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Synthesis of Hydroxy Derivatives of Chlorin e_6

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*There is a simple scheme of synthesis of new chlorin photosensitizers (PS) based on chlorin e_6 hydroxy derivatives. For the disclosure of exocycle of the initial compounds – pheophorbide a and its methyl ester we used aliphatic aminoalcohols with 2-6 carbon atoms in the alkyl chain. The reaction was carried out under mild conditions in chloroform/dichloromethane with heating up to 40 °C. The structure of all compounds obtained was confirmed by means of electronic, IR, ^{1}H NMR spectroscopy and mass-spectrometry. The yields of compounds **2a-e** and **3b-e** were 60–75 %. It is necessary to note that chlorin e_6 hydroxy derivatives **2a-e** could be soluble in water using alkaline compounds as excipients (namely KOH, NaOH). This fact is important and valuable because many effective porphyrin and chlorin PS are insoluble in water systems and obtaining of chlorin e_6 is time-consuming and hard work. Thus, in this paper we propose a reliable scheme of synthesis of new chlorin's photosensitizers which are promising agents for PDT.*

Keywords: Chlorin e_6, synthesis, hydroxy derivatives, photodynamic therapy (PDT).

Синтез гидроксипроизводных хлорина e_6

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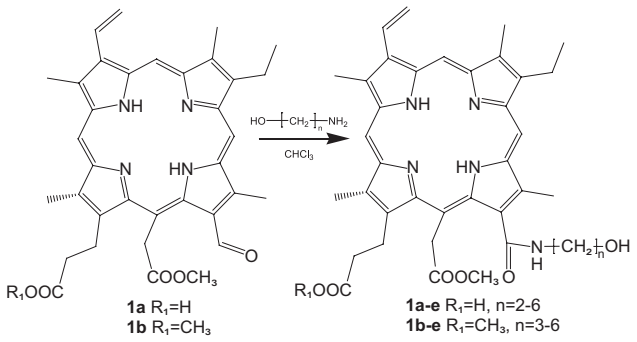
*Осуществлён синтез гидроксипроизводных хлорина e_6 путём присоединения аминоспиртов к феофорбиду а и его метиловому эфиру. Гидроксиамидные производные хлорина e_6 **2a-e** растворимы в щелочных водных растворах и являются перспективными агентами для ФДТ.*

Ключевые слова: Хлорин e_6, синтез, гидроксипроизводные, фотодинамическая терапия (ФДТ).

Nowadays photodynamic therapy plays an important role in oncology diseases treatment.[1-3] Due to high efficiency, minimal contraindications, good patient acceptability and excellent cosmetic effect PDT finds an application for treatment of different types of tumors.[4-5] Unfortunately, there are some limits for photosensitizers used in medicine (namely selectivity, light depth penetration, stability *etc.*). Because of PDT's significance and actuality, development of new effective photosensitizers is an actual task at the moment.[6]

Pharmaceuticals based on chlorin e_6 approve themself to be reliable photosensitizers.[4,7] But its synthesis is time-consuming. One of the possible ways for obtaining of chlorin's photosensitizers is opening of cyclopentanone fragment in pheophorbide *a*.[8-10] Following this idea alkylamides,[11,12] aminoamides[13,14] and hydroxyamides[14,15] of chlorin e_6 were synthesized.

Our investigations are based on synthesis of chlorin photosensitizers from methyl ester of pheophorbide *a* using amino alcohols. This type of reaction was earlier provided for 17(3)-methyl ester of pheophorbide *a* with 2-aminoethanol as nucleophilic agent.[14] We expanded the number of amino alcohols with 3-6 carbon atoms in the alkyl chain (Scheme 1) and succeeded in opening of cyclopentanone fragment in pheophorbide *a*. We used for our synthesis this sequence of amino alcohols to evaluate the dependence of physicochemical properties on length of the hydrocarbon chain. The reactions were carried out under mild conditions with good yields 60–75 %. During the experiment we



Scheme 1.

used a 30-fold excess of the amino alcohol relatively the pheophorbide *a* and its methyl ester (**1a** and **1b**).

The reaction was monitored by TLC and electronic spectroscopy. We observed the hypsochromic shift of the Soret and Q absorption bands from 413 and 668 nm to 403 and 663 nm respectively in the electronic spectrum.

The compounds obtained were purified by column chromatography and characterized by IR, ^{1}H NMR spectroscopy and mass spectrometry. To demonstrate the purification efficacy and accuracy of the results the ^{1}H NMR spectrum fragment of **3d** is shown in Figure 1.

It is interesting to note that the compounds **2a-e** were soluble in water using alkaline substances as excipients. In the extraction process (washing after reaction complete) these substances remained in water layer. Using 3 % HCl solution allowed us to separate compounds **2a-e**. After all steps of purification (including column chromatography) compounds **2a-e** were soluble in alkaline water. Thus, these photosensitizers **2a-e** are readily synthesized chlorin e_6 derivatives that could be transferred in water-soluble forms. Moreover, we can regard them as perspective agents for PDT.

Experimental

Electronic spectra were recorded on a spectrophotometer JASCO UV/VIS 7800 (Japan) in the range of 350–750 nm in chloroform. Mass-spectra were recorded on a Ultraflex TOF/TOF using MALDI method and 2,5-dihydroxybenzoic acid as a matrix. ^{1}H NMR spectra were recorded on a Bruker DPX-300 (Germany) in $CDCl_3$ at 298 K. Chemical shifts were measured using signal at 7.26 ppm for residual protons of $CHCl_3$ as a reference.

*13(1)-N-(2-Hydroxyaminoethyl)amide-15(2)-methyl ester of chlorin e_6 (**2a**).* The 0.1 mL of aminoethanol (1.50 mmol) was added to the solution of 25.4 mg of pheophorbide *a* (0.043 mmol) **1a** in chloroform (2 mL). The reaction mixture was stirred for 2 hours under an inert atmosphere by heating to 40 °C. The reaction mixture was poured into 3 % HCl solution, organic layer was separated, washed with water to p*H*=7, dried with Na_2SO_4 and then concentrated to dryness. The residue was purified by silica gel (0.040–0.063 mm, Merck, Germany) column chromatography using chloroform/methanol (5:1 by volume) to get pure hydroxy derivative of chlorin e_6. Yield 12 mg (43 %). UV-Vis ($CHCl_3$) λ_{max} nm: 403.0; 502.3; 529.8; 663.2. ^{1}H NMR ($CDCl_3$) δ ppm: 9.85 (s, 1H, 10-H); 9.78 (s, 1H, 5-H); 8.98 (s, 1H, 20-H); 8.07 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-H); 6.34 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-H); 6.21 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-H); 5.61 d. and 5.37 d. (1H each, *J*=19.03 Hz, 15(1)-H); 4.58–4.46 (m, 2H 17-H, 18-H); 4.04–3.71 (m, 4H, 13(3,4)-CH_2-CH_2-OH); 3.90 (s, 3H, 15(3)-CH_3); 3.64–3.53 (m, 5H, 8(1)-CH_2, 12(1)-CH_3); 3.52–3.49 (s, 3H, 2(1)-CH_3); 3.36–3.32 (m, 3H, 7(1)-CH_3); 2.52–2.05 (m, 4H, 17(1)-H, 17(2)-H); 1.73 (d, 3H, 18(1)-H, *J*=6.9 Hz); 1.65 (t, 3H, 8(2)-CH_3). Mass-spectrum, *m/z*: calculated for $[C_{37}H_{43}N_6O_5]^+$ 653.321, found: 653.154.

*13(1)-N-(2-Hydroxyaminopropyl)amide-15(2)-methyl ester of chlorin e_6 (**2b**)*. Compound was obtained similarly to **2a**. Yield 16 mg (47 %) from 30.3 mg of **1a**. UV-Vis ($CHCl_3$) λ_{max} nm: 403.6; 502.1; 527.8; 663.3. ^{1}H NMR ($CDCl_3$) δ ppm: 9.74 (s, 1H, 10-H); 9.68 (s, 1H, 5-H); 8.89 (s, 1H, 20-H); 8.04 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-H); 6.33 (dd, 1H, *J*=17.82 Hz, *trans*-3(2)-H); 6.16 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-H); 5.52 d. and 5.29 d. (1H each, *J*=18.86 Hz, 15(1)-H); 4.49 (m, 1H, 18-H); 4.41 (m, 1H, 17-H); 3.83–3.7 (m, 4H, 13(2)-CH_2, 13(4)-CH_2-OH); 3.80 (s, 3H, 15(3)-CH_3); 3.61–3.50 (m, 5H, 8(1)-CH_2, 12(1)-CH_3); 3.48 (s, 3H, 2(1)-CH_3); 3.30 (s, 3H, 7(1)-CH_3); 2.6–1.9 (m, 4H, 17(1)-H, 17(2)-H); 1.75–1.62 (m, 8H, 18(1)-CH_3, 8(2)-CH_3, 13(3)-CH_2). Mass-spectrum, *m/z*: calculated for $[C_{38}H_{45}N_6O_5]^+$ 667.337, found: 667.310.

*13(1)-N-(2-Hydroxyaminobutyl)amide-15(2)-methyl ester of chlorin e_6 (**2c**)*. Compound was obtained similarly to **2a**. Yield 19 mg (53.5 %) from 31 mg of **1a**. UV-Vis ($CHCl_3$) λ_{max} nm: 404.2; 500.9; 531.2; 663.0. ^{1}H NMR ($CDCl_3$) δ ppm: 10.06 (s, 1H, 10-H); 9.99 (s, 1H, 5-H); 9.17 (s, 1H, 20-H); 8.09 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-H); 6.38 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-H); 6.32 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-H); 5.89 d. and 5.39 d. (1H each, *J*=19.87 Hz, 15(1)-H); 4.67–4.54 (m, 2H, 18-H, 17-H); 3.97–3.75 (m, 4H, 13(2)-

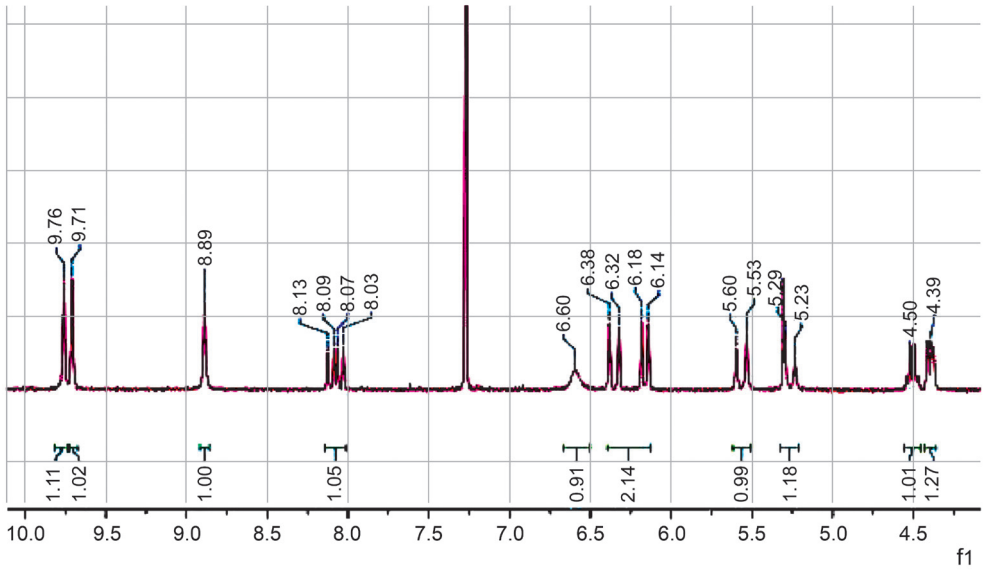


Figure 1. Fragment of ^{1}H NMR spectrum of **3d**.

CH_2, 13(5)-CH_2-OH); 3.83 (s, 3H, 15(3)-CH_3); 3.66–3.57 (m, 5H, 8(1)-CH_2, 12(1)-CH_3); 3.42 (s, 3H, 2(1)-CH_3); 3.35 (s, 3H, 7(1)-CH_3); 2.6–2.3 (m, 4H, 17(1)-H, 17(2)-H); 1.82–1.57 (m, 10H, 18(1)-H, *J*=7.31Hz, 8(2)-CH_3, 13(3,4)-CH_2-CH_2). Mass-spectrum, *m/z*: calculated for $[C_{39}H_{47}N_6O_5]^+$ 681.353, found: 681.815.

13(1)-N-(2-Hydroxyaminopentyl)amide-15(2)-methyl ester of chlorin e_6 ***(2d)***. Compound was obtained similarly to **2a**. Yield 24.8 mg (70.5 %) from 30.06 mg of **1a**. UV-Vis ($CHCl_3$) λ_{max} nm: 403.4; 502.3; 663.2. ^{1}H NMR ($CDCl_3$) δ ppm: 9.73 (s, 1H, 10-H); 9.69 (s, 1H, 5-H); 8.88 (s, 1H, 20-H); 8.05 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-H); 6.33 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-H); 6.15 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-H); 5.53 d. and 5.31 d. (1H each, *J*=18.46 Hz, 15(1)-H); 4.49 (m, 1H, 18-H); 4.40 (m, 1H, 17-H); 3.86–3.7 (m, 4H, 13(2)-CH_2, 13(6)-CH_2-OH); 3.76 (s, 3H, 15(3)-CH_3); 3.58–3.50 (m, 5H, 8(1)-CH_2, 12(1)-CH_3); 3.48 (s, 3H, 2(1)-CH_3); 3.31 (s, 3H, 7(1)-CH_3); 2.11–2.61 (m, 4H, 17(1)-H, 17(2)-H); 2.0–1.68 (m, 9H, 18(1)-CH_3, *J*=7.37 Hz, 13(3,4,5)-CH_2-CH_2-CH_2); 0.85 (t, 3H, 12(2)-CH_3).

13(1)-N-(2-Hydroxyaminohexyl)amide-15(2)-methyl ester of chlorin e_6 ***(2e)***. Compound was obtained similarly to **2a**. Yield 15 mg (50.5 %) from 24.9 mg of **1a**. UV-Vis ($CHCl_3$) λ_{max} nm: 403.9; 503.0; 532.8; 663.0. ^{1}H NMR ($CDCl_3$) δ ppm: 9.78 (s, 1H, 10-H); 9.74 (s, 1H, 5-H); 8.93 (s, 1H, 20-H); 8.06 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-H); 6.34 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-H); 6.18 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-H); 5.56 d. and 5.32 d. (1H each, *J*=18.49 Hz, 15(1)-H); 4.55–4.39 (m, 2H, 18-H, 17-H); 3.83–3.74 (m, 4H, 13(2)-CH_2, 13(7)-CH_2-OH); 3.80 (s, 3H, 15(3)-CH_3); 3.56–3.51 (m, 5H, 8(1)-CH_2, 12(1)-CH_3); 3.49 (s, 3H, 2(1)-CH_3); 3.32 (s, 3H, 7(1)-CH_3); 2.7–1.99 (m, 4H, 17(1)-H, 17(2)-H); 1.90–1.4 (m 17H, 18(1)-CH_3, 13(3,4,5,6)-CH_2-CH_2-CH_2-CH_2, 8(2)-CH_3, 8(2)-CH_3). Mass-spectrum, *m/z*: calculated for $[C_{41}H_{51}N_6O_5]^+$ 709.384, found: 709.944.

13(1)-N-(2-Hydroxyaminopropyl)amide-15(2),17(3)-dimethyl ester of chlorin e_6 ***(3b)***. The 0.12 mL 3-aminopropanol (1.47 mmol) was added to the solution of 29.9 mg of 17(3)-methyl ester of pheophorbide *a* (0.049 mmol) **1b** in chloroform (2 mL). The reaction mixture was stirred for 2 hours under an inert atmosphere at heating to 40 °C. The reaction mixture was washed with water to p*H*=7, organic layer was separated, dried with Na_2SO_4 and then concentrated to dryness. The residue was purified by silica gel (0.040–0.063 mm, Merck, Germany) column chromatography using chloroform/methanol (10:1 by volume) to get pure hydroxy derivative of chlorin e_6. Yield 19.8 mg (59 %). UV-Vis ($CHCl_3$) λ_{max} nm: 403.5; 500.8; 663.4. ^{1}H NMR ($CDCl_3$) δ ppm: 9.73 (s, 1H, 10-H); 9.68 (s, 1H, 5-H); 8.92 (s, 1H, 20-H); 8 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-CH);7.2 (br. t, 1H, 13(1)-NH; 6.33 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-CH_2); 6.16 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-CH_2); 5.48 d. and 5.19 d. (1H each, *J*=18.85 Hz, 15(1)-CH_2); 4.51 (m, 1H, 18-H); 4.39 (m, 1H, 17-H); 3.85–3.75 (m, 4H, 13(2)-CH_2, 13(4)-CH_2-OH); 3.81 (s, 3H, 15(3)-CH_3); 3.63 (s, 3H, 12(1)-CH_3); 3.50 (s, 3H, 2(1)-CH_3); 3.29 (s, 3H, 7(1)-CH_3); 2.12–2.62 (m, 4H, 17(1)-CH_2, 17(2)-CH_2); 1.83–1.75 (m, 5H, 18(1)-CH_3, *J*=7,37 Hz, 13(4)-CH_2); 1.67 (t, 3H, 8(2)-CH_3); –1.94 (br. s, 2H, 21-NH and 23-NH). Mass-spectrum, *m/z*: calculated for $[C_{39}H_{47}N_6O_5]^+$ 681.353, found: 681.348.

13(1)-N-(2-Hydroxyaminobutyl)amide-15(2),17(3)-dimethyl ester of chlorin e_6 ***(3c)***. Compound was obtained similarly to **3b**. Yield 19.7 mg (57.2 %) from 30.03 mg of **1b**. UV-Vis ($CHCl_3$) λ_{max} nm: 402.9; 502.6; 530.8; 663.2. ^{1}H NMR ($CDCl_3$) δ ppm: 9.73 (s, 1H, 10-H); 9.67 (s, 1H, 5-H); 8.88 (s, 1H, 20-H); 8.05 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-CH); 6.74 (br. t, 1H, 13(1)-NH; 6.33 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-CH_2); 6.13 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-CH_2); 5.53 d. and 5.23 d. (1H each, *J*=18.65 Hz, 15(1)-CH_2); 4.51 (m, 1H, 18-H); 4.39 (m, 1H, 17-H); 3.88–3.73 (m, 4H, 13(2)-CH_2, 13(5)-CH_2-OH); 3.85 (s, 3H, 15(3)-CH_3); 3.68-3.61 (m, 5H, 17(3)-CH_3, 8(1)-CH_2); 3.51 (s, 3H, 12(1)-CH_3); 3.49 (s, 3H, 2(1)-CH_3); 3.31 (s, 3H, 7(1)-CH_3); 2.12–2.60 (m, 4H, 17(1)-CH_2, 17(2)-CH_2); 1.82–1.62 (m, 11H, 18(1)-CH_3, 13(3,4)-CH_2-CH_2, 8(2)-CH_3); –1.88 (br. s, 2H, 21-NH and 23-NH).

13(1)-N-(2-Hydroxyaminopentyl)amide-15(2),17(3)-dimethyl ester of chlorin e_6 ***(3d)***. Compound was obtained similarly to **3b**. Yield 25.4 mg (72.3 %) from 30.03 mg of **1b**. UV-Vis ($CHCl_3$) λ_{max} nm: 403.3; 500.7; 528.5; 663.0. ^{1}H NMR ($CDCl_3$) δ ppm: 9.76 (s, 1H, 10-H); 9.71 (s, 1H, 5-H); 8.89 (s, 1H, 20-H); 8.08 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-CH); 6.6 (br. t, 1H, 13(1)-NH; 6.35 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-CH_2);6.16 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-CH_2); 5.55 d. and 5.26 d. (1H each, *J*=18,84 Hz, 15(1)-CH_2); 4.50 (m, 1H, 18-H); 3.94 (s, 3H, 15(3)-CH_3); 4.39 (m, 1H, 17-H); 3.91–3.72 (m, 4H, 13(2)-CH_2, 13(6)-CH_2-OH); 3.69–3.6 (m, 5H, 17(3)-CH_3, 8(1)-CH_2; 3.55 (s, 3H, 12(1)-CH_3); 3.50 (s, 3H, 2(1)-CH_3); 3.33 (s, 3H, 7(1)-CH_3); 2.11–2.63 (m, 4H, 17(1)-CH_2, 17(2)-CH_2); 1.8-1.43 (m, 11H, 18(1)-CH_3, 13(3, 4, 5)-CH_2-CH_2-CH_2, 8(2)-CH_3); –1.87 (br. s, 2H, 21-NH and 23-NH).

13(1)-N-(2-Hydroxyaminohexyl)amide-15(2),17(3)-dimethyl ester of chlorin e_6 ***(3e)***. Compound was obtained similar to **3b**. Yield 16.7 mg (69.7 %) from 20.08 mg of **1b**. UV-Vis ($CHCl_3$) λ_{max} nm: 403.2; 502.7; 663.2. ^{1}H NMR ($CDCl_3$) δ ppm: 9.78 (s, 1H, 10-H); 9.72 (s, 1H, 5-H); 8.89 (s, 1H, 20-H); 8.09 (dd, 1H, *J*=17.8 Hz, *J*=11.5 Hz, 3(1)-CH); 6.56 (br. t, 1H, 13(1)-NH; 6.37 (dd, 1H, *J*=17.8 Hz, *trans*-3(2)-CH_2); 6.18 (dd, 1H, *J*=11.5 Hz, *cis*-3(2)-CH_2); 5.58 d. and 5.27 d. (1H each, *J*=18.85 Hz, 15(1)-CH_2); 4.51 (m, 1H, 18-H); 4.39 (m, 1H, 17-H); 3.95-3.72 (m, 4H, 13(2)-CH_2, 13(7)-CH_2-OH); 3.81 (s, 3H, 15(3)-CH_3); 3.70–3.6 (m, 5H, 17(3)-CH_3, 8(1)-CH_2); 3.63 (s, 3H, 12(1)-CH_3); 3.57 (s, 3H, 2(1)-CH_3); 3.35 (s, 3H, 7(1)-CH_3); 2.0–2.7 (m, 4H, 17(1)-CH_2, 17(2)-CH_2); 1.89-1.41 (m. 14H, 18(1)-CH_3, 13(3,4,5,6)-CH_2-CH_2-CH_2-CH_2, 8(2)-CH_3); –1.87 (br. s, 2H, 21-NH and 23-NH). Mass-spectrum, *m/z*: calculated for $[C_{42}H_{53}N_6O_5]^+$ 723.399, found: 723.892.

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