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Heterocyclic Derivatives of Natural Chlorins as a Basis for the Creation of New Theranostic Agents with Tunable Properties

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Dedicated to the outstanding scientist, developer of domestic photosensitizers for PDT of cancer and a great friend of the Moscow school of porphyrin chemistry, Oskar Iosifovich Koifman

The functionalization of the periphery of the tetrapyrrole macrocycle in natural chlorins allows, on the one hand, to expand the aromatic system of the macroheterocycle, fundamentally changing its electronic structure, on the other hand, it allows introducing various structural blocks into the molecule, varying their type and quantity, the distance between them and their mutual orientation. The purpose of this study was to develop methods for the functionalization of natural chlorins by introducing heterocyclic fragments. The use of formyl chlorins to obtain heterocycle-substituted derivatives made it possible to obtain β-imidazolyl substituted chlorins by the Debus-Radzishevsky reaction. In this way, two new chlorins containing phenanthreneimidazole and benzimidazole in the pyrrole ring A of chlorin e_6 were obtained.

Keywords: Photosensitizers, photodynamic therapy, annealing, chlorin e_6, heterocycles.

Гетероциклические производные природных хлоринов в качестве основы для создания новых тераностических агентов с настраиваемыми свойствами

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Посвящяется выдающемуся ученому, разработчику отечественных фотосенсибилизаторов для ФДТ рака и большому другу московской школы порфириновой химии Оскару Иосифовичу Койфману

Функционализация периферии тетрапиррольного макроцикла у природных хлоринов позволяет, с одной стороны, расширить ароматическую систему макрогетероцикла, принципиально меняя его электронную структуру, с другой – позволяет вводить в молекулу различные структурные блоки, варьируя их тип и количество, расстояние между ними и их взаимную ориентацию. Целью настоящего исследования явилась разработка методов функционализации природных хлоринов путем введения гетероциклических фрагментов. Использование формилхлоринов для получения гетероциклзамещенных производных позволило получить по реакции Дебуса-Радзишевского β-имидазолилзамещенные хлорины. Таким путем были получены два новых хлорина, содержащих фенантренимидазол и бензимидазол в пиррольном кольце А хлорина e_6.

Ключевые слова: Фотосенсибилизаторы, фотодинамическая терапия, аннелирование, хлорин e_6, гетероциклы.

Introduction

Porphyrins and their hydrogenated analogues – chlorins and bacteriochlorins – possess unique physicochemical and spectral characteristics, which determine their role as an attractive platform for the development of new materials, including ones with biomedical properties.[1] Structural modification of natural chlorins allows the tuning of their physicochemical characteristics and, as a consequence, expands the range of their possible applications.[2-6] Modified natural chlorins attract attention as photosensitizers for fluorescence diagnostics and photodynamic therapy of cancer, as contrast agents for magnetic resonance imaging (MRI) and as fluorescent probes for theranostic applications. Heterocyclic annelation reactions leading to conjugated systems are of particular interest.[7-10] This type of functionalization, on the one hand, allows to expand the aromatic system of the macroheterocycle, fundamentally changing its electronic structure, on the other hand, allows to introduce different structural blocks into the molecule, varying their type and number, the distance between them and their mutual orientation.[11-14]

In the present work, methods for the synthesis of derivatives of natural chlorins containing benzimidazole and phenanthreneimidazole fragments have been developed, the physicochemical properties of the obtained chlorins have been studied, and the influence of the introduced heterocycles onto the spectral characteristics of the photosensitizers has been evaluated.

Experimental

General

The solvents were purified and prepared according to standard methods. The following categories are used in the work: potassium hydroxide, hydrochloric acid, N-methyl-N-nitrosourea, sodium periodate, osmium tetraoxide, ammonium acetate, sodium hydrosulchite, acetic acid, potassium carbonate. Methyl ester of pheophorbide *a* (**1**) was obtained *Spirulina platensis* using a well-known technique.[15]

Silica gel 40/60 (Merck, Germany) was used for column chromatography. Silica gel 5/40 (Vecton, Russia) was used for preparative TLC. The analytical solution was obtained on the basis of Kieselgel 60 F_{245} (Merck, Germany).

NMR spectra were recorded in a deuterated $CDCl_3$ solvent on a Bruker pulsed Fourier spectrometer with an operating frequency of 600 MHz. The internal standard is tetramethylsilane. The values of chemical shifts (δ) are given in millionths (ppm). MALDI mass spectra were recorded on a Bruker Ultraflex TOF/TOF mass spectrometer using 2,5-dihydroxybenzoic acid as a matrix. Absorption spectra were recorded on the Shimadzu UV1800 UV/VIS spectrometer in CH_2Cl_2.

HPLC-MS analysis conditions are as follows:

Parameter	Conditions
Column	Pyramid C_{18}, 2×75 mm, 3 μm
Mobile phase	Solvent A: deionized water; Solvent B: isopropyl alcohol
Flow rate	0.4 mL/min
Injection volume	3.00 μL
Column temp.	40°C
Elution mode	Gradient
Ionization mode	ESI
Detection	FTMS

Synthesis

*Trimethyl ester of chlorin e_6 (**2**).* 50 mL of acetone and a solution of 7.4 g (0.132 mol) KOH in 50 mL of H_2O were degassed for 2 h. 500 mg (0.825 mmol) of methyl ester of pheophorbide *a* (**1**) was dissolved in degassed acetone and KOH solution was added. The reaction was carried out by stirring in a water bath (50 °C) with a return refrigerator for 1.5 h. The course of the reaction was controlled according to TLC data in the methylene chloride-methanol system (20:1). The reaction mass was diluted with H_2O and 1M HCl solution was adjusted to p*H* 4.5. The resulting suspension was centrifuged and filtered. The precipitate was dissolved in acetone; the solvent was evaporated in vacuum. The resulting mixture was dissolved in methylene chloride and treated with an excess of diazomethane solution in diethyl ester in an ice bath. The course of the reaction was monitored using the TLC method in the methylene chloride-methanol system (50:1). The solvent was evaporated at reduced pressure. The product was isolated by column chromatography in the methylene chloride-methanol system (150:1) and crystallized from methylene chloride on a watch glass. 498 mg of compound **2** (94.8%) was obtained. ^{1}H NMR ($CDCl_3$) δ ppm: 1.62–1.81 (m, 6H, 8^2-CH_3, 18^3-CH_3), 2.06–2.31 (m, 2H, 17^2-CH_2), 2.45–2.67 (m, 2H, 17^1-CH_2), 3.29 (s, 3H, 7^1-CH_3), 3.46 (s, 3H, 2^1-CH_3), 3.56 (q, *J*=7.2 Hz, 2H, 8^1-CH_2), 3.62 (s, 3H, 12^1-CH_3), 3.75 (s, 3H, 15^3-CH_3), 3.78 (s, 3H, 17^4-CH_3), 4.24 (s, 3H, 13^2-CH_3), 4.32–4.49 (m, 2H, 17-H, 18-H), 5.21 (d, *J* = 18.4 Hz, 1H, 15^1-CH_2), 5.34 (d, *J* = 18.8 Hz, 1H, 15^1-CH_2), 6.13 (dd, *J* = 1.3, 11.7 Hz, 1H, 3^2-CH(cis), 6.34 (dd, *J* = 1.3, 18.9 Hz, 1H, 3^2-CH(trans), 8.05 (dd, *J* = 17.9, 11.6 Hz, 1H, 3^1-CH), 8.72 (s, 1H, 20-H), 9.55 (s, 1H, 5-H), 9.68 (s, 1H, 10-H). UV-Vis (CH_2Cl_2) λ_{max} nm (log ε): 403 (5.17), 501 (4.09), 530 (3.78), 613 (3.72), 664 (4.63).

*Trimethyl ester of 3-formylchlorin e_6 (**3**).* To 498 mg (0.780 mmol) trimethyl ester of chlorin e_6 (**2**) dissolved in 20 mL of THF, a solution of 670 mg (3.133 mmol) $NaIO_4$ in 5 mL H_2O and 300 μL of a solution of 2.75 g (0.039 mmol) OsO_4 in 90 mL methylene chloride was added. The reaction was carried out by stirring in an argon atmosphere and cooling to 0 °C for 3 h. The course of the reaction was controlled according to TLC data in the hexane–ethyl acetate system (1:1). Then a saturated $NaHSO_3$ solution in 10 mL of methanol was added to the reaction mixture and stirred for another 15 minutes. The reaction mixture was extracted with methylene chloride (1×30 mL). The resulting extract was washed with water (3×100 mL), dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The product was isolated by column chromatography in the hexane–ethyl acetate (2:1) system and crystallized from methylene chloride on a watch glass. 206 mg of compound **3** (41.0%) was obtained in the form of purple crystals. ^{1}H NMR ($CDCl_3$) δ ppm: 1.66–1.79 (m, 6H, 8^2-CH_3, 18^3-CH_3), 2.12–2.30 (m, 2H, 17^2-CH_2), 2.50–2.66 (m, 1H, 17^1-CH_2), 3.33 (s, 3H, 7^1-CH_3), 3.57 (s, 3H, 2^1-CH_3), 3.59 (q, *J*=7.2 Hz, 2H, 8^1-CH_2), 3.64 (s, 3H, 12^1-CH_3), 3.80 (s, 3H, 15^3-CH_3), 3.83(s, 3H, 17^4-CH_3), 4.27 (s, 3H, 13^2-CH_3), 4.39–4.52 (m, 2H, 17-H, 18-H), 5.25 (d, *J* = 18.8 Hz, 1H, 15^1-CH_2), 5.38 (d, *J* = 18.8 Hz, 1H, 15^1-CH_2), 8.94 (s, 1H, 20-H), 9.67 (s, 1H, 5-H), 10.27 (s, 1H, 10-H), 11.55 (s, 1H, 3^1-CH). Mass spectrum (MALDI-TOF): for $C_{36}H_{40}N_4O_7^+$ calculated: 640.290, found: 640.909 $[M]^+$. UV-Vis (CH_2Cl_2) λ_{max} nm (log ε): 416 (4.24), 512 (3.28), 547 (3.36), 634 (3.06), 691 (3.98).

*Trimethyl ester of 3-(benzimidazole-2-yl) chlorin e_6 (**4**).* 50 mg (0.080 mmol) of compound **3** was dissolved in 5 mL of *ortho*-dichlorobenzene and 43.1 mg (0.399 mmol) of *ortho*-phenylenediamine was added. The reaction was carried out for 18 h in an argon atmosphere under reflux. The course of the reaction was controlled according to TLC data in the methylene chloride-methanol system (50:1). At the end of the reaction, the solvent was evaporated at reduced pressure. The product was isolated by the method of preparative TLC in the methylene chloride-methanol system (40:1) and crystallized from methylene chloride

on a watch glass. 52.6 mg of compound **4** (92.3%) was obtained in the form of brown crystals. ^{1}H NMR ($CDCl_3$, δ, ppm): –1.80 (s, 2H, NH), 1.51 (d, J = 7.4 Hz, 3H, 8^2-CH_3), 1.63 (t, J = 7.8 Hz, 3H, 18^3-CH_3), 1.93–2.31 (m, 2H, 17^1-CH_2, 17^2-CH_2), 2.60 (ddd, J = 15.8, 8.8, 6.9 Hz, 2H, 17^1-CH_2, 17^2-CH_2), 2.73 (s, 3H, 7^1-CH_3), 2.90 (s, 3H, 2^1-CH_3), 3.56 (q, J = 7.2 Hz, 2H, 8^1-CH_2), 3.59 (s, 3H, 12^1-CH_3), 3.66 (s, 3H, 8^1-CH_2), 3.78 (s, 3H, 15^3-CH_3), 4.25–4.39 (dd, J = 2.4, 9.6 Hz, 1H, 17-H), 4.44 (q, J = 7.2 Hz, 1H, 18-H), 4.29 (s, 3H, 13^2-CH_3), 5.24 (d, J = 19.3 Hz, 1H, 15^1-CH_2), 5.35 (d, J = 19.3 Hz, 1H, 15^1-CH_2), 7.22 (d, J = 7.7 Hz, 1H, Ph-H^3), 7.27 (d, J = 7.8 Hz, 1H, Ph-H^2), 7.30 (d, J = 7.8 Hz, 1H, Ph-H^4), 8.04 (d, J = 7.9 Hz, 1H, Ph-H^1), 8.75 (s, 1H, 20-H), 9.71 (s, 1H, 5-H), 9.72 (s, 1H, 10-H). Mass spectrum (MALDI-TOF): for $C_{42}H_{44}N_6O_6^+$ calculated: 729.336, found: 729.341 $[M+H]^+$. UV-Vis (CH_2Cl_2) λ_{max} nm (log ε): 407 (5.21), 505 (4.42), 534 (4.34), 620 (4.30), 674 (4.82). HPLC-MS t_R min (*m/z*): 7.81 (729.3389).

*Trimethyl ester of 3-(phenanthrenoimidazole-2-yl) chlorin e_6 (**5**).* To a solution of 25 mg (0.040 mmol) of compound **3** in a mixture of $CHCl_3$/AcOH (5%), 16.6 mg (0.080 mmol) phenanthrenedione and 61.5 mg (0.798 mmol) NH_4OAc were added in two doses with an interval of 7 hours when boiling. The course of the reaction was controlled according to TLC data in the hexane-ethyl acetate system (1:1). At the end of the reaction, the mixture was washed with a saturated NaCl solution, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The product was isolated by the method of preparative TLC in the methylene chloride-methanol system (50:1) and crystallized from methylene chloride on a watch glass. 22.6 mg of compound **5** (69.5%) was obtained. ^{1}H NMR ($CDCl_3$) δ ppm): –1.79 (s, 1H, NH), 1.61 (t, J = 7.6 Hz, 4H, 8^2-CH_3), 1.76 (d, J = 7.3 Hz, 3H, 18^3-CH_3), 2.10–2.66 (m, 3H, 17^1-CH_2, 17^2-CH_2), 3.13 (s, 3H, 7^1-CH_3), 3.56 (s, 3H, 2^1-CH_3), 3.59 (q, J=7.2 Hz, 2H, 8^1-CH_2), 3.63 (s, 3H, 12^1-CH_3), 3.69 (q, J=7.2 Hz, 2H, 8^1-CH_2), 3.76 (s, 3H, 15^3-CH_3), 4.26 (s, 3H, 13^2-CH_3), 4.40 (d, J = 10.8 Hz, 1H, 17-H), 4.44 (q, J = 7.2 Hz, 1H, 18-H), 5.24 (d, J = 19.0 Hz, 1H, 15^1-CH_2), 5.35 (d, J = 19.0 Hz, 1H, 15^1-CH_2), 7.62 (s, 3H, Ph-H^3, Ph-H^4), 8.63 (s, 4H, Ph-H^1, Ph-H^2), 8.82 (s, 1H, 20-H), 9.57 (s, 1H, 5-H), 10.09 (s, 1H, 10-H). Mass spectrum (MALDI-TOF): for $C_{50}H_{48}N_6O_6^+$ calculated: 829.367, found: 829.379 $[M+H]^+$. UV-Vis (CH_2Cl_2) λ_{max} nm (log ε): 407 (4.51), 505 (3.63), 536 (3.52), 622 (3.04), 674 (4.30). HPLC-MS t_R min (*m/z*): 9.81 (829.3701).

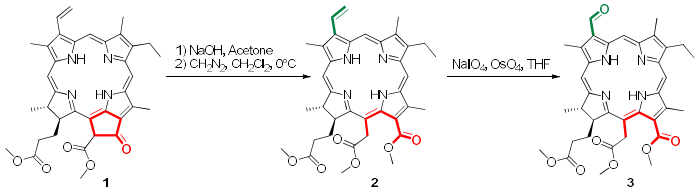
Results and Discussion

In order to obtain the target natural chlorin derivatives, methylpheophorbide *a* (**1**) was chosen as the starting compound, the vinyl group of which was oxidized to formyl in the pyrrole ring A of the macrocycle (Scheme 1).

The oxidation was carried out on trimethyl ester of chlorin e_6 to force the reaction to proceed unambiguously.[15] The opening of the exocycle was immediately recognized in the absorption spectrum as a slight hypsochromic shift of all absorption bands (Figure 1).

The oxidation of the vinyl group in pyrrole A of the obtained trimethyl ester of chlorin e_6 (**2**) was carried out in the typical way by the Lemieux-Johnson reaction with sodium periodate and osmium tetraoxide in THF medium (Scheme 1),[16] in which olefins undergo oxidative cleavage to form two ketone or aldehyde units. The reaction proceeds in 2 steps: first, the vinyl group is converted to cis-diol by OsO_4, which is subsequently cleaved by $NaIO_4$. The main advantage of this method is that it allows the oxidation to be carried out selectively to the aldehyde.

A significant bathochromic shift from 664 to 691 nm is observed in the absorption spectrum, indicating the replacement of the vinyl group with a formyl group (Figure 2). Instead of the characteristic signals of the protons of the vinyl group, a signal of the formyl proton (11.55, s, 1H) can be seen in the ^{1}H NMR spectrum.



Scheme 1. Preparation of trimethyl ester of chlorin`s derivatives.

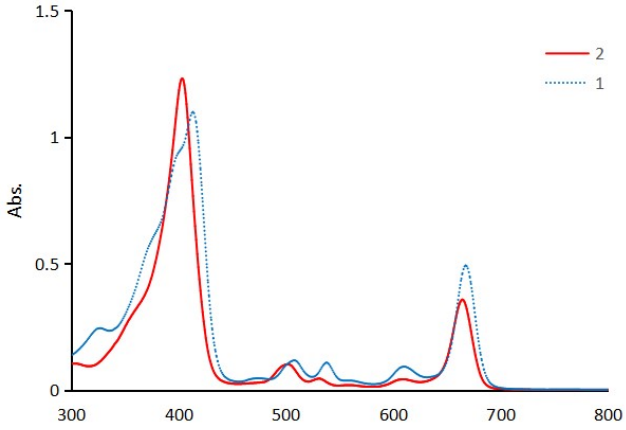


Figure 1. Absorption spectra of compounds **1** and **2**.

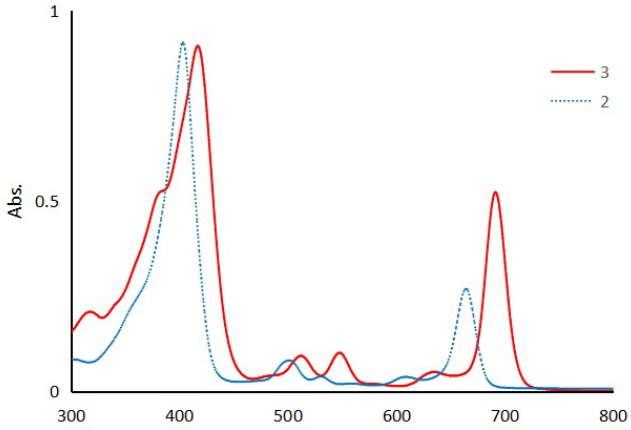
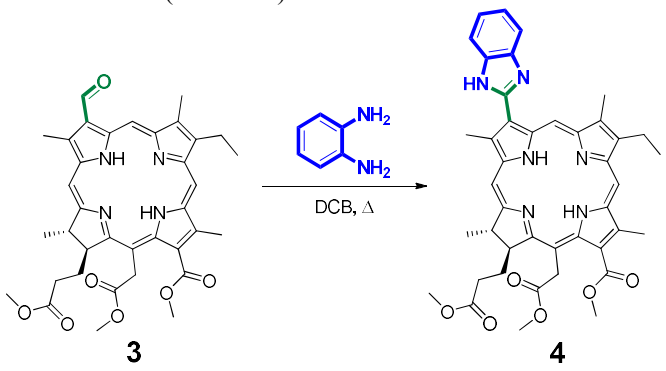


Figure 2. UV-Vis absorption spectra of compounds **2** and **3**.

In the present work, the trimethyl ester of 3-formylchlorin e_6 (**3**) was the key compound for the preparation of heterocycle-substituted chlorins, containing benzimidazole and phenanthreneimidazole moieties. The preparation of benzimidazole derivative of chlorin was realized by the Phillips-Ladenburg reaction[17] as one of the methods for the preparation of benzimidazole derivatives

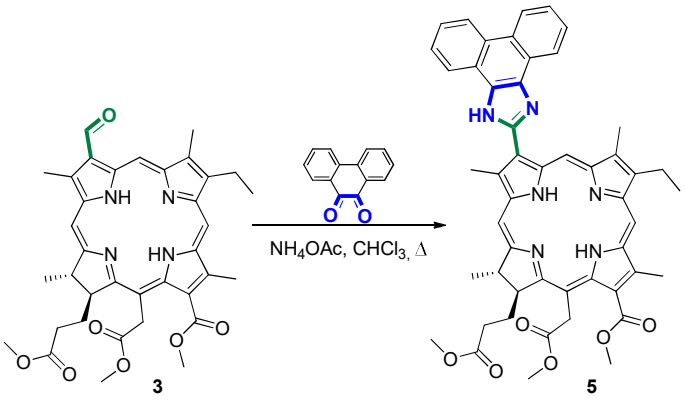
involving condensation of formyl chlorin **3** with *o*-phenylenediamine in *o*-dichlorobenzene medium upon reflux for 18 h (Scheme 2).



Scheme 2. Preparation of trimetyl ester of 3-(benzimidazol-2-yl) chlorin e_6 (**4**).

During the reaction, the final compound **4** exhibited a slight bathochromic shift of the absorption bands by 7 nm compared to the initial methylpheophorbide **1** and by 10 nm compared to trimethyl ester of chlorin e_6 **2** (Figure 3). The purity and identification of compound **4** was carried out by high-resolution chromato-mass spectrometry (Figure 4), as well as by MALDI-TOF mass spectrometry and ^{1}H NMR spectroscopy. According to the ^{1}H NMR spectrum the absence of a proton signal of the formyl group was confirmed and benzimidazole signals were detected (7.22, d, 1H, Ph-H^3; 7.27, d, 1H, Ph-H^2; 7.30, d, 1H, Ph-H^4; 8.04, d, 1H, Ph-H^1).

The Debus-Radziszewski condensation,[18-21] which is a multicomponent reaction, where the first step is condensation of dicarbonyl compound with two ammonia molecules to form diimine and the second step is condensation of diimine with aldehyde to form imidazole, afforded the phenanthreneimidazole derivative of chlorin **5**. The reaction was carried out with phenanthrenedione and ammonium acetate in a mixture of $CHCl_3$:AcOH upon reflux for 24 h (Scheme 3).



Scheme 3. Preparation of trimethyl ester of 3-(phenanthrene-imidazol-2-yl) chlorin e_6 (**5**).

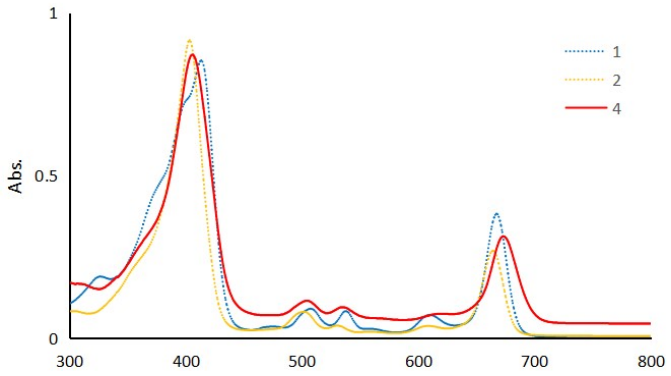


Figure 3. UV-Vis absorption spectra of compounds **1**, **2** and **4**.

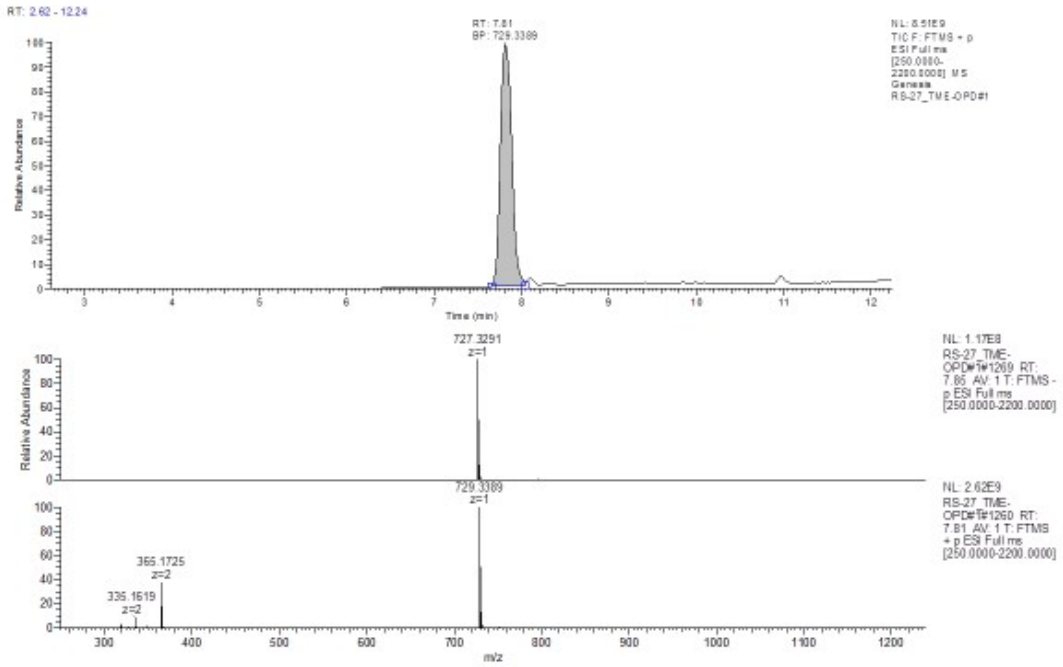


Figure 4. Chromato-mass spectrometry data of compound **4**.

A shift of the absorption band was observed for compound **5** similar to chlorin **4** with benzimidazole moiety (Figure 5). The purity and identification of compound **5** was carried out by high-resolution chromato-mass spectrometry (Figure 6), as well as by MALDI-TOF mass spectrometry and ^{1}H NMR spectroscopy. Also proton signals of aromatic rings of phenanthrenimidazole can be seen on the ^{1}H NMR spectrum (7.62, s, 4H, Ph-H^{3}, Ph-H^{4}; 8.63, s, 2H, Ph-H^{1}).

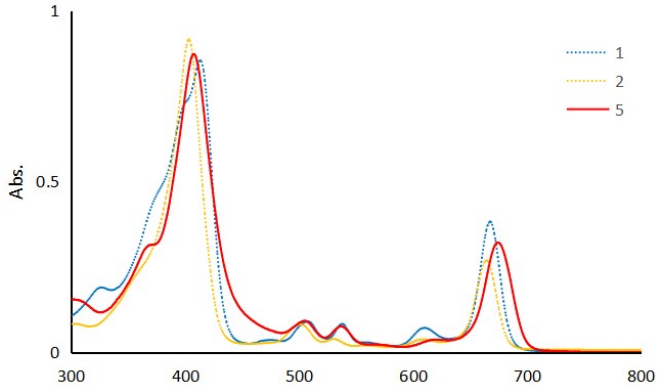


Figure 5. UV-Vis absorption spectra of compounds **1**, **2** and **5**.

Conclusions

Thus, in the present work, the derivatives of natural chlorins, containing benzimidazole and phenanthrene-imidazole fragments in their structure, were prepared for the first time. The target compounds were characterized by a set of physicochemical methods of analysis and it was shown that the introduction of heterocyclic fragments to the periphery of the core macrocycle affects the redistribution of electron density in the molecule. The main characteristic of photosensitizers for their use in PDT are spectral properties, including the electronic absorption spectrum. The bathochromic shift of the main absorption band of Q2 to the near-infrared region of the spectrum allows the use of dyes for the treatment of deep-lying and pigmented tumors. The expansion of the conjugation chain in chlorin derivatives with annelated cycles should cause a bathochromic shift depending on the nature and location of the heterocycles.

In the present work, the strong +M effect of aromatic substituents did not significantly improve the spectral properties, however, further functionalization of such compounds, including the introduction of electron acceptor groups, will make it possible to obtain chlorines with the required (tunable) properties.

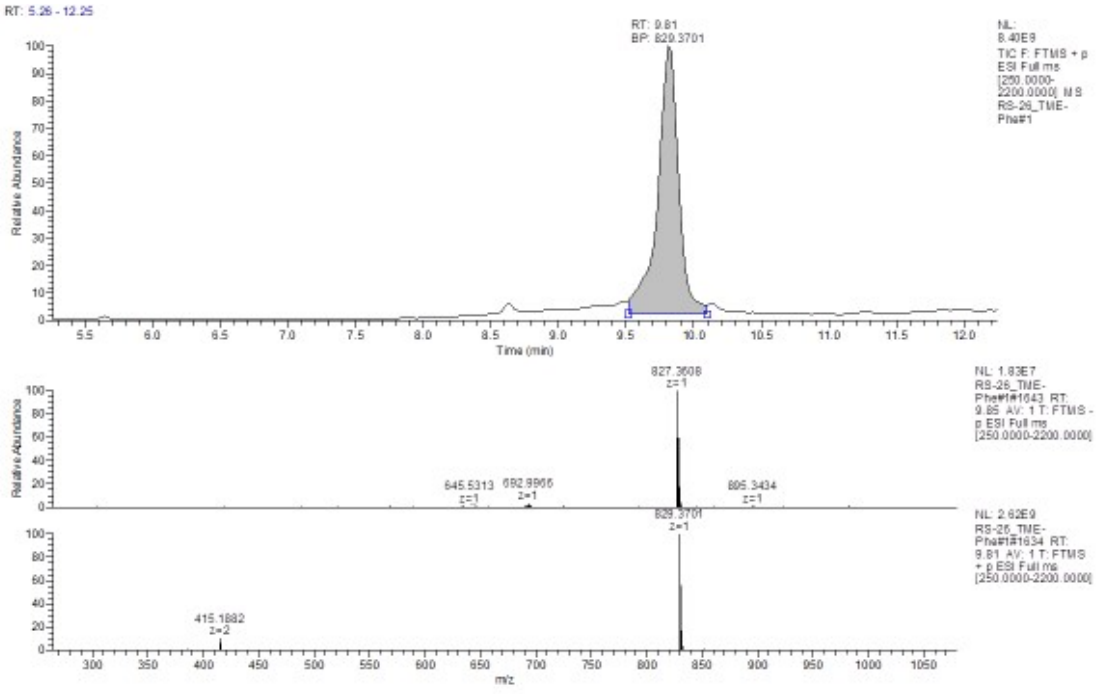


Figure 6. Chromato-mass spectrometry data of compound **5**.

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