Novel pH–Independent Amphiphilic Chlorophyll a Derivatives with Oligoethylene Glycol Substituents as a Hydrophilic Part: Synthesis and Hydrophilicity Estimation

D. V. Belykh,@ O. M. Startseva, and S. A. Patov

Institute of Chemistry, Komi Scientific Center, Ural Division, Russian Academy of Sciences, 167982 Syktyvkar, Russia
@Corresponding author E-mail: belykh-dv@chemi.komisc.ru, belykh-dv@mail.ru

Several novel pH-independent amphiphilic chlorophyll a derivatives with oligoethylene glycol substituents as a hydrophilic part were synthesized, and hydrophilicity estimation was carried out using their mobility on reverse phase HPLC data. It was shown, that the oligoethylene glycol substituent insertion significantly increases the hydrophilicity of the whole molecule. The most important structural factors affecting hydrophilicity are the presence or absence of the exocycle (exocycle opening results in hydrophobicity decrease in case of the same length oligoethylene glycol chain), and the position of the oligoethylene glycol substituent (increase in length of the spacer between the macrocycle and oligoethylene glycol substituent leads to increase in hydrophilicity). Oligoethylene glycol chain elongation does not lead to appreciable increase in hydrophilicity. So more available di-, tri- and tetaethylene glycols may be used for chlorophyll a derivatives hydrophilization instead of the less available penta- and hexamers.

Keywords: Chlorophyll a derivatives, methylpheophorbide a, chlorin e₆, photosensitizes, hydrophilicity, oligoethylene glycol.

Новые рН–независимые амфифильные производные хлорофилла а с фрагментами олигоэтиленгликолей в качестве гидрофильной части: синтез и оценка гидрофильности

Д. В. Белых,@ О. М. Старцева, С. А. Патов

Институт химии Коми научного центра Уральского отделения Российской академии наук, 167982 Сыктывкар, Россия
@E-mail: belykh-dv@chemi.komisc.ru, belykh-dv@mail.ru

Синтезирован ряд новых pH-независимых амфифильных производных хлорофилла а с фрагментами олигоэтиленгликолей в качестве гидрофильной части и выполнена оценка гидрофильности полученных соединений на основе данных об их хроматографической подвижности на обращенной фазе. Показано, что внедрение олигоэтиленгликолевого фрагмента значительно увеличивает гидрофильность молекулы в целом. Из структурных факторов наиболее сильно влияет наличие/отсутствие экзоцикла (размыкание экзоцикла приводит при одинаковой длине олигоэтиленгликольной цепочки к уменьшению гидрофобности), а так же положение олигоэтиленгликолевого фрагмента (увеличение длины спейсера между фрагментом олигоэтиленгликолей и макроциклом приводит к повышению гидрофильности). Удлинение олигоэтиленгликольной цепочки не приводит к заметному увеличению гидрофильности. В связи с этим для гидрофилизации производных хлорофилла а можно использовать более доступные ди-, три- и тетраэтиленгликоли вместо менее доступных пента- и гексамеров.

Ключевые слова: Производные хлорофилла а, метилфенофобид а, хлорин e₆, гидрофильность, фотосенсибилизаторы, олигоэтиленгликоль.
Novel Amphiphilic Chlorophyll \(a\) Derivatives with Oligoethylene Glycol Substituents

Introduction

It is known that chlorophyll \(a\) derivatives are intensively investigated as photosensitizers (PS) for photodynamic therapy (PDT) in various fields of medicine (oncology,\[^{14}\] otolaryngology,\[^{7,8}\] ophthalmology,\[^{9,10}\] surgery,\[^{11}\] treatment of fungal diseases\[^{12}\]). Some of them have been already used in clinical practice.\[^{1-3}\] The formation of amphiphilic properties of chlorin PS molecule enhances photodynamic action through more effective interaction of PS with cell membranes, that increases the efficiency of PDT in many cases.\[^{13,14}\] Taking into account that the porphyrin macrocycle is hydrophobic the hydrophilic moieties introduction to the macrocycle periphery is of great interest. The oligoethylene glycol substituents (where the number of ethylene glycol units varies from 2 to 6) were used as hydrophobic moiety here. There is only fragmentary information about such derivatives with di- or triethylene glycol substituents.\[^{15-18}\] And the influence of the structure of these compounds on the hydrophilicity was not studied systematically. Here we report the synthesis of several phorbines (6-21) and chlorins (22-32) with di-, tri-, tetra-, penta- and hexaethylene glycol substituents using methyl pheophorbide \(a\) (1) and its derivatives (2-5) as an initial material (Scheme 1). The influence of the oligoethylene glycol chain length, its position at the macrocycle periphery and the structure of macrocycle on the hydrophilicity of compounds obtained was estimated using their mobility on the reverse phase HPLC data.

Experimental

\(^1\)H NMR spectra were recorded in CDCl\(_3\) on spectrometer Bruker Avance II (working frequency 300 MHz). IR spectra were recorded on spectrometer Shimadzu IR Prestige 21 in KBr (diffuse reflection). HPLC was carried out by Thermo finnigan surveyor (PDA) instrument, pump with auto assembler, Hypersil C18 column 100×2/1 mm, temperature 22°C, gradient elution (from a mixture of 1% aqueous trifluoroacetic acid-methanol, 40:60 by volume, to pure methanol for 50 min, flow rate 0.4 ml/min). UV-Vis detection was realized at 400 nm. Mass spectra were obtained by Thermo finnigan LCQ Flut (ESI) instrument. UV-Vis spectra were recorded on spectrometer Shimadzu UV-1700 (PharmaSpec) in CHCl\(_3\), in 200-1100 nm range in 10 mm quartz cuvettes, using CHCl\(_3\) as comparison sample. Monitoring the reaction proceeding was performed by TLC on Silufol plates, eluent – CC\(_4\)-acetone (4:1 vol). Column chromatography was carried out using silica gel Alfa Aesar 70/230\(\mu\). Methyl pheophorbide \(a\) (1) was obtained according to\[^{19}\]. Methyl pyropheophorbide \(a\) (2) and chlorin \(e_6\)\(13\)-(1-)-N-methylamide-\(15,17\)-dimethyl ester (4) was obtained according to\[^{20}\].

i: collidine, reflux, 30-40 min; ii: \(\text{CH}_3\text{NH}_2/\text{H}_2\text{O}, \text{THF}, \text{r.t.}, 1-2\) h; iii: \(\text{H}_2\text{O}-\text{HCl/acetone}; \) iv: \(\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{OCH}_2\text{OH} (n = 1-3), \) \(\text{H}_2\text{SO}_4(\text{conc}), \text{r. t.} 12-16\) h; v: \(\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{OCH}_2\text{OH} (n = 4, 5), 2\)-chloro-\(\text{N}\)-methylpyridinium iodide, DMAP, \(\text{THF}, \text{reflux} 1-2\) h.

![Scheme 1](image)

\(n = 1 \ (6, 11, 14, 19, 22, 27, 30); \ n = 2 \ (7, 12, 15, 20, 23, 28, 31); \ n = 3 \ (8, 13, 16, 21, 24, 29, 32); \ n = 4 \ (9, 17, 25); \ n = 5 \ (10, 18, 26)\)

Макрогетероциклы / Macroheterocycles 2014 7(4) 401-413
Trans-esterification of the ester group at position 13(2) of the starting compound — methylpyridinium iodide in 5 ml of toluene for 3 hours at full conversion of the starting compound. Mass spectrum (ESI) m/z: for MH (C_{51}H_{48}N_{15}O_{3}) calculated 725.3, found 725.3; for M-n-CH (C_{50}H_{47}N_{15}O_{2}) calculated 747.3 found 747.5. UV-Vis (CHCl_3) \( \lambda \text{nm} \) (relative intensity, %): 468 (66.6%), 611 (51.9%), 538 (10.5%), 507 (11.2%), 414 (100%).

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH]. Trans-esterification of the ester group at position 13(2) of the starting compound — methylpyridinium iodide in 5 ml of toluene for 3 hours at full conversion of the starting compound. Mass spectrum (ESI) m/z: for MH (C\(_{51}\)H\(_{48}\)N\(_{15}\)O\(_{3}\)) calculated 725.3, found 725.3; for M-n-CH (C\(_{50}\)H\(_{47}\)N\(_{15}\)O\(_{2}\)) calculated 747.3 found 747.5. UV-Vis (CHCl\(_3\)) \( \lambda \text{nm} \) (relative intensity, %): 468 (66.6%), 611 (51.9%), 538 (10.5%), 507 (11.2%), 414 (100%).

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH].

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH].

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH].

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH].

**Methyl pheophorbide a 13(2) triethylene glycol ester (7).** 7.37 mg (67%) of compound 7 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to \( \lambda \text{nm} \). The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue after evaporation was chromatographed on silica gel (eluent: CCl\(_4\)-acetone from 1:0 to 1:1). The eluate containing the major product was evaporated. 25.2 mg (42%) of compound 3 was obtained as dark-blue crystals. Spectral data of the compound obtained are identical to those described in^2^1^. H NMR (CDCl\(_3\), 300 MHz) \( \delta \) ppm: 9.73 s (1H, H\(^\beta\)), 8.83 s (1H, H\(^\beta\)), 8.12 dd [1H, 3-(CH=CH\(_2\))], 1.45 s [3N, III-NH].
Макрогетероциклы / Macroheterocycles

<table>
<thead>
<tr>
<th>Номер строки</th>
<th>Содержание</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.36 t (2H, 13(2)-COOC_CHO_CHO_CHO_CHO_CHO_OH), 3.36 t (2H, 13(2)-COOC_CHO_CHO_CHO_CHO_OH, J 4.4 Hz), 3.82-3.64 m 5H and 3.57-3.41 m 4H [8-(CH_2_CH_2]</td>
</tr>
<tr>
<td>2</td>
<td>Methyl phosphorib a 13(2) pentaethylene glycol ester (10). 66.7 mg (47%) of compound 10 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to 'H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of I, 0.5 mg (0.991 mmol) of tetraethylene glycol, 60.0 mg (0.491 mmol) of DMAP and 60.0 mg (0.317 mmol) of 2-chloro-N-methylpyridinium iodide in 5 ml of toluene for 3 hours at full conversion of the starting compound I. Mass-spectrum (ESI) m/z: for MH(^+) (C(<em>{47})H(</em>{61})N(<em>4)O(</em>{11})), 681.4, found 681.3 (M(<em>{\text{calc}}) = 681.4), 641.3 (M(</em>{\text{calc}}) = 641.3), 601.2 (M(<em>{\text{calc}}) = 601.2), 561.1 (M(</em>{\text{calc}}) = 561.1), 521.0 (M(<em>{\text{calc}}) = 521.0), 481.9 (M(</em>{\text{calc}}) = 481.9), 441.8 (M(<em>{\text{calc}}) = 441.8), 401.7 (M(</em>{\text{calc}}) = 401.7), 361.6 (M(<em>{\text{calc}}) = 361.6), 321.5 (M(</em>{\text{calc}}) = 321.5), 281.4 (M(<em>{\text{calc}}) = 281.4), 241.3 (M(</em>{\text{calc}}) = 241.3), 201.2 (M(<em>{\text{calc}}) = 201.2), 161.1 (M(</em>{\text{calc}}) = 161.1), 121.0 (M(<em>{\text{calc}}) = 121.0), 81.0 (M(</em>{\text{calc}}) = 81.0), 41.0 (M(_{\text{calc}}) = 41.0).</td>
</tr>
<tr>
<td>3</td>
<td>Novel Amphiphilic Chlorophyll a Derivatives with Oligoethylene Glycol Substituents</td>
</tr>
</tbody>
</table>
mixture was chromatographed on silica gel (eluent: CC13-acetone from 70:1 to 2:1). The eluate containing the major product was evaporated and residue after evaporation was re-purified from chloroform-hexane mixture.

**Phytophora b 17-diethylenglycol ester (II).** 57.1 mg (51%) of compound 11 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 6:1 according to 1H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 100 mg (0.165 mmol) of 1H in a mixture of 10 ml of diethyl glycol, 0.3 ml of concentrated sulfuric acid and 2 ml of chloroform for 19 hours at complete conversion of starting compound 1. Mass-spectrum (ESI) m/z: for MH+ (C13H18N4O7) calcd. 618.3, found 618.3. UV-Vis (CHCl3) λ nm (relative intensity, %): 686 (45.1%), 611 (9.5%), 538 (11.2%), 508 (12.1%), 414 (100%). IR (KBr) cm-1: 3464 (ν OH), 3395 (ν NH of chlorin cycle); 2957 (ν2 CH3); 2926 (ν3 CH3); 2780 (ν3 CH3); 2739 (ν3 CH3; O-glycol); 1736 (ν CO, ester); 1697 (ν 2 CO, exo cycle); 1616 (schlorin bands). 1H NMR (CDCl3, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.54 s (1H, H8), 9.40 s (1H, H9), 8.60 s (1H, H10), 8.01 dd (1H, 3-J, J 17.6 and 11.4 Hz), 6.32 dd (1H, 2-J, J17.6 Hz), 5.92 s (1H, H11, H14 Hz), 4.50 q (1H, H3, J7.3 and 1.5 Hz), 4.27 br.d (1H, H12, J7.9 and 2.2 Hz), 4.21-4.05 m [2H, 17-CH2COOCH2CH(OH)CH2OCH(OH)], 3.91 s (3H, 13(2)-COOC2H5), 3.72 s (3H, 12-CH3), 3.44 s (3H, 2-CH2), 3.25 s (3H, 7-CH3), 3.38-3.36 m (6H, 8-CH3, 17-CH3COOCH2CH(OH)CH2OCH(OH)), 2.75-2.59 m (2H, 17-CH2COOCH2CH(OH)CH2OCH(OH)), 2.48-2.34 and 2.32-2.19 (both m 1H, 17-CH2COOCH2CH(OH)CH2OCH(OH)), 1.86 s (3H, 18-CH3, J7.3 Hz), 1.72 s (1H, 8-CH3, J7.3 Hz). 1.58 br.s (1H, 13(2)-S diastereomer).

Phytophthora b 17-triethylenglycol ester (II) 21.7 mg (36%) of compound 12 (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 2:1 according to 1H NMR) as a dark blue-black crystalline was obtained with transesterification of 50 mg (0.082 mmol) of 1 in a mixture of 3 ml of triethyl glycol, 0.2 ml of concentrated sulfuric acid for 20 hours at complete conversion of starting compound 1. Mass-spectrum (ESI) m/z: for MH+ (C14H20N4O10) calcd. 725.4, found 725.3. UV-Vis (CHCl3) λ nm (relative intensity, %): 668 (45.8%), 610 (8.9%), 538 (10.4%), 508 (11.1%), 414 (100%). IR (KBr) cm-1: 3464 (ν OH), 3393 (ν NH of chlorin cycle); 2957 (ν2 CH3); 2926 (ν3 CH3); 2780 (ν3 CH3); 2739 (ν3 CH3; O-glycol); 1736 (ν CO, ester); 1695 (ν 2 CO, exo cycle); 1616 (schlorin bands). 1H NMR (CDCl3, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.51 s (1H, H8), 9.36 s (1H, H9), 8.54 s (1H, H10), 8.05-7.94 m (1H, 3(1)-H), 6.34 (d 1H, 3(2)-H, J 11.7 Hz), 6.20 s (1H, J 11.7 Hz), 4.53 brq (1H, H3, J7.2 Hz), 4.34 br.t (1H, H12, J 7.7 Hz), 4.21-4.05 m [2H, 17-CH2COOCH2CH(OH)CH2OCH(OH)], 3.87 s (3H, 13(2)-COOC2H5), 3.71 s (3H, 12-CH3), 3.42 s (3H, 2-CH2), 3.24 s (3H, 7-CH3), 3.82-3.36 m [8H [8-CH2CH3]], 17-CH2COOCH2CH(OH)CH2OCH(OH)), 2.75-2.49 m (2H, 17-CH2COOCH2CH(OH)CH2OCH(OH)), 2.48-2.34 and 2.32-2.19 (both m 1H, 17-CH2COOCH2CH(OH)CH2OCH(OH)), 1.86 s (3H, 18-CH3, J 17.3 Hz), 1.72 s (1H, 8-CH3, J 7.3 Hz), 0.67 br.s (1H, 13(2)-S diastereomer).
Novel Amphiphilic Chlorophyll a Derivatives with Oligoethylene Glycerol Substituents

3H (17-CH₂CHOOCOCH₂CH₂OCH₂CHOH), 3H 3.53 t (2H, 17-CH₂CHOOCOCH₂CH₂OCH₂CHOH, J 4.4 Hz), 2.85-2.55 m (2H, 17-CH₂CHOOCOCH₂CH₂OCH₂CHOH), 2.45-2.29 m (2H, 17-CH₂CHOOCOCH₂CH₂OCH₂CHOH), 1.86 d (3H, 18-CH₃, J 7.3 Hz), 1.73 t (3H, 8-CH₂CH₃, J 7.3 Hz), 0.48 brs (1H, 1-I-NH), -1.63 brs (1H, III-NH).

Phytophthora 17-β-lactam glucoside (15): 35.5 mg (29%) yield was obtained as a dark blue-black crystalline powder. It was obtained by transesterification of 100 mg (0.182 mmol) of 2 in a mixture of 5 ml of triethylene glycol, 0.25 ml of concentrated sulfuric acid for 18 hours at complete conversion of starting compound 2.

Mass-spectrometry (ESI): m/z for MH⁺ (C₄₂H₅₁N₄O₁₁⁺) calcld. 843.4, found 843.3. UV-Vis (CHCl₃): λ nm (%): 668 (44.9%), 610 (9.7%), 538 (11.4%), 507 (12.9%), 414 (100%). IR (KBr cm⁻¹): 3458 (v OH); 3393 (v NH of chloroform); 2959 (v₃(CH₃)); 2872 (v₃(CH₃)); 2736 (v₃(CH₃)-O, glycol); 1736 (v C-O, ester); 1697 (v CH2-CH2); 1607 (v NH) Hz.

Phytophthora 17-β-lactam glucoside (16): 37.7 mg (28%) of compound 16 as a dark blue-black crystalline powder was obtained with transesterification of 100 mg (0.182 mmol) of 2 in a mixture of 5 ml of triethylene glycol, 0.25 ml of concentrated sulfuric acid for 18 hours at complete conversion of starting compound 2.

Mass-spectrometry (ESI): m/z for MH⁺ (C₄₆H₅₉N₄O₁₁⁺) calcld. 843.4, found 843.3. UV-Vis (CHCl₃): λ nm (%): 668 (44.9%), 610 (9.7%), 538 (11.4%), 507 (12.9%), 414 (100%). IR (KBr cm⁻¹): 3458 (v OH); 3393 (v NH of chloroform); 2959 (v₃(CH₃)); 2872 (v₃(CH₃)); 2736 (v₃(CH₃)-O, glycol); 1736 (v C-O, ester); 1697 (v CH2-CH2); 1607 (v NH) Hz.

Phytophthora 17-β-lactam glucoside (17): 46.0 mg (42%) of compound 17 (13,2-diastereomers mixture, 13-2/12-3: S 7:1 according to 'H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 50 mg (0.095 mmol) of 7 in a mixture of 5 ml of triethylene glycol, 0.25 ml of concentrated sulfuric acid for 18 hours at complete conversion of starting compound 7. Mass-spectrometry (ESI): m/z for MH⁺ (C₄₆H₅₉N₄O₁₁⁺) calcld. 843.4, found 843.3. UV-Vis (CHCl₃): λ nm (%): 668 (44.9%), 610 (9.7%), 538 (11.4%), 507 (12.9%), 414 (100%). IR (KBr cm⁻¹): 3458 (v OH); 3393 (v NH of chloroform); 2959 (v₃(CH₃)); 2872 (v₃(CH₃)); 2736 (v₃(CH₃)-O, glycol); 1736 (v C-O, ester); 1697 (v CH2-CH2); 1607 (v NH) Hz.
(0.099 mmol) of 8 in 5 ml of tetrahydrofuran glycol, 0.25 ml of concentrated sulfuric acid for 19 hours at complete conversion of starting compound 8. Mass-spectrum (ESI) m/z: for MH\(^+\) ([C\(_{53}H_57N_6O_9\)]). 931.5, found 931.5; for MNA\(^+\) ([C\(_{53}H_57N_6O_9\)] Na) calc'd 953.5, found 953.4; for MK\(^+\) ([C\(_{53}H_57N_6O_9\)] K) calc'd 969.4, found 969.3. UV-Vis (CHCl\(_3\)) \(\lambda\) nm (relative intensity, %): 669 (41.5%), 612 (8.3%), 535 (11.6%), 414 (100%). IR (KBr) cm\(^{-1}\): 3385 (ν OH, 3H, 17-CH\(_2\)COOCH), 3377 (ν OH, 3H, 17-CH\(_2\)COOCH), 3340 (ν OH, 3H, 15-CH\(_2\)COOCH), 3293 (ν OH, 3H, 15-CH\(_2\)COOCH), 3287 (ν CH\(_2\)), 2736 (ν CH\(_2\), -glycol), 1734 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 (ν C=O, "amide I"); 1616 (ν C=O, "chlorin band").

**Chlorin e\(13(1)-\)N-methylamidine-17-methyl-15-triethylene glycol ester (23).** 38.7 mg (74%) of compound 23 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous dimethylglycol solution (1 ml) on 50 mg (0.069 mmol) of compound 7 in 5 ml of THF for 20 min at complete conversion of starting compound 7. Mass-spectrum (ESI) m/z: for MH\(^+\) ([C\(_{53}H_57N_6O_9\)] Na) calc'd 756.4, found 756.3. UV-Vis (CHCl\(_3\)) \(\lambda\) nm (relative intensity, %): 662 (30.8%), 607 (3.8%), 501 (9.9%), 403 (100%). IR (KBr) cm\(^{-1}\): 3380 (ν OH, 309) 3393 (ν NH of chlorin cycle); 2868 (ν CH\(_3\)); 2737 (ν CH\(_3\), -glycol). 1734 (ν C=O, ester); 1651 (ν C=O, "amide I"); 1549 ("amide-II"); 1551 ("amide-III"). NMR (CDCl\(_3\)), 300 MHz) \(\delta\) ppm: 9.74 s (1H, H\(^5\)), 9.69 s (1H, H\(^8\)), 8.18 s (1H, H\(^9\)), 8.13 dd (1H, 3=CH, J \(=\) 18.0 and 11.4 Hz), 7.16-7.04 m (4H, 17-CONFC\(_3\)), 6.40-6.35 m (4H, 17-CONFC\(_3\)), 4.51 q (1H, Н, J \(=\) 7.3 Hz), 4.44 br.d (1Н, Н, J \(=\) 7.3 Hz), 1.72 d (3H, 18-CH\(_3\)), -1.61 brs (1H, 1-NH), -1.32 brs (1H, 3-NH).

**Chlorin e\(13(1)-\)N-methylamidine-17-methyl-15-tetraethylene glycol ester (24).** 33.5 mg (62%) of compound 24 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous dimethylglycol solution (1 ml) on 50 mg (0.065 mmol) of compound 8 in 5 ml of THF for 20 min at complete conversion of starting compound 8. Mass-spectrum (ESI) m/z: for MH\(^+\) ([C\(_{53}H_57N_6O_9\)] Na) calc'd 800.4, found 800.3, for МNa\(^+\) ([C\(_{53}H_57N_6O_9\)] Na) calc'd 822.4, found 822.4. UV-Vis (C\(_44\)H\(_58\)N\(_5\)O\(_9\)) \(\lambda\) nm: 662 (30.8%), 607 (3.8%), 501 (9.9%), 403 (100%). IR (KBr) cm\(^{-1}\): 3380 (ν OH, 309); 3393 (ν NH of chlorin cycle); 2868 (ν CH\(_3\)); 2737 (ν CH\(_3\), -glycol); 1734 (ν C=O, ester); 1651 (ν C=O, "amide I"); 1549 ("amide-II"); 1551 ("amide-III"). NMR (CDCl\(_3\), 300 MHz) \(\delta\) ppm: 9.75 s (1H, H\(^5\)), 9.70 s (1H, H\(^8\)), 8.18 s (1H, H\(^9\)), 8.45 dd (1H, 3=CH, J \(=\) 18.3 and 11.7 Hz), 7.47-7.34 m (4H, 17-CONFC\(_3\)), 6.40 (4H, 17-CONFC\(_3\)), 4.51 (4H, 17-CONFC\(_3\)), 3.52-3.09 m (6H, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH), 2.65-2.02 m (4H, 17-CONFC\(_3\)), 1.70-1.06 m (5H, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH, 15-CH\(_2\)COOCH), 1.75 t (3H, 8-CH\(_3\)), -1.61 brs (1H, 1-NH), -1.18 brs (1H, 3-NH).

**Chlorin e\(13(1)-\)N-methylamidine-17-methyl-15-tetraethylene glycol ester (25).** 36.8 mg (71%) of compound 25 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous dimethylglycol solution (1 ml) on 50 mg (0.062 mmol) of compound 9 in 5 ml of THF for 20 min at complete conversion

---

D. V. Belykh et al.
of starting compound 9. Mass-spectrum (ESI) m/z: for MH⁺ (C_{42}H_{53}N_{5}O_{8}Na) calcld. 864.4 found 865.4, for MNa⁺ (C_{42}H_{52}N_{5}O_{8}Na) calcld. 882.4 found 882.3. UV-Vis (CHCl₃) λ nm (relative intensity, %): 656 (32.2%), 602 (4.9%), 498 (11.0%), 398 (100%). IR (KBr) cm⁻¹: 3380 (vOH), 3309 (vNH of chlorine cycle); 2925 (v_C≡N CH₂), 2868 (v_C=N CH_{2}-O-, glycol), 1732 (v C=O, ester); 1651 (v C=O, cis, 13-CONH₂); 1545 (vamide-I), 1501 (chlorbion band); 1410 (v(C=O), 12.0 Hz), 8.62 s (1H, 3-CH_{2}CH=O), 3.30 d (3H, 13-CONH₂, J 4.3 Hz), 3.19-2.79 m (18H, 15-СН₂CH₂COO⁻), 2.62-2.00 m (4H, 17-CH₂CH=O(OH), 1.76 t (3H, 8-CH₂ CH=O), J 7.7 Hz), 1.72 d (3H, 18-CH₃, J 7.0 Hz), -1.63 brs (1H, 1-NH), -1.85 brs (1H, III-NH).

Chlorin e₁₁(11-)N-methylamide-17-methyl-15-hexaethyleneglycol ester (26). 29.5 mg (57%) of compound 26 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methanol solution (1 ml) on the 50 mg (0.058 mmol) of compound 10 in 5 ml of THF for 20 min at complete conversion of starting compound 10. Mass-spectrum (ESI) m/z: for MH⁺ (C_{40}H_{50}N_{5}O_{7}Na) calcld. 765.0 found 765.4, for MNa⁺ (C_{40}H_{49}N_{5}O_{7}Na) calcld. 787.4 found 787.8, for MCl⁺ (C_{40}H_{48}N_{5}O_{7}Cl) calcld. 794.3 found 794.3. UV-Vis (CHCl₃) λ nm (relative intensity, %): 663 (31.6%), 605 (5.4%), 500 (11.7%), 402 (100%). IR (KBr) cm⁻¹: 3382 (v OH), 3307 (v NH of chlorin cycle); 2925 (v_C=O CH₂), 2866 (v_C=N CH₂), 2733 (v_C=O CH₂-O, -glycol); 1734 (v C=O, ester); 1647 (v C=O, amide-I), 1601 (chlobion band); 1551 (vamide-II). 

Chlorin e₁₁(11-)N-methylamide-15-methyl-17-tetraethyleneglycol ester (29). 10.3 mg (21%) of compound 29 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methanol solution (1 ml) on the 20 mg (0.026 mmol) of compound 13 in 3 ml of THF for 1 h at complete conversion of starting compound 13. Mass-spectrum (ESI) m/z: for MH⁺ (C_{40}H_{50}N_{5}O_{7}Na) calcld. 880.4, found 880.3, for MNa⁺ (C_{40}H_{49}N_{5}O_{7}Na) calcld. 883.4 found 883.4, for MCl⁺ (C_{40}H_{48}N_{5}O_{7}Cl) calcld. 887.4. UV-Vis (CHCl₃) λ nm (relative intensity, %): 663 (31.6%), 605 (5.4%), 500 (11.7%), 402 (100%). IR (KBr) cm⁻¹: 3382 (v OH), 3306 (v NH of chlorin cycle); 2925 (v_C=O CH₂), 2866 (v_C=N CH₂), 2735 (v_C=O CH₂-O, -glycol); 1734 (v C=O, ester); 1651 (v C=O, amide-Ib), 1601 (chlobion band); 1549 (vamide-Ilink).
crystalline powder was obtained by the action of 33% aqueous methanol solution (1 ml) on the 30 mg (0.040 mmol) of compound 19 in 3 ml of THF for 1 h at complete conversion of starting compound 19. Mass-spectrum (ESI) m/z: for MH⁺ (C₁₇H₂₇N₅O₃) calcd. 386.4, found 386.3. UV-Vis (CHCl₃) λ nm (relative intensity, %): 231 (94%), 310 (52%), 350 (22%). (IR) KBr cm⁻¹: 3392 (v O-H), 2960, 2926, 2855 (v C-H).

3.1 Hz), 3.85 q (2H, 8-СН₂, 4.8 Hz), 2.59-2.22 m (4Н, 17-СН₂), 4.54 q (1Н, Н, 3-CH=CH₂, 4.50 q (1Н, Н, 3-CH=CH₂, 5.17 Hz), 3.92 (s, 2H, 8-CH₂, 5.7 Hz), 3.64-3.30 m 22H and 3.11-2.82 m 8H (17-CН₂C=O, 15-CH=CH₂, 17-СН₂), 1.72 t (3H, 8-CH₂, 7.7 Hz), 1.70 d (3H, 18-CH₂, 7.7 Hz), -1.76 brs (1H, 1-NH), -1.90 brs (1H, III-NH).

Pyropheophorbide a 17-pentaethylene glycol ester (17). To a solution of 30.0 mg (0.055 mmol) of pyropheophorbide a (3) in 5 ml of chloroform 15.0 mg of DMAP, 18.1 mg 2-chloro-N-methylpyridinium iodide and 0.1 ml of pentaethylene glycol was added. The mixture was boiled under reflux for 1 h. The reaction was monitored by TLC (eluent: CC1₃-acetone = 1:1). The reaction mixture was diluted with 50 ml chloroform, transferred to a separatory funnel and washed with 5-10% hydrochloric acid for removing of DMAP and 2-chloro-N-methylpyridinium iodide excess. And then hydrochloric acid was washed by distilled water until neutral reaction of wash waters. The resulting solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure at 40-50 °C. The residue after evaporation was chromatographed on silica gel (eluted with CC1₃-acetone in ratios ranging from 3:1 to 1:1). The fraction containing the basic substance was evaporated and precipitated with hexane. 15 mg (36%) of compound 17 was obtained. Mass-spectrum (ESI) m/z: for MH⁺ (C₄₃H₅₅N₄O₉) calcd. 774.4, found 774.4, (МК + Na) calcd. 821.4, found 821.5, МК Na) calcd. 786.4, found 785.3. UV-Vis (СНCl₃) λ nm (relative intensity, %): 668 (46.9%), 611 (9.3%), 538 (10.7%), 414 (100%).

Chlorin e (13)-N-methylamide 15,17-bis(triethylene glycol) ester (32). 15 mg (46%) of compound 31 as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methanol solution (1 ml) on the 30 mg (0.040 mmol) of compound 20 in 3 ml of THF for 1 h at complete conversion of starting compound 20. Mass-spectrum (ESI) m/z: for MH⁺ (C₁₆H₂₃N₄O₇) calcd. 384.0, found 383.3. UV-Vis (CH₂Cl₂) λ nm (relative intensity, %): 236 (90%), 320 (58%), 350 (20%). (IR) KBr cm⁻¹: 3392 (v O-H), 3230 (v N-H), 2960, 2929, 2855 (v C-H).

В. Д. Белях et al.
Novel Amphiphilic Chlorophyll a Derivatives with Oligoethylene Glycol Substituents

2-CH₃, 3.78-3.46 m (24H, 8-CH₂), CH₂CH₂COOCH₂CH₂O(CH₂OH)₂, CH₂CH₂O(CH₂OH)₂, 3.24 s (3H, 7-CH₃), 2.83-2.57 m [2H, 17-CH₂CH₂COOCH₂(CH₂OCH₂)₂CH₂OH], 2.44-2.29 m (2H, 17-CH₂CH₂COOCH₂(CH₂OCH₂)₂CH₂OH), 1.86 d (3H, 18-CH₂, J 7.0 Hz), 1.73 t (8-CH₂, J 7.3 Hz), 0.43 br.s (1H, I-NH), -1.67 br.s (1H, III-NH).

Results and Discussion

The transesterification reaction of the ester groups at positions 17 and 13(2) (under acid catalysis and with the activation of 2-chloro-N-methylpyridinium iodide, respectively) and the esterification of the carboxyl group at position 17 were used for insertion of oligoethylene glycol substituent’s to the macrocycle periphery (compounds 6-32, Scheme 1). The transformation of phorbins to chlorins was carried out by exocyclic opening under the action of methylamine. The structure of the compounds obtained was confirmed using IR, UV-Vis and NMR spectroscopy and mass spectrometry data. The insertion of oligoethylene glycol substituent leads to a decrease in the chromatographic mobility on normal phase (TLC Silufol) compared with the both initial ester and carboxylic acid derivatives. The peaks of protonated molecular ions and, in many cases, the peaks of sodium and potassium adduction cations of compounds 6-32 are observed in mass spectra (ESI). The oligoethylene glycol fragment is manifested in the IR spectrum as a weak band at 2730-2750 cm⁻¹ region, this band corresponds to the stretching vibrations of the methylene group linked to the etheric oxygen atom C-H bond. In the ¹H NMR spectra the oligoethylene glycol fragments appear as multiplets at the regions of 4.60-4.00 and 3.90-3.00 ppm, typical for the methylene protons near the ester, alcohol and ether oxygen atoms. The trans-esterification of the ester group leads to absence of the corresponding methyl singlet in the ¹H NMR spectrum of the product that allows to distinguish methoxyl substitution at the positions 13(2) and 17. Chemical shifts of these proton signals in the methyl phosphoribide ¹H NMR spectra differ significantly from each other and, at the same time, slightly change during the transition from one to another derivative. So the ester methyl group signals can provide a reliable source of information about the direction of the reaction (see Figure 1, which presents the ¹H NMR spectra of methylphosphoribide a (1) and its diethylen glycol esters (6 and 11) with different positions of glycol substituent as an example). The investigation of ¹H NMR spectra of all 13(2)-carbomethoxy derivatives shows that all of them are 13(2) diastereomer mixture with a significant prevalence of 13(2)-R diastereomer.

Opening of phorbin derivatives exocycle is manifested in the IR and NMR spectra by the same way as more simple derivatives we have observed previously.[22-26] In the IR spectra of chlorin e₅ derivatives 22-32 the 13(1)-keto group absorption band about 1700 cm⁻¹ is absent and absorption bands of amide groups (“amide-I” in the region of 1640-1650 cm⁻¹ and “amide-II” in the region 1530-1550 cm⁻¹) are present. The singlet of the proton in position 13(2) at 6.25-6.35 ppm is absent and the signals of protons of the methylene group which is formed by opening exocycle (AB multiplet system at 5-6 ppm region) as well as the methylamide group proton signals (broad quartet or unresolved multiplet of NH proton and doublet of the methyl moiety) are observed in the ¹H NMR spectra of compounds 22-32. Preparation of di-, tri- and tetrachlorophyll glycol 17-esters was carried out by the action of the corresponding diol excess on the corresponding 17-methyl ester at presence of sulfuric acid. Di-, tri- and tetrachlorophyll glycol acted simultaneously as a reactant and a solvent. In the case of derivatives 1-3, the solubility of which in a mixture of sulfuric acid and oligoethylene glycol is low, a small amount of chloroform was added to reaction mixture up to the complete dissolution of the starting chlorin precipitate. As a result, the trans-esterification of the ester group at the 17-position substituent to form the target products takes place. Exocycle ester group trans-esterification does not occur under these conditions. Esterification of chlorins 3 and 5 carboxy group by penta- and hexaethyleneglycol, stimulated by 2-chloro-N-methylpyridinium iodide as activating agent, was used for corresponding esters synthesis because of low availability of penta- and hexaethyleneglycols.[27-32] The corresponding derivatives were obtained in the case of pyropheophorbide a. Under the action of penta- and hexaethyleneglycol on chlorin 5 at the same conditions, there was a formation of a complex mixture of unidentified compounds, but the target products were not obtained. The same activating agent was also used by us to synthesize 13(2) ethers and methylphorphoribides 6-10 with the di-, tri-, tetra-, penta- and hexaethyleneglycol fragments: it is known that the ester group exocycle methylphorphoribide has a relatively high chemical activity and, therefore, can undergo a trans-esterification reaction.[33-36] Synthesis of chlorin e₅ derivatives with oligoethylene glycol substituents at position 15 (22-26) was carried out by the action of methylamine on phorbin derivatives 6-10. Chlorin e₅ derivatives with oligoethylene glycol substituents at position 17 (27-29) were obtained by the same way (the phorbin derivatives 11-13 exo ring recovering by the action of methylamine).

Trans-esterification of phorbin derivatives (6-10) ester groups at position 17 was used for synthesis of phorbin derivatives with two fragments of oligoethylene glycol (19-21). Chlorin e₅ derivatives with two oligoethylene glycol fragments (30-32) can also be synthesized by the action of methylamine on phorbin derivatives 19-21. Efforts to obtain the same derivatives directly from methylamide 4 by trans-esterification of both ester groups of this compound were unsuccessful.

Separation of even a slight excess of the diol from the reaction product is the most time-consuming step of the process. The more polar is the derivative obtained, the more difficult is its separation. In this regard, the synthesis of oligoethylene glycol derivatives should be designed so, that the step involving interaction with oligoethylene glycol would lead to the production of the most possible hydrophobic compound and subsequent conversion to form more hydrophilic derivatives held without oligoethylene glycols. Thus, when two substituents are inserted (compounds 30-32), it is advisable to obtain phorbin derivatives 19-21 first, and thereafter exocycle opening. Similarly, chlorin e₅ derivatives with oligoethylene glycol fragments at position 17 (27-29) are more convenient to receive via appropriate 17-ester pyropheophorbide a 11-13.

For the hydrophilicity estimation of biologically active substances the characteristics of their distribution between...
the aqueous and «fat phase» are used and currently octanol is commonly used as the «fat phase».[37] Furthermore, it was shown that the ratio of distribution correlates with retention times of compounds by reverse phase chromatography.[38] Thus the chromatographic mobility of the compounds by reverse phase chromatography may serve as a quantitative criterion for the hydrophilic properties estimation along with the distribution between octanol and water. The higher the mobility, the greater the hydrophilicity of the compounds investigated, and the greater the difference in retention times, the more different hydrophilicity. The insertion of any oligoethylene glycol fragment in any position of the macrocycle significantly increases chromatographic mobility on reversed phase (retention time is reduced by 3-5 minutes). A similar effect is achieved by the introduction of the second oligoethylene glycol fragment. Comparison of the oligoethylene glycol derivatives 6-32 chromatographic characteristics (Table 1) reveals the following structure features influencing on the hydrophilicity of the compounds obtained. The exocycle presence/absence and oligoethylene glycol fragment position in the macrocycle are the structural factors of a most significant influence. Transition from phorbin derivatives to chlorin derivatives leads to increase in the hydrophilicity of the compounds when other structural characteristics (oligoethylene glycol chain length and number of identical oligoethylene glycol alternates) are equal. For example, the transition of 13(2)-glycol derivatives 6-10 to the corresponding chlorins 22-26 leads to retention time decreasing of approximately 0.5-1.5 min. Similarly, retention time of 2.3 min decreased in case of transition from phorbin derivatives with glycol fragment in position 17 (11-13) to chlorin derivatives with the same fragment at the same position (27-29). When other structural characteristics are equal the isomeric derivatives with oligoethylene glycol moiety at position 17 have higher chromatographic mobility than derivatives with oligoethylene glycol moiety at position 13(2) (in the case of phorbin derivatives) or at position 15 (in the case of chlorins). For example, the retention time of chlorin ε derivatives with oligoethylene glycol moiety at position 17 (27-29) is approximately 2 min lower than the retention time of analogous derivatives with oligoethylene glycol moiety at position 15 (6-8). In the case of phorbin derivatives the difference in the retention time for analogous pairs is about 1 min. The oligoethylene glycol chain length influencing on the chromatographic mobility of derivatives is significantly lower than the effect of other structural factors. The retention time of these derivatives is similar and the difference of retention time values for structural analogs is lower than 0.5 min in most cases. It is interesting that the monotonous increasing of chromatographic mobility with oligoethylene glycol chain length growing was not observed in many cases because of complex interactions of oligoethylene glycol moiety with stationary phase. Thus, results of hydrophylicity estimation of the oligoethylene glycol chlorophyll a derivatives reported above allowed to conclude that more available di-, tri- and tetraethylene glycol

Figure 1. $^1$H NMR spectra of methylpheophorbide $\alpha$ (I) and its diethylene glycol esters 6 (B) and 11 (C) (CDCl$_3$, 300 MHz, 3-4 ppm).

D. V. Belykh et al.
Table 1. Retention time of chlorins with oligoethylene glycol fragments (Thermo finnigan surveyor (PDA, column Hypersil C18 100×2/1 mm, gradient elution from a mixture of 1% aqueous trifluoroacetic acid - methanol (40:60 by volume) to pure methanol for 50 min, flow rate 0.4 ml/min) (*) – chlorophyll a derivatives without oligoethylene glycol fragments for comparison.

<table>
<thead>
<tr>
<th>n</th>
<th>X = Gl</th>
<th>Y = OCH3</th>
<th>X = OCH3</th>
<th>Y = Gl</th>
<th>X = OCH3</th>
<th>Y = Gl</th>
<th>X = Y = Gl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.76</td>
<td>36.68</td>
<td>29.13</td>
<td>41.64</td>
<td>36.14</td>
<td>34.01</td>
<td>27.03</td>
</tr>
<tr>
<td>2</td>
<td>37.54</td>
<td>36.56</td>
<td>33.28</td>
<td>41.48</td>
<td>36.46</td>
<td>34.43</td>
<td>31.19</td>
</tr>
<tr>
<td>3</td>
<td>36.81</td>
<td>36.39</td>
<td>31.90</td>
<td>41.22</td>
<td>36.22</td>
<td>33.98</td>
<td>30.09</td>
</tr>
<tr>
<td>4</td>
<td>36.46</td>
<td>43.09</td>
<td>27.03</td>
<td></td>
<td>35.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36.58</td>
<td>40.74</td>
<td>27.03</td>
<td>35.93</td>
<td>36.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(*)</td>
<td>41.16</td>
<td>45.92</td>
<td>27.03</td>
<td>40.96</td>
<td>27.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

can be used for the synthesis of hydrophilic derivatives instead of the less available penta- and hexamers.

Conclusion

Thus, chlorophyll a phorbin and chlorin derivatives with oligoethylene glycol fragments at the macrocycle periphery were synthesized in this study and the hydrophilicity estimation of the compounds obtained based on their chromatographic mobility on reverse phase was carried out. The introduction of oligoethylene glycol moiety has been shown to increase significantly the hydrophilicity of the whole molecule. Among structural factors the presence/absence of exocycle (exocycle opening leads to the hydrophobicity decrease), as well as position of oligoethylene glycol fragment (the moving of oligoethylene glycol fragment from the macrocycle leads to the increase in hydrophilicity due to more effective solvation of this fragment) are the most important. The monotonous increase of chromatographic mobility with oligoethylene glycol chain length growing was not observed in many cases, the most likely, due to the complex nature of oligoethylene glycol moiety interaction with the stationary phase. Oligoethylene glycol chain lengthening does not lead to any appreciable increase in hydrophilicity, so for hydrophilizing chlorophyll derivatives may be used more available di-, tri- and tetraethylene glycol instead of less available penta- and hexamers.

Acknowledgements. This work was supported by RFBR (grant № 14-03-01061 a)

References


D. V. Belykh et al.

Received 08.05.2014
Accepted 24.05.2014