydrolysis) leads to isomeric **85** as a mixture of positional isomers (Scheme 20) [171].

To be sure of the final molecular structure, especially of the carboxylation degree, and to avoid the formation of oligomeric structures, octacarboxy Zn and Cu phthalocyanines **82** have been prepared from diesterified phthalonitrile **90** obtained in four steps from *o*-xylene **86** [182]. **90** is cyclotetramerised into the octaesterified phthalocyanine **91**, with a final hydrolysis of the esters groups to regenerate the carboxyle groups (Scheme 21) [183].



Scheme 21. Synthesis of octacarboxylic acid substituted phthalocyanine **82** [183].



Scheme 22. Preparation of octacarboxytetrapyrazinoporphyrazines **96** [185].

Octacarboxylated Cu phthalocyanine has been described as a ternary complex, with two axial pyridine ligands [184].

Metallated octacarboxytetrapyrazinoporphyrazines **96** are obtained in a three-step synthesis [185]. The condensation of diaminomaleodinitrile **92** with diethyl dioxosuccinate **93** leads to the diesterified phthalonitrile **94**. Its cyclotetramerisation assisted by different metal salts lead to the octaethoxycarbonyl derivative **95**, and the alkaline hydrolysis of the Cu and Zn compounds lead to **96** derivatives (M: Cu and Zn) (Scheme 22).

2.3.1.3. Asymmetric substitution pattern. All the carboxylated phthalocyanines having an asymmetric substitution pattern are of AB3 type and have been obtained by mixed statistical condensation of two different precursors.

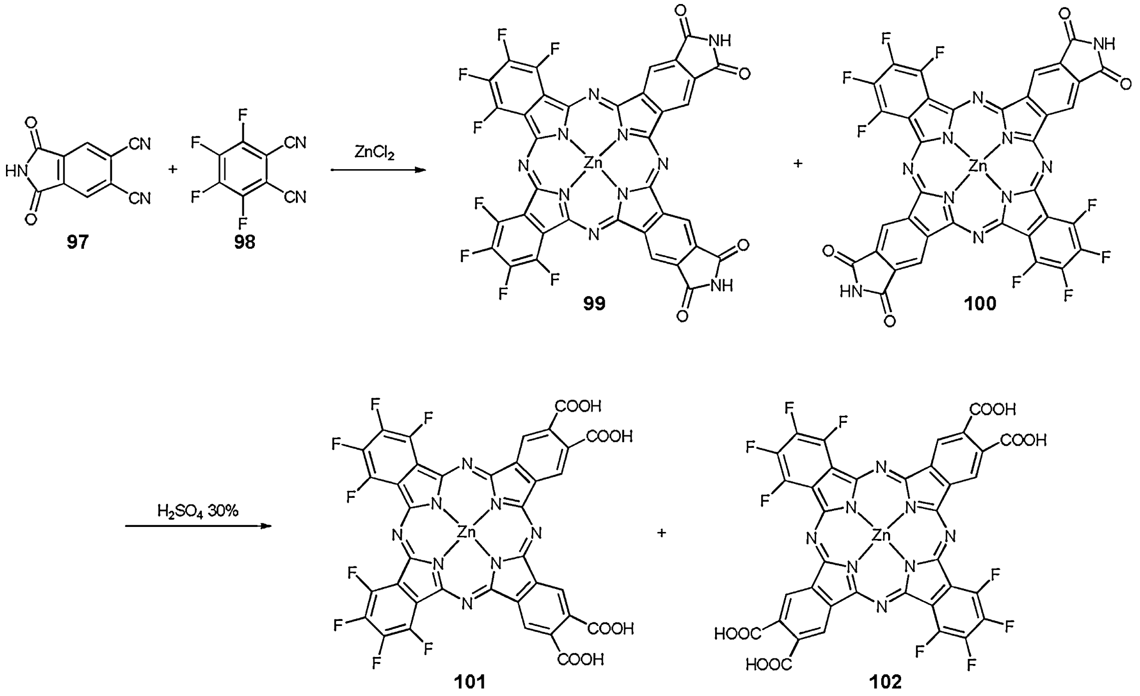
In order to obtain asymmetric substitution pattern with carboxylic groups directly borne by the macrocycle and alternated with fluorine atoms, carboxylic function was introduced on the phthalocyanine under a phthalimide form (phthalonitrile **97**), converted after a mixed cyclotetramerisation with tetrafluorophthalonitrile **98** into asymmetric phthalocyanines **99** and **100**, followed by a strongly acidic hydrolysis into respectively **101** and **102** (Scheme 23), that are highly amphiphilic [186].

Octa[4,5]carboxyphthalocyanine tetraanhydrides **103** [187–189] react easily with amines. Asymmetric carboxyphthalocyanine **104** bearing one rhodamine moiety was prepared from cobalt phthalocyanine **103** and is soluble in aqueous basic media (Scheme 24) [190].

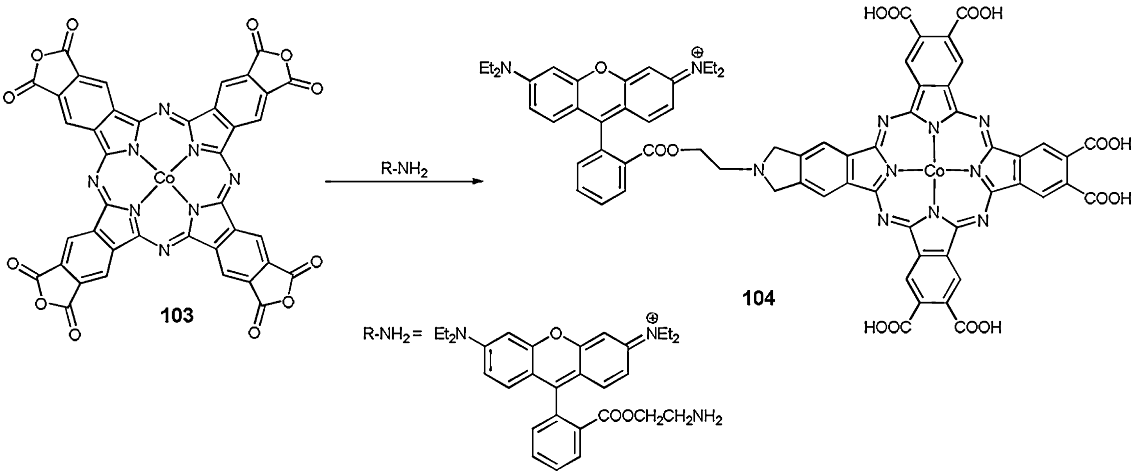
The water-solubilizing properties of directly macrocycle-carboxylated phthalocyanines allowed the formation of asymmetric labellisable phthalocyanines. Thus, carboxylated naphthalonitrile **105** [115], when undergoing a mixed condensation with 4-nitrophthalonitrile, leads to **106** easily converted into isothiocyanated phthalocyanine **108** in two steps: reduction of the nitro function and functionalization by 1,1′-thiocarbonyldi-2(1H)-pyridone **109** (Scheme 25) [191].

2.3.2. Carboxylic functions on spacer

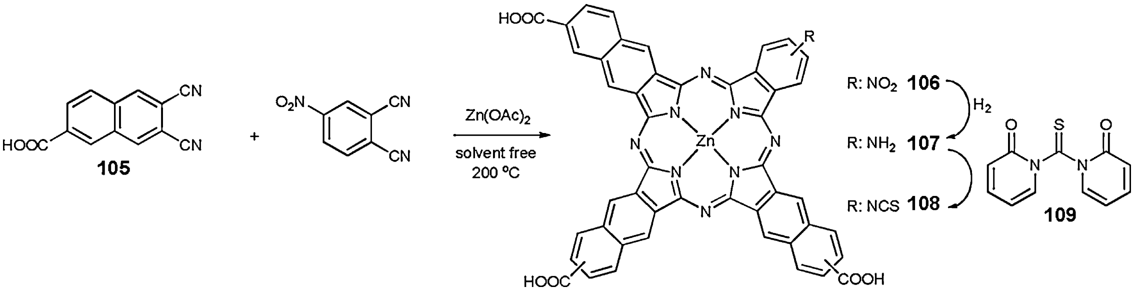
Alternative ways have been developed to access carboxylated phthalocyanines, in which the carboxylic functions are borne by spacers. This carboxylic function is either present on the



Scheme 23. Preparation of fluoro and carboxylic acid substituted phthalocyanines **101** and **102** [186].



Scheme 24. Preparation of rhodamine substituted hexacarboxylated phthalocyanine **104** [190].



Scheme 25. Preparation of isothiocyanate substituted phthalocyanine **108** [191].

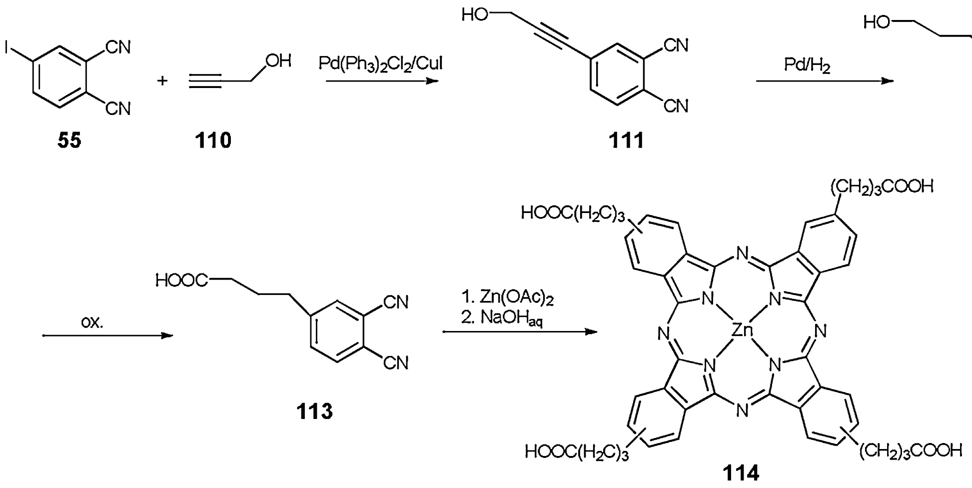
phthalocyanine precursor or introduced later on a functionalized phthalocyanine. Carboxylated precursors are generally phthalonitriles bearing one or two carboxylic functions possibly protected by esterification.

2.3.2.1. From carboxylated phthalonitriles. As the use of ammonia required in the synthesis of phthalocyanine when the precursor is a phthalic derivative, leads to tetraamido groups which are difficult to hydrolyze [172], van Lier and coworkers prepared the tetrapropionic acid substituted phthalocyanine **114** directly from carboxylated phthalonitrile **113**, obtained by a three-step sequence from the iodophthalonitrile **55** and propargylic alcohol **110** (Scheme 26) [161].

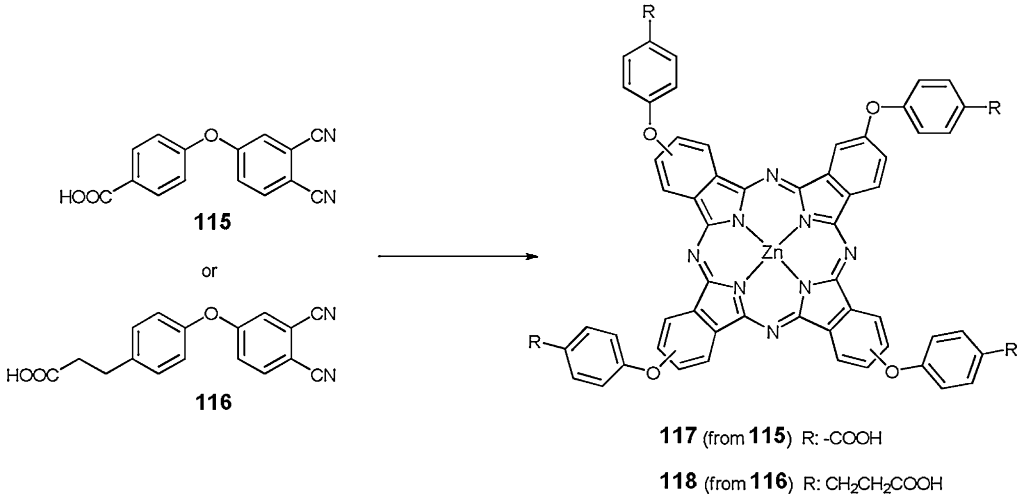
4-(3,4-Dicyanophenoxy)-benzoic acid [106] **115** and 3-[4-(3,4-dicyanophenoxy)phenyl] propionic acid **116** have similarly been used for the preparation of the tetracarboxylated phthalocyanine **117** and **118** (Scheme 27) [119].

115 was used in mixed cyclotetramerisation together with nitrophthalonitrile to produce precursor of labellisable phthalocyanines [191].

Dendrimeric structure **120**, in which phthalocyanine is the core, contains numerous carboxylic functions at the periphery of the molecule resulting in significant lowering of aggregation [192]. The starting phthalonitrile bears free carboxyl, but the cyclotetramerisation conditions in *n*-pentanol lead to the formation of esterified phthalocyanine, the carboxyl groups being regenerated



Scheme 26. Synthetis of tetracarboxylated phthalocyanine **114** [161].



Scheme 27. Preparation of tetracarbophthalocyanines **117** and **118** [119].

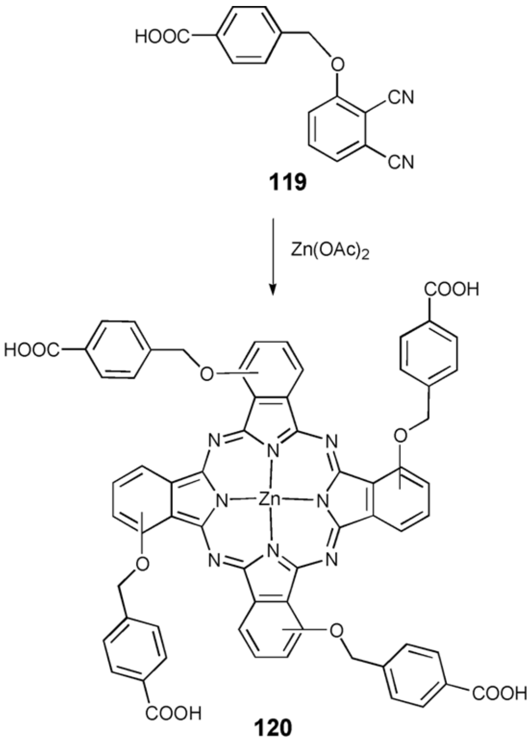
afterward by a methanolic solution saturated by sodium hydroxide (Scheme 28).

Mg and Zn tetrapyrazinoporphyrazines **124** substituted by four carboxyl groups were prepared from the phthalonitrile derivative **123** (Scheme 29) [193]. While the Mg is directly introduced during the cyclotetramerisation step of **123**, the Zn derivative is obtained from the free-base derivative, the latter resulting from the hydrolysis of the Li_2 derivative.

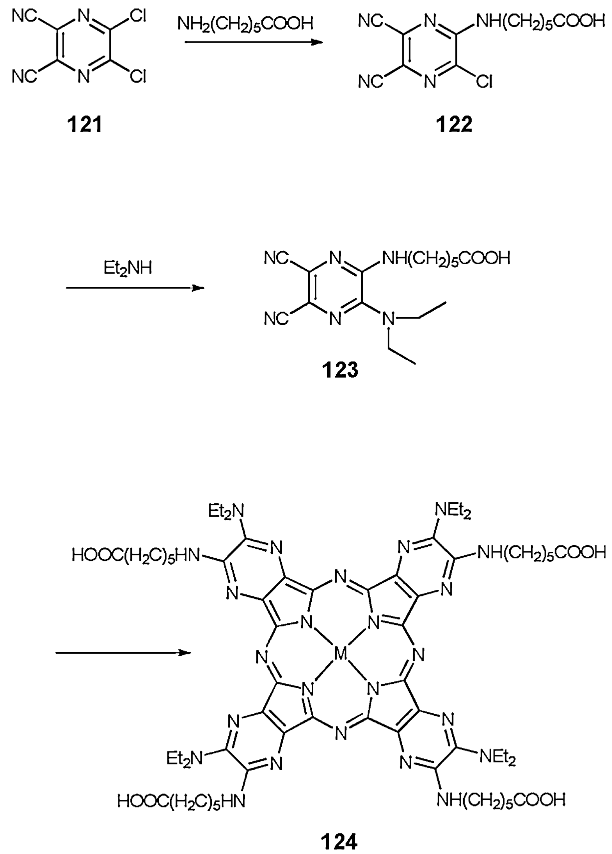
2.3.2.2. From esterified phthalonitriles. Dimethyl 5-hydroxyisophthalate is widely used for dendrimer synthesis. 4-Nitrophthalonitrile was substituted by various [G*n*]-OH, G being one unit of dimethyl 5-hydroxyisophthalate **125**, and $n = 0–2$. The resulting phthalonitriles underwent cyclotetramerisation and subsequent hydrolyis of the ester function, leading to the dendrimeric water-soluble phthalocyanines **126a–c** (Fig. 9) [194,195]. The aggregation, which also exists for dendrimeric phthalocyanines [196], is adequately inhibited in this case.

Ng [197] and Vicente and coworkers [198] published nearly concomitantly the synthesis of hexadecacarboxylated phthalocyanine **128** from the dicarboxylated phthalonitrile **127**, obtained by the condensation of dimethyl 5-hydroxyisophthalate **125** on 4,5-dichlorophthalonitrile. The metallation occurred either directly during the phthalocyanine formation or by further metallation of the free-base phthalocyanine (Scheme 30).

The carboxylic function of the coumarine substituted phthalocyanine **130** [199] is in its lactonized form. During the opening



Scheme 28. Preparation of tetracarboxylated ZnPc **120** [192].



Scheme 29. Preparation of tetracarboxy tetrapyrazinoporphyrazines **124** [193].

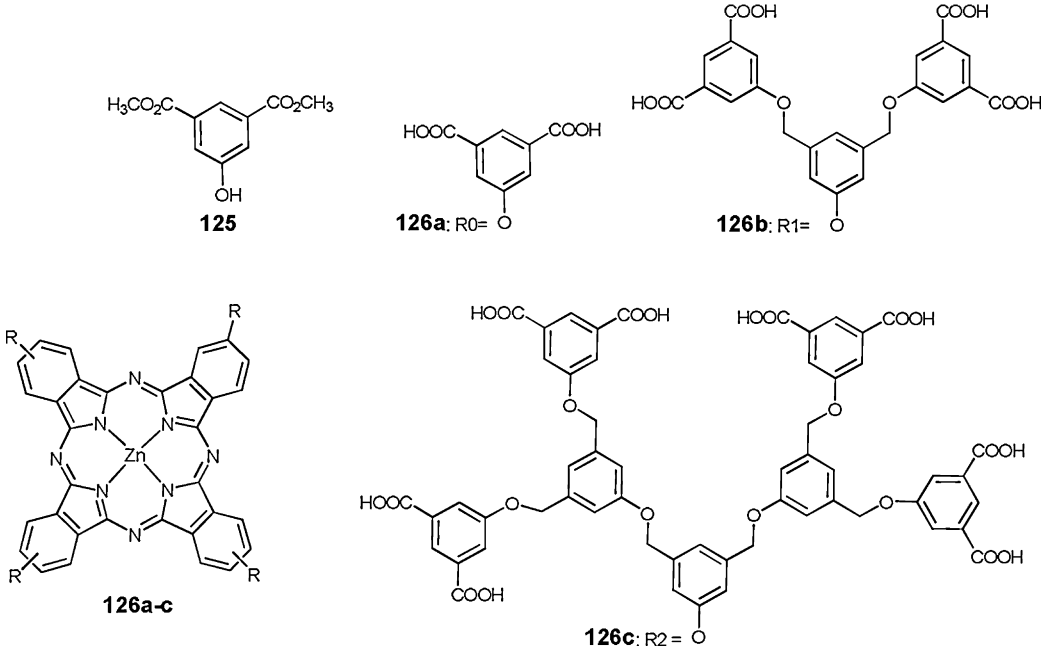
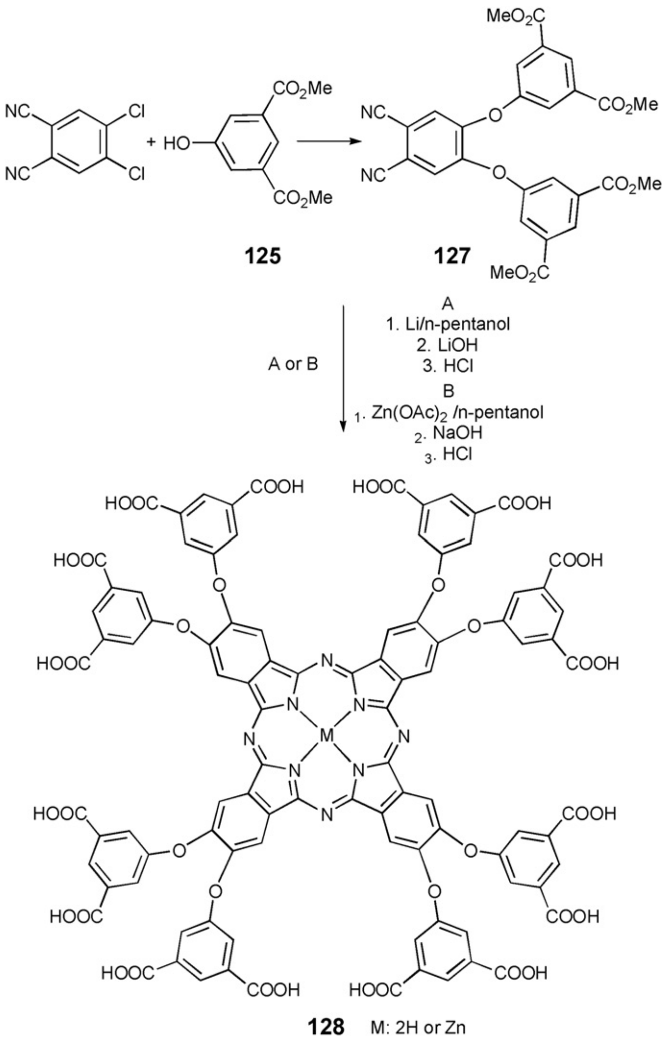
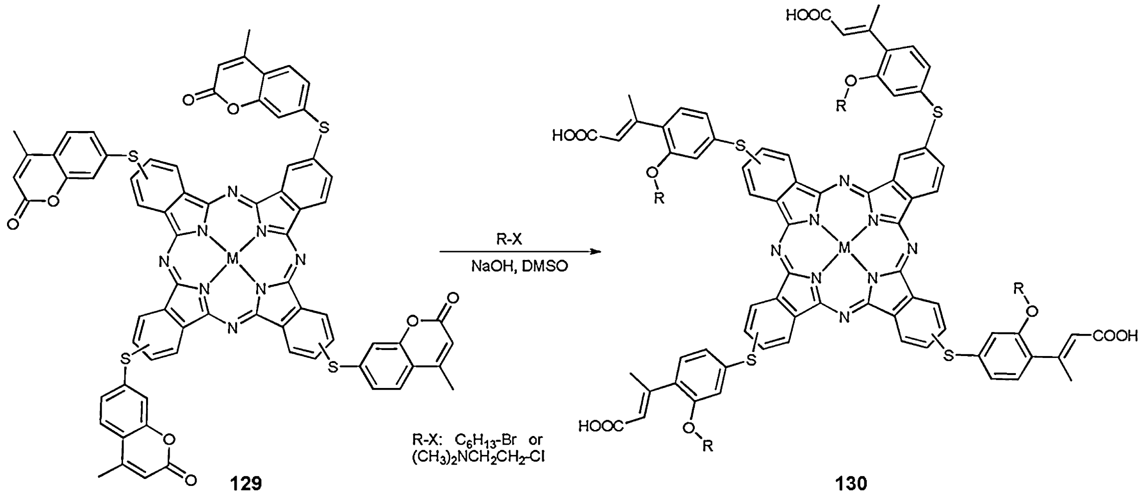


Fig. 9. Dendrimeric phthalocyanines **126a**–**c** [194,195].



Scheme 30. Preparation of dendrimeric hexadecacarboxylated phthalocyanine **128** [197–198].



Scheme 31. Opening of the coumarine rings of **129** to prepare **130** [199–200].

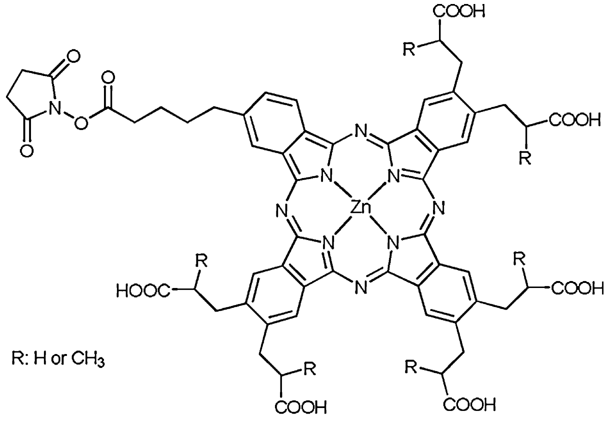
of a lactone (in **129**) by sodium hydroxide [200], the hydroxyl groups formed readily react on halogenoalkanes (Scheme 31). The resulting carboxylic function can then be deprotonated by aqueous sodium hydroxide solutions, giving rise to the highly water-soluble phthalocyanines **130**.

Hanack and coworkers reported in 1999 the synthesis of several carboxylated phthalocyanines [201], all being water-soluble. Carboxylic functions were borne by various spacers, among which highly elaborated substituents such as amino acid groups bearing α-carboxylic function. Phthalocyanine **134** was obtained from the phthalonitrile **133**, itself prepared in two steps from bromocatechol **131** and ethyl 2-bromopropionate (Scheme 32).

Another starting compound, 3,4-dihydroxyphenylalanine (DOPA, **135**), after protecting the carboxy and amino groups, was converted into the activated bistriflate **137**, and underwent subsequent conversion into the phthalonitrile **138** by a palladium-catalyzed substitution. The source of cyanide is $Zn(CN)_2$. This method was later on extended to difficult substrates [202]. The cyclotetramerisation followed by the regeneration of the carboxylic acid functions lead to the amino acid substituted phthalocyanine **139**, exhibiting an excellent water-solubility (Scheme 33) [201].

A serine-substituted phthalocyanine was synthesized from the reaction of 3,4-dibromobenzoyl chloride with a protected serine, followed by conversion to the corresponding phthalonitrile and then cyclotetramerisation, before final hydrolytic steps [201].

Tetracarboxylated phthalocyanine **146** was prepared from the protected catechol **140** reacting with the bromo derivative **141** after deprotonation by butyl lithium (Scheme 34).

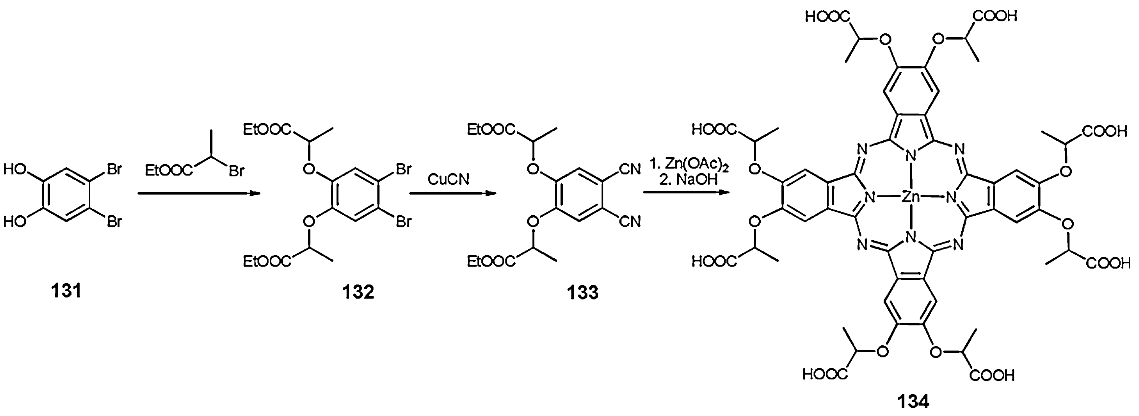


147

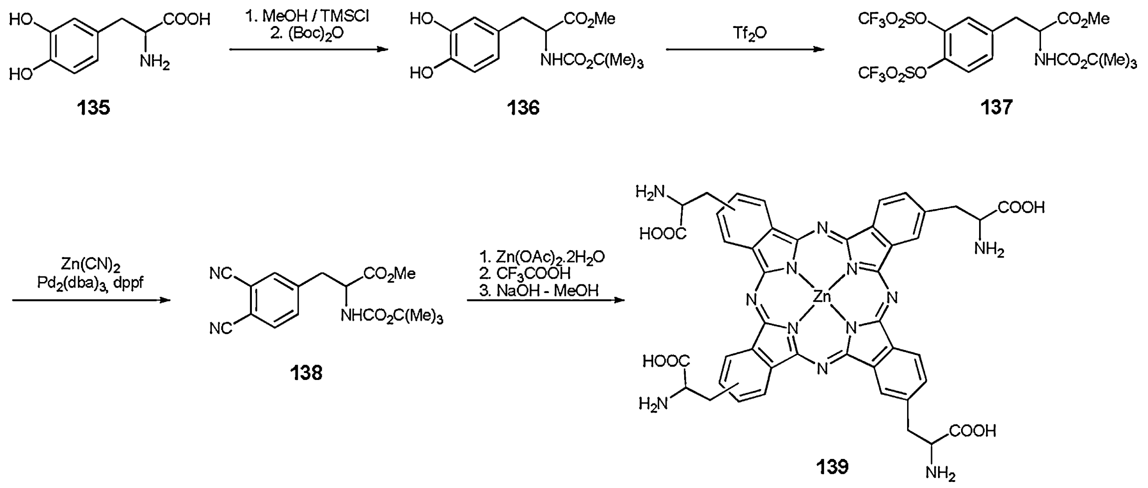
Fig. 10. Asymmetrically substituted carboxyphthalocyanine **147** [201].

Asymmetric statistical cyclotetramerisation lead to AB3 type phthalocyanines **147** (Fig. 10) bearing three protected carboxylic acid functions. The fourth substituent can easily react with proteins, thus antibodies [201].

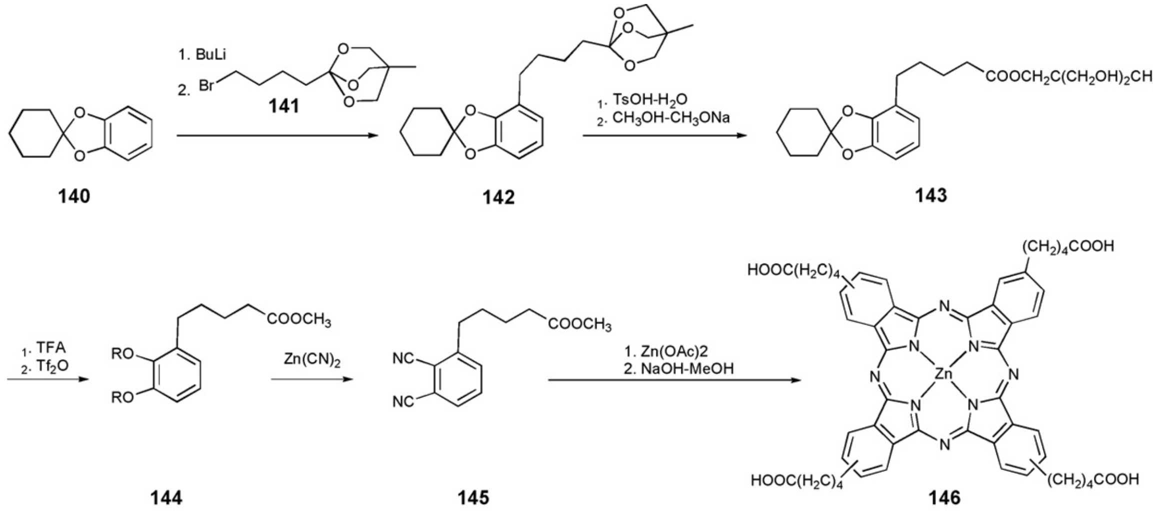
Carboxy amino acid having their carboxylic function esterified can be condensed to phthalonitrile, and the carboxy functions are then regenerated after the cyclotetramerisation step (Scheme 35) [203].



Scheme 32. Preparation of phthalocyanine **134** [201].



Scheme 33. Synthesis of aminoacid substituted phthalocyanine **139** [201].



Scheme 34. Preparation of phthalocyanine **146** [201].

Another original molecule in which a CoPc bears four closo-carborane cages (Scheme 36) is described, water-solubility resulting from carboxylate sodium salt, the latter introduced in a very original way using dimethyl malonate [204]. The carboneboronate substituted phthalonitrile **161**, when undergoing cyclotetramerisation, leads to a mixture of partially decarboxylated phthalocyanines. The complete decarboxylation was achieved during the hydrolysis of the ester, leading to the water-soluble phthalocyanine **162**.

2.3.2.3. Generation of the carboxylic function on preformed phthalocyanine. Easily obtainable tetrasulfonyl chloride phthalocyanine **48**, which can readily be converted to sulfonamide derivatives, reacts with the amino acid glycine or with 6-aminohexanoic acid and yields tetracarboxylated phthalocyanines **163a** [178] and **163b** [205] with four sulfonamide functions (Scheme 37).

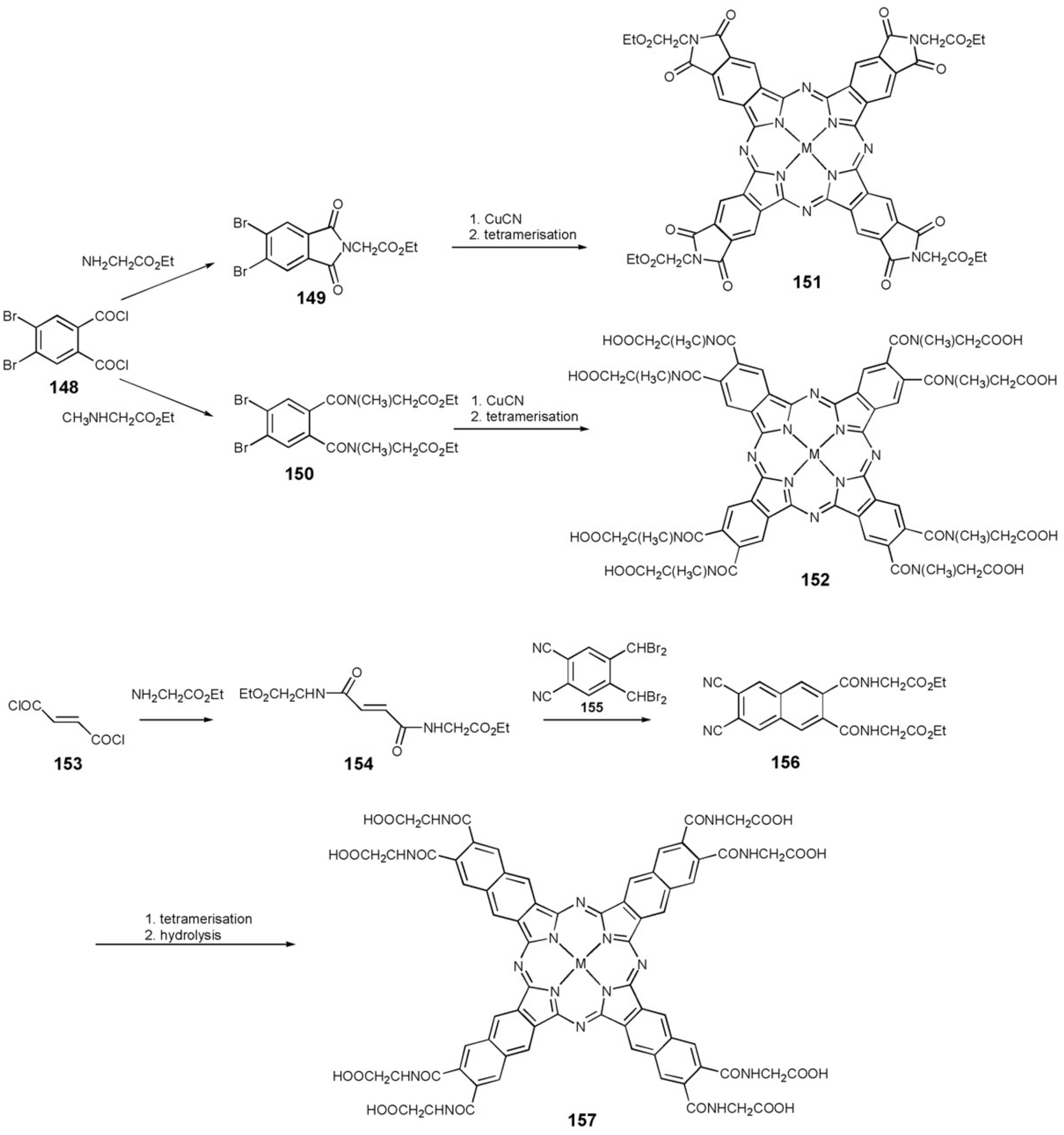
Selective synthesis of tricarboxylate substituted phthalocyanines can also be achieved via palladium-catalyzed coupling reactions of asymmetrically substituted triiodo phthalocyanines (prepared by the ring expansion of triiodosubphthalocyanines by the Kobayashi method [206] using various diiminoisoindolines) with terminal alkynes bearing carboxylic acids functions [207].

Axially carboxylated subphthalocyanine **165** has been prepared by substituting the chloride of **164** by hydrobenzoic acid in basic medium [208]. The water-solubility is increased by the carboxylic proton exchange with amine, yielding **166** (Scheme 38).

3. Cationic water-soluble phthalocyanines

Cationic groups are obtained by the quaternization of aliphatic or aromatic nitrogen atom. The quaternization occurs at the end of the synthetic pathway, on the formed phthalocyanine. The nitrogen atom which will be quaternized is present during the phthalocyanine formation in the form of an amine or pyridine derivative, or can be part of the macrocycle itself (case of the tetrapyridinoporphyrazines). A few examples describe its introduction on a previously formed functionalized phthalocyanine [209,210]. As far as we could find out, both types of cationic quaternized phthalocyanines: alkyl or aromatic, were described concomitantly for the first time in 1989, slightly preceded by quaternized tetrapyridinoporphyrazines.

A special chapter will be devoted to the quaternization of the nitrogen atom belonging to the macrocycle of azaphthalocyanines (tetrapyridino and tetrapyrazinoporphyrazines).



Scheme 35. Preparation of phthalocyanine **157** [203].

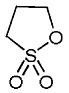
3.1. Quaternization agents

When the sole quaternization is targeted, multimethylation is the simplest way. It is achieved by several quaternization agents that are commonly used: methyl bromide/iodide and dimethylsulfate. All the methylating agents are potentially dangerous and must be used with care, as they are likely to methylate DNA. Some halogenated compounds utilized as quaternizing agents are functionalized, such as bromoethylvalerate [211] or monochloroacetic acid [212]. When one aims at modulating the amphiphilic balance of the water-soluble quaternized phthalocyanine, iodoalkane of various alkyl chain length or iodopolyethylene glycol of general formula $CH_3(OCH_2CH_2)_nI$ can be utilized.

1,3-Propanesultone **167** (Fig. 11) [213] is a special quaternizing agent as it is used in producing zwitterionic salts.

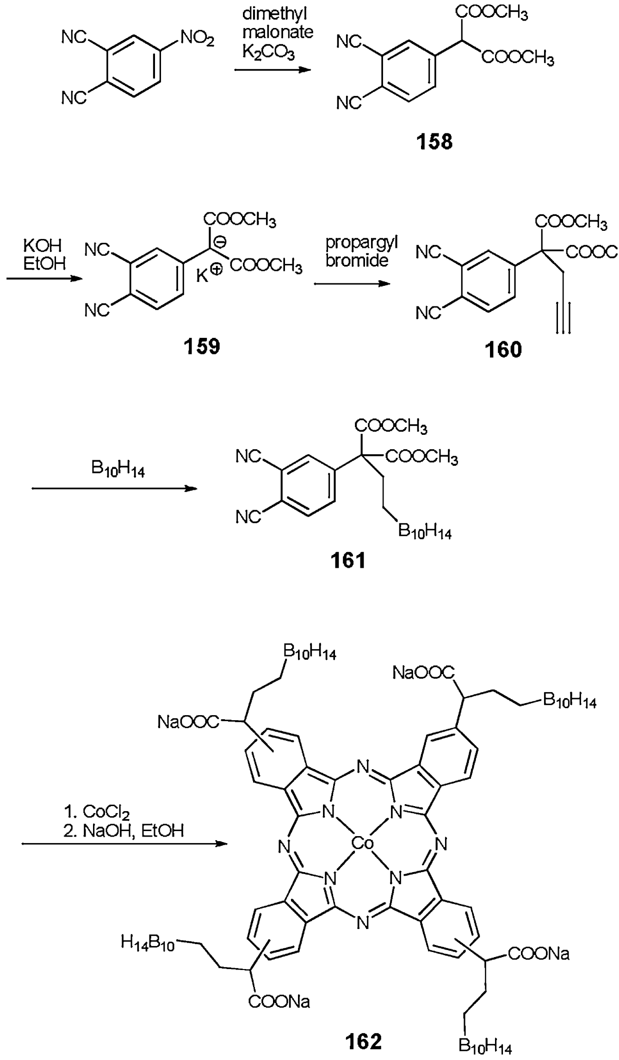
3.2. Quaternized amines

The main synthetic point is the introduction of the amino group, knowing that the quaternization always occurs on the phthalocyanine, and is in most of the cases the last step of the synthesis. The amino group itself can be introduced prior to the formation of the macrocycle, or on a preformed phthalocyanine bearing suitable substituents.



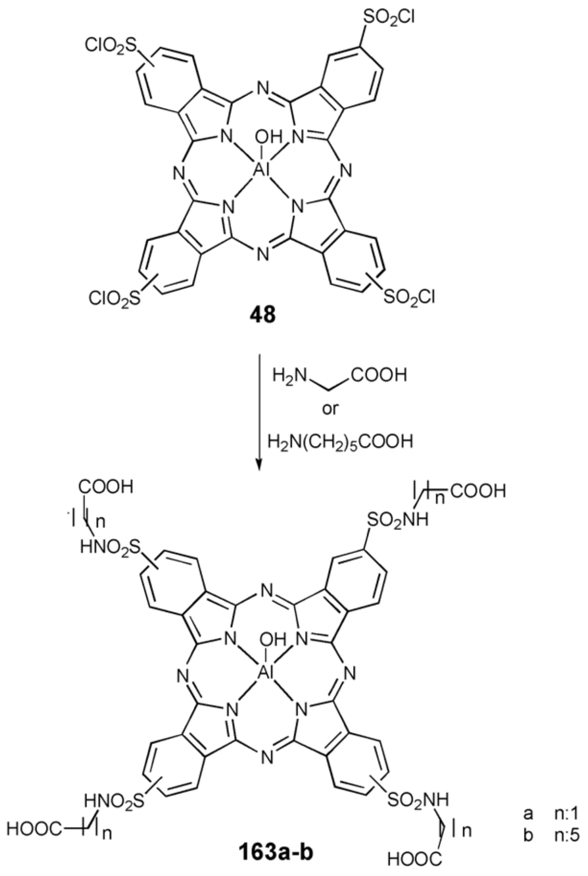
167

Fig. 11. Structure of 1,3-propanesultone (**167**).



Scheme 36. Preparation of o-carboranyl substituted CoPc **162** [204].

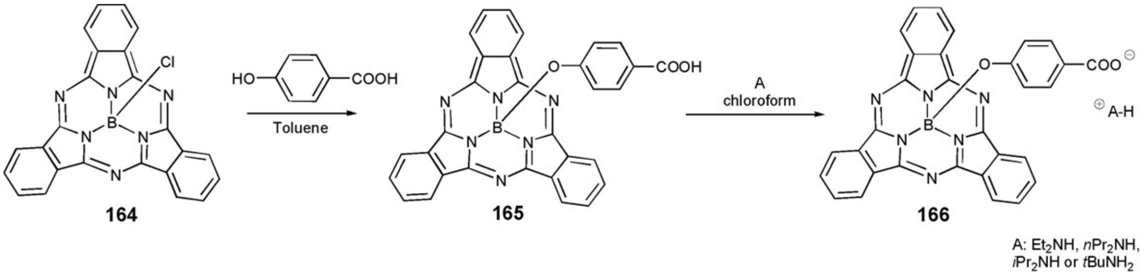
The first cationic phthalocyanine **174** bearing quaternized amines was prepared by Leznoff et al. [214]. 3-*N*,*N*′-Diethylaminoprop-1-yne (**168**) was coupled to iodophthalonitrile **55** (bistriphenylphosphine, copper iodide) [215], then the triple bond was reduced, leading to the alkylaminophthalonitrile **170**. The metal free phthalocyanine **172** was obtained from the corresponding diiminoisoindoline **171**, metallated by Zn and then quaternized by iodomethane, leading to **174** (Scheme 39). Later on cobalt and copper quaternized derivatives obtained by the same method, were described [216].



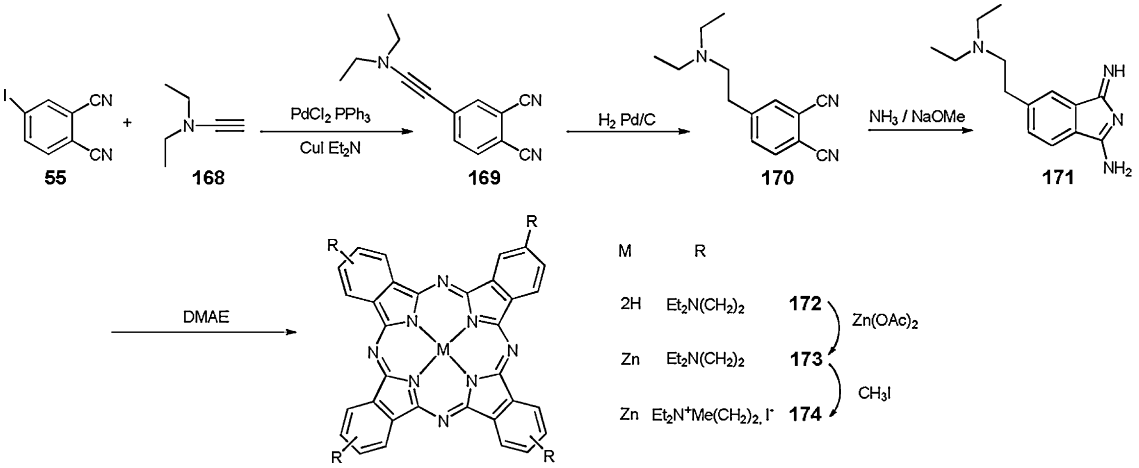
Scheme 37. Sulfonamidification of **48** leading to tetracarboxylated phthalocyanines **163** [178,205].

This first quaternized phthalocyanine was used for the comparison of their different properties with those of anionic and neutral ones. Since this pioneering work, many phthalonitriles mono or disubstituted bearing amino functions have been prepared, the amino function being quaternized after the phthalocyanine formation. A large choice of central metals is reported.

Functionalized tertiary amine or its hydrochloride salts, such as 2-(dimethylamino) ethanethiol [217–219], 2-(diethylamino)ethanethiol [220], 1,3-bis(dimethylamino)-2-propanol [221,222], 2-(dimethylamino)ethanol, 3-(diethylamino)phenol, 3-(dimethylamino)phenol, 3-aminothiophenol [223] or 8-hydroxy julolidine (2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-8-ol) [224] have been widely and commonly grafted by ether or thioether functions [225,226] on various precursors such as 3- or 4-nitrophthalonitrile, 4,5-dichlorophthalonitrile, 5,6-dichloropyrazine-2,3-dicarbonitrile [227,228] or more complex



Scheme 38. Preparation of axially carboxylate substituted subphthalocyanines **166** [208].



Scheme 39. Synthesis of the first cationic phthalocyanine bearing quaternized amines [214,215].

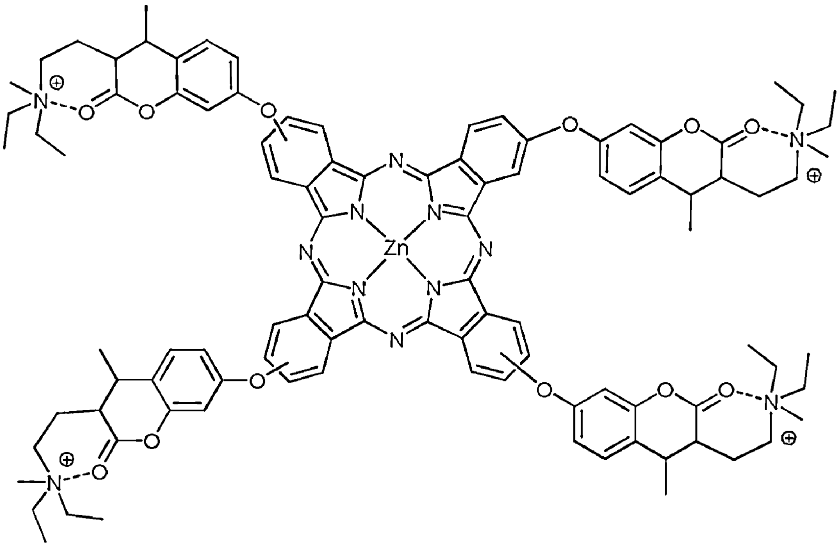
phthalonitrile derivatives [229], leading (after quaternization) to water-soluble phthalocyanines bearing generally four or eight quaternized amines. In the case of the coumarine substituted phthalocyanine **175**, 3-[(2-diethylamino)ethyl]-7-hydroxy-4-methylcoumarin was condensed on 4-nitrophthalonitrile, and after quaternization, hydrogen bonds were established between the ammonium groups with the vicinal carbonyl (Fig. 12) [230].

A record has been registered with 12 quaternized amino groups on a Pd(II) phthalocyanine, obtained from 2,4,6-tris(*N*,*N*′-dimethylaminomethyl)phenol grafted on 4-nitrophthalonitrile. After cyclotetramerisation of the resulting phthalonitrile **176**, full methylation of the twelve tertiary amines leads to the phthalocyanine **177** absolutely non-aggregated in water (Scheme 40) [231].

More complex synthetic pathways have been developed, enlarging the number of available molecules. Successive bromination and Rosenmund–von Braun dinitrilation of aromatic compounds bearing protected amines is one of these methods (Scheme 41) [232]: 1-chloro-2-methyl-2-phenylpropane **178** undergoes a nucleophilic substitution by potassium phthalimide **179**. The resulting **180** is dibrominated into **181** by bromine used as the solvent, since the usual conditions (bromine in dichloromethane or acetic acid, in presence of ferric chloride) were probably too mild for the poorly reactive **180**. After dinitrilation leading to **182** and its cyclotetramerisation, the removal of the protecting phthalimide occurs on the phthalocyanine **183** leading to **184**. This is followed by the quaternization step, leading to the quaternized water-soluble Zn(II) phthalocyanine **185** [233,234].

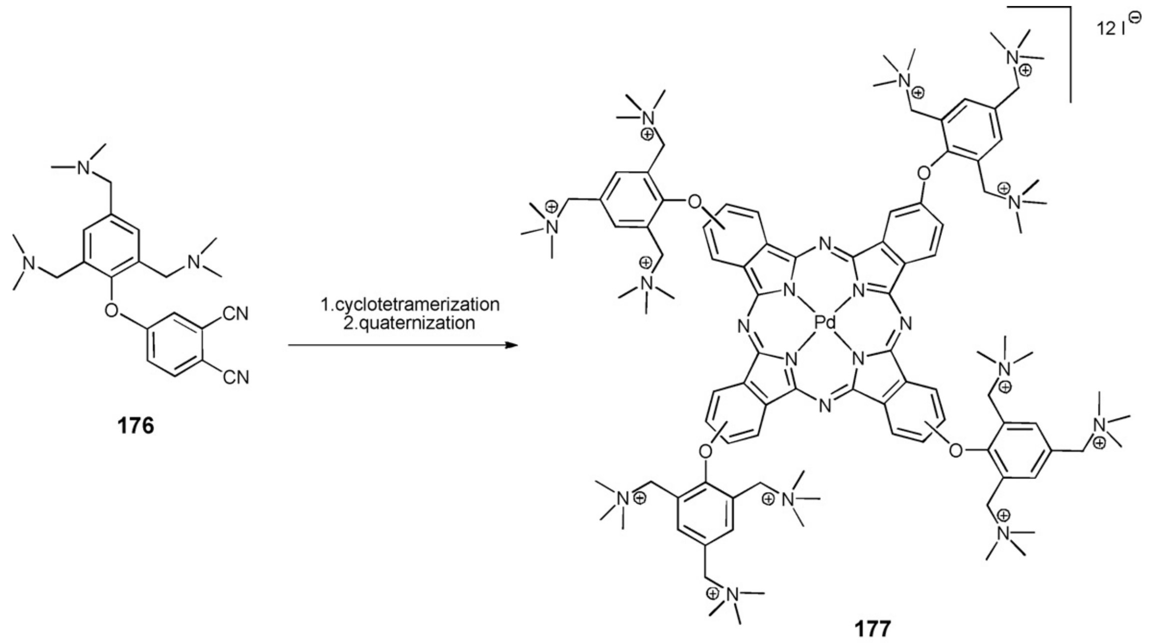
A synthetic strategy involving the reduction of the eight amide functions of an octasubstituted phthalocyanine into an amine is reported as well (Scheme 42) [235]. In this case, pyrocatechol is the starting compound. After a disubstitution by ethylbromoacetate and bromination leading to respectively **186** and **187**, the ester function is converted by a four-step sequence into the corresponding dimethylamide **188**. This derivative undergoes the Rosenmund–von Braun dinitrilation (**189**) and a subsequent tetramerisation into the octa substituted Zn(II) phthalocyanine **190**. Two more steps achieved on the phthalocyanine itself lead respectively to **191**, then to the water-soluble phthalocyanine **192**.

Starting with 2-(4,5-dibromo-2-methylbenzyl)-1H-isoindoline-1,3(2H)-dione **193** [236], the amphiphilic quaternized phthalocyanine **201** was obtained in a eight-step sequence [237], and is partially soluble in water despite the long alkyl chain used for the quaternization (Scheme 43).

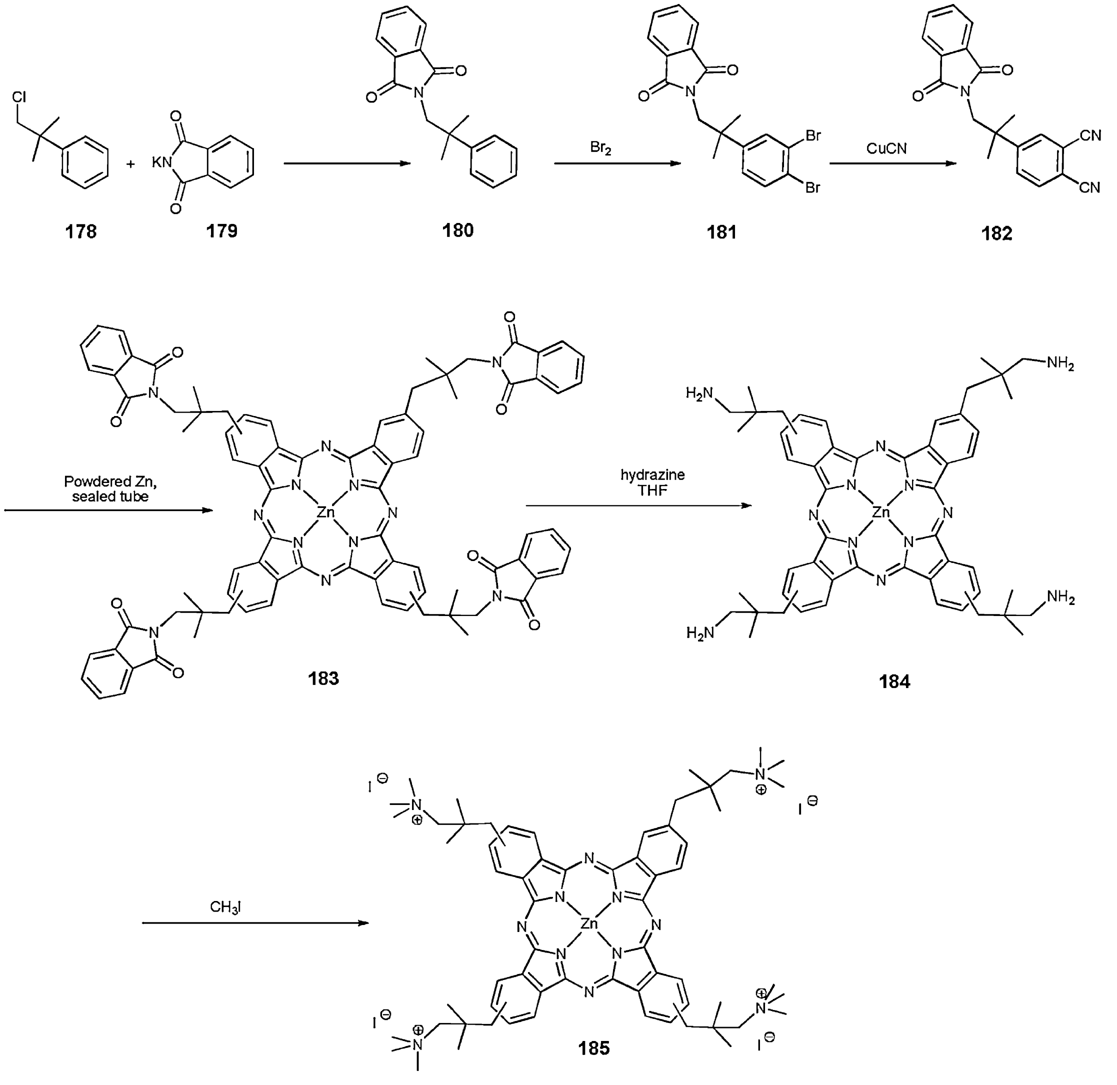


175

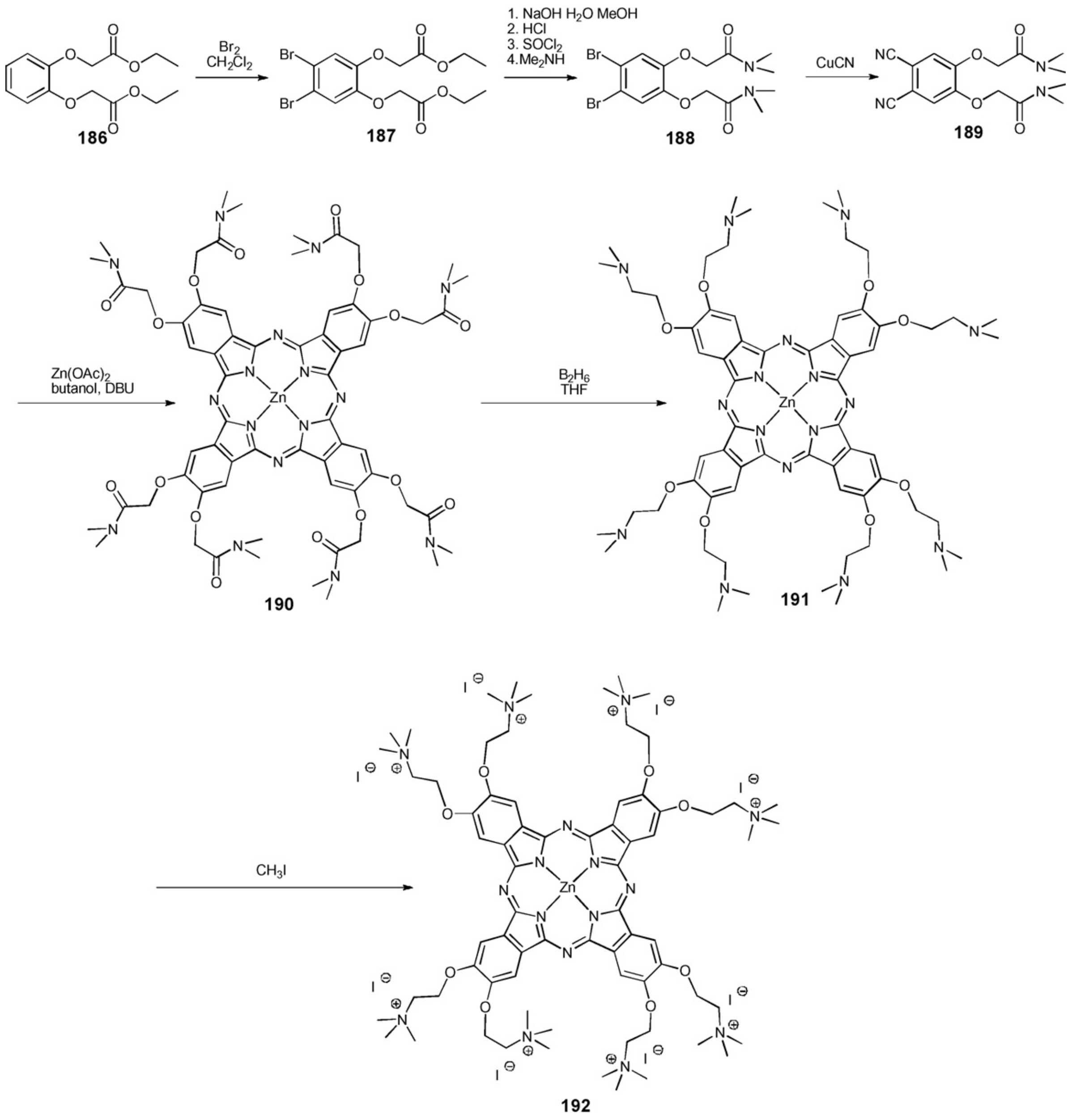
Fig. 12. Structure of phthalocyanine **175** bearing coumarine substituted by quaternized amines [230].



Scheme 40. The dodecaammonium substituted Pd(II) phthalocyanine **177** [231].



Scheme 41. Preparation of the quaternized phthalocyanine **185** [233,234].



Scheme 42. Preparation of octasubstituted quaternized phthalocyanine **192** [235].

Transition metal catalyzed coupling on halogenated phthalonitriles are another strategy to introduce amino functions. An original synthetic pathway was developed to couple alkylated aniline moieties with halogenated phthalonitriles (Scheme 44) [238]: 4-bromo-*N*,*N*′-dimethylaniline was converted first of all to its Grignard derivative, then to the corresponding boronic acid **203**. This latest intermediate is then coupled to 4-iodophthalonitrile (**55**) [239] or dibromophthalonitrile (**202**) [240].

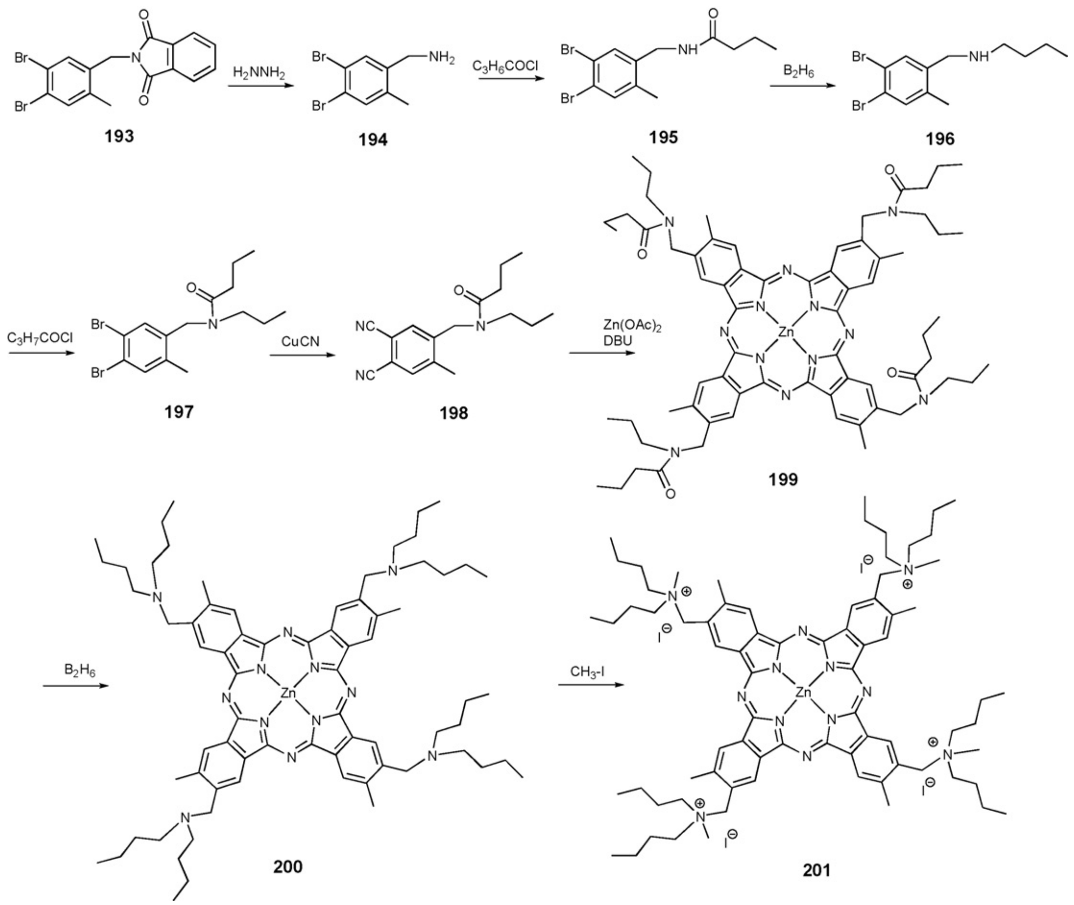
In addition, to the phthalocyanines having symmetric substitution pattern, sulfonated ABAB type phthalocyanines **208** and **209** are described as well (Fig. 13) [241]. The latter one is, as far as we could find out, the only case in which a reduction reaction is achieved, resulting in a quaternized phthalocyanine.

In the following example, the amino functions are introduced on a functionalized phthalocyanine [242]. The 2,3:9,10:16,17:23,24-tetrakis (dicarboxanhydride) phthalocyanine **210**, obtained from benzene-1,2,4,5-tetracarboxylic acid dianhydride [243], reacts with *N*,*N*′-diethylethylenediamine to yield *N*-substituted imid substituted phthalocyanines **211**. The diethylamino moiety is then quaternized by R-X leading to highly water-soluble complexes **212** (Scheme 45), water-solubility being modulated nevertheless by the central metal.

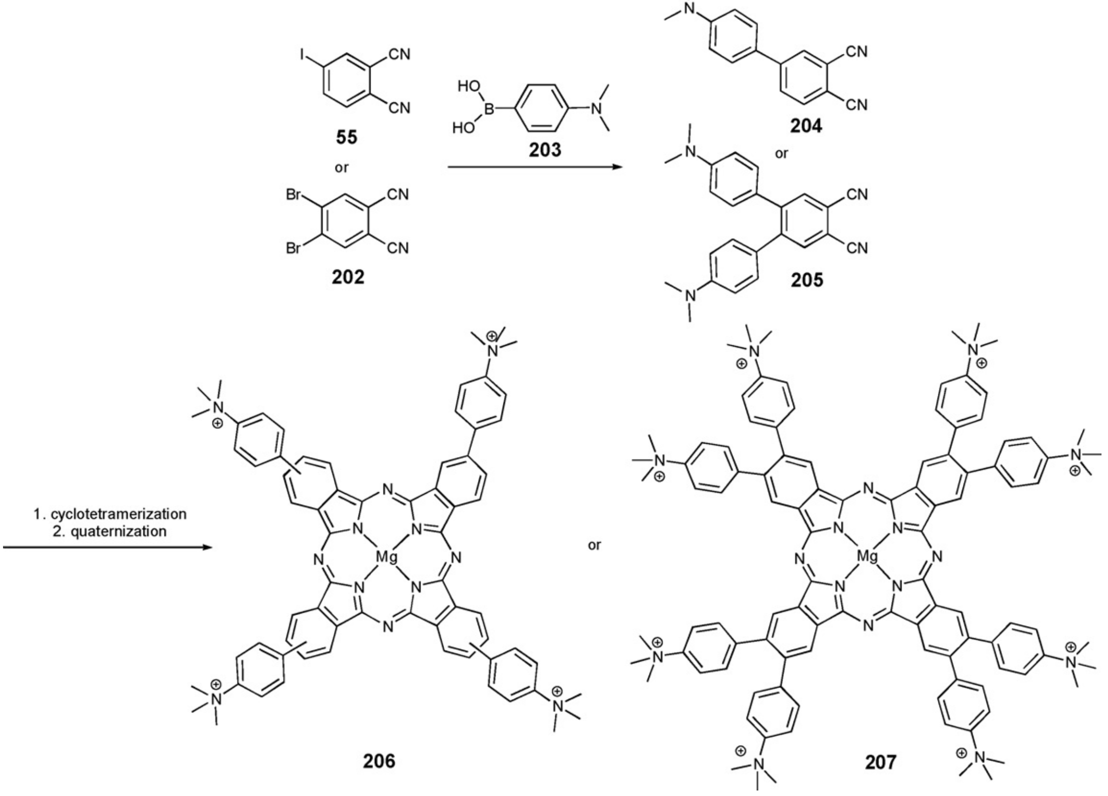
Ammonium functions may be provided by amine containing biological unit moieties, such as choline or 5-aminolevulinic acid (ALA).

Octa(cholinyl)phthalocyanine oxo-titanium TiOPcChol$_8$ **213** (Fig. 14) was prepared recently by heating octakis(chloromethyl) TiOPc with an excess of 2-dimethylaminoethanol [244].

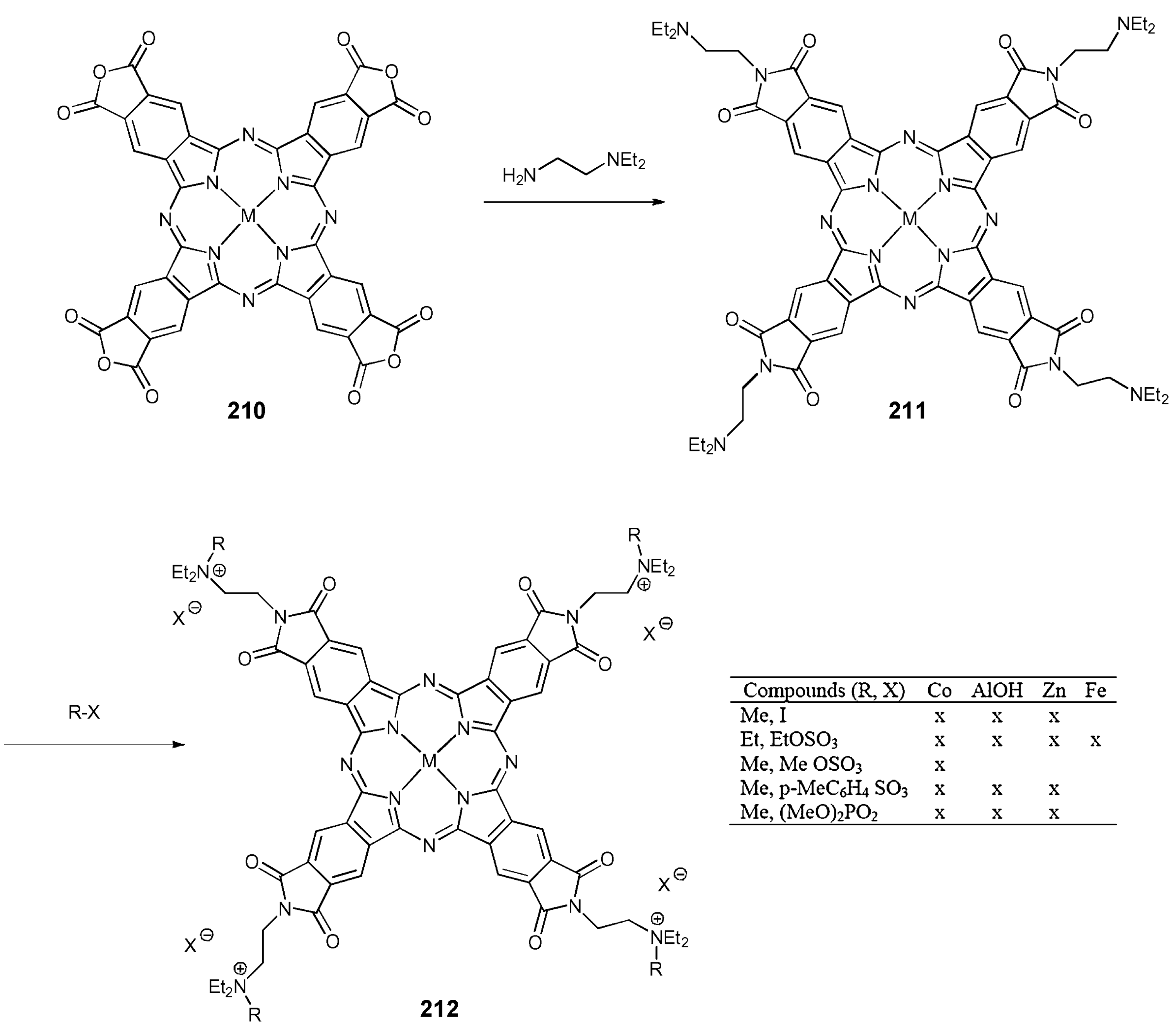
Two phthalocyanines conjugated to 5-aminolevulinic acid (ALA) have been recently described [245], one with a symmetric substitution pattern (**216**) bearing four esterified ALA units, the second one with only one unit and three menthol (**219**) (Scheme 46) whose bulkiness aims at inhibiting aggregation and increasing the



Scheme 43. Synthesis of tetraquaternized phthalocyanine **201** [237].



Scheme 44. Preparation of tetra- and octasubstituted phthalocyanines **206** and **207** [238–240].



210 **211** **212**

Compounds (R, X)	Co	AlOH	Zn	Fe
Me, I	x	x	x	
Et, $EtOSO_3$	x	x	x	x
Me, Me OSO_3	x			
Me, p-MeC_6H_4 SO_3	x	x	x	
Me, $(MeO)_2PO_2$	x	x	x	

Scheme 45. Preparation of quaternized phthalocyanine **212** [243].

uptake of phthalocyanine **219** in tumor cells [246]. Menthol was chosen since its efficiency as a formulating agent had previously been demonstrated. The precursor phthalonitrile **214** bearing a protected hydroxyl function leads by symmetric or asymmetric (in the presence of the menthol-substituted phthalonitrile **217**) cyclotetramerisation to the symmetrically substituted phthalocyanine **215** or the asymmetric one **218**, that are esterified by the hydrochloride salt of ALA after deprotection of the tetrahydropyrane moieties, leading respectively to the water-soluble phthalocyanines **216** and **219**. Though the amine function of ALA is not tetraalkylated, the water-solubility is provided by its cationic character.

Phthalocyanines **221** tetrasubstituted by guanidinium groups were obtained by reaction of tetraamino Zn(II)Pc **220** with various carbodiimides, under conditions known to remove the central metal [247,248]. Zn was thus re-incorporated at the end of the synthetic pathway (Scheme 47). The isopropyl derivative proved to be the one having the best water-solubility.

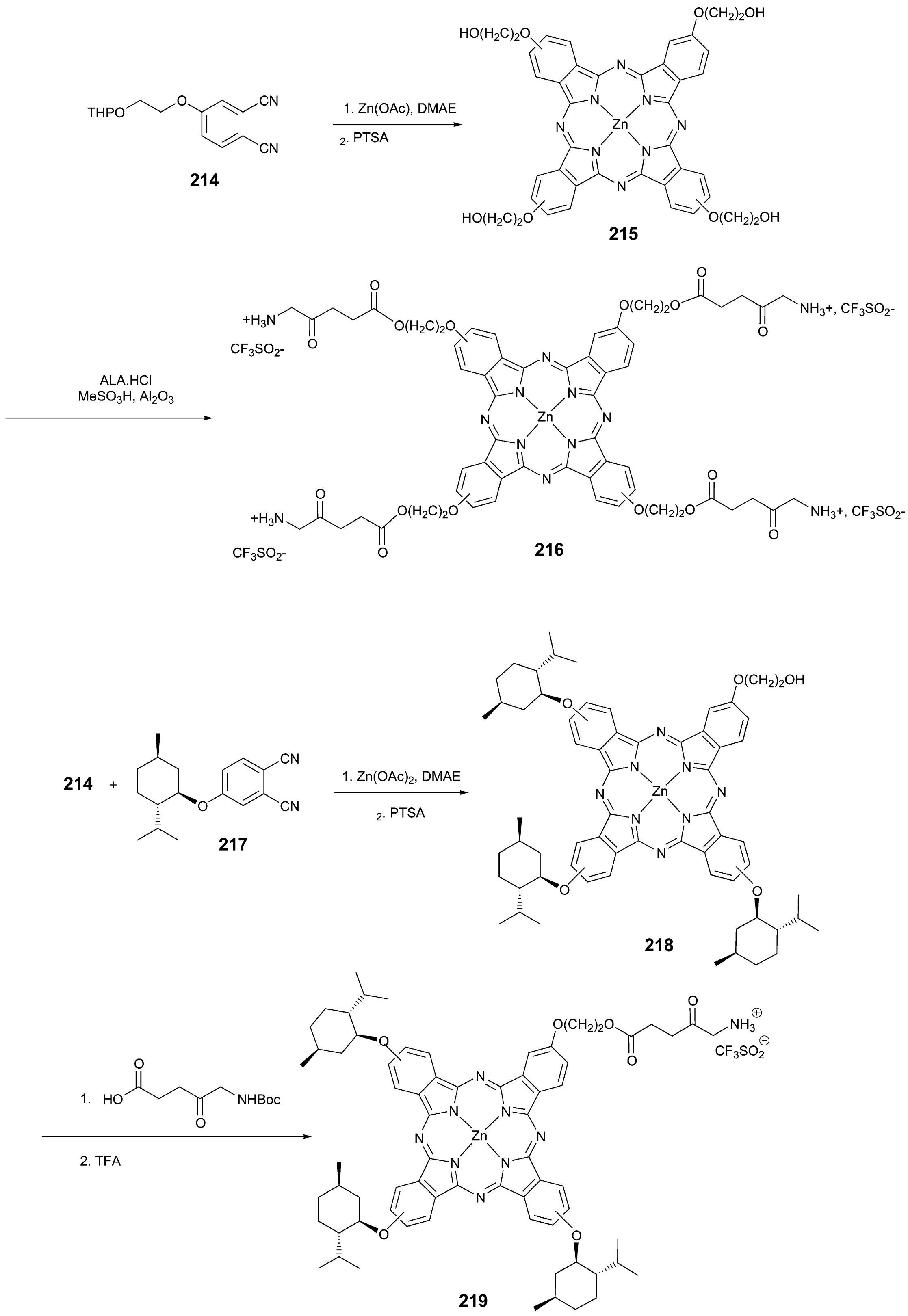
The axially substituted cationic subphthalocyanine **223** is described: the quaternized moiety is borne by the boron atom. 2-(Dimethylamino)ethanol replaced firstly the axial chloride of the unsubstituted subphthalocyanine **164**, leading to **222**, that undergoes quaternization to yield **223** (Scheme 48) [208].

Aza crown ether is a particular class of substituent likely to be quaternized. A few papers describe the synthesis of quaternized azacrown ether substituted phthalocyanines, such as the monoaza crown ether **227** and **230**, and the tetraaza crown **234** ethers substituted derivatives.

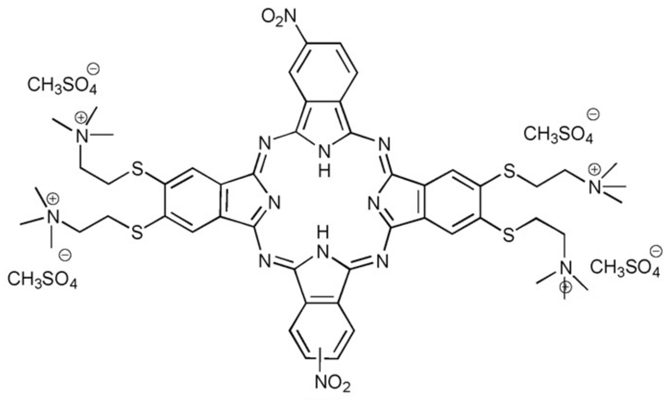
First monoazacrown ether substituted phthalocyanines were prepared from the dibrominated derivative **224**, directly converted into the copper phthalocyanine **227**-**Cu** by strong heating in pyridine in presence of CuCN [249] and quaternized by dimethylsulfate. The preparation of other metallated phthalocyanines **227** (M = 2H, Ni, Pb) requires more steps [250], as **224** was first quaternized into **225** then converted into the quaternized phthalonitrile **226**. The phthalonitrile was then cyclotetramerised in presence of adequate metal salts (Scheme 49).

This is the only description of a Rosenmund–von Braun dinitrilation applied to quaternized dibromo derivatives. Attempts to synthesize **227** from a more expected strategy: protection by acylation of the nitrogen on **224**, dinitrilation, cyclotetramerisation into **228**, desacetylation in acidic medium and subsequent quaternization proved to be unsatisfactory. The concomitant desacetylation and quaternization of acetylated **228** by an excess of dimethylsulfate in chloroform gave better yields.

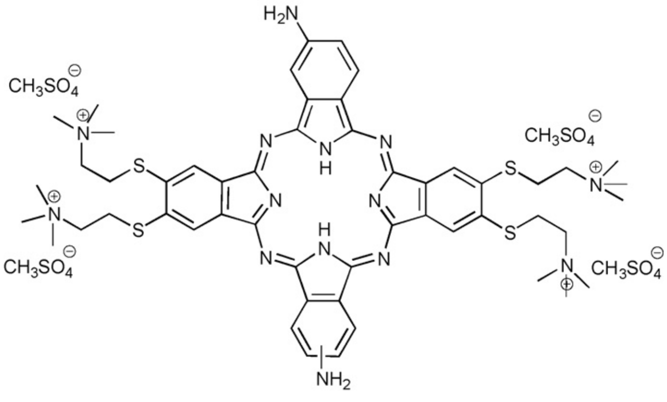
Corresponding quaternized Lu homoleptic dimer **230** is obtained in its neutral form by the quaternization of the



Scheme 46. Preparation of symmetric and asymmetric ALA-substituted phthalocyanines **216** and **219** [245].



208



209

Fig. 13. Quaternized ABAB type phthalocyanines **208** and **209** [241].

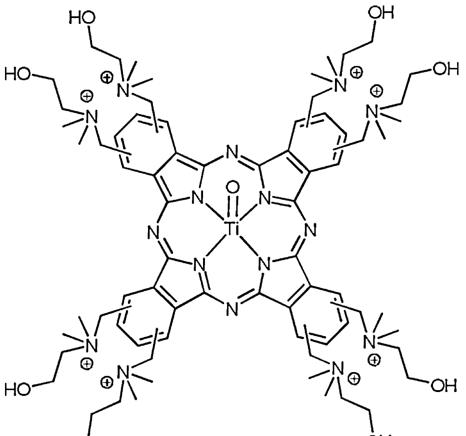
acetylated Lu bis(phthalocyaninato) derivative **229** (Scheme 50) [250,251].

Phthalocyanines **227** and **230** proved to be extraordinarily soluble in water and in polar solvents.

Four 15-membered tetraazamacrocycle substituted phthalocyanine **234** is as expected highly soluble in water. It was prepared from **232** and the tetratosylated tetraamine **231** (Scheme 51) [252].

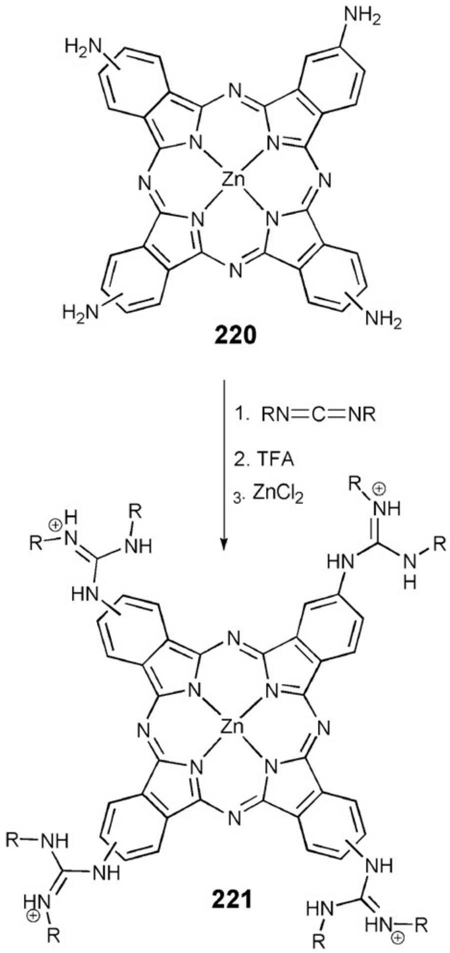
3.3. *Quaternized aromatic nitrogen atoms*

These derivatives are expected to be water-soluble, but probably due to the flatness of the pyridinium aromatic rings, being less

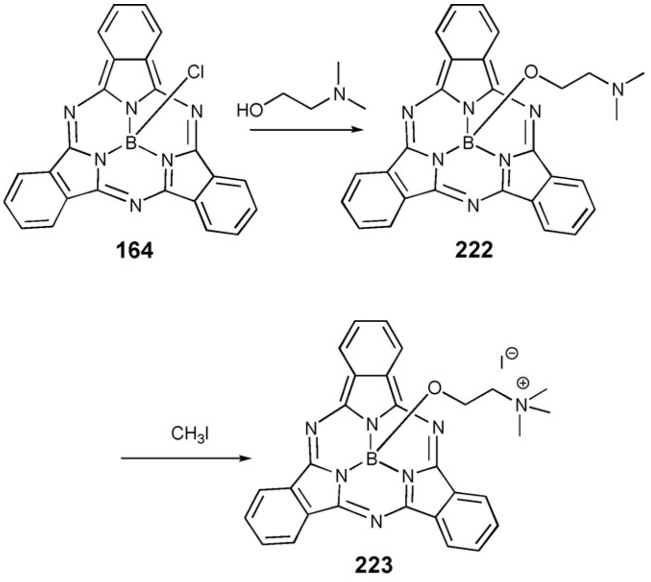


213

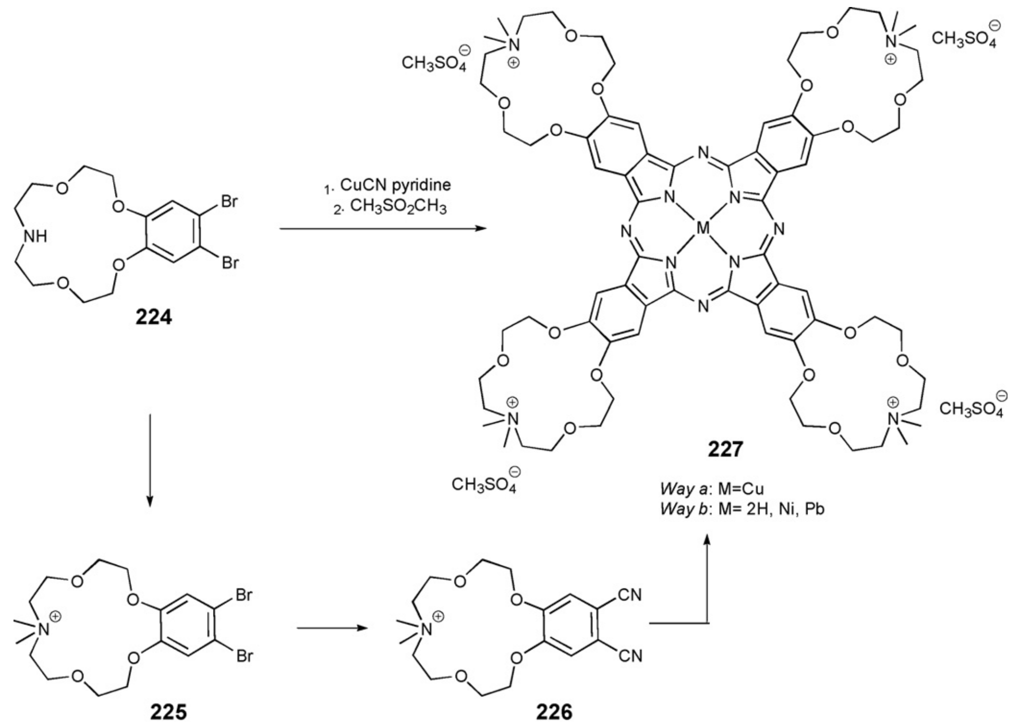
Fig. 14. Structure of TiOPcChol$_8$ **213** [244].



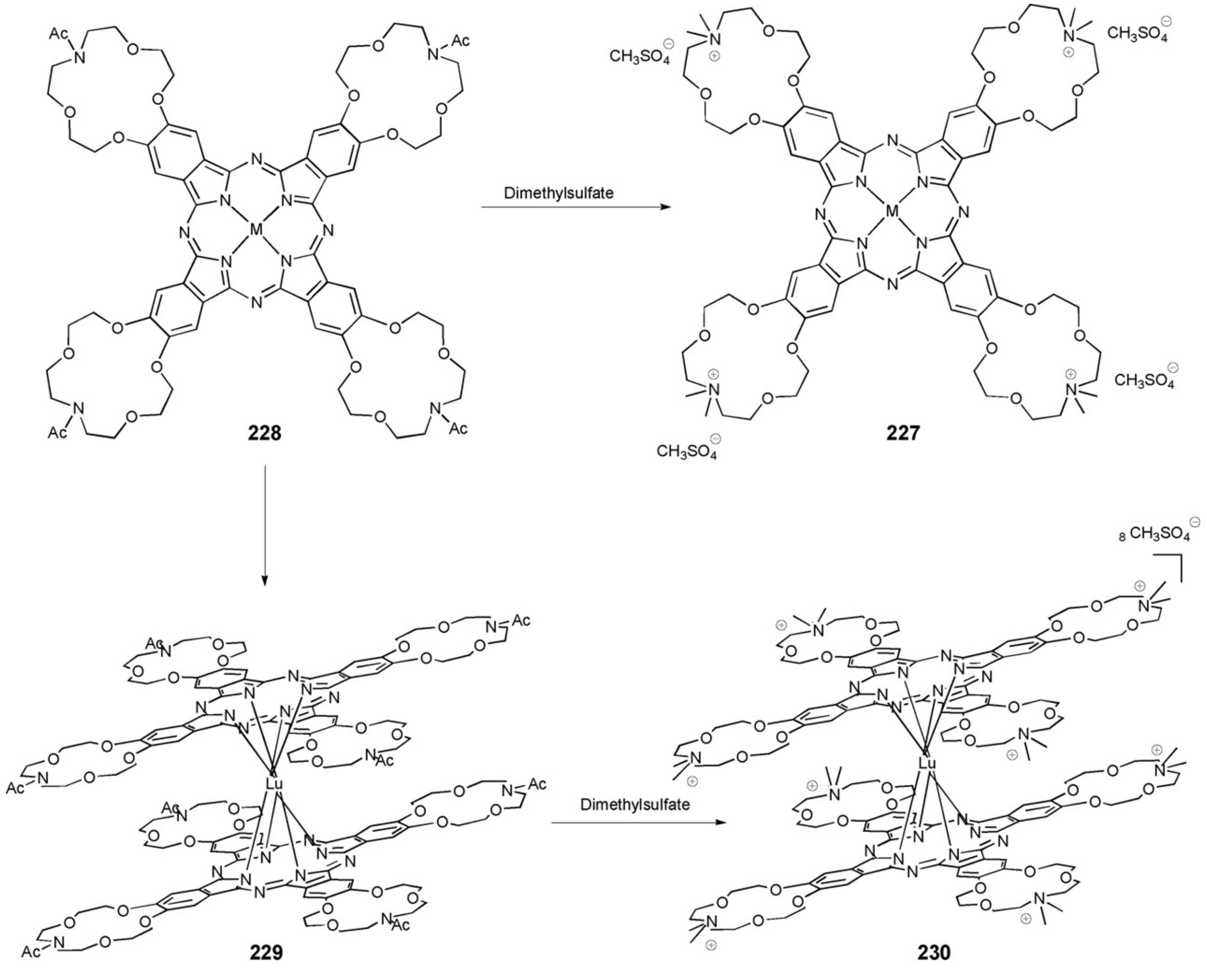
Scheme 47. Preparation of phthalocyanine **221** [247].



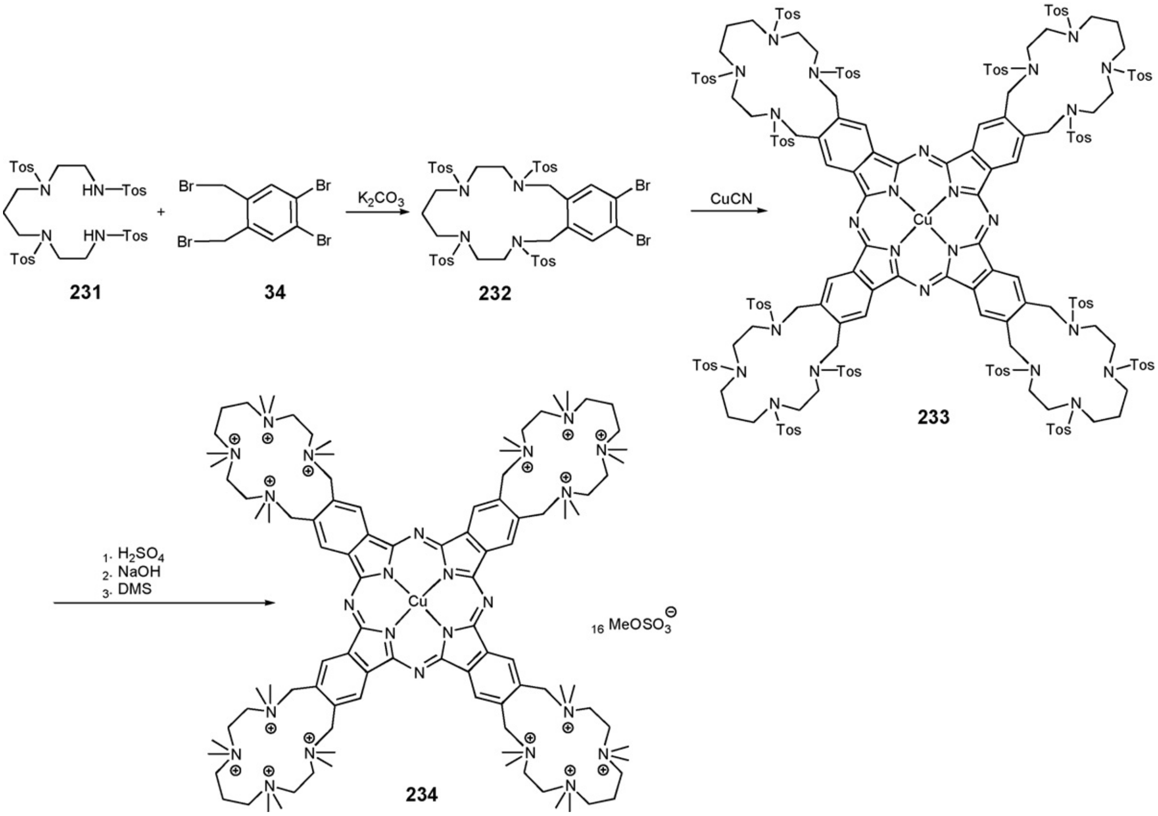
Scheme 48. Preparation of axially ammonium substituted subphthalocyanine **223** [208].



Scheme 49. Preparation of phthalocyanine **227** [249,250].



Scheme 50. Preparation of quaternized double-decker **230** [250,251].



Scheme 51. Preparation of quaternized tetraazasubstituted Cu phthalocyanine **234** [252].

bulky than the previously alkylated derivatives, they are generally more aggregated than alkyl ammonium phthalocyanines bearing the same number of quaternized charges [244].

3.3.1. Synthesis from pyridine substituted precursors

Tetrapyridinium substituted phthalocyanines are generally prepared following a three-step pathway. Functionalized pyridines react with 3- or 4-phthalonitrile to obtain a mono-pyridine substituted phthalonitrile. The most commonly used pyridine derivatives are: 4-hydroxypyridine [253–255], 3-hydroxypyridine [101,256–261], 2-hydroxypyridine [106], 2-mercaptopyridine [262–265], 4-hydroxymethylpyridine [266].

After cyclotetramerisation, the pyridine's nitrogen is quaternized, leading to tetrasubstituted phthalocyanines which are eventually water-soluble, and more or less aggregated (Scheme 52). Cyclotetramerisation is attempted in the presence of various metal salts and requires sometimes the preparation of the corresponding diiminoisoindoline [261].

Tricationic subphthalocyanine **237** bearing three pyridinium moieties on the macrocycle is prepared by similar method, employing BCl_3 as the metal salt (Scheme 53) [267]. A similar subphthalocyanine axially substituted by a phenoxy instead of a chloride has also been described [268].

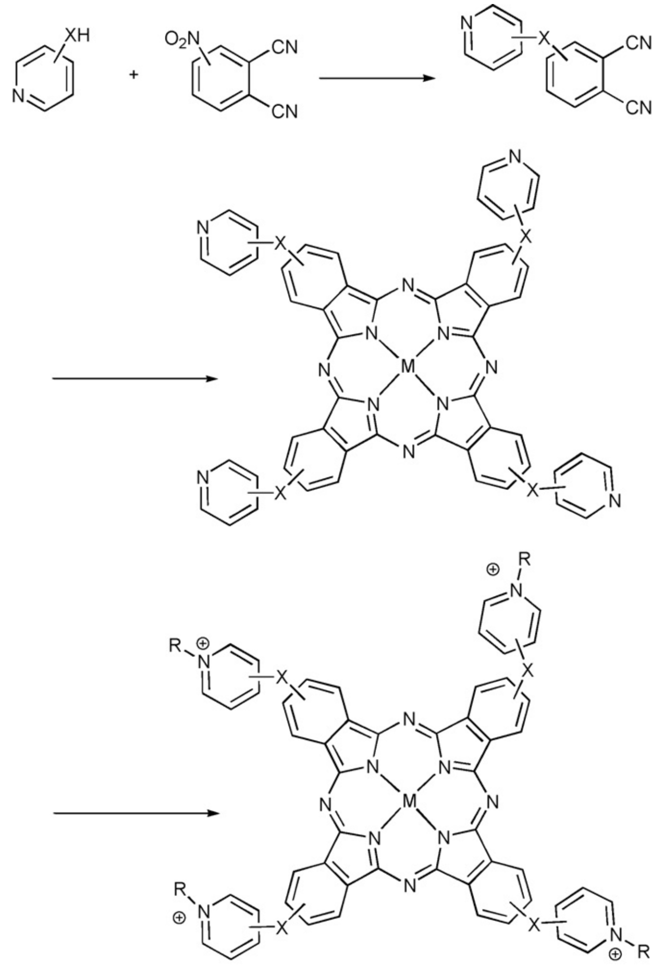
A pyridine phthalocyanine (**238**) may be quaternized into **239a**–**d** by different alkyl iodide for further studies of the effect of the chain length in modulating the amphiphilicity of the molecule, and thus its potential properties (Scheme 54) [101,268,269].

Octapyridinium substituted phthalocyanines are commonly obtained following Wöhrle's method [270], by reacting 3-hydroxypyridine on 4,5-dichlorophthalonitrile, leading to **240** and its eventual conversion into the corresponding diiminoisoindoline **241** followed by conversion into **242** in the presence of In [271], Zn or Si [272] salts. In the case of Si, and as the quaternization is always the last step of the synthesis, axial substitution on the silicon atom by bulky substituents aiming at inhibiting aggregation is previously performed. The quaternization of **242c**–**e** is achieved by several iodinated derivatives (methyl iodine and 1-iodo-3,6,9-trioxadecane) (Scheme 55). This quaternization provides as expected water-solubility for the silicon derivatives **243a**–**d** but analogous quaternized Zn(II) phthalocyanines as well as octamethylated indium phthalocyanine remain highly aggregated in water.

Related octacationic octakis(N-methylpyridinium) pyrazinoporphyrazines **248** and **249** are described. The starting phthalonitrile derivative **245** can be prepared by reacting diaminomaleonitrile **92** with α-diketones-2,2′-pyridil **244**, the reaction conditions being variable [273,274]. Cyclotetramerization is achieved without solvent and assisted only by a few drops of DBU leading to the free-base derivative [274], or in template assisted conditions [273] (**245** dissolved in dioxane followed by addition to a propyloxymagnesium slurry, or dissolved in DMF to which $CuCl_2$ is added). The quaternization by methylation proved to be more efficient on a metallated derivative than on the corresponding free-base [275,276], the latter is subsequently reacted with magnesium salt (Scheme 56) [277]. The quaternization occurs on the pyridine nitrogen atoms but not on the macrocyclic pyrazine's ones.

Quaternized quinoline tetra- and octasubstituted phthalocyanines **250** and **251** (Fig. 15) are currently under investigation by us [278].

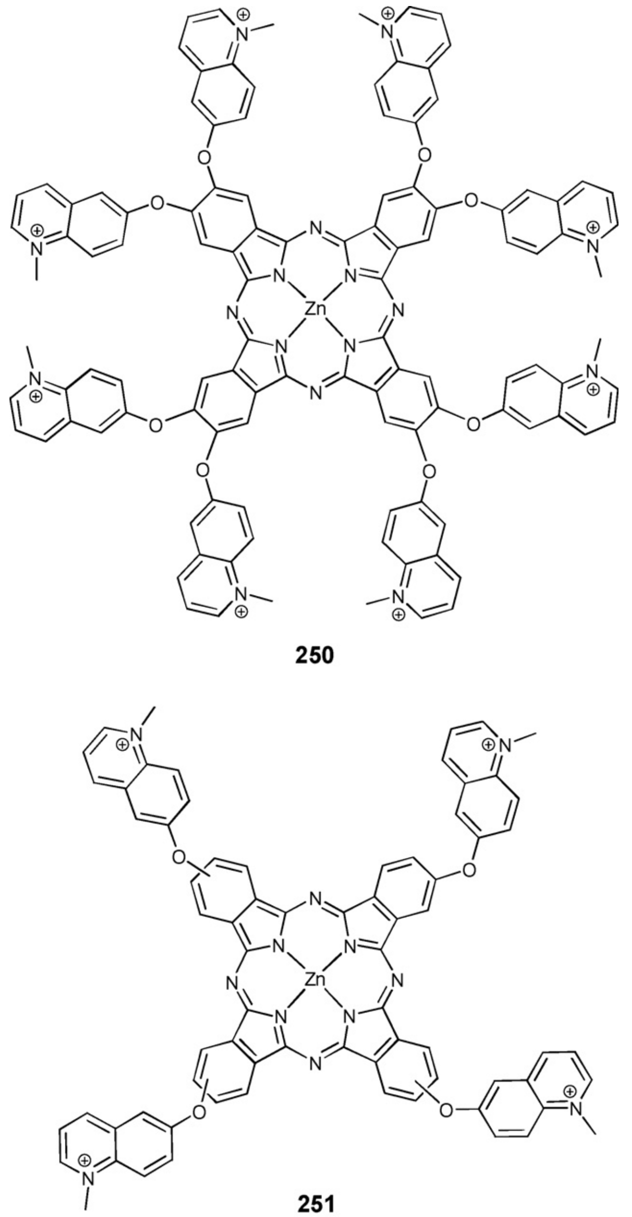
A modulation of the amphiphilicity is achieved by preparing asymmetric phthalocyanines, by statistical condensation of mono- or di-2-pyridyloxy substituted phthalonitriles **252** or **240** with hydrophobic phthalonitrile **253**, the quaternization of the resulting phthalocyanine **254** leading to amphiphilic water-soluble phthalocyanines **255** (Scheme 57) [279]. The water-solubility increases with the number of quaternized groups.



X = O, S, CH_2O

R= C_nH_{2n+1}

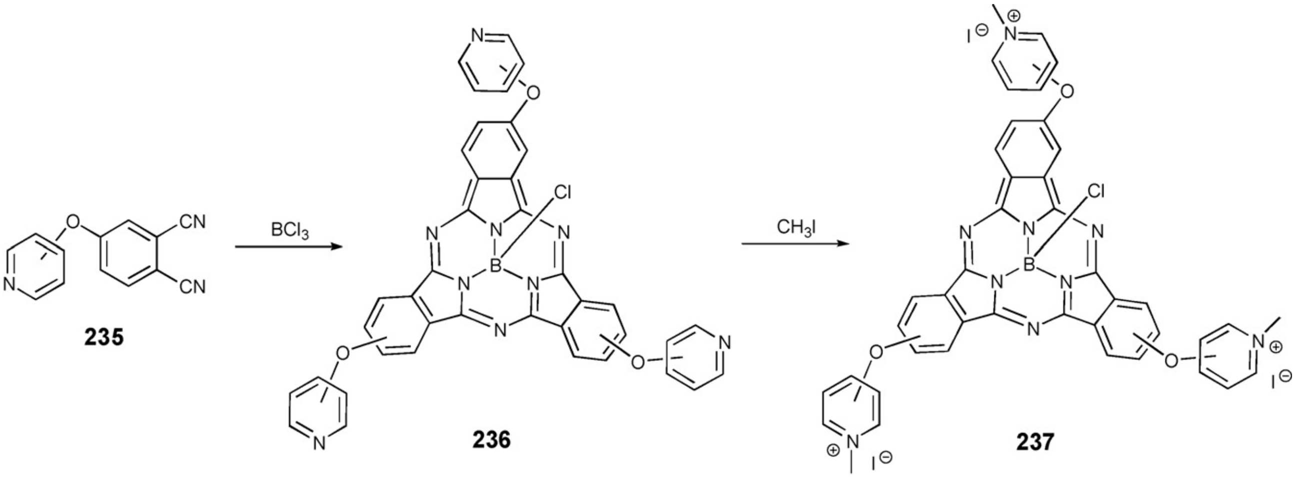
Scheme 52. General synthetic pathway to quaternized pyridyl substituted phthalocyanines.



250

251

Fig. 15. Structure of quaternized quinoline substituted ZnPcs **250** and **251** [278].



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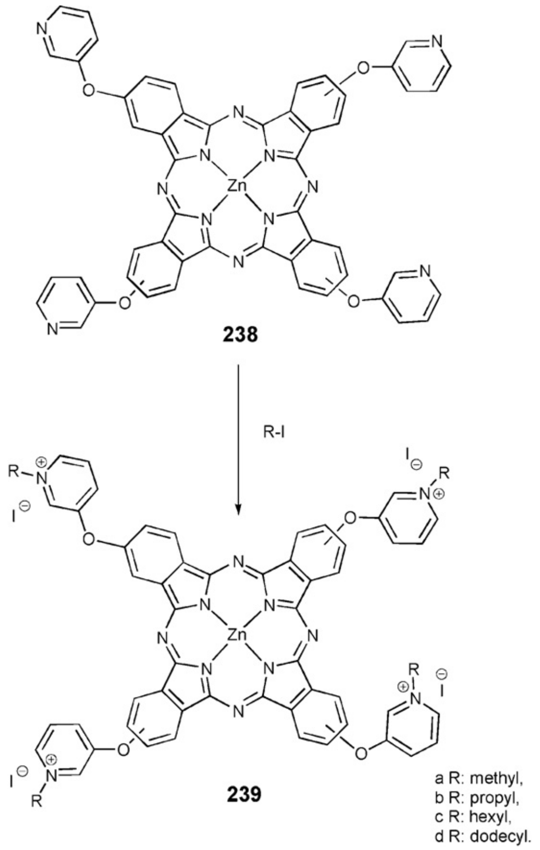
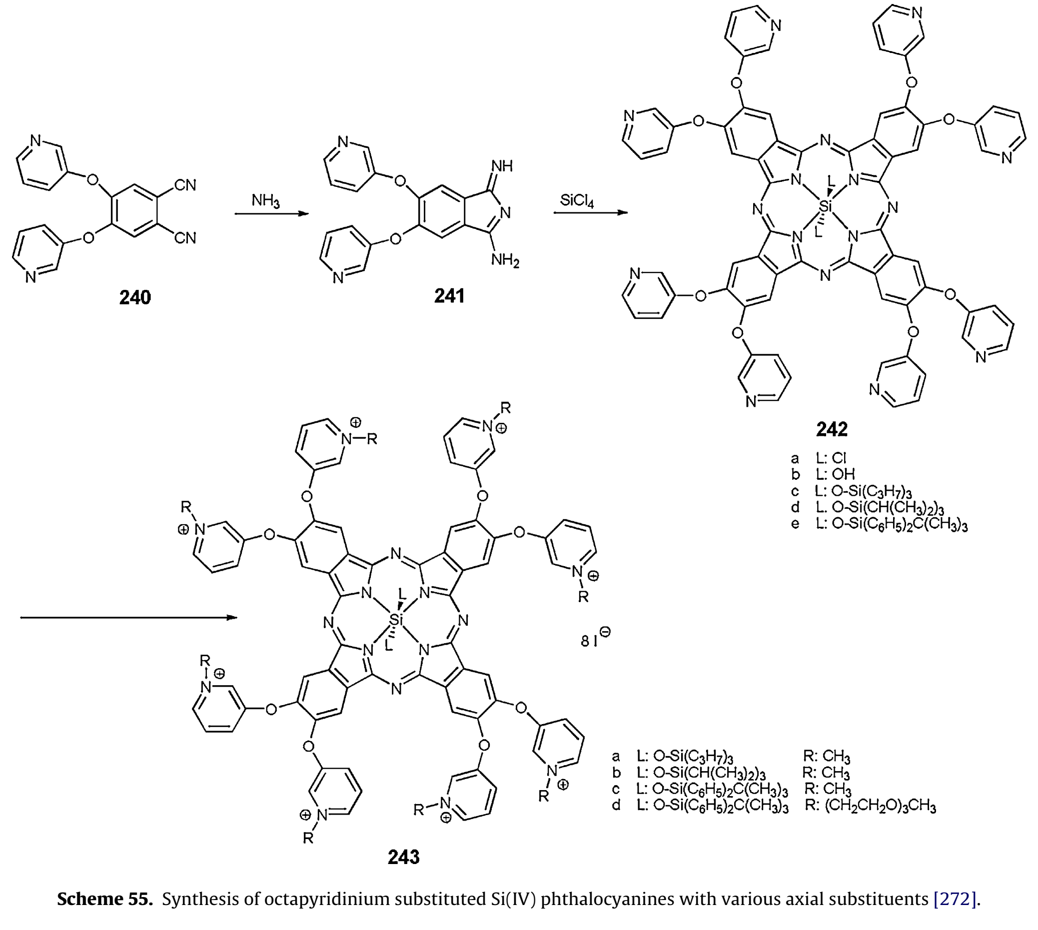
236

237

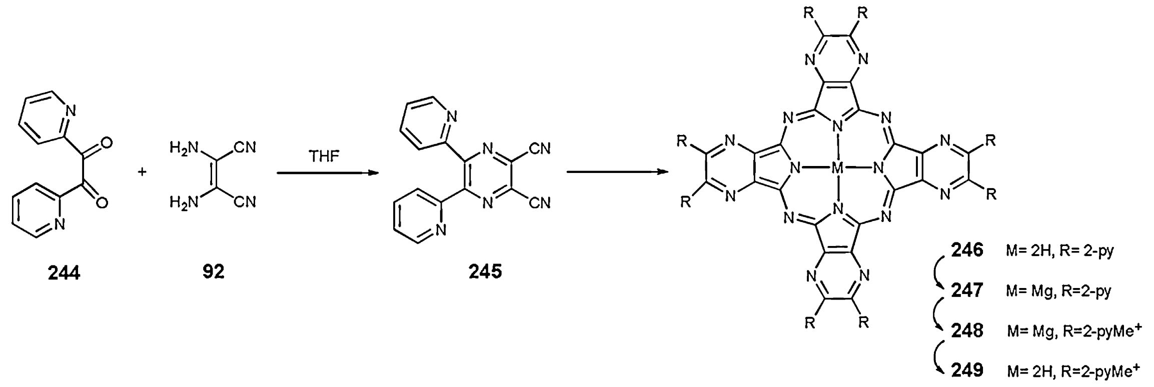
Scheme 53. Preparation of tri quaternized pyridyl substituted subphthalocyanine **237** [267].



Scheme 54. Alkylation of pyridine substituted phthalocyanine **238** by various iodoalkanes [101,268,269].



Scheme 55. Synthesis of octapyridinium substituted Si(IV) phthalocyanines with various axial substituents [272].



Scheme 56. Preparation of octacationic octakis(N-methylpyridinium) pyrazinoporphyrazines **248**–**249** [277].

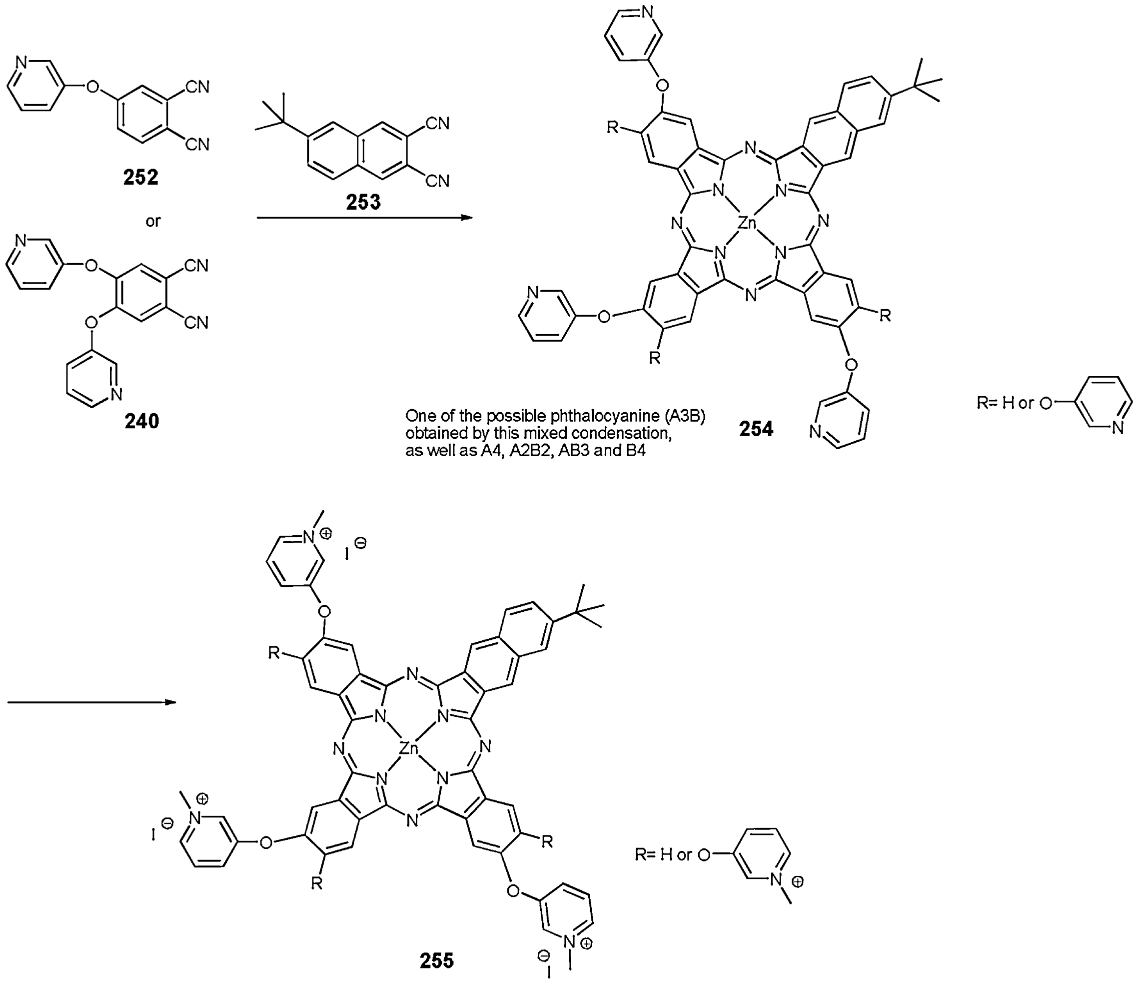
3.3.2. Introduction of pyridine on preformed phthalocyanines

The pyridine moiety may be introduced on preformed Pc suitably functionalized, generally by iodo, hydroxyl or carboxyl functions. In the case of Zn(II) and free-base phthalocyanines containing tetrapyridinium hydrochloride fragments, a tetrahydroxylated phthalocyanine (**257**) was firstly prepared, undergoing later on nucleophilic substitution on 4-bromopyridine (slight excess of 4.5 or 5 equivalents per phthalocyanine) (Scheme 58). In this case, the pyridine groups are introduced on a preformed phthalocyanine, with high yields: around 80% [210].

Gül's team prepared the tetra(2-hydroxyethylthio)phthalocyanine [209] **259** and esterified it by a strong excess of 4-pyridinecarboxylic acid (isonicotinic acid) **260**, leading to **261** (Scheme 59) [280]. Pyridine function were quaternized or used also to coordinate VO(acac)$_2$.

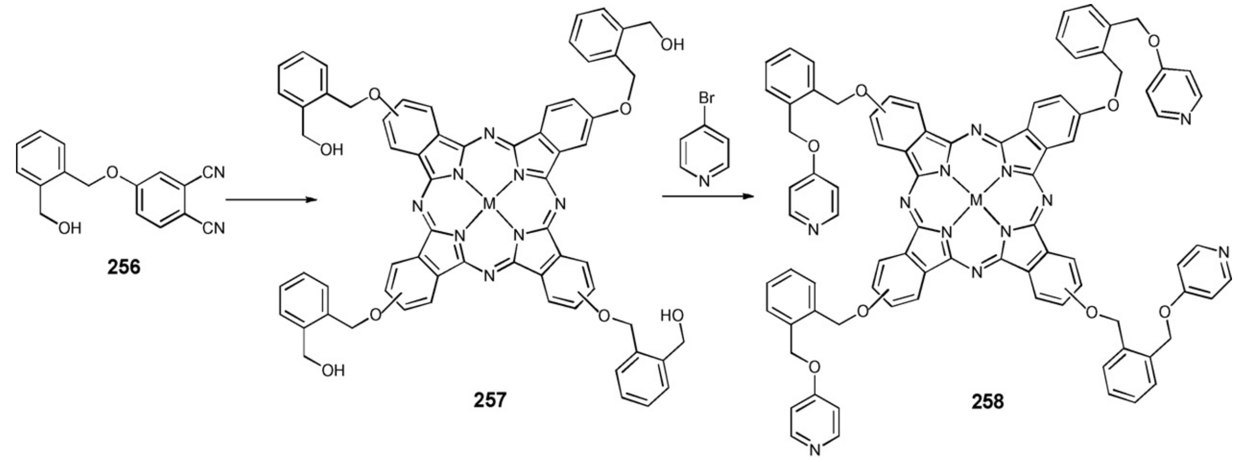
The synthesis of AB3-type asymmetric phthalocyanines bearing three pyridinium functions follows a method also used for tetracarboxylated phthalocyanines (Scheme 60) [207]: 2- or 3-ethynylpyridine (A substituent) are coupled to triiodophthalocyanines (**262**) and subsequently quaternized into **264**. The B moiety is either an unsubstituted benzene or naphtha group, or a tBu, modulating the solubility of the phthalocyanine.

An axially phenyl-substituted analogous triiodoboron subphthalocyanine (**265**) was coupled with 2- and 3-ethynylpyridine by a Sonogashira reaction [213]. 3-Pyridinylethynyl moieties sub-

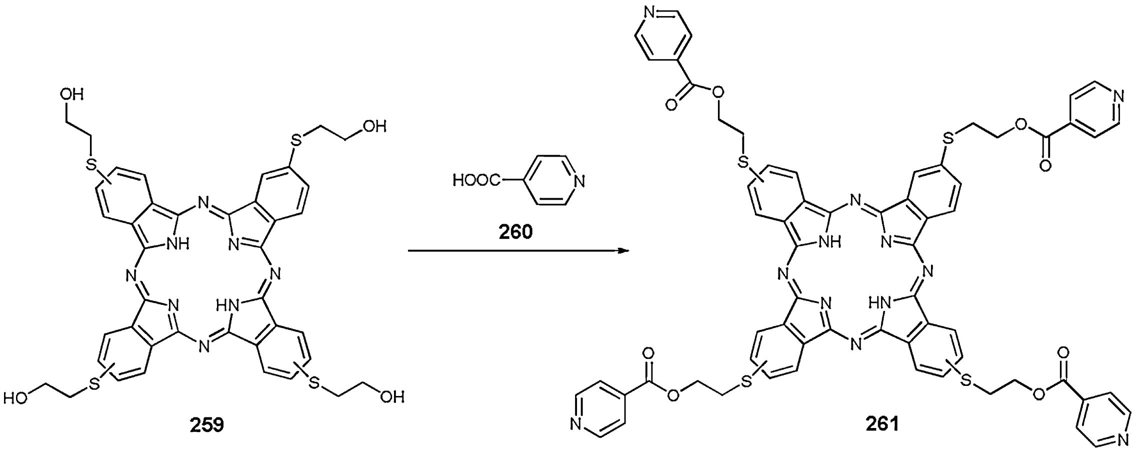


One of the possible phthalocyanine (A3B) obtained by this mixed condensation, as well as A4, A2B2, AB3 and B4

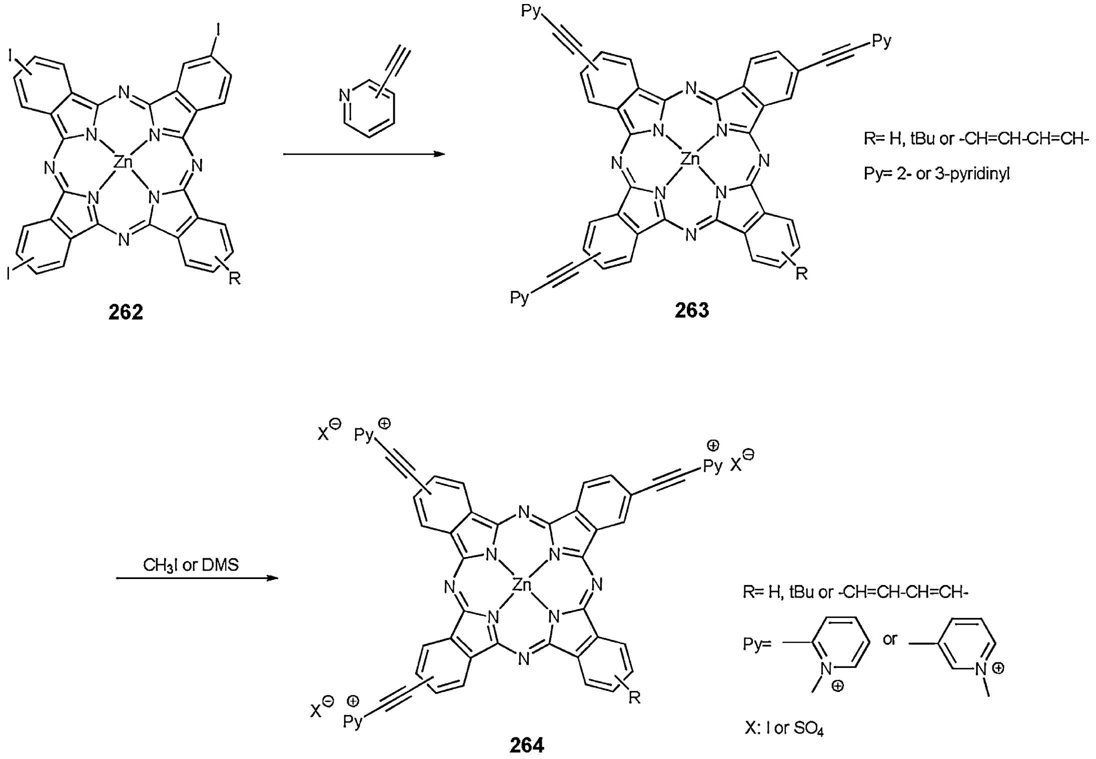
Scheme 57. Preparation of tri- and hexaquaternized phthalocyanines [279].



Scheme 58. Introduction of pyridine on **257** via aromatic substitution (M: 2H or Zn) [210].



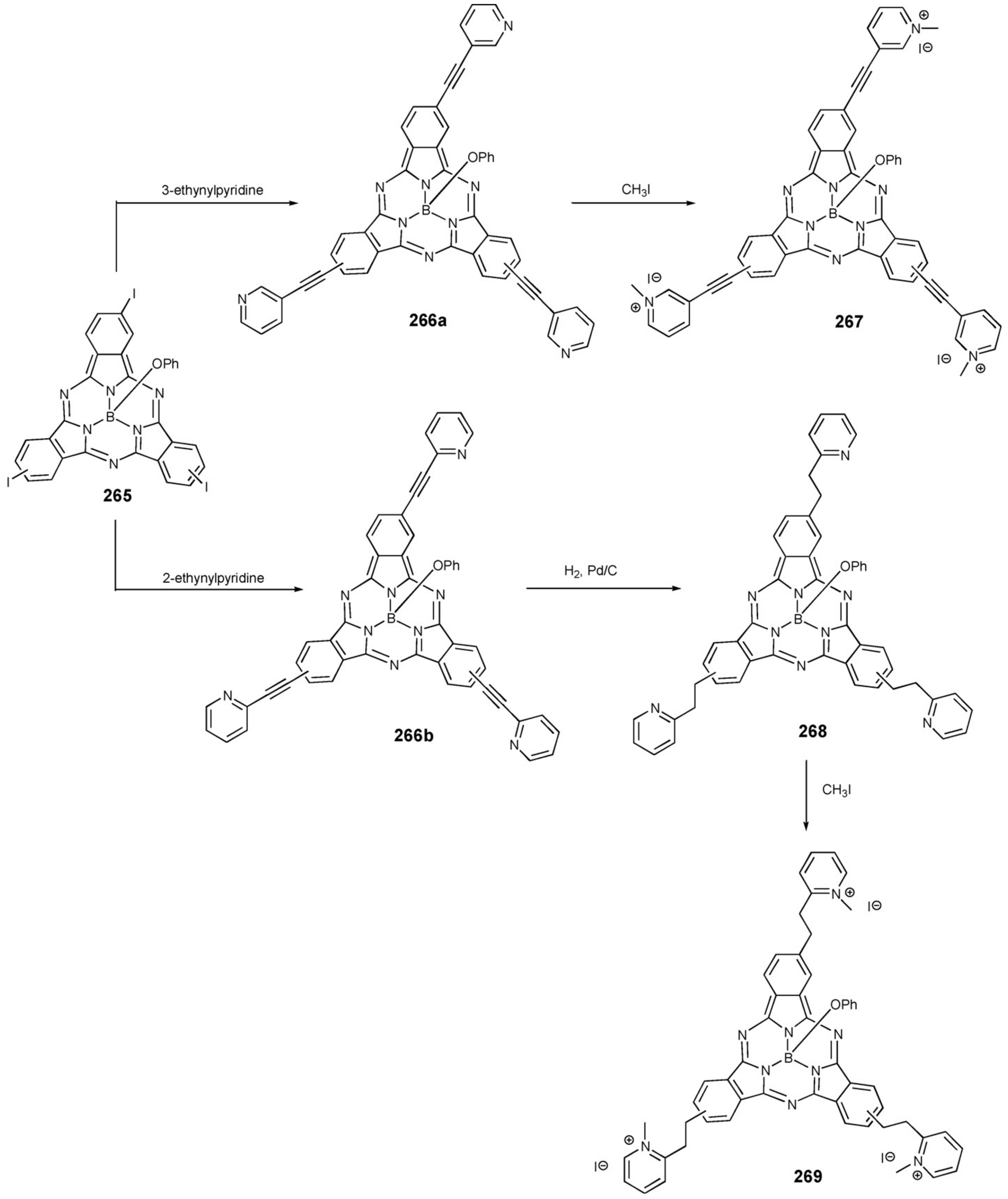
Scheme 59. Esterification of **259** by isonicotinic acid [280].



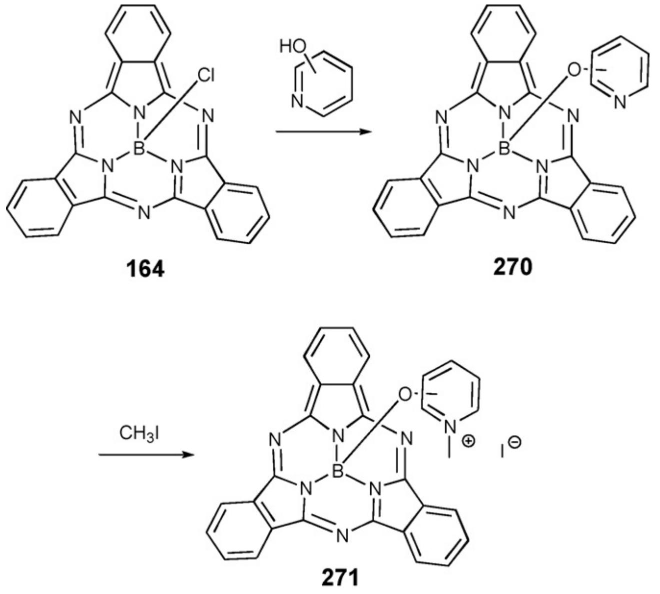
Scheme 60. Preparation of asymmetric quaternized phthalocyanines **264** [207].

stituted phthalocyanine **266a** was then quaternized into **267**, when the triple bonds of the 2-pyridinylethynyl moieties of **266b** underwent a reduction prior to their quaternization, yielding **269** (Scheme 61).

Bischloromethylated phthalocyanines (the main product obtained in chloromethylation conditions) are easily accessible and can react with trialkylamines or pyridines, leading to methyl ammonium or pyridinium chloride salts. In this case,



Scheme 61. Preparation of pyridinium substituted subphthalocyanines **267** and **269** [213].



Scheme 62. Preparation of axially pyridinium substituted subphthalocyanine **271** [208].

the phthalocyanine itself is the quaternizing agent [178]. This method was used by Lukyanets as well on polychloromethylated phthalocyanines [244,281].

Unsubstituted boron subphthalocyanine **164** bearing an axial halogen can undergo a nucleophilic substitution by 3- and 4-hydroxypyridine. Subsequent quaternization leads to water-soluble subphthalocyanine **271** (Scheme 62) [208].

3.4. Quaternized tetrapyridinoporphyrazines

The case of the tetrapyridinoporphyrazines bearing macrocyclic quaternized nitrogen atoms (general formula in Fig. 16) is treated separately from the previous section, as the water-solubility providing function is not borne by a substituent but is introduced directly on the macrocyle). These phthalocyanine analogues have been earlier depicted by Linstead et al. [282] and the first investigations of their properties focused on unsubstituted derivatives, prepared from pyridine-2,3-dicarboxylic acid or dicyanopyridine [283,284] with a large choice of central metals at the center of tetramethylated quaternized derivatives: Pd, Pt [285], Co [286], Ge, Si, Zn, Sn [287].

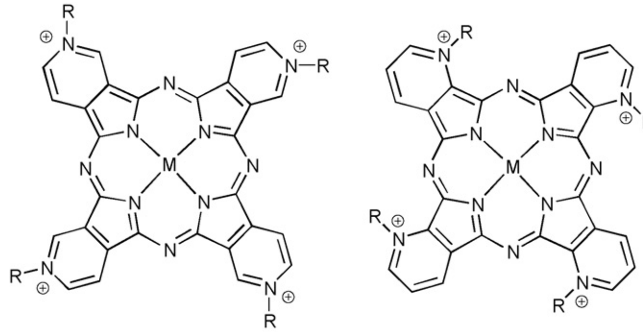
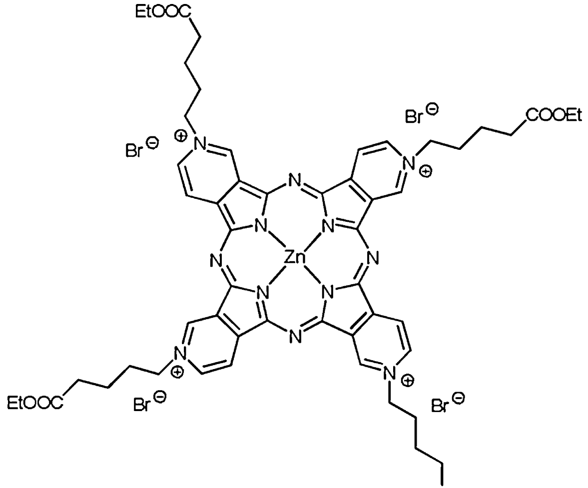


Fig. 16. General representation of quaternized tetrapyridinoporphyrazines.



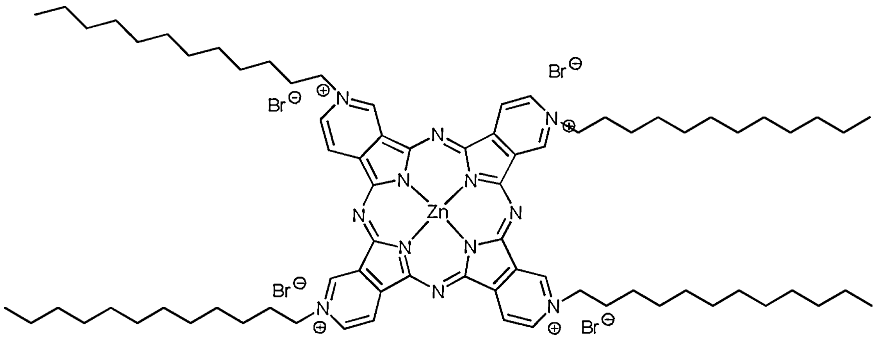
272

Fig. 17. A tetrapyridinobenzoporphyrazine quaternized by ethylbromovalerate [211,212].

The pair of electrons of the pyridine ring is not involved in the aromaticity of the macrocycle [75], thus its quaternization is as easy [288] as those of a pyridine. This has been widely used to produce water-soluble tetrapyridinoporphyrazines. The first quaternization were achieved by methylation, using bromo- or idodomethane, or dimethylsulfate [289].

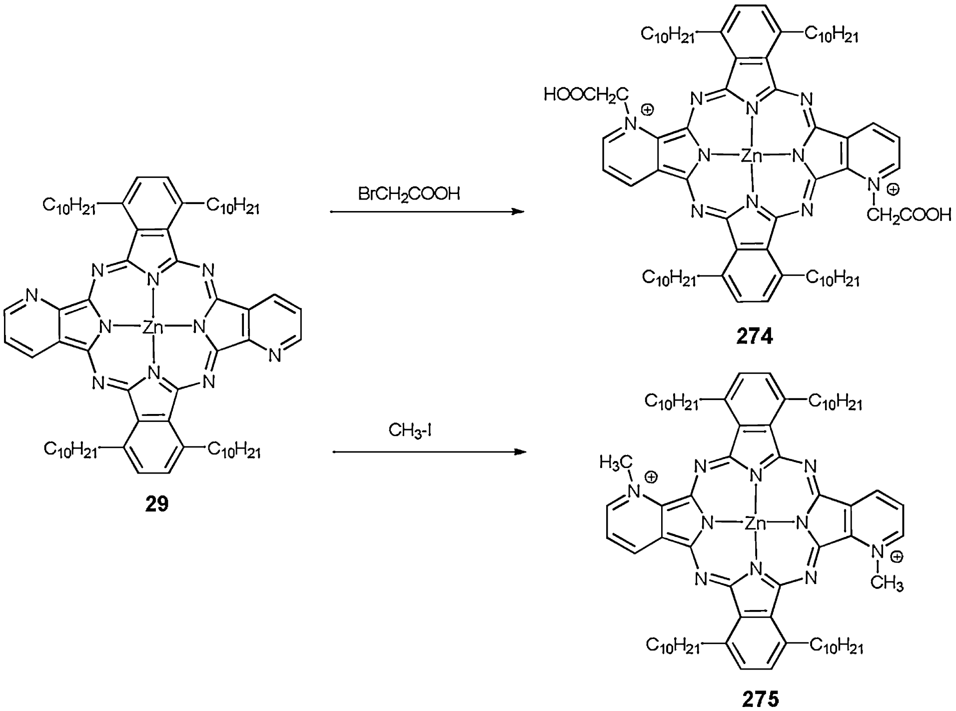
Later on, different halogen derivatives bearing functional group have been used, such as ethyl 5-bromovalerate, leading to **272**, or monochloroacetic acid [211,212] (Fig. 17).

The water-solubility depends on the nature of the alkylating agent, when it is a dodecyl chain (**273**, Fig. 18), the tetracationic nature of the molecule is not sufficient to confer water-solubility to the molecule which forms monolayer at the air–water interface [290]. For the same reason, photodynamic activity evaluations of **273** are achieved in reverse micelle phase [291].



273

Fig. 18. **273**, A quaternized tetrapyridinoporphyrazine not soluble in water [291].



Scheme 63. Water-soluble quaternized crosswise bispyridinoporphyrazines **274** and **275** [138,139].

When strongly amphiphilic molecules are targeted, asymmetric structures such as ABAB type derivatives (Scheme 63) are good options, with either external [212] or internal [138,139] macrocyclic nitrogen. In this case as well the choice of the quaternizing agent offers interesting flexibility to tailor the properties. Even if halogenated compounds are suitable to quaternize the pyrazinic nitrogen atoms, the common agent dimethyl or even more so diethylsulfate lead preferentially to the sulfonation of the pyridine groups instead of the expected quaternization [137]. These results update Scott's ones [292], who was the first to describe a quaternized pyridinoporphyrazine [283].

4. Zwitterionic phthalocyanines

Only a few molecules bearing simultaneously anionic and cationic charges are reported. They are generally a result of the quaternization of substituent nitrogen by propanesultone **167**. This reagent bears a hidden sulfonate function that appears after the opening of the ring during the quaternization. This is the case of the tetrapyridino Zn(II) phthalocyanine **276a** [101], of the analogous Ge derivative **276b** [261], and of the Si(OH)$_2$ derivative **276c** [260] quaternized by propanesultone **167** (Fig. 19), all combining four positive charges on pyridine nitrogen atoms and four sulfonate negative functions.

Quaternization of the 3-ethynylpyridinyl substituted subphthalocyanine **266a** by 1,3-propanesultone **167** provides the zwitterionic subphthalocyanine **277** that has concomitantly pyridinium and sulfonate functions (Scheme 64) [213].

Cobaltacarborane substituted asymmetric phthalocyanine **278** (Fig. 20), despite its zwitterionic character, is not soluble in water [293].

5. Non-ionic water-soluble phthalocyanines

Several types of non-ionic substituents are also able to confer water-solubility to phthalocyanines. They can be divided into three main types: polyethyleneglycol, carbohydrate substituted phthalocyanines and other polyhydroxylated substituted derivatives.

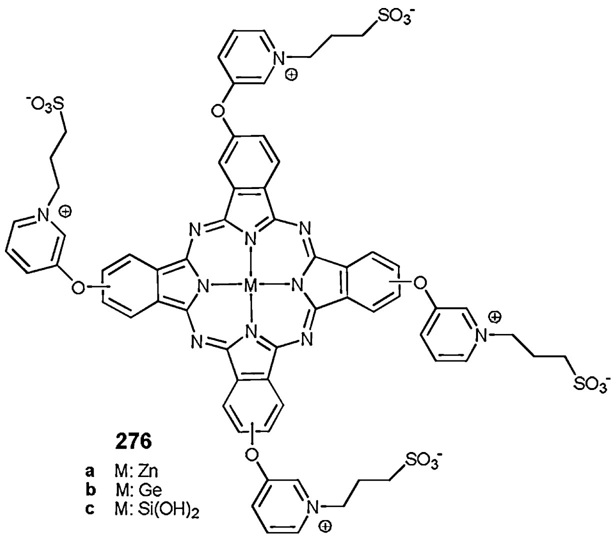


Fig. 19. Zwitterionic phthalocyanine **276** [101,260,261].

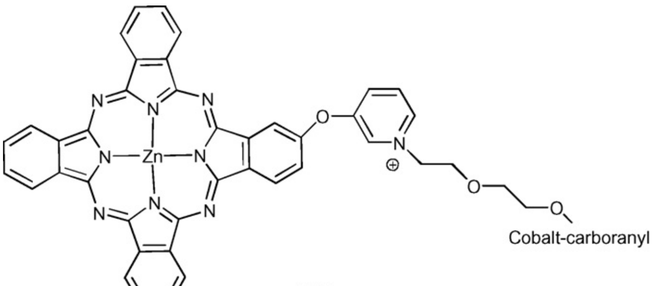
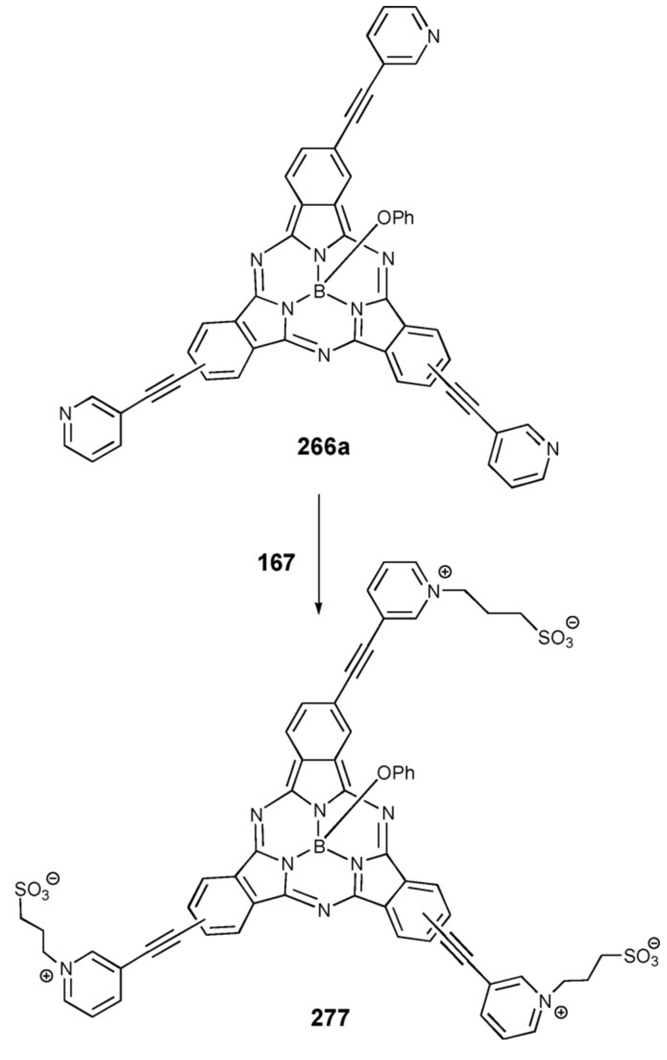


Fig. 20. Cobalt–carboranyl substituted phthalocyanine **278** [293].



Scheme 64. Zwitterionic subphthalocyanine **277** [213].

5.1. Polyethylene glycol substituted phthalocyanines

Polyethylene glycol (PEG) substitution is a classical means to confer water-solubility to molecular materials [294,295].

Numerous phthalocyanines bearing polyethylene glycol chains are reported, with many variations on the chain number and/or various ethyleneglycol units. However, from the available data, some of these phthalocyanines are either not water-soluble (but all said to be highly soluble in very polar solvents), or this property was not investigated, depending on the authors' aims [296–298]. Lyotropism, a weak water-solubility, is a common property of PEG substituted phthalocyanines [299–305].

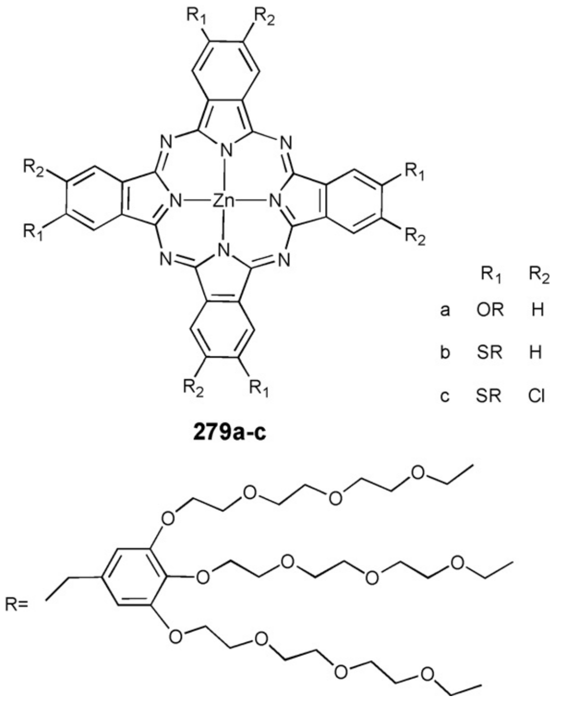


Fig. 21. Structure of dodecaPEG substituted phthalocyanines **279** [307].

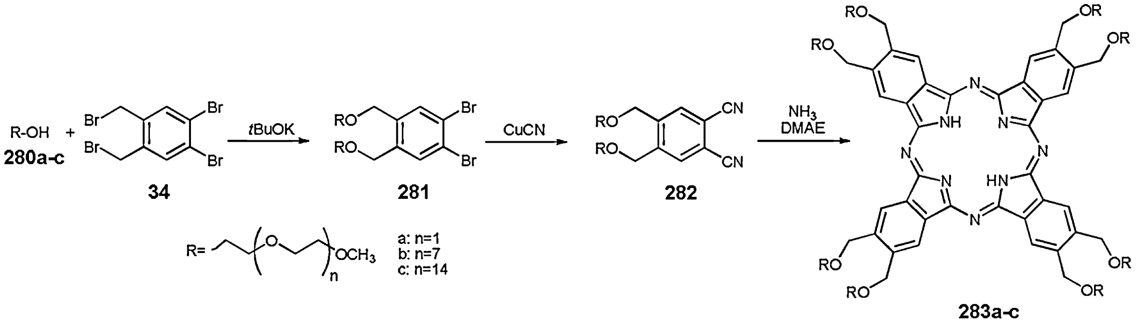
For the few of them reported to be water-soluble, the water-solubility is submitted to fine structural variations, and various aggregation degrees in water. Increasing the number and length of polyoxo chains helps generally to overcome this problem [296,306], but this is not a universal rule: phthalocyanines **279a**–**c** bearing 12 ethylated PEG chain units (Fig. 21) are not even water-soluble [307].

In the case of asymmetric substitution pattern, the hydrophobic nature of the other substituents inhibits water-solubility [308], but the presence of the polyoxo chain lead to interesting behaviors [309].

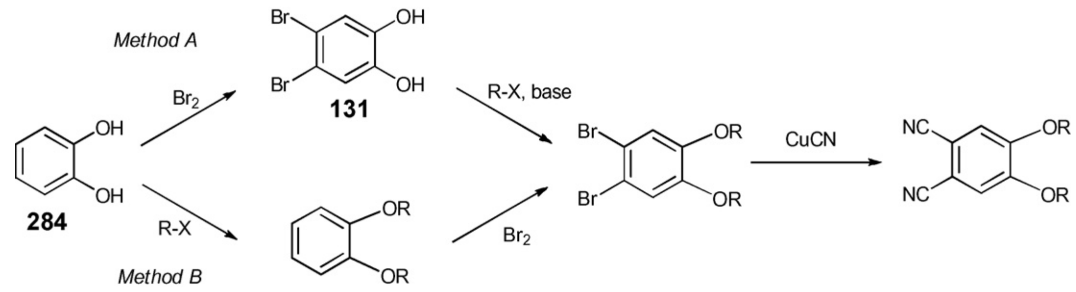
The first described derivatives contained one or two PEG chains directly on the isoindole subunit, then branched substituents were described, leading to phthalocyanines bearing eight or sixteen chains depending on their tetra- or octasubstitution pattern.

5.1.1. Linear substitution pattern

The first reported phthalocyanines **283a**–**c** bearing polyethylene glycol chains form a series consisting of three octasubstituted unmetallated phthalocyanines. The polyethyleneglycol chains are methylated at the end and consist of one, seven or fourteen ethylene glycol units (Scheme 65) [310]. Subsequently metallated derivatives were reported [305]. These compounds are indeed highly aggregated but nevertheless water-soluble. Their classical



Scheme 65. Synthesis of octasubstituted phthalocyanine **283** [310].



Scheme 66. Synthetic methods leading to di-O-alkyl phthalonitriles.

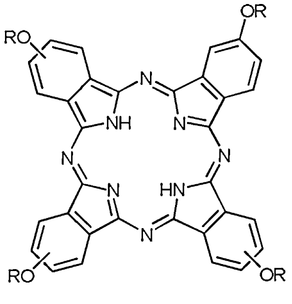
synthetic pathway consists of condensing the selected starting alcohols **280a**–**c** on **34** into **281**, proceeding to the dinitrilation and converting the resulting phthalonitrile **282** into the expected phthalocyanine under ammonia atmosphere.

In the subsequent studies, an alkyl moiety was introduced between the phthalocyanine core and the PEG part [311]. The PEG chain is connected directly to the macrocycle by an ether bond. The synthesis of the starting phthalonitrile follows one of the two general synthetic pathways shown on Scheme 66, starting from pyrocatechol **284**. The resulting phthalocyanines **288** prepared in three steps following method A, from bromocathechol **131** and the brominated derivative **285** (Scheme 67) are far more amphiphilic but still soluble in water.

Octa- and tetrasubstituted phthalocyanines **292** [312] and **293** [300,312] bearing the PEG moiety directly linked to the macrocycle are also reported (Scheme 68). They are prepared by substituting **289** onto 3-nitrophthalonitrile or by following the synthetic method B described in Scheme 66 [313].

Tetrasubstituted PEG phthalocyanines **294** and **295** (Fig. 22) illustrate the structural sensitivity towards water-solubility [299].

The presence of hydroxyl groups at the end of the chain considerably enhances the water-solubility [314,315]. The position of the substituents has an effect as well. Phthalonitriles **296** and **297** are prepared by the condensation of 4-nitrophthalonitrile with an excess of respectively mono- and tetraethylene glycol. Their cyclotetramerisation is achieved in solvent-free conditions in presence of hydroquinone for the free-base derivatives **298a** and **299a**. Ni, Co and Cu derivatives were prepared in quinoline in presence of the required metal salt (Scheme 69).



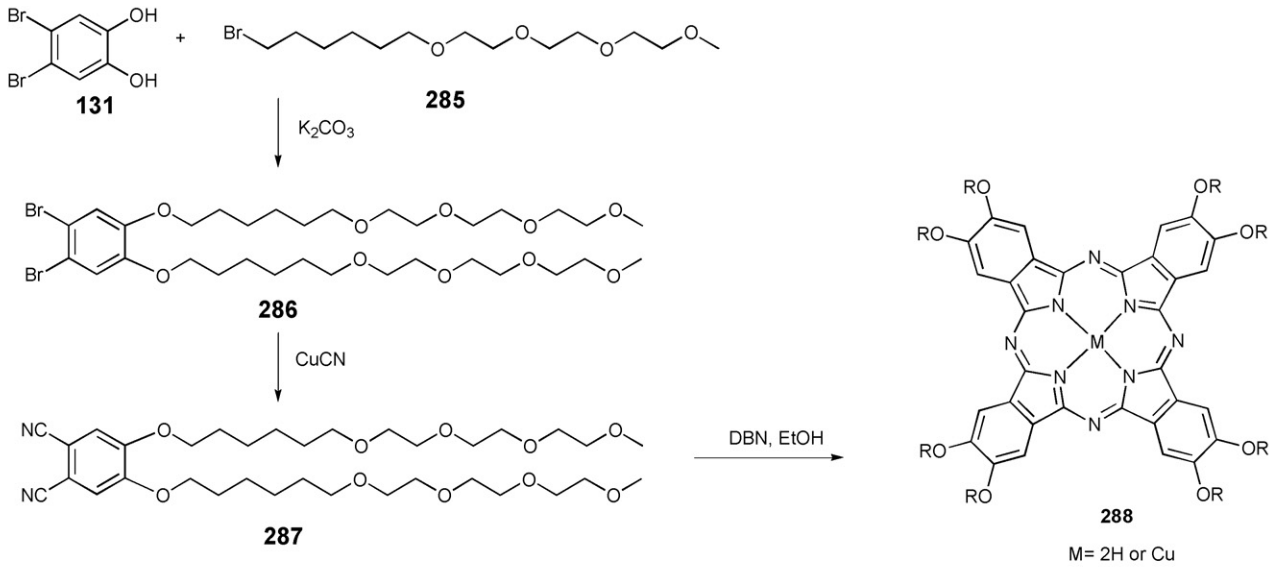
294: R=-$(CH_2CH_2O)_3CH_3$

295: R=-$(CH_2CH_2O)_8CH_3$

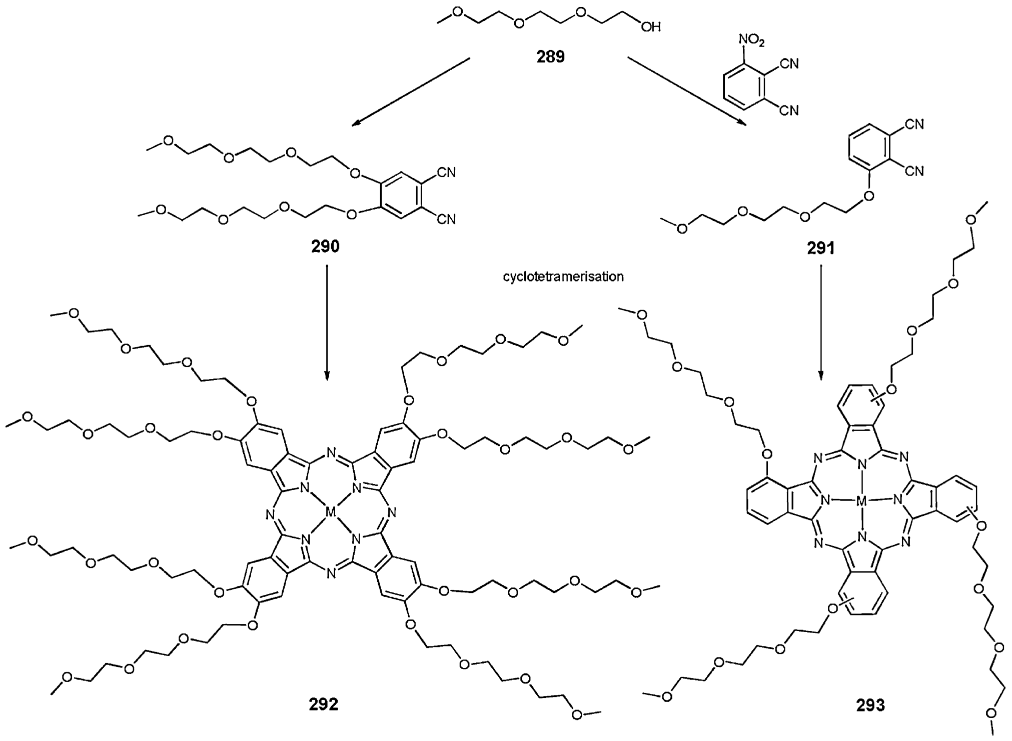
Fig. 22. Phthalocyanines **294** and **295** bearing four methylated polyethylene glycol chains [299].

A series of tetraethyleneglycol substituted ZnPc (**300**, **301**, **302**, Fig. 23) prepared by us exhibit as expected excellent water-solubility.

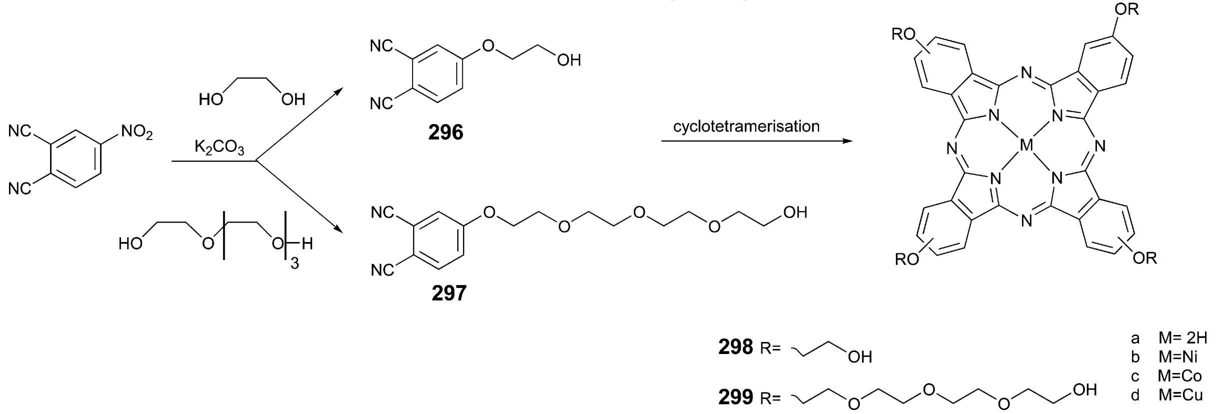
Both water-soluble homoleptic lutetium double decker **303** bearing 16 PEG chains, and heteroleptic **305** were reported by us [313]. **303** was prepared directly from the phthalonitrile **290** heated in presence of $Lu(OAc)_3\cdot 3H_2O$ in a DBU–hexanol system (Scheme 70), whereas **305** was obtained by mixing (15-C-5)4PcLu(OAc) prepared following a known procedure [316] with **292-2H** (Scheme 71).



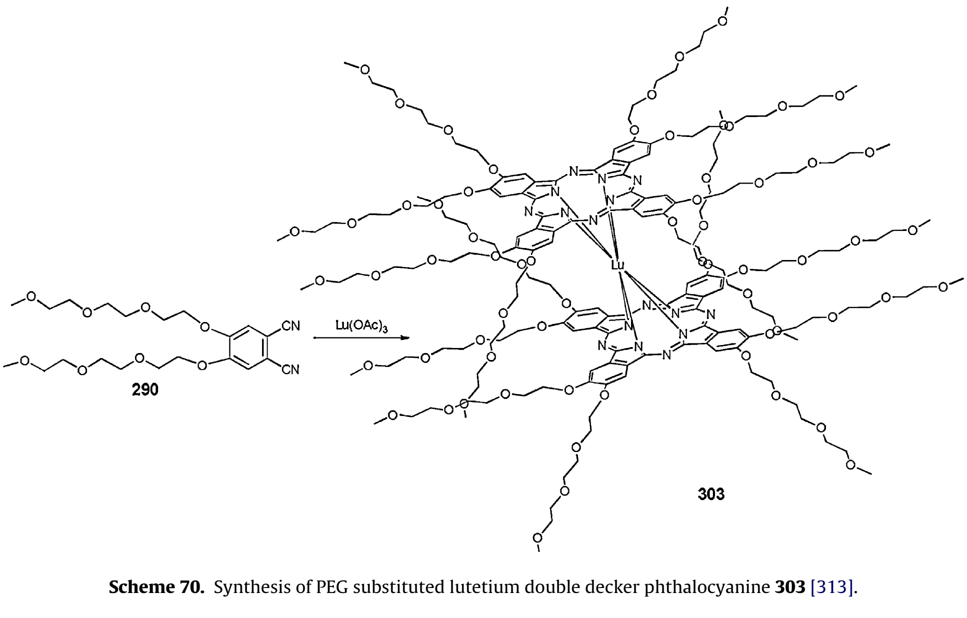
Scheme 67. Preparation of phthalocyanine **288** [311].



Scheme 68. M: 2H or Zn [300,312].



Scheme 69. Preparation of polyethylene glycol substituted phthalocyanines **298** and **299** [314,315].



Scheme 70. Synthesis of PEG substituted lutetium double decker phthalocyanine **303** [313].

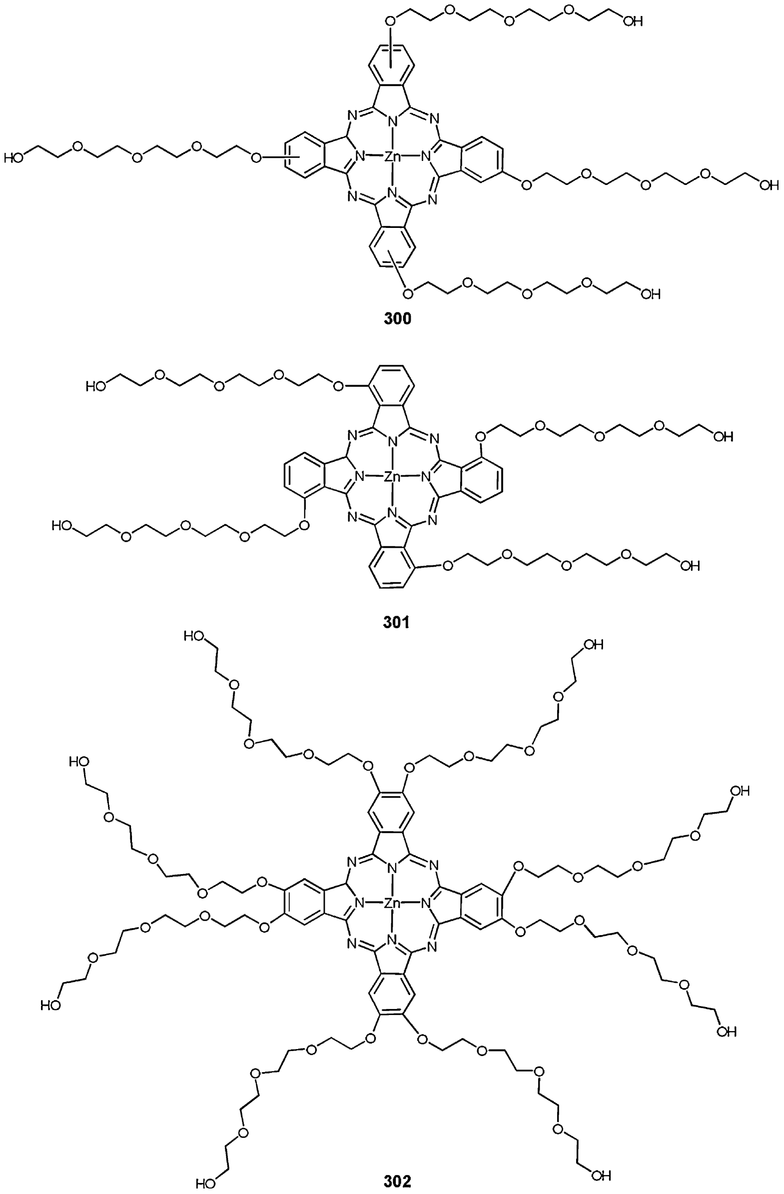
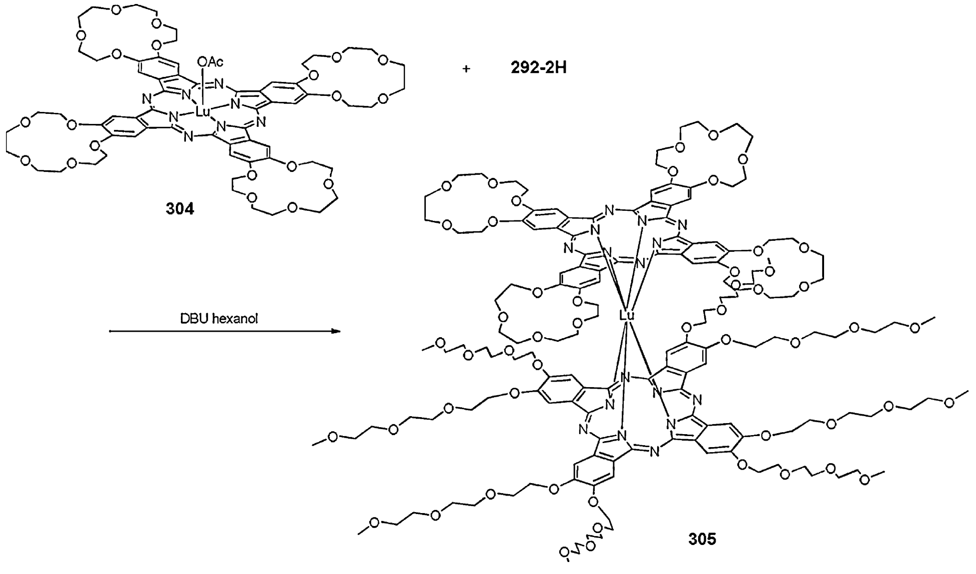
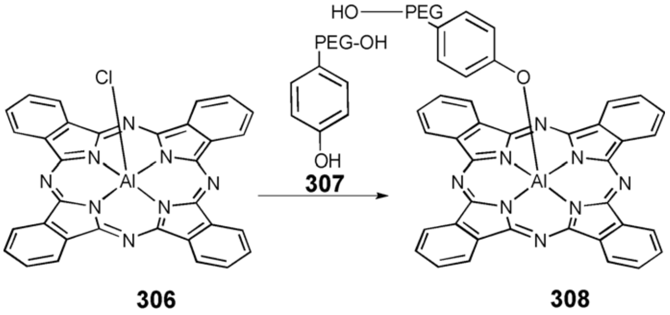


Fig. 23. Hydroxylated polyethylene glycol substituted phthalocyanines [314].



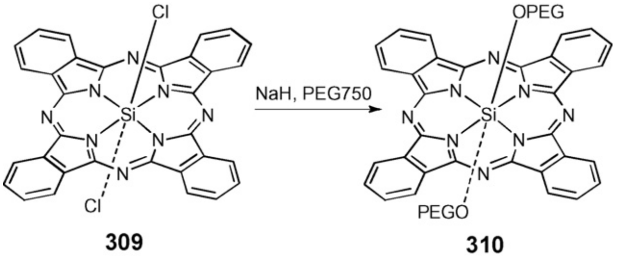
Scheme 71. Preparation of heteroleptic double-decker **305** [316].



Scheme 72. Axial substitution of AlPc [318].

PEG may be introduced on the axial position of appropriately metalated phthalocyanines: a few PEG axially substituted phthalocyanines and naphthalocyanines [317] are reported. The axial substitution of unsubstituted chloroaluminium phthalocyanine **306** by the activated PEG derivative **307** leads to the water-soluble phthalocyanine **308** (Scheme 72) [318].

Highly water-soluble (>5 mg mL^{-1}) Si(PEG750)$_2$Pc (**310**) was prepared in one step by the substitution of the axial chloride of unsubstituted SiPc (**309**) by PEG 750 (Scheme 73) [319].

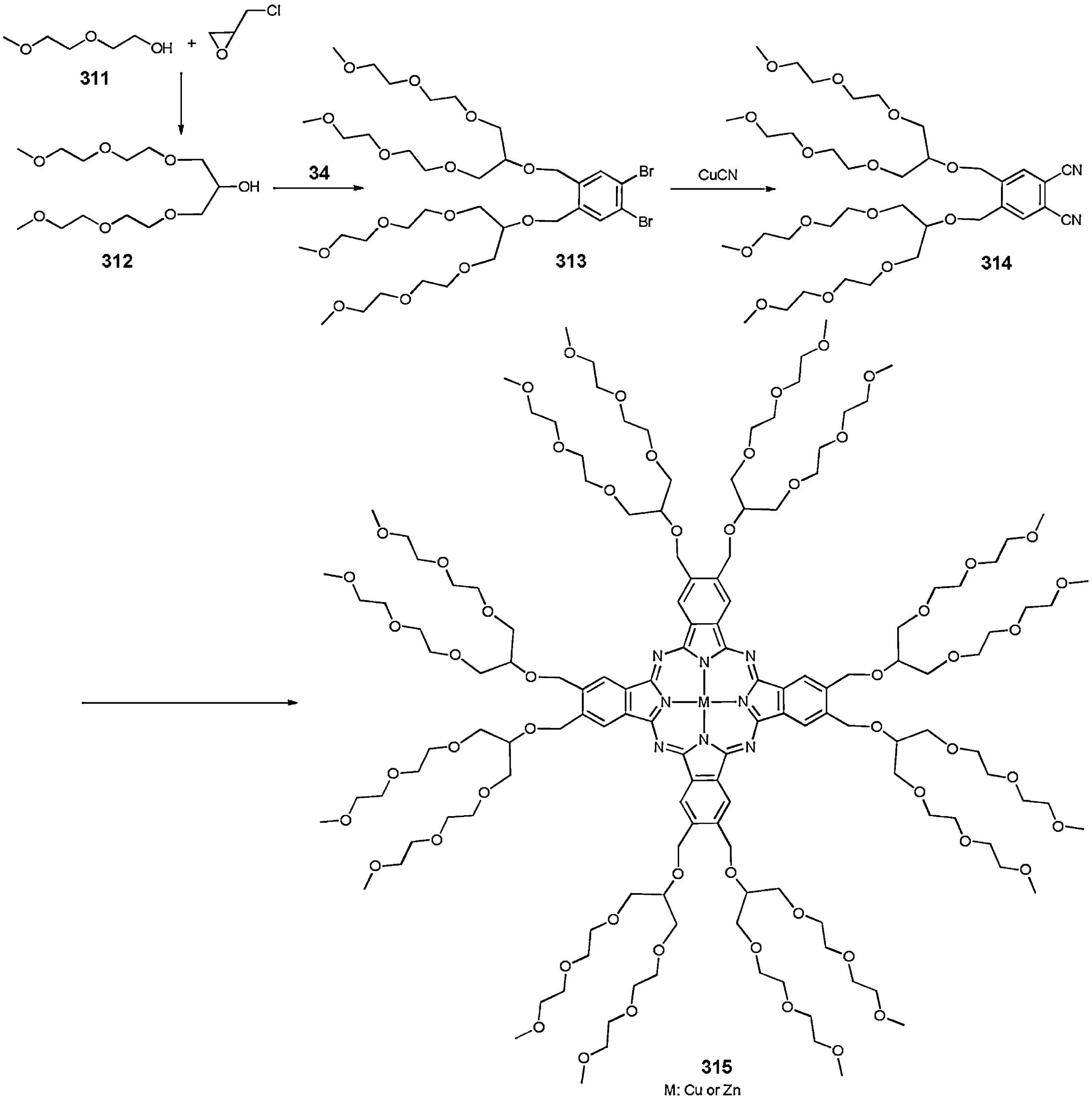


Scheme 73. Axial substitution by polyethylene glycol chain of Si(IV)Pc [319].

The strong hydrophilic nature of PEG is the key in providing the satisfactory water solubility in addition to inhibiting aggregation when located in the axial position.

5.1.2. Branched substitution pattern

The synthetic pathway previously presented Scheme 65 was applied to the synthesis of phthalocyanine **315**, from the phthalonitrile **314** (Scheme 74). **314** was prepared in three steps: **311** opens epichlorhydrine in basic conditions, the resulting branched alcohol achieves a nucleophilic substitution on **34** followed by the dinitrilation step leading to phthalonitrile **314**. After cyclotetramerization,

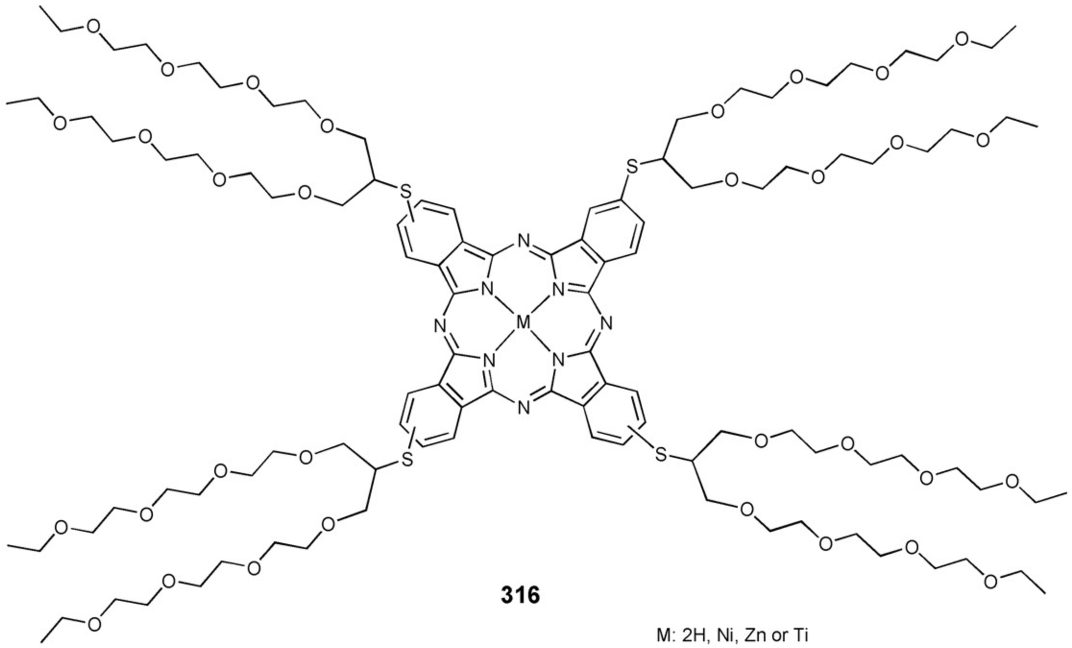


Scheme 74. Preparation of phthalocyanine **315** [296].

the resulting phthalocyanine **315** exhibits water-solubility much better than the unbranched octasubstituted **298a** [296].

Phthalocyanines **316**, **317** and **318** (Fig. 24) are of closely related structures, the main difference lying on the methylene sulfur bridge. Following the evolution of our research interests, the water-solubility of the free-base and Ni derivatives was not investigated at first [320]. The water-solubility of the Zn [321] and the Ti [322] derivatives, prepared in order to be tested as type II photosensitisers, was better for the octasubstituted derivatives than for the tetrasubstituted ones.

The synthesis of all these phthalocyanines is based on the preparation of 1,3-di[2-2-(2-ethoxyethoxy)ethoxy)]-2-propanethiol



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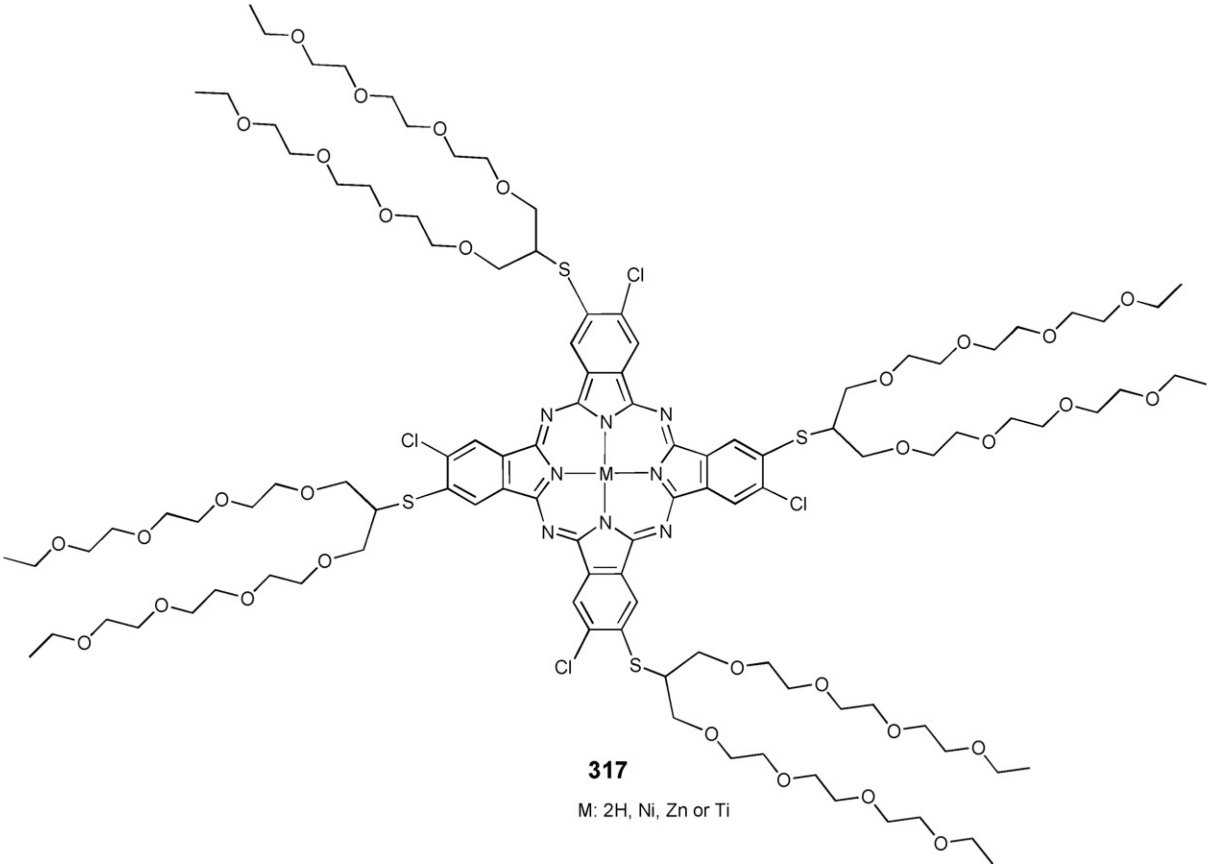
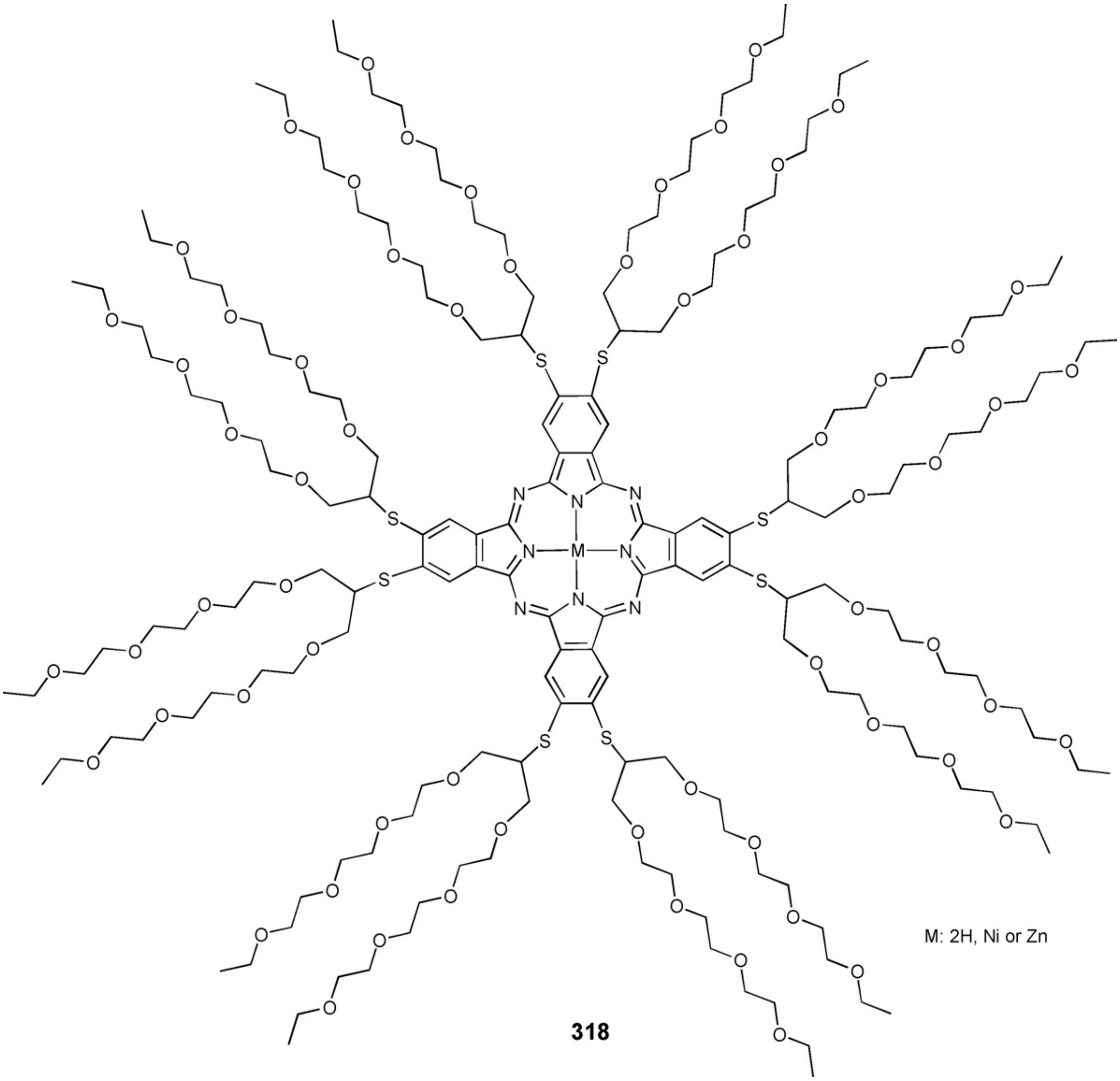


317

Fig. 24. M: 2H, Ni or Zn. Only one of the isomer of **317** (obtained as an isomeric mixture) is represented [320–322].



318

Fig. 24. (*Continued*).

321, in two steps from 1,3-di[2-(2 ethoxyethoxy)ethoxy]-2-propanol **319** [296], via the tosylated intermediate **320**. **321** reacts then with 4-nitrophthalonitrile and 4,5-dichlorophthalonitrile to give the three starting phthalonitriles **322**, **323** and **324** (Scheme 75).

5.2. Carbohydrate substituted phthalocyanines

Since the publication of the first carbohydrate substituted phthalocyanine **325** (Fig. 25) in 1989 [323], only a few examples of carbohydrate substituted phthalocyanines have been reported in the literature, with a significantly increasing interest for such compounds since 2005. Up to now, mainly Zn(II) and Si(IV) carbohydrate substituted phthalocyanines are reported, probably because they were designed for PDT applications. Most of these carbohydrate substituted phthalocyanines have a symmetric substitution pattern (mainly tetrasubstitution) and only a few are asymmetrically substituted.

Carbohydrate units can be attached to the phthalocyanine either by a glycosidic bond (with a selective anomeric configuration or a mixed one) or by one of its other functional groups. This increases the number of possible isomers (in addition to the isomeric mixtures of tetrasubstituted phthalocyanines), rendering the characterization of the mixture quite difficult [324]. The synthesis of carbohydrate octasubstituted water-soluble phthalocyanine consisting of only one isomer (or still being a diastereoisomeric mixture because of anomeric structures) was achieved more recently.

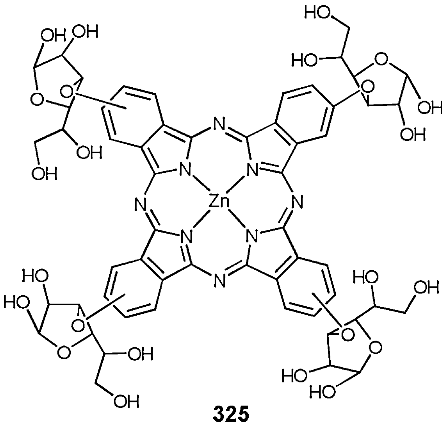


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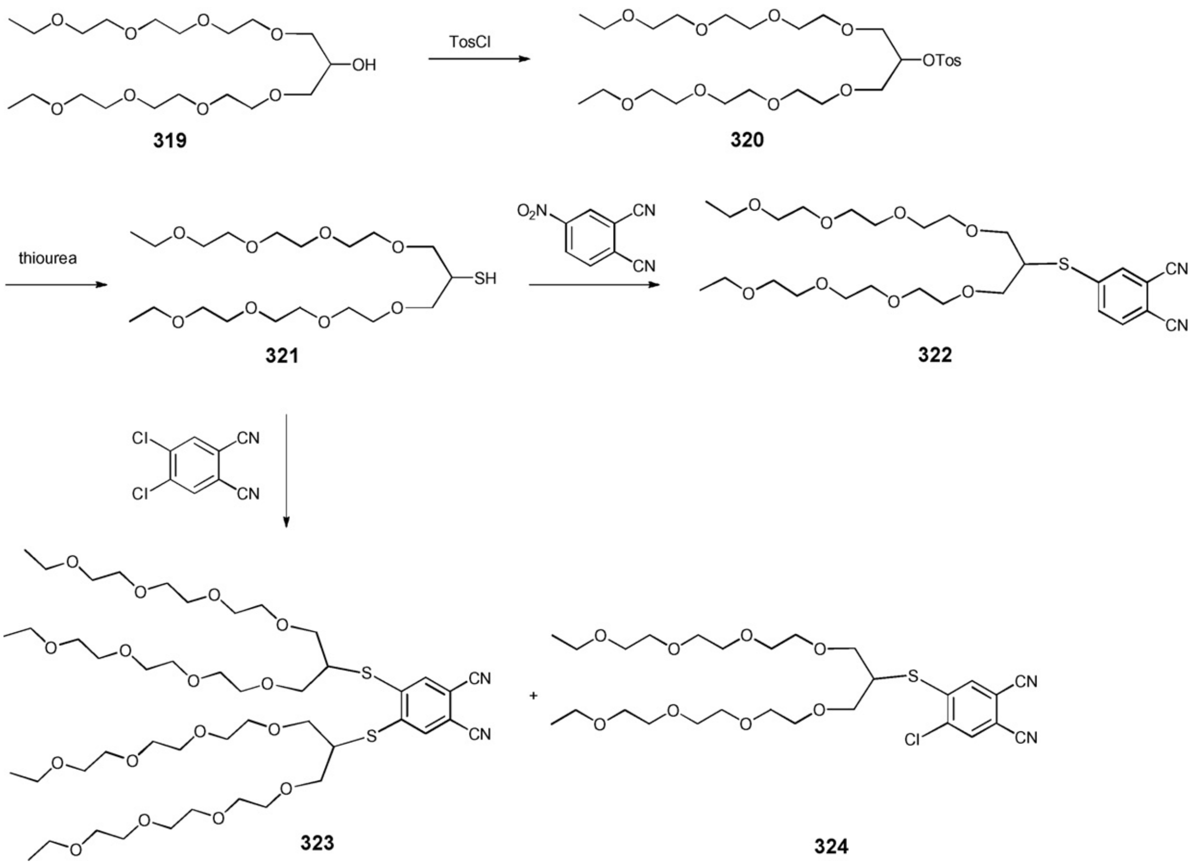
Fig. 25. The first carbohydrate substituted phthalocyanine (**325**) [323].



Scheme 75. Preparation of branched polyethylene glycol substituted phthalonitriles **322**, **323** and **324** [320–322].

Two strategies are employed to obtain water-soluble carbohydrate substituted phthalocyanines: from protected carbohydrates phthalonitriles or directly from unprotected carbohydrate substituted phthalonitriles. In this first case, water-solubility is obtained only after the removing of protecting groups on the carbohydrate units, and anyway depends on the overall substitution pattern of the molecule. If highly hydrophobic substituents are present as well on asymmetrically substituted phthalocyanines, the presence of carbohydrate may not be sufficient to have water-solubility, which may actually not be the aim of making the molecules [325–328]. In the second case, the formation of the macrocycle is the last step of the synthetic pathway, the resulting phthalocyanine being water-soluble without requiring further steps. Several phthalocyanines substituted by carbohydrates at the peripheral or axial position are reported without the removal of the protecting groups, therefore without the desired water-solubility property. This is the case of some axially substituted Si(IV) [329,330] or Zn(II) phthalocyanines [324,331] that have nevertheless been tested as PDT agents.

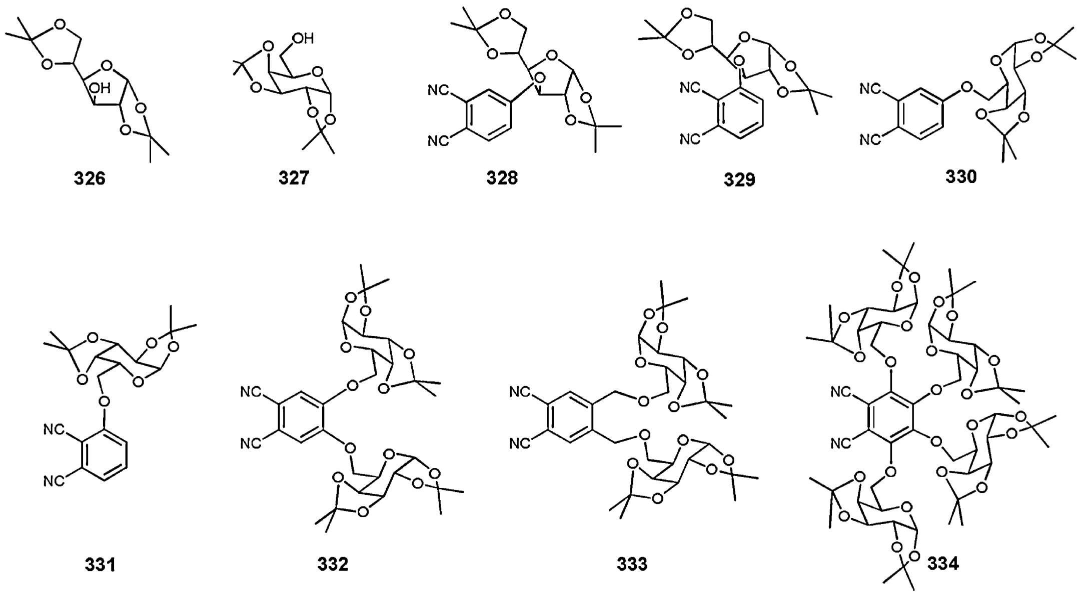
5.2.1. Symmetric substitution pattern

5.2.1.1. Tetrasubstitution by non-glycosidic bond. As stated above, the first phthalocyanine substituted by carbohydrate units (**325**) was prepared by Maillard et al. [323], in two steps starting from the phthalonitrile **328**. After cyclotetramerisation, acidic hydrolysis of the protecting acetal groups led to a diastereoisomeric mixture of **325**. Acetalated carbohydrates, particularly 1,2:5,6-diisopropylidene-D-glucofuranose **326** and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **327** have been widely used to produce carbohydrate substituted phthalocyanines. Their free hydroxyl is easily condensed on 3-, 4-, di- or tetrafluorophthalonitriles, leading to starting materials **328**–**334** (Fig. 26). These nucleophilic substitutions are achieved in yields similar to those involving aliphatic alcohols.

Phthalocyanines prepared from **328**, **329** and **330** were not characterized after their acidic hydrolysis, due to the tedious identification of the resulting isomeric mixture. However, phthalocyanine **335** obtained by the cyclotetramerisation of **330** (Fig. 27) was unprotected and fully characterized [332].

5.2.1.2. Tetrasubstitution by glycosidic bond. The synthesis of the first glycosylated phthalonitriles **337a**–**c** (in which the carbohydrate unit, glucose, is linked to the phthalonitrile via a glycosidic bond) was achieved in 2006. Synthetic strategy based on the cyclotetramerization of **337a**–**c** with further removal of the protecting groups (acetyl, benzoyl or benzyl) proved to be inadequate: either the complete cleavage of the benzyl groups remained unsuccessful or the acyl groups degradated during the phthalocyanine formation [333]. The method was thus modified: the protecting groups were removed from the glucosylated phthalonitriles, the resulting phthalonitrile **338** being directly (Scheme 76) converted into the water-soluble tetraglucosylated phthalocyanine **339** under smoother conditions: reaction at 100 °C with zinc acetate in a 2:1 dimethylacetamide/n-butanol mixture.

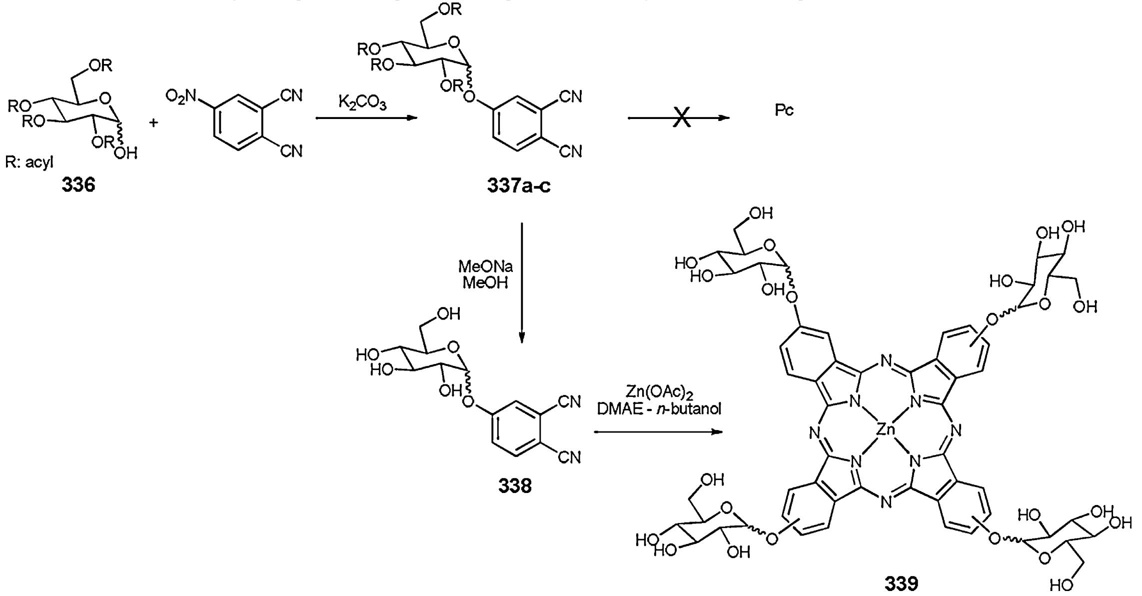
This new method of aryl glycosylation, created by Hanack and Ziegler for the preparation of protected 3,4-dicyanophenyl D-glycopyranosides, exploites a common reaction of phthalonitrile chemistry: the nitrite displacement on 4-nitrophthalonitrile by an alcolate. It was then rapidly extended onto various acylated carbohydrates including thioaldoses [334,335], and was applied by us to obtain the tetragalactose Zn(II) derivative [336]. As this method does not allow an anomeric control, mixture of anomeres α/β are obtained, in an average 1:10 proportion.



326 **327** **328** **329** **330**

331 **332** **333** **334**

Fig. 26. Up-to-now reported acetal protected carbohydrate substituted phthalonitriles.



Scheme 76. Anomerically glucose substituted ZnPc **339** [333].

Nitro- or fluoronaphthalodinitrile could not be successfully utilized for similar reactions, and naphthalonitrile **349** was obtained by a three-step synthesis (Scheme 77) [337].

The corresponding unprotected glycosylated naphthalocyanine **350** (Fig. 28) is less soluble in water than the analogous phthalocyanine **339**, due to the increased hydrophobic character of the molecule.

Phthalonitriles bearing a glycosylated carbohydrate on a spacer are reported [335]. In this case, ethyleneglycol in high excess is monoglycosylated by the α-bromoglycosylation donors **343** (glucose or galactose), the remaining hydroxyl of **351** is tosylated leading to **352-Glc** [338] and **352-Gal**, then substituted by dicyanophenol **355** (prepared in two steps by the reaction of benzylic alcohol **353** on 4-nitrophthalonitrile followed the reductive removal of the benzyl moiety of **354**), leading to the acetylated glycosylated phthalonitriles **356**. The crude desacetylated glycosides **357** are then engaged in the cyclotetramerisation reaction in presence of Zn salts and leading directly to the tetraglycosylated phthalocyanines **358** (Scheme 78).

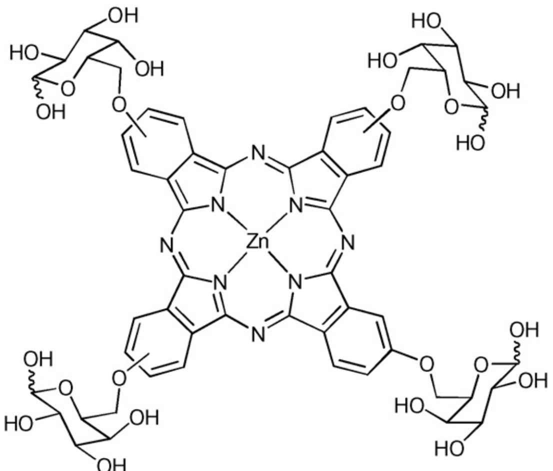


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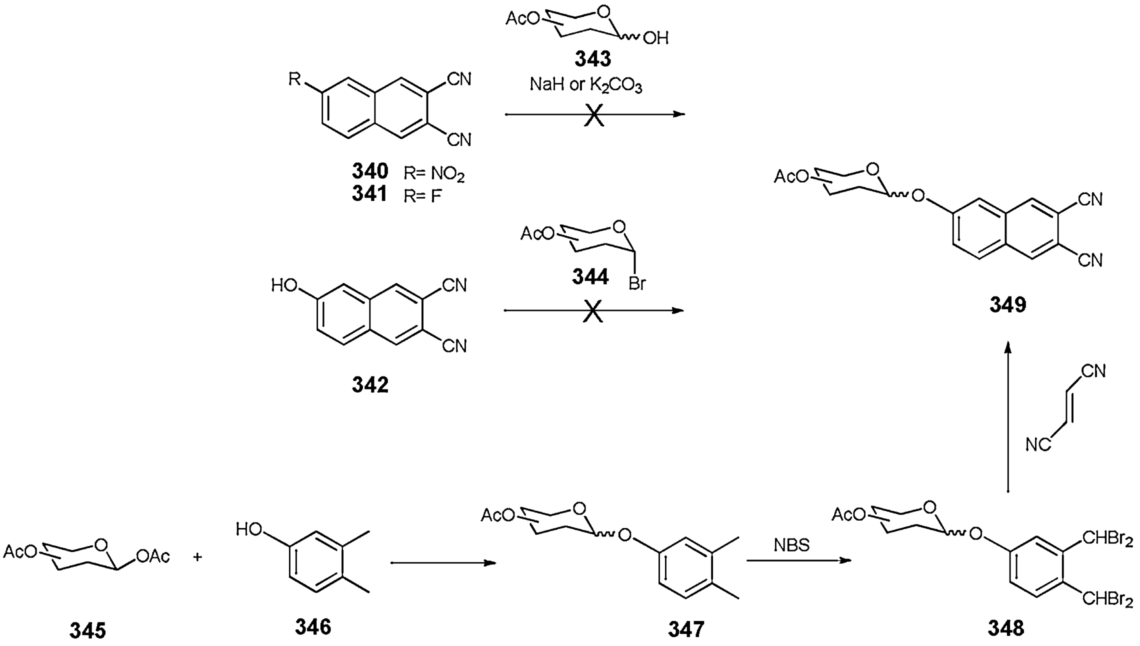
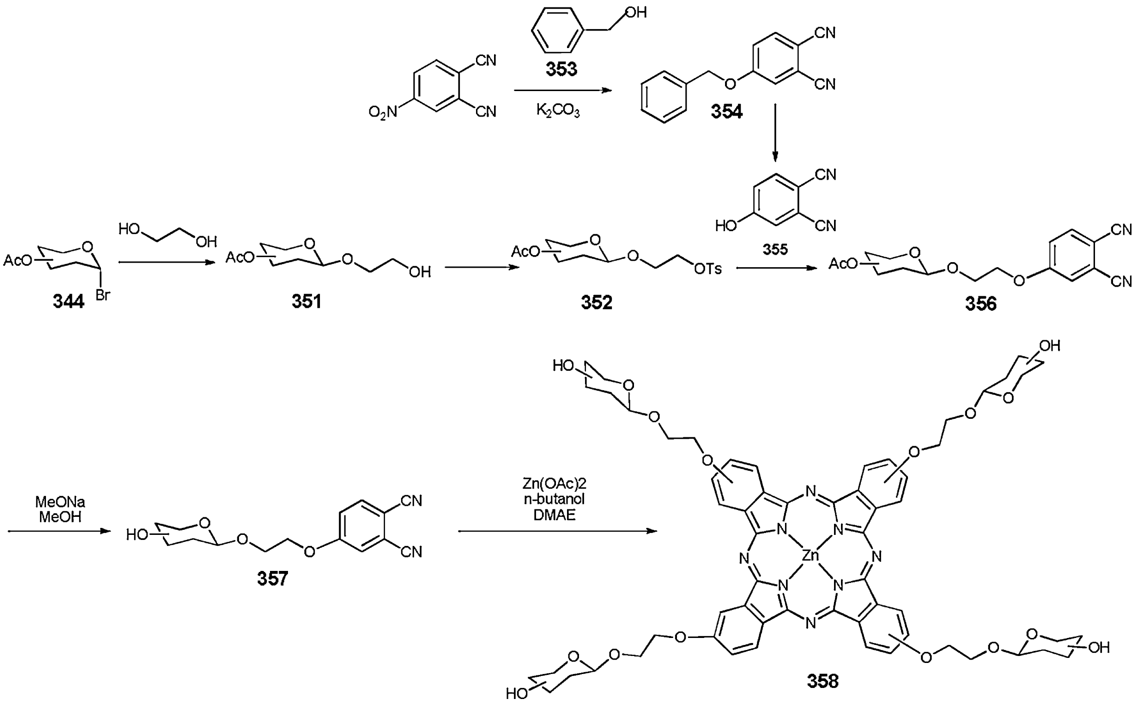
Fig. 27. Tetragalactose substituted ZnPc **335** [332].



Scheme 77. Preparation of glycosylated naphthlonitriles **349** [337].



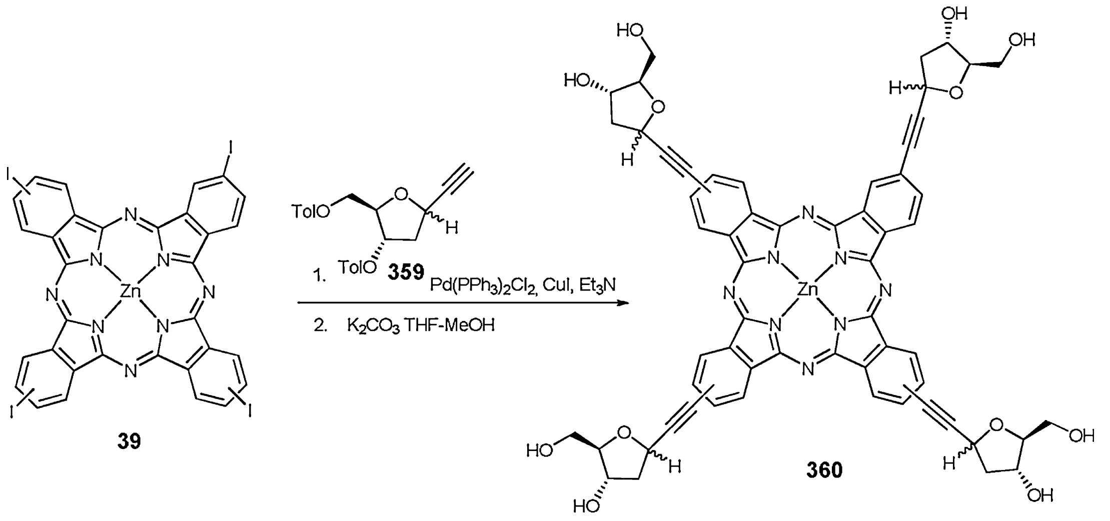
Scheme 78. Preparation of phthalocyanine **358** [338].

Carbohydrates may be grafted as well on preformed phthalocyanines: this is the case of phthalocyanine-linked C-ribofuranosyl **360** [339], obtained in two steps via a Sonogashira coupling between the C-allyl ribofuranose **359** and the tetraiodophthalocyanine **39** [340], followed by the removal of the toluoyl protecting groups (Scheme 79).

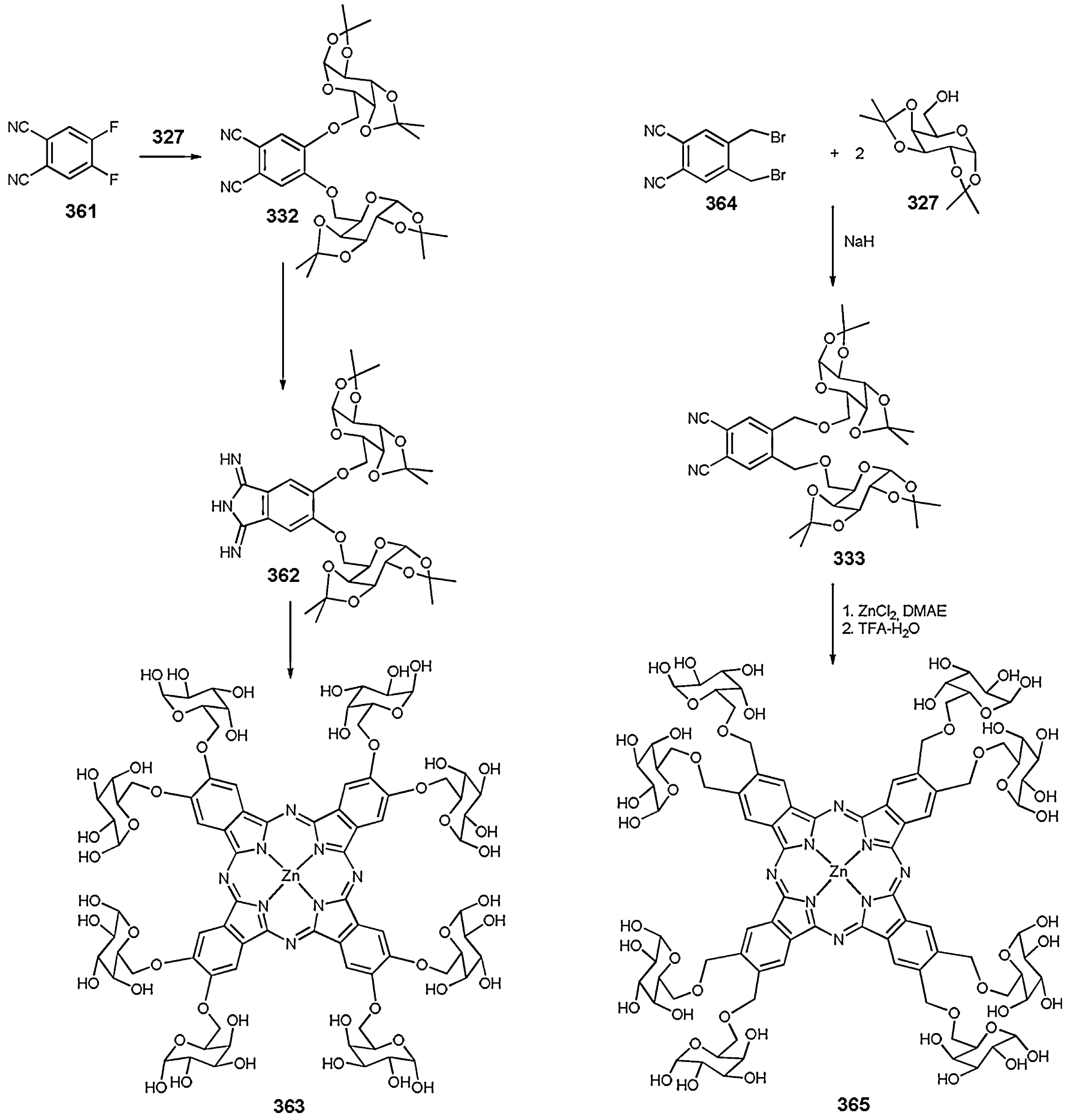
5.2.1.3. Octasubstitution. The synthesis of octacarbohydrate substituted phthalocyanines is far more recent, with two similar phthalocyanines (**363** and **365**, Scheme 80) concomitantly published by respectively Hanack and Torres [332,341]. Disubstituted phthalonitriles **332** and **333** were prepared by reacting **327** with 4-bromo-5-nitrophthalonitrile (with low yields, the monosubstituted product being the major one), 4,5-difluorophthalonitrile **361** [202] (nearly quantitatively) or 4,5-bis(bromomethyl)phthalonitrile **364** (27%) [342].

5.2.2. Asymmetric substitution pattern

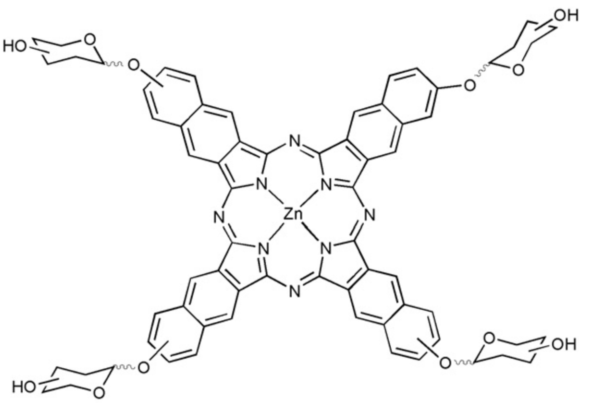
A few asymmetrically carbohydrate substituted phthalocyanines are reported. Their design aims at modulating their



Scheme 79. Coupling of C-allyl ribofuranose leading to phthalocyanine **360** [339].



Scheme 80. Synthesis of octagalactose substituted Zn phthalocyanines **363** and **365** [332,341].



350

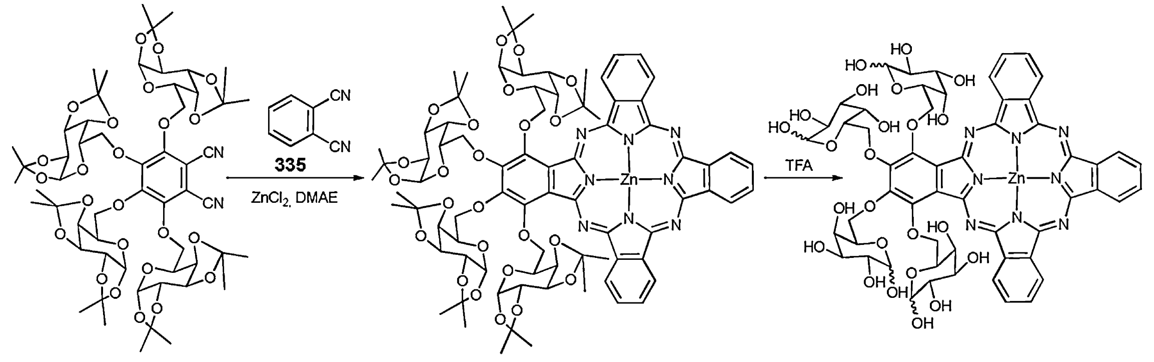
Fig. 28. Carbohydrate substituted naphthalocyanine **350** [337].

amphiphilic balance. Depending on the nature of the substituents facing the carbohydrate moieties, the resulting phthalocyanines may not be water-soluble.

Phthalonitrile **334** was engaged in a mixed statistical cyclotetramerisation with phthalonitrile, in presence of $ZnCl_2$. The expected AB3-type phthalocyanine **366** was obtained in 30%, and converted into the water-soluble **367** by acidic hydrolysis of the protecting acetals (Scheme 81) [343].

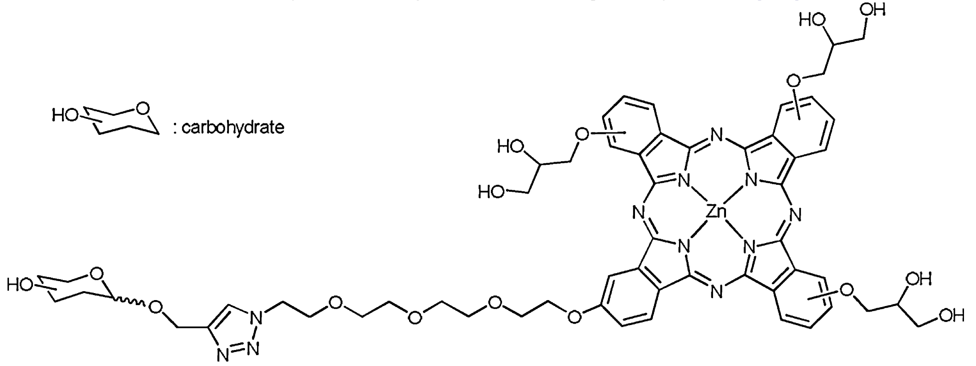
Cyclodextrines (CD) are a particular association of carbohydrates and also provide water-solubility, as demonstrated for a single β-cyclodextrine on an asymmetric amphiphilic phthalocyanine [344]. Here again the phthalocyanines **370a–b** were formed from the unprotected phthalonitrile **369**, obtained by the condensation of an excess of the cyclodextrine βCD (**368**) on 4-nitrophthalonitrile via a C6 hydroxyl (Scheme 82).

Phthalocyanines **371** (Fig. 29) substituted by three glycerol at the non-peripheral position and one carbohydrate linked by



334 **366** **367**

Scheme 81. Asymmetric tetragalactose substituted phthalocyanine **367** [343].



371

Fig. 29. Structure of **371** bearing clicked carbohydrates [345].

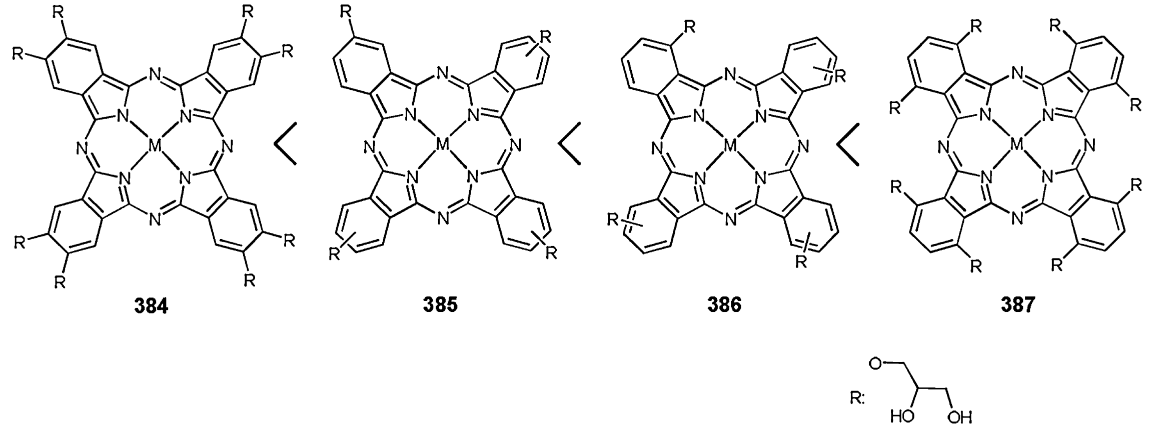
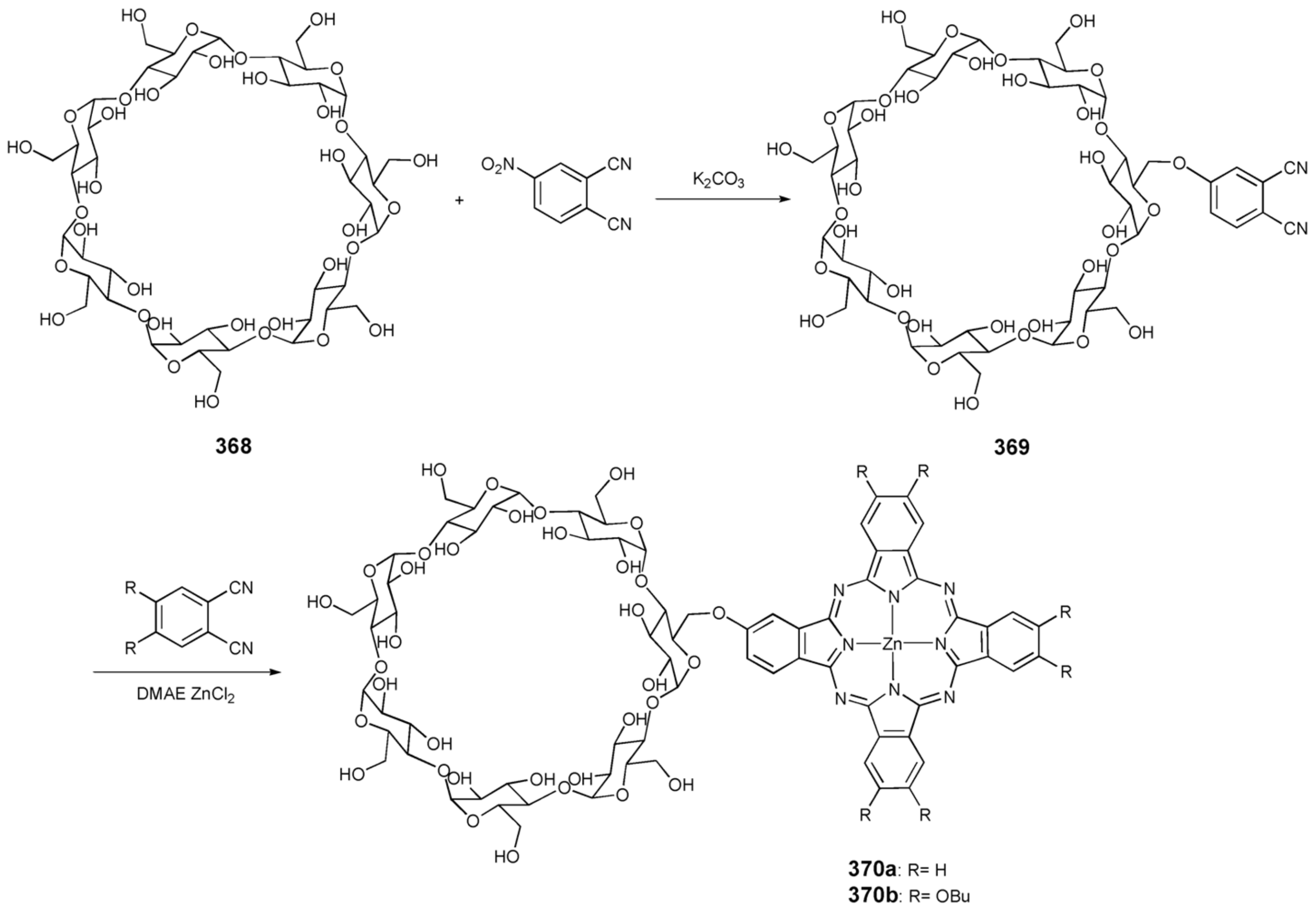


Fig. 30. Variation of the water-solubility of glycerol substituted phthalocyanines depending on the positions and number of the substituents [345,355].



Scheme 82. Preparation of β-cyclodextrine substituted Zn phthalocyanines **370** [344].

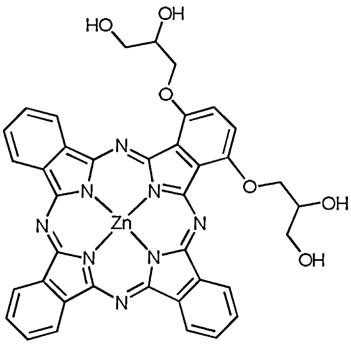
a tetraethyleneglycol bridge to the phthalocyanine macrocycle proved to be highly water-soluble [345].

5.3. *Polyhydroxylated and related compounds*

5.3.1. *Polyhydroxylation*

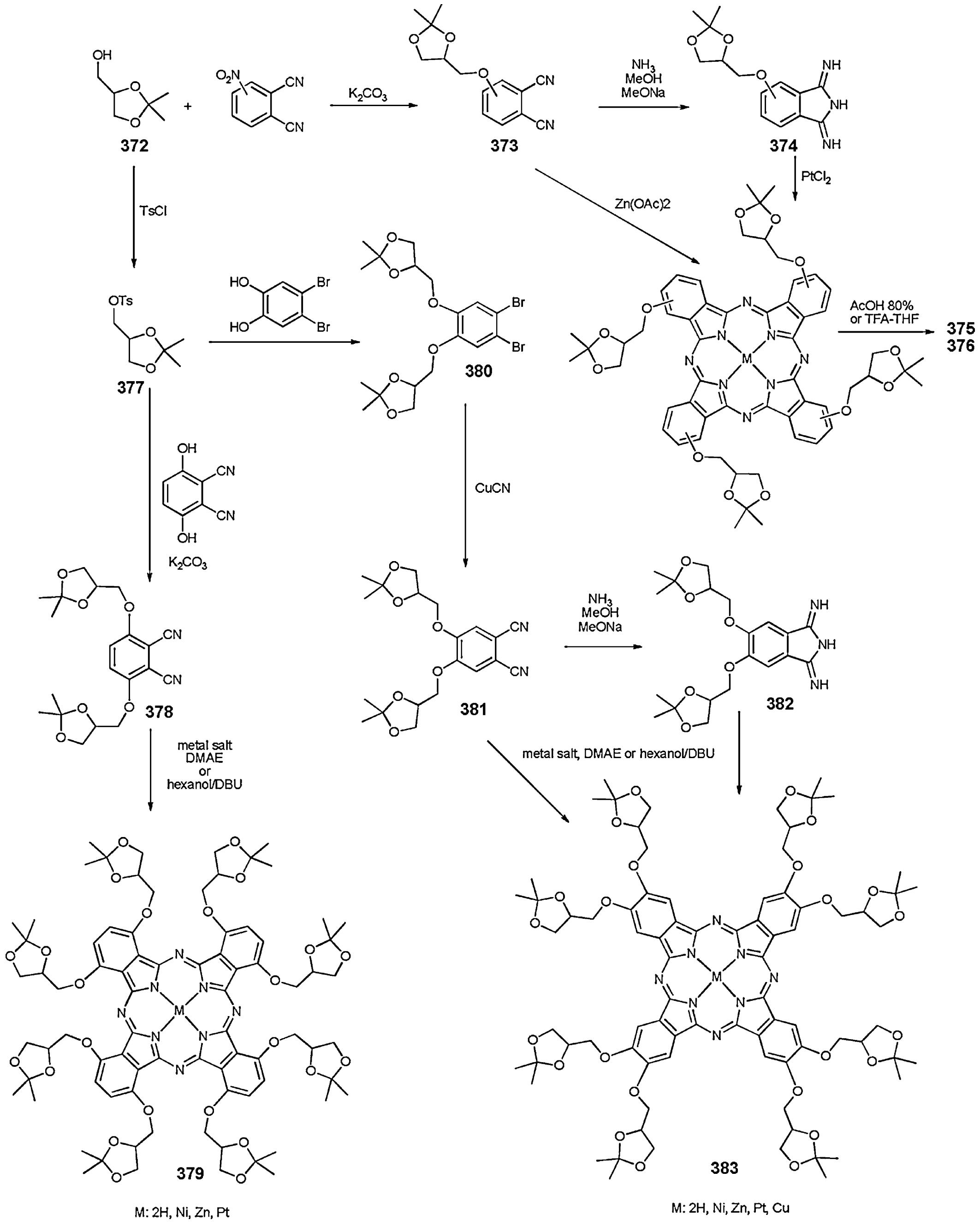
Polyhydroxylation is a common means to make a molecule to be water-soluble. The presence of several hydroxyl groups on a phthalocyanine increases its potential water-solubility. Even though several phthalocyanines polyhydroxylated directly on the macrocycle are described [346–348], no observations were made about their water-solubility. The sole presence of hydroxyl groups is not always sufficient to ensure of water-solubility. Comparative observations between our results [336] and Kobayashi's ones [349,350] demonstrate the fact that for glycerol substituted phthalocyanines, the position of the substituents is more important than the total number of hydroxyl groups. Glycerol is a cheap and versatile synthon [351,352], available under its protected form: solketal (**372**). Despite the fact that its structure is closely related to that of carbohydrates, it is not an aldose nor a ketose, but the reduced form of one of the smallest carbohydrate unit: glyceraldehyde. Several phthalocyanines substituted by glycerol units are reported. The synthesis of such phthalocyanines results from the acidic hydrolysis of solketal substituted ones, prepared by the cyclotetramerization of solketal substituted phthalonitriles [353] (or diiminoisoindolines if required, as in the case of platinum phthalocyanine derivatives [354]). Solketal reacts with 3- or 4-nitrophthalonitrile. The resulting phthalonitriles can be directly cyclotetramerized or are previously converted into the activated diiminoisoindolines. Octasubstituted phthalocyanines are obtained via the formation of a disubstituted phthalonitrile (prepared from tosylated solketal **377**) by the same method (Scheme 83).

The water-solubility of symmetrically glycerol substituted phthalocyanines is astonishingly increased on going from octaperipheral **384** (totally insoluble in water) [319,350], to tetraperipheral **385** [336], tetra-non-peripheral **386** and octa-non-peripheral **387** which are perfectly water-soluble (Fig. 30) [355].

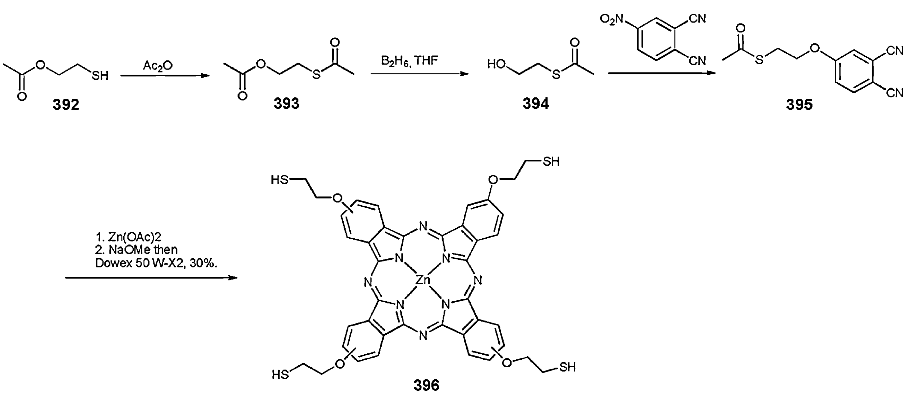


388

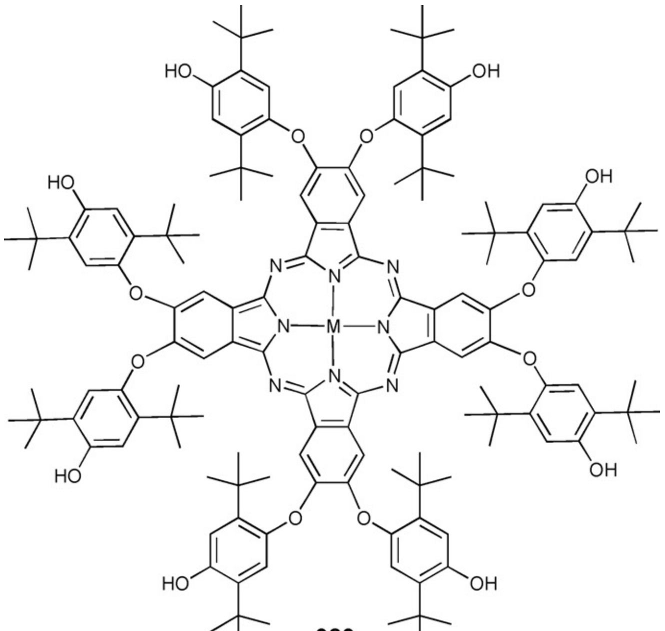
Fig. 31. Asymmetric di-glycerol substituted phthalocyanine **388** [356].



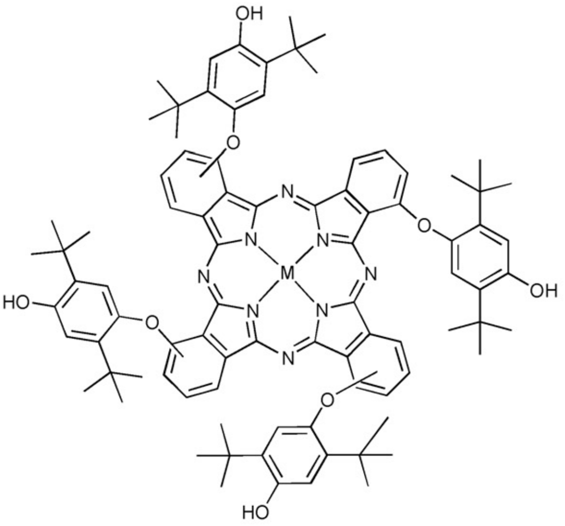
Scheme 83. Synthetic pathways to solketal substituted phthalocyanines [336,350–354].



Scheme 84. Preparation of thiol substituted phthalocyanine **396** [358].



389



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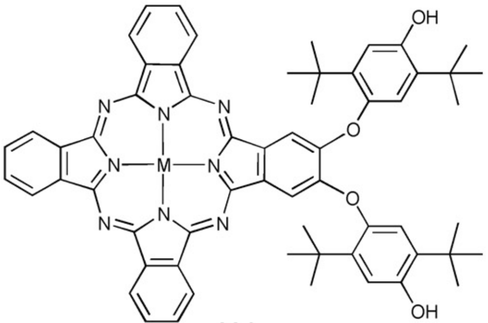

391

Fig. 32. Structures of hydroxylated phthalocyanines **389**, **390** and **391** [357].

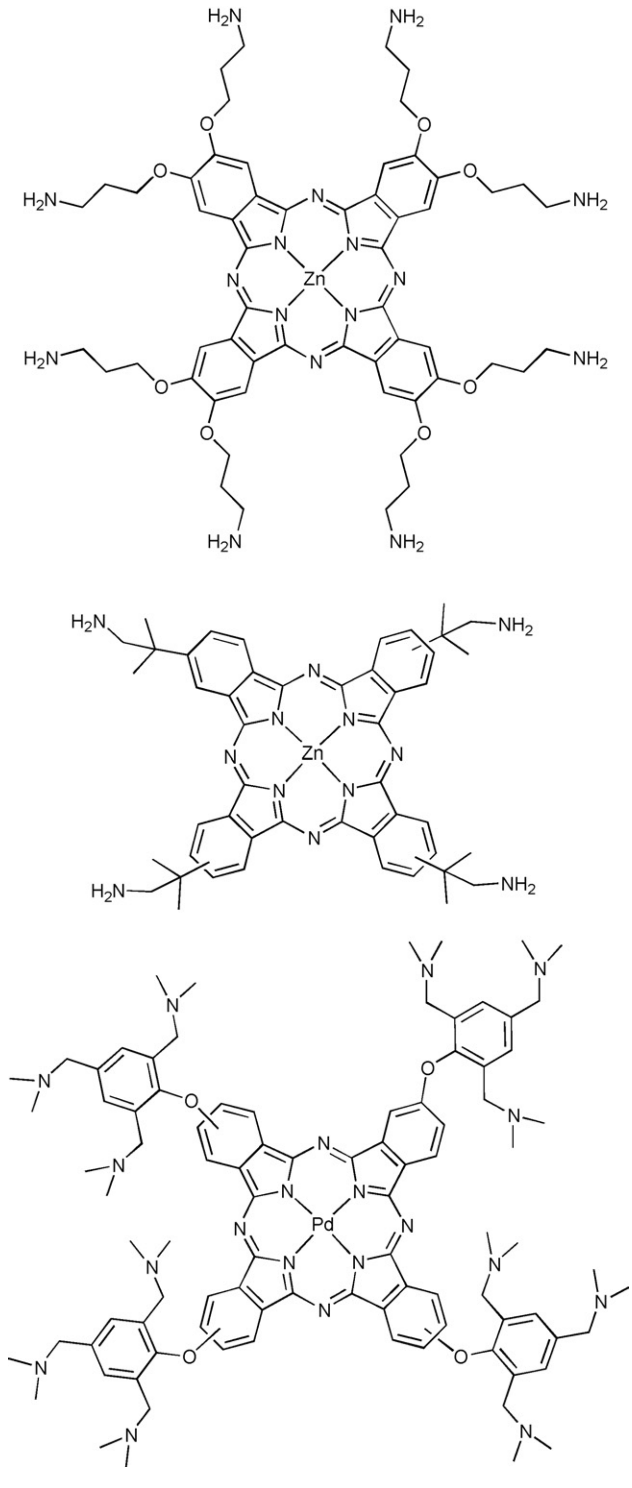

Fig. 33. Structure of amino substituted phthalocyanines [231–233,359].

Following this argument, the asymmetric Zn phthalocyanine **388** (Fig. 31) is not sufficiently substituted to be water-soluble [356].

Thanks to the bulkiness of the substituents inhibiting aggregation and despite the low number of hydroxyl groups, **389**, **390** and **391** (Fig. 32) are soluble in buffer [357].

5.3.2. *Thiols*

Thiol groups also have the ability to provide water-solubility, as shown by a recent work: phthalocyanine is partially water-soluble

[358]. This phthalocyanine was prepared in five steps from methyl 3-mercaptopropionate (**392**). Its acetylation into **393** is followed by the selective hydrolysis of the ester and the resulting alcohol **394** is condensed on 4-nitrophthalonitrile. The thioester **395** underwent a cyclotetramerisation and is subsequently unprotected leading to the phthalocyanine **396** (Scheme 84).

5.3.3. *Amines*

Amino functionalized phthalocyanines (Fig. 33) are also slightly water-soluble [231–233,359] and are likely to be more soluble in aqueous acidic medium.

6. Conclusion and outlook

Water-solubility is a required property for agents of several biological, medical or environmental related applications. The different ways to provide phthalocyanines with it have been reviewed here. This article, in addition to its exhaustive state of the art in terms of recent advances in phthalocyanine synthesis, is aimed at reflecting the outstanding potential of phthalocyanines, and particularly water-soluble ones, in finding some answers to worldwide health and environmental preoccupations.

Acknowledgements

The Scientific and Technological Research Council of Turkey (TUBITAK) and the Gebze Institute of Technology are gratefully acknowledged for their grants supporting our researches. This work was supported by the Department of Science and Technology (DST) and National Research Foundation (NRF), South Africa through DST/NRF South African Research Chairs Initiative for Professor of Medicinal Chemistry and Nanotechnology and Rhodes University.

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