Quo vadis porphyrin chemistry?

V. KRÁL¹,²*, J. KRÁLOVÁ³, R. KAPLÁNEK¹,⁴, T. BŘÍZA¹,⁴, P. MARTÁSEK⁴*

¹Department of Analytical Chemistry, Institute of Chemical Technology, ²Zentiva R & D, ³Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, ⁴First Medical Faculty, Charles University, Prague, Czech Republic

Received March 22, 2006
Accepted June 23, 2006

Summary
This review summarizes recent developments in the area of porphyrin chemistry in the direction of biological applications. Novel synthetic methodologies are reviewed for porphyrin synthesis, porphyrin analog synthesis, stable porphyrinogens - calixpyrroles, expanded porphyrins. Unique biological properties of those compounds are described with focus on photodynamic therapy (PDT) and molecular recognition properties. Special attentions given to metalloporphyrins with potential to affect heme degradation and CO formation.

Key words
Porphyrins • Synthesis • Expanded porphyrins • Photosensitizers • Molecular recognition • Metalloporphyrins

1. Porphyrin skeleton in nature

Naturally occurring porphyrins are synthesized by living matter. Among the best known natural structures utilizing porphyrin skeleton are vitamin B₁₂ (Fig. 1), chlorophyll (Fig. 3), uroporphyrins, coproporphyrins and heme (Fig. 2).

In the natural system, vitamin B₁₂ is known to have a contracted porphyrin framework which is known as corrin (Battersby 1994).

Heme, iron-containing tetrapyrrrole, is indispensable for life. It is utilized by a whole host of proteins involved in numerous cellular processes such as oxygen transport (hemoglobin), respiration (cytochrome oxidase), vascular homeostasis (nitric oxide synthases), detoxification (cytochromes P₄₅₀), and cell death (cytochrome c). Heme is produced in the mitochondrion by a complex cellular machinery comprising eight enzymes that are evolutionarily conserved from bacteria to humans.

Heme is ferroprotoporphyrin complex. The basis of the structure is the porphyrin skeleton, which is formed by four pyrroles linked with four methine bridges. The substituents, four methyls, two vinyls and two propionic side chains, in beta positions of pyrroles, can be arranged by fifteenth modality, but only one of these isomers, called Protoporphyrin IX, is present in living systems. The biological functions are ensured by its metallocomplex with iron.

Chlorophyll is one of the prevalent spread structures utilizing a porphyrin skeleton. This structure is present in all green plants. In this structure, porphyrin form a complex with magnesium, and the magnesium complex is the key compound in photosynthesis. The main purpose of this magnesium complex is in absorption of irradiation. The absorption of the photons is attributed...
to π-electrons in conjugated double bonds of molecules of chlorophyll.

2. Synthetic porphyrins

These porphyrins form the second part of porphyrins, porphyrins which are not present in nature and human body. Therefore their synthesis in laboratory is the only way that they can be obtained. Nowadays, many porphyrins have been synthesized. These structures are derived from the simplest porphyrin called *porphyne* (Fig. 4).
Porphyrs (which comes from the Greek πορφυρός means “purple, scarlet”) are based on 16-atom rings containing four nitrogen atoms. They are macrocycles that contain only sp²-hybridized bridging meso carbon atoms within their framework. The structure is fully aromatic, contains 18 π-electrons. They are of perfect size to bind nearly all metal ions.

By substitution of hydrogens in the meso-position of some substituents, the porphyrs are obtained. Depending on synthesis, the substituents in the meso-position can either be the same or different.

The basic porphyrin skeleton can be synthesized by several routes based on condensation reactions between aldehydes, pyrroles, dipyrrylmethanes or similar precursors under acidic conditions and following oxidation. The first synthesis of porphyrin - tetraphenylporphyrin (TPP) (Fig. 5), was first accomplished using benzaldehyde and pyrrole in 1936 by Rothmund (Rothmund 1936). Since that time, a series of both symmetrical and asymmetrical porphyrs, has been prepared.


An example of an asymetric porphyrin prepared by Lindsey (Lee et al. 1995), containing four different meso-substituents is shown below (Fig. 6).
3. Analogues of porphyrin

From a single porphyrin, several isomers which can be derived differ by the position of the methine link between pyrrole rings. The study of artificial porphyrin analogs started in 1960s. The first isomer of this type, porphycene, ([18]porphyrin-(2.0.2.0) which differs in the pyrrole linking carbon chain ([18]porphyrin-(1.1.1.1), was synthesized by Vogel et al. in 1986 (Vogel et al. 1986, Gosmann and Franck 1986).

Since then, the other configurational isomers containing the same C20H14N4 composition, such as corrphycene ([18]porphyrin-(2.1.0.1) (Sessler et al. 1994, Aukauloo and Guilard 1994), hemiporphycene ([18]porphyrin-(2.1.1.0) (Callot et al. 1995), isoporphycene ([18]porphyrin-(3.0.1.0) (Vogel 1996) (Fig. 7) and so on, have been reported.

4. Inverted, confused and fused porphyrins

First, the terms confusion, inversion, and fusion must be defined. In the normal porphyrin framework, a and $\alpha'$ linkage is ordinary. Confusion is defined as a linkage at the $\alpha$ and $\beta$ ($\beta'$) positions of pyroles or other hetero-pentacycles. Inversion means that the pyrrole or other pentacycle rings are turning round and inverted is a state of pyrrole NH pointing outward. Fusion is used for the formation of a tripentacyclic ring by connection of a pyrrole ring to a neighbouring inverted pyrrole with its nitrogen (Fig. 8).

N-confused porphyrin (NCP) is a porphyrin isomer that is different largely from the parent porphyrin, particularly in the physical, chemical, structural, and coordination properties. Introduction of the confused pyrrole into the normal and expanded porphyrins leads to generation of the confused porphyrinoids, which have rich structural diversity.

The first NCP was synthesized through the Rothemund type reaction, namely, the acid-catalyzed condensation of pyrrole and benzaldehyde, with concurrent formation of normal porphyrin. In 1994, Latos-Grażyński et al. and another working groups independently isolated a completely different isomer of [18]-[1.1.1.1] type (Latos-Grażyński 1999, Sessler 1994, Geier et al. 1999, Furuta et al. 1994, Chmielewski et al.1994) (Fig. 9).

---

**Fig. 7.** Porphyrin analogues

**Fig. 8.** Inverted and fused porphyrins
5. Contracted and expanded porphyrins

On the other hand, increasing attention has been paid to a class of porphyrin analogs with different core sizes, namely, expanded (Fig. 10) and contracted (Fig. 11) porphyrins. The higher homolog with all methine-bridges, pentaphyrin, was reported by Gossauer in 1983 and shown to sustain a 22 \(\pi\)-aromatic periphery (Gossauer 1983).

In 1964, Johnson et al. synthesized the first contracted porphyrin with an 18 \(\pi\)-electron system, corrole, wherein one of the meso-carbons was missing in the skeleton, by the cyclization of a tetapyrrolic precursor (Johnson and Kay 1964). Efficient one-pot syntheses of meso-substituted corroles were reported recently (Gross et al. 1999, Gryko and Jadach 2001). In 1966, Woodward reported the first example of an expanded porphyrin with a 22 \(\pi\)-electron system,
sapphyrin, which contained five pyrrole rings and four meso-carbons (Woodward 1966).

6. Porphyrins with heteroatoms

Porphyrin analogs containing heteroatoms such as O, S, Se and Te have also been synthesized (Fig. 12, 13) by the groups of Lee and Latos-Grażyński (Heo et al. 1996, Heo and Lee 1996, Lee and Kim 1997, Lee et al. 1999, Yoon and Lee 2000, Sprutta and Latos-Grażyński 1999, Pacholska et al. 2000, Sprutta and Latos-Grażyński 2001, Pushpan et al. 2001).

Furthermore, Lash and co-workers reported syntheses of a series of CNNN- and CNCN-core
porphyrins including ‘true’ carbaporphyrins, which contain a cyclopentadienyl unit in the macrocycle (Fig. 14) (Lash and Hayes 1997, Hayes et al. 1998, Lash et al. 1999).

7. Calixpyrrols

Calix[n]pyrroles are porphyrin analogs that contain pyrroles bridged exclusively by sp³ meso carbon centers. In contrast to porphyrins they are not planar and display remarkable anion-binding properties (Sessler et al. 2001). The most simple calixpyrrol – porphyrinogen (Fig. 15) can be seen as a reduced form of porphyne. Examples of anion binding (Gale et al. 1996) of chlorine and fluorine are shown below (Fig. 16). Picture a shows X-ray structure binding of chlorine and picture b – shows X-ray structure binding of fluorine anion.

8. Calixphyrins

Calixphyrins are a class of hybrid molecules that lie at the structural crossroads between porphyrins and calixpyrroles. Calixphyrins encompass all porphyrin analogs that contain a mixture of sp²- and sp³-hybridized bridging meso carbon centers. In the case of hybrid systems containing four pyrroles, calix[4]phyrins, this definition encompasses systems with one, two, and three sp³-hybridized bridging meso carbons. This leads to partial interruptions in the conjugation pathway of the molecule, introduces novel structural features, and leads to interesting anion and cation recognition properties (Sessler et al. 2001). There are known porphomethenes (one sp²-hybridized meso carbon atom), porphodimethenes (two sp²-hybridized meso carbon atoms, arranged in either a “cis-” or “trans-like” (i.e., 5,10 or 5,15) fashion across the macrocycle), isoporphyrins (three sp²-hybridized meso carbon atoms, one NH hydrogen atom), and phlorins (three sp²-hybridized meso carbon atoms, three NH hydrogen atoms) (Fig. 17).

In addition to porphyrins, the calixphyrins can also form expanded species (Fig. 18).

9. Applications

Photodynamic therapy (PDT)

History of PDT

While the term PDT is relatively new, this binary modality of treating diseases can be traced far back in history. The ancient Egyptians used the combination of orally ingested plants (containing light-activated psoralens) and sunlight to successfully treat vitiligo over 4000 years ago (Edelson 1988). The use of ultraviolet light and psoralens for the treatment of psoriasis (PUVA) has been accepted throughout the world (Baden 1984). Contemporary PDT began when Raab described, in 1900, the action of acridine dyes and light on Paramecia, where he showed that these unicellular organisms could be effectively killed with this combination (Raab 1900). Tappeiner treated, in 1903, a skin cancer with topically applied eosin and light (Tappeiner 1903). In 1913 Meyer-Betz injected himself with 200 milligrams of hematoporphyrin (1) and registered no ill effects until he exposed himself to sunlight, whereupon he suffered extreme swelling, this photosensitivity remained for several months (Laurens 1933, Meyer-Betz 1913). In 1925 Policard examined the ability of porphyrins to produce a phototoxic effect (Policard 1925) and is indeed, the most recent photoactive based drug therapies utilize porphyrin-based chromophores in combination with visible light. Phototherapy was dormant for several decades, although the idea that light could be a therapeutic modality was well explored. For instance, a book published in 1933 lists over a thousand papers exploring UV light for the treatment of a wide variety of ailments, which included arthritis, colitis, lupus, and mental diseases (Gauvain 1933). The usefulness of high dose light might, at first
sight, not seem rational for the treatment of such diseases but in the case of auto-immune disorders, the immuno-suppressing nature of UV light is now well established (Luger and Schwartz 1995).

Photodynamic therapy (PDT), a new treatment modality, involves administration of a tumor-localizing photosensitizing agent (PS) followed by activation of the agent by light of a specific wavelength resulting in a sequence of photochemical and photobiological processes that cause irreversible photodamage of tumor tissues. The hallmark of PDT is intracellular oxidative stress mediated by reactive oxygen species (Fig. 19).

In order to achieve the most efficient photosensitizing effect on tumor cells, the sensitizer must enter the cell and become closely associated with the subcellular structure(s). Photosensitizers may enter cells either directly through the plasma membrane or by endocytosis. Uptake over the plasma membrane may occur by simple or facilitated diffusion or by an active transport mechanism. The incubation parameters and mode of delivery as well as the chemical nature of the photosensitizer (molecular size, charge, water-lipid partition coefficient, concentration), the type and physiological state of the cell, the environmental conditions and the nature of the carrier can all influence subcellular localization, creating a number of potential targets for photodamage (Gomer 1991, Henderson and Dougherty 1992).

Mechanism of the tumor localising effect in PDT
(i) Cancer cells, in common with other rapidly proliferating cells, may have an increased requirement for cholesterol for membrane biosynthesis. They may therefore upregulate the expression of the low-density lipoprotein (LDL) receptor (which recognises the apoB/E lipoprotein) (Maziere et al. 1991). It is known that lipoproteins are major carriers of lipophilic porphyrins in the bloodstream (Jori et al. 1984) and may therefore be a means of entry of these compounds into cells.
(ii) A decreased intratumoral pH may affect the ionization of porphyrin species with weakly acidic pK values, thus retaining them within tumours (Pottier and Kennedy 1990).
(iii) Tumours often contain increased numbers of lipid bodies and particularly neutral lipid droplets, in addition their cell membranes may be more hydrophobic than...
those of normal cells. Both phenomena might explain the accumulation of hydrophobic photosensitisers (Freitas 1990).

(iv) A combination of “leaky” tumour vasculature and reduced lymphatic drainage might encourage the build-up of porphyrins (whether as aggregates or protein complexes) in the interstitial space (Bugelski et al. 1981).

(v) Tumour cells may have increased capabilities for phagocytosis or pinocytosis of porphyrin aggregates (Jori 1989).
Tumour-associated macrophages (TAM) may be largely responsible for the concentration in tumours (Korbelik 1992), Korbelik et al. have found that TAM may contain up to nine times the porphyrin levels present in tumour cells (Korbelik et al. 1991). Many experimental tumours can comprise up to 80% TAM (Milas et al. 1987).

And even in human cancers TAM can make up 20-50% of the cellular content. A high macrophage content is also a common factor with all the other sites of photosensitiser accumulation listed above.

Photodynamic therapy induces a highly complex series of changes in cells. The sequence of events in PDT are shown in following figure, from which it can be seen that complete establishment of the protocol requires wider study of biochemical and photochemical phenomena (Fig. 20).

It is likely to affect multiple cell targets, of which cell membranes and mitochondria are of particular importance (Kessel and Luo 1999). But which may also include lysosomes, endoplasmic reticulum, DNA and microtubules (Henderson and Dougherty 1992, Morgan and Oseroff 2001, Berg and Moan 1997). Following exposure, cells experience a rapid increase in calcium concentration accompanied or followed by other electrolyte changes as membrane damage progresses. Sublethal damage may, via various signal transduction pathways, result in apoptosis characterized by a drop in mitochondrial potential, concurrent with a drop in ATP level and a decrease in cell respiration, translocation of phosphatidylserine of the plasma membrane, DNA fragmentation, appearance of apoptotic bodies and eventually loss of plasma membrane integrity (Carre et al. 1999). The signaling cascades involved in this process are under investigation. The involvement of components of signalling network such as cell surface death receptor Fas (Ahmad et al. 2000), tumor necrosis factor (TNF) and TNF-related apoptosis-inducing ligand TRAIL (Granville et al. 2001) as well as downstream molecules such as caspases (Granville et al. 1997) and Bcl-2 family members (Srivastava et al. 2001) have been demonstrated in various PDT-induced models of cell death. Recently, protein phosphorylation as an important regulator of the apoptotic process has been highlighted (Anderson 1997). Apoptotic signalling cascade in photosensitized human epidermal carcinoma cells was mediated by two-stage activation of the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) (Chan et al. 2000).

Very essential for in vivo efficacy of PDT is the selective retention of PS in neoplastic tissues. It is determined, among other factors, by the hydrophobicity and aggregated state of the PS, decreased pH in tumors, tumor neovascular effects, poorly developed tumor lymphatics, differences in the stromal cells and heterogeneity of the cells within the tumor (Hasan and Parrish 1996). The asymmetry of charge distribution has also been suggested as an explanation for the higher uptake of PS (Kessel et al. 1987). The underlying mechanism reveals a complex interaction of direct and indirect antitumor effects triggered by PDT, which may act to mediate tumor destruction. A direct tumor cell killing results from lethal events initiated by reactive oxygen species. Indirect PDT effects represent necrosis resulting from damage of tumor-associated vasculature with subsequent infarctive death of the tumor cells and initiating a post-treatment immune response directed against tumor cells (Henderson and Dougherty 1992, Dougherty et al. 1998). The effects of PDT were found to be modulated by dose, or dose rate changes, conjugations of photosensitizers to lipoproteins or liposomes, or by the addition of chemotherapeutic agents. The response of different tumors to PDT is highly variable, ranging from high sensitivity to extreme resistance. Factors such as photosensitiser localization properties at different levels (tumor tissue, cellular and intracellular distribution) and tumor oxygenation/vascularity have been identified as the parameters determining tumor sensitivity to PDT. However, a number of other physiological properties characterizing individual tumors may exert a marked influence on the therapeutic outcome. One such property appears to be tumor immunogenicity, since immune reaction induced by PDT against treated tumors can substantially contribute to the cure. Local level of nitric oxide (NO), which directly influences multiple events participating in the antitumor effect of PTD, is another
important, but less recognized parameter (Ali and Olivo 2003). The relevance of this radical, whose production varies considerably in different cancers, to the process of PDT mediated tumor destruction, has been the subject of recent studies.

Many reports in the current literature are confusing, and often apparently contradictory. There is clearly scope for much greater understanding and future studies should more systematically address phenomena in a range of cell types, photosensitizers, and treatment conditions.

**Desirable Properties For PDT Drug**

The drug (photosensitizer) is the essential part in PDT. An ideal drug should have the following properties:

(i) Proper absorption wavelenagth: Due to light absorption by endogenous chromophores, mainly hemoglobin and light scattering, the effective light penetration through tissue is very poor in the low wavelength region of the visible spectrum (Wilson 1989). As the wavelength increases, the effective light penetration increases as well. Experiments indicate the light penetrates effectively through tissue in the red to the near infrared region (≥650 nm) (Wainwright 1996, Lown 1997). As a result, the ideal drug is one that exhibits a strong absorption in such a region (≥650 nm).

(ii) High preference for accumulation in the tumor: The drug must have a selectivity for enrichment in the tumorous tissue vs the normal tissue. Since singlet oxygen is also detrimental to the healthy tissues, a differentiation of drug concentration between biological compartments must be achieved before the irradiation. This ensures that the efficient destruction of the diseased tissue takes place while the healthy tissue remains intact or experiences less ill effect.

(iii) Low dark toxicity and quick metabolization: The PDT drug itself should be non-toxic in the absence of light. The drug should be excreted or metabolized quickly in a way that does not generate toxic metabolites of any kind after the treatment is complete.

(iv) From the standpoint of chemical synthesis, the drug should be made from readily available materials and the protocol of synthesis should be simple and able to be scaled up to an industrial scale. It should contain groups, such as phenyl group which allows easy derivatization or variation in order to optimize various properties of the drug.

(v) It should exhibit some preferred physical or photophysical properties for drug administration, such as good solubility in water and in the body's tissue fluid, easy formulation (Woodburn et al. 1994), high quantum yield of triple formulation, with a triplet energy greater than 94 kJ/mol, and high singlet oxygen quantum yield.
Structure of photosensitzizers

All sensitisers to date are based upon porphyrin-like molecules e.g. porphyrins, chlorins, bacteriocholins and phalocyanines. The in-vivo photodynamic properties of tetrapyrrolic pigments such as porphyrins has been known since the early 1900’s when Meyer-Betz self-administered haematoporphyrin (Hp) to determine its biological effect. To date the water soluble haematoporphyrin derivative (HpD) I, and its purified form commercialised under the trade name Photofrin II, have been used extensively in clinically treating a variety of malignancies. In particular, Photofrin II and complex mixture of porphyrins originated by chemical modification of haematoporphyrin (Hp) (Byrne et al. 1990) has been recently approved for the PDT of specific tumors at a clinical level in several countries (McDonald and Dougherty 2001). At present, a few thousand patients have been treated by PDT with Photofrin worldwide with objectively positive results (Schmidt-Erfurth et al. 1997, Stewaert et al. 1998). HpD is formed by the treatment of haematoporphyrin with a mixture of acetic and sulphuric acids to give a complex mixture of dimers and oligomers. The active component of HpD is believed to be either the dihaematoporphyrin ether II or di-haematoporphyrin ester (DHE). Clinical trials using HpD have proven PDT to be an effective cancer therapy and has shown considerable success in many human tumors. Further various expanded porphyrins have been synthesized and investigated for medical applications such as photodynamic therapy (PDT) (Bonnett 1995). On the following picture some photosensitzizers are shown (Fig. 21).

Saccharide recognition

Porphytrins represent an important class of naturally occurring compounds with unique optical properties. Porphyrins exhibit characteristic sharp and intense absorption maxima in the visible region of spectra (Soret band) and also in fluorescence, both of these properties are very advantageous for analytical applications. The introduction of suitable meso-substituent the planar porphyrin core allows to obtain three dimensional cage, cavity and cleft structures, which are effective for substrate entrapping. Taking into account all these factors porphyrin can be considered as perspective sensing molecule for recognition of bioanalyts. Water-soluble porphyrins have been recently extensively studied, mainly due to their possible madico-biological applications. The use of porphyrins and their derivatives (Fig. 22) for molecular recognition of saccharides is a very promising approach in such intriguing problem as molecular recognition of saccharides and modern bioanalytical chemistry (Lu 2006, Dukh et al. 2003, Rusin et al. 2001, Rusin et al. 2002, Murakami et al. 1994, Král et al. 2000, James et al. 1996).

Other applications

We have recently demonstrated (Králová et al. 2003) application of designed positively charged porphyrins for antisense and antigen application in terms of facilitated oligonucleotide transport. Leading structures are summarized below (Fig. 23).

Metalloporphyrins in connection with poly(ethylene glycol) (PEG) units have been used as
One rational approach to designing tumor-targeting platinum(II) complexes (Sohn et al. 2003) is to introduce a suitable carrier ligand which tends to accumulate in the tumor tissue. Some porphyrins are known to selectively accumulate in the tumor tissue. The tumor-targeting properties of porphyrins are known to be dependent on their hydrophobicity and hydrophilicity balance. In general, the insolubility of most porphyrin derivatives in aqueous solution causes serious problems in biological applications, but some amphiphilic porphyrins are known to selectively accumulate in tumor tissues. A systematic variation of the amphiphilic properties requires a regiochemical arrangement of hydrophobic and hydrophilic substituents in the structure.
A new series of platinum (II) complexes (Sohn et al. 2003) of pegylated hematoporphyrin derivatives with controlled hydrophobic/hydrophilic balance was synthesized by introducing different kinds of poly(ethylene glycol) and amine ligands to the porphyrin ring (Fig. 24).

The antitumor activity of the porphyrin–platinum(II) conjugates was assayed in vitro and in vivo against the leukemia L1210 cell line and various human tumor cell lines. The present complexes exhibited high antitumor activity and improved water solubility as well as considerable lipophilicity.

Porphyrin-peptide conjugates bearing a nuclear localizing sequence SV40 or a fusogenic peptide (HIV-1Tat 40-60 or octa-arginine) linked by low molecular weight poly(ethylene glycol) have been prepared (Vicente et al. 2006) and utilized in in vitro studies using human HEp2 cells. The porphyrins were designed to
contain a peptide sequence (NLS or fusogenic peptide) linked by a low molecular weight PEG in order to minimize intramolecular interactions between the porphyrin and the peptide moieties and to enhance their water solubility (Fig. 25).

Previous studies have shown that PEG-drug conjugates display enhanced water solubility, serum life, and tumor accumulation. The studies show that the cellular uptake of the conjugates depends significantly on the nature and sequence of amino acids in the peptide and on the nature of the substituents on the porphyrin macrocycle. The fusogenic peptide sequences HIV-1Tat 40-60 and octa-arginine were the most effective in delivering the conjugates to the cells.

The new tri(ethyleneglycol)-derivatized Mn(III) porphyrins were synthesized (Dewhirst et al. 2006) with...
the aim of increasing their bioavailability, and blood-circulating half-life (Fig. 26).

Substitution with 1-(2-(2-(2-methoxyethoxy)ethoxy)ethyls in ortho positions of meso pyridyl and imidazolyl substituents significantly increased blood-circulating half-life and decreased unfavorable interactions with biological molecules. The presence of oxygen atoms in substituents on pyridyls and imidazolys eliminated their surfactant-like properties. Consequently, they were not toxic in a simple model of oxidative stress,
SOD-deficient E. coli. They possess the highest ability to disproportionate $O_2$ among meso-substituted porphyrins.

Selective delivery of 10B to tumours is one of the major remaining problems in boron neutron capture therapy (BNCT) of cancer. Because the porphyrins are selectively accumulated in tumours, they were used in connection with carboran units. The solubility was ensured with PEG substitution. Thus two series of carborane-carrying porphyrins (Threadgill et al. 2003) were constructed, with additional functionality for attachment of uncharged potentially water solubilising polyethers. Meso-substituted porphyrins carrying carboranes and oligo(ethylene glycol) units have been used for potential applications in boron neutron capture therapy.

Zinc protoporphyrin (ZnPP) was conjugated with poly(ethylene glycol) (PEG) with a molecular weight of 5000 kDa, to make ZnPP, a water-soluble compound (PEG-ZnPP), and to improve its tumor-targeting efficiency (Maeda et al. 2002), (Maeda et al. 2003), (Maeda et al. 2004) (Fig. 27).

The divalent zinc cation was chelated into the protoporphyrin ring to obtain PEG-ZnPP. PEG-ZnPP became highly water-soluble, and formed multimolecular associations with molecules larger than 70 kDa in aqueous media. PEG-ZnPP inhibited splenic microsomal HO activity in vitro in a competitive manner in the presence of hemin, with an apparent inhibitory constant of 0.12 µM. Most important, PEG-ZnPP injected intravenously significantly suppressed intratumor HO activity in a murine solid tumor model, which suggests that tumor-targeted inhibition of HO is possible with the use of PEG-ZnPP.

A number of metallo-deuteroporphyrins have been synthesized and tested for their ability to modulate HO (Maines 2005). For example, zinc deuteroporphyrin IX 2,4-bis glycol (Fig. 28) dramatically inhibits heme oxygenase activity. This structure which was prepared and tested in 1988 (Martásek et al. 1988) showed the highest inhibition of HO from prepared metallocomplexes. The zinc metallocomplex has been intensively explored in the field of HO (Atzori et al. 2004).

Acknowledgement
The financial support from the Ministry of Education of the Czech Republic (grants no. MSM 0021620806 and 1M683785002), the Grant Agency of the Czech Republic (grants No. GA301/04/1315, GA303/05/0335) is gratefully acknowledged.

References


GAUVAIN H: Actinotherapy Technique; The Sollux Publishing Co: Slough, UK. 1933.


---

**Reprint requests**

Vladimir Král, Department of Analytical Chemistry, Institute of Chemical Technology, Technická 5, 166 28, Prague 6, Czech Republic; Pavel Martásek, First Medical Faculty, Charles University,Kateřinská 1660/32, 120 00 Prague, Czech Republic
Quo vadis porphyrin chemistry? Article. Full-text available. Feb 2006. Vladimir Kral, Jarmila Kralova, Robert Kaplánек. Porphyrins have been receiving much attention in a wide area of chemistry as functional dyes, non-linear optical materials, ligands for a variety of metals, structural motifs in supramolecules, and so forth. However, they have been receiving much attention in a wide area of chemistry as functional dyes, non-linear optical materials, ligands for a variety of metals, structural motifs in supramolecules, and so forth. However, they have View. or. Discover by subject area. Recruit researchers. Join for free. Department of Organic Chemistry cordially invite you to Lecture: Catalysis: "Awakening Affinities" for Organic Synthesis given by Prof. Roderick W. Bates, from Division of Chemistry and Biological Chemistry, Nanyang Technological University, Singapore. The lecture takes place on 15th of October 2018 at 3 p.m. in auditorium CH2, Hlavova 8, Prague 2. When.