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Study on Synthesis, Characterization and Biological Activity of Some New Nitrogen Heterocycle Porphyrins

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Abstract—Seven new nitrogen heterocycle porphyrins, 5,10,15,20-tetra[4-(*N*-pyrrolidinyl)phenyl]porphine ($TBPPH_2$), 5,10,15,20-tetra[4-(4′-ethylpiperazinyl)phenyl]porphine ($TEPPH_2$), 5,10,15,20-tetra [4-(4′-butylpiperazinyl)phenyl]porphine ($TUPPH_2$), 5,10,15,20-tetra[4-(4′-heptylpiperazinyl) phenyl]porphine ($THPPH_2$), 5-[4-(4′-ethylpiperazinyl)phenyl]-10,15,20-triphenylporphine ($MEPPH_2$), 5-[4-(4′-buthylpiperazinyl)phenyl]-10,15,20-triphenylporphine ($MUPPH_2$) and piperazine bridge porphine dimer *N*,*N*′-di(5,10,15,20-tetraphenylporphinato)piperazine ($DiPPH_2$) have been synthesized by the direct condensation of nitrogen heterocycle substituted benzaldehydes with pyrrole. Each porphine bears one or four substituted pyrrolidine or piperazine moieties that have been used as drugs. Their structures were characterized by elementary analysis, MS, ^{1}H NMR, IR and UV–vis. These nitrogen heterocycle porphyrins aggregates in water and THF solution were studied by the spectrophotofluorimetry. The anticancer activity of these porphines for the liver cancer cells, the stomach tumor cells and the nasopharyngeal carcinoma cancer cells were tested by the MTT assay. Compared with *cis*-platinum (*cis*-Pt) and 5-Fluorouracil (5-Fu), the nitrogen heterocycle porphyrins have the better biological activity and might have potential application in medicine.

During the last decades, people have been interested in the synthesis of porphine compounds as drugs because they both tend to accumulate in neoplastic tissue to higher concentrations than in surrounding normal tissue and they might convert dioxygen into singlet state oxygen which can destroy the cancer cells when irradiated by light. The photodynamic therapy (PDT) for cancers was established based on these characteristics of porphine compounds.[1] People found that cationic porphine complexes containing a tertiary amine have a good affinity for nucleic acids and are efficient catalysts for DNA cleavage.[2] In the last few years, a great deal of interest has been focused on the synthesis of porphines bearing glycosylated groups owing to good solubility in aqueous solution and specific membrane interaction.[3] So far, porphines with sugar moieties have been applied in cancer PDT[4,5] as new photosensitizers. Although a number of porphine-based photosensitizers have been approved for clinical trials, it is necessary to keep patients from darkness for a long time during the PDT treatment.[6] Moreover, PDT treatment also was not suitable for therapy of the cancer locating at the deeper tissue of the body.[7]

Statistics of the drugs in late development or on the market shows that 68% of drugs contain the heterocyclic structures.[8] Nitrogen heterocyclic compounds are widely used in the pharmaceutical industry. But so far, all clinical chemical anticancer drugs, including nitrogen heterocyclic drugs, inevitably have side effects for patients. The cytotoxicity of drugs on cancer cells and on normal cells is identical because drugs can not efficiently concentrate in tumor tissue. People have to reduce the dosages of the drugs in clinical use to mitigate the side effects of drugs. But this will prevent the drugs from bringing its efficacy into play and results in the curative effect decreasing. Therefore, it is very promising to synthesize some new compounds as anticancer drugs that can concentrate to higher concentrations in malignant tumors than in normal tissue.

It seems a good idea to link a drug moiety to a porphine ring. Porphines bearing drug moieties could make the concentration of the drugs in tumor tissue higher than in surrounding normal tissue by the transport of porphines. So, it is possible to avoid or mitigate the side effect of drugs at the same dosages of the drugs. Pyrrolidine or piperazine are the heterocyclic compounds used most widely in the drugs, especially in anticancer drugs, and some substituted pyrrolidine or

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piperazine compounds have distinctive anticancer activity.[9–13]

In this paper we report the design and synthesis of 7 new porphines bearing pyrrolidine or piperazine substituents. To achieve this we have developed routes to 7 substituted benzaldehydes and have converted them to the corresponding porphines. We have investigated the aggregation and preliminary anticancer activity of these new porphines bearing pyrrolidine or piperazine substituents as the drugs. These studies established molecular design issues for the synthesis of the porphine-containing chemical anticancer drugs.

Results and Discussion

Molecular design

We sought to develop an anticancer drug approach that can accumulate in neoplastic tissue to higher concentrations than in surrounding normal tissue. The major design constrains include:

1. can accumulate in neoplastic tissue.
2. achieve high anticancer activity.
3. form the desired product in high yield.

Our approach to porphine-based drugs makes use of a convenient reaction for converting an aldehyde and pyrrole to the corresponding *meso*-substituted porphine. The reaction provides a means for converting prefunctionalized benzaldehyde to the corresponding porphine. In this paper the functional groups selected are those drugs that be used in the treatment of cancers.

Synthesis of aldehydes

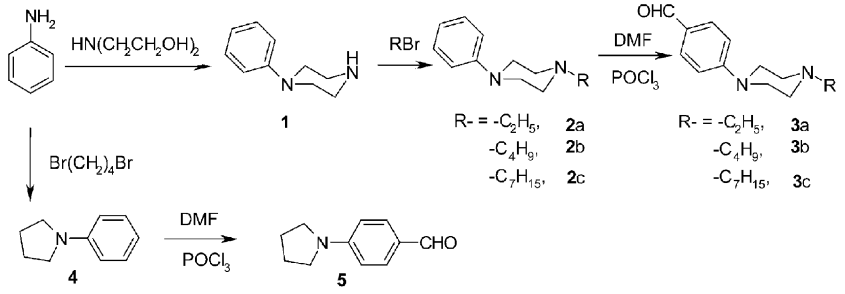
Benzaldehydes bearing substituted piperazines or pyrrolidine were prepared according to literature,[14–16] the synthetic routes were shown in Scheme 1.

N,*N*′-di(4-formylphenyl)piperazine (**8**) was prepared according to Scheme 2.

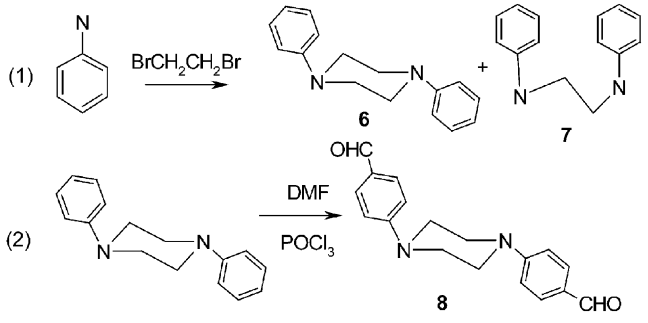
The reaction of aniline with 1,2-dibromoethane in benzene gave the product *N*,*N*′-diphenylpiperazine (**6**) and the by-product *N*,*N*′-diphenylethandiamine (**7**). The yield of *N*,*N*′-diphenylpiperazine was varied with the mole ratio of aniline to 1, 2-dibromoethane. The yield is the highest when the ratio is 1:1. Formylation of *N*, *N*′-diphenylpiperazine with Vilsmeier reagents was found to give the product *N*,*N*′-di(4-formylphenyl) piperazine (**8**), the yield of *N*,*N*′-di(4-formylphenyl)-piperazine is the highest when the mole ratio of *N*,*N*′-diphenylpiperazine to $POCl_3$ is 1:2.1.

Synthesis of nitrogen heterocycle substituted porphines

The keys of the synthesis of the nitrogen heterocyclic porphines are how to introduce nitrogen heterocyclic to the porphine ring. We tried to couple iodoporphine with various nitrogen heterocyclic compounds to synthesize target molecules at room temperature according to the Buchwald method.[17] However, the reaction did not proceed, even after stirring over an extended period of time. The couple 5,10,15,20-tetra(4-aminophenyl)porphine ($TAPPH_2$) with 1,4-dibromobutane or *N*,*N*′-di(2-bromoethyl)alkylamine at room temperature can obtain the corresponding nitrogen heterocyclic porphines, but the components of products are too complicated to purify.



Scheme 1. Synthetic routes of *N*-alkyl-*N*′-(4-formylphenyl) piperazine and *N*-(4-formylphenyl) pyrrolidine.



Scheme 2. Synthetic route of *N*-*N*′-di(4-formylphenyl) piperazine.

We synthesized six new nitrogen heterocyclic porphines by the routes in Scheme 3.

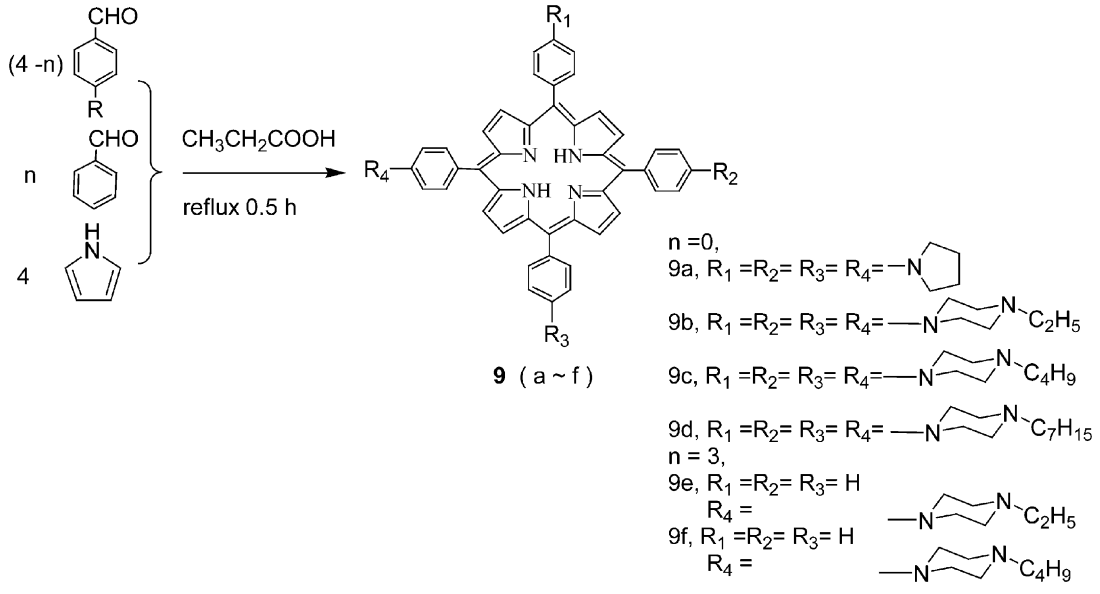
5,10,15,20 - Tetra[4 - (*N* - pyrrolidinyl)phenyl]porphine ($TBPPH_2$, **9a**), 5,10,15,20-tetra [4-(4′-ethylpiperazinyl)-phenyl]porphine ($TEPPH_2$, **9b**), 5,10,15,20-tetra [4-(4′-butylpiperazinyl)phenyl]porphine ($TUPPH_2$, **9c**), and 5,10,15,20-tetra [4-(4′-heptylpiperazinyl)phenyl]porphine ($THPPH_2$, **9d**) are symmetrical nitrogen heterocyclic porphine; 5-[4-(4′-ethylpiperazinyl)phenyl]-10,15,20-triphenylporphine ($MEPPH_2$, **9e**) and 5-[4-(4′-buthylpiperazinyl) phenyl]-10,15,20-triphenylporphine ($MUPPH_2$, **9f**) are unsymmetrical nitrogen heterocyclic porphines.

The structures of all nitrogen heterocyclic porphines were characterized by elementary analysis, MS, ^1H NMR, IR and UV–vis. The ^1H NMR spectra at $-2.40 \sim -2.70$ ppm show the characteristic single peak for porphines. Their molecular ion peaks and elementary analysis further confirmed their structures.

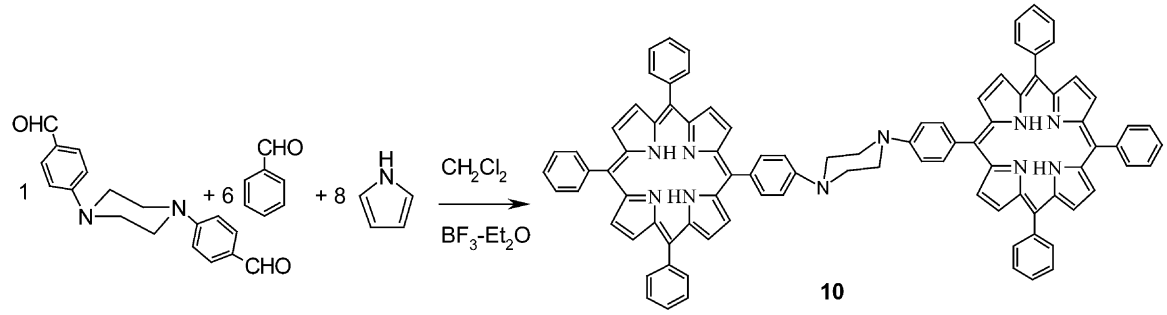
Symmetric *meso*-tetraarylporphines (**9a**–**9d**), each bearing four identical functional groups, were synthesized by the direct condensation of pyrrole with the appropriate benzaldehyde (**3a**–**3c** and **5**) under Adler's conditions.[18] Asymmetric tetraarylporphines bearing two different substituents around the porphine periphery can be achieved in an expedient manner by the condensation of mixed aldehyde with pyrrole. The condensation of aldhyde (**3b** or **3c**), benzaldehyde with pyrrole affords a mixture of six porphines that is separated chromatographically. For example, the reaction of **3b** and benzaldehyde with pyrrole in the ratio of 1:3:4 afforded porphine **9**e bearing three phenyl groups and one nitrogen heterocyclic groups in 2.0% yield.

Synthesis of porphine dimers

In the last decade, a number of porphine dimers used in photodynamic therapy (PDT) for the treatment of cancers have been reported in the literature.[19] The dimeric and trimeric species also showed the significant biological activity. The piperazine bridge porphine dimer (**10**, $DiPPH_2$) was obtained according to Lindsey' method[20] by condensation of pyrrole with benzaldehyde and *N*,*N*′-di(4-formylphenyl)piperazine at 8:6:1 in CH_2Cl_2. The procedure is shown in Scheme 4.



Scheme 3. Synthetic routes of porphyrin monomer.



Scheme 4. Synthetic routes of piperazine bridge porphyrin dimer.

Study of porphine aggregation

The biologic functions of biomolecules are closely linked to their structure and existing states. It had been found that some porphines as the active center of bacteriochlorophyll and chlorophyll in the nature take the form of the aggregates.[21] In the solution, porphine molecules tend to aggregate due to the π–π interaction. The porphine aggregates have many different characters from monomers, such as fluorescence lifetimes are reduced, fluorescence intensity quenched, the Soret band of UV–vis spectra with hypochromicity, the shape and numbers of Q bands changed.[22] Especially, the change of porphine aggregates can affect the interaction between porphines and target biomolecules.[23] Porphine compounds have characteristic fluorescence spectra and UV–vis spectra. Based on the notable influence of aggregation on spectrum, the aggregate forms of porphines could be studied by measuring the change of UV–vis spectra and fluorescence spectra of porphines in different systems. We studied the properties of porphine aggregate with $TBPPH_2$ (**9a**) and $TEPPH_2$ (**9b**) as representatives.

The influence of ψ(H_2O) on fluorescence spectra of porphines

The nitrogen heterocyclic substituted porphines are insoluble in water, but soluble in THF, so a mixture of THF and H_2O was used to dissolve these porphines. In the different volume ratio ψ(H_2O) of H_2O to THF solution systems, the fluorescence spectra properties of $TBPPH_2$ and $TEPPH_2$ were shown in Table 1.

Table 1 shows that the fluorescence intensity (*F*) of $TBPPH_2$ and $TEPPH_2$ decreased with ψ(H_2O) increasing. The wavelength of the maximum excited and emission of $TBPPH_2$ increased with the increase of ψ(H_2O). When the ψ(H_2O) was up to 1.5, the fluorescence intensity of $TBPPH_2$ was very weak. But the wavelength of maximum excited and maximum emission of $TEPPH_2$ was decreased with the increase of ψ(H_2O).

Table 1. The influence of ψ(H_2O) on the fluorescence spectra of $TBPPH_2$ and $TEPPH_2$

	ψ (H_2O)	0	0.25	0.67	1.50	3.00
$TBPPH_2$	EX (nm)	437.7	438.8	441.1	442.4	444.5
	EM (nm)	672.1	697.5	700.2	701.1	703.1
	F	128.0	94.0	85.6	29.8	23.6
$TEPPH_2$	EX (nm)	430.0	427.5	426.5	426.0	425.5
	EM (nm)	673.0	671.5	671.0	669.5	667.5
	F	198.0	176.0	164.2	148.0	116.2

ψ (H_2O) is the volume ratio of H_2O to THF; *F* is the peak fluorescence intensity.

The influence of ψ(H_2O) on UV–vis spectra of porphines

The Soret regions of porphyrins are usually very sensitive to many factors such as solvent, concentration, aggregation, ionic strength.[23] The change of UV–vis spectra of two synthetic porphines with the change of ψ (H_2O) were investigated. The results are shown in Table 2.

Table 2 shows that the absorbance of Soret band of $TBPPH_2$ and $TEPPH_2$ decreased with ψ(H_2O) increasing. When the ψ(H_2O) was up to 1.5, the wavelength of the Soret band would shift from 441 to 451 nm. But the maximum wavelength of the Soret band of $TEPPH_2$ decreased as ψ(H_2O) increased. When the ψ (H_2O) was up to 3.0, the wavelength of the Soret band shifted from 430.5 to 426.5 nm, and was accompanied with apparent hypochromicity.

The work of Barber[24] showed that porphines had two typical aggregate formations in solutions, and the differences of the aggregate formations caused the changes of the Soret bands of porphines. The extent of the aggregation increased as ψ(H_2O) increased. The porphines are H-aggregate formation when the wavelength of the Soret band is blue-shifted, and J-aggregate formation when the wavelength of the Soret band is red-shifted. So $TBPPH_2$ is J-aggregate formation, and $TEPPH_2$ is H-aggregate formation. This may result from the hydrophobic forces, steric hindrance, and resolvability of hydrophilic moieties of pyrrolidine and ethyl piperazine substitutes.

In vitro antitcancer activity tests

In order to study whether these nitrogen heterocycle porphines have the anticancer activities for cancer cells, the porphyrin $TEPPH_2$ and two common anticancer drugs, *cis*-platinum (*cis*-Pt) and 5-fluorouracil (5-Fu), were use to test in vitro against three human tumor cell lines, Bel-7404, liver cancer cells, MCG, stomach tumor cells, and HNE1, a nasopharyngeal carcinoma cancer cells by the MTT assay. The results of the pre-screenings are given in Table 3.

One can see from Table 3 that three tumor cells death rates for $TEPPH_2$ are greater compared with *cis*-Pt and 5-Fu. This means that tumor cells are more sensitive to $TEPPH_2$ than *cis*-Pt and 5-Fu.

Table 2. The influence of ψ (H_2O) on the Soret band of UV–vis spectra of $TBPPH_2$ and $TEPPH_2$

	ψ (H_2O)	0.00	0.25	0.67	1.50	3.00
$TBPPH_2$	Wavelength (nm)	441.00	441.00	441.5	446.50	446.50
	ε ($10^5 cm^{-1}mol^{-1}$ L)	1.42	1.05	0.84	0.45	0.44
$TEPPH_2$	Wavelength (nm)	430.50	430.00	428.00	426.5	425.0
	ε ($10^5 cm^{-1}mol^{-1}$ L)	1.14	1.07	0.94	0.82	0.66

ψ (H_2O) is the volume ratio of H_2O to THF; ε is the molar extinction coefficient of Soret band.

Table 3. The comparison of the anticancer activity of $TEPPH_2$, *cis*-platin and 5-Fu

Compound	Concentration (μg/mL)	Cells death rate (%)		
		Bel-7404	MCG	HNE1
$TEPPH_2$	6.25	45	41	44
cis-Pt	6.25	38	40	33
5-Fu	6.25	30	29	43

Table 4. ID_{50} values in μg/mL of compounds $TEPPH_2$, $TAPPH_2$, $DiPPH_2$ and **3a**

Compound	Bel-7404	MCG	HNE1
$TEPPH_2$	9	10	8
$TAPPH_2$	33	24	28
3a	25	18	17

Structurally, the nitrogen heterocycle porphine $TEPPH_2$ consists of two parts: tetraaminoporphine $TAPPH_2$ and nitrogen heterocycle compound **3a**. In order to study the contribution of each fragment in the $TEPPH_2$ molecule for the anticancer activities (cells death rate), the ID_{50} values of three cancer cells by compounds $TAPPH_2$, **3a** and $TEPPH_2$ were tested. The study results are listed in Table 4.

Table 4 shows that $TEPPH_2$ exhibits stronger activities since it displays lower ID_{50} values than others. The molecular mechanism for the anticancer activities of nitrogen heterocycle porphines is being further studied.

Experimental

Instruments and reagents

Infrared spectra were recorded on a Perkin–Elmer model 783 IR spectrophotometer. ^1H NMR spectra were recorded on a Varian FT-80A spectrometer, and the chemical shifts were reported on the δ scale relative to TMS. Elemental analyses were obtained on A Perkin–Elmer 2400 elementary analyzer. Mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer. UV–vis absorption spectra were obtained with a Perkin–Elmer L-17 UV–vis spectrophotometer. All fluorescence measurements were made with a Hitachi M850 fluorescence spectrophotometer by using 1-cm quartz cells, and with both excitation slit and emission at 10 nm.

Compounds **1**, **2** (**a**–**c**), **3** (**a**–**c**), **4** and **5** were synthesized according to literature.[14,15] The pyrrole and propionic acid were distilled before use. Other chemicals were used as received. Column chromatography was performed using silica gel (200–300 mesh) or alumina (80–200 mesh). 5-Fluorouracil (5-Fu) and 3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were from Sigma Chemical Co. (USA). *cis*-Platinum (*cis*-Pt, Shandong Qilu Pharmaceutical Corp., Shandong, China). Three human tumor cell lines, Bel-7404, MCG and HNE1, were obtained from Shanghai Institute of Cell Biology, Chinese Academy of Science.

Cell survival assay

The cytotoxic effects of some compounds on Bel-7404, MCG and HNE1 cells were determined using the MTT assay.[25] Cells were plated in 100 μL medium at a concentration of 1×10^3 cells per well in 96-well microtiter plates. Plates were then incubated for 18 h at 37 °C under an atmosphere of air containing 5% CO_2. Medium (100 μL) containing the tested drug dissolved in appropriate solvent was added to quadruplicate wells and incubated for an additional 96 h. The medium was then removed from the wells and 200 μL MTT (1 μg/mL in complete medium) was added to each well followed by a 3-h incubation. The formazan crystals were dissolved in 100 μL dimethyl sulfoxide buffered with 25 μL glycine–NaCl solution (0.1 M glycine, 0.1 M NaCl, pH 10.5). The absorbance was measured in an enzyme-linked immunoabsorbent assay plate reader (Bio-Rad) at a wavelength of 570 nm. Concentration 50% cell death (ID_{50}) was determined for the various compounds tested.

Synthesis of compounds

***N*,*N*′-Diphenylpiperazine (6).** A mixture of aniline (0.2 mol), 1,2-dibromethane (0.2 mol), potassium carbonate (0.45 mol), and benzene (200 mL) was stirred at room temperature for 20 h. The product was purified with column chromatography (neutral alumina, 200–300 mesh; petroleum/ethyl acetate, 5:1). Yield, 14.0 g, 60%. MS *m*/*z*: 238 (M^+). IR (KBr): 3000, 2956, 2876, (C–H), 1596, 1494 (C=C). ^1H NMR ($CDCl_3$), δ6.67–7.40 (10H, Ar-H), 3.11–3.61 (8H, NCH_2).

***N*,*N*′-Di(4-formylphenyl)piperazine (8).** *N*,*N*′-di(4-formylphenyl)piperazine was synthesized according to the procedure of the synthesis of *N*-ethyl-*N*′-(4-formylphenyl)piperazine. *N*, *N*′-diphenylpiperazine (0.01 mol), phosphoryl trichloride (0.021 mol), dimethylformamide (10 mL) were used. Yield, 2.1 g, 72%. MS *m*/*z* 294 (M); IR (KBr): 2964, 2928 (C–H), 1668 (C=O), 1600, 1500 (C=C); ^1H NMR ($CDCl_3$), δ9.82 (2H, CHO), 6.86–8.00 (8H, ArH), 3.59–4.10 (8H, NCH_2).

5,10,15,20 - Tetra - [4 - (*N* - pyrrolidinyl)phenyl]porphine ($TBPPH_2$, 9a). A literature procedure[18] was used. A solution of pyrrole (0.02 mol), *N*-(4-formylphenyl)pyrrolidine (0.02 mol), and propionic acid (100 mL) were allowed to reflux for 30 min and then stored overnight in a freezer at 0 °C. The green precipitate was purified with column chromatography (silica gel, $CHCl_3$). Yield, 0.36 g, 8.5%. Anal. calcd for $C_{60}H_{58}N_8$: C, 80.90; H, 6.52; N, 12.58%; found: C, 81.01; H, 6.58; N, 12.41%. MS *m*/*z*: 891($M^+ + 1$); ^1H NMR ($CDCl_3$), δ: 8.89 (8H, pyrrolic), 6.68–8.11 (16H, ArH), 3.26–3.57 (16H, pyrrolidinyl NCH_2), 2.03–2.57 (16H, pyrrolidinyl CH_2), −2.48 (2H, N–H)ppm; IR (KBr, cm^{-1}): 3320, 1604, 1510; UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in THF: 325.5 (259.1), 441 (203.9), 521 (16.7), 571 (21.4), 612 (18.0), 668 (9.6).

5,10,15,20-Tetra-[4-(*N*-ethylpiperazinyl)phenyl]porphine ($TEPPH_2$, 9b). 5,10,15,20-Tetra-[4-(*N*-ethylpiperazinyl)phenyl]porphine was synthesized according to the procedure of the synthesis of 5,10,15,20-tetra-[4-(*N*-pyrrolidinyl)phenyl]porphine. Pyrrole (0.02 mol), propionic acid (100 mL) and *N*-ethyl-*N*′-(4-formylphenyl)piperazine (0.02 mol) were used. The purple precipitate was purified with column chromatography (neutral alumina, 200–300 mesh; ethanol). Yield, 0.24 g, 4.5%. Anal. calcd for $C_{68}H_{78}N_{12}$: C,76.84; H, 7.34; N, 15.82%; Found: C, 77.03; H, 7.40; N,15.57%; MS *m*/*z*: 1063 ($M^+ + 1$);^{1}H NMR ($CDCl_3$), δ 8.62–8.66 (8H, pyrrolic), 6.97–7.33 (16H, ArH), 2.82–3.57 (40H, N–CH_2), 1.22–1.67 (12H, Me), −2.46 (2H, NH). IR (KBr): 3324, 1606, 1512 cm^{-1} ;UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 426 (203.9), 525 (16.7), 569 (21.4), 612 (18.0), 656 (9.6).

5,10,15,20-Tetra[4-(*N*-butylpiperazinyl)phenyl]porphine ($TUPPH_2$, 9c). 5,10,15,20-Tetra[4-(*N*-butylpiperazinyl)phenyl]porphine was synthesized according to the procedure of the synthesis of 5,10,15,20-tetra-[4-(*N*-pyrrolidinyl)phenyl]porphine. Pyrrole (0.02 mol), propionic acid (100 mL) and *N*-butyl-*N*′-(4-formylphenyl)piperazine (0.02 mol) were used. Yield, 0.15 g, 2.5%. Anal. calcd for $C_{76}H_{94}N_{12}$:C, 77.68; H, 8.01; N, 14.31%; found: C,77.73; H, 8.04; N, 14.23%; MS *m*/*z*: 1175 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$), δ 8.72–8.86 (8H, pyrrolic), 6.85–7.20 (16H, ArH), 2.64–3.62 (40H, N–CH_2), 1.22–1.46 (16H, CH_2), 0.80–1.00 (12H, Me), −2.48 (2H, NH); IR (KBr): 3306, 1600 cm^{-1}; UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 430.5 (179.2), 524 (5.8), 566 (7.6), 658(6.3).

5,10,15,20-Tetra[4-(*N*-heptylpiperazinyl)phenyl]porphine ($THPPH_2$, 9d). 5,10,15,20-Tetra[4-(*N*-heptylpiperazinyl)phenyl]porphine was synthesized according to the procedure of the synthesis of 5,10,15,20-tetra-[4-(*N*-pyrrolidinyl)phenyl]porphine. pyrrole (0.02 mol), propionic acid (100 mL) and *N*-heptyl-*N*′-(4-formylphenyl)piperazine (0.02 mol) were used. Yield, 0.2 g, 3.0%. Anal. calcd for $C_{88}H_{118}N_{12}$: C, 78.69; H, 8.79; N, 12.52%; found: C, 78.76; H, 8.82; N, 12.42%; MS *m*/*z*: 1343 ($M^+ + 1$);^{1}H NMR ($CDCl_3$), δ 8.22–8.86 (8H, pyrrolic), 7.12–7.43 (16H, ArH), 2.62–3.60 (40H, N–CH_2), 1.22–1.42 (40H, CH_2), 0.82–1.06 (12H, Me), −2.58 (2H, NH); IR (KBr): 3316, 1608, 1510 cm^{-1}; UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 432 (228.5), 525 (13.4), 568 (18.0), 658 (9.4).

5-[4-(*N*-Ethylpiperazinyl)phenyl]-10,15,20-triphenylporphine ($MEPPH_2$, 9e). 5-[4-(*N*-Ethylpiperazinyl)phenyl]-10,15,20-triphenylporphine was synthesized according to the procedure of the synthesis of 5,10,15,20-tetra-[4-(*N*-pyrrolidinyl)phenyl]porphine. Pyrrole (0.02 mol), benzldehyde (0.015 mol), *N*-ethyl-*N*′-(4-formylphenyl)piperazine (0.005 mol) and propionic acid (100 mL) were used. Yield, 0.07 g, 2.0%. Anal. calcd for $C_{50}H_{42}N_6$: C, 82.64; H, 5.78; N,11.57%; Found: C, 82.72; H, 5.84; N, 11.44%; MS *m*/*z*: 727 ($M^+ + 1$);^{1}H NMR ($CDCl_3$), δ 8.72–8.84 (8H, pyrrolic), 7.12–7.86 (19H, ArH), 2.80–3.68 (10H, N–CH_2), 1.20–1.60 (3H, Me), −2.68 (2H, NH); IR (KBr, cm^{-1}) :3320 (N–H), 1598, 1506 (C=C) cm^{-1}; UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 431 (166.8), 524 (13.3), 566 (14.1), 657 (7.4).

5-[4-(*N*-Buthylpiperazinyl)phenyl]-10,15,20-triphenylporphine ($MUPPH_2$, 9f). 5-[4-(*N*-Buthyl piperazinyl)-phenyl]-10,15,20-triphenylporphine was synthesized according to the procedure of the synthesis of 5,10,15,20-tetra-[4-(*N*-pyrrolidinyl)phenyl]porphine. Pyrrole (0.02 mol), benzldehyde (0.015 mol), *N*-butyl-*N*′-(4-formylphenyl)piperazine (0.005 mol) and propionic acid (100 mL) were used. Yield, 0.07 g, 1.8%. Anal. calcd for $C_{52}H_{46}N_6$: C, 82.76; H, 6.10; N, 11.14%; Found: C, 82.82; H, 6.15; N, 11.03%; MS *m*/*z*: 755 ($M^+ + 1$);^{1}H NMR ($CDCl_3$), δ 8.72–8.80 (8H, pyrrolic), 6.97–8.12 (19H, ArH), 2.82–3.82 (10H, N–CH_2), 1.22–1.32 (4H, CH_2), 0.82–1.02 (3H, Me), −2.60 (2H, NH); IR (KBr, cm^{-1}): 3316 (N–H), 1600, 1510 (C=C); UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 432 (157.8), 526 (14.2), 568(16.2), 659 (5.7).

***N*,*N*′-Di(5,10,15,20-tetraphenylporphinato)piperazine ($DiPPH_2$, 10).** *N*,*N*′-Di(5,10,15,20-tetraphenylporphinato)piperazine was prepared following literature procedures.[20] A 600 mL reaction was performed of *N*,*N*′-di(4-formylphenyl)piperazine (2 mmol), benzaldehyde (12 mmol), and pyrrole (16 mmol) in CH_2Cl_2 with BF_3–Et_2O (0.6 mL of 2.5 M stock solution) and oxidation with *p*-chloranil (12 mmol) at reflux for 1 h. Column chromatography (silica, CH_2Cl_2) affords 47 mg (1.8%) of porphine. Anal. calcd for $C_{92}H_{66}N_{10}$: C, 84.27; H, 5.04; N, 10.69%; Found: C, 84.36; H, 5.08; N, 10.56%; MS *m*/*z*: 1311 ($M^+ + 1$);^{1}H NMR ($CDCl_3$), δ 8.62–8.82 (16H, pyrrolic), 6.78–8.08 (38H, ArH), 2.84–3.62 (8H, N–CH_2), −2.70 (4H, NH); IR (KBr, cm^{-1}): 3296 (N–H), 1596, 1498 (C=C); UV–vis [λ_{max}, nm ($\varepsilon\times10^{-3}$ cm^{-1} mol^{-1} L)] in CH_2Cl_2: 418 (212.2), 463 (19.7), 515 (16.8), 553 (22.3), 657 (7.8).

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