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New Promising Porphyrazine-Based Agents for Optical Theranostics of Cancer

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Abstract—New porphyrazine bases containing peripheral benzyloxyphenyl groups have been synthesized by the template method. The procedure includes condensation of aromatic aldehydes with malononitrile, transformation of arylmethylidenemalononitriles to arylethenetricarbonitriles, template assembly of porphyrazine macrocycle on bis(indenyl)ytterbium(II) complex, and removal of the central metal ion. Luminescence properties of the synthesized porphyrazines and their dependence on the viscosity of the medium were studied, and the light and dark toxicities of the porphyrazines have been estimated. The obtained results suggest the possibility of using these porphyrazines as optical theranostic agents of new generation.

Keywords: porphyrazines, template synthesis, ytterbium complexes, optical theranostic agents, photosensitizers, optical intracellular viscosity probes

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Porphyrazines belong to a huge family of aromatic tetrapyrrole macrocycles. Interest in these compounds is determined by the fact that they can be regarded as porphyrin analogs in which the *meso*-CH groups are replaced by nitrogen atoms. Tetrapyrrole macrocycles occupy a central position in modern bioorganic chemistry due to their ability to selectively accumulate in tumor tissues and then, under irradiation at an appropriate wavelength, produce singlet oxygen which induces cell death. This concept underlies photodynamic therapy of cancer.

Over a long time, design of new drugs has been based on the concept of separate diagnostic and therapeutic approaches in medicine. However, in recent time there is a strong tendency to create medications that efficiently combine diagnostic and therapeutic functions. Such medications are called theranostic agents. In particular, as applied to oncology, they make it possible to not only precisely localize tumors in an organism and exert therapeutic effect thereon but also ensure direct monitoring of individual therapeutic response to the treatment procedure [1].

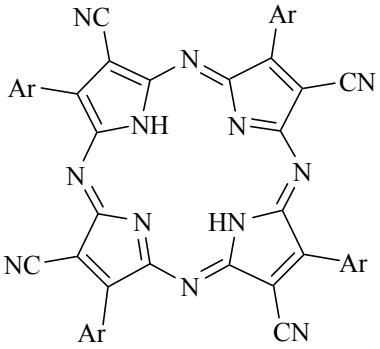
It has recently been found that photodynamic effect is accompanied by a strong increase of intracellular viscosity [2, 3]. This means that intracellular viscosity may be an important parameter allowing real-time monitoring of dynamic processes occurring in cancer cells during their photoinduced destruction. Thus, photosensitizers acting as intracellular viscosity sensors, i.e., showing fluorescence sensitivity to viscosity of the environment, acquire additional potentialities as theranostic agents [2–4].

We previously reported the synthesis and photophysical properties of new fluorescent porphyrazine dyes which revealed a unique combination of properties as efficient photodynamic therapy sensitizers and optical sensors for intracellular viscosity [3, 4]. It is known that the relation between photphysical properties and viscosity depends on the rate of rotation of particular molecular fragments of some dyes upon photoexcitation [2, 5]. Highly viscous medium hampers internal rotation of molecules and hence dissipation of the excitation energy. As a result, the fluorescence intensity sharply increases. By contrast,

low-viscosity media facilitate internal motion of molecular fragments, so that fluorescence in such media is strongly weakened. Dyes characterized by strong dependence of the fluorescence parameters (such as fluorescence quantum yield and lifetime, as well as rate constants of radiative transition from the excited state to ground state) on solvent viscosity are called fluorescent molecular rotors [5].

By measuring fluorescence parameters of a molecular rotor in a living cell, we can monitor some intracellular processes by the change of local viscosity. Modern bioimaging technologies, especially fluorescence lifetime imaging microscopy (FLIM), ensure mapping of molecular rotor distribution over a cell or tissue by the fluorescence lifetime [6]. This method features a high sensitivity, non-invasiveness, and almost instantaneous response, which allows real-time monitoring of processes occurring in cells or tissues [2]. Thus, a combination of fluorescent molecular rotor and photodynamic therapy sensitizer properties in a dye molecule gives rise to a very convenient optical theranostic agent.

We have recently demonstrated the above approach by performing monitoring of photodynamic therapy and quantitative assessment of intracellular viscosity before and after photodynamic therapy on cell cultures by measuring the fluorescence lifetime of a new photosensitizer and fluorescent molecular rotor, tetrakis(4-fluorophenyl)tetracyanoporphyrazine **1** [3].

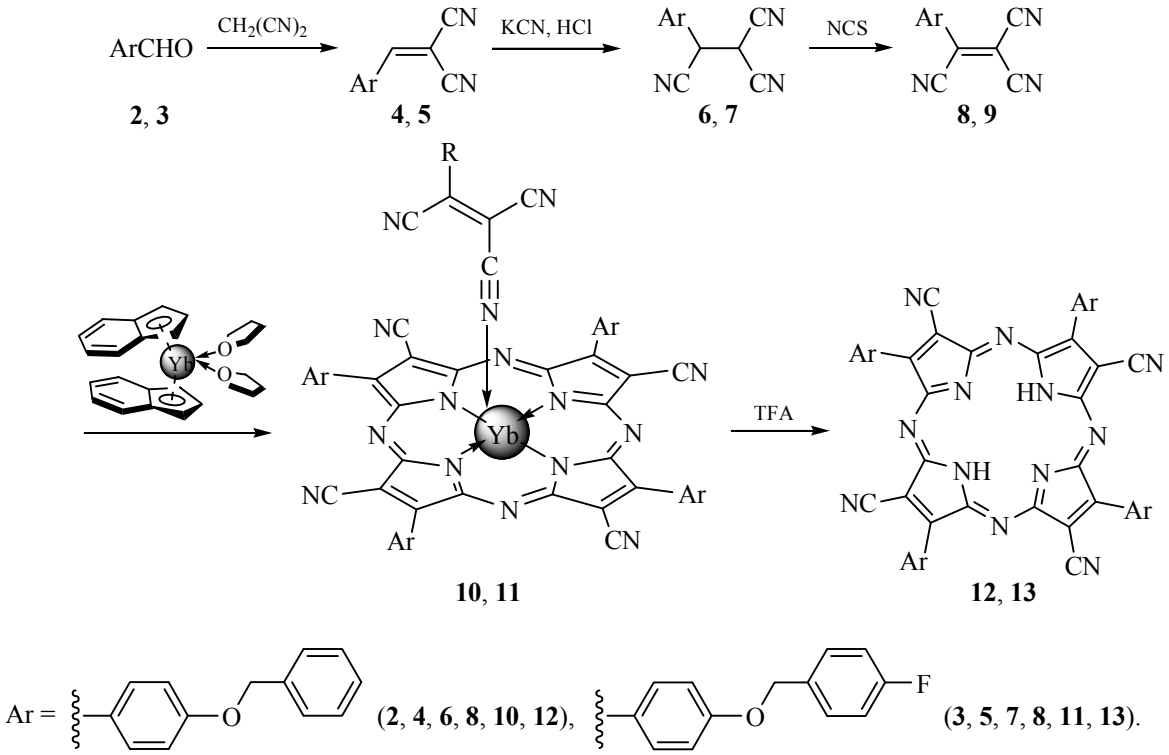


1

Ar = 4-FC_6H_4.

The goal of the present work was to obtain porphyrazines with enhanced photodynamic activity compared to compound **1** by varying peripheral substituents on the macrocycle. For this purpose, we synthesized new porphyrazine bases **12** and **13** containing additional donor substituents and studied the possibility of using them as optical theranostic agents (Scheme 1).

Scheme 1.



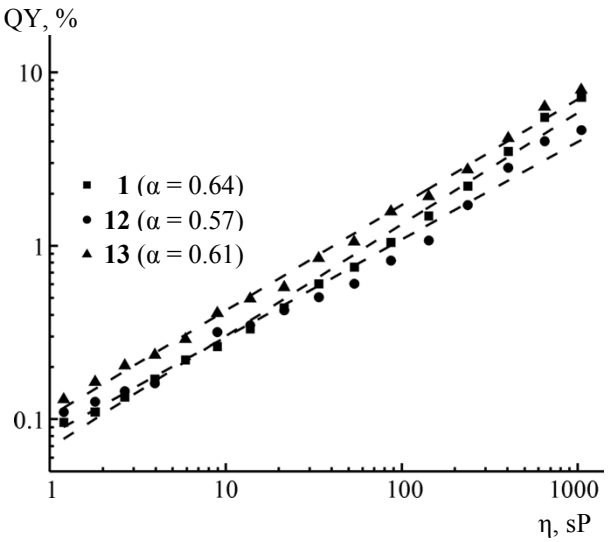
Compounds **12** and **13** were synthesized starting from aromatic aldehydes **2** and **3** which were converted to arylethylenetricarbonitriles **8** and **9**, followed by template assembly of macrocycles **10** and **11** on Yb^{3+} complex and removal of the central metal ion. Analogous scheme was used by us previously for the synthesis of porphyrazine **1** [3]. As we showed in this work, replacement of the fluorine atom in the initial benzaldehyde by benzyloxy group does not impair synthetic potential of the procedure. As a result, new porphyrazines **12** and **13** were isolated in overall yields of 32 and 33%, respectively (calculated on the initial benzaldehydes **2** and **3**).

To estimate the potential of **12** and **13** as multimodal cancer theranostic agents and compare their properties with those of previously described porphyrazine **1**, we examined their spectral properties, quantitatively estimated their dark and photoinduced cytotoxicities, and determined viscosity dependence of the fluorescence quantum yield.

Table 1 contains the long-wave absorption and fluorescence maxima and fluorescence quantum yields of porphyrazines **1**, **12**, and **13** in water. On the whole, introduction of benzyloxy groups resulted in red shift of the absorption and fluorescence maxima, which is favorable for photodynamic therapy due to enhancement of the permeability of living tissues for radiation both on excitation and emission measurement.

The data in Table 1 also show some increase of the red fluorescence quantum yield (QY) in aqueous medium in the series **1** < **12** < **13** upon excitation at λ 590 nm. Interestingly, the presence of a fluorine atom in the *para* position of the benzyloxy groups increases the fluorescence quantum yield of in **13** compared to **12** (see figure). Analogous pattern was observed by us previously for 4-fluorophenyl-substituted tetracyanoporphyrazine [7]. Obviously, the favorable effect of *para*-fluorine substitution on the red fluorescence intensity of teraaryltetracyanoporphyrazines as potential photodynamic therapy sensitizers should be taken into account in further design of peripheral environment of tetrapyrrole macrocycle.

The improved potential of new tetra(aryl)tetracyanporphyrazines as photosensitizers was demonstrated by quantitative assessment of their dark and photoinduced cytotoxicities against human epidermoid carcinoma A431 cell line. A widely used experimental procedure for such assessment is based on measurement of the inhibitory concentration IC_{50}, i. e., concentration of a drug inducing 50% cell growth inhibition (or death). This parameter was measured both in the dark and under irradiation. The IC_{50} values are given in Table 2. It is seen that compounds **1**, **12**, and **13** insignificantly differ from each other in photoinduced cytotoxicity [IC_{50}(light)] which characterizes cell survival rate under irradiation. However, the dark inhibitory concentrations of benzyloxy-substituted porphyrazines **12** and **13** [IC_{50}(dark)] were considerably higher than that of **1**, the most impressive difference being observed for compound **13**. The intrinsic cytotoxicity of **13** (i.e., cytotoxicity not related to photodynamic process) is lower by more than an order of magnitude than that of compound **1** having no oxygen atoms in the peripheral substituents. Therefore, porphyrazines **12** and **13** are potentially more efficient photodynamic sensitizers than **1** since their photoinduced cytotoxicity is determined mainly



Viscosity dependence of the fluorescence quantum yield of porohyrazines **1**, **12**, and **13**: QY = αη.

Table 1. Long-wave absorption and fluorescence maxima and fluorescence quantum yields of porphyrazines **1**, **12**, and **13** in water (c = 4.0 μM)

Parameter	**1**	**12**	**13**
Absorption maximum (Q band), nm	580	590	591
Excitation wavelength, nm	590	590	590
Fluorescence maximum, nm	650	670	670
Fluorescence quantum yield,[a] %	0.096	0.11	0.13

[a] Relative to Rhodamine 6G.

Table 2. Dark and photoinduced cytotoxicities (IC_{50}) of porphyrazines **1**, **12**, and **13**

Porphyrazine no.	IC_{50}(light), M	IC_{50}(dark), M	IC_{50}(dark)/ IC_{50}(light)
1	8.2×10^{-7}	6.3×10^{-6}	7.7
12	1.0×10^{-6}	4.0×10^{-5}	40.0
13	8.9×10^{-7}	7.4×10^{-5}	83.1

by just photoinduced cell death rather than by undesirable intrinsic cytotoxicity. A quantitative parameter characterizing the efficiency of a photosensitizer is the ratio IC_{50}(dark)/IC_{50}(light) or so-called therapeutic index. This parameter reflects the range of safe administration of a drug and is the ratio of the toxic dose to the effective therapeutic dose. Compound **1** showed a very low therapeutic index in cell cultures (7.7), whereas the corresponding value of **13** is 83. These findings lead us to expect high therapeutic index of **13** *in vivo*.

It should be noted that high dark cytotoxicity of drugs for photodynamic therapy is an important problem related to serious undesirable side effects in patients. Therefore, we believe that our results are useful for further design of fluorescent tetrapyrrole structures with reduced dark cytotoxicity.

A unique feature of porphyrazine **1** (for details, see [3]) is a combination of its photodynamic activity with high sensitivity of its fluorescence parameters to viscosity of the medium, so that compound **1** can be used as intracellular viscosity sensor. We examined the dependence of the fluorescence quantum yield of porphyrazines **12** and **13** on the solvent viscosity and revealed strong increase of the fluorescence intensity and quantum yield with increase of the viscosity of ethanol–glycerol mixtures (see figure). It is seen that introduction of benzyloxy and 4-fluorobenzyloxy groups into the *para* position of peripheral phenyl substituents does not reduce the sensitivity of their fluorescence parameters to viscosity as compared to compound **1**.

In summary, we have synthesized new fluorescent porphyrazine macrocycles exhibiting enhanced photodynamic activity. A combination of photodynamic sensitizer and intracellular viscosity sensor properties of these compounds makes them promising as optical theranostic agents of new generation.

EXPERIMENTAL

The IR spectra were recorded in mineral oil on an FSM 1201 spectrometer with Fourier transform. The electronic absorption spectra in the UV and visible regions were measured on a Perkin Elmer Lambda 25 spectrophotometer. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance II+ instrument at 400, 100, and 375 MHz, respectively, at 25°C. Fluorescence measurements were performed in a stationary mode on a Perkin Elmer LS 55 instrument in the range λ 300–800 nm. The mass spectra (MALDI TOF) were obtained on a Bruker Microflex LT mass spectrometer. The dynamic viscosities of binary ethanol (methanol)–glycerol mixtures were measured with an accuracy of ±0.35% on an Anton Paar SVM 3000 Stabinger viscometer. Porphyrazines were dissolved by mechanical stirring and ultrasonic treatment for at least 15 min.

The survival rate of cell culture was estimated by MTT assay [8]. Cells were distributed over a 96-well plate (4000 cells per well) and were incubated overnight. The nutrient medium in the wells was replaced by 100 μL of a medium containing porphyrazine PZ1, PZ2, or PZ3 at different concentrations, and the plate was incubated for 4 h. The medium in the wells was then replaced by fresh portions of nutrient medium.

The cells in 96-well plates were irradiated with a radiation source with a replaceable LED module ensuring uniform light flux [9]; the radiation dose was 20 J/cm^2 (λ 615–635 nm) at a power density of of 20 mW/cm^2. After irradiation for 24 h, 3-(4,5-dimethyl-1,3-thiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT reagent, Alfa Aesar, UK) was added to a concentration of 0.5 mg/mL, and the cells were incubated for 4 h. The incubation medium was withdrawn, and colored MTT formazan crystals were dissolved in 100 μL of dimethyl sulfoxide. The optical density for each well was measured at λ 570 nm with a BioTek Synergy MX microplate spectrophotometer (USA). The cell survival rate was estimated by the ratio of the optical densities of the formazan solution for each well and that of control (not irradiated). The dark cytotoxicity was determined without irradiation.

All operations in the synthesis and analysis of porphyrazines were carried out in purified anhydrous solvents. *N*-Chlorosuccinimide, malononitrile, 4-hydroxybenzaldehyde, benzyl chloride, and 4-fluorobenzyl chloride were commercial products (from Acros Organics). Bis(indenyl)ytterbium was synthesized according to the procedure described in [10].

Tetracyanotetrakis(4-fluorophenyl)porphyrazine **1** was synthesized by us previously [3].

Aldehydes 2 and *3 (general procedure)*. Aldehydes **2** and **3** were synthesized by alkylation of 4-hydroxybenzaldehyde according to modified procedure [11]. A mixture of 30 mL of DMF, 6.1 g (50 mmol) of 4-hydroxybenzaldehyde, 48 mmol of benzyl or 4-fluorobenzyl chloride, 6.9 g (50 mmol) of potassium carbonate , and 83 mg (0.5 mmol) of potassium iodide was heated for 3 h at 100°C on an oil bath. The mixture was cooled to room temperature and diluted with 200 mL of water, and the precipitate was filtered off, washed several times with water, and dried.

4-(Benzyloxy)benzaldehyde (2). Yield 8.9 g (88%), white solid, mp 70°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.18 s (2H, CH_2), 7.11 d (2H, J = 8.7 Hz), 7.38–7.47 m (5H), 7.87 d (2H, J = 8.7 Hz), 9.91 s (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 70.29, 115.18, 127.50, 128.35, 128.75, 130.16, 132.01, 135.98, 163.77, 190.80. Mass spectrum: *m*/*z* 212 (I_{rel} 100%) $[M]^+$.

4-(4-Fluorobenzyloxy)benzaldehyde (3). Yield 9.4 g (85%), white solid, mp 99°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.13 s (2H, CH_2), 7.08–7.13 m (4H), 7.45–7.42 m (2H), 7.87 d (2H, J = 8.7 Hz), 9.91 s (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 69.60, 115.12, 115.69 d (J_{CF} 21.6 Hz), 129.41 d (J_{CF} = 8.2 Hz), 130.27, 131.88, 132.02, 162.69 d (J_{CF} = 246.0 Hz), 163.55, 190.75. ^{19}F NMR spectrum ($CDCl_3$): δ_F –113.50 ppm. Mass spectrum: *m*/*z* 230 (I_{rel} 100%) $[M]^+$.

Arylethenetricarbonitriles 8 and 9 *(general procedure)* [12, 13]. Aldehyde **2** or **3**, 10 mmol, was dissolved in 100 mL of ethanol, 0.56 g (10 mmol) of malononitrile and two drops of piperidine were added, and the mixture was stirred for 24 h at room temperature. The precipitate was filtered off, washed with water (4×80 mL), and dried at room temperature under reduced pressure. The crude product (2-arylmethylidenemalononitrile) was dissolved in 150 mL of ethanol, a solution of 1.62 g (25 mmol) of potassium cyanide in 80 mL of water was added, 240 mL of water was then added, and the mixture was stirred for 45 min at room temperature. The mixture was treated with 6 mL of 37% aqueous HCl and cooled in an ice bath, and the precipitate was filtered off, thoroughly washed with water, and dried at room temperature under reduced pressure. Crude 2-arylethane-1,1,2-tricarbonitrile thus obtained was dissolved in 100 mL of diethyl ether, 1.20 g (9 mmol) of *N*-chlorosuccinimide was added, and the mixture was stirred for 1 h on cooling with an ice bath. Water, 150 mL, was added, the organic phase was separated and washed with water (3×150 mL), the solvent was removed under reduced pressure, and the product was purified by vacuum sublimation.

2-(4-Benzyloxyphenyl)ethene-1,1,2-tricarbonitrile (8). Yield 72%, yellow solid, mp 153°C. IR spectrum, ν, cm^{-1}: 2222, 2236 (C≡N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.21 s (2H), 7.14 d (2H, J = 9.1 Hz), 7.42 m (5H), 8.09 d (2H, J = 9.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 70.94, 87.69, 111.91, 111.96, 113.84, 116.49, 121.59, 127.55, 128.75, 128.93, 132.53, 135.02, 140.27, 165.10. Found, %: C 76.95; H 3.81; N 14.19. $C_{18}H_{11}N_3O$. Calculated, %: C 75.78; H 3.89; N 14.73.

2-(4-Fluorobenzyloxyphenyl)ethene-1,1,2-tricarbonitrile (9). Yield 66%, yellow solid, mp 127°C. IR spectrum, ν, cm^{-1}: 2222, 2239 (C≡N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.17 s (2H), 7.11 m (4H), 7.41 m (2H), 8.10 d (2H, J = 9.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 70.19, 87.87, 111.82, 111.87, 113.77, 115.87 d (J_{CF} = 21.8 Hz), 116.38, 121.65, 129.51 d (J_{CF} = 8.3 Hz), 130.80, 132.48, 140.22, 162.86 d (J_{CF} = 246.0 Hz), 164.81. ^{19}F NMR spectrum ($CDCl_3$): δ_F –113.50 ppm. Found, %: C 72.38; H 3.24; N 13.34; F 6.12. $C_{18}H_{10}FN_3O$. Calculated, %: C 71.28; H 3.32; N 13.85; F 6.26.

Ytterbium complexes 10 and 11 *(general procedure)*. A solution of 2.3 mmol of tricyanoethylene **8** and **9** in 5 mL of preliminarily degassed THF was added in small portions in an inert atmosphere to a solution of 0.25 g (0.46 mmol) of bis-indenyl ytterbium(II) complex in 5 mL of THF. After 24 h, the precipitate was filtered off under reduced pressure, washed with preliminarily degassed toluene until colorless washings, and dried under reduced pressure.

[Tetrakis(4-benzyloxyphenyl)tetracyanoporphyrazinato]ytterbium(II) (10). Yield 53%, black solid, mp > 300°C. IR spectrum, ν, cm^{-1}: 2204, 2118 (C≡N); 1687, 1678 (C=N), 1601 (C=C); 1219, 1024 (C_{arom}–O–C). Found, %: C 62.46; H 4.03; N 12.63; Yb 12.99. $C_{72}H_{49}N_{12}O_7Yb$. Calculated, %: C 63.25; H 3.61; N 12.29; Yb 12.66.

{Tetracyanotetrakis[4-(4-fluorobenzyloxy)phenyl]-porphyrazinato}ytterbium(II) (11). Yield 73%, black solid, mp > 300°C. IR spectrum, ν, cm^{-1}: 2204, 2119 (C≡N); 1687 (C=N), 1603 (C=C); 1224, 1029

(C_{arom}–O–C); 1158, 1101 (C–F). Found, %: C 60.89; H 3.37; F 5.08; N 11.35; Yb 12.46. $C_{72}H_{45}F_4N_{12}O_7Yb$. Calculated, %: C 60.09; H 3.15; F 5.28; N 11.68; Yb 12.02.

Porphyrazines 12 and 13 *(general procedure).* A solution of 0.14 mmol of complex **10** or **11** in 2 mL of trifluoroacetic acid was stirred for 30 min at room temperature. The mixture was diluted with 30 mL of water, and the precipitate was separated by cetrifugation and thoroughly washed with water until neutral washings. The product was purified by column chromatography on Silica gel 60 (40–60 μm) using THF as eluent.

Tetrakis(4-benzyloxyphenyl)tetracyanoporphyrazine (12). Yield 83%, black solid, mp > 300°C. IR spectrum, ν, cm^{-1}: 3400 (N–H), 2205 (C≡N); 1687, 1678 (C=N), 1600 (C=C); 1218, 1025 (C_{arom}–O–C). UV spectrum (THF), λ_{max}, nm: 361, 397 (Soret band), 617 (*Q* band). Found, %: C 76.70; H 4.16; O 5.4; N 14.02. $C_{72}H_{46}N_{12}O_4$. Calculated, %: C 75.64; H 4.06; O 5.6; N 14.70.

Tetracyanotetrakis[4-(4-fluorobenzyloxy)phenyl]-porphyrazine (13). Yield 69%, black solid, mp > 300°C. IR spectrum, ν, cm^{-1}: 3403 (N–H), 2201 (C≡N), 1681 (C=N), 1603 (C=C); 1218, 1038 (C_{arom}–O–C); 1164, 1102 (C–F). UV spectrum (THF), λ_{max}, nm: 356, 397 (Soret band), 610 (*Q* band). Found, %: C 72.16; H 3.56; F 6.11; N 13.19. $C_{72}H_{42}F_4N_{12}O_4$. Calculated, %: C 71.16; H 3.48; F 6.25; N 13.83.

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