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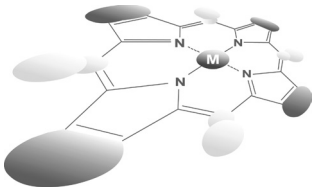

Synthesis and photodynamic activities of a new metronidazole-appended porphyrin and its Zn(II) complex

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ABSTRACT: One novel porphyrin 5,10,15-tris(phenyl)-20-[4-(2-(2-methyl-5-nitro-imidazolyl)ethoxyl) phenyl] porphyrin and its zinc(II) metalloporphyrin were synthesized and characterized by IR, UV-vis, ^{1}H NMR, MS and elemental analysis. The single crystal structure of zinc(II) porphyrin shows that the Zn(II) ion is coordinated with four nitrogen atoms of porphyrin ring and one oxygen atom of ethanol from axial, forming a five-coordinated square pyramidal geometry. Their cytotoxicity and photodynamic activity against breast cancer cells were studied. The results indicate that both of the porphyrins display high phototoxicity to the breast cancer cells with the negligible dark toxicity. In addition, the photodynamic activity of zinc(II) porphyrin was obviously higher than that of the free porphyrin.

KEYWORDS: porphyrin, zinc(II) porphyrin, photodynamic therapy (PDT), cytotoxicity, phototoxicity, breast cancer.

INTRODUCTION

During the past decades, there has been a growing interest in using porphyrins as photosensitizers in the photodynamic therapy (PDT) of cancer [1–7]. Compared with conventional treatment methods, such as surgery, chemotherapy and radiation, PDT is a promising therapeutic modality for the treatment of a variety of premalignant and malignant diseases, which utilizes suitable illumination that can be replaced in the same site if necessary [8, 9]. Because of its low cytotoxicity, no surface damage, the capacity of highly selective, destroying cancer cells without harming normal tissues and relatively lower cost than surgery, PDT is a valuable therapy method. In the process of PDT, the porphyrins as photosensitizers generally accumulate in cancer tissues with a relative high concertration and generate the cytotoxic singlet oxygen ($^1O_2$), which can induce damages to cancer cells and result in their death [10, 11].

Introducing additional functional groups onto the porphyrin skeleton has been effectively employed to extending the functionalities of tetrapyrrole chromophores [12]. In order to develop new porphyrin photosensitizers, several modified porphyrin derivatives, like porphyrins linked with amino acid, steroid, imidazole and nucleotide have been employed and investigated in the treatment of cancers in recent years [13–17]. Metronidazole (MTZ), the Food and Drug Administration (FDA)-approved pharmaceutical intermediate [18], which plays a significant role in biological metabolism, particularly against the disabled cells. Its anti-inflammation and antibacterial function make this medicine popular and heat-sensing among the medical domain. So introducting metronidazole as a group into the porphyrin may further increase the anticancer activity of porphyrin.

It has been reported that a range of metalloporphyrins have been investigated as photosensitizers in cancer treatment, and among those porphyrins, Zn, Ru and Co metalloporphyrins showed dramatic and diverse biological activities in preclinical studies [19]. In addition, as one life essential element, Zn(II) ion plays

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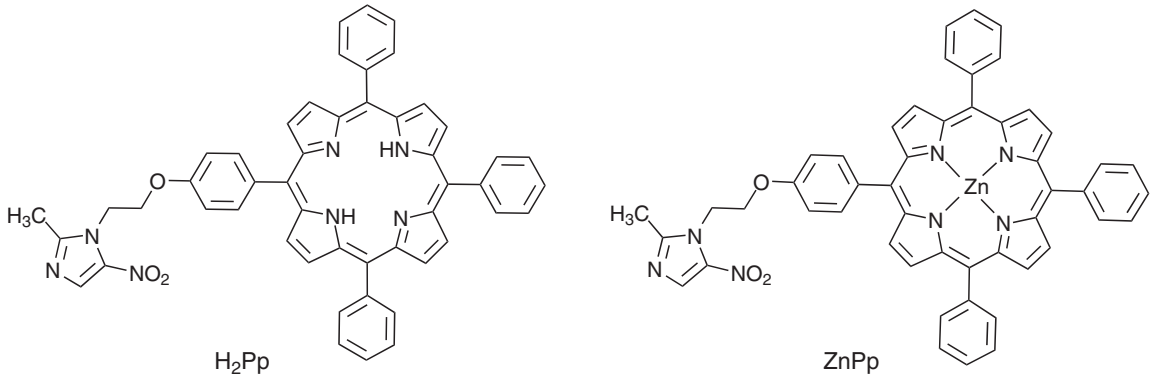


Fig. 1. The structure of porphyrins **H_2Pp** and **ZnPp**

vital roles in cellular metabolism, gene expression, apoptosis, neurotransmission, and so forth [20, 21]. It is also associated with physical growth retardation and neurological disorders such as cerebral ischemia and Alzheimer's disease [22].

For the above reasons, in this paper, we synthesized a new metronidazole-appended porphyrin, 5,10,15-tris (phenyl)-20-[4-(2-(2-methyl-5-nitro-imidazolyl)ethoxyl) phenyl]porphyrin **H_2Pp** and its corresponding zinc(II) porphyrin **ZnPp** (Fig. 1). Their cytotoxicities and photo-toxicities against breast cancer cells were also studied.

RESULTS AND DISCUSSION

Synthesis of H_2Pp and ZnPp

The synthetic route of **H_2Pp** and Zn(II) porphyrin was outlined in Scheme 1. **H_2Pp** was synthesized by the reaction of 5-(4-bromophenyl)-10,15,20-tri(phenyl) porphyrin and metronidazole in DMF in the presence of K_2CO_3 at room temperature with the yield about 70%. The **ZnPp** was obtained by reaction of **H_2Pp** with excess of $Zn(Ac)_2$ in a 25 mL teflon-lined stainless reactor at 90 °C. The purple bulk-like single crystals were collected in 72% yield.

Characterization of H_2Pp and ZnPp

The structures of **H_2Pp** and **ZnPp** were characterized by elemental analysis, mass spectrometry, UV-vis, FT-IR and ^{1}H NMR.

From the UV-vis spectra in Fig. 2, we can find that the free porphyrin **H_2Pp** exhibits the Soret band at 418 nm and four weak Q-bands in the 510–650 nm region, while the ZnPp has the Soret band at 420 nm, and only two weak Q-bands at 548 nm and 588 nm respectively. The insertion of zinc(II) ion into the porphyrin ring causes a decreasing number of Q-bands, due to the increasing symmetry of the porphyrin ring when the H ions of N–H are replaced by Zn(II) ion. Also a red shift of the Soret

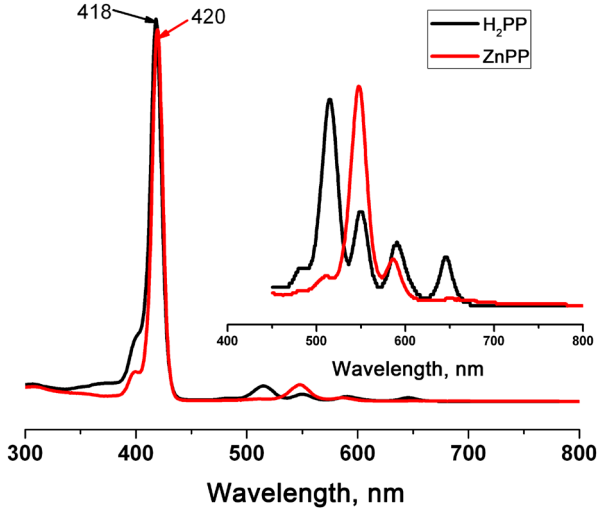


Fig. 2. UV-vis spectra of **H_2Pp** and **ZnPp**

band can be found in the metalloporphyrin spectrum (418 and 420 nm for **H_2Pp** and **ZnPp** respectively). This is induced by the delocalized π bonds which decrease the average electron density in metalloporphyrin.

In the FT-IR spectroscopy data (Table 1), the absorption peaks around 3436 and 962 cm^{-1}, observed in **H_2Pp**, are related to the stretching and bending vibrations of the central N–H of porphyrin ring, and the two peaks are absent for **ZnPp** because of the coordination of four N atoms with Zn(II) ion. The bands at 1545 cm^{-1} and 1548 cm^{-1}, found in the spectra of both **H_2Pp** and metalloporphyrin, are associated with the stretching vibrations of $-NO_2$; and the bands around 1250, 1160, 1100 cm^{-1} are attributed to the stretching vibrations of Ph–O–C.

The ^{1}H NMR spectrum of the porphyrin **H_2Pp** has been determined in $CDCl_3$. It is showed that the chemical shift of eight β-pyrrolic proton resonances is around at δ = 8.79–8.88 ppm, and the peaks at 8.21, 8.11, 7.93, 7.75 ppm are the resonance of 19 protons of the benzene

Table 1. Data of mass spectroscopy and FT-IR spectroscopy of **H_2Pp** and **ZnPp**

Porphyrin	MS (m/z, $[M + 1]^+$)	FT-IR (U, cm^{-1})
H_2Pp	799.7	3436 (U_{NH}), 1545 ($U_{C\text{-}NO2}$), 1284 ($U_{Ph\text{-}O\text{-}C}$), 1171 ($U_{Ph\text{-}O\text{-}C}$), 1047 ($U_{Ph\text{-}O\text{-}C}$), 962 (U_{NH})
ZnPp	877.3	1548 ($U_{C\text{-}NO2}$), 1176 ($U_{Ph\text{-}O\text{-}C}$), 1064 ($U_{Ph\text{-}O\text{-}C}$))

rings. The double peaks at δ = 7.17 ppm can be ascribed to the proton of imidazole. The multiple peaks of $–CH_2–$ protons from $–CH_2–CH_2–O–$ are detected at 4.42 ppm. Then, the single peak around 2.66 ppm belongs to the protons of the $–CH_3$. In the end, the single peak around δ = -2.78 ppm is from the protons of the –NH group in porphyrinic core.

X-ray powder diffraction (PXRD)

PXRD experiment has been carried out to check the phase purity of the complex **ZnPp**. The experimental and computer-simulated PXRD patterns are shown in Fig. 3. All the characteristic peaks are well-matched with that of simulated one, which suggest that they are identical samples.

Crystal structure description

The single crystal X-ray diffraction analysis illustrated that the complex **ZnPp** crystallized in the triclinic crystal system and P-1 space group. As shown in Fig. 4(a), the Zn(II) ion inserted into the core of porphyrin by coordinating to four pyrrole nitrogen atoms. At the same time, an oxygen atom of ethanol coordinated to Zn(II) ion in the axial direction to form a pyramidal geometry. The coordination bond lengths of Zn–N ranged from 2.067(12) to 2.080(10)Å, and the bond length of Zn(2)–O(4) is 2.108(11) Å. The angle of N(3)–Zn(2)–O(4) measured to be 97.6(5)°.

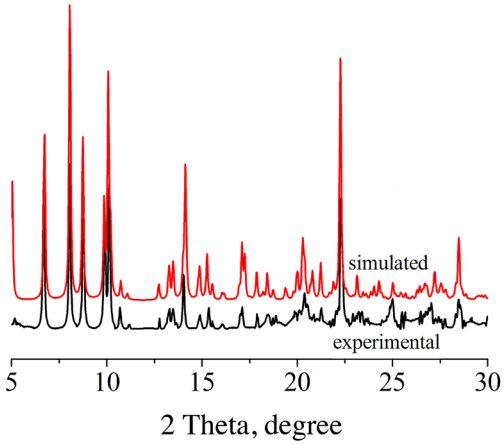
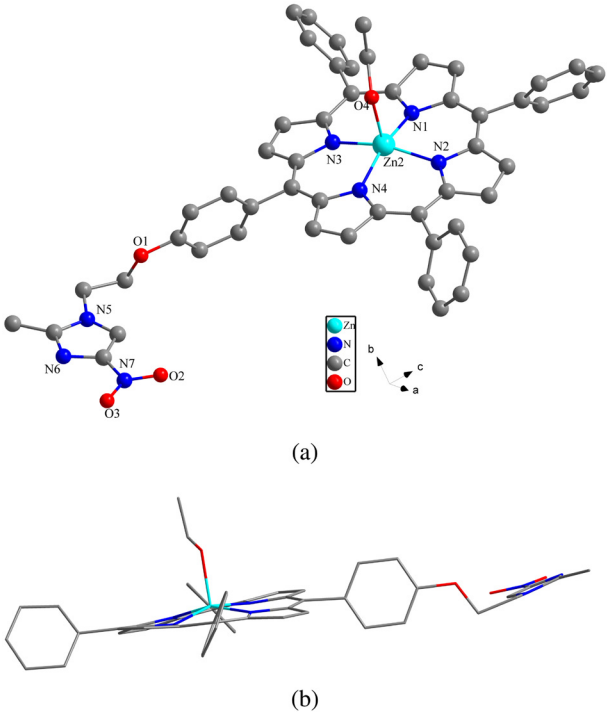


Fig. 3. PXRD patterns of Zn(II) porphyrin



(a)

(b)

Fig. 4. The coordination environment of Zn(II) (a), and the structural conformation of **ZnPp** (b)

The porphyrin macrocycle in **ZnPp** displays a distorted configuration owing to the four pyrrole rings slightly distorted in an alternant pattern either upward or downward with respect to the mean plane of the porphyrin core. The angles of the two aryl rings in para-position and the aryl ring with metronidazole ethoxy to its para-position aryl ring were measured to be 65.66°, 9.68° respectively, shown in Fig. 4(b).

Cytotoxicity and phototoxicity

The dark cytotoxicities of **H_2Pp** and **ZnPp** were investigated with the breast cancer cells at the concentration of 0 μM, 0.25 μM, 0.5 μM, 1.0 μM, 5 μM, 10 μM, respectively, and viabilities of the breast cancer cells were determined by using the MTT assay. As shown in Fig. 5 orange bars, both **H_2Pp** and **ZnPp** exhibited very low dark cytotoxicities with the survival rate above 80%. However, after being exposed to metal halide lamp (50 $mW.cm^{-2}$) for 30 min, they were found to be phototoxic towards the breast cancer cells. The results,

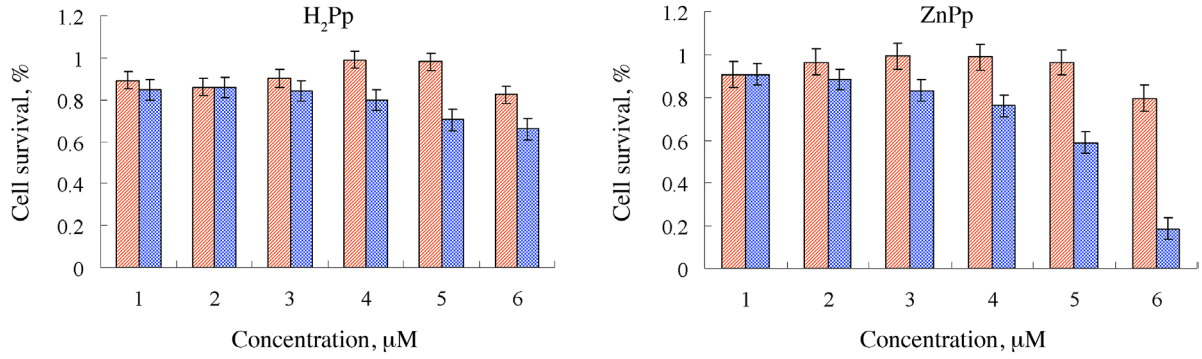


Fig. 5. Cytotoxicity (orange bars) and phototoxicity (blue bars) of the **H_2Pp** and **ZnPp** in different concentrations (0 μM, 0.25 μM, 0.5 μM, 1.0 μM, 5 μM, 10 μM respectively) on breast cancer cells

represented in Fig. 5 blue bars, showed cells survival rates decreased to 65.3% and 17.8% respectively with the increase of porphyrins concentration, and the anti-cancer activity of **ZnPp** was obviously higher than that of **H_2Pp**.

As reported in Ref. [23], Vicente *et al.* used the Zn(II) *meso*-tetra[4-(nidocarboranyl)phenyl] porphyrin to human K562 cells, after treatment with this porphyrin in the dark and in the presence of light, the cells survival rates decreased to 89% and 86% respectively. Obviously, **ZnPp** shows high inhibition rate to breast cancer cells compared with one reported Zn(II) porphyrin. We likely credit the contribution to the role of the peripherial metronidazole group.

EXPERIMENTAL

Chemicals and instruments

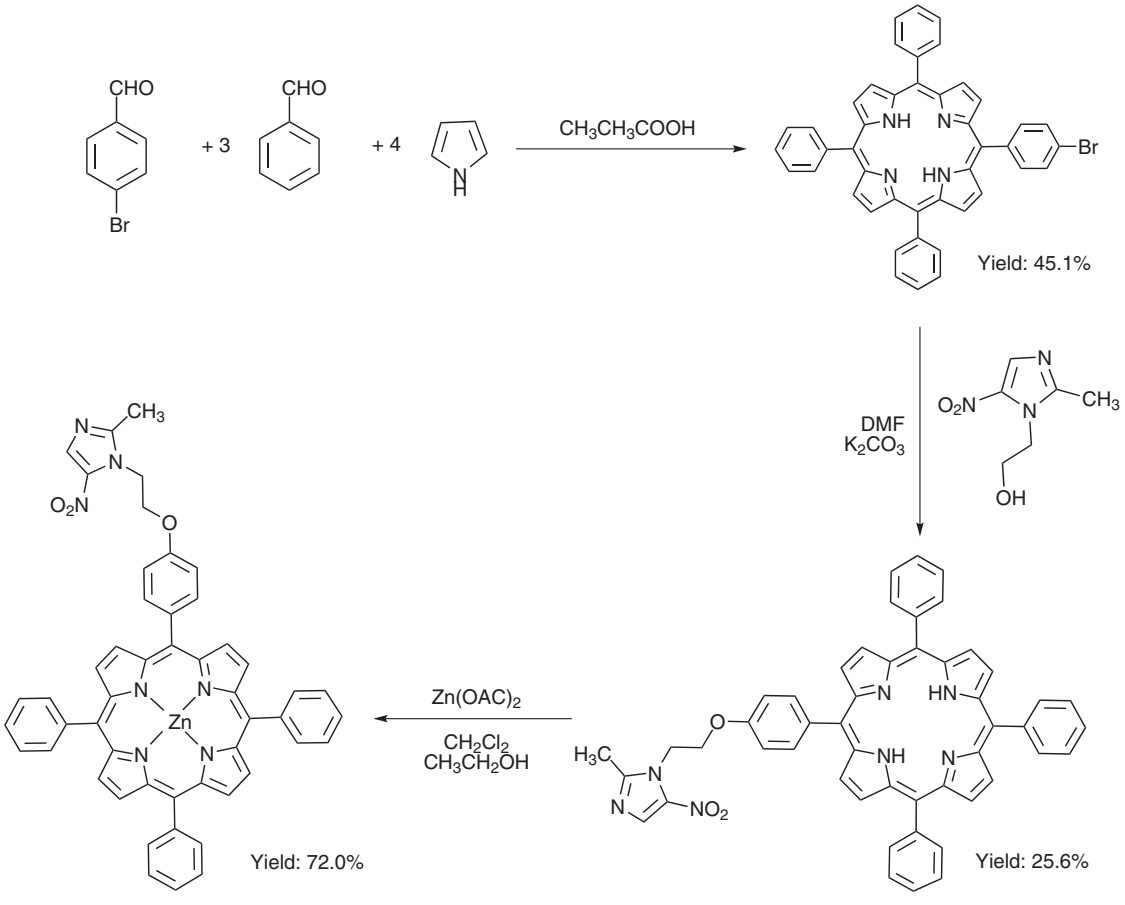
4-Bromobenzaldehyde, benzaldehyde and pyrrole were purchased from Sinopharm Chemical Reagents Company. 1,3-Diphenylisobenzofuran (DPBF), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and other reagents were obtained from Beijing chemical, reagents company. They were used without further purification except pyrrole and *N*,*N*-dimethyl formamide (DMF), which were distilled before use. Dimethyl sulfoxide (DMSO) was dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Chromatographic separations were carried out on silica gel (100–200 mesh).

Elemental analyses (C, H and N) were performed by Vario EL-α CHNOS instrument. UV-vis spectra were measured on a Shimadzu UV 1800 UV-vis-NIR spectrophotometer. FT-IR spectra were recorded on a BEQUZNDX-550 spectrometer on samples embeded in KBr pellets. Mass spectrometry (MS) analysis were carried out on a matrix assisted laser desorption/ionization time of flight mass spectrometer (MALDI-TOF MS, Krato Analytical Company of Shimadzu Biotech, Manchester, Britain). The ^{1}H NMR spectra were recorded using a Bruker Advance 400 MHz NMR spectrometer. The powder X-ray diffraction (PXRD) patterns were taken with a Bruker D8 diffractometer using graphite monochromatic copper radiation (Cu Kα) at 40 kV, 30 mA over the 2θ range from 5 to 30°.

Synthesis

5,10,15-Tris(phenyl)-20-[4-(2-(2-methyl-5-nitro-imidazolyl)ethoxyl)phenyl]porphyrin (H_2Pp). 5,10,15-tris(phenyl)-20-[4-(2-(2-methyl-5-nitro-imidazolyl) ethoxyl)phenyl]porphyrin was synthesized by following the two steps, shown in Scheme 1. Firstly, 4-bromobenzaldehyde (1.84 g, 0.01 mol), benzaldehyde (1.06 g, 0.03 mol) and pyrrole (0.04 mol, 2.5 mL) were dissolved in 150 mL propionic acid in a three-necked bottle. The mixture was heated to reflux and was stirred for about 50 min. Then the solution was cooled to room temperature, and two-thirds of solvent was removed under vacuum and 40 mL C_2H_5OH was added. The mixture was cooled overnight in refrigerator and filtered under vacuum. Then the crude products were purified by chromatography on a silica-gel column with CH_2Cl_2 as eluant to give 5-(4-bromophenyl)-10,15,20-tri(phenyl)porphyrin as a purple solid. Yield 45.1%.

Subsequently, the desired porphyrin was obtained by metronidazole (0.17g, 0.001mol) and 5-(4-bromophenyl)-10,15,20-tri(phenyl)-porphyrin (0.69 g, 0.003 mol) was mixed in 20 mL DMF and stirred in the presence of K_2CO_3 for nearly 24 h in the darkness at room temperature, which was monitored by TLC. After the reaction was completed, DMF was removed under vacuum. The residue was purified by chromatography on a silica-gel column with CH_2Cl_2 as eluent, porphyrin **H_2Pp** was obtained. Yield 25.6%. mp > 250 °C, Anal. calcd. (found) for $C_{50}H_{37}N_7O_3$: C 76.67 (76.61), H 4.74 (4.76), N 12.49 (12.51). ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 8.88–8.79 (m, 8H, β position of the pyrrol), 8.21 (d, J = 6.1 Hz, 6H, Ar), 8.11 (d, J = 8.5 Hz, 2H, Ar), 7.93 (s, 2H, Ar), 7.75 (d, J = 7.3 Hz, 9H, Ar), 7.17 (d, J = 8.6 Hz, 1H, imidazole), 4.42 (dd, J = 10.6, 4.0 Hz, 4H, –CH_2–), 2.61 (s, 3H,



Scheme 1. The Synthesis of **H_2Pp** and **ZnPp**

$-CH_3$), -2.78 (s, 2H, –NH). FT-IR (KBr): ν, cm^{-1} 3436, 2921, 2359, 1641, 1601, 1544, 1499, 1465, 1397, 1336, 1284, 1239, 1171, 1047, 962, 797, 736, 702, 646. UV-vis ($CHCl_3$): λ_{max}, nm 418 (Soret), 515 (QI), 550 (QII), 590 (QIII), 645 (QIV). MS: *m/z* 799.7 $[M + 1]^+$ amu.

Zn(II) 5,10,15-tris(phenyl)-20-[4-(2-(2-methyl-5-nitro-imidazolyl)ethoxyl)phenyl]porphyrin (ZnPp). To a solvent of 5 mL CH_2Cl_2 and 2 mL anhydrous ethanol, added **H_2Pp** (0.001 mol 0.78 g) and $Zn(CH_3COO)_2{\cdot}2H_2O$ (0.003 mol, 0.65 g) with stir until their fully dissolution. Then sealed the solution in a 25 mL teflon-lined stainless reactor and heated slowly to 90 °C in 2 h and kept for 72 h. After that, it was cooled to the room temperature within 24 h. The purple bulk-like single crystals were collected in 72.0% yield. Anal. calcd. (found) for $C_{52}H_{40}N_7O_3Zn$ (%): C 71.11 (71.04), H 4.49 (4.44), N (11.37). IR spectrum (KBr): ν, cm^{-1} 3457, 2925, 2365, 1652, 1506, 1380, 1340, 1242, 1176, 1064, 995, 799, 701, 569. MS: *m/z* 877.7 $[M + 1]^+$ amu.

Crystallographic data collection and refinement

The crystallographic data-set was obtained on a Bruker SMART CCDC diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Absorption correction was performed by using SADABS program [24]. The structure was solved by direct method and refined by full-matrix least-squares techniques using the program SHELXL-97 [25]. Anisotropic thermal parameters were assigned to all non-hydrogen atoms. The hydrogen atoms on carbon were placed in geometrically calculated positions with a fixed C–H distance (0.97 Å). The crystal parameters of the complex ZnPp were given in Table 2. Selected bonds distances and angles were listed in Table 3.

Study on breast cancer cells

Cell culture conditions. Breast cancer cells were cultured in plastic culture flasks at 36.5 ± 0.5 °C and 5% CO_2 humidified sterile incubator, by using DMEM/F-12 medium with penicillin (100 $UI.mL^{-1}$), streptomycin (100 $\mu g.mL^{-1}$) and 10% heat-activated fetal bovine serum. When cells were in the exponential growth phase, the medium was removed and washed with 5 mL of phosphate buffer saline (PBS) for three times, and treated with trypsin 2 mL to separate them from the flasks and collected into a centrifuge tube containing 4 mL of the culture medium.

Cytotoxicity and phototoxicity. During the cytotoxicity test, the same concentrations of cells were suspended in

Table 2. The crystal parameters of complex **ZnPp**

Complex	**ZnPp**
Empirical formula	$C_{50}H_{35}N_7O_3Zn$ $C_{56}H_{36}N_{12}Mn$
M, g.mol^{-1}	1843.16
θ range, °	1.16–28.25
Crystal system	triclinic
T, K	296
Space group	*P-1*
a, Å	9.986(7)
b, Å	13.628(9)
c, Å	17.615(11)
α, °	94.055(14)
β, °	92.306(15)
γ, °	104.930(13)
V, Å^3	2306(3)
Z	1
Dcalc, g.cm^{-3}	1.327
F(0 0 0)	916
μ, mm^{-1}	0.580
R_1/wR_2 [I > 2θ(I)]	R_1[a] = 0.1544 wR_2[b] = 0.2833
R_1/wR_2 (all reflections)	R_1 = 0.4368 wR_2 = 0.4353
Goodness-of-fit	1.044
Largest diff. peak and hole, eÅ^{-3}	0.597 and -0.989

[a] $R_1 = \sum(|F_o|-|F_c|)/E|F_o|$, [b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

Table 3. Selected bond lengths (Å) and angles (°) for ZnPp

Bond lengths, Å			
Zn(2)-N(3)	2.067 (12)	Zn(2)-N(4)	2.080 (10)
Zn(2)-N(1)	2.070 (12)	Zn(2)-O(4)	2.108 (11)
Zn(2)-N(2)	2.077 (11)	O(1)-C(74)	1.436 (18)
Angles,°			
N(3)-Zn(2)-N(2)	161.2 (5)	N(3)-Zn(2)-O(4)	97.6 (5)
N(1)-Zn(2)-N(2)	89.0 (5)	N(1)-Zn(2)-O(4)	97.7 (5)
N(3)-Zn(2)-N(4)	89.2 (5)	N(2)-Zn(2)-O(4)	101.2 (5)
N(1)-Zn(2)-N(4)	163.2 (5)	N(4)-Zn(2)-O(4)	99.1 (5)
N(2)-Zn(2)-N(4)	87.6 (4)	C(22)-N(2)-C(20)	106.8 (12)

Dulbecco's modified eagle medium (DMEM) and were ultrasonicated for 30 s to prevent agglomeration. To evaluate the toxicity of the porphyrins, the breast cancer cells were cultured in 200 mL growth medium at a concentration of 2×10^4 cells.well^{-1} in 96-well microtiter plates containing 200 μL culture medium per well, and incubated for 24 h in growth medium in a humidified 5% CO_2 incubator at 37 °C. Then, the free porphyrin and the zinc porphyrin dissolved in DMSO were added to the quintuplicate wells, in different concentration of 0 μM, 0.25 μM, 0.5 μM, 1.0 μM, 5 μM and 10 μM respectively.

After 24 h incubation, the 20 μL MTT (5 mg.mL^{-1}) was added to each well and incubated for 4 h. The culture medium was removed and the MTT reduzate was dissolved by adding 150 μL DMSO. After 20 min oscilation, the absorbance was measured using an enzyme-linked immuneoabsorbent assay plate reader (Bio-Rad) at 680 nm. The survival rate of cells was given as the percentage compared to the untreated cells.

In the phototoxicity test, the breast cancer cells were cultured as described above. Then, the **H_2Pp** and **ZnPp** were dissolved in DMSO and added to the quintuplicate wells respectively, developed for another 24 h in the darkness. Then the cells were immediately exposed to metal halide lamp (50 mW.cm^{-1}) for 30 min and after 24 h incubation. The viability of cells was measured by the MTT assay [26, 27].

CONCLUSION

In summary, a novel metronidazole-based porphyrin derivative and its complex zinc(II) metalloporphyrin were synthesized, then the crystal structure of **ZnPp** was analyzed. Their cytotoxicities and phototoxicities were evaluated with the MTT assay. The results indicate that they exhibit nearly no cytotoxicity towards breast cancer cells in the absence of light, however, after UV irradiation for a certain period of time, they display different degrees of phototoxicity, and the phototoxicity of the zinc(II) porphyrin is obviously higher than that of the free porphyrin, which may provide some valuable reference for these porphyrin derivatives applied in PDT for non-invasive treatment of cancer in the future.

Acknowledgements

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Supporting information

Crystallographic data for Zn(II) porphyrin have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under numbers CCDC-952593. Copies can be obtained on request, free of charge, *via* www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033 or email: data_request@ccdc.cam.ac.uk).

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