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Synthesis and properties of Cu- and Pd-complexes of cyclen conjugates with pheophorbide and bacteriopheophorbide

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Objectives. *Chlorin and bacteriochlorin photosensitizers are effective agents for cancer photodynamic therapy and fluorescence imaging. They are also excellent chelators forming stable metal complexes. Besides, ^{64}Cu and ^{109}Pd isotopes can serve as emitters for nuclear medicine. Chelation of these metals with cyclen conjugates with chlorin and bacteriochlorin photosensitizers can become a simple and universal strategy for the synthesis of diagnostic and therapeutic radiopharmaceuticals for nuclear medicine. This article reports on the synthesis of similar Cu and Pd complexes of cyclen conjugates with pheophorbide and bacteriopheophorbide and the study of their photophysical properties.*

Methods. *Metalation of cyclen conjugates was carried out with palladium and copper acetates. For bacteriochlorins, 6-O-palmitoyl-L-ascorbic acid was additionally used as a reducing agent. MALDI mass spectrometry, which was carried out on a time-of-flight mass spectrometer Bruker Ultraflex TPF/TOF and a Bruker Daltonics Autoflex II confirmed the structure of the compounds obtained. Electronic absorption spectra were obtained on a Shimadzu 3101 spectrophotometer. Fluorescence and phosphorescence spectra were obtained on a FluoTime 300 PicoQuant spectrofluorometer.*

Results. *Photophysical studies of metal complexes showed that the introduction of palladium cations quenches fluorescence and increases the quantum yield of singlet oxygen generation to 0.98 for the chlorin conjugate. Besides, it decreases the quantum yield of fluorescence to 0.10 and increases the quantum yield of singlet oxygen generation to 0.72 for the bacteriochlorin conjugate. Introducing a copper cation to cyclen conjugates with pheophorbide and bacteriopheophorbide leads to photophysical characteristics quenching.*

Conclusions. *Due to the stability of the synthesized metal complexes in acidic media, as well as the short metalation time (5, 20, 10, and 15 minutes) it is reasonable to expect the successful development of effective imaging agents for positron emission tomography and radionuclide therapy. In addition, the residual fluorescence of bacteriochlorins makes it possible to use fluorescence diagnostics in combination with these methods.*

Keywords: *metal complexes, bacteriochlorins, chlorins, theranostics, cyclen, palladium, copper, photodynamic therapy.*

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Синтез и свойства Cu- и Pd-комплексов конъюгатов циклена с феофорбидом и бактериофеофорбидом

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Цели. *Фотосенсибилизаторы на основе хлоринов и бактериохлоринов являются эффективными агентами для фотодинамической терапии и флуоресцентной визуализации рака. Кроме того, они представляют собой отличные хелаторы, образующие стабильные металлокомплексы, а изотопы ^{64}Cu и ^{109}Pd могут служить в качестве излучателей для ядерной медицины. Хелатирование таких металлов с конъюгатами циклена с хлориновыми и бактериохлориновыми фотосенсибилизаторами может стать простой и универсальной стратегией синтеза диагностических и терапевтических радиофармацевтических препаратов для ядерной медицины. В настоящем исследовании сообщается о синтезе подобных Cu- и Pd-комплексов конъюгатов циклена с феофорбидом и бактериофеофорбидом и исследовании их фотофизических свойств.*

Методы. *Металлирование конъюгатов циклена проводилось ацетатами палладия и меди, для бактериохлоринов дополнительно использовали 6-O-пальмитоил-L-аскорбиновой кислоты в качестве восстановителя. Структуру полученных соединений подтверждали с помощью MALDI-масс-спектрометрии, которую проводили на время-пролетном масс-спектрометре Bruker Ultraflex TPF/ TOF и Bruker Daltonics Autoflex II. Электронные спектры поглощения регистрировали на спектрофотометре Shimadzu 3101. Спектры флуоресценции и фосфоресценции были получены на спектрофлуориметре FluoTime 300 PicoQuant.*

Результаты. *Фотофизические исследования металлокомплексов показали, что введение катионов палладия приводит к тушению флуоресценции и увеличению квантового выхода синглетного кислорода до 0.98 для хлоринового конъюгата, а также уменьшению квантового выхода флуоресценции до 0.10 и увеличению квантового выхода синглетного кислорода до 0.72 для бактериохлориного конъюгата. Введение катиона меди к конъюгатам циклена с феофорбидом и бактериофеофорбидом приводит к тушению фотофизических характеристик.*

Заключение. *Устойчивость синтезированных металлокомплексов в кислых средах, а также небольшое время металлирования (5, 20, 10 и 15 мин соответственно) позволяет ожидать успешное создание эффективных визуализирующих агентов для позитронно-эмиссионной томографии и радионуклидной терапии, а остаточная флуоресценция бактериохлоринов делает возможным применение флуоресцентной диагностики в комбинации с данными методами.*

Ключевые слова: *металлокомплексы, бактериохлорины, хлорины, тераностика, циклен, палладий, медь, ФДТ.*

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Introduction

Various physical methods can be used for the molecular imaging of malignant neoplasms. Among them, an important place is occupied by single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), and fluorescence diagnostics (FD). Each of these image processing methods has both merits and demerits. Combining different methods makes it possible to overcome the existing limitations. Compounds possessing different, but complementary physical properties play an important role in this. In this case, it is possible to combine two modal units, for example, a fluorescent dye and a chelator containing Gd, with the formation of a bifunctional agent for simultaneous use in FD/MRI. This type of agents is designed for 1:1 ratio (e.g., a bimetallic complex with

a 1:1 Gd/Cu ratio) [1]. In the case of MRI and PET, due to the different sensitivity of the methods, this system can be used only upon diluting the radioactive isotope with "cold" copper ions. Tei et al reported the synthesis of a heterodimeric polyaminocarboxylate ligand DO3A-AAZTA (1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid – 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine) and its hetero-ditopic Gd(III)-Ga(III) complex for use as a contrast agent in MRI/PET [2]. Guerin and coworkers described the synthesis of a series of new bimodal probes combining zinc phthalocyanine (ZnPc) to form fluorescence and ^{68}Ga/1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA) or ^{64}Cu/1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) for PET images [3]. Kim et al describe the synthesis of a bimodal Gd(III)/^{125}I-RGD-DOTA probe for SPECT/MRI [4]. Desbois and colleagues obtained dimeric ligands with two different chelating macrocycles: one based on a DOTA derivative for Gd(III) complexation to enhance the contrast in the MRI method and another using a corrin macrocycle for ^{64}Cu chelation in radionuclide visualization [1]. Waghorn et al used ^{109}Pd as a radioisotope for radionuclide therapy (RT) in their work. They showed that hematoporphyrin with ^{64}Cu and ^{109}Pd isotopes has significant tropism regarding tumors, mainly those localized in mitochondria [5].

Interestingly, a chelating DOTA-like tetraaza-macrocycle can be used for the complexation of various metal ions usually leading to stable heterobimetallic complexes. For example, the gadolinium complex of DOTA is currently used as an extravascular contrast agent for MRI [6].

Various chelating ligands were suggested for copper radionuclides, such as polyaminocarbonoxylates, cyclic polyamines, tetraazamacrocycles and bis-thiosemicarbazones [7]. Selection of the reagents depends on the stability of the formed complexes. Acyclic chelates do not have sufficient kinetic stability. Therefore, macrocyclic ligands are preferred [8]. The thermodynamic stability of the respective classes of ligands for Cu(II) complexes decreases in the following order: hexa aza cages > tetraazamacrocycles > polyaminophosphonates > polyaminocarboxylate macrocycles > acyclic aminocarboxylates [7]. DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is the most commonly used macrocyclic chelator of metals, including ^{64}Cu, in radiopharmaceutical studies [9]. However, DOTA is not an ideal ligand for ^{64}Cu because of the slow reaction kinetics [10]. 1,4,7-Triazacyclononane-1,4,7-triacetyl acid, as well as cross-bridged 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid are more stable as compared to DOTA, but they require harsh conditions of radioactive labeling [11]. The most common ^{64}Cu complex is diacetylbis(*N*-4-methylthiosemicarbazone) (ATSM) [12]. The lipophilic molecules of this complex are selectively absorbed by hypoxic tissues and therefore may be used to detect such areas with cardiac system disorders.

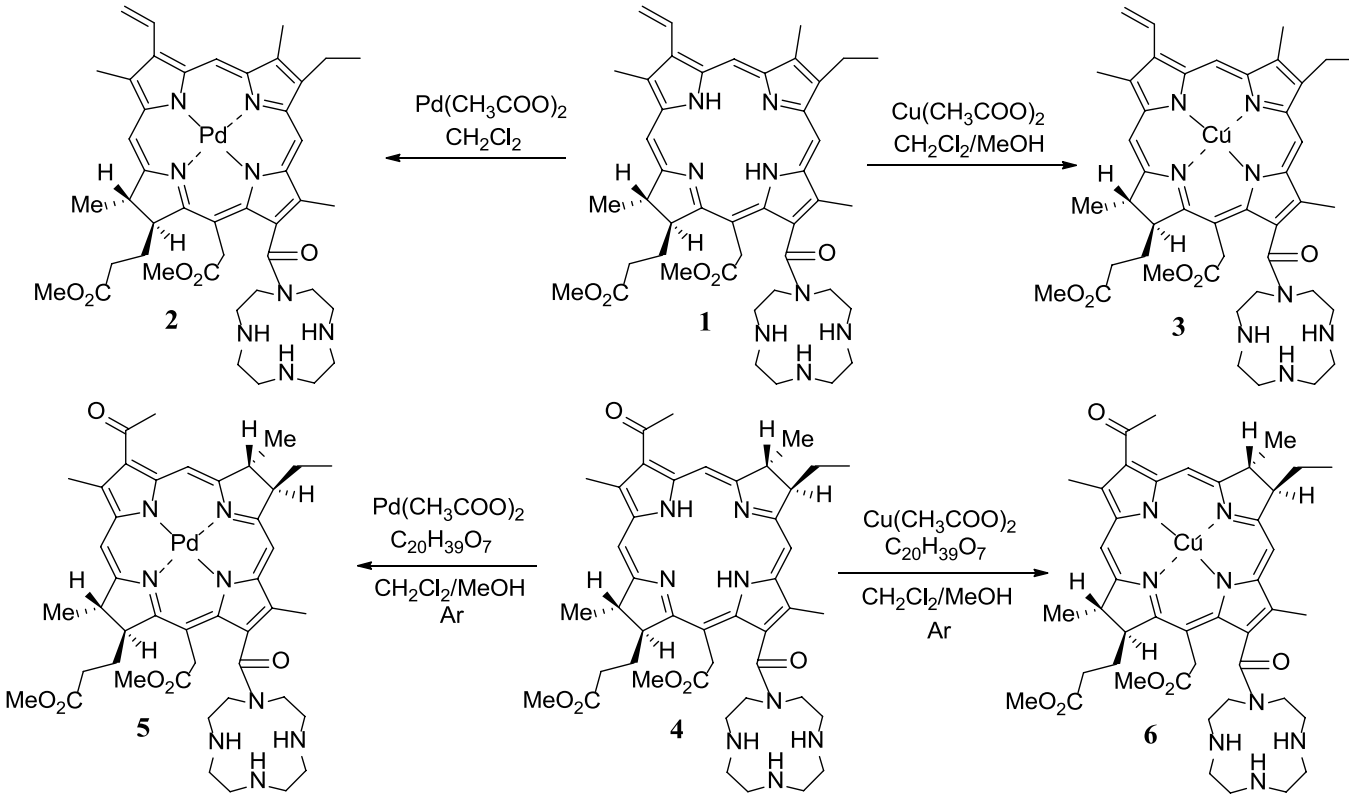
On the other hand, the rapid complexation of metal ions with a ligand is an important criterion in the development of radiopharmaceuticals, because in some cases the lifetime of a radioisotope is comparable with the time of the complex's preparation and use. This is a serious limitation of many radioactive labeling techniques, in which long incubation times (up to 1 hour) and an excess of the ligand are used to achieve a sufficient complexation yield. In some cases, the presence of an excess of the ligand in the compositions is undesirable, because many target agents have their own biological activity.

An extensive class of natural and synthetic porphyrins occupies a prominent place among numerous chelating ligands. This is due to the high affinity of these compounds to various metals and increased tropism for malignant neoplasms [13]. The metal complexes of porphyrins and of their hydrogenated analogues (chlorins and bacteriochlorins) are widely used in photodynamic therapy (PDT) for cancer. The well-known photosensitizer Padeliporfin (a Pd complex of bacteriochlorin) is used for the fluorescence diagnostics and therapy of various tumor types [14]. Porphyrins and their hydrogenated analogues are promising chelators and vehicles to deliver copper radioisotopes to diseased tissues [15]. They have the ability to chelate metal ions through a system of four nitrogen atoms in the macrocycle with an ionic radius of about 70 pm (the ionic radius of Cu^{2+} is 72 pm). Although the complexes are characterized by the high values of stability constants, they have relatively poor formation kinetics. This limitation was removed by using a mechanism including a SAT (sitting-a-top) complex formation [16]. The chelating properties are substantially independent of the type and number of substituents in the ring, which allows using a suitable amphiphilic conjugate for PET-imaging.

In this work, we developed methods for the preparation of palladium and copper complexes with derivatives of natural chlorins with DOTA, the synthesis of which we previously described [17], as potential diagnostic and therapeutic radiopharmaceuticals for nuclear medicine. The use of ^{109}Pd and ^{64}Cu isotopes in the porphyrin macrocycle followed by the introduction of Gd or Ga into the cyclic cavity will make it possible to obtain multifunctional probes for combining diagnostic and therapeutic methods (PD/RT/PET, PD/MRI/PDT, etc.).

Results and Discussion

The introduction of metal cations into chlorin and bacteriochlorin macrocycles fundamentally changes the properties of the structures and is a promising direction to generate contrast agents for diagnostics and therapy. It is known that the bathochromic shift of the main absorption band Q in the series porphyrins–chlorins–bacteriochlorins is accompanied by a decrease in the intrinsic fluorescence of these compounds. The introduction of metals into porphyrins and chlorins, but not into bacteriochlorins, extinguishes fluorescence, which greatly limits the possibility of studying such structures in further biological tests. As shown previously, the presence of two coordination cavities in conjugates **1** and **4** makes it possible to obtain homo- and heteronuclear metal complexes. The latter can be in demand in fluorescence diagnostics, magnetic resonance, and positron emission tomography as well as in radionuclide therapy and photodynamic therapy for cancer [17].



Scheme. Introduction of metal ions into the coordination sphere for conjugates of methylpheophorbide *a* and methylbacteriopheophorbide *a* with cyclen.

A regioselective introduction of the palladium cation into the chlorin macrocycle of conjugate **2** was carried out under mild conditions without heating using palladium acetate (Scheme). The reaction's progress and the formation of metal complex **2** were monitored by the hypsochromic shift of the absorption band from 664 to 624 nm. Similarly, the reaction was carried out to obtain copper complex **3**. The formation of the metal complex was monitored by the hypsochromic shift of the absorption band from 664 to 640 nm (Fig. 1).

The presence of palladium and copper cations in conjugates **2** and **3** was clearly confirmed via MALDI mass spectra by the presence of molecular ions and signal groups corresponding to the main isotopes of palladium and copper.

It follows from Table 1 data that when the Pd^{2+} cation is introduced into the chlorin macrocycle, the initial conjugate **1** fluorescence is significantly suppressed, while the photosensitizing activity of the metal complex **2**, which was estimated on the basis of the quantum yield of singlet oxygen generation

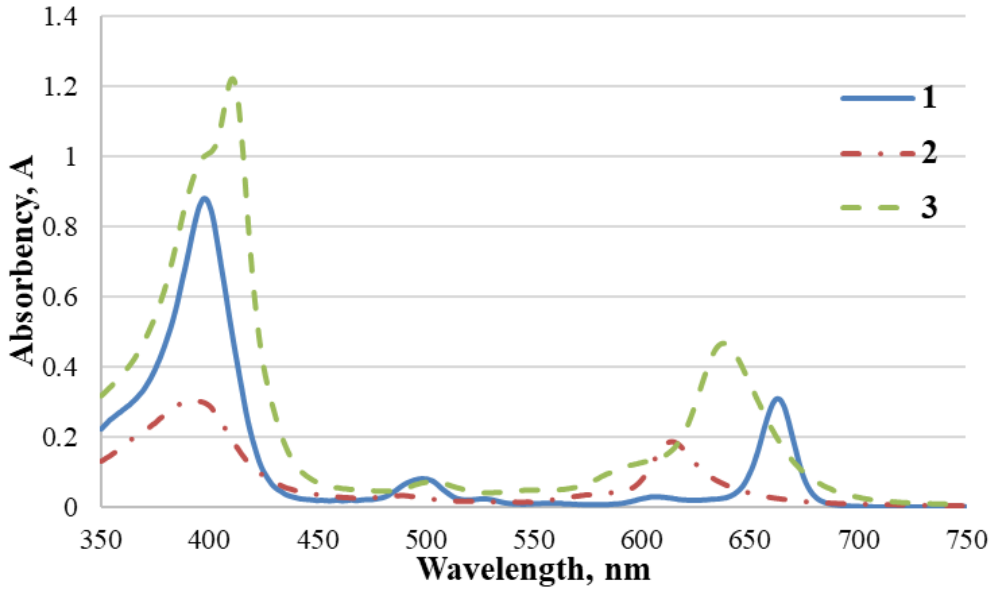


Fig. 1. Absorption spectra for methylpheophorbide *a* conjugate with cyclen (**1**), Pd complex of chlorin-cyclen conjugate (**2**), and Cu complex of chlorin-cyclen conjugate (**3**).

(Φ_Δ) using 1,3-diphenylisobenzofuran (DPIBF) as a chemical trap, it increased to 98%. This makes it possible to conclude that the photodynamic potential of this metal complex is high. The introduction of Cu^{2+} cation, in turn, results in the characteristic suppression of the main photophysical characteristics, Φ_Δ and Φ_F.

Table 1. Quantum yields for fluorescence (Φ_F) and singlet oxygen generation (Φ_Δ) of the chlorin-cyclen conjugate and its Pd complex

Compound	Fluorescence quantum yield Φ_F	Singlet oxygen generation quantum yield Φ_Δ
1	0.266±0.005	0.71
2	0.0005	0.98
3	–	–

Next, we obtained the palladium and copper complexes of bacteriopheophorbide *a* conjugate with cyclen **4**. Previously, Scherz with coworkers showed that the introduction of a metal into bacteriochlorins is much faster in the presence of reducing agents [18]. Using these data, we treated conjugate **4** with palladium acetate in the presence of 6-*O*-palmitoyl-L-ascorbic acid. The reaction was controlled spectrophotometrically by the hypsochromic shift of the main absorption band from 522 to 515 nm, as well as by the reduction of fluorescence intensity, which indicated the formation of Pd complex **5**. Similarly, metalation was performed with copper acetate. The bathochromic shift of the spectrum in the band from 758 to 767 nm as well as the almost complete absence of fluorescence, indicate the formation of Cu complex **6** (Fig. 2, Fig. 3).

The presence of palladium and copper cations in conjugates **5** and **6** was clearly confirmed via MALDI mass spectra by the presence of molecular ions and groups of signals corresponding to the main isotopes of palladium and copper.

It follows from the data of Table 2 that introducing the Pd^{2+} cation into the bacteriochlorin macrocycle results in a slight decrease in conjugate **5** fluorescence, and the fluorescence lifetime remains unchanged. The combination of such parameters in Pd complex **5** maintains its therapeutic and diagnostic potentials. In turn, the introduction of the Cu^{2+} cation quenches the photophysical characteristics of complex **6** while maintaining residual fluorescence with a maximum identical to compound **4**, which is due to the partial introduction of copper according to the SAT mechanism [5].

Conclusions

Due to the stability of the synthesized metal complexes in acidic media, as well as the short metalation time (5, 10, 20, and 15 min., respectively) it is reasonable to expect successful development of

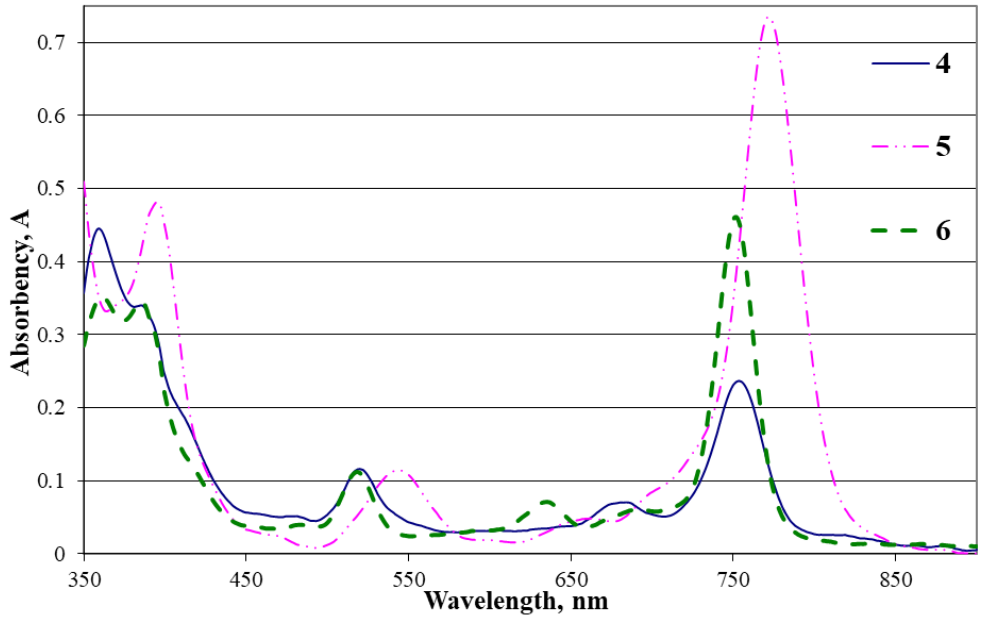


Fig. 2. Absorption spectra of methylbacteriopheophorbide *a* conjugate with cyclen (**4**), of the Pd complex of bacteriochlorin-cyclen conjugate (**5**), and of the Cu complex of bacteriochlorin-cyclen conjugate (**6**).

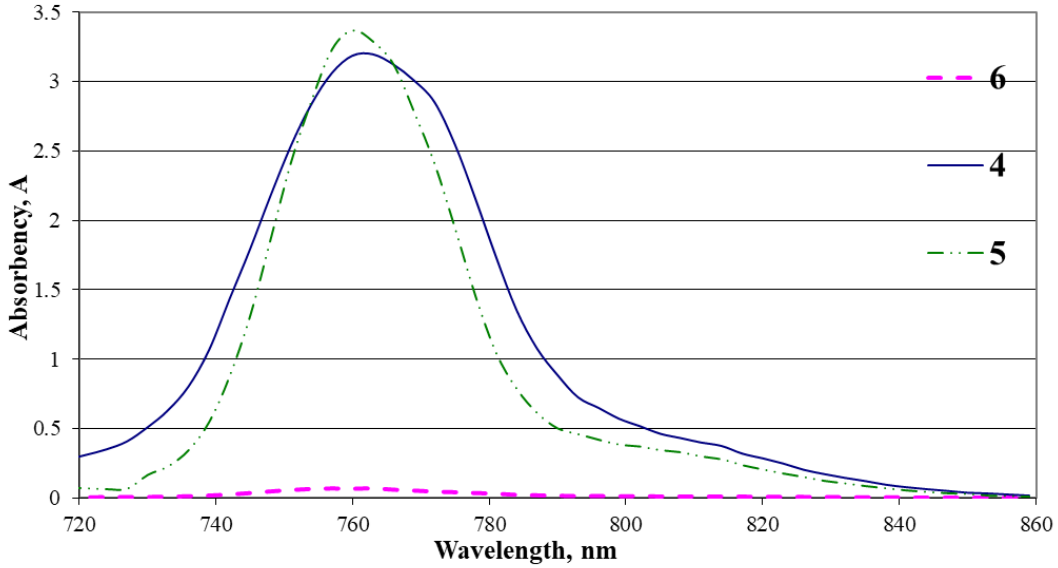


Fig. 3. Fluorescence spectra of methylbacteriopheophorbide *a* conjugate with cyclen (**4**), of the Pd complex of bacteriochlorin-cyclen conjugate (**5**), and of the Cu complex of bacteriochlorin-cyclen conjugate (**6**).

Table 2. Quantum yield of fluorescence (Φ_F), of singlet oxygen generation (Φ_Δ) and fluorescence lifetime (τ_S) for methylbacteriopheophorbide *a* conjugate with cyclen (**4**), for the Pd complex of bacteriochlorin-cyclen conjugate (**5**), and for the Cu complex of bacteriochlorin-cyclen conjugate (**6**)

Compound	Fluorescence quantum yield Φ_F	Fluorescence lifetime, τ_S, ns	Singlet oxygen generation quantum yield Φ_Δ
4	0.13	1.75	0.68
5	0.1	1.79	0.72
6	0.0013	–	–

effective visualizing agents for PET and radionuclide therapy (RT). At the same time, the virtual absence of fluorescence excludes the use of the compounds **2**, **3**, and **6** in the fluorescence diagnostics.

Therefore, the combination of physicochemical, photophysical, and spectral characteristics along with the short time of cyclen conjugates with pheophorbide and bacteriopheophorbide metalation with palladium and copper promotes the further study of metal complexes of natural chlorins for use in nuclear medicine.

Materials and Methods

Electronic absorption spectra were obtained on a *Shimadzu* 3101 spectrophotometer. Fluorescence and phosphorescence spectra were obtained on a *FluoTime 300 PicoQuant* spectrofluorometer. Mass spectra were obtained on *Bruker Ultraflex* TPF/TOF and *Bruker Daltonics Autoflex* II time-of-flight mass-spectrometers using the MALDI method; 2,5-dihydroxybenzoic acid (DHB) and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propylidene] malononitrile (DCTB) were used as matrices.

Solvents were purified and prepared according to standard procedures. All reactions were carried out using degassed solvents under protection from direct light in an argon atmosphere. For preparative TLC, silica gel 60 (*Merck*) 20×20 cm plates with a layer thickness of 1 mm were used. Analytical TLC was performed on Kieselgel 60 F245 plates (*Merck*).

Pd complex of pheophorbide *a* methyl ester with cyclen (2). Twenty-five mg of methyl pheophorbide a with cyclen (**1**) and 10 mg of palladium acetate were dissolved in 4 ml of CH_2Cl_2. The reaction's progress was monitored spectrophotometrically by recording the reaction's mixture absorbance spectrum every 5 min. After the completion, the mixture was transferred to a separating funnel with water and extracted with DCM (2×20 ml) to remove excess metalation agent. The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed in the vacuum of a water-jet pump. The resulting product was dissolved in a minimal amount of DCM and purified by preparative TLC using a DCM/methanol mixture (v/v 30:1). The purified conjugate was recrystallized from hexane. Yield: 23.75 mg. Electronic spectrum, λ_{max}, nm ($\varepsilon\times10^{-3}$, $M^{-1}cm^{-1}$): 390 (100), 500 (10), 621 (18). Mass spectrum (MALDI), *m/z*: 893.157 (M^+).

Cu complex of pheophorbide *a* methyl ester with cyclen (3). Twenty-five mg of conjugate **1** in 4 ml of CH_2Cl_2 and 4 mg of copper acetate were dissolved in 2 ml of CH_3OH. The reaction mixture was stirred under argon. The reaction's progress was monitored spectrophotometrically by recording the reaction's mixture absorbance spectrum every 5 min. The reaction was completed after 10 minutes. The mixture was transferred to a separating funnel with water and extracted with DCM (2×20 ml) to remove excess copper acetate. The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed in the vacuum of a water-jet pump. The resulting product was dissolved in a minimum of DCM and purified by preparative TLC using DCM/methanol mixture (v/v 30:1). The purified conjugate was recrystallized from hexane. Yield: 22.25 mg. Electronic spectrum, λ_{max}, nm ($\varepsilon\times10^{-3}$, $M^{-1}cm^{-1}$): 388 (100), 502 (12), 638 (35). Mass spectrum (MALDI), *m/z*: 667.875 (M^+).

Pd complex of bacteriopheophorbide *a* methyl ester with cyclen (5). Twenty-five mg of bacteriopheophorbide a methyl ester conjugate with cyclen (**4**) and 17 mg of palladium acetate were dissolved in 4 ml of CH_2Cl_2 and mixed with a solution of 76 mg of 6-*O*-palmitoyl-L-ascorbic acid in 8 mL of CH_3OH. The reaction mixture was stirred under argon. The reaction's progress was monitored spectrophotometrically. The reaction was completed was completed after 20 minutes. The mixture was diluted with water and extracted with DCM (2×20 ml) to remove excess metalation agent. The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed in the vacuum of a water-jet pump. The resulting product was dissolved in a minimum of DCM and purified by preparative TLC using DCM–methanol mixture (v/v 30:1). The purified conjugate was recrystallized from hexane. Yield: 21.25 mg. Electronic spectrum, λ_{max}, nm ($\varepsilon\times10^{-3}$, $M^{-1}cm^{-1}$): 351 (75), 515 (43), 750 (112). Mass spectrum (MALDI), *m/z*: 900.033 (M^+).

Cu complex of bacteriopheophorbide *a* methyl ester with cyclen (6). Twenty mg of conjugate **4** and 7 mg of copper acetate were dissolved in 4 ml of CH_2Cl_2 and mixed with a solution of 38 mg of 6-*O*-palmitoyl-L-ascorbic acid in 4 ml of CH_3OH. The reaction mixture was stirred under argon. The reaction's progress was monitored spectrophotometrically. The reaction was completed after 15 minutes. The mixture was transferred to a separating funnel with water and extracted with DCM (2×20 ml). A trace amount of water from the organic layer I was removed by sodium sulfate and the solvent was evaporated under a vacuum. The resulting product was dissolved in a minimal amount of DCM and purified by preparative TLC using DCM–methanol mixture (v/v 30:1). Conjugate **6** was recrystallized from hexane. Yield: 17.2 mg. Electronic spectrum, λ_{max}, nm ($\varepsilon\times10^{-3}$, $M^{-1}cm^{-1}$): 389 (100), 542 (75), 767 (245). Mass spectrum (MALDI), *m/z*: 858.529 (M^+).

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The authors declare no conflicts of interest.

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