

Химия и технология лекарственных препаратов
и биологически активных соединений
Chemistry and technology of medicinal compounds
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RESEARCH ARTICLE

Synthesis and biological activity of new *meso*-arylporphyrin and erlotinib conjugate

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Abstract

Objectives. This study set out to develop approaches for creating new photodynamic agents that incorporate a tumor-targeting ligand and a photoactive photosensitizer component within their structure. The work continues a series of investigations into the influence of the chemical structure of photosensitizers and type of conjugation with the targeting moiety on the antitumor efficacy of photodynamic therapy. The work proposed the design and synthesis of a new conjugate based on *meso*-aryl-substituted porphyrin and erlotinib, a low-molecular-weight tyrosine kinase inhibitor, which ensures selective delivery of the photosensitizer to the tumor.

Methods. In order to obtain the target compound, erlotinib was modified, the porphyrin was synthesized, and the conjugate of these two components was prepared using a click reaction. The compounds were characterized by ¹H and ¹³C nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry.

Results. The target water-soluble conjugate of *meso*-arylporphyrin and erlotinib was obtained and characterized. Its biological activity was studied against conditionally normal (Normal Kidney Epithelial, NKE) and tumor (MCF-7, MDA-MB-231, A431) cell lines. The target conjugate demonstrated photoinduced activity in the submicromolar range and low dark toxicity. A relatively high dark-to-light toxicity ratio (~30 times) was shown for the conjugate.

Conclusions. The proposed design of a photodynamic agent based on the obtained conjugate of *meso*-arylporphyrin and erlotinib may facilitate progress in addressing the challenge of targeted photosensitizer delivery for use in photodynamic therapy.

Keywords

photodynamic therapy, synthesis, *meso*-arylporphyrins, erlotinib, antitumor activity

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НАУЧНАЯ СТАТЬЯ

Синтез и биологическая активность нового конъюгата мезо-арилпорфирина и эрлотиниба

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Аннотация

Цели. Данное исследование заключается в разработке подходов к созданию новых фотодинамических агентов, содержащих в своей структуре нацеливающие на опухоль лиганд и фотоактивный компонент — фотосенсибилизатор. Представленная работа является продолжением исследований по изучению влияния химической структуры фотосенсибилизатора и типа связывания с ним нацеливающего фрагмента на противоопухолевую эффективность фотодинамической терапии. В работе был предложен дизайн и осуществлен синтез нового конъюгата на основе мезо-арилзамещенного порфирина и низкомолекулярного ингибитора тирозинкиназы, эрлотиниба, обеспечивающего селективную доставку фотосенсибилизатора в опухоль.

Методы. Для получения целевого соединения произведена модификация эрлотиниба, синтез порфирина и получен конъюгат из данных двух компонент на основе click-реакции. Соединения охарактеризованы ¹H и ¹³C спектроскопией ядерного магнитного резонанса и масс-спектрометрией высокого разрешения.

Результаты. Получен и охарактеризован целевой водорастворимый конъюгат мезо-арилпорфирина и эрлотиниба. Изучена его биологическая активность по отношению к условно-нормальной (Normal Kidney Epithelial, NKE) и опухолевым (Michigan Cancer Foundation-7, MCF-7, MDA-MB-231, A431) клеточным линиям. Целевой конъюгат показал фотоиндуцированную активность в субмикромольном диапазоне концентраций и низкую темновую токсичность. Показано достаточно высокое соотношение темной и световой токсичностей (~30 раз) для конъюгата.

Выводы. Таким образом, в работе получен конъюгат мезо-арилпорфирина и эрлотиниба. Предложенный дизайн может обеспечить прогресс в решении проблемы нацеленного транспорта фотосенсибилизатора для использования в фотодинамической терапии.

Ключевые слова

фотодинамическая терапия, синтез, мезо-арилпорфирины, эрлотиниб, противоопухолевая активность

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INTRODUCTION

One of the most critical challenges in modern medicine consists in developing means for enhancing the efficacy of cancer treatment modalities. The primary limitation of conventional therapeutic approaches, such as chemotherapy and radiotherapy, lies in their insufficient selectivity for malignant cells. Consequently, achieving a positive clinical response necessitates the administration of increased drug doses. Since such highly toxic therapeutic regimens tend to affect healthy cells within the human organism, severe adverse side effects are frequently encountered [1].

Currently, alternative therapeutic approaches characterized by enhanced safety, efficacy, and accessibility are being actively developed. Photodynamic therapy (PDT) represents one such innovative modality [2, 3]. Owing to its unique properties, including spatiotemporal selectivity, low systemic toxicity, absence of induced resistance, and minimal invasiveness, PDT has established itself as a successful method for treating a wide range of neoplasms of various types and localizations [4, 5]. The therapeutic agents fundamental to PDT are photoactive compounds, known as photosensitizers, and laser irradiation. The interaction between these agents generates reactive oxygen species,

which can be used to destroy vital structures within tumor cells [6].

Due to their photophysical characteristics, which satisfy the requirements of PDT, synthetic porphyrins are widely employed as photoactive agents [7–9]. Among the advantages of utilizing tetrapyrrole photosensitizers consists in the possibility of modifying their hydrophilic-lipophilic balance by varying the peripheral substituents. However, the application of synthetic tetrapyrroles is often limited by the hydrophobicity of the tetrapyrrole macrocycle, non-selectivity, and aggregation [10].

Nowadays, the advancement of PDT is associated with the development of novel combined photosensitizers and the optimization of methods for their selective delivery to tumor tissues [11, 12]. Literature sources indicate that one promising approach for regulating the biodistribution of photodynamic agents and consequently enhancing their overall efficacy upon systemic administration involves modifying photosensitizers with ligands that specifically bind to target molecules or are recognized by receptors overexpressed in tumor cells [13–15].

Among various receptor types, epidermal growth factor receptors (EGFRs) [16] and vascular endothelial growth factor receptors [17] are regarded as some of the most promising targets for active tumor targeting due to their overexpression in a broad range of malignancies and their involvement in key processes within cancer cells. EGFRs, which belong to the receptor tyrosine kinase family, function as key mediators in cellular signaling pathways that regulate proliferation, angiogenesis, and metastatic dissemination of cancer cells [17–19].

One of the main strategies for targeting tyrosine kinases involves the use of their small-molecule inhibitors. Agents such as erlotinib, dasatinib, and other substances approved for clinical application in anticancer

therapy can be employed as targeting vectors for the development of conjugates to enable the selective delivery of photosensitizers to tumors [20, 21]. Several recent studies have investigated the antitumor activity of photosensitizers based on phthalocyanines [22], chlorins [23, 24], and porphyrins incorporating tyrosine kinase inhibitors into their structure [25, 26]. In each case, a significant enhancement in the efficacy of antitumor PDT was achieved compared to the use of sensitizers lacking targeting moieties.

Despite significant advances in the development of targeted photosensitizers, numerous avenues remain insufficiently explored. These include investigations into the relationship between antitumor activity and the structure of both the photosensitizer and the targeting vector, the method of their conjugation, as well as studies on the effects and mechanisms of action of such compounds.

Previously, our research group reported on the design of novel photosensitizers based on EGFR-targeted *meso*-arylporphyrins through the incorporation of the low-molecular-weight tyrosine kinase inhibitor erlotinib into their structure for application in PDT [25]. The erlotinib molecule is expected to serve a dual function: first, to selectively deliver the photosensitizer to cancer cells through preferential binding to EGFRs, which are overexpressed in many tumor types; and second, to exert a cytotoxic effect resulting from the inhibition of the receptor tyrosine kinase domain activity. In a previous work, we established that the presence of a spacer positively influenced the biological activity of the resulting compound. The alternative design for a porphyrin–erlotinib conjugate—**UB-4** (Fig. 1) developed on this basis in the present study involves modifying the type of spacer and the distance between the photosensitizer fragment and the erlotinib moiety. Synthesis of the target compound a copper(I)-catalyzed

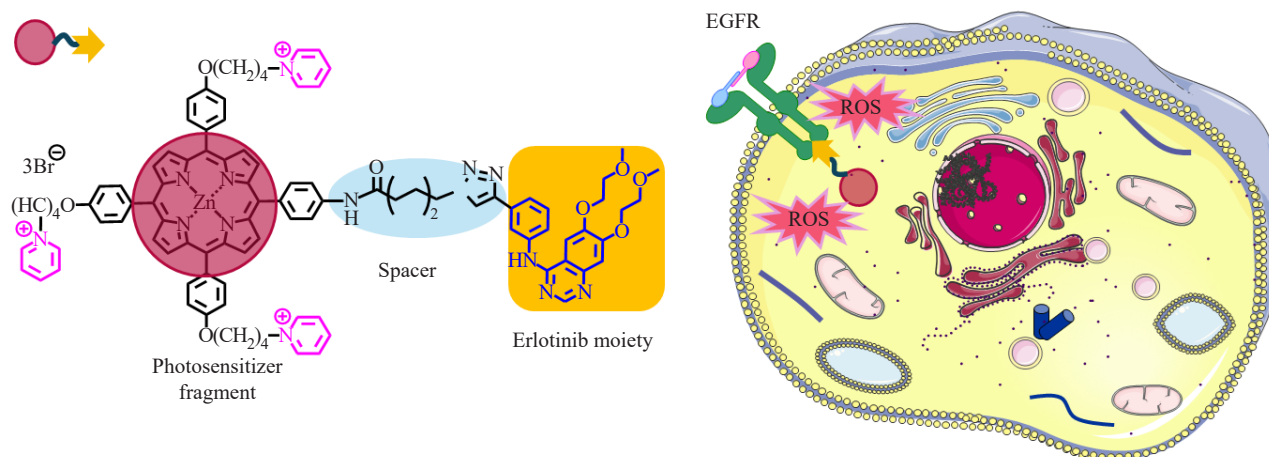


Fig. 1. Mechanism of action of the photosensitizer **UB-4**

azide-alkyne cycloaddition (CuAAC, click) reaction was carried out. The antitumor activity of the obtained conjugate was investigated *in vitro*.

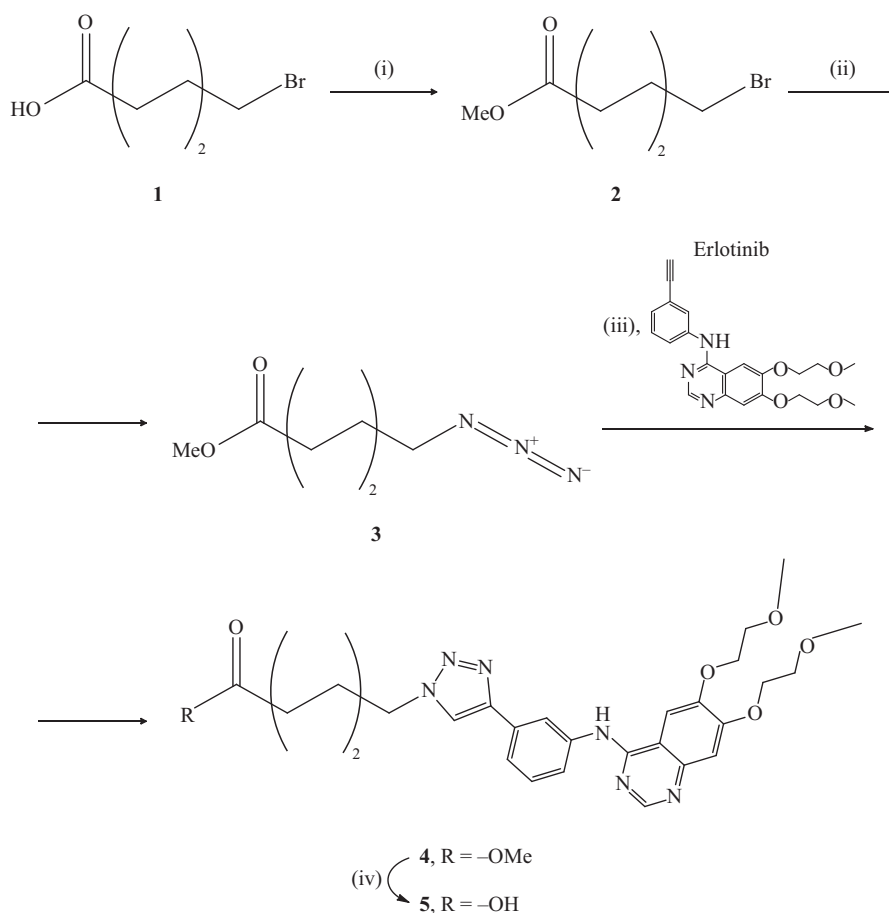
RESULTS AND DISCUSSION

The novel multifunctional phototherapeutic agent presented in this study incorporates a porphyrin-based photosensitizer and an erlotinib vector molecule, which is separated from the macrocycle by an aliphatic spacer consisting of five methylene units. The synthesis strategy for the conjugate was based on the formation of an amide bond between a tetrapyrrole bearing an active amino group and an erlotinib derivative modified with a carboxylic acid.

Modification of erlotinib

At the initial stage, a strategy was developed for conjugating erlotinib with ω -bromohexanoic acid via the formation of a bifunctional 1,2,3-triazole linker under CuAAC conditions (Scheme 1). The modification of 6-bromohexanoic acid **1** involved the preparation of its methyl ester **2**, which was subsequently converted to the primary azide **3** through a substitution reaction

in dimethylformamide (DMF) at 80°C to afford a near-quantitative yield. The incorporation of the hexanoic acid moiety into the structure of erlotinib, which contains a terminal alkyne group, was achieved via CuAAC. The Cu(I) species was generated *in situ* by reduction of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5 equiv.) in the presence of sodium ascorbate (3 equiv.) in an aqueous-organic medium. The optimal solvent ratio was found to be tetrahydrofuran (THF)/ H_2O = 3 : 1. The 1,3-dipolar cycloaddition product **4** was isolated by column chromatography using a dichloromethane/methanol (20 : 1) eluent system. Subsequent saponification of the methoxycarbonyl group with potassium hydroxide in a THF/EtOH/ H_2O mixture afforded the corresponding carboxylic acid in near-quantitative yield. Compound **5** was isolated by extraction with ethyl acetate/water, followed by acidification of the aqueous phase with 1 M HCl to convert the potassium carboxylate salt into the free carboxylic acid. The signal at a chemical shift of 3.62 ppm corresponding to the protons of a methyl group disappears in the ^1H nuclear magnetic resonance (NMR) spectrum. The ratio of the integral signal intensities in the ^1H NMR spectra corresponds to the number of chemically equivalent protons in the structures of compounds **4** and **5**. Data from



Scheme 1. Modification of erlotinib. (i) SOCl_2 , MeOH, Ar, 0°C, 30 min, then 20°C, 12 h; (ii) NaN_3 , DMF, 80°C, 5 h; (iii) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, NaAsc, Ar, THF/ H_2O , 64°C, 8 h; (iv) KOH, THF/EtOH/ H_2O (6/3/1, v/v/v), 64°C, 3 h

matrix-assisted laser desorption/ionization (MALDI) mass-spectrometry of compound **4** confirm the presence of a molecular ion peak $[M+H]^+$ at 565.484 Da, which corresponds to the calculated molecular weight for the modified erlotinib molecule.

SYNTHESIS OF THE CATIONIC CONJUGATE

The zinc complex of aminoporphyrin **6**¹ was synthesized according to a previously reported procedure [25] employing the mixed-aldehyde monopyrrole condensation method. The choice of Zn(II) as the central metal ion for the tetrapyrrole macrocycle was guided by its ability to enhance the hydrophilicity of the photodynamic agent, as well as to increase the quantum yield of singlet oxygen (¹O₂) generation.

The key step in the synthesis of *meso*-arylporphyrin conjugates with the targeting ligand involved the *N*-acylation of aminoporphyrin **6** using erlotinib functionalized with a carboxylic acid group. Initial attempts to synthesize the conjugate via the carbodiimide method with nucleophilic additives (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), 4-dimethylaminopyridine (DMAP), and 1-hydroxybenzotriazole (HOBt)) resulted in only trace amounts of the target compound. Consequently, an optimized acyl chloride approach was employed, which entailed the initial activation of the carboxylic acid group of modified erlotinib **5**, followed by amide bond formation with the amino-substituted *meso*-arylporphyrin **6** (Scheme 2). Activation of the carboxylic acid moiety of compound **5** was achieved by refluxing with an excess of thionyl chloride (10 equiv.) under an inert atmosphere for 3 h. The resulting acyl chloride was then subjected to acylation with aminoporphyrin **6** in the presence of a weak nucleophilic base, Et₃N, under an inert gas flow. The reaction medium comprised anhydrous THF dried over 5 Å molecular sieves. The target conjugate **7** was extracted using a dichloromethane/water system, followed by neutralization of the aqueous phase with 1 M acetic acid. Purification of the target compound was

achieved by normal-phase column chromatography using a chloroform/ethanol/pyridine (10 : 1 : 0.05) eluent system.

Cationic derivatives of the erlotinib–porphyrin conjugate-bearing terminal pyridinium groups separated from the macrocycle by aliphatic spacers were synthesized according to a standard procedure for nitrogen quaternization. The bromine-substitute precursor **7** was refluxed in pyridine for 8 h (Scheme 2). The target conjugate **8** (**UB-4**) precipitated during the reaction was subsequently recrystallized from an Et₂O/MeOH solvent system. The obtained **UB-4** conjugate was characterized by liquid chromatography–mass spectrometry (LC–MS) to reveal a peak corresponding to the triply charged molecular ion $[M-3Br]^{3+}$ at m/z 567.3. In the ¹H NMR spectrum of product **UB-4**, signals from protons of the pyridine fragment were detected at 8.96, 8.61, and 8.11 ppm. The ratio of the integrated signals from erlotinib and the porphyrin fragment corresponds to the structure of the **UB-4** conjugate.

The electronic absorption spectra and two-band emission spectra of conjugate have a typical appearance for metalloporphyrins with a maximum of the Soret band near 430 nm and two Q bands in the range of 560–610 nm (Table 1, Fig. 2). A comparison of the spectral and luminescent properties

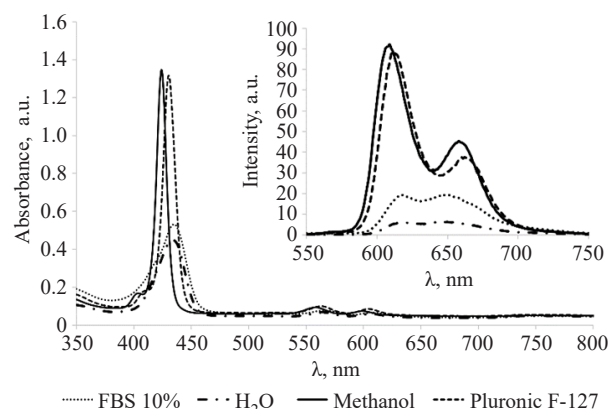


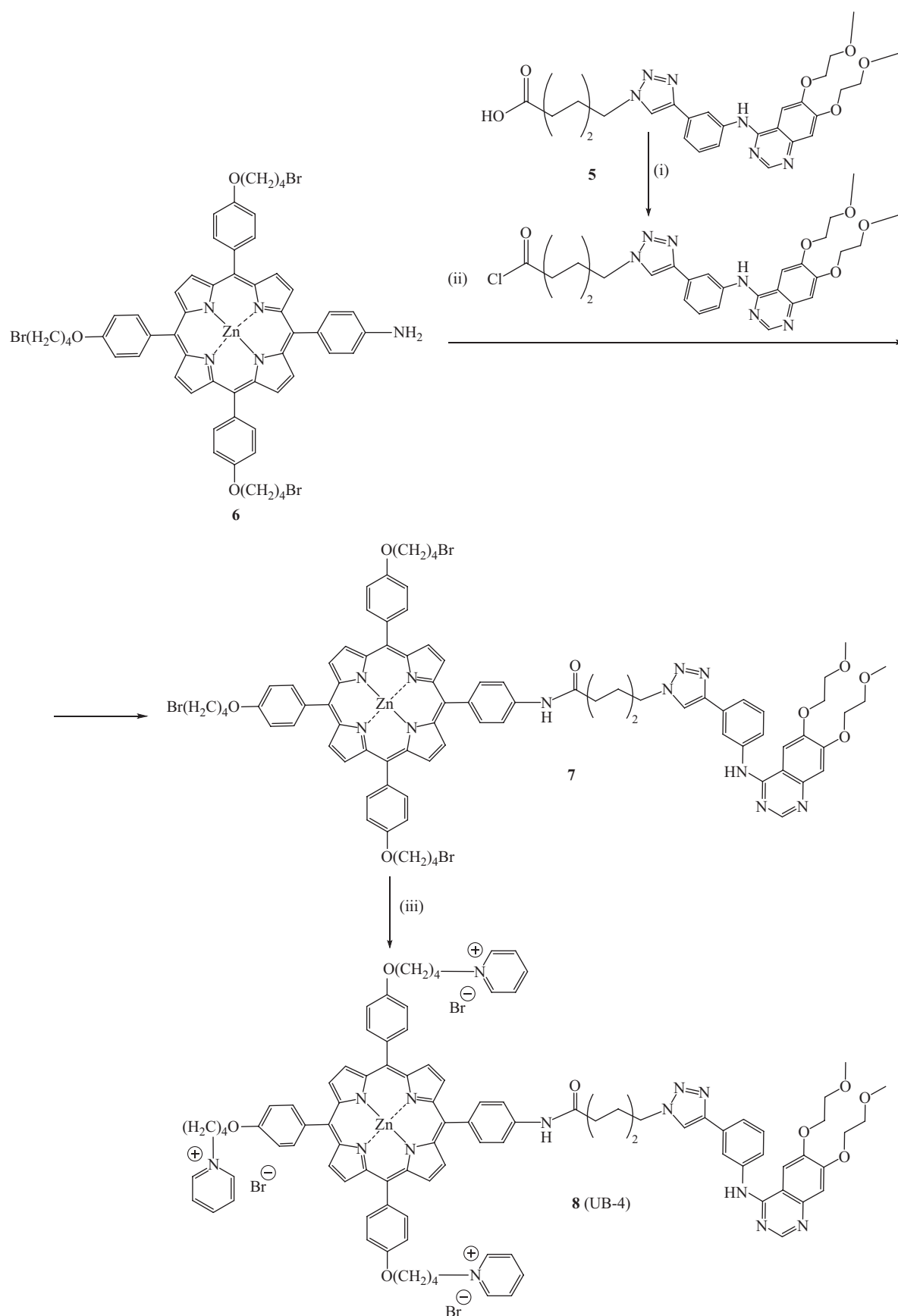
Fig. 2. Electronic absorption spectra and electronic fluorescence spectra ($\lambda_{\text{ex}} = 430$ nm) of **UB-4** (concentration of **UB-4** was 1.10 μM) in DMSO, in water and in aqueous solutions of solubilizers (FBS 10% and Pluronic® F-127)

Table 1. Physicochemical properties of compound **UB-4** in DMSO

Compound	Soret bands		Q bands				Emission		Log <i>P</i>
	λ_1	lgε	λ_1	lgε	λ_2	lgε	λ_{em1}	λ_{em2}	
UB-4	430	6.18	566	4.75	608	4.26	610	660	-1.59 ± 0.08

Note: λ is an absorption wavelength, nm; ϵ is a molar extinction coefficient, $\text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$; λ_{em} is an emission wavelength, nm; *P* is an octanol-water partition coefficient.

¹ Aminoporphyrin and *meso*-arylporphyrin are the names of the same compound. The name *meso*-arylporphyrin focuses on the heterocyclic structure of the compound. The name aminoporphyrin indicates the presence of a functional group that modifies the compound.



Scheme 2. Preparation of cationic conjugate of *meso*-arylporphyrin with erlotinib. (i) SOCl₂, Ar, 76°C, 3 h; (ii) Et₃N, THF, Ar, 64°C, 12 h; (iii) pyridine, 115°C, 8 h

of metalloporphyrin in dimethyl sulfoxide (DMSO), H₂O, micellar solutions of Pluronic® F-127 and aqueous solution with 10% fetal bovine serum (FBS) reveals effective stabilization of the monomolecular fluorescently active forms of the target compound **UB-4** in 1% Pluronic® F-127 solution.

Biological activity *in vitro*

In order to carry out a preliminary assessment of the biological activity of the obtained **UB-4** conjugate, its dark and photoinduced toxicity were evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on a human normal kidney epithelial (NKE) cell line, as well as on the tumor cell lines MCF7 (breast ductal adenocarcinoma), MDA-MB-231 (human breast adenocarcinoma), and A431 (human epidermoid carcinoma) in the absence and presence of FBS. For the *in vitro* experiments, a formulation of the target compound with Pluronic® F-127 (1%, v/v) was prepared. This approach yields the target compound in its monomolecular form, thus preventing compound aggregation. Such a strategy is widely reported in the literature, as well as having been successfully applied by us previously [25, 27–29].

First, cellular uptake of **UB-4** was estimated by flow cytometry in A431 cells. Cells were accumulated during 15 and 30 min, 1, 2, 4, 6, and 24 h. Figure 3 shows that cellular uptake of **UB-4** increased with the increasing of incubation time. At 6 h of incubation time almost complete accumulation was achieved for **UB-4**.

In the absence of FBS it was established that the cytotoxic effect of the **UB-4** conjugate upon irradiation reveals in the submicromolar concentration range for all studied cell lines (Table 2 and Fig. 4). Specifically, the half-maximal inhibitory concentration (IC₅₀) values for the EGFR overexpressing A431 and MDA-MB-231 cell lines were 0.20 and 0.36 μM, respectively. Notably, a significant difference (27–33 fold) was observed between the dark toxicity and the photoinduced toxicity of **UB-4** for all four cell lines. It is worth noting that the highest IC_{50dark}/IC_{50light} ratio was observed for the A431 cell line, which is characterized by the highest level of EGFR expression. We have previously reported the synthesis of erlotinib-based photosensitizers, such as **UB-3** [23]. However, for the photosensitizer **UB-3** the ratio between dark and photoinduced toxicity was only 3–10 fold. For the newly synthesized conjugate **UB-4**, this parameter has been improved by more than 5 times. Furthermore, **UB-4** exhibits significantly better solubility in biological media as compared to **UB-3**, which forms a precipitate at concentrations above 1.4 μM. Accordingly, the 1-octanol/water partition coefficient (log*P*) [27] for **UB-4** is -1.59 ± 0.07 , while for **UB-3** it is -1.10 ± 0.03 .

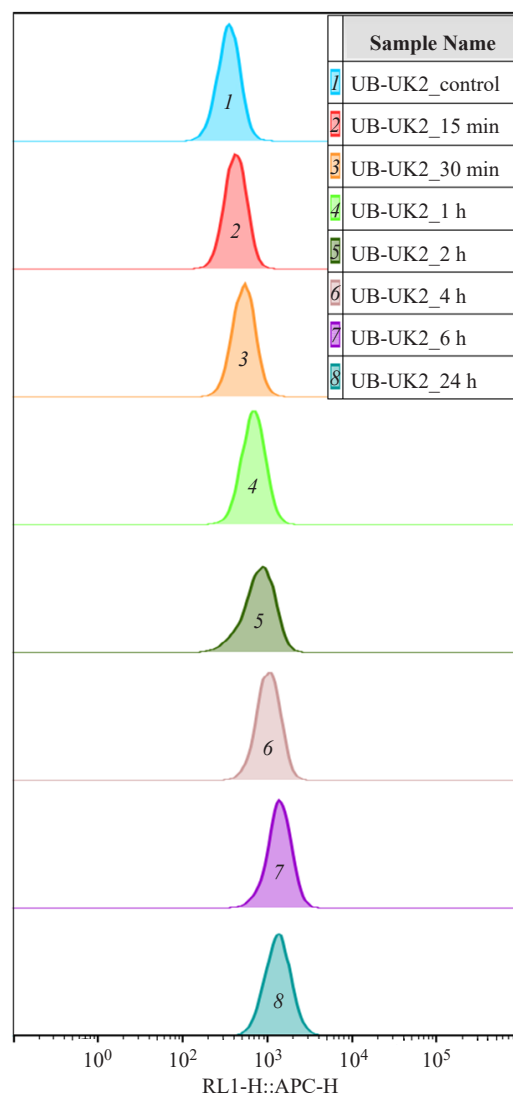


Fig. 3. Flow cytometry analysis of A431 cells treated with 1 μM of **UB-4** in Pluronic® F-127 for 15 min (2, red), 30 min (3, yellow), 1 h (4, green), 2 h (5, dark green), 4 h (6, rose), 6 h (7, purple), 24 h (8, turquoise), nontreated control cells marked in blue (1)

Table 2. Dark and Light IC₅₀ values for **UB-4** in the absence of FBS

Cell lines	UB-4		
	IC _{50dark} , μM	*IC _{50light} , μM	IC _{50dark} /IC _{50light}
NKE	7.5 ± 0.7	0.28 ± 0.08	27
MCF7	6.9 ± 0.6	0.23 ± 0.03	30
A431	12.0 ± 1.5	0.36 ± 0.03	33
MDA-MB-231	5.6 ± 0.07	0.20 ± 0.02	28

* Irradiation was performed using a Medical Therapy Philips TL 20W/52 lamp (total irradiation dose 8.1 J/cm²). NKE and MCF7 (rose) are EGFR-low-expressed cell lines; A431 and MDA-MB-231 (green) are EGFR-overexpressed cell lines.

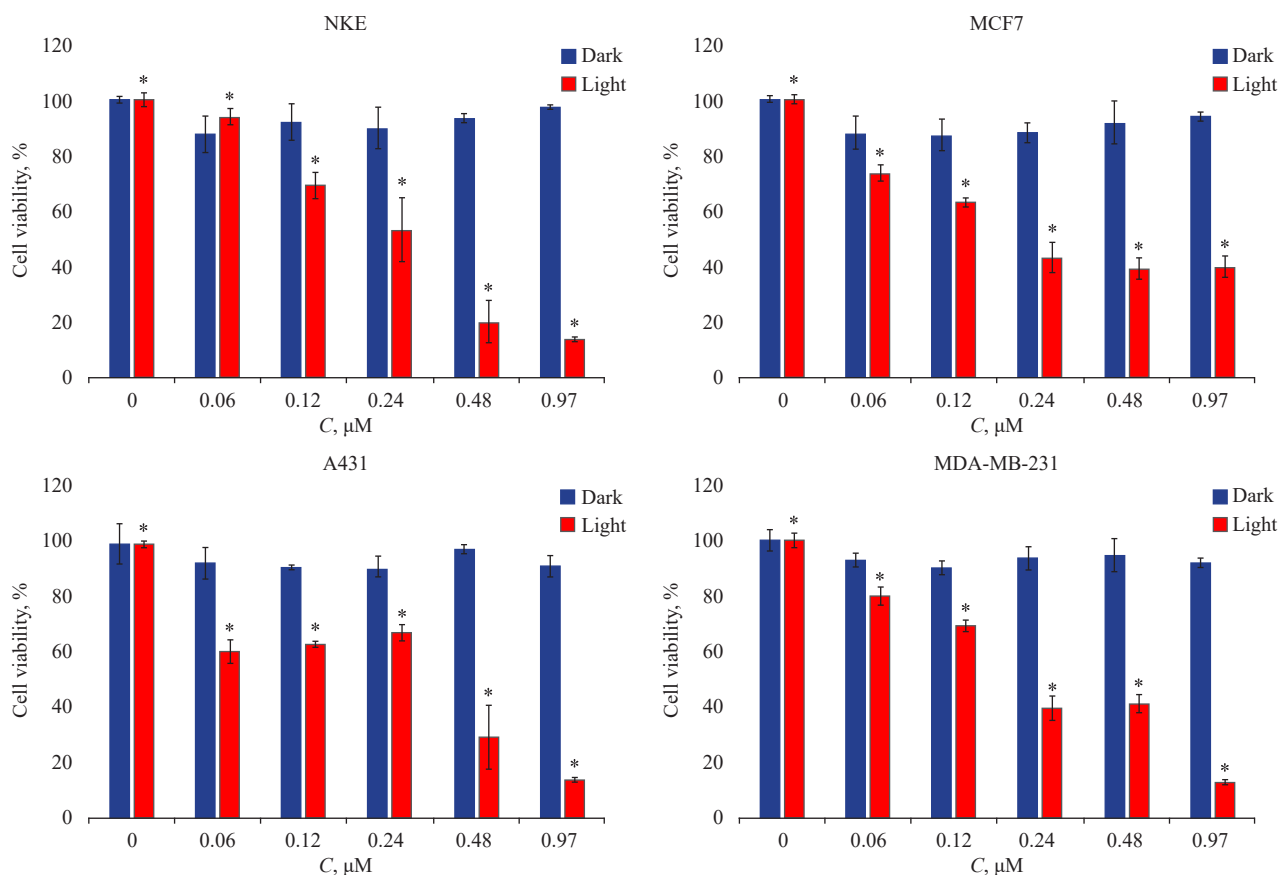


Fig. 4. Effect of compounds **UB-4** in the micellar form on the viability of cell lines NKE, MCF7, A431, MDA-MB-231. Cells were irradiated for 90 min using the Medical Therapy Philips TL 20W/52 lamp (total irradiation dose was 8.1 J/cm²). Incubation of cells with the compound 24 h.

* Statistically significant differences in cell survival relative to the values with zero concentration of the compound (p (false-positive probability) < 0.05) were noted

Next, we evaluated the dark and photoinduced toxicity of the micellar form of the **UB-4** conjugate in the presence of 10% FBS on MDA-MB-231 and NKE cell lines (Table 3, Fig. 5). For both cell lines, a significant decrease in $IC_{50\text{dark}}/IC_{50\text{light}}$ ratio was

observed in medium containing 10% serum (1.7-fold for MDA-MB-231 and 3.3-fold for NKE) compared to the parameters obtained in serum-free medium. The main contribution to this change in the ratio comes from a two-fold increase in dark toxicity, which is most

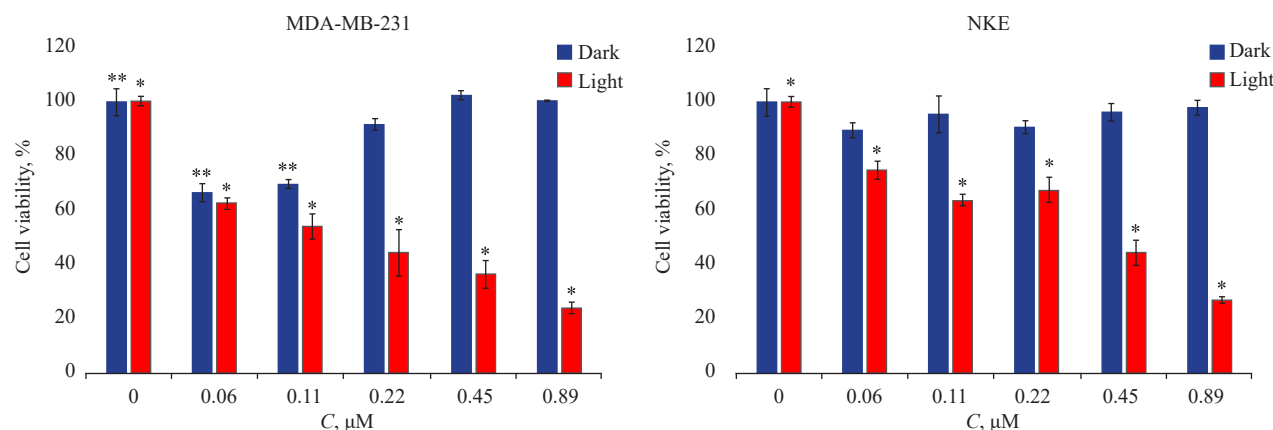


Fig. 5. Effect of compound **UB-4** in the micellar form on the viability of cell lines MDA-MB-231 and NKE in the presence of 10% FBS. Cells were irradiated for 90 min using the Medical Therapy Philips TL 20W/52 lamp (irradiation dose of 8.1 J/cm²). Incubation of cells with the compound 24 h.

* Statistically significant differences in cell survival relative to the values with zero concentration of the compound (p < 0.05) were noted

likely associated with more active cellular metabolism in the presence of 10% FBS. Photoinduced toxicity remained unchanged for the MDA-MB-231 tumor line but decreased 1.5-fold for the conditionally normal NKE line. Compared to the data in serum-free medium, where the IC_{50} values for all cell lines were similar, the photoinduced toxicity against the MDA-MB-231 tumor line in the presence of serum is twice as high as the photoinduced toxicity against the conditionally normal NKE line.

Table 3. Dark and light IC_{50} values for **UB-4** in the presence of FBS

Cell lines	UB-4		
	$IC_{50\text{dark}}, \mu\text{M}$	$^*IC_{50\text{light}}, \mu\text{M}$	$IC_{50\text{dark}}/IC_{50\text{light}}$
NKE	3.40 ± 0.03	0.41 ± 0.09	8
MDA-MB-231	2.90 ± 0.06	0.20 ± 0.04	15

* Cells were irradiated for 90 min using the Medical Therapy Philips TL 20W/52 lamp (total irradiation dose was 8.1 J/cm^2).

It can be additionally noted that IC_{50} of the cells under irradiation in the experiments without FBS is practically the same for normal and malignant cells. Conversely, in the presence of FBS photoinduced toxicity of **UB-4** was two times lower for the normal NKE cells comparing malignant MDA-MB-231 cells. It is likely that the absence of FBS and consequent reduction in cellular exchange processes in terms of their ability to divide leads to a decrease in the differences between cell lines and to the similar accumulation and effect of the **UB-4** compound. All these findings indicate the promise of further biological investigation of **UB-4**.

EXPERIMENTAL

Commercially available reagents: 6-bromohexanoic acid ($\geq 98.0\%$, *abcr GmbH*, Germany), SOCl_2 ($\geq 99.5\%$, *Acros Organics*, USA), sodium azide ($\geq 99.0\%$, *Sigma-Aldrich*, USA), erlotinib ($\geq 99.6\%$, *abcr GmbH*, Germany), copper(II) sulfate pentahydrate ($\geq 98.0\%$, *Fisher Chemical*, USA), sodium ascorbate ($\geq 95.0\%$, *Sigma-Aldrich*, USA), KOH ($\geq 98.0\%$, *Aldosa*, Russia) were used without further purification. The solvents were purified according to standard procedures. The purity of the obtained compounds was confirmed by thin-layer chromatography (TLC) on TLC Silicagel 60 F254 plates (*Merck*). Macherey-Nagel Kieselgel 60 silica gel (230–400 mesh, 38–63 μm) was used for column chromatography. The electronic

absorption spectra were recorded on a HACHDR-4000V instrument (*Hach-Lange*, USA) in the wavelength range 320–800 nm in 1 nm increments in quartz cuvettes with an optical path length of 10 mm at 25°C . Steady-state fluorescence spectra were recorded using a Cary Eclipse fluorescence spectrophotometer (*Agilent Technologies*, Malaysia) under similar conditions at a monochromator slit width of 10 nm and excitation wavelength corresponding to the maximum of the Soret band. Concentrations of porphyrin solutions were $1.10 \mu\text{M}$. NMR spectra were obtained on a high-resolution AVANCE DPX NMR spectrometer (*Bruker Analytik GmbH*, Germany) with an operating frequency of 300 MHz, measurements were carried out on the δ scale, the internal tetramethylsilane (TMS) standard, the solvent CDCl_3 , CD_3OD and $\text{DMSO}-d_6$. Matrix-activated laser desorption/ionization spectrometry with a time-of-flight analyzer (*Bruker Daltonics Inc.*, Bremen, Germany), for which 3,5-dihydroxybenzoic acid was used to record mass spectra. The mass spectra were recorded using an electrospray ionization (ESI) mass spectrometer (*Agilent Technologies*, USA).

Syntheses

Synthesis of 6-bromohexanoic acid methyl ester (**2**)

3.0 g (0.015 mol) of 6-bromohexanoic acid was dissolved in 20 mL of methanol. Then SOCl_2 (5 mL) was added to the carboxylic acid solution. The reaction mass was stirred at 0°C under an inert atmosphere for 2 h, then allowed warming to 20°C . After 8 h of stirring, the reaction mixture was concentrated and extracted with a methylene chloride/water system. The degree of reactions was controlled by TLC. Yield was 3.12 g (99%). Retention factor $R_f = 0.5$ (methylene chloride).

Synthesis of 6-azidohexanoic acid methyl ester (**3**)

1.0 g (7.68 mmol) of 6-bromohexanoic acid methyl ester **2** and 1.40 g (23.05 mmol) of sodium azide were dissolved in DMF (15 mL). The reaction mixture was stirred at 80°C under an inert atmosphere for 5 h. Then the reaction mass was concentrated under reduced pressure and extracted with a methylene chloride/water system. Yield was 0.706 g (95%). $R_f = 0.5$ (methylene chloride). ^1H NMR (CDCl_3 , δ , ppm): 3.65 (3H, s, $-\text{COOCH}_3$), 3.38 (2H, t, $J = 3.10 \text{ Hz}$, $\text{N}_3\text{CH}_2(\text{CH}_2)_4\text{COOCH}_3$), 2.31 (2H, t, $J = 3.20 \text{ Hz}$, $\text{N}_3(\text{CH}_2)_4\text{CH}_2\text{COOCH}_3$), 1.85 (2H, m, $\text{N}_3\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{COOCH}_3$), 1.63 (2H, m, $\text{N}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{COOCH}_3$), 1.45 (2H, m, $\text{N}_3(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{COOCH}_3$).

Synthesis of 6-(4-(3-(6,7-bis(2-methoxyethoxy)-quinazoline-4-ylamino)phenyl)-1H-1,2,3-triazol-1-yl)hexanoic acid methyl ether (**4**)

0.543 g (1.81 mmol) of erlotinib was added to a solution of 0.200 g (2.17 mmol) of compound **3** in THF (10 mL). The resulting mixture was treated with a solution of 1.637 g (6.52 mmol) of copper(II) sulfate pentahydrate and 2.120 g (10.87 mmol) of sodium ascorbate in water (5 mL). The reaction mixture was refluxed for 8 h. Then the mixture was extracted with methylene chloride/water. The collected organic layer was dried over sodium sulfate and evaporated on a rotary evaporator. A viscous yellow liquid was purified by column chromatography on G60 silica gel. Elution of compounds **4** was carried out by methylene chloride/methanol (20 : 1, v/v). Yield was 0.781 g (82%). R_f = 0.3 (methylene chloride/methanol = 20 : 1). ^1H NMR (CDCl_3 , δ , ppm): 8.58 (1H, s, H-pyrimidine), 8.23 (1H, br. s, -NH), 8.07 (1H, s, H-triazole), 7.80 (1H, s, 8-H-quinazoline), 7.71 (1H, s, 5-H-quinazoline), 7.44 (2H, m, 4,6-H-Ph), 7.32 (1H, m, 5-H-Ph), 7.15 (1H, s, 2-H-Ph), 4.30 (2H, t, J = 3.10 Hz, $-\text{NCH}_2(\text{CH}_2)_4\text{COOCH}_3$), 4.18 (4H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 3.76 (2H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 3.71 (2H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 3.62 (3H, s, $-\text{COOCH}_3$), 3.38 (3H, s, $-\text{OCH}_3$), 3.36 (3H, s, $-\text{OCH}_3$), 2.26 (2H, t, J = 2.90 Hz, $-\text{N}(\text{CH}_2)_4\text{CH}_2\text{COOCH}_3$), 1.87 (2H, m, $-\text{NCH}_2\text{CH}_2(\text{CH}_2)_3\text{COOCH}_3$), 1.61 (2H, m, $-\text{N}(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{COOCH}_3$), 1.26–1.36 (2H, m, $\text{N}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{COOCH}_3$). ^{13}C NMR ($\text{DMSO}-d_6/\text{CDCl}_3$, (20/1, v/v), δ , ppm): 171.59, 155.76, 149.49, 148.89, 145.73, 137.36, 131.64, 129.55, 123.80, 123.06, 121.52, 120.99, 114.77, 107.20, 104.43, 69.78, 68.80, 68.71, 67.27, 58.38, 51.43, 49.24, 48.84, 39.52, 33.97, 30.27, 26.33, 25.50. MALDI-TOF-MS, m/z : calculated for $\text{C}_{29}\text{H}_{36}\text{N}_6\text{O}_6$ 564.27 $[\text{M}]^+$, found 565.484 $[\text{M}+\text{H}]^+$.

Synthesis of 6-(4-(3-(6,7-bis(2-methoxyethoxy)-quinazolin-4-ylamino)phenyl)-1H-1,2,3-triazol-1-yl)hexanoic acid (**5**)

Intermediate compound **4** (0.250 g, 0.044 mmol) was dissolved in THF (12 mL). Subsequently, an excess of KOH (17 equiv.) dissolved in ethanol (6 mL) and water (3 mL) was added. The reaction mixture was stirred at 64°C for 3 h. The cooled reaction mixture was concentrated under reduced pressure and extracted using an ethyl acetate/water system; a 1 M hydrochloric acid solution was used to neutralize the alkali. The product was recrystallized from ethyl acetate. Yield was 0.242 g (98%). R_f = 0.4 (methylene chloride/methanol = 10 : 1). ^1H NMR (CDCl_3 , δ , ppm): 9.19 (1H, br. s, $-\text{COOH}$), 8.52 (1H, s, H-pyrimidine), 8.02 (1H, s, H-triazole), 7.87 (1H, s, 8-H-quinazoline), 7.67 (1H, s, 5-H-quinazoline), 7.44

(2H, m, 4,6-H-Ph), 7.10 (1H, t, J = 5.70 Hz, 5-H-Ph), 7.01 (1H, s, 2-H-Ph), 4.32 (2H, t, J = 3.55 Hz, $\text{NCH}_2(\text{CH}_2)_4\text{COOCH}_3$), 4.18 (2H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 4.08 (2H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 3.75–3.71 (4H, m, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 3.40 (3H, s, $-\text{OCH}_3$), 3.38 (3H, s, $-\text{OCH}_3$), 2.32 (2H, m, $\text{N}(\text{CH}_2)_4\text{CH}_2\text{COOCH}_3$), 1.88 (2H, m, $\text{NCH}_2\text{CH}_2(\text{CH}_2)_3\text{COOCH}_3$), 1.64 (2H, m, $\text{N}(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{COOCH}_3$), 1.31 (2H, m, $\text{N}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{COOCH}_3$). ^{13}C NMR (CDCl_3 , δ , ppm): 173.87, 154.47, 148.91, 147.49, 139.58, 131.26, 129.41, 121.74, 121.19, 120.05, 119.05, 108.32, 102.82, 70.85, 70.49, 69.03, 68.37, 59.23, 51.60, 50.16, 33.67, 29.96, 25.97, 24.22.

The zinc complex of *meso*-arylporphyrin arylporphyrin **6** was synthesized according to a previously reported procedure [25] employing the mixed-aldehyde monopyrrole condensation method.

Synthesis of conjugate of *meso*-arylporphyrin with erlotinib (**7**)

At the first stage, 0.050 g (0.091 mmol) of compounds **5** and SOCl_2 (2 mL) were dissolved in methylene chloride (10 mL). The reaction mixture was stirred at 75°C for 3 h under an inert atmosphere. Next, the reaction mass was concentrated under a reduced pressure. At the second stage, the formed acyl chloride of compound **4** was dissolved in THF (7 mL). Then 0.065 g (0.059 mmol) of aminoporphyrin **6**, dissolved in THF (7 mL), and 150 μL of Et_3N were added to the resulting solution. The reaction mass was stirred at 64°C for 12 h under an inert atmosphere. The cooled reaction mass was concentrated under a reduced pressure and extracted using a methylene chloride/water, followed by pH adjustment to a neutral medium with 1 M acetic acid solution. The purple solid was purified by column chromatography on G60 silica gel. Compound **7** was eluted by the chloroform/pyridine (100 : 0.05) with a further increase in the polarity of the system to the chloroform/ethanol/pyridine ratio (10 : 1 : 0.05). Yield was 0.040 g (42%). R_f = 0.4 (chloroform/ethanol = 5 : 1). Electronic absorption spectrum (EAS) (λ_{max} , nm, CH_2Cl_2 (lg ϵ)): 423.9 (6.11), 556.1 (4.19), 595.2 (4.06). ^1H NMR (CDCl_3 , δ , ppm): 8.84 (8H, m, $\beta\text{-CH}$ -pyrrole), 8.63 (1H, s, H-pyrimidine), 8.41 (1H, s, H-triazole), 8.09 (8H, 2,6-ArH and $\alpha\text{-ArNH}$), 7.83 (1H, s, 8-H-quinazoline), 7.71 (1H, s, 5-H-quinazoline), 7.26–7.15 (11H, m, 3,5-ArH, $\beta\text{-ArNH}$, and 4,5,6-H-Ph), 6.64 (1H, s, 2-H-Ph), 4.51 (2H, m, $-\text{NCH}_2(\text{CH}_2)_4\text{C}(\text{O})\text{NH}-$), 4.20 (10H, m, $2\times-\text{OCH}_2\text{CH}_2\text{OCH}_3$ and $3\times-\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Br}$), 3.74 (10H, m, $2\times-\text{OCH}_2\text{CH}_2\text{OCH}_3$ and $3\times-\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Br}$), 3.45 (3H, s, $-\text{OCH}_3$), 3.39 (3H, s, $-\text{OCH}_3$), 2.47 (2H, m, $-\text{N}(\text{CH}_2)_4\text{CH}_2\text{C}(\text{O})\text{NH}-$), 2.17–2.06 (12H, m, $3\times-\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Br}$), 1.77 (4H, m, $-\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}-$), 1.61 (2H, m,

$-\text{N}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{C}(\text{O})\text{NH}-$). MALDI-TOF-MS, m/z : calculated for $\text{C}_{84}\text{H}_{82}\text{Br}_3\text{N}_{11}\text{O}_8\text{Zn}$ 1676.31 $[\text{M}]^+$, found 1677.874 $[\text{M}+\text{H}]^+$.

Synthesis of the cationic conjugate of *meso*-arylporphyrin with erlotinib **UB-4 (8)**

0.042 g (0.024 mmol) of compound **7** was dissolved in anhydrous pyridine (15 mL). The reaction mixture was refluxed for 8 h. The resulting precipitate was washed with diethyl ether and filtered. The target compound was recrystallized from the diethyl ether/methanol. Yield was 0.032 g (91%). $R_f = 0.15$ (CH_3OH). EAS (λ_{max} , nm, CH_3OH (lgε)): 431.8 (6.18), 559.0 (4.75), 599.9 (4.26). ^1H NMR (CD_3OD , δ, ppm): 8.96 (7H, m, 3×2,6- $\underline{\text{H}}$ -Py and $\underline{\text{H}}$ -pyrimidine), 8.92–8.77 (8H, m, β- $\underline{\text{CH}}$ -pyrrole), 8.61 (3H, t, 3×4- $\underline{\text{H}}$ -Py), 8.32 (1H, s, $\underline{\text{H}}$ -triazole), 8.11 (6H, m, 3×3,5- $\underline{\text{H}}$ -Py), 8.03 (1H, s, 8- $\underline{\text{H}}$ -quinazoline), 7.91 (9H, m, 2,6-Ar $\underline{\text{H}}$; α-ArNH and 5- $\underline{\text{H}}$ -quinazoline), 7.10 (8H, dd, 3,5-Ar $\underline{\text{H}}$ and β-ArNH), 7.02 (3H, m, 4,5,6- $\underline{\text{H}}$ -Ph), 6.75 (1H, s, 2- $\underline{\text{H}}$ -Ph) 4.58 (8H, m, $-\text{NCH}_2(\text{CH}_2)_4\text{C}(\text{O})\text{NH}-$ and 3× $-\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Py}^+$), 4.26 (8H, m, 2× $-\text{OCH}_2\text{CH}_2\text{OCH}_3$), 4.07 (6H, m, 3× $-\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Py}^+$), 3.43 (3H, s, $-\text{OCH}_3$), 3.41 (3H, s, $-\text{OCH}_3$), 2.46 (2H, m, $-\text{N}(\text{CH}_2)_4\text{CH}_2\text{C}(\text{O})\text{NH}-$), 2.10–1.99 (8H, m, 3× $-\text{O}(\text{CH}_2)_2\text{CH}_2\text{CH}_2\text{Py}^+$ and $-\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}-$), 1.93–1.80 (8H, m, 3× $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_2\text{Py}^+$ and $-\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}-$), 1.60 (2H, m, $-\text{N}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{C}(\text{O})\text{NH}-$). ^{13}C NMR (CD_3OD_3 , δ, ppm): 157.88, 155.51, 153.41, 149.95, 146.62, 145.64, 140.25, 136.62, 135.12, 130.81, 129.50, 129.25, 128.29, 126.61, 123.87, 123.68, 113.73, 110.12, 107.85, 103.84, 84.09, 83.49, 79.46, 78.53, 73.21, 71.58, 71.35, 69.79, 69.30, 68.16, 62.56, 61.94, 59.16, 49.00, 30.34, 30.00, 29.30, 26.66, 26.24. ESI-HRMS, m/z : calculated for $\text{C}_{99}\text{H}_{93}\text{N}_{14}\text{O}_8\text{Zn}^{3+}$ 577.89 $[\text{M}-3\text{Br}]^{3+}$, found 577.9 $[\text{M}-3\text{Br}]^{3+}$.

1-*n*-Octanol/phosphate-buffered saline (PBS) partition coefficients

The partition coefficient ($\log P$) of compound **UB-4** under study were assessed using a previously reported protocol [27]. Briefly, 1.0–1.5 mg of each porphyrin was dissolved in 1-*n*-octanol pre-equilibrated with PBS. An equal volume of PBS pre-saturated with 1-*n*-octanol was subsequently introduced. The biphasic mixture was subjected to ultrasonication for 30 min followed by mechanical agitation at 25°C. Phase separation was achieved by centrifugation. The partition coefficients were calculated from electronic absorption spectra by measuring the absorbance ratio of the Soret band in the organic and aqueous phases, taking into account the respective dilution factors as analogously determined. Final values are expressed as $\log P$.

Biological activity *in vitro*

This experiment was performed using four cell lines: NKE (human renal tubule epithelium), MCF-7 (human breast adenocarcinoma), A431 (human epidermoid carcinoma), and MDA-MB-231 (human breast adenocarcinoma). For the *in vitro* experiments, a formulation of the target compound with Pluronic® F-127 (1%, *v/v*) was prepared. During the experiment, cells were seeded in 96-well plates (*SPL Lifesciences*, Korea) at density of $7 \cdot 10^3$ cells/well in 180 μL of culture medium and incubated for 24 h at +37°C in a humidified atmosphere containing 5% CO_2 . On the day of the experiment, the medium was replaced with a similar serum-free medium to avoid interaction of the tested compounds with it. Serial dilutions of the compounds were made in Milli-Q water and added to the cell culture by 20 μL. The cell culture was irradiated for 90 min using a Medical Therapy Philips TL 20W/52 lamp (400–500 nm wavelength) with 2.3 mW of power. Subsequently the plates were placed in an incubator and left for 24 h at +37°C in 5% CO_2 . Parallel incubation of cell culture with compounds without irradiation was performed in a similar manner. After 24 h, 10 μL of MTT reagent solution (5 mg/mL) was added to the cell medium and incubated for another 3.5 h. The formazan formed in the cells was dissolved in 100 μL of DMSO. MultiScan MCC 340 (*Thermo Fisher Scientific*, USA) spectrophotometer was used to determine the optical density of the solution at 540 nm. Experiments were repeated at least 3 times. The titration curves were used to calculate the concentration of the compound that induced 50% of the maximum toxicity effect (IC_{50}). The Excel program package (*Microsoft Corporation*, USA) was utilized for statistical processing of the obtained data.

Flow cytometry

For the experiment, A431 cells were seeded into 6-well plates (*SPL Lifesciences*, Korea) at a rate of $2.5 \cdot 10^5$ cells/well in Dulbecco's Modified Eagle Medium (DMEM) nutrient medium (*PanEco*, Russia) and incubated for 24 h at 37°C in 5% CO_2 . After this, the cell medium was changed to a similar medium that did not contain fetal bovine serum and the test compound were added to a final concentration of 1 μM. Incubation was carried out for 15 and 30 min, 1, 2, 4, 6, and 24 h at 37°C in 5% CO_2 in the absence of light. Cells were removed from the substrate using 0.02% Versene (*PanEco*, Russia) and 0.25% trypsin solutions (*PanEco*, Russia) and washed twice with phosphate-salt buffer (*PanEco*, Russia). Fluorescence intensity was measured using

a LongCyte flow cytometer (*Challenbio*, China) equipped with a $\lambda_{\text{ex}} = 635$ nm laser and a 665/20 nm bandpass filter. Statistical processing of the obtained data was performed using the FlowJo software (*Becton Dickinson*, USA).

CONCLUSIONS

In this study, a novel EGFR-targeted photosensitizer was designed and synthesized based on a cationic porphyrin-erlotinib conjugate. After efficiently assembling the conjugate via CuAAC click chemistry, its structure, along with those of all intermediates, was confirmed by comprehensive physicochemical analysis. The compound exhibited submicromolar cytotoxicity against tumor cell lines and a high photodynamic index due to a significant differential between photoinduced and dark toxicity. These results identify this conjugate as a promising antitumor agent for further development.

REFERENCES

1. Jin H., Wang L., Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nat. Rev. Drug Discov.* 2023;22:213–234. <https://doi.org/10.1038/s41573-022-00615-z>
2. Gunaydin G., Gedik M.E., Ayan S. Photodynamic Therapy—Current Limitations and Novel Approaches. *Front. Chem.* 2021;9:691697. <https://doi.org/10.3389/fchem.2021.691697>
3. Fang L., Chen Z., Dai J., Pan Y., Tu Y., Meng Q., Diao Y., Yang S., Guo W., Li L., Liu J., Wen H., Hua K., Hang L., Fang J., Meng X., Ma P., Jiang G. Recent Advances in Strategies to Enhance Photodynamic and Photothermal Therapy Performance of Single-Component Organic Phototherapeutic Agents. *Adv. Sci.* 2025;12(7):2409157. <https://doi.org/10.1002/advs.202409157>
4. Condorelli A.G., Motolese A., Borgia F., Bartolomeo L.D., Bianchi L., Rossi P.G., Ottone M., Guarneri F., Motolese A. Photodynamic therapy for superficial basal cell carcinomas: Clinical features of partial responses and recurrences. *Photodiagn. Photodyn. Ther.* 2022;37:102727. <https://doi.org/10.1016/j.pdpdt.2022.102727>
5. Kim T.E., Chang J.-E. Recent Studies in Photodynamic Therapy for Cancer Treatment: From Basic Research to Clinical Trials, *Pharmaceutics*. 2023;15(9):2257. <https://doi.org/10.3390/pharmaceutics15092257>
6. Przygoda M., Bartusik-Aebischer D., Dynarowicz K., Cieřlar G., Kawczyk-Krupka A., Aebischer D. Cellular mechanisms of singlet oxygen in photodynamic therapy. *Int. J. Mol. Sci.* 2023;24(23):16890. <https://doi.org/10.3390/ijms242316890>
7. Akbar A., Khan S., Chatterjee T., Ghosh M. Unleashing the power of porphyrin photosensitizers: illuminating breakthroughs in photodynamic therapy. *J. Photochem. Photobiol. B: Biol.* 2023;248:112796. <https://doi.org/10.1016/j.jphotobiol.2023.112796>
8. Usanyov A.Yu., Sukoreva S.M., Prokopova N.V., Gradova M.A., Karpechenko N.Yu., Bragina N.A., Zhdanova K.A. Synthesis and photophysical properties of a new glycoconjugate based on meso-arylporphyrin. *Mendeleev Commun.* 2025;35(6):667–669. <https://doi.org/10.71267/mencom.7791>
9. Zhdanova K.A., Savelyeva I.O., Markova A.A., Nguyen M.T., Egorov A.E., Voitova A.V., Rybkin A.Yu., Filatova N.V., Bondarenko S.D., Mishchenko D.V., Gradova M.A., Karpechenko N.Yu., Maksimova V.P., Popova V.G., Govorov N.D., Bezborodova O.A., Kuzmin V.A., Bragina N.A. Novel π -extended cationic meso-arylporphyrins as photosensitizers for photodynamic therapy: Synthesis, photoinduced toxicity and *in vivo* fluorescence. *J. Photochem. Photobiol. B: Biol.* 2026;281:113497. <https://doi.org/10.1016/j.jphotobiol.2026.113497>
10. Gradova M.A., Gradov O.V., Bychkova A.V., Motyakin M.V., Ionova I.S., Lobanov A.V. Interaction between meso-tetra-(4-hydroxyphenyl) porphyrin and SDS in aqueous solutions: premicellar porphyrin-surfactant J-aggregate formation. *Chem. Phys.* 2022;562:111655. <https://doi.org/10.1016/j.chemphys.2022.111655>
11. Yan T., Alimu G., Zhu L., Fan H., Zhang L., Du Z., Ma R., Chen S., Alifu N., Zhang X. PpIX/IR-820 Dual-Modal Therapeutic Agents for Enhanced PDT/PTT Synergistic Therapy in Cervical Cancer. *ACS Omega.* 2022;7(49):44643–44656. <https://doi.org/10.1021/acsomega.2c02977>
12. Kustov A.V., Morshnev P.K., Smirnova N.L., Kustova T.V., Zorina T.E., Zorin V.P., Gagua A.K., Fomin N.S., Lyapin D.S., Fomichev M.D., Berezin D.B., Abramova O.B. Natural Chlorin e_6 Derivative Containing a Cationic Dimethyl Piperazinyl Moiety for Efficient Photodynamic Therapy of Cancer. *ACS Omega.* 2026;11(4):5271–5280. <https://doi.org/10.1021/acsomega.5c07979>

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Authors' contributions

Yu.S. Bortnevskaya—data collecting, processing and writing the text of the article.

A.A. Notarova—performing a synthesis experiment.

N.A. Bragina—scientific consulting at all stages of the work.

N.Yu. Karpechenko—performing an experiment to study biological activity.

K.A. Zhdanova—concept, idea, and design of research, data collecting and processing.

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13. Chakraborty S., Agrawalla B.K., Stumper A., Vegi N.M., Fischer S., Reichardt C., Kögler M., Dietzek B., Feuring-Buske M., Buske C., Rau S., Weil T. Mitochondria Targeted Protein-Ruthenium Photosensitizer for Efficient Photodynamic Applications. *J. Am. Chem. Soc.* 2017;139(6):2512–2519. <https://doi.org/10.1021/jacs.6b13399>
14. Didamson O.C., Chandran R., Abrahamse H. Synthesis, characterisation, and anti-tumour activity of nano-immuno-conjugates for enhanced photodynamic therapy of oesophageal cancer stem cells. *Biomed. Pharmacother.* 2024;181:117693. <https://doi.org/10.1016/j.biopha.2024.117693>
15. Kuzmina N.S., Fedotova E.A., Jankovic P., Gribova G.P., Nyuchev A.V., Fedorov A.Y., Otvagin V.F. Enhancing precision in photodynamic therapy: innovations in light-driven and bioorthogonal activation. *Pharmaceutics*. 2024;16(4):479. <https://doi.org/10.3390/pharmaceutics16040479>
16. Sigismund S., Avanzato D., Lanzetti L. Emerging Functions of the EGFR in Cancer. *Mol. Oncol.* 2018;12(1):3–20. <https://doi.org/10.1002/1878-0261.12155>
17. Kaufman N.E., Dhirga S., Jois S.D., Vicente M.D.G.H. Molecular Targeting of Epidermal Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor Receptor (VEGFR). *Molecules*. 2021;26(4):1076. <https://doi.org/10.3390/molecules26041076>
18. Koseska A., Bastiaens P.I. Processing Temporal Growth Factor Patterns by an Epidermal Growth Factor Receptor Network Dynamically Established in Space. *Annu. Rev. Cell Dev. Biol.* 2020;36(1):359–383. <https://doi.org/10.1146/annurev-cellbio-013020-103810>
19. Maity P., Chatterjee J., Patil K.T., Arora S., Katiyar M.K., Kumar M., Samarbakhsh A., Joshi G., Bhutani P., Chugh M., Gavande N.S., Kumar R. Targeting the Epidermal Growth Factor Receptor with Molecular Degradable: State-of-the-Art and Future Opportunities. *J. Med. Chem.* 2023;66(5):3135–3172. <https://doi.org/10.1021/acs.jmedchem.2c01242>
20. Cheruku R.R., Cacaccio J., Durrani F.A., Tabaczynski W.A., Watson R., Sifers K., Missert J.R., Tracy E.C., Dukh M., Guru K., Koya R.C., Kalinski P., Baumann H., Pandey R.K. Synthesis, Tumor Specificity, and Photosensitizing Efficacy of Erlotinib-Conjugated Chlorins and Bacteriochlorins: Identification of a Highly Effective Candidate for Photodynamic Therapy of Cancer. *J. Med. Chem.* 2021;64(1):741–767. <https://doi.org/10.1021/acs.jmedchem.0c01735>
21. Wu W., Luo C., Zhu C., Cai Z., Liu J. A Novel Boron Dipyrromethene-Erlotinib Conjugate for Precise Photodynamic Therapy against Liver Cancer. *Int. J. Mol. Sci.* 2024;25(12):6421. <https://doi.org/10.3390/ijms25126421>
22. Zhang F.L., Huang Q., Liu J.Y., Huang M.D., Xue J.P. Molecular-Target-Based Anticancer Photosensitizer: Synthesis and *in vitro* Photodynamic Activity of Erlotinib–Zinc(II) Phthalocyanine Conjugates. *ChemMedChem*. 2015;10(2):312–320. <https://doi.org/10.1002/cmdc.201402373>
23. Otvagin V.F., Kuzmina N.S., Kudriashova E.S., Nyuchev A.V., Gavryushin A.E., Fedorov A.Y. Conjugates of Porphyrinoid-Based Photosensitizers with Cytotoxic Drugs: Current Progress and Future Directions Toward Selective Photodynamic Therapy. *J. Med. Chem.* 2022;65(3):1695–1734. <https://doi.org/10.1021/acs.jmedchem.1c01953>
24. Krylova L.V., Otvagin V.F., Gribova G.P., Kuzmina N.S., Fedotova E.A., Zelepukin I.V., *et al.* Developing chlorin/arylaminquinazoline conjugates with nanomolar activity for targeted photodynamic therapy: design, synthesis, SAR, and biological evaluation. *J. Med. Chem.* 2025;68(2):1901–1923. <https://doi.org/10.1021/acs.jmedchem.4c02643>
25. Bortnevskaia Y.S., Zakharov N.S., Senkov V.S., Gradova M.A., Karpechenko N.Yu., Nikolskaya E.D., Mollaeva M.R., Yabbarov N.G., Novikov A.S., Bragina N.A., Zhdanova K.A. Synthesis, molecular docking, and biological activity of new EGFR-targeted photosensitizers based on cationic porphyrins encapsulated into Pluronic F127 micelles. *Mol. Pharm.* 2025;22(6):3308–3330. <https://doi.org/10.1021/acs.molpharmaceut.5c00247>
26. Huang K., Niu Y., Yuan G., Yan M., Xue J., Chen J. EGFR-targeted photosensitizer for enhanced photodynamic therapy and imaging therapeutic effect by monitoring GSH decline. *Sens. Actuators. B: Chem.* 2022;355:131275. <https://doi.org/10.1016/j.snb.2021.131275>
27. Ormond A.B., Freeman H.S. Effects of substituents on the photophysical properties of symmetrical porphyrins. *Dyes Pigm.* 2013;96(2):440–448. <https://doi.org/10.1016/j.dyepig.2012.09.011>
28. Nechaeva I.A., Parfenova A.S., Filippova A.S., Filonov A.E. Solubilization of *n*-hexadecane by micellar solutions of trehalolipid – surfactants of biological origin. *Fine Chem. Technol.* 2024;19(5):418–428. <https://doi.org/10.32362/2410-6593-2024-19-5-418-428>
29. Kustov A.V., Morshnev P.K., Kukushkina N.V., Smirnova N.L., Berezin D.B., Karimov D.R., Shukhto O.V., Kustova T.V., Belykh D.V., Mal'shakova M.V., Zorin V.P., Zorina T.E. Solvation, cancer cell photoinactivation and the interaction of chlorin photosensitizers with a potential passive carrier non-ionic surfactant Tween 80. *Int. J. Mol. Sci.* 2022;23(10):5294. <https://doi.org/10.3390/ijms23105294>

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