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Synthesis, separation and characterization of amphiphilic 2,10-di-sulfonato-18,26-di-phthalimidomethyl phthalocyanine zinc di-potassium salt by template reaction

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Abstract

An amphiphilic 2,10-di-sulfonato-18,26-di-phthalimidomethyl phthalocyanine zinc di-potassium salt (**3**) was synthesized by first direct condensation of hydrophilic precursor 4-sulfonic phthalic acid mono-potassium salt (**1**) with hydrophobic precursor 4-phthalimidomethyl phthalic acid (**2**). Then the condensed mixture was separated by reverse HPLC method and further purified by a membrane separation method. The composition of the title compound was characterized by elemental analysis, UV, ^{1}H NMR, ^{13}C NMR as well as TG and DTA, and its C_{4h}-structure was identified according to the ^{1}H NMR signal of submethyl protons of the phthalimidomethyl groups in the phthalocyanine ring, polarity and synthetic mechanism. In vivo antitumor activity of the title compound as photosensitizer showed that its inhibitory rate was up to 90.3%. This amphiphilic photosensitizer has a potential application in the photodynamic therapy of cancer.

Keywords: 2,10-Di-sulfonato-18,26-di-phthalimidomethyl phthalocyanine zinc; Synthesis; Separation; Characterization; Photodynamic therapy

1. Introduction

In the last few years, phthalocyanine (Pc) and their substituted derivatives (Pcs) have been intensively studied as second-generation photosensitizers for photodynamic therapy (PDT) of cancer [1,2]. The presence of both hydrophobic and hydrophilic groups in the Pc ring would be beneficial for better performance in tumor selectivity [3]. On the other hand, an amino or imido substituted Pc seems to have advantages because of its hydrophobic characteristic and its possibility of high interaction with proteins or covalent bonding with monoclonal antibodies [4]. Adopting this concept, our research group has successfully synthesized a new photosensitizer disulfonato diphthalimidomethyl phthalocyanine zinc di-potassium salt ($ZnPcS_2P_2K_2$) [5] with amphiphilic character. In vivo and in vitro assay showed that it has good anticancer activities and low toxicity. This compound, the method of making it and the application in the anticancer drug was the subject of Chinese patent, No: ZL 96117137.5 [6]. In that patent, the method for preparation of this amphiphilic metal phthalocyanine compound ($ZnPcS_2P_2K_2$) comprised two steps: firstly, the synthesis of the un-substituted phthalocyanine zinc, then the introduction of the both 4-sulfonic and phthalimidomethyl groups into the Pc ring system simultaneously by the “in a plot” reaction [7]. As the “in a plot” reaction lacked region-selectivity, it unavoidably led to a complicated mixture which was

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difficult to be separated by common chromatographic methods.

Therefore, an efficient synthetic route was required. The alternative procedure for the preparation of this amphiphilic metal phthalocyanine was the mixed-condensation of two types of precursors (hydrophilic and hydrophobic) which differ substantially in their physical properties and reactivates, required a detailed study of optimal reaction conditions. Up to date, we still have not seen a successful example. Kudrevich et al. [8] synthesized a series of amphiphilic metal phthalocyanines containing both sulfonic and *tert*-butyl groups by multi-step reaction. The detailed procedure was described as: first, condensation of two hydrophobic precursors with similar properties, 3-nitro phthalinitrile with 4-*tert*-butyl phthalinitrile, then via the Meerwein reaction to obtain mono-sulfonato-tri-*tert*-butyl phthalocyanine zinc. However, di- and tri-sulfonato phthalocyanine cannot be obtained using this synthetic route.

In order to improve the "in a plot" reaction method and avoid the problems associated with the reaction of incompatibility of the hydrophilic and hydrophobic precursors, we directly condensed hydrophobic precursor 4-phthalimidomethyl phthalic acid (**2**) with hydrophilic precursor 4-sulfonic phthalic acid mono-potassium salt (**1**) by template reaction. The separation of $ZnPcS_2P_2K_2$ was accomplished by reverse HPLC method. The structure of $ZnPcS_2P_2K_2$ was characterized by spectroscopic techniques.

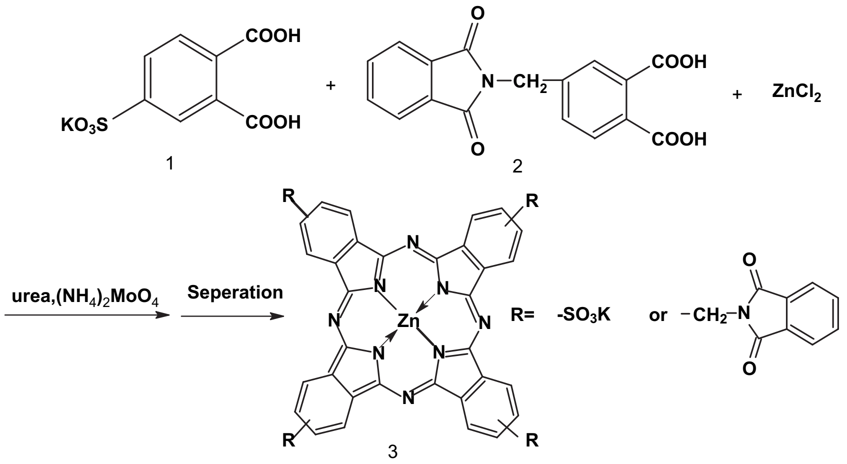
2. Result and discussion

The hydrophilic precursor 4-sulfonic phthalic acid mono-potassium salt (**1**), its corresponding tetra-sulfonato phthalocyanine zinc tetra-potassium salt ($ZnPcS_4K_4$) [9] and the hydrophobic precursor phthalimidomethyl phthalic acid (**2**), its corresponding tetra-phthalimethyl phthalocyanine zinc ($ZnPcP_4$) [10], had been prepared in our previous study.

The mixed-condensation of (**1**) with (**2**) (1 equiv) was carried out with zinc chloride anhydrate as template agent and $(NH_4)_2MoO_4$ as catalyst (Scheme 1). Precursor (**1**) turned out to be more reactive than (**2**) and, to a large extent, underwent self condensation after some hours. It was therefore necessary to add (**1**) periodically until all the precursor (**2**) had reacted (see Section 4). Moreover, in order to reduce self-condensation of (**2**) in the absence of (**1**), an equimolecular of chloride zinc anhydrate with respect to the amount of (**1**) was added with each portion of latter. Under these conditions, a mixture composed of all possible structure was obtained.

In order to find the optimal conditions for synthesis of $ZnPcS_2P_2K_2$, trials were performed at different material molar rate, reaction time and reaction temperature of precursors (**1**) and (**2**) of 2:2, 2.5:2, 2:2.5; 6 h, 12 h, 16 h and 180 °C, 200 °C, 220 °C. The optimal condition was found through polar difference analytic method by comparing the HPLC curve peak area of $ZnPcS_2P_2K_2$ of each trial. The optimum conditions were found to be: (**1**) to (**2**) 2:2, reaction time 16 h and reaction temperature 200 °C.

Tetra-sulfonato phthalocyaninato zinc tetra-potassium salt ($ZnPcS_4K_4$), produced by self-condensation of precursor (**1**) was separated from other fractions by washing with a large volume of water. In order to achieve the desired $ZnPcS_2P_2K_2$, several separation methods such as micellar electrokinetic capillary chromatography method (MECK), ion exchange method and solvent extractive method were examined. The reverse High Performance Liquid Chromatograms (HPLC) method showed to be the better one. The separation was accomplished on Dynamax model



Scheme 1. Synthesis of $ZnPcS_2P_2K_2$.

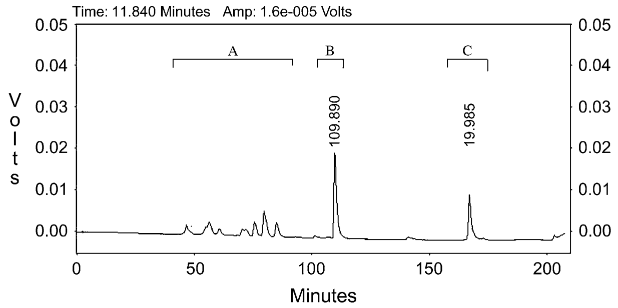


Fig. 1. HPLC chromatogram of phthalocyanine zinc mixture. Mobile phase: 10 mmol KOH–KH_2PO_4 phosphate buffer/95% ethanol, gradient: 95% ethanol (0–200 min, 0–100%), detection wavelength: 670 nm, temperature: 25 °C.

HPLC apparatus produced by Varian-Rainin Inc. Analytical separate curve shown in Fig. 1 was achieved on Rainin C18 (5 μm, 10 nm) 250 mm × 4.6 nm stainless column, and separation was carried out on Rainin C18 (8 μm, 10 nm) 250 mm × 41.4 nm stainless column. The membrane separation method of whose cut off molecular weight 450 was used to remove phosphate and methanol introduced in the chromatography process. The obtained solution was concentrated and refrigerated to dryness.

The fractions A, B and C (Fig. 1.) were collected, respectively, according to the retention time. Then, they were vacuum dried at 100 °C for more than 12 h. Elemental analysis was done to determine the composition of each fraction. The constitution of B was: calculated (%): C, 49.81; H, 3.06; N, 12.40; found: C, 50.04; H, 2.33; N, 11.67. This result basically conformed the composition of di-sulfonato-di-phthalimidomethyl phthalocyanine zinc di-potassium salt whose formula was $C_{50}H_{24}N_{10}S_2K_2Zn{\cdot}4H_2O$.

IR spectrum of fraction B indicated the existence of both sulfonic groups and phthalimido-methyl groups by the intense absorption at 1185–1028 cm^{-1} (S–O stretching vibration), 614 cm^{-1} (C–S stretching vibration), 1725 cm^{-1}(C=O stretching vibration) and 2926–2856 cm^{-1}($C(sp^3)$–H stretching vibration).

UV/Vis spectra of B in DMSO showed only one peak for its characteristic Q band at 672 nm and it did not split.

The ^1H NMR and ^{13}C NMR data of fraction B (D_2SO_4, 500 MHz) were listed in Tables 1 and 2. In the submethyl groups region there was only one signal ($\delta = 4.201$ ppm). On the other hand, there were eight signals in the aromatic region. Due to the stronger sulfonic withdrawing groups, $\delta = 9.803$ ppm, 9.462–9.446 ppm and 8.579–8.563 ppm were assigned to the signal of H1, H4 and H3, respectively. $\delta = 9.803$ ppm was assigned to signal of H1, because of no other proton in vicinity, it showed single. $\delta = 9.462$–9.446 ppm was corresponding to signal of H4, whose coupling constant was $^3J = 8$ Hz, as the coupling action of H3, it showed doublet. $\delta = 8.579$–8.563 ppm was contributed to the signal of H3, whose coupling constant was $^3J = 8$ Hz, it also showed doublet which was caused by the coupling of H4. As H4 was closer to Pc ring than H3, it showed bigger shift. $\delta = 9.292$, 8.178 and 8.070 ppm were corresponding to signal of H20, H17 and H19, because of the relative weaker phthalimidomethyl withdrawing group. $\delta = 9.292$ ppm was contributed to signal of H17, as no other proton in vicinity, it showed single. $\delta = 8.178$ ppm was corresponding to signal of H20, as the coupling action of H19, it showed doublet. $\delta = 8.070$ ppm was designed to the signal of proton H19, it also showed doublet which was caused by the coupling of H20. As H20 was closer to Pc ring than H19, it showed bigger shift. The last two signals $\delta = 7.628$, 7.567 in the aromatic region were assigned to the protons of the phthalimidomethyl groups. They corresponded to the protons of Hd and He, respectively.

The ^{13}C NMR spectrum of the $ZnPcS_2P_2K_2$ showed that there were carbons of amide's and submethyl's existing in the compound, the corresponding shifts were 167.561 and 38.624, respectively.

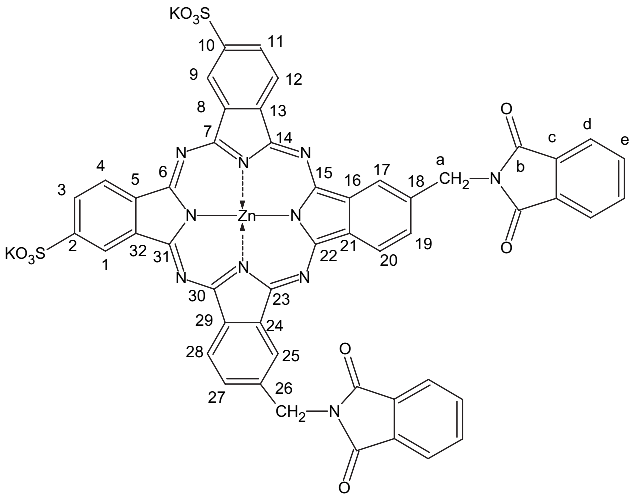


Table 1
^1H NMR data of $ZnPcS_2P_2K_2$

Protons	δ (ppm)	
H1, H9	9.803	(s, 2H)
H20, H28	9.462	(d, 2H, $^3J = 8$ Hz)
H3, H11	9.292	(d, 2H, $^3J = 8$ Hz)
H4, H12	8.579	(d, 2H, $^3J = 8$ Hz)
H17, H25	8.178	(S, 2H)
H19, H27	8.070	(d, 2H, $^3J = 8$ Hz)
He	7.628	m, 4H
Hd	7.567	(d, 4H, $^3J = 9$ Hz)
Ha	4.201	S, 4H

Table 2
^{13}C NMR data of $ZnPcS_2P_2K_2$

Carbon	δ (ppm)
Cb	167.561
C6, C31, C7, C14, C15, C22, C23, C30	153.481
C2, C10	153.260
C18, C26	152.835
Cc	150.273
C5, C13	148.768
C8, C32	138.267
C4, C12	138.121
C1, C9	137.875
C3, C11	132.257
C16, C24	130.212
C20, C28	130.011
C17, C25, Ce	128.527
C19, C27	122.837
C21, C29	122.510
Cd	120.475
Ca	38.624

The thermal stability of the fraction B under nitrogen gas was studied by TG and DTA method. The thermal analytical procedure was deduced: from 51 °C to 133 °C, there was a range of decomposition of crystallized water. The experimental weight loss rate was 6.61%, and the calculated value was 6.26%. This suggested that each molar fraction B contained four molar crystal waters. From 220 °C to 437 °C was the temperature range of decomposition of the phthalimidomethyl groups. The experiment weight loss rate was 22.36% the calculated value was 23.15%. It was therefore deduced that each molar fraction B contained two molar phthalimidomethyl groups. 437–628 °C was the range of decomposition of Pc ring. 628–799 °C was the range of the sulfonic groups eliminated from the Pc fragment ring. The experiment weight loss rate was 19.88%, and the calculated value was 20.17%. It was deduced that each molar $ZnPcS_2P_2K_2$ contains two molar sulfonic potassium groups.

According to the above experimental results, including element analysis, IR, UV/Vis, ^{1}H NMR, ^{13}C NMR, TG and DTA, it was believed that the chemical composition of fraction B was in good agreement with the formula $ZnPcS_2P_2K_2 \cdot 4H_2O$. As for the structural configuration concerning the arrangement of the substituent, there would be a detailed discussion in the later.

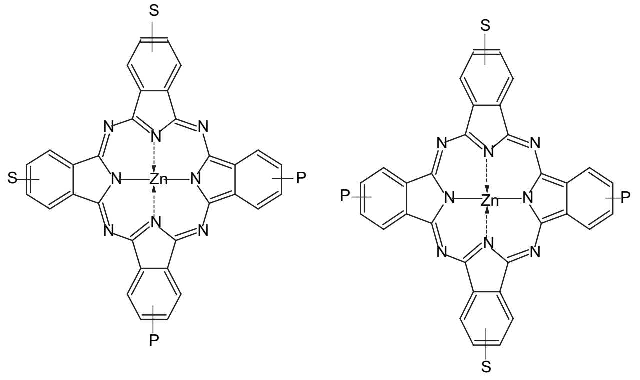


Fig. 2. *Trans*- and *cis*-configurations of $ZnPcS_2P_2K_2$ (P: phthalimidomethyl group, S: sulfonic group).

As mentioned, there were two possible configurations (Fig. 2) for four substituted groups (two sulfonic groups and two phthalimidomethyl groups) in the Pc ring. The *trans*-one possessed nearly central symmetry, and it has no polarity or very small polarity. While the *cis*-one had higher polarity. The solubility of $ZnPcS_2P_2K_2$ indicated that it was readily dissolved in polar solvents such as *n*-octanol, ethanol, methanol, pyridine, while less dissolved in toluene and dimethylbenzene, and it was insoluble in non-polar solvents such as benzene and tetrachloride carbon. This suggested that $ZnPcS_2P_2K_2$ may be *cis*-structure for four substitutions leading to the higher polarity.

The *cis*-configurations of $ZnPcS_2P_2K_2$ consisted of 16 stereo-isomers listed in Table 3. No. 2 has the same structure as 5, 3 as 7, 4 as 15, 8 as 16, 13 as 14, so only 10 kinds of isomers were possible.

Which structure is the $ZnPcS_2P_2K_2$? The signal of protons of the submethyl groups of the ^{1}H NMR spectrum showed some important clues for determining the structure of $ZnPcS_2P_2K_2$. In our previous study [10], tetra-phthalimidomethyl phthalocyanine zinc ($ZnPcP_4$) was synthesized by using phthalimidomethyl phthalic acid and phthalimidomethyl phthalonitrile as precursors through "ammonium molybdate method" and "DBU method", respectively. Different products were obtained: a C_{4h} $ZnPcP_4$ isomer was obtained by using the former method with only one signal of submethyl protons at 4.742 ppm, and its corresponding HPLC

Table 3
Stereo-isomers of *cis*-configurations of $ZnPcS_2P_2K_2$

No.	Arrangements order	No.	Arrangements order	No.	Arrangements order	No.	Arrangements order
1	PHHPHSSH	2	HPPHHSSH	3	HPHPHSSH	4	PHPHHSSH
5	PHHPSHHS	6	HPPHSHHS	7	HPHPSHHS	8	PHPHSHHS
9	PHHPSHSH	10	HPPHSHSH	11	HPHPSHSH	12	PHPHSHSH
13	PHHPHSHS	14	HPPHHSHS	15	HPHPHSHS	16	PHPHHSHS

P: Phthalimidomethyl group, S: sulfonic group, H: hydrogen. Arrangements order: from R1 to R8 (Fig. 3).

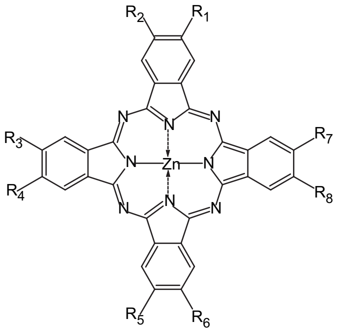


Fig. 3. Possible arrangements of substituted group.

analytic curve also indicated that only one structural isomer existed. While a mixture $ZnPcP_4$ isomer was obtained through latter method with multi-split signals of submethyl protons at $\delta = 4.812$, 4.570, 4.657 ppm, and its corresponding HPLC analytic curve also showed that multi-structural isomers existed.

Only one peak ($\delta = 4.201$ ppm) was corresponding to the signal of submethyl in the ^{1}H NMR spectrum of $ZnPcS_2P_2K_2$. This recommended that there was only two types of magnetically equivalent isoindoline units connected with phthalimidomethyl group in the Pc ring [11,12]. Of the 10 possible isomers listed in Table 3, only five (No. 1, 2, 5, 6 and 12) isomers' isoindolines connected with phthalimidomethyl groups were magnetically equivalent. Therefore, the possible structure may be these five isomers. The possible structural isomer of $ZnPcS_2P_2K_2$ was further identified with the help of the synthetic mechanism.

The process of synthesis of $ZnPcS_2P_2K_2$ involved three steps: firstly, synthesis of two precursors with sulfonic and phthalimidomethyl substituted groups at β position of phthalic acid, and then two precursors were direct-condensed with zinc chloride anhydrate as template agent and $(NH_4)_2MoO_4$ as catalyst, at last, separation of the condensed mixtures by HPLC method. This process was bound to have two limitations: (1) each precursor bearing only one substituted group, (2) the substituted group being at β position of each precursor.

Even with such limitations, there are still many configurations for $ZnPcS_2P_2K_2$ bearing four substituted groups. According to the postulated mechanism for the formation of the Pc ring [13], only two isomers can be rationalized: due to the effect of the substituted group, the two cyano groups of the starting materials have different electronic position, the carbon of the cyano group with higher electronic position was easily attacked by the N of the cyano group with lower electronic position in the other molecular, whereby, a dimer species was obtained (Fig. 4). An alternative type Pc (Fig. 5) isomer was also formed by further connection of the two dimer species.

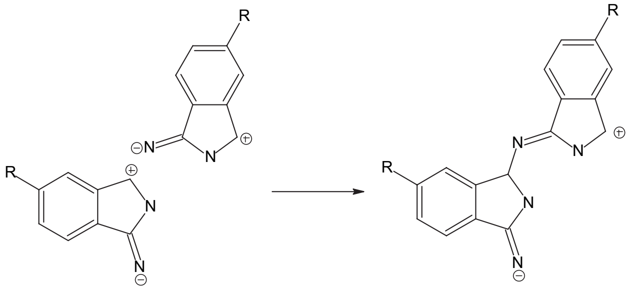


Fig. 4. Possible dimer species of $ZnPcS_2P_2K_2$.

It was worth to point out that, this kind of alternative C_{4h} isomer was the most familiar with. For example, Gaspard [14] obtained single tetra-butyl phthalocyanine zinc C_{4h} isomer. $ZnPcP_4$ and $ZnPcS_4K_4$ were also C_{4h} isomers [9,10]. Of the five possible structures, only No. 12 was the alternative type, and the arrangement of four substituted groups in Pc ring was with C_{4h} structure. Therefore, the structure of $ZnPcS_2P_2K_2$ was regarded as C_{4h} isomer (Fig. 5).

Although much analysis has been adopted to deduce the structure of the $ZnPcS_2P_2K_2$, the culture single crystal work was still in the progress.

2.1. In vivo activity

An in vivo experimental data of $ZnPcS_2P_2K_2$ were listed in Table 4. From these data, it can be concluded that $ZnPcS_2P_2K_2$ inhibited significantly the growth of S_{180} solid tumor transplanted in mice with irradiation of laser light with 670 nm wavelength. Its inhibitory rate was up to 90.3% for S_{180} when dosage of drug was 2 mg/kg and the dosage of light was 100 J/cm^2.

3. Conclusions

An amphiphilic 2,10-di-sulfonato-18,26-di-phthalimidomethyl phthalocyanine zinc di-potassium salt was

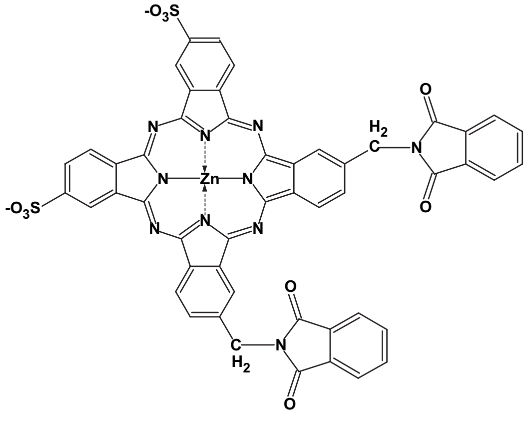


Fig. 5. Structure of $ZnPcS_2P_2K_2$.

Table 4
PDT activity of $ZnPcS_2P_2K_2$ against S_{180} carcinoma in mice

Drug	Dosage (kg^{-1})	Number of mice	Mean weight of tumor (g)	Inhibitory rate (%)
$ZnPcS_2P_2K_2$	2	10	0.060 ± 0.080	90.3
Solvent	–	10	0.605 ± 0.232	2.3
Blank	–	10	0.619 ± 0.181	0.0

synthesized and characterized. The ^1H NMR signal of submethyl protons of the phthalimidomethyl groups in Pc ring, polarity and synthetic mechanism allowed $ZnPcS_2P_2K_2$ as C_{4h} isomer. In vivo antitumor activity showed that it was a hopeful potential photosensitizer for clinic use in photodynamic therapy of cancer.

4. Experimental section

4.1. General

All material were commercial available and all solvents were purified according to standard methods. NMR spectra were recorded on the UNITY Plus model of the Varian company, UV/Vis spectra on the Perkin–Elmer Lambda 9 UV/Vis/IR spectrometers, IR spectra on Perkin–Elmer PE-983G spectrometers, and thermal analysis on the Perkin–Elmer Dta-1700 and TGA-7 apparatus.

4.2. Mixed-condensation of (1) with (2)

4-Sulfonic phthalic acid mono-potassium salt (**1**) (1.8 g, 0.033 mol), 4-phthalimidethyl phthalic acid (3.25 g, 0.01 mol), NH_4Cl (1.28 g, 0.2 mol), urea (9.6 g, 0.16 mol), ammonium molybdate (0.02 g, 0.0002 mol) and zinc chloride anhydrous (0.45 g, 0.033 mol) were mixed together and grounded to be homogeneous powder. The mixture was put into a 500 mL three necks flask equipped with a stirrer, a reflux condenser, pumped, and heated to 180 °C at which point urea decomposed to yield NH_3. After 30 min, the temperature was raised to 200 °C and, after 4 h, the same amounts of (**1**) (1.8 g, 0.033 mol) and zinc chloride anhydrous (0.45 g, 0.033 mol) were added. After heating for 4 h, (**1**) (1.8 g, 0.033 mol) and zinc chloride anhydrous (0.45 g, 0.033 mol) were added again. The reaction was heated for another 8 h and, after cooling, it was dispersed in 50 mL 1 mol/L hydrochloric acid saturated with potassium chloride, then the solution and the accompanying undissolved material were briefly heated to boiling, cooled to room temperature and filtered, the resulting solid was dissolved in 1 mol/L potassium hydroxide, the solution was heated to 80 °C for 12 h, the filtrate was collected and vaporized. The separation of the condensed mixture was performed by HPLC using C18 as solid phase and 95% ethanol–phosphate buffer solution as mobile phase. $ZnPcS_2P_2K_2$ was obtained by collecting the fraction whose retention time was 109 min, and was further purified by membrane separation method. Yield: 39.45%. IR: ν_{max}/cm^{-1} 3422(–OH), 2926 cm^{-1}, 2865 cm^{-1}(–CH_2), 1637 cm^{-1}, 1485 cm^{-1}(C=C of Pc ring), 960 cm^{-1}, 720 cm^{-1}(CH_2), 1185 cm^{-1}, 1119 cm^{-1}, 1088 cm^{-1} and 1028 cm^{-1}(SO_3^-), 1725 cm^{-1}(C=O). UV/Vis (DMSO): λ_{max}/nm (log[ϵ/$dm^3\,mol^{-1}\,cm^{-1}$]) 672 (5.61), 608 (4.01), 340 (5.16).

4.3. In vivo photodynamic activity against cancer assay

The same male KM strain mice (18–22 g body weigh, cleanness grade) were obtained from Shanghai Ciplerpiker Animal Inc. The S_{180} carcinoma was transplanted into the right black of mice. After 5–6 d, when the tumor had reached a diameter of 0.5 cm or so, the mice were randomly distributed into five groups, and then the experimental group mice were injected intravenously with the $ZnPcS_2P_2K_2$ aqueous solvent which consisted of Cremophor EL2%(v/v), propanediol 20%(v/v) and 0.9% sodium chloride (weight percent). The negative control mice were injected with solvent. After 12 h, the tumors were irradiated with 670 nm light delivered by SPECTRA-PHYSICS 171-09, 375B argon ion laser. The light fluence rate was 200 mW cm^{-2} and irradiation time was 500 s, so the dosage of light was 100 J/cm^2.

After irradiation, the mice were fed in dark room and butchered after 4–5 d, the tumors were peeled off, and the inhibitory rates against tumor were counted.

Acknowledgments

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Reference

[1] Moser JD. Photodynamic tumor therapy 2nd and 3rd generation photosensitizer. New Delhi: Harwood Academic Publishers; 1998.

[2] Leznoff CC, Lever ABP. In: Phthalocyanine—properties and applications, vol. 1. New York: VCH; 1989.

[3] Passcali U, Cynthia M, Allen RL, Carole LM, Johan EVL. J Porphyrins Phthalocyanines 2001;5:151–4.

[4] Oda K, Ogura S, Okura I. J Photochem Photobiol B: Biol 2000;59:20–6.

[5] Huang JL, Chen NS, Huang JD, Liu ES, Xue JP, Yang SL. Sci China B 2000;12:481–5.

[6] Huang JL, Chen NS, Huang JD, Liu ES, Xue JP, SL. Chinese Patent, Patent No. ZL96117137.5.

[7] J.D. Huang. Ph. D. dissertation of Fuzhou University, China, 1998. p. 112–24.

[8] Kudrevich SV, Ali H, Vanlier JE, S. J Chem Soc Perkin Trans 1994:2767–71.
[9] Peng YR, Chen NS, Lin ZP, Huang JL. Chinese Apply Chem 2002;19:730–4.
[10] Peng YR, Lin ZP, Chen NS, Huang JL. Chin J Inorg Chem 2002;1:23–7.
[11] Maria PDF, Donata D, Lia LF, Gabrio R. Tetra Lett 2000;41:9143–5.
[12] Huang JL, Peng YR, Chen NS. Chin J Struct 2001;20:144–8.
[13] Morgade SR, Hanack M. Chem Eur J 1997;3:1042–51.
[14] Gaspard S, Mangold P, Hanack M. Tetrahedron 1991;56: 3501–3.