Synthesis of cobalt bis(dicarbollide) conjugates with natural chlorins by the Sonogashira reaction

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Novel boron-containing conjugates based on the alkynylated cobalt bis(dicarbollide) anion and chlorin e_6 and purpurinimide *p*-iodophenyl derivatives were synthesized by the Sonogashira reaction. These conjugates can accumulate in the cancer cell cytoplasm and can be considered as potential candidates for using in boron neutron capture therapy of tumors.

Key words: cobalt bis(dicarbollide), chlorin e_6, purpurinimide, the Sonogashira reaction, boron neutron capture therapy of tumors, photosensitizers, fluorescence microscopy, tumor cells.

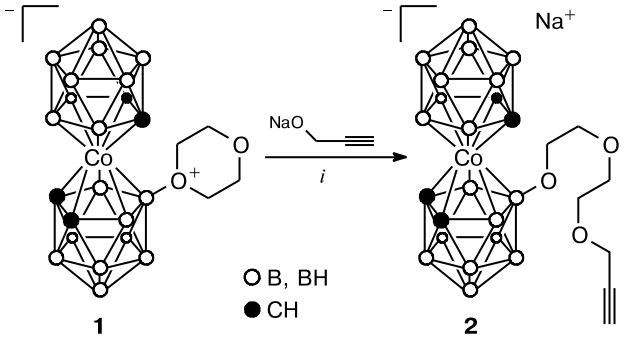
Boron neutron capture therapy (BNCT) is one of the new and promising methods for cancer treatment.[1—4] The further development of this method is inseparably associated with the design of new boron-containing drugs that can selectively accumulate in the tumor tissue. Amino acids, peptides, nucleotides, and some other molecules tropic to tumors can be used as molecules performing the targeted boron transport to the tumor. The ability of porphyrins to be accumulated in cancer cells is well known. This ability in combination with the photoinduced generation of reactive oxygen species makes it possible to use them as photosensitizers in anticancer photodynamic therapy (PDT).[5—7] Photosensitizers based on natural chlorophylls with the enhanced tropicity to tumors, low toxicity, and an intense absorption in the near-IR spectral region, providing the laser radiation action on deeply localized layers of cancer tissues, are of special interest. Therefore, synthesis of conjugates of polyhedral boron compounds with natural porphyrins is a topical issue.[8—16] The porphyrin fragment in these compounds provides the transportation of the boron-containing conjugate to cancer cells and a possibility of visualization of the tumor. The subsequent irradiation of the cells with thermal neutrons and their interaction with the ^{10}B isotope of boron compounds selectively accumulated in cancer cells should result in the selective destruction of malignant neoplasms.

In the present work, the Sonogashira reaction, which is actively employed in modern organic chemistry,[17,18] was used for the synthesis of boron-containing conjugates of natural porphyrins.

Results and Discussion

The reaction of sodium propynolate with the oxonium derivative of cobalt bis(dicarbollide) (**1**) afforded the cobalt bis(dicarbollide) derivative with the terminal acetylene group (**2**) linked with the boron polyhedron through a flexible hydrophilic spacer, being the di(ethylene glycol) fragment (Scheme 1).

Scheme 1



Reagents and conditions: *i*. MeCN, 0 °C, 48 h.

The acylation of amino-containing chlorins **3** and **4** with *p*-iodobenzoyl chloride gave the second component of the Sonogashira reaction, namely, chlorin e_6 and purpurinimide *p*-iodophenyl derivatives (**5** and **6**) (Scheme 2).

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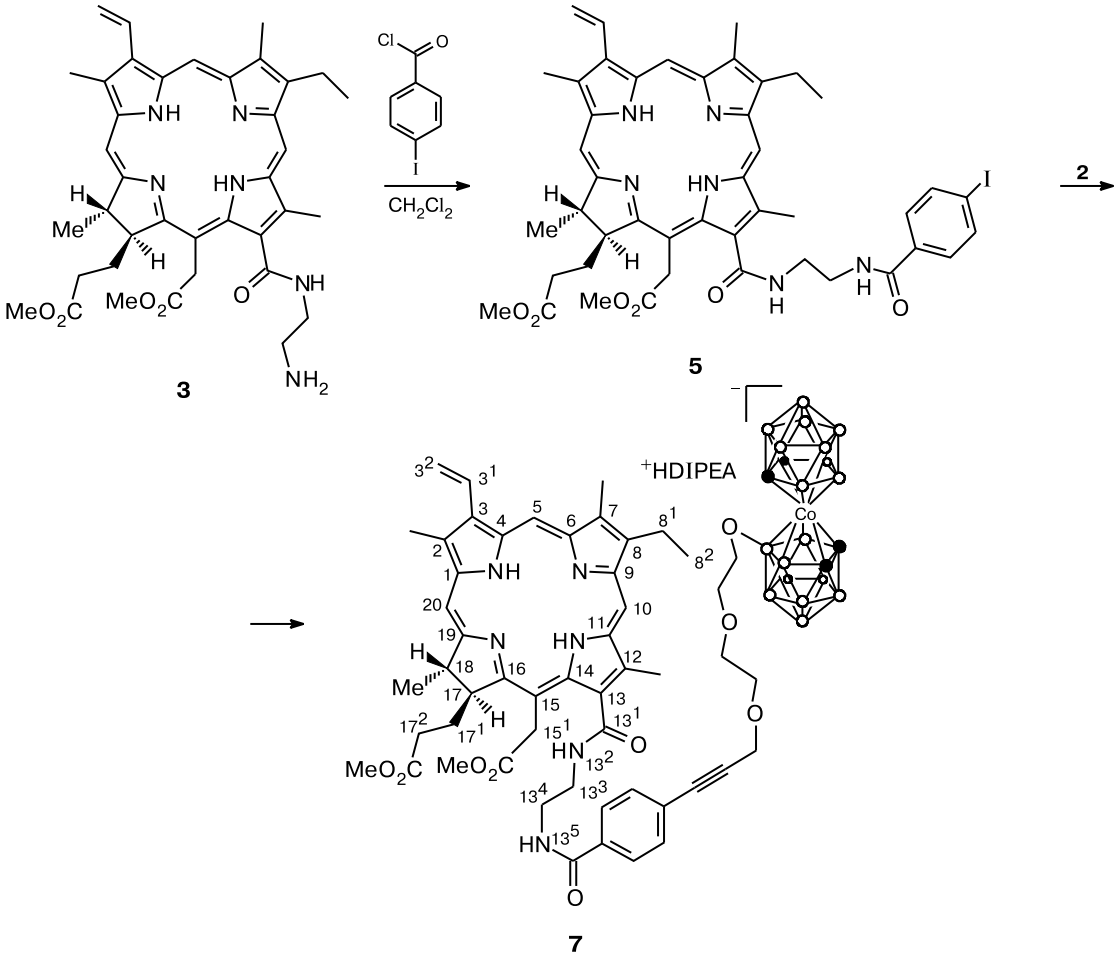
Scheme 2



The ^{1}H NMR spectra of compounds **5** and **6** exhibit signals for protons of the 1,4-disubstituted benzene ring in the region δ 7.7—7.4.

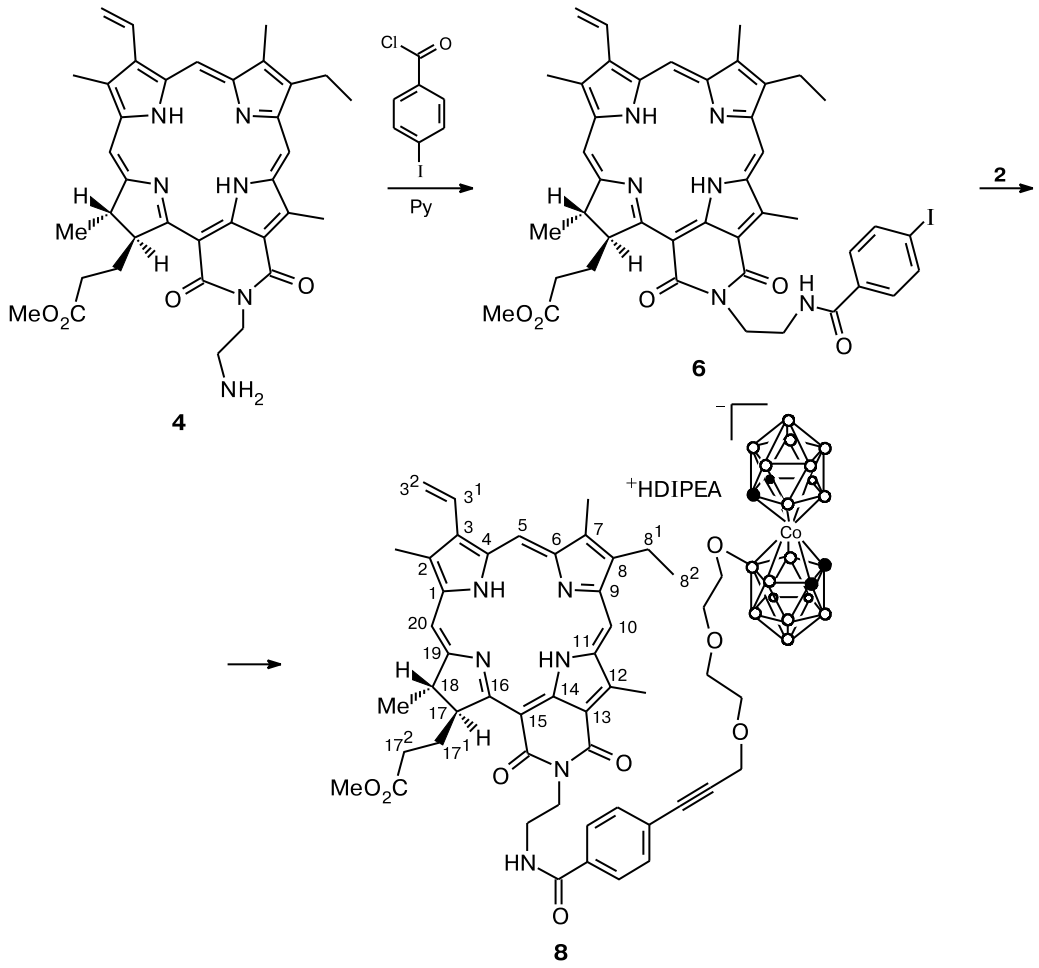
The Sonogashira reaction was carried out in the presence of $Pd_2(dba)_3$ and Ph_3P in an argon atmosphere in a 5 : 1 benzene—diisopropylethylamine (DIPEA) mixture for 48 h (see Schemes 2 and 3). Compounds **7** and **8** were isolated by preparative TLC. The spectral characteristics of the synthesized conjugates confirm the presence of the boron polyhedron in the molecules. The ^{1}H NMR spectra contain distinct signals for the CH protons of cobalt bis(dicarbollide) at δ 4.30 and 4.16 for compounds **7** and **8**, respectively, and a broadened signal for the BH groups at δ 3.5—1.5. The IR spectra of the synthesized compounds contain an intense band at 2550 cm^{-1} corresponding to stretching vibrations of the B—H bond.

Boron-containing conjugates **7** and **8** are hydrophobic compounds. They are well soluble in organic solvents and insoluble in water. Solubilization of these conjugates for *in vivo* studies was carried out using the biologically compatible solubilizer Cremophor EL (CrEL), which, as we have shown previously,[19—22] provides the stabilization of monomeric forms of various hydrophobic tetrapyrrole compounds in aqueous solutions. Compounds **7** and **8** were dissolved in a 5% emulsion of CrEL, their concentration being 0.5 mmol L^{-1}. The study of the stability of these solutions showed neither precipitation, nor changes in the absorption spectra of the studied compounds on storage in the dark at 4 °C for 3 months.

The ability of chlorin e_6 as a component of a conjugate to fluoresce in the red spectral region makes it possible to use fluorescence microscopy for studying the interaction of compounds **7** and **8** with cancer cells.

In the present work, cell studies were carried out on A549 human lung adenocarcinoma cells, which are traditionally used in the investigation of diverse porphyrin derivatives[19—22] and enable a standardized comparison of the cytotoxicity and photoinduced cytotoxicity of different compounds. It is known that the ability (or inability) of porphyrin derivatives to penetrate into cancer cells and the character of the intracellular distribution are almost independent of the choice of the cell model. That is why, the

Scheme 3



results obtained for the A549 cells allow one to predict the behavior of the studied compounds with respect to other cancer cells.

It was established by laser scanning confocal microscopy that compounds **7** and **8** penetrate into the A549 human lung adenocarcinoma cells and accumulate in the cytoplasm for the both conjugates; the intracellular distribution is alike: they are concentrated in granular cell structures of the submicron size (Fig. 1). The conjugates do not penetrate into the cell nucleus and do not accumulate in the plasma membrane.

It was found that compounds **7** and **8** are nontoxic for the A549 cells at their concentration in the medium up to 16 μmol L^{-1} and an incubation time of 3 h. Nontoxicity

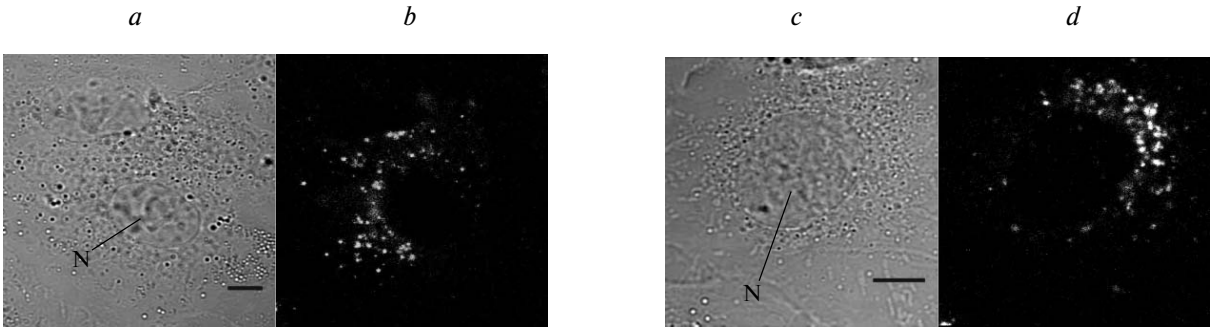


Fig. 1. Distribution of compounds **7** (*a*, *b*) and **8** (*c*, *d*) (4 μmol L^{-1}) in the A549 cells after incubation for 3 h; *b*, *d*, the intracellular distribution measured with a confocal laser scanning microscope. The label corresponds to 5 μm; N is the cell nucleus.

for the cells in the absence of an activating action (light, neutron flux) is a favorable property of the compounds developed for PDT and BNCT because this makes it possible to avoid the general toxicity characteristic of drugs used in chemotherapy and to enhance the selectivity of the effect. Chlorin e_6 is known to be a photosensitizer, *i.e.*, a substance capable of producing reactive oxygen species under the action of light and inducing death of cancer cells. To characterize the properties of compounds **7** and **8** as photosensitizers, we studied their photoinduced cytotoxicity. As found by counting alive and dead cells, the irradiation of the A549 cells with the red light after the 3-h incubation with compound **7** or **8** in the concentration range from 0.5 to 16 μmol L^{-1} does not result in cell death.

Thus, a method for the synthesis of conjugates of natural chlorins with boron clusters based on the Sonogashira reaction was developed in the present work. Compounds **7** and **8** synthesized can penetrate and accumulate in cancer cells. Their localization in the cytoplasm and nonpenetration into the nucleus are typical of the most part of the porphyrin derivatives developed as photosensitizers[19—26] and of the known porphyrin conjugates with the polyhedral boron compounds.[12,27—29] Each molecule transports 18 boron atoms to the cell cytoplasm, and these compounds can be considered as potential candidates for using in boron neutron capture therapy of cancer.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX spectrometer (300 MHz). IR and UV spectra were measured on a Bruker EQUINOX 55 spectrometer and a Jasco 7800 spectrophotometer, respectively. Mass spectra were obtained on a Bruker Ultraflex TOF/TOF spectrometer by the MALDI method using dihydroxybenzene (DHB) as the matrix and on a Bruker Daltonics Autoflex II spectrometer by the MALDI method using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (for conjugates) as the matrix. Preparative TLC was carried out using glass plates with Kiselgel 60H (200×200×1 mm, Merck). Plates with Kieselgel 60 F245 (Merck) were used for analytical TLC. Dioxane derivative **1**, chlorin e_6 amide **3**, and purpurinimide **4** were synthesized according to earlier published procedures.[30—32]

Synthesis of cobalt sodium 8-[2(2-(propargyloxyethoxy)]-bis(1,2-dicarbollide), [(8-HC≡C—CH_2O—(CH_2CH_2O)$_2$—3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$))$^-$ Na^+] (2). Compound **2** was synthesized by the modification of a described procedure.[33] A freshly prepared solution of sodium propynolate (3 mg of sodium per 1 mL of propargyl alcohol) was added at 0 °C to a solution of compound **1** (41 mg, 0.1 mmol) in acetonitrile (10 mL), and the mixture was left for 48 h. The reaction course was monitored by TLC. Water (100 μL) was added after the end of the reaction. The solvent was evaporated *in vacuo*. The yield was 46 mg (95.2%).

^{1}H NMR (acetone-d_6), δ: 4.19 (d, 2 H, C$\underline{H}_2$C≡CH, J = 2.4 Hz); 3.81 (s, 2 H, CH_{carb}); 3.74 (m, 2 H, OCH_2CH_2O); 3.69 (m, 2 H, OCH_2CH_2O); 3.66 (m, 2 H, OCH_2CH_2O); 3.60 (m, 2 H, OCH_2CH_2O); 3.53 (s, 2 H, CH_{carb}); 2.47 (t, 1 H, CH_2C≡C$\underline{H}$, J = 2.4 Hz). IR (KBr), ν/cm^{-1}: 3291 (CH_{carb}), 2536 (BH), 2129 (C≡CH).

Synthesis of 13^1-[2-*N*-(4-iodobenzoyl)aminoethylcarbamoyl]-isochlorin e_4 dimethyl ester (5). A mixture of amino derivative of chlorin **3** (17 mg, 0.025 mmol), *p*-iodobenzoyl chloride (7 mg, 0.025 mmol), and DIPEA (10 μL) was stirred in CH_2Cl_2 (2 mL) for 1 h. The solvent was removed *in vacuo*. The product was isolated by preparative multiple gradient development TLC in CH_2Cl_2—methanol (0—20%) solvent systems. The yield of the product was 18 mg (79%). MALDI MS (*m*/*z*): 897 $[M]^+$. UV-Vis ($CHCl_3$), λ_{max}/nm (I_{rel}): 402 (the Soret band) (1.00), 526 (0.03), 609 (0.04), 665 (0.30). ^{1}H NMR ($CDCl_3$), δ: 9.56 (s, 1 H, C(5)H); 9.40 (s, 1 H, C(10)H); 8.81 (s, 1 H, C(20)H); 7.85 (dd, 1 H, H_2C=C$\underline{H}$—C(3)H, J = 18 Hz, J = 12 Hz); 8.81 (t, 1 H, N(13^2)H, J = 3.6 Hz); 7.57 (d, 2 H, C_6H_4, J = 8.7 Hz); 7.45 (d, 2 H, C_6H_4, J = 8.7 Hz); 6.56 (s, 1 H, N(13^5)H); 6.13 (d, 1 H, *E*-$\underline{H}_2$C=CH—C(3)H, J = 18 Hz); 5.94 (d, 1 H, *Z*-$\underline{H}_2$C=CH—C(3), J = 12 Hz); 5.26 (d, 1 H, C(15^1)H_2, J = 19 Hz); 5.07 (d, 1 H, C(15^2)H_2, J = 19 Hz); 4.50 (q, 1 H, C(18)H, J = 7 Hz); 4.35 (d, 1 H, C(17)H, J = 9 Hz); 3.65 (br.m, 2 H, C(8^1)H_2); 3.62 (s, 3 H, C(15^2)OOMe); 3.60 (s, 3 H, C(12)H_3); 3.38 (s, 3 H, C(17^3)OOMe); 3.36—3.15 (m, 4 H, $NHCH_2CH_2NH$); 3.13 (s, 3 H, C(2)H_3); 2.93 (s, 3 H, C(7)H_3); 2.61 (m, 2 H, C(17^1)H_2); 2.25 (m, 2 H, C(17^1)H_2, C(17^2)H_2); 1.85 (m, 2 H, C(17^2)H_2); 1.74 (d, 3 H, C(18)H_3, J = 7 Hz); 1.62 (t, 3 H, C(8^2)H_3, J = 8 Hz); −1.64 (s, 1 H, NH); −1.85 (s, 1 H, NH). IR (KBr), ν/cm^{-1}: 3410 (ν_{NH}), 1728 ($\nu_{C=O}$), 1640 (amide I), 1520 (amide II).

Synthesis of [2-*N*-(4-iodobenzoyl)aminoethyl]purpurinimide methyl ester (6). A mixture of amino derivative of chlorin **4** (16 mg, 0.025 mmol) and *p*-iodobenzoyl chloride (7 mg, 0.025 mmol) was stirred in pyridine (2 mL) for 1 h. The solvent was removed *in vacuo*. The product was isolated by multiple gradient development preparative TLC in CH_2Cl_2—methanol (0—20%) systems. The yield of the product was 18 mg (83%). MALDI MS (*m*/*z*): 851 $[M]^+$. UV-Vis ($CHCl_3$), λ_{max}/nm (I_{rel}): 366 (the Soret band) (1.00), 417 (0.03), 548 (0.04) 639 (0.07), 705 (0.30). ^{1}H NMR ($CDCl_3$), δ: 9.35 (s, 1 H, C(5)H); 9.16 (s, 1 H, C(10)H); 8.52 (s, 1 H, C(20)H); 7.85 (s, 1 H, $NCH_2CH_2N\underline{H}$); 7.78 (dd, 1 H, *E*-$\underline{H}_2$C=CH—C(3)H, J = 18 Hz, J = 12 Hz); 7.74 (d, 2 H, C_6H_4, J = 8.6 Hz); 7.54 (d, 2 H, C_6H_4, J = 8.6 Hz); 6.23 (d, 1 H, *E*-C(3^2)H, J = 18 Hz); 6.12 (d, 1 H, *Z*-$\underline{H}_2$C=CH—C(3)H, J = 12 Hz); 5.26 (d, 1 H, C(17)H, J = 9 Hz); 4.84 (m, 2 H, NCH_2CH_2NH); 4.47 (q, 1 H, C(18)H, J = 7 Hz); 4.06 (m, 2 H, NCH_2CH_2NH); 3.69 (s, 3 H, C(12)H_3); 3.57 (s, 3 H, C(17^3)OOMe); 3.47 (br.m, 2 H, C(8^1)H_2); 3.31 (s, 3 H, C(2)H_3); 3.02 (s, 3 H, C(7)H_3); 2.71 (m, 1 H, C(17^1)H_2); 2.43 (m, 2 H, C(17^1)H_2, C(17^2)H_2); 2.00 (m, 1 H, C(17^2)H_2); 1.75 (d, 3 H, C(18)H_3, J = 7 Hz); 1.57 (t, 3 H, C(8^2)H_3, J = 8 Hz); 0.14 (s, 1 H, NH); −0.12 (s, 1 H, NH). IR (KBr), ν/cm^{-1}: 3428 (ν_{NH}), 1732 ($\nu_{C=O}$), 1645 (amide I), 1521 (amide II).

Synthesis of conjugate 7. A mixture of chlorin derivative **5** (22 mg, 0.025 mmol), compound **2** (23 mg, 0.05 mmol), PPh_3 (3 mg, 0.03 mmol), and $Pd_2(dba)_3$ (3 mg, 0.003 mmol) in a 5 : 1 benzene—DIPEA mixture (3 mL) was heated to 60 °C. The reaction was carried out for 48 h. The reaction course was monitored by TLC. The solvent was removed *in vacuo*. The product was isolated by multiple gradient development preparative TLC in CH_2Cl_2—methanol (0—20%) systems. The yield of the product was 20 mg (60%). MALDI MS (*m*/*z*): 1234 $[M]^-$. UV-Vis ($CHCl_3$), λ_{max}/nm (I_{rel}): 402 (the Soret band) (1.00), 526 (0.03),

609 (0.04), 665 (0.30). ^{1}H NMR ($CDCl_3$), δ: 9.70 (s, 1 H, C(5)H); 9.68 (s, 1 H, C(10)H); 9.21 (s, 1 H, C(20)H); 8.47 (t, 1 H, N(13^2)H, J = 5 Hz); 8.21 (s, 1 H, N(13^5)H); 8.18 (dd, 1 H, C(3^1)H, J = 18 Hz, J = 12 Hz); 7.76 (m, 2 H, C_6H_4, J = 8.4 Hz); 7.45 (m, 2 H, C_6H_4, J = 8.4 Hz); 6.37 (d, 1 H, *E*-$\underline{H}_2$C=CH—C(3), J = 18 Hz); 6.13 (d, 1 H, *Z*-$\underline{H}_2$C=CH—C(3), J = 12 Hz); 5.57 (d, 1 H, C(15^1)H_2, J = 19 Hz); 5.33 (d, 1 H, C(15^2)H_2, J = 19 Hz); 4.73 (q, 1 H, C(18)H, J = 7 Hz); 4.56 (d, 1 H, C(17)H, J = 9 Hz); 4.40 (s, 2 H, C≡CC$\underline{H}_2$O); 4.30 (br.s, 4 H, CH_{carb}); 3.83 (br.m, 4 H, NHCH_2CH_2NH); 3.7—3.5 (DIPEA); 3.70 (s, 3 H, C(15^2)OOMe); 3.67 (br.m, 4 H, OCH_2CH_2O); 3.62 (s, 3 H, C(12)H_3); 3.60 (m, 2 H, C(8^1)H_2); 3.52 (s, 3 H, C(17^3)OOMe); 3.38 (s, 3 H, C(2)H_3); 3.33 (br.m, 4 H, OCH_2CH_2O); 3.20 (s, 3 H, C(7)H_3); 2.80 (DIPEA); 2.74 (m, 1 H, C(17^1)H_2); 2.38 (m, 2 H, C(17^1)H_2); 2.31 (m, 1 H, C(17^2)H_2); 1.75 (d, 3 H, C(8^2)H_3, J = 7 Hz); 1.21 (t, 3 H, C(18)H_3, J = 8 Hz); 1.63 (DIPEA); −2.15 (s, 1 H, NH); −2.24 (s, 1 H, NH). IR (KBr), ν/cm^{-1}: 3413, 2923, 2554, 1731, 1098.

Synthesis of conjugate 8 was carried out similarly from chlorin derivative **6** (21 mg, 0.025 mmol) and compound **2** (23 mg, 0.05 mmol) in the presence of PPh_3 (3 mg, 0.03 mmol) and $Pd_2(dba)_3$ (3 mg, 0.003 mmol) in a 5 : 1 benzene—DIPEA mixture (3 mL). Compound **8** was obtained in a yield of 22 mg (68%). MALDI MS (*m/z*): 1188 [M]$^-$. UV-Vis ($CHCl_3$), λ_{max}/nm (I_{rel}): 366 (the Soret band) (1.00), 417 (0.03), 548 (0.04) 639 (0.07), 705 (0.30). ^{1}H NMR ($CDCl_3$), δ: 9.33 (s, 1 H, C(5)H); 9.20 (s, 1 H, C(10)H); 8.53 (s, 1 H, C(20)H); 7.97 (t, 1 H, NCH_2CH_2N$\underline{H}$, J = 4 Hz); 7.80 (dd, 1 H, C(3^1)H, J = 18 Hz, J = 12 Hz); 7.76 (m, 2 H, C_6H_4, J = 8.1 Hz); 7.48 (m, 2 H, C_6H_4, J = 8.1 Hz); 6.26 (d, 1 H, *E*-$\underline{H}_2$C=CH—C(3), J = 18 Hz); 6.14 (d, 1 H, *Z*-$\underline{H}_2$C=CH—C(3), J = 12 Hz); 5.25 (d, 1 H, C(17)H, J = 9 Hz); 4.82 (m, 2 H, NC$\underline{H}_2$C$\underline{H}_2$NH); 4.35 (s, 2 H, C≡CCH_2O); 4.30 (q, 1 H, C(18)H, J = 7 Hz); 4.16 (br.s, 4 H, CH_{carb}); 4.02 (m, 2 H, NC$\underline{H}_2$C$\underline{H}_2$NH); 3.70 (br.m, 2 H, OCH_2CH_2O); 3.69 (s, 3 H, C(12)H_3); 3.65—3.51 (br.m, 6 H, OCH_2CH_2O, C(8^1)H_2); 3.6—3.4 (DIPEA); 3.49 (s, 3 H, C(17^3)OOMe); 3.32 (s, 3 H, C(2)H_3); 3.03 (s, 3 H, C(7)H_3); 3.00 (DIPEA); 2.69 (m, 1 H, C(17^1)H_2); 2.35 (m, 2 H, C(17^1)H_2, C(17^2)H_2); 2.00 (m, 1 H, C(17^2)H_2); 1.73 (d, 3 H, C(18)H_3, J = 8 Hz); 1.58 (t, 3 H, C(8^2)H_3, J = 7 Hz); 1.65 (DIPEA); 0.07 (s, 1 H, NH); −0.1 (s, 1 H, NH). IR (KBr), ν/cm^{-1}: 3432, 2539, 1734, 1648, 1525.

Experiments on the cell culture. The A549 human lung adenocarcinoma cells were cultured in the Eagle-MEM medium with the addition of 2 *mM* L-glutamine and 8% fetal calf serum at 37 °C in a wet atmosphere containing 5% CO_2.

To study the intracellular accumulation and the distribution of conjugates **7** and **8**, the cells were seeded on cover glasses into 24-well plates (seeding density 5×10^4 cell mL^{-1}). After 24 h, compounds **7** and **8** in a concentration of 4 μmol L^{-1} were introduced into the medium from a 0.5 *mM* concentrated solution in 5% CrEL. After 3 h of incubation, the cells were transferred onto a slide, covered with a cover glass (under which a fresh medium (60 μL) was introduced), and placed in a microscope for investigation.

The intracellular distribution of compounds **7** and **8** was studied by an LSM510META confocal laser scanning microscope (Zeiss, Germany). The confocal fluorescence images (see Fig. 1) were obtained using a water-immersion 63× objective (C-Apochromat, numerical aperture 1.2). The lateral resolution was 0.3 μm, and the axial resolution was 1.5 μm. The fluorescence of compounds **7** and **8** was excited with an Ar^+ laser (514.5 nm). The long-wavelength barrier filter with a boundary of 650 nm was used to detect the fluorescence.

To determine the cytotoxicity of conjugates **7** and **8**, the A549 cells were seeded into 96-well plain-bottom plates. The substances to be tested were introduced into the wells 24 h after seeding, varying the concentration from 0.5 to 16 μmol L^{-1}. To estimate the cytotoxicity, the fluorescent dyes Hoechst 33342 (4 μmol L^{-1}) and propidium iodide (PI) (6 μmol L^{-1}) were introduced into the wells after 3 h of incubation of the cells with conjugates **7** or **8**. After 15 min, the plate with the cells was placed on the sample stage of an Axio Observer inverted fluorescence microscope (Zeiss, Germany) to count alive and dead cells. The cells, whose wells contained an equivalent amount of the solvent (buffer solution with CrEL), were used as reference.

The Hoechst 33342 dye stains nuclei of both alive and dead cells, while PI penetrates only through the damaged membrane of dead cells and begins to fluoresce, binding with DNA. The fluorescence of the Hoechst 33342 dye was excited in a region of 359—371 nm and detected at the wavelengths >397 nm. The fluorescence of PI was excited at 530—585 nm and excited in the wavelength region >615 nm. The total number of cells and the amount of dead cells were counted for each concentration of compounds **7** and **8** (at least 500—700 cells in each sampling were analyzed), and the fraction of dead cells was calculated.

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