Boronated Porphyrins and Chlorins as Potential Anticancer Drugs†

Valentina A. Ol'shevskaya, Andrey V. Zaytsev, Arina N. Savchenko, Alexander A. Shtil,‡ Chan Seong Cheong,§ and Valery N. Kalinin*

*A.N. Nesmeyanov Institute of Organoelement Compounds, Moscow 119991, Russia. *E-mail: vkalin@ineos.ac.ru*
‡N.N. Blokhin Cancer Center, Moscow 115478, Russia
§Korea Institute of Science and Technology, Seoul 130-650, Korea
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Analyzed are recent advances in design of novel boronared conjugates of synthetic and natural porphyrins and chlorins. These compounds showed high efficacy as cytotoxic agents for tumor cells in culture and as phototoxins in photodynamic therapy of tumor xenografts. Thus, boronated porphyrins and chlorins emerge as promising class of anticancer agents with potentially multiple advantages: the chemotherapeutic drugs alone and photo- and radiosensitizers in binary treatments.

Key Words : Carboranes, Porphyrins, Drug resistance, Photodynamic therapy, Boron neutron capture therapy

Introduction

Boronated derivatives of porphyrins and structurally close chlorins have been the subject of an extensive investigation as tentative agents for binary anticancer treatment, *i.e.*, photodynamic therapy (PDT) and boron neutron capture therapy (BNCT).[1] Use of these compounds is based on the accumulation of porphyrins in malignant tumors and activation by thermal neutrons (BNCT) or laser light (PDT).[2,3] The path length of particles $^4_2$He and $^7_3$Li (BNCT) or singlet oxygen $^1O_2$ (PDT) generated in the tumor is comparable with the cell diameter. This provides an opportunity to selectively destroy the tumor with minimal damage to healthy tissues. Some porphyrin-containing pharmaceuticals such as Fotogem[4] or its analogue Photofrin[5] are used in the clinic as PDT agents. Moreover, the second generation of the chlorin-based photosensitizers (PSs) for PDT is under development.[5] Chlorins are more promising PSs for PDT because they absorb light in the red spectral region (λ = 650-660 nm). This property of chlorins, first, provides deeper penetration of tissue photodamage compared with that achievable with porphyrins. Second, radiation used for excitation of chlorins is less absorbable by surrounding tissues. Therefore, the synthesis of boronated porphyrins and chlorins makes it possible to obtain compounds with the properties advantageous for both BNCT and PDT: the tropicity to neoplasms, phototoxicity, and the ability to generate local radioactive reaction and cytotoxic particles generated by thermal neutrons. To develop an efficient dual sensitizer for BNCT/PDT, general (dark) toxicity of the porphyrin-type structures should be low, as higher doses of the drug are usually required for BNCT compared to PDT.

† This paper is dedicated to Professor Sang Chul Shim on the occasion of his honorable retirement.

Ol'shevskaya Valentina Antonovna received her Ph. D. in 1984 from Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS) under supervision of Prof. L.I. Zakharkin. From 1987 she was a senior researcher in Prof. L.I. Zakharkin's laboratory and from 2001 in Prof. V.N. Kalinin's laboratory. Her research interests are focused on the development of biologically active carboranes, including boronated porphyrins and chlorines for photodynamic therapy and boron neutron capture therapy

Zaytsev Andrey Viktorovich received his Ph. D. in 2005 from Moscow State Academy of Fine Chemical Technology and Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS) under supervision of Prof. A.F. Mironov and Dr. V.A. Ol'shevskaya. From 2006 he is a scientific researcher in the laboratory of Prof. V.N. Kalinin in INEOS. His research interest is focused on development of biologically active compounds on the base of carboranes, porphyrins and chlorines.

Savchenko Arina Nikolaevna received her Ms. D. in 2007 from Moscow State Academy of Fine Chemical Technology and Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS) under supervision of Dr. V.A. Ol'shevskaya. Now she is a post-graduate student in the laboratory of Prof. V.N. Kalinin in INEOS. Her research interest is focused on development of boron-containing porphyrins and chlorines for BNCT and PDT.

Shtil Alexander Albertovich received his Ph.D. in Moscow Research Institute of Otorhinolaryngology (1990). In 1990-93 he served as surgeon-oncologist and experimental cancer researcher at Blokhin Cancer Center, Moscow. In 1994-2002 Dr.Shtil worked in leading laboratories in the USA (with I.Roninson, W.Dalton and K.Scotto) studiyng the molecular and cellular biology of multidrug resistance in cancer. After returning to Russia in 2002 Dr.Shtil started his laboratory of tumor cell death at Blokhin Cancer Center. His current interests are mechanisms of cell death induced by chemotherapeutic drugs.

Chan Seong Cheong received his MS and PhD in chemistry under Professor Kwan Soo Kim from Yonsei University in 1988 and 1993 and worked on enzymatic reactions with Professor R.J. Kazlauskas at McGill University, Canada as a Postdoctoral Fellow in 1997. From 1979 to the present time, he has studied process developments for synthesizing various organic chemicals including agrochemicals and pharmaceuticals at Korea Institute of Science and Technology. Other work is to develop new chemical groups to optimize the biological activity for T-type channel blocker. Additionally, his current interests include the biotransformation of the materials which are modulators for the biological or physical properties.

Kalinin Valery Nikolaevich received his Ph. D. in 1967 from Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS) under supervision of Prof. L.I. Zakharkin. All his scientific life is connected with INEOS where in 1989 he was appointed to Full Professor. He was honored with the State Prize in 1996. His research interest is development of biologically active substances on the base of carboranes, morphine alkaloids, mesoionic compounds etc.

A number of synthetic routes toward the boronated porphyrins and chlorins have been developed but the suitability of these compounds for medicinal application can be estimated only after the *in vitro* and *in vivo* biological testing. We have developed a strategy of synthesis of carboranylporphyrins *via* classical route[6] using condensation of carborane aldehydes with pyrrole and by introducing the carborane polyhedra into the synthetic or natural porphyrins.[3] In this review our recent results of synthesis and anticancer properties of boronated porphyrins and chlorins are analyzed.

Boronated Derivatives of 5,10,15,20-Tetraphenylporphyrin

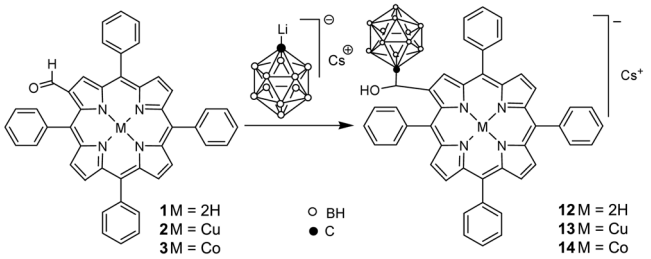
We developed a series of carboranylporphyrins based on functional derivatives of 5,10,15,20-tetraphenylporphyrin and various neutral and anionic polyhedral carboranes. Our choice of 5,10,15,20-tetraphenylporphyrin as a basic compound for chemical modifications was dictated by (i) availability of this compound, (ii) suitability for introducing different functional groups, and (iii) easiness of obtaining final products with reasonable yields and high purity.

To obtain functionally substituted hydrophilic boronated porphyrins, we employed general approach based on the interactions of carborane carbanions with aldehydes.[7,8] The reaction of 2-formyl-5,10,15,20-tetraphenylporphyrin (**1**), its copper (**2**) and cobalt (**3**) complexes with 1-lithium-2-methyl-*o*-carborane or 1-isopropyl-7-lithium-*m*-carborane yielded neutral carboranylporphyrin alcohols **4-8** (Scheme 1).

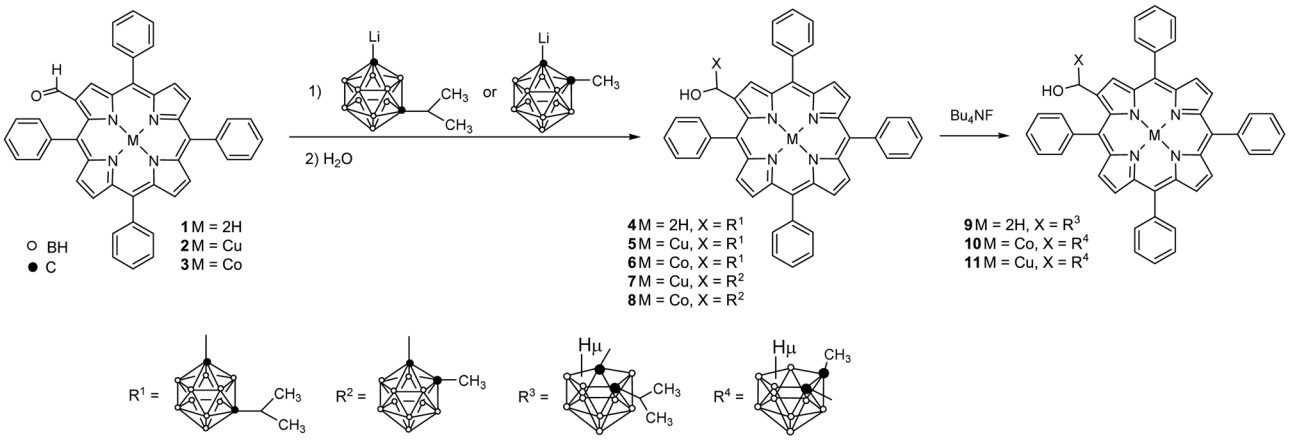
The anionic *nido*-carboranylporphyrin alcohols **9-11** were synthesized by deboronation[9] of *closo*-analogues **4**, **6** and **7** with $Bu_4NF{\cdot}2H_2O$ in THF and isolated as tetrabutylammonium salts (Scheme 1).

Also, we synthesized a new type of anionic carboranylporphyrin alcohols as synthones for water soluble analogues.[3,7] We used hydrophilic *closo*-monocarbon carborane anion, *closo*-$CB_{11}H_{11}^-$, which is isoelectronic to neutral *closo*-$C_2B_{10}H_{12}$ carboranes. This compound was chosen because (i) monocarbon carborane is stable in air and aqueous media, suggesting its stability in the body; (ii) some salts of monocarbon carborane and its hydrophilic derivatives are water soluble due to anionic charge; this is advantageous over neutral carboranes and allows for obtaining hydrophilic boronated porphyrins. We found that the reaction of 1-lithium- *closo*-monocarbon carboranyl cesium with formylporphyrins **1-3** in THF resulted in the formation of anionic monocarbon carboranylporphyrin alcohols **12-14** in high yields (70-85%) (Scheme 2).

Among the novel monocarbon carborane substituted porphyrins, only cesium salt of monocarbon carborane alcohol **12** was, to some extent, soluble in water. Our preliminary data suggest that substitution of cesium cation by sodium or lithium cations results in higher amphiphilicity (not shown). All carboranylporphyrins were tested for their ability to kill cultured human tumor cells.[7] The compounds showed differential activity. We found that *closo*-alcohols **4**, **6**, **8** as well as *nido*-alcohols **9**, **10** demonstrated little or no cytotoxicity for leukemia and breast carcinoma cell lines (not shown). However, 5,10,15,20-tetraphenylporphyrin caused death of K562 leukemia cells with $IC_{50} = 52.6 \pm 4.3$ μM as determined in the colorimetric test based on conversion of 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyl tetrazolium bromide into formazan (MTT-test) after 72 h of continuous xposure (Figure 1A). Comparison of activities of *closo*- and *nido*-carboranyl-substituted derivatives of Cu-5,10,15,20-tetraphenylporphyrin complex (compounds **5**, **7** and **11**) and monocarbon carborane substituted copper (II) complex of 5,10,15,20-tetraphenylporphyrin (**13**) identified compound **13** as the most active ($IC_{50} = 4.6 \pm 2.2$ μM) (Figure 1A). Next, **13** demonstrated higher activity for MCF-7 breast



Scheme 2. Synthesis of anionic monocarbon carboranylporphyrin alcohols.



Scheme 1. Synthesis of neutral and anionic carboranylporphyrins.

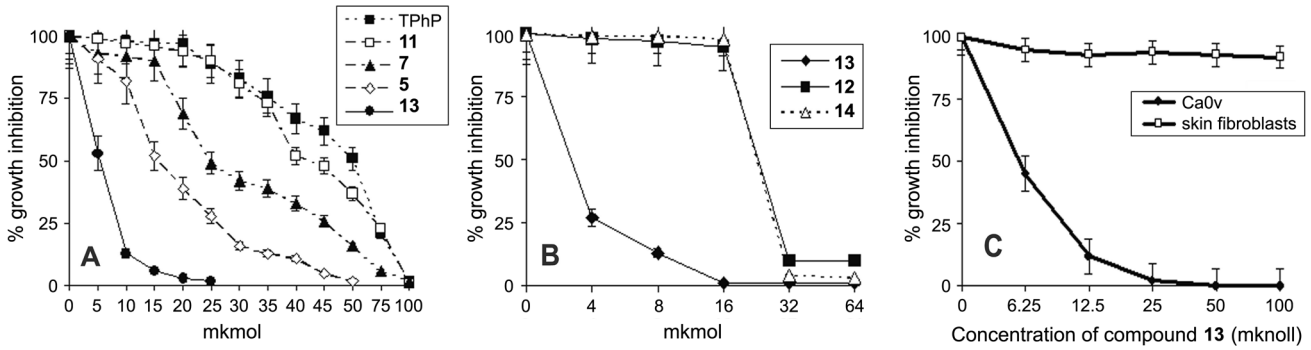


Figure 1. Cytotoxicity of 5,10,15,20-tetraphenylporphyrin (TPhP) and its carborane derivatives.

carcinoma cell line than structurally related cobalt (II) salt **12** and metal free **14** carborane derivatives of 5,10,15,20-tetraphenylporphyrin (Figure 1B). Importantly, **13** was virtually inert for non-malignant human skin fibroblasts at concentrations up to 100 μM whereas this compound potently killed ovarian carcinoma CaOv cells (Figure 1C). Only at higher concentrations at which **13** formed precipitates in aqueous solutions, this agent was toxic for fibroblasts. These experiments provide evidence that monocarbon carboranes conjugated with Cu (II) salt of 5,10,15,20-tetraphenylporphyrin could be perspective for further investigation as anticancer agents.[7]

Pleiotropic refractoriness of tumor cells to exogenous stimuli remains a major reason for therapeutic failure. The transmembrane transporter P-glycoprotein (Pgp; ABCB1) frequently mediates the intrinsic (prior to chemotherapy) resistance to apoptosis as well as multidrug resistance (MDR) acquired in the course of treatment.[10-12] To study the potency of carboranylporphyrins for sublines with Pgp-mediated MDR, we chose **13** because this compound was the most active against parental leukemia and breast cancer cells. We first addressed the role of Pgp in the cytotoxicity of **13** by comparing the survival of K562 cells and the K562i/S9 subline that expresses Pgp without selection.[13] The K562i/S9 cells were significantly more resistant than K562 cells to vincristine, the conventional chemotherapeutic drug transported by Pgp (IC_{50}s = 56.1 ± 4.5 nM *versus* 6.2 ± 2.1 nM, respectively; resistance index 9.0). In striking contrast, survival of both cell lines in the presence of **13** differed only moderately: the respective IC_{50}s were 10.5 ± 2.0 μM *versus* 5.2 ± 1.7 μM; resistance index 2.0). These data suggest that **13** is a weaker substrate of Pgp-mediated transport than vincristine. Nevertheless, inhibition of Pgp function with verapamil (VER)[14] dramatically potentiated the cytotoxicity of **13**. Death of K562i/S9 cells after 24 h of exposure to 4 μM **13** + 20 μM VER (Figure 2) was almost as pronounced as death of the same cells treated with 16 μM **13** alone. Only marginal MTT conversion (Figure 2) and clearly detectable morphological signs of apoptosis such as cell shrinkage and nuclear fragmentation were found in K562i/S9 cells treated with 2 μM **13** + 20 μM VER for 48 h. No significant changes in MTT reduction were detected in these cells after exposure to 4 μM **13** or 20 μM VER alone (Figure 2).

To study the potency of **13** for cells that acquired Pgp-

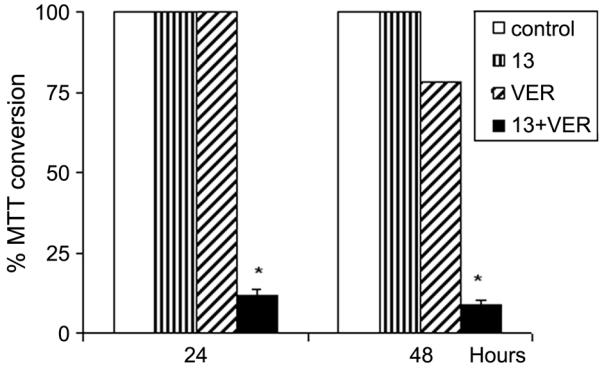


Figure 2. VER potentiates the cytotoxicity of compound **13** for Pgp-expressing leukemia cells.

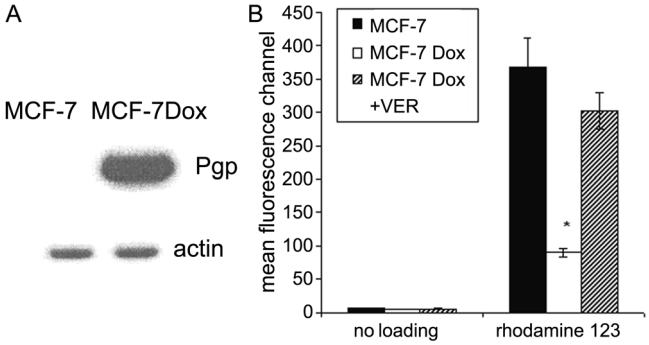


Figure 3. MCF-7Dox cells express functional Pgp.

mediated MDR during multistep selection with conventional drugs, we compared the cytotoxicity of **13** for MCF-7 cells and the MCF-7Dox variant selected for long-term survival in the presence of doxorubicin (**DOX**). The MCF-7Dox subline displayed Pgp-mediated MDR as determined by higher resistance to Pgp-transported chemotherapeutics **DOX**, vincristine, mitoxantrone and taxol (Table 2), elevated amount of Pgp and increased efflux of Pgp-transported fluorescent dye rhodamine 123[15] (Figure 3A, B). Importantly, prolonged (72 h) exposure to **13** demonstrated slightly higher (resistance index ~2) survival of MCF-7Dox cells compared with MCF-7 cells (Figure 4).

Thus, although carboranylporphyrins are currently studied as tentative anticancer agents, anionic monocarbon carboranes such as $CB_{11}H_{12}^-$ are poorly investigated. We demonstrate that this class of boron containing porphyrins could be

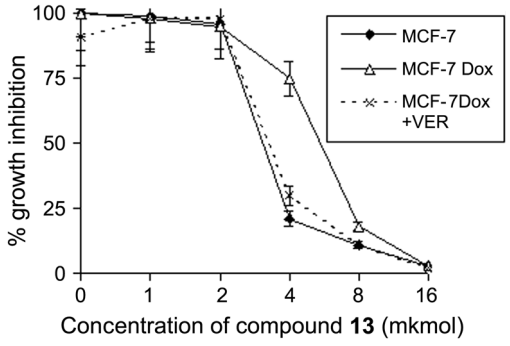


Figure 4. VER sensitizes MCF-7Dox cells to compound **13**.

perspective since **13**, the water soluble Cu (II) salt of monocarboranyl substituted 5,10,15,20-tetraphenylporphyrin, potently killed human tumor cells otherwise resistant to many apoptotic stimuli.[7]

A key prerequisite for overcoming pleiotropic irresponsiveness should be delivery of the amount of the drug sufficient to activate as many death pathways as possible.[16] Our results provide evidence that **13** is relatively poor substrate for Pgp-mediated efflux. Indeed, the cytotoxicity of **13** for Pgp-negative and -positive cells did not differ as substantially as it did for Pgp transported drugs, making **13** (and potentially other agents of this class) perspective for circumventing the resistance.

Our data demonstrate that, for tumor cells, boronated porphyrins are toxic even as single agents; one may expect that this activity would potentiate the efficacy of these compounds as photo/radiosensitizers in binary treatments. The potency of Cu(II) salt of monocarbon carboranyl substituted 5,10,15,20-tetraphenylporphyrin for cells with altered stress response proves the applicability of this chemical class for circumventing anticancer drug resistance.

It should be noted that the efficacy of binary treatments depends on the accumulation of the sensitizing agent in the tumor cells. Direct calculations revealed[13] that the therapeutic efficacy of boronated porphyrins is higher if the agent is accumulated in the nucleus compared with the cytoplasmic localization. Furthermore, generation of free oxygen burst in the vicinity of the nucleus would enhance the cytotoxic effect. Despite an extensive search for new compounds for BNCT and PDT, the problem of optimization of boron delivery systems has not been addressed in detail. Therefore, optimization of boronated porphyrins as photo/radiosensitizers presumes the design of DNA-interacting compounds. The desired selectivity can be attained by attaching carborane cages to various tumor-seeking biomolecules or by introducing functional groups into the carborane cage. The key point is to choose appropriate functionalities whose transformations eventually yield active compounds. We chose the isocyanate group, an attractive moiety from the standpoint of design of non-toxic compounds for BNCT and PDT. We found that 1-lithium-9-isocyanato-*o*- and *m*-carboranes readily reacted with the aldehyde group of porphyrin (**1**) and its metal complexes (**2**, **15-17**) to form corresponding porphyrin alcohols **18-27**, containing N=C=O group at the boron atom of carborane polyhedron[17] (Scheme 3).

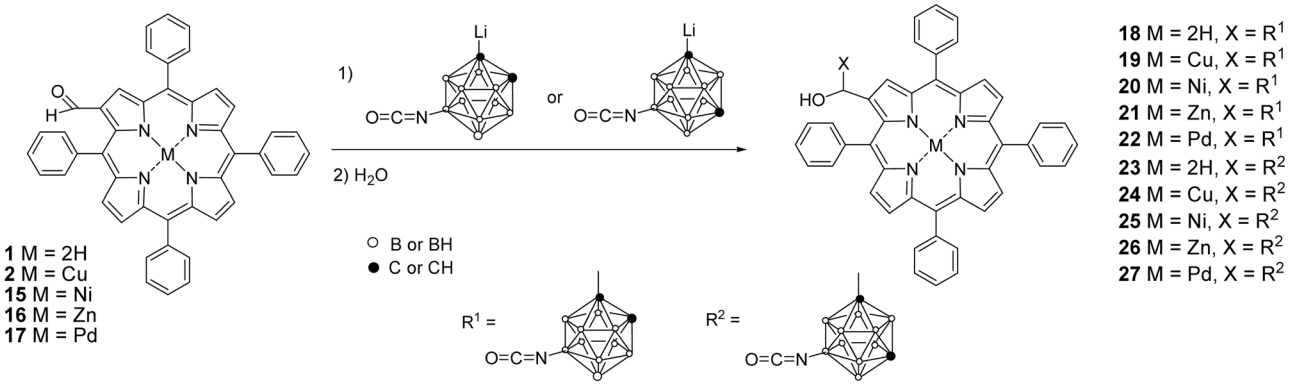
Isocyanates (**19**, **24**) can be readily transformed to urethanes (**28-29**) and water soluble ammonium derivatives (**30-31**) in quantitative yields (Scheme 4).

Cytotoxicity of compounds **18-27** was studied using human K562 leukemia cells and non-malignant skin fibroblasts. Importantly, **18**, **20-23**, **25-27** were not toxic for fibroblasts whereas **19** and **24** killed leukemia cells. These data imply that the compounds of this series can potentially be useful given their differential cytotoxicity for non-malignant and tumor cells.

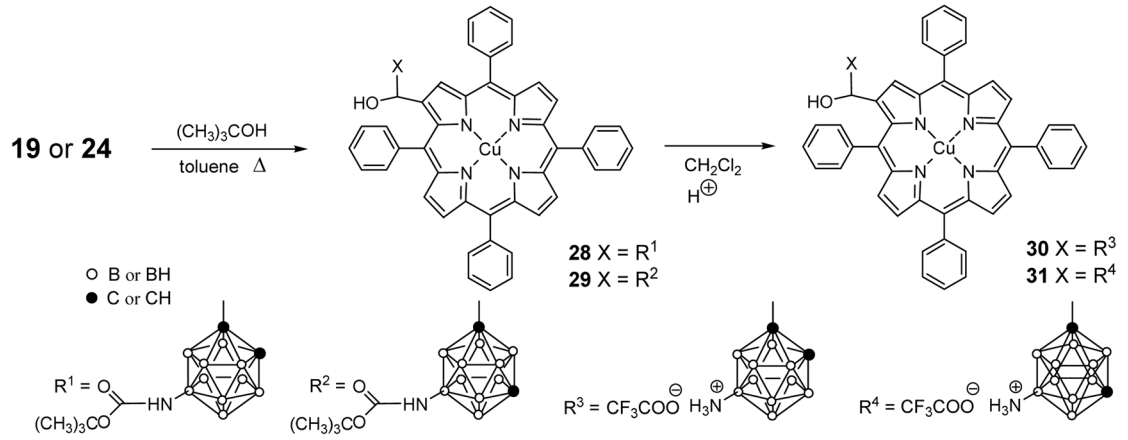
Binding of compounds **19**, **22**, **24** and **27** with double stranded DNA was investigated using spectrophotometry. Compounds **19**, **22**, **24** caused a decrease of DNA absorption without shifting its maximum, suggesting that these agents do not interact with DNA. In contrast, **27** shifted the maximum from 260 to 272 nm, indicating the formation of a complex between this compound and the duplex DNA.

So, the introduction of isocyanatocarboranes into the porphyrin macrocycle allow to obtain carboranylporphyrins with two functional groups, one of which bound to the boron atom of polyhedron. This allows for modifying hydrophobic/hydtophilic properties of boronated conjugates as well as to improve their selective uptake by tumor sells.

Boronated Derivatives of Protohemin IX and Chlorin e_6



Scheme 3. Conjugation of 2-formyl 5,10,15,20-tetraphenylporphyrin with 9-isocyanato-carboranes.



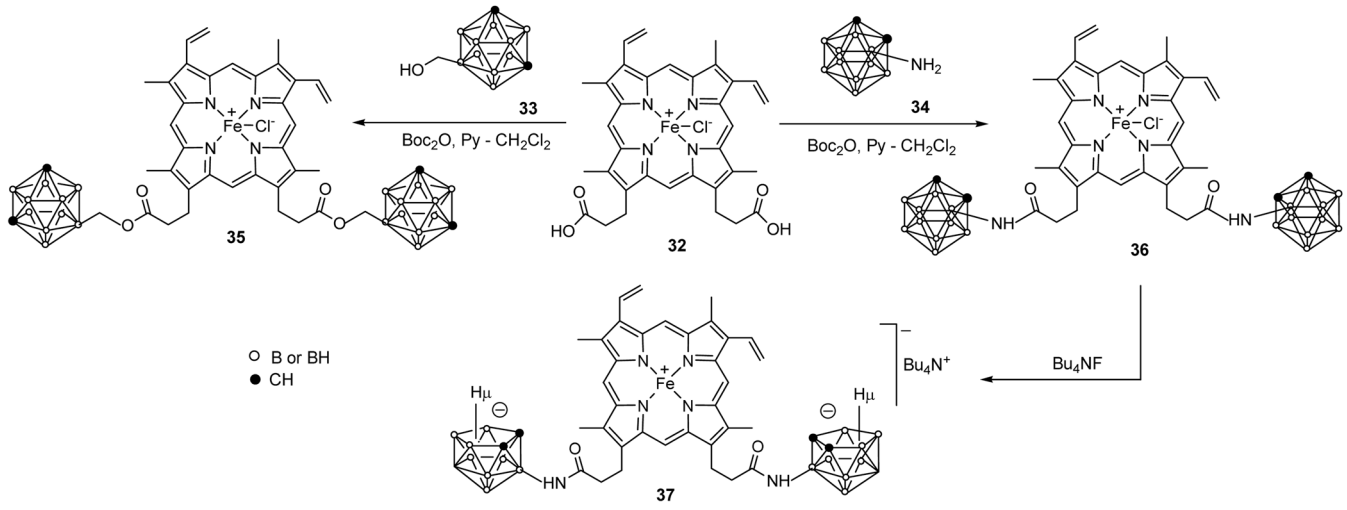
Scheme 4. Chemical transformations of isocyanate-substituted boronated porphyrins.

A major problem that limits clinical use of porphyrin based compounds is general (dark) toxicity. Although the boronated porphyrins demonstrate therapeutic efficacy due to high ratio of tumour-to-tissue content and the ability to generate intratumoural ionization processes,[2,3,18] these compounds (**13** for example) may cause toxicity prior to irradiation. Photofrin®, a mixture of porphyrin oligomers derived from natural products, recently entered clinical trials as a photosensitizer for PDT of bladder, stomach, lung, esophageal and cervical tumours. However, skin photosensitivity emerged as an unfavourable effect, and a series of novel porphyrins and chlorins have been synthesized to obtain active antitumour compounds with attenuated general toxicity.[20] Studies of BOPP [tetrakiscarborane carboxylate ester of 2,4-bis(α,β-dihydroxyethyl) deuteroporphyrin IX disodium salt], a water-soluble boronated porphyrin, demonstrated its excellent characteristics such as the selective tumour uptake, mitochondrial localization and anticancer effect in PDT of experimental intracranial tumours and in phase I clinical trials.[1,19] Still, thrombocytopenia was a dose-limiting factor, and skin photosensitivity should be taken into consideration.[21]

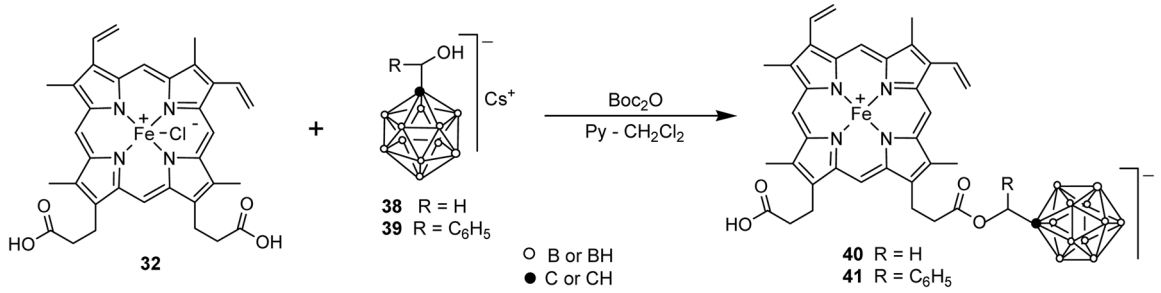
For this reason we have developed the synthesis[22] of carboranyl and monocarbon carboranyl derivatives of protohemin IX (**32**), a component of heme containing proteins. Using the activation of porphyrin (**32**) carboxylic groups with di-*tert*-butyl pyrocarbonate (Boc_2O) or pivaloyl chloride[23] the neutral and anionic congeners in which the boron polyhedra are linked to the porphyrin ring by ester (**35**) or amide bonds (**36**) were prepared (Scheme 5).

Hydrophilic boronated derivatives (**40**, **41**) of protohemin IX were prepared by the direct introduction of anionic *closo*-monocarbon carborane polyhedron into the porphyrin system (Scheme 6). In this case we prepared only mono-substituted zwitter-ionic monocarbon carboranylporphyrins **40** and **41**.

The water soluble 1,3,5,8-tetramethyl-2,4-divinyl-6(7)-[2'-(*closo*-monocarbon carborane-1"-yl)methoxycarbonyl-ethyl]-7(6)-(2'-carboxyethyl)porphyrin Fe (III) (**40**) exerted no discernible cytotoxicity for cultured mammalian cells, nor did it cause general toxicity in rats. Importantly, **40** demonstrated the dose dependent activity as a phototoxin in PDT of M-1 sarcoma bearing rats. In animals injected with 20 mg/kg of **9** the tumours shrank by day 3 after one single irradiation of the tumour with red laser light. By days 7-14 post irradiation 77.8% of rats were tumour free; no



Scheme 5. Synthesis of carboranyl derivatives of protohemin IX.



Scheme 6. Synthesis of monocarbon carboranyl derivatives of protohemin IX.

recurrence of the disease was detectable within at least 90 days. Protohemin IX alone was without effect, indicating that boronation is important for the phototoxic activity of **9**. The applicability in PDT broadens the therapeutic potential of boronated porphyrins beyond their conventional role as radiosensitizers in boron neutron capture therapy.

Aiming at optimization of antitumor characteristics of compound **40** we developed the methods of conjugation of L-amino acids with carboxy group of porphyrin **40**. We hypothesized that amino acid residues should ensure high amphiphilicity and therefore good tissue accumulation of the conjugates. Moreover, it has been suggested that amino acids facilitate transmembrane transport and stabilize carboranylporphyrin-DNA complexes.[24]

We obtained the amide L-amino acid derivatives of **40** in the reaction of methyl esters of serine, valine and phenylalanine with Boc-activated carboxy group of **40** (ref. 25; Scheme 7).

The reaction of compound **40** with oxazaborolidine complexes[26] of L-serine (**46**) or L-threonine (**47**) and subsequent hydrolysis of intermediates **48** and **49** yielded the amino acid conjugates **50** and **51** in which the amino acid residue was linked to the porphyrin macrocycle via ester bond (Scheme 7). Importantly, **50** and **51** contain free amino- and hydroxy groups that increases their water solubility.

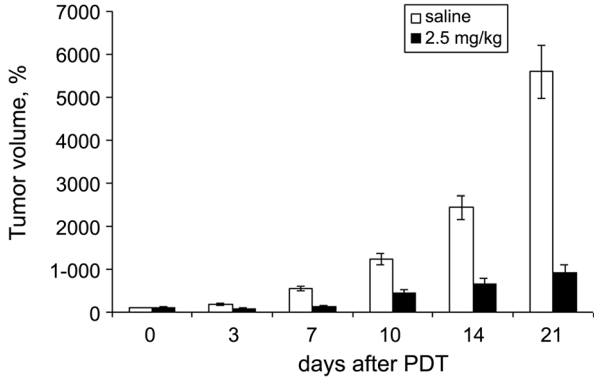
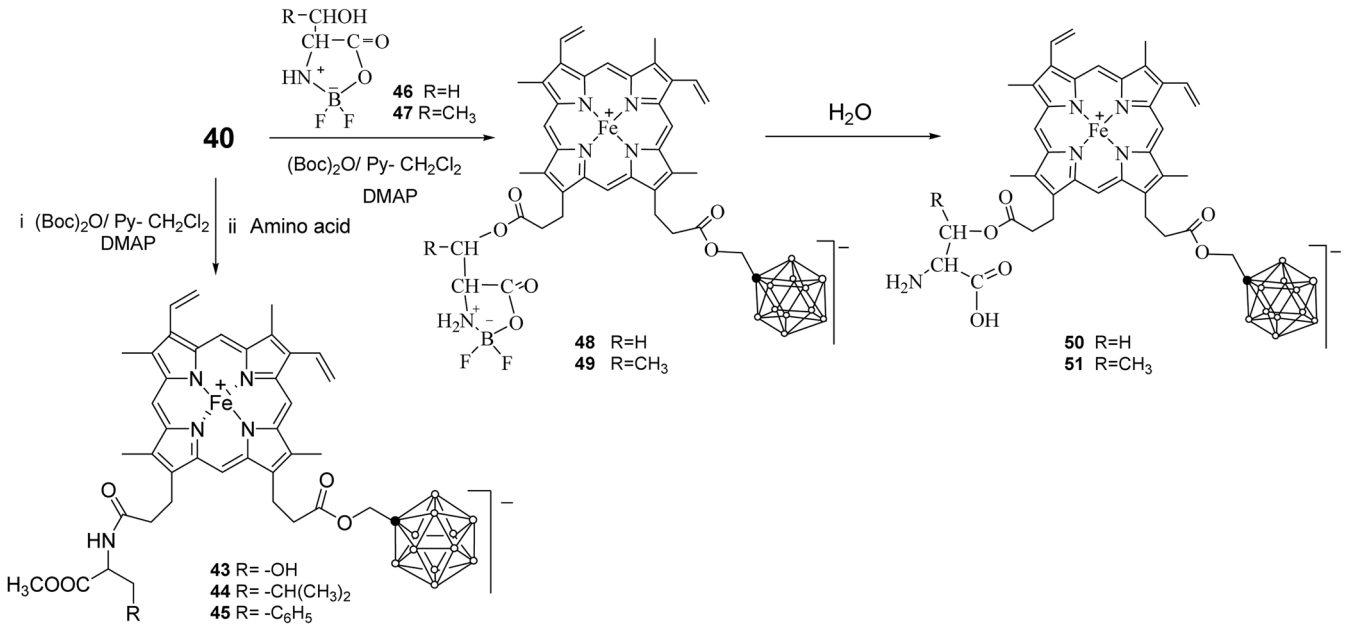
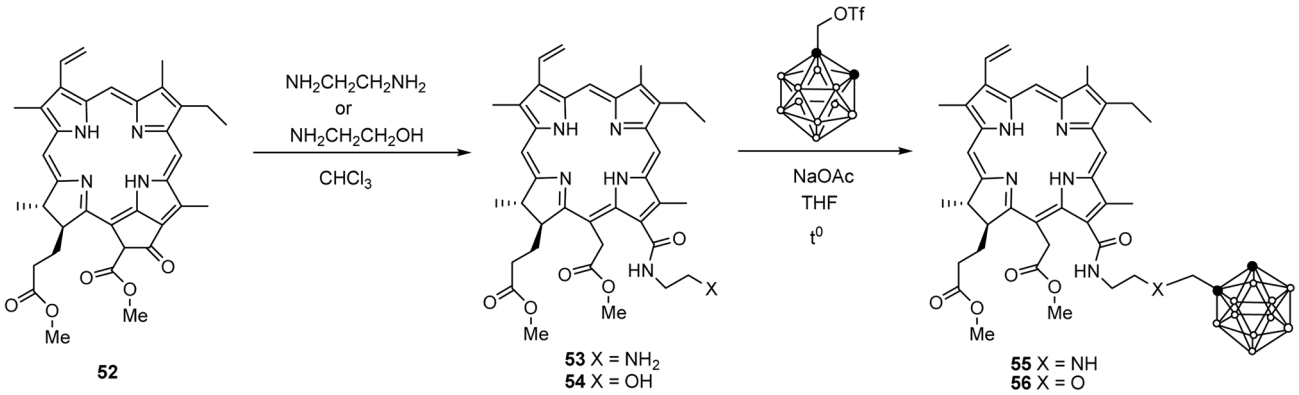


Figure 5. Phototoxic activity of compound **40**.

Screening of novel compounds for cytotoxicity revealed that their potency was **43** > **44** >> **45**, **50**, **51**. Compound **43** triggered complex pattern of cell death. This multiplicity of death pathways induced by **43** implies that our novel amino acid derivatives of boronated porphyrins can be potent for tumor cells in which death signaling was impaired during their natural history and/or preceding therapy.



Scheme 7. Synthetic route to L-amino acid amide and ester derivatives of boronated protohaemin IX.



Scheme 8. Synthesis of boronated derivatives of chlorin e_6.

Finally, we obtained[27] previously unknown carborane derivatives of chlorin e_6 by alkylation of amino and hydroxy groups of chlorins **53** and **54** with carboranylmethyl triflate (Scheme 8). As a result carboranylchlorins **55** and **56** were formed.

Both **55** and **56** did not cause cell death at concentrations of 1-50 μM during 72 h. It should be noted that compounds **55** and **56** are soluble in water at concentrations up to 25 μM. Thus, these carboranylchlorins are non-toxic for cultured cells at concentrations that do not affect the solubility. The toxicity of the new compounds and their efficacy in PDT and BNCT will be determined in animal studies.

Conclusion

In summary, progress in the synthesis of boronared conjugates of porphyrins and chlorins yielded the reliable methods for obtaining the compounds potent as cytotoxic agents for tumor cells in culture and as phototoxins in photodynamic therapy of tumor xenografts. Boronated porphyrins and chlorins deserve further development as promising class of antitumor agents due to their applicability as the chemotherapeutic drugs alone and photo- and radiosensitizers in binary treatment strategies.

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