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EDN OOWRYZ

RESEARCH ARTICLE

Platinum(II) complexes based on derivatives of natural chlorins with pyridine-containing chelate groups as prototypes of drugs for combination therapy in oncology

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Abstract

Objectives. To synthesize Pt-containing derivatives of natural chlorins as potential agents for the combination therapy in oncology. Platinum compounds are known to occupy an important place as chemotherapeutic agents in the treatment of oncological diseases. However, Pt(II) complexes are highly toxic to the body and are not selectively accumulated in tumor cells. If photodynamic and chemotherapy methods are combined in a single drug, the pigments are responsible for the selectivity of conjugate accumulation in the tumor, while a chemotherapeutic agent based on Pt(II) complexes is responsible for the cytotoxic effect on tumor cells. This will not affect healthy cells and thereby minimize the systemic toxicity of the drug to the body.

Methods. Methods for the synthesis of pyridine-containing derivatives of natural chlorins and their metal complexes for use as potential binary agents in oncology were applied. As part of the study, the structures of the compounds obtained were confirmed by mass spectrometry, nuclear magnetic resonance spectroscopy, ultraviolet spectroscopy, and high-resolution chromatography-mass spectrometry. Preparative methods, including thin-layer and column chromatography, centrifugation and recrystallization, were used to isolate and purify the compounds obtained.

Results. Platinum(II) complexes of pyridine-containing derivatives of natural chlorins were obtained for application in combination therapy in oncology. The schemes for synthesizing the target photosensitizers were optimized, in order to increase the yields and for subsequent transfer to industrial sites.

Conclusions. It was found that pyridine-containing derivatives of natural chlorins could be obtained in high yields, that they possess chelating properties for platinum, and can be considered as binary agents in cancer therapy after successful preclinical trials.

Keywords

photodynamic therapy, chlorins, bacteriochlorins, platinum complexes, photosensitizer, combination therapy, pyridines

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НАУЧНАЯ СТАТЬЯ

Комплексы платины(II) на основе производных природных хлоринов с пиридинсодержащими хелатными группами: прототипы лекарств для комбинированной терапии в онкологии

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Аннотация

Цели. Целью настоящей работы является синтез Pt-содержащих производных природных хлоринов как потенциальных агентов для комбинированной терапии в онкологии. Известно, что соединения платины в качестве химиотерапевтических агентов занимают важное место в лечении онкологических заболеваний. Однако комплексы Pt(II) высокотоксичны для организма и не обладают селективностью накопления в опухолевых клетках. При комбинировании методов фотодинамической и химиотерапии в составе одного препарата пигменты будут отвечать за селективность накопления конъюгата в опухоли, а химиотерапевтический агент на основе комплексов Pt(II) — за цитотоксический эффект в отношении опухолевых клеток, не затрагивая здоровые клетки и, тем самым, минимизируя системную токсичность препарата на организм.

Методы. В работе реализованы методы синтеза пиридинсодержащих производных природных хлоринов и их металлокомплексов для применения их в качестве потенциальных бинарных агентов в онкологии. В ходе выполнения работы структуры полученных соединений были подтверждены методами масс-спектрометрии, спектроскопии ядерного магнитного резонанса, ультрафиолетовой спектроскопии, а также хромато-масс-спектрометрии высокого разрешения. При выделении и очистке полученных соединений применялись препаративные методы, включая тонкослойную и колоночную хроматографию, центрифугирование и перекристаллизацию.

Результаты. Получены комплексы платины(II) пиридинсодержащих производных природных хлоринов с целью их применения в комбинированной терапии в онкологии, а также оптимизированы схемы синтеза целевых фотосенсибилизаторов для увеличения их выходов и последующего трансфера на промышленные площадки.

Выводы. Установлено, что пиридинсодержащие производные природных хлоринов обладают хелатирующими свойствами в отношении платины, могут быть получены с высокими выходами и после успешных доклинических испытаний могут рассматриваться как бинарные агенты в терапии рака.

Ключевые слова

фотодинамическая терапия, хлорины, бактериохлорины, комплексы платины, фотосенсибилизатор, комбинированная терапия, пиридины

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INTRODUCTION

Chemotherapy is one of the primary and most efficient methods of cancer treatment [1]. Its main advantage is the direct cytotoxic effect of chemotherapeutic drugs on tumor cells. However, these drugs feature many of side effects due to their effect on normal cells [2, 3][1]. Platinum-based antitumor drugs occupy an important place in cancer chemotherapy, both in monotherapy, and as part of combination therapy. However, they cause serious side effects and are not always efficient due to the drug resistance of tumor cells. Therefore,

[1] Ostroverkhov P.V. *Theranostics based on natural chlorins for non-invasive diagnostic methods and therapy in oncology:* Diss. Cand. Sci. (Chem.). Moscow: 2022, 115 p.

significant efforts on the part of drug developers are aimed at creating platinum-containing drugs with higher selectivity of action.

Over past decades, platinum-based mixed-ligand complexes have been produced and their biological activity has been studied (Fig. 1). Since the discovery of the cytotoxic effect of platinum by Rosenberg in 1964 [4] about 30 drugs have undergone clinical trials. Of the drugs studied, in addition to Cisplatin, only Carboplatin and Oxaliplatin are used in clinical practice. Other drugs are used locally. For example, nedaplatin has been approved in Japan for the treatment of various types of cancer; Lobaplatin is used in China for the treatment of metastatic breast cancer, chronic myeloid leukemia, and small cell lung cancer; and Heptaplatin is used in Korea to treat stomach cancer [5].

The mechanism of the action of platinum-group drugs involves internalization into the cell where they undergo hydrolysis before binding to purine bases in DNA, formation of cross-links between DNA branches, and initiation of the cell apoptosis process. The formation of cross-linked adducts leads to disruption of DNA expression (Fig. 2).

The use of photodynamic therapy in combination with chemotherapy has shown a high degree of efficiency both in *in vitro* and *in vivo* studies, and in clinical practice. Analysis of publications distinguishes two approaches. The first involves the use of photodynamic therapy (PDT) and chemotherapy with various variants of their combination, while in the second approach, new combination drugs have been developed [6].

In the monotherapy regimen, PDT and chemotherapy have their own drawbacks and limitations. In clinical practice, combination therapy is currently being widely used, in order to enhance the efficiency of antitumor treatment by using two different methods of affecting the

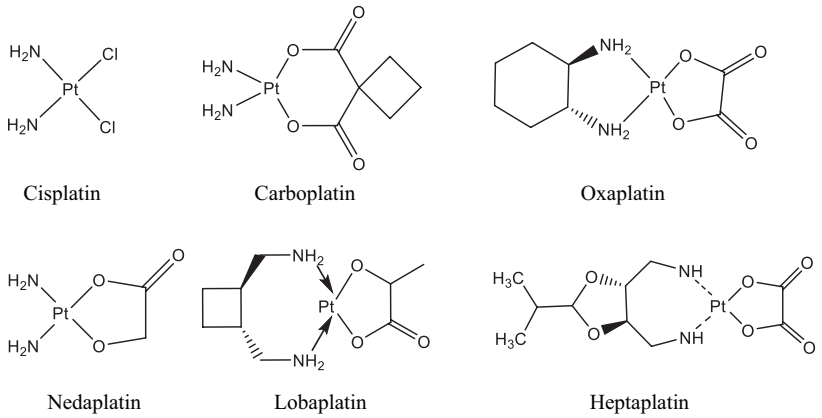


Fig. 1. Structure of platinum complexes

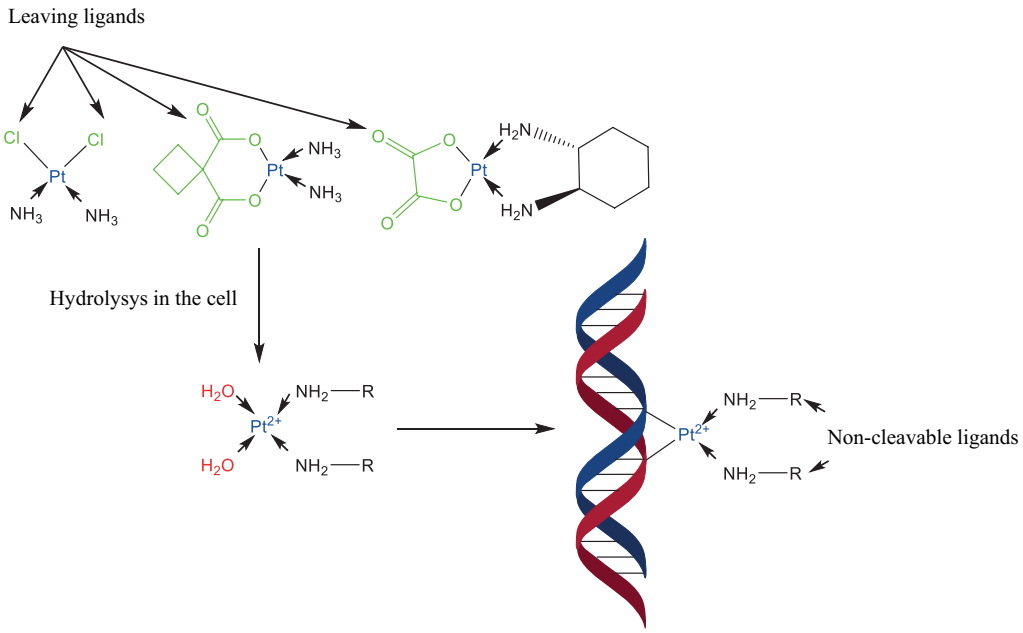


Fig. 2. Simplified mechanism of action of platinum preparations in the cell

tumor. This multimodal approach allows for synergistic effects and better healing results.

Tae-Gyu *et al*. estimated the combined effects of Cisplatin chemotherapy and PDT on EMT6 breast carcinoma in *in vivo* experiments using Nude mice [7].

Kaplan *et al*. presented data on the efficiency of the combined treatment of rats with M-1 sarcoma using Photolon and Cisplatin as photodynamic and cytotoxic agents [8]. The authors used various treatment regimens and drug doses. The treatment effect was assessed by the absolute rate of tumor growth, inhibition of tumor growth, and complete tumor regression. The most efficient treatment regimen was found to involve photodynamic therapy with irradiation 2 h after photosensitizer administration followed by Cisplatin 1 and 4 days after PDT with a total chemotherapeutic agent dose of 2.5 mg/kg. By the end of the study, complete regression of the tumor was observed in 88.9% of the animals, and inhibition of tumor growth was observed in the vast majority of tumor-bearing animals. The results of the study allowed the authors to conclude that the combination of photodynamic therapy with Cisplatin therapy is more efficient than monotherapy since it leads to a synergistic effect and helps reduce the dose of Cisplatin.

One of the first examples of the preparation of conjugates of platinum and a photosensitizer was reported by Brunner *et al*. in 1994. They assumed that the selectivity of tumor treatment with Cisplatin could be enhanced by combining it with a protoporphyrin IX derivative, since the latter has some affinity for low-density lipoprotein receptors. The resulting carboxylate complex of platinum and the protoporphyrin derivative exhibited a pronounced synergistic effect both in the dark and upon irradiation on MDA-MB-231 human breast cancer cells [9].

In later studies, Brunner showed that the nature of the non-cleavable ligands bound to platinum strongly affected the anticancer activity of the entire conjugate [10–12].

In addition to protoporphyrins, synthetic porphyrins with pegylated substituents are also used for conjugation with platinum [13]. It is interesting to note that replacement of protoporphyrin with synthetic derivatives did not lead to significant changes in the antiproliferative properties of the conjugates on incubation with MDA-MB-231 cells.

Mao obtained new platinum-phthalocyanine conjugates based on silicon phthalocyanines with axial pyridine ligands for binding to Cisplatin [14]. The steric hindrance which can arise between axial ligands after complexation with Cisplatin prevents the aggregation of phthalocyanines, ensuring the preservation of photophysical characteristics and photodynamic activity.

In 2014, Springler *et al*. suggested tetrakis-(4-pyridyl)porphyrin containing four pyridyl moieties as a substance for complexation with platinum [15]. A number of porphyrin derivatives with various *cis*- and *trans*-platinum complexes showed significant toxicity to several tumor cell lines under irradiation. Among these, the conjugate with transplatin was found to be the most active. It showed a low level of dark cytotoxicity, while the photoinduced toxicity was in the nanomolar concentration range.

Later, Alberto *et al*. studied the effect of replacing the porphyrin ligand with a chlorin or bacteriochlorin ligand [16]. It was shown that, along with enhanced absorption in the long-wavelength region, the reduction of the porphyrin ligand decreased the hydrolysis rate of the conjugated platinum complex. This, in turn, can lead to a decrease in undesirable side toxicity which is related, among other things, to the rate of formation of platinum aqua complexes [17].

In 2021, Springler's research team obtained a synthetic bacteriochlorin with an absorption maximum in the region of 750 nm containing pyridine moieties for complexation with platinum, as well as fluoro- and chloro-substituted phenyl and sulfonamide groups for increasing resistance of the macrocycle to oxidation [18, 19]. *In vitro* studies of the activity of the resulting bacteriochlorins with platinum on various cell lines showed an increase in cytotoxicity by an order of magnitude, when compared to the metal-free bacteriochlorins.

MATERIALS AND METHODS

The solvents were purified and prepared according to the standard procedures[2]. The following reagents were used in the study: potassium hydroxide (*Sigma-Aldrich*, USA), hydrochloric acid (reagent grade) (*Merck*, Germany), *N*-methyl-*N*-nitrosourea (*Sigma-Aldrich*, USA), sodium periodate (*Acros Organics*, Belgium), osmium tetroxide (*Tokyo Chemical Industry*, Japan), ammonium acetate (*Sigma-Aldrich*, USA), sodium hydrosulfite (*Sigma-Aldrich*, USA), acetic acid (reagent grade) (*ALDOSA*, Russia), potassium carbonate (*Merck*, Germany), hydrazine hydrate (*Sigma-Aldrich*, USA), hydroxylamine hydrochloride (*Sigma-Aldrich*, USA), Cisplatin (*Clearsynth*, India), silver nitrate (*Merck*, Germany), diazabicycloundecene (*Sigma-Aldrich*, USA), isoniazid (*Sigma-Aldrich*, USA), trifluoroacetic acid (*ALDOSA*, Russia), and phenanthrolinediketone (*Sigma-Aldrich*, USA). Thin layer chromatography (TLC)

[2] Gordon A.J., Ford R.A. *The Chemist's Companion*. New York: Wiley-Interscience; 1972.

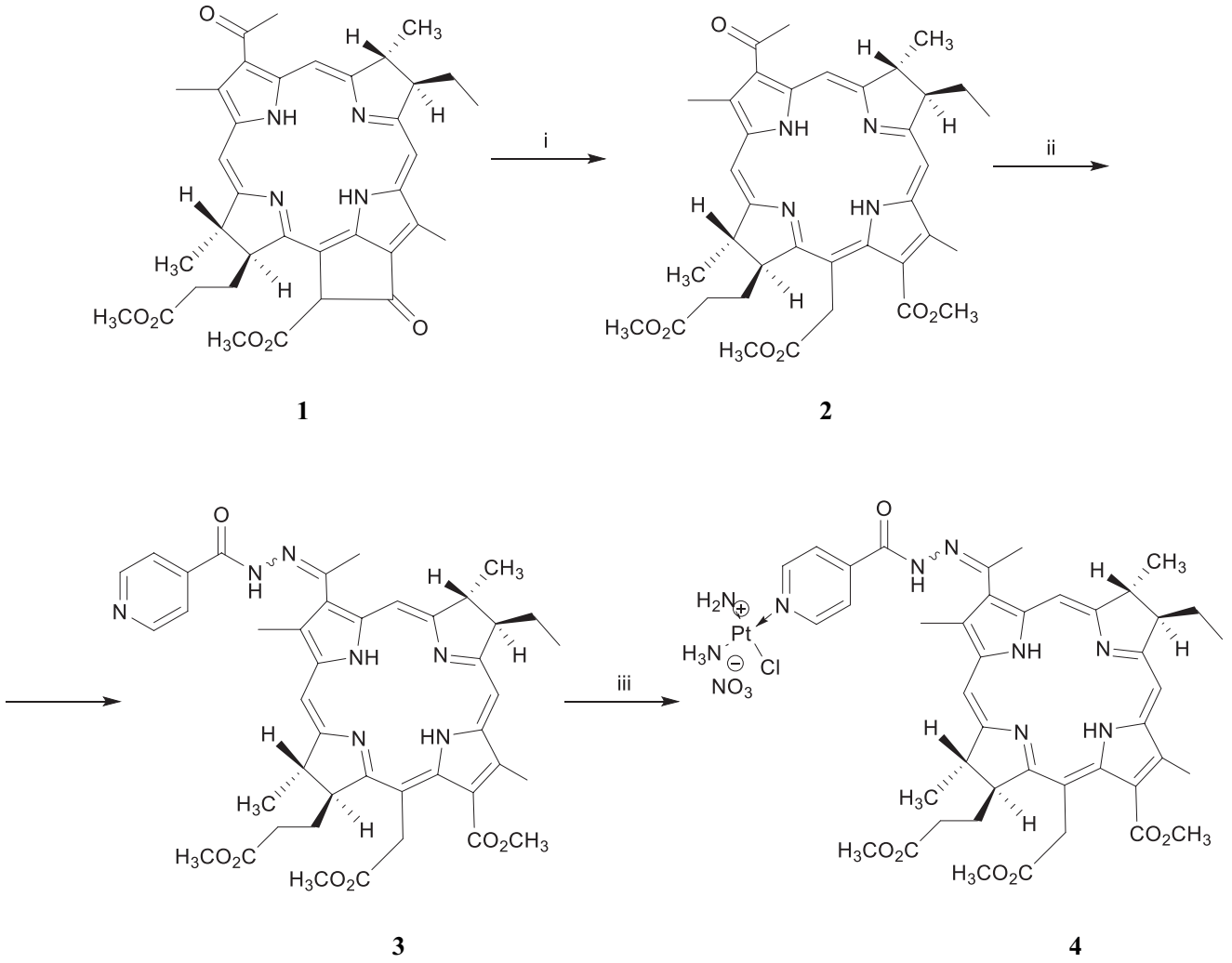
was performed using TLC-Kieselgel 60 F_{254} and TLC Aluminumoxide 60 F_{254} neutral plates (*Merck*, Germany). Column chromatography was performed on Silica gel 60 (*Merck*, Germany). For preparative TLC, Aluminum oxide 60 G neutral (type E) and Silica gel 60 G (*Merck*, Germany) were used. Chromatography was carried out in the dichloromethane–methanol system in various ratios. Nuclear magnetic resonance (NMR) spectra were recorded in deuterochloroform on a DPX-300 spectrometer (*Bruker*, Germany) with an operating frequency of 300 MHz. High-resolution mass spectra were recorded on an Orbitrap Elite mass spectrometer (*Thermo Scientific*, USA) and on a micrOTOF II instrument (*Bruker*, Germany) using electrospray ionization (ESI). Electronic absorption spectra were obtained on an Ultrospec 2100 Pro spectrophotometer (*GE HealthCare*, USA), in 10 mm thick quartz cells. All the spectral studies were performed at 25°C. Sedimentation was carried out on a Hermle Z 206 A centrifuge (*Hermle*, Germany).

RESULTS AND DISCUSSION

In continuation of the studies described above performed by various research teams, this work obtained pyridine-containing complexes of natural chlorins and their complexes with Pt(II) as prototypes of drugs for combined photodynamic and chemotherapy.

Bacteriopheophorbide (**1**) obtained from bacteriochlorophyll, which in turn was isolated by the standard method from *Rhodobacter spheroids* bacteria [20], was chosen as the initial compound. It was then converted into bacteriochlorin e_6 by nucleophilic opening of the cyclopentanone ring by treatment with a solution of NaOH in acetone at 50°C for 1.5 h.

Bacteriochlorin e_6 was converted to its trimethyl ester (**2**) by treatment with diazomethane (Scheme 1). The chromatographic mobility of the product increased significantly, enabling its chromatographic purification to be performed efficiently. Next, Schiff base (**3**) was prepared by treatment of compound (**2**) with isonicotinic



Scheme 1. Preparation of bacteriochlorin *e* derivative with isoniazid and its complex with Pt(II). i: (1) NaOH, H_2O/Acetone; (2) HCl, H_2O/Acetone; (3) CH_2N_2, Et_2O/CH_2Cl_2, 1 h; ii: isonicotinic acid hydrazide, TosOH, *N*,*N*-dimethylformamide (DMF), Ar, 24 h; iii: $Pt(NH_3)_2(H_2O)Cl$, DMF, 24 h

acid hydrazide. The reaction was carried out in *N,N*-dimethylformamide (DMF) in an inert environment for 96 h using *p*-toluenesulfonic acid as the catalyst. Chromatography of the product (**3**) showed the presence of two compounds with similar retention coefficients R_f and identical molar masses, suggesting the formation of that *syn*- and *anti*-isomers.

Incorporation of an isonicotinic acid moiety leads to a hypsochromic shift of the main absorption band by 15 nm (Fig. 3).

Next, a platinum complex of isonicotinyl-containing bacteriochlorin (**4**) was obtained by the reaction of compound (**3**) with Cisplatin in 5 : 1 ratio using an equimolar ratio (1 : 1) of silver nitrate to compound (**3**). Excess of Cisplatin was required, in order to increase the overall yield of the reaction, since platinum can be reduced during activation with silver nitrate. As a result of the reaction, silver chloride precipitated and was separated by centrifugation. The reaction was performed in an argon atmosphere for 48 h.

Analysis of the electronic absorption spectra showed that platinum is coordinated at the periphery of the macrocycle rather than the internal cavity of the latter (Fig. 4).

The structure of the resulting compound was confirmed by mass spectrometry (Fig. 5) where splitting of the molecular ion $[M+H]^+$ 1118.3 Da matching the isotopic composition of platinum atoms was observed.

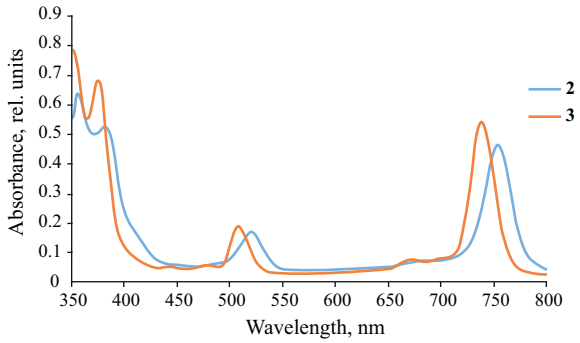


Fig. 3. Absorption spectra of compounds (**2**) and (**3**)

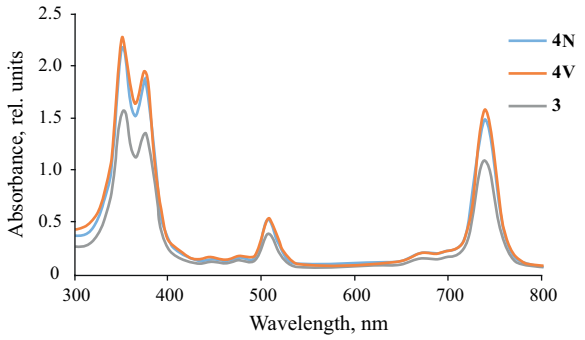


Fig. 4. Absorption spectra of compounds (**3**) and (**4**)

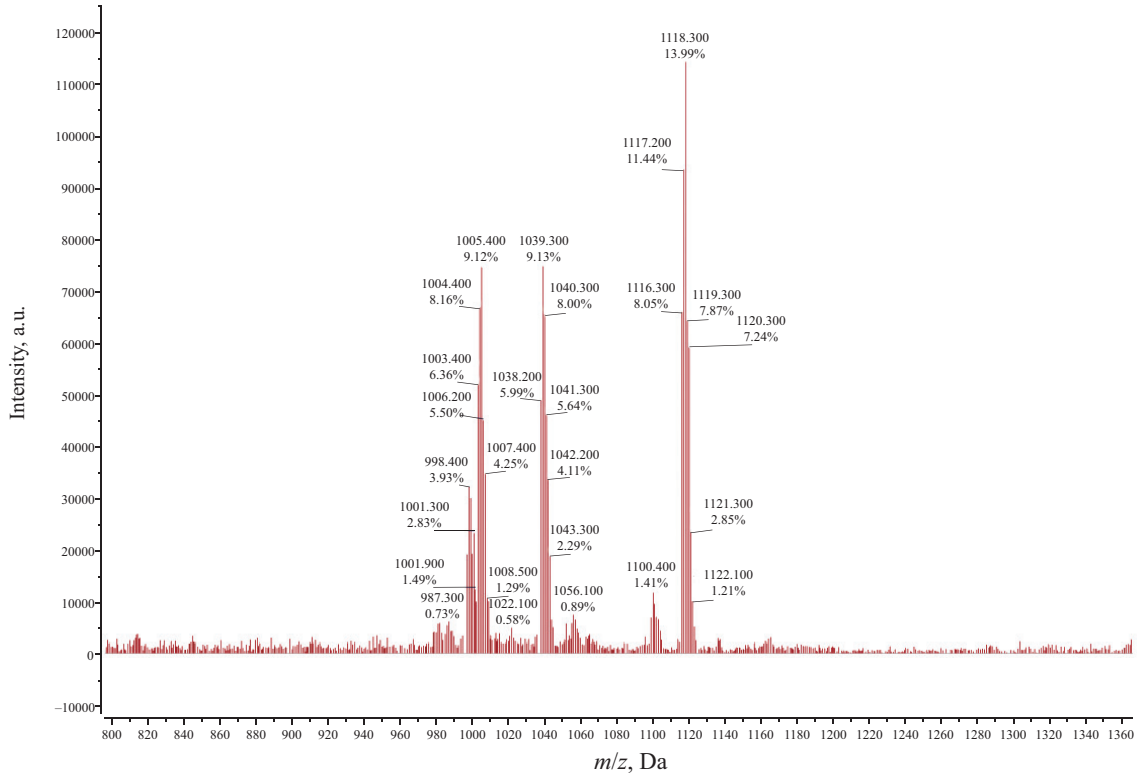
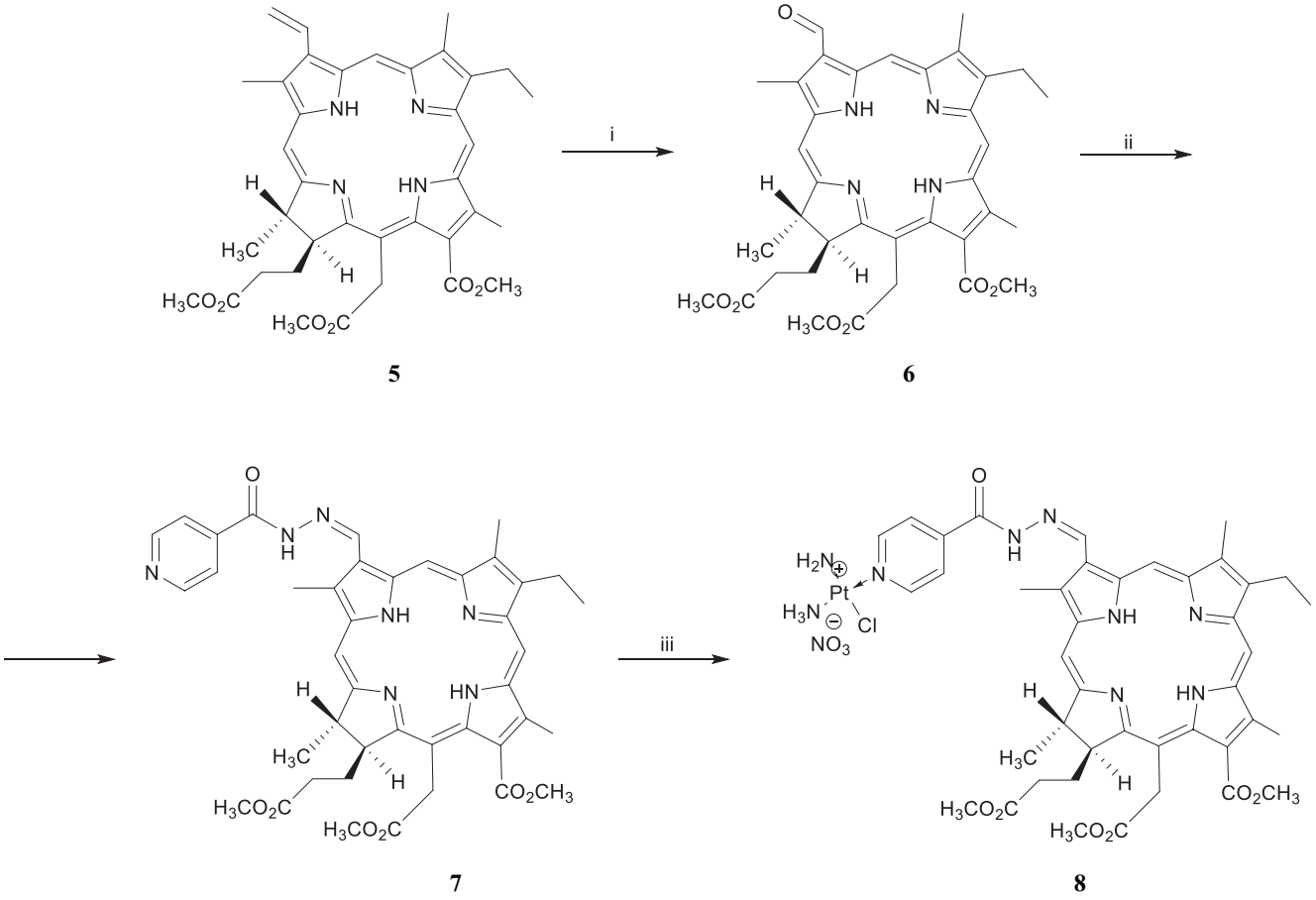


Fig. 5. Mass spectrum of compound (**4**)

In a similar way, we obtained a monopyridyl platinum complex of natural chlorin (Scheme 2). The starting compound was formylchlorin e_6 (**6**) obtained by the Lemieux–Johnson reaction from trimethyl ester of chlorin e_6 (**5**) using OsO_4 and $NaIO_4$ [21]. This method was used due to the presence of a vinyl group in pyrrole A, and mild oxidation reaction conditions which do not affect the chlorin macrocycle. The platinum complex of the monopyridyl derivative of chlorin e_6 was prepared according to a scheme involving the preparation of enimine (**7**) followed by metalation with dichlorodiaminoplatinum.

The resulting metal complex (**8**) was characterized using chromatography-mass spectrometry (Fig. 6). Here



Scheme 2. Preparation of a chlorin e_6 derivative with isoniazide and its complex with Pt(II). i: $NaIO_4$, OsO_4, tetrahydrofuran (THF), 1 h; ii: isonicotinic acid hydrazide, TosOH, DMF, Ar, 24 h; iii: $Pt(NH_3)_2(H_2O)Cl$, DMF, 24 h

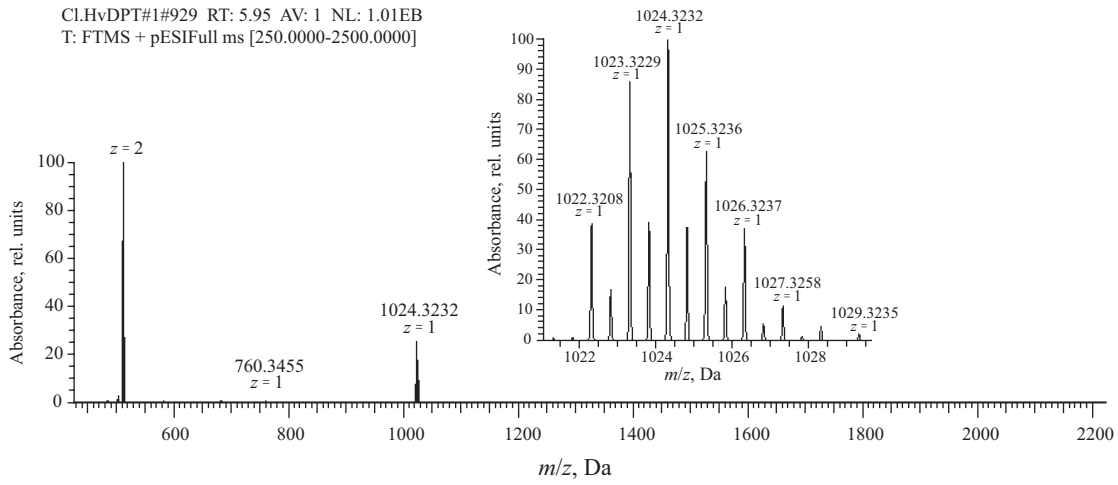


Fig. 6. Chromato-mass spectrum of compound (**8**)

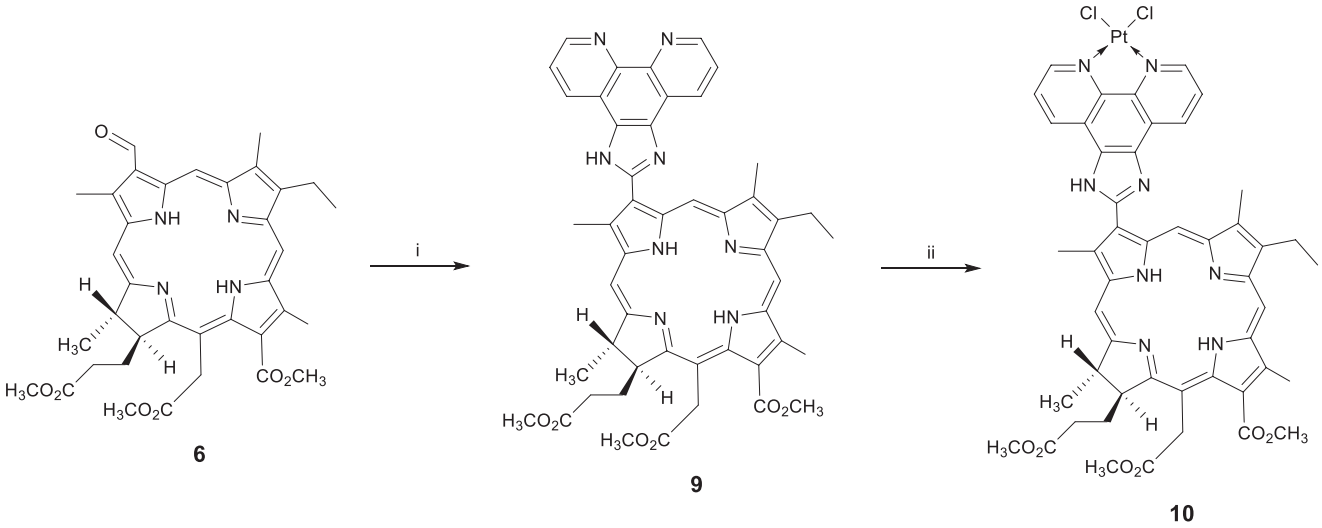
a molecular ion peak M^+ = 1024.3232 Da with isotopic splitting characteristic of platinum compounds was observed.

In the next experiment, a phenanthroline residue was introduced into the chlorin macrocycle as a chelating moiety. The Debus–Radziszewski condensation of formylchlorin e_6 (**6**) with phenanthrolinedione was used to this end, resulting in the phenanthroline imidazole derivative of chlorin (**9**) [22–25]. The reaction was carried out in the presence of ammonium acetate in a chloroform-acetic acid mixture under reflux for 24 h (Scheme 3).

Incorporation of an electron-acceptor substituent into pyrrole A leads to a bathochromic shift of the long-wave absorption band of chlorin by 21 nm relative to the methyl ester of pheophorbide *a* and by 24 nm relative to the trimethyl ester of chlorin e_6 (**5**) (Fig. 7).

Logical continuation for modifying the conjugate of chlorin with a phenanthrolinimidazole moiety is to incorporate a Pt atom on the periphery of the macrocycle by the reaction of the pigment with potassium tetrachloroplatinate refluxing in DMF for 18 h. The resulting metal complex (**10**) can be considered as a prototype of an antitumor drug with combined photodynamic and chemotherapeutic effects.

The binding of nitrogen atoms in the phenanthroline ring to the platinum cation caused a hypsochromic shift in the long-wavelength absorption band of the pigment (Fig. 8).



Scheme 3. Preparation of a chlorin e_6 derivative with phenanthroline and its complex with Pt(II). i: phenanthrolinedione, $CHCl_3$/AcOH, NH_4OAc, reflux, 12 h; ii: $K_2[PtCl_4]$, DMF/H_2O, Ar, 18 h

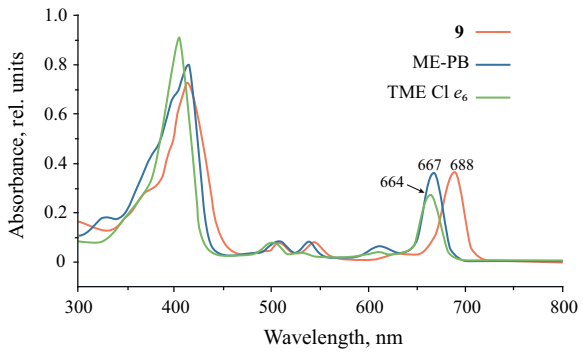


Fig. 7. Electronic absorption spectrum of compound (**9**). ME-PB—methyl ester of pheophorbide *a*, TME CL—trimethyl ester of chlorin e_6

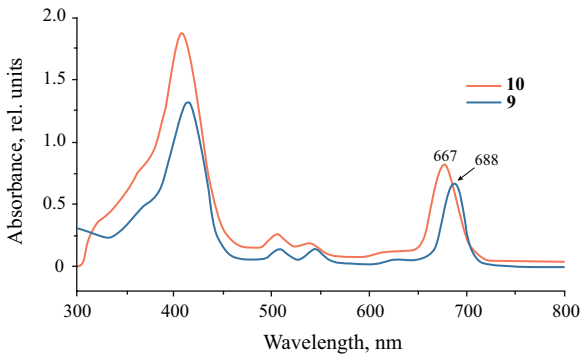


Fig. 8. Electronic absorption spectra of compounds (**9**) and (**10**)

The mass spectrum of compound (**10**) exhibited a molecular ion peak $[M+H]^+$ = 1097.260 Da and an accompanying isotope splitting characteristic of platinum compounds (Fig. 9).

Terpyridine was the next pyridine-containing chelating moiety used for complexation with platinum. Bacteriochlorin *N*-aminocycloimide methyl ester (**11**) [26] was the starting compound. It was reacted with bromotolyl terpyridine in tetrahydrofuran in the presence of diisopropylethylamine (Scheme 4). The substitution reaction occurs at the exocyclic primary amino group of the pigment, enabling the formation of mono- and disubstituted amines. In order to obtain the monosubstituted product (**12**), a molar ratio of reagents of 1 : 1 and dilution of the reaction mixture were used. A 2–3-fold excess of the alkylating agent was used [27] in order to obtain the disubstituted product.

Product (**12**) was purified using preparative TLC on neutral alumina since due to high polarity, the target pigments are "stretched" on the silica gel plate.

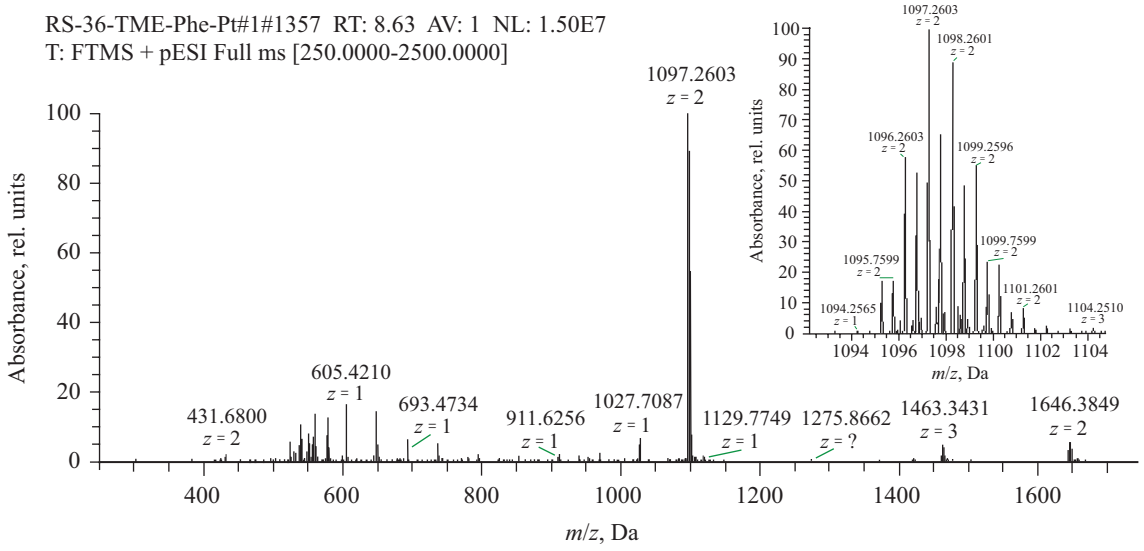
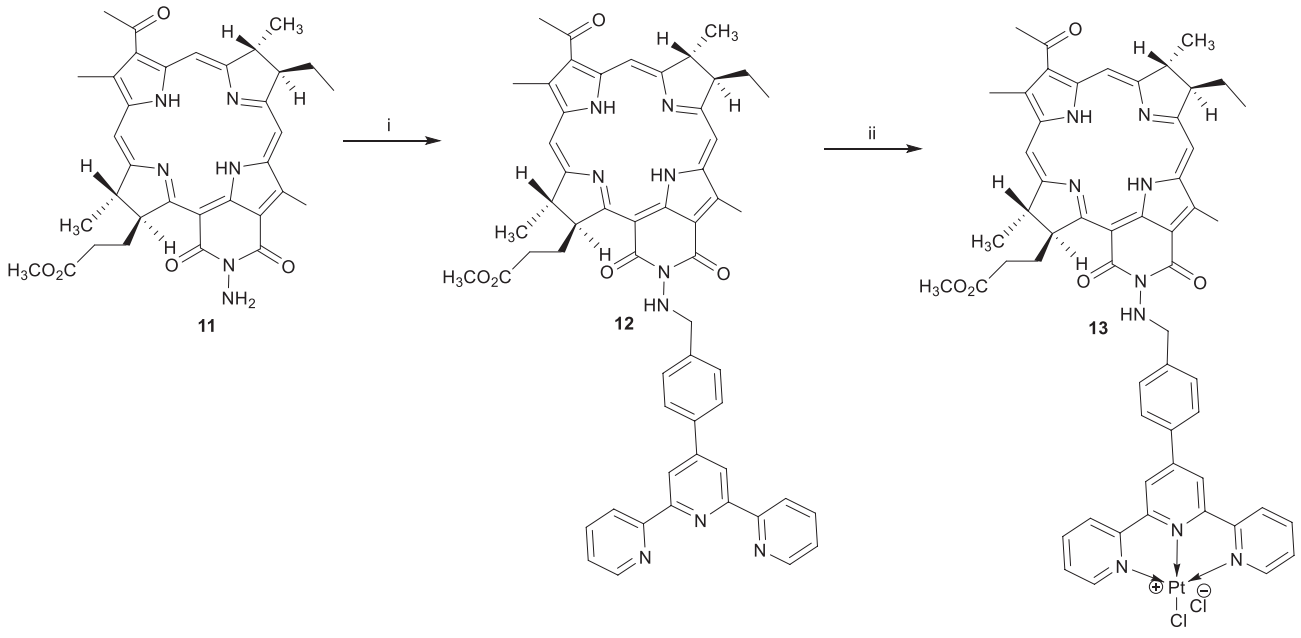


Fig. 9. Electrospray ionization Fourier transform mass spectrum of compound (**10**)



Scheme 4. Preparation of the *N*-NH_2-bacteriopurpurinimide derivative with terpyridine and its complex with Pt(II).
i: 4′-(4-bromomethylphenyl)-2,2′:6′,2″- terpyridine, THF, reflux, 8 h; ii: $K_2[PtCl_4]$, DMF/H_2O, Ar, 75°C, 4 h

In the case of monosubstituted bacteriochlorin, a hypsochromic shift is observed in the electronic absorption spectrum from 834 to 828 nm with respect to the parent compound (**11**). The ^{1}H NMR spectra of both compounds contain characteristic signals of the protons in the pyridine rings of the tolyl terpyridine moiety in the region of 8 ppm.

The metallation of terpyridine-containing bacteriochlorin was carried out using potassium tetrachloroplatinate in DMF in the presence of a small amount of water. The progress of the reaction was monitored using analytical TLC on alumina, since the chromatographic mobility of the resulting metal complex decreases abruptly.

The electrospray ionization + high-resolution mass spectrometry (ESI-HRMS) showed a molecular ion peak with isotopic splitting characteristic of platinum compounds (Fig. 10).

Another way of incorporating a terpyridine moiety into a bacteriochlorin molecule involves the use of *N*-hydroxybacteriopurpurinimide oxime (**14**) synthesized previously in the Preobrazhensky laboratory of the Department of Chemistry and Technology of Biologically Active Compounds at the Lomonosov Institute of Fine Chemical Technologies (Scheme 5) [28]. The presence of two reaction centers in the molecule of the latter results in an ambiguous reaction. Due to enhanced acidity, the substitution reaction at the OH group of the exocycle occurs more readily (**15**), while replacement of the OH group of the oxime requires refluxing for 15 h to give the disubstituted reaction product (**16**) in 38% yield. The structure of the resulting compounds was reliably confirmed by a combination of physicochemical analytical methods.

Since the formation of the metal complex of compound (**16**) is difficult due to the steric properties of the molecule, mono-Pt-containing photosensitizer (**17**) was obtained by the method reported for the synthesis of compound (**13**) involving the use of potassium tetrachloroplatinate in DMF and heating.

The resulting complex (**17**) was characterized by electrospray ionization mass spectrometry (ESI-MS) where a molecular ion peak with isotopic splitting characteristic of platinum compounds was observed.

Thus, as a result of the work described above, pyridine-containing chelator groups such as residues of isonicotinic acid, phenanthroline, and terpyridine, which show affinity to the platinum atom and form stable complexes with it, were incorporated into the structure of natural chlorins. On the one hand, the resulting metal complexes can exhibit photodynamic activity on irradiation into the absorption band of the chlorin used. On the other hand, platinum complexes have a cytotoxic effect, alkylating DNA and exerting an antiproliferative effect. After conducting biological tests and confirming the synergistic effect, the metal complexes obtained can be considered as binary photosensitizers for photodynamic and chemotherapy in oncology.

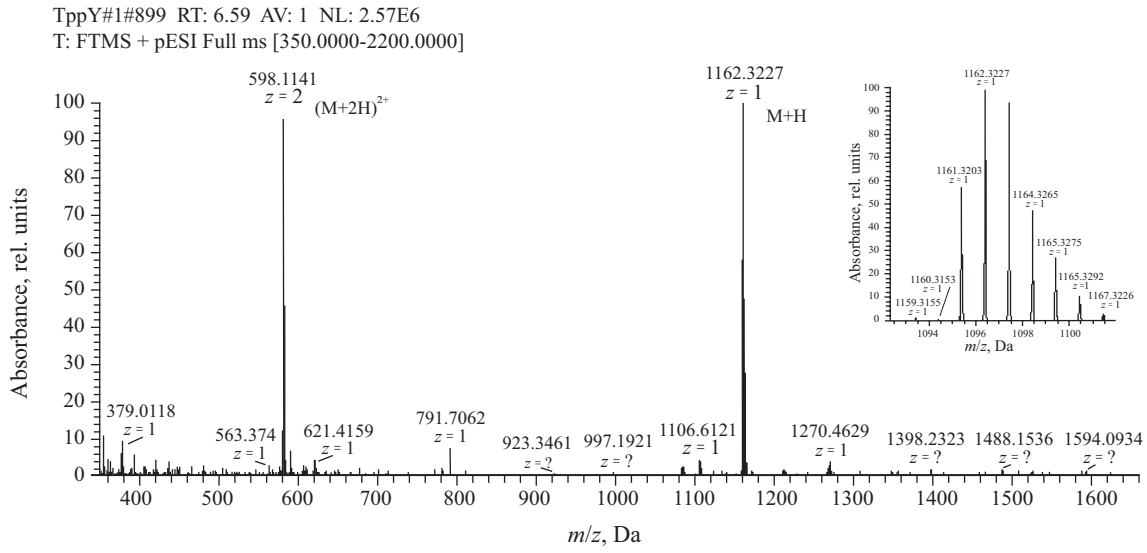
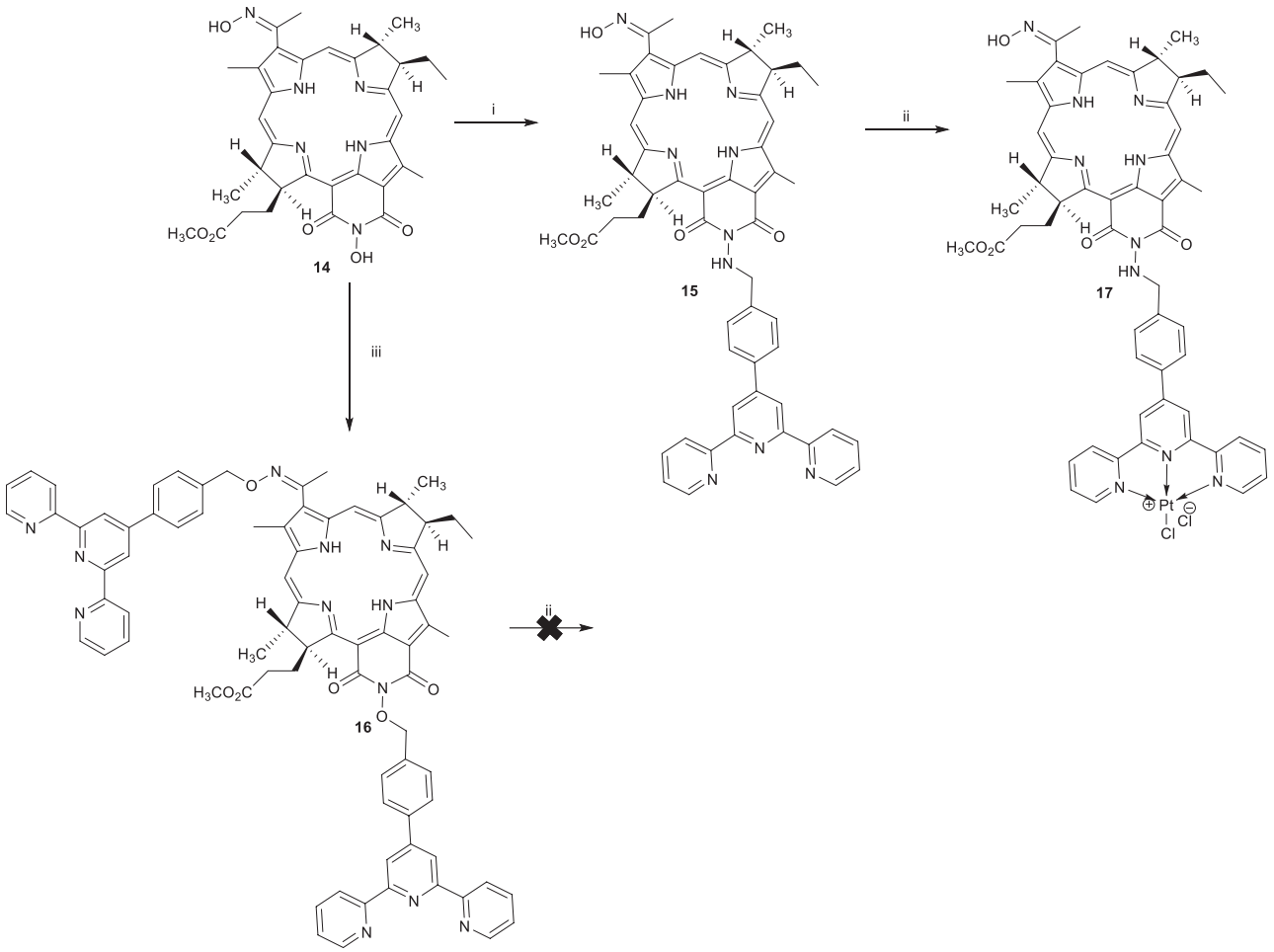


Fig. 10. ESI-HRMS spectrum of compound (**13**)



Scheme 5. Preparation of *N*-OH-bacteriopurpurinimide derivatives with terpyridine and its complex with Pt(II).
i: 4′-(4-bromomethylphenyl)-2,2′:6′,2″- terpyridine, diazabicycloundecene (DBU), $CHCl_3$, 1 h; ii: $K_2[PtCl_4]$, DMF/H_2O, Ar, 75°C, 4 h; iii: 4′-(4-bromomethylphenyl)-2,2′:6′,2″- terpyridine (2eq), DBU, $CHCl_3$, 15 h

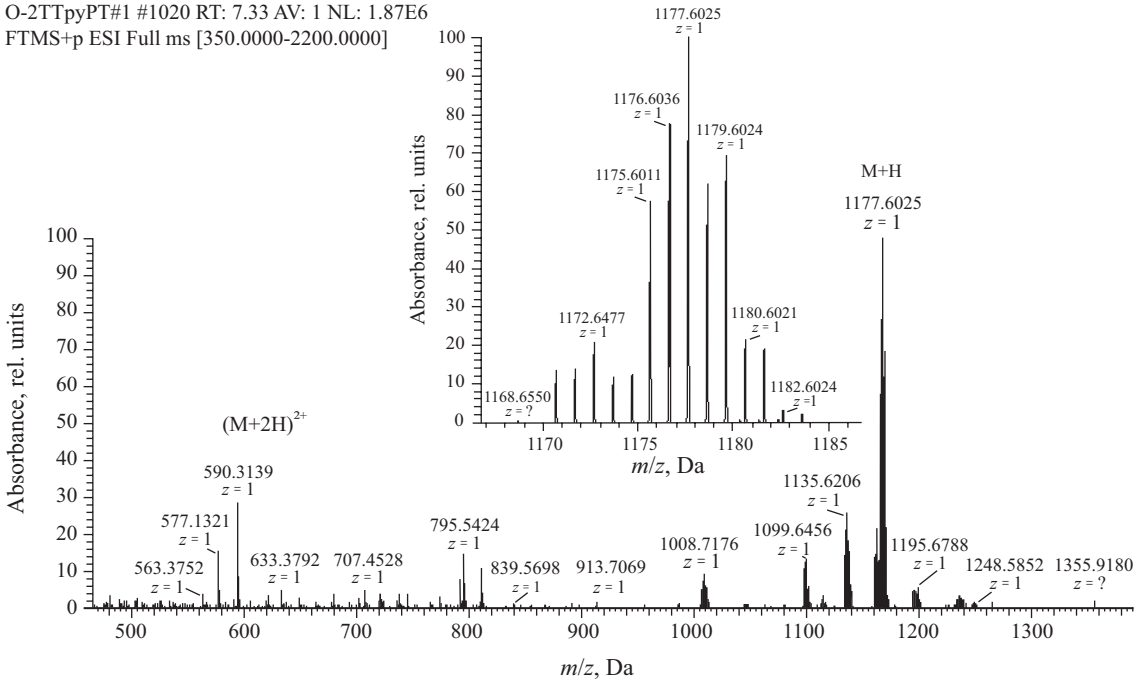


Fig. 11. ESI-MS spectrum of compound (**17**)

EXPERIMENTAL

Bacteriochlorin trimethyl ester e_6 (2). Bacteriopheophorbide *a* (**1**) (250 mg, 0.409 mmol) was dissolved in 28 mL of degassed acetone. The reaction mixture was degassed for 10 min in an ultrasonic bath, then argon was bubbled through it for 5 min with stirring. A degassed aqueous solution (28 mL) of potassium hydroxide (3.64 g, 0.065 mol) was added to the reaction mixture. Then the reaction mixture was heated in a water bath for 1.5 h at 51°C. The reaction progress was monitored by TLC on silica gel in the CH_2Cl_2 : MeOH (5 : 1) solvent system. Next, the reaction mixture was diluted with water and adjusted to pH 4.5 with hydrochloric acid. The precipitate formed was separated, an aqueous solution of hydrochloric acid with pH 4.6 was added, and the suspension was then centrifuged for 10 min (6000 rpm). The supernatant was removed and the procedure was repeated two more times. Then, 15 mL of a solution of freshly prepared diazomethane in diethyl ether was added. The reaction mixture was stirred for 1 h at room temperature (25°C). The reaction progress was monitored by TLC in the dichloromethane/methanol (50 : 1) system to give 160 mg (80%) of compound **2**.

^{1}H NMR ($CDCl_3$, δ, ppm): 9.29 (s, 5-H), 8.69 (s, 10-H), 8.63 (s, 20-H), 5.20 (s, 15-CH_2^a), 5.16 (s, 15-CH_2^b), 4.38–4.15 (m, 7-H, 18-H, 17-H, 13-$COOCH_3$), 3.76 (m, 15-$COOCH_3$), 3.67 (m, 8-H), 3.65 (s, 17-$COOCH_3$), 3.61 (s, 2-Me), 3.37 (s, 12-Me), 3.21 (s, 3^2-Me), 2.38–1.92 (m, 17^1-CH_2, 8^2-CH_2 , 17^2-CH_2), 1.86 (d, *J* = 7.2 Hz, 7-Me), 1.67 (d, *J* = 7.1 Hz, 18-Me), 1.10 (t, *J* = 7.3 Hz, 8^3-Me), −1.12 (s, NH), −1.20 (s, NH).

Mass spectrum, *m/z*: $[M+H]^+$; calculated for $C_{37}H_{44}N_4O_7$ + H: 656.32; obtained: 657.3.

Conjugate of bacteriochlorin with isonicotinic acid (3). Bacteriochlorin e_6 trimethyl ester (**2**) (62.4 mg, 0.095 mmol), isonicotinic acid hydrazide (65.15 mg, 0.475 mmol), and TosOH·H_2O (18.07 mg, 0.095 mmol) were dissolved in 2 mL of DMF, after which argon was bubbled through the solution for 15 min. The reaction mixture was stirred for 24 h at room temperature. The reaction progress was monitored by TLC on silica gel in the CH_2Cl_2:MeOH (100 : 1) solvent system. The product was purified using preparative TLC on neutral alumina in the dichloromethane/methanol solvent system (80 : 1) to give 49.6 mg (79.5%) of compound **3**.

^{1}H NMR ($CDCl_3$, δ, ppm): 9.43 (s, 5-H), 8.77–8.66 (m, N-CH-Nic), 8.37 (d, 20-H), 8.23 (m, CH-Nic), 8.01 (s, NH-Nic), 5.40–5.05 (m, 15^1-CH_2), 4.40–4.27 (m, 7-H,17-H,18-H), 4.24 (s, 13-$COOCH_3$), 3.78 (s, 15-$COOCH_3$), 3.71–3.67 (m, 8-H), 3.66 (s, 17-$COOCH_3$), 3.40 (s, 2-Me), 3.36 (s, 12-Me), 3.00 (s, 3^2-Me), 2.46–1.97 (m, 8^2-CH_2, 17^1-CH_2, 17^2-CH_2), 1.84 (d, 18-Me), 1.71 (d, 7-Me), 1.06 (t, 8^3-Me), (−1.61)–(−1.31) (m, NH).

Mass spectrum, *m/z*: $[M+H]^+$ calculated for $C_{43}H_{49}N_7O_7$ + H: 775.37; obtained: 776.3.

Bacteriochlorin platinum complex (4). Silver nitrate (2.82 mg, 0.017 mmol) and Cisplatin (5 mg, 0.011 mol) were suspended in 1.5 mL of DMF in an inert environment without access of light, after which the mixture was stirred for 12 h at room temperature. The suspension was then centrifuged for 5 min (10000 rpm), after which the supernatant was added to compound **7** (5 mg, 0.007 mmol). The solution was stirred for 12 h at room temperature in an argon atmosphere without access of light. The reaction progress was monitored by TLC in the dichloromethane/methanol solvent system (10 : 1). After reaction completion, the reaction mixture was concentrated in the vacuum of an oil pump to give 4.98 mg (99.6%) of compound **4**.

Mass spectrum, *m/z*: $[M+H]^+$ calculated for $C_{43}H_{49}N_7O_7PtClNO_3(NH_2)_2$ + H: 1118.292; obtained: 1118.3.

3-Formylchlorin e_6 trimethyl ester (6). Chlorin e_6 trimethyl ester (**5**) (498 mg, 0.780 mmol) was dissolved in 20 mL of THF, then a solution of $NaIO_4$ (670 mg, 3.133 mmol) in 5 mL of H_2O and 300 μL of OsO_4 solution (2.75 g, 0.039 mmol) in 90 mL of dichloromethane were added. The reaction was carried out using stirring in an argon atmosphere and cooling to 0°C for 3 h. The progress of the reaction was monitored by TLC in a hexane/ethyl acetate (1 : 1) system. A saturated solution of $NaHSO_3$ in 10 mL of methanol was then added to the reaction mixture that was stirred for another 15 min. The reaction mixture was extracted with dichloromethane (1 × 30 mL). The resulting extract was washed with water (3 × 100 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was isolated using column chromatography in a hexane/ethyl acetate system (2 : 1) and crystallized from dichloromethane on a watch glass to give 206 mg (41.0%) of compound **6** as 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, *m/z*: $[M]^+$ calculated for $C_{36}H_{40}N_4O_7^+$: 640.290, obtained: 640.909 $[M]^+$.

Ultraviolet and visible (UV/VIS) radiation (CH_2Cl_2), maximum wavelengths λ_{max}, nm ($\log_\varepsilon$): 416 (4.24), 512 (3.28), 547 (3.36), 634 (3.06), 691 (3.98).

Chlorin conjugate with isonicotinic acid (7). Formyl derivative of chlorin e_6 (**6**) (62.4 mg, 0.095 mmol), isonicotinic acid hydrazide (65.15 mg, 0.475 mmol), and diazabicycloundecene (18.07 mg, 0.095 mmol) were dissolved in 3 mL of DMF, after which argon was bubbled for 10 min through the solution. The reaction mixture was stirred for 36 h at room temperature. The reaction progress was monitored by TLC on silica gel in the dichloromethane/methanol (100 : 1) solvent system. The product was isolated using preparative TLC on neutral alumina in the CH_2Cl_2 : MeOH (80 : 1) solvent system to give 52.7 mg (81.3%) of compound **7**.

^{1}H NMR ($CDCl_3$, δ, ppm): 9.43 (s, 5-H), 8.77–8.66 (m, N-CH-Nic), 8.37 (d, 20-H), 8.23 (m, CH-Nic), 8.01 (s, NH-Nic), 5.40–5.05 (m, 15^1-CH_2), 4.40–4.27 (m, 7-H,17-H,18-H), 4.24 (s, 13-$COOCH_3$), 3.78 (s, 15-$COOCH_3$), 3.71–3.67 (m, 8-H), 3.66 (s, 17-$COOCH_3$), 3.40 (s, 2-Me), 3.36 (s, 12-Me), 3.00 (s, 3^2-Me), 2.46–1.97 (m, 8^2-CH_2, 17^1-CH_2, 17^2-CH_2), 1.84 (d, 18-Me), 1.71 (d, 7-Me), 1.06 (t, 8^3-Me), (−1.61)–(−1.31) (m, NH).

Mass spectrum, *m*/*z*: $[M+H]^+$ calculated for $C_{42}H_{44}N_7O_7$ + H: 759.421; obtained: 760.5.

Platinum complex of monopyridyl chlorin derivative (8). Silver nitrate (2.82 mg, 0.017 mmol) and Cisplatin (5 mg, 0.011 mol) were suspended in 1 mL of DMF in an inert environment without access of light, after which the mixture was stirred for 12 h at room temperature. The suspension was then centrifuged for 5 min (10000 rpm), after which the supernatant was added to compound **7** (5 mg, 0.007 mmol). The solution was stirred in an argon atmosphere for 12 h at room temperature without access of light. The reaction progress was monitored by TLC in the dichloromethane/methanol (10 : 1) solvent system. After completion of the reaction, the reaction mixture was concentrated in the vacuum of an oil pump to give 5.54 mg (99.7%) of compound **8**.

Mass spectrum, *m*/*z*: $[M+H]^+$ calculated for $C_{42}H_{44}N_7O_7PtClNO_3(NH_2)_2$ + H: 1204.3243; obtained: 1204.3232.

3-(Phenanthrolinoimidazol-2-yl) chlorin e_6 trimethyl ester (9). To a solution of compound **6** (25 mg, 0.039 mmol) in a mixture of $CHCl_3$/AcOH (5%), phenanthrolinedione (16.4 mg, 0.078 mmol) and NH_4OAc (60.2 mg, 0.781 mmol) were added in two portions with an interval of 7 h under reflux conditions. The progress of the reaction was monitored by TLC in the hexane/ethyl acetate system (1 : 1). At the end of the reaction, the mixture was washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was isolated using preparative TLC in the dichloromethane/methanol (50 : 1) system and crystallized from dichloromethane on a watch glass to give 24.8 mg (77%) of compound **9**.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 2.18 (s, 1H, NH), 1.39 (t, *J* = 7.6 Hz, 3H, 8^2-CH_3), 1.94 (d, *J* = 7.2 Hz, 3H, 18^3-CH_3), 2.72–3.02 (m, 4H, 17^1-CH_2, 17^2-CH_2), 3.22 (s, 3H, 7^1-CH_3), 3.44 (s, 3H, 2^1-CH_3), 3.76 (s, 2H, 17^1-CH_3), 3.95 (s, 3H, 12^1-CH_3), 4.38 (s, 3H, 13^2-CH_3), 4.53 (d, *J* = 10.1 Hz, 1H, 17-H), 4.62 (d, *J* = 7.3 Hz, 1H, 18-H), 5.54–5.31 (m, 2H, 15^1-CH_2), 6.83 (s, 1H, NH), 7.47 (s, 2H, Ph-H^2), 8.09 (s, 2H, Ph-H^1), 8.76 (s, 2H, Ph-H^3), 8.85 (s, 1H, 20-H), 9.09 (s, 1H, 5-H), 10.50 (s, 1H, 10-H).

Mass spectrum, *m*/*z*: $[M]^+$: calculated for $C_{48}H_{46}N_8O_6^+$: 832.361; obtained: 832.300.

UV/VIS (CH_2Cl_2), λ_{max}, nm (ε × 10^{-3}, $M^{-1}\cdot cm^{-1}$): 413 (5.49), 508 (4.50), 543 (4.55), 631 (4.14), 688 (5.19).

High performance liquid chromatography – mass spectrometry (HPLC-MS) (CH_3CN), retention time t_R, min (*m*/*z*): 10.95 (832.3445).

Platinum complex of 3-(phenanthrolinoimidazol-2-yl)chlorin trimethyl ester e_6 (10). To compound **9** (32 mg, 0.039 mmol) dissolved in 4 mL of DMF, a solution of $K_2[PtCl_4]$ (24 mg, 0.058 mmol) in 1 mL of H_2O was added. The reaction was carried out with stirring for 18 h. The progress of the reaction was monitored by TLC in the dichloromethane/methanol (20 : 1) system. The reaction mixture was extracted with dichloromethane. The resulting extract was washed three times with saturated NaCl solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Next, the product was isolated using preparative TLC in the dichloromethane/methanol (20 : 1) system and crystallized from dichloromethane on a watch glass to give 6.4 mg (15%) of compound **10**.

Mass spectrum, *m*/*z*: $[M]^+$: calculated for $C_{48}H_{46}N_8O_6Cl_3Pt^+$: 1097.256; obtained: 1097.260.

HPLC-MS (CH_3CN), t_R, min (*m*/*z*): 8,63 (1097.2603).

Bacteriochlorin 13,15-(*N*-(4-([2,2′:6′,2″-terpyridin]-4′-yl)benzyl)amino)cycloimide methyl ester (12). Bacteriochlorin 13,15-(*N*-amino)cycloimide methyl ester (15 mg, 0.025 mmol), *N,N*-diisopropylethylamine (9.6 μL, 0.055 mmol) and 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine (11.1 mg, 0.028 mmol) were dissolved in 15 mL of THF and refluxed for 8 h in a stream of argon. The reaction mixture was diluted with 10 mL of chloroform and washed with 50 mL of water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified using preparative TLC on neutral alumina in a dichloromethane/methanol system (200 : 1) to give 14.4 mg (63%) of compound **12**.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm), terpyridine moiety (TTpy): 9.19 (1H, s, 10-H), 8.79 (1H, s, 5-H), 8.75–8.55 (9H, m, 20-H and TTpy-H), 7.94–7.79 (4H,

TTpy-H), 7.36–7.31 (2H, m, TTpy-H), 5.22 (1H, m, 17-H), 4.56 (2H, s, TTpy-CH_2), 4.27 (1H, m, 18-H), 4.08 (1H, m, 7-H), 3.88 (1H, m, 8-H), 3.71 (3H, s, 12-CH_3), 3.57 (3H, s, 17^5-CH_3) 3.53 (3H, s, 2-CH_3), 3.17 (3H, s, 3^2-CH_3), 2.61 (2H, m, 8^1-CH_2), 2.39 (2H, m, 17^2-CH_2), 2.04 (2H, m, 17^1-CH_2), 1.81 (3H, d, J = 7 Hz, 7-CH_3), 1.69 (3H, d, J = 7.8 Hz, 18-CH_3), 1.11 (3H, t, J = 7.4 Hz, 8^2-CH_3), −0.34 (1H, br.s, s, NH), −0.56 (1H, br.s, s, NH).

ESI-HRMS, *m/z*: $[M+H]^+$: calculated for $C_{56}H_{53}N_9O_5$ + H: 932.42; obtained: 932.42.

UV/VIS (CH_2Cl_2), λ_{max}, nm (ε × 10^{-3}, $M^{-1}\cdot cm^{-1}$): 365 (49.2), 417 (42.7), 551(33.4), 828(40.5).

Platinum complex of compound 12 (13). Compound **12** (3.5 mg, 0.0037 mmol) was dissolved in 2 mL of DMF. $K_2[PtCl_4]$ (1.7 mg, 0.0041 mmol) was dissolved in 0.5 mL of water and added to the DMF solution. The reaction mixture was stirred for 6 h at 75°C. The reaction mixture was diluted with 10 mL of chloroform and washed with 50 mL of water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator to give 0.9 mg (21%) of compound **13**.

UV/VIS (CH_2Cl_2), λ_{max}, nm (ε × 10^{-3}, $M^{-1}\cdot cm^{-1}$): 349 (46.2), 368 (83.7), 418 (42.7), 541(33.4), 799 (40.5).

ESI-HRMS, *m/z*: $[M+H]^+$: calculated for $C_{56}H_{53}Cl_2N_9O_5Pt$ + H: 1162.4170; obtained: 1162.4248.

Bacteriochlorin 13,15-(N-(4-([2,2′:6′,2″-terpyridin]-4′-yl)benzyl)oxy)cycloimide oxime methyl ester (15). Bacteriochlorin 13,15-(*N*-hydroxy)cycloimide methyl ester **14** [28] (28.9 mg, 0.046 mmol), diazabicycloundecene (13.8 μL, 0.092 mmol), and 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine (20.4 mg, 0.042 mmol) were dissolved in 3 mL of chloroform and stirred for 1 h. The reaction mixture was washed with 30 mL of water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified using preparative TLC on neutral alumina in a dichloromethane/methanol system (200 : 1) to give 29.8 mg (66%) of compound **15**.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 8.80 (1H, s, 5-H), 8.75–8.36 (10H, m, 10-H, 20-H and TTpy-H), 7.99–7.71 (4H, m, J = 8 Hz, TTpy-H), 7.43–7.35 (2H, m, TTpy-H), 5.18 (1H, m, 17-H), 4.27–4.22 (2H, m, TTpy-CH_2), 4.19–4.10 (2H, m, 7-H, 18-H), 4.05 (1H, m, 8-H), 3.58 (3H, s, 12-CH_3), 3.50 (3H, s, 17^5-CH_3) 3.22 (3H, s, 2-CH_3), 2.78 (3H, s, 3^2-CH_3), 2.32 (2H, m, 17^2-CH_2), 2.22 (2H, m, 8^1-CH_2), 2.02 (2H, m, 17^1-CH_2), 1.95 (3H, d, J = 7.3 Hz, 7-CH_3), 1.75 (3H, d, J = 7 Hz, 18-CH_3), 1.09 (3H, t, J = 7.3 Hz, 8^2-CH_3), 0.03 (1H, br.s, s, NH), −0.23 (1H, br.s, s, NH).

UV/VIS (CH_2Cl_2), λ_{max}, nm (ε × 10^{-3}, $M^{-1}\cdot cm^{-1}$): 349 (46.2), 368 (83.7), 418 (42.7), 541(33.4), 799 (40.5).

ESI-HRMS, *m/z*: $[M+H]^+$: calculated for $C_{56}H_{53}N_9O_6$ + H: 948.41; obtained: 948.40.

Methyl ester of 13,15-(*N*-(4-([2,2′:6′,2″-terpyridin]-4′-yl)benzyl)oxy)cycloimide 3-devinyl-3-(((4-([2,2′:6′,2″-terpyridin]-4′-yl)benzyl)oxy)imino) bacteriochlorin (16). 13,15-(*N*-Hydroxy)cycloimide bacteriochlorin methyl ester **14** (30 mg, 0.048 mmol), diazabicycloundecene (28.6 μL, 0.191 mmol), and 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine (38.6 mg, 0.096 mmol) were dissolved in 3 mL of chloroform and stirred for 15 h under reflux. The reaction mixture was washed with 30 mL of water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified using preparative TLC on neutral alumina in a dichloromethane/methanol system (200 : 1) to give 23.1 mg (38%) of compound **16**.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 9.15 (1H, s, 10-H), 8.70 (1H, s, 5-H), 8.69–7.53 (27H, m, 20-H and TTpy-H), 5.30 (1H, m, 17-H), 4.92 (2H, m, TTpy-CH_2), 4.23 (2H, m, 7-H, 18-H), 4.10 (1H, m, 8-H), 3.89 (2H, m, TTpy-CH_2'), 3.73 (3H, s, 12-CH_3), 3.65 (3H, s, 17^5-CH_3) 3.55 (3H, s, 2-CH_3), 3.24 (3H, s, 3^2-CH_3), 3.27–2.12 (4H, m, 8^1-CH_2, 17^2-CH_2), 1.98 (2H, m, 17^1-CH_2), 1.75 (3H, d, J = 7.3 Hz, 7-CH_3), 1.72 (3H, d, J = 7.2 Hz, 18-CH_3), 1.08 (3H, t, J = 7.4 Hz, 8^2-CH_3), −0.26 (1H, br.s, s, NH), −0.64 (1H, br.s, s, NH).

ESI-HRMS, *m/z*: $[M+H]^+$: calculated for $C_{56}H_{53}N_9O_6$ + H: 1268.91; obtained: 1268.92.

Platinum complex compound 15 (17). Compound **15** (15 mg, 0.016 mmol) was dissolved in 2 mL of DMF. $K_2[PtCl_4]$ (9.86 mg, 0.024 mmol) was dissolved in 0.5 mL water and added to the DMF solution. The reaction mixture was stirred for 6 h at 75°C. The reaction mixture was then diluted with 10 mL of chloroform and washed with 50 mL of water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator to give 3.5 mg (18%) of compound **17**.

UV/VIS (CH_2Cl_2), λ_{max}, nm (ε × 10^{-3}, $M^{-1}\cdot cm^{-1}$): 349 (46.2), 368 (83.7), 418 (42.7), 541(33.4), 799 (40.5).

ESI-HRMS, *m/z*: $[M+H]^+$: calculated for $C_{56}H_{53}Cl_2N_9O_6Pt$ + H: 1177.63; obtained: 1177.60.

CONCLUSIONS

In this study, a series of platinum complexes of pyridine-containing derivatives of natural chlorins and bacteriochlorins were obtained for potential use in combination therapy in oncology. The structure of all the compounds obtained was reliably confirmed by a combination of physicochemical methods of analysis. The study demonstrated the high chelating ability of pyridine-containing derivatives of natural chlorins. Biological tests of photoinduced and dark cytotoxicity of the leader compounds have been scheduled along with an assessment of the antitumor activity at the organism level.

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Authors' contributions

N.S. Kirin—data collecting and processing on terpyridine derivatives of natural bacteriochlorins and their metal complexes, phenanthroline-containing natural chlorin and its metal complex, and writing the text of the article.

P.V. Ostroverkhov—data collecting and processing on isonicotinyl-containing derivatives of natural chlorins and bacteriochlorins and their metal complexes.

M.N. Usachev—selection of optimal conditions and chromatographic purification of the compounds obtained.

K.P. Birin—scientific consulting at all stages of the work.

M.A. Grin—concept, idea, and design of research, data collecting and processing.

The authors declare no conflicts of interest.

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