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Spectroscopical study of bacteriopurpurinimide–naphthalimide conjugates for fluorescent diagnostics and photodynamic therapy

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A B S T R A C T

Two novel bis(chromophoric) dyads **ABPI-NI1** and **ABPI-NI2** containing 1,8-naphthalimide and bacterio-purpurinimide units linked by *p*-phenylene-methylene (**ABPI-NI1**) and pentamethylene (**ABPI-NI2**) spacers were prepared to test their ability to be used in the design of effective agents for both photodynamic therapy (PDT) and fluorescent tumor imaging. Photophysical studies revealed that the emission from the naphthalimide chromophore in both conjugates was partially quenched due to resonance energy transfer between the photoactive components. Compound **ABPI-NI2** with more sterically flexible oligomethylene group demonstrated higher fluorescence intensity as compared with that for **ABPI-NI1**. © 2014 Elsevier B.V. All rights reserved.

Keywords:

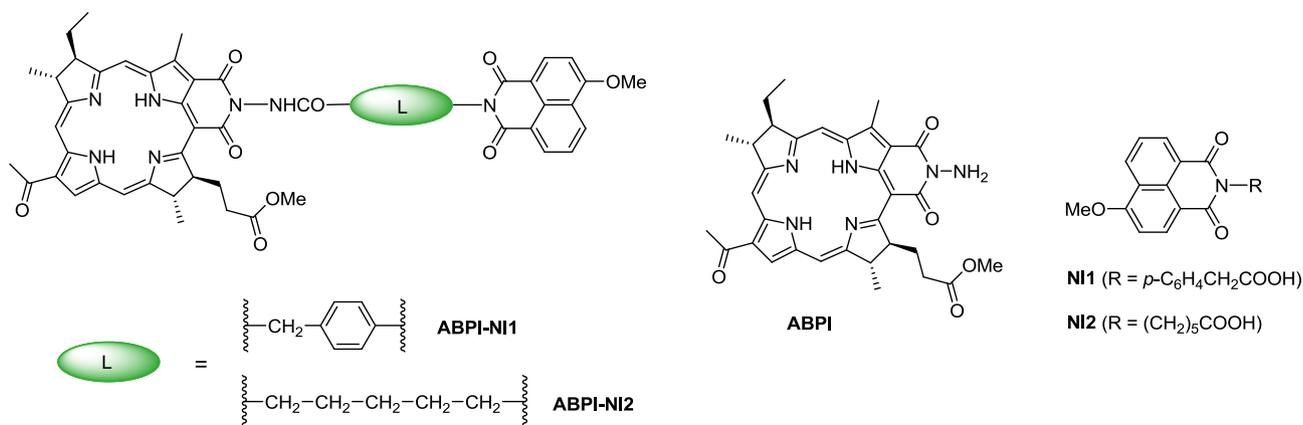
1,8-Naphthalimide; Bacteriopurpurinimide; Conjugate; Photodynamic therapy; Fluorescence imaging; Resonance energy transfer; PM6 semiempirical calculations

1. Introduction

Cancer is known to be one of the deadliest diseases of our time and throughout the world. Current treatment modalities for patients afflicted by cancer include surgery, radiation therapy, chemotherapy, and a relatively novel option called photodynamic therapy [1,2]. Surgery is used to excise abnormal growths and surrounding tissue, but the procedure is invasive and may be complicated by relapse of the cancer if not all of the tumor cells are removed. Chemotherapy employs different cytotoxic chemicals to attack or block specific cellular and molecular mechanisms that aid tumor growth. Unfortunately, patients on chemotherapeutics suffer from side effects due to adverse drug toxicities. Radiation uses ionizing energy to attack neoplastic cells, but it is nonspecific and may cause damage to surrounding healthy tissue, which can lead to the occurrence of secondary cancers. PDT uses a drug known as a photosensitizer, light, and oxygen to destroy tumors and their surrounding vasculature. PDT has several advantages in that (i) there is no systemic, organ, or tissue toxicity, (ii) it is noninvasive, and (iii) it can be used repeatedly as a primary or adjuvant treatment [3,4].

Porphyrin-based photosensitizing agents for PDT possess unique advantages due to their ability to be retained in tumors and to produce cytotoxic singlet oxygen upon exposure to an appropriate wavelength of light. UV/Vis absorption spectra of porphyrins contains strong $\pi-\pi^*$ transition around 400 nm (Soret band) and satellite Q-bands in the visible region between 600 and 800 nm, which coincidentally drop into “therapeutic window” where tissues exhibit the best light penetration ability [2]. Therefore only Q-bands are useful for PDT. To date, many porphyrins have been obtained to test their efficiency in PDT and some of them are currently at different stages of clinical or preclinical trials [5–9].

In addition to therapy, the difference in concentration of the photosensitizer in malignant and normal tissue could be the basis of fluorescent imaging. Noninvasive in nature, fluorescent imaging instruments are simple and not expensive to operate and can allow precise assessment of the location and size of a tumor, providing information on its invasiveness in adjacent tissue [10,11]. Unfortunately, porphyrins and most of the tumor-avid long-wavelength photosensitizers (e.g. chlorins and bacteriochlorins) have very small wavelength differences between their NIR absorption and emission bands (Stokes shifts). Such an inherent property limits application of these molecules for imaging. To overcome this difficulty a new approach have been recently developed by Pandey



and co-workers [12,13], who offered the construction of tumor-specific imaging agents by conjugating of organic fluorophores with appropriate photophysical properties to porphyrin-based compounds. Thus, the excitation of the labeled fluorescent species is expected to produce the strong emission signal, which could be used to monitor tumor responses to treatment. Further excitation by another light wavelength corresponding to the absorption maxima of porphyrin leads to formation of singlet oxygen responsible for cancer cell damage.

The work discussed herein describes the study of spectral properties of novel dyad compounds **ABPI-NI1** and **ABPI-NI2** (Scheme 1) bearing *N*-aminobacteriopurpurinimide (ABPI) and naphthalimide (NI) chromophores aimed to determine their ability to be used in the design of effective agents for both PDT and tumor imaging. Bacteriopurpurinimide type photosensitizer was chosen since the presence of fused imide cycle in the macrocyclic system is known to enhance pigment stability and result in the red shift of longwavelength Q_y -band in the absorption spectrum compared to chlorins and bacteriochlorins [14]. Yet, in spite of their promising optical properties **ABPI** and its derivatives exhibit high light-induced cytotoxicity on A-549 human adenocarcinoma cells [15]. As a basic fluorophore responded for the imaging effect we used 1,8-naphthalimide. Due to strong emission in the visible region, large Stokes shifts and excellent photostability compounds of this type are considered to be good candidates for the construction of fluorescent probes [16,17], organic electroluminescent devices [18], laser dyes [19] and optical brighteners [20]. Moreover, the utility of naphthalimides as fluorescent markers in cells has also been demonstrated [21,22].

2. Materials and methods

2.1. Synthesis of the compounds

For the synthesis of conjugates **ABPI-NI1** and **ABPI-NI2**, *N*-aminobacteriopurpurinimide **ABPI** was prepared from Bacteriochlorophyll *a* by following the literature procedure [23,24], which was afforded from the frozen biomass containing *Rhodospirillum rubrum*. Reaction of **ABPI** with acyl chlorides derived from **NI1** and **NI2** gave the target compounds. The experimental details concerning the synthesis of **ABPI-NI1**, **ABPI-NI2** and naphthalimides **NI1** and **NI2** are described in [Supplementary Information data file](#).

2.2. Steady-state and time-resolved optical measurements

The absorption spectra were taken on a Varian-Cary 5G spectrophotometer. The fluorescence quantum yield measurements were performed using a Varian-Cary 5G spectrophotometer and a

FluoroMax-3 spectrofluorimeter. Spectral measurements were carried out in air-saturated solutions at 20 ± 1 °C. Acetonitrile (Aldrich) and dimethylsulfoxide (Spectro) of spectrophotometric grade were used. The concentrations of studied compounds were of about $0.5\text{--}1.0 \times 10^{-5}$ M. All measured fluorescence spectra were corrected for the nonuniformity of detector spectral sensitivity. Quinine sulfate in 1N H_2SO_4 ($\phi^f = 0.55$) [25] and Coumarin 481 in acetonitrile ($\phi^f = 0.08$) [26] were used as a reference for the fluorescence quantum yield measurements. Fluorescence lifetimes were determined according to the method described earlier [27].

2.3. Computational details

The three dimensional structures of conjugates **ABPI-NI1** and **ABPI-NI2** were built with MOPAC program package using PM6 semiempirical method [28]. The calculations were performed at optimized geometries, which reached gradient variations less than 0.01 kcal/mol. The solvent effect was included in geometry optimizations following the «Conductorlike Screening Model» (COSMO) implemented in MOPAC. A dielectric constant of $\epsilon = 40$ and a refraction index of solvent (n) such that $n^2 = 2$ were used.

3. Results and discussion

The conjugates of bacteriopurpurinimide derivatives with the fluorescent dyes, in which the linker groups separate two photoactive components, can be considered as bis(chromophoric) systems, where the optical characteristics of the individual chromophores might be perturbed to some extent as a result of mutual energy/electron transfer process or exciplex formation originating from the feasible stereoelectronic properties of the excited state. Regarding the application of conjugates in PDT, one could reveal that the occurrence of such additional deactivation pathways, non-radiative in nature, would impair singlet oxygen sensitization or, alternatively, quench the emission of the fluorophore dye.

In order to avoid the decrease in emission efficiency of naphthalimide unit in the designed conjugates caused by fluorescence resonance energy transfer (FRET) to bacteriopurpurinimide, we followed the rule, according to which the FRET-process could occur whenever the emission spectrum of a donor fluorophore (naphthalimide) overlaps with the absorption spectrum of acceptor (**ABPI**) [29]. As it can be seen from Fig. 1, the absorption spectrum of **ABPI** in acetonitrile contains the interval between 440 and 520 nm, where the absorption values are relatively low. At the same time, it is well-known that photophysical properties of 1,8-naphthalimides are strongly dependent on the nature of the substituent at C-4 involved in the charge transfer interaction with carboximide moiety and, in general, the derivatives with alkoxy

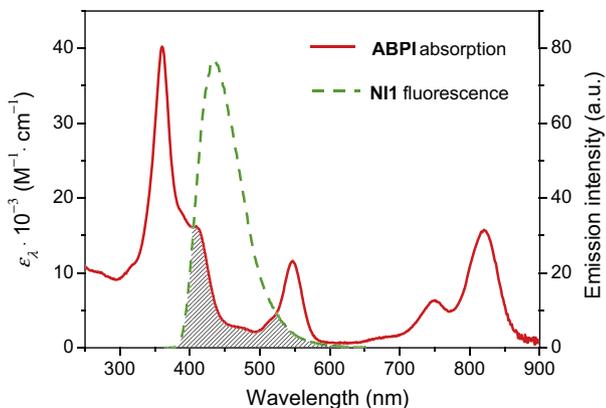


Fig. 1. Overlap between the **ABPI** absorption and **NI1** fluorescence spectrum in acetonitrile.

groups exhibit blue fluorescence in the region of 430–470 nm [30–31]. Indeed, the low overlapping of methoxynaphthalimide **NI1** emission band with **ABPI** absorption was observed (Fig. 1) implying good fluorescent characteristics for conjugate **ABPI-NI1**.

Contrary to our expectations, we found that **ABPI-NI1** showed very low fluorescence signal at 437 nm compared with the reference compound **NI1** (Fig. 2b) and 85-fold reduction in the quantum yield (ϕ^f for **NI1** and **ABPI-NI1** in MeCN are 0.58 and 0.0068 respectively, Table 1). Such difference in ϕ^f values could be accounted for the fact that excitation light (with wavelength 360 nm) used by us to collect the emission spectra is absorbed by both chromophores in **ABPI-NI1** (see Fig. 2a for the comparison of absorption of **ABPI-NI1** and **NI1** at 360 nm) and thus, less amount of excitation energy is consumed to produce the emission of naphthalimide fragment. To estimate the magnitude of this effect we compared the fluorescence quantum yields for the solution of **ABPI-NI1** and the solution containing equimolar mixture of **ABPI** and **NI1** (Table 1), and it was found that ϕ^f value for the mixture of chromophores (0.17) is 25 times higher compared to the value observed for **ABPI-NI1** (0.0068). This result indicates that emission of naphthalimide in the conjugate **ABPI-NI1** is quenched by a kind of non-radiative process which competes fairly well with the fluorescence in the excited state.

To clarify our assumption whether FRET is a reason of quenching of naphthalimide emission in **ABPI-NI1**, we calculated the rate constant k_{FRET} for FRET deactivation pathway on the basis of Förster resonance theory [29]. In this treatment k_{FRET} is given by Eq. (1):

$$k_{FRET} = \frac{1}{\tau_D} \left(\frac{R_0}{r} \right)^6 \quad (1)$$

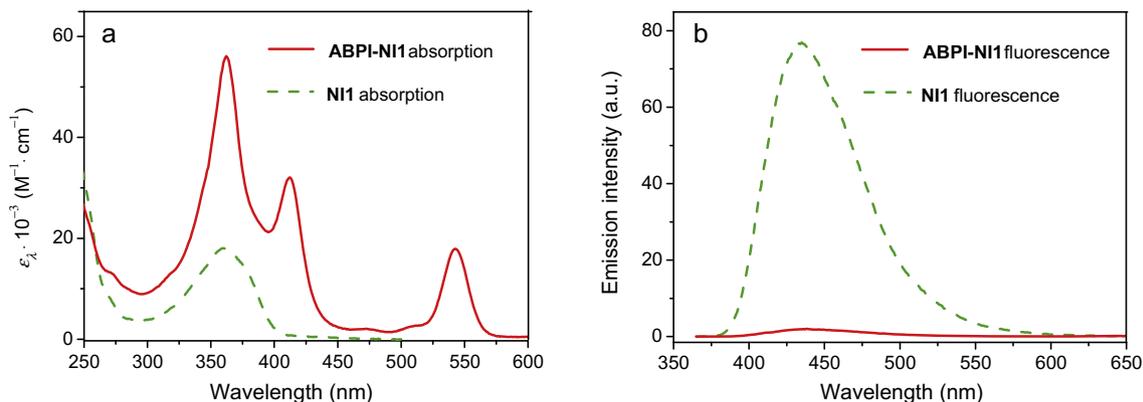


Fig. 2. Absorption (a) and fluorescence (b) spectra of conjugate **ABPI-NI1** and naphthalimide **NI1** in acetonitrile. Concentrations of compounds are both 5.8×10^{-6} M.

where τ_D is the excited state lifetime of the donor chromophore (naphthalimide) in the absence of acceptor (bacteriopurpurinimide) and r is the donor–acceptor separation. As a parameter τ_D we used the fluorescence lifetime of compound **NI1** in MeCN ($\tau_D = 7.5$ ns). The distance between donor and acceptor chromophores ($r = 13.0$ Å) was found from the PM6 optimized ground state geometry of **ABPI-NI1** (see Fig. 3a). R_0 is a distance calculated according to the Eq. (2):

$$R_0^6 = \frac{9000 \ln 10 \kappa^2 \phi_D^f}{128 \pi^2 N_A n^4} \int_0^\infty F_D(\lambda) \epsilon_A(\lambda) \lambda^4 d\lambda \quad (2)$$

where κ^2 is a factor which describes the relative orientations of the donor and acceptor, ϕ_D^f is the donor emission quantum yield in the absence of the acceptor, n is the refractive index of the medium, N_A is Avogadro constant ($N_A = 6.02 \times 10^{23} \text{ mol}^{-1}$) and the integral defines the amount of overlap between the normalized emission spectrum of the donor $F_D(\lambda)$ and the acceptor absorption spectrum $\epsilon_A(\lambda)$. In terms of Förster resonance theory, R_0 corresponds to the donor–acceptor distance at which 50% of the excited donors undergo energy transfer to an acceptor and is usually known as the critical distance. Values of R_0 are typically 50–100 Å when the transitions in both donor and acceptor are allowed and there is good overlap between the donor emission and acceptor absorption spectra [29]. Assuming that $\kappa^2 = 2/3$ (for a random orientation) and $\phi_D^f = 0.58$ (the quantum yield of **NI1** in MeCN) we found the rate constant k_{FRET} to be as high as $7.1 \times 10^{10} \text{ s}^{-1}$, with the distance R_0 being 37.1 Å (Table 1). On the other hand, the relaxation rate of donor naphthalimide chromophore in the absence of the acceptor can be well estimated by the sum of radiative (k_r) and non-radiative (k_{nr}) constants describing the excitation energy loss in the compound **NI1**, which is derived from the known fluorescence lifetime of **NI1** as given in Eq. (3):

$$k_r + k_{nr} = \frac{1}{\tau_D} = \frac{1}{7.5 \times 10^{-9} \text{ s}} = 1.3 \times 10^8 \text{ s}^{-1} \quad (3)$$

The performed calculations reveal that the resonance energy transfer rate for the conjugate **ABPI-NI1** could be higher compared with the emission rate at least by 2 orders of magnitude, and this could be the reason of fluorescence quenching. Apparently, the high k_{FRET} value is a result of a rather short distance between naphthalimide and **ABPI** chromophores ($r = 13.0$ Å) lying within the range $0 < r < 0.5R_0$ (18.5 Å), where transfer efficiency (E) is usually close to 100% [29]. As it can be seen from Table 1, transfer efficiencies E for **ABPI-NI1** obtained from theoretical calculations and steady-state fluorescence measurements are both higher than 95%.

To avoid the decrease of naphthalimide fluorescence due to FRET to **ABPI** fragment we modified the structure of linker by using less rigid pentamethylene chain instead of *p*-phenylene–methylene

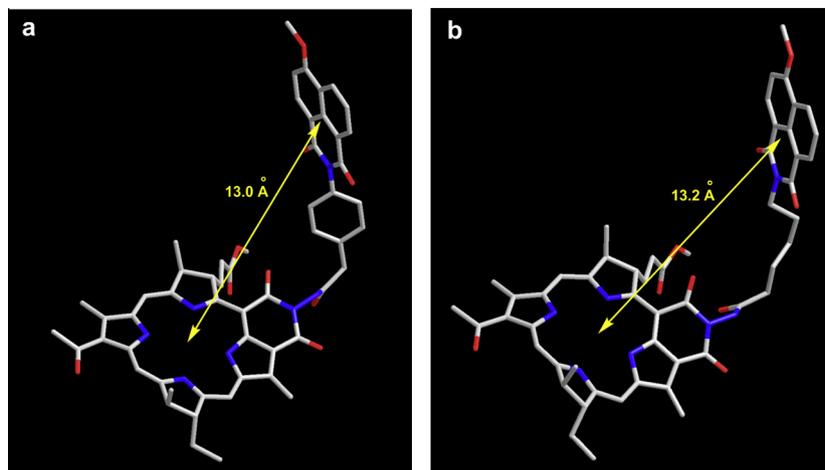


Fig. 3. PM6 optimized ground state geometry of the compounds **ABPI-NI1** (a) and **ABPI-NI2** (b).

group. This idea was realized in the conjugate **ABPI-NI2**. In this case, the molecule is expected to be more sterically flexible resulting in a more easy achievement of a conformation with nearly orthogonal orientation of dipole transition moments of chromophores at which energy transfer rate is close to zero. Although there are a large variety of conformers for **ABPI-NI2**, there could be some conformers where the FRET is hampered, and thus fluorescent characteristics could be improved to some extent with respect to **ABPI-NI1**. As it has been shown by Pandey and coworkers who conducted molecular modeling and photophysical studies for conjugates of purpurinimide with cyanine dyes, the increase of the number of relative orientations of two chromophores on going to a molecule with more flexible linker provides the better fluorescence imaging capabilities [13]. Following this design logic, we used the linker with almost same length as in the case of **ABPI-NI1** (the distance between NI and ABPI fragments in **ABPI-NI2** is 13.2 Å, see Fig. 3b), but with increased sterical flexibility. We did not further extend the oligomethylene chain in **ABPI-NI2**, because at a very high number of CH₂ groups (higher than 5) the molecule could adopt a conformation where the ABPI and NI moieties are arranged as a small H-aggregate stabilized by π -stacking interaction, in which the formation of non-emissive excimer state could be suggested. It should be noted that the quenching of naphthalimide fluorescence in excimers or exciplexes with π -donor aromatic compounds has been reported in literature [32–33].

The fluorescence quantum yields of **ABPI-NI2**, **NI2** and equimolar mixture of **ABPI** and **NI2** are presented in Table 1, the

absorption and emission spectra displayed in Fig. S2 (Supplementary information). As the comparison of φ^{fl} values shows, the emission intensity of naphthalimide is only 2 times quenched when going from the mixture **ABPI + NI2** to **ABPI-NI2** solution, which corresponds to 50.0% efficiency of FRET against 96.0% in the conjugate **ABPI-NI1**. Considering the observation that the overlap integral ($3.30 \times 10^{14} \text{ M}^{-1} \text{ cm}^{-1} \text{ nm}^4$, Table 1) and distance between the chromophores ($r = 13.2 \text{ \AA}$) for **ABPI-NI2**, as well as the measured fluorescence quantum yield and lifetime of **NI2** ($\varphi_b^{\text{fl}} = 0.56$, $\tau_D = 6.7 \text{ ns}$) which are very close to the corresponding parameters of **ABPI-NI1** and **NI1**, one can see that the inhibition of FRET process in **ABPI-NI2** could be only a result of conformational changes leading to the different relative orientation of chromophores with the orientation factor κ^2 (Eq. (2)) decreased to some extent. The high theoretical efficiency of energy transfer for **ABPI-NI2** (Table 1) which does not agree with the experimental data could be explained by the choice of the same of κ^2 value (2/3) used by us for the calculation of rate constant k_{FRET} and Förster distance R_0 as in the case of **ABPI-NI1**. Obviously, the steric structure of studied conjugates is different and cannot be described within the same orientation of donor and acceptor chromophores. Because of size of molecules and their complex structure, we did not carry out the detailed quantum chemical calculations to explore the conformation flexibility of these conjugates and to estimate the factor κ^2 in each case, however, the performed results clearly indicate that these are steric reasons that respond for the different fluorescent characteristics of compounds **ABPI-NI1** and **ABPI-NI2**.

Table 1

Fluorescence quantum yields, fluorescence band maximum positions and resonance energy transfer characteristics for the compounds **NI1**, **NI2**, **ABPI-NI1**, **ABPI-NI2** and equimolar mixtures of **ABPI + NI1** and **ABPI + NI2**.^a

	φ^{fl}	$\lambda_{\text{max}}^{\text{fl}}$ (nm)	R_0 (Å)	Overlap integral ($\text{M}^{-1} \text{ m}^{-1} \text{ nm}^4$) ^b	k_{FRET} (s^{-1})	E (%)	
						Theory ^c	Experiment ^d
NI1	0.58	434	–	–	–	–	–
ABPI + NI1	0.17	436	–	–	–	–	–
ABPI-NI1	0.0068	436	37.1	2.49×10^{14}	7.1×10^{10}	99.8	96.0
NI2	0.56	446	–	–	–	–	–
ABPI + NI2	0.11	448	–	–	–	–	–
ABPI-NI2	0.055	448	36.3	3.30×10^{14}	6.4×10^{10}	99.8	50.0

^a The data for **ABPI-NI1**, **NI1** and **ABPI + NI1** were obtained using acetonitrile as a solvent and 360 nm excitation light (λ_{ex}), the data for **ABPI-NI2**, **NI2** and **ABPI + NI2** – using dimethylsulfoxide and $\lambda_{\text{ex}} = 340 \text{ nm}$.

^b Calculated from the absorption spectra of **ABPI** and emission spectra of compounds **NI1** and **NI2** (see Fig. 1 and Fig. S1 in Supplementary information data file) according to Eq. (2).

^c Calculated as $R_0^6/(R_0^6 + r^6)$ [29], where R_0 is a critical Förster distance and r is the distance between donor (NI) and acceptor (ABPI) chromophores.

^d Calculated as $1 - (\varphi^{\text{fl}}/\varphi_b^{\text{fl}})$, where φ^{fl} and φ_b^{fl} are quantum yields of donor chromophore in the presence and absence of acceptor respectively [29]. As a φ^{fl} we used quantum yields of conjugates, while φ_b^{fl} values were approximated by the quantum yields of solutions containing the equimolar mixtures **ABPI + NI1** and **ABPI + NI2**.

4. Conclusions

In summary, we have prepared two bacteriopurpurinimide-naphthalimide dye conjugates **ABPI-NI1** and **ABPI-NI2**. Evaluation of spectral properties has shown that the fluorescence intensity of naphthalimide residue is decreased with respect to compounds **NI1** and **NI2**, which can be rationalized in terms of FRET interaction occurring from the fluorophore (NI) to photosensitizer (ABPI). The magnitude of the quenching effect is strongly dependent on the structure of the linker group. Upon the excitation at the absorption maxima of naphthalimide, compound **ABPI-NI2** with more sterically flexible pentamethylene group exhibited higher emission intensity compared with that for **ABPI-NI1** containing *p*-phenylene-methylene linker unit. Thus, through the studied molecules, conjugate **ABPI-NI2** seems to be the better candidate for the application as a photosensitizing and imaging agent.

Our study illustrates a new approach for targeting highly emissive fluorophores to tumors, which is of great importance for simultaneous cancer diagnosis and therapy. The bifunctional conjugates provide an opportunity to independently select and associate appropriate photosensitizers and fluorophores. Our future work in this field will continue investigating the applicability of naphthalimide derivatives as signaling components in such systems. Due to facilely modified spectral characteristics, emission maxima of 1,8-naphthalimides can be shifted close to NIR region [22,34] where the fluorescent contrast agents can provide planar and tomographic images at millimeter to centimeter depth, with millimeter to sub-millimeter resolution and very high sensitivity. Related research is currently in progress.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jphotobiol.2014.03.008>.

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