There is a simple scheme of synthesis of new chlorin photosensitizers (PS) based on chlorin e₆ 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, ¹H NMR spectroscopy and mass-spectrometry. The yields of compounds 2a-e and 3b-e were 60–75 %. It is necessary to note that chlorin e₆ 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 e₆ 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 e₆, synthesis, hydroxy derivatives, photodynamic therapy (PDT).

Синтез гидроксипроизводных хлорина е₆

О. И. Гущина, М. Ю. Гришина, Е. А. Ларкина, В. С. Лебедева, А. Ф. Миронов

Московский технологический университет (Институт тонких химических технологий), 119571 Москва, Россия

Осуществлён синтез гидроксипроизводных хлорина е₆ путём присоединения аминоспиртов к феофорбиду а и его метиловому эфиру. Гидроксиамидные производные хлорина е₆ 2а-е растворимы в щелочных водных растворах и являются перспективными агентами для ФДТ.

Ключевые слова: Хлорин е₆, 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 e₆ 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.[6-10] Following this idea alkylamides,[11,12] aminoamides,[13,14] and hydroxyamides[14,15] of chlorin e₆ 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

DOI: 10.6060/mhc161072g
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 respectively in the electronic spectrum.

The compounds obtained were purified by column chromatography and characterized by IR, 1H NMR spectroscopy. To demonstrate the purification efficacy and accuracy of the results the 1H 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 exipients. 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 ε6 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. 1H NMR spectra were recorded on a Bruker DPX-300 (Germany) in CDCl3, at 298 K. Chemical shifts were measured using signal at δ ppm: 1.65 (t, 3H, 8(2)-CH3); 1.73 (d, 3H, 18(1)-CH3); 2.52–2.05 (m, 4H, 17(1)-H, 17(2)-H); 1.17 (t, 3H, 8(2)-CH3). Mass-spectrum, m/z: calculated for [C13H11N2O4]+ 653.321, found: 653.154.

13(1)-N-(2-Hydroxymethyl)amidine-15(2)-methyl ester of chlorin ε6 (2a). Compound was obtained similarly to 2a. Yield 16 mg (47 %) from 30.3 mg of 1a. UV-Vis (CHCl3) λ max nm: 403.6; 502.1; 527.8; 663.3. 1H NMR (CDCl3) 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); 6.16 (dd, 1H, J=11.5 Hz, 3(1)-H); 4.88–4.46 (m, 2H 17(1)-H, 17(2)-H); 4.04–3.71 (m, 5H, 8(1)-CH3, 12(1)-CH3); 3.52–3.49 (s, 3H, 2(1)-CH3); 3.36–3.32 (m, 3H, 7(1)-CH3); 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)-CH3). Mass-spectrum, m/z: calculated for [C13H11N2O4]+ 653.321, found: 653.154.

13(1)-N-(2-Hydroxymethyl)amidine-15(2)-methyl ester of chlorin ε6 (2b). Compound was obtained similarly to 2a. Yield 16 mg (47 %) from 30.3 mg of 1a. UV-Vis (CHCl3) λ max nm: 403.6; 502.1; 527.8; 663.3. 1H NMR (CDCl3) 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); 6.16 (dd, 1H, J=11.5 Hz, 3(1)-H); 4.88–4.46 (m, 2H 17(1)-H, 17(2)-H); 4.04–3.71 (m, 5H, 8(1)-CH3, 12(1)-CH3); 3.52–3.49 (s, 3H, 2(1)-CH3); 3.36–3.32 (m, 3H, 7(1)-CH3); 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)-CH3). Mass-spectrum, m/z: calculated for [C13H11N2O4]+ 653.321, found: 653.154.

13(1)-N-(2-Hydroxymethyl)amidine-15(2)-methyl ester of chlorin ε6 (2c). Compound was obtained similarly to 2a. Yield 19 mg (53.5 %) from 31 mg of 1a. UV-Vis (CHCl3) λ max nm: 404.2; 500.9; 531.2; 663.0. 1H NMR (CDCl3) 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, 3(2)-H); 5.65 d. and 5.39 d. (1H each, J=11.5 Hz, 3(2)-H); 4.67–4.54 (m, 2H, 18, 18-H, 17-H); 3.97–3.75 (m, 4H, 13(2)-
Macroheterocycles / Macrocycles and Hybrids 10(1) 81-83

O. I. Gushchina et al.

13(1)-N-(2-Hydroxynaphthylnitroporphyrin)amide-15(2),17(3)-dimethyl ester of chlorin e₆ (3d). Compound was obtained similarly to 3b. Yield 25.4 mg (72.3 %) from 30.03 mg of 1b. UV-Vis (CHCl₃) λₘₐₓ nm: 403.3, 500.7, 528.5, 663.0. ¹H NMR (CDCl₃) δ ppm: 9.76 (s, 1H, 10-H); 9.31 (s, 1H, 15(6)-H); 8.89 (s, 1H, 17-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)-CH₂) 0.16 (dd, 1H, J = 11.5 Hz, 3(1)-CH); 5.55 d. and 5.26 d. (1H each, J = 18.84 Hz, 15(1)-CH₃); 4.50 (m, 1H, 18-H); 3.94 (s, 3H, 15(3)-CH); 4.39 (m, 1H, 17-H); 3.91–3.72 (4H, 13(2)-CH₃, 13(6)-CH-OH); 3.69–3.6 (m, 5H, 17(3)-CH₃); 3.55 (s, 3H, 12(1)-CH₃); 3.50 (s, 3H, 2(1)-CH₃); 3.33 (4H, 3(1)-CH₃); 2.11–2.63 (4H, 17(1)-CH₁, 17(2)-CH₂); 1.84 (m, 13(1), 18(1)-CH₁, 13(3), 5(5)-CH₃-CH₃, 8(2)-CH₂); 1.87 (br. s, 2H, 21-NH and 23-NH).

Yield 16.7 mg (69.7 %) from 20.08 mg of 1b. UV-Vis (CHCl₃) λₘₐₓ nm: 403.2, 502.7, 663.2. ¹H NMR (CDCl₃) δ ppm: 9.78 (s, 1H, 10-H); 9.72 (s, 1H, 5-H); 8.89 (s, 1H, 17-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)-CH₂); 6.18 (dd, 1H, J = 11.5 Hz, cis-3(2)-CH₂); 5.36 d. and 5.32 d. (1H each, J = 18.49 Hz, 15(1)-CH₃); 4.51 (m, 1H, 18-H); 4.39 (m, 1H, 17-H); 3.95–3.72 (4H, 15(1)-CH₃, 17(2)-CH₂-OH); 3.81 (s, 3H, 15(3)-CH₃); 3.70–3.6 (m, 5H, 17(3)-CH₃); 3.63 (s, 3H, 12(1)-CH₃); 3.57 (s, 3H, 2(1)-CH₃); 3.35 (4H, 3(1)-CH₃); 2.3 (s, 21-H); 2.0–2.7 (4H, 17(1)-CH₁, 17(2)-CH₂); 1.89–1.41 (14H, 17(1)-CH₁, 13(3), 5(5)-CH₃-CH₃, 8(2)-CH₂); 1.87 (br. s, 2H, 21-NH and 23-NH). Mass-spectrum, m/z: calculated for [CH₂N₃O₇]⁺ 723.399, found: 723.892.

Acknowledgements. The work was financially supported by the RFSc project №16-33-10092.

References


Received 25.10.2016
Revised 11.01.2017
Accepted 14.01.2017