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An efficient route to VEGF-like peptide porphyrin conjugates via microwave-assisted 'click-chemistry'

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ABSTRACT

Synthetic cyclopeptides, and particularly those derived from VEGF sequence, present considerable interest for the development of nanodevices devoted to tumour imaging or targeting. In order to provide selective peptide-targeted tetrapyrrolic structures, we designed two *meso*-porphyrin derivatives anchored to a 17-residue-long cyclopeptide, potent antagonist of VEGF receptors, via a flexible tetraethylene glycol chain. Anchoring was achieved by two different strategies: a classical secondary amide bond formation and microwave-assisted Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition ('click-chemistry'). These compounds appear to be promising candidates for applications in PDT.

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1. Introduction

Photodynamic therapy (PDT) is an emerging method aimed at destroying diseased tissue or pathogenic organisms.[1] Applied to a variety of human disorders, this curative approach has received considerable attention in recent years for fighting cancer.[2] This technique relies upon accumulation of photosensitizing molecules, such as porphyrins, into tumours followed by exposure of the affected area to visible light. Upon light, the excited state of the photosensitizer generates singlet oxygen that in turn induces cell damage and ultimately leads to cell death.[3] Healthy cells, however, are also able to uptake photosensitizers, leading to systemic and prolonged photosensitization syndromes, and therefore to severe limitations of PDT.[4] As a result, more selective photosensitizers, named third-generation photosensitizers are desired.[5] Until now, most of the efforts in the development of tumour-targeting photosensitizers have focused on the targeting of markers overexpressed by tumour cells themselves.[6] Indeed neoangiogenesis is a key phenomenon in regard to tumour growth. As capillaries supply oxygen and nutrients to cancer cells, destroying neovessels by PDT appears as an attractive goal. To this aim, we have designed synthetic routes to porphyrin derivatives designed for tumour targeting and more specifically neovascularization.

A novel and potentially powerful approach to improving selective delivery of porphyrins consists in conjugating these molecules to oligopeptide vectors,[7] preferably with cyclic structures[8] in order to increase their in vivo half life.[9] Biological functions of vascular endothelial growth factor (VEGF) are mediated through binding to several receptors, among which Type 2 VEGF receptor (VEGF-R2) is the most efficient towards tumoural neoangiogenesis. These interactions are mainly achieved through three basic residues: R82, K84 and H86. We have previously demonstrated that synthetic cyclopeptides, designed from the structural requirements for VEGF activity, present a very high affinity for VEGF-R2 and subsequently a high level of antitumoural in vivo activity.[10] CBO-P11, one of these cyclopeptides, is presently under preclinical development as anticancer agent and studies to use it for anticancer drug delivery or tumour imaging are in progress.

Abbreviations: Abs_{301}, absorbance at 301 nm; AcOH, acetic acid; All, allyl; Boc, *tert*-butoxycarbonyl; Da, dalton; DIEA, *N*,*N*-diisopropylethylamine; DMAc, *N*,*N*-dimethylacetamide; DMF, *N*,*N*-dimethylformamide; EDC, 1-ethyl-3(3′-dimethylaminopropyl)carbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; HBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; MALDI, matrix-assisted laser desorption/ionization; MsCl, mesyl chloride; NHS, *N*-hydroxysuccinimide; NMM, *N*-methylmorpholine; NMR, nuclear magnetic resonance; Pbf, 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl; PDT, PhotoDynamicTherapy; PyBOP, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; SPPS, solid-phase peptide synthesis; TEG, triethyleneglycol; THF, tetrahydrofuran; TIS, triisopropylsilane; Trt, trityl; VEGF, vascular endothelial growth factor; VEGF-R2, vascular endothelial growth factor receptor 2.

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The main aim of the present work is the design and synthesis of two new bio-conjugate photosensitizers consisting of *meso*-porphyrin derivatives bearing an ethylene glycol spacer arm attached to CBO-P11 (Fig. 1). Two synthetic strategies are depicted in: grafting of the tetraethylene glycol spacer arm by classic peptidic synthetic reaction between carboxyphenylporphyrin **8** and the amino function of spacer (Schemes 1 and 2), and microwave-assisted Cu(I)-catalyzed alkyne dipolar cycloaddition ('*click-chemistry*') (Schemes 1 and 3). These two porphyrins CBO-P11 derivatives were characterized by ^{1}H NMR, MALDI Mass spectrometry, absorption and fluorescence spectroscopies in aqueous solution, and we tested their ability to produce singlet oxygen upon illumination.

2. Results and discussion

2.1. Synthesis of CBO-P11

CBO-P11 was synthesized as previously described, in order to prevent chemical modifications of essential residues occurred in natural VEGF that interacting with VEGF-R2 receptors (Arg82, Lys84 and His86).[11] Accordingly, cyclopeptide **4** (Fig. 1) thus obtained possesses a single deprotected carboxylic group (γ-carboxyl of the glutamate residue) for controlled introduction of molecular decoration. For this purpose, we performed the total synthesis of CBO-P11 on the extremely acid-labile 2-chlorotrityl chloride resin. This resin was loaded by formation of an ester bond

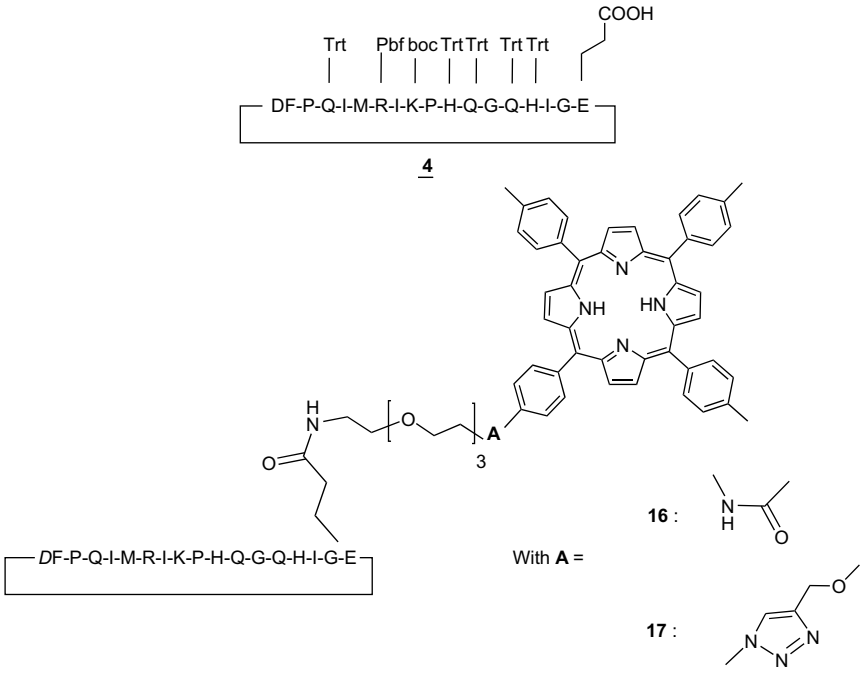
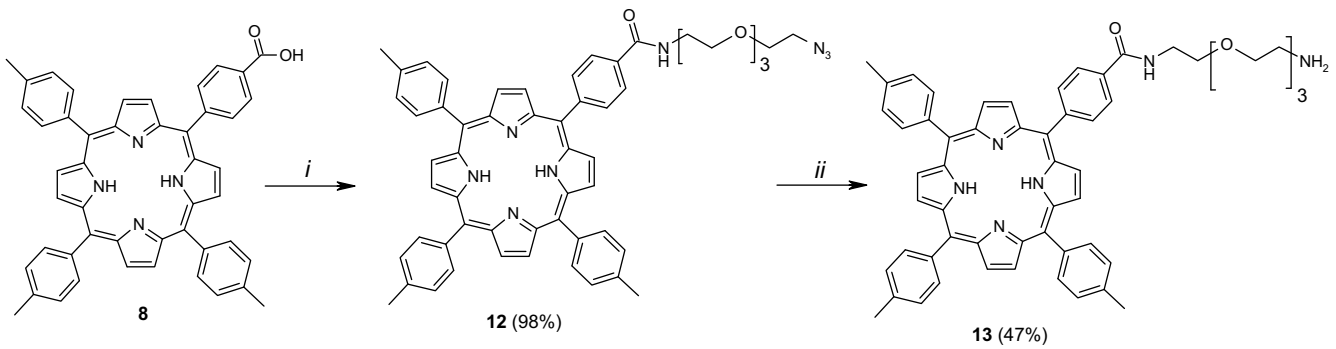


Figure 1. Structures of *cyclo*-VEGI **4** and CBO-11 porphyrins derivatives **16** and **17**.

Scheme 1. Reagents and conditions: (i) MsCl (1.1 equiv), Et_3N in DCM (−5 °C to rt, 90 min); (ii) NaN_3 (4.0 equiv) in EtOH/DMAc (4:1), reflux 6 h; (iii) PPh_3 (1.0 equiv) in Et_2O/HCl (1 M) mixture, rt, 2 h.



Scheme 2. Reagents and conditions: (i) EDC (2.0 equiv), NHS (1.5 equiv) in $CHCl_3$, rt, 45 min, **7** (2.0 equiv), rt, 6 h; (ii) PPh_3 (3.0 equiv) in $CHCl_3$, H_2O (100 μL) in THF (1 mL), rt, 6 h.

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