Synthesis and Biological Evaluation of Novel Chalcone-Porphyrin Conjugates

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

Studies on the synthesis, structural characterization and biological evaluation of novel chalcone-porphyrin derivatives are described. The photodynamic effect, intracellular localization and cellular uptake of the new conjugates were evaluated in vitro in COS-7 cells. All derivatives exhibited high stability and yielded good fluorescence under light irradiation. None of the chalcone-porphyrins proved to be cytotoxic and/or phototoxic for COS-7 cells.

Keywords: porphyrins, chalcones, medicinal applications, fluorophores, fluorine

1. Introduction

For the last two decades, interdisciplinary studies performed with porphyrin macrocycles pointed out the great potential applications of this type of compounds in various fields like medicine, catalysis and as components of new electronic materials.1

Concerning biomedical applications, photodynamic therapy (PDT) is an emergent and promising technique for the treatment of several cancer pathologies. Among the different types of photosensitizers being used in PDT, porphyrins are the most extensively studied, due to their photophysical and biological properties, and because a few of them are already approved for clinical use.2 At the same time, porphyrins have been studied in relation to cancer photodetection (PD), due to their characteristic red emission fluorescence. In this way, most of the porphyrinic fluorescent agents used in PD were developed for PDT use. However, the strategies for developing fluorescent markers should be different. Besides the required fluorescence, high selectivity and uptake by tumour cells, the fluorescence markers for photodetection shouldn’t, ideally, show either cytotoxicity or photocytotoxicity.

Some carotenoporphyrins without phototoxicity have already been synthesized,3,6 but in vivo studies revealed that a large amount of the dye accumulated in the liver.6 Photodiagnosis based on tumour target exogenous fluorophores does not cover the entire cancer diagnosis research field. Recent promising work has also been reported regarding the autofluorescence levels of blood components.7 This method has given good results to distinguish normal and cancer patients at different stages, but is not able to differentiate the type of cancer. Another interesting area in recent development is based on 19F NMR applications.8–11 This technique implies the use of fluorinated molecules and can be quite advantageous in vivo due to the lack of fluorine compounds in biological systems.

Recently, several epidemiological and animal studies tend to suggest a protective effect of flavonoids against some cancer types.12 They also have revealed potent antioxidant activity, by scavenging reactive oxygen species that can predispose to cancer development. In particular, chalcones demonstrated anticancer activity against some cancer types like human leukaemia,13–16 B16 mouse melanoma,17 and breast cancer cell lines.18 In addition, so-
me 2-hydroxychalcones also inhibit 4-NOO induced carcinoma formation in the tongue.\(^{19}\)

In this study, following our interest on the development of compounds with potential application in medicine we describe, for the first time, the synthesis of non fluorinated and fluorinated chalcone-porphyrin derivatives 4, 6 and 7. Preliminary biological tests were performed in vitro in COS-7 cells, in order to establish the effect of the porphyrinic substituents on photocytotoxicity, on cellular uptake and on intracellular localization. We have found that chalcone derivatives accumulate in the nucleus and/or at perinuclear membranes and give good fluorescent images of the cell organelles.

**2. Results and Discussion**

**2.1 Chemistry**

For these studies on chalcone-porphyrin conjugates we decided to choose an easily accessible chalcone 3,\(^{20}\) with only one free hydroxyl group, to be coupled to the selected porphyrins 1 (Scheme 1) and 5 (Scheme 2). The choice of porphyrin 1 was based on the knowledge that porphyrins with meta-methoxyphenyl groups in meso positions show high cellular uptake.\(^{21}\) The presence of the carboxyl group in one of the phenyl substituents appeared to us to be an easy option for the connection to the chalcone unit.

The simple substitution of the para fluorine atoms by nucleophiles on meso-tetakis(pentafluorophenyl)porphyrin 5,\(^{22-23}\) prompted us to select that compound as our second porphyrin. On the other hand, the newly synthesised derivatives containing fluorine atoms could be considered potential markers to be used in \(^{19}\)F magnetic resonance imaging (MRI).

Porphyrins 1 and 5 were obtained according to literature procedures from Rothemund and crossed-Rothemund reactions using the appropriate substituted benzaldehydes and pyrrole.\(^{24-26}\) The chalcone-porphyrin 4 was obtained in excellent yield (97%) from the reaction of the activated ester 2 with chalcone 3 (Scheme 1). The coupling reaction was carried out in DMSO in the presence of potassium carbonate, at room temperature. The activated ester 2, isolated also in excellent yield (97%), was prepared by generating firstly the acyl chloride of porphyrin, followed by the addition of \(N\)-hydroxysuccinimide. Attempts to couple directly the acyl chloride of porphyrin 1 with 3 were not successful.

Compounds 6 and 7 were obtained from the reaction of porphyrin 5 with chalcone 3, in DMSO in the presence of \(\text{Na}_2\text{CO}_3\) (Scheme 2). In order to favor the substitution of only one para fluorine atom, an excess of porphyrin 5

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**Schema 1.** i) (a) SOCl\(_2\), dry pyridine, 30 min, r.t.; (b) \(N\)-hydroxysuccinimide, 3 h, 50 °C. \(\text{ii) } \text{K}_2\text{CO}_3\), DMSO, r.t., 1.5 h.
relatively to 3 was used and the reaction was performed at 50 °C; under these conditions the derivative 6 was isolated in 44% yield and 50% of the starting porphyrin was recovered. When a large excess of chalcone 3 was used and the reaction performed at 100 °C, the substitution of all para fluorine atoms occurred, leading to derivative 7 in moderate yield (33%).

The structures of all chalcone-porphyrin derivatives were confirmed by NMR, UV-visible, mass spectrometry, and elemental analysis. Unequivocal proton and carbon assignments were based on two-dimensional COSY, HSQC and HMBC experiments.

The $^1$H NMR spectrum of compound 4 shows a complex pattern due to the overlap of the signals of the chalcone unit with the ones due to the aryl groups of the porphyrin moiety. Based on two-dimensional NMR studies and by comparison with the $^1$H NMR spectrum of compounds 6 and 7 we were able to identify the resonances due to the protons of the chalcone unit between ca. 5 and 8 ppm. The major difference in the $^1$H NMR spectra of compounds 6 and 7 is in the low field region where the signals due to the resonances of the β-pyrrolic protons appear. For compound 7 those resonances occur as a singlet at 8.95 ppm, while for compound 6 two doublets and a singlet are observed at $\delta$ 9.00 (d), 9.02 (s) and 9.08 (d). Due to the deshielding mesomeric effect of the chalcone carbonyl group in the $^1$H NMR spectra of compounds 4, 6 and 7, the resonance signal of H-β appears at a higher frequency than the signal of H-α. The trans configuration of the chalcone double bond is confirmed by the values of the coupling constants obtained (ca. 16 Hz) for all the chalcone-porphyrin derivatives.

The $^{19}$F NMR spectra of the fluorinated derivatives 6 and 7 also confirm the proposed structure, namely the number of the para-fluorine atoms substituted by the chalcone unit. The $^{19}$F NMR spectrum of compound 6 revealed the presence of a multiplet between $\delta$ –161.8 and –161.6 ppm due to the resonances of the three para-fluorine atoms. On the other hand, the absence of similar signals due to the resonance of para-fluorine atoms in the $^{19}$F NMR spectrum of compound 7 is in accordance with the tetra-substituted structure.

2. 2. Biological Assays

2. 2. 1. Photostability of the Compounds

The photostability of the target compounds is an important parameter to assess, as exposure of the porphyrins to visible light can cause an irreversible photodestruction of the tetrapyrrolic macrocycle. This process is generally defined as photobleaching.27

To induce photobleaching, aerated solutions of compounds 1, 4–7 (1 μM in DMF), under magnetic stirring,
were irradiated using the same conditions as in the biological assays (white light, fluence rate of 33.3 mW/cm²). The UV-VIS spectra of these compounds were recorded at different times of irradiation (0 and 40 minutes) and did not show any absorbance decay of the Soret and Q bands during the total irradiation period. The results indicate that all studied compounds are highly stable under such conditions. As an example, the UV-VIS spectra of compound 7 at two irradiation times are shown in Figure 1.

Figure 1. UV-vis spectra of compound 7 (1 μM, DMF) after two irradiation times with white light, 33.3 mW/cm²

### 2.2.2. Cytotoxicity and Photocytotoxicity Studies

The biological activity of the porphyrinic compounds was monitored in COS-7 cells, an immortalized monkey kidney cell line. Cells were maintained in complete DMEM (Dulbecco’s Modified Eagle’s Medium; Sigma-Aldrich), at 37 °C and 5% CO₂.

The compounds cytotoxicity and photocytotoxicity were evaluated on the basis of cell viability. Cells were incubated with different concentrations of compounds 1, 4–7 (0 to 100 μM in DMEM). After 2 h in the dark at 37 °C, cells were washed thoroughly with PBS and irradiated, or not, with white light (400–800 nm) for 10 min at a fluence rate of 33.3 mW/cm² (20 J/cm²). Then, cells were further incubated in compound-free DMEM for an additional 24 h period in the dark, upon which cellular viability was assessed by the MTT assay. Concentrations above 100 μM were not tested since this appeared to be near their upper solubility limit. Toxicity results obtained are shown in Figure 2.

No significant effects on cellular viability were observed with compounds 5, 6 and 7, for all concentrations tested and even when cells were exposed to the light dose used. Additionally, the morphology of the cells, observed by light microscopy, remained always unaltered (data not shown).

Compound 1 and its derivative 4 exhibited differences in their biological activity. Cells exposure to compound 1 for 2 h without irradiation yielded a statistically significant decrease in viability of ∼20% at the higher concentrations tested (50 and 100 μM). Light irradiation appeared to aggravate compound 1 cytotoxicity, although a statistically significant potentiation effect was only observed at 100 μM (∼55% viability). Lower concentrations of compound 1 were tested under both light conditions without exhibiting toxicity (data not shown). Thus, compound 1 induced cytotoxicity in a dose-dependent manner, which was potentiated by light irradiation at 100 μM. In contrast, no significant changes in COS-7 cells viability were observed for compound 4 under all conditions tested. Furthermore, alterations in cellular morphology were also observed with compound 1 that were not similarly elicited by compound 4 (Figure 3). The observed morphologic alterations are commonly associated with cell death.

### 2.2.3. Cellular Uptake

In order to study the time-dependent uptake of each compound into COS-7 cells, these were incubated with 10 μM of compounds 1, 4–7 from 0 to 24 h. After each incubation period, cells were washed with PBS and collected with 2% SDS. Total protein concentration of each sample was quantified by the BCA protein assay. The intracellular uptake was determined by following the fluorescence intensity of cellular extracts at different incubation times (0, 0.5, 1, 2, 4 and 24 h). Results obtained are presented in Figure 4. Compound 5 aggregated strongly to the cell sur-
face and, even after several washes, can not be removed inter-
fering with the accurate determination of the cellular 
uptake for this compound. The other compounds exhibited 
some significant differences in terms of their cellular up-
take. The tetra-substituted chalcone-porphyrin 7 showed a 
higher uptake than the mono-substituted one (6) at each ti-
me point. However, the best accumulation was always ob-
served, at all incubation times, for porphyrin 1. After 24 h, 
an uptake 15 times higher than for the corresponding chal-
cone-porphyrin 4 was observed. Porphyrin 4 reached its 
highest uptake (118.19 ± 2.27 nmol porphyrin/μg of pro-
tein; ∼3x higher than 6 and 7) after 2 h of incubation. After 
24 h its uptake (63.70 ± 8.99 nmol porphyrin/μg of protein) 
was lower than the one obtained for the fluorinated porphy-
rin 7 (98.46 ± 9.89 nmol porphyrin/μg of protein). These 
findings suggest that chalcone groups may be involved in 
modulation of the cellular uptake of the porphyrin.

2. 2. 4. Subcellular Localization

The intrinsic fluorescence and subcellular localization 
of the five porphyrinic compounds was analyzed. Cells were incubated for 2 h at 37 °C in DMEM contain-
ing 10 μM of the indicated compound. Following four 
washings with PBS, the intrinsic fluorescence of the 
porphyrinic compounds was analysed using an Olympus 
IX-81 inverted epifluorescence microscope, with the filter 
set indicated in Figure 5.

A characteristic punctate pattern of intracellular 
staining was observed for the five compounds (Figure 5). 
Intense red fluorescence was mainly observed to localize 
in the nucleus and/or perinuclear loci, where the porphyrin-
ic compounds appear to concentrate. As expected, none 
of the tested compounds produced fluorescence in the in-
tercellular space. The observed fluorescence correspon-
ded solely to internalized porphyrins.

Figure 3. Phase contrast microphotographs of COS-7 cells treated or not (C), with 100 μM of compounds 1 and 4, for 2 h in the dark. Compounds 
were then removed by washing with PBS and cells were irradiated, or not, with white light (400–800 nm) for 10 min at a fluence rate of 33.3 
MW/cm² (20 J/cm²). All cells were further incubated in compound-free DMEM for an additional 24 h period at 37 °C in the dark.

Figure 4. Cellular uptake (nmol porphyrin/μg of protein) of compounds 1, 4, 6 and 7 (10 μM) in COS-7 cells at different incubation 
times. *Values are means of three experiments

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3. Conclusion

The novel chalcone-porphyrinic conjugates described were efficiently synthesized in reasonable to good yields. These compounds are highly photostable and give good cellular fluorescence images. Upon internalization by an immortalized cell line, all the synthesized compounds localized mainly near the nuclear area. Nonetheless, the tetra-substituted chalcone-porphyrin 7 showed a higher uptake than the mono-substituted 6, reflecting an advantageous replacement of the \( para \) fluorine atoms by chalcone moieties in COS-7 cellular uptake. All the chalcone-porphyrinic derivatives show similar non cytotoxic and non photocytotoxic profiles. However, the chalcone-free porphyrin 1 induced COS-7 cell toxicity in a concentration-dependent manner. Therefore, the lack of cytotoxicity induced by compound 4 suggests that the chalcone moiety induces a protective effect concerning the cytotoxic characteristics of the precursor porphyrin 1. The fluorinated derivatives 6 and 7 may also be good candidates for cancer diagnosis using \( ^{19}F \) NMR imaging. The absence of photocytotoxic effects for these porphyrinic derivatives encourages further biological assays and these chalcone-porphyrin conjugates appear to be good potential agents for cancer diagnosis.

4. Experimental

\( ^1H, ^13C \) and \( ^{19}F \) solution NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300.13, 75.47 and 282.38 MHz, respectively. CDCl\(_3\) was used as solvent and TMS was used as internal reference for \( ^1H \) and \( ^13C \) NMR spectra, while \( C_7F_8 \) was used in the \( ^{19}F \) NMR. The chemical shifts are expressed in \( \delta \) (ppm) and the coupling constants \( (J) \) in hertz (Hz). Mass spectra were recorded on a VG AutoSpecQ mass spectrometer using DMSO or CHCl\(_3\) as solvent and NBA as matrix. The UV-vis spectra were recorded on a Uvikon 922 spectrophotometer. Elemental analyses were performed with a Leco 932 CHNS analyser. Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. Column chromatography was carried out in silica gel (35–70 mesh, Merck). Preparative thin-layer chromatography was carried out on 20 \( \times \) 20 cm glass plates coated with silica gel (0.5 mm thick, Merck). When required, the solvents were purified or dried according to literature procedures. All the experiments with light were performed with white light from an interchangeable fiber optic probe (400–800 nm) coupled to a 250 W quartz/halogen lamp (LC-122 LumaCare, USA). The light was delivered and fluence rate measured with a radiometer LI-COR Model LI-250.

5-(4-Carboxyphenyl)-10,15,20-tris(3-methoxyphenyl) porphyrin (1): 4-Formylbenzoic acid (1.62 g, 10.8 mmol) and 3-methoxybenzaldehyde (2.63 mL, 21.6 mmol) were added to a refluxing mixture of glacial acetic acid (200 mL) and nitrobenzene (150 mL). After the dissolution of the 4-formylbenzoic acid, pyrrole (2 mL, 28.9 mmol) was added dropwise (ca. 4 min) to the mixture. The reaction mixture was then refluxed for 1 h. The solvents were distilled under reduced pressure and the crude material was taken into chloroform and directly chromatographed on a silica column using chloroform as eluent. The first fraction was identified as 5,10,15,20-tetakis(3-methoxyphenyl)porphyrin (130.6 mg, 3 %). The second fraction, eluted with the same solvent, gave porphyrin 1 (634 mg, 8% yield) after evaporation of the solvent and recrystallization from chloroform/light petroleum. \( ^1H \) NMR (300.13 MHz, CDCl\(_3\)) \( \delta \): 2.80 (s, 2H, NH), 3.99 (s, 9H, 10,15,20-Ar-OCH\(_3\)), 7.34 (dd, \( J = 8.2 \) Hz and 2.1 Hz, 3H, 10,15,20-Ar-p-H), 7.63–7.68 (m, 3H, 10,15,20-Ar-m-H), 7.79–7.83 (m, 6H, 10,15,20-Ar-o-H). 8.35 (d, \( J = 7.6 \) Hz, 2H, 5-Ar-o-H), 8.51 (d, \( J = 7.6 \) Hz, 2H, 5-Ar-m-H), 8.80 and 8.92 (AB, \( J = 4.9 \) Hz, 4H, pyrrolic \( \beta \)-H), 8.90 (s, 4H, pyrrolic \( \beta \)-H); MS (FAB\(^+\)) \( m/z: 749 \) (M\(^+\)H\(^+\)).

5-4-[Succinimide-N-oxycarbonyl]phenyl]-10,15,20-tris(3-methoxyphenyl)porphyrin (2): To a stirred solution of porphyrin 1 (31 mg, 21 \( \mu \)mol) in dry pyridine was added SOCl\(_2\) (0.1 mL, 163 mmol). The reaction mixture was maintained in the dark, protected from moisture with silica gel, during 30 min at room temperature. Then, N-hydroxysuccinimide (74 mg, 643 \( \mu \)mol) was added and the temperature rise to 50 °C. The reaction progress was monitored by TLC. When the reaction was complete (3 hours), the solvent was removed under reduced pressure and the crude material was taken into chloroform.
Chalcone-porphyrin conjugate (4): Chalcone 3 (55 mg, 167 μmol) was dissolved in dry DMSO (1.5 mL) and an excess of K₂CO₃ (150 mg) was added to this solution. The porphyrinic activated ester 2 (20.0 mg, 24.1 μmol) was then added and the reaction mixture was stirred in the dark for 1 h at room temperature, protected from moisture with silica gel. The coupling reaction was monitored by TLC using dichloromethane/petroleum ether (1:1) as eluent and was purified by flash chromatography (silica gel) using dichloromethane/light petroleum (1:2) as eluent. The first fraction was identified as the unchanged chalcone 5 (50%) and the second one showed to be a mixture of three products. This fraction was then purified by preparative TLC (silica) using dichloromethane/light petroleum (1:2) as eluent and afforded the desired chalcone-porphyrin 6 as the major constituent (15.8 mg, 44%). mp 289–290 °C; UV-vis (DMSO) λ max (log ε) 411 (54.7), 536 (not calculated), 506 (4.35), 579 (3.85), 632 nm (2.91). ⁱH NMR (300 MHz, CDCl₃/TFA) δ 5.22 (s, 2H, Chalc-CH₂), 7.14 (d, J 8.8 Hz, 2H, Chalc-H₃,5), 7.34 (d, J 8.3 Hz, 1H, Chalc-H'), 7.43 (d, J 15.8 Hz, 1H, Chalc-H'), 9.00 and 9.08, (AB, J 5.0 Hz, 4H, pyrrolic β-H), 9.02 (s, 4H, pyrrolic β-H). ¹³C NMR (75.47 MHz, CDCl₃/TFA) δ 71.0 (OCH₃), 116.3, 123.2, 125.3, 128.3, 128.8, 128.9, 130.0, 131.0, 132.1, 134.1, 135.7, 145.3, 146.1, 146.3, 153.4, 154.4 (C²'), 162.5, 196.7 (CO). ¹⁹F NMR (282.38 MHz CDCl₃/TFA) δ −183.4 to −183.3 (m, 2F, 5-Ar-F), −175.7 to −175.6 (m, 6F, 10,15,20-Ar-F), −168.8 to −161.6 (m, 3F, 10,15,20-Ar-F), −161.9 (d, J = 14.1 Hz, 2F, 5-Ar-F), −161.6 (d, J = 14.1 Hz, 6F, 10,15,20-Ar-F). MS (FAB⁺) m/z: 1284 (M⁺). Anal. Calcd for C₆₆H₂₇N₄O₃F₁₉·H₂O: C 60.84, H 2.24, N 4.30. Found: C 61.04, H 2.14, N 4.41.

Chalcone-porphyrin conjugate (7): Chalcone 3 (41.4 mg, 125 μmol) was dissolved in dry DMSO (1.5 mL) and an excess of K₂CO₃ (80 mg) was added to this solution. Porphyrin 5 (21.1 mg, 21.7 μmol) was then added and the reaction mixture was stirred in the dark for 3 h at 100 °C under nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and then washed with water (2 × 100 mL) and extracted with chloroform. The organic layer was dried (Na₂SO₄), concentrated and the crude material was submitted to column chromatography (silica gel) using dichloromethane/light petroleum (1:2) as eluent.
δ 5.14 (s, 8H, Chalc-CH2), 7.07 (d, J 8.8 Hz, Chalc-H3,5), 7.31 (d, J 8.4 Hz, 4H, Chalc-H3'), 7.33–7.42 (m, 24H, Chalc-H1,3'), 7.69 (d, J 8.8 Hz, 8H, Chalc-H2,6), 7.71–7.73 (m, 4H, Chalc-H4'), 7.84 (dd, J 8.8 Hz, 4H, Chalc-H5'), 7.69 (d, J 7.6 Hz and 1.6 Hz, 4H, Chalc-H6'), 7.87 (d, J 15.6 Hz, Chalc-Hβ) δ 35.8 (Chalc-C1), 127.5 (Chalc-C2',6''-Bn), 128.4 (pyrrolic C), 130.8 (Chalc-C6'), 131.5 (Chalc-C2,6), 133.7 (Chalc-C4''-Bn), 128.7 (Chalc-C3''-5''-Bn), 129.4 (pyrrolic Cβ), 130.8 (Chalc-C6'), 135.9 (Chalc-C1'-Bn), 145.9 (pyrrolic Cα), 151.0 (Chalc-Cβ), 154.3 (Chalc-C2'), 156.8 (Chalc-CO). 19F NMR (282.38 MHz CDCl3/TFA) δ −175.5 (d, J = 14.1 Hz, 8F, 5,10,15,20-Ar-F), 161.6 (d, J =14.1 Hz, 8F, 5,10,15,20-Ar-p-F). MS (FAB+) m/z: 2214 (M+). Anal. Calcd. for C35H27F8N4O12F16: C 71.54, H 3.55, N 2.73. Found: C 71.49, H 3.61, N 2.78.

5. Acknowledgements

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Povzetek

Opisana je študija strukturne karakterizacije in biološke evalvacije novih chalcone-porfirinskih derivatov. Fotodinamični efekt in cepljenje novih konjugatov je bil testiran in vitro na COS-7 celicah. Vsi derivati so pokazali visoko stabilnost in dobre fluorescenčne lastnosti pri obsevanju s svetlobo. Pri nobedem od chalcone-porfirinskih derivatov ni bila opažena citotoksičnost in fototoksičnost na COS-7 celicah.