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Enhanced anti-microbial effect through cationization of a mono-triazatricyclodecane substituted asymmetric phthalocyanine

Huajian Lin[a], Jincan Chen[b], Yaxin Zhang[b], Azeem Ulla[b], Jianyong Liu[a], Fan Lin[c], Longguang Jiang[a], Mingdong Huang[a,b,*]

[a] College of Chemistry, Fuzhou University, Fujian 350118, China
[b] State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Fuzhou, Fujian 350002, China
[c] Qingdao Sundynamic Technology Co., Ltd, Qingdao, Shandong 266000, China

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ABSTRACT

Antimicrobial photodynamic therapy (aPDT) is an effective way to combat infectious diseases and antibiotic resistance. Photosensitizer is a key factor of aPDT and has triggered extensive research interest. In this study, a new asymmetric Zn(II) phthalocyanine mono-substituted with a triazatricyclodecane moiety (compound **3**) and its cationic *N*-methylated derivative (compound **4**) were synthesized. Their photodynamic antimicrobial activities were evaluated using bioluminescent bacterial strains. Compound **3** showed phototoxicity only toward the Gram-positive bacteria, whereas the cationic derivative compound **4** exhibited strong anti-bacterial activity against both Gram-positive and Gram-negative strains. These bacterial species were eradicated (> 4.0 logs or 99.99% killing) at appropriate concentrations of compound **4** with 12.7 J/cm^2 of red light, demonstrating compound **4** as a potent aPDT agent.

1. Introduction

Phthalocyanines have many important industrial applications, including dyes and pigments in fabric, demonstrating that they are safe and environment-friendly materials. They also possess remarkable stability and unique photochemical and photophysical properties, broadening their uses in many high technology fields, including semiconductor materials [1,2], solar cells [3,4], optical data storage [5], chemical sensors [6,7], oxidation-reduction catalysts [8–11] and photocatalysts [12], as well as photodynamic therapy (PDT) for antimicrobial [13–15] or antitumor applications [16–18]. The emergence of multi-resistant bacteria due to the over-use of antibiotics has become a global challenge [19,20]. Phthalocyanines have emerged as a new class of photosensitizer possessing potent antimicrobial effect, even toward drug-resistant bacterial strains separated from hospitals [21–24].

In this study, we designed a new asymmetric Zn(II) phthalocyanine (ZnPc): triazatricyclo-substituted Zn(II) phthalocyanine (compound **3**) by conjugating with a Nitrogen-rich compound (1,3,5-triazatricyclo [3.3.1.1(3, 7)] decane-7-amine, Scheme 1). The substituent is quite bulky in size and can reduce the aggregation of phthalocyanine. Aggregation of Pc typically leads to the quench of photodynamic effect. Moreover, the triazatricyclodecane is water soluble, and will be protonated at aqueous solution, potentially rendering the conjugate aqueous solubility and positive charges in a weakly acidic environment. The positive charge is a common property of antimicrobial agents, which allows the adsorption and binding to bacterial surface that carry large amount of negative charges [25,26]. We also wanted to avoid the positional isomer on ZnPc during conjugation because single compound is a key for approval by regulatory agent, should the compound proceeds to clinical trial stage.

It turned out that compound **3** was not water soluble, and did not show desirable antimicrobial effect toward bacterial strains. We suspect that the compound **3** was not protonated at aqueous solution. Quaternization of aliphatic or aromatic nitrogen atom at the end of the synthetic pathway of phthalocyanine is a common way to prepare cationic phthalocyanine [27]. Most of the published cationic phthalocyanines with quaternary amine groups exhibit excellent photodynamic antimicrobial effect [28–32]. Moreover, it was discovered recently by Hamblin group that aPDT can be greatly enhanced by the addition of simple inorganic salts especially iodine ion at micromolar concentration [33]. Thus, we carried out methylation on the tertiary amine group of compound **3** in a hope to form an cationic phthalocyanine compound **4**. Photophysical and photochemical properties including UV–Vis spectra,

* Corresponding author at: College of Chemistry, Fuzhou University, Fujian 350118, China.
E-mail address: HMD_lab@fzu.edu.cn (M. Huang).

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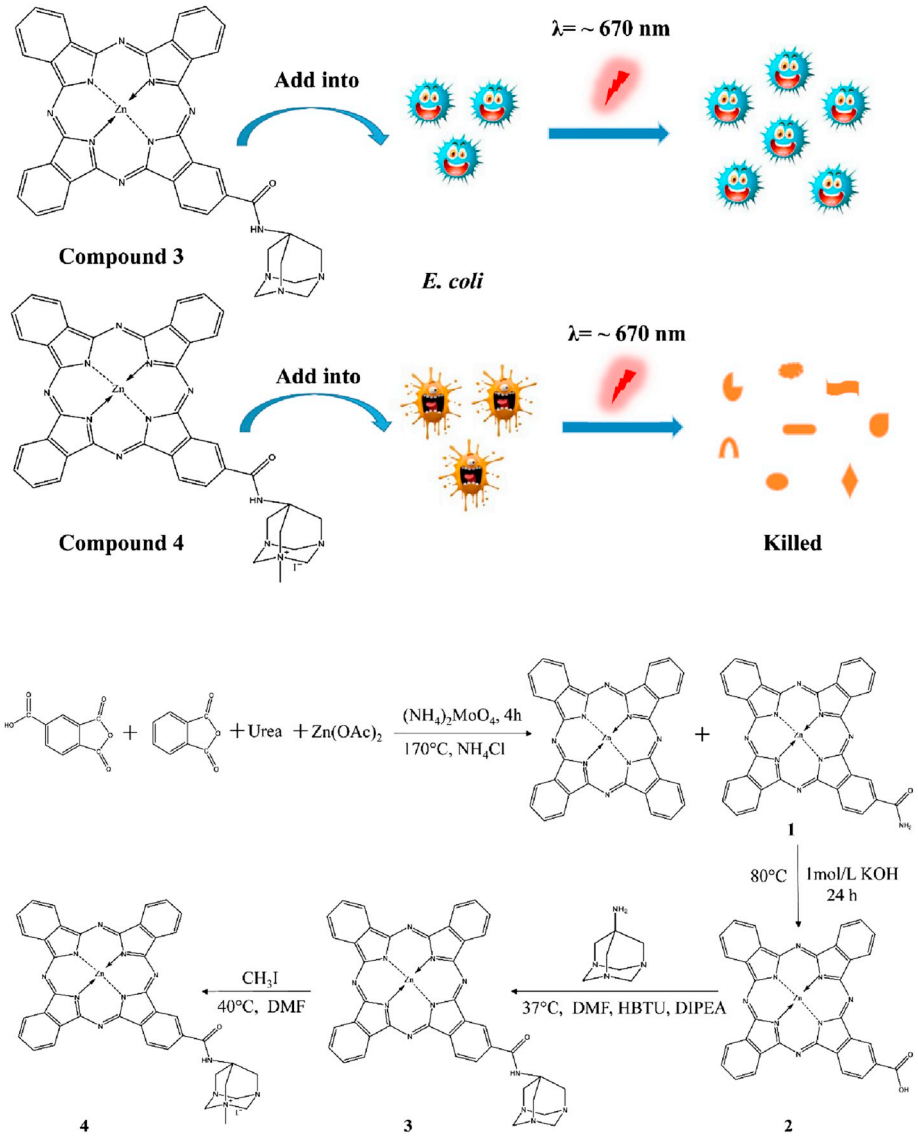

Scheme 1. Synthesis of compound **3** and **4**.

photodynamic antibacterial and hemolysis activities of these compounds were characterized and evaluated. Encouragingly, the compound **4** exhibited very potent antimicrobial effect.

2. Results and discussion

2.1. Synthesis of compound 3

The target compound (**3**) was synthesized using the scheme shown in Scheme 1. The intermediate compound (**1**) was prepared by statistic condensation method. Condensation of trimellitic anhydride or phthalic anhydride in the presence of urea and catalyst at high temperature can produce tetra-formamido-phthalocyanine or phthalocyanine, respectively. Using a mixture of trimellitic anhydride and phthalic anhydride at a ratio of 1:7 for condensation, we made a mixture of 2-formamidophthalocyanine zinc (**1**) and phthalocyanine zinc with only trace amount presumably polycarboxy substituted phthalocyanine zinc. The amide group of compound **1** was hydrolyzed to carboxy group, leading to 2-carboxyphthalocyanine (compound **2**), which was separated out of the mixture to a high purity (> 90%, Fig. S1). It is important to carry out the hydrolysis before the purification, because the separation of the compound **1** out of the condensation mixture was quite difficult. The purified carboxy compound **2** was then conjugated to compound 1,3,5-triazatricyclo [3.3.1.1(3, 7)] decan-7-amine by amine coupling chemistry. The product was precipitated out with water and collected by centrifugation, followed by washing with deionized water, acetonitrile and CH_2Cl_2, and dried to give blue solid. The compound **3** was further purified by semi-preparative HPLC system. The structure of compound **3** was fully confirmed by ^{1}H, ^{13}C NMR spectrum (Figs. S2, S3) and mass spectrometry measurement (Electrospray Ionization, ESI, Fig. S4, *m/z* calculated for compound **3** $[M + H]^+$ 757.1879, found 757.1846).

2.2. Antimicrobial effects of compound 3

Phthalocyanine and its derivatives are highly potent photosensitizers in photodynamic antimicrobial therapy. They sensitize oxygen under red light (~670 nm) to generate reactive oxygen species (ROS) and damage effectively nearby bacteria or cells [34]. In this study we evaluated the photodynamic antibacterial activity of compound **3** against two luminescent bacterial strains, Gram-positive (*S. aureus*) and Gram-negative (*E. coli*). These are genetically engineered bacterial strains expressing both luciferase and luciferase substrate, and are luminescent while alive with bioluminescence intensity (relative

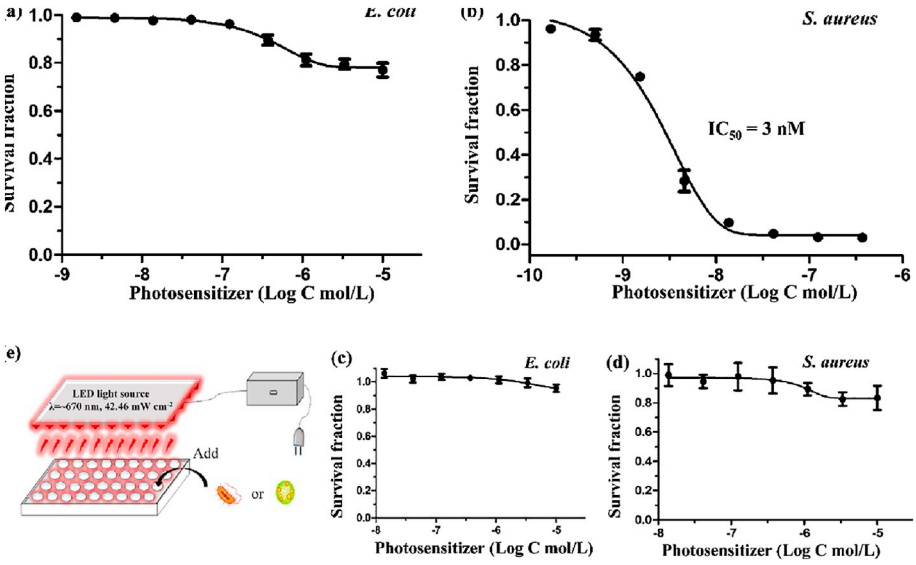

Fig. 1. Photo cytotoxicity of compound **3** against *E. coli* (a) and *S. aureus* (b); dark cytotoxicity of compound **3** against *E. coli* (c) and *S. aureus* (d); panel (e) shows the LED array light source used in this assay (λ = ~670 nm, fluency rate = 42.5 mW/cm^2, illumination time = 5 min to a light dose of 12.7 J/cm^2).

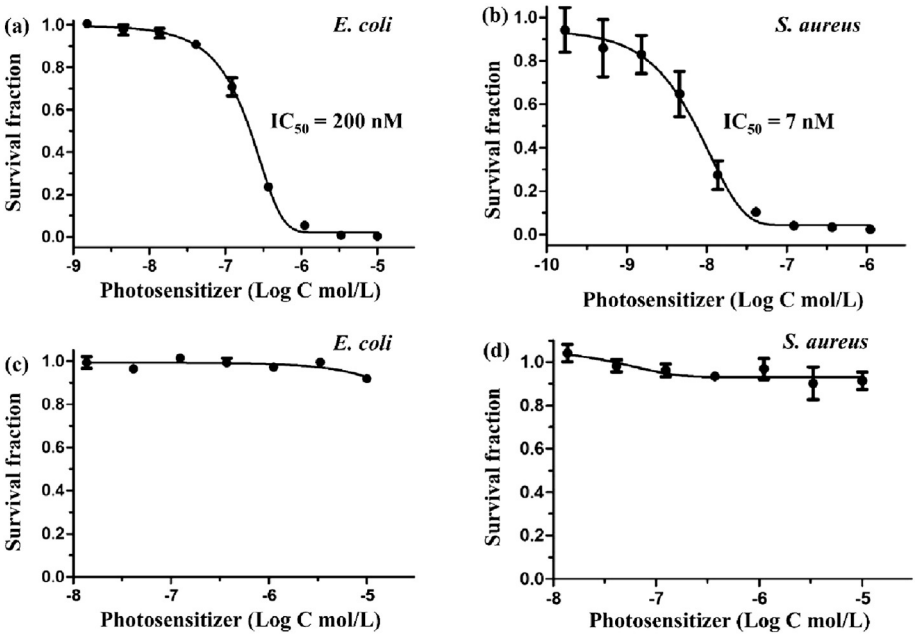

Fig. 2. Photo cytotoxicity of compound **4** against *E. coli* (a) and *S. aureus* (b); dark cytotoxicity of compound **4** against *E. coli* (c) and *S. aureus* (d) (λ = ~670 nm, fluency rate = 42.5 mW/cm^2, illumination time = 5 min to a light dose of 12.7 J/cm^2).

luminescence units, RLU) proportional to the number of live cells, allowing the real time evaluation of photodynamic bacterial inactivation effect. An array of light-emitting diode (LED, fluency rate = 42.5 mW/cm^2) light source was designed for this assay on 96-well plates (5 min, to a light dose of 12.7 J/cm^2). The advantage of this LED light source is its capability to illuminate all 96 wells of microplate evenly at the same time and without generating too much heat, thus reducing the systemic error of the experiments (Fig. 1). In our assay, the phosphate buffered saline (PBS) suspensions of bacterial strains *S. aureus* or *E. coli* were added to the 96-well plate at a density of about 10^6 CFU/ml and incubated at 37 °C in dark for 10 or 15 min (10 min for *S. aureus*, 15 min for *E. coli*) with the compound **3**. The compound **3** was first dissolved in DMSO, and diluted into the assay buffer keeping the final assay concentration of DMSO at < 1%. After the illumination, the luminescence intensity of the wells was monitored for 50 min. As shown in the results of antibacterial assay, the compound **3** did not show potent antimicrobial effect against the Gram-negative strains, even at concentrations up to 10 μM, but it did have potent antimicrobial effect against the Gram-positive strains with a IC_{50} value at nanomolar range (Fig. 1B). In addition, the dark toxicity measurement of compound **3** was performed under the same conditions. The compound **3** did not show any noticeable toxic toward these strains in the absence of light at concentrations up to 10 μM to either for *S. aureus* or *E. coli*. We suspected that compound **3** cannot be protonated at neutral aqueous solution presumably due to high rigidity of triazatricyclodecane moiety. Thus, the methylation of tertiary amine group was carried out in order to get the cationic phthalocyanine (compound **4**) [35].

2.3. Synthesis of compound 4

The cationic compound **4** was synthesized through methylation of compound **3** in anhydrous DMF using excess amount of iodomethane

(Scheme 1). Interestingly, only one tertiary amino group was methylated despite the used of excess amount of iodomethane during the reaction, as shown by both proton NMR spectra (Fig. S5) and ESI mass spectra (Fig. S6). We do not know why only one tertiary amino group was methylated. It is likely that the bulky nature of the triazatricyclodecane moiety prevents further methylation.

2.4. Antimicrobial efficacy of compound 4

The cationic compound **4** now exhibited high cytotoxicity toward both types of bacteria with IC_{50} values at nanomolar range (7.2 nM and 200 nM for *S. aureus* and *E. coli*, respectively, Fig. 2). This observation can be attributed to the difference in morphology of their membranes. The Gram-negative species contains an inner cytoplasmic membrane and an out membrane which are separated by the periplasmic region, covered by a tightly organized outer cell wall that imparts a high permeability barrier for the photosensitizer. The Gram-positive strains has a membrane covered by a relatively porous cell wall composed of peptidoglycan and lipoteichoic acid that allows photosensitizer to bind or cross. It was found that, most of the neutral, anionic or cationic photosensitizers can efficiently kill Gram-positive bacteria, whereas only cationic photosensitizer are able to kill Gram-negative species [36,37].

Colony counting method was further used to validate the antimicrobial efficacy (Fig. 3), and we found that compound **4** killed > 4 logs of bacteria (> 99.99%) of *S. aureus* at a concentration of 1.6 μM, and induced similar anti-bacterial effect against *E. coli* at 8.0 μM (Figs. 4, S8). These results are consistent with the measurements using luminescent bacteria.

In addition, the dark toxicity measurement of compound **4** was performed under the same conditions in dark. The compound **4** did not showed noticeable dark toxicity toward these strains at concentrations up to 10 μM for either *S. aureus* or *E. coli*.

2.5. UV–Vis and fluorescence spectra of compounds 3 and 4

Both compounds **3** and **4** did not have any solubility in water. In DMSO, they showed UV–Vis spectra similar to each other with a B-band at 346–347 nm, a vibronic band at 606 nm, and an intense sharp Q-band at 677 nm (Fig. 5). The absence of absorption at 630 nm demonstrated that they were non-aggregated in the organic solvent. Both compound **3** and **4** showed a strong fluorescence emission at 690 nm in DMSO (exc = 610 nm, Fig. 5). The molar extinction coefficients data of the two compounds was available in supporting information (Table S1).

2.6. Safety of compound 4 toward blood red cells

A molecule containing high positive charge density will induce toxicity to mammalian cells and restrict its clinical applications [38–40]. To evaluate whether compound **4** will show toxicity toward mammalian erythrocytes, we carried out hemolysis assay with red blood cells of healthy mice at compound concentrations between 0.1 and 10 μM which was dissolved in PBS containing 1% DMSO [41]. We observed negligible lytic activities at these concentrations (Fig. 6). These results demonstrated the potential safety of compound **4** for the mammalian cells. For future clinical application, additional long term toxicity and systemic toxicity evaluation need to be carried out.

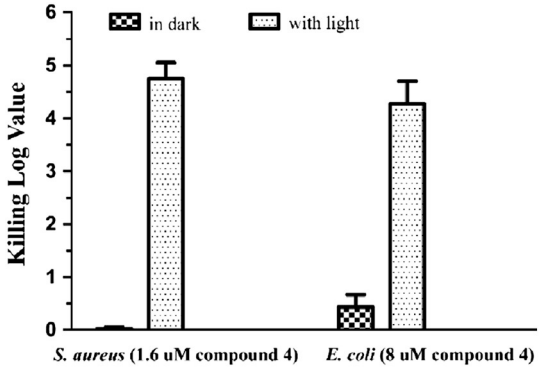

Fig. 4. Photo cytotoxicity and dark cytotoxicity of compound **4** against *E. coli* and *S. aureus* (λ = ~670 nm, fluency rate = 42.5 mW/cm^2, illumination time = 5 min to a light dose of 12.7 J/cm^2).

3. Experimental

3.1. Materials and instruments

All the reactions were carried out under the atmosphere of nitrogen. The beta-carboxy Zn(II) phthalocyanine compound **2** was synthesized in our lab according to our previously published method [42]. 1,3,5-Triazatricyclo [3. 3. 1. 1 (3, 7)] decan-7-amine, O-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluorophosphate (HBTU), *N*,*N*-diisopropylethylamine (DIPEA), dimethyl sulfoxide-d_6 and dry DMF (dried with molecular sieves) were purchased from the J & K Scientific LTD. The common solvents such as acetonitrile, CH_2Cl_2 and diethyl ether were purchased from the Sinopharm Chemical Reagent Co., Ltd. and dehydrated before use. All organic reagents purchased from commercial source were of analytical purity. The planar light-emitting diode (LED, λ = 660 nm ± 25 nm, 42.46 mW/cm^2) light source used in the inactivation experiments was custom-made by Uniglory Electronics (HK) Co., Ltd. The light intensity was measured by Spectra-Physics Model 407A Power Meter.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III 400 and Bruker Avance III 500 spectrometers (400 and 500 MHz) in deuterated solvent and the spectras were referenced internally by using the residual solvent (DMSO-d_6) resonances relative to $SiMe_4$. Electrospray ionization (ESI) mass spectra were recorded on a Thermo Finnigan LCQ Deca XP Max mass spectrometer. The compounds were dissolved in DMSO and the methyl alcohol was used as the mobile phase. UV–Vis and fluorescence spectrum were measured with a BioTek Synergy 4 multi-mode microplate reader in a 96-well plate under room temperature.

3.2. Synthesis

3.2.1. Synthesis of compound 3

The compound **2** (80.6 mg), HBTU (100.7 mg) and DIPEA (46.9 mg) were added to a solution of anhydrous DMF (40 ml), and then stirred at

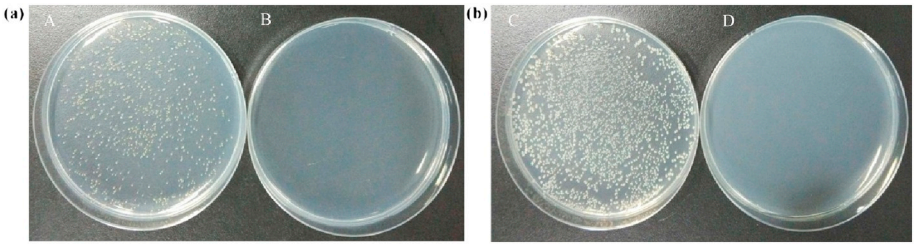

Fig. 3. Antimicrobial effect of compound **4** against *S. aureus* (a) and *E. coli* (b). *S. aureus* (B) or *E. coli* (D) were incubated with compound **4** (1.6 and 8.0 μM respectively) for 10 or 15 min, for *S. aureus* and *E. coli*, respectively, followed by illumination with red light at a dose of 12.7 J/cm^2, and counted on agar plates. A and C were the controls (no compound **4** but with light).

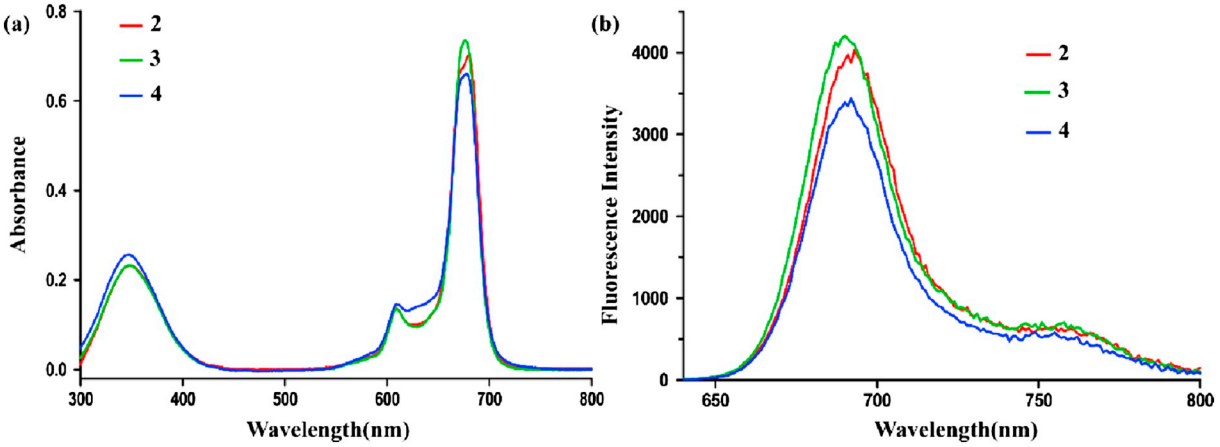

Fig. 5. (a) UV–Vis spectra of compounds **2**, **3** and **4** in DMSO. (b) Fluorescence spectrum of compounds **2**, **3** and **4** in DMSO (exc = 610 nm).

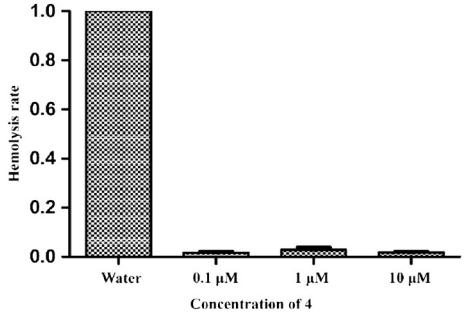

Fig. 6. Hemolysis assay of cationic compound **4** (0.1–10 μM) using mice erythrocytes. Erythrocytes incubated with distilled water were used as the positive control.

room temperature for about 40 min, followed by the addition of 1, 3, 5-triazatricyclo [3. 3. 1. 1(3, 7)] decan-7-amine (33.5 mg) and further reaction at 37 °C overnight (about 17 h). The mixture was dumped into water (about 1:4, v/v) to give the blue precipitate, which was collected by centrifugation at 10,000 rpm, washed with deionized water, acetonitrile and CH_2Cl_2, and then dried in a lyophilizer to give blue solid compound **3** (69.2 mg, 60.6%). The purity of compound **2** and compound **3** were confirmed on HPLC by C18 column. Both compounds were eluted with H_2O/DMF gradient (50–100%, containing 0.1% TFA) in 30 min. The HPLC chromatograms of compounds **2** and **3** showed that they have high purities (> 95%). The final product compound **3** was eluted faster (22 min vs 24 min) on C18 column compared to its precursor compound **2**, indicating higher hydrophilicity of compound **3** compared to its precursor. The structure of compound **3** was fully confirmed by ^1H, ^{13}C NMR spectrum (Figs. S2, S3) and mass spectrometry measurement (Electrospray Ionization, ESI, Fig. S4), which are available in supporting information. UV–Vis (DMSO): λ_{max} = 677 nm, HRMS (ESI): *m/z* calculated for $C_{40}H_{29}N_{12}OZn^+$ $[M + H]^+$ 757.1879, found 757.1846. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ = 9.49 (s, 1H, Pc-H_α), δ = 8.86–9.17 (m, 7H, Pc-H_α), δ = 8.54 (d, J = 8.0 Hz, 1H, Pc-H_β), δ = 8.47 (s, 1H, - HN-CO-), δ = 7.98–8.19 (m, 6H, Pc-H_β), δ = 4.00–4.46 (m, 6H, N-CH_2-N), δ = 3.87 (s, 6H, N-CH_2-C). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): δ = 167.96, 153.15, 153.10, 152.96, 152.87, 152.31, 152.16, 151.53, 151.01, 139.42, 138.00, 137.91, 137.86, 137.31, 135.62, 129.63, 129.56, 129.51, 128.66, 122.57, 122.55, 122.49, 122.35, 122.08, 72.90, 59.60, 43.50 (some of the signals were overlapped).

3.2.2. Synthesis of compound 4

Iodomethane (1.5 ml) was added to a mixture of compound **3** (30.0 mg) in anhydrous DMF (10 ml), and then stirred at 40 °C for about 40 h in the absence of light. After removing the volatiles in vacuo, the remained solution was dumped into diethyl ether (about 1:5, v/v) to give the blue precipitate, which was collected by centrifugation at 10000 rpm, washed with diethyl ether, ethyl acetate and acetonitrile, and then dried in lyophilizer to give blue solid. The structure of compound **4** was fully confirmed by proton NMR spectrum (Fig. S5) and mass spectrometry measurement (Electrospray Ionization, ESI, Fig. S6), which are available in supporting information. UV–Vis (DMSO): λ_{max} = 677 nm, HRMS (ESI): *m/z* calculated for $C_{41}H_{31}N_{12}OZn^+$ $[M - I]^+$ 771.2035, found 771.2043. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ = 9.57 (s, 1H, Pc-H_α), δ = 9.00–9.28 (m, 7H, Pc-H_α), δ = 8.96 (s, 1H, - HN-CO-), δ = 8.59 (d, J = 8.0 Hz, 1H, Pc-H_β), δ = 8.02–8.27 (m, 6H, Pc-H_β), δ = 4.26–4.54 (m, 4H, N-CH_2-N^+), δ = 3.99 (d, J = 8.0 Hz, 2H, N-CH_2-N), δ = 3.69 (s, 2H, C-CH_2-N^+), δ = 3.39 (s, 3H, CH_3-N^+), δ = 2.59 (s, 4H, C-CH_2-N).

3.3. Bacteria strain and culture conditions

The bioluminescent bacterial strains Gram-positive *S. aureus*, luminescent *Staphylococcus aureus* Xen29 were purchased from Shanghai Biofeng Company (China). The Gram-negative bacteria, *Escherichia coli* (*E. coli* DH5α), were transformed with bioluminescent plasmid (pAKlux2.1) in our laboratory. They were also grown in Luria-Bertani medium (LB medium) at 37 °C overnight. Then 100 μl of suspension of the bioluminescent bacteria was added into fresh medium (10 ml) to grow again until their optical density at 600 nm (OD600) reached about 0.6 (10^8 CFU/ml). The luminescent bacteria were further diluted with PBS to give a relative luminescence intensity of roughly 2.0×10^5 for *E. coli* and 1.0×10^5 for *S. aureus* in opaque white 96-well plate and read with Synergy 4 multi-mode microplate reader. The luminescence intensity was proportional to the amount of live bacteria within certain range.

The Gram-positive *S. aureus* ATCC6538 and Gram-negative *E. coli* ATCC25922 were grown in LB medium at 37 °C with agitation of 220 rpm for 7 h firstly. Then 60 μl of the suspension was added into fresh medium (2 ml) to grow again (about 7 h for *S. aureus*, and 6 h for *E. coli*) to mid log phase. The cells were harvested at 4000 rpm for 5 min, washed twice and re-suspended with PBS. The bacteria suspension (about 10^6 CFU/ml) was obtained after the dilution of 100 folds with PBS.

3.4. Photodynamic inactivation of bacteria

The photosensitizers (PS) were dissolved in DMSO (1 ml) to 2.0 mM and kept in the absence of light until use. After dilution with water by 10 folds, it was further diluted into concentration gradients with DMSO:water (1:9). These PS gradients (20 μl each) were transferred

into opaque 96-well microplates containing bacteria suspension (about 10^6 CFU/ml, 180 μl). Final concentration of DMSO was kept to be low (1%) and nontoxic to the bacteria. Then the bacteria were incubated at 37 °C in the dark (10 min for *S. aureus*, and 15 min for *E. coli*). After that, the microplate was illuminated with a planar LED light source ($\lambda = 660$ nm ± 25 nm, fluency rate = 42.5 mW/cm^2) for 5 min to give a light dose of 12.7 J/cm^2. After the illumination, the luminescence intensity of the microplate was monitored on microplate reader for 50 min with 2 min interval (Fig. S7). The survival fractions S_l were calculated as following formula:

$$S_l = (Le/Lc) \times 100\%$$

Here, Le and Lc were luminescence intensity of the experimental and control group, respectively.

To measure antimicrobial effect on Gram-positive *S. aureus* ATCC6538 and Gram-negative *E. coli* ATCC25922, the PS was added to bacteria at various concentrations in transparent 96-well microplate under the same condition, incubated (10 min for *S. aureus*, and 15 min for *E. coli*), and illuminated for 5 min using our LED light source. To count the number of alive bacteria, 100 μl of the bacteria suspension from each well was taken out for serial dilution with PBS. Then 100 μl of the each diluted bacteria suspension was added into agar plate and incubated at 37 °C overnight for counting of viable colonies (the agar plates were prepared with LB medium one day in advance). The survival fractions S were calculated as following formula:

$$S = (Ne/Nc) \times 100\%$$

Here, Ne and Nc were colony amount of the experimental and control group, respectively.

3.5. Safety evaluation of compound 4 in blood lysis activity toward red blood cells

In Eppendorf tubes, 450 μl 0.9% NaCl was mixed with the same volume of 2% erythrocytes from healthy mice and 100 μl compound **4** which was dissolved in PBS containing 10% DMSO was added to adjust the final concentration of the photosensitizer into gradient concentrations (0.1–10 μM). Ultrapure water (550 μl) was used as positive control to induce hemolysis, and 0.9% NaCl (450 μl) was used as negative control. Samples were incubated at 37 °C in water bath for 1 h, then followed by centrifugation for 10 min at 800 rpm. The OD of 576 nm of supernatants were measured in a 96-well plate with 200 μl of samples. The hemolysis percentage Q was calculated with the following formula:

$$Q = (As-An)/(Ac-An) \times 100\%$$

Here, As, An, and Ac were absorbance of samples, negative control, and positive control, respectively.

3.6. Statistical analysis

All the data of the assays was obtained after at least three parallel experiments, and the results were expressed as mean value and standard deviation.

4. Conclusions

In conclusion, a new asymmetric mono-substituted Zn(II) phthalocyanine compound **3** and its cationic derivative compound **4** were synthesized and characterized. The photodynamic antimicrobial data showed that compound **3** only inactivated Gram-positive bacterial strains. However, the cationic compound **4** induced > 4 logs antimicrobial effect against both of Gram-positive and Gram-negative strains under short incubation time and low light dose. In addition, the compound **4** exhibited negligible toxicity in the hemolysis experiment, suggesting its potential safety for mammalian cells and feasibility for in vivo application as anti-microbial agent.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2018.10.001.

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