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Novel Dicationic Chlorin e_6 Derivatives

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Number of dicationic chlorins with additional hydrophobic (alkyl) and hydrophilic (polyether) groups were synthesized on the basis of methyl pheophorbide a. Novel dicationic amphiphilic chlorins with different hydrophobic part size were obtained by alkylation of tertiary amino groups of twice aminomethylated chlorin e_6 derivatives by methyl iodide. It has been shown that several of the dicationic chlorins obtained can form true solutions in water and introduction of hydrophobic substituents to amide group (starting with two methyl groups or one ethyl) leads to a loss of solubility. Cationic derivatives with polyether moieties at the macrocycle periphery are unexpectedly insoluble in water, despite of hydrophilic moieties presence.

Keywords: Methyl pheophorbide *a*, chlorin e_6, dicationic chlorins.

Новые дикатионные производные хлорина e_6

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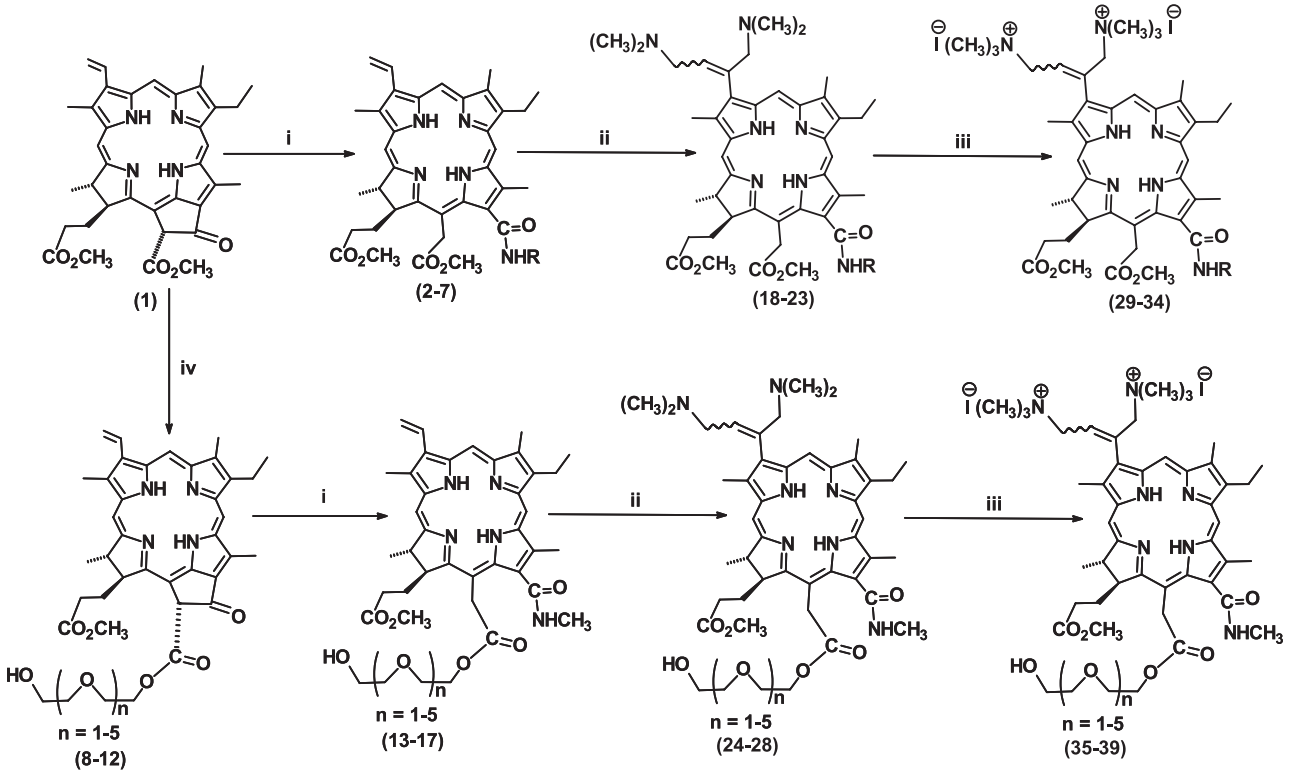
На основе метилфеофорбида а синтезирован ряд дикатионных хлоринов с дополнительными гидрофобными (алкильными) и гидрофильными (полиэфирными) группами. Алкилированием третичных амино-групп дважды аминометилированных производных хлорина e_6 йодистым метилом получены не описанные ранее амфифильные дикатионные хлорины, различающиеся размером гидрофобной части. Показано, что некоторые из полученных дикатионных хлоринов могут образовывать истинные растворы в воде, причем внедрение в амидную группу гидрофобных заместителей (начиная с двух метильных или одной этильной группы) приводит к потере растворимости. Катионные производные с полиэфирными фрагментами на периферии макроцикла неожиданно оказались нерастворимыми в воде, несмотря на наличие гидрофильных фрагментов.

Ключевые слова: Метилфеофорбид *а*, хлорин e_6, дикатионные хлорины.

Introduction

The porphyrin compounds photosensitizing properties are intensively studed and used in various fields of medicine, such as oncology,[1-6] otolaryngology,[7,8] ophthalmology,[9,10] surgery,[11] the treatment of bacterial[6] and fungal[12] diseases. A number of preparations based on porphyrins are in clinical practice now.[1-6,11-17] Some chlorophyll *a* derivatives were found to be highly active photo sensitizers (PS) with low dark toxicity.[1-6,13-16] Thus, new medical PS searching among chlorophyll *a* derivatives is of a good chance. Modification of chlorins chemical structure features such as charge, hydrophobicity and steric properties leads to the significant changing of the pigments ability to insert into the cell which can define their photodynamic effectivity.[17,18] The cationic groups insertion results in hydrophilicity increasing as well as selective binding with mitochondria membrane.[2,6] Therefore such PS cause selective organelles damage which significantly increases their efficiency and leads to apoptosis of malignant neoplasms which is more advantageous from the viewpoint of therapeutic effect. Also the cationic PSs show photoinduced antibacterial activity against gram-negative bacteria.[6] The activity against these bacteria caused by the negatively charged external membrane is an effective barrier to permeation of hydrophobic and anionic molecules. The cationic groups presence in the PS molecule promotes the interaction with negatively charged outer membrane of these bacteria, resulting in an effective photodamage and death of the bacteria. Gram negative bacteria are known to be most pathogens and resistant to various types of impacts, however, development of resistance in relation to the photodynamic action is impossible.[6] Thus, the development of methods for the cationic groups introduction to the such derivatives molecule is an urgent task. The tertiary amino groups quaternization were used for the formation of cationic substituent. This approach was used in the case of synthetic porphyrins[19-25] as well as in the case of natural porphyrins.[26-29] We have previously developed the method of aminomethylation of chlorin e_6 derivatives vinyl group by action of *bis*(*N,N*-dimethylamino)methane.[30] This method allows to obtain chlorin e_6 derivatives with two dimethylamino substituents in vinyl group. Quaternization of the dimethylaminomethyl group allows to synthesize compounds with two cationic groups, which are localized in one part of the molecule. So, the dicationic amphiphilic derivatives with different size of hydrophobic part may be synthesized. The combination of cationic groups with electrically neutral hydrophilic polyether fragments in one molecule is of significant interest for new water-soluble cationic photosensitizers development. At present work a series of dicationic chlorins with additional hydrophobic (alkyl) and hydrophilic (polyether) groups were synthesized based on methylpheophorbide *a* (**1**) (Scheme 1).



R = CH_3 (**2, 18, 29**); C_2H_5 (**3, 19, 30**); C_4H_9 (**4, 20, 31**); C_6H_{13} (**5, 21, 32**); C_8H_{17} (**6, 22, 33**); $(CH_2)_2OH$ (**7, 23, 34**); n = 1 (**8, 13, 24, 35**); n = 2 (**9, 14, 25, 36**); n = 3 (**10, 15, 26, 37**); n = 4 (**11, 16, 27, 38**); n = 5 (**12, 17, 28, 39**).

i: the reactions were carried out according to[30-33]; ii: $((CH_3)_2N)_2CH_2$, THF/AcOH, refluxing, 20-30 min, derivatives **18-23** were obtained according to[30], **23-28** were obtained similarly to [30], yielding **24** (50 %), **25** (47 %), **26** (45 %), **27** (43 %), **28** (51 %); iii: CH_3I, THF or CH_2Cl_2, r. t., 60 min (yields are quantitative); iv: reactions were carried out according to[33].

Scheme 1.

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). 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. Mass spectra were obtained by Thermo finnigan LCQ Flut (ESI) instrument. 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.

Chlorin e_6 13(1)-*N*-methylamide-15(2),17(3)-dimethyl ester (**2**), chlorin e_6 13(1)-*N*-ethylamide-15(2),17(3)-dimethyl ester (**3**), chlorin e_6 13(1)-*N*-hydroxyethylamide-15(2),17(3)-dimethyl ester (**7**) were obtained according to [31,35].

Chlorin e_6 13(1)-*N*-(*n*-butyl)-amide-15(2),17(3)-dimethyl ester (**4**), chlorin e_6 13(1)-*N*-(*n*-hexyl)-amide-15(2),17(3)-dimethyl ester (**5**), chlorin e_6 13(1)-*N*-(*n*-octyl)-amide-15(2),17(3)-dimethyl ester (**6**) were obtained according to [32].

Methyl pheophorbide *a* 13(2)-diethylene glycol ester (**8**), methyl pheophorbide *a* 13(2)-triethylene glycol ester (**9**), methyl pheophorbide *a* 13(2)-tetraethylene glycol ester (**10**), methyl pheophorbide *a* 13(2)-pentaethylene glycol ester (**11**), methyl pheophorbide *a* 13(2)-hexaethylene glycol ester (**12**), chlorin e_6 13(1)-*N*-methylamide 17-methyl-15-diethylene glycol ester (**13**), chlorin e_6 13(1)-*N*-methylamide 17-methyl-15-triethylene glycol ester (**14**), chlorin e_6 13(1)-*N*-methylamide 17-methyl-15-tetraethylene glycol ester (**15**), chlorin e_6 13(1)-*N*-methylamide 17-methyl-15-pentaethylene glycol ester (**16**), chlorin e_6 13(1)-*N*-methylamide 17-methyl-15-hexaethylene glycol ester (**17**) were obtained according to [33].

Chlorin e_6 Amides Aminomethylation

Chlorin e_6 amides interaction with bis(N,N-dimethylamino) methane (general procedure). To a solution of chlorin e_6 13-amides (**2-7**, **13-17**) (30-100 mg, 0.036-0.113 mmol) in a mixture of equal volumes of THF and acetic acid (3–7 ml) *bis*(*N,N*-dimethylamino) methane (0.1–0.5 ml, 0.73–3.7 mmol) was added. The resulted mixture was refluxed for 20–60 minutes, then diluted with chloroform, washed with water, dried by anhydrous sodium sulfate and evaporated to dryness under reduced pressure at 40–50 °C. The residue after evaporation was chromatographed on silica gel (eluent: CCl_4-acetone, 60:1–1:1 then $CHCl_3$-C_2H_5OH, 30:1–1:1). The eluate containing main substance, was evaporated under reduced pressure.

3(1),3(2)-Bis(*N,N*-dimethylamino)chlorin e_6 13(1)-*N*-methylamide-15(2),17(3)-dimethyl ester (**18**), *3(1),3(2)*-bis(*N,N*-dimethylamino)chlorin e_6 13(1)-*N*-butylamide-15(2),17(3)-dimethyl ester (**20**), *3(1),3(2)*-bis(*N,N*-dimethylamino)chlorin e_6 13(1)-*N*-hexylamide-15(2),17(3)-dimethyl ester (**21**), 3(1),3(2)-bis(*N,N*-dimethylamino)chlorin e_6 13(1)-*N*-octylamide-15(2),17(3)-dimethyl ester (**22**) were obtained according to [30].

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-ethylamide-15(2),17(3)-dimethyl ester (**19**), 3(1),3(2)-bis(N,N-dimethylamino)chlorin e_6 13(1)-N-2-hydroxyethylamide-15(2),17(3)-dimethyl ester (**23**)* were obtained analogously to **18**. Compound **19** (50 mg, 54 % yield) was prepared from 79 mg of compound **3**. UV-Vis (CH_2Cl_2) λ nm: 398.0 (100%), 498.0 (7%), 554.0 (1%), 604.0 (3%), 659.0 (33%). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.86 s (1H, H^{10}), 9.74 s (1H, H^5), 8.82/8.83* s (1H, H^{20}), 7.38-7.30 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.42 br.t (1H, 13^1-CON*H*C_2H_5), 5.58 d (1H, $H^{15(1)}{}_A$, *J* 19.2 Hz), 5.29 d (1H, $H^{15(1)}{}_B$, *J* 19.2 Hz), 4.49 q (1H, H^{18}, *J* 6.9 Hz), 4.39 br.d (1H, H^{17}, *J* 9.6 Hz), 3.96-3.85 m (2H, 13^1-CONHC*H*$_2$$CH_3$), 3.85-3.75 m [2H, 8-(C*H*$_2$$CH_3$)], 3.80-3.50 m [4H, 3-C(C*H*$_2$$N(CH_3)_2$)=CH(C*H*$_2$$N(CH_3)_2$)], 3.83 s (3H, 15^2-COOC*H*$_3$), 3.63/3.62* s (3H, 2-CH_3), 3.60 s [3H, 17-(CH_2CH_2COOC*H*$_3$)], 3.55 s (3H, 12-CH_3), 3.37 s (3H, 7-CH_3), 2.98-2.70 m [2H, 17-(C*H*$_2$$CH_2$COOC$H_3$)], 2.60-2.00 m [2H, 17-(CH_2C*H*$_2$COOCH_3)], 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.30 s (6H), 2.26 s (3H), 2.23 s (3H); 1.78-1.69 m (6H, 18-CH_3, 8-CH_2C*H*$_3$), 1.48 t (3H, 13^1-CONHCH$_2$C*H*$_3$, *J* 7.5 Hz), -1.70 br.s (1H, III-NH), -1.91 br.s (1H, I-NH). Compound **23** (33 mg, 37 % yield) was prepared from 77 mg of compound **7**. UV-Vis (CH_2Cl_2) λ nm: 399.0, 499.0, 604.0, 660.0. NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.84 s (1H, H^{10}), 9.73 s (1H, H^5), 8.84 s (1H, H^{20}), 7.36-7.30 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.92 t (1H, 13-CON*H*CH_2CH_2OH, *J* 4.2 Hz), 5.62 d (1H, $H^{15(1)}{}_A$, *J* 18.3 Hz), 5.34 d (1H, $H^{15(1)}{}_B$, *J* 18.3 Hz), 4.47 q (1H, H^{18}, *J* 7.2 Hz), 4.43 br.d (1H, H^{17}, *J* 9.6 Hz), 4.07 t (2H, 13^1-CONHCH$_2$C*H*$_2$OH), 4.00-3.92 m (2H, 13^1-CONHC*H*$_2$$CH_2OH$), 3.85-3.79 m [2H, 8-(C*H*$_2$$CH_3$)], 3.80-3.40 m [4H, 3-C(C*H*$_2$$N(CH_3)_2$)=CH(C*H*$_2$$N(CH_3)_2$)], 3.77 s (3H, 15^2-COOC*H*$_3$), 3.62 s (3H, 2-CH_3), 3.61 s [3H, 17-(CH_2CH_2COOC*H*$_3$)], 3.56 s (3H, 12-CH_3), 3.37 s (3H, 7-CH_3), 2.84-2.50 m [4H, 17-(C*H*$_2$C*H*$_2$COOCH$_3$)], 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.33 s (6H), 2.26/2.23* s (3H), 2.20 s (3H); 1.78-1.68 m (6H, 18-CH_3, 8-CH_2C*H*$_3$), -1.66 br.s (1H, III-NH), -1.88 br.s (1H, I-NH).

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-methylamide-15(2)-diethylene glycol 17(3)-methyl ester (**24**).* Compound **24** (54.0 mg, 50 % yield) was prepared from 90.0 mg of compound **13**. MS (ESI) *m/z*: 829.1 $(M+4H)^+$. UV-Vis (CH_2Cl_2) λ nm: 656 (33%), 602 (5%), 522 (4%), 498 (11%), 397 (100%). IR (cm^{-1}, KBr): 2957 ($\nu_{CH}{}^{as}$ CH_3); 2933 ($\nu_{CH}{}^{as}$ CH_2); 2866 ($\nu_{CH}{}^{s}$ CH_3); 2769 (ν_{CH} CH_2-O-, glycol); 1736 (ν C=O, ester); 1651 («amide-I»); 1605 («chlorin band»); 1551 («amide-II»). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.86 s (1H, H^{10}), 9.77 s (1H, H^5), 8.85 s (1H, H^{20}), 7.37-7.31 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.12 br.m (1H, 13^1-CON*H*CH_3), 5.58 d (1H, 15-C$H_A$$H_B$$COOCH_2CH_2OCH_2CH_2OH$, *J* 18.3 Hz), 5.42 d (1H, 15-$CH_A$$H_B$$COOCH_2CH_2OCH_2CH_2OH$, *J* 18.4 Hz), 4.56-4.41 m (2H, H^{18}, H^{17}), 4.37-4.20 m (2H, 15-CH_2COOC*H*$_2$$CH_2OCH_2CH_2OH$), 3.94-3.67 m [6H, 8-(C*H*$_2$$CH_3$), 3-C(C*H*$_2$$N(CH_3)_2$)=CH(C*H*$_2$$N(CH_3)_2$)], 3.64 s (3H, 17-($CH_2CH_2$COOC*H*$_3$), 3.60 s (3H, 12-$CH_3$), 3.57 s (3H, 2-$CH_3$), 3.40 s (3H, 7-$CH_3$), 3.31 d (3H, 13^1-CONHC*H*$_3$, *J* 4.7 Hz), 3.67-3.16 m (6H, 15-CH_2COOCH$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OH), 2.86-2.44 m [2H, 17-(CH_2C*H*$_2$COOCH$_3$)], 2.43-1.99 [3-C(C*H*$_2$$N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.37 s (6H), 2.27/2.25* s (3H), 2.04 s (3H)]; 1.76 d (3H, 18-CH_3, *J* 6.0 Hz),1.71 t (3H, 8-CH_2C*H*$_3$, *J* 7.9 Hz), -1.92 br.s (1H, I-NH), -2.19 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-methylamide 15(2)-triethylene glycol 17(3)-methyl ester (**25**).* Compound **25** (28.4 mg, 38 % yield) was prepared from 61.4 mg of compound **14**. MS (ESI) *m/z*: 873.5 $(M+4H)^+$. UV-Vis (CH_2Cl_2) λ nm: 655 (33%), 602 (4%), 549 (3%), 498 (10%), 397 (100%). IR (cm^{-1}, KBr): 2955 ($\nu_{CH}{}^{as}$ CH_3); 2924 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2769 (ν_{CH} CH_2-O-, glycol); 1732 (ν C=O, ester); 1645 («amide-I»); 1609 («chlorin band»); 1551 («amide-II»). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.87 s (1H, H^{10}), 9.77 s (1H, H^5), 8.86 s (1H, H^{20}), 7.41-7.31 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.39-7.32 m (1H, 13^1-CON*H*CH_3), 5.59 d (1H, 15-C$H_A$$H_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 18.7 Hz), 5.42 d (1H, 15-$CH_A$$H_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 17.6 Hz), 4.57-4.10 m (2H, H^{17}, H^{18})], 4.34-4.16 m (2H, 15-CH_2COOC*H*$_2$$CH_2OCH_2CH_2OCH_2CH_2OH$), 3.94-3.67 m (6H, 8-C*H*$_2$$CH_3$), 3.70-3.60 m [4H, 3-C(C*H*$_2$$N(CH_3)_2$)=CH(C*H*$_2$$N(CH_3)_2$)], 3.62 s (3H, 17-($CH_2CH_2$COOC*H*$_3$), 3.61 s (3H, 12-$CH_3$), 3.57 s (3H, 2-$CH_3$), 3.39 s (3H, 7-$CH_3$), 3.30 d (3H, 13^1-CONHC*H*$_3$, *J* 4.4 Hz), 3.57-3.23 m (10H, 15-CH_2COOCH$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OH), 2.78-2.46 m (4H, 17-C*H*$_2$C*H*$_2$COOCH$_3$), 2.42-2.02 m 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.36 s (6H), 2.27 s (3H),

2.24 s (3H); 1.76 t (3H, 8-CH_2CH_3, *J* 7.9 Hz),1.71 d (3H, 18-CH_3, *J* 6.1 Hz), -1.86 br.s (1H, I-NH), -1.97 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-methylamide 15(2)- tetraethylene glycol 17(3) methyl ester (**26**).* Compound **26** (15.0 mg, 42 % yield) was prepared from 31.0 mg of compound **15**. MS (ESI) *m/z*: 917.2 $(M+4H)^+$. UV-Vis (CH_2Cl_2) λ nm: 656 (31%), 601 (3%), 549 (2%), 498 (9%), 397 (100%). IR (cm^{-1}, KBr): 2955 ($\nu_{CH}{}^{as}$ CH_3); 2926 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2764 (ν_{CH} CH_2-O-, glycol); 1736 (ν C=O, ester); 1647 («amide-I»); 1605 («chlorin band»); 1551 («amide-II»). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.85 s (1H, H^{10}), 9.77 s (1H, H^5), 8.86 s (1H, H^{20}), 7.44-7.37 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.36-7.32 m [1H, 13^1-(CON*H*CH_3)], 5.61 d (1H, 15-C$H_AH_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 19.6 Hz), 5.42 d (1H, 15-CH_AH_BCO$OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 18.0 Hz), 4.57-4.42 m [(2H, H^{17}, H^{18})], 4.35-4.14 m (2H, 15-$CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 3.95-3.60 m [6H, (8-C$H_2CH_3$), 3-C(C$H_2N(CH_3)_2$)=CH(C$H_2N(CH_3)_2$)], 3.63 s (3H, 17-($CH_2CH_2COOCH_3$), 3.62 s (3H, 12-$CH_3$), 3.57 s (3H, 2-$CH_3$), 3.40 s (3H, 7-$CH_3$), 3.30 d (3H, 13^1-CONHCH_3, *J* 4.3 Hz), 3.13-2.75 m (14H, 15-C$H_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.45-2.00 m 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.42 s (6H), 2.28 s (3H), 2.26 s (3H); 2.16-1.89 m (4H, 17-C$H_2CH_2COOCH_3$), 1.81-1.67 m (6H, 8-CH_2CH_3, 18-CH_3), -1.88 br.s (1H, I-NH), -1.99 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-methylamide 15(2)- pentaethylene glycol 17(3) methyl ester (**27**).* Compound **27** (13.0 mg, 37 % yield) was prepared from 30.0 mg of compound **16**. MS (ESI) *m/z*: 961.4 $(M+4H)^+$. UV-Vis (CH_2Cl_2) λ nm: 668 (44.4%), 610 (8.5%), 539 (9.9%), 509 (11.0%), 414 (100%). IR (cm^{-1}, KBr): 2955 ($\nu_{CH}{}^{as}$ CH_3); 2927 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2785 (ν_{CH} CH_2-O-, glycol); 1734 (ν C=O, ester); 1651 («amide-I»); 1603 («chlorin band»); 1551 («amid-II»). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.86 s (1H, H^{10}), 9.77 s (1H, H^5), 8.86 s (1H, H^{20}), 7.50-7.41 m [1H, C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.40-7.32 m [1H, 13^1-(CON*H*CH_3)], 5.61 d (1H, 15-CH_AH_BCO$OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 19.4 Hz), 5.41 d (1H, 15-$CH_AH_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 19.4 Hz), 4.58-4.42 m (2H, H^{17}, H^{18})], 4.33-4.14 m (2H, 15-$CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 3.93-3.67 m [6H, (8-C$H_2CH_3$), 3-C(C$H_2N(CH_3)_2$)=CH(C$H_2N(CH_3)_2$)], 3.63 c (3H, 17-($CH_2CH_2COOCH_3$), 3.62 s (3H, 12-$CH_3$), 3.58 s (3H, 2-$CH_3$), 3.41 s (3H, 7-$CH_3$), 3.31 d (3H, 13^1-CONHCH_3, *J* 4.0 Hz), 3.20-2.72 m (18H, 15-$CH_2CO$$OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.46-2.00 m 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.39 s (6H), 2.28 s (3H), 2.25 s (3H); 2.45-1.83 m (4H, 17-C$H_2CH_2COOCH_3$), 1.81-1.67 m (6H, 8-CH_2CH_3, 18-CH_3), -1.87 br.s (1H, I-NH), -1.99 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N-dimethylamino)chlorin e_6 13(1)-N-methylamide 15(2)-hexaethylene glycol 17(3)-methyl ester (**28**).* Compound **28** (57.3 mg, 51 % yield) was prepared from 100.0 mg of compound **17**. MS (ESI) *m/z*: 1005.3 $(M+4H)^+$; 1026.4 $(MNa+H_2)$; 1043.0 $(MK+H_2)$. UV-Vis (CH_2Cl_2) λ nm: 655 (31%), 600 (3%), 550 (2%), 498 (9%), 397 (100%). IR (cm^{-1}, KBr): 2953 ($\nu_{CH}{}^{as}$ CH_3); 2926 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2781 (ν_{CH} CH_2-O-, glycol); 1736 (ν C=O, ester); 1651 («amide-I»); 1603 («chlorin band»); 1551 («amide-II»). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.89 ***s*** (1H, H^{10}), 9.77 s (1H, H^5), 8.86 s (1H, H^{20}), 7.51-7.42 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.39-7.33 m [1H, 13^1-(CON*H*CH_3)], 5.60 d (1H, 15-C$H_AH_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, *J* 17.2 Hz), 5.52-5.36 m (1H, 15-$CH_AH_B$$COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 4.60-4.40 m (2H, H^{17}, H^{18})], 4.35-4.15 m (2H, 15-$CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 3.94-3.79 m (2H, 8-C$H_2CH_3$), 3.76-3.60 m [4H, 3-C(C$H_2N(CH_3)_2$)=CH(C$H_2N(CH_3)_2$)], 3.63 s (3H, 17-($CH_2CH_2COOCH_3$), 3.62 s (3H, 12-CH_3), 3.57 s (3H, 2-CH_3), 3.40 s (3H, 7-CH_3), 3.30 d (3H, 13^1-CONHCH_3, *J* 4.0 Hz), 3.20-2.72 m (22H, 15-$CH_2CO$$OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), 2.41-2.16 m 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$): 2.32 s (6H), 2.27 s (3H), 2.25 s (3H); 2.15-1.96 m (4H, 17-C$H_2CH_2COOCH_3$), 1.82-1.64 m (6H, 8-CH_2CH_3, 18-CH_3), -1.72 br.s (1H, I-NH), -1.97 br.s (1H, III-NH).

General procedure for alkylation of chlorins dimethylamino groups by methyl iodide. 0.1 ml of iodomethane was added to a solution of 5–50 mg of starting chlorin (**18**–**28**) in 5 ml of THF or methylene chloride. The resulting mixture was allowed to stay for 15-45 minutes at room temperature, then the solvent and iodomethane were evaporated under reduced pressure, and the residue after evaporation was reprecipitated with pentane. Alkylation products **29**–**39** were obtained in quantitative yields in all cases. Spectral characteristics of the compounds obtained are shown below.

*3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-methylamide 15(2),17(3)-dimethyl ester (**29**).* MS (ESI) *m/z* (Chl I_2): 783.7 $(Chl^{2+}+H_2+\bar{e})^+$, 769.32 $(Chl^{2+}+H_2-CH_2^+)^+$, 650.39 $(Chl^{2+}+H_2-2N(CH_3)_3-CH_3^+)^+$. UV-Vis ($CHCl_3$) λ nm: 660.0 (14%), 641.5 (15%), 599.0 (2%), 524.5 (4%), 499.0 (4%), 405.0 (100%). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.66/9.67* s (1H, H^{10}), 9.60/9.64* s (1H, H^5), 8.85 s (1H, H^{20}), 7.10 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.76 br.q [1H, 13^1-(CON*H*CH_3), *J* 4.5 Hz], 5.56/5.57* d (1H, $H^{15(1)}{}_A$, *J* 18.1 Hz), 5.30/5.32* d (1H, $H^{15(1)}{}_B$, *J* 18.1 Hz), 4.48 q (1H, H^{18}, *J* 7.2 Hz), 4.36 br.d (1H, H^{17}, *J* 9.3 Hz), 3.74-3.58 m [6H, 8-(CH_2CH_3), 3-C(C$H_2N(CH_3)_2$)=CH(C$H_2N(CH_3)_2$)], 3.83 s (3H, 13^2-$COOCH_3$), 3.62/3.63* s (3H, 2-CH_3), 3.53 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.51/3.53* s (3H, 7-CH_3), 3.27/3.29* s (3H, 12-CH_3), 3.27 d (3H, 13^1-CONHCH_3, 5.4 Hz), 3.03-2.04 m [4H, 17-(C$H_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 1.56 s (6H), 2.25/2.28* s (3H), 2.51/2.54* s (9H); 1.71-1.60 m (6H, 18-CH_3, 8-CH_2CH_3), -1.86 br.s (1H, III-NH), -2.10 br.s (1H, I-NH).

*3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-ethylamide 15(2),17(3)-dimethyl ester (**30**).* MS (ESI) *m/z* (Chl I_2): 922.8 $(Chl^{2+}I^-)^+$, 795.0 $(Chl^{2+}+\bar{e})^+$, 783.4 $(Chl^{2+}+H_2-CH_2^+)^+$, 664.4 $(Chl^{2+}+2H_2-2N(CH_3)_3-CH_3^+)^+$, 520.4 $(Chl^{2+}-2N(CH_3)_3-OCH_3-H^+-2C_2H_2-CONHC_2H_5)^+$. UV-Vis ($CHCl_3$) λ nm: 661.0 (15%), 642.0 (15%), 610.0 (3%), 524.5 (4%), 500.0 (4%), 405.5 (100%). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.70/9.69* s (1H, H^{10}), 9.64/9.62* s (1H, H^5), 8.85 s (1H, H^{20}), 7.16-7.08 m [1H, 3-C(C$H_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.66 m (1H, 13^1-CON*H*CH_2CH_3), 5.59/5.58* d (1H, $H^{15(1)}{}_A$, *J* 19.2 Hz), 5.31/5.30* d (1H, $H^{15(1)}{}_B$, *J* 19.2 Hz), 4.48 q (1H, H^{18}, *J* 8.9 Hz), 4.38 br.d (1H, H^{17}, *J* 9.0 Hz), 3.92-3.20 m [8H, 8-(CH_2CH_3), 3-C(C$H_2N^+(CH_3)_3$)=CH(C$H_2N^+(CH_3)_3$), 13^1-(CONHCH_2CH_3)], 3.82 s (3H, 13^2-$COOCH_3$), 3.76/3.75* s (3H, 2-CH_3), 3.61/3.60* s [3H, 17-($CH_2CH_2COOCH_3$)], 3.55/3.53* s (3H, 7-CH_3), 3.31/3.30* s (3H, 12-CH_3), 3.22-2.77 m [4H, 17-(C$H_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.61/2.60* s (12H), 2.29/2.27 s (6H); 1.90-1.40 m [6H, 18-CH_3, 8-CH_2CH_3], 1.46 t [3H, 13^1-(CONHCH$_2$CH_3), *J* 9.0 Hz], -1.76 br.s (1H, I-NH), -2.08 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-butylamide 15(2),17(3)-dimethyl ester (**31**).* MS (ESI) *m/z* (Chl I_2): 950.9 $(Chl^{2+}I^-)^+$, 825.24 $(Chl^{2+}+H_2+\bar{e})^+$, 827.4 $(Chl^{2+}+2H_2+\bar{e})^+$, 811.2 $(Chl^{2+}+H_2-CH_2^+)^+$, 692.3 $(Chl^{2+}+2H_2-2N(CH_3)_3-CH_3^+)^+$, 518.82 $(Chl^{2+}-2N(CH_3)_3-OCH_3^+-H_2-2C_2H_2-CONHC_4H_9)^+$. UV-Vis ($CHCl_3$) λ nm: 660.5 (14%), 642.0 (15%), 612.5 (3%), 524.5 (4%), 500.0 (4%), 405.5 (100%). NMR ^1H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.67 s (1H, H^{10}), 9.61/9.64* s (1H, H^5), 8.86 s (1H, H^{20}), 7.10 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.67 m (1H, 13^1-CON*H*$(CH_2)_3CH_3$), 5.58 d (1H, $H^{15(1)}{}_A$, *J* 18.0 Hz), 5.30 d (1H, $H^{15(1)}{}_B$,

J 18.0 Hz), 4.49 q (1H, H^{18}, *J* 9.0 Hz), 4.34 br.d (1H, H^{17}, *J* 9.0 Hz), 3.90-3.80 m [2H, 8-(CH_2CH_3)], 3.75-3.60 m [4H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$)], 3.83 s (3H, 15^2-$COOCH_3$), 3.61/3.62* s (3H, 2-CH_3), 3.54 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.50/3.53* s (3H, 7-CH_3), 3.28/3.30* s (3H, 12-CH_3), 3.32 m [2H, 13^1-($CONHCH_2(CH_2)_2CH_3$)], 3.03-2.00 m [4H, 17-($CH_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.24 s (6H), 2.53 s (12 H); 1.80-1.40 m [10H, 13^1-($CONHCH_2(CH_2)_2CH_3$), 18-CH_3, 8-CH_2CH_3], 0.92 m [3H, 13^1-($CONH(CH_2)_3CH_3$)], -2.15 br.s (1H, I-NH), -1.88 br.s (1H, III-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-hexylamide 15(2),17(3)-dimethyl ester ***(32)***. MS (ESI) *m/z* (Chl I_2): 950.9 ($Chl^{2+}I^-$)$^+$, 855.4 (Chl^{2+}+$2H_2$+ē)$^+$, 839.4 (Chl^{2+}+H_2-CH_2^+)$^+$, 810.4 (Chl^{2+}+$2H_2$-CH_3^+-C_2H_5)$^+$, 720.5 (Chl^{2+}+$2H_2$-2N$(CH_3)_3$-CH_3^+)$^+$. UV-Vis ($CHCl_3$) λ nm: 660.5 (17%), 642.5 (15%), 524.5 (4%), 499.0 (5%), 405.5 (100%). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.67 s (1H, H^{10}), 9.61/9.64* s (1H, H^5), 8.86 s (1H, H^{20}), 7.11 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.69 m (1H, 13^1-CO N*H*(CH_2)$_5CH_3$), 5.58 d (1H, $H^{15(1)}{}_A$, *J* 18.0 Hz), 5.30 d (1H, $H^{15(1)}{}_B$, *J* 18.0 Hz), 4.49 q (1H, H^{18}, *J* 9.0 Hz), 4.34 br.d (1H, H^{17}, *J* 9.0 Hz), 3.90-3.80 m [2H, 8-(CH_2CH_3)], 3.75-3.60 m [4H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$)], 3.83 s (3H, 15^2-$COOCH_3$), 3.61/3.62* s (3H, 2-CH_3), 3.54 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.51/3.53* s (3H, 7-CH_3), 3.29/3.30* s (3H, 12-CH_3), 3.32 m [2H, 13^1-($CONHCH_2(CH_2)_4CH_3$)], 3.03-2.00 m [4H, 17-($CH_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.24/2.27* s (6H), 2.54 s (12 H); 1.80-1.40 m [14H, 13^1-($CONHCH_2(CH_2)_4CH_3$), 18-CH_3, 8-CH_2CH_3], 0.98 m [3H, 13^1-($CONH(CH_2)_5CH_3$)], -1.85 br.s (1H, III-NH), -2.14 br.s (1H, I-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-octylamide 15(2),17(3)-dimethyl ester ***(33)***. MS (ESI) *m/z* (Chl I_2): 950.9 ($Chl^{2+}I^-$)$^+$, 883.5 (Chl^{2+}+$2H_2$+ē)$^+$, 867.5 (Chl^{2+}+H_2-CH_2^+)$^+$, 825.6 (Chl^{2+}+$2H_2$-CH_3^+-C_3H_7)$^+$. UV-Vis ($CHCl_3$) λ nm: 660.5 (16%), 642.0 (15%), 524.5 (3%), 499.0 (4%), 405.5 (100%). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.68 s (1H, H^{10}), 9.61/9.65* s (1H, H^5), 8.86 s (1H, H^{20}), 7.10 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 6.67 m (1H, 13^1-CON*H*(CH_2)$_7CH_3$), 5.58 d (1H, $H^{15(1)}{}_A$, *J* 17.7 Hz), 5.31 d (1H, $H^{15(1)}{}_B$, *J* 17.7 Hz), 4.48 q (1H, H^{18}, *J* 5.0 Hz), 4.37 br.d (1H, H^{17}, *J* 7.5 Hz), 3.90-3.80 m [2H, 8-(CH_2CH_3)], 3.75-3.60 m [4H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$)], 3.83 s (3H, 15^2-$COOCH_3$), 3.61/3.62* s (3H, 2-CH_3), 3.56 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.51/3.53* s (3H, 7-CH_3), 3.29/3.31* s (3H, 12-CH_3), 3.34 m [2H, 13^1-($CONHCH_2(CH_2)_6CH_3$)], 3.03-2.00 m [4H, 17-($CH_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.26/2.30* s (6H), 2.51 s (12 H); 1.80-1.40 m [18H, 13^1-($CONHCH_2(CH_2)_6CH_3$), 18-CH_3, 8-CH_2CH_3], 0.93 m [3H, 13^1-($CONH(CH_2)_7CH_3$)], -1.84 br.s (1H, III-NH), -2.12 br.s (1H, I-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-(2-hydroxyethyl)amide 15(2),17(3)-dimethyl ester ***(34)***. MS (ESI) *m/z* (Chl I_2): 950.9 ($Chl^{2+}I^-$)$^+$, 813.4, (Chl^{2+}+H_2+ē)$^+$, 815.4 (Chl^{2+}+$2H_2$+ē)$^+$, 799.4 (Chl^{2+}+H_2-CH_2^+)$^+$, 680.4 (Chl^{2+}+H_2-2N$(CH_3)_3$-CH_3^+)$^+$. UV-Vis ($CHCl_3$) λ nm: 660.0 (14%), 641.5 (15%), 599.0 (2%), 524.5 (4%), 499.0 (4%), 405.0 (100%). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.53/9.50* s (1H, H^{10}), 9.38/9.26* s (1H, H^5), 8.79 s (1H, H^{20}), 7.39-7.30 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.03-6.90 m (1H, 13^1-CON*H*CH_2-CH_2OH), 5.65-5.51 m (1H, $H^{15(1)}{}_A$), 5.36-5.20 m (1H, $H^{15(1)}{}_B$), 4.51-4.26 m (2H, H^{18}, H^{17}), 4.03-3.81 m (4H, 13^1-CONHCH_2CH_2OH, 13^1-CONHCH_2CH_2OH), 3.80-2.92 m [8H, 8-(CH_2CH_3), 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$), 3.75 s (3H, 15^2-$COOCH_3$), 3.60/3.58* s (3H, 2-CH_3), 3.45/3.43* s [3H, 17-($CH_2CH_2COOCH_3$)], 3.41 s (3H, 7-CH_3), 3.13/3.07* s (3H, 12-CH_3), 2.70-2.38 m [4H, 17-($CH_2CH_2COOCH_3$)], 3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.22/2.18* s (3H), 1.99/1.94 s (6H), 171-1.58 m (9H); 1.45-1.22 m [6H, 18-CH_3, 8-CH_2CH_3], -1.964 br.s (I-NH), -2.20/-2.24* br.s (III-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorine e_6 13(1)-N-2-methylamide 15(2)-diethylene glycol 17(3)-methyl ester ***(35)***. MS (ESI) *m/z* (Chl I_2): 757.54 (Chl^{2+}+H_2+ē)$^+$, 843.4 (Chl^{2+}+H_2-CH_2^+)$^+$, 724.4 (Chl^{2+}+H_2-2N$(CH_3)_3$-CH_3^+)$^+$. UV-Vis ($CHCl_3$) λ nm: 659 (33%), 604 (3%), 524 (2%), 498 (9%), 398 (100%). IR (cm^{-1}, KBr): 2957 ($\nu_{CH}{}^{as}$ CH_3); 2928 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2743 (ν_{CH} CH_2-O-, glycol); 1736 (ν C=O, ester); 1645 («amide-I»); 1605 («chlorin band»); 1549 («amide-II»). NMR ^{1}H ($CDCl_3$, Me_4-Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.71 s (1H, H^{10}), 9.67 s (1H, H^5), 8.87 s (1H, H^{20}), 7.26-7.18 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.16-7.07 m [1H, 13^1-(CON*H*CH_3)], 5.58 d (1H, 15-C$H_A$$H_B$COOC$H_2CH_2OCH_2CH_2$OH, *J* 20.3 Hz), 5.47-5.31 m (1H, 15-C$H_A$$H_B$COOC$H_2CH_2OCH_2CH_2$OH), 4.55-4.38 q (2H, H^{18}, H^{17}), 4.30-4.13 m (2H, 15-CH_2COOCH_2CH_2OCH_2CH_2OH), 3.83-3.68 m [6H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$), 8-CH_2CH_3], 3.63 s (3H, 17-($CH_2CH_2COOCH_3$), 3.56 s (3H, 12-CH_3), 3.53 s (3H, 2-CH_3), 3.35 s (3H, 7-CH_3), 3.29 d (3H, 13^1-CONHCH_3, *J* 4.0 Hz), 3.85-3.09 m (6H, 15-CH_2COOCH_2CH_2OCH_2CH_2OH), [3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.56/2.49* s (6H), 2.31 s (3H), 2.29 s (3H); 2.92-1.97 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.79-1.60 m (6H, 18-CH_3, 8-CH_2CH_3), -1.62 br.s (1H, I-NH), -2.12 br.s (1H, III-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-2-methylamide 15(2)-triethylene glycol 17(3)-methyl ester ***(36)***. MS (ESI) *m/z* (Chl I_2): 843.4 (Chl^{2+}+H_2-CH_2^+)$^+$. UV-Vis ($CHCl_3$) λ nm: 660 (34%), 604 (3%), 554 (2%), 498 (9%), 398 (100%). IR (cm^{-1}, KBr): 2955 ($\nu_{CH}{}^{as}$ CH_3); 2926 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2747 (ν_{CH} CH_2-O-, glycol); 1734 (ν C=O, ester); 1647 («amide-I»); 1605 («chlorin band»); 1549 («amide-II»). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.72 s (1H, H^{10}), 9.70 s (1H, H^5), 8.88 s (1H, H^{20}), 7.26-7.18 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.22-7.09 m [1H, 13^1-(CON*H*CH_3)], 5.59 d (1H, 15-C$H_A$$H_B$COOC$H_2CH_2OCH_2CH_2OCH_2CH_2$OH, *J* 16.9 Hz), 5.47-5.41 m (1H, 15-$CH_A$$H_B$COOC$H_2CH_2OCH_2CH_2OCH_2CH_2$OH), 4.50 q (1H, H^{18}, *J* 7.7 Hz), 4.44 br.d (1H, H^{17}, *J* 8.8 Hz), 4.32-4.13 m (2H, 15-CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH), 3.90-3.66 m [6H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$), 8-CH_2CH_3], 3.63 s (3H, 17-($CH_2CH_2COOCH_3$), 3.56 s (6H, 12-CH_3, 2-CH_3), 3.35 s (3H, 7-CH_3), 3.28 d (3H, 13^1-CONHCH_3, *J* 4.4 Hz), 3.20-2.72 m (10H, 15-CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH), 2.70-2.27 [3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.70/2.66* s (6H), 2.33 s (3H), 2.30 s (3H)]; 2.27-1.94 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.78-1.56 m (6H, 18-CH_3, 8-CH_2CH_3), -1.89 br.s (1H, I-NH), -2.12 br.s (1H, III-NH).

3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-2-methylamide 15(2)-tetraethylene glycol 17(3)-methyl ester ***(37)***. MS (ESI) *m/z* (Chl I_2): 945.4, (Chl^{2+}+H_2+ē)$^+$, 947.4 (Chl^{2+}+$2H_2$+ē)$^+$, 931.8 (Chl^{2+}+H_2-CH_2^+)$^+$, 812.5 (Chl^{2+}+H_2-2N$(CH_3)_3$-CH_3^+)$^+$. UV-Vis ($CHCl_3$) λ nm: 660 (34%), 605 (3%), 498 (9%), 398 (100%). IR (cm^{-1}, KBr): 2955 ($\nu_{CH}{}^{as}$ CH_3); 2926 ($\nu_{CH}{}^{as}$ CH_2); 2868 ($\nu_{CH}{}^{s}$ CH_3); 2747 (ν_{CH} CH_2-O-, glycol); 1734 (ν C=O, ester); 1645 («amide-I»); 1605 («chlorin band»); 1549 («amide-II»). NMR ^{1}H ($CDCl_3$, Me_4Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.86/9.61* s (1H, H^{10}, H^5), 8.91 s (1H, H^{20}), 7.51-7.40 m [1H, 3-C($CH_2N(CH_3)_2$)=C*H*($CH_2N(CH_3)_2$)], 7.25-7.12 m [1H, 13^1-(CON*H*CH_3)], 5.61 d (1H, 15-C$H_A$$H_B$COOC$H_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$OH, *J* 19.4 Hz), 5.50-5.33 m (1H, 15-$CH_A$$H_B$COOC$H_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$OH), 4.52 q (1H, H^{18}, *J* 7.0 Hz), 4.46 br.d (1H, H^{17}, *J* 9.0 Hz), 4.33-4.11 m (2H, 15-CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH), 3.98-3.67 m [6H, 3-C($CH_2N(CH_3)_2$)=CH($CH_2N(CH_3)_2$), 8-CH_2CH_3], 3.63 s (3H, 17-($CH_2CH_2COOCH_3$), 3.59 s (6H, 12-CH_3, 2-CH_3), 3.37 s (3H, 7-CH_3), 3.29 d (3H, 13^1-CONHCH_3, *J* 4.9 Hz), 3.69-3.07 m (14H, 15-CH_2COOCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH), [3-C($CH_2N^+(CH_3)_3$)=CH($CH_2N^+(CH_3)_3$): 2.80 s (6H), 2.34 s (3H),

2.30 s (3H); 2.64-1.79 m [4H, 17-(C*H*$_2$C*H*$_2$COOCH$_3$)], 1.76-1.66 m (6H, 18-CH$_3$, 8-CH$_2$C*H*$_3$), -1.81 br.s (1H, I-NH), -2.15 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorine$_6$13(1)-N-2-methylamide 15(2)-pentaethylene glycol 17(3)-methyl ester (**38**).* MS (ESI) *m/z* (Chl I$_2$): 1117.4 (Chl^{2+}+HI+ē)$^+$, 989.4 (Chl^{2+}+H$_2$+ē)$^+$, 975.6 (Chl^{2+}+H$_2$-CH$_2^+$)$^+$, 933.7 (Chl^{2+}+3H$_2$-N(CH$_3$)$_3^+$)$^+$, 856.6 (Chl^{2+}+H$_2$-2N(CH$_3$)$_3$-CH$_3^+$)$^+$. UV-Vis (CHCl$_3$) λ nm: 659 (33%), 603 (5%), 523 (5%), 498 (11%), 398 (100%). IR (cm^{-1}, KBr): 2955 (ν_{CH}^{as} CH$_3$); 2926 (ν_{CH}^{as} CH$_2$); 2868 (ν_{CH}^{s} CH$_3$); 2745 (ν_{CH} CH$_2$-O-, glycol); 1732 (ν C=O, ester); 1647 («amide-I»); 1605 («chlorin band»); 1549 («amide-II»). NMR ^{1}H (CDCl$_3$, Me$_4$Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.86 s (1H, H^{10}), 9.77 s (1H, H^5), 8.86 s (1H, H^{20}), 7.50-7.41 m [1H, C(CH$_2$N(CH$_3$)$_2$)=C*H*(CH$_2$N(CH$_3$)$_2$)], 7.40-7.32 m [1H, 13^1-(CON*H*CH$_3$)], 5.61 d (1H, 15-C*H*$_A$H$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 5.41 d (1H, 15-CH$_A$*H*$_B$COOCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH, *J* 19.4 Hz), 4.58-4.42 m (2H, H^{17}, H^{18})], 4.33-4.14 m (2H, 15-CH$_2$COOC*H*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.93-3.67 m [6H, (8-C*H*$_2$CH$_3$), 3-C(C*H*$_2$N(CH$_3$)$_2$)=CH(C*H*$_2$N(CH$_3$)$_2$)], 3.63 s (3H, 17-(CH$_2$CH$_2$COOC*H*$_3$), 3.62 s (3H, 12-CH$_3$), 3.58 s (3H, 2-CH$_3$), 3.41 s (3H, 7-CH$_3$), 3.31 d (3H, 13^1-CONHC*H*$_3$, *J* 4.0 Hz), 3.20-2.72 m (18H, 15-CH$_2$COOCH$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OH), 3-C(CH$_2$N$^+$(C*H*$_3$)$_3$)=CH(CH$_2$N$^+$(C*H*$_3$)$_3$): 2.39 s (6H), 2.28 s (3H), 2.25 s (3H); 2.45-1.83 m (4H, 17-C*H*$_2$C*H*$_2$COOCH$_3$), 1.81-1.67 m (6H, 8-CH$_2$C*H*$_3$, 18-CH$_3$), -1.87 br.s (1H, I-NH), -1.99 br.s (1H, III-NH).

*3(1),3(2)-Bis(N,N,N-trimethylaminoiodide)chlorin e_6 13(1)-N-2-methylamide 15(2)-hexaethylene glycol 17(3)-methyl ester (**39**).* MS (ESI) *m/z* (Chl I$_2$): 1019.6 (Chl^{2+}+H$_2$-CH$_2^+$)$^+$. UV-Vis (CHCl$_3$) λ nm: 659 (32%), 604 (3%), 522 (3%), 498 (9%), 398 (100%). IR (cm^{-1}, KBr): 2953 (ν_{CH}^{as} CH$_3$); 2926 (ν_{CH}^{as} CH$_2$); 2870 (ν_{CH}^{s} CH$_3$); 2749 (ν_{CH} CH$_2$-O-, glycol); 1734 (ν C=O, ester); 1649 («amide-I»); 1607 («chlorin band»); 1551 («amide-II»). NMR ^{1}H (CDCl$_3$, Me$_4$Si, *the signals of *cis*- and *trans*-isomers with different chemical shifts, 300 MHz) δ ppm: 9.90 s (1H, H^{10}), 9.68 s (1H, H^5), 8.95 s (1H, H^{20}), 7.51-7.40 m [1H, 3-C(CH$_2$N(CH$_3$)$_2$)=C*H*(CH$_2$N(CH$_3$)$_2$)], 7.25-7.12 m [1H, 13^1-(CON*H*CH$_3$)], 5.63 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* 19.3 Hz), 5.40-5.33 m (1H, 15-CH$_A$*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), 4.59-4.40 m (2H, H^{18}, H^{17}), 4.36-4.12 m (2H, 15-CH$_2$COOC*H*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH), 3.92-3.67 m [6H, 3-C(C*H*$_2$N(CH$_3$)$_2$)=CH(C*H*$_2$N(CH$_3$)$_2$), 8-C*H*$_2$CH$_3$], 3.65 s (3H, 17-(CH$_2$CH$_2$COOC*H*$_3$), 3.61 s (6H, 12-CH$_3$, 2-CH$_3$), 3.39 s (3H, 7-CH$_3$), 3.31 d (3H, 13^1-CONHC*H*$_3$, *J* 4.4 Hz), 3.69-3.07 m (22H, 15-CH$_2$COOCH$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$OH), 2.88-2.72 and 2.38-2.22 both m [3-C(CH$_2$N$^+$(C*H*$_3$)$_3$)=CH(CH$_2$N$^+$(C*H*$_3$)$_3$): 2.36/2.34* s (6H), 2.29 s (3H), 2.26 s (3H); 2.64-1.79 m [4H, 17-(C*H*$_2$C*H*$_2$COOCH$_3$)], 1.76-1.66 m (6H, 18-CH$_3$, 8-CH$_2$C*H*$_3$), -1.99 br.s (1H, I-NH), -2.22 br.s (1H, III-NH).

Results and Discussion

As it was mentioned above alkylation of tertiary amino groups can be used for the cationic substituent formation. The previously developed method of aminomethylation of vinyl group by *bis*(N,N-dimethylamino)methane at the presence of acetic acid which allows to realize two dimethylaminomethyl substituents insertion was used here. Aminomethylated chlorin e_6 derivatives **18-23** described previously[30] were obtained for synthesis of dicationic derivatives with different size of hydrophobic part. The same method was convenient for aminomethylation of chlorin e_6 derivatives with glycol substituents (**13-17**). The resulted aminomethylated chlorin e_6 derivatives **24-28** were used for hydrophylised dicationic derivatives. The aminomethylation of chlorins **13-17** occurs by the same way as for alkylamides **2-7**, but the yields of reaction products **24-28** are lower. The spectral changers resulted from transition to aminomethylated derivatives **24-28** are similar to the observed by us before.[30] The disappearance of two from three vinyl proton signals in the NMR ^{1}H spectra of compounds obtained is evident to double substitution in vinyl group. *Cis*- and *trans*-isomers mixture of **18-28** is formed in this reaction as well as in cases described previously.[30,34] In addition there are *N,N*-dimethylaminomethyl substituent's methyl group signals at 2.40-2.00 ppm in the NMR ^{1}H spectra of compounds **24-28**. Mass spectra of aminomethylated derivatives **24-28** can be obtained by electrospray ionization (ESI) (at EI-MS conditions there are some plasma formation difficulties for aminomethylated derivatives **24-28** as well as for initial glycol derivatives **8-17**, **24-28**). Electrospray ionization leads to particular reduction (hydrogenisation) of the molecules as a side process (addition of 2 and sometimes 4 hydrogen atoms occurs) and corresponding protonated molecular ions are observed. Sometimes the formation of adducts with sodium is observed. Quaternization of twice aminomethylated dimethylaminomethyl groups of chlorin e_6 derivatives was carried out by methyl iodide action (Scheme 1). Series of novel dicationic chlorins **29-39** was obtained as a result. The structure of compounds obtained was proved by NMR ^{1}H, IR and UV-Vis spectroscopies and mass spectrometry. The electronic absorption spectrum of the dication derivatives obtained retained chlorin chromophore bands. The main bands of chlorin e_6 13-amide fragment are observed in the IR spectrum. The methyl groups signal in the NMR ^{1}H spectrum of quaternized derivatives **29-39** have downfield shift and increased intensity in comparison with the spectra of the starting compounds **18-28** (the typical changes in this region are shown in Figure 1). In addition, there is a shift in a weak field of substituted vinyl group proton signals. Downfield shifts of the proton signals can be explained by the electron-accepting nature of the cationic groups.

The resulting quaternized derivatives **29-39** are salt-like compounds which can be represented by the general formula ChlI$_2$ (where Chl – dication chlorin moiety) and dissociate in the solution according to the equation:

$$ChlI_2 \leftrightarrows ChlI^{2+} + 2I^-$$

The best ionization method for investigation of such compounds by mass spectrometry is electrospray ionisation (ESI) using solutions of the testing compounds in polar solvents. The peak of greatest intensity in the mass spectra (ESI) of all dicationic derivatives obtained is a peak of ions formed as a result of hydrogenation and elimination of CH_2^+ cation from dicationic chlorin part (Chl^{2+}+H$_2$-CH$_2^+$)$^+$ (the spectrum of compound **37** is shown as an example in Figure 2). In addition, there are low-intensity peaks corresponding to electron capture by dication particle Chl^{2+} in the spectra of some dicationic derivatives (Chl^{2+} + ē). Besides the peaks corresponding to dication particle electron capture the peaks of dication chlorin particles with an anion of iodine adducts (ChlI$^+$) are observed and these peaks also have a low intensity. The intensity of these peaks is low, apparently because of

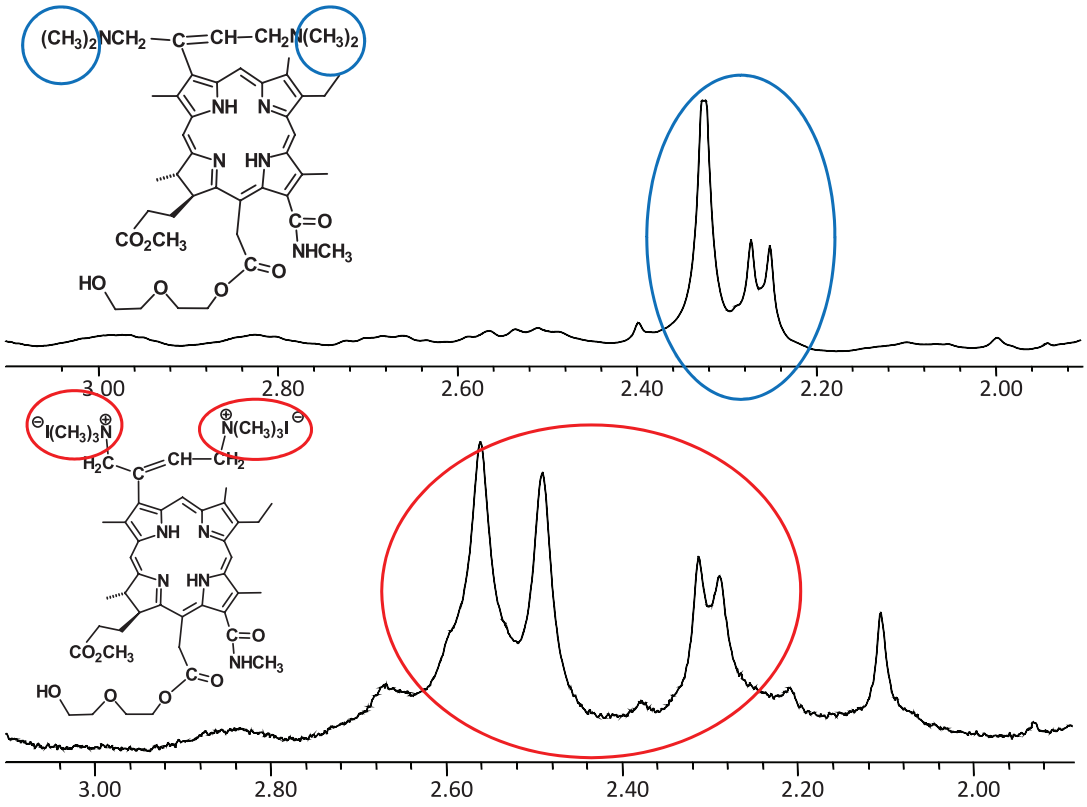


Figure 1. ^{1}H NMR spectra of aminomethylated derivative **24** and the product of its reaction with methyl iodide (**35**) (region 3.2-1.8 ppm, $CDCl_3$, 300 MHz).

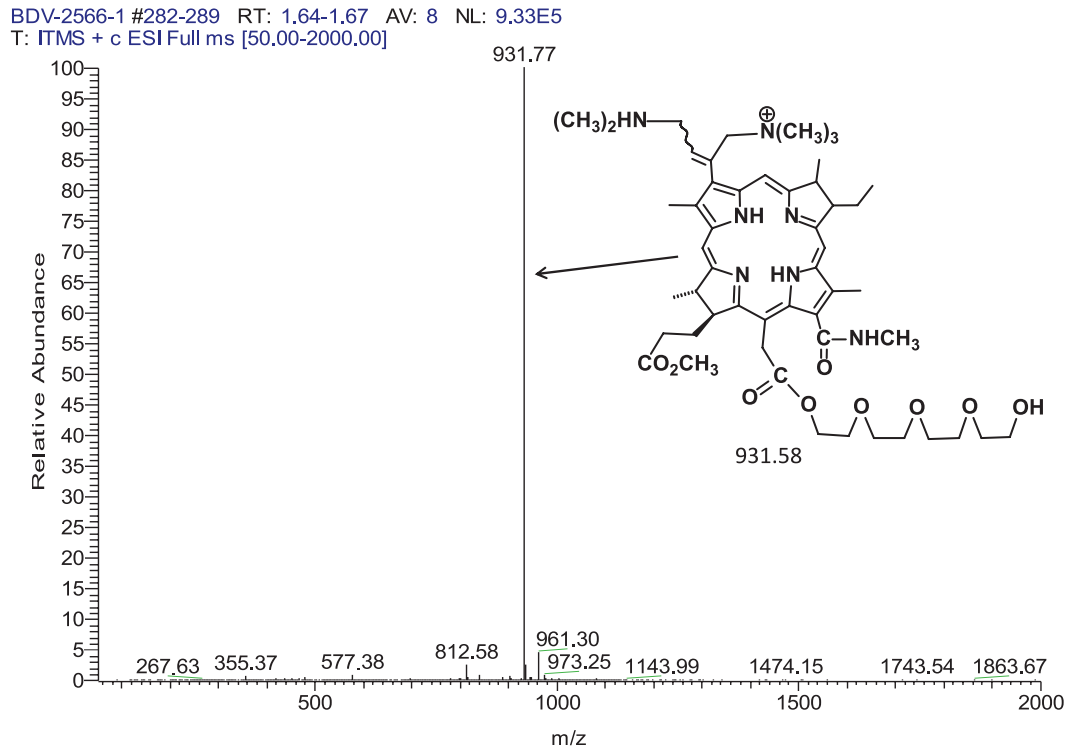


Figure 2. Mass spectrum (ESI) of the compound **37**.

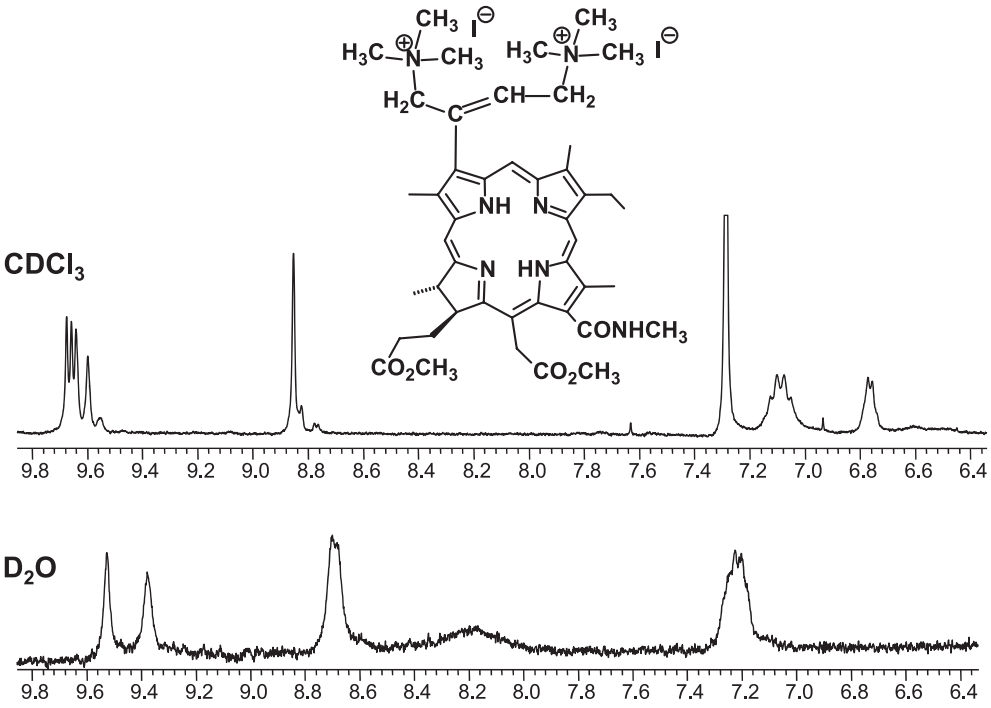


Figure 3. [1]H NMR spectrum of **29** in deuterochloroform and deuterated water (300 MHz, *meso* protons signals area).

little likelihood of formation of these particles. In addition, there are fragment ions peaks associated with the elimination of trimethylamine molecule, methyl and methoxy groups. Thus, the NMR spectroscopy and mass spectrometry data combined with IR and UV-Vis spectroscopic data allow to establish unambiguously the structure of dicationic derivatives obtained.

The solubility in water of chlorins obtained was studied here. It was found that compound **29** with a relatively small hydrophobic fragment is soluble in water and forms a true solution. The study of solution of this chlorin dication in deuterated water by [1]H NMR reveals signals of chlorin macrocycle protons not participating in the exchange reactions (Figure 3). In the case of formation of colloidal solutions the macrocycle proton signals cannot be observed. The introduction of ethyl and large size groups leads to a loss of solubility in water. The presence of hydrophilic moiety in amide group also gives solubility in water. For example, the hydroxy derivative **34**, as well as the compound **29**, form a true solution in water. Cationic derivatives with polyether moieties at the macrocycle periphery are unexpectedly insoluble in water, despite the presence of hydrophilic moieties.

Conclusion

A series of novel dicationic chlorins with additional hydrophobic (alkyl) and hydrophilic (polyether) groups were synthesized on the basis of methylpheophorbide *a*. New amphiphilic dicationic chlorins varying in size of the hydrophobic part were obtained by alkylation of tertiary amino groups of twice aminomethylated chlorin e_6 derivatives by methyl iodide. It was shown that several of the dicationic chlorins obtained can form true solutions in water and the introduction of hydrophobic substituents to amide group (starting with two methyl groups or one ethyl) leads to a loss of solubility. The cationic derivatives with polyether fragments at the macrocycle periphery are unexpectedly insoluble in water despite the presence of hydrophilic moieties.

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