Hematoporphyrin-Derived Soluble Porphyrin−Platinum Conjugates with Combined Cytotoxic and Phototoxic Antitumor Activity

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To combine the cytotoxic activity of cisplatin and the phototoxicicity of hematoporphyrin derivatives in the same molecule, hematoporphyrin was derivatized at the two secondary alcohol positions by etherification with oligo- and poly(ethylene glycol) units. The two carboxylic acid groups of the propionate side chains were used to bind platinum fragments. The antiproliferative activity of 35 platinum complexes (0.5, 1, and 5 μM) differing in solubility and type of the platinum fragment and the corresponding porphyrin ligands were studied in tests with TCC-SUP and J82 transitional bladder cancer cells in the dark and after irradiation ($\lambda = 600-730$ nm, 24 J/cm^2). The most active compounds were found among the porphyrin−platinum conjugates bearing the diammine and (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane ligand. These porphyrin−platinum conjugates, especially the water-soluble species, such as diammine{7,-12-bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II), are promising candidates for the development of a novel type of photosensitizers with intrinsic cytotoxicity, which due to the porphyrin constituent may selectively enrich in tumor tissues.

Introduction

In many industrialized countries, bladder carcinoma has a high prevalence, which is in part a consequence of the disease's strong association with cigarette smoking and the use of organic solvents in a number of occupations, e.g., the rubber industry.[1] Bladder cancer rates are stable at around 20 per 100 000,[2] and it is estimated that globally there are approximately 200 000 new cases per annum,[3] with more than 66 000 new cases diagnosed yearly in Europe.[4] A total of 90−95% of the bladder cancers arise from the urothelium, and 70% of the patients at the initial medical examination are diagnosed with superficial transitional cell carcinoma (TCC). In principle, TCC of the urothelium is considered a chemosensitive tumor.[5] Nonetheless, chemotherapy confers only a modest survival benefit to the patients, and metastatic disease remains essentially incurable with only a small number of patients achieving long-term disease control.

Most often, combination chemotherapy for advanced and metastatic TCC of the urothelium has been based on cisplatin and methotrexate yielding single-agent response rates of 30−35%.[6] Nowadays, a MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) combination is considered the standard treatment of metastatic bladder cancer[7] with responses from 40 to 72%[8−12] and median survival times of 12−13 months.[13,14] However, polychemotherapy with MVAC is associated with a number of adverse effects, i.e., myelosuppression, nausea, and vomiting.[15] Intravesical immunotherapy with bacille Calmette-Guérin (BCG) is one of the most effective treatments of superficial TCC decreasing tumor recurrences, disease progression, and bladder cancer-specific mortality.[16,17] Photodynamic therapy (PDT) after intravenous or intravesical administration of a photosenisitizer with subsequent in situ intravesical activation by using visible laser light is another therapeutic approach for bladder cancer as in the case of BCG incompatibility. So far, hematoporphyrin derivative (e.g., Photofrin) is the only approved photosensitizer for clinical use. However, Photofrin has several disadvantages including (i) prolonged light sensitivity in treated patients, (ii) weak absorption at the 630 nm maximum, and (iii) difficulties in characterization as Photofrin is a mixture of products.[18−21]

Because of the deficiencies of the current therapies, the development of novel treatment modalities for bladder cancer has been a challenge for many years. A combination of chemotherapy and PDT is one of several preclinical attempts, which have been made with promising results.[22,23]

This motivated us to synthesize compounds in which a cytostatic group is combined with a photosensitizer in the same molecule: porphyrin−platinum conjugates.[24−27] For such porphyrin−platinum conjugates, we expect a cytotoxic effect of the platinum component in the dark and, on irradiation, an additional photodynamic effect of the porphyrin sensitizer. In addition, porphyrin−platinum conjugates should have the great advantage of tumor selectivity as compared to platinum compounds. Whereas porphyrin derivatives enrich in neoplastic tissues, platinum complexes such as cisplatin and carboplatin unselectively penetrate all tissues, especially fast-growing tissues, leading to the side effects mentioned above. With porphyrin−platinum conjugates, we attempt a selective enrichment of platinum compounds in tumors. Because porphyrins are important in the PDT and platinum compounds in the cytostatic therapy of bladder cancer, porphyrin−plati-

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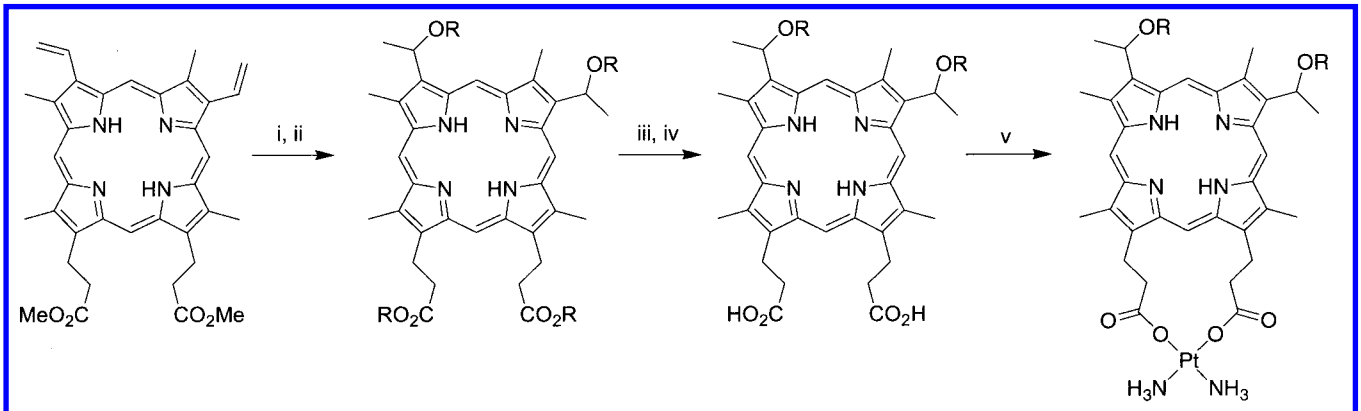
Scheme 1[a]



1

2: R = $(CH_2CH_2O)_2CH_3$
3: R = $(CH_2CH_2O)_3CH_3$
4: R = $(CH_2CH_2O)_4CH_3$
5: R = $(CH_2CH_2O)_5CH_3$
6: R = $(CH_2CH_2O)_{\sim 12}CH_3$
7: R = $(CH_2CH_2O)_{\sim 17}CH_3$

8: R = $(CH_2CH_2O)_2CH_3$
9: R = $(CH_2CH_2O)_3CH_3$
10: R = $(CH_2CH_2O)_4CH_3$
11: R = $(CH_2CH_2O)_5CH_3$
12: R = $(CH_2CH_2O)_{\sim 12}CH_3$
13: R = $(CH_2CH_2O)_{\sim 17}CH_3$

21: R = $(CH_2CH_2O)_2CH_3$
22: R = $(CH_2CH_2O)_3CH_3$
23: R = $(CH_2CH_2O)_4CH_3$
24: R = $(CH_2CH_2O)_5CH_3$
25: R = $(CH_2CH_2O)_{\sim 12}CH_3$
26: R = $(CH_2CH_2O)_{\sim 17}CH_3$

[a] Reagents: (i) 33% HBr in HOAc, 24 h; (ii) excess ROH, 2 d; (iii) 20% KOH in MeOH, reflux, 2 d; (iv) 7% HCl, H_2O; (v) diammine(diaqua)platinum(II) hydroxide, H_2O, EtOH, >18 h.

num conjugates seem an especially promising approach to the treatment of this disease.[28−30] Focusing the light on the tumor only would additionally increase the effectiveness.[31] Here, we describe the synthesis of 35 new porphyrin−platinum conjugates and their antitumor activity on two transitional bladder cancer cell lines.[32]

Chemical Results and Discussion

Synthesis of the Porphyrin Ligands and the Platinum Precursors. Hemin was transferred to protoporphyrin dimethylester **1**,[33] from which all of the subsequent reactions started (Scheme 1). First, protoporphyrin dimethylester **1** was treated with 30% hydrobromic acid in acetic acid to give the labile Markovnikoff adduct of HBr to the two vinyl double bonds,[34] which was reacted with different types of alcohols to replace bromide by the corresponding alkoxides. As alcohols, we chose hydrophilic oligo- and poly(ethylene glycol) monomethyl ethers. During the etherification, the HBr that formed catalyzed the transesterification of the methylesters into the esters of the corresponding alcohols (Scheme 1). The etherified hematoporphyrin esters **2**−**7** were purified by column chromatography. The carboxylic acids **8**−**13**, which were required for coordination to the platinum(II) moieties, were prepared by hydrolysis of the esters **2**−**7** with 20% methanolic KOH solution (Scheme 1).

1,2-Diaminoethane, 1,3-diaminopropane, (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane, and 2,2′-bipyridine were commercially available and used as ligands to prepare the corresponding dichloroplatinum(II) complexes **14**−**17** according to literature procedures.[35−37]

Ethyl (*R*/*S*)-2,3-diaminopropionate dihydrochloride, ethyl (*S*)-2,4-diaminobutanoate dihydrochloride, and diethyl *meso*-4,5-diaminosuberate dihydrochloride were synthesized according to literature procedures[38−41] and used as ligands for the preparation of the corresponding diiodoplatinum(II) complexes **18**−**20**.[42]

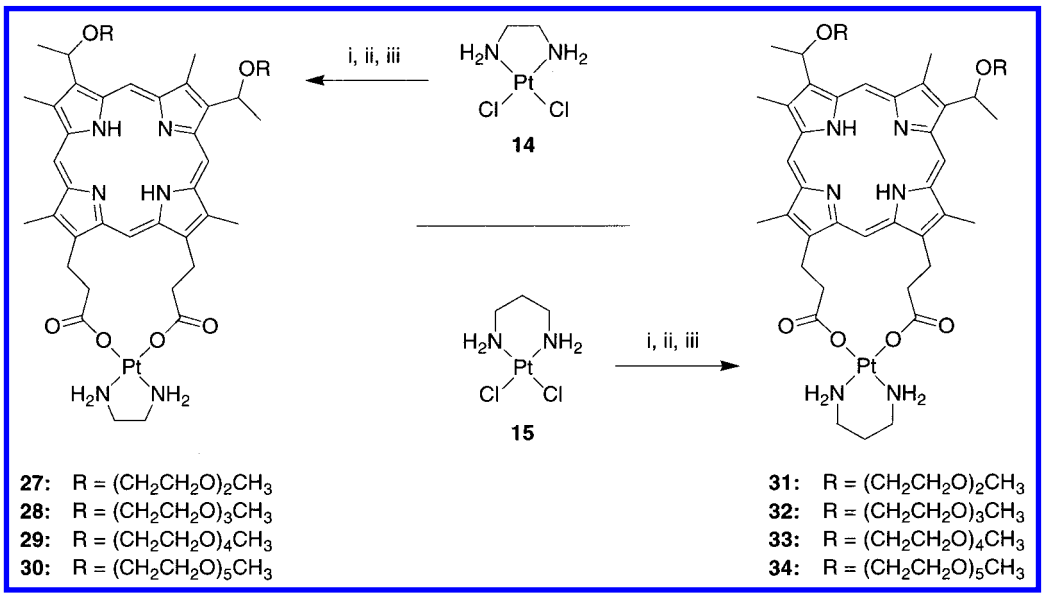
Synthesis of the Platinum Complexes. Reaction of the porphyrin carboxylic acids **8**−**13** with cisplatin did not result in the desired complexes. Therefore, cisplatin had to be activated by conversion into diammine(diaqua)platinum(II) hydroxide,[27] which was reacted with an equimolar amount of the porphyrin ligand in a mixture of ethanol and water or, in the case of the water-soluble ligands **12** and **13**, in pure water. The resulting diammine(dicarboxylato)platinum(II) complexes **21**−**24** precipitated. To the reaction mixtures of the water-soluble complexes **25** and **26**, CH_2Cl_2 was added to remove neutral impurities before the aqueous phase was evaporated to obtain the products (Scheme 1).

The diamine(dichloro)platinum(II) precursors **14**−**17** were activated by conversion into diamine(dihydroxy)-platinum(II) species,[43] which were reacted with an equimolar amount of the respective porphyrin carboxylic acid in a mixture of ethanol and water or, in the case of the water-soluble ligands **12** and **13**, in pure water. The complexes **27**−**38**, **40**, and **41** precipitated. To the water-soluble complex **39**, CH_2Cl_2 was added to remove neutral impurities and the aqueous phase was evaporated to obtain the product (Schemes 2 and 3).

For the reaction with the porphyrincarboxylic acids, it is necessary to activate the diamine(diiodo)platinum-(II) complexes **18**−**20** by conversion into diamine-(dinitrato)platinum(II) species,[43] which are water-soluble. In this form, they were reacted with an equimolar amount of the porphyrin ligand (**8**−**11**) in a mixture of ethanol and water or, in the case of the water-soluble ligand **13**, in pure water. The water-insoluble complexes **42**−**45**, **47**−**50**, and **52**−**55** precipitated after concentrating the solution. The water-soluble complexes **46** and **51** were isolated by chromatography on silica (Schemes 4 and 5).

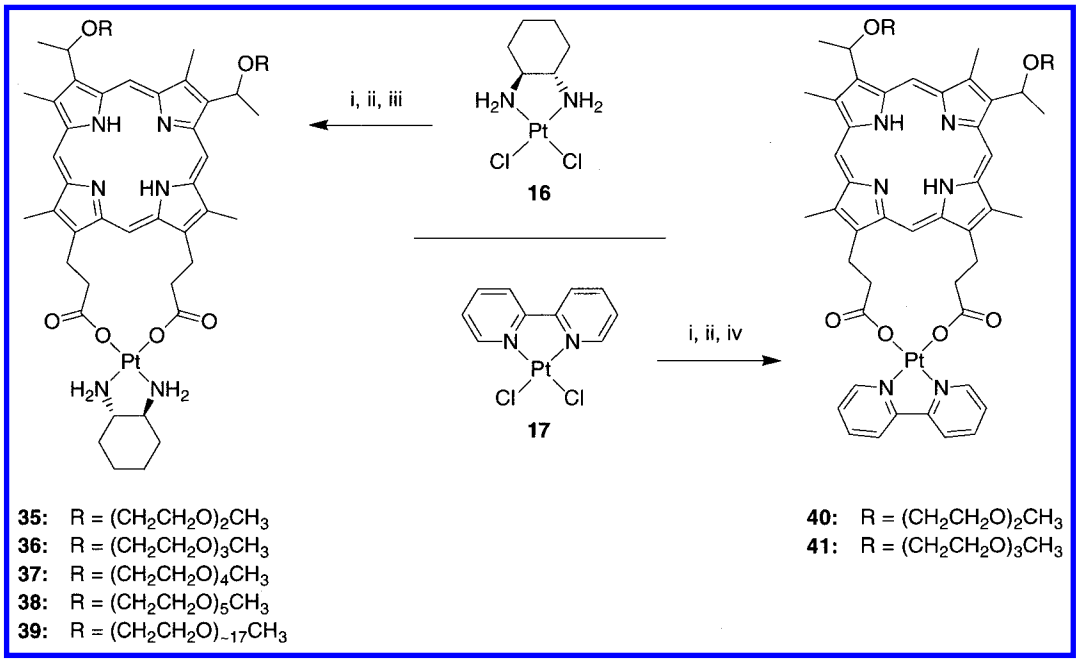
The porphyrindicarboxylatoplatinum(II) complexes **21**−**55** are soluble in dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO), except **29**, **33**, and **37**. The complexes **24**, **30**, **34**, **38**, **45**, **50**, and **55**, which contain

Scheme 2[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) ion-exchanger; (iii) **8**−**11**, EtOH, H_2O.

Scheme 3[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) ion-exchanger; (iii) **8**−**11** and **13**, EtOH, H_2O; (iv) **8** and **9**, EtOH, H_2O.

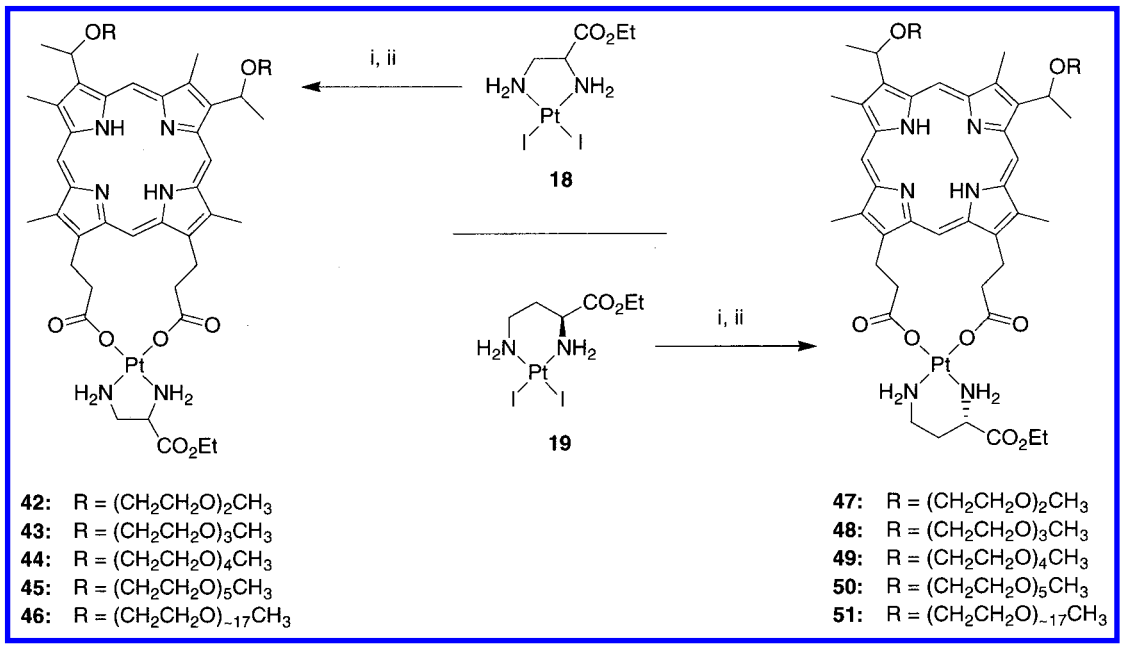
pentaethylene glycol monomethyl ether side chains, are soluble in CH_2Cl_2 and $CHCl_3$ as well. The complexes **25**, **26**, **39**, **46**, and **51** can even be dissolved in water because of their poly(ethylene glycol) monomethyl ether side chains.

Spectroscopy. For most of the reactions described, IR spectroscopy is a useful method to monitor the course of the reactions. The porphyrin backbone shows the characteristic and sharp NH absorption of pyrrole at 3300 cm^{-1}. The shift of the CO absorption of the esters **2**−**7** (1730−1720 cm^{-1}) during hydrolysis to the porphyrindicarboxylic acids **8**−**13** (1720−1715 cm^{-1}) can be used to check the completion of the conversion. The complexation of the porphyrindicarboxylic acids with the platinum fragments results in compounds with CO absorptions between 1690 and 1600 cm^{-1}. Porphyrin−platinum conjugates with nitrogen ligands containing ester groups show an additional CO absorption (1740−1705 cm^{-1}).

All of the porphyrins exhibit a characteristic $\pi-\pi^*$ transition (Soret band) with a wavelength λ of about 400 nm and a molar extinction coefficient ϵ up to 400 000 L mol^{-1} cm^{-1}. The hematoporphyrin derivatives show absorption spectra of the etio type. The sequence of the visible satellite band intensity is IV > III > II > I. The satellite band I appears at 620 nm, II at 570 nm, III at 530 nm, and IV at 500 nm. For measuring these absorption spectra, the porphyrins and porphyrin−platinum conjugates were dissolved in DMSO or DMF in concentrations of about 1×10^{-5} mol L^{-1}.

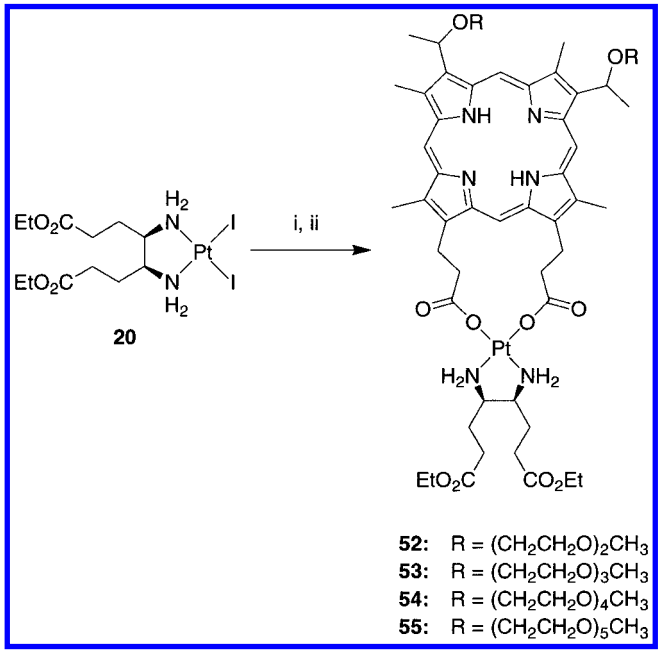
The strong magnetic anisotropy of the macrocyclic porphyrins expands the ^1H nuclear magnetic resonance

Scheme 4[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) **8-11** and **13**, EtOH, H_2O.

Scheme 5[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) **8-11**, EtOH, H_2O.

(NMR) spectra up to 15 ppm. The signals of the four methine bridges of the hematoporphyrin derivatives are found at about 10 ppm. The two NH protons show a broad signal at about −4 ppm due to a fast interchange. The methyl groups of the hematoporphyrin derivatives in the positions 2, 7, 12, and 18 are strongly affected by the anisotropy and appear at 3.7 ppm. The signals of the α-methylene groups in the positions 13 and 17 show up at 4.4 ppm, and those of the *β*-methylene groups show up at 3.3 ppm. The OCH_2CH_2 groups give rise to characteristic AA′BB′ spin systems, which frequently result in multiplets. The ^1H NMR signals of the platinum complexes tend to broaden.[32]

All of the synthesized compounds were examined by mass spectrometry (MS) with electron ionization (EI), PI−fast atom bombardment (FAB), and electrospray ionization (ESI) techniques. For PI−FAB MS, the porphyrins or the porphyrin−platinum compounds were embedded in a matrix consisting of glycerol and DMSO. The more easily soluble compounds were embedded in a matrix of 3-nitrobenzyl alcohol and CH_2Cl_2, $CHCl_3$, or MeOH. For ESI MS, the compounds were dissolved in MeOH, MeCN, CH_2Cl_2, or MeOH/CH_2Cl_2 always containing 1% acetic acid to ease protonation. Interestingly, most of the porphyrin−platinum compounds exhibit the molecular ion peaks establishing their composition.[32] The mass spectra of the oligo- and poly(ethylene glycol) derivatives are characterized by a successive loss of ethylene glycol units.

Biological Results and Discussion

Cell Lines and General Prodecure. To determine the antiproliferative activity of the new porphyrin ligands and the corresponding platinum complexes with different amine nonleaving groups, two bladder cancer cell lines TCC-SUP and J82 were selected as in vitro models. The TCC-SUP line was isolated in 1974 from a 67 year old female patient suffering from an anaplastic TCC grade IV in the neck of the urinary bladder,[44] whereas the J82 cell line was established from a TCC of a 58 year old caucasian male.[45]

For the evaluation of the sensitivity of the cancer cell lines against the test compounds, we used a computerized (kinetic) chemosensitivity assay based on the quantification of biomass by staining cells with crystal violet.[46,47] To discriminate between the cytotoxic and the phototoxic effects, all experiments were carried out in duplicate. The cells were seeded into microplates, and the test compounds were added after 48 h. One batch of the microplates was kept in the dark until the end of the experiment, whereas the other microplates were irradiated 48 h after addition of the substances for 10 min with a light dose of 24 J cm^{-2}, before the plates were reincubated in the dark.

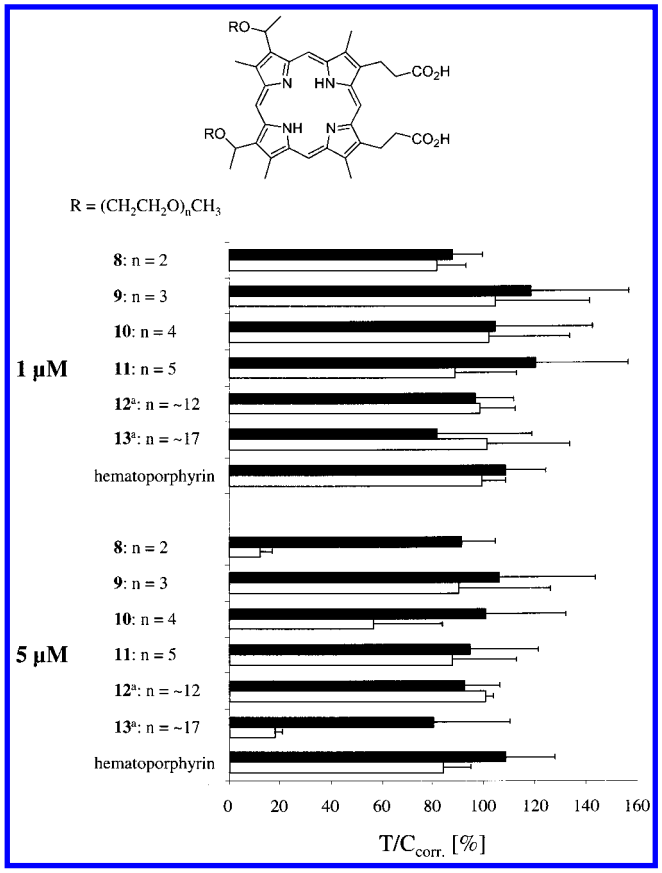


Figure 1. Effect of the porphyrin ligands and the reference hematoporphyrin (stock solution in DMF) on the proliferation of TCC-SUP cells (in passage 53 from origin) without (filled bars) and with (open bars) irradiation (λ = 600−730 nm, 10 min, 24 J cm^{-2}). The cells were exposed to the substances for 96 h. Irradiation was performed 48 h after the addition of the test compounds. Superscript a represents the stock solution of the ligands in H_2O.

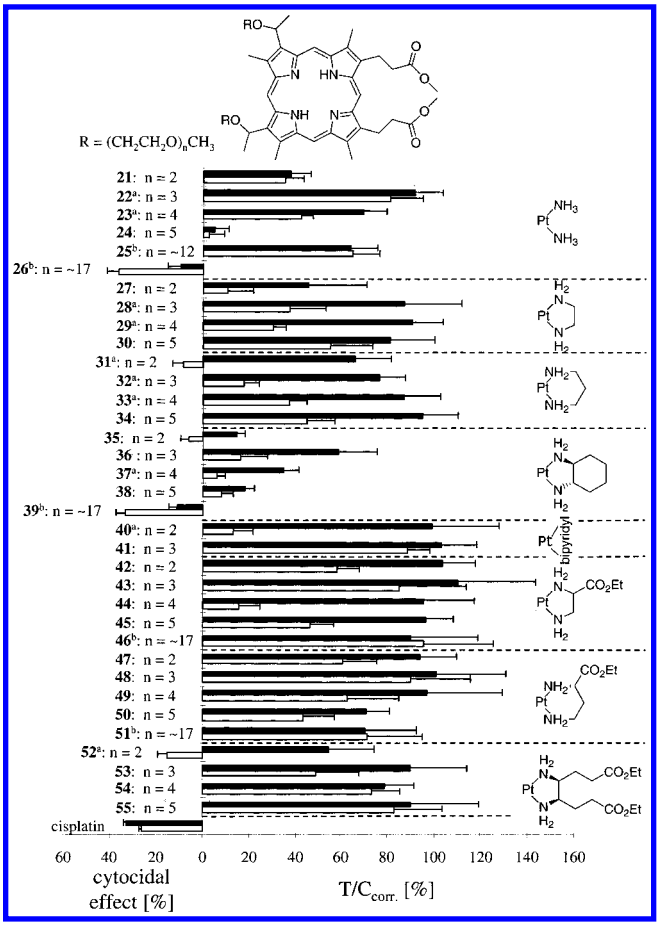


Figure 2. Effect of the porphyrin−platinum conjugates and the reference cisplatin (stock solution in DMF) at a concentration of 5 μM on the proliferation of TCC-SUP cells (in passage 53 from origin) without (filled bars) and with (open bars) irradiation (λ = 600−730 nm, 10 min, 24 J cm^{-2}) as a function of the different nonleaving groups. The cells were exposed to the substances for 96 h. Irradiation was performed 48 h after the addition of the test compounds. Superscript a represents the stock solution of the complexes in DMSO; superscript b represents the stock solution of the complexes in H_2O.

End Point Chemosensitivity Assay. TCC-SUP cells were incubated for 4 days with 1, 5, and 10 μM porphyrin ligand, porphyrin−platinum conjugate, and hematoporphyrin and cisplatin as reference.

The dark and light-induced effects of the porphyrin ligands **8**−**13**, the putative leaving groups of the porphyrin−platinum complexes, and hematoporphyrin are comparatively shown in Figure 1. At a dosage of 1 and 5 μM, no statistically significant cytotoxicity was observed in the dark (Figure 1). At a dosage of 10 μM, there was no dark toxicity for **9**−**12** and hematoporphyrin, whereas the cytotoxic effects of compounds **8** and **13** amounted to a $T/C_{corr.}$ value (see Experimental Section) of approximately 60%. At a concentration of 1 μM, there was also no light-induced toxicity for all substances, whereas at 5 μM compounds **8**, **10**, and **13** showed a phototoxic effect after irradiation (Figure 1). Interestingly, the photoactivation was most effective for porphyrins with the shortest (n = 2) and the longest (n = ~17) side chains. This effect was dose-dependent, i.e., more pronounced at the 10 μM concentration (data not shown).

At a dosage of 1 μM, both the dark and the phototoxicity of the porphyrin−platinum conjugates are influenced by the type of nonleaving group. The platinum complexes with 2,2′-bipyridyl (**40** and **41**), ethyl (*R*/*S*)-2,3-diaminopropionate (**42**−**46**), ethyl (*S*)-2,3-diaminobutanoate (**47**−**51**), and diethyl *meso*-4,5-diaminosuberate (**52**−**55**) ligands were inactive at a concentration of 1 μM, both in the dark and after irradiation. The compounds bearing 1,2-diaminoethane (**27**−**30**) and 1,2-diaminopropane (**31**−**34**) nonleaving groups were also inactive against TCC-SUP cells. The most interesting porphyrin−platinum conjugates were those with the diammine (**21**−**26**) and the (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane (**35**−**39**) ligands. Within these series of compounds, the water-soluble complexes **26** and **39** were most active with $T/C_{corr.}$ values of around 30 and 15%, respectively. At 1 μM concentration, the reference cisplatin had a $T/C_{corr.}$ value of approximately 2%. At this dosage, there was no statistically significant enhancement of the cytotoxicity by irradiation of the bladder cancer cells.

An increase in the concentration of complexes **40**−**55** to 5 μM resulted in no or only marginal augmentation of the dark toxicity (Figure 2). For most of these complexes, the phototoxicity is not much higher than the cytotoxicity observed without irradiation. However, for **42**, **45**, **47**, **49**, **50**, and **53**, there is a distinct effect, and for **40** and **44**, a very strong effect on the proliferativation of the TCC-SUP cells upon irradiation is

observed (Figure 2). The highest synergism was found for compound **52** resulting in the lysis of the tumor cells.

Apart from cisplatin, the highest antitumor activities were measured within the series of porphyrin−platinum conjugates bearing diammine (**21**−**26**) and (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane (**35**−**39**) nonleaving groups. The differences between dark and light-induced toxicities were best for the water-soluble porphyrin−platinum complexes **26** and **39** with a side chain length of $n = \sim 17$ in positions 7 and 12 of the porphyrin leaving group. All of the ethylenediamine and propylenediamine complexes **27**−**34** showed a remarkable light-induced toxicity (Figure 2).

The analysis of the structure−activity relationship (SAR) of several thousand platinum complexes[48,49] revealed some common characteristics, which are supposed to be responsible for antitumor activity.[50−52] Most of the cisplatin analogues are prodrugs and must be activated by solvolysis prior to the coordination with the target bionucleophiles DNA, RNA, and proteins.[51] In contrast to carboplatin where the two carboxylate groups are part of a favored six-membered chelate ring, the replacement of the porphyrin leaving groups in the title compounds should be faster due to the increased ring size. Therefore, these compounds should be stable enough to enter the cell as intact prodrugs but labile enough to react with intracellular biomolecules, resulting in the antitumor activity.

It is widely accepted that the structure of the nonleaving group primarily determines the pharmacokinetic properties of platinum complexes as well as their penetration through the cell membrane. However, quantitative SAR studies suggest that in the case of amine ligands at least one H atom at the nitrogen is essential for cytotoxicity.[53−55] This fact is in agreement with the inactivity of **40** and **41**, both lacking in H atoms at the nitrogens of the bipyridyl nonleaving group.

In the present study, the most active porphyrin−platinum conjugates contained two ammonia ligands (**21**−**26**) and (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane (**35**−**39**) nonleaving groups. This is not surprising since analogous platinum derivates with these ligands are the commercially available drugs cisplatin and oxaliplatin.[56,57]

In addition to the discussed SARs, the differences in antitumor activities can be partly explained by a differential uptake of the various porphyrin−platinum complexes by the tumor cells. We assume that in addition to the aforementioned contribution of the nonleaving group the structure of the hematoporphyrin ligand also affects cell penetration. According to these considerations, the cytocidal activity of porphyrin−platinum conjugates **26** and **39** can be explained by the favorable properties of the nonleaving groups in combination with their high solubility in water.

Multiple Point Chemosensitivitiy Assay. The antitumor activity of the most promising porphyrin−platinum compound **26** was analyzed in detail on the J82 bladder cancer cell line in a kinetic assay. This procedure provides information concerning quality of action (cytotoxic, cytostatic, or cytocidal), inactivation of the test compounds, and potential development of drug resistance.[46,47]

The J82 cells were seeded into microplates, and hematoporphyrin, the porphyrin ligand **13**, cisplatin alone, a combination of cisplatin and hematoporphyin, and the water-soluble porphyrin−platinum conjugate **26** were added after 48 h at a concentration of 0.5 μM. By analogy, to the end point experiment with the TCC-SUP cells, irradiation was performed 24 h after addition of the substances for 10 min with a light dose of 24 J cm^{-2} as indicated by the arrows in Figures 3 and 4. $T/C_{corr.}$ values and the percent cytocidal effect (left ordinate) for the test compounds were plotted together with the absorbances of the untreated solvent control (right ordinate) vs the time of drug exposure.

In these plots of $T/C_{corr.}$ vs time of incubation, time zero indicates the time at which the drug was added. According to the equation of $T/C_{corr.}$, any growth curve for a drug-treated cell population can be reconstructed from the $T/C_{corr.}$ values (filled and open squares) and

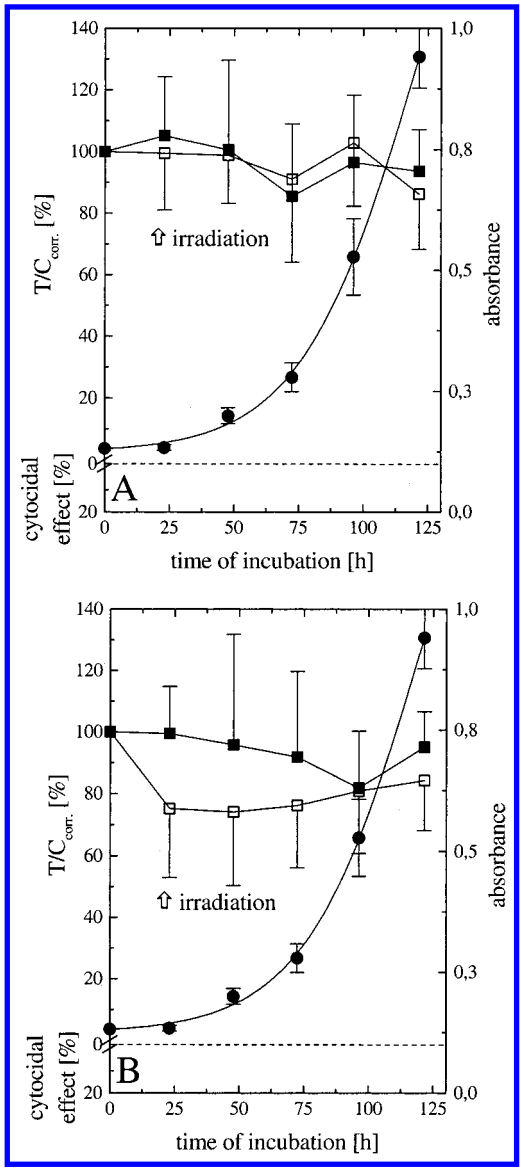


Figure 3. Effect of the reference hematoporphyrin and the porphyrin ligand **13** on the proliferation of long-term incubated J82 bladder cancer cells (in passage 23 from origin) without (filled squares) and with (open squares) irradiation ($\lambda = 600-730$ nm, 10 min, 24 J cm^{-2}) at a concentration of 0.5 μM. Irradiation was performed 24 h after the addition of the test compounds. ●, Proliferation kinetics of the corresponding controls (absorbance at 578 nm); A, hematoporphyrin; (DMF) B, porphyrin ligand **13** (water).

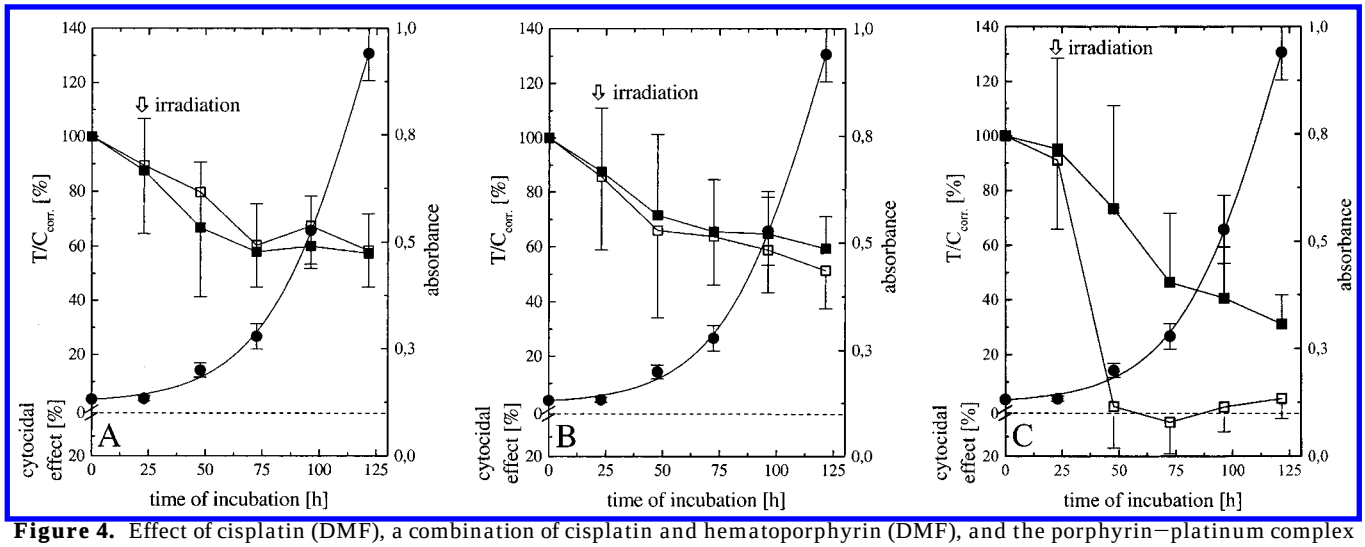


Figure 4. Effect of cisplatin (DMF), a combination of cisplatin and hematoporphyrin (DMF), and the porphyrin−platinum complex **26** (water) on the proliferation of long-term incubated J82 bladder cancer cells (in passage 23 from origin) without (filled squares) and with (open squares) irradiation ($\lambda = 600-730$ nm, 10 min, 24 J cm^{-2}) at a concentration of 0.5 μM. Irradiation was performed 24 h after the addition of the test compounds. ●, Proliferation kinetics of the corresponding controls (absorbance at 578 nm); A, cisplatin; B, cisplatin/hematoporphyrin; C, porphyrin−platinum complex **26**.

the growth curve data of the corresponding solvent control (filled circles). In these experiments, the drug-containing culture media was left unchanged throughout the incubation period.

As shown in Figure 3A, at the dosage of 0.5 μM, clinically established hematoporphyrin did not affect the proliferation of the J82 cells, neither in the dark nor after irradiation. There was also no intrinsic toxicity of the porphyrin ligand **13**, whereas irradiation with incoherent light for 10 min and at 24 J cm^{-2} became effective immediately resulting in cytostasis at a level of approximately 80% $T/C_{corr.}$ (Figure 3B). As expected, the proliferation of the irradiated cell population in the presence of 0.5 μM cisplatin did not differ from that of the nonirradiated cells (Figure 4A). During the course of the experiment, the $T/C_{corr.}$ value dropped from 100 to 60% due to cisplatin's cytotoxicity. Similar cytotoxicities were determined for the combination of 0.5 μM cisplatin and 0.5 μM hematoporphyrin (Figure 4B). A comparison of Figures 3A and 4A,B revealed that there was no synergism of the drug mixture upon irradiation. In the dark, the cytotoxicity of the porphyrin−platinum conjugate **26** is higher than that of cisplatin (Figure 4C). On irradiation, there is a dramatic increase in cytotoxicity, indicated by a steep drop of the $T/C_{corr.}$ curve. The number of the irradiated cells is reduced to the level of the beginning of the experiment (C_0). The light-induced efficacy of the porphyrin−platinum complex **26** exceeds the sum of the phototoxicity of the corresponding porphyrin ligand **13** and the cytotoxicity of cisplatin (Figures 3B and 4A,C).

Conclusion

We synthesized porphyrin-based platinum derivatives bearing a phototoxic ligand, which enhances the cellular uptake and increases the antitumor activity by an additional light-induced toxicity. The water-soluble complexes **26** and **39** are the most promising new porphyrin−platinum conjugates. Provided the hematoporphyrin ligand is responsible for the penetration across the cell membrane and the increased intracellular concentration, the phototoxic effect on TCC-SUP cells observed for the porphyrin−platinum conjugates should be at least as intense as for the corresponding free porphyrin ligand **8**−**13**. This was the case for porphyrin−platinum complexes **27**, **31**, **35**, **40**, and **52** with the 1,4,7-trioxaoctyl groups in positions 7 and 12 of the porphyrin moiety as well as for water-soluble complexes **26** and **39** with the poly(ethylene glycol)-750-monomethyl ether-substituted porphyrins. The weak phototoxic effect observed after incubation of the TCC-SUP cells with **21**, **42**, **46**, **47**, and **51** indicates limited penetration or loss of the porphyrin ligand.

Our ongoing studies are focused on the interrelation of the stability of the porphyrin−platinum conjugates, their accumulation in cells, and the intracellular distribution to understand the mechanism of action of these new photosensitizers having a cytotoxic component in the same molecule. Moreover, we currently optimize the photochemical properties of the porphyrin moiety with respect to an increase in the absorption at a higher wavelength. In this context, it should be mentioned that the used light dose of 24 J cm^{-2} is on the lower level of the intensity range, as there are light doses up to 48 J cm^{-2} in the literature.[58−60] Therefore, we do expect further reduction of the biomass by increasing the light dose. Pharmacokinetic and pharmodynamic in vivo experiments must show whether the new porphyrin−platinum conjugates will contribute to an improved therapy of transitional bladder cancer.

Experimental Section

Chemistry. IR: Beckman spectrometer 4240. ^{1}H NMR: Bruker WM 250 (250 MHz); chemical shifts are given in parts per million; tetramethylsilane was used as internal standard. MS: Finnigan MAT 95 and MAT 112 S, ThermoQuest Finnigan TSQ 7000. The respective molecules are designated as M; in complexes, the porphyrin ligands are designated as L. Mp: Büchi SMP 20; the melting points are not corrected. UV/vis: Kontron Instruments spectrophotometer UVIKON 922.

Solid reagents were used as obtained from commercial suppliers without further purification; liquids were freshly distilled before use. Oligoethylene glycol monomethyl ethers up to four CH_2CH_2O units are commercially available, and pentaethylene glycol monomethyl ether was synthesized ac-

cording to a literature procedure.[61] Column chromatographies were performed using alumina 90 (63−200 μm). The reaction progress was determined by thin-layer chromatography (TLC) analysis on alumina 60 F_{254} (Merck, Darmstadt, Germany).

The nomenclature of the porphyrins and their complexes was based on the recommendation of the IUPAC and the International Union of Biochemistry (IUB).[62] The synthesis of dimethyl 7,12-divinyl-3,8,13,17-tetramethylporphyrin-2,18-dipropionate **1** was performed as described in the literature.[33]

General Procedure 1 (GP 1). A mixture of **1** (3.00 g, 5.08 mmol) and 250 mL of a 33% solution of HBr in glacial acetic acid (Merck) was stirred under a N_2 atmosphere for 24 h at room temperature. After the solvent was removed, 250 mL of the respective alcohol was added to the residual dibromide. The resulting dark purple solution was stirred for 5 d at 50 °C. Besides the etherification of the CH(Me)Br groups, an esterification of the propionic acid side chains occurred. To remove excess alcohol, the reaction mixture was diluted with 300 mL of CH_2Cl_2 and washed with H_2O (5 × 250 mL). The ruby-colored organic layer was dried with Na_2SO_4, and the solvent was removed. The residual reddish brown oil was purified by column chromatography on alumina (40 × 5 cm) using $CHCl_3$ as eluent. The products eluted as broad, red bands, which were isolated, evaporated, and dried in high vacuum.

Bis(1,4,7-trioxaoctyl) 7,12-Bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionate (2). According to GP 1, 250 mL of diethylene glycol monomethyl ether was reacted with the dibromide. Yield: 5.03 g (4.99 mmol, 98%), dark red oil. IR (film): 1730 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 401 (5.31), 498 (4.23), 532 (4.01), 567 (3.93), 621 (3.66), 661 nm (3.56). ^{1}H NMR ($CDCl_3$): δ 10.59 (s, 1H, CH), 10.57 (s, 1H, CH), 10.11 (s, 1H, CH), 10.09 (s, 1H, CH), 6.19 (q, ^3J = 6.7 Hz, 2H, C*H*CH_3), 4.43 (t, ^3J = 7.8 Hz, 4H, CCH_2), 4.21 (m, 4H, $CO_2CH_2CH_2O$), 3.97−2.94 (m, 28H, OCH_2), 3.70 (s, 3H, CCH_3), 3.69 (s, 3H, CCH_3), 3.66 (s, 3H, CCH_3), 3.65 (s, 3H, CCH_3), 3.39 (s, 12H, 4 OCH_3), 3.30 (t, ^3J = 7.8 Hz, 2H, CH_2CO_2), 3.29 (t, ^3J = 7.8 Hz, 2H, CH_2CO_2), 2.27 (d, ^3J = 6.7 Hz, 6H, 2 CHC*H*$_3$), −3.72 (bs, 2H, NH). MS (FAB) *m*/*z* (relative intensity): 1007 (MH, 100). Anal. ($C_{54}H_{78}N_4O_{14}$, 1007.2) C, H, N.

Bis(1,4,7,10-tetraoxaundecyl) 7,12-Bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,-18-dipropionate (3). According to GP 1, 250 mL of triethylene glycol monomethyl ether was reacted with the dibromide. Yield: 5.10 g (4.31 mmol, 85%), dark red oil. IR (film): 1725 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 401 (5.18), 499 (4.11), 532 (3.89), 567 (3.80), 621 (3.53), 660 nm (3.43). ^{1}H NMR ($CDCl_3$): δ 10.55 (s, 1H, CH), 10.52 (s, 1H, CH), 10.12 (s, 1H, CH), 10.08 (s, 1H, CH), 6.17 (q, ^3J = 6.7 Hz, 2H, 2 C*H*CH_3), 4.42 (t, ^3J = 7.6 Hz, 4H, 2 CCH_2), 4.21 (m, 4H, $CO_2CH_2CH_2O$), 3.92−3.44 (m, 44H, OCH_2), 3.69 (s, 3H, CCH_3), 3.66 (s, 3H, CCH_3), 3.64 (s, 3H, CCH_3), 3.63 (s, 3H, CCH_3), 3.38 (s, 12H, 4 OCH_3), 3.27 (t, ^3J = 7.6 Hz, 4H, 2 CH_2CO_2), 2.26 (d, ^3J = 6.7 Hz, 6H, 2 CHC*H*$_3$), 3.74 (bs, 2H, NH). MS (FAB) *m*/*z* (relative intensity): 1183 (MH, 100). Anal. ($C_{62}H_{94}N_4O_{18}$, 1183.4) C, H, N.

Bis(1,4,7,10,13-pentaoxatetradecyl) 7,12-Bis[1-(1,4,7,-10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionate (4). According to GP 1, 250 mL of tetraethylene glycol monomethyl ether was reacted with the dibromide. Yield: 3.30 g (2.43 mmol) dark red, oily product. IR (film): 1720 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 401 (4.75), 498 (3.67), 532 (3.46), 567 (3.38), 622 (3.13), 645 (3.32), 659 nm (3.30). ^{1}H NMR ($CDCl_3$): δ 10.57 (s, 1H, CH), 10.54 (s, 1H, CH), 10.11 (s, 1H, CH), 10.10 (s, 1H, CH), 6.19 (q, ^3J = 6.8 Hz, 2H, 2 C*H*CH_3), 4.43 (t, ^3J = 7.7 Hz, 4H, 2 CCH_2), 4.20 (m, 4H, $CO_2CH_2CH_2O$), 3.94−3.41 (m, 60H, OCH_2), 3.70 (s, 3H, CCH_3), 3.68 (s, 3H, CCH_3), 3.66 (s, 3H, CCH_3), 3.65 (s, 3H, CCH_3), 3.40 (s, 12H, 4 OCH_3), 3.29 (t, ^3J = 7.7 Hz, 4H, 2 CH_2CO_2), 2.27 (d, ^3J = 6.8 Hz, 6H, 2 CHC*H*$_3$), −3.73 (bs, 2H, NH). MS (FAB) *m*/*z* (relative intensity): 1359 (MH, 3), 1315 (MH − OCH_2CH_2, 23), 1271 (MH − 2 OCH_2CH_2, 66), 1227 (MH − 3 OCH_2CH_2, 74), 1183 (MH − 4 OCH_2CH_2, 33). Anal. ($C_{70}H_{110}N_4O_{22}$, 1359.6) C, H, N.

Bis(1,4,7,10,13,16-hexaoxaheptadecyl) 7,12-Bis[1-(1,4,7,-10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionate (5). According to GP 1, 250 mL of pentaethylene glycol monomethyl ether was reacted with the dibromide. Yield: 7.50 g (4.88 mmol), red oil. IR (film): 1730 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 401 (5.16), 499 (4.21), 532 (3.91), 567 (3.82), 621 (3.48), 663 nm (3.78). ^{1}H NMR ($CDCl_3$): δ 10.57 (s, 1H, CH), 10.54 (s, 1H, CH), 10.11 (s, 1H, CH), 10.10 (s, 1H, CH), 6.19 (q, ^3J = 6.5 Hz, 2H, 2 C*H*CH_3), 4.43 (t, ^3J = 7.6 Hz, 4H, 2 CCH_2), 4.21 (m, 4H, $CO_2CH_2CH_2O$), 3.94−3.42 (m, 76H, OCH_2), 3.70 (s, 3H, CCH_3), 3.69 (s, 3H, CCH_3), 3.66 (s, 3H, CCH_3), 3.65 (s, 3H, CCH_3), 3.39 (s, 12H, 4 OCH_3), 3.30 (t, ^3J = 7.6 Hz, 2H, CH_2CO_2), 3.29 (t, ^3J = 7.6 Hz, 2H, CH_2CO_2), 2.27 (d, ^3J = 6.5 Hz, 6H, 2 CHC*H*$_3$), −3.73 (bs, 2H, NH). MS (ESI) *m*/*z* (relative intensity): 1535 (MH, 2), 1447 (MH − 2 OCH_2CH_2, 10), 1359 (MH − 4 OCH_2CH_2, 45), 1271 (MH − 6 OCH_2CH_2, 100). Anal. ($C_{78}H_{126}N_4O_{26}$, 1535.8) C, H, N.

Bis(poly(ethylene glycol)-550-monomethyl ether-1-yl) 7,12-Bis[1-(poly(ethylene glycol)-550-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionate (6). According to GP 1, 250 mL of poly(ethylene glycol)-550-monomethyl ether was reacted with the dibromide. Yield: 10.4 g (3.76 mmol) red, oily solid. IR (film): 1730 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.35), 499 (4.30), 534 (4.10), 568 (4.05), 621 (3.75), 662 nm (4.08). ^{1}H NMR ($CDCl_3$): δ 10.56 (s, 1H, CH), 10.55 (s, 1H, CH), 10.10 (s, 1H, CH), 10.09 (s, 1H, CH), 6.20 (q, ^3J = 6.7 Hz, 2H, 2 C*H*CH_3), 4.44 (t, ^3J = 7.6 Hz, 4H, 2 CCH_2), 4.21−2.75 (m, 220H, OCH_2, CCH_3, OCH_3, CH_2CO_2), 2.29 (d, ^3J = 6.7 Hz, 6H, 2 CHC*H*$_3$), −3.72 (bs, 2H, NH). MS (FAB) *m*/*z* (relative intensity): 2577 (MH − CH_3 − 4OCH_2CH_2, 10), 2401 (MH − CH_3 − 8OCH_2CH_2, 12), 2225 (MH − CH_3 − 12OCH_2CH_2, 14). Anal. ($C_{134}H_{238}N_4O_{54}$, 2769.3).

Bis(poly(ethylene glycol)-750-monomethyl ether-1-yl) 7,12-Bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionate (7). According to GP 1, 250 mL of poly(ethylene glycol)-750-monomethyl ether, which had been melted at 50 °C, was reacted with the dibromide. Yield: 14.1 g (3.86 mmol, 76%), red oil. IR (film): 1725 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.23), 499 (4.19), 534 (4.02), 568 (3.92), 622 (3.63), 662 nm (3.94). ^{1}H NMR ($CDCl_3$): δ 10.58 (s, 1H, CH), 10.56 (s, 1H, CH), 10.10 (s, 1H, CH), 10.08 (s, 1H, CH), 6.19 (q, ^3J = 6.7 Hz, 2H, 2 C*H*CH_3), 4.43 (t, ^3J = 7.6 Hz, 4H, 2 CCH_2), 4.37−2.52 (m, 300H, OCH_2, CCH_3, OCH_3, CH_2CO_2), 2.27 (d, ^3J = 6.7 Hz, 6H, 2 CHC*H*$_3$), −3.73 (bs, 2H, NH). MS (FAB) *m*/*z* (relative intensity): 2577 (MH − CH_3 − 24OCH_2CH_2, 12), 2401 (MH − CH_3 − 28OCH_2CH_2, 16), 2225 (MH − CH_3 − 32OCH_2-CH_2, 17). Anal. ($C_{174}H_{318}N_4O_{74}$, 3650.4).

General Procedure 2 (GP 2). About 2.00 mmol of the respective porphyrin ester was dissolved in 300 mL of a 20% methanolic KOH solution. The resulting mixture was heated to reflux, and the reaction progress was monitored by TLC analysis on alumina with CH_2Cl_2/MeOH 100:1. After 3 h, the reaction was finished and both ester groups were hydrolyzed. The mixture was allowed to cool to room temperature, stirred for another 24 h, and concentrated to about 50 mL. The alkaline mixture was acidified with 7% aqueous HCl solution (pH 4) while cooling with ice and then extracted with CH_2Cl_2 (400 mL). The organic layer was washed three times with water slightly acidified with hydrochloric acid and dried with Na_2SO_4. The solvent was removed, and the red or reddish brown residue was dried in high vacuum.

7,12-Bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionic Acid (8). Compound **2** (2.00 g, 1.99 mmol) was hydrolyzed according to GP 2. Yield: 33 g (1.66 mmol, 83%) reddish brown, oily substance. IR (film): 1715 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.20), 457 (3.99), 498 (4.15), 533 (3.96), 567 (3.86), 621 nm (3.59). ^{1}H NMR ($CDCl_3$): δ 10.63 (s, 1H, CH), 10.58 (s, 1H, CH), 10.03 (s, 1H, CH), 9.93 (s, 1H, CH), 6.19 (q, ^3J = 6.5 Hz, 2H, 2 C*H*CH_3), 4.35 (d, 4H, 2 $CHCH_3OCH_2CH_2$), 4.19 (d, 4H, 2 $CHCH_3$-OCH_2CH_2), 4.02−3.15 (m, 28H, OCH_2, CCH_3, $CCH_2CH_2CO_2$), 3.39 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 2.28 (d, ^3J = 6.5 Hz,

3H, CHC*H*$_3$), 2.26 (d, ^3J = 6.5 Hz, 3H, CHC*H*$_3$). The CO_2H and NH signals could not be detected. MS (FAB) *m/z* (relative intensity): 803 (MH, 100). Anal. ($C_{44}H_{58}N_4O_{10}$, 803.0) H, C: calcd, 65.82; found, 65.37. N: calcd, 6.98; found, 6.50.

7,12-Bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionic Acid (9). Compound **3** (2.40 g, 2.03 mmol) was hydrolyzed according to GP 2. Yield: 1.42 g (1.59 mmol, 79%) reddish brown, oily product. IR (film): 1720 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ): 401 (5.27), 498 (4.18), 532 (3.97), 567 (3.88), 621 (3.61), 661 nm (3.31). ^{1}H NMR ($CDCl_3$): δ 10.60 (s, 1H, CH), 10.58 (s, 1H, CH), 10.06 (s, 1H, CH), 9.99 (s, 1H, CH), 6.20 (q, ^3J = 6.3 Hz, 1H, C*H*CH$_3$), 6.19 (q, ^3J = 6.3 Hz, 1H, C*H*CH$_3$), 4.41 (d, 4H, 2 CHCH$_3$OC*H*$_2$CH$_2$), 4.31 (d, 4H, 2 CHCH$_3$OCH$_2$C*H*$_2$), 4.00−3.20 (m, 42H, OCH$_2$, CCH$_3$, CCH$_2$CH$_2$CO$_2$, OCH$_3$), 2.29 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$), 2.28 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$). The CO_2H and NH signals could not be detected. MS (FAB) *m/z* (relative intensity): 891 (MH, 100). Anal. ($C_{48}H_{66}N_4O_{12}$, 891.1) C: calcd, 64.70; found, 65.17. H: calcd, 7.47; found, 7.95. N: calcd 6.29; found, 5.55.

7,12-Bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,-13,17-tetramethylporphyrin-2,18-dipropionic Acid (10). Compound **4** (2.75 g, 2.02 mmol) was hydrolyzed according to GP 2. Yield: 1.94 g (1.98 mmol, 98%) dark red oil. IR (film): 1720 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (4.84), 498 (3.77), 533 (3.56), 568 (3.50), 621 (3.21), 662 nm (3.17). ^{1}H NMR ($CDCl_3$): δ 10.63 (s, 1H, =CH), 10.58 (s, 1H, =CH), 10.03 (s, 1H, =CH), 9.93 (s, 1H, =CH), 6.17 (q, ^3J = 6.5 Hz, 2H, 2 C*H*CH$_3$), 4.39−3.13 (m, 52H, OCH$_2$, CCH$_3$, CCH$_2$CH$_2$CO$_2$), 3.38 (s, 6H, 2 OCH$_3$), 2.25 (d, ^3J = 6.5 Hz, 6H, 2 CHC*H*$_3$). The CO_2H and the NH signals could not be detected. MS (FAB) *m/z* (relative intensity): 979 (MH, 39), 935 (MH − CO_2, 100), 891 (MH − 2 CO_2, 66). Anal. ($C_{52}H_{74}N_4O_{14}$, 979.2) C, H, N: calcd, 5.72; found, 4.80.

7,12-Bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionic Acid (11). Compound **5** (3.10 g (2.02 mmol) was hydrolyzed according to GP 2. Yield: 2.13 g (2.00 mmol, 99%) red oil. IR (film): 1715 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (4.82), 499 (3.57), 533 (3.26), 568 (3.12), 622 (2.67), 662 nm (2.33). ^{1}H NMR ($CDCl_3$): δ 10.58 (s, 1H, CH), 10.56 (s, 1H, CH), 10.07 (s, 1H, CH), 10.02 (s, 1H, CH), 6.18 (q, ^3J = 6.5 Hz, 2H, 2 C*H*CH$_3$), 4.40−3.16 (m, 60H, OCH$_2$, CCH$_3$, CCH$_2$CH$_2$CO$_2$), 3.38 (s, 3H, OCH$_3$), 3.37 (s, 3H, OCH$_3$), 2.28 (d, ^3J = 6.5 Hz, 6H, 2 CHC*H*$_3$). The CO_2H and the NH signals could not be detected. MS (ESI) *m/z* (relative intensity): 1067 (MH, 10), 979 (MH − 2OCH$_2$-CH$_2$, 28), 891 (MH − 4OCH$_2$CH$_2$, 23). Anal. ($C_{56}H_{82}N_4O_{16}$, 1067.3) C: calcd, 63.02; found, 63.43. H: calcd, 7.74; found, 8.17. N: calcd 5.25; found, 4.70.

7,12-Bis[1-(poly(ethylene glycol)-550-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionic Acid (12). Compound **6** (5.50 g, 1.99 mmol) was hydrolyzed according to GP 2. Yield: 3.32 g (1.97 mmol, 99%) red oil. IR (film): 1715 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.05), 498 (3.99), 532 (3.77), 567 (3.68), 621 (3.44), 648 nm (3.42). ^{1}H NMR ($CDCl_3$): δ 10.56 (s, 1H, CH), 10.54 (s, 1H, CH), 10.01 (s, 1H, CH), 9.99 (s, 1H, CH), 6.14 (q, ^3J = 6.5 Hz, 2H, 2 C*H*CH$_3$), 4.38−3.29 (m, 122H, OCH$_2$, CCH$_3$, CCH$_2$CH$_2$CO$_2$, OCH$_3$), 2.26 (d, ^3J = 6.5 Hz, 6H, 2 CHC*H*$_3$). The CO_2H and the NH signals could not be detected. MS (ESI) *m/z* (relative intensity): 1684 (MH, 65), 1640 (MH − OCH$_2$-CH$_2$, 45), 1596 (MH − 2OCH$_2$CH$_2$, 17). Anal. ($C_{84}H_{138}N_4O_{30}$, 1684.0).

7,12-Bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionic Acid (13). Compound **7** (7.30 g, 2.00 mmol) was hydrolyzed according to GP 2. After the pH was adjusted to 4 with 7% hydrochloric acid and extracted with CH_2Cl_2, a crude product was obtained, which still contained much poly(ethylene glycol). Thus, a strongly basic ion exchanger (Merck, Ionenaustauscher III) was activated with 100 mL of 2 N NaOH and flushed with water until the eluate was neutral. Then, the crude product was dissolved in water and brought onto the ion exchanger, which led to immobilization of the porphyrindicarboxylic acid at the ion exchanger matrix. Excess poly(ethylene glycol) could be removed with water. After 2 N aqueous HCl was put onto the ion exchanger, the porphyrin was eluted, and after the solvent was removed, the product **13** was obtained. Yield: 4.21 g (1.98 mmol, 99%) reddish brown oil. IR (film): 1720 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ): 404 (5.13), 503 (4.13), 536 (3.95), 572 (3.88), 662 nm (3.55). ^{1}H NMR ($CDCl_3$): δ 10.64 (s, 1H, CH), 10.60 (s, 1H, CH), 10.11 (s, 1H, CH), 10.05 (s, 1H, CH), 6.16 (q, ^3J = 6.3 Hz, 2H, 2 C*H*CH$_3$), 4.50−2.93 (m, 162H, OCH$_2$, CCH$_3$, CCH$_2$CH$_2$CO$_2$, OCH$_3$), 2.29 (d, ^3J = 6.3 Hz, 6H, 2 CHC*H*$_3$). The CO_2H and the NH signals could not be detected. MS (FAB) *m/z* (relative intensity): 2124 (MH, 85), 2080 (MH − OCH$_2$CH$_2$, 90), 2036 (MH − 2OCH$_2$CH$_2$, 90), 1992 (MH − 3OCH$_2$CH$_2$, 100). Anal. ($C_{104}H_{178}N_4O_{40}$, 2124.5).

1,2-Diaminoethane(dichloro)platinum(II) (14). Compound **14** was prepared according to a literature procedure.[35] Yield: 70% fine, yellow needles, mp >250 °C. IR (KBr): 3260, 3220, 3180, 2920, 2860, 310 cm^{-1}. Anal. ($C_2H_8Cl_2N_2Pt$, 326.1) C, H, N.

1,3-Diaminopropane(dichloro)platinum(II) (15). Compound **15** was synthesized according to a literature procedure.[35] After recrystallization from hot 3% aqueous HCl solution, the orange product was dried in high vacuum. Yield: 59% orange, shiny plates, mp >250 °C. IR (KBr): 3240, 3200, 3170, 3100, 2940, 2900, 2860 cm^{-1}. Anal. ($C_3H_{10}Cl_2N_2Pt$, 340.1) C, H, N.

(*RR*/*SS*)-*trans*-1,2-Diaminocyclohexane(dichloro)-platinum(II) (16). Compound **16** was synthesized according to a literature procedure.[36] For purification, the crude product was recrystallized from a mixture of acetone/water. Yield: 92% fine, yellow needles, mp >250 °C. IR (KBr): 3260, 3190, 3100, 2920, 2860 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 5.56 (m, 4H, NH_2), 2.11 (m, 2H, C_6H_{10}), 1.86 (m, 2H, C_6H_{10}), 1.45 (m, 2H, C_6H_{10}), 1.23 (m, 2H, C_6H_{10}), 0.99 (m, 2H, C_6H_{10}). Anal. ($C_6H_{14}Cl_2N_2$-Pt, 380.2) C, H, N.

2,2′-Bipyridyl(dichloro)platinum(II) (17). Compound **17** was prepared according to a literature procedure.[36] The crude olive-yellow product was extracted with acetone in a Soxhlet apparatus. Yellow needles crystallized, which were dried in high vacuum. Yield: 65% yellow needles, mp >250 °C. IR (KBr): 3100, 3070, 3050, 3020, 1610, 1600, 340 cm^{-1}. Anal. ($C_{10}H_8Cl_2N_2Pt$, 422.2) C, H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate Dihydrochloride. The title compound was prepared according to a literature procedure.[38] Yield: 98% nearly colorless powder. IR (KBr): 2990, 2930, 1755, 1600, 1500 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.97 (s, 6H, NH_3+), 4.44 (m, 1H, CH), 4.25 (q, ^3J = 7.1 Hz, 2H, 2 $CO_2CH_2CH_3$), 3.36 (m, 2H, CH_2), 1.27 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2CH_3$). MS (FAB) *m/z* (relative intensity): 205 (MH, 18), 133 (MH − 2 HCl). Anal. ($C_5H_{12}N_2O_2$·2HCl, 205.1) C, H, N.

Ethyl (*S*)-2,4-Diaminobutanoate Dihydrochloride. The title compound was prepared according to a literature procedure.[39] Yield: 94%. IR (KBr): 2980, 2920, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 6H, NH_3+), 4.24 (m, 3H, CH, CO_2CH_2-CH_3), 2.98 (m, 2H, NCH_2CH_2), 2.13 (m, 2H, NCH_2CH_2), 1.26 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2CH_3$). MS (FAB) *m/z* (relative intensity): 423 (MH − 2HCl + 3glycerol, 2), 331 (MH − 2HCl + 2glycerol, 9), 239 (MH − 2HCl + glycerol, 15), 147 (MH − 2HCl, 100). Anal. ($C_6H_{14}N_2O_2$ · 2HCl, 219.1) C, H, N.

***meso*-5,5′-Di-2-pyrrolidonyl.** The title compound was prepared according to a literature procedure.[40] After the mixture was dried in high vacuum, a meso/rac mixture 1:1 was obtained in 6.4% yield as a colorless powder (mp >260 °C). The diastereomer mixture was recrystallized from hot H_2O. Colorless needles of the meso diastereomer formed after 10 h at 5 °C, which were washed with acetone and dried in high vacuum. Yield: 2.5%, mp >300 °C. IR (film): 3200, 3090, 2980, 2920, 2880, 1680 cm^{-1}. ^{1}H NMR (DMSO-d_6, meso/rac mixture): δ 7.85 (s, 2H, *meso*-NH), 7.59 (s, 2H, *rac*-NH), 3.44 (m, 4H, CH), 2.10 (m, 8H, CH_2), 1.69 (m, 8H, CH_2). ^{1}H NMR (DMSO-d_6, meso diastereomer): δ 7.86 (s, 2H, NH), 3.41 (m, 2H, CH), 2.08 (m, 4H, CH_2), 1.73 (m, 4H, CH_2). MS (EI) *m/z*

(relative intensity): 168 (M, 3), 84 (M/2, 100). Anal. ($C_8H_{12}N_2O_2$, 168.2) C, H, N.

Diethyl *meso*-4,5-Diaminosuberate Dihydrochloride. The title compound was prepared according to a literature procedure.[41] Yield: 87% slightly brown colored, sticky crystals. IR (KBr): 2970, 2890, 2860, 1715 cm^{-1}. ^1H NMR (CF_3CO_2D): δ 4.34 (q, ^3J = 7.1 Hz, 4H, 2 $CO_2CH_2CH_3$), 4.30 (m, 2H, CH), 2.94 (m, 4H, CH_2CO_2), 2.41 (m, 4H, CH_2), 1.39 (t, ^3J = 7.1 Hz, 6H, 2 $CO_2CH_2CH_3$). The NH_3^+ protons could not be detected. MS (FAB) *m*/*z* (relative intensity): 521 ((M − 2HCl)$_2$H, 4), 333 (MH, 7), 261 (MH − 2HCl, 100). Anal. ($C_{12}H_{24}N_2O_4$·2HCl, 333.3) C, H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate(diiodo)platinum-(II) (18). Compound **18** was prepared according to a literature procedure.[39] Yield: 72% yellow solid, mp >228 °C dec. IR (KBr): 3260, 3240, 3180, 3100, 2980, 2940, 2920, 2890, 1740, 280 cm^{-1}. ^1H NMR (DMF-d_7): δ 5.86−5.28 (m, 4H, NH_2), 4.21 (q, ^3J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.89−3.77 (m, 1H, CH), 3.02−2.97 (m, 2H, CH_2), 1.25 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2CH_3$). MS (FAB) *m*/*z* (relative intensity): 659 (MH + DMSO, 2), 610 (LPtI(DMSO)$_2$, 2), 532 (LPtI(DMSO), 14). Anal. ($C_5H_{12}I_2N_2O_2$-Pt, 581.1) C, H, N.

Ethyl (*S*)-2,4-Diaminobutanoate(diiodo)platinum(II) (19). Compound **19** was prepared according to a literature procedure.[39] Yield: 59% yellow crystals, mp >218 °C dec. IR (KBr): 3240, 3220, 3160, 3100, 2970, 2950, 2900, 2870, 1700, 310 cm^{-1}. ^1H NMR (DMF-d_7): δ 6.46−4.91 (m, 4H, NH_2), 4.21 (q, ^3J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.90−3.52 (m, 1H, CH), 3.03−2.77 (m, 2H, NCH_2CH_2), 2.35−1.92 (m, 2H, NCH_2CH_2), 1.26 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2CH_3$). MS (FAB) *m*/*z* (relative intensity): 673 (MH + DMSO, 2), 623 (LPtI(DMSO)$_2$, 11), 545 (LPtI(DMSO), 100), 467 (LPtI, 4). Anal. ($C_6H_{14}I_2N_2O_2Pt$, 595.1) C, H, N.

Diethyl *meso*-4,5-Diaminosuberate(diiodo)platinum-(II) (20). To a solution of K_2PtCl_4 (480 mg, 1.15 mmol) in 10 mL of H_2O, KI (1.90 g, 11.4 mmol) was added and the solution was stirred for 24 h at room temperature. The mixture was evaporated, and the residue was dissolved in 60 mL of abs EtOH. Then, 380 mg (1.14 mmol) of diethyl *meso*-4,5-diaminosuberate dihydrochloride and 86.4 mg (2.16 mmol) of NaOH were added. After the mixture was stirred for 5 h, the precipitate was filtered off and washed with EtOH. The yellow solid was recrystallized from 100 mL of acetone/H_2O 1:1 (after cooling to 5 °C), washed with H_2O, and dried in high vacuum. Yield: 153 mg (0.216 mmol, 19%) yellow crystals, mp >190 °C dec. IR (KBr): 3240, 3210, 3130, 2990, 2940, 2910, 1730, 320 cm^{-1}. ^1H NMR (DMF-d_7): δ 5.72−5.04 (m, 4H, NH_2), 4.11 (q, ^3J = 7.1 Hz, 4H, 2 $CO_2CH_2CH_3$), 3.01−2.96 (m, 2H, CH), 2.65 (t, ^3J = 7.6 Hz, 4H, 2 CH_2CO_2), 2.12 (m, 4H, $NCHCH_2$), 1.22 (t, ^3J = 7.1 Hz, 6H, 2 $CO_2CH_2CH_3$). MS (FAB) *m*/*z* (relative intensity): 865 (MH + 2DMSO, 1), 787 (MH + DMSO, 11), 659 (LPtI(DMSO), 100), 518 (LPtI, 10). Anal. ($C_{12}H_{24}I_2N_2O_4Pt$, 709.2) C, H, N.

General Procedure 3 (GP 3). Diammine(diaqua)platinum(II) hydroxide was synthesized from diammine(dichloro)-platinum(II) (cisplatin) as previously described.[24] After the solvent was removed, a glassy solid was obtained, which was dissolved in a 1:1 mixture of water/ethanol just before reaction with the respective porphyrindicarboxylic acid ligands. Compounds **8**−**11** were dissolved in ethanol, and the water-soluble ligands **12** and **13** were dissolved in water before an equimolar amount of diammine(diaqua)platinum(II) hydroxide was added. The solution was stirred for at least 18 h at room temperature. The precipitated complexes **21**−**24** were filtered off, washed with water and ethanol, and dried in vacuo. In the case of the water-soluble complexes **25** and **26**, CH_2Cl_2 was added to the aqueous solution and the mixture was extracted with water. The aqueous phase was evaporated to obtain the product.

Diammine{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,-17-tetramethylporphyrin-2,18-dipropionato}platinum-(II) (21). According to GP 3, **8** (80.3 mg, 0.100 mmol) was dissolved in 6 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum(II) hydroxide solution, and stirred for 20 h. Yield: 23.0 mg (22.3 μmol, 22%) dark brown powder, mp >250 °C. IR (KBr): 1640, 1630 (C═O); 375 cm^{-1} (PtO). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.05), 502 (4.07), 536 (3.89), 570 (3.81), 622 (3.53), 662 nm (3.27). MS (FAB) *m*/*z* (relative intensity): 1030 (MH, 100). Anal. ($C_{44}H_{62}N_6O_{10}$-Pt, 1030.1) C: calcd, 51.30; found, 50.75. H: calcd, 6.07; found, 5.49. N.

Diammine{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}-platinum(II) (22). According to GP 3, **9** (89.1 mg, 0.100 mmol) was dissolved in 10 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum(II) hydroxide solution, and stirred for 4 d. Yield: 40.0 mg (35.8 μmol, 36%) brown powder, mp >250 °C. IR (KBr): 1630, 1620 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (4.64), 502 (3.66), 536 (3.49), 570 (3.36), 623 (3.10) nm. MS (FAB) *m*/*z* (relative intensity): 1179 (MH − NH_3 + DMSO, 40). Anal. ($C_{48}H_{70}N_6O_{12}Pt$, 1118.2) C: calcd, 51.56; found, 50.97. H, N.

Diammine{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)-ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}-platinum(II) (23). According to GP 3, **10** (97.9 mg, 0.100 mmol) was dissolved in 5 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum(II) hydroxide solution, and stirred for 18 h. Yield: 16.0 mg (13.3 μmol, 13%) dark brown powder, mp >250 °C. IR (KBr): 1630, 1620 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.38), 503 (4.45), 536 (4.32), 572 (4.24), 623 nm (4.04). MS (FAB) *m*/*z* (relative intensity): 1267 (MH − NH_3 + DMSO, 80). Anal. ($C_{52}H_{78}N_6O_{14}$-Pt, 1206.3) C: calcd, 51.78; found, 51.21. H, N.

Diammine{7,12-bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (24). According to GP 3, **11** (107 mg, 0.100 mmol) was dissolved in 10 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum-(II) hydroxide solution, and stirred for 2 d. Yield: 21.0 mg (16.2 μmol, 16%) dark brown solid, mp >250 °C. IR (KBr): 1620, 1600 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.13), 499 (4.05), 534 (3.85), 568 (3.76), 621 (3.49), 662 nm (3.27). ^1H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H, ═CH), 10.53 (s, 1H, ═CH), 10.10 (s, 1H, ═CH), 10.01 (s, 1H, ═CH), 6.18 (q, ^3J = 6.6 Hz, 2H, 2 $CHCH_3$), 4.48−2.88 (m, 66H, OCH_2, CCH_3, $CCH_2CH_2CO_2$, OCH_3), 2.33 (d, ^3J = 6.6 Hz, 6H, 2 $CHCH_3$), −3.78 (bs, 2H, NH). The NH_3 signals could not be detected. MS (ESI) *m*/*z* (relative intensity): 1294 (MH, 17), 1206 (MH − 2OCH_2CH_2, 65), 1118 (MH − 4OCH_2CH_2, 65). Anal. ($C_{56}H_{86}N_6O_{16}Pt$, 1294.4) C: calcd, 51.96; found, 51.01. H, N.

Diammine{7,12-bis[1-(poly(ethylene glycol)-550-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (25). According to GP 3, **12** (168 mg, 0.100 mmol) was dissolved in 10 mL of H_2O, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum-(II) hydroxide solution, and stirred for 5 d. Yield: 39.0 mg (20.4 μmol, 20%) brown powder, mp >250 °C. IR (KBr): 1640, 1630 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.14), 499 (4.10), 5.35 (3.96), 569 (3.88), 621 (3.60), 649 (3.63), 662 (3.59) nm. MS (FAB) *m*/*z* (relative intensity): 1911 (MH, 48), 1867 (MH − OCH_2CH_2, 52), loss of 2−8 OCH_2CH_2 units, int. 70−94, 1515 (MH − 9OCH_2CH_2, 100). Anal. ($C_{84}H_{142}N_6O_{30}Pt$, 1911.1).

Diammine{7,12-bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (26). According to GP 3, **13** (212 mg, 0.100 mmol) was dissolved in 10 mL of H_2O, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum-(II) hydroxide solution, and stirred for 3 d. Yield: 71.8 mg (30.5 μmol, 31%) dark purple powder, mp >250 °C. IR (KBr): 1630, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.46), 504 (4.43), 537 (4.27), 574 (4.15), 625 (3.83), 664 (3.52) nm. MS (ESI) *m*/*z* (relative intensity): 1454 (MH − NH_3 − 20OCH_2CH_2, 62), loss of 21−23 OCH_2CH_2 units, int. 74−95, 1278 (MH − NH_3 − 24OCH_2CH_2, 100). Anal. ($C_{104}H_{182}N_6O_{40}Pt$, 2351.7).

General Procedure 4 (GP 4). About 0.100 mmol of the respective diamine(dichloro)platinum(II) complex was suspended in ca. 15 mL of water. After 10 min of ultrasonic treatment, the 2-fold amount of $AgNO_3$ was added and the mixture was stirred for 7 d in the dark. The precipitated AgCl

was filtered off and washed with H_2O. Fifteen grams of a strongly basic ion exchanger (Merck, Ionenaustauscher III) was activated with 100 mL of 2 N NaOH and flushed with water until the eluate was neutral. The filtrate was brought onto the ion exchanger and eluted with water. The eluate was evaporated. The residue was dissolved in 15 mL of water, before it was combined with a solution of the respective porphyrindicarboxylic acid (0.100 mmol) in H_2O or EtOH. After the mixture was stirred for 2 d in the dark at room temperature, the reaction mixture was concentrated. The precipitated product was filtered off, washed with water and EtOH, and dried in vacuo.

1,2-Diaminoethane{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}-platinum(II) (27). According to GP 4, 80.3 mg (0.100 mmol) of **8** in 10 mL of EtOH was reacted with 0.100 mmol of activated **14**. Yield: 33.0 mg (31.2 μmol, 31%) brown solid, mp >250 °C. IR (KBr): 1620, 1600 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ): 403 (4.88), 503 (3.83), 536 (3.64), 572 (3.54), 623 (3.19) nm. MS (ESI) *m/z* (relative intensity): 1056 (MH, 100), 528.5 (M + 2H, dipositive cation, 92). Anal. ($C_{46}H_{64}N_6O_{10}Pt$, 1056.1) C, H: calcd, 6.11; found, 5.68. N: calcd, 7.96; found, 8.36.

1,2-Diaminoethane{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (28). According to GP 4, 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH was reacted with 0.100 mmol of activated **14**. Yield: 37.0 mg (32.3 μmol, 32%) dark purple powder, mp >250 °C. IR (KBr): 1630, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.10), 499 (4.08), 534 (3.87), 568 (3.79), 622 (3.50), 662 (3.19) nm. MS (ESI) *m/z* (relative intensity): 1144 (MH, 24), 572.5 (M + 2H, dipositive cation, 100). Anal. ($C_{50}H_{72}N_6O_{12}Pt$, 1144.2) C, H, N.

1,2-Diaminoethane{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (29). According to GP 4, 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH was reacted with 0.100 mmol of activated **14**. Yield: 40.0 mg (32.5 μmol, 33%) dark purple solid, mp >250 °C. IR (KBr): 1630, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 404 (4.93), 503 (4.03), 537 (3.86), 572 (3.76), 622 (3.50), 663 nm (3.24). MS (FAB) *m/z* (relative intensity): 1233 (MH, 100). Anal. ($C_{54}H_{80}N_6O_{14}Pt$, 1232.3) C: calcd, 52.63; found, 52.04. H, N.

1,2-Diaminoethane{7,12-bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (30). According to GP 4, 107 mg (0.100 mmol) of **11** in 10 mL of EtOH was reacted with 0.100 mmol of activated **14**. Yield: 46.0 mg (34.8 μmol, 35%) dark blue solid, mp >250 °C. IR (KBr): 1620, 1600 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.22), 499 (4.15), 534 (3.93), 568 (3.82), 621 (3.56), 661 (3.16) nm. MS (ESI) *m/z* (relative intensity): 1321 (MH, 20), 1233 (MH − $2OCH_2CH_2$, 73), 1145 (MH − $4OCH_2CH_2$, 59), 661 (M + 2H, dipositive cation, 15), 617 (M − $2OCH_2CH_2$ + 2H, dipositive cation, 60), 573 (M − $4OCH_2CH_2$ + 2H, dipositive cation, 100). Anal. ($C_{58}H_{88}N_6O_{16}$-Pt, 1320.4) C: calcd, 52.76; found, 51.94. H, N.

1,3-Diaminopropane{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}-platinum(II) (31). According to GP 4, 80.3 mg (0.100 mmol) of **8** in 10 mL of EtOH was reacted with 0.100 mmol of activated **15**. Yield: 25.0 mg (23.4 μmol, 23%) dark brown solid; mp 245 °C. IR (KBr): 1640, 1620 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 407 (5.13), 504 (4.12), 537 (3.94), 573 (3.86), 622 (3.48), 663 nm (3.27). MS (ESI) *m/z* (relative intensity): 1070 (MH, 21). Anal. ($C_{47}H_{66}N_6O_{10}Pt$, 1070.1) C: calcd, 52.75; found, 52.14. H, N: calcd, 7.85; found, 7.42.

1,3-Diaminopropane{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (32). According to GP 4, 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH was reacted with 0.100 mmol of activated **15**. Yield: 26.0 mg (22.4 μmol, 22%) dark brown powder; mp 237 °C. IR (KBr): 1640, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.27), 503 (4.26), 536 (4.07), 570 (3.95), 622 (3.65), 662 nm (3.20). MS (ESI) *m/z* (relative intensity): 1158 (MH, 6). Anal. ($C_{51}H_{74}N_6O_{12}Pt$, 1158.2) C: calcd, 52.89; found, 51.92. H, N.

1,3-Diaminopropane{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (33). According to GP 4, 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH was reacted with 0.100 mmol of activated **15**. Yield: 29.0 mg (23.3 μmol, 23%) dark brown solid; mp 250 °C. IR (KBr): 1630, 1620 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 404 (5.23), 503 (4.25), 536 (4.07), 571 (3.96), 622 (3.67), 661 nm (3.27). MS (ESI) *m/z* (relative intensity): 1246 (MH, 8), 1202 (MH − OCH_2CH_2, 31), 1158 (MH − $2OCH_2CH_2$, 24). Anal. ($C_{55}H_{82}N_6O_{14}Pt$, 1246.4) C: calcd, 53.00; found, 52.27. H, N.

1,3-Diaminopropane{7,12-bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,-18-dipropionato}platinum(II) (34). According to GP 4, 107 mg (0.100 mmol) of **11** in 10 mL of EtOH was reacted with 0.100 mmol of activated **15**. Yield: 10.2 mg (7.64 μmol, 8%) dark brown powder; mp >250 °C. IR (KBr): 1635, 1610 cm^{-1} (C═O). 403 (5.16), 501 (4.12), 536 (3.92), 570 (3.83), 622 (3.55), 663 nm (3.24). MS (ESI) *m/z* (relative intensity): 1335 (MH, 16), 1247 (MH − $2OCH_2CH_2$, 84), 1159 (MH − $4OCH_2CH_2$, 81). Anal. ($C_{59}H_{90}N_6O_{16}Pt$, 1334.5) C: calcd, 53.10; found, 52.31. H, N.

(*RR/SS*)-*trans*-1,2-Diaminocyclohexane{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (35). According to GP 4, 80.2 mg (0.100 mmol) of **8** in 10 mL of EtOH was reacted with 0.100 mmol of activated **16**. Yield: 23.4 mg (21.1 μmol, 21%) reddish brown solid; mp >250 °C. IR (KBr): 1620, 1600 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ): 405 (5.22), 503 (4.19), 536 (4.02), 573 (3.95), 662 (3.64) nm. MS (ESI) *m/z* (relative intensity): 1110 (MH − $4H_2O$, 100), 555.5 (M − $4H_2O$ + 2H, dipositive cation, 80). Anal. ($C_{50}H_{70}N_6O_{10}Pt\cdot 4\ H_2O$, 1182.3) C, H: calcd, 6.65; found, 6.10. N: calcd, 7.11; found, 7.54.

(*RR/SS*)-*trans*-1,2-Diaminocyclohexane{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (36). According to GP 4, 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH was reacted with 0.100 mmol of activated **16**. Yield: 18.7 mg (15.6 μmol, 16%) dark purple powder; mp >250 °C. IR (KBr): 1630, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 405 (4.94), 503 (4.00), 537 (3.85), 572 (3.76), 623 (3.51) nm. MS (ESI) *m/z* (relative intensity): 1199 (MH, 100), 600 (M + 2H, 73). Anal. ($C_{54}H_{78}$-$N_6O_{12}Pt$, 1198.3) C: calcd, 54.12; found, 53.51. H, N: calcd, 7.01; found, 7.35.

(*RR/SS*)-*trans*-1,2-Diaminocyclohexane{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (37). According to GP 4, 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH was reacted with 0.100 mmol of activated **16**. Yield: 35.4 mg (25.7 μmol, 26%) dark brown solid; mp >250 °C. IR (KBr): 1620, 1600 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 405 (4.99), 504 (4.13), 536 (3.97), 573 (3.86), 623 (3.62) nm. MS (ESI) *m/z* (relative intensity): 1287 (MH − $5H_2O$, 4), 1243 (MH − $5H_2O$ − OCH_2CH_2, 13), 1199 (MH − $5H_2O$ − $2OCH_2CH_2$, 9). Anal. ($C_{58}H_{86}N_6O_{14}Pt\cdot 5H_2O$, 1376.5) C, H, N.

(*RR/SS*)-*trans*-1,2-Diaminocyclohexane{7,12-bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (38). According to GP 4, 107 mg (0.100 mmol) of **11** in 10 mL of EtOH was reacted with 0.100 mmol of activated **16**. Yield: 25.5 mg (17.2 μmol, 17%) reddish brown powder; mp 245 °C. IR (KBr): 1630, 1600 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.18), 499 (4.10), 534 (3.90), 568 (3.80), 621 (3.52), 661 (3.31) nm. ^{1}H NMR ($CDCl_3$): δ 10.58 (s, 1H, CH), 10.55 (s, 1H, CH), 10.07 (s, 1H, CH), 10.04 (s, 1H, CH), 6.18 (q, ^3J = 6.4 Hz, 2H, 2 C*H*CH_3), 4.47−3.03 (m, 62H, CH_2O, CCH_3, CCH_2-CH_2CO_2, C*H*NH_2), 3.38 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.28 (d, ^3J = 6.4 Hz, 6H, 2 CHC*H*$_3$), 1.25 (m, 8H, CH_2), −3.76 (bs, 2H, NH). The NH_2 signals could not be detected. MS (ESI) *m/z* (relative intensity): 1375 (MH − $6H_2O$, 9), 1287 (MH − $6H_2O$ − $2OCH_2CH_2$, 32), 1199 (MH − $6H_2O$ − $4OCH_2CH_2$, 100), 688 (M − $6H_2O$ + 2H, dipositive cation, 5), 644 (M −

$6H_2O - 2OCH_2CH_2 + 2H$, dipositive cation, 20), 600 (M − $6H_2O - 4OCH_2CH_2 + 2H$, dipositive cation, 28). Anal. ($C_{62}H_{94}N_6O_{16}Pt \cdot 6H_2O$, 1482.6) C: calcd, 50.23; found, 49.02. H: calcd, 7.21; found, 6.33. N: calcd, 5.67; found, 6.41.

(*RR*/*SS*)-*trans*-1,2-Diaminocyclohexane{7,12-bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (39). According to GP 4, 212 mg (0.100 mmol) of **13** in 10 mL of H_2O was reacted with 0.100 mmol of activated **16**. CH_2Cl_2 was added to the solution, and the reaction mixture was extracted with water. The aqueous phase was evaporated to obtain the product. Yield: 46.8 mg (19.2 μmol, 19%) dark purple powder; mp >250 °C. IR (KBr): 1630, 1610 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 404 (5.19), 503 (4.21), 537 (4.04), 572 (3.93), 624 (3.61) nm. MS (ESI) *m*/*z* (relative intensity): 1023 (MH − $32OCH_2CH_2$, 5), 979 (MH − $33OCH_2CH_2$, 8), 935 (MH − $34OCH_2CH_2$, 11). Anal. ($C_{110}H_{190}N_6O_{40}Pt$, 2431.8).

2,2′-Bipyridyl{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (40). A 42.2 mg (0.100 mmol) amount of **17** was suspended in 15 mL of H_2O. After 10 min of ultrasonic treatment, 34.0 mg (0.200 mmol) of $AgNO_3$ was added and the mixture was stirred for 4 d in the dark at room temperature. The precipitated AgCl was filtered off and washed with water. The filtrate containing the activated platinum(II) complex was evaporated. The residue was dissolved in 5 mL of H_2O and combined with a solution of **8** (80.3 mg, 0.100 mmol) in 10 mL of EtOH. After the mixture was stirred for 20 h at 50 °C and cooled to room temperature, the precipitated solid was filtered, washed with water and EtOH, and dried in vacuo. Yield: 64.0 mg (55.5 μmol, 55%) dark purple powder; mp >250 °C. IR (KBr): 1720 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.04), 503 (4.09), 536 (3.91), 571 (3.86), 623 (3.58) nm. MS (FAB) *m*/*z* (relative intensity): 1152 (MH, 49), 1078 (MH − $OCH_2CH_2OCH_3$, 100), 1003 (MH − $2OCH_2CH_2OCH_3$; 98). Anal. ($C_{54}H_{64}N_6O_{10}Pt$, 1152.2) C, H, N.

2,2′-Bipyridyl{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (41). As described for complex **40**, 89.1 mg (0.100 mmol) of **9** was reacted with 0.100 mmol of **17**. Yield: 28.7 mg (23.1 μmol, 23%) dark purple solid; mp 201 °C. IR (KBr): 1720 cm^{-1} (C═O). UV/vis (DMF) λ_{max} (log ϵ): 402 (5.14), 502 (4.15), 533 (3.99), 569 (3.93), 623 (3.72), 664 (3.40) nm. MS (FAB) *m*/*z* (relative intensity): 1241 (MH, 45), 1122 (MH − $OCH_3 - 2OCH_2CH_2$, 100), 1003 (MH − $2OCH_3 - 4OCH_2CH_2$, 82). Anal. ($C_{58}H_{72}N_6O_{12}Pt$, 1240.3) C: calcd, 56.17; found, 56.64. H: calcd, 5.85; found, 6.34. N.

General Procedure 5 (GP 5). The respective diamine(diiodo)platinum(II) complex (0.100 mmol) was suspended in 15 mL of water. After 3 h of ultrasonic treatment, 34.0 mg (0.200 mmol) of $AgNO_3$ was added and the mixture was stirred for 7 d in the dark. The precipitated AgI was filtered off and washed with H_2O. The filtrate was evaporated. The glassy residue was dissolved in 15 mL of water, before it was combined with a solution of the respective porphyrindicarboxylic acid (0.100 mmol) in H_2O or EtOH. The pH of the solution was adjustified to 6 with 0.1 M NaOH, and the reaction mixture was stirred for 2 d in the dark at room temperature. After the solution was concentrated, the precipitated product was filtered off, washed with water and EtOH, and dried in vacuo.

Ethyl (*R*/*S*)-2,3-Diaminopropionate{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (42). According to GP 5, 58.1 mg (0.100 mmol) of **18** was reacted with a solution of 80.2 mg (0.100 mmol) of the porphyrindicarboxylic acid **8** in 10 mL of EtOH. Yield: 51.1 mg (43.9 μmol, 44%) reddish brown powder; mp 250 °C. IR (KBr): 1740, 1730 (C═O, ester), 1640, 1630 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.29), 499 (4.22), 534 (4.01), 568 (3.90), 621 (3.62) nm. ^{1}H NMR (DMSO-d_6): δ 10.71 (s, 1H, CH), 10.62 (s, 1H, CH), 10.57 (s, 1H, CH), 10.25 (s, 1H, CH), 6.26 (q, ^3J = 6.3 Hz, 1H, C*H*CH$_3$), 6.14 (q, ^3J = 6.3 Hz, 1H, C*H*CH$_3$), 4.40−2.60 (m, 47H, OCH_2-CH_2, CCH_3, $CCH_2CH_2CO_2$, OCH_3, NCH, NCH_2, $CO_2CH_2CH_3$), 2.19 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$), 2.17 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$), 0.88 (t, ^3J = 6.9 Hz, 3H, $CO_2CH_2CH_3$), −3.96 (bs, 2H, NH). The NH_2 signals could not be detected. MS (FAB) *m*/*z* (relative intensity): 1128 (MH − $2H_2O$, 100). Anal. ($C_{49}H_{68}N_6O_{12}Pt \cdot 2H_2O$, 1164.2) C, H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (43). According to GP 5, 58.1 mg (0.100 mmol) of **18** was reacted with a solution of 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH. Yield: 10.9 mg (8.96 μmol, 9%) purple powder; mp >250 °C. IR (KBr): 1735 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.31), 499 (4.19), 533 (3.99), 567 (3.87), 622 (3.59) nm. MS (FAB) *m*/*z* (relative intensity): 1216 (MH, 100). Anal. ($C_{53}H_{76}N_6O_{14}Pt$, 1216.3) C: calcd, 52.34; found, 51.65. H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (44). According to GP 5, 58.1 mg (0.100 mmol) of **18** was reacted with a solution of 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH. Yield: 26.6 mg (19.3 μmol, 19%) reddish brown solid; mp >250 °C. IR (KBr): 1740, 1730 (C═O, ester), 1640, 1630 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.22), 500 (4.18), 534 (3.98), 570 (3.87), 623 (3.59), 661 (3.23) nm. MS (ESI) *m*/*z* (relative intensity): 1327 (MNa − $4H_2O$, 20), 1305 (MH − $4H_2O$, 32), 1283 (MNa − $4H_2O - OCH_2CH_2$, 43), 1261 (MH − $4H_2O - OCH_2CH_2$, 100), 1239 (MNa − $4H_2O - 2OCH_2CH_2$, 18), 1217 (MH − $4H_2O - 2OCH_2CH_2$, 84). Anal. ($C_{57}H_{84}N_6O_{16}Pt \cdot 4H_2O$, 1376.5) C: calcd, 49.74; found, 48.90. H: calcd, 6.74; found, 5.81. N: calcd, 6.11; found, 6.85.

Ethyl (*R*/*S*)-2,3-Diaminopropionate{7,12-bis[1-(1,4,7,10,13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (45). According to GP 5, 58.1 mg (0.100 mmol) of **18** was reacted with a solution of 107 mg (0.100 mmol) of **11** in 10 mL of EtOH. Yield: 10.9 mg (7.83 μmol, 8%) reddish brown solid; mp >250 °C. IR (KBr): 1730, 1720 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (CH_2Cl_2) λ_{max} (log ϵ): 402 (5.17), 499 (4.08), 534 (3.87), 569 (3.77), 622 (3.49), 662 (3.02) nm. MS (ESI) *m*/*z* (relative intensity): 1393 (MH, 2), 1305 (MH − $2OCH_2CH_2$, 11), 1217 (MH − $4OCH_2CH_2$, 25). Anal. ($C_{61}H_{92}N_6O_{18}Pt$, 1392.49) C: calcd, 52.61; found, 52.15. H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate{7,12-bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (46). According to GP 5, 58.1 mg (0.100 mmol) of **18** was reacted with a solution of 212 mg (0.100 mmol) of **13** in 10 mL of H_2O. After the mixture was stirred for 2 d in the dark, the reaction mixture was evaporated and the residue was chromatographed on silica (15 cm × 1.5 cm). With CH_2Cl_2/MeOH 5:1, the product eluted as a broad, red band. Yield: 69.0 mg (28.2 μmol, 28%) brown, oily solid. IR (KBr): 1740, 1730 (C═O, ester), 1640, 1630 cm^{-1} (C═O, carboxylate). UV/vis (H_2O) λ_{max} (log ϵ): 397 (4.91), 499 (3.88), 435 (3.68), 568 (3.64), 619 (3.44), 650 (3.56) nm. MS (FAB) *m*/*z* (relative intensity): 2449 (MH, 60), 2405 (MH − OCH_2CH_2, 71), loss of 2−5 OCH_2CH_2 units, int. 73−80. Anal. ($C_{109}H_{188}N_6O_{42}Pt$, 2449.8).

Ethyl (*S*)-2,4-Diaminobutanoate{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (47). According to GP 5, 59.5 mg (0.100 mmol) of **19** was reacted with a solution of 80.2 mg (0.100 mmol) of **8** in 10 mL of EtOH. Yield: 19.3 mg (15.7 μmol, 16%) black powder; mp >250 °C. IR (KBr): 1730 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 403 (5.24), 502 (4.18), 535 (3.99), 569 (3.89), 622 (3.58) nm. ^{1}H NMR (DMF-d_7): δ 10.84 (s, 1H, CH), 10.73 (s, 1H, CH), 10.68 (s, 1H, CH), 10.33 (s, 1H, CH), 6.40 (m, 2H, C*H*CH$_3$), 4.38 (m, 4H, CCH_2), 4.02−3.04 (m, 40 H, OCH_2CH_2, CCH_3, CH_2CO_2, OCH_3, $CO_2CH_2CH_3$), 2.39 (m, 1H, NCH_2CH_2), 2.19 (m, 1H, NCH_2CH_2), 2.24 (d, ^3J = 5.9 Hz, 6H, 2 CHC*H*$_3$), 0.99 (t, ^3J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), −3.66 (bs, 2H, NH). The

NCH and NCH_2 signals could not be detected. MS (FAB) *m/z* (relative intensity): 1142 (MH − $5H_2O$, 100). Anal. ($C_{50}H_{70}N_6O_{12}Pt·5H_2O$, 1232.3) C, H: calcd, 6.54; found, 6.11. N.

Ethyl (*S*)-2,4-Diaminobutanoate{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (48). According to GP 5, 59.5 mg (0.100 mmol) of **19** was reacted with a solution of 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH. Yield: 31.2 mg (25.4 μmol, 25%) purple solid; mp 90 °C. IR (KBr): 1725 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.10), 498 (4.01), 533 (3.78), 568 (3.70), 621 (3.39), 658 (3.28) nm. ^1H NMR ($CDCl_3$): δ 10.57 (s, 1H, CH), 10.45 (s, 1H, CH), 10.09 (s, 1H, CH), 9.90 (s, 1H, CH), 6.16 (q, ^3J = 6.3 Hz, 2H, 2 C*H*CH_3), 4.50−2.64 (m, 52H, OCH_2CH_2, CCH_3, $CCH_2CH_2CO_2$, OCH_3, $CO_2CH_2CH_3$), 2.27 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$), 2.22 (d, ^3J = 6.3 Hz, 3H, CHC*H*$_3$), 2.23 (m, 2H, NCH_2CH_2), 0.85 (t, ^3J = 6.3 Hz, 3H, $CO_2CH_2CH_3$), −4.08 (bs, 2H, NH). The NCH and NCH_2 signals could not be detected. MS (FAB) *m/z* (relative intensity): 1230 (MH, 100). Anal. ($C_{54}H_{78}N_6O_{14}Pt$, 1230.3) C: calcd, 52.72; found, 54.50. H: calcd, 6.39; found, 6.94. N: calcd, 6.83; found, 5.84.

Ethyl (*S*)-2,4-Diaminobutanoate{7,12-bis[1-(1,4,7,10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (49). According to GP 5, 59.5 mg (0.100 mmol) of **19** was reacted with a solution of 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH. Yield: 16.9 mg (12.8 μmol, 13%) reddish brown powder; mp >250 °C. IR (KBr): 1735 (C═O, ester), 1640, 1630 cm^{-1} (C═O, carboxylate). UV/vis (DMF) λ_{max} (log ϵ): 403 (4.93), 502 (3.90), 536 (3.73), 572 (3.62), 623 (3.34) nm. MS (FAB) *m/z* (relative intensity): 1319 (MH, 100). Anal. ($C_{58}H_{86}N_6O_{16}Pt$, 1318.4) C: calcd, 52.84; found, 52.26. H, N.

Ethyl (*S*)-2,4-Diaminobutanoate{7,12-bis[1-(1,4,7,10,-13,16-hexaoxaheptadecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (50). According to GP 5, 59.5 mg (0.100 mmol) of **19** was reacted with a solution of 107 mg (0.100 mmol) of **11** in 10 mL of EtOH. Yield: 23.7 mg (16.9 μmol, 17%) dark purple powder; mp 190 °C. IR (KBr): 1730 (C═O, ester), 1630, 1610 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.03), 499 (4.05), 532 (3.69), 569 (3.64), 622 (3.32), 659 (3.19) nm. MS (ESI) *m/z* (relative intensity): 1407 (MH, 5), 1319 (MH − $2OCH_2CH_2$, 18), 1231 (MH − $4OCH_2CH_2$, 70). Anal. ($C_{62}H_{94}N_6O_{18}Pt$, 1406.5) C, H, N: calcd, 5.98; found, 5.49.

Ethyl (*S*)-2,4-Diaminobutanoate{7,12-bis[1-(poly(ethylene glycol)-750-monomethyl ether-1-yl)ethyl]-3,8,13,-17-tetramethylporphyrin-2,18-dipropionato}platinum-(II) (51). According to GP 5, 59.5 mg (0.100 mmol) of **19** was reacted with a solution of 212 mg (0.100 mmol) of **13** in 10 mL of H_2O. After the mixture was stirred for 2 d in the dark, the reaction mixture was evaporated and the residue was chromatographed on silica (15 cm × 1.5 cm). With CH_2Cl_2/MeOH 5:1, the product eluted as a broad, red band. Yield: 46.0 mg (18.7 μmol, 19%) greenish brown, oily solid. IR (KBr): 1720 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 396 (4.79), 498 (3.80), 536 (3.62), 571 (3.66), 613 (3.50), 669 (3.68) nm. MS (FAB) *m/z* (relative intensity): 2464 (MH, 55), 2420 (MH − OCH_2CH_2, 56), loss of 2−4 OCH_2CH_2 units, int. 58−67. Anal. ($C_{110}H_{190}N_6O_{42}Pt$, 2463.8).

Diethyl *meso*-4,5-Diaminosuberate{7,12-bis[1-(1,4,7-trioxaoctyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (52). According to GP 5, 70.9 mg (0.100 mmol) of **20** was reacted with a solution of 80.3 mg (0.100 mmol) of **8** in 10 mL of EtOH. Yield: 20.7 mg (16.5 μmol, 17%) reddish brown solid; mp 220 °C. IR (KBr): 1725 (C═O, ester), 1630, 1620 cm^{-1} (C═O, carboxylate). UV/vis (DMF) λ_{max} (log ϵ): 404 (5.05), 503 (4.15), 536 (4.00), 573 (3.91), 623 (3.66), 663 (3.46) nm. MS (ESI) *m/z* (relative intensity): 1256 (MH, 44), 628.5 (M + 2H, dipositive cation, 100). Anal. ($C_{56}H_{80}N_6O_{14}Pt$, 1256.3) C: calcd, 53.54; found, 53.98. H, N.

Diethyl *meso*-4,5-Diaminosuberate{7,12-bis[1-(1,4,7,10-tetraoxaundecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (53). According to GP 5, 70.9 mg (0.100 mmol) of **20** was reacted with a solution of 89.1 mg (0.100 mmol) of **9** in 10 mL of EtOH. Yield: 47.0 mg (35.0 μmol, 35%) dark purple powder; mp 200 °C. IR (KBr): 1720 (C═O, ester), 1620, 1600 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.14), 498 (4.07), 532 (3.84), 567 (3.77), 621 (3.48), 644 (3.30), 660 (3.29) nm. MS (ESI) *m/z* (relative intensity): 1345 (MH, 60), 673 (M + 2H, dipositive cation, 100). Anal. ($C_{60}H_{88}N_6O_{16}Pt$, 1344.5) C, H, N: calcd, 6.25; found, 6.68.

Diethyl *meso*-4,5-Diaminosuberate{7,12-bis[1-(1,4,7,-10,13-pentaoxatetradecyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (54). According to GP 5, 70.9 mg (0.100 mmol) of **20** was reacted with a solution of 97.9 mg (0.100 mmol) of **10** in 10 mL of EtOH. Yield: 33.1 mg (23.1 μmol, 23%) reddish brown solid; mp 225 °C. IR (KBr): 1720 (C═O, ester), 1620, 1600 cm^{-1} (C═O, carboxylate). UV/vis (DMF) λ_{max} (log ϵ): 403 (4.88), 503 (4.11), 536 (3.98), 571 (3.90), 623 (3.71), 664 (3.69) nm. MS (ESI) *m/z* (relative intensity): 1433 (MH, 25), 717 (M + 2H, dipositive cation, 100). Anal. ($C_{64}H_{96}N_6O_{18}Pt$, 1432.6) C: calcd, 53.66; found, 53.18. H: calcd, 6.75; found, 6.25. N: calcd, 5.87; found, 6.42.

Diethyl *meso*-4,5-Diaminosuberate{7,12-bis[1-(1,4,7,-10,13,16-hexaoxahepta-decyl)ethyl]-3,8,13,17-tetramethylporphyrin-2,18-dipropionato}platinum(II) (55). According to GP 5, 70.9 mg (0.100 mmol) of **20** was reacted with a solution of 107 mg (0.100 mmol) of **11** in 10 mL of EtOH. Yield: 23.4 mg (15.4 μmol, 15%) brown powder; mp 187 °C. IR (KBr): 1720 (C═O, ester), 1620, 1600 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ): 402 (5.19), 499 (4.10), 533 (3.88), 568 (3.80), 621 (3.48), 661 (3.29) nm. MS (ESI) *m/z* (relative intensity): 1521 (MH, 22), 1433 (MH − $2OCH_2CH_2$, 100), 1345 (MH − $4OCH_2CH_2$, 94), 761 (M + 2H, dipositive cation, 7), 717 (M − $2OCH_2CH_2$ + 2H, dipositive cation, 30), 673 (M − $4OCH_2CH_2$ + 2H, dipositive cation, 41). Anal. ($C_{68}H_{104}N_6O_{20}Pt$, 1520.7) C: calcd, 53.71; found, 52.97. H: calcd, 6.89; found, 6.45. N.

Cell Culture. The human TCC-SUP[44] and J82[45] bladder cancer cell lines were obtained from the American Type Culture Collection (ATCC) (Rockville, MD). Cell line banking and quality control were performed according to the "seed stock concept" reviewed by Hay.[63] The TCC-SUP (ATCC No. HTB-5) and the J82 (ATCC No. HTB-1) cells were maintained in Eagle's Minimum Essential Medium (Sigma, Deisenhofen, Germany), containing L-glutamine, $NaHCO_3$ (2.2 g/L), sodium pyruvate (110 mg/L) (Serva, Heidelberg, Germany), and 5% fetal calf serum (Biochrom KG seromed, Berlin, Germany) using 75 cm^2 culture flasks (Nunc, Wiesbaden, Germany) in a water-saturated atmosphere (95% air/5% CO_2) at 37 °C. The cells were serially passaged weekly following trypsinization using 0.05% trypsin/0.02% ethylenediaminetetraacetic acid (Roche Diagnostics, Mannheim, Germany). Mycoplasma contamination was routinely monitored and only Mycoplasma-free cultures were used. All additional reagents (A-grade purity) were obtained from Merck (Darmstadt, Germany).

Drugs. Cisplatin (gold label) was obtained from Sigma-Aldrich (Steinheim, Germany) and hematoporphyrin from Fluka (Neu-Ulm, Germany). Both substances were dissolved in DMF. As the porphyrin−platinum complexes, with the exception of **25**, **26**, **39**, **46**, and **51**, were not soluble in water or phosphate-buffered saline (PBS), they were dissolved in DMF or DMSO. For all drugs, 10 mM stock solutions were prepared. After appropriate dilution, feed solutions were made. The drugs (feed solutions) were added to the culture medium such that the final DMF, DMSO, or water concentration was 0.1% (v/v).

Chemosensitivity Assay. For chemosensitivity testing, the cells were seeded (100 μL/well) in 96 well flat-bottomed microtitration plates (Greiner) at an appropriate density of approximately 15 cells/microscopic field (Leitz, Diavert, 320×). After 48 h, the medium was carefully removed by suction and replaced by fresh medium (200 μL/well) containing drugs (feed solutions were diluted 1:1000 with culture medium) or pure solvent. On every plate, 16 wells served as controls (reference)

and 16 wells were used per drug concentration. After various times of incubation, the culture medium was shaken off and the cells were fixed with 100 μL 1% glutardialdehyde in PBS/well for 25 min. The fixative was replaced by 180 μL of PBS/well, and the plates were stored in a refrigerator (4°C). At the end of the experiment, the cells were simultaneously stained with 0.02% aqueous crystal violet solution (100 μL/well) for 20 min. Excess dye was removed by rinsing the microplates with water for 20 min. The stain bound by the cells was redissolved in 70% ethanol (180 μL/well) while shaking the microplates for about 3 h. Absorbance, a parameter proportional to cell mass,[64] was measured at 578 nm using a Bio-Tek 309 Autoreader (Winooski).

Drug effects were expressed as corrected *T*/*C* values for each group according to

$$T/C_{\text{corr.}}\ [\%] = \frac{T - C_0}{C - C_0} \cdot 100\ [\%]$$

where T is the mean absorbance of the treated cells, C is the mean absorbance of the controls, and C_0 is the mean absorbance of the cells at the time ($t = 0$) when the drug was added.

When the absorbance of treated cells T is less than that of the culture at $t = 0$ (C_0), the extent of cell killing must be calculated as

$$\text{cytocidal effect}\ [\%] = \frac{C_0 - T}{C_0} \cdot 100\ [\%]$$

The relationship between growth kinetics of a drug-treated cell population and the plot of corrected *T*/*C* values vs time is discussed in detail elsewhere.[46,47]

Irradiation of the Cells. Irradiation occurred for 10 min with an incoherent light source, namely, a Waldmann PDT 700 lamp (Waldmann-Medizintechnik, Villingen-Schwennigen, Germany). With the aid of dichroic edge filters, the wavelength range was kept between 600 and 730 nm. The microplate to be irradiated was set in a black-coated 96 well template. The wells of the template exactly aligned with the 96 wells of the microplate. To minimize reflection, irradiation was carried out in a black box. The distance from lamp to microplate was 0.5 m corresponding to a fluence rate of 40 mW cm^{-2} and a light dose of 24 J cm^{-2}.

End Point Chemosensitivity Assay. To obtain both the cytotoxic and the phototoxic effect, two microplates were prepared in duplicate for the same substances. After an incubation time of 2 d, one batch of plates was irradiated with the Waldmann PDT 700 lamp. After irradiation, the irradiated and the nonirradiated plates were incubated for another 2 d at 37 °C. The drug-containing culture medium was left unchanged throughout the incubation period.

Multiple Point Chemosensitivity Assay. The cultivation and the seeding of the J82 cells, the preparation of the stock solutions of the porphyrin−platinum conjugates, cisplatin and hematoporphyrin, and the preparation of the wells of the microplates were carried out as described above. The plates were prepared for each substance in a concentration of 0.5 μM for five different periods of incubation. Twenty-four hours after the incubation with the porphyrin−platinum conjugates, cisplatin and hematoporphyrin corresponding to $t = 0$ (the time zero indicates the time at which the drug was added), one series of the plates was irradiated. The first time point of the kinetics was made immediately after the irradiation by fixating an irradiated plate together with one of the nonirradiated plates. In 24 h intervals, the next time points followed. The concentration of the tested substances was 0.5 μM throughout the test series, i.e., the drug-containing culture medium was left unchanged throughout the incubation period. In both series, one additional plate was used to determine the initial cell density.

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References

(1) Burch, J. D.; Rohan, T. E.; Howe, G. R.; Risch, H. A.; Hill, G. B.; Steele, R.; Miller, A. B. Risk of bladder cancer by source and type of tabacco exposure; A case-control study. *Int. J. Cancer* **1989**, *44*, 622−628.

(2) Manhert, B.; Tauber, S.; Kreigmair, M.; Schmitt, U. M.; Hasholzer, U.; Reiter, W.; Hofmann, K.; Schmeller, N.; Stieber, P. BTA TRAK−A useful diagnostic tool in urinary bladder cancer? *Anticancer Res.* **1999**, *19*, 2615−2620.

(3) Halachmi, S.; Linn, J. F.; Amiel, G. E.; Moskovitz, B.; Nativ, O. Urine cytology, tumor markers and bladder cancer. *Br. J. Urol.* **1998**, *82*, 647−654.

(4) Black, R. J.; Bray, F.; Ferlay, J.; Parkin, D. M. Cancer incidence and mortality in the European Union: Cancer registry data and estimates of national incidence for 1990. *Eur. J. Cancer* **1997**, *33*, 1075−1107.

(5) Von der Maase, H. Gemcitabine and cisplatin in locally advanced and/or metastatic bladder cancer. *Eur. J. Cancer* **2000**, *36*, 13−16.

(6) Roth, B. J. Chemotherapy for advanced bladder cancer. *Semin. Oncol.* **1996**, *5*, 633−644.

(7) Scher, H.; Bahnson, R.; Cohen, S.; Eisenberger, M.; Herr, H.; Kozlowski, J.; Lange, P.; Montie, J.; Pollack, A.; Raghaven, D.; Richie, J.; Shipley, W. NCCN urothelial cancer practice guidelines. National Comprehensive Cancer Network. *Oncology* **1998**, *12*, 225−271.

(8) Dodd, P. M.; McCaffrey, J. A.; Herr, H.; Mazumdar, M.; Bacik, J.; Higgins, G.; Boyle, M. G.; Scher, H. J.; Bajorin, D. F. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. *J. Clin. Oncol.* **1999**, *17*, 2546−2552.

(9) Tannock, I.; Gospodaowicz, M.; Connolly, J.; Jewett, M. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: the Princess Margaret Hospital experience. *J. Urol.* **1989**, *142*, 289−292.

(10) Igawa, M.; Ohkuchi, T.; Ueki, T.; Ueda, M.; Okada, K.; Usui, T. Usefulness and limitations for methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. *J. Urol.* **1990**, *144*, 662−665.

(11) Connor, J. P.; Olsson, C. A.; Benson, M. C.; Rapoport, F.; Sawczuk, I. S. Long-term follow-up in patients treated with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) for transitional cell carcinoma of urinary bladder: cause of concern. *Urology* **1989**, *34*, 353−356.

(12) Boutan-Laroze, A.; Mahjoubi, M.; Droz, J. P.; Charrot, P.; Fargeot, P.; Kerbrat, P.; Caty, A.; Voisin, P. M. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced carcinoma of the bladder. *Eur. J. Cancer* **1991**, *27*, 1690−1694.

(13) Loehrer, P.; Einhorn, L. H.; Elson, P. J.; Crawford, E. D.; Kuebler, P.; Tannock, I.; Raghavan, D.; Stuart-Harris, R.; Sarosdy, M. F.; Lowe, B. A. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a Cooperative Group study. *J. Clin. Oncol.* **1992**, *10*, 1066−1073.

(14) Logothetis, C. J.; Dexeus, F. H.; Finn, L.; Sella, A.; Amato, R. J.; Ayala, A. G.; Kilbourn, R. G. A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J. Clin. Oncol.* **1990**, *8*, 1050−1055.

(15) Witjes, J. A.; Wullink, M.; de Mulder, P. Toxicity and results of MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy in advanced urothelial carcinoma. *Eur. Urol.* **1997**, *31*, 414−419.

(16) Lockyer, C. R. W.; Gillatt, D. A. BCG immunotherapy for superficial bladder cancer. *J. R. Soc. Med.* **2001**, *94*, 119−123.

(17) Kamat, A. M.; Lamm, D. L. Intravesical therapy for bladder cancer. *Urology* **2000**, *55*, 161−168.

(18) Dougherty, T. J.; Gomer, C. J.; Henderson, B. W.; Jori, G.; Kessel, D.; Korbelik, M.; Moan, J.; Peng, Q. Photodynamic Therapy. *J. Natl. Cancer Inst.* **1998**, *90*, 889−905.

(19) Peng, O.; Moan, J.; Ma, L. W.; Nesland, J. M. Uptake, Localization and Photodynamic Effect of *meso*-Tetra(hydroxyphenyl)-porphine and its Corresponding Chlorin in Normal and Tumor Tissues of Mice Bearing Mammary Carcinoma. *Cancer Res.* **1995**, *55*, 2620−2626.

(20) Henderson, B. W.; Dougherty, T. J. How Does Photodynamic Therapy Work? *Photochem. Photobiol.* **1992**, *55*, 145−157.

(21) Sharman, W. M.; Allen, C. M.; van Lier, J. E. Photodynamic Therapeutics: Basic Principles and Clinical Applications. *Drug Discovery Today* **1999**, *4*, 507−517.

(22) Datta, S. N.; Allman, R.; Loh, C.; Mason, M.; Matthews, P. N. Effect of photodynamic therapy in combination with mitomycin C on a mitomycin-resistant bladder cancer cell line. *Br. J. Cancer* **1997**, *76*, 312−317.
(23) Canti, G.; Nicolin, A.; Cubeddu, R.; Taroni, P.; Bancieramonte, G.; Valentini, G. Antitumor efficacy of the combination of photodynamic therapy and chemotherapy in murine tumors. *Cancer Lett.* **1998**, *125*, 39−44.
(24) Brunner, H.; Maiterth, F.; Treittinger, B. Synthese und Antitumoraktivität neuer Porphyrin-Platin(II)-Komplexe mit an den Porphyrin-Seitenketten gebundenem cytostatischen Platin-Rest. *Chem. Ber.* **1994**, *127*, 2141−2149.
(25) Brunner, H.; Obermeier, H. Platin(II)-Komplexe mit Porphyrinliganden—additive cytotoxische und photodynamische Wirkung. *Angew. Chem.* **1994**, *106*, 2305−2306; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2214−2216.
(26) Brunner, H.; Obermeier, H.; Szeimies, R.-M. Platin(II)-Komplexe mit Porphyrinliganden: Synthese und Synergismen bei der photodynamischen Tumortherapie. *Chem. Ber.* **1995**, *128*, 173−181.
(27) Brunner, H.; Schellerer, K.-M.; Treittinger, B. Synthesis and in vitro testing of hematoporphyrin type ligands in platinum(II) complexes as potent cytostatic and phototoxic antitumor agents. *Inorg. Chim. Acta* **1997**, *264*, 67−79.
(28) Wong, E.; Giandomenico, C. M. Current Status of Platinum-Based Antitumor Drugs. *Chem. Rev.* **1999**, *99*, 2451−2466.
(29) Kelland, L. R.; Sharp, S. Y. Platinum compounds in cancer therapy. *Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs* **1999**, *1*, 380−385.
(30) Walker, E. M., Jr.; Walker, S. M. Evolution of chemotherapy with platinum compounds. *Ann. Clin. Lab. Sci.* **1999**, *29*, 263−274.
(31) Moan, J.; Berg, K. Yearly review. Photochemotherapy of cancer: experimental research. *Photochem. Photobiol.* **1992**, *55*, 931−948.
(32) Bart, K.-C. Ph.D. Thesis, Universität Regensburg, 2001.
(33) Caughey, W. S.; Alben, J. O.; Fujimoto, W. Y.; York, J. L. Substituted deuterioporphyrins. I. Reactions at the periphery of the porphyrin ring. *J. Org. Chem.* **1966**, *31*, 2631−2640.
(34) Neilands, J. B.; Tuppy, H. Crystalline synthetic porphyrin c. *Biochim. Biophys. Acta* **1960**, *38*, 351−353.
(35) Basolo, F.; Bailar, J. C.; Rapp Tarr, B. The stereochemistry of complex inorganic compounds. X. The stereoisomers of dichlorobis-(ethylenediamine)-platinum(IV) chloride. *J. Am. Chem. Soc.* **1950**, *72*, 2433−2438.
(36) Kidani, Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. Antitumor activity of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 ascites form. *J. Med. Chem.* **1978**, *21*, 1315−1318.
(37) Morgan, G. T.; Burstall, F. H. Researches on residual affinity and coordination. Part XXXIV. 2: 2′-Dipyridyl platinum salts. *J. Chem. Soc.* **1934**, 965−971.
(38) Capretta, A.; Maharajh, R. B.; Bell, R. A. Synthesis and characterization of cyclomaltoheptaose-based metal chelants as probes for intestinal permeability. *Carbohydr. Res.* **1995**, *267*, 49−63.
(39) Kasina, S.; Fritzberg, A. R.; Johnson, D. L.; Eshima, D. Tissue distribution properties of technetium-99m-diamide-dimercaptide complexes and potential use as renal radiopharmaceuticals. *J. Med. Chem.* **1986**, *29*, 1933−1940.
(40) Pesaro, M.; Felner-Caboga, I.; Eschenmoser, A. Rac.-di-2-pyrrolidonyl-(5,5′), ein Zwischenprodukt zur Synthese von Corrinkomplexen. *Chimia* **1965**, *19*, 566−567.
(41) Frydman, B.; Los, M.; Rapoport, H. Synthesis of substituted 1,5- and 1,7-naphthyridines and related lactams. *J. Org. Chem.* **1971**, *36*, 450−454.
(42) Noji, M.; Hanamura, S.; Suzuki, K.; Tashiro, T.; Kidani, Y. Antitumor activity of Pt(II) complexes containing diaminocarboxylates and their ester derivatives. *Chem. Pharm. Bull.* **1986**, *34*, 2487−2493.
(43) Holler, E. Mechanism of Action of Tumor-Inhibiting Metal-Complexes. In *Metal Complexes in Cancer Chemotherapy*, 1st ed.; Keppler, B. K., Ed.; VCH Verlagsgesellschaft: Weinheim, 1993; p 41.
(44) Nayak, S. K.; O'Toole, C.; Price, Z. H. A cell line from an anaplastic transitional cell carcinoma of human urinary bladder. *Br. J. Cancer* **1977**, *35*, 142−151.
(45) O'Toole, C. M. Human Bladder Cancer Cell Lines: HLA Class I and Class II Antigen Espression and susceptibility to Cytostatic and cytolytic Effects In Vitro. In *In Vitro Models for Cancer Research*; Webber, M. M., Ed.; CRC Press: Baco Raton, FL, 1986; Vol. IV, pp 103−125.
(46) Reile, H.; Birnböck, H.; Bernhardt, G.; Spru*β*, T.; Schönenberger, H. Computerized determination of growth kinetic curves and doubling times from cells in microculture. *Anal. Biochem.* **1990**, *187*, 262−267.
(47) Bernhardt, G.; Reile, H.; Birnböck, H.; Spru*β*, T.; Schönenberger, H. Standardized kinetic microassay to quantitate differential chemosensitivity based on proliferative activity. *J. Cancer Res. Clin. Oncol.* **1992**, *118*, 35−43.
(48) Keppler, B. K. Metallkomplexe in der Krebstherapie. *Nachr. Chem. Technol. Lab.* **1987**, *35*, 1029−1036.
(49) Hollis, L. S. New approaches to the design of platinum antitumor agents. In *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Howell, S. B., Ed.; Plenum Press: New York, 1991; pp 115−125.
(50) Connors, T. Platinum Compounds. In *Cancer Medicine*, 2nd ed.; Holland, J. F., Frei, E., Eds.; Lea and Febinger: Philadelphia, 1981; pp 843−850.
(51) Lippert, B.; Beck, W. Platin-Komplexe in der Krebstherapie. *Chemie Unserer Zeit* **1983**, *17*, 190−199.
(52) Pasini, A.; Zunino, F. Neue Cisplatin-Analoga—auf dem Weg zu besseren Cancerostatica. *Angew. Chem.* **1987**, *99*, 632−641; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 615−624.
(53) Kjøller-Larsen, I. DNA and cell growth in chemotherapy of cancer. In *A Textbook of Drug Design and Development*; Krogsgaard-Larsen, P., Bundgaard, H., Eds.; Harwood Academic Publishers: Chur, 1991; pp 192−241.
(54) Reedijk, J. The mechanism of action of platinum antitumor drugs. *Pure Appl. Chem.* **1987**, *59*, 181−192.
(55) Butour, J. L.; Alvinerie, P.; Souchard, J. P.; Colson, P.; Houssier, C.; Johnson, N. P. Effect of amine nonleaving group on the structure and stability of DNA complexes with cis-[$Pt(R\text{-}NH_2)_2$-$(NO_3)_2$]. *Eur. J. Biochem.* **1991**, *202*, 975−980.
(56) Wiseman, L. R.; Adkins, J. C.; Plosker, G. L.; Goa, K. L. Oxaliplatin: A review of its use in the management of metastatic colorectal cancer. *Drugs Aging* **1999**, *14*, 459−475.
(57) Misset, J. L.; Bleiberg, H.; Sutherland, W.; Bekradda, M.; Cvitkovic, E. Oxaliplatin clinical activity: a review. *Crit. Rev. Oncol./Hematol.* **2000**, *35*, 75−93.
(58) Fickweiler, S.; Szeimies, R.-M.; Bäumler, W.; Steinbach, P.; Karrer, S.; Goetz, A. E.; Abels, C.; Hofstädter, F.; Landthaler, M. Indocyanine green: intracellular uptake and phototherapeutic effects in vitro. *J. Photochem. Photobiol. B* **1997**, *38*, 178−183.
(59) Karrer, S.; Szeimies, R.-M.; Ebert, A.; Fickweiler, S.; Abels, C.; Bäumler, W.; Landthaler, M. Dose-dependent Photodynamic Effects of 9-Acetoxy-2,7,12,17-tetrakis-(*β*-methoxyethyl)-porphycene In Vitro. *Lasers Med. Sci.* **1997**, *12*, 307−312.
(60) Abels, C.; Fickweiler, S.; Weiderer, P.; Bäumler, W.; Hofstädter, F.; Landthaler, M.; Szeimies, R.-M. Indocyanine green (ICG) and laser irradiation induced photooxidation. *Arch. Dermatol. Res.* **2000**, *292*, 404−411.
(61) Kocian, O.; Chiu, K. W.; Demeure, R.; Gallez, B.; Jones, C. J.; Thornback, J. R. Synthesis and characterization of new polyethyleneoxy substituted salicylaldimine Schiff bases and some corresponding reduced tetra- and pentaaza ligands and their gadolinium(III) complexes: new potential contrast agents in magnetic resonance imaging. *J. Chem. Soc., Perkin Trans. 1* **1994**, 527−535.
(62) Moss, G. P. Nomenclature of tetrapyrroles. *Pure Appl. Chem.* **1987**, *59*, 779−832.
(63) Hay, R. J. The seed stock concept and quality control for cell lines. *Anal. Biochem.* **1988**, *171*, 225−237.
(64) Spru*β*, T.; Bernhardt, G.; Schickaneder, E.; Schönenberger, H. Different response of murine and human mammary tumor models to a series of diastereoisomeric [1,2-bis(difluorophenyl)-ethylenediamine]dichloroplatinum(II) complexes. *J. Cancer Res. Clin. Oncol.* **1991**, *117*, 435−443.

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