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Effective monofunctional azaphthalocyanine photosensitizers for photodynamic therapy

Accessory Publication

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Content

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Synthesis

4,5-bis(*tert*-butylsulfanyl)phthalonitrile (12): NaH (60% mineral oil dispersion, 2.46 g, 61 mmol) has been washed from the mineral oil by dry hexane and dried using the argon stream. Anhydrous DMF (100 mL) was added and the dispersion was cooled down to 0°C with water/ice. 2-methylpropan-2-thiol (54 mmol, 6.1 mL) has been added dropwise under argon atmosphere. After the stop of the gas evolution, Cu_2O (52 mmol, 7.38 g) and 4,5-dichlorophthalonitrile (25 mmol, 4.84 g) were added and the mixture was heated for 30 min at 90°C. The mixture was stirred and left to cool down at r.t. for next 30 min and poured into ice cold water (500 mL). The suspension was filtered and the solid was extracted several times by chloroform. The filtrate was also washed 3 times with chloroform and organic layer was dried. The chloroform solutions of crude **12** were combined, evaporated and purified by column chromatography on silica (chloroform/toluene 2:1) to receive white-yellow solid (4.85 g, 65%). Mp 157.5-158°C (methanol) (lit.[1] 150-152°C). (Found: C 62.81, H 6.50, N 8.83%. $C_{16}H_{20}N_2S_2$ requires: C 63.12, H 6.62, N 9.20%.) δ_H ($CDCl_3$) 1.44 (s, 18H, CH_3), 7.86 ppm (s, 2H, aromH). δ_C ($CDCl_3$) 30.9, 49.6, 112.5, 115.2, 136.9, 146.9 ppm.

5,6-bis(*tert*-butylsulfanyl)pyrazine-2,3-dicarbonitrile (15): Aqueous NaOH solution (34.5 mL, 34.5 mmol) was slowly stirred at room temperature and 2,2-dimethyl-propane-1-thiol (4.0mL, 35.5 mmol) was added by syringe. Care was taken to put the thiol directly to the solution of hydroxide. Mixture was stirred at r.t. for 30 min and a solution of 5,6-dichloropyrazine-5,6-dicarbonitrile[2] (3.0 g, 15 mmol) in THF (80 mL) was added. Reaction was stirred for 15 min, ethyl-acetate was added and two layers were separated. The water layer was washed two more times with ethyl-acetate and discarded. Organic layers were combined, dried and evaporated. The crude product was purified by flash chromatography on silica (toluene) to give yellow solid (4.3 g, 93%). Mp 161.8-162.3°C (methanol)(lit.[1] 161-162°C). (Found: C 54.81, H 5.80, N 18.53%. $C_{14}H_{18}N_4S_2$ requires: C 54.87, H 5.92, N 18.28%.) δ_H ($CDCl_3$) 1.64 ppm (s, 9H, CH_3). δ_C ($CDCl_3$) 29.6, 52.3, 113.8, 125.0, 161.0 ppm.

[2,11(12),20(21),29(30)-Tetracarboxytetra[2,3]quinoxalinoporphyrazinato] magnesium (II) (5): Anhydrous butanol (10 mL) was refluxed with magnesium (7 mmol, 168 mg) and a small

crystal of iodine for 3 h. Compound **17** (1 mmol, 224 mg) was added and the reflux continued for next 24 h. Solvent was evaporated and the green solid was stirred with 50% acetic acid (50 mL) for 30 min. Crude product was filtered off and washed thoroughly and sonicated with 50% acetic acid, water, acetone, pyridine, diethylether and dried. Black-blue solid (125 mg, 55%). Compound is soluble in 1M aqueous NaOH (see Figure S1).

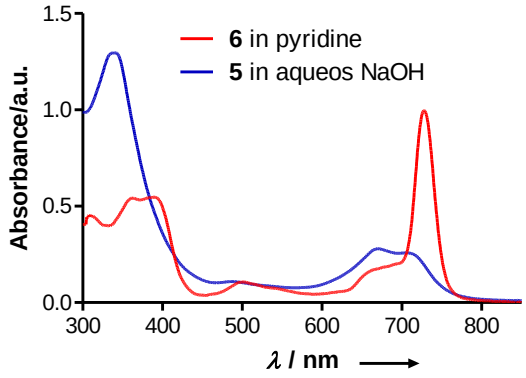
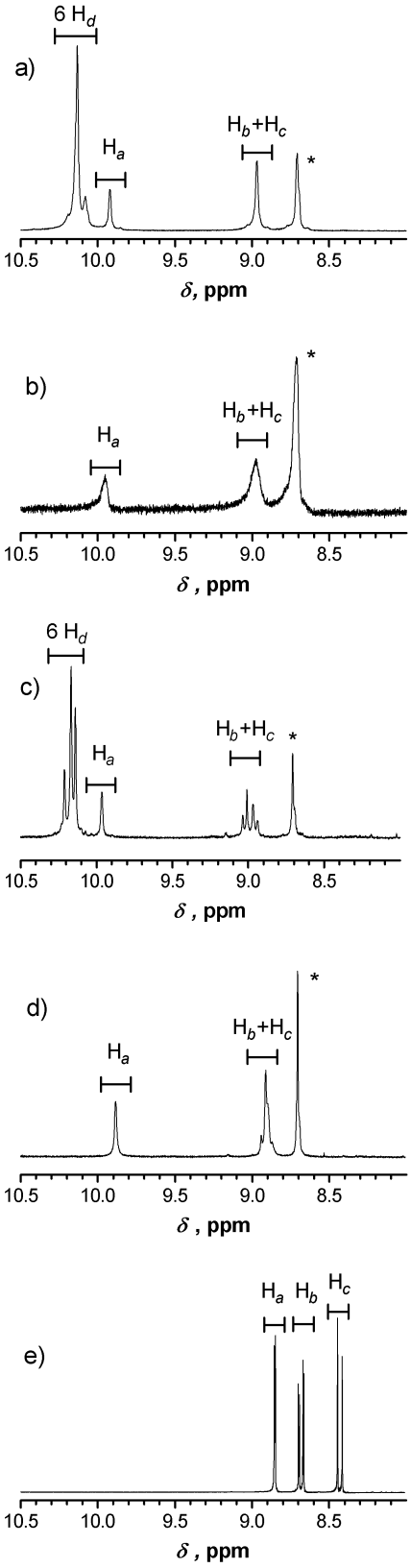


Figure S1: UV-vis spectra of compound **5** in aqueous NaOH (1M) (blue) and compound **6** in pyridine (red). Broad Q-band of **5** together with much stronger B-band than Q-band indicate strong aggregation.

NMR spectra



The signals of aromatic hydrogens of quinoxaline ring in dyes **1**-**4** are shifted to lower fields comparing to precursors. The closer to centre of the macrocycle, the stronger shift of aromatic hydrogens was observed. Thus signal of hydrogen H_a was detected close to 10 ppm and hydrogens H_b and H_c fused together to form one broad signal around 9 ppm. Even stronger effect can be observed for hydrogens H_d of benzene rings in **1** and **3** which are located closer to the centre of macrocycle than hydrogens H_a, H_b and H_c. The signal of these aromatic hydrogens in phthalonitrile **12** appears at 7.86 ppm (in $CDCl_3$). After tetramerization, these hydrogens are detected over 10 ppm (C_5D_5N).

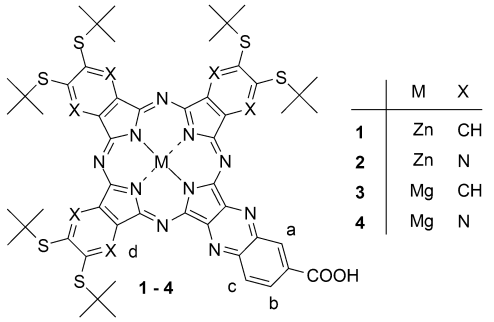


Figure S2. NMR spectra of a) **1**, b) **2**, c) **3**, d) **4** in [D_5]-pyridine and e) **16** in [D_6]-acetone. Asterisk indicates residuals of non-deuterated solvent.

UV-vis absorption, fluorescence emission and fluorescence excitation spectra

For all following figures: solvent pyridine, UV-vis absorption spectra (red), fluorescence excitation spectra (blue), fluorescence emission spectra (green). Emission spectra were taken after excitation at 375 nm. Wavelengths of emission that was observed during collecting the excitation spectra differ and are mentioned for each compound.

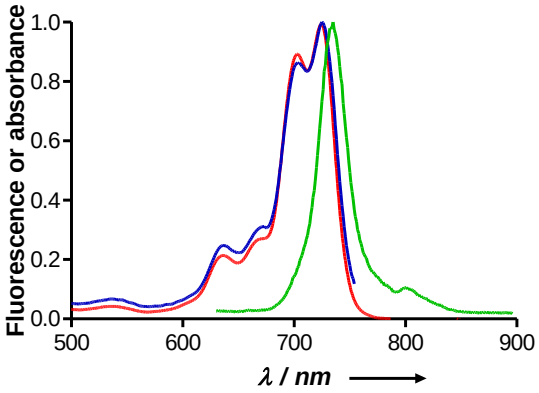


Figure S3: Compound **1**, emission wavelength 770 nm.

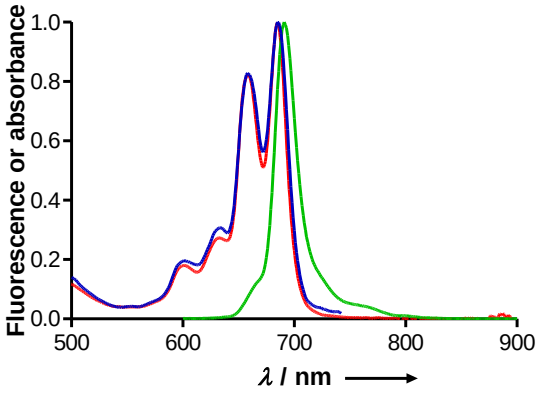


Figure S4: Compound **2**, emission wavelength 750 nm.

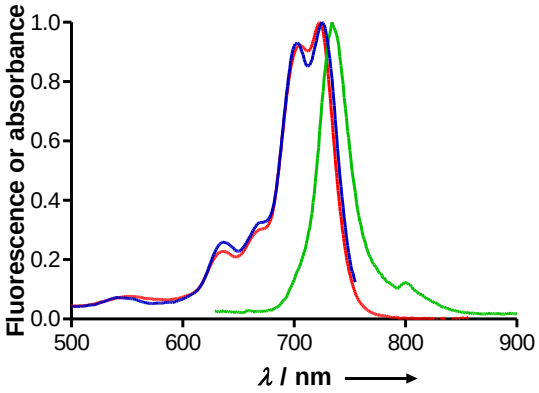


Figure S5: Compound **3**, emission wavelength 770 nm.

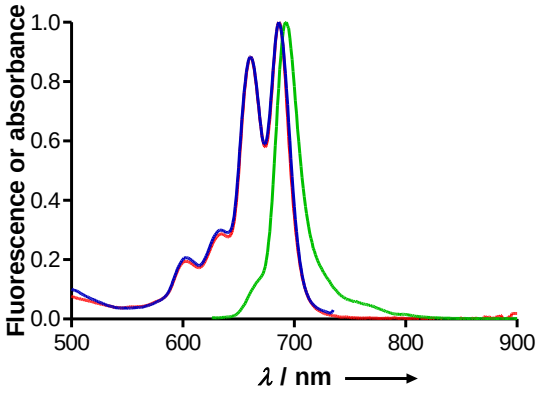


Figure S6: Compound **4**, emission wavelength 750 nm.

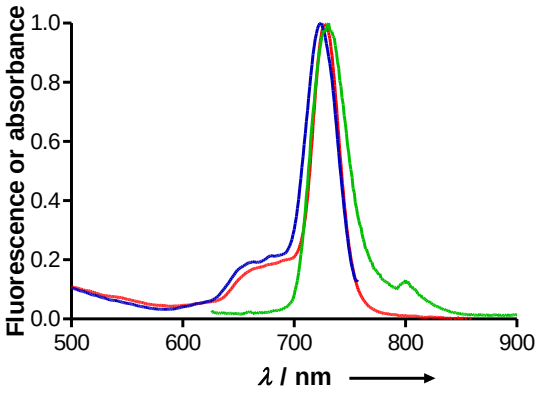


Figure S7: Compound **6**, Emission wavelength 800 nm.

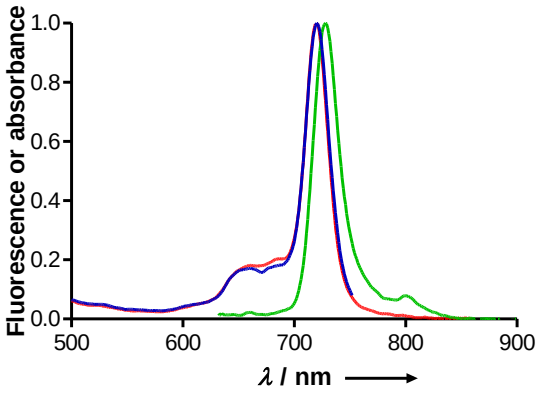


Figure S8: Compound **7**, Emission wavelength 800 nm.

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MS (MALDI-TOF) spectra

Enlarged parts of the MALDI-TOF spectrum of compound **7** (measured without addition of TFA) and corresponding calculated isotope distributions. For comparison also the spectra calculated for $[M+2X-H]^+$ (where X is Na or K) are shown. The loss of one proton would explain only one charge but the calculated spectra do not correspond to measured values.

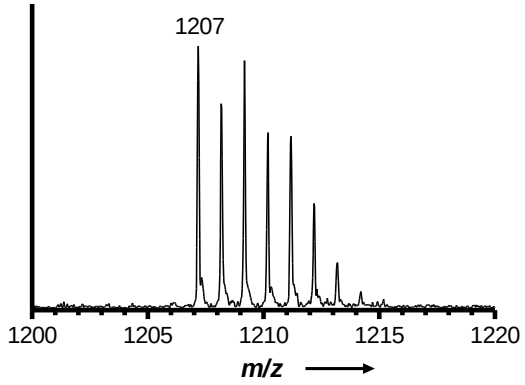

Figure S9: $[M+Na]^+$ measured.

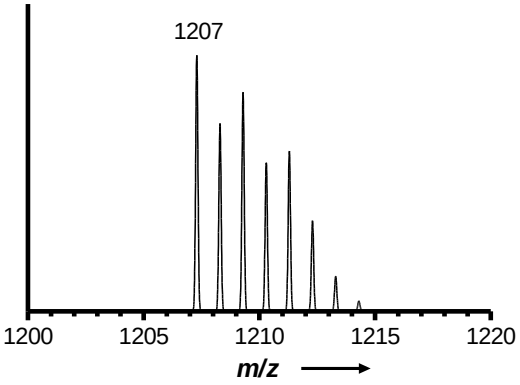

Figure S10: Calculated isotope distribution for $[M+Na]^+$.

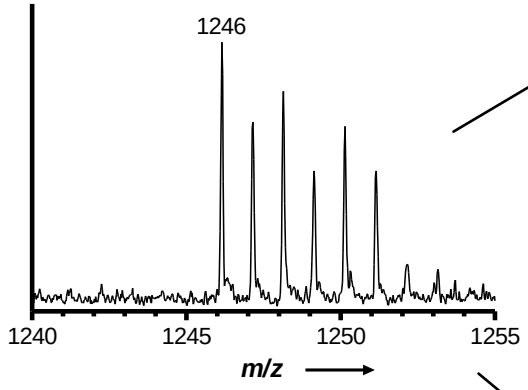

Figure S11: $[M+Na+K]^+$ measured.

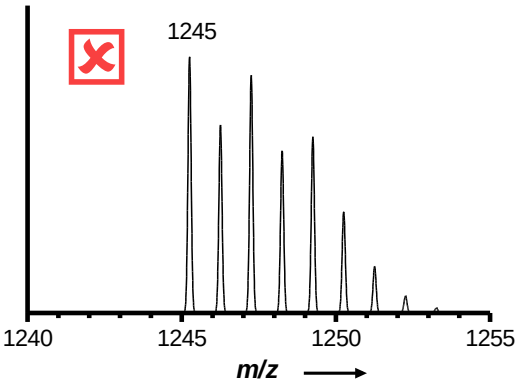

Figure S12: Calculated for $[M+Na+K-H]^+$.

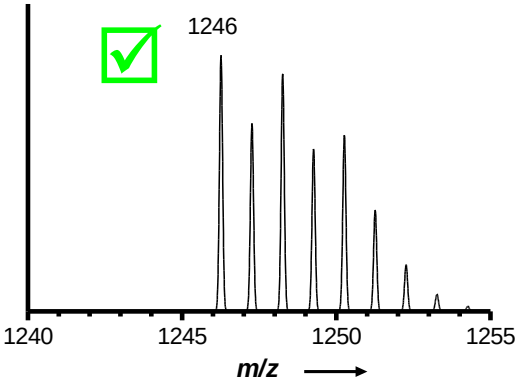

Figure S13: Calculated for $[M+Na+K]^+$.

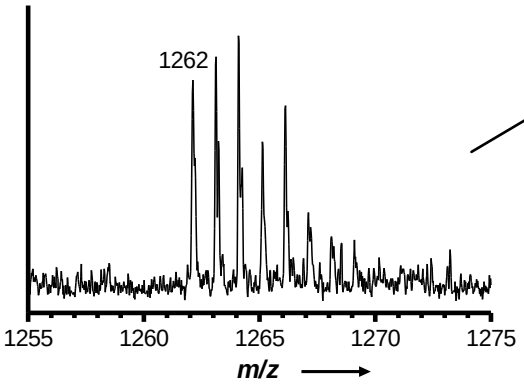

Figure S14: $[M+2K]^+$ measured.

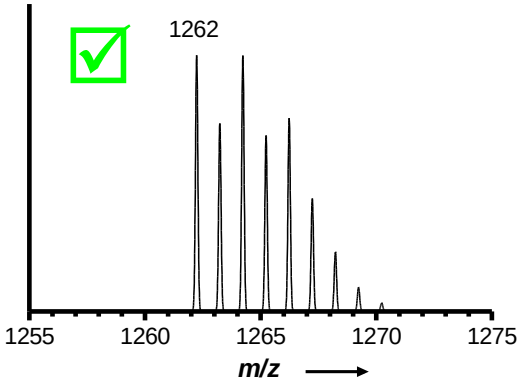

Figure S15: Calculated for $[M+2K]^+$.

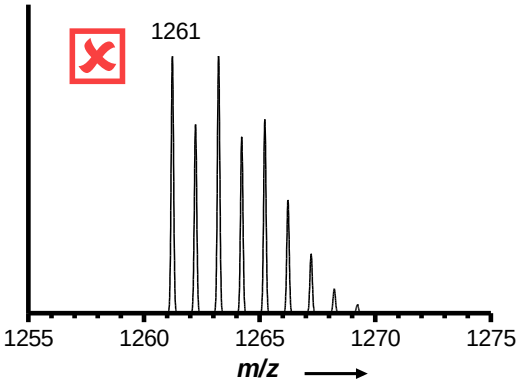

Figure S16: Calculated for $[M+2K-H]^+$.

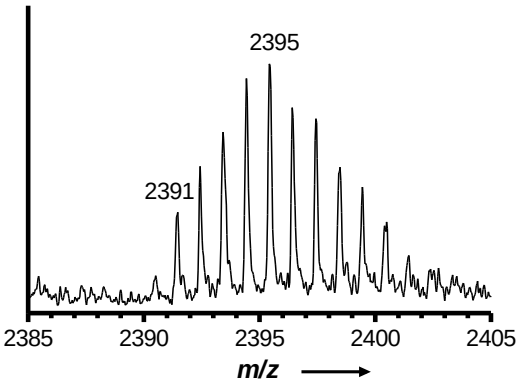

Figure S17: $[2M+Na]^+$ measured.

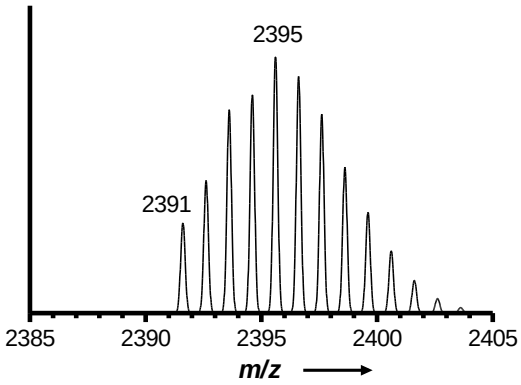

Figure S18: $[2M+Na]^+$ calculated.

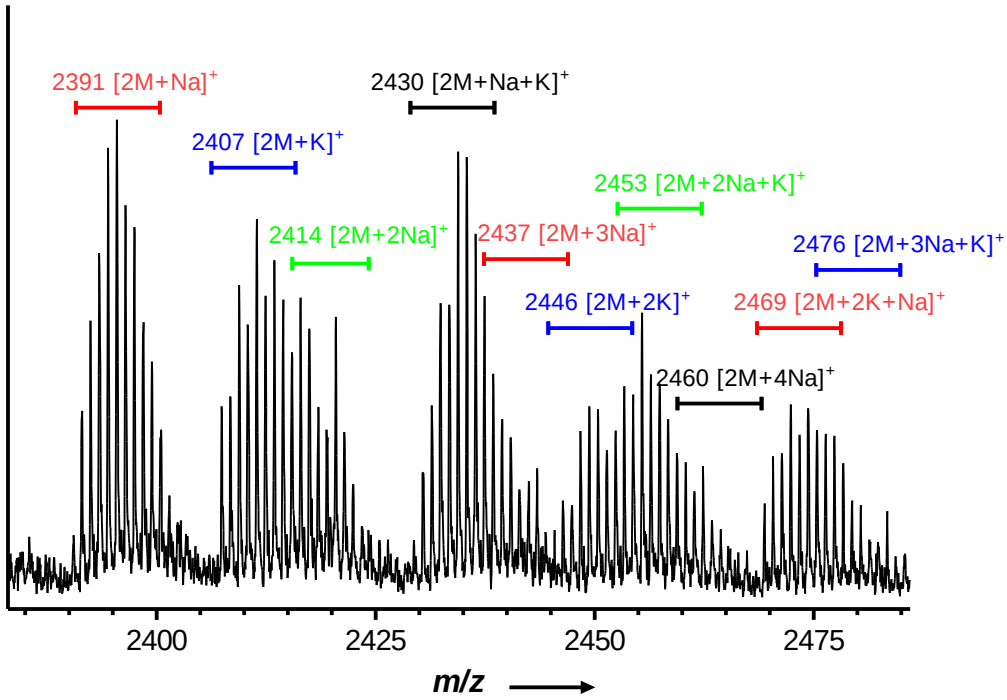

Figure S19: Dimer area of MALDI-TOF spectrum of **7** with analysis of the adducts.

References:

[1] M. Kostka, P. Zimcik, M. Miletin, P. Klemera, K. Kopecky, Z. Musil, *J. Photochem. Photobiol. A: Chem.* **2006**, *178*, 16.

[2] E. H. Mørkved, L. T. Holmaas, H. Kjøsen, G. Hvistendahl, *Acta Chem. Scand.* **1996**, *50*, 1153.

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