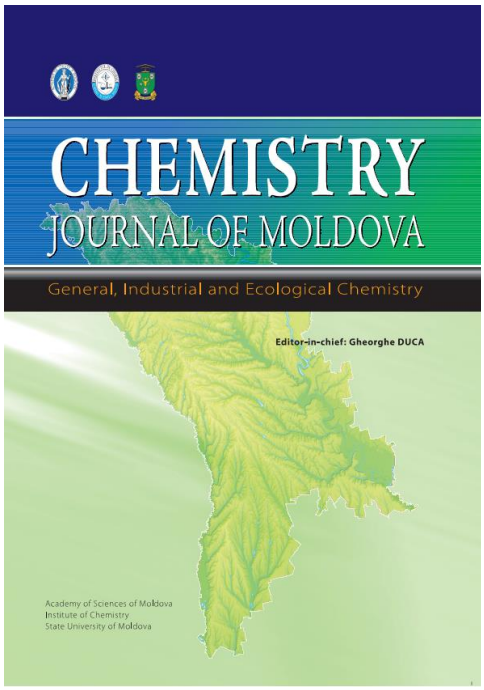

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Accepted version posted online: 04 June 2025

To cite this article: S. Robu, T. Potlog, I. Bulimestru, I. Lungu, O. Sadohina, A. Druta, P. Bulmaga, I. Gutu. Synthesis of Chitosan Grafted with Aminomethyl Zinc Phthalocyanine for Photodynamic Therapy. *Chemistry Journal of Moldova, 2025,* DOI: doi.org/10.19261/cjm.2025.1217

CHEMISTRY JOURNAL OF MOLDOVA. General, Industrial and Ecological Chemistry
ISSN (p) 1857-1727 ISSN (e) 2345-1688
http://cjm.ichem.md
https://doi.org/10.19261/cjm.2025.1217

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Abstract. This paper reports the synthesis of a substituted aminomethyl zinc phthalocyanine (AmPcZn) and its covalent grafting onto chitosan *via* an ethyl chloroformate-mediated reaction. Chitosan-based copolymers containing 10%, 20%, 30%, and 60% (w/w) AmPcZn were successfully obtained. The chemical structure of the synthesized AmPcZn was confirmed by ^{1}H-NMR spectroscopy and elemental analysis, which were consistent with the expected molecular composition. The grafting reaction and structural integrity of the resulting copolymers were investigated using Fourier-transform infrared (FTIR) and UV-Vis spectroscopies. FTIR spectra revealed characteristic amide and carbonyl stretching bands, confirming covalent bond formation between chitosan and AmPcZn. UV-Vis measurements showed a concentration-dependent increase in absorbance and a typical splitting of the Q-band with band at 605 nm and 715 nm, indicating the successful incorporation of the phthalocyanine moiety into the polymeric matrix.

Keywords: ZnPc derivative, chitosan, grafting reaction, UV-Vis spectroscopy, FTIR spectroscopy.

Received: 06 November 2024/ Revised final: 2 June 2025/ Accepted: 4 June 2025

Introduction

Photodynamic therapy (PDT) is classified as the fourth most promising cancer treatment method, alongside surgery, chemotherapy and radiotherapy, due to its high specificity and selectivity at the tumour tissue level [1,2]. The essential component of PDT is the photosensitizer (PS), a light-sensitive compound that is selectively absorbed by tumour cells. In a typical PDT process, the photosensitizer is activated by a laser with a specific wavelength, generating reactive oxygen species (ROS) capable of destroying tumour cells [3]. Among various photosensitizers used in PDT, metallophthalocyanines (MePc) have garnered significant interest as second-generation photosensitizers [3]. They are characterized by strong absorption at long wavelengths (λ> 660 nm), advantageous for deep tissue penetration due to reduced light scattering and absorption by biological tissues [4]. They also have a high extinction coefficient (ε> 10^5 L·mol^{-1}·cm^{-1}), meaning they can efficiently absorb light and convert it into chemical energy [6-10]. Additionally, the photophysical and photochemical properties of phthalocyanines can be adjusted through chemical modifications, making them versatile for various therapeutic applications. To enhance the solubility and biocompatibility of MePc, they are often grafted with water-soluble polymers or copolymers. For example, some studies have successfully coupled metallophthalocyanines with polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP), resulting in water-soluble polymeric materials through the interaction of the -OH terminal groups of PEG [11] with the aromatic nuclei of the metallophthalocyanine [12]. Another example includes graft copolymers from N-vinylpyrrolidone (N-VP) oligomers with acryloyl chloride and zinc phthalocyanine, which have shown advanced photodynamic properties and solubility in DMSO-water solutions [13,14]. Chitosan, a natural polysaccharide, is frequently used in nanomedicine as a carrier due to its excellent biocompatibility, biodegradability, and possibilities for chemical modification [15,16]. Ke, M.R., *et al.* demonstrated that tetra-*α*-substituted ZnPcs exhibit reduced aggregation tendency, higher

photostability, and increased photocytotoxicity against human gastric carcinoma cells compared to tetra-*β*-substituted counterparts [17]. In another study, a nanocarrier, based on chitosan modified with polyethylene glycol-polylactic acid, was designed to improve the water solubility of ZnPc [18]. However, the drug encapsulation efficiency of the nanocarrier is limited by the amphiphilicity of modified chitosan, which is challenging to control.

The aim of this work was to develop natural chitosan polymers grafted with aminomethyl zinc phthalocyanine (AmPcZn), in weight percentages ranging from 5% to 60%, for photodynamic therapy applications, aiming to enhance the solubility, stability, and targeted delivery of ZnPc.

Experimental

Materials

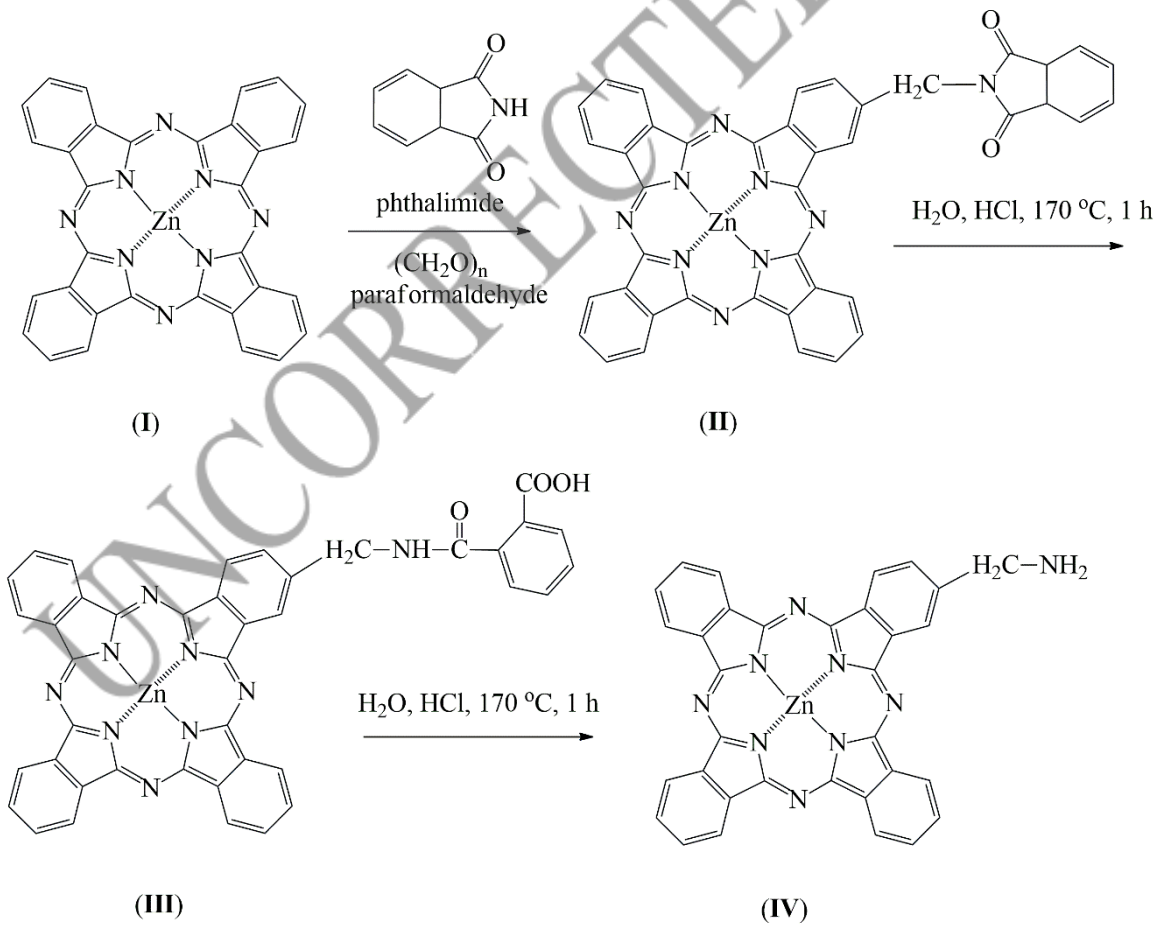
The reagents used were chitosan, phthalimide, HCl, dimethylformamide (DMF, anhydrous), paraformaldehyde, triethylamine, ethyl chloroformate, and diethyl ether, all purchased from Sigma-Aldrich.

Equipment

UV-Vis spectroscopy was performed using a Cary 300 UV-Vis spectrophotometer (Agilent Technologies) in the spectral range of 200–800 nm. This instrument, equipped with deuterium and halogen light sources and a photomultiplier detector, provides a spectral resolution of up to 0.1 nm and a photometric accuracy of ±0.005 Abs. FTIR spectra were recorded using a BRUKER ALPHA spectrometer in the 4000–400 cm^{-1} region, at room temperature, in the scientific research laboratory "Advanced Materials in Biopharmaceutics and Technics" of Moldova State University. ^{1}H-NMR spectra were recorded in DMSO-d_6 using a Bruker Avance III 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in ppm, with coupling constants (J) in Hz. The NMR analysis was conducted to confirm the chemical structure of AMZnPc by identifying the expected proton environments.

Synthesis of aminomethyl zinc phthalocyanine

The synthesis of aminomethyl zinc phthalocyanine (AmPcZn) was carried out according to the method described before [19], and is illustrated in Scheme 1.



Scheme 1. Synthesis of aminomethyl zinc phthalocyanine.

Steps of synthesis: Zinc phthalocyanine (I) reacts with paraformaldehyde and phthalimide to form compound (benzimidomethyl zinc phthalocyanine) (II), which easily transforms into (*o*-carboxybenzamidomethyl zinc phthalocyanine (III). In the final stage, when treated with HCl solutions (12% by mass), it is heated for four hours at a temperature of 170°C to form aminomethyl zinc phthalocyanine (IV). The total yield is about 72%.

Synthesis of chitosan-zinc aminomethyl phthalocyanine copolymers

The synthesis of chitosan–zinc aminomethyl phthalocyanine (AmPcZn) copolymers containing 5–60% AmPcZn by mass was achieved *via* a chemical grafting method, as depicted in Scheme 2. This process followed the methodology described in patent [19], with the exception that the intermediate product resulting from the treatment of chitosan with ethyl chloroformate and triethylamine was not isolated. Initially, 1.0 g of chitosan was dissolved in 50 mL of anhydrous dimethylformamide (DMF) under continuous magnetic stirring at 60°C for 1 hour, forming a homogeneous, viscous, and slightly opaque solution (Solution 1). This condition ensured adequate swelling and dispersion of chitosan in the organic solvent. Separately, 0.1 g of AmPcZn was dissolved in 50 mL of DMF to prepare Solution 2. To Solution 1, 0.25 mL of triethylamine was added under stirring at room temperature, followed by 0.20 mL of ethyl chloroformate after 20 minutes. The reaction mixture was cooled to 2–3°C and stirred for 10–15 minutes to activate the functional groups on chitosan. Solution 2 was then added dropwise, and the reaction was maintained under stirring for 15–20 minutes at room temperature, followed by continued stirring for 2–3 hours. The solvent was removed under vacuum to a final volume of approximately 15–20 mL (corresponding to 12–15% concentration), and the product was purified by precipitation in diethyl ether. A blue to dark blue-violet solid was obtained and dried to constant weight. The colour change confirmed the successful grafting of AmPcZn onto chitosan chains, supporting the chemical nature of the bonding, in agreement with the structures proposed in Schemes 2 and 3. The reaction yield was around 72%, and the resulting grafted copolymers were soluble in a DMSO–H_2O (1:1) mixture, in contrast to unmodified chitosan.

The synthesis of the copolymers from chitosan with AmPcZn was carried out according to Scheme 2 [20].

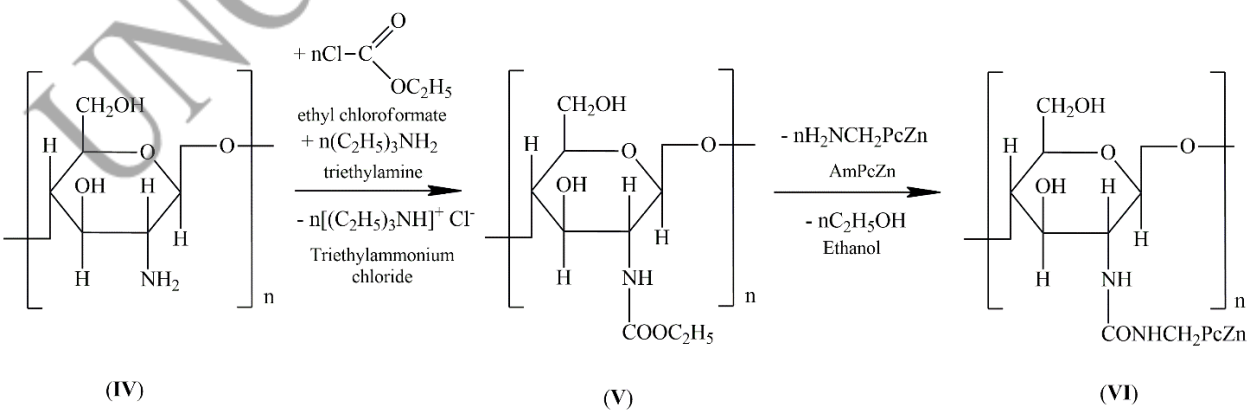
Results and discussion

To validate the formation of the metallophthalocyanine compounds (I, III, and IV), elemental analysis was performed, with particular focus on the nitrogen content - an essential element in the structure of these compounds. As shown in Table 1, the experimental nitrogen values are close to the theoretical ones, confirming the successful synthesis of the targeted compounds.

Table 1

Elemental analysis of ZnPc, AM-PcZn, and CBAM-PcZn.

Nr.	*Samples*	*Content, %*					
		N		*C*		*H*	
		Experimental	*Theoretic*	*Experimental*	*Theoretic*	*Experimental*	*Theoretic*
I	ZnPc	18.69	19.38	64.69	66.45	2.11	2.77
III	CBAM-PcZn	14.53	16.93	61.73	64.52	2.69	3.22
IV	AM-PcZn	19.16	20.72	66.02	65.14	2.83	3.29



Scheme 2. Grafting of aminomethyl zinc phthalocyanine onto chitosan.

For compound III (CBAM-PcZn), a significant decrease in nitrogen content is observed (from 16.93% to 14.53%), which can be attributed to the formation of a structure incorporating a terephthalic acid residue, thereby reducing the relative nitrogen proportion in the compound.

In contrast, compound IV (AmPcZn) shows an increase in nitrogen content up to 19.16%, supporting the formation of the aminomethyl derivative, which was subsequently used for grafting onto chitosan macromolecules.

The ^{1}H-NMR spectrum of the CBAM-PcZn compound exhibits distinct signals at 9.42, 8.27, 7.89, 5.46, 3.38 and 2.51 ppm. The signal at 9.42 ppm is highly deshielded and can be attributed to the protons located either on the extended aromatic system of the phthalocyanine core or to a weakly shielded amide proton. The signals at 8.27 and 7.89 ppm are characteristic of aromatic protons. Specifically, the signal at 7.89 ppm is assigned to the proton on the ortho-substituted benzene ring bearing –COOH and –CONH– groups, while the one at 8.27 ppm likely originates from the phthalocyanine aromatic core. A prominent signal appears at 5.46 ppm, corresponding to the amide proton (–NH–) of the benzamide moiety, which is typically observed in this region when measured in DMSO-d_6. At 3.38 ppm, a methylene (–CH_2–) signal is observed, attributed to the group bridging the phthalocyanine nucleus and the benzamide fragment through a nitrogen atom. Finally, the signal at 2.51 ppm is assigned to the DMSO-d_6 solvent used in the spectrum acquisition.

The ^{1}H-NMR spectrum of the AM-PcZn compound shows signals at 9.42, 8.27, 3.40, and 2.51 ppm. As in the case of CBAM-PcZn, the signal at 9.42 ppm can be attributed to the protons on the aromatic phthalocyanine ring, strongly deshielded due to the extended conjugation. The signal at 8.27 ppm is characteristic of aromatic protons, reflecting the conjugated structure of the phthalocyanine system. The signal at 3.40 ppm corresponds to the methylene group (–CH_2–NH_2), present in this compound. Finally, the 2.51 ppm signal originates from the DMSO-d_6 solvent.

When comparing the two spectra, it is evident that CBAM-PcZn has a more complex structure, as indicated by the higher number of signals and the presence of a characteristic amide proton signal at 5.46 ppm, along with an additional aromatic proton signal at 7.89 ppm, which is absent in the spectrum of AM-PcZn. This difference confirms the incorporation of the benzamide moiety into CBAM-PcZn and provides a clear structural distinction between the two zinc phthalocyanine derivatives.

In the study by Groves, E. *et al*., the authors separate the intermediate product (IV) before coupling it with compounds containing active NH_2, OH, and COOH groups [21]. In our proposed methodology, the separating step for intermediate (V) was omitted, and the synthesis was performed in a one-pot reaction without purification of the intermediate. Experimental results confirmed that this simplification does not significantly affect the grafting efficiency of AmPcZn onto chitosan, while significantly reducing the total reaction time.

Chitosan has useful properties for biomedicine, pharmacology, and wastewater treatment. Grafting of zinc aminomethyl phthalocyanine onto chitosan was achieved using ethyl chloroformate according to Scheme 2. The process consists of two stages. In stage one, chitosan reacts with ethyl chloroformate to form a slightly stable intermediate compound (V), which readily reacts with zinc aminomethyl phthalocyanine to form the final product (VI). To remove traces of AmPcZn, product (VI) is dissolved in water and filtered. After evaporating the water from the filtrate, the grafted copolymer Chitosan-AmPcZn, soluble in water, is obtained. The reaction yield is approximately 30%. For the first time, composition of the obtained polymer analogues Chitosan-AmPcZn with a content of zinc aminomethyl phthalocyanine from 5% to 60% was confirmed using FTIR spectroscopy.

As described by Zheng, B. *et al*, the process consists of two stages [8]. In the first stage, the product obtained from the interaction of chitosan with ethyl chloroformate in the presence of triethylamine is separated and dried in a vacuum flask. Subsequently, the reaction mixture is treated with a solution of zinc aminomethylphthalocyanine dissolved in DMF. The final product is purified by sedimentation and then dried in air and finally in a vacuum flask until a constant mass is achieved. Our study follows the procedure proposed by Zheng, B. *et al*. [9], conduct the synthesis in a single step. The intermediate product is cold treated with the solution of aminoderivative. The product obtained from the reaction between chitosan and AmPcZn was purified by water extraction. The resulting copolymer was first dissolved in distilled water under stirring at room temperature, forming a clear, viscous solution. After filtration to remove any insoluble residues, the aqueous phase was subjected to evaporation. The solid obtained after complete removal of water was dried to constant

mass. No precipitation in diethyl ether was performed at this stage. The final product, a water-soluble chitosan-AmPcZn grafted copolymer, corresponds to the structure shown in Figure 1.

The obtained copolymer was characterized by FTIR and UV-Vis spectroscopy to confirm the structure and the success of the grafting reaction. As can be observed in the FTIR spectra (Figure 2), for the grafted copolymer Chitosan-AmPcZn, new bands appear at 3050-3100 cm^{-1}, characteristic of the amide NH-CO-NH groups, confirming the chemical linkage between the amine groups of chitosan and the amine groups of zinc aminomethyl zinc phthalocyanine. The appearance of strong bands at 2500-2600 cm^{-1}, characteristic of NH^- groups, also confirms the presence of the Chitosan-AmPcZn chemical linkage, while 1600 and 1722 cm^{-1} signals are characteristic for C=O groups (Figure 3).

The completely different spectra of the mechanical mixture of chitosan with AmPcZn (80:20) (Figure 3), compared to that of the copolymer described above, confirms that a chemical reaction occurred during synthesis between the confirmed amine groups of chitosan and the amine groups of aminomethyl zinc phthalocyanine.

The UV-Vis spectra of chitosan-AmPcZn copolymer in DMSO, presented in Figure 4*(a)*, shows two broadened bands. The *Q*-band is split in two distinct peaks located at λ= 605 nm and λ= 715 nm. It can be observed that the absorbance increases with increasing AmPcZn concentration in the Chitosan-AmPcZn solution.

Comparing the Q and Soret bands positions with unsubstituted zinc phthalocyanine (ZnPc), at 672 nm and 343 nm, respectively, it can conclude that the substitution with amino methyl shift both B and Q bands in the UV and IR regions. The calibration curve in Figure 4(*b*) was plotted, depicting the variation in absorbance at a 715 nm wavelength as a function of AmPcZn concentration in the mixture, showing a good linear dependence which excludes the possibility of dimer formation over this concentration range.

This characteristic renders Chitosan-AmPcZn highly beneficial for use in photodynamic therapy and various other medical applications.

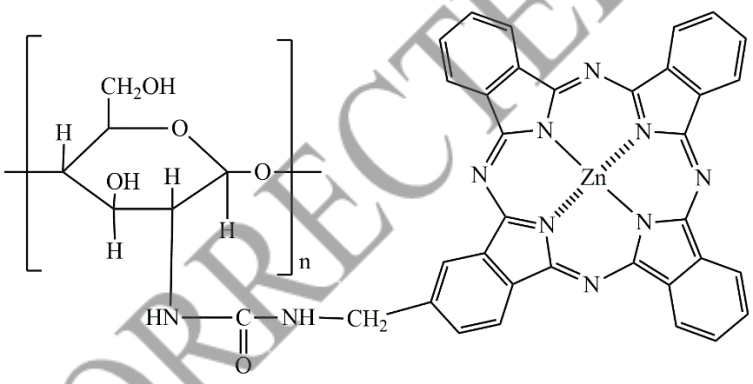


Figure 1. Structural formula of the copolymer Chitosan-AmPcZn.

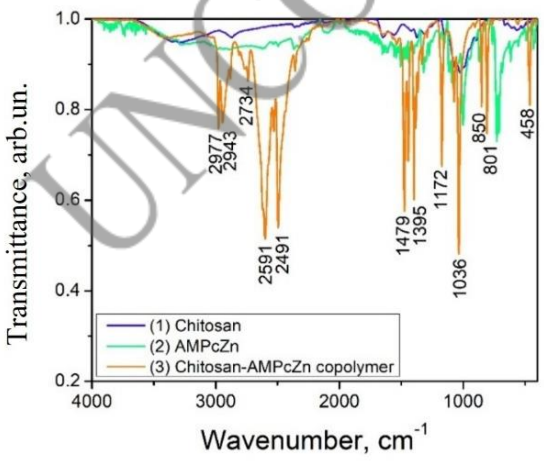


Figure 2. FTIR spectra of Chitosan (1), AmPcZn (2), and the copolymer Chitosan-AmPcZn with ratio 80:20 (3).

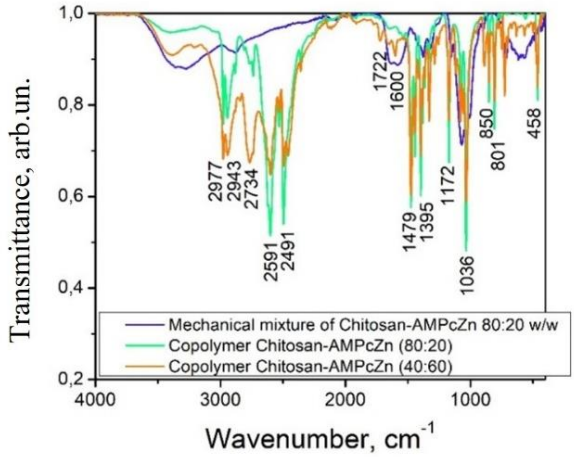
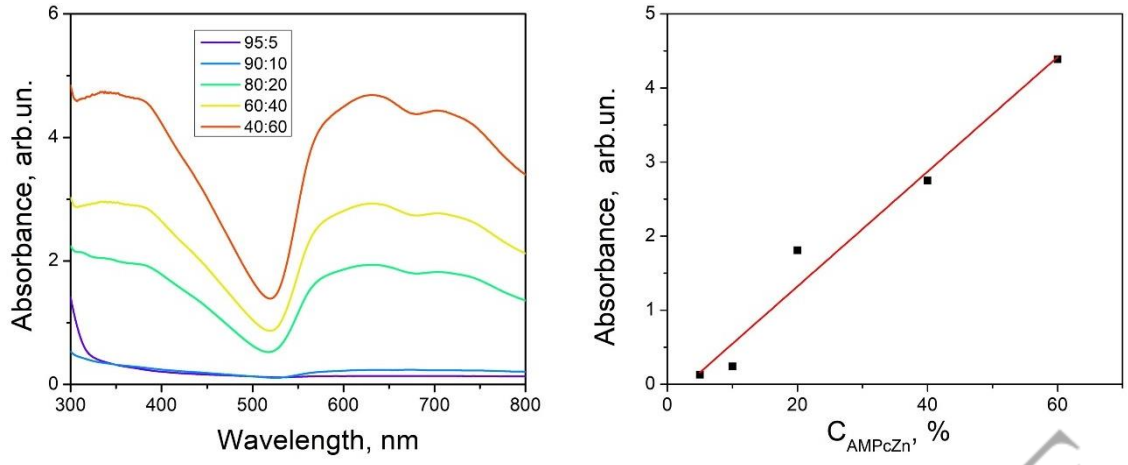


Figure 3. FTIR spectra of the copolymer Chitosan-AmPcZn (80:20) (1), the mechanical mixture of Chitosan-AmPcZn 80:20 w/w (2) and copolymer Chitosan-AmPcZn (40:60) (3).



(a) *(b)*

Figure 4. UV-Vis spectra of Chitosan-AmPcZn in DMSO solution *(a)* and calibration curve showing absorbance as a function of AmPcZn concentration in the copolymer at λ= 715 nm *(b)*.

Conclusions

Zinc aminomethylphthalocyanine was successfully synthesized using an original scheme, achieving a yield of over 72%. Additionally, grafted copolymers of chitosan with zinc aminomethylphthalocyanine were synthesized with AmPcZn contents ranging from 10% to 60% by mass. The chemical composition of these chitosan-AmPcZn copolymers was confirmed using FTIR spectroscopy, which revealed new vibrations at 3100–3200 cm^{-1} characteristic of -NH-CO-NH- groups, as well as distinct vibrations associated with $-NH_2$. From the calibration curve of Chitosan-AmPcZn, the composition of the copolymer was estimated. UV-Vis spectroscopy demonstrated that the chitosan-AmPcZn copolymers exhibited a broader Q band extending into the IR region beyond 800 nm, indicating their potential suitability for applications in photodynamic therapy.

Acknowledgments

This research paper was financially supported by the Ministry of Education and Research of the Republic of Moldova, subprogram "Design of supramolecular architectures based on metal phthalocyanine derivatives - functionalized nanoparticles for medicine", #011209.

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