Soluble Tetraarylporphyrin−Platinum Conjugates as Cytotoxic and Phototoxic Antitumor Agents

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A series of asymmetric tetraarylporphyrins was synthesized from pyrrole, para-substituted oligo- or poly(ethylene glycol) monomethyl ether benzaldehyde and from 4-hydroxybenzaldehyde etherified with diethyl bromomalonate according to the Lindsey method. After hydrolysis of the tetraarylporphyrin esters, the resulting carboxylic acid groups were used to bind platinum fragments. In comparison to analogous hematoporphyrin−platinum conjugates, the title compounds are characterized by a 30 nm bathochromic shift of their absorption bands. The antiproliferative activity of 18 platinum complexes (1, 5, and 10 μM) differing in solubility, type of the platinum fragment, and the corresponding tetraarylporphyrin ligands were studied on TCC-SUP transitional bladder cancer cells in the dark and after irradiation (λ = 600−730 nm; 24 J/cm^2). The most active compounds were among the tetraarylporphyrin−platinum conjugates bearing the diammine and (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane ligands.

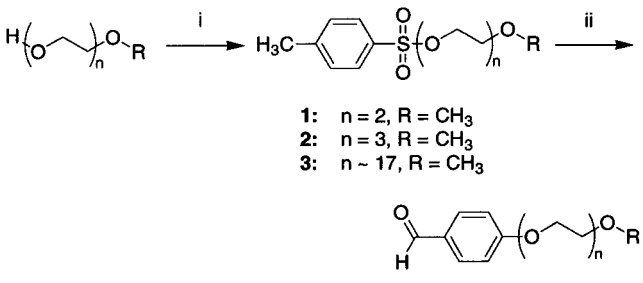
Introduction

As described in the preceding paper we tried to combine the cytostatic therapy with platinum complexes and the photodynamic therapy with porphyrins by assembling platinum fragments and porphyrin systems in the same molecule. The cytostatic effect of the platinum component and, on irradiation, the additional photodynamic effect of the porphyrin sensitizer were proven for hematoporphyrin−platinum conjugates. The crucial limitation of the photodynamic effect is the small depth of light penetration into the tissue depending on the wavelength of the absorption maximum of the sensitizer, which corresponds to the irradiation wavelength. Comparing hematoporphyrins with tetraarylporphyrins, the maxima of tetraarylporphyrins show a bathochromic shift of about 30 nm. Therefore, we switched from hematoporphyrins to tetraarylporphyrins expecting an increase in the penetration depth due to the red-shift of the irradiation wavelength. In the present paper, the synthesis, characterization, and antitumor properties of 18 tetraarylporphyrin−platinum derivatives are described. Ethylene glycol units solubilize the new compounds in DMF, DMSO, and, in particular, water.

Chemical Results and Discussion

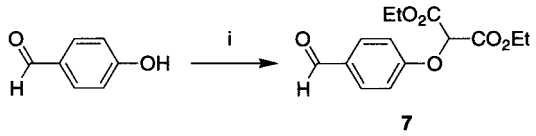
Synthesis of the Substituted Benzaldehydes. For the reaction with 4-hydroxybenzaldehyde, the respective oligo- and poly(ethylene glycol) monomethyl ethers had to be activated at their alcohol terminus with tosyl chloride according to a literature procedure.[1] The etherification was performed by refluxing the tosylated alcohols **1**−**3** and 4-hydroxybenzaldehyde together with K_2CO_3 in DMF.[2] The substituted benzaldehydes **4**−**6** were separated by filtration and purified by column chromatography (Scheme 1).

Scheme 1[a]



[a] Reagents: (i) tosyl chloride, CH_2Cl_2, NaOH, benzyltriethylammonium chloride, phase-transfer catalysis, 20 °C, 20 h; (ii) 4-hydroxybenzaldehyde, DMF, K_2CO_3, reflux, 48 h.

Scheme 2[a]



[a] Reagents: (i) diethyl bromomalonate, NaOH, DMF, 20 °C, 24 h.

For platinum coordination to the tetraarylporphyrins to be synthesized it is necessary to introduce two adjacent carboxylic acid groups in one of the substituted benzaldehydes. Therefore, 4-hydroxybenzaldehyde was etherified with diethyl bromomalonate under alkaline conditions (Scheme 2). The diethyl 2-(4-formylphenoxy)-malonate **7** was used together with the substituted benzaldehydes **4**−**6** for the synthesis of asymmetric tetraarylporphyrins.

Synthesis of the Porphyrin Ligands. The synthesis of the asymmetric tetraarylporphyrins was performed using the Lindsey method.[3] Pyrrole and the respective benzaldehydes were reacted under Lewis acid catalysis to porphyrinogens, which were oxidized with *p*-chloranil to the corresponding porphyrins. The tetra-

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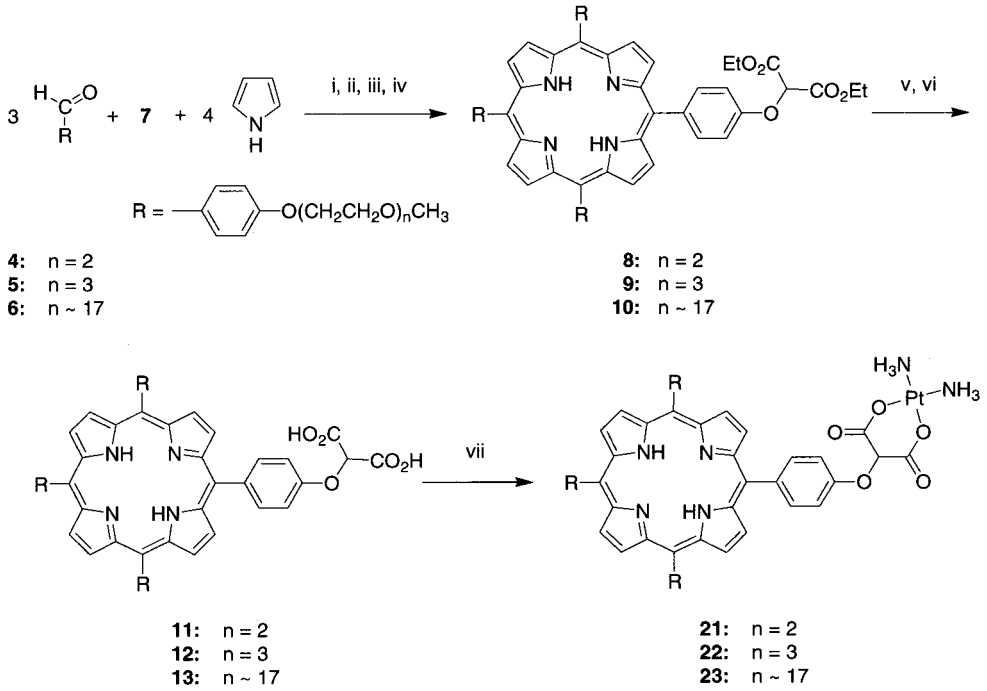
Scheme 3[a]



[a] Reagents: (i) CH_2Cl_2, N_2, $BF_3{\cdot}Et_2O$, 20 °C, 1 h; (ii) triethyl orthoacetate, 20 °C, 15 min; (iii) $BF_3{\cdot}Et_2O$, 20 °C, 1 h; (iv) *p*-chloranil, 20 °C, 24 h; (v) $CHCl_3$ (only for the synthesis of **11** and **12** necessary), 20% methanolic KOH solution, reflux, 3 h; (vi) 7% aqueous HCl solution; (vii) diammine(diaqua)platinum(II) hydroxide, H_2O, EtOH, $CHCl_3$ (only for the synthesis of **21** and **22** necessary), >18 h.

arylporphyrin esters **8**−**10** were purified by several column chromatographies. The carboxylic acids **11**−**13**, which were required for coordination to the platinum(II) fragments, were prepared by hydrolysis of the esters **8** and **9** with a mixture of $CHCl_3$ and 20% methanolic KOH solution. For the hydrolysis of **10**, pure 20% methanolic KOH solution was used (Scheme 3).

Synthesis of the Platinum Precursors. 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.[4−6]

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[7−10] and used for the preparation of the corresponding diiodoplatinum(II) complexes **18**−**20**.[11]

Synthesis of the Platinum Complexes. For the reaction with the porphyrincarboxylic acids **11**−**13**, cisplatin had to be activated by conversion into diammine(diaqua)platinum(II) hydroxide.[12] It was reacted with an equimolar amount of the porphyrin ligand in a mixture of $CHCl_3$, ethanol, and water or, in the case of the water-soluble ligand **10**, in pure water. The resulting diammine(malonato)platinum(II) complexes **21** and **22** precipitated. To the reaction mixture of the water-soluble complex **23** was added CH_2Cl_2 to remove neutral impurities. The aqueous phase was evaporated to obtain the product (Scheme 3).

The diamine(dichloro)platinum(II) precursors **14**−**17** were activated by conversion into diamine(dihydroxy)platinum(II) species,[13] which were reacted with an equimolar amount of the respective porphyrinmalonic acid in a mixture of CH_2Cl_2, ethanol, and water or, in the case of the water-soluble ligand **13**, in pure water. The complexes **24**−**29**, **31**, and **32** precipitated. To the water-soluble complex **30** was added CH_2Cl_2 to remove neutral impurities before the aqueous phase was evaporated to obtain the product (Schemes 4 and 5).

For the reaction with the porphyrinmalonic acids it was necessary to activate the diamine(diiodo)platinum(II) complexes **18**−**20** by conversion into diamine(dinitrato)platinum(II) species,[13] which are water-soluble. In this form they were reacted with an equimolar amount of the porphyrin ligands **11** and **12**, respectively, in a mixture of CH_2Cl_2, ethanol, and water. The water-insoluble complexes **33**−**38** precipitated after concentrating the solutions (Schemes 6 and 7).

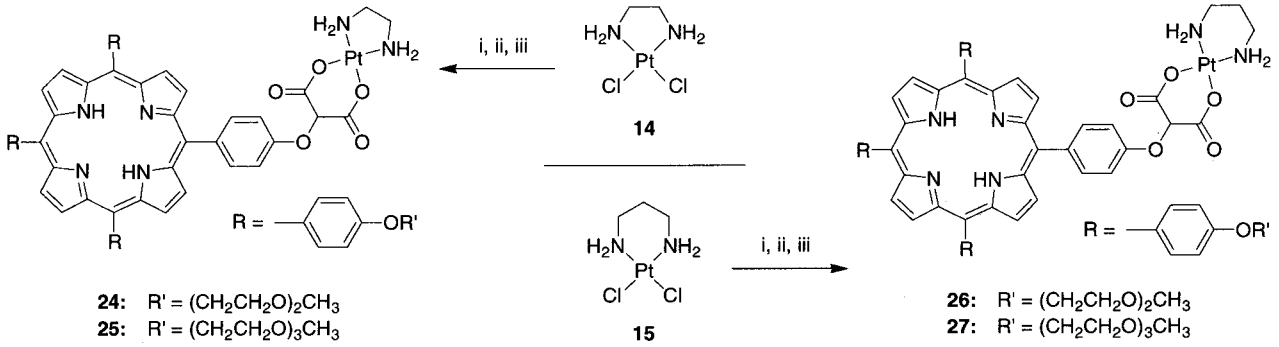
The tetraarylporphyrin−platinum(II) conjugates **21**−**38** are easily soluble in CH_2Cl_2 and $CHCl_3$, but only slightly soluble in DMF or DMSO. The complexes **23** and **30** can be dissolved in water because of their poly(ethylene glycol) monomethyl ether side chains.

The spectral data for the individual compounds are given in the Experimental Section. Most of the general points discussed in the preceding paper apply. The tetraarylporphyrin derivatives exhibit UV/vis spectra with absorption maxima at 650, 590, 555, and 520 nm. In comparison with the spectra of the hematoporphyrin derivatives described in the preceding paper, the maxima of the tetraarylporphyrins show a bathochromic shift of about 30 nm. The malonate substituent renders the tetraarylporphyrin backbone asymmetric. Thus, in the ^1H NMR spectra, the methine protons of the porphyrin system form two different AB spin systems. Some of them coincide, resulting in singlets.[14]

Biological Results and Discussion

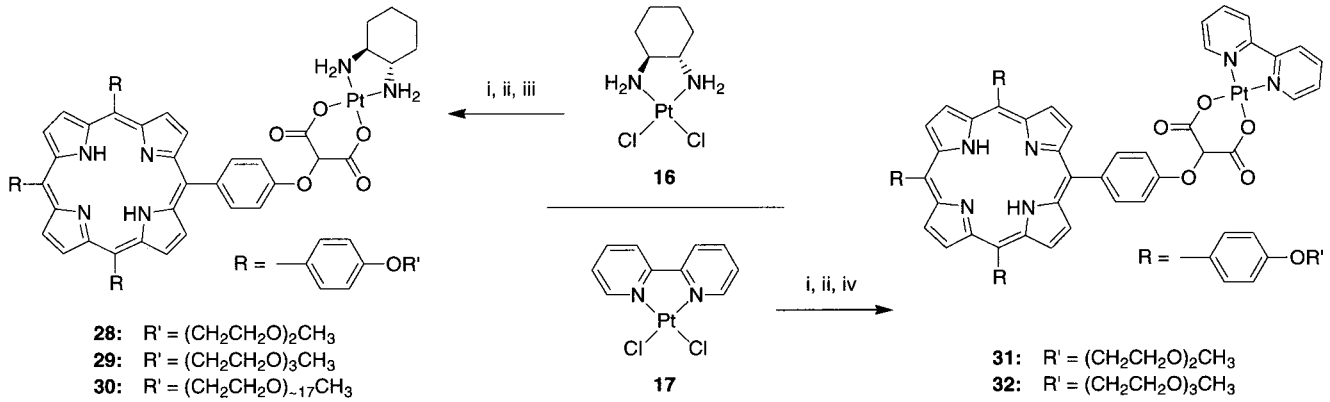
The antiproliferative activity of the new tetraarylporphyrin ligands and the corresponding platinum com-

Scheme 4[a]



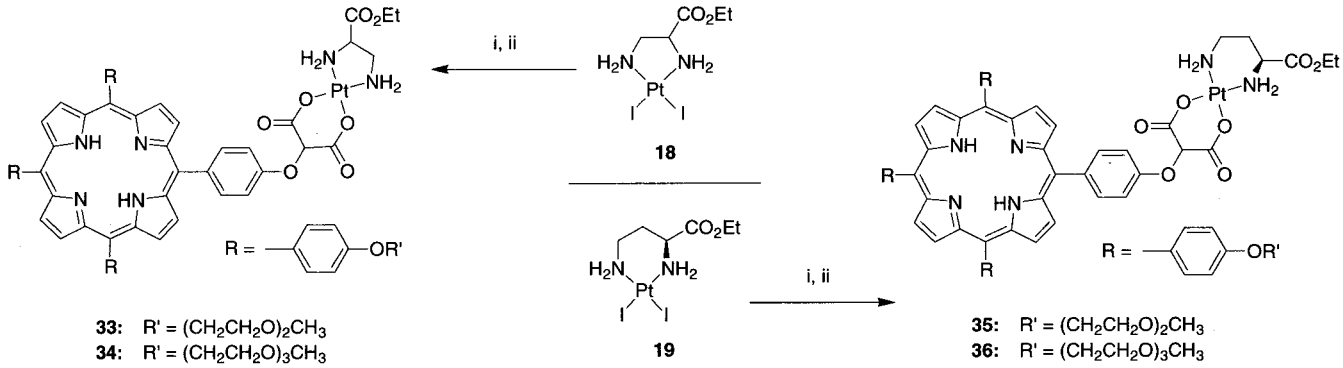
[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) ion exchanger; (iii) **11** and **12**, CH_2Cl_2, EtOH, H_2O.

Scheme 5[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) ion exchanger; (iii) **11**−**13**, CH_2Cl_2 (only for the synthesis of **28** and **29** necessary), EtOH, H_2O; (iv) **11** and **12**, CH_2Cl_2, EtOH, H_2O.

Scheme 6[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) **11** and **12**, CH_2Cl_2, EtOH, H_2O.

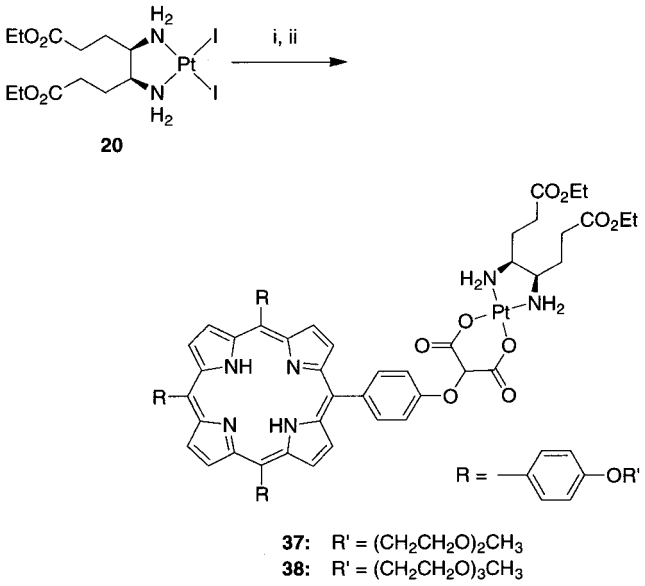
plexes with different amine nonleaving groups were determined on TCC-SUP bladder cancer cells.[15] The evaluation of the sensitivity of the cancer cells with respect to the test compounds was performed in a computerized (kinetic) chemosensitivity assay.[16,17] The technical details of the chemosensitivity assay, the irradiation, and the evaluation of the results have been described in the preceding paper.

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

The dark and the light-induced effects of the tetraarylporphyrin ligands **11**−**13**, the putative leaving groups of the tetraarylporphyrin−platinum complexes, and hematoporphyrin are comparatively shown in Figure 1. At a dosage of 1 μM and 5 μM (Figure 1) and 10 μM (data not shown) no statistically significant cytotoxicity was observed in the dark. In contrast to the ethylene glycol substituted hematoporphyrins reported in the preceding paper, a marked light-induced toxicity of the tetraarylporphyrins **11** and **12** was observed at a concentration of 1 μM ($T/C_{corr.}$ = 37%), whereas the photoactivation of **13** (n = ~17) was low.

At a dosage of 1 μM and 5 μM, both the dark- and phototoxicity of the tetraarylporphyrin−platinum conjugates **21**−**38** were highly influenced by the type of the nonleaving group, the results agreeing with those of the hematoporphyrin−platinum complexes discussed in the preceding paper. Compounds **23**, **29**, and **30** were the most active tetraarylporphyrin−platinum conjugates

Scheme 7[a]



[a] Reagents: (i) $AgNO_3$, H_2O, 7 d; (ii) **11** and **12**, CH_2Cl_2, EtOH, H_2O.

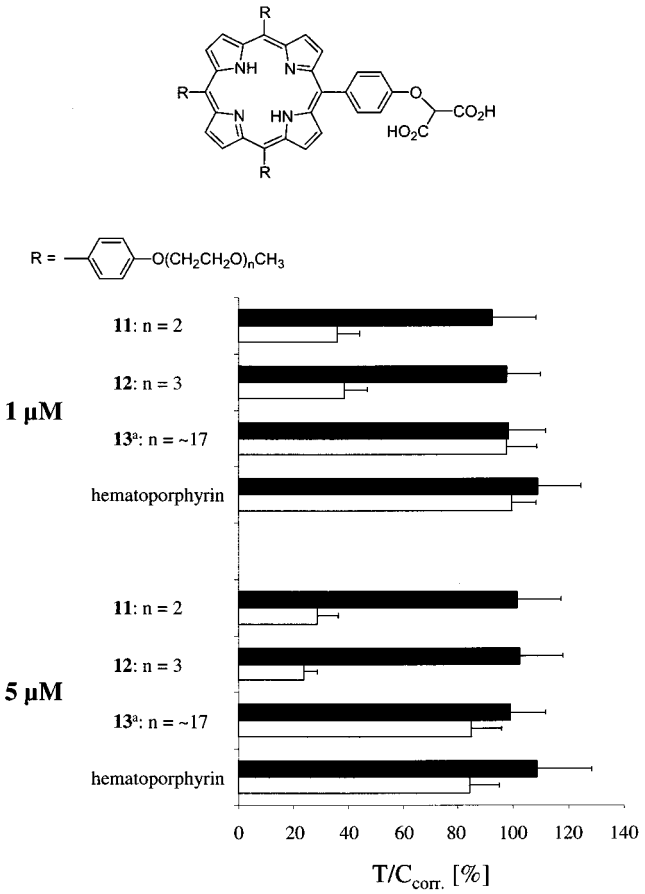


Figure 1. Effect of the tetraarylporphyrin ligands **11**−**13** and the reference hematoporphyrin (stock solution in DMF) on the proliferation of TCC-SUP cells (in passage 55 from origin) without (filled bars) and with (open bars) irradiation (λ = 600−730 nm; 10 min; 24 J cm^{-2}). The cells were exposed to the substances for 96 h. Irradiation was performed 48 h after the addition of the test compounds. [a]Stock solution of ligand **13** in H_2O.

with $T/C_{corr.}$ values of around 37%, 57%, and 63%, respectively, at 1 μM concentration. This is analogous

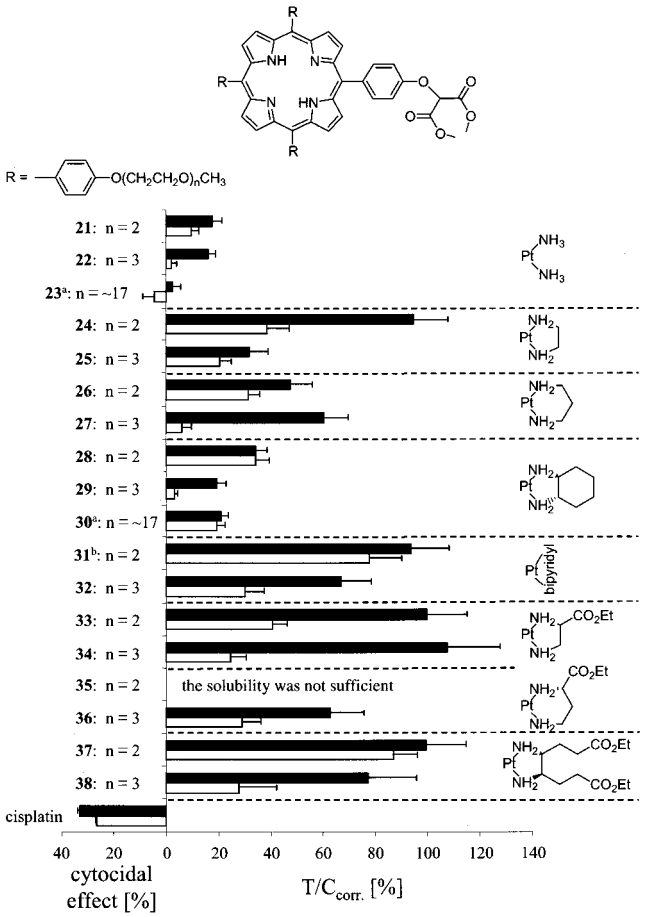


Figure 2. Effect of the tetraarylporphyrin−platinum conjugates **21**−**38** and the reference cisplatin (stock solution in DMF) at a concentration of 5 μM on the proliferation of TCC-SUP cells (in passage 55 from origin) without (filled bars) and with (open bars) irradiation (λ = 600−730 nm; 10 min; 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. [a] Stock solution of the complexes **23** and **30** in H_2O. [b] Stock solution of complex **31** in DMSO.

to the hematoporphyrin−platinum complexes, the most active of which were those with the diammine or the (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane nonleaving groups. At 1 μM concentration, there was only a slight enhancement of the cytotoxicity of the tetraarylporphyrin−platinum conjugates with the side chain length n = 2 and n = 3 upon irradiation. On the average, the light-induced $T/C_{corr.}$ values were approximately 20% lower than the dark-only cytotoxicities (data not shown).

An increase in the concentration of the complexes to 5 μM enhanced the dark effects and the phototoxicities as shown in Figure 2. Apart from cisplatin, the highest antitumor activities were measured for the tetraarylporphyrin−platinum conjugates bearing diammine (**21**−**23**) and (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane (**28**−**30**) nonleaving groups. The differences between dark and light-induced toxicities were best for the tetraarylporphyrin−platinum complexes **24**, **27**, **32**−**34**, **36**, and **38** with a side chain length of n = 2 or n = 3.

Multiple Point Chemosensitivitiy Assay. The antitumor activity of the tetraarylporphyrin−platinum compound **22** was analyzed on the TCC-SUP bladder cancer cell line in a kinetic assay,[16,17] as **22** was one of the most active tetraarylporphyrin−platinum conju-

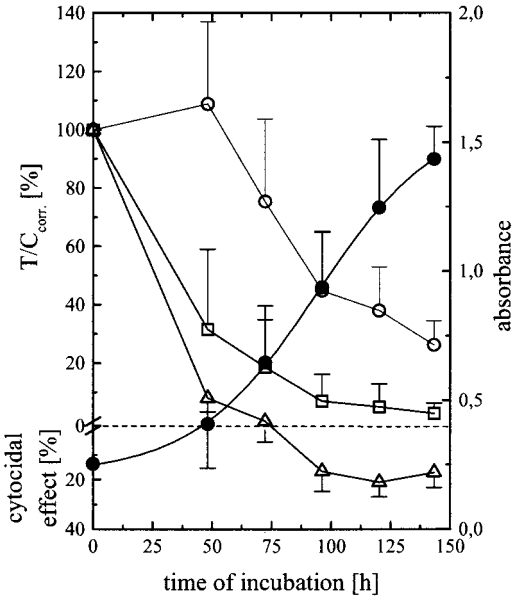


Figure 3. Dose−response relationship of the tetraarylporphyrin−platinum conjugate **22** (stock solution in DMF) on the proliferation of long-term incubated TCC-SUP bladder cancer cells (in passage 56 from origin) at a concentration of 1 μM (○), 5 μM (□), and 10 μM (△). Proliferation kinetics of the corresponding control (absorbance at 578 nm) (●).

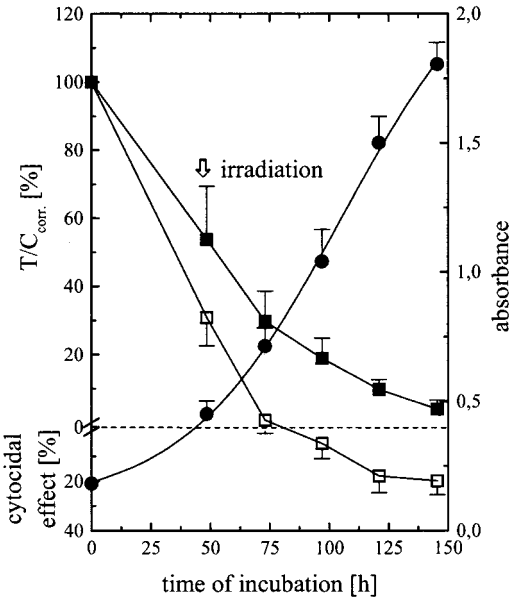


Figure 4. Effect of the tetraarylporphyrin−platinum conjugate **22** (stock solution in DMF) on the proliferation of long-term incubated TCC-SUP bladder cancer cells (in passage 56 from origin) without (filled square) and with (open square) irradiation (λ = 600−730 nm; 10 min; 24 J cm^{-2}) at a concentration of 5 μM. Irradiation was performed 48 h after the addition of the test compound. Proliferation kinetics of the corresponding control (absorbance at 578 nm) (●).

gates in the end-point chemosensitivity assay at 5 μM concentration and the antiproliferative effect was clearly improved by irradiation (Figure 2). Dose−response relationship of the dark toxicity and enhancement of its antitumor activity by irradiation is exemplarily shown in Figures 3 and 4.

The TCC-SUP cells were seeded into microplates, and the tetraarylporphyrin−platinum conjugate **22** was added after 48 h at a concentration of 1, 5, and 10 μM for the dose−response relationship experiment (Figure 3) and at 5 μM for the study of the phototoxicity of the complex (Figure 4). By analogy to the end-point experiment, irradiation was performed 48 h after addition of the substances for 10 min with a light dose of 24 J cm^{-2} as indicated by the arrow in Figure 4. For Figures 3 and 4, $T/C_{corr.}$ and the percent cytocidal effect (left ordinate) for the test compound 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. In both plots, the growth-curve data of the corresponding solvent control are given by filled circles. In these experiments, the drug containing culture medium was left unchanged throughout the incubation period.

As obvious from Figure 3, the tetraarylporphyrin−platinum complex **22** shows a classical dose−response relationship. A clear antiproliferative effect is observed as a function of time for all three concentrations resulting in $T/C_{corr.}$ values of 26.2% and 2.8% for 1 μM and 5 μM concentration, and a cytocidal effect of 17.1% at 10 μM concentration after an incubation period of 144 h.

On irradiation, there is an increase in cytotoxicity indicated by a steep drop of the $T/C_{corr.}$ curve. At the end of the experiment, the number of the irradiated cells is lower than the number at the beginning of the experiment (C_0) (Figure 4). Thus, photoactivation of the tetraarylporphyrin−platinum complex **22** improved the antitumor activity from the $T/C_{corr.}$ value of 4%, resulting from the platinum moiety to a cytocidal effect of 20%.

In summary, we synthesized tetraarylporphyrin-based platinum derivatives bearing a phototoxic ligand which increases the antitumor activity of the platinum moiety by an additional light-induced toxicity, which is improved compared to their hematoporphyrin analogues due to the red-shift of the irradiation wavelength. In contrast to the ethylene glycol substituted hematoporphyrin ligands discussed in the preceding paper, the new tetraarylporphyrin ligands showed a phototoxic effect already at 1 μM by irradiation of the tumor cells for 10 min with a light dose of 24 J cm^{-2} (λ = 600−730 nm), which is attributed to the bathochromic shift of about 30 nm. The largest difference between dark and light-induced antitumor activity was found for the tetraarylporphyrin−platinum conjugates **22**, **24**, **27**, **29**, **32**−**34**, **36**, and **38** bearing the 1,4,7-trioxaoctyl and the 1,4,7,10-tetraoxaundecyl groups.

Our ongoing studies will focus on a further improvement of the photophysical properties of the platinum conjugates by replacing the hematoporphyrin or the tetraarylporphyrin system with chlorins, phthalocyanines, or naphthalocyanines to induce a further bathochromic shift of the absorption bands.

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. Column chromatographies were performed using alumina 90 (63−200 μm). Reaction progress was determined by 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).[18]

General Procedure 1 (GP 1). A total of 150 mmol of the respective alcohol were dissolved in 150 mL of CH_2Cl_2. Next, 1.37 g (6.00 mmol) of benzyltriethylammonium chloride and 120 mL of a 30% aqueous NaOH solution were added. Then a solution of 4-toluenesulfonyl chloride (30.1 g, 160 mmol) in 150 mL of CH_2Cl_2 was added dropwise, and the reaction mixture was stirred for 20 h at 20 °C. The white precipitate, which formed in the organic layer, was dissolved by adding 200 mL of H_2O. The organic phase was separated, washed with 3 × 150 mL of water, and dried with Na_2SO_4. The solvent was removed, and the residue was purified by chromatography over SiO_2 (15 × 10 cm).

3,6-Dioxaheptyl 4-Toluenesulfonate (1). According to GP 1, 18.0 g (150 mmol, 17.5 mL) of diethylene glycol monomethyl ether was reacted with 30.1 g (160 mmol) of 4-toluenesulfonyl chloride. The resulting crude yellow product was purified by column chromatography over SiO_2 with CH_2Cl_2. The first yellow bands were discarded before the colorless product eluted. Yield: 22.1 g (80.6 mmol, 54%) colorless oil. IR (film): 1380, 1180 cm^{-1} (S═O). ^1H NMR ($CDCl_3$) δ (ppm): 7.80 (d, ^3J = 8.3 Hz, 2H, aryl-H2,6), 7.34 (d, ^3J = 8.3 Hz, 2H, aryl-H3,5), 4.17 (d, 2H, aryl-$SO_3CH_2CH_2$), 3.69 (d, 2H, aryl-SO_3-CH_2CH_2), 3.58 (d, 2H, OCH_2CH_2), 3.48 (d, 2H, OCH_2CH_2), 3.35 (s, 3H, OCH_3), 2.45 (s, 3H, aryl-CH_3). MS (EI) *m*/*z* (rel int.): 274 (M, 10); 242 (M − MeOH, 28); 229 (M − $MeOCH_2$, 4); 199 (M − OCH_2CH_2OMe, 17); 155 (M − $O(CH_2CH_2O)_2Me$, 42); 91 (C_7H_7, 100); 59 ($MeOCH_2CH_2$, 78); 45 ($MeOCH_2$, 64); 31 (MeO, 14). Anal. ($C_{12}H_{18}O_5S$, 274.3) C, H.

3,6,9-Trioxadecyl 4-Toluenesulfonate (2). According to GP 1, 24.6 g (150 mmol, 23.7 mL) of triethylene glycol monomethyl ether was reacted with 30.1 g (160 mmol) of 4-toluenesulfonyl chloride. The yellow oil obtained was purified by column chromatography over SiO_2 with CH_2Cl_2/MeOH 40:1. After yellow impurities were removed, the colorless product eluted. Yield: 22.1 g (80.6 mmol, 54%) colorless oil. IR (film): 1345, 1160 cm^{-1} (S═O). ^1H NMR ($CDCl_3$) δ (ppm): 7.80 (d, ^3J = 8.3 Hz, 2H, aryl-H2,6), 7.34 (d, ^3J = 8.3 Hz, 2H, aryl-H3,5), 4.16 (d, 2H, aryl-$SO_3CH_2CH_2$), 3.69 (d, 2H, aryl-SO_3-CH_2CH_2), 3.61 (d, 2H, OCH_2CH_2), 3.59 (m, 4H, OCH_2CH_2-OCH_3), 3.53 (d, 2H, OCH_2CH_2), 3.37 (s, 3H, OCH_3), 2.45 (s, 3H, aryl-CH_3). MS (EI) *m*/*z* (rel int.): 318 (M, 2); 243 (M − OCH_2CH_2OMe, 9); 199 (M − $O(CH_2CH_2O)_2Me$, 92); 172 (TosOH, 2); 155 (Tos, 50). Anal. ($C_{14}H_{22}O_6S$, 318.4) C, H.

Poly(ethylene glycol)-750-monomethyl ether-1-yl 4-Toluenesulfonate (3). According to GP 1, 113 g (150 mmol) of poly(ethylene glycol)-750-monomethyl ether was reacted with 30.1 g (160 mmol) of 4-toluenesulfonyl chloride. The resulting yellow, waxy product was purified by column chromatography over SiO_2 with CH_2Cl_2/MeOH 20:1. The first yellow bands were discarded before the product eluted. Yield: 88.4 g (94.5 mmol, 63%) colorless wax. IR (film): 1355, 1180 cm^{-1} (S═O). ^1H NMR ($CDCl_3$) δ (ppm): 7.80 (d, ^3J = 8.3 Hz, 2H, aryl-H2,6), 7.34 (d, ^3J = 8.3 Hz, 2H, aryl-H3,5), 4.16 (d, 2H, aryl-$SO_3CH_2CH_2$), 3.69 (d, 2H, aryl-$SO_3CH_2CH_2$), 3.68−3.53 (m, 64H, OCH_2), 3.38 (s, 3H, OCH_3), 2.45 (s, 3H, aryl-CH_3). ($C_{42}H_{78}O_{20}S$, 935.1).

General Procedure 2 (GP 2). A total of 8.33 g (68.2 mmol) of 4-hydroxybenzaldehyde, 28.3 g (205 mmol) of K_2CO_3, and 75.0 mmol of the respective 4-toluenesulfonate were dissolved in 200 mL of absolute DMF under N_2 atmosphere and heated to reflux. After a period of 48 h, the conversion was quantitative, which was monitored by TLC. The mixture was filtered, and the filtrate was evaporated. The residue was diluted with CH_2Cl_2 and filtered once more to separate insoluble components. The filtrate was evaporated and purified as described below.

4-(1,4,7-Trioxaoctyl)benzaldehyde (4). According to GP 2, 8.37 g (68.5 mmol) of 4-hydroxybenzaldehyde was reacted with 20.7 g (75.3 mmol) of 3,6-dioxaheptyl 4-toluenesulfonate **1** and 28.5 g (206 mmol) of K_2CO_3. The crude product was purified by column chromatography over SiO_2 with CH_2Cl_2. After the solvent was removed, a solid was obtained, which was recrystallized from ether/petroleum ether (40/60). Yield: 13.2 g (58.9 mmol, 86%) fine, colorless needles, mp 41−42 °C. IR (film): 1670 cm^{-1} (C═O). ^1H NMR ($CDCl_3$) δ (ppm): 9.89 (s, 1H, CHO), 7.83 (d, ^3J = 8.7 Hz, 2H, aryl-H2,6), 7.02 (d, ^3J = 8.7 Hz, 2H, aryl-H3,5), 4.23 (d, 2H, aryl-OCH_2CH_2), 3.90 (d, 2H, aryl-OCH_2CH_2), 3.73 (d, 2H, OCH_2CH_2), 3.59 (d, 2H, OCH_2CH_2), 3.40 (s, 3H, OCH_3). MS (EI) *m*/*z* (rel int.): 224 (M, 16); 121 ($OHCC_6H_4O$, 13); 59 ($CH_3OCH_2CH_2$, 100). Anal. ($C_{12}H_{16}O_4$, 224.3) C, H.

4-(1,4,7,10-Tetraoxaundecyl)benzaldehyde (5). According to GP 2, 8.34 g (68.3 mmol) of 4-hydroxybenzaldehyde was reacted with 23.9 g (75.1 mmol) of 3,6,9-trioxadecyl 4-toluenesulfonate **2** and 28.3 g (205 mmol) of K_2CO_3. The crude product was purified by column chromatography over SiO_2 with CH_2Cl_2. Yield: 16.9 g (63.0 mmol, 92%) nearly colorless, viscous oil. IR (film): 1680 cm^{-1} (C═O). ^1H NMR ($CDCl_3$) δ (ppm): 9.89 (s, 1H, CHO), 7.83 (d, ^3J = 8.7 Hz, 2H, aryl-H2,6), 7.02 (d, ^3J = 8.7 Hz, 2H, aryl-H3,5), 4.22 (d, 2H, aryl-OCH_2CH_2), 3.89 (d, 2H, aryl-OCH_2CH_2), 3.75 (d, 2H, OCH_2CH_2), 3.69 (d, 2H, OCH_2CH_2), 3.65 (d, 2H, $OCH_2CH_2OCH_3$), 3.56 (d, 2H, OCH_2CH_2-OCH_3), 3.38 (s, 3H, OCH_3). MS (EI) *m*/*z* (rel int.): 268 (M, 9); 149 (M − $O(CH_2CH_2O)_2Me$, 15); 121 ($OHCC_6H_4O$, 22). Anal. ($C_{14}H_{20}O_5$, 268.3) C: calcd, 62.67; found, 62.21. H.

4-(Poly(ethylene glycol)-750-monomethyl ether-1-yl)-benzaldehyde (6). According to GP 2, 8.33 g (68.2 mmol) of 4-hydroxybenzaldehyde was reacted with 70.1 g (75.0 mmol) of poly(ethyleneglycol)-750-monomethyl ether-1-yl 4-toluenesulfonate **3** and 28.3 g (205 mmol) of K_2CO_3. The brown, waxy crude product was purified by column chromatography over SiO_2 with CH_2Cl_2. Yield: 25.1 g (28.4 mmol, 42%) yellowish, viscous oil. IR (film): 1680 cm^{-1} (C═O). ^1H NMR ($CDCl_3$) δ (ppm): 9.88 (s, 1H, CHO), 7.83 (d, ^3J = 8.7 Hz, 2H, aryl-H2,6), 7.02 (d, ^3J = 8.7 Hz, 2H, aryl-H3,5), 4.22 (d, 2H, aryl-OCH_2-CH_2), 3.89 (d, 2H, aryl-OCH_2CH_2), 3.76−3.53 (m, 64H, OCH_2-CH_2), 3.38 (s, 3H, OCH_3). MS (ESI) *m*/*z* (rel int.): 923 (MK, 38); 907 (MNa, 70); 902 (M + NH_4, 40); 879 (MK − OCH_2CH_2, 36); 863 (MNa − OCH_2CH_2, 80). ($C_{42}H_{76}O_{19}$, 885.0).

Diethyl 2-(4-Formylphenoxy)malonate (7). A total of 12.2 g (100 mmol) of freshly sublimated 4-hydroxybenzaldehyde and 23.9 g (100 mmol, 16.8 mL) of diethyl bromomalonate were dissolved under N_2 atmosphere in 120 mL of absolute DMF. A total of 4.00 g (100 mmol) of pulverized NaOH was added, and the mixture was stirred for 24 h at room temperature. The orange solution was diluted with 300 mL of water and extracted with 3 × 200 mL of CH_2Cl_2. The combined organic phases were washed with 3 × 200 mL of H_2O and dried with Na_2SO_4. After the solvent was removed and the mixture was dried in a vacuum, a yellow oil was obtained, which was purified by bulb tube distillation. At 70−75 °C in a vacuum, excessive diethyl bromomalonate and DMF were distilled. At 90−130 °C in high vacuum, the product **49** condensed in the first bulb. Yield: 20.0 g (71.4 mmol, 71%) colorless, viscous oil. IR (film): 1755, 1730 (C═O, ester); 1680 cm^{-1} (C═O, aldehyde). ^1H NMR ($CDCl_3$) δ (ppm): 9.91 (s, 1H, CHO), 7.86 (d, ^3J = 8.7 Hz, 2H, aryl-H2,6), 7.07 (d, ^3J = 8.7 Hz, 2H, aryl-H3,5), 5.31 (s, 1H, CH), 4.34 (q, ^3J = 7.1 Hz, 4H, 2 CO_2CH_2-CH_3), 1.32 (t, ^3J = 7.1 Hz, 6H, 2 $CO_2CH_2CH_3$). MS (EI) *m*/*z* (rel int.): 280 (M, 70); 207 (M − CO_2Et, 25); 135 (MH − CO_2-Et, 100). Anal. ($C_{14}H_{16}O_6$, 280.3) C, H.

General Procedure 3 (GP 3). In a 2 L three-necked flask with gas tap containing 1.2 L of dry CH_2Cl_2, 805 mg (12.0 mmol, 840 μL) of freshly distilled pyrrole and 12.0 mmol of the respective substituted benzaldehydes were added under N_2 atmosphere. The resulting 10^{-2} M solution was stirred for 15 min before 170 mg (1.20 mmol, 150 μL) of $BF_3 \cdot Et_2O$ was added and the solution was stirred for an additional 75 min in the dark at room temperature. Then 1.95 g (12.0 mmol, 2.18 mL) of triethyl orthoacetate was added. After the mixture was

stirred for 15 min, 150 μL of $BF_3{\cdot}Et_2O$ was added once more and the mixture was stirred for 1 h. The resulting porphyrinogens were oxidized to the corresponding porphyrins with the addition of 2.22 g (9.00 mmol) of *p*-chloranil. After being stirred for 20 h at room temperature in the dark, the reaction mixture was concentrated and 5−10 g of SiO_2 were added. The solvent was removed with a rotary evaporator, the resulting powder was put on the top of a chromatography column, which had been dry filled with SiO_2, and eluted with 500 mL of CH_2Cl_2/petroleum ether (40/60) 1:1 and 500 mL of pure CH_2Cl_2 to remove multicolored pigments. The porphyrin fraction eluted with CH_2Cl_2/MeOH 20:1 in form of a thick, purple band. The different substituted porphyrins could be separated by further chromatographies.

5,10,15,20-Tetrakis[4-(1,4,7-trioxaoctyl)phenyl]porphyrin. According to GP 3, 2.02 g (9.00 mmol) of 4-(1,4,7-trioxaoctyl)benzaldehyde **4** and 841 mg (3.00 mmol) of diethyl 2-(4-formylphenoxy)malonate **7** were reacted with 805 mg (12.0 mmol, 840 μL) of pyrrole. After the first chromatography, the crude product mixture was chromatographed over SiO_2 (65 × 3 cm) with CH_2Cl_2/MeOH 160:1 eluting two small red bands, which contain porphyrins with more than one diethyl malonate group. If the methanol concentration of the solvent was increased up to CH_2Cl_2/MeOH 150:1, compound **8** eluted in form of a thick, purple band. Using a mixture of CH_2Cl_2/MeOH 140:1, the product eluted, which was recrystallized from CH_2Cl_2/cyclohexane. Yield: 221 mg (0.203 mmol, 2.3%) purple needles, mp > 250 °C. IR (KBr): 3330 cm^{-1} (═NH). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.56); 518 (4.22); 556 (4.07); 593 (3.79); 650 nm (3.79). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.85 (s, 8H, ═CH), 8.10 (d, ^3J = 8.7 Hz, 8H, 4 aryl-H2,6), 7.29 (d, ^3J = 8.7 Hz, 8H, 4 aryl-H3,5), 4.44 (d, 8H, 4 aryl-OCH_2CH$_2$), 4.06 (d, 8H, 4 aryl-OCH$_2$CH_2), 3.87 (d, 8H, 4 OCH_2CH$_2$), 3.69 (d, 8H, OCH$_2$CH_2), 3.47 (s, 12H, 4 OCH$_3$), −2.77 (bs, 2H, ═NH). MS (FAB) *m*/*z* (rel int.): 1087 (MH, 100). Anal. ($C_{64}H_{70}N_4O_{12}$, 1087.3) C: calcd, 70.70; found, 70.24. H, N.

Diethyl 2-(4-{10,15,20-Tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonate (8). The synthesis and work up was carried out according to 5,10,15,20-tetrakis[4-(1,4,7-trioxaoctyl)phenyl]porphyrin. The crude product was purified by chromatography over SiO_2 (30 × 3 cm) with CH_2Cl_2/MeOH 200:1. Yield: 455 mg (0.398 mmol, 4.4%) purple powder, mp 192 °C. IR (KBr): 3300 (═NH); 1760, 1740 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 419 (5.59); 518 (4.25); 555 (4.05); 593 (3.63); 650 nm (3.68). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.86 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.81 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.85 (s, 4H, ═CH pos. 12, 13, 17, 18), 8.14 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 7.35 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 8.10 (d, ^3J = 8.7 Hz, 6H, C_6H_4 pos. 10, 15, 20), 7.29 (d, ^3J = 8.7 Hz, 6H, C_6H_4 pos. 10, 15, 20), 5.53 (s, 1H, CH), 4.47 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.46 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.44 (d, 6H, 3 aryl-OCH_2CH$_2$), 4.06 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.86 (d, 6H, 3 OCH_2CH$_2$), 3.69 (d, 6H, 3 OCH$_2$CH_2), 3.47 (s, 9H, 3 OCH$_3$), 1.43 (t, ^3J = 7.1 Hz, 6H, 2 CO$_2$CH$_2$CH_3), −2.78 (bs, 2H, ═NH). MS (ESI) *m*/*z* (rel int.): 1143 (MH, 20); 572 (M + 2 H, dipositive cation, 100). Anal. ($C_{66}H_{70}N_4O_{14}$, 1143.3) C, H, N.

5,10,15,20-Tetrakis[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin. According to GP 3, 2.41 g (9.00 mmol) of 4-(1,4,7,-10-tetraoxaundecyl)benzaldehyde **5** and 841 mg (3.00 mmol) of diethyl 2-(4-formylphenoxy)malonate **7** were reacted with 805 mg (12.0 mmol, 840 μL) of pyrrole. After the first chromatography the crude product mixture was chromatographed over SiO_2 (65 × 3 cm) with CH_2Cl_2/MeOH 200:1 up to 180:1, eluting two small red bands, which contain porphyrins with more than one diethyl malonate group. If the methanol concentration of the solvent was increased from CH_2Cl_2/MeOH 150:1 up to 80:1, compound **9** eluted in form of a thick, purple band. Using a mixture of CH_2Cl_2/MeOH 60:1, the product eluted, which was recrystallized from CH_2Cl_2/cyclohexane. Yield: 258 mg (0.204 mmol, 2.3%) purple needles, mp 154 °C. IR (KBr): 3310 cm^{-1} (═NH). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 419 (5.59); 518 (4.33); 555 (4.17); 593 (3.81); 650 nm (3.92). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.85 (s, 8H, ═CH), 8.10 (d, ^3J = 8.7 Hz, 8H, 4 aryl-H2,6), 7.28 (d, ^3J = 8.7 Hz, 8H, 4 aryl-H3,5), 4.41 (d, 8H, 4 aryl-OCH_2CH$_2$), 4.04 (d, 8H, 4 aryl-OCH$_2$CH_2), 3.87 (d, 8H, 4 OCH_2CH$_2$), 3.79 (d, 8H, 4 OCH$_2$CH_2), 3.73 (d, 8H, 4 OCH_2CH$_2$OCH$_3$), 3.62 (d, 8H, 4 OCH_2CH$_2$OCH$_3$), 3.42 (s, 12H, OCH$_3$), −2.76 (bs, 2H, ═NH). MS (ESI) *m*/*z* (rel int.): 1264 (MH, 40); 632.5 (M + 2 H, dipositive cation, 100). Anal. ($C_{72}H_{86}N_4O_{16}$, 1263.5) C, H, N.

Diethyl 2-(4-{10,15,20-Tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonate (9). The synthesis and work up was carried out according to 5,10,15,20-tetrakis[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin. The crude product was purified by chromatography over SiO_2 (40 × 3.5 cm) with CH_2Cl_2/MeOH 100:1. Yield: 478 mg (0.375 mmol, 4.2%) purple, shiny crystals, mp 130−131 °C. IR (KBr): 3300 (═NH); 1760, 1740 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.50); 518 (4.13); 555 (3.97); 592 (3.70); 649 nm (3.69). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.86 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.81 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.86 (s, 4H, ═CH pos. 12, 13, 17, 18), 8.14 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 7.35 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 8.10 (d, ^3J = 8.7 Hz, 6H, C_6H_4 pos. 10, 15, 20), 7.30 (d, ^3J = 8.7 Hz, 6H, C_6H_4 pos. 10, 15, 20), 5.53 (s, 1H, CH), 4.47 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.46 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.43 (d, 6H, 3 aryl-OCH_2CH$_2$), 4.06 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.89 (d, 6H, 3 OCH_2CH$_2$), 3.80 (d, 6H, 3 OCH$_2$CH_2), 3.75 (d, 6H, 3 OCH_2CH$_2$OCH$_3$), 3.62 (d, 6H, 3 OCH$_2$CH_2OCH$_3$), 3.43 (s, 9H, 3 OCH$_3$), 1.43 (t, ^3J = 7.1 Hz, 6H, 2 CO$_2$CH$_2$CH_3), −2.78 (bs, 2H, ═NH). MS (FAB) *m*/*z* (rel int.): 1275 (MH, 100). Anal. ($C_{72}H_{82}N_4O_{17}$, 1275.4) C: calcd, 67.80; found, 67.31. H, N.

Diethyl 2-(4-{10,15,20-Tris[4-(poly(ethylene glycol)-750-monomethyl ether-1-yl)phenyl]porphyrin-5-yl}phenoxy)malonate (10). According to GP 3, 7.97 g (9.00 mmol) of 4-(poly(ethylene glycol)-750-monomethyl ether-1-yl)benzaldehyde **6** and 841 mg (3.00 mmol) of diethyl 2-(4-formylphenoxy)malonate **7** were reacted with 805 mg (12.0 mmol, 840 μL) of pyrrole. After the first chromatography the crude product mixture was chromatographed over SiO_2 (65 × 3 cm) with CH_2Cl_2/MeOH 100:1 up to 30:1, eluting several small bands, which contain porphyrins with more than one diethyl malonate group. If the methanol concentration of the solvent was increased up to CH_2Cl_2/MeOH 20:1, the product eluted as a purple band. Yield: 800 mg (0.256 mmol, 2.8%) dark red oil. IR (film): 3300 (═NH); 1765, 1740 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.54); 518 (4.17); 555 (3.99); 593 (3.68); 650 nm (3.65). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.88 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.81 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.85 (s, 4H, ═CH pos. 12, 13, 17, 18), 8.13 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 7.34 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 5), 8.10 (d, ^3J = 8.7 Hz, 4H, C_6H_4 pos. 10, 20), 7.30 (d, ^3J = 8.7 Hz, 4H, C_6H_4 pos. 10, 20), 8.09 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 15), 7.29 (d, ^3J = 8.7 Hz, 2H, C_6H_4 pos. 15), 5.53 (s, 1H, CH), 4.47 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.46 (q, ^3J = 7.1 Hz, 2H, CO$_2$CH_2CH$_3$), 4.43 (d, 6H, 3 aryl-OCH_2CH$_2$), 4.06 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.87 (d, 6H, 3 aryl-OCH$_2$CH$_2$OCH_2CH$_2$), 3.80 (d, 6H, 3 aryl-OCH$_2$CH$_2$OCH$_2$CH_2), 3.73−3.53 (m, 168H, OCH$_2$CH$_2$), 3.48 (s, 9H, 3 OCH$_3$), 1.43 (t, ^3J = 7.1 Hz, 6H, 2 CO$_2$CH$_2$CH_3), −2.78 (bs, 2H, ═NH). MS (ESI) *m*/*z* (rel int.): 3125 (MH, 22); loss of 2 CO$_2$CH$_3$ units and 1−16 OCH$_2$CH$_2$ units; 2231 (MH − 2 CO$_2$CH$_3$ − 17 OCH$_2$CH$_2$, 100). ($C_{156}H_{250}N_4O_{59}$, 3125.6).

2-(4-{10,15,20-Tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonic Acid (11). 310 mg (0.271 mmol) of diethyl 2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonate **8** was dissolved in 85 mL of CH_2Cl_2. 200 mL of a 20% methanolic KOH solution and 3 mL of water were added. The mixture was heated to reflux for 3 h and stirred for 12 h at room temperature. After concentrating the solution to ca. 50 mL, it was cooled with ice and acidified with a 7% aqueous HCl solution (pH 4). The resulting green precipitate was filtered off, dissolved in CH_2Cl_2, and washed with H_2O until the aqueous phase is neutral. The purple organic phase was dried with Na_2SO_4, evaporated, and dried in a vacuum. Yield: 295 mg (0.271 mmol, 100%) dark blue, shiny solid, mp 202−203 °C. IR (KBr): 3310 (═NH); 1710 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.52); 458 (4.75); 518

(4.17); 555 (4.03); 594 (3.78); 651 (3.91); 697 nm (4.13). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.86−8.61 (m, 8H, =CH), 8.48 (d, 2H, C_6H_4 pos. 5), 7.57 (d, 2H, C_6H_4 pos. 5), 8.11 (d, 6H, C_6H_4 pos. 10, 15, 20), 7.32 (d, 6H, C_6H_4 pos. 10, 15, 20), 5.42 (s, 1H, CH), 4.46 (d, 6H, 3 aryl-OCH_2CH$_2$), 4.08 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.87 (d, 6H, 3 OCH$_2$CH$_2$), 3.69 (d, 6H, 3 OCH$_2$CH$_2$), 3.47 (s, 6H, 2 OCH_3 pos. 10, 20), 3.37 (s, 3H, OCH_3 pos. 15), −2.81 (bs, 2H, =NH). The CO_2H signals could not be detected. MS (ESI) *m*/*z* (rel int.): 1087 (MH, 100); 1043 (MH − CO_2, 60); 544 (M + 2 H, dipositive cation, 17); 522 (M − CO_2 + 2 H, dipositive cation, 11). Anal. ($C_{62}H_{62}N_4O_{14}$, 1087.2) C, H, N: calcd, 5.15; found, 4.49.

2-(4-{10,15,20-Tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]-porphyrin-5-yl}phenoxy)malonic Acid (12). 400 mg (0.314 mmol) of diethyl 2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonate **9** was dissolved in 100 mL of CH_2Cl_2. 300 mL of a 20% methanolic KOH solution and 5 mL of water were added. The mixture was heated to reflux for 3 h and stirred 12 h at room temperature. After concentrating the solution to ca. 50 mL, it was cooled with ice and acidified with a 7% aqueous HCl solution (pH 4). The resulting green precipitate was filtered off, dissolved in CH_2Cl_2, and washed with H_2O until the aqueous phase was neutral. The purple organic phase was dried with Na_2SO_4, evaporated, and dried in a vacuum. Yield: 383 mg (0.314 mmol, 100%) greenish blue solid, mp > 250 °C. IR (KBr): 3300 (=NH); 1740, 1730 cm^{-1} (C=O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.53); 518 (4.08); 555 (3.89); 593 (3.47); 650 nm (3.54). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.80−8.64 (m, 8H, =CH), 8.12 (d, 2H, C_6H_4 pos. 5), 7.28 (d, 2H, C_6H_4 pos. 5), 7.89 (d, 6H, C_6H_4 pos. 10, 15, 20), 7.28 (d, 6H, C_6H_4 pos. 10, 15, 20), 5.42 (s, 1H, CH), 4.31−3.55 (m, 36H, OCH$_2$CH$_2$), 3.36 (s, 9H, 3 OCH_3), −2.80 (bs, 2H, =NH). The CO_2H signals could not be detected. MS (ESI) *m*/*z* (rel int.): 1219 (MH, 8); 1175 (MH − CO_2, 10); 610 (M + 2 H, dipositive cation, 100); 588 (M − CO_2 + 2 H, dipositive cation, 88). Anal. ($C_{68}H_{74}N_4O_{17}$, 1219.3) C: calcd, 66.98; found, 66.50. H: calcd, 6.12; found 5.54. N.

2-(4-{10,15,20-Tris[4-(poly(ethyleneglycol)-750-monomethyl ether-1-yl)phenyl]porphyrin-5-yl}phenoxy)malonic Acid (13). A total of 800 mg (0.256 mmol) of diethyl 2-(4-{10,15,20-tris[4-(poly(ethyleneglycol)-750-monomethyl ether-1-yl)phenyl]porphyrin-5-yl}phenoxy)malonate **10** was dissolved in 120 mL of a 20% methanolic KOH solution, heated to reflux for 3 h, and stirred for 12 h at room temperature. After the solution was concentrated to ca. 50 mL, it was cooled with ice, acidified with a 7% aqueous HCl solution (pH 4), and extracted with 250 mL of CH_2Cl_2. The organic layer was washed with 2 × 100 mL of water, dried with Na_2SO_4, and evaporated obtaining a green oil. Now 100 g of a strong basic ion exchanger (Fa. Merck, Ionenaustauscher III) was activated with 100 mL of 2 M NaOH and eluted with water, until the eluate was neutral. Then the crude product was dissolved in 10 mL of H_2O and put on the top of the ion exchanger. The porphyrindicarboxylic acid was immobilized on the ion exchanger matrix so that the excessive poly(ethylene glycol) could be eluted with 1 L of water. With 2 M aqueous HCl, the immobilized porphyrin could be eluted, which was extracted with CH_2Cl_2. After drying the organic layer with Na_2SO_4, the solvent was removed and the product was dried in a vacuum. Yield: 400 mg (0.130 mmol, 51%) red oil. IR (film): 3310 (=NH); 1745, 1730 cm^{-1} (C=O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 424 (5.53); 519 (4.15); 558 (4.06); 594 (3.67); 652 nm (3.77). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.86−8.54 (m, 8H, =CH), 8.17−7.28 (m, 16H, C_6H_4), 4.56−3.54 (m, 204 H, OCH$_2$CH$_2$), 3.37 (s, 9H, 3 OCH_3). The CO_2H, =NH, and CH signals could not be detected. MS (ESI) *m*/*z* (rel int.): 3068 (MH, 20); loss of CO_2 and 1−16 OCH$_2$CH$_2$ units; 2320 (MH − CO_2 − 16 OCH$_2$CH$_2$, 97); 2276 (MH − CO_2 − 17 OCH$_2$CH$_2$, 100). ($C_{152}H_{242}N_4O_{59}$, 3069.5).

General Procedure 4 (GP 4). Diammine(diaqua)platinum(II) hydroxide was synthesized from diammine(dichloro)-platinum(II) (cisplatin) as previously described. After removal of the solvent, 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 **11** and **12** were dissolved in a mixture of $CHCl_3$ and EtOH, and the water-soluble ligand **13** was 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** and **22** were filtered off, washed with water and ethanol, and dried in a vacuum. In the case of the water-soluble complex **23**, 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[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (21). According to GP 4, **11** (109 mg, 0.100 mmol) was dissolved in 10 mL of $CHCl_3$ and 20 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum(II) hydroxide solution and stirred for 20 h. Yield: 81.0 mg (54.2 μmol, 54%) purple powder, mp 213−214 °C. IR (KBr): 1680, 1660 cm^{-1} (C=O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 424 (5.05); 520 (4.16); 556 (3.98); 593 (3.69); 650 nm (3.66). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.52 (m, 8H, =CH), 7.94 (d, 8H, 4 aryl-H2,6), 7.19 (d, 8H, 4 aryl-H3,5), 4.34 (d, 6H, 3 aryl-OCH_2CH$_2$), 3.94 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.78 (d, 6H, 3 OCH_2CH$_2$), 3.62 (d, 6H, 3 OCH$_2$CH_2), 3.39 (s, 9H, 3 OCH_3), −3.01 (bs, 2H, =NH). The NH_3 and CH signals could not be detected. MS (ESI) *m*/*z* (rel int.): 1315 (MH − 10 H_2O, 23); 1087 (LH, 8); 1043 (LH − CO_2, 7); 999 (LH − 2 CO_2, 6); 658 (M − 10 H_2O + 2 H, dipositive cation, 100). Anal. ($C_{62}H_{66}N_6O_{14}Pt$·10 H_2O, 1494.5) C: calcd, 49.83; found, 49.19. H, N: calcd, 5,62; found, 6.09.

Diammine[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum-(II) (22). According to GP 4, **12** (122 mg, 0.100 mmol) was dissolved in 10 mL of $CHCl_3$ and 30 mL of EtOH, combined with 0.100 mmol of the aqueous diammine(diaqua)platinum-(II) hydroxide solution, and stirred for 20 h. Yield: 54.4 mg (37.6 μmol, 75%) purple powder, mp 197−198 °C. IR (KBr): 1640, 1625 cm^{-1} (C=O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.39); 518 (4.20); 557 (4.06); 594 (3.72); 651 nm (3.76). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.52 (m, 8H, =CH), 7.99 (d, 8H, 4 aryl-H2,6), 7.20 (d, 8H, 4 aryl-H3,5), 4.38 (d, 6H, 3 aryl-OCH_2CH$_2$), 4.05 (d, 6H, 3 aryl-OCH$_2$CH_2), 3.76 (d, 6H, 3 OCH_2CH$_2$), 3.62 (d, 6H, 3 OCH$_2$CH_2), 3.49 (d, 6H, 3 OCH_2CH$_2$OCH$_3$), 3.41 (d, 6H, 3 OCH$_2$CH_2OCH$_3$), 3.42 (s, 9H, OCH_3), −2.99 (bs, 2H, =NH). The NH_3 and CH signals could not be detected. MS (ESI) *m*/*z* (rel int.): 1447 (MH, 28); 1219 (LH, 100); 724 (M + 2 H, dipositive cation, 42); 610 (L + 2 H, dipositive cation, 55). Anal. ($C_{68}H_{78}N_6O_{17}Pt$, 1446.5) C: calcd, 56.46; found, 56.01. H, N.

Diammine[2-(4-{10,15,20-tris[4-(poly(ethyleneglycol)-750-monomethyl ether-1-yl)phenyl]porphyrin-5-yl}-phenoxy)malonato]platinum(II) (23). According to GP 4, **13** (307 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 20 h. To the resulting solution was added CH_2Cl_2, and the mixture was extracted with H_2O. The aqueous phase was evaporated to obtain the product. Yield: 48.2 mg (14.6 μmol, 15%) brown, sticky solid. IR (KBr): 1635, 1620 cm^{-1} (C=O). UV/vis (DMSO) λ_{max} (log ϵ) 423 (5.56); 519 (4.26); 557 (4.17); 595 (3.78); 651 nm (3.88). MS (ESI) *m*/*z* (rel int.): 2357 (MH − CH_3 − 21 OCH$_2$CH$_2$, 34); loss of CH_3 and 22−25 OCH$_2$CH$_2$ units; 2181 (MH − CH_3 − 25 OCH$_2$CH$_2$, 100); 2137 (MH − CH_3 − 26 OCH$_2$CH$_2$, 100). ($C_{152}H_{246}N_6O_{59}Pt$, 3296.7).

General Procedure 5 (GP 5). About 0.100 mmol of the respective diamine(dichloro)platinum(II) complex were suspended in ca. 15 mL of water. After 10 min 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. A total of 15 g 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 CH_2Cl_2/EtOH. After being 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 a vacuum.

1,2-Diaminoethane[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum-(II) (24). According to GP 5, 109 mg (0.100 mmol) of **11** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated 1,2-diaminoethane(dichloro)platinum(II). Yield: 52.0 mg (38.8 μmol, 39%) purple powder, mp 252 °C. IR (KBr): 1650, 1630 cm^{-1} (C═O). UV/vis (DMF) λ_{max} (log ϵ) 422 (5.48); 519 (4.12); 557 (4.05); 596 (3.67); 652 nm (3.74). MS (ESI) *m*/*z* (rel int.): 1341 (MH, 1); 1087 (LH, 28); 544 (L + 2 H, 100). Anal. ($C_{64}H_{68}N_6O_{14}Pt$, 1340.3) C: calcd, 57.35; found, 56.83. H, N.

1,2-Diaminoethane[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]-platinum(II) (25). According to GP 5, 122 mg (0.100 mmol) of **12** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated 1,2-diaminoethane(dichloro)-platinum(II). Yield: 70.8 mg (48.0 μmol, 48%) purple powder, mp 207−208 °C. IR (KBr): 1665, 1640 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ) 422 (5.53); 518 (4.19); 556 (4.10); 594 (3.75); 651 nm (3.82). MS (ESI) *m*/*z* (rel int.): 1473 (MH, 19); 737 (M + 2 H, dipositive cation, 100). Anal. ($C_{70}H_{80}N_6O_{17}Pt$, 1472.5) C: calcd, 57.10; found, 56.57. H, N.

1,3-Diaminopropane[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (26). According to GP 5, 109 mg (0.100 mmol) of **11** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated 1,3-diaminopropane(dichloro)platinum(II). Yield: 72.0 mg (53.2 μmol, 53%) light purple powder, mp 212 °C. IR (KBr): 1645, 1630 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 422 (5.11); 441 (4.91); 521 (4.19); 556 (4.01); 595 (3.79); 651 nm (3.71). MS (ESI) *m*/*z* (rel int.): 1355 (MH, 7); 1087 (LH, 15); 678 (M + 2 H, dipositive cation, 100); 544 (L + 2 H, dipositive cation, 70). Anal. ($C_{65}H_{70}N_6O_{14}Pt$, 1354.4) C, H, N.

1,3-Diaminopropane[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]-platinum(II) (27). According to GP 5, 122 mg (0.100 mmol) of **12** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated 1,3-diaminopropane(dichloro)-platinum(II). Yield: 82.6 mg (55.6 μmol, 56%) purple solid, mp 202−203 °C. IR (KBr): 1650, 1630 cm^{-1} (C═O). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 386 (4.66); 422 (5.44); 442 (5.02); 520 (4.31); 556 (4.12); 595 (3.86); 651 nm (3.81). MS (ESI) *m*/*z* (rel int.): 1487 (MH, 64); 744 (M + 2 H, dipositive cation, 100). Anal. ($C_{71}H_{82}N_6O_{17}Pt$, 1486.5) C, H, N.

(*RR*/*SS*)-*trans*-1,2-Diaminocyclohexane[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)-malonato]platinum(II) (28). According to GP 5, 109 mg (0.100 mmol) of **11** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane(dichloro)platinum(II). Yield: 72.0 mg (50.3 μmol, 50%) purple powder, mp 238 °C. IR (KBr): 1660, 1645 cm^{-1} (C═O). UV/vis (DMF) λ_{max} (log ϵ) 422 (5.49); 519 (4.16); 556 (4.05); 594 (3.64); 651 nm (3.74). MS (ESI) *m*/*z* (rel int.): 1395 (MH − 2 H_2O, 47); 698 (M − 2 H_2O + 2 H, dipositive cation, 100). Anal. ($C_{68}H_{74}N_6O_{14}Pt \cdot 2H_2O$, 1430.5) C, H, N.

(*RR*/*SS*)-*trans*-1,2-Diaminocyclohexane[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}-phenoxy)malonato]platinum (II) (29). According to GP 5, 122 mg (0.100 mmol) of **12** in 10 mL of CH_2Cl_2 and 20 mL of EtOH was reacted with 0.100 mmol of activated (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane(dichloro)platinum(II). Yield: 113 mg (73.9 μmol, 74%) purple solid, mp 208 °C. IR (KBr): 1650, 1630 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ) 423 (5.52); 520 (4.17); 555 (4.02); 595 (3.65); 650 nm (3.69). MS (ESI) *m*/*z* (rel int.): 1527 (MH, 57); 764 (M + 2 H, dipositive cation, 100). Anal. ($C_{74}H_{86}N_6O_{17}Pt$, 1526.6) C, H, N.

(*RR*/*SS*)-*trans*-1,2-Diaminocyclohexane[2-(4-{10,15,20-tris[4-(poly(ethylene glycol)-750-monomethyl ether-1-yl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (30). According to GP 5, 307 mg (0.100 mmol) of **13** in 10 mL of H_2O was reacted with 0.100 mmol of activated (*RR*/*SS*)-*trans*-1,2-diaminocyclohexane(dichloro)platinum(II). CH_2Cl_2 was added to the reaction mixture, and it was extracted with water. The aqueous phase was evaporated to obtain the product. Yield: 190 mg (56.3 μmol, 56%) purple, sticky solid. IR (KBr): 1655, 1640 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ) 424 (5.57); 489 (3.71); 519 (4.18); 557 (4.09); 594 (3.68); 651 nm (3.79). MS (ESI) *m*/*z* (rel int.): 3112 (MH − 6 OCH_2CH_2, 33); loss of 7−13 OCH_2CH_2 units; 2804 (MH − 13 OCH_2CH_2, 90). ($C_{158}H_{254}N_6O_{59}$-Pt, 3376.8).

2,2′-Bipyridyl[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)-phenyl]porphyrin-5-yl}phenoxy)malonato]platinum-(II) (31). A total of 42.2 mg (0.100 mmol) of 2,2′-bipyridyl-(dichloro)platinum(II) was suspended in 15 mL of H_2O. After a 10 min ultrasonic treatment, 34.0 mg (0.200 mmol) of $AgNO_3$ was added, and the mixture was stirred for 7 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 **11** (109 mg, 0.100 mmol) in 10 mL of $CHCl_3$ and 20 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 a vacuum. Yield: 92.4 mg (64.3 μmol, 64%) purple powder, mp 235−236 °C. IR (KBr): 1690, 1660 cm^{-1} (C═O). UV/vis (DMSO) λ_{max} (log ϵ) 421 (5.54); 518 (4.11); 555 (3.96); 593 (3.60); 649 nm (3.64). MS (ESI) *m*/*z* (rel int.): 1459 (MNa, 100); 1437 (MH, 17); 741 (M + 2 Na, dipositive cation, 49); 730 (MH + Na, dipositive cation, 100); 719 (M + 2 H, dipositive cation, 35). Anal. ($C_{72}H_{68}N_6O_{14}Pt$, 1436.4) C, H, N.

2,2′-Bipyridyl[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (32). According to the synthesis of **31**, 2,2′-bipyridyl-(dichloro)platinum(II) (42.2 mg, 0.100 mmol) was reacted with 122 mg (0.100 mmol) of **12**. The precipitated solid was filtered, washed with water and EtOH, and dried in a vacuum. Yield: 67.9 mg (43.3 μmol, 43%) purple solid, mp 237 °C. IR (KBr): 1690, 1660 cm^{-1} (C═O). UV/vis (DMF) λ_{max} (log ϵ) 422 (5.54); 518 (4.20); 556 (4.11); 595 (3.78); 651 nm (3.84). ^1H NMR ($CDCl_3$) δ (ppm): 8.85 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.70 (d, ^3J = 4.8 Hz, 2H, 2 ═CH), 8.81 (d, ^3J = 1.4 Hz, 2H, 2 ═CH), 8.70 (d, ^3J = 1.4 Hz, 2H, 2 ═CH), 8.13 (d, ^3J = 8.6 Hz, 2H, C_6H_4 pos. 5), 8.79 (d, ^3J = 8.6 Hz, 2H, C_6H_4 pos. 5), 7.99 (d, ^3J = 8.6 Hz, 4H, C_6H_4 pos. 10, 20), 7.23 (d, ^3J = 8.6 Hz, 4H, C_6H_4 pos. 10, 20), 7.99 (d, ^3J = 8.6 Hz, 2H, C_6H_4 pos. 15), 7.17 (d, ^3J = 8.6 Hz, 2H, C_6H_4 pos. 15), 7.80 (m, 2H, bipy), 7.05 (m, 2H, bipy), 6.84 (m, 2H, bipy), 5.77 (m, 2H, bipy), 5.09 (s, 1H, CH), 4.43 (d, 2H, aryl-OCH_2CH$_2$ pos. 15), 4.04 (d, 2H, aryl-OCH$_2$CH_2 pos. 15), 4.32 (d, 4H, 2 aryl-OCH_2CH$_2$ pos. 10, 20), 3.94 (d, 4H, 2 aryl-OCH$_2$CH_2 pos. 10, 20), 3.86 (d, 2H, OCH_2-CH$_2$ pos. 15), 3.60 (d, 2H, OCH$_2$CH_2 pos. 15), 3.77 (d, 4H, 2 OCH_2CH_2 pos. 10, 20), 3.53 (d, 4H, 2 OCH_2CH_2 pos. 10, 20), 3.71 (d, 6H, 3 O$CH_2CH_2OCH_3$), 3.62 (d, 6H, 3 $OCH_2CH_2OCH_3$), 3.41 (s, 3H, OCH_3 pos. 15), 3.34 (s, 6H, 2 OCH_3 pos. 10, 20), −3.29 (bs, 2H, ═NH). MS (FAB) *m*/*z* (rel int.): 1569 (MH, 100). Anal. ($C_{78}H_{80}N_6O_{17}Pt$, 1568.6) C: calcd, 59.73; found, 59.27. H: calcd, 5.14; found, 4.59. N: calcd, 5.36; found, 4.90.

General Procedure 6 (GP 6). The respective diamine-(diiodo)platinum(II) complex (0.100 mmol) was suspended in 10 mL of water. After a 3 h 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 10 mL of water, before it was combined with a solution of the respective porphyrindicarboxylic acid (0.100 mmol) in a mixture of 10 mL of CH_2Cl_2 and 40 mL of EtOH. The pH of the solution was adjusted 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 the solvent used above, and dried in a vacuum.

Ethyl (*R*/*S*)-2,3-Diaminopropionate[2-(4-{10,15,20-tris-[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)-malonato]platinum(II) (33). According to GP 6, ethyl (*R*/*S*)-2,3-diaminopropionate(diiodo)platinum(II) (58.1 mg, 0.100 mmol) was reacted with 109 mg (0.100 mmol) of **11**. Yield: 67.0 mg (47.4 μmol, 47%) purple powder, mp 210−215 °C. IR (KBr): 1725 (C═O, ester); 1655, 1630 cm^{-1} (C═O, carboxylate). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.25); 519 (4.00); 557 (3.85); 594 (3.48); 651 nm (3.52). MS (ESI) *m*/*z* (rel int.): 1413 (MH, 6); 1087 (LH, 28); 544 (L + 2 H, dipositive cation, 100). Anal. ($C_{67}H_{72}N_6O_{16}Pt$, 1412.4) C: calcd, 56.98; found, 56.54. H, N.

Ethyl (*R*/*S*)-2,3-Diaminopropionate[2-(4-{10,15,20-tris-[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (34). According to GP 6, ethyl (*R*/*S*)-2,3-diaminopropionate(diiodo)platinum(II) (58.1 mg, 0.100 mmol) was reacted with 122 mg (0.100 mmol) of **12**. Yield: 76.9 mg (49.8 μmol, 50%) purple solid, mp 170 °C. IR (KBr): 1730 (C═O, ester); 1640, 1630 cm^{-1} (C═O, carboxylate). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.55); 519 (4.32); 555 (4.16); 594 (3.86); 650 nm (3.88). MS (ESI) *m*/*z* (rel int.): 1545 (MH, 24); 773 (M + 2 H, dipositive cation, 100). Anal. ($C_{73}H_{84}N_6O_{19}Pt$, 1544.6) C, H, N.

Ethyl (*S*)-2,4-Diaminobutanoate[2-(4-{10,15,20-tris[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (35). According to GP 6, ethyl (*S*)-2,4-diaminobutanoate(diiodo)platinum(II) (59.5 mg, 0.100 mmol) was reacted with 109 mg (0.100 mmol) of **11**. Yield: 95.0 mg (56.6 μmol, 57%) purple powder, mp 234−235 °C. IR (KBr): 1725 (C═O, ester); 1655, 1630 cm^{-1} (C═O, carboxylate). ^{1}H NMR ($CDCl_3$, 5 drops CD_3OD) δ (ppm): 8.73 (m, 8H, ═CH), 8.02 (d, 8H, 4 aryl-H2,6), 7.24 (d, 8H, 4 aryl-H3,5), 4.36 (d, 6H, 3 aryl-OCH_2CH_2), 3.99 (d, 6H, 3 aryl-OCH_2CH_2), 3.79 (d, 6H, 3 OCH_2CH_2), 3.63 (d, 6H, 3 OCH_2CH_2), 3.40 (s, 9H, OCH_3), −2.86 (bs, 2H, ═NH). The CH signal and the signals of the nonnucleofuge could not be detected. MS (ESI) *m*/*z* (rel int.): 1427 (MH − 14 H_2O, 13); 1087 (LH, 100). Anal. ($C_{68}H_{74}N_6O_{16}$-Pt · 14 H_2O, 1678.6) C, H, N.

Ethyl (*S*)-2,4-Diaminobutanoate[2-(4-{10,15,20-tris[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (36). According to GP 6, ethyl (*S*)-2,4-diaminobutanoate(diiodo)platinum(II) (59.5 mg, 0.100 mmol) was reacted with 122 mg (0.100 mmol) of **12**. Yield: 61.8 mg (39.7 μmol, 40%) purple solid, mp 201−203 °C. IR (KBr): 1730 (C═O, ester); 1650, 1620 cm^{-1} (C═O, carboxylate). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.54); 519 (4.26); 556 (4.12); 594 (3.81); 650 nm (3.83). MS (ESI) *m*/*z* (rel int.): 1559 (MH, 84); 780 (M + 2 H, dipositive cation, 100). Anal. ($C_{74}H_{86}N_6O_{19}Pt$, 1558.6) C, H, N: calcd, 5.39; found, 4.94.

Diethyl *meso*-4,5-Diaminosuberate[2-(4-{10,15,20-tris-[4-(1,4,7-trioxaoctyl)phenyl]porphyrin-5-yl}phenoxy)-malonato]platinum(II) (37). According to GP 6, diethyl *meso*-4,5-diaminosuberate(diiodo)platinum(II) (70.9 mg, 0.100 mmol) was reacted with 122 mg (0.100 mmol) of **11**. Yield: 65.3 mg (42.4 μmol, 42%) dark purple powder, mp 206 °C. IR (KBr): 1720, 1705 (C═O, ester); 1640, 1625 cm^{-1} (C═O, carboxylate). UV/vis (DMSO) λ_{max} (log ϵ) 423 (5.57); 519 (4.24); 557 (4.16); 594 (3.75); 651 nm (3.86). MS (ESI) *m*/*z* (rel int.): 1540 (MH, 25); 1087 (LH, 80); 770.5 (M + 2 H, dipositive cation, 60); 544 (L + 2 H, dipositive cation, 100). Anal. ($C_{74}H_{84}N_6O_{18}Pt$, 1540.6) C, H. N: calcd, 5.46; found, 6.03.

Diethyl *meso*-4,5-Diaminosuberate[2-(4-{10,15,20-tris-[4-(1,4,7,10-tetraoxaundecyl)phenyl]porphyrin-5-yl}phenoxy)malonato]platinum(II) (38). According to GP 6, diethyl *meso*-4,5-diaminosuberate(diiodo)platinum(II) (70.9 mg, 0.100 mmol) was reacted with 122 mg (0.100 mmol) of **12**. Yield: 87.2 mg (52.1 μmol, 52%) purple solid, mp 191−192 °C. IR (KBr): 1730 (C═O, ester); 1650, 1630 cm^{-1} (C═O, carboxylate). UV/vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.55); 518 (4.21); 556 (4.04); 593 (3.64); 650 nm (3.72). MS (ESI) *m*/*z* (rel int.): 1673 (MH, 100); 837 (M + 2 H, dipositive cation, 75). Anal. ($C_{80}H_{96}N_6O_{21}Pt$, 1672.7) C, H: calcd, 5.78; found, 5.31. N.

Cell Culture. The human TCC-SUP bladder cancer cell line[15] was 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.[19] The maintenance and the routine treatment of the TCC-SUP (ATCC No.: HTB-5) cells is described in the preceding paper.

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 complexes, with the exception of **23** and **30**, were not soluble in water or 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. The general procedure for chemosensitivity testing is described in the preceding paper.

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

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

where T is the mean absorbance of the treated cells, C the mean absorbance of the controls, and C_0 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 versus time is discussed elsewhere.[16,17]

Irradiation of the Cells. In brief, irradiation occurred for 10 min with an incoherent light source, namely a Waldmann PDT 700 lamp (Waldmann-Medizintechnik, Villingen-Schwenningen, Germany). The wavelength range was between 600 and 730 nm. The distance from lamp to irradiated 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 culture and the seeding of the TCC-SUP cells, the preparation of the stock solutions of the tetraarylporphyrin−platinum conjugates, cisplatin, and hematoporphyrin, and the preparation of the wells of the microplates were carried out as described in the preceding paper. For the dose−response relationship experiment, the compounds were tested at 1, 5, and 10 μM concentration. For studying the dark and light-induced toxicity, the test compounds were used at 5 μM concentration. At 48 h after incubation with the tetraarylporphyrin−platinum conjugates corresponding to $t = 0$ (the time zero indicates the time at which the drug was added), one series of the plates was irradiated. The data of the first time point of the kinetics were obtained immediately after the irradiation. 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) 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.

(2) Leblanc, J.-P.; Rorrer, K.; Gibson, H. W. Synthesis of a Star-Shaped Tris(Reissert Compound). *J. Org. Chem.* **1994**, *59*, 674−675.

(3) (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. Synthesis of tetraphenylporphyrins under very mild conditions. *Tetrahedron Lett.* **1986**, *27*, 4969−4970. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. Rothemund and Adler-Longo reactions revisited: synthesis of tetraphenylporphyrins under equilibrium conditions. *J. Org. Chem.* **1987**, *52*, 827−836.

(4) 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.

(5) 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.

(6) 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.

(7) 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.

(8) 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.

(9) Pesaro, M.; Felner-Caboga, I.; Eschenmoser, A. Rac.-di-2-pyrrolidonyl-(5,5′), ein Zwischenprodukt zur Synthese von Corrinkomplexen. *Chimia* **1965**, *19*, 566−567.

(10) 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.

(11) 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.

(12) 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.

(13) 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.

(14) Bart, K.-C. Ph.D. Thesis, Universität Regensburg, 2001.

(15) 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.

(16) 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.

(17) 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.

(18) Moss, G. P. Nomenclature of tetrapyrroles. *Pure Appl. Chem.* **1987**, *59*, 779−832.

(19) Hay, R. J. The seed stock concept and quality control for cell lines. *Anal. Biochem.* **1988**, *171*, 225−237.

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