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Novel Conjugates of Galactose with Dimeric Chlorophyll *a* Derivatives

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The article is dedicated to memory of Academician Oskar I. Koifman

In this work, new conjugates of galactose with dimeric derivatives of chlorophyll a with different hydrophilicity were synthesized. The change in the hydrophilicity of dimeric chlorins is achieved by introducing into the molecule one or two tertiary amino groups containing two galactose fragments as substituents at the nitrogen atom.

Keywords: Methylpheophorbide *a*, chlorin e_6, chlorin e_6 dimer derivatives, galactose, alkylation.

Новые конъюгаты галактозы с димерными производными хлорофилла *a*

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В настоящей работе синтезированы новые конъюгаты галактозы с димерными производными хлорофилла а с различной гидрофильностью. Изменение гидрофильности димерных хлоринов достигнуто путем внедрения в молекулу одной или двух третичных аминогрупп, содержащих два фрагмента галактозы в качестве заместителей при атоме азота.

Ключевые слова: Метилфеофорбид *a*, хлорин e_6, димерные производные хлорина e_6, галактоза, алкилирование.

Introduction

Photodynamic therapy (PDT) of oncological diseases is one of the rapidly developing areas in modern medicine, therefore, the synthesis of new compounds – potential photosensitizers (PS) for PDT is of great interest.[1-22] One of the possible directions for improving of PS for medical use is to combine two chlorin macrocycles in one molecule.[1] The use of porphyrin dimers as PS is advantageous due to a larger photon absorption cross-section compared to monomenetic porphyrins and increased membranotropicity, leading to more effective damage to cell membranes.[1] Lipophilicity, caused by the presence of two porphyrin macrocycles in the molecule, in addition to increasing membranotropicity, leads to decreased solubility in water and physiological fluids and, accordingly, a decrease in bioavailability. It is known that the introduction of carbohydrate fragments to the periphery of the macrocycle of porphyrins and their analogues, including chlorophyll *a* derivatives, helps to increase the hydrophilicity of the compounds.[2-24] In some cases, when carbohydrate fragments are introduced, chlorophyll *a* derivatives acquire the ability to form true solutions.[2,22-24] Thus, for chlorins **1** and **2**, which we previously synthesized, with one and two tertiary amino groups with galactose fragments as substituents[22] it is possible to obtain an aqueous solution

containing at least 3 mg/mL of a solute without the use of excipients. The solubility of chlorophyll *a* derivatives in water in this case refers to the ability of a compound to form colored solutions (usually swamp green) that produce red luminescence when illuminated with violet or green light. The ability to luminesce means the presence of single molecules in a solution. However, this does not mean that all water-soluble chlorin molecules are single in solution. We have shown[25] that water-soluble cationic derivatives of chlorophyll *a* **3**-**5** in an aqueous solution form colloidal particles that are in equilibrium with single molecules and are destroyed when the solution is diluted. Thus, an equilibrium between single molecules and larger aggregates (up to colloidal particles) ensures good bioavailability of such compounds. Apparently, similar processes occur in the case of water-soluble conjugates with carbohydrates.

Solubility in water depends in a complex way not only on the number of carbohydrate fragments, but also on their nature and method of binding to the macrocycle. For example, chlorin **6**[26] with two galactose fragments connected to the macrocycle by an ester bond is not soluble in water, but chlorin **7** with one fructose fragment is soluble in water.[22] The introduction of a tertiary amino group with two galactose fragments not only makes it possible to obtain water-soluble derivatives with a high probability, but is also convenient in processing and gives high yields of the target compounds.[22,23] Such a modification can promote the solubility of dimeric derivatives of chlorophyll *a* in water. However, the complex dependence of the compound solubility in water on the number of carbohydrate fragments, their nature, modes of binding to the macrocycle and other factors does not allow us to unhesitatingly predict the effect of chemical modification on the solubility of compounds. This question can be resolved experimentally only. In this regard, here we synthesized dimeric derivatives of chlorophyll *a* with one and two tertiary amino group with two galactose fragments as substituents at the nitrogen atom in order to evaluate the possibility of imparting solubility to dimeric derivatives of chlorophyll *a* by introducing such substituents to the periphery of macrocycles.

Experimental

Materials and Methods

^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded on Bruker AVANCE-II-300 (working frequency 300 MHz and 75 MHz for NMR ^{1}H and ^{13}C, respectively) using standard impulse Bruker software for one and two-dimensional experiments. Infrared spectra were measured in KBr tablets on the "IR Prestige 21" device (Shimadzu). Mass spectra were recorded on the "Thermo-Finnigan LCQ Fleet" device. UV-Vis spectra were recorded on a spectrometer UV-1700 (Shimadzu) with the wave-length range of 200–1100 nm. The samples were analyzed in quartz cuvettes (10 mm thick). The reaction was controlled using TLC method on Sorbfil slides. Isolation of the reaction products was done using column chromatography on silica gel Alfa Aesar 70–230 mesh.

Synthesis

Chlorin e_6 derivatives **8**,[22] **10**,[27] **13**,[28] **14**[29] and 1,2:3,4-di-*O*-isop-ropylidene-1-*O*-(trifluoromethanesulfonyl)-D-galacto-pyranose **16**[30] were obtained according to literature methods.

Compound ***9***. To the 500 mg (0.43 mmol) of compound **8**, 5 mL of ethylendiamine was added. The mixture was stirred at room temperature (~23 ºC) for 20 h (TLC: $CHCl_3$–CH_3OH, 8:1). Next, the reaction mixture was diluted with chloroform (100 mL), washed with water until neutral p*H*, the organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated *in vacuo*. A residue after the evaporation was chromatographed on silica gel (eluent: $CHCl_3$–CH_3OH, 20:1). 330 mg (65%) of compound **9** was obtained as a dark green crystalline powder. UV-Vis (CH_2Cl_2) λ_{max} nm ($I_{relative}$ (%)): 662 (29), 606 (3), 527 (3), 500 (9), 401 (100). IR (KBr) ν cm^{-1}: 1739 (C=O, ester), 1680 ("amide-I"), 1602 ("chlorin band"), 1540 ("amide-II"). MS (ESI) *m*/*z*: 1201.6 (calcd. for $[MNa]^+$ 1201.6), 1179.5 (calcd. for $[MH]^+$ 1179.6), 590.9 (calcd. for $[(M+2H)H_2]^{2+}$ 591.3), 394.2 (calcd. for $[(M+2H)H_3]^{3+}$ 394.6). ^{1}H NMR ($CDCl_3$) δ_H ppm: –1.78 (1H, s, I-NH); –1.60 (1H, s, III-NH); 0.69 (6H, s), 1.06 (6H, s), 1.25 (6H, s) and 1.46 (6H, s) (8^a-CH_3, 9^a-CH_3, 11^a-CH_3, 12^a-CH_3, 8^b-CH_3, 9^b-CH_3, 11^b-CH_3, 12^b-CH_3); 1.75 (3H, d, 18(1)-CH_3, J = 6.6 Hz); 1.76 (3H, t, 8(2)-CH_3, J = 6.9 Hz); 1.85-2.12 (3H, m) and 2.29-2.41 (1H, m) (17(1)-CH_2, 17(2)-CH_2); 2.45 (2H, t, 17(5)-NH_2, J = 5.6 Hz); 2.89–3.07

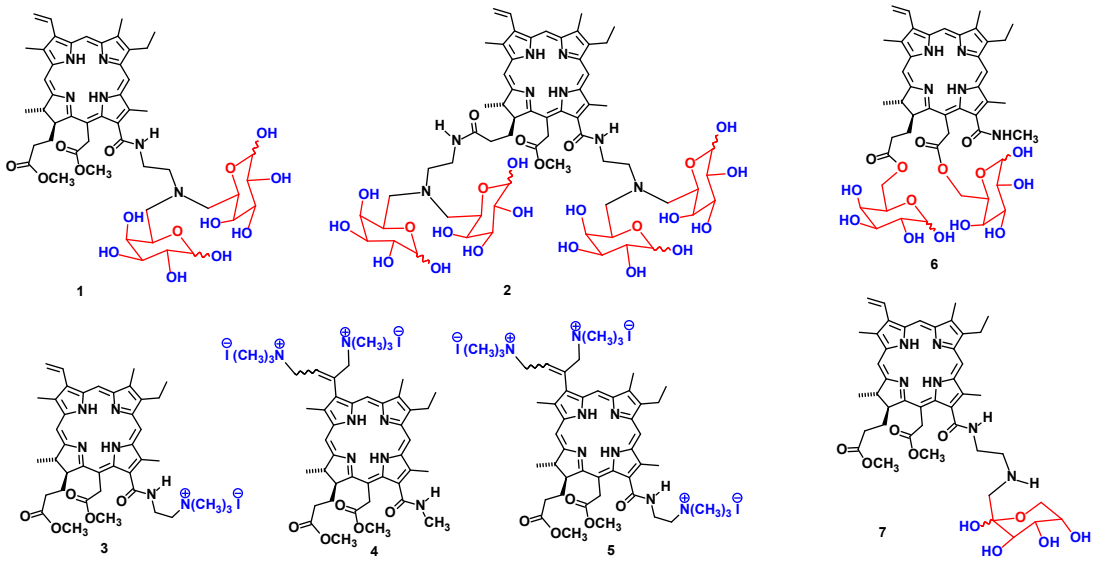


Figure 1. Hydrophilic derivatives of chlorophyll *a*.

(8H, m), 3.16-3.29 (2H, m) and 3.67-3.80 (2H, m) (17(4)-CH_2, 17(5)-CH_2, 13(2)-CH_2, 13(3)-CH_2, 6^a-CH_2, 6^b-CH_2); 3.37 (3H, s, 7(1)-CH_3); 3.52 (3H, s, 2(1)-CH_3); 3.62 (3H, s, 12(1)-CH_3); 3.85 (3H, s, 15(3)-CH_3); 3.80–3.91 (2H, m, 8(1)-CH_2); 4.05–4.12 (2H, m), 4.14 (2H, dd, J = 2.1, 5.1 Hz), 4.27 (2H, d, J = 8.1 Hz), 4.45 (2H, dd, J = 1.4, 6.0 Hz) and 4.49–4.57 (2H, m) (17-H, 18-H, 2^a-H, 2^b-H, 3^a-H, 3^b-H, 4^a-H, 4^b-H, 5^a-H, 5^b-H); 5.38 (2H, d, 1^a-H, 1^b-H, J = 5.1 Hz); 5.53 (1H, m, 17(3)-NH); 15(1)-CH_2: 5.37 (1H, d, J = 17.4 Hz), 5.54 (1H, d, J = 19.2 Hz); 6.17 (1H, d, 3(2)-H (*cis*), J = 10.8 Hz); 6.39 (1H, d, 3(2)-H (*trans*), J = 18.3 Hz); 7.93 (1H, m, 17(3)-NH); 7.76 (1H, t, 13(1)-NH, J = 5.4 Hz); 8.12 (1H, dd, 3(1)-H, J = 11.7, 17.4 Hz); 8.32 (1H, s, 20-H); 9.68 (1H, s, 5-H); 9.73 (1H, s, 10-H).

Compound ***11***. To the solution of 320 mg (0.27 mmol) of compound **9** in 25 mL of CH_2Cl_2, 170 mg (0.27 mmol) of compound **10**, 69 mg (0.27 mmol) of 2-chloro-1-methylpyridinium iodide and 33 mg (0.27 mmol) of DMAP were added. The mixture was refluxed for 2 h (TLC: $CHCl_3$–CH_3OH, 5:0.25). The mixture was cooled, diluted with dichloromethane (60 mL), washed with 3% aqueous HCl (150 mL) and then washed with water until neutral p*H*, the organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated *in vacuo*. A residue after the evaporation was chromatographed on silica gel (eluent: CCl_4–acetone, 1:1). 220 mg (45 %) of compound **11** was obtained as a dark green crystalline powder. UV-Vis (CH_2Cl_2) λ_{max} nm ($I_{relative}$ (%)): 663 (30), 608 (3), 528 (3), 501 (10), 402 (100). IR (KBr) ν cm^{-1}: 3084 (C–H, vinyl group), 1736 (C=O, ester), 1657 ("amide-I"), 1601 ("chlorin band"), 1539 ("amide-II"). MS (ESI) *m*/*z*: 1784.5 (calcd. for $[MH]^+$ 1784.9), 904.2 (calcd. for $[(M+2H)HNa]^{2+}$ 904.0), 897.5 (calcd. for $[(M+2H)H_2]^{2+}$ 897.5). ^{1}H NMR ($CDCl_3$) δ_H ppm: –1.88 (1H, s) and –1.85 (1H, s) (I-NH, I′-NH); –1.66 (2H, s, III-NH, III′-NH); 1.02 (6H, s), 1.21 (6H, s), 1.32 (6H, s) and 1.44 (6H, s) (8^a-CH_3, 9^a-CH_3, 11^a-CH_3, 12^a-CH_3, 8^b-CH_3, 9^b-CH_3, 11^b-CH_3, 12^b-CH_3); 1.28 (3H, s, 13′(1)-CH_3), 1.51–1.62 (6H, m) and 1.67–1.79 (6H, m) (18(1)-CH_3, 8(2)-CH_3, 18′(1)-CH_3, 8′(2)-CH_3); 1.95–2.07 (2H, m), 2.16-2.24 (2H, m), 2.39–2.50 (1H, m) and 2.56–2.66 (3H, m) (17(1)-CH_2, 17(2)-CH_2, 17′(1)-CH_2, 17′(2)-CH_2); 2.87-3.04 (8H, m), 3.12-3.28 (2H, m) and 3.48–3.53 (2H, m) (17(4)-CH_2, 17(5)-CH_2, 13(2)-CH_2, 13(3)-CH_2, 6^a-CH_2, 6^b-CH_2); 3.32 (3H, s) and 3.35 (3H, s) (7(1)-CH_3, 7′(1)-CH_3); 3.39 (3H, s) and 3.40 (3H, s) (2(1)-CH_3, 2′(1)-CH_3); 3.45 (3H, s) and 3.46 (3H, s) (12(1)-CH_3, 12′(1)-CH_3); 3.55 (3H, s) and 3.73 (3H, s) (15(3)-CH_3, 15′(3)-CH_3); 3.74-3.86 (4H, m, 8(1)-CH_2, 8′(1)-CH_2); 4.03-4.16 (4H, m) and 4.20-4.45 (8H, m) (17-H, 18-H, 17′-H, 18′-H, 2^a-H, 2^b-H, 3^a-H, 3^b-H, 4^a-H, 4^b-H, 5^a-H, 5^b-H); 5.35 (2H, d, 1^a-H, 1^b-H, J = 5.1 Hz); 5.10-5.28 (2H, m) and 5.38-5.62 (2H, m) (15(1)-CH_2, 15′(1)-CH_2); 6.06 (1H, d, J = 10.5 Hz) and 6.08 (1H, d, J = 11.4 Hz) (3(2)-H (*cis*), 3′(2)-H (*cis*)); 6.26 (1H, d, J = 17.7 Hz) and 6.29 (1H, d, J = 18.0 Hz) (3(2)-H (*trans*), 3′(2)-H (*trans*)); 6.37-6.47 (2H, m, 17(3)-NH, 17′(3)-NH); 7.63-7.74 (2H, m, 13(1)-NH, 13′(1)-NH); 7.88-8.10 (2H, m, 3(1)-H, 3′(1)-H); 8.72 (1H, s) and 8.76 (1H, s) (20-H, 20′-H); 9.62 (2H, s, 5-H, 5′-H); 9.73 (2H, s, 10-H, 10′-H). ^{13}C NMR ($CDCl_3$) δ_C ppm: 11.33 (2C, 7(1), 7′(1)); 11.84 (2(1)); 12.04 (3C, 12(1), 12′(1), 2′(1)); 17.67 and 17.72 (8(2), 8′(2)); 19.68 (2C, 8(1), 8′(1)); 23.03 and 23.13 (18(1), 18′(1)); 23.57 (2C), 24.59 (2C), 25.64 (2C) and 26.01 (2C) (8^a, 9^a, 11^a, 12^a, 8^b, 9^b, 11^b, 12^b); 29.72 (2C), 30.44 and 30.47 (17(1), 17(2), 17′(1), 17′(2)); 32.27, 32.46, 37.77 and 38.19 (13(2), 13(3), 17(4), 17(5)); 39.11 and 39.35 (15(1), 15′(1)); 49.28 and 49.33 (18, 18′); 51.91 and 52.08 (15(3), 15′(3)); 52.95 (13′(2)); 53.14 (17, 17′); 53.85 and 54.75 (6^a, 6^b); 65.30 (2C), 70.39 (2C), 70.67 (2C) and 71.79 (2C) (2^a, 3^a, 4^a, 5^a, 2^b, 3^b, 4^b, 5^b); 93.55 and 93.64 (20, 20′); 96.41 (2C, 1^a, 1^b); 98.66 (2C, 5, 5′); 101.06 and 101.29 (10, 10′); 102.34 and 102.63 (15, 15′); 108.33 (2C) and 108.93 (2C) (7^a, 10^a, 7^b, 10^b); 121.56 and 121.63 (3(2), 3′(2)); 128.22 and 128.98 (13, 13′); 129.34 and 129.37 (3(1), 3′(1)); 129.81 and 129.85 (12, 12′); 130.14 and 130.31 (2, 2′); 134.48 and 134.57 (7, 7′); 134.60 and 134.70 (4, 4′); 134.81 and 134.99 (11, 11′); 135.07 and 135.25 (3, 3′); 135.96 and 136.00 (1, 1′); 138.77 and 138.93 (8, 8′); 144.59 and 144.66 (14, 14′); 148.78 (2C, 9, 9′); 153.86 (2C, 6, 6′); 166.70 (2C, 16, 16′); 169.07 and 169.34 (19, 19′); 169.48 and 169.69 (13(1), 13′(1)); 172.95 and 173.26 (17(3), 17′(3)); 173.90 and 174.24 (15(2), 15′(2)).

Compound ***12***. To the 150 mg (0.08 mmol) of compound **11** 5 mL of 90% aqueous trifluoroacetic acid (TFA) was added. The reaction mixture was stirred at room temperature (~23 ºC) for 4 h. Next, the excess of the trifluoroacetic acid was evaporated at low pressure. A residue after the evaporation was diluted with 5 mL of $CHCl_3$–CH_3OH (5:0.1) mixture, the resulting mixture was chromatographed on silica gel (eluent: $CHCl_3$–C_2H_5OH (95% aqueous), 1:1; TLC: $CHCl_3$–CH_3OH, 3:1)). 104 mg (80%) of compound **12** was obtained as a dark green crystalline powder. UV-Vis (CH_2Cl_2:CH_3OH, 4:1) λ_{max} nm ($I_{relative}$ (%)): 662 (29), 606 (3), 528 (3), 500 (9), 401 (100). IR (KBr) ν cm^{-1}: 1680 ("amide-I"), 1601 ("chlorin band"), 1545 ("amide-II"). MS (ESI) *m*/*z*: 1624.6 (calcd. for $[MH]^+$ 1624.8), 824.4 (calcd. for $[(M+2H)HNa]^{2+}$ 824.9), 813.6 (calcd. for $[(M+2H)H_2]^{2+}$ 813.9). ^{1}H NMR (DMSO-D_6) δ_H ppm: –2.11 (1H, s) and –2.01 (1H, s) (I-NH, I′-NH); -1.83 (1H, s) and –1.77(1H, s, III-NH, III′-NH); 1.60–1.74 (12H, m, 18(1)-CH_3, 8(2)-CH_3, 18′(1)-CH_3, 8′(2)-CH_3); 2.01–2.24 (4H, m) and 2.27–2.49 (4H, m) (17(1)-CH_2, 17(2)-CH_2, 17′(1)-CH_2, 17′(2)-CH_2); 3.07–3.21 (8H, m) and 3.35-3.46 (4H, m) (17(4)-CH_2, 17(5)-CH_2, 13(2)-CH_2, 13(3)-CH_2, α,β-6^a-CH_2, α,β-6^b-CH_2); 3.31 (6H, s, 7(1)-CH_3, 7′(1)-CH_3); 3.48 (3H, s) and 3.49 (3H, s) (2(1)-CH_3, 2′(1)-CH_3); 3.50 (3H, s) and 3.56 (3H, s) (12(1)-CH_3, 12′(1)-CH_3); 3.68 (6H, s) and 3.73 (3H, s) (15(3)-CH_3, 15′(3)-CH_3, 13′(1)-CH_3); 3.76–3.89 (10H, m) and 3.96–4.09 (4H, m) (8(1)-CH_2, 8′(1)-CH_2, α,β-1^a-OH, α,β-1^b-OH, α,β-2^a-OH, α,β-2^b-OH, α,β-3^a-OH, α,β-3^b-OH, α,β-4^a-OH, α,β-4^b-OH); 4.11-4.19 (2H, m), 4.30-4.68 (8H, m) and 5.04–5.17 (2H, m) (17-H, 18-H, 17′-H, 18′-H, α,β-2^a-H, α,β-2^b-H, α,β-3^a-H, α,β-3^b-H, α,β-4^a-H, α,β-4^b-H, α,β-5^a-H, α,β-5^b-H); 5.28 (0.8H, d, J = 7.8 Hz, β-1^a-H, β-1^b-H); 5.35 (1.2H, d, J = 7.8 Hz, α-1^a-H, α-1^b-H); 5.03–5.19 (2H, m) and 5.43–5.62 (2H, m) (15(1)-CH_2, 15′(1)-CH_2); 6.15 (2H, d, J = 11.4 Hz, 3(2)-H (*cis*), 3′(2)-H (*cis*)); 6.41 (2H, d, J = 18.0 Hz, 3(2)-H (*trans*), 3′(2)-H (*trans*)); 7.99-8.12 (2H, m, 17(3)-NH, 17′(3)-NH); 8.25 (1H, dd, J = 3.9, 12.0 Hz) and 8.31 (1H, dd, J = 4.2, 11.7 Hz) (3(1)-H, 3′(1)-H); 7.63-7.74 (2H, m, 13(1)-NH, 13′(1)-NH); 9.03 (1H, q, J = 4.9 Hz, 13′(1)-N<u>H</u>CH_3); 9.36-9.50 (1H, m, 13(1)-N<u>H</u>CH_2); 9.11 (2H, s, 20-H, 20′-H); 9.73 (1H, s) and 9.74 (1H, s) (5-H, 5′-H); 9.79 (1H, s) and 9.81 (1H, s) (10-H, 10′-H). ^{13}C NMR (DMSO-D_6) δ_C ppm: 11.47 (2C, 7(1), 7′(1)); 12.16 and 12.24 (2(1), 2′(1)); 12.48 (2C, 12(1), 12′(1)); 18.25 (2C, 8(2), 8′(2)); 19.41 (2C, 8(1), 8′(1)); 23.47 (2C, 18(1), 18′(1)); 29.46 (2C) and 30.91 (2C) (17(1), 17(2), 17′(1), 17′(2)); 32.81, 32.90, 37.08 and 37.46 (13(2), 13(3), 17(4), 17(5)); 38.91 (2C, 15(1), 15′(1)); 48.78 (2C, 18, 18′); 52.21 (2C, 15(3), 15′(3)); 52.45 (13′(2)); 53.27 (2C, 17, 17′); 56.50 and 56.76 (6^a, 6^b); 68.71, 69.35, 72.12, 73.55, 76.46, 77.63 and 83.04 (2C) (2^a, 3^a, 4^a, 5^a, 2^b, 3^b, 4^b, 5^b); 93.45 and 94.62 (20, 20′); 97.93 (2C, 1^a, 1^b); 98.93 (2C, 5, 5′); 101.13 and 102.44 (10, 10′); 103.08 and 103.23 (15, 15′); 122.37 and 122.46 (3(2), 3′(2)); 129.25 (2C, 13, 13′); 129.82 (2C, 3(1), 3′(1)); 129.96 and 130.40 (12, 12′); 130.56 and 130.65 (2, 2′); 134.08 and 134.17 (7, 7′); 134.32 and 134.35 (4, 4′); 135.25 and 135.41 (11, 11′); 135.48 and 135.59 (3, 3′); 136.62 and 136.66 (1, 1′); 138.33 and 138.58 (8, 8′); 144.74 and 144.89 (14, 14′); 148.78 (2C, 9, 9′); 153.16 and 153.45 (6, 6′); 168.76, 168.85 (2C) and 168.93 (16, 16′, 19, 19′); 169.94 and 170.27 (13(1), 13′(1)); 172.53 (2C, 17(3), 17′(3)); 173.27 and 173.34 (15(2), 15′(2)).

Compound ***15***. To the 400 mg (0.33 mmol) of compound **14** in 15 mL of $CHCl_3$, 2 mL of ethylendiamine was added. The mixture was stirred at room temperature (~23 ºC) for 5 h (TLC: $CHCl_3$–C_2H_5OH (95% aqueous)–NH_3 (25% aqueous), 2.5:1:0.01). Next, the reaction mixture was diluted with chloroform (100 mL), washed with water until neutral p*H*, the organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated *in vacuo*. 410 mg (93%) of compound **15** was obtained as a dark green crystalline powder. UV-Vis (CH_2Cl_2:CH_3OH, 10:1) λ_{max} nm ($I_{relative}$ (%)): 663 (30), 607 (3), 529 (3), 500 (9), 402 (100). IR

(KBr) ν cm^{-1}: 1734 (C=O, ester), 1655 ("amide-I"), 1601 ("chlorin band"), 1539 ("amide-II"). MS (ESI) *m/z*: 1329.5 (calcd. for $[MH]^+$ 1329.7), 665.7 (calcd. for $[MH_2]^{2+}$ 665.4), 444.2 (calcd. for $[MH_3]^{3+}$ 443.9). ^{1}H NMR (DMSO-D_6) δ_H ppm: –2.10 (2H, s, I-NH, I′-NH); –1.81 (2H, s, III-NH, III′-NH); 1.57–1.74 (12H, m, 18(1)-CH_3, 8(2)-CH_3, 18′(1)-CH_3, 8′(2)-CH_3); 1.91–2.28 (6H, m) and 2.40-2.50 (2H, m) (17(1)-CH_2, 17(2)-CH_2, 17′(1)-CH_2, 17′(2)-CH_2); 2.91 (4H, t, 13(3)-NH_2, 13′(3)-NH_2, *J* = 6.5 Hz); 3.05–3.29 (12H, m, 13(2)-CH_2, 13(3)-CH_2, 13′(2)-CH_2, 13′(3)-CH_2, 17(4)-CH_2, 17′(4)-CH_2); 3.32 (6H, s, 7(1)-CH_3, 7′(1)-CH_3); 3.50 (6H, s, 2(1)-CH_3, 2′(1)-CH_3); 3.53 (6H, s, 12(1)-CH_3, 12′(1)-CH_3); 3.69 (6H, s, 15(3)-CH_3, 15′(3)-CH_3); 3.83 (4H, q, 8(1)-CH_2, 8′(1)-CH_2, *J* = 7.0 Hz); 4.35 (2H, d, 17-H, 17′-H, *J* = 9.9 Hz); 4.59 (2H, q, 18-H, 18′-H, *J* = 6.8 Hz); 5.32 (2H, d, *J* = 18.3 Hz) and 5.58 (2H, d, *J* = 19.5 Hz) (15(1)-CH_2, 15′(1)-CH_2); 6.15 (2H, d, (3(2)-H (*cis*), 3′(2)-H (*cis*), *J* = 11.7 Hz); 6.41 (2H, d, 3(2)-H (*trans*), 3′(2)-H (*trans*), *J* = 17.7 Hz); 7.95-8.04 (2H, m, 17(3)-NH, 17′(3)-NH); 8.28 (2H, dd, 3(1)-H, 3′(1)-H, *J* = 12.0, 18.0 Hz); 8.33-8.38 (2H, m, 13(1)-NH, 13′(1)-NH); 9.12 (2H, s, 20-H, 20′-H); 9.74 (2H, s, 5-H, 5′-H); 9.79 (2H, s, 10-H, 10′-H). ^{13}C NMR (DMSO-D_6) δ_C ppm: 11.47 (2C, 7(1), 7′(1)); 12.16 (2C, 2(1), 2′(1)); 12.49 (2C, 12(1), 12′(1)); 18.28 (2C, 8(2), 8′(2)); 19.42 (2C, 8(1), 8′(1)); 23.49 (2C, 18(1), 18′(1)); 30.88 (2C) and 32.91 (2C) (17(1), 17(2), 17′(1), 17′(2)); 37.21 (2C), 38.88 (2C) and 41.71 (2C) (13(2), 13(3), 13′(2), 13′(3), 17(4), 17′(4)); 43.92 (2C, 15(1), 15′(1)); 48.76 (2C, 18, 18′); 52.25 (2C, 15(3), 15′(3)); 53.30 (2C, 17, 17′); 94.58 (2C, 20, 20′); 98.97 (2C, 5, 5′); 101.10 (2C, 10, 10′); 103.21 (2C, 15, 15′); 122.30 (2C, 3(2), 3′(2)); 129.84 (2C, 13, 13′); 130.01 (2C, 3(1), 3′(1)); 130.35 (2C, 12, 12′); 130.64 (2C, 2, 2′); 134.05 (2C, 7, 7′); 134.12 (2C, 4, 4′); 135.25 (2C, 11, 11′); 135.61 (2C, 3, 3′); 136.66 (2C, 1, 1′); 138.25 (2C, 8, 8′); 144.76 (2C, 14, 14′); 148.95 (2C, 9, 9′); 153.30 (2C, 6, 6′); 168.43 (2C, 16, 16′); 168.87 (2C, 19, 19′); 169.80 (2C, 13(1), 13′(1)); 172.45 (2C, 17(3), 17′(3)); 173.34 (2C, 15(2), 15′(2)).

Compound ***17***. To the solution of 350 mg (0.26 mmol) of compound **15** in 20 mL of THF, 500 mg (1.27 mmol) of 1,2:3,4-di-*O*-isopropylidene-1-*O*-(trifluoromethanesulfonyl)-D-galactopyranose **16** and 104 mg (1.27 mmol) of anhydrous CH_3COONa were added. The mixture was refluxed for 5 h (TLC, CCl_4–acetone, 1:1). The mixture was cooled, filtered from excess of sodium acetate and the solvent (THF) was evaporated *in vacuo*. A residue after the evaporation was diluted with chloroform (100 mL), washed with 3% aqueous HCl (200 mL) and then washed with water until neutral p*H*, the organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated *in vacuo*. A residue after the evaporation was chromatographed on silica gel (eluent: CCl_4–acetone, 2:1). 280 mg (47%) of compound **17** was obtained as a dark green crystalline powder. UV-Vis (CH_2Cl_2) λ_{max} nm ($I_{relative}$ (%)): 663 (30), 607 (3), 529 (3), 500 (10), 402 (100). IR (KBr) ν cm^{-1}: 1736 (C=O, ester), 1659 ("amide-I"), 1601 ("chlorin band"), 1518 ("amide-II"). MS (ESI) *m/z*: 1150.2 (calcd. for $[H_2M]^{2+}$ 1150.6), 767.9 (calcd. for $[(M+2H)H_3]^{3+}$ 767.4), 575.2 (calcd. for $[MH_4]^{4+}$ 575.3). ^{1}H NMR ($CDCl_3$) δ_H ppm: –1.82 (2H, s, I-NH, I′-NH); –1.61 (2H, s, III-NH, III′-NH); 0.65 (12H, s), 1.04 (12H, s), 1.22 (12H, s) and 1.45 (12H, s) (8^a-CH_3, 9^a-CH_3, 11^a-CH_3, 12^a-CH_3, 8^b-CH_3, 9^b-CH_3, 11^b-CH_3, 12^b-CH_3, 8^c-CH_3, 9^c-CH_3, 11^c-CH_3, 12^c-CH_3, 8^d-CH_3, 9^d-CH_3, 11^d-CH_3, 12^d-CH_3); 1.65 (6H, d, 18(1)-CH_3, 18′(1)-CH_3, *J* = 6.9 Hz); 1.76 (6H, t, 8(2)-CH_3, 8′(2)-CH_3, *J* = 7.4 Hz); 1.81–2.05 (6H, m) and 2.10–2.26 (2H, m) (17(1)-CH_2, 17(2)-CH_2, 17′(1)-CH_2, 17′(2)-CH_2); 2.78-3.01 (12H, m), 3.15-3.30 (4H, m) and 3.65-3.76 (4H, m) (13(2)-CH_2, 13(3)-CH_2, 13′(2)-CH_2, 13′(3)-CH_2, 17(4)-CH_2, 17′(4)-CH_2, 6^a-CH_2, 6^b-CH_2, 6^c-CH_2, 6^d-CH_2); 3.36 (6H, s, 7(1)-CH_3, 7′(1)-CH_3); 3.46 (6H, s, 2(1)-CH_3, 2′(1)-CH_3); 3.62 (6H, s, 12(1)-CH_3, 12′(1)-CH_3); 3.79 (6H, s, 15(3)-CH_3, 15′(3)-CH_3); 3.84 (4H, q, 8(1)-CH_2, 8′(1)-CH_2, *J* = 7.4 Hz); 4.03-4.18 (8H, m), 4.21-4.29 (4H, m) and 4.35-4.48 (8H, m) (17-H, 17′-H, 18-H, 18′-H, 2^a-H, 2^b-H, 2^c-H, 2^d-H, 3^a-H, 3^b-H, 3^c-H, 3^d-H, 4^a-H, 4^b-H, 4^c-H, 4^d-H, 5^a-H, 5^b-H, 5^c-H, 5^d-H); 5.36 (4H, d, 1^a-H, 1^b-H, 1^c-H, 1^d-H, *J* = 5.1 Hz); 5.28 (2H, d, *J* = 19.5 Hz) and 5.54 (2H, d, *J* = 18.9 Hz) (15(1)-CH_2, 15′(1)-CH_2); 5.68-5.81 (2H, m, 17(3)-NH, 17′(3)-NH); 6.14 (2H, d, (3(2)-H (*cis*), 3′(2)-H (*cis*), *J* = 11.4 Hz); 6.35 (2H, d, 3(2)-H (*trans*), 3′(2)-H (*trans*), *J* = 18.0 Hz); 7.65–7.75 (2H, m, 13(1)-NH, 13′(1)-NH); 8.08 (2H, dd, 3(1)-H, 3′(1)-H, *J* = 11.6, 17.9 Hz); 8.78 (2H, s, 20-H, 20′-H); 9.66 (2H, s, 5-H, 5′-H); 9.72 (2H, s, 10-H, 10′-H). ^{13}C NMR ($CDCl_3$) δ_C ppm: 11.32 (2C, 7(1), 7′(1)); 12.08 (4C, 2(1), 2′(1), 12(1), 12′(1)); 17.73 (2C, 8(2), 8′(2)); 19.71 (2C, 8(1), 8′(1)); 23.14 (2C, 18(1), 18′(1)); 23.56 (4C), 24.62 (4C), 25.64 (4C) and 26.02 (4C) (8^a, 9^a, 11^a, 12^a, 8^b, 9^b, 11^b, 12^b, 8^c, 9^c, 11^c, 12^c, 8^d, 9^d, 11^d, 12^d); 30.70 (2C) and 31.60 (2C) (17(1), 17(2), 17′(1), 17′(2)); 32.55 (2C), 37.65 (2C) and 38.22 (2C) (13(2), 13(3), 13′(2), 13′(3), 17(4), 17′(4)); 39.61 (2C, 15(1), 15′(1)); 49.37 (2C, 18, 18′); 52.13 (2C, 15(3), 15′(3)); 53.16 (4C, 6^a, 6^b, 6^c, 6^d); 54.81 (2C, 17, 17′); 65.31 (4C), 70.41 (4C), 70.67 (4C) and 71.79 (4C) (2^a, 3^a, 4^a, 5^a, 2^b, 3^b, 4^b, 5^b, 2^c, 3^c, 4^c, 5^c, 2^d, 3^d, 4^d, 5^d); 93.51 (2C, 20, 20′); 96.42 (4C, 1^a, 1^b, 1^c, 1^d); 98.71 (2C, 5, 5′); 101.12 (2C, 10, 10′); 102.65 (2C, 15, 15′); 108.35 (4C) and 108.94 (4C) (7^a, 10^a, 7^b, 10^b, 7^c, 10^c, 7^d, 10^d); 121.55 (2C, 3(2), 3′(2)); 129.01 (2C, 13, 13′); 129.51 (2C, 3(1), 3′(1)); 129.92 (2C, 12, 12′); 130.12 (2C, 2, 2′); 134.46 (2C, 7, 7′); 134.60 (2C, 4, 4′); 134.71 (2C, 11, 11′); 135.30 (2C, 3, 3′); 136.01 (2C, 1, 1′); 138.76 (2C, 8, 8′); 144.58 (2C, 14, 14′); 148.92 (2C, 9, 9′); 153.94 (2C, 6, 6′); 166.69 (2C, 16, 16′); 169.14 (2C, 19, 19′); 169.25 (2C, 13(1), 13′(1)); 173.30 (2C, 17(3), 17′(3)); 174.00 (2C, 15(2), 15′(2)).

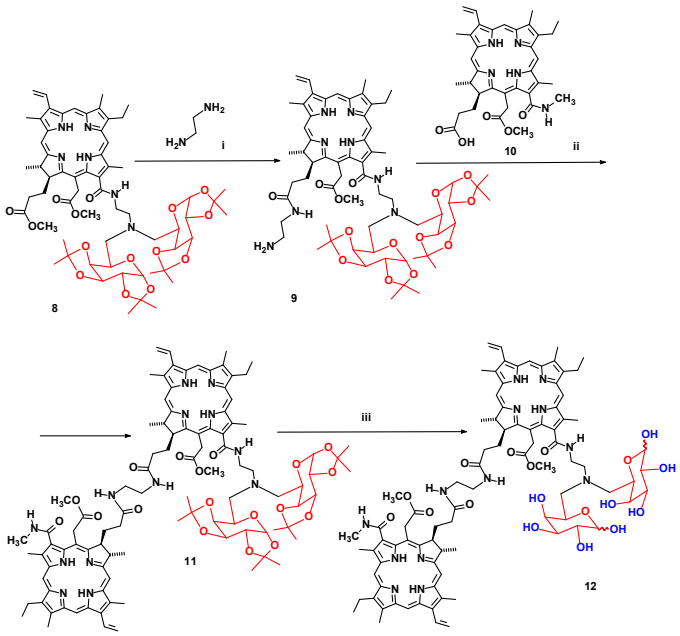
Compound ***18***. To the 210 mg (0.09 mmol) of compound **17** 4 mL of 90% aqueous trifluoroacetic acid (TFA) was added. The reaction mixture was stirred at room temperature (~23 ºC) for 4 h. Next, the excess of trifluoroacetic acid was evaporated at low pressure. A residue after the evaporation was diluted with 5 mL of $CHCl_3$–CH_3OH (5:0.5) mixture, the resulting mixture was chromatographed on silica gel (eluent: $CHCl_3$–C_2H_5OH (95% aqueous)–H_2O–NH_3 (25% aqueous), 10:20:5:1; TLC: $CHCl_3$–C_2H_5OH (95% aqueous)–NH_3 (25% aqueous), 1:2:0.2). 130 mg (82%) of compound **18** was obtained as a dark green crystalline powder. UV-Vis (DMSO) λ_{max} nm ($I_{relative}$ (%)): 663 (30), 608 (3), 529 (3), 501 (9), 403 (100). IR (KBr) ν cm^{-1}: 1722 (C=O, ester), 1645 ("amide-I"), 1603 ("chlorin band"), 1543 ("amide-II"). MS (ESI) *m/z*: 989.7 (calcd. for $[H_2M]^{2+}$ 989.5). ^{1}H NMR (DMSO-D_6) δ_H ppm: –2.11 (2H, s, I-NH, I′-NH); –1.81 (2H, s, III-NH, III′-NH); 1.64 (6H, d, 18(1)-CH_3, 18′(1)-CH_3, *J* = 6.9 Hz); 1.70 (6H, t, 8(2)-CH_3, 8′(2)-CH_3, *J* = 7.4 Hz); 1.93–2.48 (8H, m, 17(1)-CH_2, 17(2)-CH_2, 17′(1)-CH_2, 17′(2)-CH_2); 2.94-3.17 (12H, m) and 3.39-3.48 (8H, m) (13(2)-CH_2, 13(3)-CH_2, 13′(2)-CH_2, 13′(3)-CH_2, 17(4)-CH_2, 17′(4)-CH_2, α,β-6^a-CH_2, α,β-6^b-CH_2, α,β-6^c-CH_2, α,β-6^d-CH_2); 3.33 (6H, s, 7(1)-CH_3, 7′(1)-CH_3); 3.50 (6H, s, 2(1)-CH_3, 2′(1)-CH_3); 3.53 (6H, s, 12(1)-CH_3, 12′(1)-CH_3); 3.70 (6H, s, 15(3)-CH_3, 15′(3)-CH_3); 3.56–3.89 (20H, m, 8(1)-CH_2, 8′(1)-CH_2, α,β-1^a-OH, α,β-1^b-OH, α,β-1^c-OH, α,β-1^d-OH, α,β-2^a-OH, α,β-2^b-OH, α,β-2^c-OH, α,β-2^d-OH, α,β-3^a-OH, α,β-3^b-OH, α,β-3^c-OH, α,β-3^d-OH, α,β-4^a-OH, α,β-4^b-OH, α,β-4^c-OH, α,β-4^d-OH); 3.90–4.24 (6H, m), 4.25–4.43 (6H, m) and 4.47–4.78 (8H, m) (17-H, 17′-H, 18-H, 18′-H, α,β-2^a-H, α,β-2^b-H, α,β-2^c-H, α,β-2^d-H, α,β-3^a-H, α,β-3^b-H, α,β-3^c-H, α,β-3^d-H, α,β-4^a-H, α,β-4^b-H, α,β-4^c-H, α,β-4^d-H, α,β-5^a-H, α,β-5^b-H, α,β-5^c-H, α,β-5^d-H); 4.94-5.06 (3H, m) and 5.14-5.37 (1H, m) (α,β-1^a-H, α,β-1^b-H, α,β-1^c-H, α,β-1^d-H); 5.26 (2H, d, *J* = 17.7 Hz) and 5.55 (2H, d, *J* = 17.6 Hz) (15(1)-CH_2, 15′(1)-CH_2); 6.17 (2H, d, (3(2)-H (*cis*), 3′(2)-H (*cis*), *J* = 12.0 Hz); 6.43 (2H, d, 3(2)-H (*trans*), 3′(2)-H (*trans*), *J* = 17.7 Hz); 7.11-7.29 (2H, m, 17(3)-NH, 17′(3)-NH); 7.93-8.03 (2H, m, 13(1)-NH, 13′(1)-NH); 8.30 (2H, dd, 3(1)-H, 3′(1)-H, *J* = 11.9, 17.9 Hz); 9.10 (2H, s, 20-H, 20′-H); 9.75 (2H, s, 5-H, 5′-H); 9.78 (2H, s, 10-H, 10′-H). ^{13}C NMR (DMSO-D_6) δ_C ppm: 11.27 (2C, 7(1), 7′(1)); 11.49 (2C, 2(1), 2′(1)); 12.50 (2C, 12(1), 12′(1)); 18.28 (2C, 8(2), 8′(2)); 19.45 (2C, 8(1), 8′(1)); 23.46 (2C, 18(1), 18′(1)); 28.84 (2C) and 30.29 (2C) (17(1), 17(2), 17′(1), 17′(2)); 32.88 (2C), 37.26 (2C) and 38.85 (2C) (13(2), 13(3), 13′(2), 13′(3), 17(4), 17′(4)); 38.88 (2C, 15(1), 15′(1)); 48.74 (2C, 18, 18′); 52.31 (2C, 15(3), 15′(3)); 53.30 (2C, 17, 17′); 67.92 (4C, 6^a, 6^b, 6^c, 6^d); 69.29 (4C), 72.64 (4C), 72.74 (4C) and 74.10 (4C) (2^a, 3^a, 4^a, 5^a, 2^b, 3^b, 4^b, 5^b, 2^c, 3^c, 4^c, 5^c, 2^d, 3^d, 4^d, 5^d); 93.20 (2C, 20,

20′); 94.56 (2C) and 98.04 (2C) (1[a], 1[b], 1[c], 1[d]); 98.97 (2C, 5, 5′); 101.09 (2C, 10, 10′); 103.19 (2C, 15, 15′); 122.34 (2C, 3(2), 3′(2)); 129.13 (2C, 3(1), 3′(1)); 129.99 (2C, 13, 13′); 130.38 (2C, 12, 12′); 130.47 (2C, 2, 2′); 132.21 (2C, 7, 7′); 134.05 (2C, 4, 4′); 134.13 (2C, 11, 11′); 135.62 (2C, 3, 3′); 136.67 (2C, 1, 1′); 138.26 (2C, 8, 8′); 144.75 (2C, 14, 14′); 148.95 (2C, 9, 9′); 153.30 (2C, 6, 6′); 166.96 (2C, 16, 16′); 168.91 (2C, 19, 19′); 169.84 (2C, 13(1), 13′(1)); 172.49 (2C, 17(3), 17′(3)); 173.26 (2C, 15(2), 15′(2)).

Results and Discussion

To form a dimeric chlorin molecule with one tertiary amino group with two galactose fragments, we have synthesized aminochlorin **9** by acting on the preliminary obtained ethylenediamine derivative **8**. Then acylation of aminochlorin **9** with carboxychlorin **10** activated by CMPI gives the corresponding dimer **11** with two diisopropylidene galactose fragments (Scheme 1). Deprotection of isopropylidene with 10% aqueous trifluoroacetic acid (TFA) gives the target dimeric derivative **12** with two galactose moieties.

The amidation of the ester group of the substituent at position 17 of the starting chlorin **8** occurs chemo-selectively, similarly to the previously described reaction of ethylenediamine with simpler amide derivatives.[24] The introduction of one ethylenediamine fragment and the chemo-selectivity of the process are confirmed by IR and NMR spectroscopy data, as well as mass spectrometry. In the mass spectrum of the amidation product, the peaks with *m/z* values corresponding to the protonated molecular ion of compound **9** (MH^+) and the adduct of its molecule with the sodium cation (MNa^+), as well as doubly and triply charged ions $[(M+2H)H_2]^{2+}$ and $[(M+2H)H_3]^{3+}$, formed during two and threefold protonation of molecule **9** hydrogenated during ionization are observed. It is interesting that the peak of the doubly charged ion has the highest intensity, which can be explained by the relatively large size of the molecule and the presence of a basic amino group in it. These structural factors determine the possibility of interaction with two protons. The absorption band of the ester group preserved in the IR spectrum additionally confirms monoamidation. In the ^{1}H NMR spectrum of the resulting compound, there is no singlet corresponding to the ester group in the propionate substituent at position 17, and the singlet corresponding to the ester group at position 15 is retained (Figure 2).



Scheme 1. i – Ethylendiamine, 20 h (~23ºC); ii – **10**, CMPI, DMAP, CH_2Cl_2, reflux, 2 h; iii – TFA-H_2O, 4 h (~23ºC).

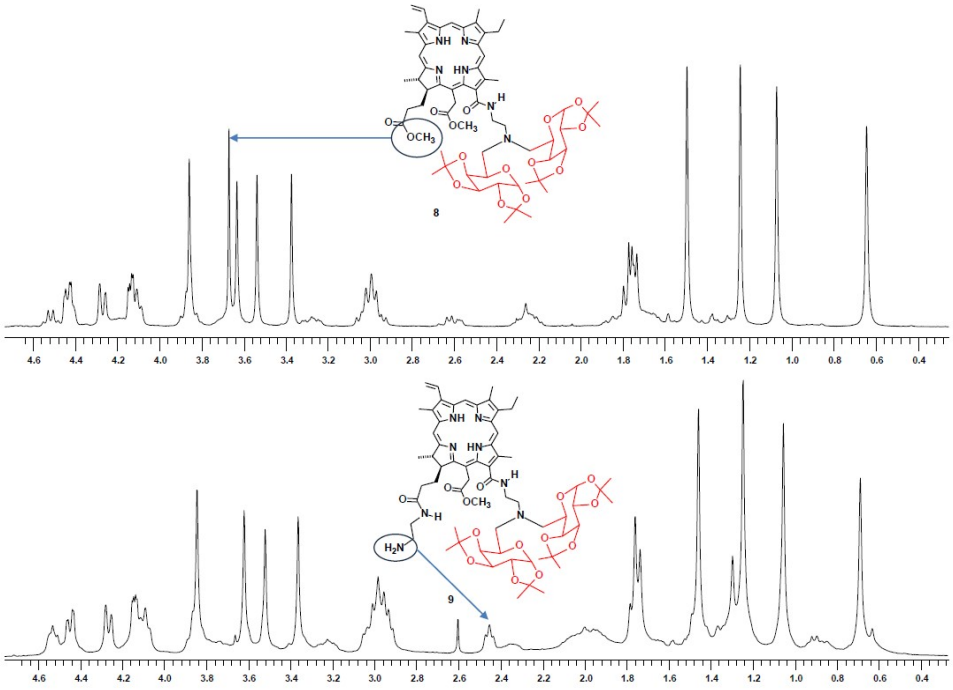


Figure 2. ^{1}H NMR spectra of chlorin **8** and the product of its reaction with ethanolamine **(9)** (0.4–4.6 ppm, $CDCl_3$, 300 MHz).

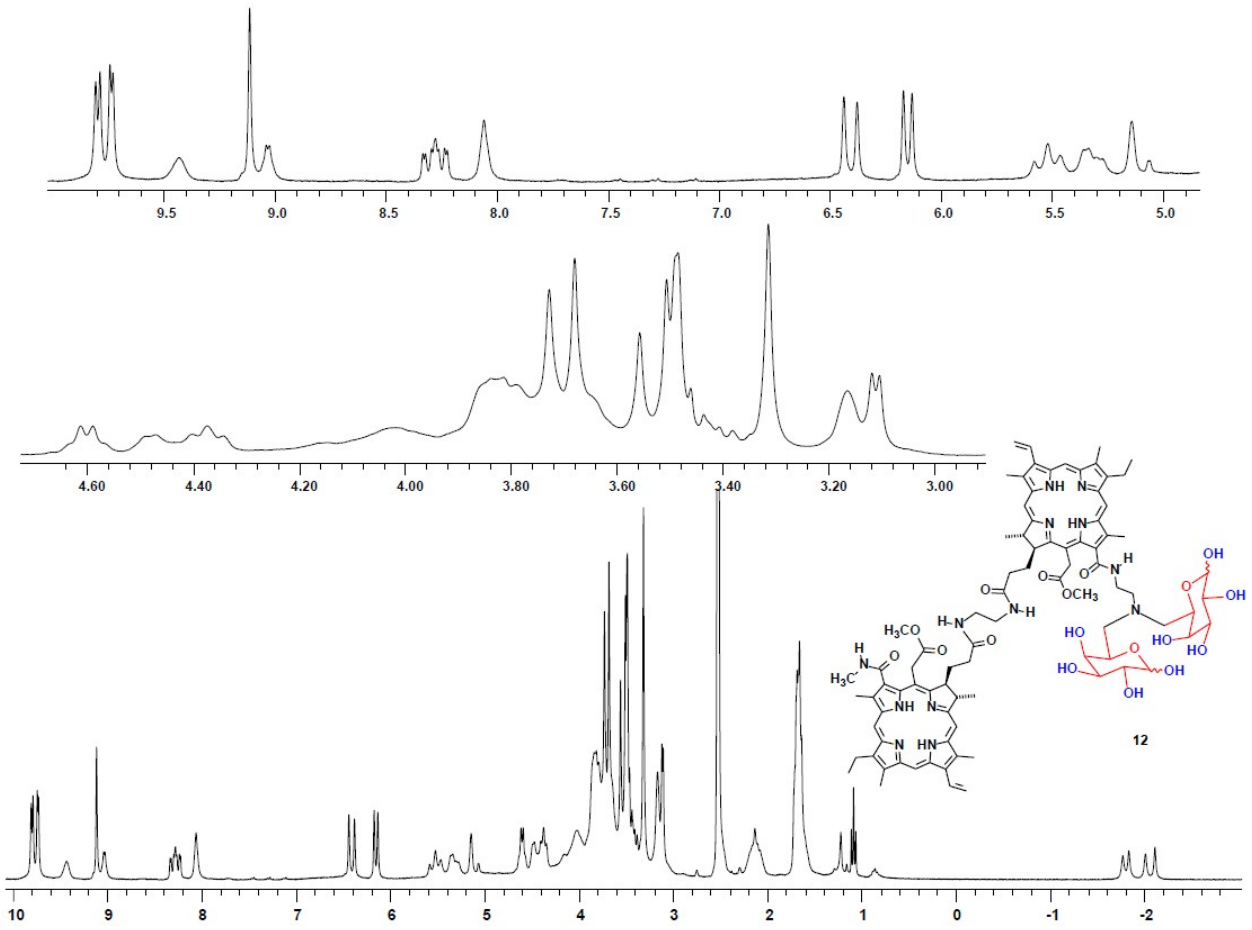
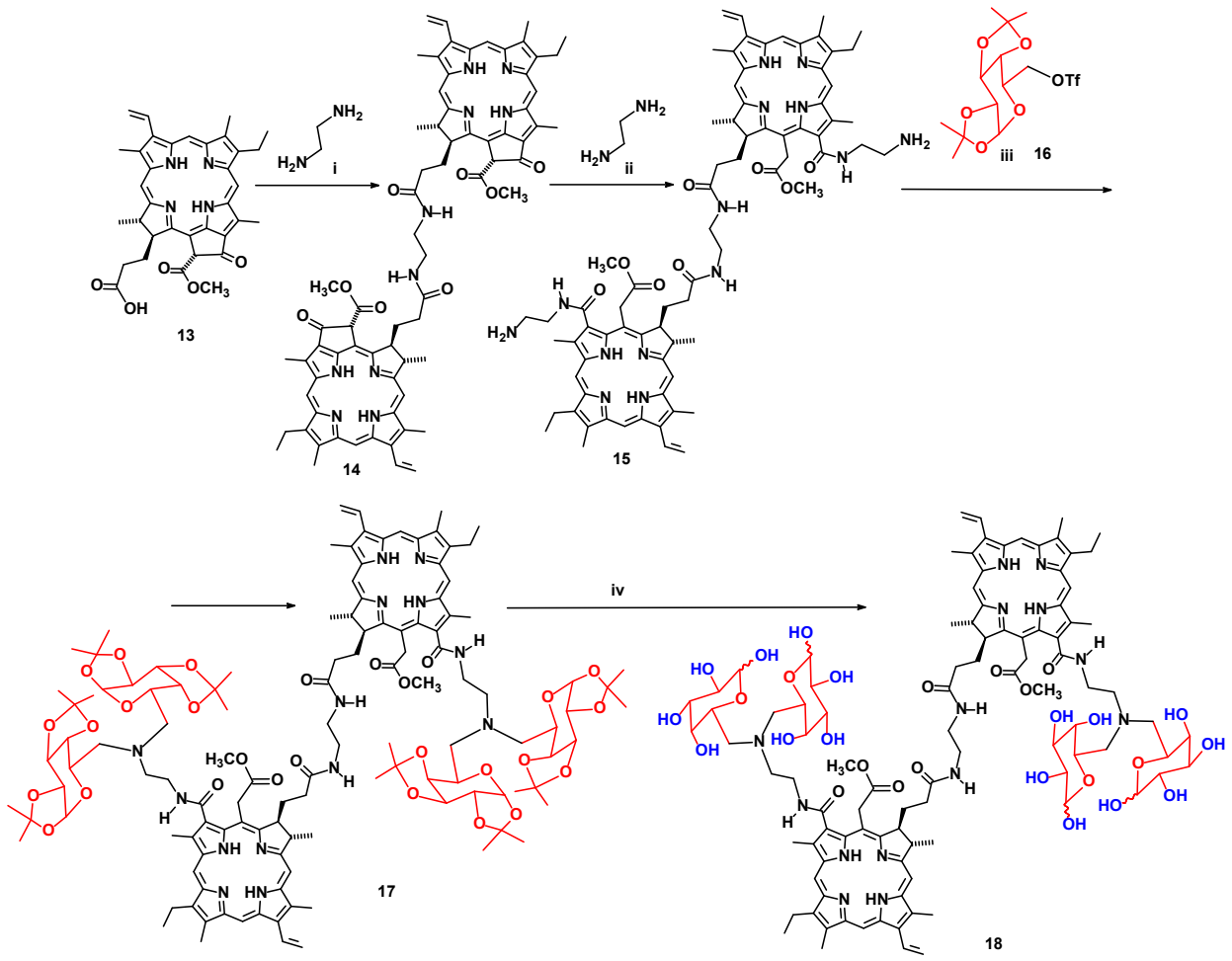


Figure 3. ^{1}H NMR spectrum of dimer **12** (DMSO-D_6, 300 MHz).

These facts indicate the amidation of the propionate substituent. The introduced ethylenediamine fragment appears in the ^{1}H NMR spectrum as multiplet signals of the methylene groups protons, a multiplet of an additional amide proton, and a two-proton triplet of the amino group. The proton signals of diisopropylidene galactose fragments remain almost unchanged compared to the spectrum of compound **8**, which indicates that these fragments are retained in the molecule (Figure 2).

In the mass spectrum of the compound **11** (the product of compound **9** acylation with CMPI-activated carboxychlorin **10**), the peaks with *m/z* values corresponding to the protonated molecular ion of compound **11** (MH^+) and doubly charged ions formed as a result of double protonation (ion $[(M+2H)H_2]^{2+}$), and with the participation of the sodium cation (ion $[(M+2H)HNa]^{2+}$) are observed. The intensity of the doubly charged ions peaks, is significantly higher than the intensity of the singly charged ions peaks as in the case of compound **9**. The ^{1}H and ^{13}C NMR spectra of dimer **11** show signals from protons and carbon atoms of two structurally similar macroheterocycles. The ratio of the signal intensities of the protons of carbohydrate and porphyrin fragments in the ^{1}H NMR spectrum corresponds to two fragments of diisopropylidene galactose per two chlorin macrocycles, which is in agreement with the structure of dimer **11**. The removal of isopropylidene protection with the formation of the target chlorin **12** is manifested in the ^{1}H and ^{13}C NMR spectra by the absence of signals from the methyl groups of the isopropylidene fragment, while the signals of other protons and carbon atoms of the galactose fragments are saved and the signals of the hydroxyl groups protons appear. The ^{1}H and ^{13}C NMR spectra of dimer **11** show signals from protons and carbon atoms of two structurally similar macroheterocycles (Figure 3). In the mass spectrum of compound **12**, peaks of one and two charged ions ($[MH]^+$, $[(M+2H)HNa]^{2+}$ and $[(M+2H)H_2]^{2+}$) are observed, the *m/z* values of which correspond to the structure of **12**, similar to the ions in the mass spectrum of **11**.

The previously described dimer formation under the action of a small excess of ethylenediamine on pheophorbide *a* **13**, the carboxyl group of which is "activated" by di-*tert*-butyl pyrocarbonate (Boc_2O)[29] were used for synthesis of the chlorin e_6 dimeric derivative with four galactose fragments. A dimeric pheophorbide *a* derivative **14** is formed as a result; the phorbin exocycle of the start compound **13** does not react with ethylenediamine under these conditions.[29] Opening of the phorbin fragments exocycles of dimer **14** under the action of excess ethylenediamine gives the corresponding dimeric chlorin e_6 derivative **15**, each macrocycle of which contains an amino group. Alkylation of the amino groups of dimer **15** by the action of diisopropylidene galactose triflate **16** according to the method used for obtaining of compound **8** from the corresponding amino derivative,[22] allows one to obtain dimer **17**, which is an analogue of compound **8**: two fragments of compound **8** are conjugated in it by a covalent spacer. Deprotection of isopropylidene leads to compound **18** similar to the monomeric chlorin **1**.



Scheme 2. i – CH_2Cl_2-Py, Boc_2O, ethylendiamine 1 h (~23ºC);[30] ii – ethylendiamine, $CHCl_3$, 5 h (~23ºC); iii – **16**, THF, CH_3COONa, reflux, 5 h; iv – TFA-H_2O, 4 h (~23ºC).

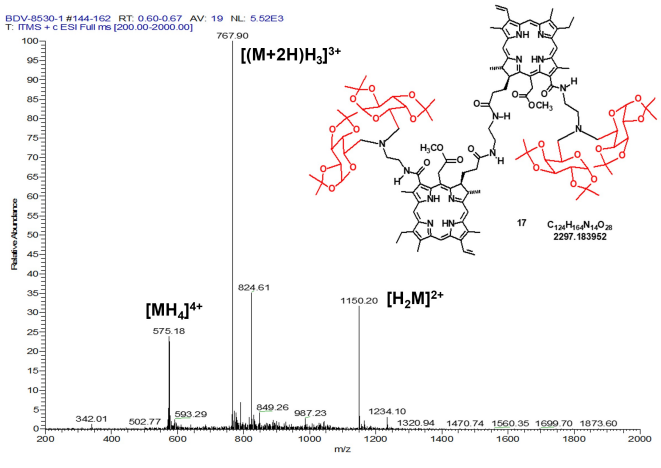


Figure 4. Mass spectrum (ESI) of compound **17**.

The opening of exocycles of the pheophorbide *a* dimeric derivative **14** under the action of ethylenediamine with the formation of dimer **15** is manifested in the ^{1}H NMR spectra by the absence of a singlet corresponding to protons in positions 13(2) of the exocycle and the presence of doublets corresponding to methylene groups in positions 15 of both macrocycles, formed during the exocycles opening. In addition, in the ^{1}H and ^{13}C NMR spectra of compound **15**, signals from the protons and carbon atoms of the ethylenediamine fragment are observed. The chlorin macrocycles in dimer **15** are magnetically equivalent, and the chemical shifts of the signals of protons and carbon atoms of chlorin fragments in the ^{1}H and ^{13}C NMR spectra of dimer **15** coincide with each other. In the mass spectrum of diamine derivative **15**, peaks are observed, the *m/z* values of which correspond to single, double and triple charged ions formed as a result of single, double and triple protonation of the molecule **15** during ionization (ions $[MH]^+$, $[MH_2]^{2+}$ and $[MH_3]^{3+}$), which is quite expected for a large molecule with two amino groups. In the ^{1}H and ^{13}C NMR spectra of compound **17**, formed upon alkylation of the amino groups of dimer **15** with triflate **16**, signals of diisopropylidene galactose fragments protons and carbon atoms are observed. The ratio of the integral intensity of the chlorin and carbohydrate fragments protons signals in the ^{1}H NMR spectrum corresponds to the introduction of four diisopropylidene galactose fragments. As in the case of dimer **15**, the macrocycles of dimer **17** are magnetically equivalent and chemically equivalent and the chemical shifts of the signals of protons and carbon atoms of both chlorin and carbohydrate fragments in the ^{1}H and ^{13}C NMR

spectra of dimer **17** coincide with each other. The relative molecular weight of compound **17** (2297.2) does not allow us to observe singly charged ions of this compound on the instrument at our disposal (the upper limit of the determined *m/z* is 2000). However, ions with higher charges are available for study and can be used to obtain structural information. In the mass spectrum of dimer **10**, the peaks with *m/z* values corresponding to two-, three-, and four-charged ions formed by protonation and hydrogenation of molecule **17** during electrospray ionization ($[H_2M]^{2+}$, $[(M+2H)H_3]^{3+}$ and $[MH_4]^{4+}$, Figure 4) are observed.

The conclusions about the structure of compound **17** are in agreement with the information on the structure of compound **18** obtained by deprotection of isopropylidene from galactose moieties. The peak with *m/z*=989.7 corresponding to a doubly protonated molecular ion ($[H_2M]^{2+}$) is observed in the mass spectrum of compound **18**. There are no signals of the protons and carbon atoms of the isopropylidene protection in the ^1H and ^{13}C NMR spectra of compound **18** and the ratio of the signal intensities of the protons of the chlorin macrocycle and galactose fragments corresponds to two carbohydrate fragments per macrocycle. So, the data described are in agreement with the structure of **18** and indicate complete removal of isopropylidene protection. Other spectral characteristics of dimer **18** are similar to those of dimer **17** (Figure 5).

Thus, in this work, dimers with one (dimer **12**) and two (dimer **18**) tertiary amino groups with two galactose fragments as substituents at the nitrogen atom were synthesized. As noted above, in this work we consider a compound to be soluble in water if it forms a colored solution that gives red luminescence when illuminated with violet light when added to water. The estimation of the solubility in water of the compounds obtained allows us to note the following. The addition of one more chlorin macrocycle to the molecule (compared to compound **1**) (dimer **12**) leads to loss of solubility in water. The covalent binding of two fragments of water-soluble compound **1** in dimer **18** leads to loss of solubility, despite the fact that the number of galactose fragments in dimer **18** and the mode of their binding with macrocycle completely coincides with those of compound **1**. Apparently, the covalent binding of chlorin macrocycles prevents the destruction of the crystal lattice during dissolution. It is possible that the covalent binding of macrocycles promotes stacking interactions between macrocycles within the dimer and the formation of larger aggregates.

Conclusions

Thus, in this work, new conjugates of galactose with dimeric derivatives of chlorophyll *a* with different hydrophilicity were synthesized. The change in the hydrophilicity of dimeric chlorins is achieved by introducing into the molecule one or two tertiary amino groups containing two galactose fragments as substituents at the nitrogen atom.

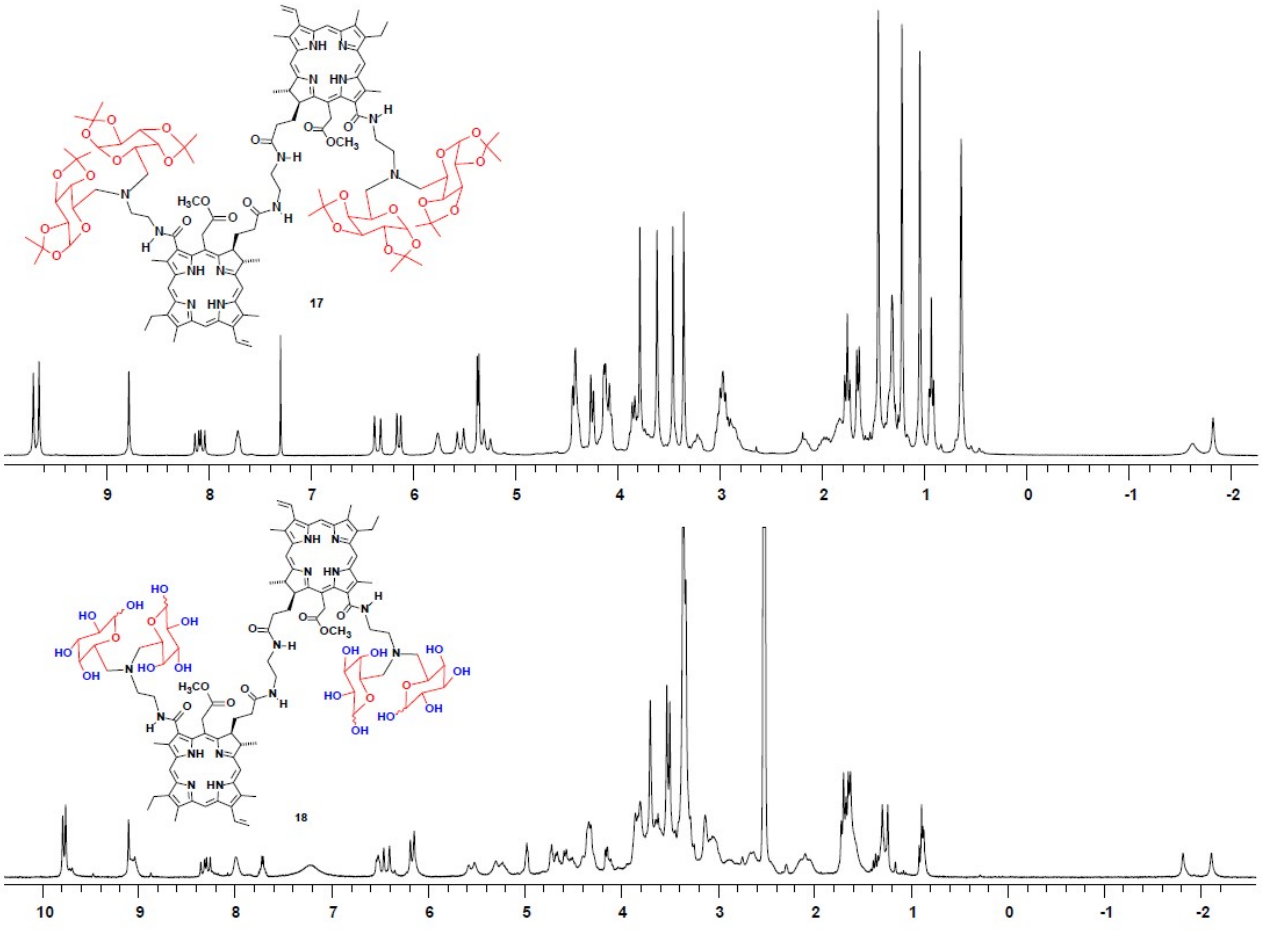


Figure 5. ^1H NMR spectra (300 MHz) of dimers **17** ($CDCl_3$) and **18** (DMSO-D_6).

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