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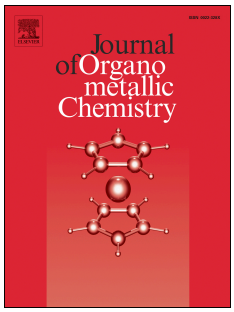

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Synthesis of Boronated *meso*-Arylporphyrins via Copper-catalyzed 1,3-Dipolar Cycloaddition Reaction and Their Binding Ability Towards Albumin and Low Density Lipoproteins

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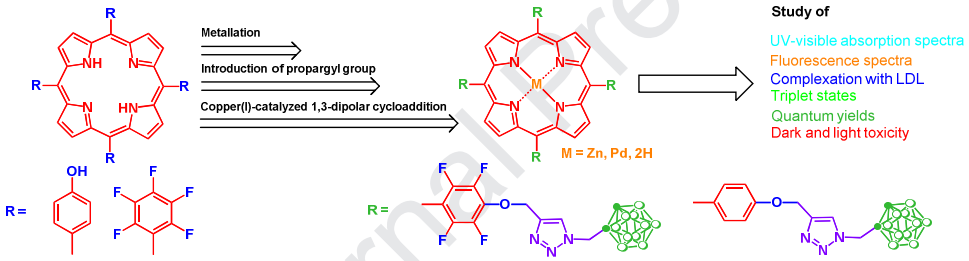
Graphical abstract



A series of novel *meso*- triazoloporphyrin-carborane conjugates were prepared in good yields starting from propargyl derivatives of tetrakis(pentafluorophenyl)porhyrin and tetrakis(4-hydroxyphenyl)porphyrin and azidometyl carborane. Their photophysical properties, complexation with LDL, triplet states, quantum yields and cytotoxicity were investigated.

Abstract

A series of novel *meso*- triazoloporphyrin-carborane conjugates was prepared in good yields via the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction of Zn(II) or Pd(II) 5,10,15,20-tetrakis[4-(2-propargyloxy)-2,3,5,6-tetrafluorophenyl]porphyrin or Zn(II) 5,10,15,20-tetra(*p*-propargyloxyphenyl)porphyrin with 1-azidomethyl-*o*-carborane in CH_2Cl_2. Zinc metalloporphyrins were demetallated under acidic conditions to afford the corresponding free-base triazolo-carborane porphyrins in excellent yields. All new compounds were characterized by MS, NMR and UV-vis spectroscopy and their photophysical properties were studied.

Key words

porphyrins, triazoles, carboranes, fluorescence, triplet state, phototoxicity.

Highlights

Novel triazole-carborane porphyrin conjugates were synthesized.
Synthesized compounds were structurally characterized by conventional spectroscopy.
Binding constants for albumin and LDL with synthesized compounds were obtained.
Singlet oxygen quantum yields of synthesized compounds were measured.
All compounds are nontoxic and show pronounced photoinduced cytotoxicity.

1. Introduction

Porphyrins and their derivatives represent an important class of macroheterocycles that have important applications in a number of fields, including catalysis [1], polymer synthesis [2], materials [3]. As photoactive compounds they are used as photosensitizers (Ps) in photodynamic therapy (PDT) for treatment of oncological cancer diseases [4]. PDT is based on excitation of Ps with light of specific wavelengths initiating of type I and type II photochemical reactions that may result in the primary tumor destruction via the local generation of reactive oxygen species (ROS) [5-7]. PDT is a complex modality for destruction of cancer cells, and results of the treatment depend on multiple parameters including the chemical and photochemical properties of the PS, light delivery system, and subcellular localization of Ps in organelles of the tissue.

Numerous porphyrin derivatives as bases for PDT application have been reported and some of them are currently used in preclinical and clinical trials [8]. Nevertheless, intensive investigations are carried out on the improvement of the structural characteristics of Ps in the hope to get newer derivatives with the higher anticancer PDT activity. One of the approaches includes the functionalization of porphyrins with well-established pharmacophore structural fragments. Small nitrogen heterocycles are substituents of particular interest, providing sites for metal coordination, hydrogen bonding, alkylation, and thus affecting on the electronic and physico-chemical properties of the porphyrin macrocycle.

Among nitrogen heterocycles five-membered 1,2,3-triazoles are important scaffold due to their extensive biological activities. Copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes leading to 1,4-substituted 1,2,3-triazoles plays an important role in the preparation of biologically active compounds [9]. It employs stable and readily available chemical reagents (azides and alkynes) which react rapidly at ambient temperature, tolerates a wide range of functional groups, including unprotected alcohols, carboxylic acids, and amines, and shows little sensitivity to steric factors [10-12]. This simple reaction is considered as an efficient approach for linking two organic fragments by triazole bridge. But the role of triazoles is not limited to the role of a convenient linker for organic groups. A great number of compounds containing 1,2,3-

triazole moieties have been reported to show a broad spectrum of biological activities, including fungicidal, antimicrobial, anticonvulsant, analgesic, and antitumor behavior [13-16]. Triazole compounds containing three nitrogen atoms in the five-membered aromatic ring are able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus modulating versatile biological activities [17] Moreover, this heterocycle is stable towards metabolic degradation and can improve the stability of molecules. So, coupling porphyrins to triazoles may lead to the multi-chromophore conjugates with improved biological activity possessing the potential for medical applications. With regard to porphyrins, it is extremely important to have available and simple synthetic methods for functionalization of macrocycle backbone in order to obtain derivatives with desirable characteristics. Via click chemistry, porphyrins have been connected with various structural units such as fullerene [18], ferrocene [19], carbohydrate [20-21] and also with triazole units and peripheral alkyl chains [22-23] in a single molecular framework for the study of their photophysical and therapeutic properties.

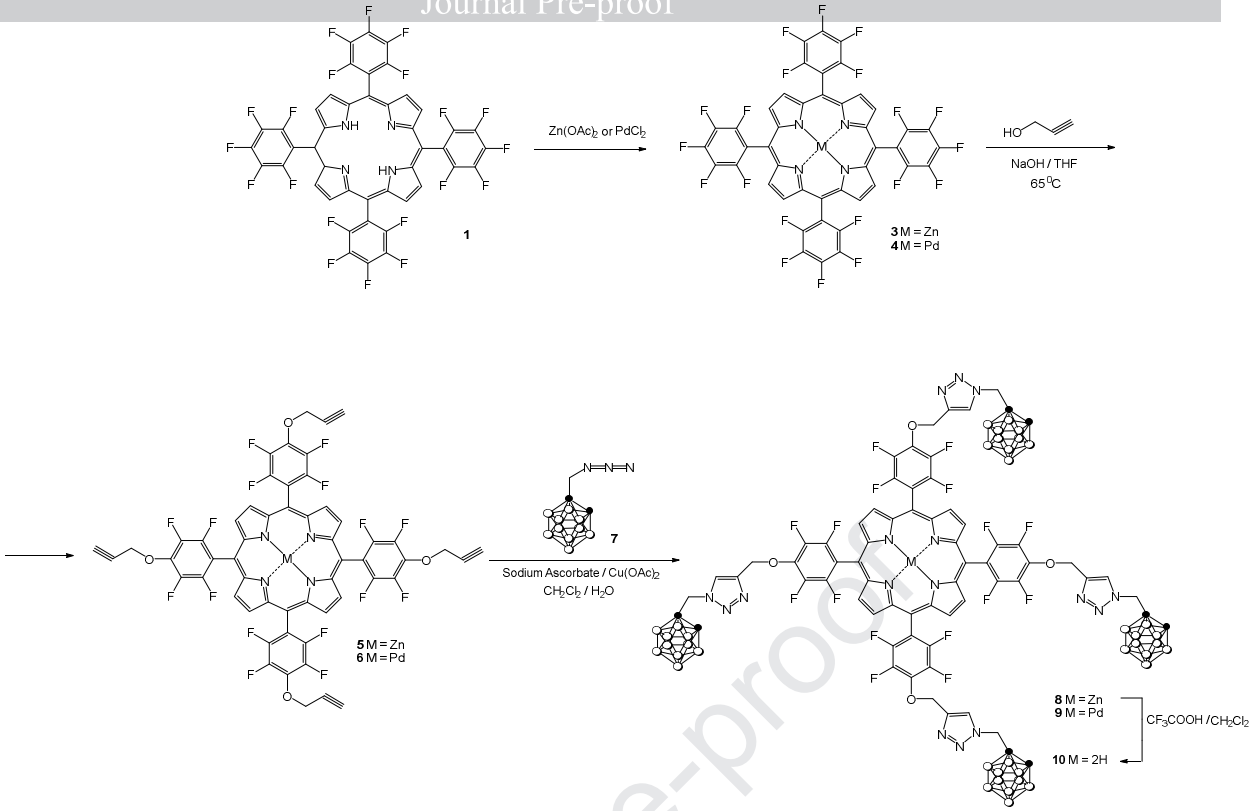
Polyhedral carboranes due to their unique chemical and structural properties[24] has attracted much attention as promising systems for various practical applications, including the biomedical ones [25].They also prospective for drug therapy as the hydrophobic pharmacophores targeting of biomolecules with suitable hydrophobic binding sites [26-27]. As a class of efficient photosensitizers, porphyrin conjugates with boron polyhedra have been under extensive study for PDT [28], since it was evidenced that carboranyl-substituted porphyrins demonstrated a higher PDT efficiency than comparable non-boronated analogues [29]. Furthermore, conjugation of carborane polyhedra to porphyrins yields dual efficacy antitumor photo/radiosensitizers allowing to carry out simultaneously both neutron capture therapy (BNCT) and PDT [30-31]. For the preparation of triazole-substituted boronated porphyrins *meso*-tetraarylporphyrins were used due to their straightforward syntheses and the availability of a wide variety of aryl-functionalized derivatives [32]. Most aryl derivatives do not change the electronic properties of the porphyrin macrocycles chromophore in any major way [33], but this does not apply to *meso*-tetrakis-(pentafluorophenyl)porphyrin which contain 20 strongly electron-withdrawing fluorine atoms having a significant inductive effect on porphyrin core. So the chemical and physical properties of this porphyrin and its functional derivatives may be altered when compared to non-fluorinated phenyl-substituted macrocycles [34-39]. The presence of pentafluorophenyl groups in this macrocycle enables its further simple modification at the peripheral parts by aromatic nucleophilic substitution [40-41]. In living organisms porphyrins, as prosthetic groups of enzymes, play an important role for electron transport in oxidation– reduction processes of cells and oxygen transport [42]. So, extensive studies have been carried out with respect to their

interaction with some cell compartments for estimation their therapeutic value. By considering the anticancer significance of porphyrins and biological dependence of the peripheral substituents of porphyrins on their properties it was contemplated to synthesize new porphyrin structures combining porphyrin macrocycle (fluorinated and parent phenyl-substituted), carborane and 1,2,3-triazole moiety within one molecule and to study binding ability and transport of prepared conjugates with albumin and low density lipoproteins (LDL).

2.Results and discussion

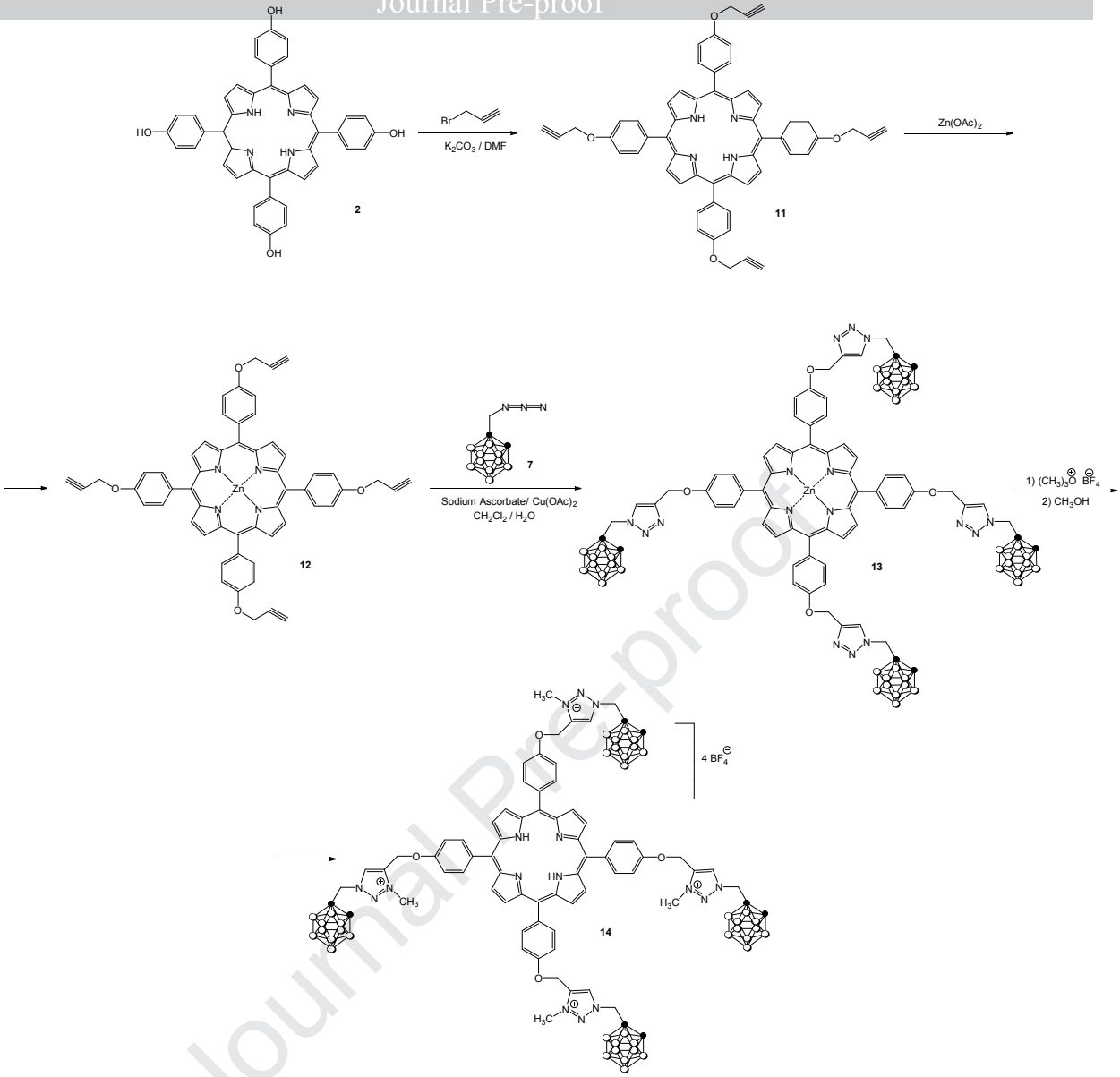
2.1. Synthesis

In this work for the preparation of porphyrins functionalized with carborane polyhedra and 1,2,3-triazole heterocycle commercially available 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (**1**) [43] and 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (**2**) [44] were used as starting compounds. Porphyrin **1** containing four pentafluorophenyl substituents easily enters into the nucleophilic para-regioselective S_NAr aromatic substitution reactions with various nucleophiles [45-49] and this reaction widely applied in pharmaceutical and chemical research, providing a broadly useful platform for the modification of aromatic ring scaffolds. In our study the functionalization of porphyrin **1** was achieved through two simple reaction steps. It was found that zinc (**3**) [50] or palladium (**4**) [51] complexes of porphyrin **1** readily reacted with excess of propargyl alcohol to afford porphyrins **5**, **6** via the substitution of fluorine atoms in the para position of pentafluorophenyl units with four propargyloxy groups. The reaction was performed in boiling THF in the presence of NaOH (powder). The crude products were purified by column chromatography to afford the porphyrins **5** and **6** with a yield of 94% and 92%, respectively. Porphyrins **5**, **6** are valuable substrates to use in Huisgen copper catalyzed 1,3-dipolar cycloaddition reaction [52-53] which give an opportunity to easily connect various types of molecular units. We have found that reaction of 1-azidomethyl-*o*-carborane (**7**) [54] with alkynyl-substituted porphyrins **5** and **6** under "click-chemistry" conditions proceeded smoothly and chemoselectively by heating in CH_2Cl_2 affording boronated porphyrin-triazole conjugates **8**, **9** in 72-79 % yields. Free base conjugate **10** was obtained in 95% yield by the removal of zinc from compound **8** under the action of trifluoroacetic acid in $CHCl_3$ – MeOH mixture (**Scheme 1.**).



Scheme 1. Synthesis of carboranyl triazole conjugates **8**-**10** based on porphyrin **1**.

To study the influence of porphyrin chromophore structure on the properties of boronated triazole conjugates we have synthesized similar derivatives based on non-fluorinated porphyrin **2** as starting compound. Reaction between porphyrin **2** and excess of propargyl bromide in DMF in the presence of K_2CO_3 (Williamson coupling reaction) led to the formation of 5,10,15,20-tetra(propargyloxyphenyl)porphyrin (**11**) [55] in 85% yield. To avoid undesirable metalation of porphyrin ring with copper ions during click reaction zinc complex (**12**) was synthesized in 92% yield by reaction of porphyrin **11** with $Zn(OAc)_2$ in CH_2Cl_2-MeOH mixture at ambient temperature. Next, the terminal triple bonds of propargylated porphyrin **12** were introduced into reaction with azide **7** in the presence of copper(II) acetate/sodium ascorbate catalyst under argon atmosphere at boiling in a mixture of solvent CH_2Cl_2/H_2O leading to porphyrin **13** containing 1,2,3-triazole linkers between porphyrin macrocycle and carborane polyhedra (**Scheme 2**.).



Scheme 2. Synthesis of carboranyl triazole conjugates **13**, **14** based on porphyrin **2**.

Alkylation of porphyrin **13** with the excess of trimethyloxonium tetrafluoroborate [56] in CH_2Cl_2 resulted in non-metallated tetracationic triazolium salt **14** in quantitative yield. This reaction is accompanied by the zinc removal from the coordination sphere of porphyrin. We suggest that the zinc removal occurs after the final treatment of the reaction mass with MeOH, which, interacting with the remaining trimethyloxonium tetrafluoroborate, gives HBF_4 acid, which removes zinc from the coordination sphere of porphyrin [57]. The structures of all newly prepared compounds were identified by IR and ^{1}H, ^{11}B, ^{11}B $\{^{1}H\}$, ^{19}F NMR spectroscopies and mass spectrometry. The IR spectra of boronated compounds **8**, **9**, **10**, **13** and **14** contains absorption band at 2580-2588 cm^{-1} assigned to the BH-stretching vibration in the *closo*-carborane polyhedron. The formation of propargyl-substituted porphyrins **5**, **6, 11** and **12** was confirmed by the presence of an absorption band in the region of 2119-2130 cm^{-1} due to the stretching vibration of the

terminal C≡C triple bond. ^{1}H NMR spectra of porphyrins **5**, **6**, **8** – **14** exhibit singlet signals of the *β*-pyrrole protons at δ = 8.86-9.25 ppm and broadened singlets of the porphyrin NH protons at δ = –2.77- –2.86 ppm for porphyrins **10**, **11** and **14**. The presence of characteristic singlet signals in ^{1}H NMR corresponding to triazolyl =CH protons in the region of 8.26 – 9.34 ppm confirmed the formation of triazole ring. The formation of porphyrin triazoles was also confirmed by the presence in ^{1}H NMR spectra for porphyrins **8** – **10**, **13** of two types of methylene proton groups in the region of 5.72-5.81 ppm and 5.37 – 5.58 ppm, respectively. The carborane CH protons for **8** – **10**, **13** were observed at δ = 4.92 - 5.28 ppm. ^{19}F NMR spectra are also in good agreement with the structures of porphyrins **8** – **10** demonstrating two sets of fluorine nuclei signals of tetrafluorophenylfragments corresponding to multiplet ones at δ -137.3 – -139.5 ppm (eight *o*-fluorine atoms) and at δ -152.6 – -156.1 ppm (eight *m*-fluorine atoms), respectively. The ^{11}B {^{1}H} NMR spectra for porphyrins **8** – **10**, **13** were sufficiently well-resolved to allow integration and contained set of signals between δB - 1.0 – (-19.0) ppm characteristic for the *closo*-structure of carborane polyhedra.

2.2. Physico-chemical properties

2.2.1. Absorption spectra

The absorption spectra of compounds **8, 9, 10, 13, 14** have an intense absorption in the region of 400-425 nm (S-band) and absorption in the red region of 500-660 nm (Q-band) (**Fig. 1**), which allowed us to consider these compounds as potential photosensitizers for PDT.

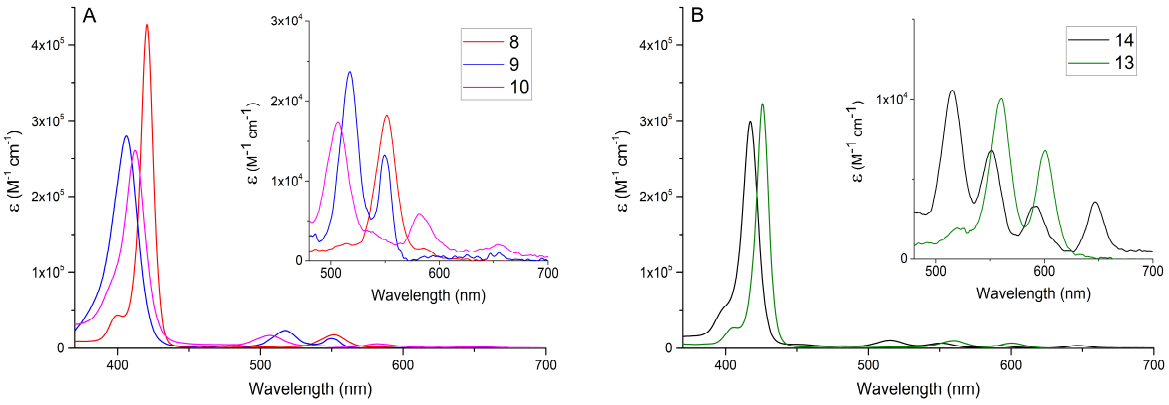


Fig. 1. (A) Absorbance spectra of **8, 9, 10** compounds in acetonitrile; (B) Absorbance spectra of **13, 14** compounds in acetonitrile.

2.2.2. Complexation with HSA

HSA has a complex molecular structure and the structure of binding sites is well known [58]. During complexation, porphyrin primarily binds to FA1 site located in subdomain IB of human serum albumin, and the rigidity of the structure of porphyrin increases and fluorescence increases as a result [59-60]**.** Formation of complexes between **8, 13** and HSA strongly changed the spectral characteristics. Binding constant determined from the absorption spectra (**Fig. 2A**) was $K_{b\_abs} = 3.5\times10^5\ M^{-1}$ for 8 and $K_{b\_abs} = 2.2\times10^5\ M^{-1}$ for 13. Binding constant calculated from the fluorescence spectra (**Fig. 2B**) estimated to be $K_{b\_fl} = 3.3\times10^5\ M^{-1}$ for 8. Similar values of these constants indicated that the replacement of hydrogen atoms with fluorine atoms in the structure of boronated mesoarylporphyrins caused no significant changes in binding constants of complexes. In the complexes of the porphyrin with albumin, a rigid molecular structure is formed, and relaxation of the excited singlet state of the porphyrin to the ground state becomes difficult. For this reason, the lifetime of fluorescence of the porphyrin in the complex with HSA is increased. The measured fluorescence lifetime for **8** in propanol-1 is 1.6 ns. Meanwhile in the complex with albumin the fluorescence lifetime is 3.2 ns which is consistent with the assumed strong interaction between the porphyrin and the amino acids in the binding site of albumin.

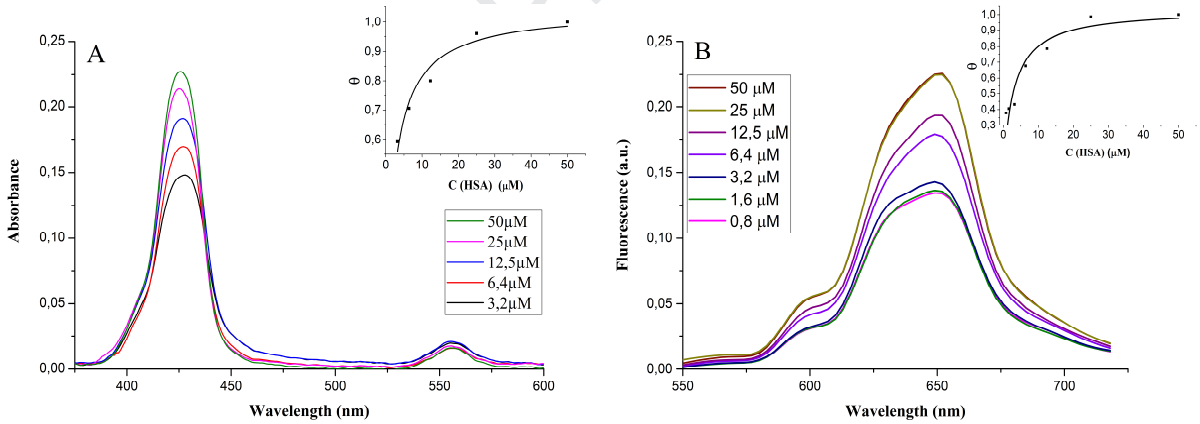


Fig. 2. (A) Absorbance spectra of **8** in phosphate buffer, pH = 7.0 with HSA ($3.2 \times 10^{-6} – 5 \times 10^{-5}$ M). Inset: Experimental values of θ as a function of the protein concentration (425 nm).
(B) Fluorescence spectra of **8** (phosphate buffer, pH = 7.0, λ_{ex} 424 nm) with HSA ($8 \times 10^{-7} – 5 \times 10^{-5}$ M). Inset: Experimental values of θ as a function of the protein concentration (λ_{em} = 652 nm).

2.2.3. *Complexation with LDL*

Generally lipoproteins are soluble complexes of proteins (apolipoproteins) and lipids that provided transport of lipids to their sites in living systems [61]**.** The ability of the synthesized compounds to form complexes with low density lipoproteins (LDL) is an important property for

the delivery of photosensitizers to cancer cells. Effective delivery of the photosensitizer can also occur through the interaction of fluorophenyl boronated *meso*-arylporphyrins with LDL. The binding constants for **8**, **9**, and **10** with LDL calculated on the basis of fluorescence spectra were K_{b_flu} = 4.0×10^8, 4.7×10^8 and 7.4×10^8 M^{-1}, respectively. The binding constants for LDL are significantly larger than the constants for complexes with albumin. However, the mechanisms of interaction of fluorophenyl boronated *meso*-arylporphyrins with albumin differs significantly than the one with LDL. For albumin, interaction within its drug binding site is typical for small molecular weight compounds whereas complexation with LDL occurs when the porphyrin passes from the aqueous to the organic phases inside the vesicles formed by LDL molecules. This non-specific binding of the porphyrin to the LDL lipid phase is characterized by very high constant. According to [62], the vesicles consist of approximately 800 units of phospholipids. Taking into account the amounts of the protein that interact with the drug, the true binding constants for LDL ($K_{b(LDL)}$) are ~3 orders of magnitude smaller ($K_{b(LDL)}=K_{(b\_flu)}/800$) and approximately correspond to the binding constants calculated for HSA.

2.2.4. Triplet states

Using flash photolysis, we obtained the spectral-kinetic characteristics of the triplet state of **9** in propanol. Photoexcitation of the oxygen free **9** solution was carried out in the S-band. Differential absorption spectra of the triplet of **9** (**Fig. 3**) correspond to the bleaching of S/Q bands and the formation of two absorption bands at 440-500 and 530-800 nm. The triplet lifetime was 0.6 ms. The quenching of **9** triplets by oxygen occurs with a constant typical for triplet quenching k_q = 2×10^9 M^{-1} s^{-1} as a result of energy transfer to oxygen and generation of singlet oxygen.

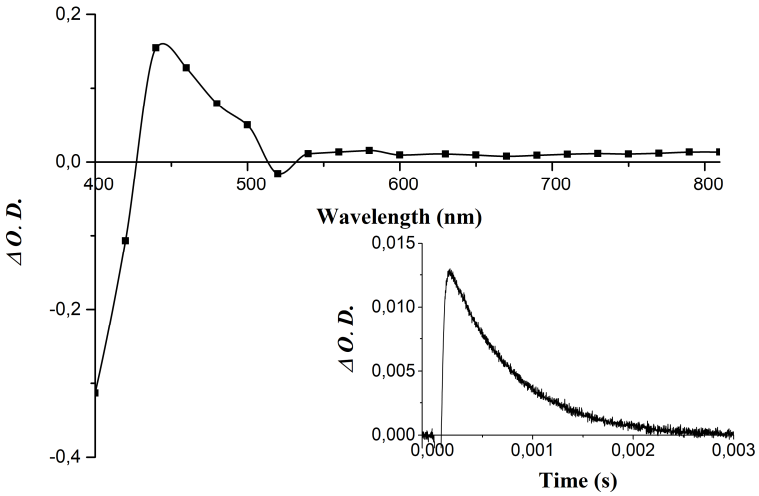


Fig. 3. Differential triplet-triplet absorption spectra of **9** (~ 10^{-7} M) in propanol-1 (200 μs after flash). Inset: kinetic trace of the triplet at 710 nm, $k_T = 1.6 \times 10^3$ s^{-1}.

2.2.5. Quantum yields

The phosphorescence spectra of singlet oxygen (**Fig. 4**) in acetonitrile (λ_{max} ~ 1270 nm) were obtained upon irradiation (xenon lamp, photoexcitation at 511 nm for **9**, **10**, **14**, 549 nm for **8**, **13**) of air-saturated solutions.

The quantum yields of singlet oxygen for **8, 9, 10, 13, 14** in acetonitrile were determined by comparison with the standard tetraphenylporphyrin (TPP) (**Fig 4.**) [63-64].

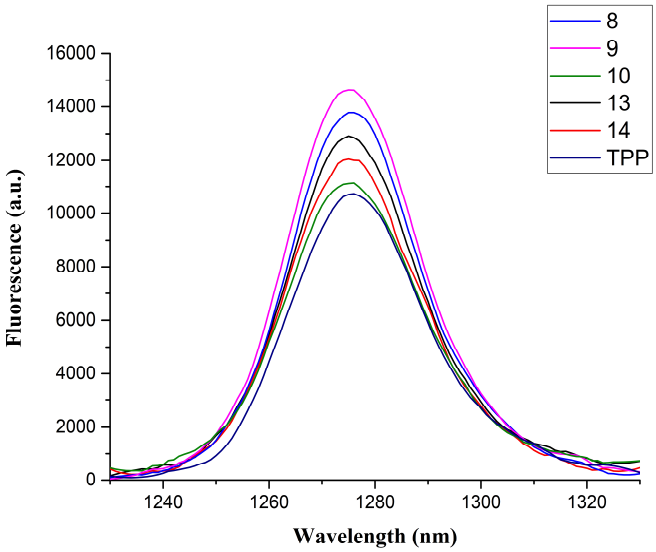


Fig. 4. Phosphorescence spectra of singlet oxygen ($^1O_2$) in acetonitrile.

Singlet oxygen forms as a result of quenching of the triplet by the ground state oxygen and singlet oxygen quantum yield correlates with quantum yield of triplet state. According to heavy atom effect introduction of Zn (**8**, **13)** and Pd (**9)** into the structure of these compounds enhances intersystem crossing and results in the increase of quantum yield of triplet state. At the same time singlet oxygen quantum yield increases (**8**, **9**, **13**).

Porphyrin	TPP	**8**	**9**	**10**	**13**	**14**
Φ ($^1O_2$)	0.60	0.75	0.80	0.66	0.72	0.67

Table 1. Quantum yields of singlet oxygen Φ ($^1O_2$) for porphyrins in air-saturated solutions of acetonitrile.

Quantum yield of triplet states for all new compounds remains sufficient (~0.6-0.8), so that singlet oxygen is formed as a result of quenching of the triplet by the ground state of oxygen.

Thus, fluorophenyl boronated *meso*-arylporphyrins **8**, **9**, **13** have high quantum yield of singlet oxygen and this peculiarity could make these compounds potential new photosensitizers.

2.3. Dark and light toxicity

All studied photosensitizers showed low dark cytotoxicity. 50% cell death in the dark did not reach a concentration in the range studied (0.1–50 μM) (**Fig. 5.**). The control compound in the dark experiment was doxorubicin at the same concentrations as the photosensitizers. Doxorubicin exhibits cytotoxicity upon HCT116 cells and is a suitable positive control in the dark cytotoxicity experiment at low IC50 values of the experimental compounds. Photoinduced cytotoxicity of the studied porphyrins was characterized; 50% cell death in the light experiment occurred at submicromolar concentrations (**Fig. 6.**) (IC_{50} values are shown in **Table 2**.). The highest photo-induced cytotoxicity showed compound **9**. The compound **8** showed the average value in the synthesized series. IC_{50} values one order higher were shown by the compounds **10**, **13**, **14**. Non-boronated porphyrins, 5,10,15,20-tetraphenylporphyrin (TPP) and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (F-TPP) did not exhibit dark and photo-induced cytotoxicity. The introduction of carborane-containing substituents on the periphery of porphyrin macrocycle increases the photosensitivity of HCT116 cells, while the rather low dark cytotoxicity of the synthesized carboranes remains. This data are consistent with our previous results [65]. All studied compounds show slight dark cytotoxicity with pronounced photoinduced cytotoxicity, which characterizes them as potential photosensitizers for antitumor PDT.

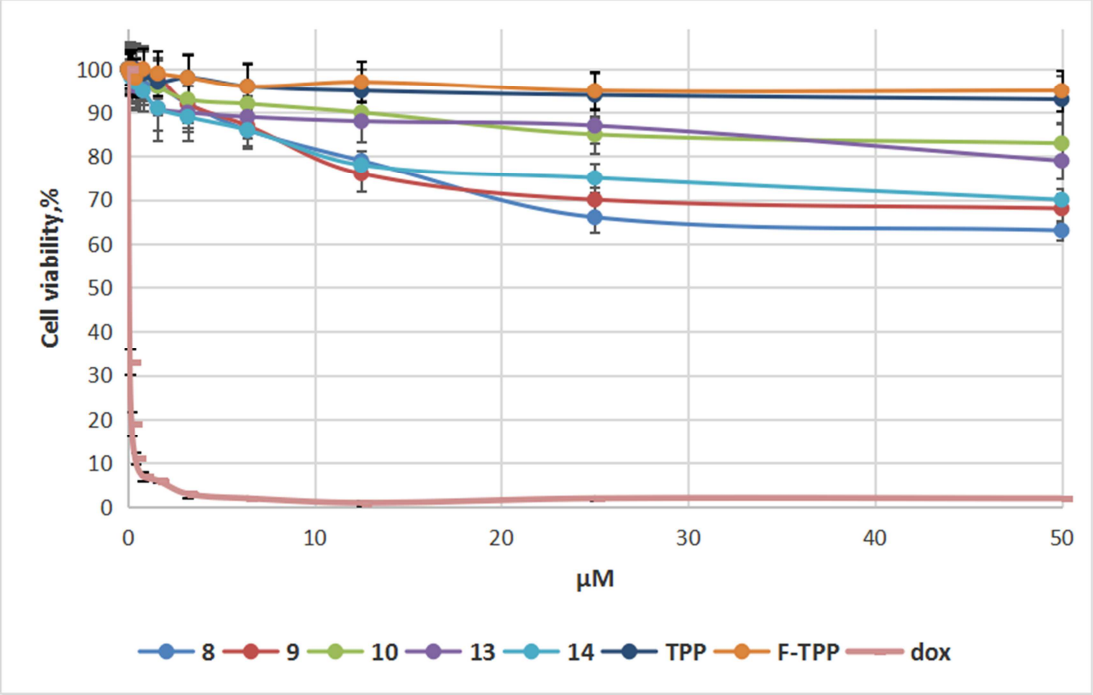


Fig. 5. Dark cytotoxity

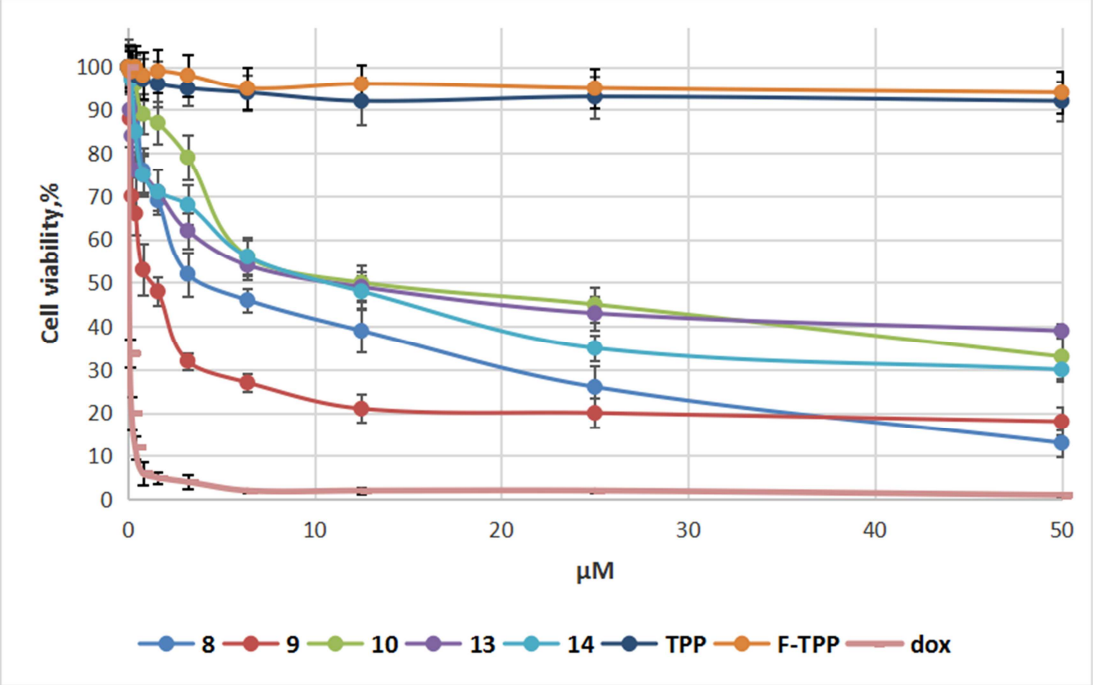


Fig. 6. Photoinduced cytotoxity

Compound	IC_{50}, μM	
	Light experiment	Dark experiment
8	3.9±1.2	>50
9	1.2±0.6	>50
10	12.9±5.3	>50
13	11.1±4.2	>50
14	10.9±3.1	>50
TPP	>50	>50
F-TPP	>50	>50
doxorubicin	0.6±0.1	0.6±0.1

Table 2. IC_{50} values of photosensitizers (MTT-assay)

3. Experimental

3.1. Synthesis and characterization

3.1.1 General Information

All reactions were performed in an atmosphere of dry argon. All solvents were dried according to the standard protocols. Dichloromethane was purified by distillation over calcium hydride. Tetrahydrofuran (THF) was stored over sodium benzophenone and distilled before use.

^{1}H and ^{11}B and ^{19}F NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400.13 MHz for ^{1}H NMR, 128.28 MHz for ^{11}B NMR and 376.5 MHz for ^{19}F NMR. Chemical shifts (δ) were referenced to the residual solvent peak $(CD_3)_2CO$, ^{1}H: 2.05 ppm; $CDCl_3$, ^{1}H: 7.26 ppm; THF-D_8 ^{1}H: 3.58 and 1.73 ppm) for ^{1}H, external $BF_3 \cdot OEt_2$ for ^{11}B and external $CFCl_3$ for ^{19}F. IR spectra were recorded on a Brucker FTIR spectrometer Tensor 37 in KBr tablets. Merck silica gel L 0.040–0.08 mesh was used for column chromatography. The identities of new compounds were verified on Sorbfil plates. The UV-vis spectra were measured on a spectrophotometer Jasco UV 7800 series in CH_3CN, $CHCl_3$ and THF. The mass spectra were obtained using VISION 2000 (MALDI) mass spectrometer, the most intense peaks were given for each compound.

The identities of new compounds were verified on TLC 60 F254 plates (Merck). Merck silica gel L 0.04-0.08 mesh was used for column chromatography (elution with chloroform-hexane 2 : 1, chloroform, and chloroform—methanol 10 : 1).

*3.1.2 Synthesis of compounds **5-6** and **8-14***

3.1.2.1. **5,10,15,20-Tetrakis[4-(2-propargyloxy)-2,3,5,6-tetrafluorophenyl]porphyrinato zinc (II) (5).** To a solution of porphyrin **3** (100 mg, 0.096 mmol) in THF (20 mL) propargyl alcohol (54 mg, 0.96 mmol) (~ 30 μL) and powdered NaOH (38 mg, 0.96 mmol) were added and the mixture was boiled for 4 h under argon atmosphere. Then the reaction mixture was poured into water (50 mL), extracted with CH_2Cl_2 (2 × 20 mL), the extracts were washed with water (3 × 20 mL), dried over Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, using $CHCl_3$— hexane mixture (2 : 1) as an eluent.

Yield 107 mg (94%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 416 (281.8), 545 (24.0). IR (KBr) ν_{max}, cm^{-1}: 2925 (porphyrin CH), 2124 (C≡C). ^1H NMR (400.13 MHz, $(CD_3)_2CO$), δ: 9.18 (s, 8H, *β*-pyrrole), 5.30 (d, *J* = 2.5 Hz, 8H, CH_2), 3.34 (d, *J* = 2.5 Hz, 4H, C≡CH). ^{19}F NMR (376.5 MHz, $(CD_3)_2CO$), δ: –139,1 (m, 8F), –156,5 (m, 8F). MS (MALDI): *m/z* [M^+] calculated for: $C_{56}H_{20}F_{16}N_4O_4Zn$ 1180.052, found: 1180.036.

3.1.2.2. **5,10,15,20-Tetrakis[4-(2-propargyloxy)-2,3,5,6-tetrafluorophenyl] porphyrinato palladium (II) (6).** To a solution of porphyrin **4** (100 mg, 0.093 mmol) in THF (20 mL) propargyl alcohol (52 mg, 0.93 mmol) (~ 29 μL) and powdered NaOH (37 mg, 0.93 mmol) were added and the mixture was boiled for 4 h under argon atmosphere. Then the reaction mixture was poured into water (50 mL), extracted with CH_2Cl_2 (2 × 20 mL), the extracts were washed with water (3 × 20 mL), dried over Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, using $CHCl_3$ – hexane mixture (2 : 1) as an eluent. Yield 105 mg (92.5%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 410 (312.6), 520 (36.9), 552 (26.1). IR (KBr) ν_{max}, cm^{-1}: 2920 (porphyrin CH), 2130 (C≡C). ^1H NMR (400.13 MHz, $(CD_3)_2CO$), δ: 8.96 (s, 8H, *β*-pyrrole), 5.23 (d, *J* = 2.5 Hz, 8H, CH_2), 2.96 (d, *J* = 2.5 Hz, 4H, C≡CH). ^{19}F NMR (376.5 MHz, $(CD_3)_2CO$), δ: –139.0 (m, 8F), –156.4 (m, 8F). MS (MALDI): *m/z* [M^+] calcd. for $C_{56}H_{20}F_{16}N_4O_4Pd$ 1222.026, found 1222.004.

3.1.2.3. **5,10,15,20-Tetrakis{4-[(1-*o*-carboranylmethyl-1,2,3-triazol-4-yl)methyloxy]-2,3,5,6-tetrafluorophenyl}porphyrinato zinc (II) (8).** To a solution of porphyrin **5** (100 mg, 0.085 mmol) and carborane **7** (102 mg, 0.51 mmol) in CH_2Cl_2 (15 mL), a solution of $Cu(OAc)_2$ (2 mg, 0.0102 mmol) in water (0.3 mL) was added, and then a solution of sodium ascorbate (4 mg, 0.0168 mmol) in water (0.3 mL) was added with stirring. The reaction mixture was boiled for 48 h, cooled to room temperature, washed with water (3 × 20 mL), dried over Na_2SO_4, filtered and solvent was removed *in vacuo*. The dry residue was washed with toluene (50 mL), dried *in vacuo*. Yield 127 mg (75.3%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 419 (427.0), 550 (28.5). IR (KBr) ν_{max}, cm^{-1}: 2925 (porphyrin CH), 2586 (BH). ^1H NMR (400.13 MHz, $(CD_3)_2CO$), δ: 9.17 (s, 8H, *β*-pyrrole), 8.58 (s, 4H, triazole CH), 5.72 (s, 8H, CH_2), 5.54 (s, 8H, CH_2), 4.92 (br.s, 4H, carborane CH). ^{11}B NMR (128.28 MHz, $(CD_3)_2CO$), δ: 2.2 (d, *J*=147 Hz, 4B), – 4.8 (d, *J*=132 Hz, 4B), –9.6 (d, *J*=150 Hz, 8B), –10.2 (d, *J*=129 Hz, 8B), –12.2 (d, *J*=142 Hz, 16B). ^{19}F NMR (376.5 MHz, $(CD_3)_2CO$), δ: –138.3 (m, 8F), –156.1 (m, 8F). MS (MALDI): *m/z* [M^+] calcd. for $C_{68}H_{72}B_{40}F_{16}N_{16}O_4Zn$ 1977.893 found 1977.855.

3.1.2.4. **5,10,15,20-Tetrakis {4-[(1-o-carboranylmethyl-1,2,3-triazol-4-yl)methyloxy]-2,3,5,6-tetrafluorophenyl} porphyrinato palladium (II) (9).** To a solution of porphyrin **6** (100 mg, 0.085 mmol) and carborane **7** (98 mg, 0.49 mmol) in CH_2Cl_2 (15 mL), a solution of $Cu(OAc)_2$ (2 mg, 0.0102 mmol) in water (0.3 mL) was added, and than a solution of sodium ascorbate (4 mg, 0.0168 mmol) in water (0.3 mL) was added with stirring. The reaction mixture was boiled for 48 h, cooled to room temperature, washed with water (3 × 20 mL), dried over Na_2SO_4, filtered and solvent was removed *in vacuo*. The dry residue was washed with toluene (50 mL), dried *in vacuo*. Yield 132 mg (79.2%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 407 (280.4), 478 (11.8), 518 (32.3), 550 (21.7), 595 (2.2). IR (KBr) ν_{max}, cm^{-1}: 2920 (porphyrin CH), 2584 (BH). ^1H NMR (400.13 MHz, $(CD_3)_2CO$), δ: 9.25 (s, 8H, *β*-pyrrole), 8.62 (s, 4H, triazole CH), 5.80 (s, 8H, CH_2), 5.58 (s, 8H, CH_2), 4.98 (br.s, 4H, carborane CH). ^{11}B NMR (128.28 MHz, $(CD_3)_2CO$), δ: –2.2 (d, *J*=150 Hz, 4B), –4.8 (d, *J*=131 Hz, 4B), –8.9 (d, *J*=150 Hz, 8B,), –10.1 (d, *J*=130 Hz, 8B,), –12.1 (d, *J*=140 Hz, 16B). ^{19}F NMR (376.5 MHz, $(CD_3)_2CO$), δ: –139.5 (m, 8F), –154,1 (m, 8F). MS (MALDI): *m/z* [M^+] calcd. for $C_{68}H_{72}B_{40}F_{16}N_{16}O_4Pd$ 2019.868 found 2019.845.

3.1.2.5. **5,10,15,20-Tetrakis{4-[(1-o-carboranylmethyl-1,2,3-triazol-4-yl)methoxy]-2,3,5,6-tetrafluorophenyl} porphyrin (10).** To a solution of porphyrin **8** (50 mg, 0.025 mmol) in a mixture of $CHCl_3$ (5mL) and MeOH (5mL), TFA (1 mL) was added and the mixture was stirred for 1 h at room temperature. Then the reaction mixture was poured into water (10 mL), washed with water to a neutral medium, evaporated, passed through a layer of silica gel, using $CHCl_3$–MeOH (10 : 1) mixture as an eluent. Yield 46 mg (95%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 412 (261.3), 506 (27.5), 584 (15.9), 657 (3.2). IR (KBr) ν_{max}, cm^{-1}: 2924 (porphyrin CH), 2580 (BH). ^1H NMR (400.13 MHz, $(CD_3)_2CO$), δ: 9.24 (s, 8H, *β*-pyrrole), 8.62 (s, 4H, triazole CH), 5.81 (s, 8H, CH_2), 5.57 (s, 8H, CH_2), 4.95 (br.s, 4H, carborane CH), –2,86 (s, 2H, porphyrin NH). ^{11}B NMR (128.28 MHz, $(CD_3)_2CO$), δ: –2.2 (d, *J*=148 Hz, 4B), –4.8 (d, *J*=130 Hz, 4B), –9.5 (d, *J*=150 Hz, 8B), –11.6 (d, *J*=132 Hz, 8B), –12.4 (d, *J*=138 Hz, 16B). ^{19}F NMR (376.5 MHz, $(CD_3)_2CO$), δ: –137.3 (m, 8F), –152.6 (m, 8F). MS (MALDI): *m/z* [M^+] calcd. for $C_{68}H_{74}B_{40}F_{16}N_{16}O_4$ 1915.980 found 1915.964.

3.1.2.6. **5,10,15,20-Tetra(*p*-propargyloxyphenyl) porphyrin (11)** was prepared according to [55] with several changes.

To a solution of porphyrin **2** (100 mg, 0.144 mmol) in anhydrous DMF (5 mL) propargyl bromide (137 mg, 1.15 mmol) and K_2CO_3 (159 mg, 1.15 mmol) were added and the mixture was stirred at 20 ^0C for 24 h under argon atmosphere. Then the reaction mixture was poured into $CHCl_3$ (20 mL), washed with water (5 × 50 mL), dried over $MgSO_4$, and solvent was removed *in*

vacuo. The residue was purified by column chromatography on silica gel, using $CHCl_3$ as an eluent.

Yield 101 mg (85%). UV-vis ($CHCl_3$): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 422 (311), 519 (12.1), 556 (8.0), 592 (4.7), 651 (5.3). IR (KBr) ν_{max}, cm^{-1}: 2922 (porphyrin CH), 2125 (C≡C). ^1H NMR (400.13 MHz, $CDCl_3$), δ: 8.86 (s, 8H, *β*-pyrrole), 8.13 (d, *J*=8.4 Hz, 8H, Ph), 7.35 (d, *J*=8.5 Hz, 8H, Ph), 4.98 (d, *J*=2.3 Hz, 8H, CH_2), 2.69 (t, *J*=2.3 Hz, 4H, C≡CH), –2.77 (br.s, 2H, porphyrin NH). MS (MALDI): *m/z* [M^+] calcd. for $C_{56}H_{38}N_4O_4$ 830,289 found 830,258.

3.1.2.7. **5,10,15,20-Tetra (*p*-propargyloxyphenyl) porphyrinato zinc (II) (12)**. To a solution of of porphyrin **11** (50 mg, 0.06 mmol) in a mixture of CH_2Cl_2 (20 mL) and methanol (2 mL) $Zn(OAc)_2$ (43 mg, 0.24 mmol) was added and the mixture was stirred at 20 ^{0}C for 3 hours. Then the reaction mixture was washed with water (4 × 10 mL), dried over $MgSO_4$, and solvent was removed *in vacuo*.

Yield 49 mg (92%). UV-vis ($CHCl_3$): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 425 (183), 553 (7.3), 595 (3.3). IR (KBr) ν_{max}, cm^{-1}: 2923 (porphyrin CH), 2119 (C≡C). ^1H NMR (400.13 MHz, $CDCl_3$), δ: 8.86 (s, 8H, *β*-pyrrole), 8.15 (d, *J*=6.5 Hz, 8H, Ph), 7.37 (d, *J*=6.5 Hz, 8H, Ph), 4.99 (d, *J*=2.3 Hz, 8H, CH_2), 2.70 (t, *J*=2.36 Hz, 4H). MS (MALDI): *m/z* [M^+] calcd. for $C_{56}H_{36}N_4O_4Zn$ 892,203 found 892,176.

3.1.2.8. **5,10,15,20-Tetrakis {4-[(1-o-carboranylmethyl-1,2,3-triazol-4-yl)methyloxy] phenyl} porphyrinato zinc (II) (13).**

To a solution of porphyrin **12** (50 mg, 0.056 mmol) and carborane **7** (67 mg, 0.336 mmol) in CH_2Cl_2 (5 mL), a solution of $Cu(OAc)_2$ (1 mg, 0.0056 mmol) in water (0.3 mL) was added, and than a solution of sodium ascorbate (2 mg, 0.0084 mmol) in water (0.3 mL) was added with stirring. The reaction mixture was boiled for 48 h, cooled to room temperature, washed with water (3 × 15 mL), dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. The dry residue was washed with diethyl ether (40 ml), dried *in vacuo*.

Yield 68 mg (75%). UV-vis (THF): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 427 (30.2), 460 (32.1), 558 (7.1), 598 (3.9). IR (KBr) ν_{max}, cm^{-1}: 2927 (porphyrin CH), 2588 (BH). ^1H NMR (400.13 MHz, THF-D_8), δ: 8.90 (s, 8H, *β*-pyrrole), 8.26 (s, 4H, triazole CH), 8.14 (d, *J*=6.2 Hz, 8H, Ph), 7.45 (d, *J*=6.2 Hz, 8H, Ph), 5.52 (s, 8H, CH_2), 5.37 (s, 8H, CH_2), 5.28 (br.s, 4H, carborane CH). ^{11}B NMR (128.28 MHz, THF-D_8), δ: –1.8 (d, *J*=147 Hz, 4B), –4.7 (d, *J*=130 Hz, 4B), –9.4 (d, *J*=151 Hz, 8B), –11.6 (d, *J*=128 Hz, 8B), –12.5 (d, *J*=140 Hz, 16B). MS (MALDI): *m/z* [M^+] calcd. for $C_{68}H_{88}B_{40}N_{16}O_4Zn$ 1689,048 found 1689,012.

3.1.2.9. **5,10,15,20-Tetrakis {4-[(1-o-carboran-1-yl)methyl-1,2,3-triazol-3-y-4-yl) methyloxy] phenyl} porphyrin terakistetrafluoroborate (14).** To a solution of compound **13** (50 mg, 0.031 mmol) in CH_2Cl_2 (20 mL) trimethyloxonium tetrafluoroborate (39 mg, 0.27 mmol) was added with stirring and the reaction mixture was stirred at room temperature for 1 hour (TLC control). After that, methanol (5 mL) was added and the reaction mixture was stirred at room temperature for another 1 hour. The solvents were removed *in vacuo*, crude product was washed with diethyl ether (20 mL) and CH_2Cl_2 (10 ml), dried *in vacuo*.

Yield: 62 mg (99.5%). UV-vis (CH_3CN): λ_{max}, nm ($\varepsilon \times 10^{-3}$): 418 (300), 517 (12.5), 551 (8.4), 592 (4.7), 648 (4.7). IR (KBr) ν_{max}, cm^{-1}: 2921 (porphyrin CH), 2580 (BH). ^1H NMR (400.13 MHz, THF-D_8), δ: 9.34 (s, 4H, triazole CH), 8.86 (m, 8H, *β*-pyrrole), 8.17 (m, 8H, Ph), 7.56 (m, 8H, Ph), 5.98 (s, 8H, N-CH_2-C), 5.88 (s, 8H, C-CH_2-O), 5.14 (br.s, 4H, carborane CH), 4.78 (s, 12H, N^+-CH_3), –2.77 (s, 2H, NH). ^{11}B NMR (128.28 MHz, THF-D_8), δ: –1.0 (s, 4B, BF_4), –2.3 (d, *J*=146 Hz, 4B), –4.2 (d, *J*=161 Hz, 4B), –10.0 (d, *J*=148 Hz, 8B), –12.2 (d, *J*=164 Hz, 20B), –19.0 (d, *J*=187 Hz, 4B). MS (MALDI): *m/z* [M^{4+}/4] calcd. for $C_{72}H_{102}B_{44}F_{16}N_{16}O_4$ 509.059 found 509.015.

3.2. Spectroscopic measurements

Electronic absorption spectra were recorded for porphyrin solutions in acetonitrile on a UV-3101PC spectrophotometer (Shimadzu, Japan) in the range of 370–800 nm in a quartz cuvette with the optical path length 1 cm at room temperature. Solutions in DMSO (5 μM) were analyzed on a UV-3101PC spectrophotometer (Shimadzu, Japan) in the range of 360–700 nm in a quartz cuvette with the optical path length 1 cm at room temperature. Steady-state singlet oxygen phosphorescence measurements were carried out on a FluoTime 300 fluorimeter equipped with a NIR PMT Module H10330-45 (Hamamatsu, Japan). A Xe-lamp was used as an excitation source. Fluorescence lifetimes were measured by the time correlated single photon counting using a FluoTime 300 fluorimeter (PicoQuant). Fluorescence spectra were obtained using a FluoTime 300 fluorimeter (PicoQuant GmbH, Germany). Excitation laser pulse (405 nm) frequency was set at 40 MHz bin width 60 ps. Fluorescence decays were fitted using a FluoFit software (PicoQuant). The triplet-triplet absorption spectra and the kinetics decay of the triplet states were measured using a conventional flash photolysis setup (optical path length 20 cm, excitation by a Xe-lamp through multi-band blue-green optical absorption filters at 400–510 nm, 80 J, 20 μs [66]). Signals were recorded on a PMT-38 photomultiplier (MELZ, USSR) at 400–800 nm. The solutions were degassed before use. The binding constants of porphyrins with HSA

were determined using absorption and fluorescence spectroscopy. The binding constant K_b was calculated from the curves according to Eq. (1) [67]:

$$\theta = (K_b[HSA])/(1 + K_b[HSA]) \quad (1)$$

where $\theta = (F - F_0)/(F_\infty - F_0)$ is the fraction of the dye bound to the protein; F_0, F_∞ and F are the fluorescence intensity or absorbance at [HSA] = 0 and at complete and intermediate binding of the dye by the protein, respectively.

3.3. Cell culture and cytotoxicity

The human HCT116 colon adenocarcinoma cell line was from American Type Culture Collection; ATCC, Manassas, VA. The HCT116 cell line was propagated in Dulbecco modified Eagle's medium (ThermoFisher Scientific, Waltham, MA). Medium was supplemented with 5% fetal bovine serum (GE Healthcare Life Sciences; Chicago, IL), 2 mM L-glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin at 37 °C in a humidified CO2-controlled atmosphere. Cells in logarithmic phase of growth were used in the experiments. New compounds were dissolved in 10% aqueous DMSO (Paneco, Russia) as 10 mM stock solutions followed by serial dilutions in culture medium immediately before experiments. All assays were performed in 96-well microtiter plates (Nunc, USA). To each well 5×104 HCT116 cells were plated and incubated overnight. Then for dark experiment experimental compounds and positive control doxorubicin (Teva, Netherlands) were added (final concentrations 0.1 µM-50 µM; DMSO < 0.5%), and cells were incubated for 48 h at 37 °C/20.9% O2/5%CO2. Cell viability was assessed in an MTT test [68]. The IC50 values were defined as the concentrations of the compound that inhibited MTT conversion by 50%. Light induced cell photodamage was evaluated after the addition of compounds (final concentrations 0.1-50 µM) to HCT116 cells in 96-well plates. Cells were incubated for 24 h at 37 °C/20.9% O2/5%CO2, washed with saline, then 190 µl of fresh culture medium was added, and cells were illuminated with a white light 33 J/cm2. Cells were further incubated for 24 h at 37 °C/95% O2/5%CO2 followed by MTT test. Cell viability (mean+S.D. of at least 3 independent experiments, each concentration in duplicate) was expressed as a percentage of the optical density after MTT conversion in cells treated with the respective compounds relative to untreated cells (100%).

4. Conclusion

Synthesis of novel caborane-substituted porphyrins was achieved using "click" chemistry approach. Fuctionalization of Zn(II) or Pd(II) tetrakis(pentafluorophenyl)porhyrin and Zn(II)

tetrakis(4-hydroxyphenyl)porphyrin with propargyl alcohol yielded in the corresponding propargyl derivatives which were successfully utilized as starting materials for the construction of a novel series of porphyrin carborane-triazole conjugates in reaction with 1-azidomethyl-*o*-carborane. The developed reaction conditions of the copper catalyzed 1,3-dipolar cycloaddtion make it possible to obtain the desired carboranyl-triazole conjugates of porphyrins in moderate to high yields (75-99%). Observed compounds showed great affinity to biomacromolecules like albumin and LDL, a major biological carrier. Porphyrin complexes with Zn and Pd demonstrated a good ability to produce singlet oxygen (quantum yields > 70%) and exhibited significant photoinduced cytotoxicity. Synthesized porphyrin conjugates may be useful as potential candidates for biological evaluations in PDT.

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Highlights

Novel triazole-carborane porphyrin conjugates were synthesized.

Synthesized compounds were structurally characterized by conventional spectroscopy.

Binding constants for albumin and LDL with synthesized compounds were obtained.

Singlet oxygen quantum yields of synthesized compounds were measured.

All compounds are nontoxic and show pronounced photoinduced cytotoxicity.

Declaration of interests

☑ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: