Synthesis of Novel Functionalised Zinc Phthalocyanines Applicable in Photodynamic Therapy

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The synthesis of several new phthalonitriles **3**, **9**, **14**, **25**, **33**, and **36**, functionalised with carboxyl groups, including two examples of amino acid derivatives is described. All new phthalonitriles were converted into their corresponding phthalocyaninatozinc compounds. The phthalocyanines, 2,3,9,10,16,17,23,24-octa(1-carboxyethyloxy)phthalocyaninatozinc (**5**), 2,9,16,23-tetra(2-amino-2-carboxyethyl)phthalocyaninatozinc (**11**), 2,9,16,23-tetra(1-carboxy-2-hydroxyethylaminocarbonyl)phthalocyaninatozinc (**16**), 1,8,15,22-tetra(carboxybutyl)phthalocyaninatozinc (**27**), 2,3,9,10,16,17,23,24-octa(carboxyalkyl)phthalocyaninatozinc (**39**), and the nonidentically substituted 9,10,16,17,23,24-hexa(carboxyalkyl)-2-[4-(*N*-succinimidyloxycarbonyl)butyl]phthaloyaninatozinc (**41**) are all sufficiently soluble in water. The nonidentically-substituted compounds are important due to their selective binding to tumor-selective antibodies. UV/Vis-spectroscopy was used to investigate the effect of more or less sterically-demanding substituents in the periphery of the phthalocyanines towards aggregation. The phototoxicity towards cancer cells of some of the new compounds was investigated in several in-vitro experiments.

Recently, zinc phthalocyanines have found applications as sensitizers in the photodynamic therapy of cancer (PDT).[1−4] To increase the selectivity of these therapeuticals, some targeting models, including the use of tumor selective antibodies, have been developed.[5] The formation of selective antibody-sensitizer conjugates follows two different strategies: the coordinative coupling of a biotinylated antibody and also biotinylated sensitizers to avidin, which is able to bind four molecules of biotin,[6] and the covalent linkage between antibody and sensitizer.[7−9] Both targeting models require sensitizers, which are sufficiently soluble in water and which show only a weak tendency to form stacked aggregates.[10] Water solubility could be achieved by introducing carboxyl groups linked to the macrocyclic system with more or less branched alkyl or alkoxy chains as spacers. Due to a certain steric demand, these spacers enlarge the distance between two neighbouring macrocycles, which significantly lowers the tendency for aggregation. As isomeric mixtures show better photodynamic properties there is no need to prepare isomerically pure compounds.[11] In this paper we wish to report the synthesis of several new substituted zinc phthalocyanines, which fulfil the demands mentioned above.

Synthesis of 2,3,9,10,16,17,23,24-Octa(1-carboxyethyloxy)phthalocyaninatozinc (5)

Scheme 1 shows the synthetic route to octasubstituted zinc phthalocyanines. Starting from 4,5-dibromocatechol (**1**), the conversion into the diether **2** is obtained by treating **1** with ethyl 2-bromopropionate in DMF in the presence of sodium methoxide.[12] Subsequent substitution of the bromo groups by cyanide in a Rosenmund−von Braun reaction using cuprous cyanide,[13] affords the corresponding phthalonitrile **3** in 50% yield. As depicted in Scheme 1, the synthesis of the zinc phthalocyanine **5** is carried out in two steps. Heating the phthalonitrile **3** in *n*-pentanol with zinc(II) acetate and catalytic amounts of DBU leads to the phthalocyanine system **4** as a diastereomeric mixture. Under these conditions, a transesterification of the ester functions to the corresponding pentyl ester **4** is observed. After chromatographic purification, the ester phthalocyanine **4** is hydrolysed to the carboxylic acid **5**.

Compound **5** is highly soluble in polar organic solvents such as MeOH, DMF, or THF, and exhibits a good water solubility at pH ≥ 6. The branched substituents in **5** lead to an increased inter-ring distance between two neighbouring macrocycles, which significantly lowers their tendency to form stacked aggregates. This behaviour is indicated in the UV-spectrum of **5**, which exhibits a highly resolved Q-band, centered at 672 nm, assigned to the monomeric species. This absorption is accompanied by two transitions into excited vibration states at 639.5 and 610.5 nm, respectively.

Synthesis of Phthalocyaninatozinc Amino Acids 11 and 16

To increase the water solubility of the compounds, we decided to introduce amino acid moieties in the periphery of the Pc macrocycles. The synthetic route to the target compound **11** is shown in Scheme 2. Because of its substitution pattern, 3,4-dihydroxyphenylalanine (DOPA, **6**) is used as starting material. To avoid undesired side reactions

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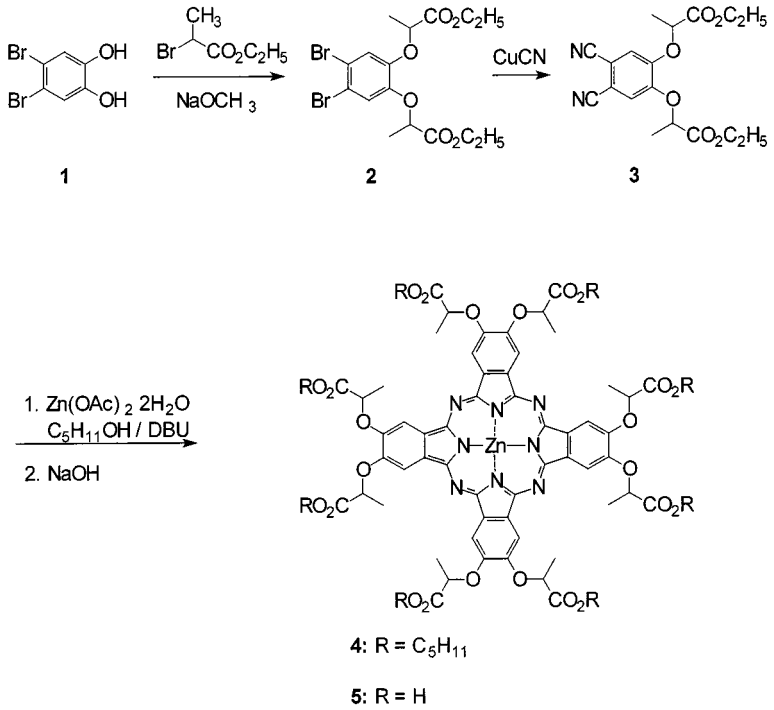
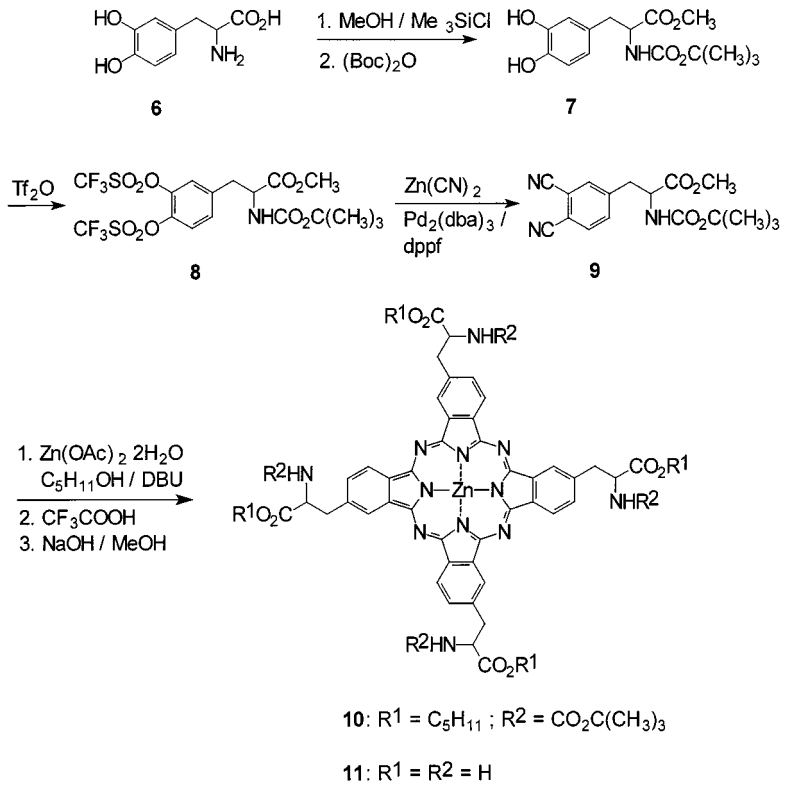


Scheme 1. Synthesis of phthalocyanine **5** starting from 4,5-dibromocatechol (**1**)

during further reaction steps it is necessary to protect the amino function as well as the carboxyl group. In a first reaction step, the carboxyl group in **6** is esterified in excess MeOH in the presence of trimethylsilyl chloride, giving the corresponding methyl ester.[14] Subsequent treatment of the amino group with di-*tert*-butyl dicarbonate leads to the base-stable *tert*-butyl carbamate **7**.[15] Compound **7** is converted into the corresponding bistriflate, **8**, by treating it with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane at −20°C.[16] The phthalonitrile derivative, **9**, is obtaind by palladium-catalysed substitution of the triflate groups by cyanide in DMF at 60°C, using $Zn(CN)_2$ as the cyanide source, tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] as the zerovalent metal species, and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) as a ligand in the catalyst system.[17] The protected zinc phthalocyanine, **10**, is obtained by heating the nitrile **9** in *n*-pentanol in the presence of zinc(II) acetate and a catalytic amount of DBU at 130°C. The Boc-protecting groups remain unchanged and the methyl ester groups are transesterified to the corresponding pentyl esters under these conditions. After chromatographic purification the amino groups are deprotected with trifluoroacetic acid, followed by subsequent cleavage of the pentyl esters through alkaline hydrolysis. The phthalocyanine tetraamino acid **11** is obtained as a mixture of diastereomeric and regioisomers in 75% yield. Compound **11** is slightly soluble in MeOH and DMF and exhibits excellent water solubility, as expected. The aggregation behaviour of tetraamino acid **11** in different solvents could be monitored by UV-spectra. In aqueous solution the most intensive absorption band is assigned to the aggregated species, whereas the Q-band of the monomeric Pc appears as a shoulder at 667 nm. Changing the solvent to MeOH leads to a reduction of the absorption of the aggregated species and a simultaneous increase of the monomer′s Q-band, which is also shifted to higher wavelengths compared to the aqueous solution. These effects are further promoted when the solvent is changed to DMF. These phenomena are readily explained by interactions between the solvent and the macrocycle′s π-system: the driving forces for the stacking are hydrophobic in character, which means that in aqueous solution no solvation of the phthalocyanine core could be expected. This effect is only partially compensated by the excellent solvation of the peripheral amino acid functions. Changing the solvent to MeOH or DMF increases the solvation of the phthalocyanine core, finally leading to a higher amount of monomers in solution. The improved interaction between solvent and π-system diminishes the distance between the macrocycle′s HOMO and LUMO, thereby producing a shift of the Q-band to higher wavelengths.

As depicted in Scheme 3, the synthetic route to the serine substituted system **16** starts from 3,4-dibromobenzoyl chloride (**12**), which is reacted with *O*-*t*Bu serine methyl ester to give the corresponding amide, **13**, in 87% yield. Subsequent treatment of **13** with cuprous cyanide in DMF affords the phthalonitrile, **14**, in 30% yield. Heating phthalonitrile **14** in the presence of $Zn(OAc)_2$ and catalytic amounts of DBU in *n*-pentanol leads to the protected phthalocyanine, **15**, in 17% yield as a diastereomeric and regioisomeric mixture. Cleavage of the protecting groups proceeds in two steps: liberation of the hydroxyl functions by treatment of **15** with trifluoroacetic acid, followed by alkaline hydrolysis affording the desired carboxylic acid **16** in 71% yield. Compound **16** is slightly soluble in acetone, highly soluble in MeOH,

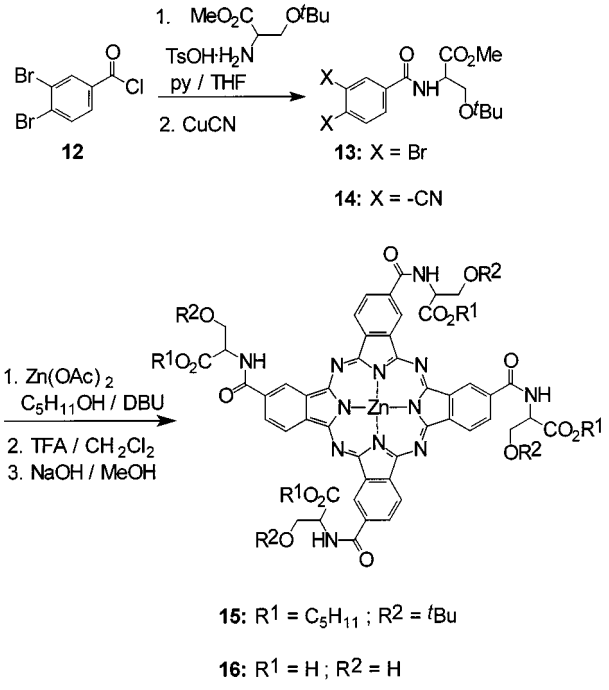


Scheme 2. Synthetic route to phthalocyaninato zinc amino acid **11**

and exhibits a good water solubility at a pH $\geq$ 8. The UV-spectrum of **16** shows the Q-band absorption of the monomeric species at 675 nm which is overlapped by the broad absorption of a small amount of aggregated macrocycles, centered at 634 nm.

Synthesis of 1,8,15,22-Tetra(4-carboxybutyl)-phthalocyaninatozinc (27)

Depending on the arrangement of two neighbouring isoindoline subunits, substituents in the 1-position could either be isolated, or arranged towards each other. Due to steric hindrance, the substituents ordered towards each other are pushed outside the plane of the macrocyclic system, which enlarges the inter-ring distance between two macrocycles. Because previously described synthetic methods are lenghty and low yielding,[18] we developed a more suitable synthetic route. Considering the strong electron-donating effect of phenolic hydroxyl groups, it is possible to metallate the 3-position of suitably protected catechol derivatives with *n*-butyllithium. The resulting phenyllithium derivative could finally be alkylated with alkyl halides.[19] Scheme 4 shows the synthetic pathway to the desired target compound, **27**. The cyclohexylidene ketal represents a sufficiently stable protecting group for the catechol function towards organolithium compounds. As shown in Scheme 4, the protected catechol, **19**, is readily metallated in 60% yield. The phenyllithium derivative prohibits the presence of a carbonyl function, hence the desired carboxyl function was masked as an *ortho* ester,[20] which is not attacked by strong nucleophiles. The *ortho* ester function in the resulting alkyl catechol, **20**, is further

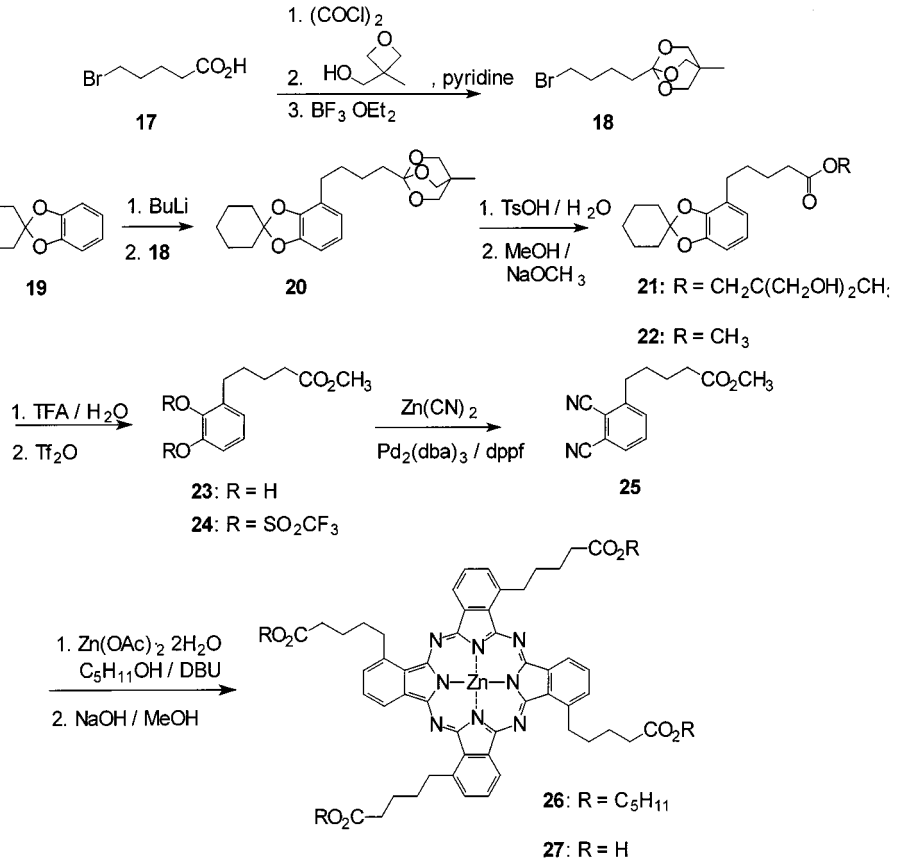


Scheme 3. Synthesis of phthalocyanine **16**

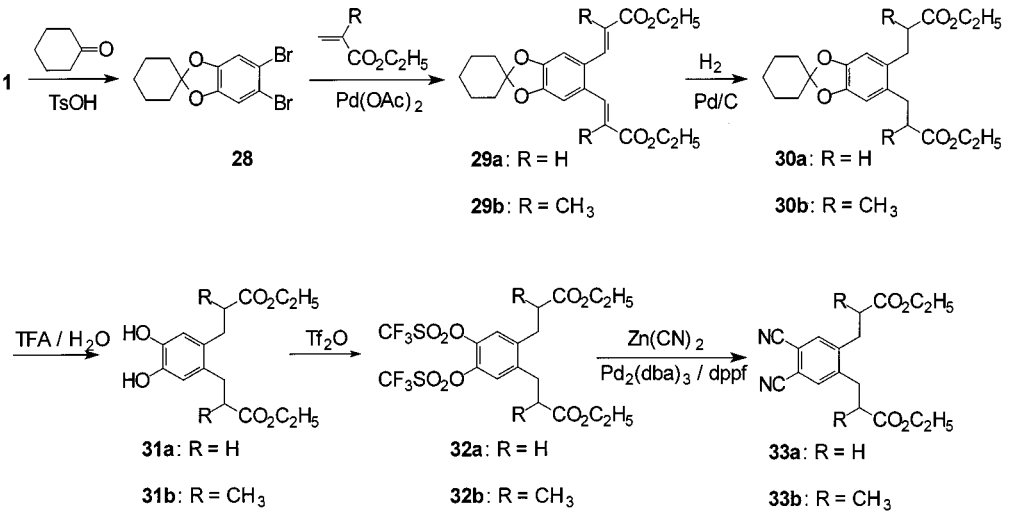
converted into the corresponding methyl ester in two steps; acid catalysed ring opening of the bicyclic system to the dihydroxy ester **21**, followed by subsequent reesterification in MeOH to give the methyl ester, **22**. During a further reaction step the ketal **22** is cleaved at room temperature using trifluoroacetic acid-water mixture (95:5). The free hydroxyl groups in **23** are first converted into the corresponding ditriflate, **24**, which is replaced by cyanide using $Zn(CN)_2$ and a palladium-dppf catalyst to give the phthalonitrile derivative, **25**, in high yields.[17] Treating phthalonitrile **25** with $Zn(OAc)_2$ in *n*-pentanol and catalytic amounts of DBU at 130°C furnishes, after chromatographic purification, the corresponding zinc phthalocyanine, **26**, as a mixture of four constitutional isomers,[21] which were not separated. Compound **26** is highly soluble in common organic solvents like hexane, chloroform, THF, or MeOH. Alkaline hydrolysis finally leads to the tetracarboxylic acid, **27**, which exhibits good water solubility. The UV-spectrum of **27** shows, as expected, a sharp Q-band at 678 nm, accompanied by transitions into excited vibration states, without any absorption of aggregated species.

Synthesis of Nonidentically-Substituted Phthalocyanines, 41

To enable a defined linkage of the phthalocyanine to the antibody, a suitable anchor group, e.g. a succinimidyl active ester, has to be introduced. In order to avoid undesired interactions between phthalocyanine and antibody,[22] this anchor group is coupled to the phthalocyanine core by an alkyl chain as spacer. These demands require nonidentically-substituted phthalocyanines carrying the anchor-spacer group as well as water solubility mediators. To prepare these nonidentically-substituted phthalocyanines, **38a** and **38b**, a suitable route is the statistical condensation of two different phthalonitriles in a specific ratio. The synthesis of the ester phthalonitriles, **33a** and **33b**, and the carboxyl phthalonitrile, **36**, are illustrated in Schemes 5 and 6, respectively. Starting from 4,5-dibromocatechol (**1**) the protection of the catechol function as cyclohexylidene ketal **28** is necessary to enable chromatographic purification in further reaction steps. The dibromo compound, **28**, is converted into the unsaturated esters **29a** or **29b** by treating it with ethyl acrylate or ethyl methacrylate, respectively, in a Heck reaction with $Pd(OAc)_2$ as catalyst.[23] Subsequent hydrogenation of the double bonds at atmospheric pressure using palladium on charcoal leads to the saturated esters **30a** and **30b**, respectively. Cleavage of the ketal, followed by triflate introduction, and finally, the substitution of the triflate groups by cyanide leads to the desired nitriles **33a** and **33b**, respectively. The phthalonitrile component carrying the carboxyl function is prepared starting from 4-iodophthalonitrile (**34**), which is alkenylated in a Heck reaction with benzyl pent-4-enoate to the corresponding benzyl ester, **35**. In a subsequent hydrogenation at atmospheric

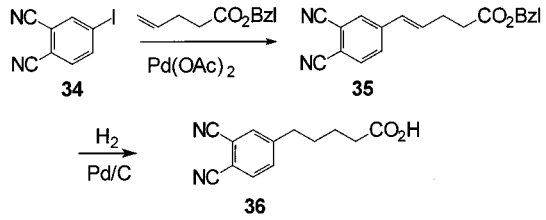


Scheme 4. Synthesis of **27** starting from the protected catechol **19**



Scheme 5. Synthesis of the phthalonitriles **33a** and **33b**

pressure using palladium on charcoal, hydrogenation of the double bond and hydrogenolysis of the benzyl group proceed simultaneously to give the phthalonitrile **36** in good yields.



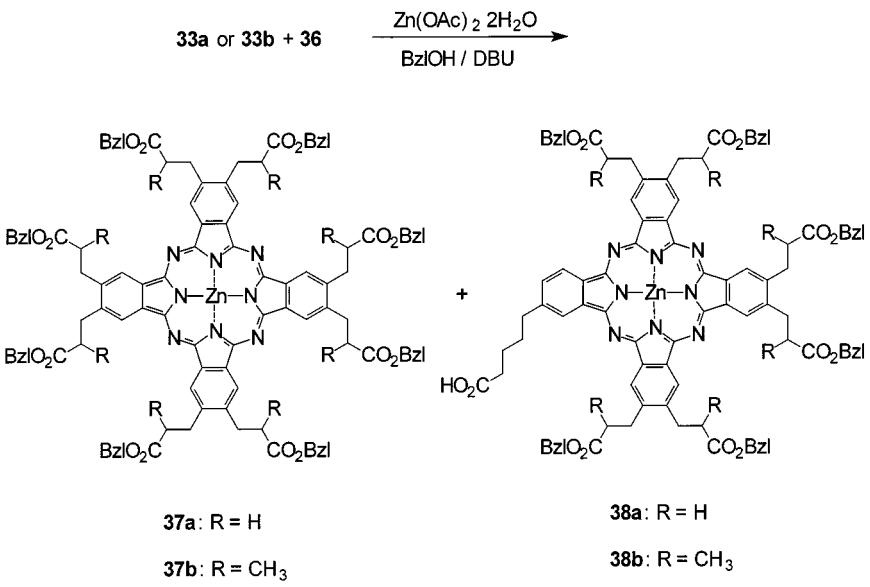
Scheme 6. Synthesis of **36**

As shown in Scheme 7, the statistical condensation[18][21] of the two different nitriles, **33a** or **33b** and **36**, in a molar ratio 6:1 is carried out in benzyl alcohol with $Zn(OAc)_2$ and catalytic amounts of DBU at 130°C. Benzyl alcohol was chosen as solvent to convert the ester functions into the corresponding benzyl esters. The desired reaction products, in our case the symmetric compounds **37a** or **37b**, and the monocarboxyl complexes **38a** or **38b**, have to be separated from the mixture using column chromatography with gradient elution. In the case of the linearly substituted phthalocyanines **37a** and **38a**, the use of $CHCl_3$/EtOAc yields the symmetric phthalocyanine **37a** as the first fraction. Changing the eluent to $CHCl_3$/THF elutes monocarboxyl compound **38a** as the second fraction. Separation of the branched systems **37b** and **38b** proceeds similarly; $CHCl_3$/EtOAc gives **37b** as the first fraction, and $CHCl_3$/EtOAc/AcOH yields **38b**, which has to be further purified in a second chromatographic step. As shown in Scheme 8, the symmetric octaesters **37a** and **37b** are hydrolysed in methanolic NaOH to the corresponding octacarboxylic acids **39a** and **39b**, respectively. The monocarboxyl phthalocyanines **38a** and **38b** are converted into the corresponding active esters **40a** and **40b**, respectively, with *N*-hydroxysuccinimide (NHS). Finally, catalytic hydrogenation at atmospheric pressure leads to the carboxylic acids **41a** and **41b**, respectively, with preservation of the active ester functions.

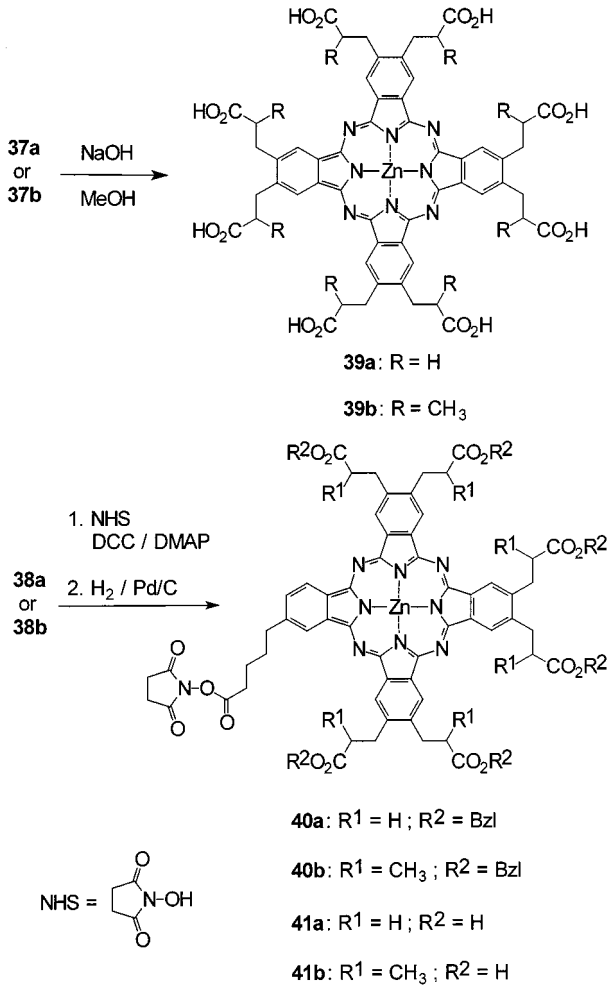
In-vitro Cytotoxicity Investigations

To investigate the phototoxicity towards cultivated T47d human mammary carcinoma cells we exemplarily chose the phthalocyanines **5**, **11**, **16**, and **27** as sensitisers. All experiments were run with an amount of $5{\cdot}10^4$ cells in phosphate buffered saline (PBS). The phthalocyanine sensitisers were dissolved in PBS containing 5% of DMSO, to give a concentration of 1 mg/mL, and were further dilluted to 10^{-1}, 10^{-2}, and 10^{-3} mg/mL. Addition of these solutions to the cell suspension finally lead to sensitiser concentrations of 0.5, $5{\cdot}10^{-2}$, $5{\cdot}10^{-3}$, and $5{\cdot}10^{-4}$ mg/mL, respectively. The cell survival rate was determined four hours after irradiation with a fluence of $5\ J{\cdot}cm^{-2}$. A laser tuned to the absorption maximum of the corresponding phthalocyanine (approx. 675 nm) was used as the light emitting source. A certain amount of cells was removed and, after lysing using a commercially available lysing solution, the content of ATP was measured by an ATP bioluminescence assay, which utilizes the ATP dependence of light emittance of the biooxidation of luciferine. The cell survival rate is determined by the ratio of ATP content after irradiation compared to the nonirradiated sample.

Figure 1 shows the results for compound **27** compared to the survival rates of the similarily treated, nonirradiated sample, and a negative control which was treated in the same way (cells + PBS + DMSO + irradiation) but *without* addition of sensitiser. Due to a significantly lower aggregation tendency, leading to higher singlet oxygen quantum yields at lower concentrations, a maximum effectiveness at $5{\cdot}10^{-2}$ mg/mL for compound **27** is observed. Further dilution leads to absolute amounts of sensitisers which are



Scheme 7. Statistical condensation of **33** and **36**



Scheme 8. Synthesis of the phthalocyanines **39**, **40** and **41**

too low to be effective. In Figure 2 the results for compound **27** are compared with those for compound **5**. It is obvious that compound **5** shows no phototoxicity over the entire concentration range, which is supposed to be the result of a diminished singlet oxygen yield caused by the substitution of the macrocycle by hetero atoms. Whereas the tetraamino acid **11** showed only a poor phototoxicity, the serine derivative **16** exhibits even a dark toxicity, which was concluded from the decrease of the cell amount under influence of compound **16** without any irradiation.

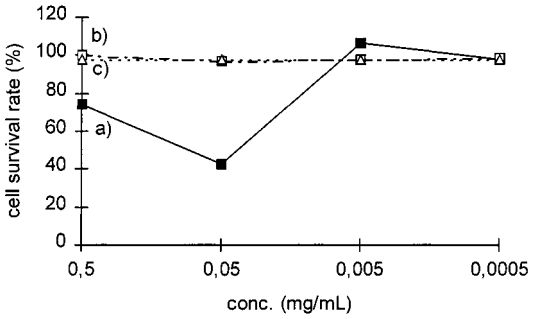


Figure 1. Cell survival rates at different sensitiser concentrations. a) Phthalocyanine **27**, irradiated; b) Phthalocyanine **27**, nonirradiated; c) Negative control, irradiation without sensitiser

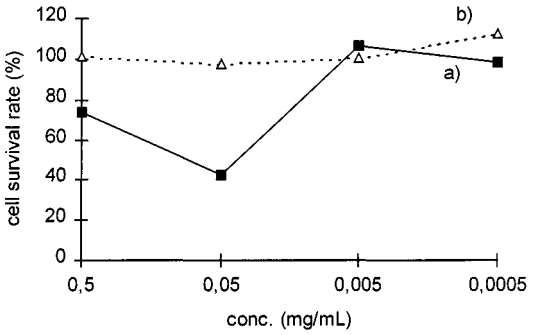


Figure 2. Comparison of different sensitisers. a) Phthalocyanine **27**; b) Phthalocyanine **5**

Conclusion

We have developed novel synthetic routes to several water-soluble zinc phthalocyanines, including carboxyl groups and, for the first time, amino acid functions in the periphery of the macrocycles. Due to a labelled anchor group, some of the new compounds could selectively be linked to tumor-selective antibodies. All new phthalocyanines exhibit only weak tendencies to form stacked aggregates in solution. These compounds should therefore be excellent sensitizers for singlet oxygen generation in the photodynamic therapy of cancer. In-vitro investigations to study the effectiveness of some of the new compounds towards cancer cells were performed. In particular, the weakly aggregated compound, **27**, showed a good phototoxicity, whereas others exhibit an acute toxicity towards the employed cells. Further investigations, involving tumor-selective antibodies are in progress.

Experimental Section

General: All melting points are uncorrected. − Commercially available starting compounds were directly used without further purification. All reactions were carried out under nitrogen atmosphere in degassed solvents, which were dried using conventional methods. The following precursors were prepared according to literature procedures: 4,5-dibromocatechol,[24] *N-tert*-butyloxycarbonyl-(3,4-dicyanophenyl)alanine methyl ester,[17] 1*O*,2*O*-cyclohexylidene catechol,[19] 4-iodophthalonitrile,[25] and 3-(hydroxymethyl)-3-methyloxetane.[26] The compounds **2**, **7**, **8**, **13**, **18**, **20**, **21**, **22**, **23**, **28**, **29**, **30**, **31**, and **35** were prepared as intermediates. It was not possible to obtain mass spectra of carboxylic acids **5**, **11**, **27**, **41a**, and **41b** with the available methods (EI, FD, FAB). Because of the incomplete combustion of these compounds no elemental analysis can be given. − FT-IR: Bruker IFS 48. − UV/Vis: Shimadzu UV-365. − MS: Varian Mat 711 (EI, FD, FAB). − ^{1}H-, ^{13}C NMR: Bruker ARX 250 (250 MHz and 62.9 MHz, for ^{1}H and ^{13}C, respectively). The deuterated solvent was used as internal standard. − Elemental Analyses: Carlo Erba Elemental Analyser 1104, 1106.

4,5-Bis[1-(ethyloxycarbonyl)ethyloxy]-1,2-dibromobenzene (2): To a suspension of sodium methoxide (2.3 g, 41.8 mmol) in DMF (20 mL) was added, dropwise, 4,5-dibromocatechol (5.6 g, 20.8 mmol) in DMF (20 mL) at 0°C. After stirring the mixture for 1 h at 0°C, ethyl 2-bromopropionate (5.4 mL, 41.8 mmol) was added. After the addition was complete, the mixture was stirred for 8−10 h at 120°C. The recooled mixture was poured into 150 mL of ice water and the product was extracted three times with 100 mL of ethyl acetate. The combined organic phases were dried with Na_2SO_4 and the solvent was removed by rotary evaporation. Column chromatography of the residue on silica gel using chloroform as eluent gave **2** (5.3 g, 54%) as a colourless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.08 Hz, 6 H, 2×$CO_2CH_2CH_3$), 1.55 (d, *J* = 6.88 Hz, 6 H, 2×CH_3), 4.14 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 4.72 (q, *J* = 6.88 Hz, 2 H, 2×OCH), 7.08 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 18.2 (CH_3), 61.2 ($CO_2CH_2CH_3$), 74.4 (OCH), 116.6 (aromatic *C*Br), 122.1 (aromatic *C*H), 147.8 (aromatic *C*OCH), 171.1 (*C*=O).

4,5-Bis[1-(ethyloxycarbonyl)ethyloxy]benzene-1,2-dicarbonitrile (3): Cu^ICN (3.6 g, 40.0 mmol) and **2** (5.3 g, 11.0 mmol) were dissolved in DMF (20 mL). The mixture was stirred at 130°C for 4−5 h. After cooling the mixture to room temp., a solution of $FeCl_3 \cdot 6\,H_2O$ (11.9 g, 40.0 mmol) and 1 mL of concd. HCl in 20 mL of water was added and the resulting mixture was heated to 70°C for 15 min. The reaction mixture was cooled to room temp. and poured into 200 mL of ice-water. The resulting mixture was extracted three times with chloroform and the combined organic phases were washed with 100 mL of dilute HCl, 100 mL of saturated aqueous $NaHCO_3$, and 100 mL of water and dried with Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography, on normal grade silica gel, using $CHCl_3$/ethyl acetate (5:1) as eluent to give **3** (2.0 g, 50.5%) as a colourless oil. − IR (film): $\tilde{\nu}$ = 2990 cm^{-1}, 2941, 2232, 1745, 1591, 1514, 1290, 1205, 1099. − ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.10 Hz, 6 H, 2×$CO_2CH_2CH_3$), 1.65 (d, *J* = 6.88 Hz, 6 H, 2×CH_3), 4.19 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 4.86 (q, *J* = 6.88 Hz, 2 H, 2×OCH), 7.12 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 18.2 (CH_3), 61.6 ($CO_2CH_2CH_3$), 74.3 (OCH), 109.7 (*C*CN), 115.3 (*C*N), 120.2 (aromatic *C*H), 151.4 (aromatic *C*OCH), 170.2 (*C*=O). − MS (EI) *m/z*: 360.2, [M$^+$] 287.1, 171.1. − $C_{18}H_{20}N_2O_6$ (360.4): calcd. C 59.99, H 5.59, N 7.77; found C 59.80, H 5.50, N 8.03.

***N*-(3,4-Dibromobenzoyl)-*O*-*tert*-butylserine Methyl Ester (13):** A solution of *O*-*tert*-butylserine methyl ester *p*-toluenesulfonyl salt (3.5 g, 10.1 mmol), 3,4-dibromobenzoyl chloride (**12**) (3.0 g, 10.1 mmol), and dry pyridine (1.63 mL) in THF (60 mL) was stirred under nitrogen at room temp. overnight. The resulting mixture was poured into 200 mL of ice water and the product was extracted three times with dichloromethane. The combined organic layers were washed with water, dried with $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using $CHCl_3$/ethyl acetate (2:1) as eluent to give **13** (3.8 g, 86.5%) as a yellowish oil. − IR (film): $\tilde{\nu}$ = 3319 cm^{-1}, 2974, 2878, 1749, 1657, 1585, 1533, 1456, 1364, 1348, 1234, 1096. − ^1H NMR ($CDCl_3$): δ = 1.07 [s, 9 H, C(C*H*$_3$)$_3$], 3.60 (m, 1 H, C*H*$_2$O*t*Bu), 3.70 (s, 3 H, CO_2CH_3), 3.81 (m, 1 H, C*H*$_2$O*t*Bu), 4.80 (m, 1 H, HNC*H*), 7.00 (d, *J* = 8.20 Hz, 1 H, N*H*), 7.45 (m, 1 H, aromatic H), 7.59 (d, *J* = 8.10 Hz, 1 H, aromatic H), 7.98 (d, *J* = 1.90 Hz, 1 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 27.1 [C(*C*H$_3$)$_3$], 52.3 (CO_2CH_3), 53.3 (HN*C*H), 61.7 (*C*H$_2$), 73.4 [*C*(CH$_3$)$_3$], 125.1 (*C*Br), 126.7 (aromatic *C*H), 128.5 (*C*Br), 132.4 (aromatic *C*H), 133.6 (aromatic *C*H), 134.4 (aromatic *C*C=O), 164.7 (Ar*C*ONH), 170.6 (*C*=O). − MS (EI) *m*/*z*: 438.0 [M^+ + 1], 262.9. − $C_{15}H_{19}Br_2NO_4$ (437.1): calcd. C 41.21, H 4.38, N 3.20; Br, 36.56; found C 40.94, H 4.35, N 3.31, Br 36.62.

***N*-(3,4-Dicyanobenzoyl)-*O*-*tert*-butylserine Methyl Ester (14):** The same procedure as for the preparation of **3** was used. Cu^ICN (3.4 g, 38.0 mmol), **13** (4.8 g, 10.9 mmol) and $FeCl_3 \cdot 6\,H_2O$ (14.9 g, 55.0 mmol) gave, after column chromatography on silica gel using $CHCl_3$/ethyl acetate (2:1), **14** (1.1 g, 30%) as a colourless powder. m.p. 108−109°C. − IR (KBr): $\tilde{\nu}$ = 3279 cm^{-1}, 2976, 2241, 1745, 1734, 1649, 1437, 872. − ^1H NMR ($CDCl_3$): δ = 1.12 [s, 9 H, C(C*H*$_3$)$_3$], 3.67 (m, 1 H, C*H*$_2$O*t*Bu), 3.76 (s, 3 H, CO_2CH_3), 3.89 (m, 1 H, C*H*$_2$O*t*Bu), 4.85 (m, 1 H, HNC*H*), 7.07 (d, *J* = 8.10 Hz, 1 H, N*H*), 7.90 (d, *J* = 8.10 Hz, 1 H, aromatic H), 8.12 (m, 1 H, aromatic H), 8.23 (d, *J* = 1.20 Hz, 1 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 27.0 [C(*C*H$_3$)$_3$], 52.4 (CO_2CH_3), 53.5 (HN*C*H), 61.4 (*C*H$_2$), 73.6 [*C*(CH$_3$)$_3$], 114.5 (*C*N), 114.6 (*C*N), 116.0 (*C*CN), 117.8 (*C*CN), 131.5 (aromatic *C*H), 132.4 (aromatic *C*H), 133.7 (aromatic *C*H), 138.3 (aromatic *C*C=O), 163.3 (Ar*C*ONH), 170.2 (*C*=O). − MS (EI) *m*/*z*: 330.1 [M^+], 299.0, 155.0, 127.0. − $C_{17}H_{19}N_3O_4$(329.4): calcd. C 62.00, H 5.81, N 12.76; found C 61.11, H 5.76, N 12.58.

1-(4-Bromobutyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (18): To a solution of **17** (13.5 g, 75.0 mmol) in dichloromethane (30 mL) was added, dropwise, oxalyl chloride (8.6 mL, 100.0 mmol) at 0°C. The resulting solution was stirred overnight at room temp. and all volatile components were removed on a rotary evaporator. The residue was redissolved in 15 mL of dichloromethane and added dropwise at 0°C to a solution of 3-(hydroxymethyl)-3-methyloxetane (7.6 g, 75.0 mmol) and dry pyridine (6.0 mL, 75.0 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temp. for 4−6 h, evaporated, and the residue was filtered over a short pad of silica gel pretreated with 10% triethylamine in dichloromethane. Evaporation to dryness gave a colourless oil, which was directly converted without further characterisation. To a solution of the obtained oil in 50 mL of dichloromethane was added, dropwise, at −15°C, freshly distilled borontrifluoride diethyl ether (2.5 mL, 20.0 mmol). After stirring for 8 h at −15°C, triethylamine (10 mL) was added and the resulting solution was poured into 150 mL of diethyl ether to precipitate the resulting borontrifluoride triethylamine complex. The filtrate was eluted over a short pad of silica gel, which had been pretreated with 10% triethylamine in dichloromethane. Evaporation of the solvent gave **18** (14.9 g, 81.5%) as a yellowish oil. − ^1H NMR ($CDCl_3$): δ = 0.70 (s, 3 H, C*H*$_3$), 1.54 (m, 4 H, 2×C*H*$_2$), 1.76 (m, 2 H, C*H*$_2$), 3.29 (t, *J* = 6.70 Hz, 2 H, BrC*H*$_2$), 3.78 (s, 6 H, 3×OC*H*$_2$). − ^{13}C NMR ($CDCl_3$): δ = 14.3 (*C*H$_3$), 21.8 (*C*H$_2$), 30.0 [(OCH$_2$)$_3$*C*CH$_3$], 32.3 (*C*H$_2$), 33.4 (*C*H$_2$), 35.4 (Br*C*H$_2$), 72.3 (O*C*H$_2$), 108.5 [CH$_2$*C*(OCH$_2$)$_3$].

1,2-Di-*O*-Cyclohexylidene-3-[4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-oct-1-yl)butyl]catechol (20): To a solution of **19** (6.6 g, 35.0 mmol) in THF (40 mL) and diethyl ether (20 mL) was added, dropwise, 1.6 M butyllithium in hexane (24.0 mL, 38.0 mmol) at −10°C. After complete addition the mixture was stirred for 1 h at 0°C, and for further 8 h at room temp. The mixture was recooled to −15°C and **18** (7.4 g, 28.0 mmol) in THF (10 mL) was added dropwise. The mixture was stirred overnight at 0°C and 2−3 h at room temp., poured into 100 mL of ice water and extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and all volatile products were removed on a rotary evaporator. The residue was purified by chromatography on silica gel with hexane/ethyl acetate (9:1) as eluent, to give **20** (6.3 g, 60%) as a yellowish oil, which was used directly without further characterisation.

1,2-Di-*O*-Cyclohexylidene-3-{4-[2,2-bis(hydroxymethyl)propyl-oxycarbonyl]butyl}catechol (21): To a solution of crude **20** (6.3 g, 16.8 mmol) in THF (50 mL) was added at, 0°C, a solution of $TsOH \cdot H_2O$ (650 mg, 3.4 mmol) in water (5 mL). After slow warming to room temp., the mixture was stirred for 3 h, poured into 150 mL of water and extracted three times with diethyl ether. The combined organic phases were washed with saturated $NaHCO_3$ and water, dried with Na_2SO_4, and the solvent was evaporated. The residue was purified chromatographically on silica gel with chloroform/ethyl acetate (2:1) to give **21** (5.4 g, 80.5%) as a yellowish oil. − ^1H NMR ($CDCl_3$): δ = 0.80 (s, 3 H, C*H*$_3$), 1.46 (m, 2 H, C*H*$_2$ cyclohexyl), 1.65 (m, 8 H, 4×C*H*$_2$), 1.84 (m, 4 H, 2×C*H*$_2$ cyclohexyl), 2.36 (t, *J* = 7.08 Hz, 2 H, C*H*$_2$CO$_2$CH$_2$), 2.55 (t, *J* = 7.10 Hz, 2 H, ArC*H*$_2$), 2.98 (s, 2 H, 2×O*H*), 3.48 (s, 4 H, 2×C*H*$_2$OH), 4.11 (s, 2 H, CH$_2$CO$_2$C*H*$_2$), 6.60 (m, 3 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 16.7 (*C*H$_3$), 23.1 (*C*H$_2$), 24.4 (*C*H$_2$), 24.5 (*C*H$_2$ cyclohexyl), 28.7 (*C*H$_2$), 28.8 (*C*H$_2$ cyclohexyl), 34.0 (Ar*C*H$_2$), 35.1 (*C*H$_2$ cyclohexyl), 40.6 [CH$_2$*C*(CH$_2$OH)$_2$CH$_3$], 66.3 (*C*H$_2$OH), 67.2 (CH$_2$CO$_2$*C*H$_2$), 106.2 [(O)$_2$*C*(CH$_2$)$_2$], 117.7 (aromatic C), 120.5 (aromatic C), 121.6 (aromatic C), 122.9 (aromatic *C*CH$_2$), 145.4 (aromatic C), 146.8 (aromatic C), 174.5 (*C*=O). − MS (EI) *m*/*z*: 392.1 .[M^+] − $C_{22}H_{32}O_6$ (392.5): calcd. C 67.32, H 8.22; found C 67.50, H, 8.23.

1,2-Di-*O*-Cyclohexylidene-3-[4-(methyloxycarbonyl)butyl]catechol (22): A solution of **21** (5.4 g, 13.7 mmol) and sodium methoxide (54 mg, 1.0 mmol) in MeOH (20 mL) was stirred at room temp. for 8 h. The solvent was removed in vacuo, and the residue was eluted with chloroform over a short pad of silica gel to give **22** (3.8 g, 91%) as a yellowish oil. − ^1H NMR ($CDCl_3$): δ = 1.48 (m, 2 H, C*H*$_2$ cyclohexyl), 1.65 (m, 8 H, C*H*$_2$), 1.87 (m, 4 H, 2×C*H*$_2$ cyclohexyl), 2.32 (t, *J* = 7.08 Hz, 2 H, C*H*$_2$CO$_2$CH$_3$), 2.53 (t, *J* = 7.10 Hz, 2 H, ArC*H*$_2$), 3.63 (s, 3 H, CO_2CH_3), 6.60 (m, 3 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 23.0 (*C*H$_2$), 24.4 (*C*H$_2$), 24.5 (*C*H$_2$ cyclohexyl), 28.8 (*C*H$_2$), 28.9 (*C*H$_2$ cyclohexyl), 33.7 (Ar*C*H$_2$), 35.0 (*C*H$_2$ cyclohexyl), 51.2 (CO_2CH_3), 106.0 [(CH$_2$)$_2$*C*(O)$_2$ cyclohexyl], 117.5 (aromatic *C*H), 120.4 (aromatic *C*H), 121.5 (aromatic *C*H), 122.9 (aromatic *C*CH$_2$), 145.3 (aromatic C), 146.7 (aromatic C), 173.8 (*C*=O). − MS (EI) *m*/*z*: 304.1 [M^+]. − $C_{18}H_{24}O_4$(304.4): C 71.03, H 7.95; found C 71.11, H 7.69.

3-[4-(Methyloxycarbonyl)butyl]catechol (23): Compound **22** (3.8 g, 12.5 mmol) was dissolved in trifluoroacetic acid (19 mL) and water (1 mL). The solution was stirred at room temp. for 1 h, poured into 150 mL of ice water and the product was extracted three times with

diethyl ether. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and water, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dried in vacuo to give **23** (1.6 g, 57%) as light brown oil. − ^{1}H NMR ([D$_4$]methanol): δ = 1.60 (m, 4 H, CH_2), 2.31 (t, J = 7.10 Hz, 2 H, CH_2CO$_2$CH$_3$), 2.58 (t, J = 7.20 Hz, 2 H, ArCH_2), 3.61 (s, 3 H, CO$_2$CH_3), 4.79 (s, 2 H, 2×OH), 6.59 (m, 3 H, aromatic H). − ^{13}C NMR ([D$_4$]methanol): δ = 24.4 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$CO$_2$CH$_3$), 33.4 (Ar*C*H$_2$), 50.7 (CH$_2$CO$_2$*C*H$_3$), 112.5 (aromatic *C*H), 118.9 (aromatic *C*H), 120.6 (aromatic *C*H), 128.7 (aromatic *C*CH$_2$), 142.9 (aromatic *C*OH), 144.5 (aromatic *C*OH), 174.8 (*C*=O).

1,2-Di-*O*-Bis(trifluoromethanesulfonyl)-3-[4-(methyloxycarbonyl)-butyl]catechol (24). − General Procedure: To a solution of trifluoromethanesulfonic anhydride (3.0 mL, 17.8 mmol) in dichloromethane (5 mL) were added **23** (1.6 g, 7.1 mmol) and triethylamine (2.5 mL, 17.8 mmol) in dichloromethane (10 mL) at −20°C over a 1 h period. After slow warming to room temp. and stirring overnight, the mixture was poured into 100 mL of ice-cold water. The product was extracted three times with dichloromethane, the combined organic phases were washed with water, dried with $MgSO_4$, and evaporated to dryness by rotary evaporation. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent to give **24** in 89% yield as yellowish oil. − IR (film): $\tilde{\nu}$ = 2955 cm^{-1}, 1740, 1431, 1225, 1138. − ^{1}H NMR (CDCl$_3$): δ = 1.65 (m, 4 H, 2×CH_2), 2.30 (t, J = 6.88 Hz, 2 H, CH_2CO$_2$CH$_3$), 2.76 (t, J = 7.38 Hz, 2 H, ArCH_2), 3.60 (s, 3 H, CO$_2$CH_3), 7.30 (m, 3 H, aromatic H). − ^{13}C NMR (CDCl$_3$): δ = 24.3 (*C*H$_2$), 28.9 (*C*H$_2$), 29.8 (*C*H$_2$CO$_2$CH$_3$), 33.3 (Ar*C*H$_2$), 51.3 (CO$_2$*C*H$_3$), 118.4 (q, J_{CF} = 314.5 Hz, *C*F$_3$), 120.7 (aromatic *C*H), 129.1 (aromatic *C*H), 130.3 (aromatic *C*H), 138.1 (aromatic *C*CH$_2$), 138.8 (aromatic *C*OTf), 141.0 (aromatic *C*OTf), 173.5 (*C*=O). − MS (EI) *m*/*z*: 489.0 [M$^+$ + 1]. − C$_{14}$H$_{14}$F$_6$S$_2$O$_8$(488.4): calcd. C 34.43, H 2.89, F 23.34, S 13.13; found C 34.66, H 2.82, F 24.04, S 13.11.

3-(4-Methyloxycarbonyl)butyl-1,2-benzenedicarbonitrile (25). − General Procedure: To a solution of tris(dibenzylideneacetone)dipalladium-chloroform adduct (260 mg, 0.25 mmol) and 1,1′-bis(diphenylphosphanyl)ferrocene (560 mg, 1.0 mmol) in DMF (15 mL) was added **24** (3.0 g, 6.2 mmol) at room temp. The resulting solution was warmed to 90°C and $Zn(CN)_2$ (870 mg, 7.4 mmol) was added in small portions over a 3 h period. After complete addition, the mixture was stirred further for 3 h at 90°C. After cooling to room temp., the solution was poured into 150 mL of ice water and the product was extracted three times with dichloromethane. The combined organic layers were washed with 0.1 N HCl, water, saturated aqueous $NaHCO_3$, and water again, dried with $MgSO_4$, and finally evaporated to dryness. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent to give **25** (1.2 g, 81%) as colourless needles. − m.p. 55°C. − IR (KBr): $\tilde{\nu}$ = 2951 cm^{-1}, 2868, 2233, 1734, 1587, 1464, 1437, 1198. − ^{1}H NMR (CDCl$_3$): δ = 1.68 (m, 4 H, 2×CH_2), 2.34 (t, J = 6.88 Hz, 2 H, CH_2CO$_2$CH$_3$), 2.89 (t, J = 7.20 Hz, 2 H, ArCH_2), 3.64 (s, 3 H, CO$_2$CH_3), 7.60 (m, 3 H, aromatic H). − ^{13}C NMR (CDCl$_3$): δ = 24.3 (*C*H$_2$), 29.9 (*C*H$_2$), 33.5 (*C*H$_2$CO$_2$CH$_3$), 34.4 (Ar*C*H$_2$), 51.6 (CO$_2$*C*H$_3$), 114.6 (aromatic *C*CN), 115.7 (*C*N), 116.4 (aromatic *C*CN), 131.2 (aromatic *C*H), 132.9 (aromatic *C*H), 133.7 (aromatic *C*H), 148.2 (aromatic *C*CH$_2$), 173.6 (*C*=O). − C$_{14}$H$_{14}$N$_2$O$_2$(242.3): calcd. C 69.41, H 5.82, N 11.56; found C 69.73, H 5.69, N 11.67.

4,5-Dibromo-1,2-di-*O*-cyclohexylidenecatechol (28): A solution of **1** (23.6 g, 100 mmol), cyclohexanone (9.8 g, 100 mmol) and TsOH · H$_2$O (1.0 g, 5.2 mmol) in toluene (300 mL) was heated under reflux overnight with azeotropic removal of the developed water. After cooling to room temp., the solution was washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of water, dried with Na_2SO_4, and the solvent was removed under vacuo. The residue was recrystallised from EtOH/water (10:1) to give **28** (26.1 g, 75%) as yellowish powder. m.p. 127−129°C. − ^{1}H NMR (CDCl$_3$): δ = 1.46 (m, 2 H, CH_2), 1.67 (m, 4 H, 2×CH_2), 1.86 (m, 4 H, 2×CH_2), 6.94 (s, 2 H, aromatic H).

4,5-Bis[2-(ethyloxycarbonyl)ethenyl]-1,2-di-*O*-cyclohexylidenecatechol (29a). − General Procedure: A mixture of **28** (6.0 g, 17.0 mmol), K_2CO_3 (9.7 g, 70.0 mmol), tetrabutylammonium bromide (8.0 g, 25.0 mmol), $Pd(OAc)_2$ (225 mg, 1.0 mmol), and ethyl acrylate (7.5 mL, 70.0 mmol) in DMF (30 mL) was heated to 90°C. The mixture was stirred at this temperature until TLC-monitoring indicated the complete conversion of **28** (5−6 h). After cooling to room temp., the mixture was poured into 150 mL of dichloromethane and filtered over a short pad of silica gel. The filtrate was washed with 0.1 N HCl, water, saturated aqueous $NaHCO_3$, and water again, dried with $MgSO_4$, and evaporated to dryness. The residue was purified by chromatography on silica gel using chloroform as eluent, to give **29a** (5.9 g, 90%) as a yellowish oil. − IR (film): $\tilde{\nu}$ = 2939 cm^{-1}, 1717, 1630, 1609, 1491, 1167. − ^{1}H NMR (CDCl$_3$): δ = 1.31 (t, J = 7.05 Hz, 6 H, 2× CO$_2$CH$_2$CH_3), 1.48 (m, 2 H, CH_2), 1.71 (m, 4 H, 2×CH_2), 1.88 (m, 4 H, 2×CH_2), 4.23 (q, J = 7.03 Hz, 4 H, 2×CO$_2$CH_2CH$_3$), 6.18 (d, J = 15.6 Hz, 2 H, 2×ArCHCH), 6.92 (s, 2 H, aromatic H), 7.98 (d, J = 15.6 Hz, 2 H, 2×ArCH). − ^{13}C NMR (CDCl$_3$): δ = 14.3 (CO$_2$CH$_2$*C*H$_3$), 23.1 (*C*H$_2$), 24.3 (*C*H$_2$), 35.2 (*C*H$_2$), 60.5 (CO$_2$*C*H$_2$CH$_3$), 106.1 [(O)$_2$*C*(CH$_2$)$_2$], 119.4 (aromatic *C*H), 120.6 (ArCH*C*H), 128.8 (aromatic *C*CH), 140.5 (aromatic C), 149.7 (Ar*C*H), 166.6 (*C*=O). − MS (EI) *m*/*z*: 386.2 [M$^+$]. − C$_{22}$H$_{26}$O$_6$ (386.4): calcd. C 68.38, H 6.78; found C 68.21, H 6.83.

4,5-Bis[2-(ethyloxycarbonyl)ethyl]-1,2-di-*O*-cyclohexylidenecatechol (30a). − General Procedure: Compound **24a** (5.9 g, 15.3 mmol) was dissolved in EtOH (100 mL) and, after addition of 10% palladium on charcoal (200 mg), hydrogenated in a hydrogenation apparatus at atmospheric pressure for 2 days. After complete reaction, the catalyst was filtered off, the filtrate was evaporated, and the residue was crystallised in the refrigerator. The title compound **30a** (5.6 g, 94%) was obtained as a yellowish powder. m.p. 69−71°C. − IR (KBr): $\tilde{\nu}$ = 2947 cm^{-1}, 1730, 1499, 1367, 1285, 1248, 1177, 1094. − ^{1}H NMR (CDCl$_3$): δ = 1.22 (t, J = 7.08 Hz, 6 H, 2×CO$_2$CH$_2$CH_3), 1.45 (m, 2 H, CH_2), 1.68 (m, 4 H, 2×CH_2), 1.84 (m, 4 H, 2×CH_2), 2.50 (t, J = 7.80 Hz, 4 H, 2×ArCH$_2$CH_2), 2.82 (t, J = 7.90 Hz, 4 H, 2×ArCH_2), 4.11 (q, J = 7.10 Hz, 4 H, 2×CO$_2$CH_2CH$_3$), 6.52 (s, 2 H, aromatic H). − ^{13}C NMR (CDCl$_3$): δ = 14.2 (CO$_2$CH$_2$*C*H$_3$), 23.1 (*C*H$_2$), 24.5 (*C*H$_2$), 27.5 (ArCH$_2$*C*H$_2$), 35.1 (*C*H$_2$), 35.7 (Ar*C*H$_2$), 60.4 (CO$_2$*C*H$_2$CH$_3$), 108.8 [(O)$_2$*C*(CH$_2$)$_2$], 118.4 (aromatic C), 130.5 (aromatic *C*H), 146.0 (aromatic *C*CH$_2$), 172.8 (*C*=O). − MS (EI) *m*/*z*: 390.2 [M$^+$]. − C$_{22}$H$_{30}$O$_6$ (390.4): C 67.67, H 7.74; found C 68.17, H 8.16.

4,5-Bis[2-(ethyloxycarbonyl)ethyl]catechol (31a): The same procedure as for the preparation of **23** was used. Reaction of **30a** (5.6 g, 14.4 mmol), TFA (19 mL), and 1 mL of water gave **31a** (3.0 g, 78%) as light brown solid. m.p. 125−127°C. − ^{1}H NMR ([D$_4$]methanol): δ = 1.21 (t, J = 7.08 Hz, 6 H, 2×CO$_2$CH$_2$CH_3), 2.51 (t, J = 7.95 Hz, 4 H, 2×CH_2CO$_2$Et), 2.79 (t, J = 7.95 Hz, 4 H, 2×ArCH_2), 4.09 (q, J = 7.10 Hz, 4 H, 2×CO$_2$CH_2CH$_3$), 4.86 (s, 2 H, 2×ArOH), 6.57 (s, 2 H, aromatic H). − ^{13}C NMR ([D$_4$]methanol): δ = 14.5 (CO$_2$CH$_2$*C*H$_3$), 28.1 (*C*H$_2$CO$_2$Et), 36.8 (Ar*C*H$_2$CH$_2$), 61.5 (CO$_2$*C*H$_2$CH$_3$), 117.1 (aromatic *C*H), 130.7 (aromatic *C*OH), 144.7 (aromatic *C*CH$_2$), 174.8 (*C*=O). − MS (EI)

m/z: 310.2 [M$^+$]. − $C_{16}H_{22}O_6$ (310.3): calcd. C 61.92, H 7.15; found C 62.11, H 7.22.

4,5-Bis[2-(ethyloxycarbonyl)ethyl]-1,2-bis(trifluoromethanesulfonyloxy)benzene (32a): The same procedure as for the preparation of **24** was used. Reaction of **31a** (3.0 g, 10.0 mmol), Tf_2O (3.9 mL, 23.0 mmol), and triethylamine (3.2 mL, 23.0 mmol) gave, after chromatographic purification on silica gel using hexane/ethyl acetate (2:1) as eluent, **32a** (4.3 g, 75%) as a light-brown oil. − IR (film): $\tilde{\nu}$ = 2986 cm^{-1}, 1734, 1501, 1433, 1244, 1140, 1040. − ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, *J* = 7.10 Hz, 6 H, 2×$CO_2CH_2CH_3$), 2.79 (t, *J* = 7.95 Hz, 4 H, 2×CH_2CO_2Et), 3.18 (t, *J* = 7.95 Hz, 4 H, 2×ArCH_2), 4.28 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 7.44 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 26.9 (CH_2CO_2Et), 34.2 (ArCH_2), 60.8 ($CO_2CH_2CH_3$), 118.5 (q, J_{CF} = 320.7 Hz, CF_3), 123.7 (aromatic *C*H), 138.5 (aromatic CSO_3CF_3), 141.1 (aromatic *C*CH_2), 171.8 (*C*=O). − MS (EI) *m/z*: 574.1 [M$^+$]. − $C_{18}H_{20}F_6S_2O_{10}$ (574.5): calcd. C 37.63, H 3.51, F 19.84, S 11.16; found C 38.32, H 3.55, F 19.92, S 11.09.

4,5-Bis[2-(ethyloxycarbonyl)ethyl]-1,2-benzenedicarbonitrile (33a): The same procedure as for the preparation of **25** was used. Reaction of **32a** (4.7 g, 8.2 mmol), $Pd_2(dba)_3$ (340 mg, 0.3 mmol), dppf (730 mg, 1.3 mmol), and $Zn(CN)_2$ (1.15 g, 9.8 mmol) gave, after chromatographic purification on silica gel with hexane/ethyl acetate (2:1), the nitrile **33a** (2.0 g, 74%) as a white powder. m.p. 76°C. − IR (KBr): $\tilde{\nu}$ = 2986 cm^{-1}, 2239, 1730, 1288, 1205. − ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.10 Hz, 6 H, 2×$CO_2CH_2CH_3$), 2.63 (t, *J* = 7.53 Hz, 4 H, 2×CH_2CO_2Et), 3.04 (t, *J* = 7.50 Hz, 4 H, 2×ArCH_2CH_2), 4.11 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 7.59 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 27.1 (CH_2CO_2Et), 33.7 (ArCH_2), 60.9 ($CO_2CH_2CH_3$), 113.6 (aromatic *C*CN), 115.3 (Ar*C*N), 133.8 (aromatic *C*H), 145.3 (aromatic *C*CH_2), 171.5 (*C*=O). − MS (EI) *m/z*: 328.0 [M$^+$]. − $C_{18}H_{20}N_2O_4$ (328.4): calcd. C 65.84, H 6.14, N 8.53; found C 65.65, H 6.10, N 8.36.

4,5-Bis[2-(ethyloxycarbonyl)prop-1-enyl]-1,2-di-*O*-cyclohexylidenecatechol (29b): The same procedure as for the preparation of **29a** was used. Reaction of **28** (7.0 g, 20.1 mmol), ethyl methacrylate (10.3 mL, 83.0 mmol), K_2CO_3 (11.5 g, 83.0 mmol), Bu_4NBr (9.4 g, 30.0 mmol), and $Pd(OAc)_2$ (265 mg, 1.2 mmol) gave, after flash chromatography on silica gel using chloroform as eluent, **29b** (6.7 g, 81%) as yellowish oil. − IR (film): $\tilde{\nu}$ = 2941 cm^{-1}, 1711, 1634, 1491, 1366, 1263, 1111. − MS (EI) *m/z*: 414.1 [M$^+$].

4,5-Bis[2-(ethyloxycarbonyl)propyl]-1,2-di-*O*-cyclohexylidenecatechol (30b): The same procedure as for the preparation of **30a** was used. Yield 95% (6.0 g) as a colourless oil. − IR (film): $\tilde{\nu}$ = 2976 cm^{-1}, 2939, 1732, 1497, 1366, 1283, 1165, 1096. − ^{1}H NMR ($CDCl_3$): δ = 1.16 (m, 12 H, 2×$CO_2CH_2CH_3$, 2×$CHCH_3$), 1.44 (m, 2 H, CH_2 cyclohexyl), 1.67 (m, 4 H, 2×CH_2 cyclohexyl), 1.81 (m, 4 H, 2×CH_2 cyclohexyl), 2.55 (m, 4 H, 2×ArCH_2), 2.89 (m, 2 H, 2×C*H*), 4.05 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 6.48 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 16.8 ($CHCH_3$), 23.1 (*C*H$_2$ cyclohexyl), 24.5 (*C*H$_2$ cyclohexyl), 35.1 (*C*H$_2$ cyclohexyl), 36.2 (Ar*C*H$_2$), 41.2 (*C*H), 60.2 ($CO_2CH_2CH_3$), 109.6 [$(O)_2C(CH_2)_2$], 118.3 (aromatic *C*H), 129.9 (aromatic *C*CH_2), 145.8 (aromatic C), 176.2 (*C*=O). − MS (EI) *m/z*: 418.1 [M$^+$]. − $C_{24}H_{34}O_6$ (418.5): calcd. C 68.88, H 8.19; found C 68.04, H, 8.06.

4,5-Bis[2-(ethyloxycarbonyl)propyl]catechol (31b): Same procedure as for the preparation of **31a**. Yield 97% (2.0 g) as a light brown oil. − IR (film): $\tilde{\nu}$ = 3404 cm^{-1}, 2980, 2937, 1728, 1709, 1607, 1522, 1454, 1290, 1180. − ^{1}H NMR ([D$_4$]methanol): δ = 1.13 (m, 12 H, 2×$CO_2CH_2CH_3$, 2×$CHCH_3$), 2.61 (m, 4 H, 2×ArCH_2), 2.78 (m, 2 H, 2×C*H*), 4.03 (q, *J* = 7.10 Hz, 4 H, 2×$CO_2CH_2CH_3$), 4.79 (s, 2 H, 2×ArO*H*), 6.54 (s, 2 H, aromatic H). − ^{13}C NMR ([D$_4$]methanol): δ = 14.4 ($CO_2CH_2CH_3$), 17.4 ($CHCH_3$), 36.9 (ArCH_2), 42.6 (*C*H), 61.4 ($CO_2CH_2CH_3$), 117.9 (aromatic *C*H), 129.9 (aromatic *C*OH), 144.5 (aromatic *C*CH_2), 178.0 (*C*=O). − MS (EI) *m/z*: 338.1 [M$^+$].

4,5-Bis[2-(ethyloxycarbonyl)propyl]-1,2-bis(trifluoromethanesulfonyloxy)benzene (32b): Same procedure as for the preparation of **32a**. Yield 78% (2.75 g) as a yellowish oil. − IR (film): $\tilde{\nu}$ = 2984 cm^{-1}, 1734, 1501, 1435, 1244, 1217. − ^{1}H NMR ($CDCl_3$): δ = 1.16 (m, 12 H, 2×$CO_2CH_2CH_3$, 2×$CHCH_3$), 2.71 (m, 4 H, 2×ArCH_2), 3.04 (m, 2 H, 2×C*H*), 4.04 (q, *J* = 7.30 Hz, 4 H, 2×$CO_2CH_2CH_3$), 7.21 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 13.9 ($CO_2CH_2CH_3$), 17.3 ($CHCH_3$), 35.7 (ArCH_2), 40.3 (*C*H), 60.7 ($CO_2CH_2CH_3$), 118.5 (q, J_{CF} = 320.9 Hz, CF_3), 124.4 (aromatic *C*H), 138.2 (aromatic CSO_3CF_3), 140.5 (aromatic *C*CH_2), 175.0 (*C*=O). − MS (EI) *m/z*: 602.2 [M$^+$]. − $C_{20}H_{24}F_6S_2O_{10}$ (602.5):calcd. C 39.87, H 4.01, F 18.92, S 10.64; found C 39.78, H 3.84, F 18.99, S 10.60.

4,5-Bis[2-(ethyloxycarbonyl)propyl]-1,2-benzenedicarbonitrile (33b): Same procedure as for the preparation of **33a**. Yield 75% (1.2 g) as a yellowish oil. − IR (film): $\tilde{\nu}$ = 2982 cm^{-1}, 2939, 2233, 1730, 1464, 1182. − ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 12 H, 2×$CO_2CH_2CH_3$, 2×$CHCH_3$), 2.69 (m, 4 H, 2×ArCH_2), 3.08 (m, 2 H, 2×C*H*), 4.05 (q, *J* = 7.08 Hz, 4 H, 2×$CO_2CH_2CH_3$), 7.55 (s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 13.9 ($CO_2CH_2CH_3$), 17.5 ($CHCH_3$), 35.8 (ArCH_2), 40.2 (*C*H), 60.7 ($CO_2CH_2CH_3$), 113.4 (aromatic *C*CN), 115.3 (Ar*C*N), 134.6 (aromatic *C*H), 144.7 (aromatic *C*CH_2), 174.6 (*C*=O). − MS (EI) *m/z*: 356.1 [M$^+$]. − $C_{20}H_{24}N_2O_4$ (356.4): calcd. C 67.40, H 6.79, N 7.86; found C 67.59, H 6.70, N 8.20.

4-(4-Carboxybutyl)-1,2-benzenedicarbonitrile (36): A mixture of 4-iodophthalonitrile (**34**) (2.0 g, 8.0 mmol), K_2CO_3 (2.8 g, 20.0 mmol), Bu_4NBr (2.4 g, 8.0 mmol), benzyl penten-4-oate (2.8 g, 15.0 mmol), and $Pd(OAc)_2$ (90 mg, 0.4 mmol) in DMF (25 mL) was stirred for 6 h at 60°C. After cooling to room temp., the dark mixture was poured into 100 mL of dichloromethane and filtered over a short pad of silica gel. The filtrate was washed with 0.1 N HCl, water, saturated aqueous $NaHCO_3$, and water again, dried with Na_2SO_4, and evaporated. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent. The benzyl ester, obtained after evaporation to dryness, was directly used without further characterisation. The oily compound was dissolved in 100 mL of THF and, after addition of 10% palladium on charcoal (200 mg), hydrogenated at atmospheric pressure until the consumption of hydrogen was finished (10−12 h). After the catalyst was filtered off, the filtrate was evaporated and the residue was crystallised by addition of 50 mL of MeOH/water (2:1) and storing in the refrigerator overnight. The title compound, **36** (730 mg, 40%), was obtained as a light brown solid. m.p. 111−113°C. − IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 2951, 2631, 2233, 1709, 1597, 1412, 1227. − ^{1}H NMR ([D$_4$]methanol): δ = 1.66 (m, 4 H, 2×CH_2), 2.32 (t, *J* = 7.10 Hz, 2 H, CH_2CO_2 H), 2.78 (t, *J* = 7.10 Hz, 2 H, ArCH_2), 7.69 (d, *J* = 8.05 Hz, 1 H, aromatic H), 7.83 (s, 1 H, aromatic H), 7.85 (d, *J* = 8.15 Hz, 1 H, aromatic H). − ^{13}C NMR ([D$_4$]methanol): δ = 24.0 (*C*H$_2$), 29.7 (*C*H$_2$), 33.1 (CH_2CO_2 H), 34.7 (Ar*C*H$_2$), 112.5 (aromatic *C*CN), 115.3 (Ar*C*N), 115.4 (aromatic *C*CN), 133.3 (aromatic *C*H), 133.4 (aromatic *C*H), 133.5 (aromatic *C*H), 149.5 (aromatic *C*CH_2), 178.8 (*C*=O). − MS (EI) *m/z*: 228.0 [M$^+$]. − $C_{13}H_{12}N_2O_2$ (228.3): calcd. C 68.41, H 5.30, N 12.27; found C 68.34, H 4.97, N 11.24.

2,3,9,10,16,17,23,24-Octa[1-(pentyloxycarbonyl)ethyloxy]phthalocyaninatozinc (4). − General Procedure: A solution of **3** (200 mg,

0.6 mmol), $Zn(OAc)_2 \cdot 2\,H_2O$ (100 mg), and catalytic amounts of DBU in 1-pentanol (5 mL) was stirred at 130°C until TLC-monitoring indicated the absence of the dinitrile. After cooling to room temp., the mixture was poured into 100 mL of MeOH/water (4:1), the precipitate was centrifuged, and purified chromatographically on silica gel using chloroform/ethyl acetate (4:1) as eluent. Drying in vacuo gave **4** (75 mg, 27%) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 2959 cm^{-1}, 2932, 1745, 1462, 1406, 1279, 1099. − UV/Vis (THF): λ_{max} = 672 nm, 642, 607, 355. − ^1H NMR ([D$_5$]pyridine): Due to the presence of different diasteomers, the signals are partially split. δ = 0.62 (m, 24 H, 8×CH_3), 1.17 (m, 16 H, 8×CH_2), 1.30 (m, 16 H, 8×CH_2), 1.74 (m, 16 H, 8×CH_2), 1.97 (m, 24 H, 8×CH_3), 4.36 (m, 16 H, 8×OCH_2), 5.74 (m, 8 H, 8×C*H*), 9.49 (m, 8 H, macrocyclic H). − ^{13}C NMR ([D$_5$]pyridine): δ = 13.9 (*C*H$_3$), 18.8 (*C*H$_3$), 22.4 (*C*H$_2$), 28.1(*C*H$_2$), 28.7 (*C*H$_2$), 65.6 (O*C*H$_2$), 75.0 (*C*H), 122.6 (macrocyclic C), 134.0 (macrocyclic C), 153.9 (macrocyclic C), 172.4 (*C*=O). − MS (FAB) *m*/*z*: 1842.7 [M$^+$]. −$C_{96}H_{128}N_8O_{24}Zn$ (1843.5): calcd. C 62.55, H 7.00, N 6.08; found C 63.12, H 7.08, N 6.68.

2,3,9,10,16,17,23,24-Octa(1-carboxyethyloxy)phthalocyaninatozinc (5). − General Procedure: To a solution of **4** (70 mg, 0.04 mmol) in MeOH (2 mL) was added 1 N NaOH (0.5 mL). The mixture was stirred overnight at room temp., acidified to pH 3 with 1 N HCl, and the resulting precipitate centrifuged, washed with water and acetone, and dried in vacuo to give **5** (50 mg, 96%) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 3431 cm^{-1}, 2935, 1724, 1630, 1275, 1094, 1045. − UV/Vis (MeOH): λ_{max} (lg ε) = 672 nm (4.69), 640 (4.17), 611 (4.07), 354 (4.43). − ^1H NMR ([D$_6$]DMSO): δ = 2.13 (m, 24 H, 8×CH_3), 5.69 (m, 8 H, 8×C*H*), 8.85 (m, 8 H, macrocyclic H).

2,9,16,23-Tetra[2-(*tert*-butyloxycarbonylamino)-2-(pentyloxycarbonyl)ethyl]phthalocyaninatozinc (10): The same procedure as for the preparation of **4** was used. After chromatography on silica gel using dichloromethane/EtOH (15:1) as eluent, **10** (97 mg, 27%) was obtained as a dark green solid. − IR (KBr): $\tilde{\nu}$ = 3431 cm^{-1}, 2959, 1740, 1718, 1491, 1167, 1092, 1053. − UV/Vis (THF): λ_{max} = 673 nm, 644, 608, 347. − ^1H NMR ([D$_5$]pyridine): δ = 0.65 (t, *J* = 6.67 Hz, 12 H, 4×CH_3), 1.14 (m, 16 H, 8×CH_2), 1.44 [s, 36 H, 4×C(CH_3)$_3$], 1.61 (m, 8 H, 4×CH_2), 4.08 (m, 8 H, 4×CH_2), 4.32 (m, 8 H, 4×OCH_2), 5.44 (m, 4 H, 4×C*H*), 8.36 (m, 4 H, macrocyclic H), 9.77 (m, 8 H, macrocyclic H). − ^{13}C NMR ([D$_5$]pyridine): δ = 13.9 (*C*H$_3$), 22.4 (*C*H$_2$), 28.2 (*C*H$_2$), 28.4 [OC(*C*H$_3$)$_3$], 28.6 (*C*H$_2$), 39.0 (*C*H$_2$), 56.8 (*C*H), 65.5 (O*C*H$_2$), 78.9 [O*C*(CH$_3$)$_3$], 129.3, 131.5, 139.6, 148.5, 156.7 (macrocyclic C), 167.9 (*C*=O), 173.2 (*C*=O). − MS (FAB) *m*/*z*: 1606.3 [M$^+$]. −$C_{84}H_{108}N_{12}O_{16}Zn$ (1607.2): calcd. C 62.77, H 6.77, N 10.46; found C 62.20, H 6.50, N 10.86.

2,9,16,23-Tetra(2-amino-2-carboxyethyl)phthalocyaninatozinc (11): To a solution of **10** (60 mg, 0.04 mmol) in dichloromethane (5 mL) was added TFA (1 mL). The resulting mixture was stirred for 1 h at room temp. The mixture was poured into 30 mL of diethyl ether and the resulting precipitate filtered off and redissolved in 3 mL of MeOH. To this solution was added 0.1 N NaOH (0.5 mL), and stirring was continued for 10−12 h. After adjusting the pH to 7 using 0.1 N HCl, and saturating the solution with NaCl, the product precipitated. The precipitate was centrifuged, washed with MeOH and dried in vacuo to give **11** (28 mg, 75%) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1}, 3036, 2953, 1622, 1491, 1398, 1339, 1096. − UV/Vis (MeOH): λ_{max} (lg ε) = 674 nm (4.31), 634 (4.30), 337 (4.40).

2,9,16,23-Tetra[2-*tert*-butyloxy-1-(pentyloxycarbonyl)ethylaminocarbonyl]phthalocyaninatozinc (15): The same procedure as for the preparation of **4** was used. Chromatography on silica gel using hexanes/THF (2:1) eluted undesired side products. Changing the eluent to hexanes/THF (1:4) gave **15** (210 mg, 17%) as a dark green solid. − IR (KBr): $\tilde{\nu}$ = 3312 cm^{-1}, 2959, 2932, 1742, 1661, 1614, 1518, 1487, 1196, 1094. − ^1H NMR ([D$_6$]DMSO): δ = 0.94 (t, *J* = 6.67 Hz, 12 H, 4×CH_3), 1.14 (m, 8 H, 4×CH_2CH$_3$), 1.41 [m, 44 H, 4×C(CH_3)$_3$, 4×CH_2], 1.80 (m, 8 H, 4×CH_2), 4.12−4.33 (m, 16 H, 4×CO$_2$CH_2, 4×CH_2O*t*Bu), 5.04 (s, 4 H, 4×C*H*), 9.45−8.52 (m, 16 H, macrocyclic H, 4×N*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 13.9 (*C*H$_3$), 21.8 (*C*H$_2$CH$_3$), 27.4 [C(*C*H$_3$)$_3$], 27.8 (*C*H$_2$), 28.1 (*C*H$_2$), 54.3 (*C*H), 61.7 (CO$_2$*C*H$_2$), 64.7 (*C*H$_2$O*t*Bu), 73.3 [*C*(CH$_3$)$_3$], 121.8 (macrocyclic *C*H), 128.4 (macrocyclic *C*H), 134.7 (macrocyclic C), 137.0 (macrocyclic C), 139.1 (macrocyclic *C*C=O), 151.2 (macrocyclic C), 167.4 (HN*C*=O), 171.0 (*C*=O). − MS (FAB) *m*/*z*: 1606.3 [M$^+$]. − UV/Vis (CHCl$_3$): λ_{max} = 682.0 nm, 614.0, 348.0. − $C_{84}H_{108}N_{12}O_{16}Zn$ (1607.2): calcd. C 62.77, H 6.77, N 10.46; found C 59.92, H 6.93, N 8.82.

2,9,16,23-Tetra(1-carboxy-2-hydroxyethylaminocarbonyl)-phthalocyaninatozinc (16): To a solution of **15** (100 mg, 0.062 mmol) in dry dichloromethane (5 mL) was added TFA (1.5 mL) at 0°C. The reaction mixture was stirred for 16 h while the solution was allowed to warm to room temp. All volatile components were removed in vacuo and the residue was redissolved in 20 mL of MeOH containing NaOH (15 mg, 0.372 mmol). Stirring was continued for further 16 h at room temp. The mixture was poured into 50 mL of water and acidified with dillute HCl to pH 3. The resulting precipitate was centrifuged, redissolved in 0.1 N NaOH and finally precipitated by addition of 0.1 N HCl. Drying in vacuo gave **16** (49 mg, 71%) as a dark green solid. − IR (KBr): $\tilde{\nu}$ = 3263 cm^{-1}, 2955, 2924, 2363, 1732, 1637, 1529, 1334, 1097. − UV/Vis (MeOH): λ_{max} (lg ε) = 675.0 nm (4.83), 634.5 (4.54), 344.5 (4.64). −^1H NMR ([D$_6$]DMSO): δ = 4.05 (d, *J* = 3.79 Hz, 8 H, 4×CH_2OH), 4.80 (m, 4 H, 4×C*H*), 9.59 (m, 16 H, macrocyclic H, 4×N*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 56.4 (*C*H), 61.6 (CH_2OH), 122.3 (macrocyclic *C*H), 122.4 (macrocyclic *C*H), 128.9 (macrocyclic *C*C=O), 134.9 (macrocyclic C), 137.9 (macrocyclic C), 140.0 (macrocyclic *C*H), 152.8 (macrocyclic C), 167.2 (*C*=O), 172.3 (*C*=O). − MS (MALDI, reflection mode, matrix 2,5-dihydroxybenzoic acid, MeOH) *m*/*z*: 1101.1 [M$^+$]. − $C_{48}H_{36}N_{12}O_{16}Zn$ (1102.3): calcd. C 52.33, H 3.29, N 15.25; found C 49.06, H 3.87, N 13.52.

1,8,15,22-Tetra[4-(pentyloxycarbonyl)butyl]phthalocyaninatozinc (26): The same procedure as for the preparation of **4** was used. Chromatographic workup on silica gel using chloroform/ethyl acetate (8:1) as eluent gave **26** (160 mg, 31%) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1}, 2930, 1734, 1462, 1396, 1335, 1171. − UV/Vis (THF): λ_{max} = 684 nm, 616, 348. − ^1H NMR ([D$_5$]pyridine): δ = 0.70 (m, 12 H, 4×CH_3), 1.11 (m, 16 H, 8×CH_2), 1.45 (m, 8 H, 4×CH_2), 2.67−2.21 (m, 24 H, 8×CH_2, 4×CH_2CO$_2$C$_5$H$_{11}$), 4.02 (m, 8 H, 4×CO$_2$CH_2), 4.67 (m, 8 H, ArCH_2), 8.11 (m, 8 H, macrocyclic H), 9.65 (m, 4 H, macrocyclic H). − ^{13}C NMR ([D$_5$]pyridine): δ = 14.0 (*C*H$_3$), 22.4 (*C*H$_2$), 25.1 (*C*H$_2$), 28.2 (*C*H$_2$), 28.6 (*C*H$_2$), 31.4 (*C*H$_2$), 33.7 (*C*H$_2$), 34.7 (*C*H$_2$CO$_2$C$_5$H$_{11}$), 64.3 (CO$_2$CH_2), 121.2 (macrocyclic *C*H), 129.4 (macrocyclic *C*H), 139.8 (macrocyclic *C*H), 141.3 (macrocyclic C), 153.7 (macrocyclic C), 154.1 (macrocyclic C), 154.9 (macrocyclic C), 173.6 (*C*=O). − MS (FAB) *m*/*z*: 1257.6 [M$^+$]. − $C_{72}H_{88}N_8O_8Zn$ (1258.9): calcd. C 68.69, H 7.05, N 8.90; found C 67.34, H 6.96, N 8.23.

1,8,15,22-Tetra(4-carboxybutyl)phthalocyaninatozinc (27): The same procedure as for the preparation of **5b** was used. Yield 89% (70 mg) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 3456 cm^{-1}, 2932, 1707, 1659, 1406, 1331, 1113, 741. − UV/Vis (MeOH): λ_{max} (lg ε) = 678 nm (4.83), 649 (4.16), 613 (4.15), 353 (4.35).

2,3,9,10,16,17,23,24-Octa[2-(benzyloxycarbonyl)ethyl]phthalocyaninatozinc (37a) and 9,10,16,17,23,24-hexa[2-(benzyloxycarbonyl)ethyl]-2-[4-(*N*-succinimidyloxycarbonyl)butyl]phthalocyaninatozinc (40a). − General Procedure: A solution of **33a** (540 mg, 1.60 mmol), **36** (62 mg, 0.27 mmol), $Zn(OAc)_2 \cdot 2\,H_2O$ (100 mg, 0.47 mmol), and catalytic amounts of DBU in benzyl alcohol (7 mL) was stirred overnight at 130°C. After cooling to room temp. the mixture was poured into 100 mL of MeOH/water (4:1) and the resulting precipitate was centrifuged. The residue was purified by chromatography on silica gel using the following eluents: Chloroform/ethyl acetate (8:1) gave 170 mg of the symmetrically substituted **37a** as dark green solid. Changing the eluent to chloroform/THF (4:1) yielded a second fraction which was, after removal of the solvent, redissolved in 3 mL of THF. To this solution NHS (30 mg, 0.25 mmol), DMAP (10 mg, 0.08 mmol), and DCC (62 mg, 0.30 mmol) were added and the resulting solution was stirred at room temp. overnight. The precipitate formed during this reaction was filtered off, the filtrate was evaporated and the residue was further purified by chromatography on silica gel using $CHCl_3$/ethyl acetate (8:1) to yield 90 mg of **40a** as dark green solid.

37a: IR (KBr): $\tilde{\nu}$ = 1732 cm^{-1}, 1622, 1489, 1454, 1285, 1161, 1097. − UV/Vis (THF): λ = 682 nm, 654, 615, 350. − ^{1}H NMR ([D$_8$]THF): δ = 3.09 (t, *J* = 8.07 Hz, 16 H, 8×C*H*$_2$CO$_2$Bzl), 3.54 (t, *J* = 8.05 Hz, 16 H, 8×ArC*H*$_2$), 5.27 (s, 16 H, 8×CO$_2$C*H*$_2$C$_6$H$_5$), 7.34 (m, 40 H, aromatic H), 8.89 (s, 8 H, macrocyclic H). − ^{13}C NMR ([D$_8$]THF): δ = 29.5 (*C*H$_2$CO$_2$Bzl), 36.2 (Ar*C*H$_2$), 66.7 (CO$_2$*C*H$_2$C$_6$H$_5$), 123.3 (macrocyclic *C*H), 128.6 (aromatic *C*H), 128.9 (aromatic *C*H), 129.1 (aromatic *C*H), 137.7 (macrocyclic C), 137.9 (macrocyclic C), 141.2 (aromatic *C*CH$_2$), 153.4 (macrocyclic *C*CH$_2$), 172.9 (*C*=O). − MS (FD) *m*/*z*: 1874.0 [M$^+$]. − $C_{112}H_{96}N_8O_{16}Zn$ (1875.4): calcd. C 71.73, H 5.16, N 5.97, found C 71.76, H 4.78, N 6.33.

40a: IR (KBr): $\tilde{\nu}$ = 1743 cm^{-1}, 1680, 1664, 1454, 1161. − UV/Vis (THF): λ_{max} = 677 nm, 648, 611, 350. − ^{1}H NMR ([D$_5$]pyridine): δ = 1.94 (m, 4 H, C*H*$_2$C*H*$_2$), 2.86 [s, 4 H, C(O)C*H*$_2$C*H*$_2$C(O)], 3.18 (m, 12 H, 6×C*H*$_2$CO$_2$Bzl), 3.62 (m, 2 H, C*H*$_2$CO$_2$N), 3.71 (m, 14 H, 7×ArC*H*$_2$), 5.30 (m, 12 H, 6×CO$_2$C*H*$_2$C$_6$H$_5$), 7.33 (m, 30 H, aromatic H), 8.08 (m, 1 H, macrocyclic H), 9.72 (m, 8 H, macrocyclic H). − ^{13}C NMR ([D$_5$]pyridine): δ = 24.9 (*C*H$_2$), 26.0 (*C*H$_2$), 26.1 (*C*H$_2$), 29.0 (*C*H$_2$CO$_2$Bzl), 31.1 (*C*H$_2$CO$_2$N), 34.3 (Ar*C*H$_2$), 35.5 (Ar*C*H$_2$), 66.5 (CO$_2$*C*H$_2$C$_6$H$_5$), 121.2 (macrocyclic *C*H), 128.4 (aromatic *C*H), 128.6 (aromatic *C*H), 128.9 (aromatic *C*H), 137.0 (aromatic C), 137.7 (macrocyclic C), 139.3 (macrocyclic *C*H), 140.0 (macrocyclic C), 153.8 (macrocyclic *C*CH$_2$), 169.5 (CH$_2$*C*O$_2$N), 170.4 (*C*=O), 172.9 (CH$_2$*C*O$_2$Bzl). − MS (FD) *m*/*z*: 1747.3 [M$^+$]. − $C_{101}H_{87}N_9O_{16}Zn$ (1748.2): calcd. C 69.39, H 5.02, N 7.21; found C 69.65, H 5.18, N, 7.22.

2,3,9,10,16,17,23,24-Octa(2-carboxyethyl)phthalocyaninatozinc (39a): The same procedure as for the preparation of **5b** was used. Yield 96% (60 mg) as dark blue solid. − IR (KBr): $\tilde{\nu}$ = 3429 cm^{-1}, 3038, 1711, 1641, 1205. − UV/Vis (MeOH): λ_{max} (lg ε) = 677 nm (4.72), 631 (4.35), 343 (4.56). − ^{1}H NMR ([D$_6$]DMSO): δ = 2.99 (t, 16 H, 8×C*H*$_2$), 3.50 (br, 16 H, 8×ArC*H*$_2$), 9.18 (s, 8 H, macrocyclic H).

9,10,16,17,23,24-Hexa(2-carboxyethyl)-2-[4-(*N*-succinimidyloxycarbonyl)butyl]phthalocyaninatozinc (41a): General Procedure: To a solution of **40a** (50 mg, 0.025 mmol) in EtOH (5 mL) was added 10% Pd on charcoal (20 mg). The resulting mixture was hydrogenated under atmospheric pressure until hydrogen consumption was finished (8−10 h). The mixture was diluted with 50 mL of EtOH and the catalyst was filtered off. The filtrate was acidified to pH 3 using 0.1 M HCl, the resulting precipitate was centrifuged, washed with water and acetone, and dried in vacuo to give **41a** (25 mg, 80%) as a dark green solid. − UV/Vis (MeOH): λ_{max} (lg ε) = 677 nm (4.62), 630 (4.18), 344 (4.41). − ^{1}H NMR ([D$_6$]DMSO): δ = 2.05 (s, 4 H, 2×C*H*$_2$), 2.39 (br, 4 H, 2×C*H*$_2$), 3.02 (m, 14 H, 6×C*H*$_2$CO$_2$ H, C*H*$_2$CO$_2$NH), 3.51 (m, 14 H, 7×ArC*H*$_2$), 8.06 (m, 1 H, macrocyclic H), 9.28 (m, 8 H, macrocyclic H).

2,3,9,10,16,17,23,24-Octa[2-(benzyloxycarbonyl)propyl]phthalocyaninatozinc (37b) and 9,10,16,17,23,24-hexa[2-(benzyloxycarbonyl)propyl]-2-[4-(*N*-succinimidyloxycarbonyl)butyl]phthalocyaninatozinc (40b): The same procedure as for the preparation of **37a** and **40a** was used. Column chromatography on silica gel using $CHCl_3$/ethyl acetate (8:1) yielded 160 mg of **37b** as first fraction. Changing the eluent to $CHCl_3$/ethyl acetate/acetic acid (20:5:1) gave a second fraction which was further purified by a second chromatography step using $CHCl_3$/ethyl acetate/EtOH (16:4:1). Treatment of this fraction with NHS gave, after chromatography on silica gel using $CHCl_3$/ethyl acetate (8:1), 72 mg of **40b** as a dark blue solid.

37b: IR (KBr): $\tilde{\nu}$ = 2934 cm^{-1}, 1732, 1489, 1454, 1157, 1099. − UV/Vis ($CHCl_3$): λ_{max} = 683 nm, 616, 351. − ^{1}H NMR ([D$_8$]THF): δ = 1.43 (m, 24 H, 8×C*H*$_3$), 3.28 (m, 16 H, 8×ArC*H*$_2$), 3.80 (m, 8 H, 8×C*H*), 5.13 (s, 16 H, 8×CO$_2$C*H*$_2$), 7.15 (m, 40 H, aromatic H), 9.31 (s, 8 H, macrocyclic H). − ^{13}C NMR ([D$_8$]THF): δ = 17.5 (*C*H$_3$), 38.0 (Ar*C*H$_2$), 42.4 (*C*H), 65.9 (CO$_2$*C*H$_2$), 124.8 (macrocyclic *C*H), 128.4 (aromatic *C*H), 128.6 (aromatic *C*H), 128.9 (aromatic *C*H), 137.4 (macrocyclic C), 138.2 (macrocyclic C), 140.8 (aromatic C), 154.4 (macrocyclic *C*CH$_2$), 175.9 (*C*=O). − MS (FAB) *m*/*z*: 1986.4 [M$^+$].

40b: IR (KBr): $\tilde{\nu}$ = 2934 cm^{-1}, 1730, 1452, 1159. − UV/Vis (THF): λ_{max} = 682 nm, 654, 615, 350. − ^{1}H NMR ([D$_5$]pyridine): δ = 1.41 (m, 18 H, 6×C*H*$_3$), 1.93 (m, 4 H, 2×C*H*$_2$), 2.86 (s, 4 H, 2×C*H*$_2$), 3.11 (m, 2 H, C*H*$_2$CO$_2$N), 3.44 (m, 14 H, 7×ArC*H*$_2$), 3.87 (m, 6 H, 6×C*H*), 5.28 (m, 12 H, 6×CO$_2$C*H*$_2$), 7.38 (m, 30 H, aromatic H), 8.08 (m, 1 H, macrocyclic H), 9.77 (m, 8 H, macrocyclic H). − ^{13}C NMR ([D$_5$]pyridine): δ = 17.5 (*C*H$_3$), 24.8 (*C*H$_2$), 26.1 (*C*H$_2$), 31.0 (*C*H$_2$), 37.6 (*C*H$_2$), 41.8 (*C*H), 66.4 (CO$_2$*C*H$_2$), 124.7 (macrocyclic *C*H), 128.3 (aromatic *C*H), 128.7 (aromatic *C*H), 136.9 (aromatic C), 137.9 (macrocyclic C), 139.8 (macrocyclic *C*H), 140.7 (macrocyclic C), 154.6 (macrocyclic *C*CH$_2$), 170.3 (CH$_2$*C*O$_2$N), 175.9 (*C*=O), 176.0 (CH$_2$*C*O$_2$Bzl). − MS (FAB) *m*/*z*: 1832.4 [M$^+$].

2,3,9,10,16,17,23,24-Octa(2-carboxypropyl)phthalocyaninatozinc (39b): The same procedure as for the preparation of **5b** was used. Yield 93% (60 mg) as a dark blue solid. − IR (KBr): $\tilde{\nu}$ = 3238 nm, 2930, 1709, 1462, 1342, 1109. − UV/Vis (MeOH): λ_{max} (lg ε) = 679 nm (4.73), 614 (3.92), 350 (4.32). − ^{1}H NMR ([D$_6$]DMSO): δ = 1.37 (m, 24 H, 8×CH$_3$), 3.15 (m, 16 H, 8×ArC*H*$_2$), 3.60 (m, 8 H, 8×C*H*), 9.20 (s, 8 H, macrocyclic H).

9,10,16,17,23,24-Hexa(2-carboxypropyl)-2-[4-(*N*-succinimidyloxycarbonyl)butyl]phthalocyaninatozinc (41b): The same procedure as for the preparation of **41a** was used. Yield 75% (16 mg) as a dark green solid. − UV/Vis (MeOH): λ_{max} (lg ε) = 679 nm (4.89), 613 (4.20), 346 (4.70). − ^{1}H NMR ([D$_6$]DMSO): δ = 1.15 (m, 18 H, 6×C*H*$_3$), 2.08 (s, 4 H, C*H*$_2$), 2.76 (m, 4 H, C*H*$_2$), 2.95−3.80 (br, 16 H, C*H*$_2$), 4.02 (m, 6 H, 6×C*H*), 7.26−9.21 (br, 9 H, macrocyclic H).

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