ORIGINAL ARTICLES

INVESTIGATIO OF THE pH-DEPENDENT HYDROLYSIS OF A CHLORIN e6 HYDRAZIDE DERIVATIVES AS A POTENTIAL PHOTOSENSITIZER FOR COMBINED ANTICANCER THERAPY

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Abstract

Oncological diseases represent a global healthcare challenge, and the development of new effective therapeutic strategies remains a pressing task. Chemotherapy and photodynamic therapy (PDT) are key treatment modalities, however, their application is associated with side effects, systemic toxicity, and the development of drug resistance. In recent years, combined approaches, including the use of pH-sensitive delivery systems, have been actively investigated. The present study was dedicated to the investigation of the pH-dependent hydrolysis of a chlorin e6 hydrazide derivative, acting as a potential photosensitizer (PS) for combined anticancer therapy. Hydrazide fragments, due to their lability in the weakly acidic environment of the tumor microenvironment (pH 4.5-6.0), are promising for the creation of targeted drug delivery systems. The decomposition of the hydrazide fragment was studied spectrophotometrically in an acetate buffer (pH 5.0) over 120 minutes. Spectral changes (bathochromic shift, appearance of a maximum at 688 nm) were recorded, indicating the formation of a protonated precursor compound. A linear dependence of product accumulation on time was obtained, characteristic of zero-order reactions. A high coefficient of determination confirmed the adequacy of the obtained model. This approach ensures controlled release of active components and demonstrates the potential of the developed PS for enhancing PDT efficacy and reducing the systemic toxicity of chemotherapy.

Key words: chlorin e6, photodynamic therapy, hydrazide, hydrolysis.

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For citations: Medvedev D.Y., Grin M.A. Investigation of the pH-dependent hydrolysis of a chlorin e6 hydrazide derivative as a potential photosensitizer for combined anticancer therapy, *Biomedical Photonics*, 2025, vol. 14, no. 4, pp. 4–10. doi:10.24931/2413–9432–2025–14-4-4-10

ИССЛЕДОВАНИЕ pH-ЗАВИСИМОГО ГИДРОЛИЗА ГИДРАЗИДНОГО ПРОИЗВОДНОГО ХЛОРИНА e6 КАК ПОТЕНЦИАЛЬНОГО ФОТОСЕНСИБИЛИЗАТОРА ДЛЯ КОМБИНИРОВАННОЙ ПРОТИВООПУХОЛЕВОЙ ТЕРАПИИ

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Резюме

Онкологические заболевания представляют собой глобальную проблему здравоохранения, и разработка новых эффективных терапевтических стратегий является актуальной задачей. Химиотерапия и фотодинамическая терапия (ФДТ) являются ключевыми методами лечения, однако их применение сопряжено с побочными эффектами, системной токсичностью и развитием лекарственной устойчивости. В последние годы активно исследуются комбинированные подходы, в том числе с использованием pH-чувствительных систем доставки. Настоящее исследование было посвящено изучению гидролиза гидразидного производного хлорина e6, выступающего в качестве потенциального фотосенсибилизатора (ФС) для комбинированной противоопухолевой терапии. Гидразидные фрагменты, благодаря своей лабильности в слабокислой среде опухолевого микроокружения (pH 4,5-6,0), являются перспективными для создания систем адресной доставки лекарств. Изучение разложения гидразидного фрагмента осуществлялось спектрофотометрически в ацетатном буфере (pH 5,0) в течение 120 мин. Были зафиксированы спектральные изменения (батохромный сдвиг, появление максимума при 688 нм), указывающие на образование протонированного соединения-предшественника. Была продемонстрирована

линейная зависимость накопления продукта от времени, характерная для реакций нулевого порядка. Высокий коэффициент детерминации подтвердил адекватность полученной модели. Данный подход обеспечивает контролируемое высвобождение активных компонентов и демонстрирует потенциал разработанного ФС для повышения эффективности ФДТ и снижения системной токсичности химиотерапии.

Ключевые слова: хлорин е6, фотодинамическая терапия, гидразид, гидролиз.

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Для цитирования: Медведев Д.Ю., Грин М.А. Исследование pH-зависимого гидролиза гидразидного производного хлорина е6 как потенциального фотосенсибилизатора для комбинированной противоопухолевой терапии // Biomedical Photonics. – 2025. – Т. 14, № 4. – С. 4–10. doi:10.24931/2413–9432–2025–14-4-4-10

Introduction

Oncological diseases are a global health problem, being the second leading cause of death in the world after cardiovascular diseases. According to forecasts, the number of new cases of malignant neoplasms, which reached 20 million in 2022, will increase by 77% to 35 million by 2050 [1]. The etiological profile of oncological diseases is characterized by the complex influence of various behavioral factors, including tobacco smoking, alcohol abuse and obesity, along with the exogenous effects of environmental factors such as atmospheric air pollution [2]. These trends highlight the urgent need for further research in the field of oncology and the development of new treatment strategies.

Among the existing therapeutic methods, chemotherapy and photodynamic therapy (PDT) are of particular interest [3]. Chemotherapy based on the use of cytotoxic drugs is aimed at suppressing the proliferation of tumor cells by disrupting their metabolism or damaging genetic material [4, 5]. Despite the wide range of effects, chemotherapy is associated with a number of serious side effects due to non-selective effects on healthy cells of the body. In addition, the development of drug resistance is one of the main reasons for the ineffectiveness of chemotherapy, requiring a constant search for new drugs and strategies for their use.

One of the most common classes of chemotherapeutic drugs are platinum compounds such as cisplatin, carboplatin, and oxaliplatin, which interact with the DNA of tumor cells and cause their death [6]. These preparations contain platinum in the oxidation state of +2 (Pt(II)) and have a square-planar geometry. Cisplatin, which is the first representative of this class, forms adducts with DNA, disrupting the processes of replication and transcription [7, 8]. Carboplatin, which has less pronounced nephrotoxicity, also interacts with DNA, forming adducts, but its use is limited by myelosuppression [9]. Oxaliplatin containing a diaminocyclohexane ligand has a wide range of activity, but it can cause neurotoxicity [10]. Despite their high efficacy, the use of platinum drugs is associated with problems of resistance and toxicity, which stimulates the development of new approaches, such as the use of Pt(IV) prodrugs and targeting the tumor microenvironment [11, 12].

In recent years, platinum pyridine complexes, which have unique properties and the potential to overcome the limitations of traditional platinum preparations, have been actively investigated [13]. Pyridine ligands coordinating with platinum can affect its reactivity and selectivity [14, 15]. In addition, pyridine complexes can be modified with various substituents to regulate their lipophilicity, charge, and ability to penetrate cell membranes. The use of pyridine complexes as antitumor agents requires further study, but their potential for the development of new effective and selective drugs is beyond doubt.

PDT is a promising method for the treatment of oncological diseases based on the use of photosensitizers (PS) activated by light of a certain wavelength to generate cytotoxic reactive oxygen species (ROS) [16-18]. ROS such as singlet oxygen cause oxidative damage to cellular components, leading to the death of tumor cells. PDT has a number of advantages over traditional treatment methods, including high selectivity of effects on tumor tissues, minimal systemic toxicity, and the possibility of repeated use [19, 20]. However, the main disadvantage of PDT is the insufficient depth of light penetration into tissues, which limits its use for the treatment of deeply localized tumors.

The combined use of chemotherapy and PDT is a promising strategy that allows combining the advantages of each method and overcoming their disadvantages [21, 22]. The synergistic interaction of chemotherapeutic drugs and PDT can lead to an increase in the effectiveness of treatment, reduce toxicity and overcome drug resistance. In particular, the combination of platinum drugs and PDT can increase the selectivity of effects on tumor cells and reduce systemic toxicity due to local activation of PS and the release of the platinum drug in the tumor microenvironment.

One of the promising approaches to increasing the selectivity and effectiveness of chemotherapy and PDT is the use of pH-sensitive delivery systems that ensure the release of drugs in the acidic environment of the tumor microenvironment [23-25]. Tumor cells are characterized by an increased level of glycolysis and lactic acid formation, which leads to a decrease in the pH of the extracellular space of the tumor [26, 27]. The use of pH-sensitive linkers that are cleaved in an acidic environment makes it possible to create conjugates of chemotherapeutic drugs and PS, which release active components only in the tumor microenvironment, minimizing their effect on healthy tissues.

Previously, our scientific group successfully obtained platinum complexes with derivatives of natural chlorines, which have a high chelating ability and promising photophysical properties [28]. Developing the previously obtained results, in this work we focused on the study of the stability of the hydrazide derivative of e6 chlorin in a slightly acidic environment simulating the tumor microenvironment.

Materials and methods

Reagents and equipment

All solvents have been cleaned and prepared according to standard procedures.

ALUGRAM Xtra SIL G/UV254 plates coated with silica gel 60 (0.2 mm) (Germany) were used for analytical chromatography. Preparative chromatography was performed both by the column method on Silica gel 60 (0.0040-0.0063 mm) silica gel (Germany) and using chromatographic plates on a glass substrate measuring 20×20 cm with the same silica gel.

Absorption spectra were recorded on a Shimadzu UV1800 UV/VIS spectrophotometer (Japan) in quartz cuvettes (0.4×1.0 cm) with an optical path length of 1 cm (spectral slit width of 1 nm).

NMR spectra were recorded on a Bruker DPX300 spectrometer (USA) in $CDCl_3$. The residual signals of the ^1H cores were used to calibrate the scale. The experiments were performed using standard Bruker techniques.

Photosensitizer

The synthesis of PS with the structural formula **1** (Fig. 1) was carried out according to the procedure described earlier [28]. Chlorin e6 was obtained from the biomass of blue-green algae *Arthrospira Platensis* by a well-known method [29] and exhaustively modified with methyl esters diazomethane in the acetone/diethyl ether system to obtain the corresponding trimethyl ether. The vinyl group of trimethyl ether of chlorin e6 in the third position of the macrocycle was further oxidized to the formyl function using the Lemieux-Johnson reaction to obtain PS with the structural formula 2. The final step was the introduction of the isoniazid residue through the Schiff base. The product was purified by column chromatography (CH_2Cl_2:CH_3OH, 15:1) and is crystallized from hexane. The yield of compound **1** was 92.2%.

^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.71 (s, 1H, 5-H), 9.58 (s, 1H, 10-H), 9.47 (s, 1H, 20-H), 8.94 (s, 1H, 33-NH), 8.80 (s, 2H, 3^6-CH, 3^8-CH), 8.56 (s, 1H, 3^1-CH), 7.75 (d, J = 25.1 Hz, 2H, 3^5-CH, 3^9-CH), 5.34 (dd, J = 36.7 Hz, 19.2 Hz, 2H, 15^1-CH_2), 4.42 (d, J = 9.0 Hz, 2H, 17-H, 18-H), 4.28 (s, 3H, 13^2-$COOCH_3$), 3.83 (s, 3H, 15^2-$COOCH_3$), 3.66 (s, 3H, 17^3-$COOCH_3$), 3.54 (s, 3H, 12^1-CH_3), 3.50 (s, 3H, 7^1-CH_3), 3.14 (d, J = 9.5 Hz, 3H, 2^1-CH_3), 2.70 – 2.11 (m, 6H, 8^1-CH_2, 17^1-CH_2, 17^2-CH_2), 1.74 (s, 3H, 18^1-CH_3), -1.68 (s, 2H, 21-NH, 23-NH).

Mass spectrum (ESI) m/z: $[M+H]^+$ calculated for $[C_{42}H_{44}N_7O_7+H]^+$ – 759.3, found – 760.5.

Acid hydrolysis of compound

The decomposition of the hydrazide fragment was studied spectrophotometrically. Compound **1** at a concentration of 1 mg/mL was incubated in a DMF/acetate buffer system (4:1) at pH 5.0 for 2 h. During the incubation, aliquots were collected at 5-min intervals and diluted to a concentration of 7.5 μmol/L, optimal for subsequent spectrophotometric analysis [30]. Optical density measurements were performed at a wavelength of 688 nm, corresponding to the absorption maximum of the protonated form of precursor compound 2, containing a formyl function at the third position of the macrocycle.

Results and Discussion

Modification of the chlorin macrocycle at position 3 of the tetrapyrrole ring represents a promising approach for improving the physicochemical properties and biological activity of compounds. The advantages of this modification include the ability to introduce various functional groups at the free carboxyl groups at positions 13, 15, and 17. In particular, the introduction of substituents at position 3 allows for effective variation of the hydrophobic/hydrophilic balance of the molecule, which is critical for its distribution in biological systems.

Studies of hydrazide degradation are of significant interest in the context of anticancer drug development, primarily due to their lability in the slightly acidic environment characteristic of the microenvironment of many malignant tumors. Accelerated metabolism in rapidly proliferating tumor cells leads to the accumulation of metabolites such as lactic acid, which lowers the pH of the extracellular space and inside tumor cells to values in the range of 4.5-7.0. Unlike the physiologically neutral environment (pH ~7.4) of healthy tissue, this slightly acidic environment

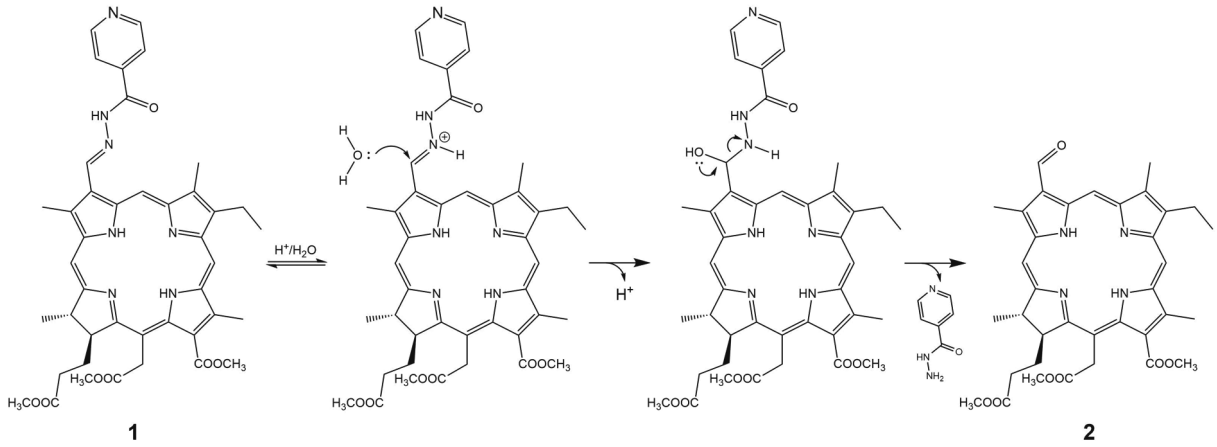

Рис. 1. Предполагаемый механизм кислотного гидролиза гидразидного фрагмента.
Fig. 1. Proposed mechanism of acid hydrolysis of the hydrazide fragment.

promotes rapid hydrolysis of the hydrazide bond. This property makes hydrazides promising for the development of targeted drug delivery systems. Conjugates containing hydrazide moieties can remain stable in the bloodstream but release a therapeutically active substance (e.g., a cytostatic agent or a PS) upon reaching tumor tissue. This mechanism increases the therapeutic efficacy of the drug by targeting it directly to the tumor and reduces systemic toxicity, minimizing side effects on healthy tissue. Studying the conditions of hydrazide hydrolysis, as well as their stability in various pH environments, is key to optimizing the design of new antitumor agents and delivery systems.

The change in spectral characteristics during incubation at pH 5.0 demonstrates chemical transformations of the hydrazide derivative of chlorin e6 (Fig. 1). The initial spectrum of compound **1** (0 min) is characterized by intense absorption bands at 410-450 nm (Soret) and 500-700 nm (Q-bands), typical of chlorin compounds. After 60 minutes of incubation, significant formation of the reaction product was detected: a noticeable bathochromic shift of the absorption bands and the formation of a distinct peak at 688 nm were observed. After 120 minutes of incubation, a further bathochromic shift of these bands is observed, with the emergence of a pronounced absorption maximum at 688 nm. This change in the absorption spectrum indicates the formation of the parent compound in a protonated form containing a formyl function at the third position of the macrocycle, consistent with the mechanism of hydrazide bond hydrolysis.

The decomposition of the hydrazide moiety and the accumulation of the formyl derivative absorbing at 688 nm were studied by analyzing the linear regression dependence of absorbance on time (Fig. 2). The resulting equation, the main parameters of which are presented in Table, demonstrates a high coefficient of

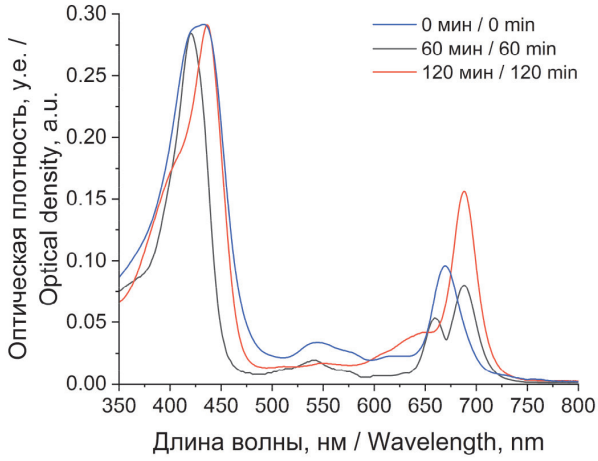

Рис. 2. Спектры поглощения раствора соединения **1** в ацетатном буфере (pH 5,0) при различных временных интервалах инкубации.
Fig. 2. Absorption spectra of compound **1** solution in acetate buffer (pH 5,0) at different incubation time intervals.

Таблица
Параметры линейной регрессии накопления продукта гидролиза во времени

Table
Parameters of linear regression for product accumulation during hydrolysis over time

Уравнение Equation	y = a + b·x
Коэффициент b Coefficient b	0,05 ± 5,32·10^{-4}
Коэффициент a Coefficient a	9,20·10^{-4} ± 7,59·10^{-4}
Остаточная сумма квадратов Residual sum of squares	1,12441
Коэффициент детерминации (R^2) Coefficient of determination (R^2)	0,99844

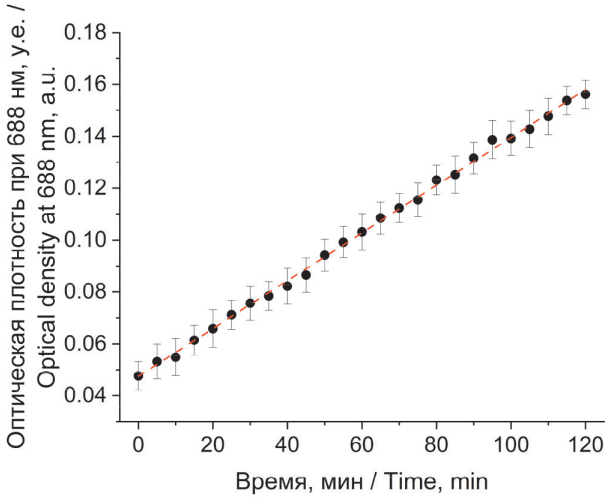

Рис. 3. Динамика накопления продукта реакции во времени.
Fig. 3. Dynamics of reaction product accumulation over time.

determination, indicating a linear fit to the experimental data. The slope of the curve reflects a constant rate of product accumulation, indicating that the process occurs at a steady state over the studied time range.

The observed linear dependence of the reaction product concentration on time is characteristic of zero-order reactions with respect to one or more initial reactants. Alternatively, a variant in which the concentration of the limiting reactant remains constant throughout the experiment is possible. This may be due either to its presence in significant stoichiometric excess or to the presence of an external factor (e.g., a catalyst or reactant source) that ensures its generation or consumption at a constant rate. Consequently, the most probable hypothesis explaining the observed linear dependence of product formation at this stage of the decomposition of the hydrazide fragment is the variant in which the rate of the process is limited by a substance whose concentration is maintained practically unchanged under the experimental conditions.

Conclusion

This study evaluated the pH-dependent hydrolysis of a hydrazide linker conjugated to a chlorin e6 derivative under conditions simulating the slightly acidic environment of a tumor microenvironment. The results demonstrate that the hydrazide can act as a pH-sensitive moiety that can be used in targeted delivery systems, providing controlled release. Thus, the developed PS has significant potential for enhancing the efficacy of photodynamic therapy for cancer and reducing the systemic toxicity of chemotherapy.

This work was supported by the Ministry of Science and Higher Education of the Russian Federation under state contract No. FSFZ-2025-0020.

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