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# Novel p*H*–Independent Amphiphilic Chlorophyll *a* Derivatives with Oligoethylene Glycol Substituents as a Hydrophilic Part: Synthesis and Hydrophilicity Estimation

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*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 hydrophylicity 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). Oligoetylene glycol chain elongation does not lead to appreciable increase in hydrophilicity. So more available di-, tri- and tetraethylene glycols may be used for chlorophyll a derivatives hydrophilization instead of the less available penta- and hexamers.*

**Keywords:** Chlorophyll *a* derivatives, methylpheophorbide *a*, chlorin $e_6$, photosensitizes, hydrophilicity, oligoethylene glycol.

# Новые p*H*–независимые амфифильные производные хлорофилла *a* с фрагментами олигоэтиленгликолей в качестве гидрофильной части: синтез и оценка гидрофильности

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*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 олигоэтиленгликольного 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 олигоэтиленгликольного фрагмента (увеличение длины спейсера между фрагментом олигоэтиленгликоля 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 *a*, метилфеофорбид *a*, хлорин $e_6$, гидрофильность, фотосенсибилизаторы, олигоэтиленгликоль.

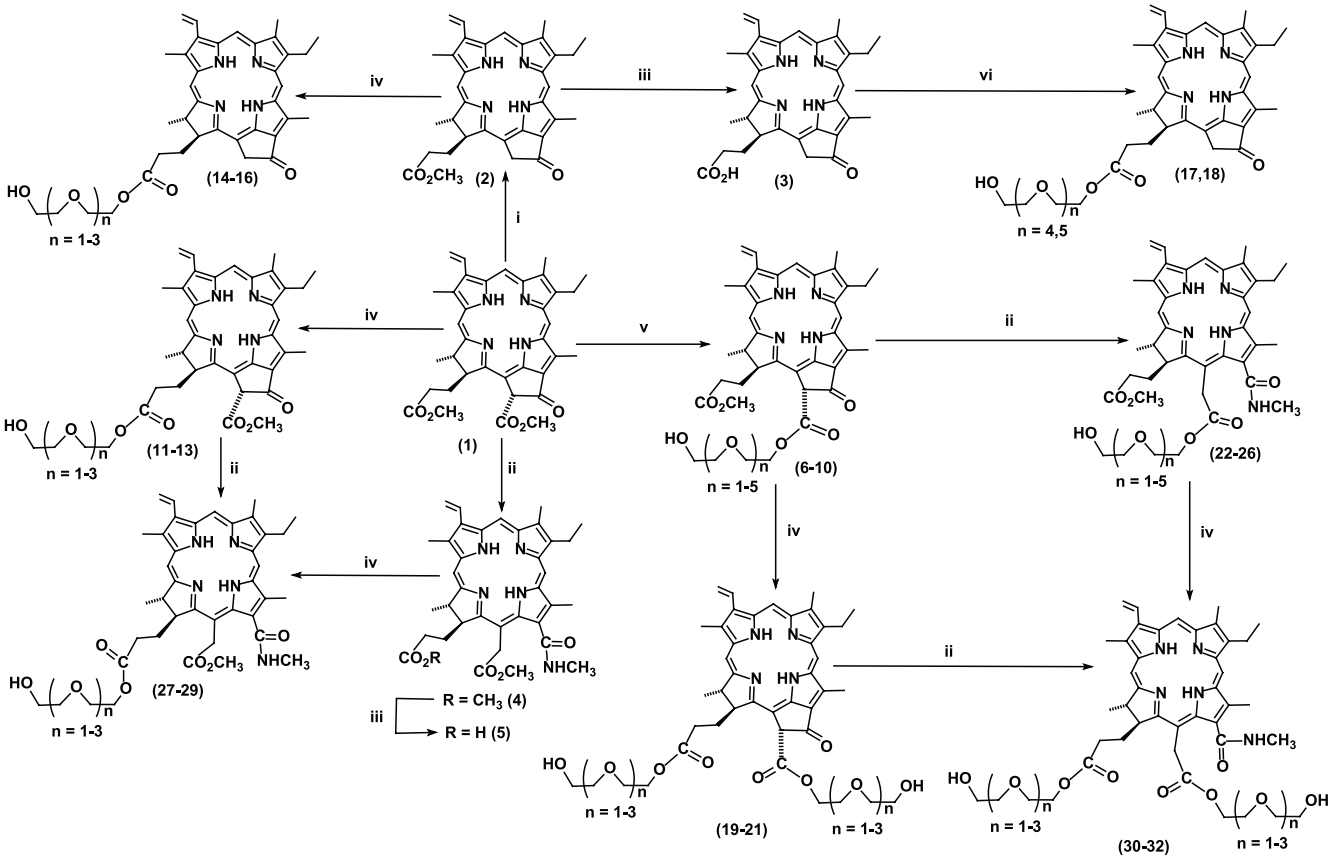
  

## Introduction

It is known that chlorophyll *a* derivatives are intensively investigated as photosensitizers (PS) for photodynamic therapy (PDT) in various fields of medicine (oncology,[1-6] 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 – $CCl_4$-acetone (4:1 vol). Column chromatography was carried out using silica gel Alfa Aesar 70/230μ. 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].




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**)

i: collidine, reflux, 30-40 min; ii: $CH_3NH_2/H_2O$, THF, r.t., 1-2 h; iii: $H_2O$-HCl/acetone; iv: $HOCH_2(CH_2OCH_2)_nOCH_2OH$ (n = 1-3), $H_2SO_{4(conc)}$, r. t. 12-16 h; v: $HOCH_2(CH_2OCH_2)_nOCH_2OH$ (n = 1-5), 2-chloro-*N*-methylpyridinium iodide, DMAP, toluene, reflux 1-3 h; vi: $HOCH_2(CH_2OCH_2)_nOCH_2OH$ (n = 4, 5), 2-chloro-*N*-methylpyridinium iodide, DMAP, THF, reflux 1-2 h.

**Scheme 1.**

*Pyropheophorbide a (**3**).* Methyl pyropheophorbide *a* (**2**) (61 mg, 0.11 mmol) was dissolved in acetone (4 ml), concentrated hydrochloric acid (0.5 mL, HCl 30-33%) was added to the resulting solution and left for 20 hours in the darkness at room temperature. The reaction mixture was diluted with chloroform (50 ml), and hydrochloric acid was removed by water until neutral reaction of washing waters. The resulted chloroform solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The evaporation residue was chromatographed on silica gel (eluent: $CCl_4$-acetone from 70:1 to 2:1). 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[21]. $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.55 s (1H, $H^{10}$), 9.44 s (1H, $H^5$), 8.61 s (1H, $H^{20}$), 8.03 dd [1H, 3-(C*H*=$CH_2$), *J* 18.0 and 11.4 Hz], 6.32 d [1H, 3-(CH=CH$H_{trans}$), *J* 17.6 Hz], 6.21 d [1H, 3-(CH=CH$H_{cis}$), *J* 11.4 Hz], 5.31 d (1H, $H^{13(2)}{}_A$, *J* 19.8 Hz), 5.16 d (1H, $H^{13(2)}{}_B$, *J* 20.1 Hz), 4.54 q (1H, $H^{18}$, *J* 7.3 Hz), 4.36 br.d (1H, $H^{17}$, *J* 7.3 Hz), 3.70 s (3H, 15-($CH_2COOCH_3$)), 3.73 q (2H, 8-$CH_2CH_3$, *J* 7.7 Hz), 3.44 s (3H, 2-$CH_3$), 3.27 s (3H, 7-$CH_3$), 2.86-2.24 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.72 t (8-$CH_2CH_3$, *J* 7.7 Hz), -1.65 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide 15-methyl ester (**5**).* Chlorin $e_6$ 13(1)-*N*-methylamide-15,17-dimethyl ester (**4**) (70 mg, 0.11 mmol) was dissolved in acetone (3 ml), concentrated hydrochloric acid (0.5 mL, HCl 30-33%) was added to the resulting solution and left for 22 hours in the darkness at room temperature. The reaction mixture was diluted with chloroform (50 ml), and hydrochloric acid was washed with water until neutral reaction of washing waters. 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 70:1 to 2:1) The eluate containing the major product was evaporated. 41.1 mg (60%) of compound **5** was obtained as dark-green crystals. Spectral data of the compound obtained are identical to those described in[21]. $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.73 s (1H, $H^{10}$), 9.67 s (1H, $H^5$), 8.83 s (1H, $H^{20}$), 8.12 dd [1H, 3-(C*H*=$CH_2$), *J* 18.0 and 11.4 Hz], 6.50-6.42 br.m (1H, 13-CON*H*$CH_3$), 6.39 d [1H, 3-(CH=CH$H_{trans}$), *J* 18.0 Hz], 6.18 d [1H, 3-(CH=CH$H_{cis}$), *J* 11.4 Hz], 5.52 d (1H, $H^{15(1)}{}_A$, *J* 19.1 Hz), 5.33 d (1H, $H^{15(1)}{}_B$, *J* 19.1 Hz), 4.47 q (1H, $H^{18}$, *J* 7.0 Hz), 4.40 br.d (1H, $H^{17}$, *J* 9.2 Hz), 3.82 s (3H, 15-($CH_2COOCH_3$), 3.88-3.78 m (2H, 8-$CH_2CH_3$), 3.58 s (3H, 12-$CH_3$), 3.52 s (3H, 2-$CH_3$), 3.35 s (3H, 7-$CH_3$), 3.28 d (3H, 13-CONH$CH_3$, *J* 4.8 Hz), 2.73-2.21 m (4H, 17-($CH_2CH_2$COOH)), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.0 Hz), 1.73 d ((3H, 18-$CH_3$, *J* 6.8 Hz), -1.82 br.s (1H, III-NH).

*Trans-esterification of the ester group at position 13(2) of methyl pheophorbide a exocycle (general procedure, preparation of derivatives **6-10**).* To a solution of 50-200 mg of methyl pheophorbide *a* (**1**) (0.083-0.330 mmol) in 10.5 mL of toluene 3-4 times molar excess of dimethylaminopyridine (DMAP), two-times molar excess of 2-chloro-*N*-methylpyridinium iodide and corresponding oligoethylene glycol (5-20 mmol) was added. The resulted mixture was heated under reflux for 1-3 hours (TLC monitoring, eluent: $CCl_4$-acetone 2:1). 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; then hydrochloric acid was removed by washing with distilled water until neutral reaction of washing waters. The resulting solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure at 40-50 ºC. The residue after evaporation was chromatographed on silica gel (eluted with $CCl_4$:acetone in ratios ranging from 40:1 to 5:1). The eluate, containing the main substance, was evaporated under reduced pressure. The residue after evaporation was crystallized first from a mixture of chloroform with hexane, and then from a mixture of chloroform with methanol.

*Methyl pheophorbide a 13(2) diethylene glycol ester (**6**).* 75.3 mg (67%) of compound **6** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of **1**, 0.5 ml (5.3 mmol) of diethylene glycol, 80.0 mg (0.656 mmol) of DMAP and 83.4 mg (0.328 mmol) of 2-chloro-*N*-methylpyridinium iodide in 5 ml of toluene for 3 hours at full conversion of the starting compound **1**. Mass spectrum (ESI), *m/z*: for $MH^+$ ($C_{39}H_{45}N_4O_7$) calcd. 681.3, found 681.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 670 (34.9%), 613 (5.5%), 531 (7.2%), 501 (9.2%), 404 (100.0%). IR (KBr) cm$^{-1}$: 3493 (ν OH); 3395 (ν NH of chlorin cycle); 2957 ($\nu_{CH}{}^{as}$ $CH_3$); 2926 ($\nu_{CH}{}^{as}$ $CH_2$); 2868 ($\nu_{CH}{}^{s}$ $CH_3$); 2739 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.55 s (1H, $H^{10}$), 9.42 s (1H, $H^5$), 8.59 s (1H, $H^{20}$), 8.03 dd [1H, 3-(C*H*=$CH_2$), *J* 18.5 and 11.6 Hz], 6.33 dd [1H, 3-(CH=CH$H_{trans}$), *J* 17.4 and 1.4 Hz], 6.32 s (1H, $H^{13(2)}$), 6.22 dd [1H, 3-(CH=CH$H_{cis}$), *J* 11.4 and 1.5 Hz], 4.61-4.45 m (3H, 13(2)-COO$CH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 br.d (1H, $H^{17}$, *J* 8.5 Hz), 3.85-3.50 m [6H, 8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OH$], 3.72 s (3H, 12-$CH_3$), 3.61 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.44 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 2.77-2.15 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.4 Hz), 0.62 br.s (1H, I-NH), -1.55 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.53 s (1H, $H^{10}$), 9.39 s (1H, $H^5$), 8.53 s (1H, $H^{20}$), 8.07-7.97 m [1H, 3-(C*H*=$CH_2$)], 6.33 dd [1H, 3-(CH=CH$H_{trans}$), *J* 17.4 and 1.4 Hz], 6.21 s (1H, $H^{13(2)}$), 6.22 dd [1H, 3-(CH=CH$H_{cis}$), *J* 11.4 and 1.5 Hz], 4.61-4.45 m (3H, 13(2)-COO$CH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 br.d (1H, $H^{17}$, *J* 8.5 Hz), 3.85-3.50 m [6H, 8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OH$], 3.69 s (3H, 12-$CH_3$), 3.48 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.42 s (3H, 2-$CH_3$), 3.27 s (3H, 7-$CH_3$), 2.77-2.15 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.4 Hz), 0.72 br.s (1H, I-NH), -1.37 br.s (1H, III-NH).

*Methyl pheophorbide a 13(2) triethylene glycol ester (**7**).* 73.7 mg (67%) of compound **7** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 9:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of **1**, 0.5 ml (3.6 mmol) of triethylene glycol, 80.0 mg (0.656 mmol) DMAP and 80.0 mg (0.325 mmol) of 2-chloro-*N*-methylpyridinium iodide in 5 ml of toluene for 3 hours at full conversion of the starting compound **1**. Mass spectrum (ESI) *m/z*: for $MH^+$ ($C_{41}H_{49}N_4O_8$) calcd. 725.3, found 725.3; for $MNa^+$ ($C_{41}H_{48}N_4O_8Na$) calcd. 747.3 found 747.5. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.6%), 611 (9.1%), 538 (10.5%), 507 (11.2%), 414 (100%). IR (KBr) cm$^{-1}$: 3460 (ν OH); 3392 (ν NH of chlorin cycle); 2957 ($\nu_{CH}{}^{as}$ $CH_3$); 2926 ($\nu_{CH}{}^{as}$ $CH_2$); 2870 ($\nu_{CH}{}^{s}$ $CH_3$); 2741 ($\nu_{CH}$ $CH_2$-O-, glycol); 1735 (ν C=O, ester); 1695 (ν C=O, exocycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: Signals of 13(2) R-diastereomer: 9.55 s (1H, $H^{10}$), 9.41 s (1H, $H^5$), 8.60 s (1H, $H^{20}$), 8.03 dd [1H, 3-(C*H*=$CH_2$), *J* 17.6 and 11.4 Hz], 6.33 dd [1H, 3-(CH=CH$H_{trans}$), *J* 17.9 and 1.1 Hz], 6.31 s (1H, $H^{13(2)}$), 6.22 dd [1H, 3-(CH=CH$H_{cis}$), *J* 11.4 and 1.4 Hz], 4.58-4.45 m (3H, 13(2)-COO$CH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 m (1H, $H^{17}$), 3.72 s (3H, 12-$CH_3$), 3.59 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.44 s (3H, 2-$CH_3$), 3.27 s (3H, 7-$CH_3$), 3.82-3.64 m 5H and 3.57-3.41 m 4H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.36 t [2H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 4.4 Hz], 3.33-3.24 m [13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.75-2.18 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.73 t (3H, 8-$CH_2CH_3$, *J* 7.7 Hz), 0.58 br.s (1H, I-NH), -1.59 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.51 s (1H, $H^{10}$), 9.37 s (1H, $H^5$), 8.53 s (1H, $H^{20}$), 8.01 dd [1H, 3-(C*H*=$CH_2$), *J* 17.6 and 11.0 Hz], 6.35-6.28 m [1H, 3-(CH=CH$H_{trans}$)], 6.23-6.19 m [1H, 3-(CH=CH$H_{cis}$)], 6.21 s (1H, $H^{13(2)}$), 4.58-4.45 m (3H, 13(2)-COO$CH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 m (1H, $H^{17}$), 3.69 s (3H, 12-$CH_3$), 3.61 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.42 s

(3H, 2-$CH_3$), 3.25 s (3H, 7-$CH_3$), 3.82-3.64 m 5H and 3.57-3.41 m 4H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.36 t [2H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], *J* 4.4 Hz], 3.82-3.64 m 5H and 3.57-3.41 m 4H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.36 t [2H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], *J* 4.4 Hz], 3.33-3.24 m [4H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.75-2.18 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.72 t (3H, 8-$CH_2CH_3$, *J* 7.0 Hz), 0.69 br.s (1H, I-NH), -1.41 br.s (1H, III-NH).

*Methyl pheophorbide a 13(2) tetraethylene glycol ester (**8**).* 63.5 mg (50%) of compound **8** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of **1**, 0.5 ml (2.9 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 **1**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{43}H_{53}N_4O_9$) calcd. 769.4, found 769.3; for $MNa^+$ ($C_{43}H_{52}N_4O_9Na$) calcd. 791.3, found 791.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.8%), 610 (9.1%), 538 (13.6%), 507 (11.2%), 414 (100%). IR (KBr) $cm^{-1}$: 3489 (ν OH); 3391 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2927 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2739 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1697 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.57 s (1H, $H^{10}$), 9.44 s (1H, $H^5$), 8.60 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.2 and 11.4 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.2 Hz), 6.30 s (1H, $H^{13(2)}$), 6.23 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 4.61-4.40 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.35-4.23 m (1H, $H^{17}$), 3.72 s (3H, 12-$CH_3$), 3.58 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.44 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.82-3.65 m 4H, 3.65-3.53 m 2H and 3.52-3.39 m 2H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.36 m [2H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.32-3.20 m [2H 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.61-2.24 m (4H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 6.9 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.58 br.s (1H, I-NH), -1.58 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.53 s (1H, $H^{10}$), 9.40 s (1H, $H^5$), 8.54 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.2 and 11.4 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.2 Hz), 6.20 s (1H, $H^{13(2)}$), 6.23 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 4.61-4.40 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.35-4.23 m (1H, $H^{17}$), 3.72 s (3H, 12-$CH_3$), 3.58 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.44 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.82-3.65 m (4H), 3.65-3.53 m (2H), 3.52-3.39 m (4H), 3.39-3.33 m (2H) and 3.32-3.20 m (4H) [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$ OH], 2.61-2.24 m (4H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 6.9 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.68 br.s (1H, I-NH), -1.41 br.s (1H, III-NH).

*Methyl pheophorbide a 13(2) pentaethylene glycol ester (**9**).* 78.1 mg (58%) of compound **9** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of **1**, 0.5 ml (2.4 mmol) of pentaethylene 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 **1**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{45}H_{57}N_4O_{10}$) calcd. 813.4, found 813.3; for $MNa^+$ ($C_{43}H_{52}N_4O_9Na$) ($C_{45}H_{57}N_4O_{10}Na$) calcd. 835.4, found 835.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (59.6%), 610 (12.2%), 538 (14.3%), 508 (15.3%), 414 (100%). IR (KBr) $cm^{-1}$: 3485 (ν OH); 3393 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2924 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2742 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.57 s (1H, $H^{10}$), 9.44 s (1H, $H^5$), 8.60 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.2 and 11.4 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 18.3 Hz), 6.30 s (1H, $H^{13(2)}$), 6.23 d (1H, 3(2)-$H_{cis}$ 11.7 Hz), 4.54-4.45 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.32-4.25 m (1H, $H^{17}$), 3.73 s (3H, 12-$CH_3$), 3.58 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.45 s (3H, 2-$CH_3$), 3.29 s (3H, 7-$CH_3$), 3.82-3.36 m 16H, 3.32-3.20 m 2H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.65-2.20 m (4H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.56 br.s (1H, I-NH), -1.59 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.54 s (1H, $H^{10}$), 9.40 s (1H, $H^5$), 8.54 s (1H, $H^{20}$), 8.12-7.97 m (1H, 3(1)-H), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 18.3 Hz), 6.23 d (1H, 3(2)-$H_{cis}$ 11.7 Hz), 6.20 s (1H, $H^{13(2)}$), 4.54-4.45 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.32-4.25 m (1H, $H^{17}$), 3.70 s (3H, 12-$CH_3$), 3.61 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.43 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.82-3.36 m 16H, 3.32-3.20 m 2H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.65-2.20 m (4H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.68 br.s (1H, I-NH), -1.33 br.s (1H, III-NH).

*Methyl pheophorbide a 13(2) hexaethylene glycol ester (**10**).* 66.7 mg (47%) of compound **10** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained in reaction of 100 mg (0.165 mmol) of **1**, 0.5 ml (1.99 mmol) of hexaethylene 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 **1**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{47}H_{61}N_4O_{11}$) calcd. 857.4, found 857.0. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.9%), 611 (8.8%), 538 (10.3%), 508 (11.1%), 414 (100%). IR (KBr) $cm^{-1}$: 3485 (ν OH); 3391 (ν NH of chlorin cycle); 2953 ($\nu_{CH}^{as}$ $CH_3$); 2922 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2743 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1618 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.56 s (1H, $H^{10}$), 9.43 s (1H, $H^5$), 8.60 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.6 and 11.4 Hz), 6.33 dd (1H, 3(2)-$H_{trans}$ *J* 17.9 and 1.1 Hz), 6.30 s (1H, $H^{13(2)}$), 6.22 dd (1H, 3(2)-$H_{cis}$, 11.4 and 1.1 Hz), 4.56-4.44 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 br.dt (1H, $H^{17}$, 8.4 and 2.9 Hz), 3.72 s (3H, 12-$CH_3$), 3.58 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.44 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.80-3.67 m 6H, 3.66-3.41 m 13H, 3.38-3.29 m 5H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.74-2.47 m (2H, 17-($CH_2CH_2COOCH_3$), 2.45-2.16 m (2H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.56 br.s (1H, I-NH), -1.60 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.53 s (1H, $H^{10}$), 9.39 s (1H, $H^5$), 8.54 s (1H, $H^{20}$), 8.04 m (1H, 3(1)-H), 6.33 dd (1H, 3(2)-$H_{trans}$ *J* 17.9 and 1.1 Hz), 6.19 s (1H, $H^{13(2)}$), 6.22 dd (1H, 3(2)-$H_{cis}$, 11.4 and 1.1 Hz), 4.56-4.44 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.28 br.dt (1H, $H^{17}$, 8.4 and 2.9 Hz), 3.71 s (3H, 12-$CH_3$), 3.59 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.43 s (3H, 2-$CH_3$), 3.26 s (3H, 7-$CH_3$), 3.80-3.67 m 6H, 3.66-3.41 m 13H, 3.38-3.29 m 5H [8-($CH_2CH_3$), 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 2.74-2.47 m (2H, 17-($CH_2CH_2COOCH_3$), 2.45-2.16 m (2H, 17-($CH_2CH_2COOCH_3$), 1.85 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.64 br.s (1H, I-NH), -1.42 br.s (1H, III-NH).

*Trans-esterification of propionate substituent in position 17 by the action of di-, tri- and tetraethylene glycol (general procedure, preparation of derivatives **11-16**, **19-21**).* 30-100 mg of the starting chlorophyll *a* derivative (about 0.049-0.165 mmol) was dissolved in a mixture of 10.5 ml of corresponding oligoethylene glycol with 0.1-0.3 ml of concentrated sulfuric acid. In case of poor solubility of the starting chlorin, 1-2 ml of chloroform was added to a mixture (until complete dissolution of the starting compound). The resulting solution was allowed to stand for 17-22 h in a dark place at 18-22 ºC. The reaction mixture was diluted with 100-300 ml of water, and the precipitate was filtered through a paper filter, washed with 200-400 ml of water and dried in air. The resulting chlorins

mixture was chromatographed on silica gel (eluent: $CCl_4$-acetone from 70:1 to 2:1). The eluate containing the major product was evaporated and residue after evaporation was re-precipitated from chloroform-hexane mixture.

*Pheophorbide a 17-diethylene glycol ester (**11**).* 57.1 mg (51 %) of compound **11** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 6:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 100 mg (0.165 mmol) of **1** in a mixture of 10 ml of diethylene 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 $MH^+$ ($C_{39}H_{45}N_4O_7$) calcd. 681.3, found 681.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (45.1%), 611 (9.5%), 538 (11.2%), 508 (12.1%), 414 (100%). IR (KBr) cm$^{-1}$: 3466 (ν OH); 3395 (ν NH of chlorin cycle); 2957 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2739 ($\nu_{CH}$ $CH_2$-O-, glycol); 1738 (ν C=O, ester); 1697 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.54 s (1H, H$^{10}$), 9.40 s (1H, H$^5$), 8.60 s (1H, H$^{20}$), 8.01 dd (1H, 3(1)-H, *J* 17.6 and 11.4 Hz), 6.32 d (1H, 3(2)-$H_{trans}$ *J* 17.6 Hz), 6.32 s (1H, H$^{13(2)}$), 6.21 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 4.50 qd (1H, H$^{18}$, *J* 7.3 and 1.5 Hz), 4.27 br.dt (1H, H$^{17}$, *J* 7.9 and 2.2 Hz), 4.21-4.05 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.91 s (3H, 13(2)-$COOCH_3$), 3.72 s (3H, 12-$CH_3$), 3.44 s (3H, 2-$CH_3$), 3.25 s (3H, 7-$CH_3$), 3.82-3.36 m [8H, 8-($CH_2CH_3$), 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$)], 2.75-2.49 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 2.48-2.34 and 2.32-2.19 (both m 1H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.72 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.58 br.s (1H, I-NH), -1.59 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.51 s (1H, H$^{10}$), 9.36 s (1H, H$^5$), 8.54 s (1H, H$^{20}$), 8.05-7.94 m (1H, 3(1)-H), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 18.3 Hz), 6.23 d (1H, 3(2)-$H_{cis}$ 11.7 Hz), 6.20 s (1H, H$^{13(2)}$), 4.53 br.q (1H, H$^{18}$, *J* 7.2 Hz), 4.34 br.t (1H, H$^{17}$, *J* 7.7 Hz), 4.21-4.05 m [2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$)], 3.87 s (3H, 13(2)-$COOCH_3$), 3.71 s (3H, 12-$CH_3$), 3.42 s (3H, 2-$CH_3$), 3.24 s (3H, 7-$CH_3$), 3.82-3.36 m [8H [8-($CH_2CH_3$), 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$)], 2.75-2.49 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 2.48-2.34 and 2.32-2.19 (both m 1H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.72 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.67 br.s (1H, I-NH), -1.42 br.s (1H, III-NH).

*Pheophorbide a 17-triethylene glycol ester (**12**).* 21.7 mg (36 %) of compound **12** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 5:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 50 mg (0.082 mmol) of **1** in a mixture of 3 ml of triethylene glycol, 0.2 ml of concentrated sulfuric acid for 20 hours at complete conversion of starting compound **1**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{41}H_{49}N_4O_8$) calcd. 725.4, found 725.3. UV-Vis ($CHCl_3$) 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 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2743 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.58 s (1H, H$^{10}$), 9.44 s (1H, H$^5$), 8.61 s (1H, H$^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.6 and 11.4 Hz), 6.34 dd (1H, 3(2)-$H_{trans}$ *J* 17.6 and 1.5 Hz), 6.31 s (1H, H$^{13(2)}$), 6.23 dd (1H, 3(2)-$H_{cis}$ 11.7 and 1.5 Hz), 4.51 br.q (1H, H$^{18}$, *J* 7.3 Hz), 4.26 br.d (1H, H$^{17}$, *J* 7.7 Hz), 4.22-4.06 m [2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$)], 3.91 s (3H, 13(2)-$COOCH_3$), 3.73 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.80-3.39 m [12H [8-($CH_2CH_3$), 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$)], 2.73-2.48 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.47-2.32 and 2.31-2.18 (both m 1H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.85 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 6.9 Hz), 0.62 br.s (1H, I-NH), -1.40 br.s (1H, III-NH).

*Pheophorbide a 17-tetraethylene glycol ester (**13**).* 57 mg (45 %) of compound **13** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 100 mg (0.165 mmol) of **1** in a mixture of 5 ml of tetraethylene glycol, 0.25 ml of concentrated sulfuric acid for 18 hours at complete conversion of starting compound **1**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{43}H_{53}N_4O_9$) calcd. 769.4, found 769.3, for $MNa^+$ ($C_{43}H_{52}N_4O_9Na$) calcd. 791.4, found 791.3, for $MK^+$ ($C_{43}H_{52}N_4O_9K$) calcd. 807.3, found 807.2. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.9%), 611 (9.3%), 558 (4.4%), 538 (10.7%), 414 (100%). IR (KBr) cm$^{-1}$: 3464 (ν OH); 3393 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2741 ($\nu_{CH}$ $CH_2$-O-, glycol); 1738 (ν C=O, ester); 1697 (ν C=O, exo cycle); 1618 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.62 s (1H, H$^{10}$), 9.48 s (1H, H$^5$), 8.65 s (1H, H$^{20}$), 8.05 dd (1H, 3(1)-H, *J* 17.6 and 11.4 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.6 Hz), 6.31 s (1H, H$^{13(2)}$), 6.24 d (1H, 3(2)-$H_{cis}$ *J* 11.7 Hz), 4.52 br.q (1H, H$^{18}$, *J* 7.7 Hz), 4.27 br.d (1H, H$^{17}$, *J* 8.1 Hz), 4.23-4.07 m [2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$)], 3.91 s (3H, 13(2)-$COOCH_3$), 3.74 s (3H, 12-$CH_3$), 3.46 s (3H, 2-$CH_3$), 3.29 s (3H, 7-$CH_3$), 3.82-3.38 m [16H [8-($CH_2CH_3$), 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$)], 2.77-2.47 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.46-2.34 and 2.33-2.17 (both m 1H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.7 Hz), 0.48 br.s (1H, I-NH), -1.61 br.s (1H, III-NH). Signals of 13(2)R-diastereomer: 9.59 s (1H, H$^{10}$), 9.44 s (1H, H$^5$), 8.60 s (1H, H$^{20}$), 8.08-7.96 m (1H, 3(1)-H), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.6 Hz), 6.24 d (1H, 3(2)-$H_{cis}$ *J* 11.7 Hz), 6.20 s (1H, H$^{13(2)}$), 4.52 br.q (1H, H$^{18}$, *J* 7.7 Hz), 4.37-4.31 m (1H, H$^{17}$), 4.23-4.07 m [2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$)], 3.87 s (3H, 13(2)-$COOCH_3$), 3.71 s (3H, 12-$CH_3$), 3.44 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.82-3.38 m [16H [8-($CH_2CH_3$), 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$)], 2.77-2.47 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.46-2.34 and 2.33-2.17 (both m 1H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.7 Hz), 0.58 br.s (1H, I-NH), -1.44 br.s (1H, III-NH).

*Pyropheophorbide a 17-diethylene glycol ester (**14**).* 15.1 mg (24 %) of compound **14** as a dark blue-black crystalline powder was obtained with transesterification of 50 mg (0.091 mmol) of **2** in a mixture of 3 ml of diethylene glycol, 0.15 ml of concentrated sulfuric acid for 18 hours at complete conversion of starting compound **2**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{37}H_{43}N_4O_5$) calcd. 623.3, found 623.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (44.7%), 611 (10.0%), 540 (11.6%), 509 (12.5%), 414 (100 %). IR (KBr) cm$^{-1}$: 3429 (ν OH); 3393 (ν NH of chlorin cycle); 2960 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2731 ($\nu_{CH}$ $CH_2$-O-, glycol); 1732 (ν C=O, ester); 1692 (ν C=O, exo cycle); 1622 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.56 s (1H, H$^{10}$), 9.44 s (1H, H$^5$), 8.61 s (1H, H$^{20}$), 8.04 dd (1H, 3(1)-H, *J* 17.8 and 11.7 Hz), 6.33 d (1H, 3(2)-$H_{trans}$ *J* 17.6 Hz), 6.22 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 5.33 d (1H, $H^{13(2)}_A$, *J* 20.2 Hz), 5.16 d (1H, $H^{13(2)}_B$, *J* 20.2 Hz), 4.54 br.q (1H, H$^{18}$, *J* 7.0 Hz), 4.39-4.30 m (1H, H$^{17}$), 4.26-4.16 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.74 q (2H, 8-($CH_2CH_3$), *J* 7.7 Hz), 3.71 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.73-3.66 m 1H and 3.66-3.57 m

3H (17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 3H 3.53 t (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$, *J* 4.4 Hz), 2.85-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 2.45-2.29 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.73 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.48 br.s (1H, I-NH), -1.63 br.s (1H, III-NH).

*Pyropheophorbide a 17-triethylene glycol ester (**15**)*. 35.5 mg (29 %) of compound **15** 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 17 hours at complete conversion of starting compound **2**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{39}H_{47}N_4O_6$) calcd. 667.3, found 667.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (45.0%), 610 (9.2%), 539 (10.8%), 509 (11.7%), 414 (100%). IR (KBr) $cm^{-1}$: 3442 (ν OH); 3393 (ν NH of chlorin cycle); 2959 ($\nu_{CH}{}^{as}$ $CH_3$); 2924 ($\nu_{CH}{}^{as}$ $CH_2$); 2868 ($\nu_{CH}{}^{s}$ $CH_3$); 2737 ($\nu_{CH}$ $CH_2$-O-, glycol); 1732 (ν C=O, ester); 1692 (ν C=O, exo cycle); 1618 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.61 s (1H, $H^{10}$), 9.49 s (1H, $H^5$), 8.65 s (1H, $H^{20}$), 8.06 dd (1H, 3(1)-H, *J* 18.0 and 11.4 Hz), 6.34 dd (1H, 3(2)-$H_{trans}$ *J* 18.0 and 1.3 Hz), 6.23 dd (1H, 3(2)-$H_{cis}$ 11.4 and 1.3 Hz), 5.34 d (1H, $H^{13(2)}{}_A$, *J* 19.8 Hz), 5.17 d (1H, $H^{13(2)}{}_B$, *J* 19.8 Hz), 4.56 qd (1H, $H^{18}$, *J* 7.3 and 2.2 Hz), 4.37 br.d (1H, $H^{17}$, *J* 7.3 Hz), 4.20 dd (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$ *J* 5.5 and 4.0 Hz), 3.76 q (2H, 8-($CH_2CH_3$), *J* 7.7 Hz), 3.73 s (3H, 12-$CH_3$), 3.46 s (3H, 2-$CH_3$), 3.30 s (3H, 7-$CH_3$), 3.67-3.48 m (11H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.86-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.45-2.28 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.36 br.s (1H, I-NH), -1.66 br.s (1H, III-NH).

*Pyropheophorbide a 17-tetraethylene glycol ester (**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 17 hours at complete conversion of starting compound **2**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{41}H_{50}N_4O_7$) calcd. 711.4, found 711.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (44.4%), 610 (8.5%), 539 (9.9%), 509 (11.0%), 414 (100%). IR (KBr) $cm^{-1}$: 3443 (ν OH); 3393 (ν NH of chlorin cycle); 2959 ($\nu_{CH}{}^{as}$ $CH_3$); 2924 ($\nu_{CH}{}^{as}$ $CH_2$); 2870 ($\nu_{CH}{}^{s}$ $CH_3$); 2734 ($\nu_{CH}$ $CH_2$-O-, glycol); 1732 (ν C=O, ester); 1692 (ν C=O, exo cycle); 1618 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.54 s (1H, $H^{10}$), 9.43 s (1H, $H^5$), 8.61 s (1H, $H^{20}$), 8.05 dd (1H, 3(1)-H, *J* 18.0 and 11.7 Hz), 6.33 d (1H, 3(2)-$H_{trans}$, *J* 18.0 Hz), 6.21 d (1H, 3(2)-$H_{cis}$, 11.3 Hz), 5.32 d (1H, $H^{13(2)}{}_A$, *J* 19.8 Hz), 5.16 d (1H, $H^{13(2)}{}_B$, *J* 19.8 Hz), 4.54 br.q (1H, $H^{18}$, *J* 7.0 Hz), 4.36 br.d (1H, $H^{17}$, *J* 7.7 Hz), 4.20 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 3.73 q (2H, 8-($CH_2CH_3$), *J* 7.9 Hz), 3.71 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.67-3.48 m (11H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.83-2.54 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.45-2.26 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.85 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.7 Hz), 0.52 br.s (1H, I-NH), -1.65 br.s (1H, III-NH).

*Pheophorbide a 13(2).17-bisdiethylene glycol ester (**19**)*. 14.1 mg (42 %) of compound **19** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 8:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 30 mg (0.040 mmol) of **6** in a mixture of 3 ml of diethylene glycol, 0.15 ml of concentrated sulfuric acid for 22 hours at complete conversion of starting compound **6**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{42}H_{51}N_4O_9$) calcd. 755.4, found 755.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (47.3%), 611 (9.9%), 539 (11.3%), 508 (11.8%), 414 (100%). IR (KBr) $cm^{-1}$: 3458 (ν OH); 3393 (ν NH of chlorin cycle); 2959 ($\nu_{CH}{}^{as}$ $CH_3$); 2926 ($\nu_{CH}{}^{as}$ $CH_2$); 2870 ($\nu_{CH}{}^{s}$ $CH_3$); 2740 ($\nu_{CH}$ $CH_2$-O-, glycol); 1734 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.61 s (1H, $H^{10}$), 9.47 s (1H, $H^5$), 8.65 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 18.0 and 11.7 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.9 Hz), 6.36 s (1H, $H^{13(2)}$), 6.24 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 4.68-4.47 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.36-4.27 m (1H, $H^{17}$), 4.25-4.13 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.88-3.48 m [16H, 8-$CH_2CH_3$, 13(2)-$COOCH_2CH_2OCH_2CH_2OH$, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.73 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.29 s (3H, 7-$CH_3$), 2.78-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 2.53-2.23 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 1.88 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.52 br.s (1H, I-NH), -1.57 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.59 s (1H, $H^{10}$), 9.44 s (1H, $H^5$), 8.59 s (1H, $H^{20}$), 8.04 dd (1H, 3(1)-H, *J* 18.0 and 11.7 Hz), 6.34 d (1H, 3(2)-$H_{trans}$ *J* 17.9 Hz), 6.24 d (1H, 3(2)-$H_{cis}$ 11.4 Hz), 6.19 s (1H, $H^{13(2)}$), 4.68-4.47 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.36-4.27 m (1H, $H^{17}$), 4.25-4.13 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.88-3.48 m [16H, 8-$CH_2CH_3$, 13(2)-$COOCH_2CH_2OCH_2CH_2OH$, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$], 3.76 s (3H, 12-$CH_3$), 3.44 s (3H, 2-$CH_3$), 3.30 s (3H, 7-$CH_3$), 2.78-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 2.53-2.23 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OH$), 1.88 d (3H, 18-$CH_3$, *J* 7.3 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.62 br.s (1H, I-NH), -1.42 br.s (1H, III-NH).

*Pheophorbide a 13(2).17-bistriethylene glycol ester (**20**)*. 40.0 mg (42 %) of compound **20** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 7:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 80 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-spectrum (ESI) *m/z*: for $MH^+$ ($C_{46}H_{59}N_4O_{11}$) calcd. 843.4, found 843.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (44.9%), 610 (9.7%), 538 (11.4%), 507 (12.9%), 414 (100%). IR (KBr) $cm^{-1}$: 3460 (ν OH); 3388 (ν NH of chlorin cycle); 2959 ($\nu_{CH}{}^{as}$ $CH_3$); 2922 ($\nu_{CH}{}^{as}$ $CH_2$); 2872 ($\nu_{CH}{}^{s}$ $CH_3$); 2736 ($\nu_{CH}$ $CH_2$-O-, glycol); 1736 (ν C=O, ester); 1697 (ν C=O, exo cycle); 1611 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.57 s (1H, $H^{10}$), 9.43 s (1H, $H^5$), 8.61 s (1H, $H^{20}$), 8.03 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.4 Hz), 6.33 d (1H, 3-CH=$CH H_{trans}$ *J* 17.6 Hz), 6.34 s (1H, $H^{13(2)}$), 6.22 d (1H, 3-CH=$CHH_{cis}$ *J* 11.7 Hz), 4.57-4.48 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.30 br.d (1H, $H^{17}$, *J* 7.7 Hz), 4.22-4.08 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.86-3.30 m [22H, 8-$CH_2CH_3$, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.72 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.27 s (3H, 7-$CH_3$), 2.78-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.53-2.23 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.57 br.s (1H, I-NH), -1.59 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.53 s (1H, $H^{10}$), 9.39 s (1H, $H^5$), 8.55 s (1H, $H^{20}$), 8.03 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.4 Hz), 6.33 d (1H, 3-CH=$CH H_{trans}$ *J* 17.6 Hz), 6.21 s (1H, $H^{13(2)}$), 6.22 d (1H, 3-CH=$CHH_{cis}$ *J* 11.7 Hz), 4.57-4.48 m (3H, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, $H^{18}$), 4.30 br.d (1H, $H^{17}$, *J* 7.7 Hz), 4.22-4.08 m [2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.86-3.30 m [22H, 8-$CH_2CH_3$, 13(2)-$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$], 3.72 s (3H, 12-$CH_3$), 3.44 s (3H, 2-$CH_3$), 3.26 s (3H, 7-$CH_3$), 2.78-2.55 m (2H, 17-$CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.53-2.23 m (2H, 17-($CH_2CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.74 t (3H, 8-$CH_2CH_3$, *J* 7.3 Hz), 0.68 br.s (1H, I-NH), -1.41 br.s (1H, III-NH).

*Pheophorbide a 13(2).17-bistetraethylene glycol ester* (**21**). 25.0 mg (27 %) of compound **21** (13(2)-diastereomers mixture, 13(2)-R/13(2)-S 5.5:1 according to $^1$H NMR) as a dark blue-black crystalline powder was obtained with transesterification of 76 mg

(0.099 mmol) of **8** in a mixture of 5 ml of tetraethylene glycol, 0.25 ml of concentrated sulfuric acid for 19 hours at complete conversion of starting compound **8**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{50}H_{67}N_4O_{13}$) calcd. 931.5, found 931.5; for $MNa^+$ ($C_{50}H_{66}N_4O_{13}Na$) calcd. 953.5, found 953.4; for $MK^+$ ($C_{50}H_{66}N_4O_{13}K$) calcd. 969.4, found 969.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 669 (41.5%), 612 (8.3%), 535 (9.5%), 504 (11.6%), 414 (100%). IR (KBr) $cm^{-1}$: 3485 (ν OH); 3393 (ν NH of chlorin cycle); 2959 ($\nu_{CH}^{as}CH_3$); 2922 ($\nu_{CH}^{as}CH_2$); 2872 ($\nu_{CH}^{s}CH_3$); 2736 ($\nu_{CH}CH_2$-O-, glycol); 1736 (ν C=O, ester); 1695 (ν C=O, exo cycle); 1616 («chlorin band»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. Signals of 13(2)R-diastereomer: 9.59 s (1H, $H^{10}$), 9.45 s (1H, $H^5$), 8.64 s (1H, $H^{20}$), 8.04 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.7 Hz), 6.33 d (1H, 3-CH=CH*H*$_{trans}$ *J* 17.6 Hz), 6.32 s (1H, $H^{13(2)}$), 6.23 d (1H, 3-CH=CHH$_{cis}$ *J* 11.7 Hz), 4.57-4.46 m (3H, 13(2)-COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, $H^{18}$), 4.30 br.d (1H, $H^{17}$, *J* 7.7 Hz), 4.21-4.05 m [2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH], 3.86-3.30 m [30H, 8-*CH*$_2$CH$_3$, 13(2)-COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$*OH*, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$*OH*], 3.72 s (3H, 12-CH$_3$), 3.45 s (3H, 2-CH$_3$), 3.28 s (3H, 7-CH$_3$), 2.78-2.55 m (2H, 17-C*H*$_2$CH$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 2.53-2.23 m (2H, 17-(CH$_2$C*H*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.86 d (3H, 18-CH$_3$, *J* 7.3 Hz), 1.73 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.7 Hz), 0.48 br.s (1H, I-NH), -1.63 br.s (1H, III-NH). Signals of 13(2)S-diastereomer: 9.56 s (1H, $H^{10}$), 9.41 s (1H, $H^5$), 8.58 s (1H, $H^{20}$), 8.02 dd (1H, 3-*CH*=$CH_2$, *J* 17.9 and 11.4 Hz), 6.33 d (1H, 3-CH=CH*H*$_{trans}$ *J* 17.6 Hz), 6.21 s (1H, $H^{13(2)}$), 6.23 d (1H, 3-CH=CHH$_{cis}$ *J* 11.7 Hz), 4.57-4.46 m (3H, 13(2)-COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, $H^{18}$), 4.30 br.d (1H, $H^{17}$, *J* 7.7 Hz), 4.21-4.05 m [2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH], 3.86-3.30 m [30H, 8-*CH*$_2$CH$_3$, 13(2)-COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$*OH*, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$*OH*], 3.72 s (3H, 12-CH$_3$), 3.44 s (3H, 2-CH$_3$), 3.27 s (3H, 7-CH$_3$), 2.78-2.55 m (2H, 17-C*H*$_2$CH$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 2.53-2.23 m (2H, 17-(CH$_2$C*H*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.86 d (3H, 18-CH$_3$, *J* 7.3 Hz), 1.73 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.7 Hz), 0.56 br.s (1H, I-NH), -1.44 br.s (1H, III-NH).

*Recovering of exocycle of chlorophyll a phorbin derivatives with oligotetraethylene glycol fragments (general procedure, synthesis of compounds **22-29**, **30-32**).* 33 % Aqueous methylamine solution (1.0-1.5 ml) was added to solution of start phorbin derivative (50-100 mg, approximately 0.081-0.165 mmol) in THF (5-7 ml) and stirred for 20-60 minutes (until complete conversion of the starting compound, control TLC). The reaction mixture was diluted with 50 ml of chloroform and washed with 1 % hydrochloric acid (200 ml) to remove an excess of methylamine and then with distilled water until neutral reaction of wash waters. The resulting solution was dried over anhydrous sodium sulfate then the solvent was distilled off. The residue after evaporation was chromatographed on silica gel (eluent - mixture of $CCl_4$:acetone = 30:1 ÷ 5:1).

*Chlorin $e_6$ 13(1)-N-methylamide-17-methyl-15-diethylene glycol ester (**22**).* 31.3 mg (60 %) of compound **22** as a dark blue-black crystalline powder was obtained by the action of 33 % aqueous methylamine solution (1 ml) on 50 mg (0.073 mmol) of compound **6** in 5 ml of THF for 20 min at complete conversion of starting compound **6**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{40}H_{50}N_5O_7$) calcd. 712.4, found 712.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (31.2%), 607 (3.9%), 501 (9.9%), 403 (100%). IR (KBr) $cm^{-1}$: 3377 (ν OH); 3305 (ν NH of chlorin cycle); 2959 2957 ($\nu_{CH}^{as}CH_3$); 2926 ($\nu_{CH}^{as}CH_2$); 2868 ($\nu_{CH}^{s}CH_3$); 2733 ($\nu_{CH}CH_2$-O-, glycol); 1734 (ν C=O, ester); 1653 (ν C=O, «amide I»); 1616 («chlorin band»); 1547 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. 9.74 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.86 s (1H, $H^{20}$), 8.13 dd (1H, 3-*CH*=$CH_2$, *J* 18.3 and 11.7 Hz), 7.31-7.22 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 18.3 Hz), 6.18 d (1H, 3-CH=CHH$_{cis}$ *J* 11.7 Hz), 5.59 d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 5.40 br.d (1H, 15-CH$_A$*H*$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 4.52 q (1H, $H^{18}$, *J* 7.0 Hz), 4.45 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.37-4.11 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OH), 3.84 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.7 Hz), 3.63 s (3H, 17-CH$_2$CH$_2$COO*CH*$_3$), 3.60 s (3H, 12-CH$_3$), 3.54 s (3H, 2-CH$_3$), 3.36 s (3H, 7-CH$_3$), 3.28 d (3H, 13-CONH*CH*$_3$, *J* 4.4 Hz), 3.19-2.79 m (6H, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 2.60-2.46 and 2.35-2.22 (both m 1H, 17-*CH*$_2$CH$_2$COOCH$_3$), 2.16-2.01 and 1.98-1.83 (both m 1H, 17-CH$_2$*CH*$_2$COOCH$_3$), 1.76 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.3 Hz), 1.72 d (3H, 18-CH$_3$, *J* 7.0 Hz), -1.63 br.s (1H, I-NH), -1.83 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide-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 methylamine 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 $MH^+$ ($C_{42}H_{54}N_5O_8$) calcd. 756.4, found 756.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 662 (30.8%), 607 (3.8%), 501 (9.9%), 403 (100%). IR (KBr) $cm^{-1}$: 3380 (ν OH); 3309 (ν NH of chlorin cycle); 2957 ($\nu_{CH}^{as}CH_3$); 2926 ($\nu_{CH}^{as}CH_2$); 2868 ($\nu_{CH}^{s}CH_3$); 2735 ($\nu_{CH}CH_2$-O-, glycol); 1734 (ν C=O, ester); 1651 (ν C=O, «amide I»); 1600 («chlorin band»); 1549 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.74 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.13 dd (1H, 3-*CH*=$CH_2$, *J* 18.0 and 11.4 Hz), 7.16-7.04 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 18.0 Hz), 6.18 d (1H, 3-CH=CHH$_{cis}$ *J* 11.4 Hz), 5.57 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.7 Hz), 5.40 br.d (1H, 15-CH$_A$*H*$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.7 Hz), 4.51 q (1H, $H^{18}$, *J* 7.3 Hz), 4.44 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.38-4.16 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.83 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.3 Hz), 3.64 s (3H, 17-CH$_2$CH$_2$COO*CH*$_3$), 3.58 s (3H, 12-CH$_3$), 3.53 s (3H, 2-CH$_3$), 3.36 s (3H, 7-CH$_3$), 3.28 br.d (3H, 13-CONH*CH*$_3$, *J* 4.0 Hz), 3.52-3.09 m (6H, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OCH$_2$CH$_2$OH), 2.65-2.02 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_3$), 2.00-1.65 m (4H, 15-CH$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$O*CH*$_2$*CH*$_2$OH), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.3 Hz), 1.72 d (3H, 18-CH$_3$, *J* 7.3 Hz), -1.61 br.s (1H, I-NH), -1.82 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide-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 methylamine solution (1 ml) on the 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 $MH^+$ ($C_{44}H_{58}N_5O_9$) calcd. 800.4, found 800.3, for $MNa^+$ ($C_{44}H_{57}N_5O_9Na$) calcd. 822.4 found 822.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (31.1%), 606 (4.5%), 501 (10.8%), 403 (100%). IR (KBr) $cm^{-1}$: 3380 (ν OH); 3309 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}CH_3$); 2926 ($\nu_{CH}^{as}CH_2$); 2868 ($\nu_{CH}^{s}CH_3$); 2737 ($\nu_{CH}CH_2$-O-, glycol); 1734 (ν C=O, ester); 1651 (ν C=O, «amide I»); 1601 («chlorin band»); 1551 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm. 9.75 s (1H, $H^{10}$), 9.70 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.14 dd (1H, 3-*CH*=$CH_2$, *J* 18.3 and 11.7 Hz), 7.43-7.34 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 18.0 Hz), 6.19 d (1H, 3-CH=CHH$_{cis}$ *J* 11.4 Hz), 5.59 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.0 Hz), 5.41 br.d (1H, 15-CH$_A$*H*$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.0 Hz), 4.51 q (1H, $H^{18}$, *J* 7.3 Hz), 4.45 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.36-4.14 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.85 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.3 Hz), 3.63 s (3H, 17-CH$_2$CH$_2$COO*CH*$_3$), 3.61 s (3H, 12-CH$_3$), 3.54 s (3H, 2-CH$_3$), 3.37 s (3H, 7-CH$_3$), 3.29 d (3H, 13-CONH*CH*$_3$, *J* 4.0 Hz), 3.19-2.79 m (12H, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 2.62-2.17 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_3$), 1.76 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.3 Hz), 1.72 d (3H, 18-CH$_3$, *J* 7.0 Hz), -1.63 br.s (1H, I-NH), -1.84 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide 17-methyl-15-pentaethylene 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 methylamine solution (1 ml) on the 50 mg (0.062 mmol) of compound **9** in 5 ml of THF for 20 min at complete conversion

of starting compound **9**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{46}H_{62}N_5O_{10}$) calcd. 844.4, found 844.3, for $MNa^+$ ($C_{46}H_{61}N_5O_{10}Na$) calcd. 866.4 found 866.3, for $MK^+$ ($C_{46}H_{61}N_5O_{10}K$) calcd. 882.4 found 882.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 656 (32.3%), 602 (4.9%), 498 (11.0%), 398 (100%). IR (KBr) $cm^{-1}$: 3380 (ν OH); 3309 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2737 ($\nu_{CH}$ $CH_2$-O-, glycol); 1732 (ν C=O, ester); 1651 (ν C=O, «amide I»); 1601 («chlorin band»); 1551 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.75 s (1H, $H^{10}$), 9.70 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.14 dd (1H, 3-*CH*=$CH_2$, *J* 18.0 and 11.4 Hz), 7.47-7.35 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 18.0 Hz), 6.19 d (1H, 3-CH=C*H*H$_{cis}$ *J* 11.4 Hz), 5.59 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 5.41 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 4.51 q (1H, $H^{18}$, *J* 7.0 Hz), 4.45 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.36-4.13 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.85 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.6 Hz), 3.64 s (3H, 17-CH$_2$CH$_2$COO*CH*$_3$), 3.62 s (3H, 12-CH$_3$), 3.54 s (3H, 2-CH$_3$), 3.37 s (3H, 7-CH$_3$), 3.30 d (3H, 13-CONH*CH*$_3$, *J* 4.3 Hz), 3.19-2.79 m (18H, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 2.62-2.00 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_3$), 1.76 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.6 Hz), 1.72 d (3H, 18-CH$_3$, *J* 7.0 Hz), -1.63 br.s (1H, I-NH), -1.85 br.s (1H, III-NH).

*Chlorin e$_6$ 13(1)-N-methylamide-17-methyl-15-hexaethylene glycol ester (**26**).* 29.5 mg (57%) of compound **26** as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methylamine 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 $MH^+$ ($C_{48}H_{66}N_5O_{11}$) calcd. 888.5, found 888.4, for $MNa^+$ ($C_{48}H_{65}N_5O_{11}Na$) calcd. 910.5 found 910.4, for $MK^+$ ($C_{48}H_{65}N_5O_{11}K$) calcd. 926.4 found 926.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (31.6 %), 607 (4.4 %), 501 (10.3 %), 403 (100 %). IR (KBr) $cm^{-1}$: 3380 (ν OH); 3308 (ν NH of chlorin cycle); 2953 ($\nu_{CH}^{as}$ $CH_3$); 2922 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2741 ($\nu_{CH}$ $CH_2$-O-, glycol); 1734 (ν C=O, ester); 1651 (ν C=O, «amide I»); 1601 («chlorin band»); 1549 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.75 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.14 dd (1H, 3-*CH*=$CH_2$, *J* 16.9 and 10.7 Hz), 7.54-7.33 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 16.9 Hz), 6.19 d (1H, 3-CH=C*H*H$_{cis}$, *J* 10.3 Hz), 5.59 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 5.41 br.d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 4.63-4.39 m (2H, $H^{18}$ and $H^{17}$), 4.37-4.10 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.93-3.79 m (2H, 8-*CH*$_2$CH$_3$), 3.64 s (3H, 17-CH$_2$CH$_2$COO*CH*$_3$), 3.62 s (3H, 12-CH$_3$), 3.54 s (3H, 2-CH$_3$), 3.36 s (3H, 7-CH$_3$), 3.30 d (3H, 13-CONH*CH*$_3$, *J* 4.3 Hz), 3.19-2.79 m (22H, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 2.62-2.00 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_3$), 1.76 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.6 Hz), 1.72 d (3H, 18-CH$_3$, *J* 7.0 Hz), -1.63 br.s (1H, I-NH), -1.84 br.s (1H, III-NH).

*Chlorin e$_6$ 13(1)-N-methylamide-15-methyl-17-diethylene glycol ester (**27**).* 30.4 mg (58%) of compound **27** as a dark blue-black crystalline powder was obtained by the action of 33 % aqueous methylamine solution (1 ml) on the 50 mg (0.073 mmol) of compound **11** in 5 ml of THF for 20 min at complete conversion of starting compound **11**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{40}H_{50}N_5O_7$) calcd. 712.4, found 712.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (29.6%), 607 (3.6%), 501 (9.2%), 403 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3308 (ν NH of chlorin cycle); 2957 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2733 ($\nu_{CH}$ $CH_2$-O-, glycol); 1734 (ν C=O, ester); 1647 (ν C=O, «amide I»); 1601 («chlorin band»); 1549 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.75 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.13 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.7 Hz), 6.58-6.46 m (1H, 13-CO*NH*$CH_3$), 6.40 dd (1H, 3-CH=CH*H*$_{trans}$, *J* 17.9 and 1.1 Hz), 6.19 dd (1H, 3-CH=C*H*H$_{cis}$, *J* 11.7 and 1.1 Hz), 5.55 d (1H, 15-C*H*$_A$H$_B$CO$_2$CH$_3$, *J* 19.0 Hz), 5.32 d (1H, 15-CH$_A$*H*$_B$CO$_2$CH$_3$, *J* 19.0 Hz), 4.51 q (1H, $H^{18}$, *J* 7.3 Hz), 4.44 br.d (1H, $H^{17}$, *J* 8.4 Hz), 4.16 dd (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 5.9 and 3.7 Hz), 3.84 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.3 Hz), 3.86 s (3H, 15-CH$_2$CO$_2$COCH$_3$), 3.60 s (3H, 12-CH$_3$), 3.53 s (3H, 2-CH$_3$), 3.67-3.49 m (5H, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$CH$_2$*OH*), 3.48-3.43 m (2H, 17-CH$_2$CH$_2$COOCH$_2$CH$_2$OCH$_2$*CH*$_2$OH), 3.36 s (3H, 7-CH$_3$), 3.31 d (3H, 13-CONH*CH*$_3$, *J* 4.8 Hz), 2.60-2.45 m 1H, 2.35-2.16 m 2H and 2.14-2.00 m 1H (17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.77 d (3H, 18-CH$_3$, *J* 7.0 Hz), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.3 Hz), -1.60 br.s (1H, I-NH), -1.78 br.s (1H, III-NH).

*Chlorin e$_6$ 13(1)-N-methylamide 15-methyl-17-triethylene glycol ester (**28**).* 5.0 mg (16%) of compound **28** as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methylamine solution (1 ml) on the 30 mg (0.041 mmol) of compound **12** in 3 ml of THF for 1 h at complete conversion of starting compound **12**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{42}H_{54}N_5O_8$) calcd. 756.4, found 756.4, for $MNa^+$ ($C_{42}H_{53}N_5O_8Na$) calcd. 778.4 found 778.4, for $MK^+$ ($C_{42}H_{53}N_5O_8K$) calcd. 794.3 found 794.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (31.6%), 608 (5.4%), 500 (11.7%), 402 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3307 (ν NH of chlorin cycle); 2957 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2733 ($\nu_{CH}$ $CH_2$-O-, glycol); 1734 (ν C=O, ester); 1647 (ν C=O, «amide-I»); 1601 («chlorin band»); 1551 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.76 s (1H, $H^{10}$), 9.70 s (1H, $H^5$), 8.87 s (1H, $H^{20}$), 8.13 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.4 Hz), 6.66-6.52 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 17.6 Hz), 6.20 d (1H, 3-CH=C*H*H$_{cis}$, *J* 11.7 Hz), 5.56 d (1H, 15-C*H*$_A$H$_B$CO$_2$CH$_3$, *J* 19.1 Hz), 5.33 d (1H, 15-CH$_A$*H*$_B$CO$_2$CH$_3$, *J* 19.1 Hz), 4.52 q (1H, $H^{18}$, *J* 7.3 Hz), 4.45 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.15 dd (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 5.1 and 4.0 Hz), 3.84 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.7 Hz), 3.86 s (3H, 15-CH$_2$CO$_2$COCH$_3$), 3.59 s (3H, 12-CH$_3$), 3.54 s (3H, 2-CH$_3$), 3.58-3.33 m (10H, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$*OH*), 3.36 s (3H, 7-CH$_3$), 3.30 d (3H, 13-CONH*CH*$_3$, *J* 4.4 Hz), 2.61-2.47 m 1H and 2.34-2.04 m 3H (17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.77 d (3H, 18-CH$_3$, *J* 7.3 Hz), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.7Hz), -1.65 br.s (1H, I-NH), -1.81 br.s (1H, III-NH).

*Chlorin e$_6$ 13(1)-N-methylamide 15-methyl-17-tetraethylene glycol ester (**29**).* 10.3 mg (21%) of compound **29** as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methylamine 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 $MH^+$ ($C_{44}H_{58}N_5O_9$) calcd. 800.4, found 800.3, for $MNa^+$ ($C_{44}H_{57}N_5O_9Na$) calcd. 822.4 found 822.4, for $MK^+$ ($C_{44}H_{57}N_5O_9K$) calcd. 838.4 found 838.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (31.5%), 607 (4.2%), 500 (10.0%), 403 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3306 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2924 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2735 ($\nu_{CH}$ $CH_2$-O-, glycol); 1734 (ν C=O, ester); 1651 (ν C=O, «amide-I»); 1601 («chlorin band»); 1549 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.74 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.86 s (1H, $H^{20}$), 8.13 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.4 Hz), 6.57-6.46 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH*H*$_{trans}$, *J* 17.6 Hz), 6.19 d (1H, 3-CH=C*H*H$_{cis}$, *J* 11.7 Hz), 5.55 d (1H, 15-C*H*$_A$H$_B$CO$_2$CH$_3$, *J* 18.7 Hz), 5.31 d (1H, 15-CH$_A$*H*$_B$CO$_2$CH$_3$, *J* 18.7 Hz), 4.52 q (1H, $H^{18}$, *J* 7.0 Hz), 4.42 br.d (1H, $H^{17}$, *J* 8.8 Hz), 4.24-4.12 m (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.86 s (3H, 15-CH$_2$CO$_2$COCH$_3$), 3.84 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.3 Hz), 3.59 s (3H, 12-CH$_3$), 3.51 s (3H, 2-CH$_3$), 3.64-3.34 m (14H, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 3.36 s (3H, 7-CH$_3$), 3.30 d (3H, 13-CONH*CH*$_3$, *J* 4.8 Hz), 2.64-2.46 m 1H and 2.36-2.05 m 3H (17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.76 d (3H, 18-CH$_3$, *J* 7.0 Hz), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.3 Hz), -1.61 br.s (1H, I-NH), -1.78 br.s (1H, III-NH).

*Chlorin e$_6$ 13(1)-N-methylamide 15,17-bis(diethylene glycol) ester (**30**).* 14.1 mg (42%) of compound **30** as a dark blue-black

crystalline powder was obtained by the action of 33% aqueous methylamine 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 $MH^+$ ($C_{43}H_{56}N_5O_9$) calcd. 786.4, found 786.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (28.8%), 607 (3.2%), 501 (8.5%), 403 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3309 (ν NH of chlorin cycle); 2957 ($\nu_{CH}^{as}$ $CH_3$); 2926 ($\nu_{CH}^{as}$ $CH_2$); 2868 ($\nu_{CH}^{s}$ $CH_3$); 2733 ($\nu_{CH}$ $CH_2$-O-, glycol); 1730 (ν C=O, ester); 1637 (ν C=O, «amide-I»); 1601 («chlorin band»); 1552 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.78 s (1H, $H^{10}$), 9.73 s (1H, $H^5$), 8.88 s (1H, $H^{20}$), 8.14 dd (1H, 3-*CH*=$CH_2$, *J* 17.8 and 11.7 Hz), 7.23-7.04 m (1H, 13-CO*NH*$CH_3$), 6.40 d (1H, 3-CH=CH$H_{trans}$, *J* 17.6 Hz), 6.20 d (1H, 3-CH=CH$H_{cis}$, *J* 11.7 Hz), 5.59 d (1H, 15-C$H_AH_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.1 Hz), 5.42 d (1H, 15-CH$_A$$H_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.1 Hz), 4.52 q (1H, $H^{18}$, *J* 7.7 Hz), 4.49 br.d (1H, $H^{17}$, *J* 8.0 Hz), 4.40-4.25 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OH), 4.21 br.t (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 4.4 Hz), 3.85 q (2H, 8-*CH*$_2$CH$_3$, *J* 8.1 Hz), 3.71-3.41 m (12H, 17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 3.60 s (3H, 12-$CH_3$), 3.54 s (3H, 2-$CH_3$), 3.37 s (3H, 7-$CH_3$), 3.30 d (3H, 13-CONH*CH*$_3$, *J* 4.4 Hz), 2.60-2.00 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.74 d (3H, 18-$CH_3$, *J* 8.0 Hz), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 8.4 Hz), -1.66 br.s (1H, I-NH), -1.85 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide 15,17-bis(triethylene glycol) ester (**31**).* 14 mg (43%) of compound **31** as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methylamine 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 $MH^+$ ($C_{47}H_{64}N_5O_{11}$) calcd. 875.5, found 874.4, for $MNa^+$ ($C_{47}H_{63}N_5O_{11}Na$) calcd. 896.4 found 896.4, $MK^+$ ($C_{47}H_{63}N_5O_{11}K$) calcd. 912.4, found 912.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (28.8%), 607 (3.2%), 501 (8.5%), 403 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3317 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2924 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2737 ($\nu_{CH}$ $CH_2$-O-, glycol); 1730 (ν C=O, ester); 1645 (ν C=O, «amide-I»); 1601 («chlorin band»); 1551 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.77 s (1H, $H^{10}$), 9.72 s (1H, $H^5$), 8.88 s (1H, $H^{20}$), 8.14 dd (1H, 3-*CH*=$CH_2$, *J* 17.6 and 11.7 Hz), 7.42-7.32 m (1H, 13-CO*NH*$CH_3$), 6.41 d (1H, 3-CH=CH$H_{trans}$, *J* 17.6 Hz), 6.20 d (1H, 3-CH=CH$H_{cis}$, *J* 11.7 Hz), 5.59 d (1H, 15-C$H_AH_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.7 Hz), 5.44 d (1H, 15-CH$_A$$H_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.7 Hz), 4.53 q (1H, $H^{18}$, *J* 7.3 Hz), 4.50 br.d (1H, $H^{17}$, *J* 8.0 Hz), 4.35-4.20 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 4.16 dd (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 4.7 and 3.1 Hz), 3.85 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.7 Hz), 3.65-3.33 m 12H and 3.22-2.80 m 8H (17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 3.61 s (3H, 12-$CH_3$), 3.51 s (3H, 2-$CH_3$), 3.37 s (3H, 7-$CH_3$), 3.29 d (3H, 13-CONH*CH*$_3$, *J* 4.8 Hz), 2.59-2.22 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.75 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.0 Hz), 1.74 d (3H, 18-$CH_3$, *J* 6.2 Hz), -1.70 br.s (1H, I-NH), -1.87 br.s (1H, III-NH).

*Chlorin $e_6$ 13(1)-N-methylamide 15,17-bis(tetraethylene glycol) ester (**32**).* 15.0 mg (46%) of compound **31** as a dark blue-black crystalline powder was obtained by the action of 33% aqueous methylamine solution (1 ml) on the 30 mg (0.040 mmol) of compound **21** in 3 ml of THF for 1 h at complete conversion of starting compound **21**. Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{51}H_{72}N_5O_{13}$) calcd. 962.5, found 962.8, for $MNa^+$ ($C_{51}H_{71}N_5O_{13}Na$) calcd. 984.5, found 984.7, $MK^+$ ($C_{51}H_{71}N_5O_{13}K$) calcd. 1000.5, found 1000.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 663 (29.7%), 607 (4.3%), 501 (10.2%), 403 (100%). IR (KBr) $cm^{-1}$: 3382 (ν OH); 3312 (ν NH of chlorin cycle); 2955 ($\nu_{CH}^{as}$ $CH_3$); 2922 ($\nu_{CH}^{as}$ $CH_2$); 2870 ($\nu_{CH}^{s}$ $CH_3$); 2743 ($\nu_{CH}$ $CH_2$-O-, glycol); 1732 (ν C=O, ester); 1645 (ν C=O, «amide-I»); 1601 («chlorin band»); 1551 («amide-II»). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.74 s (1H, $H^{10}$), 9.69 s (1H, $H^5$), 8.85 s (1H, $H^{20}$), 8.10 dd (1H, 3-*CH*=$CH_2$, *J* 18.0 and 11.7 Hz), 7.47-7.36 m (1H, 13-CO*NH*$CH_3$), 6.37 d (1H, 3-CH=CH$H_{trans}$, *J* 18.0 Hz), 6.17 d (1H, 3-CH=CH$H_{cis}$, *J* 11.7 Hz), 5.56 d (1H, 15-C$H_AH_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.3 Hz), 5.38 d (1H, 15-CH$_A$$H_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 18.3 Hz), 4.50 q (1H, $H^{18}$, *J* 7.7 Hz), 4.49-4.41 m (1H, $H^{17}$), 4.33-4.10 m (2H, 15-CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 4.12 dd (2H, 17-CH$_2$CH$_2$COO*CH*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 5.1 and 3.7 Hz), 3.82 q (2H, 8-*CH*$_2$CH$_3$, *J* 7.7 Hz), 3.64-3.30 m 22H and 3.11-2.82 m 8H (17-CH$_2$CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH, 15-CH$_2$COOCH$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$O*CH*$_2$*CH*$_2$OH), 3.58 s (3H, 12-$CH_3$), 3.49 s (3H, 2-$CH_3$), 3.34 s (3H, 7-$CH_3$), 3.26 d (3H, 13-CONH*CH*$_3$, *J* 4.4 Hz), 2.57-2.17 m (4H, 17-*CH*$_2$*CH*$_2$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 1.72 t (3H, 8-CH$_2$C*H*$_3$, *J* 7.7 Hz), 1.70 d (3H, 18-$CH_3$, *J* 7.7 Hz), -1.76 br.s (1H, I-NH), -1.90 br.s (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 hour. The reaction was monitored by TLC (eluent: $CCl_4$ -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 $CCl_4$-acetone in ratios ranging from 30:1 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 $MH^+$ ($C_{43}H_{55}N_4O_8$) calcd. 755.4, found 755.4, for $MNa^+$ ($C_{43}H_{52}N_4O_9Na$) calcd. 777.4, found 777.4, $MK^+$ ($C_{43}H_{52}N_4O_9K$) calcd. 793.4, found 793.3. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.9%), 611 (9.3%), 558 (4.4%), 538 (10.7%), 414 (100%). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.54 s (1H, $H^{10}$), 9.43 s (1H, $H^5$), 8.61 s (1H, $H^{20}$), 8.04 dd (1H, 3-C*H*=$CH_2$, *J* 18.0 and 11.7 Hz), 6.32 d (1H, 3-CH=CH$H_{trans}$, *J* 18.0 Hz), 6.21 d (1H, 3-CH=CH$H_{cis}$, *J* 11.7 Hz), 5.31 d (1H, $H^{13(2)}_A$ , *J* 20.2 Hz), 5.16 d (1H, $H^{13(2)}_B$, *J* 20.2 Hz), 4.54 q (1H, $H^{18}$, *J* 7.3 Hz), 4.36 br.d (1H, $H^{17}$, *J* 7.3 Hz), 4.25-4.16 m (2H, 17-CH$_2$CH$_2$COOC*H*$_2$CH$_2$O(CH$_2$CH$_2$O)$_3$CH$_2$CH$_2$OH), 3.73 q (2H, 8-(C*H*$_2$CH$_3$), *J* 7.3 Hz), 3.71 s (3H, 12-$CH_3$), 3.45 s (3H, 2-$CH_3$), 3.78-3.46 m (18H, CH$_2$CH$_2$COOCH$_2$*CH*$_2$O(*CH*$_2$*CH*$_2$O)$_3$*CH*$_2$*CH*$_2$OH), 3.27 s (3H, 7-$CH_3$), 2.83-2.57 m [2H, 17-*CH*$_2$CH$_2$COOCH$_2$(CH$_2$OCH$_2$)$_4$CH$_2$OH), 2.44-2.29 m [2H, 17-CH$_2$*CH*$_2$COOCH$_2$(CH$_2$OCH$_2$)$_4$CH$_2$OH), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.73 t (8-CH$_2$C*H*$_3$, *J* 7.3 Hz), 0.43 br.s (1H, I-NH), -1.67 br.s (1H, III-NH).

*Pyropheophorbide a 17-pentaethylene glycol ester (**18**).* To a solution of 33.0 mg (0.060 mmol) of pyropheophorbide *a* (**3**) in 5 ml of chloroform 15.9 mg of DMAP, 15.3 mg of 2-chloro-*N*-methylpyridinium iodide and 0.1 ml of hexaethylene glycol was added. The mixture was boiled under reflux for 1.5 hour. Hereinafter the synthesis and isolation of the reaction product was carried out analogously to the procedure of synthesis of pentaethylene glycol derivative **17**. The yield of compound **18** was 15 mg (30%). Mass-spectrum (ESI) *m/z*: for $MH^+$ ($C_{45}H_{59}N_4O_9$) calcd. 799.4, found 799.6, for $MNa^+$ ($C_{45}H_{58}N_4O_9Na$) calcd. 821.4, found 821.5, $MK^+$ ($C_{43}H_{52}N_4O_9K$) calcd. 837.4, found 837.4. UV-Vis ($CHCl_3$) λ nm (relative intensity, %): 668 (46.9%), 611 (9.3%), 558 (4.4%), 538 (10.7%), 414 (100%). $^1$H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.48 s (1H, $H^{10}$), 9.38 s (1H, $H^5$), 8.60 s (1H, $H^{20}$), 8.01 dd (1H, 3-C*H*=$CH_2$, *J* 17.5 and 11.5 Hz], 6.30 d [1H, 3-CH=CH$H_{trans}$, *J* 17.6 Hz), 6.19 d (1H, 3-CH=CH$H_{cis}$, *J* 12.1 Hz), 5.30 d (1H, $H^{13(2)}_A$ , *J* 20.0 Hz), 5.15 d (1H, $H^{13(2)}_B$, *J* 20.1 Hz), 4.53 q (1H, $H^{18}$, *J* 7.1 Hz), 4.34 br.d (1H, $H^{17}$, *J* 7.1 Hz), 4.25-4.16 m (2H, 17-CH$_2$CH$_2$COOC*H*$_2$CH$_2$O(CH$_2$CH$_2$O)$_4$CH$_2$CH$_2$OH), 3.71 s (3H, 12-$CH_3$), 3.44 s (3H,

2-$CH_3$), 3.78-3.46 m (24H, 8-C*H*$_2$CH$_3$, $CH_2CH_2COOCH_2CH_2O(CH_2CH_2O)_4CH_2CH_2OH$), 3.24 s (3H, 7-$CH_3$), 2.83-2.57 m [2H, 17-*CH*$_2$CH$_2$COOCH$_2$(CH$_2$OCH$_2$)$_4$CH$_2$OH), 2.44-2.29 m (2H, 17-CH$_2$*CH*$_2$COOCH$_2$(CH$_2$OCH$_2$)$_4$CH$_2$OH), 1.86 d (3H, 18-$CH_3$, *J* 7.0 Hz), 1.73 t (8-CH$_2$C*H*$_3$, *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 exocycle 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 adduct 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 $^1$H 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 $^1$H 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 pheophorbide *a* $^1$H 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 $^1$H NMR spectra of methylpheophorbide *a* (**1**) and its diethylen glycol esters (**6** and **11**) with different positions of glycol substituent as an example). The investigation of $^1$H 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 $e_6$ 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 $^1$H NMR spectra of compounds **22-32**. Preparation of di-, tri- and tetraethylene 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 tetraethylene 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 oligothylene 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 methylpheophorbides **6-10** with the di-, tri-, tetra-, penta- and hexaethylene glycol fragments: it is known that the ester group exocycle methylpheophorbide has a relatively high chemical activity and, therefore, can undergo a trans-esterification reaction.[33-36] Synthesis of chlorin $e_6$ derivatives with oligoethylene glycol substituents at position 15 (**22-26**) was carried out by the action of methylamine on phorbin derivatives **6-10**. Chlorin $e_6$ 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 $e_6$ 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 $e_6$ derivatives with oligoethylene glycol fragments at position 17 (**27-29**) are more convenient to receive via appropriate 17-ester pheophorbide *a* **11-13**.

For the hydrophilicity estimation of biologically active substances the characteristics of their distribution between

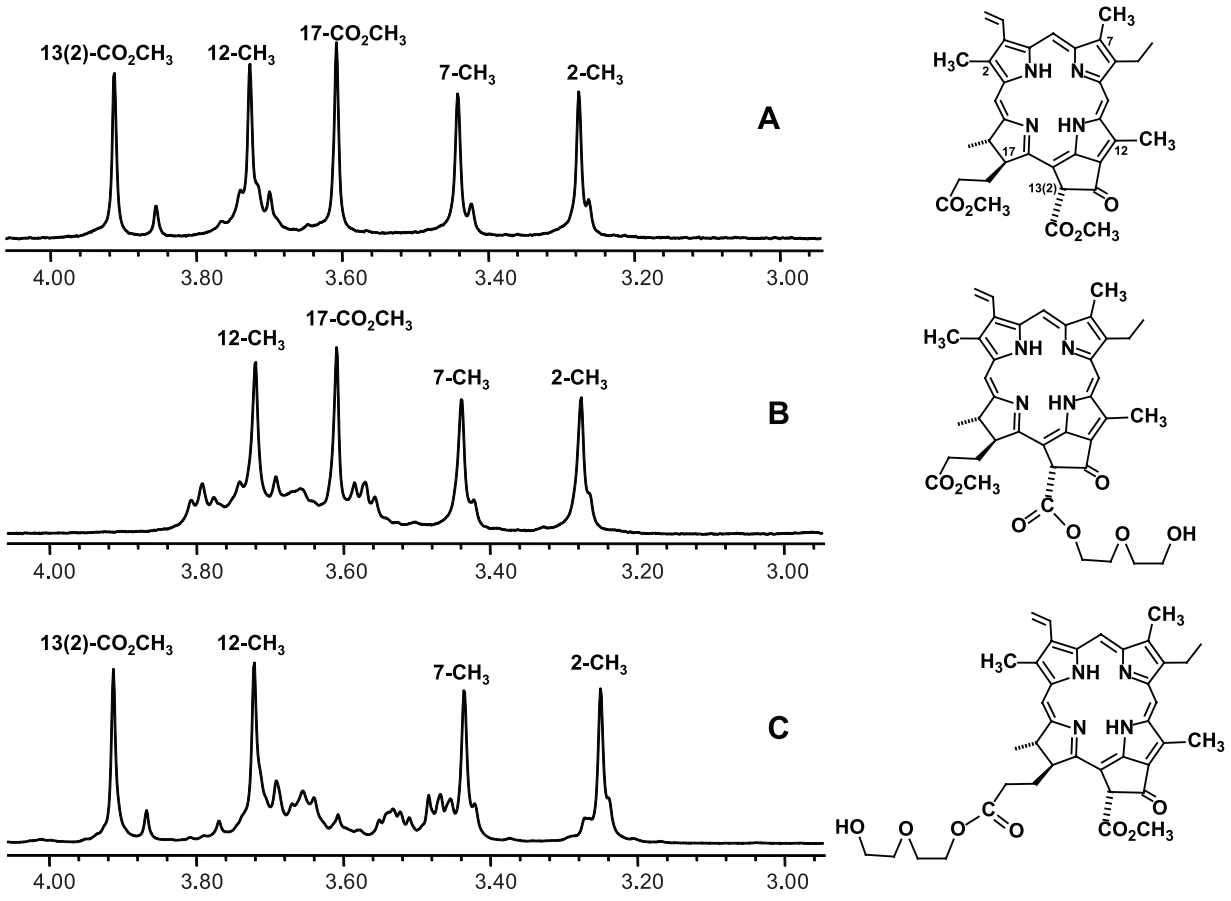
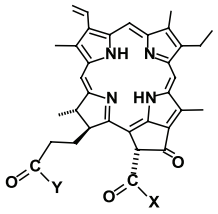
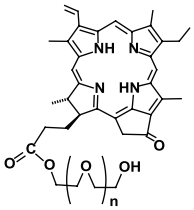
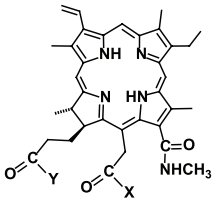



**Figure 1.** $^1$H NMR spectra of methylpheophorbide *a* (**1**) and its diethylene glycol esters **6** (B) and **11** (C) ($CDCl_3$, 300 MHz, 3-4 ppm).

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 $e_6$ 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

**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.

| n |  Gl = $OCH_2(CH_2OCH_2)_nCH_2OH$ | | |  |  Gl = $OCH_2(CH_2OCH_2)_nCH_2OH$ | | |
|---|---|---|---|---|---|---|---|
| | X = Gl Y = $OCH_3$ | X = $OCH_3$ Y = Gl | X = Y = Gl | | X = Gl Y = $OCH_3$ | X = $OCH_3$ Y = Gl | X = Y = Gl |
| 1 | 37.76 (**6**) | 36.68 (**11**) | 29.13 (**19**) | 41.64 (**14**) | 36.14 (**22**) | 34.01 (**27**) | 27.03 (**30**) |
| 2 | 37.54 (**7**) | 36.56 (**12**) | 33.28 (**20**) | 41.48 (**15**) | 36.46 (**23**) | 34.43 (**28**) | 31.19 (**31**) |
| 3 | 36.81 (**8**) | 36.39 (**13**) | 31.90 (**21**) | 41.22 (**16**) | 36.22 (**24**) | 33.98 (**29**) | 30.09 (**32**) |
| 4 | 36.46 (**9**) | | | 43.09 (**17**) | 35.93 (**25**) | | |
| 5 | 36.58 (**10**) | | | 40.74 (**18**) | 36.12 (**26**) | | |
| (*) | | 41.16 (**1**) | | 45.92 (**2**) | | 40.96 (**4**) | |

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 increases 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.

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