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Amino acids substituted phthalocyanine complexes: an overview on the synthetic approaches and UV-vis properties related to photodynamic applications

V. Mantareva[1]*, M. Aliosman[1, 3], M. Durmuş[2], I. Angelov[1]

[1] *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*
[2] *Gebze Technical University Department of Chemistry, P.O. Box 141, Gebze 41400, Kocaeli, Turkey*
[3] *Institute of Physical Chemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*

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The photosensitizers with biologically active substituents such as amino acids feature one modern strategy to achieve the target- specific photodynamic therapy (PDT). The conjugations of metal phthalocyanines (MPcs) with amino acids or the related short peptides have been studied intensively with respect to PDT applications. The known MPcs with amino acids are recognized with membrane specificity in view of cell receptors or/and with electrostatic interactions based on the charge potential of membranes. This work aims to summarize at presently existing knowledge and our expertise in respect to synthesis and photophysicochemical properties of phthalocyanine complexes conjugated with amino acids for PDT applications.

Keywords: phthalocyanine complexes, amino acids, Click reaction, Sonogashira reaction, photodynamic therapy.

INTRODUCTION

The accelerating problem with drug-resistance towards the conventional therapies reinforces the research and development of new non-traditional curative strategies for combating different pathologic conditions [1–3]. The development of resistance is a consequence of overusing of chemotherapeutics and antibiotics which are leading to adaptation and finally to lowering the effectiveness of these drugs. Photodynamic inactivation (PDI) has been featured as an approach for urgent situation in fighting the life-threatening infections [1, 2]. The procedure includes the harmless drug (photosensitizer, PS) and irradiation with soft dose light of visible or infrared spectra (630–850 nm) for drug excitation [4]. The energy of absorbed light of a PS follows Jablonski diagram. In summary, the radiation transition of a PS goes from its lowest energy singlet excited state (S_1) to the ground state (S_o) by fluorescence. Two possible non-radiative transitions can happen, one of inner conversion between the singlet states and another conversion is the intersystem crossing to the triplet excited state PS. The long-lived triplet state PS can participate in photochemical reactions including the electron or proton transfer (type I mechanism). Most probable is an energy transfer from the triplet state PS to molecular oxygen with generation of reactive singlet oxygen (type II mechanism).

Phthalocyanine complexes (MPcs) conjugated with biologically active moieties have been featured as promising photosensitizers for PDT [5–7]. Nowadays, the complexes of Zn(II)-, Al(III)- and Si(IV)-phthalocyanines are well-known as promising second generation PDT drugs. One critical limitation of these compounds is their low selectivity, followed by undesirable photocytotoxicity. MPcs are related to the natural porphyrin but with the expanded structure of addition four benzene rings. This shifts the absorption in the phototherapeutic window (670–740 nm). The planarity and symmetry in the structure of MPcs allow easy functionalization in peripheral or non-peripheral positions, or at the coordinated ions [8]. Phthalocyanine molecule as a ligand can coordinate most of the metals and semimetals from the periodic table. Moreover MPcs are more studied than their metal free counterparts because of the superior photophysicochemical properties owning to the coordinated ions [9, 10]. The Pc-molecules characterize with very low solubility and high tendency to form photo non-activable spe-

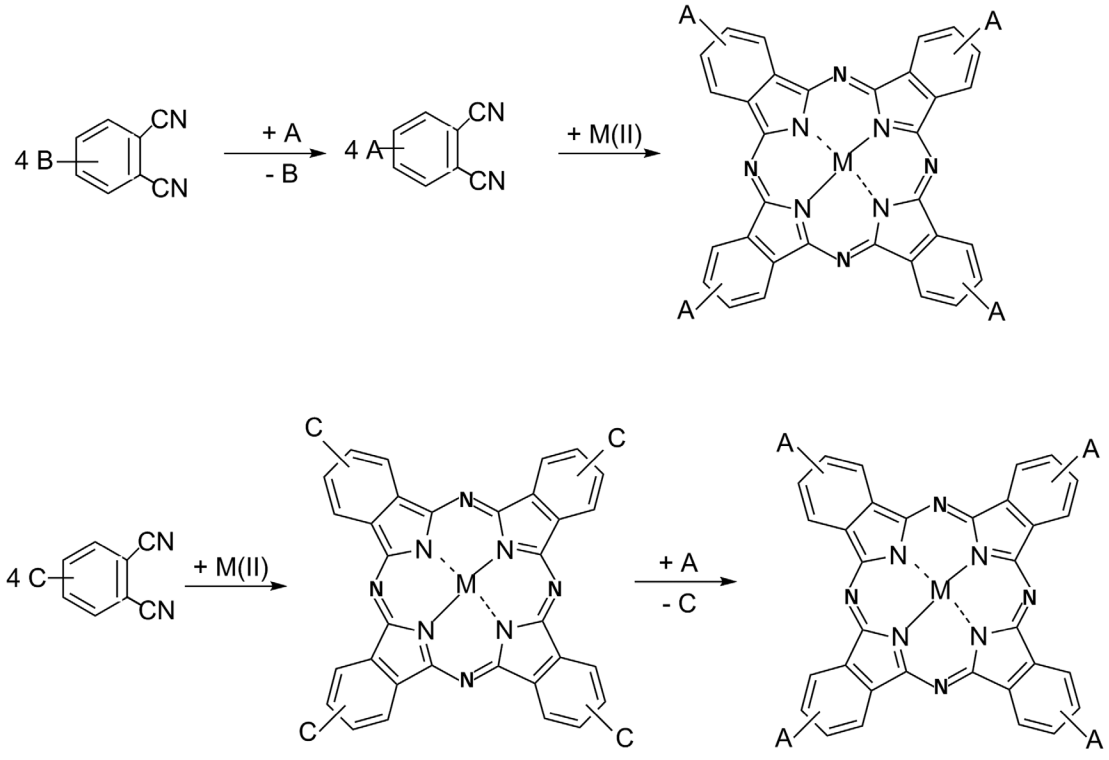
* To whom all correspondence should be sent:
E-mail: mantareva@yahoo.com

cies which is not in practical usage for biology and medicine. The proper functionalization of MPcs appears useful tool for improving their photophysicochemical properties [10]. The conjugation strategy with biomolecules such as amino acids (or short peptides) has been shown to have a great potential for enhancement of PDT properties [7]. The further improvement of MPcs includes the enhancement of their target specificity, localization ability and selectivity. Many efforts are made on the basis of Pc skeleton for structural modifications which include substitutions by different biologically-active and cell-specific molecules such as steroids [5], amino acids and short peptides [7], carbohydrates [11], and others [12].

SYNTHETIC APPROACHES FOR CONJUGATION OF PHTHALOCYANINES WITH AMINO ACIDS

There are two commonly used synthetic pathways which are applicable for preparation of functional phthalocyanine derivatives [13–15]. The so called "phthalonitrile pathway" is based on functionalization of phthalonitriles (Scheme 1**a**). The synthesis of starting phthalonitriles with substituents **A** (or AA) includes one or several steps staring from different phthalonitrile with substitution **B** and the followed up reactions lead to the desired substituted dinitrile. The second pathway known as "phthalocyanine way" includes the synthesis of Pc with reactive group C which further can be functionalized in a way to obtain the desired Pc with functional group A (Scheme 1**b**). The structural modifications on the phthalocyanine cycle can generally be performed by the insertion of hydrophilic groups or other functional substituents to the peripheral or non-peripheral position to the ring, or by changing the coordinating ion which can allow addition of bulky groups on axial position [16]. The mixtures of regioisomers which are not easy to separate are obtained in case of tetra- MPcs with peripheral substitutions [17]. Both approaches allow the synthesis of a variety of functionalized phthalocyanines conjugates with properties suitable for biomedical applications [18].

The phthalonitriles (1,2-dicyanobenzenes) are typical precursors for phthalocyanine synthesis. 1,2- Dicyanobenzene was firstly recognized as by-product of the synthesis of o-dicyanodiazoamidobenzene. In the early XX century the phthalonitrile was synthesized by refluxing acetic anhydride and phthalimide [19]. Since then several starting compounds are recognized as suitable precursors but differently substituted phthalonitriles are the most common in usage as precursors in synthetic phthalocyanine chemistry. The synthesis of precursors



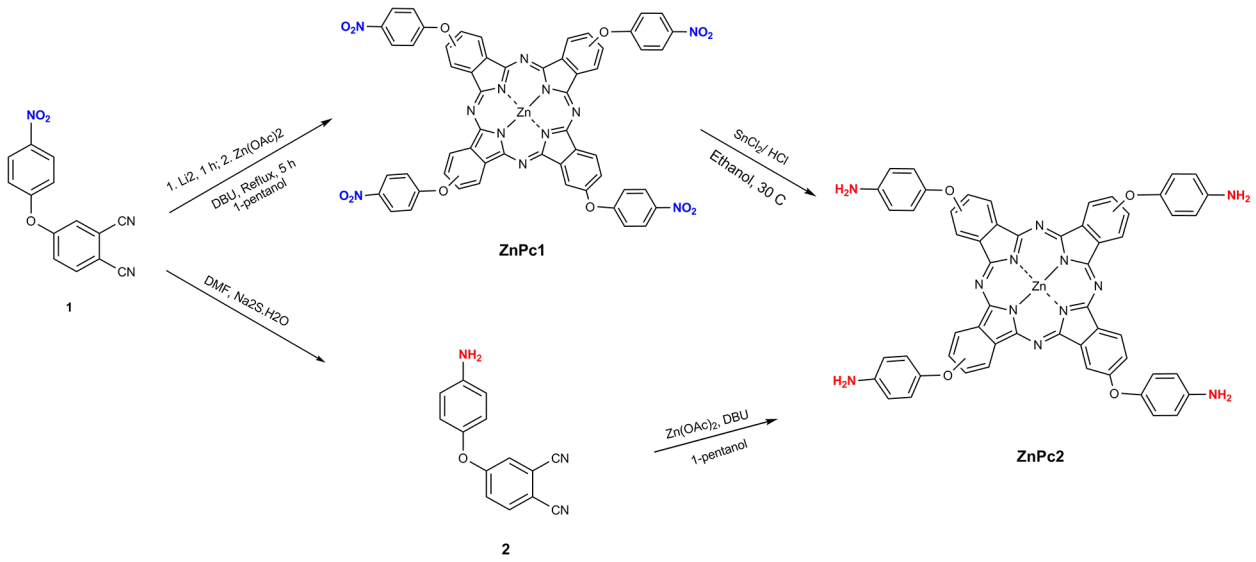
Scheme 1. Synthetic pathways for preparation of metallophthalocyanine conjugates in summarized version.

aims to obtain the starting compounds which are functional for amphiphilic, sterically hindered and soluble phthalocyanines [20, 21]. The synthetical approaches are quite common including the alcohol, base and metal salts [22]. The routine phthalocyanine synthesis starts by cyclotetramerization in a medium of alcohol and the related nucleophilic alkoxides being generated by the addition of non-nucleophilic bases such as quinoline, catalyst 1,8-diazabicyclo [5.4.0] undec-7-ene and the metal salt to serve as a template for the formation of Pc macrocycle. The expected substituted derivatives may be obtained by nucleophilic addition to the nitrile carbon atom; subsequently, the nitrogen atom will add to the other nitrile carbon atom. The second way includes the phthalonitrile molecule forming a *bis*-1,3-diiminoisoindoline which is instable compound and only a few derivatives are isolated for further studies. As mentioned above the metal ions are supposed to assist the cyclotetramerization of intermediates. The coordination, the reaction of nucleophilic additions, the elimination steps and further rearrangements resulted in formation of phthalocyanine core. Phthalocyanines without substituents are almost insoluble due to intermolecular interactions between the planar macrocyclic molecule which limits the investigation in solutions and the application in biomedicine.

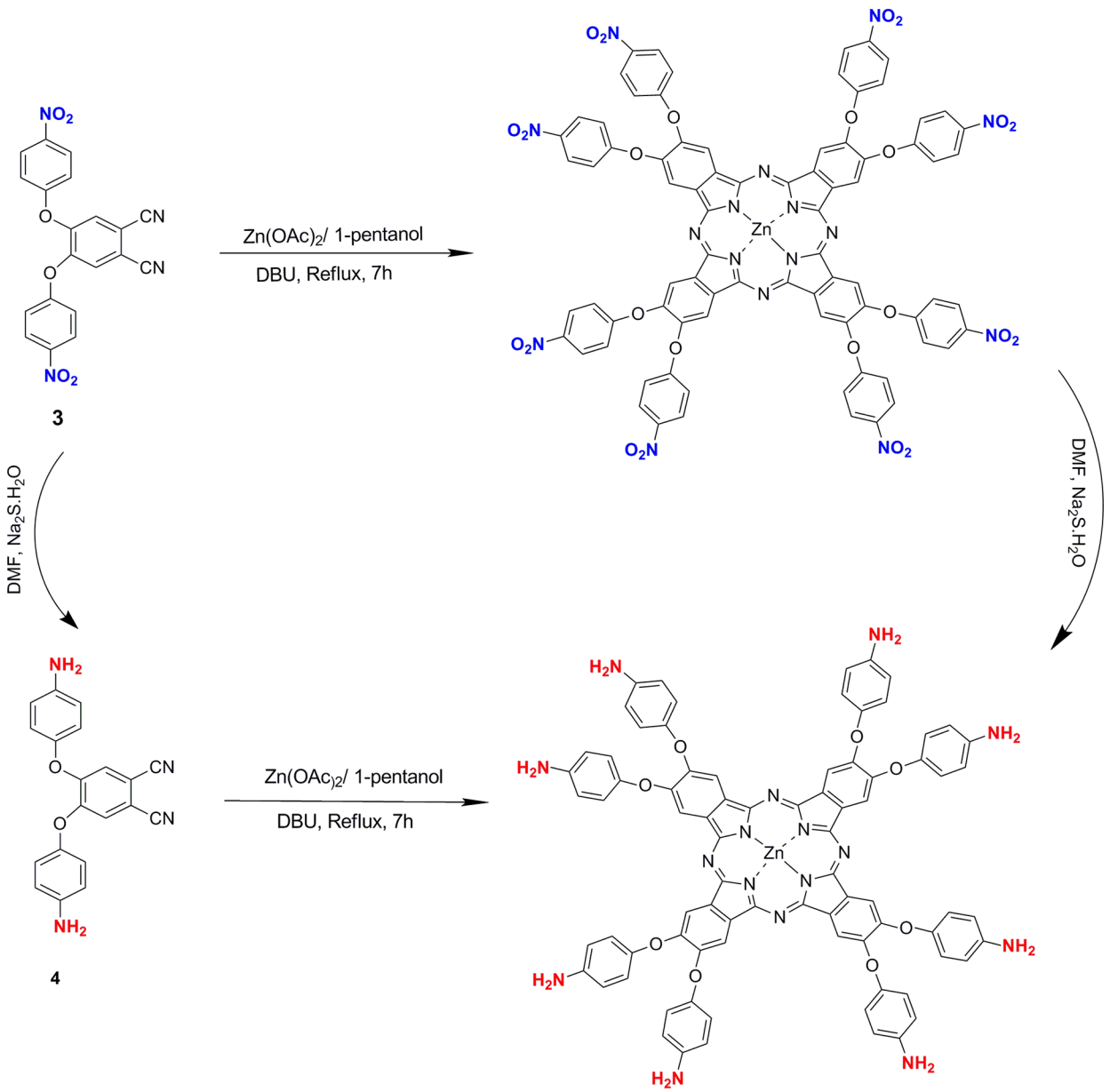
A straightforward pathway for synthesis of phthalonitriles suitable for conjugation *via* amide bond was recently proposed [23, 24]. The benefits are due to two unique molecules both with cell specific properties to facilitate the photodynamic process. The structure of amino acids includes carboxyl and amino groups which are thought to facilitate the solubility of conjugated MPcs in biological environment. The reduction of hydrophobic nature was suggested recently for ZnPcs conjugated with short peptides [25]. The biologically active peptides are well documented as suitable for functionalization with MPcs so that the final molecules are compatible in physiological conditions [26, 27]. The synthetical procedures for conjugation of phthalocyanines with biomolecules can include numerous synthetical mechanisms [28, 29]. The amide bond pathway is based on direct covalent binding (Scheme 2).

The "mirror" pathway for amide bounding includes carboxyl groups of MPcs and amino-groups from amino acids. This approach was used for conjugation between the phthalocyanine and other bioactive molecules. The addition of linker group between both molecules aims to improve the rigidity of the linker and facilitate the next reaction step. Moreover the usage of the linker assures the lack of steric hindrance which can obstruct the reaction of conjugation. The symmetrical tetra-substituted MPcs are more soluble than their octa-substituted analogues as a result of the formation of four regioisomers. However the regioisomers of tetra-substituted MPc are not easy to be separated.

The synthesis of octa-substituted phthalocyanine for conjugation with amino acids or short peptides can start from di-nitro or amino- substituted phthalonitriles in pentanol used as solvent/nucleophile (Scheme 3). However the low solubility issue leads to ineffective reaction way of direct cyclometization by using 1,2-amino-phthalonitrile as precursor [22]. The obtained product resulted in a single structure



Scheme 2. Synthetic pathways for preparation of *tetra*-aminophenoxy-substituted Zn(II)-phthalocyanine.



Scheme 3. Synthetic pathways for synthesis of *octa*aminophenoxy-substituted Zn(II)-phthalocyanine.

of the respected octa-substituted MPcs, which have better solubility and the bathochromic shifting of the absorbance in the Q bands to the near infrared region.

Most of the literatures about the conjugation of MPc with selected peptide units referred to the N-terminal position of the peptide forming a sulfonamide or amide bond [30]. However these approaches present some disadvantages if the conjugation of Pc at this position results in loss of peptide activity. The study of Ali et al. [27] reported the use of different Pd-catalyzed cross-coupling reactions (Sonogashira, Buchwald-Hartwig, and Suzuki-Miyaura) for preparation of the new MPc conjugates with selected peptides. The other possible reaction pathway involves the nucleophilic substitution reaction of s-triazine chloride with propargyl alcohol in the presence of NaH/ THF to obtain propargyl alkoxides substituted triazine [31]. This approach was often described for dual molecules with different functionality [32]. The Pc conjugation with amino acids (or short peptides) involves iodine substituted phthalonitrile to obtain the same substituted Pc and the next step is the reaction with triazine in the media of sodium ascorbate and copper sulphate at room temperature. The Cu^{I}-catalysed

azide–alkyne cycloaddition known as the "click" reaction has been developed for routine bioorthogonal ligation reactions with applications to biomaterial conjugation [33]. However, the cytotoxicity of the catalysts has hindered the common usage of this reaction especially in living systems. The "copper-free" click reaction has advantage of prevention the usage of the toxic Cu(I) ion which is not applicable for reactions with biological molecules especially within cells [34]. The solvent-free synthesis and the low-temperature synthesis as methods for synthesis of bioconjugates of phthalocyanines are well described for biologically active molecules [35–37]. Both can be featured as the future in the conjugation strategy for bioactive compounds with application as drugs. Moreover the harsh reactions condition such as toxic catalyst and high temperatures are not useful for substitution with amino functionalized MPcs including amino acids because of racemisation or hydrolysis that begin at high temperature and in the presence of the catalyst.

PHOTOPHYSICOCHEMICAL PROPERTIES OF AMINO ACIDS MPC-CONJUGATES

Properties of the singlet excited state

Phthalocyanines characterize with absorbance within the visible red and infra-red spectral region [38]. Typically the UV-vis spectrum has one sharp intensive Q-band (> 670 nm, $\varepsilon > 10^5$ $mol^{-1}.cm^{-1}$) and twice less intensive B-band (320–380 nm). The fluorescence spectra of MPcs are red shifted with small shift (8–20 nm) to the near infrared region (> 680 nm). The Q band is a result of the $\pi \rightarrow \pi^*$ transitions from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The B band is starting from the deeper π levels to LUMO transition with spectral region between 320–360 nm for known MPcs. The monomeric molecules of MPcs in solutions can be evidenced by a single (narrow) Q band in the electronic absorption spectra.

Our study with different newly synthesized ZnPcs bearing four amino acids at peripheral positions showed similarity in the absorption spectra (Fig. 1). For example conjugated ZnPcs with amino acids such as tyrosine and lysine showed maximum at ~682 nm which is red shifted by approx. 11–13 nm in respect to unsubstituted ZnPc (671 nm) for recorded UV-vis spectra in different solvents (Fig. 1a).

The similar studies of ZnPcs and SiPcs – peptide conjugates investigated in different solvents also showed the similar position of the absorption bands [39]. The spectra of the conjugates of MPcs with AA (or SPs) possess a single sharp Q band for monomeric molecules with bathochromic shift to the far red spectra. This is explained with the strong conjugation of the structure of molecule containing four, eight or one substitution to the Pc-ring. The known Zn (II)- and Si (IV)- Pcs conjugates in polar media such as buffer, showed a broad low intensity band at around 650 nm which suggested aggregation in water [40].

Recently synthesized by our group different ZnPcs with tyrosine and lysine moieties were studied to have fluorescence maxima bathochromicaly shifted (5–8 nm) in dependence on the solvents. The fluorescence emission spectra of these ZnPcs are presented in Figure 1b. As can be seen the excitation spectra were similar to absorption spectra and both of them represent the mirror images of

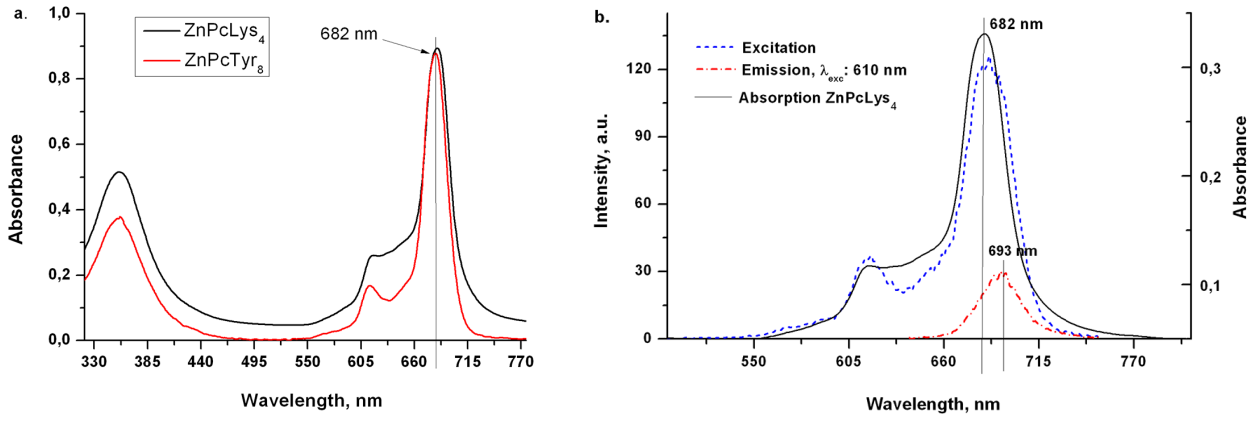


Fig. 1. UV-vis spectra of Zn(II)-phthalocyanine conjugated with amino acids: (**a**) Absorption spectra in DMSO and (**b**) fluorescence and excitation spectra of $ZnPcLys_4$ at exc: 610 nm.

the emission spectra with proves the purity of the studied ZnPcs conjugates. The studied compounds did not undergo the photodegradation during visible light excitation.

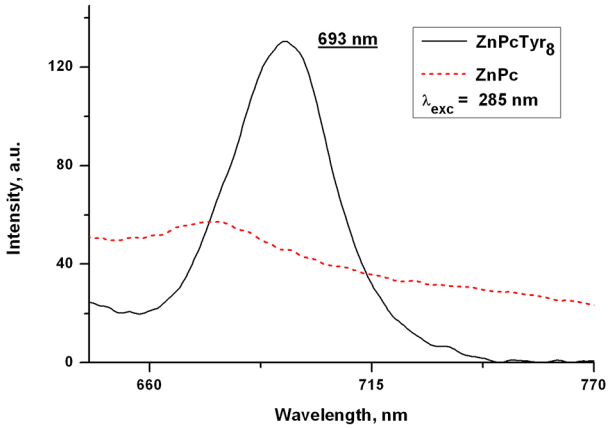


Fig. 2. Fluorescence spectra of a conjugate $ZnPcTyr_8$ (acceptor) and non-conjugate ZnPc, both recorded at exc: 285 nm as absorption maximum of Tyr (donor).

The theory considers that the non-radiative-energy-transfer (quenching) between a quencher and an energy donor proceeds in case of some extent overlap between the absorption spectrum of the quencher and the emission spectrum of the donor [38]. UV-vis study with our newly prepared ZnPc conjugates with tyrosine (ZnPcTyr) and lysine (ZnPcLys) showed the absorption spectra of ZnPc (acceptor) as a quencher and the energy of fluorescence emission of tyrosine molecules (donor) as can be seen in Figure 2. The observed spectral overlapping in the UV region (300–340 nm) suggests the possible energy transfer *via* mechanism Föster (FRET). The phenomenon of energy transfer may occur *via* the aminophenoxy linker between Pc-ring and amino acids. According to theory the distance up to 10 Å allows the energy transfer between two molecules [38]. The overlaps between absorption and fluorescence spectra are observed between spectra of both molecules of conjugate containing ZnPc and selected amino acids (Tyr or Lys). It can be concluded that for effective quenching, the energy levels of a phthalocyanine as quencher should be in a similar energy as the quenching biomolecules.

Singlet oxygen generation and photostability

The photocatalytic process of specific light applied to photosensitizer molecules in case of phthalocyanine is a generation of molecular singlet oxygen [10]. Type II pathway includes energy transfer between the triplet excited state of Pc molecule and the lowest energy state of molecular oxygen which is ground triplet state molecule. The produced other reactive oxygen species (ROS) are also in favour to the efficiency of PDT [12]. Among all possible ROS, it is only the singlet oxygen which is featured with the highest reactivity and harmful capacity towards biomolecules. Phthalocyanine macrocycle facilitates coordination with almost all of the metal and semimetal ions in the Periodic table [22]. The coordinated ion determines the properties of the triplet excited state molecules which are generated by irradiation with a proper light spectrum. The *d*-shell atoms with diamagnetic properties are achieving the optimal parameters of the triplet excited state MPcs. In addition the substitution of MPc with functional groups leads to physical quenching of the generated singlet oxygen. This phenomenon was also observed for our recently synthesized ZnPcs with amino acids tyrosine and lysine which aim to reduce the produced singlet oxygen (Fig. 3).

The photosensitizers for PDT should retain in the target tissue for proper time interval so that after receiving the suitable irradiation dose to initiate the photocatalytic reactions and the effect of photocytotoxicity. The procedure requires that the molecules to be stable without photobleaching activity for the duration of light exposure in order to be part of several cycles of photocatalytic reactions [41]. The high photostability is typical for most of the known MPcs. The presence of amide bond in the conjugated MPc complexes can lead to a limited thermal stability as well as chemical stability due to physiologically existing enzymes.

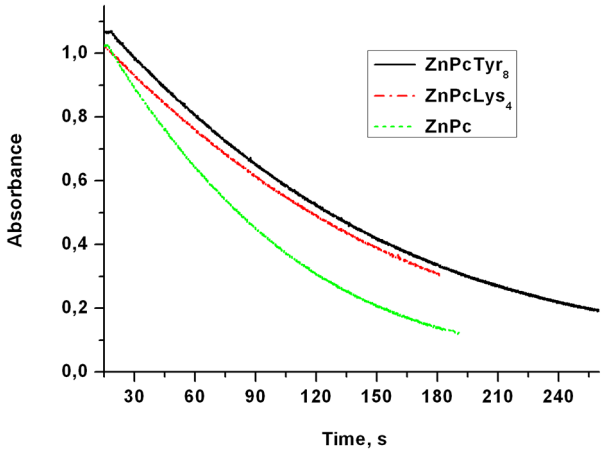


Fig. 3. Absorbance of DPBF at 417 nm as a result of singlet oxygen generation in the presence of ZnPc- amino acids conjugates and unsubstituted ZnPc for comparison.

CONCLUSIONS

A number of newly synthesized phthalocyanines conjugated with amino acids have been developed during the last decade, as well as in our research group. The newly developed ZnPc-amino acids conjugates have been synthesized by modification of different well-known synthetic pathways for chemistry of porphyrins and phthalocyanines. The ZnPc-amino acids conjugates are characterized with amphiphilic nature, with advanced photophysicochemical properties as well as an improved cellular uptake and membrane specific localization in tumor cells and pathogenic microbials. The studied optical properties are preconditions for the superior photodynamic action and finally highlight a higher PDT efficiency.

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АМИНОКИСЕЛИННИ ЗАМЕСТИТЕЛИ НА ФТАЛОЦИАНИНОВИ КОМПЛЕКСИ: ОБЗОР НА СИНТЕТИЧНИТЕ СХЕМИ И СПЕКТРАЛНИТЕ СВОЙСТВА С ПРИНОС КЪМ ФОТОДИНАМИЧНИТЕ ПРИЛОЖЕНИЯ

В. Мантарева[1]*, М. Алиосман[1, 3], М. Дурмуш[2], И. Ангелов[1]

[1] Институт по органична химия с Център по фитохимия, Българска академия на науките, 1113 София, България
[2] Технически университет в Гебзе, 41400 Кошаели, Гебзе, Турция
[3] Институт по физикохимия, Българска Академия на науките, 1113 София, България

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(Резюме)

Фотосенсибилизатори с биологично-активни заместители като аминокиселините се очертават като модерна стратегия за постигане на целева фотодинамична терапия (ФДТ). Конюгати на метални фталоцианинови комплекси (МФц) с аминокиселини или къси пептиди се отличават със свойства с принос към ФДТ. Известни МФцс с аминокиселини като заместители показват мембранна специфичност по отношение на рецептори и/или електростатични взаимодействия, основаващи се на заряда на мембраните. Настоящата работа има за цел да обобщи съществуващото научно познание както и нашия принос с нови фталоцианинови комплекси конюгати с тирозин и лизин както по отношение на синтеза, така и при изучаването на фотофизикохимичните им свойства за ФДТ приложения.