Efficient Synthesis and *in vitro* PDT Effect of Purpurin-18-*N*-Aminoimides

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Received May 10, 2010, Accepted September 15, 2010

A simple and efficient synthetic route for making purpurin-18-*N*-aminoimides is described. The purpurin-18-*N*-aminoimides are obtained by treatment of purpurin-18 methyl ester with various amines. These new compounds have long wavelength absorptions in the range of 706 - 711 nm. In preliminary screening, the purpurin-18-*N*-aminoimides have shown promising photosensitizing activity for the cancer cell by *in vitro* study in photodynamic therapy.

Key Words: Purpurin-18 methyl ester, Purpurin-18-*N*-aminoimide, Photodynamic therapy

Introduction

Photodynamic therapy (PDT) is an experimental cancer treatment modality which selectively destroys cancer cells by interaction of light with a photosensitizing dye, presumably to form singlet oxygen.[1-3] In continuing efforts to develop candidate photosensitizers for PDT, the design and synthesis of chlorin derivatives having well-defined structure with amphiphilic properties, high selectivity for tumor cell, quick elimination from health cells and strong absorption in the red region of visible spectrum are important challenges in the PDT field. In our lab, we have done a large amount of careful research about the chlorin-based photosensitizers. For example, research on Gram-positive bacterial cell *S. aureus* using troponyl methyl (pyro) pheophorbides[4] and carbohydrate-conjugated chlorin for galectin-3.[5]

DNA-intercalating agents are those antitumor agents that intercalate DNA *via* chromophores.[6] DNA intercalating ability and antitumor activity resides in a wide variety of chemical entities. Especially, imide derivative compounds have been reported as a potential class of antitumor agents containing amonafide **1**, mitonafide **2**, azonafide **3**[7-9] (Figure 1) and so on. Encouraged by this result, a group of photosensitizers featuring a chlorin ring system fused to a six-membered cyclic imide structure with a basic *N*-substituent has received considerable attention. Converting the six-membered anhydride ring of purpurin-18 into a six-membered cyclic imide structure was found to greatly increased wavelength absorption and good stability for the requirement of an improved photodynamic therapeutic agent.[10-19] Although previous report has described the synthesis of purpurin-18-*N*-(*N,N*-dimethyl)ethylimide from the chlorin p₆.[14] However, the yield of the purpurinimide formed in this reaction was low. It is therefore important to develop a new process for the synthesis of purpurinimide with a good yield. Also, there is no report regarding its *in vitro* study.

By varying the substituent on the anhydride ring nitrogen atom, the series of available purpurinimides could be extended. Thus reactions of purpurin-18 with secondary di(tri)amines could give rise of various biological active imide derivatives. In this report we wish to present a general and efficient method for the synthesis of the purpurin-18-*N*-aminoimides from the
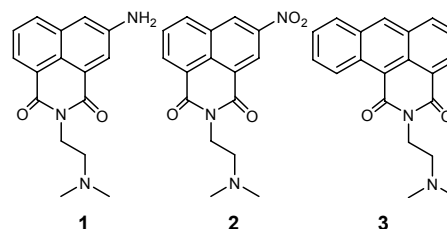

Figure 1. Structures of amonafide **1**, mitonafide **2** and azonafide **3**.

purpurin-18 methyl ester **5**. We also carried out an *in vitro* assay of cell viability with A549 cancer cells for the aim of examining preliminary photosensitizing efficacy of these new purpurinimides.

Experimental

General methods. The ¹H-NMR spectra were recorded on a Varian-500 MHz spectrometer. Chemical shifts are given as δ values using TMS as the internal standard and *J* values in Hz. The mass spectra were measured with a JEOL JMS700 spectrometer. The UV-visible spectrums were recorded on Scinco S-3100 spectrophotometer using dichloromethane as a solvent. Melting points (uncorrected) were measured on an Electrothermal IA9000 Series digital melting point apparatus. Thin-layer chromatography (TLC) was done on Merck silica gel 60 glass sheets (Cat. HX948839, layer thickness 0.25 mm). Column chromatography was performed over silica gel 60 (230 - 400 mesh). In some cases, preparative TLC plates were also used for the purification (Analtech precoated silica gel GF glass plate, Cat. 01012, layer thickness 0.5 mm). All photophysical experiments were carried out using spectroscopic grade solvents. Purpurin-18 methyl ester[12] was prepared according to literature procedure.

Methyl pheophorbide-a (4). Chlorophyll paste (*excrementum bombycis*) (100 g) was dissolved in 500 mL of 5% sulfuric acid in methanol and stirred at room temperature for 50 h under nitrogen atmosphere in dark. Following the standard workup, methyl pheophorbide-a was obtained in 5.1% yield. The analytical data are identical with those reported previously.[20]

General procedure for the preparation of purpurin-18-*N*-aminoimides. In topical experiment, purpurin-18 methyl ester **5** (200 mg) and excess of corresponding amine (0.1 mL) was dissolved in toluene (20 mL), and the mixture was refluxed under nitrogen atmosphere for 2 h. After monitoring of complete consumption of purpurin-18 methyl ester by TLC, the mixture was cooled to room temperature, solvent and excess amines were removed *in vacuum*. The crude product was purified by silica column chromatography or preparative TLC plate with an eluent of 10% methanol in dichloromethane to give corresponding purpurinimide **6a**, **6b**, **6c**, **6d** and **6e** as a purple solid, respectively.

Purpurin-18-*N*-(*N,N*-dimethyl)ethylimide 6a. Yield: 97%. mp 99 - 101 °C. UV-vis in CH_2Cl_2, λ_{max} (nm, rel. intensity log ε), 419.2 (0.98), 481.1 (0.04), 511.9 (0.05), 549.8 (0.17), 649.8 (0.06), 706.7 (0.36). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H, for 10H), 9.32 (s, 1H, for 5H), 8.56 (s, 1H, for 20H), 7.89 (dd, *J* = 17.5, 11.5 Hz, 1H, 3^{1}H), 6.30 (d, *J* = 18.0 Hz, 1H, *trans*-3^{2}H), 6.17 (d, *J* = 11.5 Hz, 1H, cis-3^{2}H), 5.33 (m, 1H for 17H), 4.74 (t, *J* = 7.0 Hz, 2H, N-*CH$_2$*-CH$_2$-N-(CH$_3$)$_2$), 4.34 (q, *J* = 7.5 Hz, 1H, 18H), 3.78 (s, 3H, 12-CH$_3$), 3.61 (q, *J* = 8.0 Hz, 2H, 8^{1}CH$_2$), 3.58 (s, 3H, 17^{2}CO$_2$CH$_3$), 3.34 (s, 3H, 2CH$_3$), 3.14 (s, 3H, 7CH$_3$), 2.76 (s, 6H, N-(CH$_3$)$_2$), 2.72-2.68, 2.43-2.37 and 2.05-1.98 (m, 6H, NCH$_2$-*CH$_2$*-N-(CH$_3$)$_2$, 2 × 17^{1}H and 2 × 17^{2}H), 1.77 (d, *J* = 7.5 Hz, 3H, 18CH$_3$), 1.65 (t, *J* = 7.5 Hz, 3H, 8^{2}CH$_3$), 0.08 and −0.08 (each br s, 1H, 2NH). Anal. calcd for $C_{38}H_{44}N_6O_4$: C, 70.35; H, 6.84; N, 12.95. Found: C, 70.47; H, 6.82; N, 12.92.

Purpurin-18-*N*-(*N,N*-diethyl)ethylimide 6b. Yield: 95%. mp 125 - 127 °C. UV-vis in CH_2Cl_2, λ_{max} (nm, rel. intensity log ε), 419.4 (1.02), 481.1 (0.04), 512.5 (0.06), 551.1 (0.19), 651.6 (0.08), 708.3 (0.37). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H, for 10H), 9.18 (s, 1H, for 5H), 8.55 (s, 1H, for 20H), 7.79 (dd, *J* = 17.5, 11.5 Hz, 1H, 3^{1}H), 6.23 (d, *J* = 18.0 Hz, 1H, *trans*-3^{2}H), 6.10 (d, *J* = 11.5 Hz, 1H, cis-3^{2}H), 5.37 (m, 1H for 17H), 4.59 (t, 2H, *J* = 7.0 Hz, N-*CH$_2$*-CH$_2$-N-(CH$_2$CH$_3$)), 4.36 (q, *J* = 7.5 Hz, 1H, 18H), 3.71 (s, 3H, 12-CH$_3$), 3.48 (q, *J* = 8.0 Hz, 2H, 8^{1}CH$_2$), 3.58 (s, 3H, 17^{2}CO$_2$CH$_3$), 3.30 (s, 3H, 2CH$_3$), 3.09 (s, 3H, 7CH$_3$), 2.90 (q, 4H, N-(*CH$_2$*CH$_3$)$_2$), 2.73-2.68, 2.44-2.37 and 2.10-1.97 (m, 6H, N-CH$_2$-*CH$_2$*-N-(CH$_2$CH$_3$)$_2$, 2 × 17^{1}H and 2 × 17^{2}H), 1.78 (d, *J* = 7.5 Hz, 3H, 18CH$_3$), 1.57 (t, *J* = 7.5 Hz, 3H, 8^{2}CH$_3$), 1.27 (t, *J* = 7.0 Hz, 6H, N-(CH$_2$-*CH$_3$)$_2$), 0.25 and −0.02 (each br s, 1H, 2NH). Anal. calcd for $C_{40}H_{48}N_6O_4$: C, 70.98; H, 7.15; N, 12.42. Found: C, 70.93; H, 7.20; N, 12.48.

Purpurin-18-*N*-(*N*-isopropylamino)ethylimide 6c. Yield: 94%. mp 116 - 118 °C. UV-vis in CH_2Cl_2, λ_{max} (nm, rel. intensity log ε), 419.8 (0.97), 480.9 (0.05), 512.6 (0.06), 552.6 (0.20), 661.4 (0.09), 710.6 (0.35). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H, for 10H), 8.97 (s, 1H, for 5H), 8.52 (s, 1H, for 20H), 7.80 (dd, *J* = 19.5, 11.5 Hz, 1H, 3^{1}H), 6.27 (d, *J* = 17.5 Hz, 1H, *trans*-3^{2}H), 6.15 (d, *J* = 11.5 Hz, 1H, cis-3^{2}H), 5.27 (m, 1H for 17H), 4.84 (m, 2H, N-*CH$_2$*-CH$_2$-NH-), 4.34 (q, *J* = 7.5 Hz, 1H, 18H), 3.59 (s, 3H, 12-CH$_3$), 3.60 (q, *J* = 6.5 Hz, 2H, 8^{1}CH$_2$), 3.57 (s, 3H, 17^{2}CO$_2$CH$_3$), 3.24 (s, 3H, 2CH$_3$), 2.82 (s, 3H, 7CH$_3$), 2.92 (m, 1H, NH-*CH*-(CH$_3$)$_2$), 2.75-2.68, 2.43-2.35 and 2.06-1.91 (m, 6H, N-CH$_2$-*CH$_2$*-NH-, 2 × 17^{1}H and 2 × 17^{2}H), 2.04 (br, 1H, NH), 1.86 (d, *J* = 8.0 Hz, 3H, 18CH$_3$), 1.54 (t, *J* = 7.0 Hz, 3H, 8^2-CH$_3$), 1.25 (d, *J* = 6.5 Hz, 6H, NH-CH-(*CH$_3$*)$_2$), 0.09 and −0.62 (each br s, 1H, 2NH). Anal. calcd for $C_{39}H_{46}N_6O_4$: C, 70.67; H,

7.00; N, 12.68. Found: C, 70.69; H, 7.06; N, 12.61.

Purpurin-18-*N*-(*N,N*-dimethylpropylamino)propylimide 6d. Yield: 97%. mp 95 - 97 °C. UV-vis in CH_2Cl_2, λ_{max} (nm, rel. intensity log ε), 419.1 (0.98), 481.0 (0.04), 511.7 (0.06), 550.0 (0.17), 651.3 (0.07), 706.9 (0.35). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H, for 10H), 9.29 (s, 1H, for 5H), 8.55 (s, 1H, for 20H), 7.86 (dd, *J* = 17.5, 13.5 Hz, 1H, 3^{1}H), 6.28 (d, *J* = 18.0 Hz, 1H, *trans*-3^{2}H), 6.15 (d, *J* = 11.5 Hz, 1H, cis-3^{2}H), 5.31 (m, 1H for 17H), 4.56 (m, 2H, N-*CH$_2$*-CH$_2$-CH2-NH-), 4.35 (q, *J* = 7.0 Hz, 1H, 18H), 3.75 (s, 3H, 12-CH$_3$), 3.57 (q, *J* = 8.5 Hz, 2H, 8^{1}CH$_2$), 3.55 (s, 3H, 17^{2}CO$_2$CH$_3$), 3.33 (s, 3H, 2CH$_3$), 3.10 (s, 3H, 7CH$_3$), 2.70-2.62, 2.41-2.10 (m, 8H, N-CH$_2$-CH$_2$-*CH$_2$*-NH-*CH$_2$*-CH$_2$-*CH$_2$*-N-(CH$_3$), 2 × 17^{1}H and 2 × 17^{2}H), 2.05 (s, 6H, N-(CH$_3$)$_2$) 1.76 (d, *J* = 7.5 Hz, 3H, 18CH$_3$), 1.63 (t, *J* = 7.0 Hz, 3H, 8^{2}CH$_3$), 1.36 (m, 2H, N-CH$_2$-*CH$_2$*-CH$_2$-NH-CH$_2$-*CH$_2$*-CH$_2$-N-(CH$_3$)), 0.08 and −0.01 (each br s, 1H, 2NH). Anal. calcd for $C_{42}H_{53}N_7O_4$: C, 70.07; H, 7.42; N, 13.62. Found: C, 70.02; H, 7.49; N, 13.60.

Purpurin-18-*N*-(*N*-imidazolyl)propylimide 6e. Yield: 96%. mp 86 - 88 °C. UV-vis in CH_2Cl_2, λ_{max} (nm, rel. intensity log ε), 418.9 (1.04), 480.8 (0.05), 511.9 (0.06), 550.4 (0.18), 651.7 (0.07), 707.6 (0.34). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H, for 10H), 9.31 (s, 1H, for 5H), 8.56 (s, 1H, for 20H), 7.88 (dd, *J* = 18.0, 11.5 Hz, 1H, 3^{1}H), 7.15, 7.08 (s, 3H, imidazole-H), 6.29 (d, *J* = 17.5 Hz, 1H, *trans*-3^{2}H), 6.16 (d, *J* = 11.5 Hz, 1H, cis-3^{2}H), 5.33 (m, 1H for 17H), 4.35 (q, *J* = 7.5 Hz, 1H, 18H), 4.55, 4.28 (each m, 2H, N-*CH$_2$*-CH$_2$-*CH$_2$*-), 3.77 (s, 3H, 12-CH$_3$), 3.59 (q, *J* = 8.0 Hz, 2H, 8^{1}CH$_2$), 3.53 (s, 3H, 17^{2}CO$_2$CH$_3$), 3.34 (s, 3H, 2CH$_3$), 3.13 (s, 3H, 7CH$_3$), 2.78-2.65, 2.55-2.48, 2.45-2.32 and 2.06-1.95(m, 6H, N-CH$_2$-*CH$_2$*-CH$_2$-, 2 × 17^{1}H and 2 × 17^{2}H), 1.77(d, *J* = 7.5 Hz, 3H, 18CH$_3$), 1.64 (t, *J* = 7.8 Hz, 3H, 8^{2}CH$_3$), 0.88 and 0.03 (each br s, 1H, 2NH). Anal. calcd for $C_{40}H_{43}N_7O_4$: C, 70.05; H, 6.32; N, 14.30. Found: C, 70.13; H, 6.37; N, 14.26.

***In vitro* photosensitizing efficacy.**

General method: A549 cells were cultured at 37 °C in a humidified 5% CO_2 incubator using RFMI 1640 growth medium supplemented with 10% fetal bovine serum and 1% penicillin/ streptomycin. For phototoxity studies, A549 cells were plated in 96-well plates at a density of $10 × 10^4$ cells well. After 24 h of incubation, 100 μL of 1 μM, 2 μM, 5 μM, 10 μM and 15 μM pur-purin-18-*N*-aminoimides were added, respectively. Plates were returned to the incubator for 24 h. And then the cells were replaced with fresh media and exposed to light (BioSpec LED, 670 - 700 nm, 2.0 J/cm^2) for 15 min. Following illumination, the plates were incubated at 37 °C in the dark. Every 3, 24, 48 hours later, WST-1 was put into each well and measure the absorbance on 450 nm wavelength after photoirradiation or without light, respectively. Each experiment was done with three replicate wells. The percentage cell survival was calculated by normalization with respect to the value for no photosensitizer treatment.

Results and Discussion

For our study, methyl pheophorbide-a (MPa) **4** was extracted from chlorophyll paste (*excrementum bombycis*) by slight modifications of the previously reported procedure in 5.1% yield.[20] MPa **4** was transformed into purpurin-18 methyl ester **5**[6] by
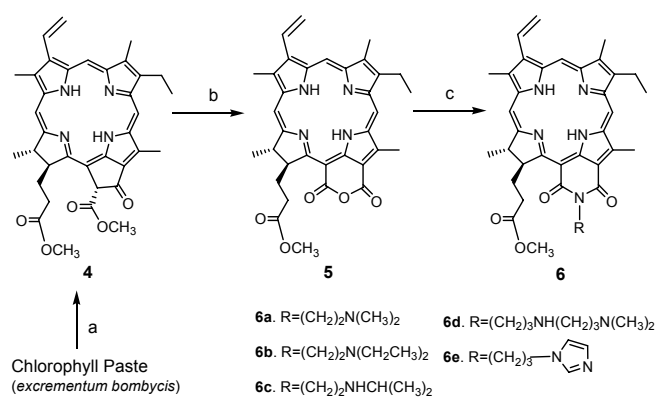
Scheme 1. Synthesis of purpurin-18-*N*-aminoimides. Reagents and conditions: a. 5% H$_2$SO$_4$/Methanol, rt; b. KOH/1-propanol/air, rt; c. Corresponding amines/toluene, reflux

Figure 2. Electronic absorption spectra of **6a-6e** in dichloromethane.

air oxidation in *n*-propanol containing KOH and was used as a substrate. As shown in Scheme 1, reaction of **5** with various amines with reflux gave the desired purpurin-18-aminoimides **6a**, **6b**, **6c**, **6d** and **6e** in 97%, 95%, 94%, 97% and 96% yield, respectively. Thus, this method appeared to be an efficient approach for preparing photosensitizers with *N*-amino-imide substituents that can be prepared in excellent yield directly from purpurin-18 methyl ester *via* one-pot synthesis.

　　The structures of the final products were confirmed by ^{1}H-NMR spectroscopy and mass spectrometry. Compared to the purpurin-18 methyl ester **5** the ^{1}H-NMR spectra of **6a-6e** showed each triplet at δ 4.74, 4.59, 4.84, 4.56 and 4.55 ppm for the protons of CO-N-*CH$_2$*-, respectively. In compounds **6a** and **6d**, N-(*CH$_3$*)$_2$ appears as a singlet at δ 2.76 and 2.05 ppm, respectively. And compound **6b** shows a triplet at δ 1.27 ppm for the protons of N-(CH$_2$*CH$_3$*)$_2$. Compound **6c** showed the appearance of a doublet at δ 1.25 ppm assigned to NH-CH-(*CH$_3$*)$_2$ protons. The imidazole protons of compound **6e** gave two singlet at δ 7.15 and 7.08 ppm.

　　The electronic absorption spectra of purpurin-18-*N*-aminoimides were compared with purpurin-18 methyl ester. All compounds showed the same pyrrole-type visible spectra in dichloromethane, but the peaks in max of Qy and Soret bands are different. As can be seen from Figure 2, all the chlorins showed similar characteristics. The Soret band was observed near 419 nm, and the long-wavelength absorption bands were observed at λ$_{max}$ = 706.7, 708.3, 710.6, 706.9 and 707.6 nm for **6a**, **6b**, **6c**, **6d** and **6e**, respectively. Thus comparing with purpurin-18 methyl ester **5** (λ$_{max}$ = 699.9 nm), the purpurin-18-aminoimides **6a**, **6b**, **6c**, **6d** and **6e**, showed a red-shift of 6.8, 8.4, 10.7, 7.0, 7.7 nm, respectively (Table 1). In other words the use of photosensitizer having long-wavelength band is desirable for better tissue penetration of excitied light *in vivo*, the purpurin-18-*N*-aminoimides may be considered as promising candidates.[19, 21]

　　The *in vitro* activities of purpurin-18 methyl ester **5** and the corresponding purpurin-18-*N*-aminoimides were determined with A549 cells. A549 cells with each compound at variable concentrations were incubated in A549 cells at 37 °C for 3 h, 24 h and 48 h respectively. As shown in Figure 3, none of the
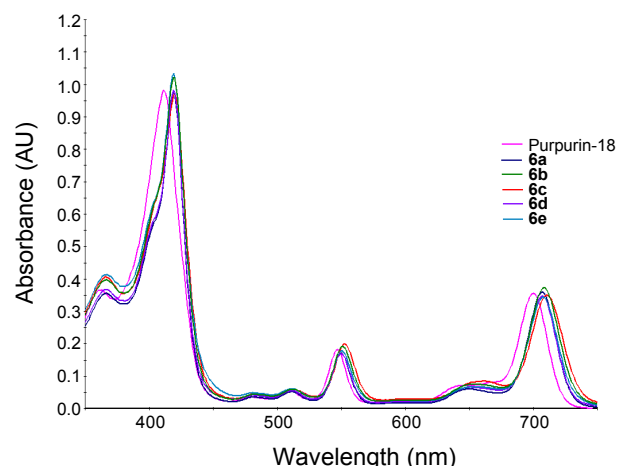
Table 1. Absorption maxima of **6a-6e** in dichloromethane and their red-shift values of the redmost Qy band

compound	Absorption maxima, nm		ΔQy (nm)
	Soret	Redmost Qy	
6	411.4	699.9	0
6a	419.2	706.7	6.8
6b	419.4	708.3	8.4
6c	419.8	710.6	10.7
6d	419.1	706.9	7.0
6e	418.9	707.6	7.7

compounds up to 15 μM concentration have any significant dark cytotoxicity at 3h and 24h. But the compounds showed little dark cytotoxicity at 48 h, presumably by light penetration errors during long time incubation. The higher concentration of the photosensitizer the more dark cytotoxicity was shown. Among the compounds investigated, compound **6b** showed the best efficacy at 3 h with 16.1% cell survival at 2 μM. After 24 h incubation in the dark, all the purpurin-18-*N*-aminoimides exhibited similar PDT efficacy. However, compared to the standard purpurin-18 methyl ester **5**, all the purpurin-18-*N*-aminoimides showed higher PDT efficacy. The *in vitro* efficacy after 24 h incubation was observed in the following order: **6c** > **6e** > **6a** > **6d** > **6b** > **5**. And the dark cytotoxicity was 3%, 5%, 3%, 3% and 5% for compounds **6a**, **6b**, **6c**, **6d** and **6e** at 2 μM after 24 h, respectively.

Conclusions

　　We have developed a simple and efficient synthetic route for preparing the purpurin 18-*N*-aminoimides. Reaction of **5** with various amines at reflux gave the corresponding imides in excellent yield (> 94%). On the basis of the preliminary *in vitro* studies, it is clearly indicated that the purpurin-18-*N*-aminoimides exhibit better PDT efficacy than the standard purpurin-18 methyl ester **5**.
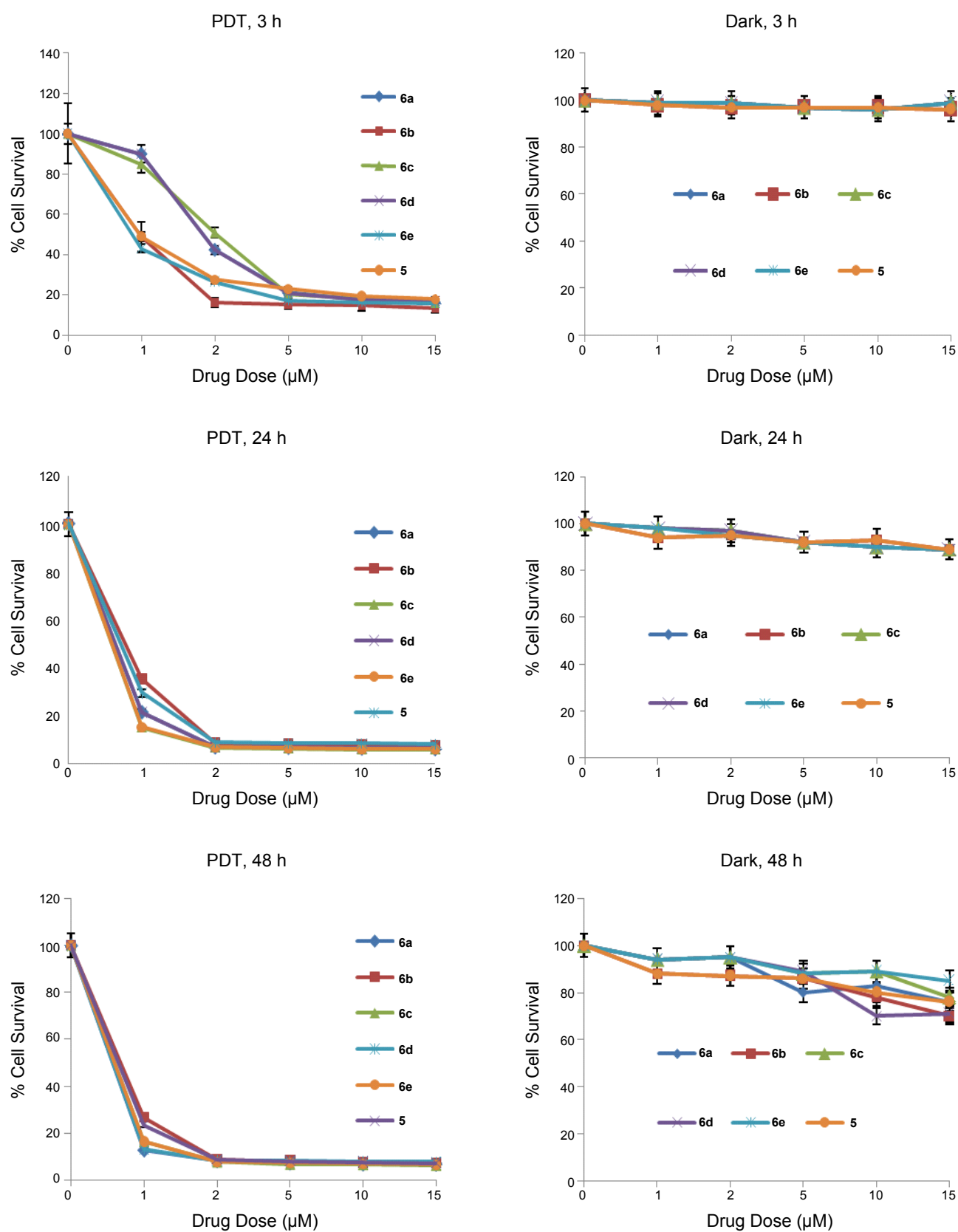
Figure 3. Cell viability results of the photosensitizers on A549 cells. The cell viability of **6a-6e** was assigned for PDT in the concentration ranges of 1 μM, 2 μM, 5 μM, 10 μM and 15 μM after 3 h, 24 h, and 48 h by comparing with those of purpurin-18 methyl ester.

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