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Aminophenoxy-substituted zinc(II) phthalocyanines as basic photosensitizers for conjugation with biologically active moieties *via* amide bond

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Photodynamic therapy with a photosensitizer functionalized with biologically active compounds such as amino acids or short peptides appears to be a promising strategy for targeted-oriented therapy. The photodynamic process is based on effective action between a photosensitizer, atmospheric molecular oxygen and specific light from visible to near infrared spectra (630 – 850 nm). Thus results in generation of singlet oxygen and other reactive oxygen species which can oxidize the varieties of biomolecules with consequential photocytotoxicity. Particular functionalization of phthalocyanine macrocycle with biologically-active units as amino acids and peptides aims to improve the solubility of the molecule of phthalocyanine as well as to enhance the cellular uptake of the photosensitizer and to improve the selectivity to the pathogenic cells.

The study presents optimization of several synthetical pathways for synthesis of tetra- and octa- aminophenoxy substituted Zn (II) phthalocyanines which functional groups namely aminophenoxy- moiety is a suitable unit for coupling through amide bond.

Keywords: phthalodinitriles, photosensitizer, Zn (II) phthalocyanine, amide bond, photodynamic therapy

INTRODUCTION

The photosensitizer conjugation to different type biomolecules such as cell penetrating, cell specific or biologically active amino acids or short peptides has been well documented as successful method to enhance the selectivity, intracellular delivery and efficacy of photodynamic method [1-7]. Peptides are attractive molecules for drug functionalization due to their relatively small size (<50 amino acid residues) which make them non-immunogenic, with a good tissue penetration, including crossing malfunctioning blood-brain barrier, and many of them interact with a given biological target without eliciting significant toxic responses. Peptides can be easily modified, allowing alterations in the sequence and straightforward conjugation to other chemical substances including phthalocyanine photosensitizers [8-10].

Phthalocyanines (Pcs) have been developed as a prospective second generation photosensitizers for biomedical applications, especially the metal complexes (MPcs) coordinated with diamagnetic ions [11-13]. The known MPcs show strong absorption (extinction coefficient $\varepsilon > 10^5$ M^{-1} cm^{-1}) at far red wavelengths (> 670 nm) and strong singlet oxygen generation abilities. The macrocyclic molecule is flexible to structural modifications which allow the binding on peripheral or non-peripheral position of different functional groups and also at the central metal ion for the metals with higher that 2 coordination number. It is also possible to bind bulky axial substitution groups. The photophysicochemical properties of MPcs are strongly dependent on the substituents around the Pc aromatic core or the central ions. The proper functionalization of MPc macrocycle aims to intense the absorption in the red region of visible light, to have non-toxic effect in the absence of light, to be selective for the targeted cells and to the normal tissue with an efficient generation of singlet oxygen. A large number of new photosensitizers have been proposed for clinical PDT; however their properties have still several limitations [14, 15].

Amino groups have ability of strong interaction and moreover the covalent bonding with biologically active molecules through carboxylic group. Hence, they are preferred functionalizations for preparation of pathogenic cell targeting photosensitizer [16].

One possible synthetical pathway for preparation of amino- substituted phthalocyanines started from synthesis of amino- substituted phthalodinitriles as precursors followed by cyclotetramerization reaction. Nyokong et. al. successfully synthesized tetraaminophenoxy substituted In(III) phthalocyanine in quinoline in the presence of urea [17].

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Most of the reported amino- substituted phthalocyanines involved phthalocyanine formation from nitro- substituted phthalodinitriles followed by cyclotetramerization reaction to obtain nitro-substituted phthalocyanine and by reduction to the amino- substituted phthalocyanines. There are reports about the possible reaction routes for synthesis of aminophenoxy- functionalized zinc(II) phthalocyanines [18-22]. Wohrle and co-authors obtained tetra aminophenoxy substituted Zn(II) phthalocyanine by reduction of the nitro analogs with $SnCl_2$ [18]. The group of Prof. Ahmet Gul obtained the aminophenoxy phthalocyanine by reduction of the nitro groups using hydrazine hydrate and 10% Pd/C [21]. Nyokong et. al. synthesized the octa- aminophenoxy substituted phthalocyanine by the reduction of nitro analogs with sodium sulfide nonahydrate [20]. The applications of phthalocyanine complexes as photosensitizers require the use of biocompatable and diamagnetic metal ions to obtain the phthalocyanine complexes for PDT.

The study presents the optimization of the synthetical pathways for synthesis of tetra- and octa- aminophenoxy- substituted Zn (II) phthalocyanines. The altering of the reaction conditions of the chemical procedures was applied in order to obtain high yield and purity of the target compounds.

EXPERIMENTAL

General

All reagents and solvents were of reagent-grade quality obtained from commercial suppliers. All solvents used for synthesis such as dimethylformamide (DMF), tetrahydrofuran (THF), 1-pentanol were dried or distilled and stored over molecular sieves (3 Å) before experiments. The salt zinc acetate (hydrate)$_2$ was dried in Glass oven over P_2O_5. The catalyst 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as received. The purity of the products was tested in each step using thin layer chromatography (TLC). Silica gel 60 Å was purchased from Merck. All reactions were carried out under nitrogen atmosphere. FT-IR spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer. ^{1}H NMR spectra were recorded on a Varian 500 MHz spectrometer (Gebze Technical University, Turkey) in DMSO-d_6,$CDCl_3$-d_1 for compounds **1**, **2**, **2a** and on Bruker 600 MHz spectrometer (Institute of Organic Chemistry with Centre of Phytochemistry) in DMSO-d_6 solutions for compounds **1a**,**3**,**4**,**5**,**6**.

Synthesis

*Synthesis of 4-(4-nitrophenoxy) phthalonitrile (**1**)*

4-Nitro phthalonitrile (1 g, 5.78 mmol) was dissolved in dry DMF and 4-nitrophenol (0,960 g 6.93 mmol) was added and stirred at room temperature under nitrogen atmosphere. Dry, powdered K_2CO_3 (800 mg, 5.79 mmol) was added as a base. After 24 h second portion K_2CO_3 (800 mg, 5.79 mmol) was added. The mixture was stirred until the ending of the starting 4-nitro phthalonitrile. Reaction was monitored by TLC. Then the reaction mixture was poured into ice water and stirred for 15 minutes. The obtained white precipitate was filtered off, washed several times with cold water dried under vacuum at 80 ^{0}C. Yield: 1.4 g (91 %). Molecular formula: $C_{14}H_7N_3O_3$. Molecular weight: 265,22 g/mol. FT-IR [ν_{max}/cm^{-1}]: 3108, 3078, 3037 (CH arom), 2232 (-C≡N), 1580, 1343 (-NO_2), 1512, 1481 (ARC=C), 1246 (Ar-O-Ar), 1309, 1213, 948, 849, 758; ^{1}HMR (d_1-$CDCl_3$), δ, ppm: 8.39-8.35 (d, 2H, CH), 7.87-7.85 (d, 1H, CH), 7.45 (d, 1H, CH), 7.40-7.38 (d, 1H, CH), 7.24-7.22 (d, 2H, CH).

*Synthesis of 4-(4-aminophenoxy) phthalonitrile (**1a**)*

4-Nitro phthalonitrile (1 g, 5.78 mmol) and 4-aminophenol (0.693 g, 6.35 mmol) were put in a round bottom flask and dry DMF was added while stirring. Dry potassium carbonate (1.6 g 11.56 mmol) was added when the mixture above became clear and after 24 h second portion potassium carbonate (0.800 g 5.78 mmol) was added. The reaction was carried out under argon atmosphere for 48 h. Then the solution was poured into ice water. The precipitated solid product was filtered off, washed with excess of water and then dried in a vacuum at 50 ^{0}C. Yield: 1.3g (91 %). Molecular formula: $C_{14}H_9N_3O$, Molecular weight: 235.25 g/mol. FT-IR [ν_{max}/cm^{-1}]: 3456, 3375 (NH_2), 3108, 3073, 3047 (CH arom), 2236 (-C≡N), 1598, 1608 (NH), 1508, 1485 (ARC=C), 1204, 1253 (C-O-C). ^{1}H-NMR (d_6-DMSO), δ, ppm: 8.03-8.01 (d, 1H, CH arom), 7.60-7.59 (d, 1H, CH arom), 7.25-7.23 (dd, 1H, CH arom), 6.86-6.83 (dt, 2H, CH arom), 6.64-6.62 (dt, 2H, CH arom), 5.17 (s, 2H, NH_2).

*Synthesis of 4,5 bis (nitrophenoxy) phthalonitrile (**2**)*

The reaction was carried out at different reaction conditions such as time, temperature and ratio in order to improve the purity and yield. A solution of 4,5-dichlorophthalonitrile (1 g, 5.08 mmol), and p-nitrophenol (2.11 g, 15.24 mmol) in dry DMF was heated while stirring at 90 ^{o}C under argon

atmosphere with the presence of dry K_2CO_3 (5,52 g 40 mmol) which was added in portions. Reaction was monitored by TLC. After finishing the starting phthalonitrile the reaction mixture was added to ice water to get precipitation and was filtered off, washed with excess of water. Obtained product was purified with column chromatography with eluent dichloromethane. Yield: 0.200 g (10%). Molecular Formula: $C_{20}H_{10}N_4O_6$, Molecular weight: 403 g/mol. FT-IR [ν_{max}/cm^{-1}]: 3105, 3077, 3037 (CH arom), 2238 (-C≡N), 1581, 1345 (NO_2), 1519, 1482 (ArC=C), 1271 (Ar-O-Ar). ^{1}H-NMR (d_6-DMSO), δ, ppm: 8.30-8.29 (d, 4H, CH arom), 7.52 (s, 2H, CH arom), 7.06-7.04 (d, 4H, CH arom).

*Synthesis of 4,5 bis (aminophenoxy) phthalonitrile (**2a**)*

A solution of (1 , 5.08 mmol) 4,5-dichlorophthalodinitrile and (1.66 g, 15.2 mmol) aminophenol in dry DMF was heated while stirring at 90 °C under argon atmosphere with the presence (5.52 g, 40 mmol) dry K_2CO_3 which was added in portions. The mixture was stirred until finishing the starting nitrile, and then the reaction mixture was added to ice water to precipitate and filtered off, washed with excess of water. The obtained crude product was purified by column chromatography with eluent dichloromethane /acetone (9:1) Yield: 0.880 g (51%). FT-IR [ν_{max}/cm^{-1}]: 3443, 3355 (-NH_2), 3110, 3047, 3000 (CH arom), 2226 (-C≡N), 1581, 1495 (ArC=C), 1204 (C-O-C). ^{1}HMR (d_6-DMSO), δ, ppm: 7.29 (s, 2H, CH), 6.85 (d, 4H, CH arom), 6.62 (d, 4H, CH arom), 5.15 (4H, NH_2).

*Synthesis of 2(3), 9(10), 16 (17), 23(24) tetra (4-nitrophenoxy) substituted Zn (II) phthalocyanine (**3**)*

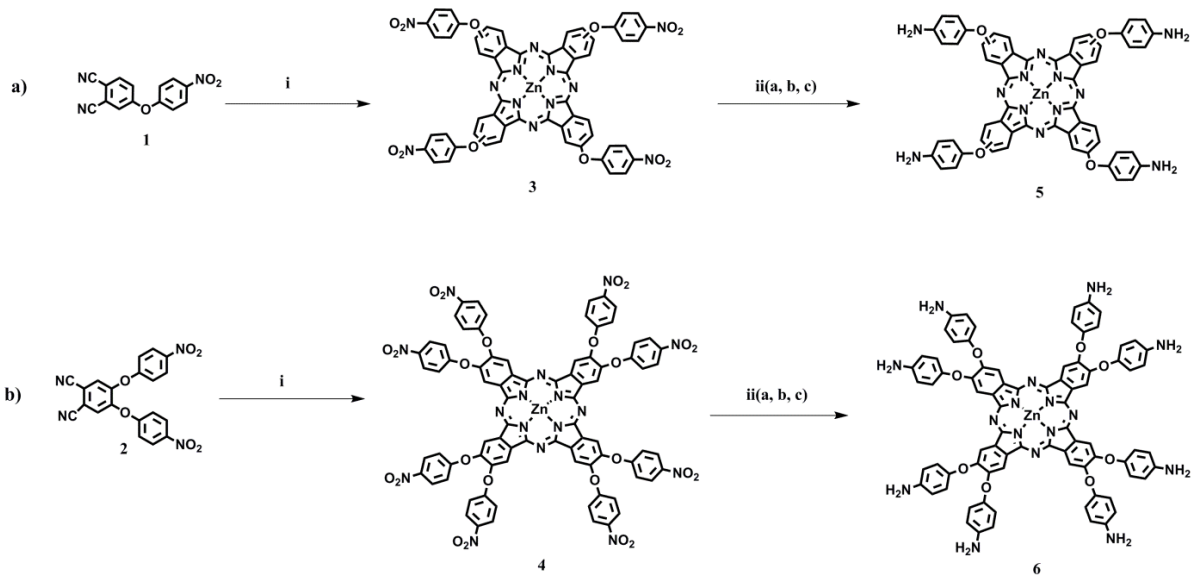
The mixture of 920 mg (3.47 mmol) of compound **1**was dissolved in 4 mL 1-pentanol and 158 mg (0.86 mmol) anhydrous zinc(II) acetate and 12 drops of DBU were added and stirred at reflux under nitrogen atmosphere. The reaction was monitored by TLC. When the reaction finished, then reaction mixture was cooled to room temperature from 137 °C and precipitated in hexane, filtrated and washed with excess of hexane, methanol and ethanol. The obtained crude product was purified by column chromatography with eluent $CHCl_3$/THF (10:1.5) Yield: 680 mg (69%). Molecular Formula: $C_{56}H_{28}N_{12}O_{12}Zn$, Molecular weight: 1126.29 g/mol. FT-IR [ν_{max}/cm^{-1}]: 2928 (CH arom), 1644, 1586, 1339 (NO_2), 1514, 1487 (ArC=C), 1393, 1236, 1110, 1084, 942, 847, 726. UV-Vis (DMF) λ_{max} (log ε): 675 (4.07), 610 (3.31), 350 (3.71). ^{1}HMR (d_6-DMSO), δ, ppm: 8.47-8.40 (m, 6H, CH Ar , 8.35-8.29 (m, 6H, CH Ar), 7.96-7.90 (m, 4H, CH Ar)), 7.73-7.53 (m, 10H, CH arom), 7,33-7.30 (d, 2H, CH arom).

*Synthesis of 2,3,9,10,16,17,23,24 octa nitrophenoxy substituted Zn(II) phthalocyanine (**4**)*

830 mg (1.97 mmol) 4,5 bis (nitrophenoxy) phthalonitrile **2** was dissolved in 4 mL 1-pentanol and then 90 mg (0.49 mmol) anhydrous zinc(II) acetate and 14 drops DBU were added and stirred under reflux at nitrogen atmosphere. The reaction was monitored with TLC. Then reaction mixture was cooled to room temperature and precipitated in hexane, filtrated and washed with excess of hexane, methanol and ethanol. The obtained crude product was purified by column chromatography with eluent $CHCl_3$/EtOH (10:1) Yield: 680 mg (82 %). Molecular Formula: $C_{80}H_{40}N_{16}O_4Zn$. Molecular weight: 1674,67 g/mol. FT-IR [ν_{max}/cm^{-1}]: 3099, 3075(CH arom), 1520, 1342(NO_2), 1515, 1488 (ArC=C), 1217. UV-Vis (DMF) λ_{max} (log ε): 675 (3.34), 645 (2.42), 610 (2.42), 350 (3.11). ^{1}HMR (d_6-DMSO), δ, ppm: 8.74 (s, 4H, CH arom), 8.22-8.20 (m, 17H, CH arom), 7.95 (s, 1H, CH arom), 7.81 (s, 2H, CH arom), 7.40 (s, 12H, CH arom), 7.20-7.19 (d, 4H, CH arom).

*Synthesis of 2(3), 9(10), 16 (17), 23(24) tetra (4-aminophenoxy) substituted Zn (II) phthalocyanine (**5**)*

520 mg (0.46 mmol) of compound **3** was dissolved in dry THF, then (40 mg) Pd/C was added and stirred under hydrogen atmosphere at ice bath. The reaction was monitored by TLC. Reaction mixture was filtrated to remove the Pd/C and washed with excess of DMF and the solvent was vacuum evaporated with pump. Yield: 280 mg (70 %). Molecular Formula: $C_{56}H_{36}N_{12}O_4Zn$; Molecular weight: 1006,36 g/mol. FT-IR [ν_{max}/cm^{-1}]: 3351, 1603 (NH), 2925,2855 (CH arom), 1505, 1483 (ArC=C), 1392, 1335, 1260, 1234. UV-Vis (DMF) λ_{max} (log ε): 685 (3.01), 615 (2.26), 350 (2.89). ^{1}HMR (d_6-DMSO), δ, ppm: 7.95 (s, 6H, CH arom), 7.77-7.75 (d, 2H, CH arom), 7.25-7.24 (d, 4H, CH arom), 7.05-7.04 (d, 3H, CH arom), 6.87-6.85 (d, 6H, CH arom), 6.65-6.64 (d, 7H, CH arom) 5.16 (s, 8H, NH_2).



Scheme 1a, b. Reaction routes for synthesis of tetra- and octa- aminophenoxy substituted Zn(II) phthalocyanines. Reagents and conditions for procedures:**a)** and **b) (i)** Zn acetate, DBU, 1-pentanol; **(iia)** dry DMF, H_2, Pd/C, ice bath; **(iib)** Ethanol, $SnCl_2$/ HCL; **(iic)** DMF, $Na_2S.H_2O$.

Synthesis of 2,3,9,10,16,17,23,24 octa aminophenoxy substituted Zn(II) phthalocyanine (6)

500 mg (0.31 mmol) of compound **4** was dissolved in dry DMF, then (80 mg) Pd/C was added and stirred at ice bath under hydrogen atmosphere. The reaction was monitored by TLC. Reaction mixture was filtrated to remove the Pd/C and washed with excess of DMF and the solvent was vacuum evaporated. Yield: 400 mg (90 %). Molecular Formula: $C_{80}H_{56}N_{16}O_8Zn$, Molecular weight: 1434 g/mol. FT-IR [ν_{max}/cm^{-1}]: 1613 (NH), 1504, 1399 (ArC=C), 1200, 1079. UV-Vis (DMF) λ_{max} (log ε): 679 (3.52), 647 (2.96), 615 (289), 301 (3.73). ^{1}HMR (d_6-DMSO), δ, ppm: 8.22-8.20 (m, 20H, CH arom), 7.20-7.19 (d, 20H, CH arom), 4.37 (s, 16H, NH).

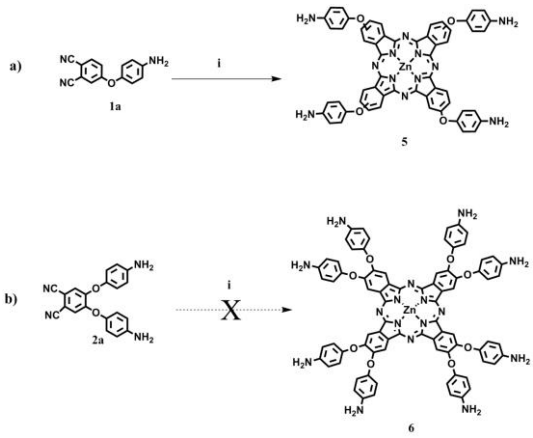
RESULTS AND DISCUSSION

Synthesis and characterizations

Two different reaction pathways were applied to obtain the desired tetra- and octa- aminophenopxy Zn(II) phthalocyanines (**Scheme 1** and **2)**. First reaction route shown in Scheme 1 started with synthesis of the corresponding nitrophenoxy-substituted phthalodinitriles, followed by the formation of the phthalocyanine molecules and by reduction of the nitro units to obtain the desired zinc(II) aminophenoxy substituted phthalocyanines. Synthetic procedure of nitrophenoxy substituted phthalonitriles is presented in **Scheme 1a and 1b.** The starting compounds 4-(4-nitrophenoxy) phthalonitrile **(1)** and 4,5-bis-(nitrophenoxy)-phthalonitrile **(2)** were prepared by modification of the known reaction procedure described elsewhere [20, 23]. Compounds **(1)** and **(2)** were synthesized with the starting 4-nitrophthalonitrile and 4, 5-dinitrophthalonitrile and p-nitrophenol in presence of K_2CO_3 in dry DMF under nitrogen atmosphere. The base catalyzed nucleophilic aromatic displacement reaction takes place. To obtain compound **(2)** different reaction conditions such as time, temperature and ratio in order to have high purity and yield were tried. The most proper reaction pathway is shown in **Scheme 1b**. The IR spectra of **(1)** and **(2)** confirmed the characteristic vibrations of the -C≡N stretching with sharp and narrow peak at position at 2232 cm^{-1}and also the characteristic vibrations of NO_2 group at positions 1345, 1580 cm^{-1} and 1345, 1581 cm^{-1}, respectively. The ^{1}H-NMR spectra of the phthalonitriles **(1)** and **(2)** were consistent with the predicted structures.

Tetra and octa nitrophenoxy- substituted Zn(II) phthalocyanines were synthesized according to the literatures [20-22]. The cyclotetramerization of the compounds **(1)** and **(2)** was carried out in the presence of anhydrous $ZnCl_2$ and DBU as catalyst in 1-pentanol at 140 °C under nitrogen atmosphere (**Scheme 1a and 1b)**. The IR spectra of Zn(II) phthalocyanines **(3)** and **(4)** clearly indicates the cyclotetramerization of the phthalonitrile derivatives **(1)** and **(2)** with the disappearance of the -C≡N peak at 2232 cm^{-1}. The ^{1}H-NMR spectra of the starting phtalonitriles **(3)** and **(4)** were consistent with the predicted structures.

Tetra- and octa- aminophenoxy substituted Zn(II) phthalocyanines **(5)** and **(6)** were synthesized by reduction of the nitro groups of compounds **(3)** and **(4)** with reaction procedures which is given in **Scheme 1a** and **b**. Several reduction procedures with different reducing agents were tested namely Na_2SxH_2O (a) and tin dichloride/HCl (b) which resulted to compounds **(5)** and **(6)** [18-22]. The most efficient reduction method was the reaction procedure of bubbling hydrogen gas in nitro-phthalocyanine solution in the presence of 10% Pd/C at ice bath. This synthetical approach was described for the first time in this study (**Scheme 1a** and **b, iia**). In the IR spectra of compound **(5)** and **(6)** the $–NH_2$ group was observed as strong peaks at 1603 and 1618 cm^{-1}, respectively and the characteristics NO_2 groups were disappeared which clearly established the formation of the target compounds. The ^{1}H-NMR spectra of **(5)** and **(6)** in deuterated DMSO solutions showed broad singlet band attributed to the $–NH_2$ protons at 5.16 and 4.37, respectively.



Scheme 2a, b. Synthethic routes of tetra- and octa-aminophenoxy substituted Zn(II) phthalocyanines. Reagents and conditions for procedures: **a)** and **b) (i)** Zn acetate, DBU, 1-pentanol.

Zn(II) phthalocyanines **(5)** and **(6)** were obtained by the second pathway which is shown in **Scheme 2a and b.** In this case the starting phthalonitriles were directly used for cyclotetramerization reaction. This allows reducing the step of the reduction reaction. For this reason the phthalonitriles **(1a)** and **(2a)** were prepared. Compound **(5)** was successfully obtained from the phthalonitrile **(1a)** in presence of anhydrous $ZnCl_2$ and DBU as catalyst in 1-pentanol at refluxing temperature under nitrogen atmosphere. However the obtained crude product was with limited solubility. Zn(II) phthalocyanine **(6)** was not obtained from the phthalonitrile **(2a**). Different reaction conditions were selected to obtain the compound **(6)** such as solvent, temperature, presence of catalyst and without catalyst and metal salt ($ZnCl_2$) to speed the complex formation. Another pathway by passing through metal free phthalocyanine was also carried out, but the reaction was not completed. The possible reasons could be the high reactivity of the amino groups which tent to form hydrogen bond between them and also of the steric hindrance effect. Therefore this synthetic pathway was not sufficient.

Ground state electronic absorption and fluorescence spectra

The electronic absorption spectra of Zn(II) phthalocyanines **(5)** and **(6)** were recorded in DMF on a Perkin Elmer Lambda 25 UV/Vis Spectrometer. (Fig.1). They showed characteristic absorption bands in the visible region with absorption maximum at 683 nm for compound **(5)** and 679 nm for compound **(6)**, respectively. In the UV region the second B band was recorded. ZnPc **(5)** was observed with band at around 350 nm with half of the intensity of absorption of the Q band. A sharp and intense B band at around 375-378 nm was observed for ZnPc **(6)**. The obtained spectra showed monomeric behavior which is evidenced by a single, narrow Q band typical for metallated phthalocyanine complexes.

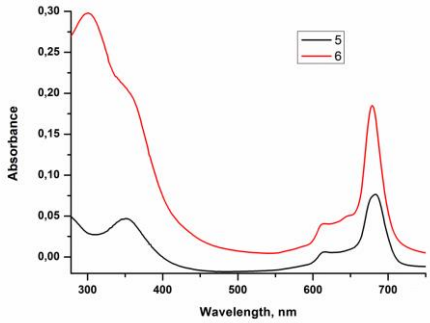


Fig.1. Absorption spectra of Zn(II) phthalocyanines **(5)** and **(6)** in DMF at concentration 12 μM.

In phthalocyanine chemistry the aggregation is usually depicted as a coplanar association of rings or physical conjugation throughout the substituents which are progressing from monomer molecule to dimer and higher associate of molecules. This phenomenon depends on the concentration, nature of the solvent, substituents, central metal ions and temperature [24]. The formation of oligomers of phthalocyanines for PDT usage should be avoided because of the lack of the proper photochemistry such as life-time and quantum yield of the triplet state of the photosensitizer. In order to evaluate the aggregation behavior of the studied ZnPc **(5)** and **(6)** the Beer's law was proven. The absorption

spectra were recorded in DMF for the concentration range between 3-16 μM for compound **(5)** and 12-2 μM for compound **(6)** in room temperature. The recorded spectra showed that, the intensity of the Q band increased with increment of the concentration. The new bands did not occur which suggested the lack of the formation of aggregates.

Fluorescence emission spectra of compounds **(5)** and **(6)** were recorded on a Perkin Elmer LS 55 Spectrometer at excitation 610 nm for the diluted solutions in DMF (Fig.2). The fluorescence emission maxima are red shifted as compared to the absorption maxima, which are as followed: 690 nm with a shift of 7 nm for compound **(5)** and 685 nm (6 nm shift) for compound **(6).**

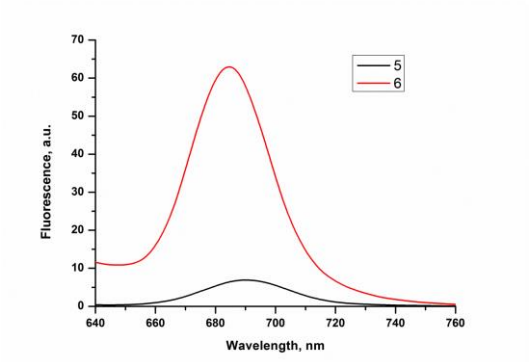


Fig.2. Fluorescence spectra of Zn(II) phthalocyanines **(5)** and **(6)** recorded in DMF. Excitation wavelength at 610 nm was used.

CONCLUSION

Tetra- and octa- aminophenoxy Zn(II) phthalocyanines were synthesized by following different reaction schemes. The efficient, simple and modified reaction conditions were chosen in order to obtain the products in a high yields and purity. A newly proposed synthetical pathway *via* reduction of the nitro- groups of tetra- and octa-nitrophenoxy- Zn(II) phthalocyanines using as reducing agent hydrogen gas, cooling and 10%Pd/C was applied for the both Zn(II) phthalocyanines with amonophenoxy- substitutions.

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АМИНОФЕНОКСИ ЗАМЕСТЕНИ ФТАЛОЦИАНИНОВИ КОМПЛЕКСИ НА ЦИНК КАТО БАЗОВИ СТРУКТУРИ ЗА КОНЮГИРАНЕ С БИОЛОГИЧНИ АКТИВНИ ГРУПИ ЧРЕЗ АМИДНА ВРЪЗКА

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(Резюме)

Фотодинамичната терапия с фотосенсибилизатори, функционализирани с биологично активни съединения като аминокиселини или къси пептиди се явява обещаваща стратегия за насочената към таргета терапия. Фотодинамичният процес е резултат от ефективното взаимодействие на фотосенсибилизатор, атмосферен молекулен кислород и специфична светлина от видимата и близката инфрачервена област (630-850 нм). В резултат на това се генерират синглетен кислород и други реактивоспособни кислородни форми, които могат да окисляват биомолекули с последваща цитотоксичност. Функционализирането на фталоциановия макроцикъл с биологично-активни пептиди цели да подобри разтворимостта на фталоцианиновата молекула, както и да повиши клетъчното усвояване на фотосенсибилизатора и да подобри таргетната му селективност спрямо органели. Пептиди като клетъчно проникващи, клетъчно специфични, биологично-активни пептиди, рецептор свързващи секвенции, вътреклетъчно локализиращи секвенции могат да повишат действието на фотосенсибилизатора чрез двойна ефективност спрямо целевите клетки и тъкани, известно като синергична фотодинамична терапия и пептидна цитотоксичност.

Настоящото научно изследване представя оптимизирането на няколко синтетични пътища за синтез на тетра- и окта аминофенокси заместени цинкови (II) фталоцианини, чиято функционална група, наречена аминофенокси- група е подходяща единица за свързване с биологично-активни пептиди.