Synthesis of porphyrin α,ω-bis(methylamino)peptide constructs‡

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New monofunctionalised electrophilic and nucleophilic derivatives of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) have been developed for controlled attachment to peptide amino and carboxyl side-chains, respectively. Reaction of 5-(4-aminophenyl)-10,15,20-triphenyl-21*H*,23*H*-porphine with 4-nitrophenyl chloroformate gave the corresponding nitrophenyl carbamate which coupled efficiently to lysine ε-amines. The aminophenylporphyrin, a poor nucleophile, was converted to a primary aliphatic amine by coupling with glycine. This glycylaminophenylporphyrin reacted readily with acyl azides derived from extended Glu side-chains. These systems offer access to novel polymeric porphinatomanganese(III) agents for contrast enhancement in MRI.

Introduction

Porphyrin complexes of Mn(III), such as chloro-5,10,15,20-tetrakis(4-sulfonatophenyl)porphinatomanganese(III) (TPPSMnCl), have been extensively explored as contrast enhancement agents in magnetic resonance imaging (MRI).[1] The porphyrin ring offers two particular advantages as a ligand. Firstly, the Mn(III) is very tightly bound, obviating problems of toxicity and inappropriate biodistribution of free Mn ions. Secondly, many tumour types have increased uptake for porphyrins.[2–4] Attachment of paramagnetic contrast-enhancing agents for magnetic resonance imaging (MRI) to macromolecules enhances the relaxivity and effectiveness of these agents by decreasing their tumbling rate in solution.[5] This effect is dependent on the rigidity of the conjugate. In some cases, the effect is higher where the contrast enhancing agent is bound near the polymer backbone than where there is a long flexible spacer.[5]

Macromolecules have also been proposed as carriers for the site-specific delivery of drugs.[6,7] Passive targeting of such conjugates is achieved through exploitation of the enhanced permeation and retention of macromolecules in solid tumours (the EPR effect).[8,9] The combination of these two properties of macromolecules could lead to enhanced MRI of the blood volume and of solid tumours.[10] Most synthetic polymers previously developed as water-soluble drug carrier systems are poorly biodegradable, leading to accumulation of high molecular weight polymers in the body.[9] Thus there is a need for a high molecular weight, degradable, non-immunogenic synthetic macromolecule with suitable functionality for attachment of MRI contrast enhancement agents. We are therefore working towards the development of such a polymer carrying Mn^{III}–porphyrins and this paper describes our approach to the controlled attachment of porphyrins to appropriate (biodegradable) peptide monomers.

Most naturally occurring porphyrins carry more than one identical electrophilic or nucleophilic group, leading to difficulty in preparing monofunctionalised porphyrins in a controlled manner. Kruper *et al.*[11] developed an efficient mononitration and subsequent reduction of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP), giving the amine **1**. In a preliminary report,[12] we outlined a method for the generation of electrophilic and nucleophilic TPP derivatives from this weakly nucleophilic amine **1**. Here we describe their efficient coupling to series of lysine- and glutamic acid-containing peptides, some of which are potentially degradable in lysosomes. These modified peptides, carrying the TPP, are functionalised at both N and C termini with methylamino groups to facilitate later polymerisation with α,ω-bis-electrophilic derivatives of poly(ethylene glycol), itself a hydrophilic, non-immunogenic and non-toxic polymer.[13]

Results and discussion

Target design

Fig. 1 shows conceptually the target constructs for this work. All the peptides carry a point of attachment for a porphyrin. The majority incorporate a sequence, GlyPheLeuGly, which has been shown[14] to be degradable by cathepsin **B**, an important lysosomal enzyme. The largest peptide also has a further functionalised amino acid which would permit attachment of tissue-targeting or other bioactive moieties. All the constructs

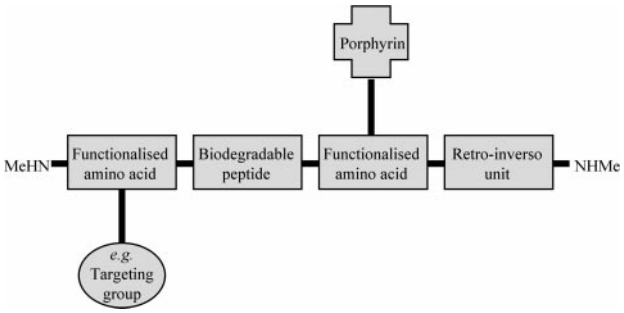

Fig. 1 Diagrammatic representation of the target porphyrin-peptide constructs.

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‡ *Supplementary material available:* spectroscopic data for compounds **2**–**5**, **11**–**20**, **22**, **24**–**31**, **33**, **34**, **37**–**41**, **43**–**48**, **50**–**52**, **54**–**65** and **69**–**79**. For direct electronic access see http://www.rsc.org/suppdata/nj/1999/1087/, otherwise available from BLDSC (No. SUP 57634, 29 pp.) or the RSC Library. See Instructions for Authors, 1999, Issue 1 (http://www.rsc.org/njc).

incorporate a retro-inverso unit ($NHCH_2CH_2NH$) enabling secondary *N*-methylamines (the amino acid sarcosine) to be presented at both N and C termini. This strategy will make both termini equally reactive in future polymerisation reactions with α,ω-bis-electrophiles.

Functionalisation of porphyrins

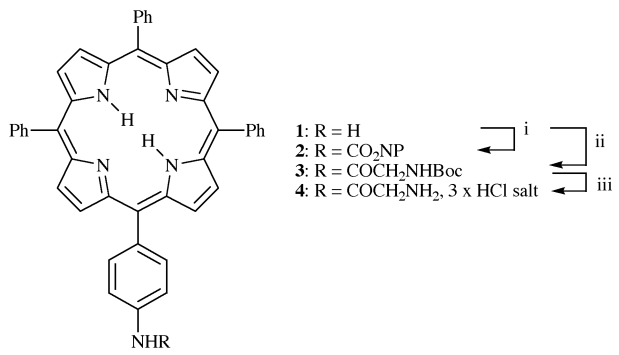
For controlled attachment of the imaging agent to peptides, we required monofunctional nucleophilic and electrophilic derivatives of *meso*-TPP. The monoaminophenylporphyrin **1** was prepared by the method of Kruper *et al.*[11] (Scheme 1). The carbamate **2** is a synthon for the isocyanate derived from **1**, which would represent a potent electrophile for reaction with the ε-amines of Lys derivatives. The amine of **1** was acylated smoothly by 4-nitrophenyl chloroformate, giving **2** as a purple solid which could be isolated, purified and characterised fully before use in coupling reactions.

Synthesis of an appropriate monofunctional nucleophilic derivative of TPP was also addressed. Compound **1** itself proved to be a very weak nucleophile. To prepare a derivative with enhanced nucleophilicity, the amine was acylated by prolonged treatment with excess BocGlyOPFP **6**,[15] giving the amide **3** (Scheme 1). Quantitative deprotection afforded the trihydrochloride salt **4**. The free base of **4**, being an unhindered primary aliphatic amine, was found to be a much more powerful nucleophile than the arylamine of **1**.

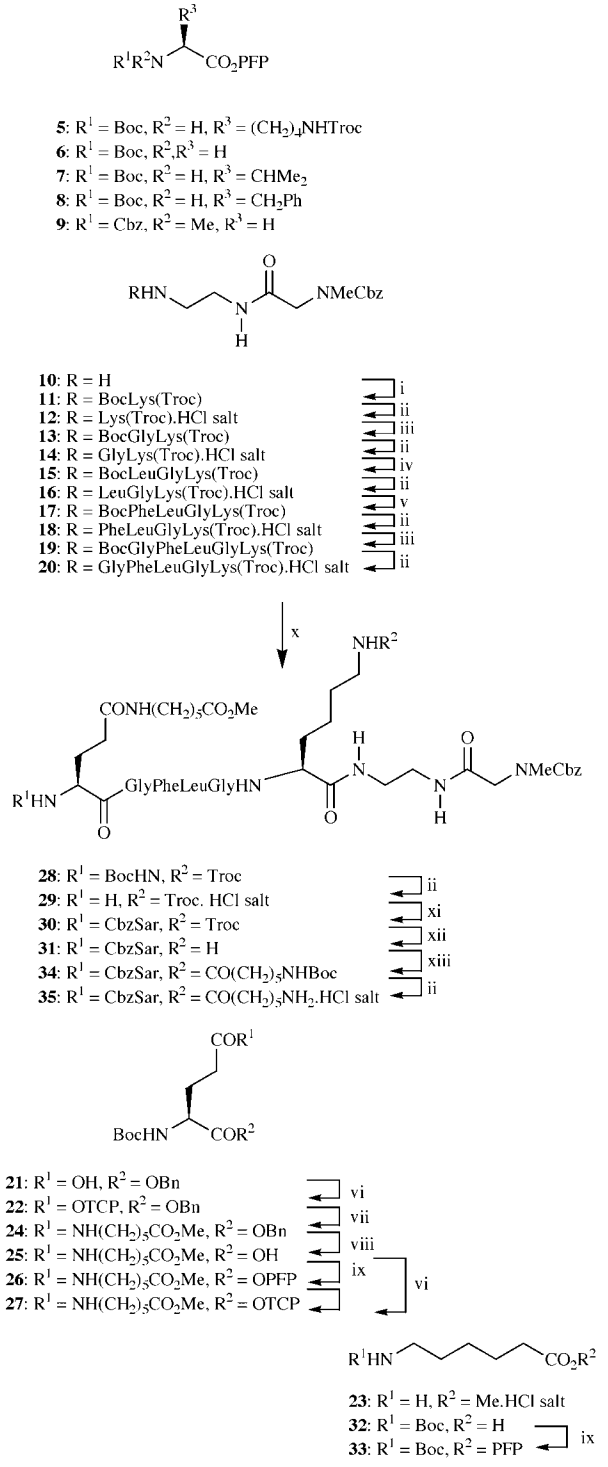
Peptide design and synthesis

In order to attach an imaging agent to the proposed biodegradable polymer, amino acids with additional side-chain functionality must be incorporated into the peptide sequence. In this work, interest has focused on lysine (nucleophilic ε-NH_2) and glutamic acid (electrophilic γ-CO_2H). To illustrate the strategies adopted for the synthesis of peptides incorporating Lys and Glu residues, our approach to the heptapeptides **30** and **35** (Scheme 2) will be presented here. These heptapeptides contain a Lys, a Glu, the cathepsin B-degradable unit and the sequence-inverting unit.

Changes in molar relaxivity (relative to the number of paramagnetic species) have been observed with variation in the length of the linker between the polymer backbone and the chelate for some polymer systems.[5] In heptapeptide **35**, the Lys side-chain has been extended with an aminohexanoyl spacer after assembly of the peptide. In the case of Glu, preliminary experiments showed the necessity of incorporating the side-chain extension prior to construction of the peptide backbone, to avoid formation of pyroglutamates. Thus BocGluOBn **21** was converted to its γ-trichlorophenyl (TCP) ester **22** (Scheme 2) which was coupled with methyl 6-aminohexanoate **23**[16] to introduce the required extended side-chain bearing the methyl ester (**24**). Hydrogenolysis of the benzyl ester exposed the α-carboxylic acid **25** which was transformed into the active esters **26** and **27**, prior to inclusion in the peptide sequence. The extended Glu ester was incorporated near the N terminus so as to be introduced as late as possible, reducing the number of steps in which the poor solubility of compounds containing this residue would cause problems.



Scheme 1 Synthesis of monofunctional electrophilic TPP derivative **2** and monofunctional nucleophilic TPP derivative **4**. NP = 4-nitrophenyl. *Reagents*: i, NPO_2CCl, Pr^i_2NEt, $CHCl_3$; ii, BocGlyOPFP **6**, $CHCl_3$; iii, HCl, $CHCl_3$.



Scheme 2 Synthesis of heptapeptides **30** and **35**, containing the sequence-inverting unit and the biodegradable GlyPheLeuGly motif with electrophilic Glu and nucleophilic Lys side-chains. DCC = N,N′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, PFP = pentafluorophenyl, TCP = 2,4,5-trichlorophenyl. *Reagents*: i, **5**, Pr^i_2NEt, CH_2Cl_2; ii, HCl, CH_2Cl_2; iii, **6**, Pr^i_2NEt, DMAP, CH_2Cl_2; iv, **7**, Pr^i_2NEt, DMAP, CH_2Cl_2; v, **8**, Pr^i_2NEt, DMAP, CH_2Cl_2; vi, TCPOH, DCC, EtOAc; vii, **23**, Pr^i_2NEt, DMAP, CH_2Cl_2; viii, H_2, Pd/C, THF; ix, PFPOH, DCC, EtOAc; x, **26**, Pr^i_2NEt, DMAP, CH_2Cl_2, DMF; xi, **29**, Pr^i_2NEt, DMAP, CH_2Cl_2; xii, Zn, MeOH, H_2O; xiii, **33**, Pr^i_2NEt, DMAP, CH_2Cl_2, DMF.

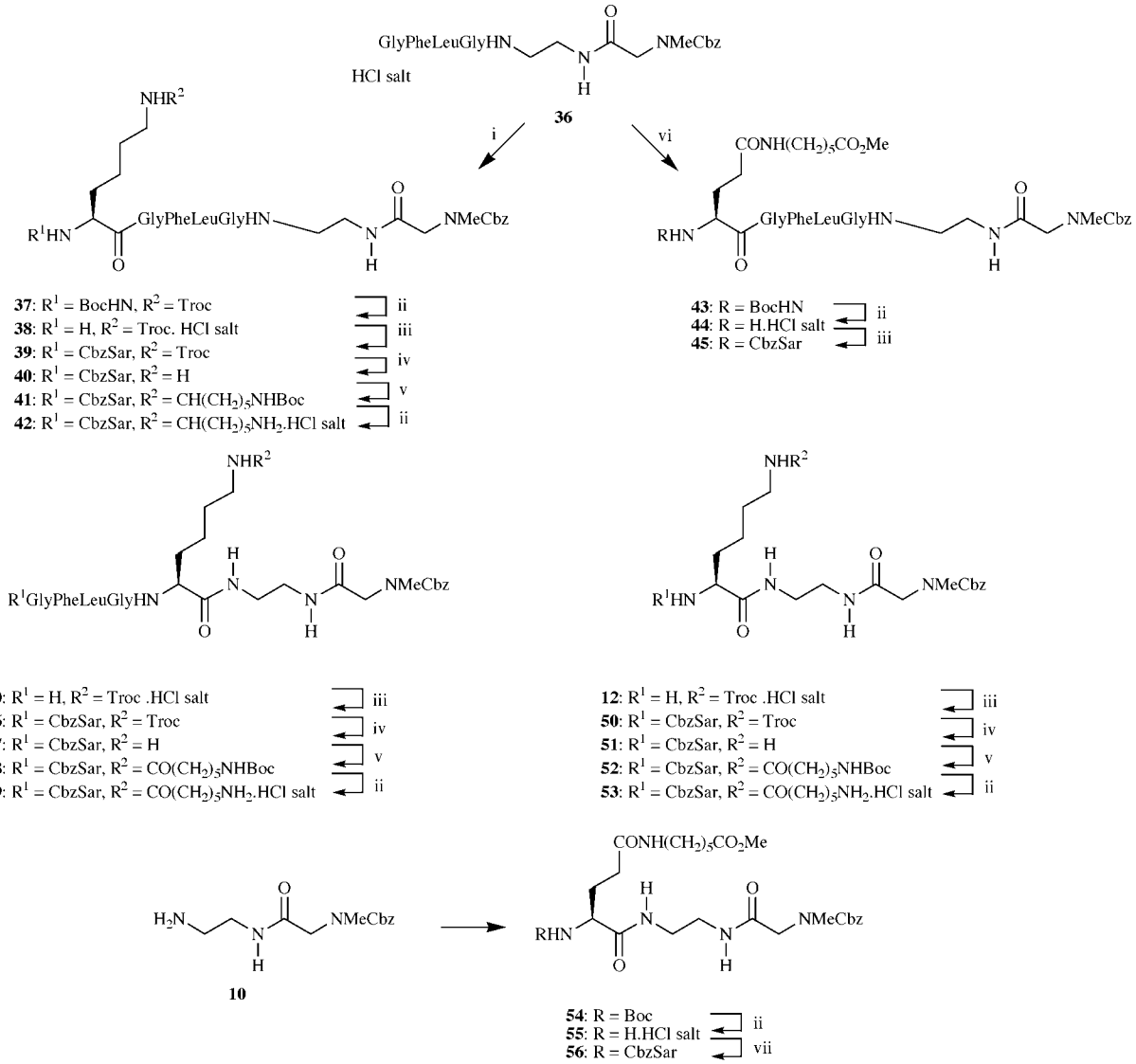
Orthogonal protection of the α- and ε-amines of L-Lys was required for construction of the peptide main chain and extension of the side-chain. BocLys(Troc)OH (prepared essentially by the method of Yajima *et al.*[17]) was activated as the pentafluorophenyl (PFP) ester **5** (Scheme 2). We have described[12] the use of ethane-1,2-diamine as a straightforward sequence-inverting "retro-inverso" unit to present amines at both termini. This was incorporated into the peptide sequence as the $CbzSarNHCH_2CH_2NHR$ unit which also gives the desired (protected) secondary amine at the C terminus. The amino acids were then incorporated in a stepwise manner involving repetitive cycles of acylation and deprotection. For example, BocLys(Troc)OPFP **5** reacted with **10** to give **11** in excellent yield. Treatment with hydrogen chloride removed the N-terminal Boc protection to give the hydrochloride salt **12**. Five similar cycles of acylation and acidolytic deprotection (BocGlyOPFP **6**,[15] BocLeuOPFP **7**,[15] BocPheOPFP **8**,[15] BocGlyOPFP **6**[15] and BocGln((CH_2)$_5CO_2$Me)OPFP **26**) and final acylation with CbzSarOPFP **9**[12] gave the fully protected heptapeptide **30**. This heptapeptide contains the "extended" Glu side-chain ready for attachment of the porphyrin.

The side-chain of the Lys could be extended in length prior to attachment of the porphyrin at this site. The extension retains an ω-primary amine. The Lys-ε-Troc protecting group was removed by reduction with powdered zinc in warm methanol. Removal was usually complete within 1 h, with no evidence of reductive removal of the Cbz protection. The newly exposed ε-amine in **31** was acylated with *N*-Boc-6-aminohexanoic acid **32**[18] (as the PFP ester **33**), affording the heptapeptide **34** with the side-chain of both Glu and Lys extended. Simple treatment with acid revealed the extended Lys ω-primary amine in **35**, ready for reaction with a porphyrin-derived electrophile.

Heptapeptides **30** and **35** contain all the required structural features. Simpler peptides were also prepared by analogous procedures (Scheme 3). These incorporate some but not all of the features shown in Fig. 1. Amongst the Lys peptides, hexapeptides **42** and **49** contain the extended Lys and the GlyPheLeuGly biodegradable units, whereas the shorter peptide **53** contains only the extended Lys. The extension of the Lys side-chains is lacking in hexapeptides **40** and **47**. Of the two simpler extended Glu peptides, hexapeptide **45** contains the GlyPheLeuGly motif but **55** does not.

Attachment of porphyrins to peptide side-chains

The porphyrin nitrophenyl carbamate **2** was designed as an electrophile for reaction with peptides carrying primary amines in the side-chains. Carbamoylation of the ω-NH_2 of the extended Lys in heptapeptide **35** was most efficiently



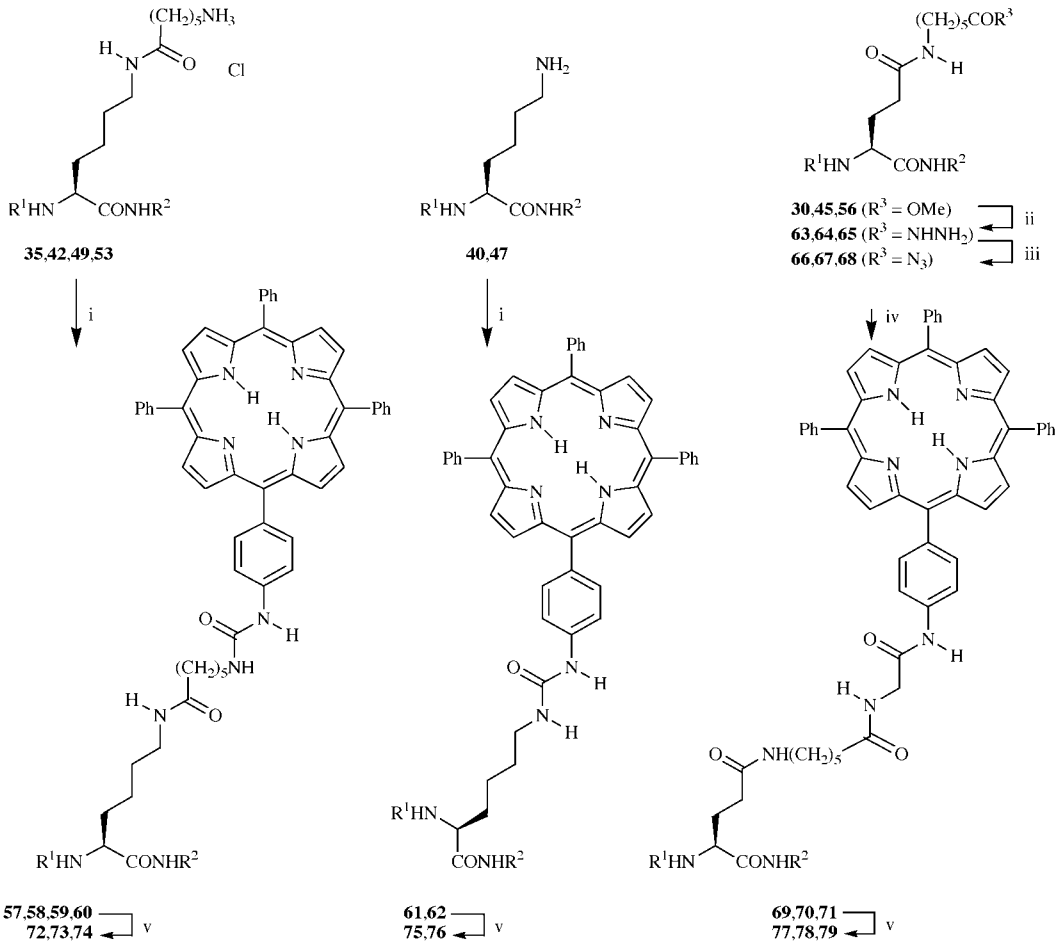
Scheme 3 Synthesis of peptides **42**, **49** and **53** (containing extended Lys side-chains), **40** and **47** (containing non-extended Lys side-chains) and **45** and **56** (containing extended Glu side-chains). DMAP = 4-(dimethylamino)pyridine. *Reagents*: i, **5**, Pr^i_2NEt, DMAP, CH_2Cl_2; ii, HCl, CH_2Cl_2; iii, **9**, Pr^i_2NEt, DMAP, CH_2Cl_2; iv, Zn, MeOH, H_2O; v, **33**, Pr^i_2NEt, DMAP, CH_2Cl_2; vi, **26**, Pr^i_2NEt, DMAP, CH_2Cl_2, DMF; vii, **9**, Pr^i_2NEt, DMAP.

carried out by reaction with 1.6 equivalents of **2** in the presence of a large excess of a tertiary amine base (Scheme 4) to give the urea-linked porphyrin-peptide **57** in good yield. Interestingly, the first step in this reaction may be base-catalysed elimination of 4-nitrophenoxide to form the isocyanate as a reactive intermediate. Similar treatment of the other extended-Lys peptides **42**, **49** and **53** with **2** provided the target porphyrin-peptide derivatives **58–60** in excellent yields. The non-extended Lys ε-amines of peptides **40** and **47** also reacted well with the TPP-derived electrophile **2**, giving **61** and **62** in very high yields (98% and 84%, respectively) after chromatography.

Surprisingly, deprotection of the side-chain methyl esters of the Glu peptides **34**, **45** and **56** proved difficult. Selective hydrolysis failed under the usual basic and acidic conditions. However, the esters were cleaved by treatment with hydrazine in hot methanol, giving the hydrazides **63–65** in very high yields (Scheme 4). In one-pot processes, these were oxidised to the electrophilic acyl azides **66–68** at low temperature and used to acylate the glycylporphyrin **4**, giving the target protected "extended" Glu-linked porphyrin-peptides **69–71** in good yields.

α,ω-Deprotection

The porphyrin-peptides **58–62** and **69–71** were treated with hydrogen bromide to effect deprotection of the N and C terminal Cbz-sarcosines (Scheme 4). The bis(methylamino)-peptide-porphyrin derivatives **72–79** were isolated as their dark green tetrahydrobromide salts. ^{1}H NMR analysis confirmed that the porphyrin ring was present as the diprotonated dicationic structure, in that two broad singlets, each integrating to two protons, were observed between δ −0.60 and δ 0.00, rather than the usual signal for the two equivalent



35,57: R^1 = CbzSarGln((CH$_2$)$_5$CO$_2$Me)GlyPheLeuGly, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
42,58: R^1 = CbzSar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
72: R^1 = Sar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$HMe.4HBr salt
49,59: R^1 = CbzSarGlyPheLeuGly, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
73: R^1 = SarGlyPheLeuGly, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$HMe.4HBr salt
53,60: R^1 = CbzSar, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
74: R^1 = Sar, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$HMe.4HBr salt
40,61: R^1 = CbzSar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
75: R^1 = Sar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$HMe.4HBr salt
47,62: R^1 = CbzSarGlyPheLeuGly, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
76: R^1 = SarGlyPheLeuGly, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$HMe.4HBr salt
30,63,66,69: R^1 = CbzSar, R^2 = GlyPheLeuGlyLys(Troc)HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
77: R^1 = Sar, R^2 = GlyPheLeuGlyLys(Troc)HN(CH$_2$)$_2$HNCOCH$_2$NMe.4HBr salt
45,64,67,70: R^1 = CbzSar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
78: R^1 = Sar, R^2 = GlyPheLeuGlyHN(CH$_2$)$_2$HNCOCH$_2$NMe.4HBr salt
56,65,68,71: R^1 = CbzSar, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMeCbz
79: R^1 = Sar, R^2 = HN(CH$_2$)$_2$HNCOCH$_2$NMe.4HBr salt

Scheme 4 Attachment of porphyrins to peptide Lys and Glu side-chains and α,ω-deprotection of peptides. DMAP = 4-(dimethylamino)pyridine. *Reagents*: i, **2**, Pr$^i_2$NEt, DMAP, $CHCl_3$, DMF; ii, $N_2H_4 \cdot H_2O$, MeOH; iii, HCl, Bu^{t}ONO, 1,4-dioxane, DMF; iv, **4**, $EtNMe_2$, 1,4-dioxane, DMF; v, HBr, HOAc.

central NH protons seen as a singlet between δ −2.5 and δ −3.5 for neutral porphyrins.

Spectroscopic characterisation

The target peptide derivatives **35**, **40**, **42**, **45**, **47**, **49**, **53** and **56**, the protected porphyrin-peptides **57**–**62** and **69**–**71** and the α,ω-deprotected porphyrin-peptides **72**–**79** were characterised by ^{1}H NMR and high resolution fast atom bombardment (FAB) mass spectrometry. As with the analogous peptides omitting Lys and Glu, the ^{1}H NMR spectra of all peptide derivatives containing CbzSar indicated rotamers about the BnO(O=C)–NMeCH$_2$R bond(s). In many cases, COSY spectra were needed for assignment of the ^{1}H NMR spectra of the larger compounds. Stereochemical purity was established *via* ^{1}H NMR by examining the resonances for the β- and γ-protons of the Leu side-chain. In all the peptides which contain the L-Phe-L-Leu sequence, both β-H resonate at higher field than the γ-H or overlap with that signal. For the diastereomeric peptides containing L-Phe-D-Leu,[19] one of the leucine β-H resonates at lower field than the γ-H.

Conclusions

The studies presented in this paper demonstrate that the monoaminotetraphenylporphyrin **1** is a readily accessible monofunctionalised porphyrin which can be converted straightforwardly into a reactive electrophile **2**, for efficient attachment to the ε-NH$_2$ of Lys and analogous extended Lys side-chains in peptides. Similarly, we have developed a method for efficient attachment of *meso*-TPP to Glu residues, using an acyl azide coupling to the highly nucleophilic monofunctional porphyrin, glycylamino-*meso*-TPP **4**. Both the urea and amide linkages are likely to be physiologically robust. All the peptides used in this study have a 'retro-inverso' sequence to present equireactive secondary amines at both termini and some incorporate the lysosomally degradable sequence GlyPheLeuGly. The processes reported here will have general use in controlled attachment of porphyrins to peptides and other compounds.

Experimental

Except where noted, (CD$_3$)$_2$SO was the solvent for NMR spectra, obtained at 20 °C, using JEOL GX270 and EX400 spectrometers. The ^{19}F NMR chemical shifts are referenced to the CF^{35}Cl$_3$ signal, *J* values are given in Hz. Mass spectra were recorded using fast atom bombardment (FAB) in positive ion mode, except where noted, using a VG ZAB-E instrument. Where high resolution MS data are shown for the pseudo-molecular ions (M + H), satisfactory data were also obtained for the isotopomers with other chlorine or carbon isotopes (data not shown). Where high resolution MS data are not shown for peptides, such data could not be obtained owing to formation of ion clusters with the mass standard. Solutions in organic solvents were dried with anhydrous MgSO$_4$. Aqueous H$_2$SO$_4$ and aqueous Na$_2$CO$_3$ refer to 10% solutions. DCC = *N*,*N*′-Dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, PFP = pentafluorophenyl, TCP = 2,4,5-trichlorophenyl, TPP = 4-(10,15,20-triphenyl-21*H*,23*H*-porphin-5-yl)phenyl, Troc = 2,2,2-trichloroethoxycarbonyl. Solvents were evaporated under reduced pressure. The chromatographic stationary phase was silica gel. Products were white or colourless, unless otherwise stated. Compounds synthesised were demonstrated to be pure by TLC in two systems. All chiral amino acids and peptides were L. BocLys(Troc)OH,[17] **6**,[15] **7**,[15] **8**,[15] **9**[20] and **32**[18] were prepared essentially by literature methods. Spectroscopic data for intermediate compounds are given as supplementary material.

Electrophilic TPP derivative

4-Nitrophenyl *N*-(4-(10,15,20-triphenyl-21*H*,23*H*-porphin-5-yl)phenyl)carbamate (2). Pr$^i_2$NEt (867 mg, 6.7 mmol) was stirred with **1**[11,12] (4.15 g, 6.7 mmol) and 4-nitrophenyl chloroformate (1.36 g, 6.7 mmol) in CHCl$_3$ (50 ml) for 20 h. Evaporation and chromatography (EtOAc–hexane, 1 : 3) gave **2** (4.51 g, 86%), purple glass: δ_H (CDCl$_3$) −2.73 (2 H, br, porphyrin 21,23-H$_2$), 7.36 (2 H, d, *J* 9.2, Ar′ 2,6-H$_2$), 7.76 (11 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 3,5-H$_2$), 8.22 (10 H, m, 3 × Ph 2,6-H$_2$ + Ar 2,6-H$_2$ + Ar′ 3,5-H$_2$), 8.84 (8 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$); *m*/*z* 795.2702 (M + H) (C$_{51}$H$_{35}$N$_6$O$_4$ requires 795.2720), 656 (M − HOC$_6$H$_4$NO$_2$).

Nucleophilic TPP derivatives

BocGlyNHTPP (3). BocGlyOPFP **6**[15] (95.6 g, 32.2 mmol) was stirred with **1**[11,12] (5.00 g, 8.2 mmol) in CHCl$_3$ (40 ml) at 40 °C for 46 h. Evaporation and chromatography (CHCl$_3$–EtOAc 10 : 1) gave **3** (6.00 g, 95%), deep purple glass: δ_H (CDCl$_3$) 1.56 (9 H, s, Bu^t), 4.09 (2 H, d, *J* 6, Gly-H$_2$), 5.48 (1 H, br, Gly NH), 7.73 (9 H, m, 3 × Ph 3,4,5-H$_3$), 7.92 (2 H, d, *J* 8.4, Ar-H$_2$), 8.18 (8 H, m, 3 × Ph 2,6-H$_2$ + Ar-H$_2$), 8.83 (s, 6 H, porphyrin 3,7,8,12,13,17-H$_6$), 8.85 (2 H, d, *J* 4.8, porphyrin 2,18-H$_2$); *m*/*z* 787.3371 (M + H) (C$_{51}$H$_{43}$N$_6$O$_3$ requires 787.3397).

GlyNHTPP·3HCl (4). HCl was passed through **3** (2.24 g, 2.9 mmol) in CHCl$_3$ (30 ml) for 1 h. Evaporation gave an emerald green glass (2.27 g, 100%). δ_H 0.34 (2 H, br) and 0.45 (2 H, br) (21,22,2,24-H$_4$), 4.07 (2 H, m, Gly-H$_2$), 7.86–8.84 (31 H, m, 3 × Ph-H$_5$ + Ar-H$_4$ + porphyrin 2,3,7,8,12,13,17,18-H$_8$ + NH + N$^+$H$_3$); *m*/*z* 687.2868 (M + H) (C$_{46}$H$_{35}$N$_6$O requires 687.2872).

Preparation of active esters

The carboxylic acid was stirred with DCC (1.0 equiv.) and either PFPOH or TCPOH (1.0 equiv.) in EtOAc (8 ml per mmol substrate) at 0 °C for 18 h. The solution was filtered and the solvent was evaporated. The following compounds were synthesised by this method: BocLys(Troc)OPFP (**5**), BocGlu(OTCP)OBn (**22**), BocGln((CH$_2$)$_5$CO$_2$Me)OPFP (**26**), BocGln((CH$_2$)$_5$CO$_2$Me)OTCP (**27**), BocNH(CH$_2$)$_5$CO$_2$PFP (**33**). Summary details are given in Table 1.

Formation of peptides and other amides

The active ester and the amine or amine hydrochloride (equimolar) were stirred with Pr$^i_2$NEt (3 equiv.) and DMAP (0.03 equiv.) in CH$_2$Cl$_2$ (10 ml per mmol substrate) for the stated time. The solvent was evaporated. The residue, in EtOAc, washed with aqueous H$_2$SO$_4$, aqueous Na$_2$CO$_3$ and brine and then dried. Evaporation and chromatography (CH$_2$Cl$_2$–MeOH 20 : 1) gave the product. The following compounds were synthesised by this method: BocLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**11**), BocGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**13**), BocLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**15**), BocPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**17**), BocGlyPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**19**), BocGln((CH$_2$)$_5$CO$_2$Me)OBn (**24**), BocGln((CH$_2$)$_5$CO$_2$Me)GlyPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**28**), CbzSarGln((CH$_2$)$_5$CO$_2$Me)GlyPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**30**), CbzSarGln((CH$_2$)$_5$CO$_2$Me)GlyPheLeuGlyLys(CO(CH$_2$)$_5$NHBoc)NH(CH$_2$)$_2$NHCOCH$_2$NMeCbz(**34**),BocLys(Troc)GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**37**), CbzSarLys(Troc)GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**39**), CbzSarLys(CO(CH$_2$)$_5$NHBoc)GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$NMeCbz (**41**), BocGln((CH$_2$)$_5$CO$_2$Me)GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$-

Table 1 Preparation of active esters

Starting carboxylic acid	Product active ester	Yield (%)	Appearance
BocLys(Troc)OH[17]	BocLys(Troc)OPFP (**5**)	91	Colourless oil
21	BocGlu(OTCP)OBn (**22**)	98	White solid: mp 78–80 °C
25	BocGln($(CH_2)_5CO_2Me$)OPFP (**26**)	100	White wax
25	BocGln($(CH_2)_5CO_2Me$)OTCP (**27**)	70[a]	White solid: mp 92–94 °C
32[18]	BocNH$(CH_2)_5CO_2$PFP (**33**)	98	White wax

[a] Product triturated (Et_2O).

NMeCbz (**43**), CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**45**), CbzSarGlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**46**), CbzSarGlyPheLeuGlyLys(CO$(CH_2)_5$NHBoc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**48**), CbzSarLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**50**), CbzSarLys(CO$(CH_2)_5$NHBoc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**52**), BocGln($(CH_2)_5CO_2Me$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**54**), CbzSarGln($(CH_2)_5CO_2Me$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**56**). Summary details are given in Table 2.

Deprotection

Removal of Boc protection. HCl was passed through the substrate in CH_2Cl_2 (10 ml per mmol) for 30 min. The solvent and excess reagent were evaporated. The following compounds were synthesised by this method: Lys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**12**), GlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**14**), LeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**16**), PheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**18**), GlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**20**), Gln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**29**), Lys(Troc)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**38**), Gln($(CH_2)_5CO_2Me$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**44**), Gln($(CH_2)_5CO_2Me$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz · HCl (**55**). Summary details are given in Table 3.

Removal of Bn ester protection. *BocGln($(CH_2)_5CO_2Me$)OH* (*25*). The ester **24** (11.97 g, 25.8 mmol) in THF (150 ml) was treated with H_2 and 10% Pd/C (2.2 g) for 24 h. Filtration (Celite®) and evaporation gave **25** (8.81 g, 91%). Summary details are given in Table 3.

Removal of Troc protection. The peptide was heated at reflux with Zn powder (40 equiv.) in MeOH–H_2O (7 : 3, 6 ml per mmol substrate) for 16 h. The suspension was filtered and the solvent evaporated. The residue, in CH_2Cl_2, was washed with water and brine and was then dried. Evaporation of the solvent yielded the desired product. The following compounds were synthesised by this method: CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLysNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**31**), CbzSarLysGlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**40**), CbzSarGlyPheLeuGlyLysNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**47**), CbzSarLysNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**51**). Summary details are given in Table 3.

Lys-linked porphyrin-peptide constructs

The amine hydrochloride was stirred with **2** (1.6 equiv.), Pr^i_2NEt (5 equiv.) and DMAP (0.05 equiv.) in $CHCl_3$–DMF 3 : 1 (20 ml per mmol substrate) for 2 d. Evaporation and chromatography ($CHCl_3$–MeOH 80 : 1 → 10 : 1) gave the product.

CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLys(CO$(CH_2)_5$NHCONHTPP)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (57). From **35**: 85%, purple glass: δ_H −2.95 (2 H, s, porphyrin 21,23-H_2), 0.78 (3 H, d, *J* 5.9, Leu Me), 0.83 (3 H, d, *J* 5.9, Leu Me), 1.18 (6 H, m, Lys γ-H_2 + 2 × hexanoyl 4-H_2 + hexyl 3-H_2), 1.30 (6 H, m, Lys β-H_2 + hexanoyl 5-H_2 + hexyl 2-H_2), 1.46 (6 H, m, Lys δ-H_2 + hexanoyl 3-H_2 + hexyl 4-H_2), 1.55–1.95 (5 H, m, Leu β,γ-H_3 + Gln β-H_2), 2.04 (4 H, m, Gln γ-H_2 + hexanoyl 2-H_2), 2.21 (2 H, m, hexyl 5-H_2), 2.76–3.18 (18 H, m,

Table 2 Formation of peptides and other amides

Starting active ester	Starting amine	Reaction time	Product	Yield (%)	Appearance
5	**10**[12]	5 h[a]	BocLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**11**)	85	Colourless glass
6[15]	**12**	3 d	BocGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**13**)	91	Colourless glass
7[15]	**14**	16 h	BocLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**15**)	92	Colourless glass
8[15]	**16**	16 h	BocPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**17**)	77	Colourless glass
6[15]	**18**	12 d	BocGlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**19**)	93	Colourless glass
22	**23**[16]	4 d	BocGln($(CH_2)_5CO_2Me$)OBn (**24**)	87	White solid: mp 60–63 °C
26	**20**	4 d[b]	BocGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**28**)	73	Colourless gum
9[12]	**29**	3 d	CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**30**)	40	White solid: mp 181–183 °C
33	**31**	2 d[c]	CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyLys(CO$(CH_2)_5$NHBoc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**34**)	89	Colourless gum
5[d]	**36**[20]	5 d	BocLys(Troc)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**37**)	97	Colourless gum
9[12,d]	**38**	4 d	CbzSarLys(Troc)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**39**)	62	Colourless gum
33	**40**	2 d	CbzSarLys(CO$(CH_2)_5$NHBoc)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**41**)	56	Colourless glass
26	**36**[20]	4 d[b]	BocGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**43**)	85	Colourless gum
9[12,d]	**44**	5 d	CbzSarGln($(CH_2)_5CO_2Me$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**45**)	47	Colourless glass
9[12,d]	**20**	2 d	CbzSarGlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**46**)	81	Colourless glass
33	**47**	2 d[b]	CbzSarGlyPheLeuGlyLys(CO$(CH_2)_5$NHBoc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**48**)	51	Colourless glass
9[12]	**12**	5 h	CbzSarLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**50**)	87	White solid: mp 77–78 °C
33	**51**	2 d	CbzSarLys(CO$(CH_2)_5$NHBoc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**52**)	85	Colourless glass
10[12]	**27**	4 d	BocGln($(CH_2)_5CO_2Me$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**54**)	72[e]	White solid: mp 88–90 °C
9[12,d]	**55**	14 d	CbzSarGln($(CH_2)_5CO_2Me$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**56**)	61	Colourless gum

[a] Pr^i_2NEt (1.1 equiv.), DMAP omitted. [b] CH_2Cl_2–DMF (3 : 1). [c] CH_2Cl_2–DMF (1 : 1). [d] 3 equiv. [e] Chromatography replaced by trituration (Et_2O).

Table 3 Deprotection

Starting material	Protecting group removed	Product	Yield (%)	Appearance
11	Boc	Lys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**12**)	99	Colourless glass
13	Boc	GlyLys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**14**)	98	Colourless gum
15	Boc	LeuGlyLys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**16**)	100	Colourless glass
17	Boc	PheLeuGlyLys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**18**)	100	Colourless glass
19	Boc	GlyPheLeuGlyLys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**20**)	100	Colourless glass
28	Boc[a]	Gln((CH_2)$_5$$CO_2$Me)GlyPheLeuGlyLys(Troc)NH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**29**)	100	Colourless glass
37	Boc	Lys(Troc)GlyPheLeuGlyNH(CH_2)$_2$NHCOCH_2NMeCbz · HCl (**38**)	92	Colourless gum
43	Boc	Gln((CH_2)$_5$$CO_2$Me)GlyPheLeuGlyNH($CH_2$)$_2$NHCO$CH_2$NMeCbz · HCl (**44**)	100	Colourless glass
54	Boc	Gln((CH_2)$_5$$CO_2$Me)NH($CH_2$)$_2$NHCO$CH_2$NMeCbz · HCl (**55**)	99	Colourless glass
24	Bn ester	BocGln((CH_2)$_5$$CO_2$Me)OH (**25**)	91	Colourless gum
30	Troc	CbzSarGln((CH_2)$_5$$CO_2$Me)GlyPheLeuGlyLysNH($CH_2$)$_2$NHCO$CH_2$NMeCbz (**31**)	89	Colourless glass
39	Troc	CbzSarLysGlyPheLeuGlyNH(CH_2)$_2$NHCOCH_2NMeCbz (**40**)	94	Colourless gum
46	Troc	CbzSarGlyPheLeuGlyLysNH(CH_2)$_2$NHCOCH_2NMeCbz (**47**)	95	Colourless gum
50	Troc	CbzSarLysNH(CH_2)$_2$NHCOCH_2NMeCbz (**51**)	97	Colourless glass

[a] CH_2Cl_2–MeOH (2 : 1).

NMe + Phe β-H_2 + Lys ε-H_2 + NCH_2CH_2N + hexanoyl-6-H_2 + hexyl 1-H_2), 3.52 (3 H, s, OMe), 3.59–3.78 (4 H, m, 2 × Gly-H_2), 3.79 (2 H, br, Sar-H_2), 3.84 (2 H, br, Sar-H_2), 4.22 (3 H, m, 3 × α-H), 4.51 (1 H, m, α-H), 4.97 (1 H, s) and 4.99 (2 H, s) and 5.02 (1 H, s) (2 × $PhCH_2O$), 6.35 (1 H, t, *J* 6, NH), 7.28 (15 H, m, 2 × Cbz Ph-H_5 + Phe Ph-H_5), 7.78 (9 H, m, 3 × Ph 3,4,5-H_3), 8.0–8.1 (8 H, m, Ar 2,6-H_2 + 6 × NH), 8.18 (11 H, m, 3 × Ph 2,6-H_2 + Ar 3,5-H_2 + 3 × NH), 8.75–8.95 (8 H, m, porphyrin 2,3,7,8,12,13,17,18-H_8); *m/z* 2001/2000/1999/1998 ($^{13}C/^{12}C$ isotope cluster for M + H).

CbzSarLys(CO(CH_2)$_5$NHCONHTPP)GlyPheLeuGlyNH(CH_2)$_2$NHCOCH_2NMeCbz (58). From **42**, 64%, purple glass: δ_H −2.90 (2 H, s, porphyrin 21,23-H_2), 0.82 (3 H, d, *J* 6.2, Leu Me), 0.87 (3 H, d, *J* 6.2, Leu Me), 1.2–1.6 (15 H, m, Lys β,γ,δ-H_6 + hexanoyl 3,4,5-H_6 + Leu β,γ-H_3), 2.10 (2 H, m, hexanoyl 2-H_2), 2.78 (1 H, m, Phe β-H), 2.85 (3 H, s, NMe) and 2.87 (3 H, NMe), 3.12 (9 H, m, hexanoyl 2-H_6 + NCH_2CH_2N + Lys ε-H_2 + Phe β-H), 3.55–3.78 (4 H, m, 2 × Gly-H_2), 3.82 (2 H, br, Sar-H_2), 3.91 (2 H, br, Sar-H_2), 4.24 (2 H, m, 2 × α-H), 4.55 (1 H, m, α-H), 5.01 (2 H, s) and 5.05 (2 H, s) (2 × $PhCH_2O$), 7.29 (15 H, m, 2 × Cbz Ph-H_5 + Phe Ph-H_5), 7.82 (11 H, m, 3 × Ph 3,4,5-H_3 + Ar 2,6-H_2), 8.06 (2 H, d, *J* 8.4, Ar 3,5-H_2), 8.25 (11 H, m, 3 × Ph 2,6-H_2 + 5 × NH), 8.80–9.00 (11 H, m, porphyrin 2,3,7,8,12,13,17,18-H_8 + 3 × NH); *m/z* 1741.8368 (M + H) ($C_{100}H_{109}N_{16}O_{13}$ requires 1741.8360).

CbzSarGlyPheLeuGlyLys(CO(CH_2)$_5$NHCONHTPP)NH(CH_2)$_2$NHCOCH_2NMeCbz (59). From **49**, 80%, purple glass: δ_H −2.91 (2 H, s, porphyrin 21,23-H_2), 0.83 (3 H, d, *J* 6.2, Leu Me), 0.86 (3 H, d, *J* 6.2, Leu Me), 1.35–1.60 (13 H, m, Lys β,γ-H_4 + hexanoyl 3,4,5-H_6 + Leu β,γ-H_3), 2.10 (2 H, m, hexanoyl 2-H_2), 2.80 (1 H, m, Phe β-H), 2.82 (1.5 H, s) and 2.85 (3 H, s) and 2.87 (1.5 H, s) (2 × NMe), 3.00–3.10 (9 H, m, Lys ε-H_2 + hexanoyl 6-H_2 + NCH_2CH_2N + Phe β-H), 3.55–3.75 (4 H, m, 2 × Gly-H_2), 3.83 (2 H, br, Sar-H_2), 3.87 (2 H, br, Sar-H_2), 4.18 (1 H, m, α-H), 4.22 (1 H, m, α-H), 4.59 (1 H, m, α-H), 5.00 (1 H, s) and 5.02 (2 H, br) and 5.05 (1 H, s) (2 × $PhCH_2O$), 6.36 (1 H, t, *J* 6, NH), 7.28 (15 H, m, 2 × Cbz Ph-H_5 + Phe Ph-H_5), 7.83 (11 H, m, 3 × Ph 3,4,5-H_3 + Ar 2,6-H_2), 7.96–8.24 (11 H, m, 3 × Ph 2,6-H_2 + Ar 3,5-H_2 + 5 × NH), 8.75–9.0 (11 H, m, porphyrin 2,3,7,8,12,13,17,18-H_8 + 3 × NH): *m/z* 1741.8386 (M + H) ($C_{100}H_{109}N_{16}O_{13}$ requires 1471.8360).

CbzSarLys(CO(CH_2)$_5$NHCONHTPP)NH(CH_2)$_2$NHCOCH_2NMeCbz (60). HCl was passed through **52** in CH_2Cl_2–MeOH 4 : 1 for 30 min. Evaporation gave crude **53**. From **53**: $CHCl_3$–DMF 3 : 1: 82%, purple glass: δ_H ($CDCl_3$) −2.78 (2 H, s, porphyrin 21,23-H_2), 1.2–1.7 (12 H, m, Lys β,γ, δ-H_6 + hexanoyl 3,4,5-H_6), 2.12 (2 H, br, hexanoyl 2-H_2), 2.93 (3 H, s, NMe), 2.99 (3 H, s, NMe), 3.0–3.3 (8 H, m, Lys ε-H_2 + hexanoyl 6-H_2 + NCH_2CH_2N), 3.77 (2 H, m, Sar-H_2), 3.86 (2 H, m, Sar-H_2), 4.36 (1 H, m, Lys α-H), 5.06 (3 H, s) and 5.07 (1 H, s) (2 × $PhCH_2O$), 5.75 (1 H, br, NH), 5.83 (1 H, br, NH), 6.39 (1 H, br, NH), 6.57 (1 H, br, NH), 6.94 (1 H, br, NH), 7.24 (10 H, brs, 2 × Ph-H_5), 7.37 (1 H, br, NH), 7.69 (11 H, m, 3 × Ph 3,4,5-H_3 + Ar 2,6-H_2), 8.06 (2 H, d, *J* 8.4, Ar 3,5-H_2), 8.15 (6 H, m, 3 × Ph 2,6-H_2), 8.79 (2 H, d, *J* 4.9, porphyrin 3,7-H_2), 8.82 (4 H, s, porphyrin 12,13,17,18-H_4), 8.87 (2 H, d, *J* 4.9, porphyrin 2,8-H_2); *m/z* 1367.6384 (M + H) ($C_{81}H_{83}N_{12}O_9$ requires 1367.6406).

CbzSarLys(CONHTPP)GlyPheLeuGlyNH(CH_2)$_2$NHCOCH_2NMeCbz (61). From **40**: 98%, purple glass: δ_H −2.90 (2 H, s, porphyrin 21,23-H_2), 0.83 (3 H, d, *J* 6.3, Leu Me), 0.88 (3 H, d, *J* 6.3, Leu Me), 1.2–1.8 (9 H, m, Lys β,γ,δ-H_6 + Leu β,γ-H_3), 2.79 (1 H, m, Phe β-H), 2.82 (1.5 H, s) and 2.86 (3 H, br) and 2.89 (1.5 H, s) (2 × NMe), 3.16 (7 H, br, NCH_2CH_2N + Lys ε-H_2 + Phe β-H), 3.68 (4 H, m, 2 × Gly-H_2), 3.82 (2 H, br, Sar-H_2), 3.98 (2 H, br, Sar-H_2), 4.32 (2 H, m, 2 × α-H), 4.59 (1 H, m, α-H), 5.00 (1 H, s) and 5.04 (3 H, s) (2 × $PhCH_2O$), 6.35 (1 H, br, NH), 7.29 (15 H, m, 2 × Cbz Ph-H_5 + Phe Ph-H_5), 7.69 (11 H, m, 3 × Ph 3,4,5-H_3 + Ar 2,6-H_2), 8.07 (2 H, d, *J* 8.2, Ar 3,5-H_2), 8.19 (11 H, m, 3 × Ph 2,6-H_2 + 5 × NH), 8.75–9.00 (11 H, m, porphyrin 2,3,7,8,12,13,17,18-H_8 + 3 × NH); *m/z* 1628.7559 (M + H) ($C_{94}H_{98}N_{15}O_{12}$ requires 1628.7519).

CbzSarGlyPheLeuGlyLys(CONHTPP)NH(CH_2)$_2$NHCOCH_2NMeCbz (62). From **47**: 84%, purple glass: δ_H −2.90 (2 H, s, porphyrin 21,23-H_2), 0.84 (3 H, d, *J* 6.3, Leu Me), 0.88 (3 H, d, *J* 6.3, Leu Me), 1.18–1.80 (9 H, m, Lys β,γ,δ-H_6 + Leu β,γ-H_3), 2.72 (1 H, m, Phe β-H), 2.83 (1.5 H, s) and 2.86 (1.5 H, s) and 2.87 (1.5 H, s) and 2.90 (1.5 H, s) (2 × NMe), 3.16 (7 H, m, NCH_2CH_2N + Phe β-H + Lys ε-H_2), 3.55–3.72 (4 H, m, 2 × Gly-H_2), 3.86 (2 H, s, Sar-H_2), 3.87 (2 H, br, Sar-H_2), 4.25 (2 H, m, 2 × α-H), 4.58 (1 H, m, α-H), 5.00 (1 H, s) and 5.04 (br, 2 H) and 5.06 (1 H, s)(2 × $PhCH_2O$), 6.36 (1 H, t, *J* 6, NH), 7.28 (15 H, m,2 × Cbz Ph-H_5 + Phe Ph-H_5), 7.84 (11 H, m, 3 × Ph 3,4,5-H_3 + Ar 2,6-H_2), 7.95–8.25 (11 H, m, 3 × Ph 2,6-H_2 + Ar 3,5-H_2 + 5 × NH), 8.8–9.0 (11 H, m, porphyrin 2,3,7,8,12,13,17,18-H_8 + 3 × NH); *m/z* 1628.7521 (M + H) ($C_{94}H_{98}N_{15}O_{12}$ requires 1628.7519).

Glu-linked porphyrin-peptide constructs

Hydrazide formation. The ester was stirred with $N_2H_4 \cdot H_2O$ (10 equiv.) in MeOH (7 ml per mmol substrate) at 40 °C for 2 d. The solvent and excess reagent were evaporated to yield the hydrazide. The following compounds were synthesised by this method: CbzSarGln((CH_2)$_5$$CONHNH_2$)Gly-

PheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**63**), CbzSarGln($(CH_2)_5$CONHNH$_2$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**64**), CbzSarGln($(CH_2)_5$CONHNH$_2$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**65**). Summary details are given in Table 4.

Acyl azides and formation of Glu-linked porphyrin-peptide constructs. HCl in 1,4-dioxane (4.0 M, 3.5 equiv.) was added to the hydrazide (1.50 g, 2.1 mmol) in DMF (1.5 ml per mmol hydrazide). The solution was taken to −20 °C and Bu^{t}ONO (0.1 ml per mmol hydrazide) was added. The solution was stirred for 3 h and taken to −60 °C. EtNMe$_2$ (4 equiv.) was added and the solution was warmed to −30 °C. EtNMe$_2$ (4 equiv.) and **4** (1.4 equiv.) were added. The solution was stirred for 24 h at 20 °C. Evaporation and chromatography (CH_2Cl_2–MeOH 20 : 1) gave the product.

CbzSarGln($(CH_2)_5$COGlyNHTPP)GlyPheLeuGlyLys(Troc)-NH$(CH_2)_2$NHCOCH$_2$NMeCbz (***69***). From **63**: 83%, purple glass: δ_H −2.94 (2 H, s, porphyrin 21,23-H$_2$), 0.83 (3 H, d, *J* 7.3, Leu Me), 0.88 (3 H, br, Leu Me), 1.18 (6 H, m, Lys γ-H$_2$ + hexyl 3-H$_2$), 1.37 (6 H, m, Lys β-H$_2$ + hexyl 2-H$_2$), 1.49 (4 H, m, Lys δ-H$_2$ + hexyl 4-H$_2$), 1.50–1.90 (7 H, m, Leu β,γ-H$_3$ + Gln β,γ-H$_4$), 2.05 (2 H, m, hexyl 5-H$_2$), 2.76–2.91 (8 H, m, Phe β-H$_2$ + 2 × NMe), 3.08 (4 H, m, hexyl 1-H$_2$ + Lys ε-H$_2$), 3.10 (4 H, br, NCH$_2$CH$_2$N), 3.69 (4 H, m, 2 × Gly-H$_2$), 3.81 (2 H, br, Sar-H$_2$), 3.89 (2 H, br, Sar-H$_2$), 4.18 (3 H, m, 3 × α-H), 4.50 (1 H, m, α-H), 4.74 (2 H, s, CH$_2$CCl$_3$), 5.01 (2 H, br, PhCH$_2$O), 5.05 (2 H, br, PhCH$_2$O), 7.30 (15 H, m, 2 × Cbz Ph-H$_5$ + Phe Ph-H$_5$), 7.70–7.76 (11 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 2,6-H$_2$), 7.96 (2 H, m, 2 × NH), 8.12 (2 H, d, *J* 8.2, Ar 3,5-H$_2$), 8.17–8.23 (12 H, m, 6 × NH + 3 × Ph 2,6-H$_2$), 8.84 (12 H, br, 4 × NH + porphyrin 2,3,7,8,12,13,17,18-H$_8$); *m/z* 2063/2062/2061/2060/2059/2058 ($^{13}C/^{12}C$ $^{37}Cl/^{35}Cl$ isotope cluster for M + H).

CbzSarGln($(CH_2)_5$COGlyNHTPP)GlyPheLeuGlyNH$(CH_2)_2$-NHCOCH$_2$NMeCbz (***70***). From **64**: 83%, purple glass: δ_H −2.95 (2 H, s, porphyrin 21,23-H$_2$), 0.79 (3 H, d, *J* 6.3, Leu Me), 0.84 (3 H, d, *J* 6.3, Leu Me), 1.2–1.6 (6 H, m, hexyl 2,3,4-H$_6$), 1.65–1.90 (5 H, m, Leu β,γ-H$_3$ + Gln β-H$_2$), 2.06 (2 H, m, Gln γ-H$_2$), 2.20 (2 H, m, hexyl 5-H$_2$), 2.75 (1 H, m, Phe β-H), 2.81 (1.5 H, s) and 2.83 (1.5 H, s) and 2.87 (1.5 H, s) and 2.89 (1.5 H, s) (2 × NMe), 2.98 (3 H, m, Phe β-H + hexyl 1-H$_2$), 3.09 (4 H, br, NCH$_2$CH$_2$N), 3.55–3.78 (6 H, m, 3 × Gly-H$_2$), 3.80 (2 H, m, Sar-H$_2$), 3.88 (2 H, m, Sar-H$_2$), 4.01 (1 H, α-H), 4.22 (1 H, m, α-H), 4.50 (1 H, m, α-H), 4.98 (1 H, s) and 5.02 (2 H, s) and 5.04 (1 H, s) (2 × PhCH$_2$O), 7.28 (15 H, m, 2 × Cbz Ph-H$_5$ + Phe Ph-H$_5$), 7.82 (9 H, m, 3 × Ph 3,4,5-H$_3$), 8.02 (2 H, d, *J* 8.6, Ar-H$_2$), 8.14 (2 H, d, *J* 8.6, Ar-H$_2$), 8.18–8.22 (6 H, m, 3 × Ph 2,6-H$_2$), 8.80 (br, 8 H, porphyrin 2,3,7,8,12,13,17,18-H$_8$); *m/z* 1755.8201 (M + H) ($C_{100}H_{107}N_{16}O_{14}$ requires 1755.8153).

CbzSarGln($(CH_2)_5$COGlyNHTPP)NH$(CH_2)_2$NHCOCH$_2$-NMeCbz (***71***). From **65**: 76%, deep purple glass: δ_H ($CDCl_3$) −2.75 (2 H, s, porphyrin 21,23-H$_2$), 0.89 (2 H, m, hexyl 3-H$_2$), 1.25–1.65 (6 H, m, hexyl 2,4-H$_4$ + Gln β-H$_2$), 1.9–2.4 (4 H, Gln γ-H$_2$ + hexyl 5-H$_2$), 3.0–3.1 (8 H, m, hexyl 1-H$_2$ + 2 × NMe), 3.35 (4 H, br, NCH$_2$CH$_2$N), 3.85–4.05 (4 H, m, 2 × Sar-H$_2$), 4.15–4.25 (2 H, m, Gly-H$_2$), 4.42 (1 H, m, Gln α-H), 5.13 (4 H, br, 2 × PhCH$_2$O), 7.25–7.33 (14 H, m, 4 × NH + 2 × Cbz Ph-H$_5$), 7.70–7.76 (1 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 2,6-H$_2$), 7.96 (2 H, m, 2 × NH), 8.12 (2 H, d, *J* 8.2, Ar 3,5-H$_2$), 8.17–8.23 (6 H, m, 3 × Ph 2,6-H$_2$), 8.84 (8 H, br, porphyrin 2,3,7,8,12,13,17,18-H$_8$); *m/z* 1381.6184 (M + H) ($C_{81}H_{81}N_{12}O_{10}$ requires 1381.6199).

Removal of α,ω-Cbz protection

The substrate was stirred with HBr in AcOH (35%, 30 ml per mmol substrate) for 45 min. Et$_2$O (100 ml per mmol substrate) was added and the mixture was stirred for 5 min. The Et$_2$O was decanted off. The precipitated solid was washed with six further portions of Et$_2$O by this method and then dried.

SarLys(CO$(CH_2)_5$NHCONHTPP)GlyPheLeuGlyNH-$(CH_2)_2$NHCOCH$_2$NHMeCbz·4HBr (72). From **58**: 100%, dark green glass: δ_H −0.52 (2 H, br s) and −0.30 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.82–0.95 (8 H, m, 2 × Leu Me + Lys δ-H$_2$), 1.30–1.45 (6 H, m, hexanoyl 4,5-H$_4$ + Lys β-H$_2$), 1.50–1.80 (7 H, m, hexanoyl 3-H$_2$ + Leu β,γ-H$_3$ + Lys γ-H$_2$), 2.13 (2 H, t, *J* 6.9, hexanoyl 2-H$_2$), 2.67 (6 H, m, 2 × NMe), 2.90 (1 H, m, Phe β-H), 3.08 (2 H, m, hexanoyl 6-H$_2$), 3.15–3.25 (6 H, m, Lys ε-H$_2$ + NCH$_2$CH$_2$N), 3.39 (1 H, m, Phe β-H), 3.60 (2 H, m, Gly-H$_2$), 3.70–3.85 (6 H, m, Gly′-H$_2$ + Sar-H$_2$ + Sar′-H$_2$), 4.10 (1 H, m, Phe α-H), 4.25 (1 H, m, Leu α-H), 4.59 (1 H, m, Lys α-H), 6.79 (1 H, br, Lys ε-NH), 7.23–7.36 (7 H, m, Phe Ph-H$_5$ + Ar 2,6-H$_2$), 7.85–7.95 (2 H, m, hexanoyl NH + Leu NH), 8.05–8.20 (13 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 3,5-H$_2$ + Gly NH + Phe NH), 8.43 (1 H, br, Gly′-NH), 8.55–8.85 (21 H, m, 3 × Ph 2,6-H$_2$ + porphyrin 2,3,7,8,12,13,17,18-H$_8$ + *H*NCH$_2$CH$_2$N*H* + Lys α-NH + 2 × N$^+$H$_2$), 9.70 (1 H, br, Ar-NH); *m/z* 1474 (M + H), 1402 (M − Sar), 1361 (M − SarNH$(CH_2)_2$NH), 1303 (M − GlyNH$(CH_2)_2$-NHCOCH$_2$NHMe), 1043 (M − PheLeuGlyNH$(CH_2)_2$-NHCOCH$_2$NHMe), 986 (M − GlyPheLeuGlyNH$(CH_2)_2$-NHCOCH$_2$NHMe), 656 (TPPNCO + H).

SarGlyPheLeuGlyLys(CO$(CH_2)_5$NHCONHTPP)NH-$(CH_2)_2$NHCOCH$_2$NHMeCbz·4HBr (73). From **59**: 100%, dark green glass: δ_H −0.55 (2 H, br s) and −0.38 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.84–0.92 (8 H, m, 2 × Leu Me + Lys δ-H$_2$), 1.32 (2 H, m, hexanoyl 4-H$_2$), 1.40 (4 H, m, Lys β-H$_2$ + hexanoyl 5-H$_2$), 1.50 (2 H, qn, *J* 7.5, hexanoyl 3-H$_2$), 1.57 (3 H, m, Leu β-H + Lys γ-H$_2$), 1.68 (1 H, m, Leu γ-H), 1.73 (1 H, m, Leu β-H), 2.15 (2 H, t, *J* 7.0, hexanoyl 2-H$_2$), 2.59 (3 H, t, *J* 4.5, NMe), 2.61 (3 H, t, *J* 5.0, NMe), 2.94 (1 H, dd, *J* 14, 7, Phe β-H), 3.16 (2 H, m, hexanoyl 6-H$_2$), 3.19 (1 H, m, Phe β-H), 3.23 (6 H, s + m, Lys ε-H$_2$ + NCH$_2$CH$_2$N), 3.72 (2 H, m, Gly-H$_2$), 3.77 (4 H, m, Gly′-H$_2$ + Sar-H$_2$), 3.85 (1 H, t, *J* 5.8) and 3.86 (1 H, t, *J* 6.2) (Sar′-H$_2$), 4.10 (1 H, m, Phe α-H), 4.20 (1 H, m, Leu α-H), 4.40 (1 H, m, Lys α-H), 6.79 (1 H, br, Lys ε-NH), 7.23–7.36 (7 H, m, Phe Ph-H$_5$ + Ar 2,6-H$_2$), 7.92 (2 H, m, hexanoyl NH + Leu NH), 8.05–8.17 (13 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 3,5-H$_2$ + Gly NH + Phe NH), 8.37 (1 H, t, *J* 5.8, Gly′-NH), 8.20–8.26 (6 H, m, 3 × Ph 2,6-H$_2$), 8.60–8.85 (15 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + *H*NCH$_2$CH$_2$N*H* + Lys α-NH + 2 × N$^+$H$_2$), 9.70 (1 H, br, Ar-NH); *m/z* 1402 (M − Sar), 1371 (M − Sar − MeNH$_2$); *m/z* (electrospray) 1028 (M − SarGlyPheLeuGly), 599.5 (M − SarGlyPhe)$^{2+}$, 673 (M − SarGly)$^{2+}$, 630

Table 4 Glu hydrazides

Starting material	Reaction temperature/°C	Product	Yield (%)	Appearance
30	55	CbzSarGln($(CH_2)_5$CONHNH$_2$)GlyPheLeuGlyLys(Troc)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**63**)	100	White solid: mp 187–189 °C
45	40	CbzSarGln($(CH_2)_5$CONHNH$_2$)GlyPheLeuGlyNH$(CH_2)_2$NHCOCH$_2$NMeCbz (**64**)	100	Colourless gum
56	40	CbzSarGln($(CH_2)_5$CONHNH$_2$)NH$(CH_2)_2$NHCOCH$_2$NMeCbz (**65**)	100	White solid: mp 140–143 °C

(TPPNH$_2$ + H), 543 (M − SarGlyPheLeu)$^{2+}$, 514.5 (M − SarGlyPheLeuGly)$^{2+}$.

SarLys(CO(CH$_2$)$_5$NHCONHTPP)NH(CH$_2$)$_2$NHCOCH$_2$-NHMe·4HBr (74). From **60**: 97%, dark green solid: mp > 300 °C: λ_{max} (MeOH + 1 drop Pr$^i_2$NEt) 406, 512, 549, 590, 645 nm; δ_H − 0.60 (2 H, br s) and − 0.38 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 1.2–1.7 (10 H, m, hexanoyl 3,4,5-H$_6$ + Lys β,γ-H$_4$), 2.13 (2 H, t, *J* 7.3, hexanoyl 2-H$_2$), 2.57 (6 H, t, *J* 5.2, 2 × NMe), 3.04 (2 H, q, *J* 6, Lys ε-H$_2$), 3.10–3.25 (6 H, m, NCH$_2$CH$_2$N + hexanoyl 6-H$_2$), 3.70 (2 H, t, *J* 5.6, Sar-H$_2$), 3.78 (2 H, t, *J* 5.5, Sar-H$_2$), 4.25 (1 H, dt, *J* 8.3, 4.9, Lys α-H), 6.73 (1 H, br, NH), 7.89 (2 H, m, 2 × NH), 8.05–8.25 (m, 19 H, 3 × Ph-H$_5$ + Ar-H$_4$), 8.54 (t, *J* 6, 1 H, NH), 8.6–8.8 (m, 14 H, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + 2 × N$^+$H$_2$ + 2 × NH), 9.58 (br, 1 H, NH); *m/z* 1099.5710 (100%) (M + H) (^{12}C$_{65}$H$_{71}$N$_{12}$O$_5$ requires 1099.5670), 550 (M + 2 H)$^{2+}$.

SarLys(CONHTPP)GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$-NHMeCbz·4HBr (75). From **61**: 100%, dark green glass: δ_H − 0.60 (2 H, br s) and − 0.40 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.83–0.93 (8 H, m, 2 × Leu Me + Lys δ-H$_2$), 1.45–1.60 (5 H, m, Lys β,γ-H$_4$ + Leu β-H), 1.64 (1 H, m, Leu γ-H), 1.75 (1 H, m, Leu β-H), 2.58 (6 H, m, 2 × NMe), 2.91 (1 H, m, Phe β-H), 3.09 (1 H, m, Phe β-H), 3.18 (2 H, m, Lys ε-H$_2$), 3.21 (4 H, br, NCH$_2$CH$_2$N), 3.40 (1 H, m, Sar-H), 3.56 (1 H, m, Sar-H), 3.70–3.90 (6 H, m, Gly-H$_2$ + Gly′-H$_2$ + Sar′-H$_2$), 4.10 (1 H, m, Phe α-H), 4.30 (1 H, m, Leu α-H), 4.43 (1 H, m, Lys α-H), 6.50 (1 H, br, Leu NH), 7.20–7.35 (7 H, m, Ar 2,6-H$_2$ + Phe Ph-H$_5$), 7.8–8.2 (21 H, m, 3 × Ph-H$_5$ + Ar 3,5-H$_2$ + Gly NH + Gly′ NH + Phe NH + Lys ε-NH), 8.60–8.85 (15 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + *H*NCH$_2$CH$_2$N*H* + Lys α-NH + 2 × N$^+$H$_2$), 9.60 (1 H, br, Ar-NH); *m/z* 1382 (M + Na), 1360 (M + H), 1247 (M − NH(CH$_2$)$_2$ NHCOCH$_2$-NHMe), 1189 (M − GlyNH(CH$_2$)$_2$ NHCOCH$_2$NHMe), 1077 (M − LeuGlyNHCH$_2$CH$_2$NHCOCH$_2$NHMe), 930 (M − PheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$NHMe), 873 (M − GlyPheLeuGlyNH(CH$_2$)$_2$NHCOCH$_2$NHMe), 656 (TPPNCO + H), 630 (TPPNH$_2$ + H).

SarGlyPheLeuGlyLys(CONHTPP)NH(CH$_2$)$_2$NHCOCH$_2$-NHMeCbz·4HBr (76). From **62**: 100%, dark green glass: δ_H − 0.55 (2 H, br s) and − 0.35 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.82–0.93 (8 H, m, 2 × Leu Me + Lys δ-H$_2$), 1.45 (2 H, m, Lys β-H$_2$), 1.57 (3 H, m, Leu β-H + Lys γ-H$_2$), 1.66 (1 H, m, Leu γ-H), 1.84 (1 H, m, Leu β-H), 2.59 (3 H, t, *J* 5, NMe), 2.61 (3 H, t, *J* 4.9, NMe), 2.92 (1 H, dd, *J* 14.3, 7.3, Phe β-H), 2.94 (2 H, m, Lys ε-H$_2$), 3.10 (1 H, br d, *J* 14, Phe β-H), 3.25 (4 H, m, NCH$_2$CH$_2$N), 3.67–3.77 (6 H, m, Gly-H$_2$ + Gly′-H$_2$ + Sar-H$_2$), 3.86 (2 H, br s, Sar′-H$_2$), 4.11 (1 H, m, Phe α-H), 4.28 (1 H, m, Leu α-H), 4.42 (1 H, m, Lys α-H), 7.13 (2 H, d, *J* 8.7, Ar 2,6-H$_2$), 7.26–7.36 (5 H, m, Phe Ph-H$_5$), 7.95 (2 H, m, Gly NH + Phe NH), 8.05–8.19 (13 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 3,5-H$_2$ + Leu NH + Lys ε-NH), 8.20–8.26 (7 H, m, 3 × Ph 2,6-H$_2$ + Gly′ NH), 8.60–8.85 (15 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + *H*NCH$_2$CH$_2$N*H* + Lys α-NH + 2 × N$^+$H$_2$), 9.70 (1 H, br, Ar-NH); *m/z* 1289 (M + H − Sar), 1247 (M − NH(CH$_2$)$_2$CONHCH$_2$NHMe), 1232 (M − SarGly), 972 (M − SarGlyPheLeu), 941 (M − SarGlyPheLeu-NHCH$_2$), 915 (M − SarGlyPheLeuGly).

SarGln((CH$_2$)$_5$COGlyNHTPP)GlyPheLeuGlyLys(Troc)-NH(CH$_2$)$_2$NHCOCH$_2$NHMe·4HBr (77). From **69**: 100%, dark green glass: δ_H − 0.55 (2 H, br s) and − 0.45 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.85–0.95 (6 H, m, 2 × Leu Me), 1.21 (4 H, m, hexyl 3-H$_2$ + Lys γ-H$_2$), 1.35 (4 H, m, hexyl 2-H$_2$ + Lys δ-H$_2$), 1.50 (5 H, m, hexyl 4-H$_2$ + Lys β-H$_2$ + Leu β-H), 1.58 (1 H, Leu β,γ-H$_2$), 1.80 (1 H, m, Gln β-H), 1.99 (1 H, m, Gln β-H), 2.12 (2 H, t, *J* 7.3, hexyl 5-H$_2$), 2.18 (2 H, m, Gln γ-H$_2$), 2.58 (3 H, t, *J* 5, NMe), 2.59 (3 H, t, *J* 5, NMe), 2.76 (1 H, m, Phe β-H), 2.92 (1 H, m, Gly-H), 3.00 (5 H, m, hexyl 1-H$_2$ + Lys ε-H$_2$ + Gly′-H), 3.10 (1 H, m, Phe β-H), 3.18 (1 H, m, Gly′-H), 3.22 (4 H, br d, *J* 5, NCH$_2$CH$_2$N), 3.40 (2 H, m, Gly-H + Gly″-H), 3.58 (1 H, m, Gly″-H), 3.70 (1 H, t, *J* 4.9) and 3.71 (1 H, t, *J* 4.9) (Sar-H$_2$), 3.75 (2 H, m, Sar′-H$_2$), 3.94 (1 H, m, Leu α-H), 4.10 (2 H, m, Lys α-H + Phe α-H), 4.21 (1 H, m, Gln α-H), 4.78 (2 H, s, CH$_2$CCl$_3$), 7.25–7.35 (5 H, m, Phe Ph-H$_5$), 7.46 (1 H, br, NH), 7.53 (2 H, d, *J* 8.5, Ar 2,6-H$_2$), 7.70 (2 H, br, Lys α-NH + Phe NH), 7.9–8.2 (15 H, m, 3 × Ph 3,4,5-H$_3$ + Gly-NH + Gly′-NH + Gly″-NH + Lys ε-NH + Gln α-NH + Gln γ-NH), 8.25 (1 H, br, Leu NH), 8.40–8.55 (10 H, m, 3 × Ph 2,6-H$_2$ + Ar 3,5-H$_2$ + *H*NCH$_2$CH$_2$N*H*), 8.65–8.80 (13 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + Ar-NH + 2 × N$^+$H$_2$); *m/z* 814/812/810/808 (GlyPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NHMe), 757/755/753/751 (PheLeuGlyLys(Troc)NH(CH$_2$)$_2$ NHCOCH$_2$-NHMe), 687 (TPPNHCOCH$_2$NH$_2$ + H), 630 (TPPNH$_2$ + H), 497/495/493/491 (GlyLys(Troc)NH(CH$_2$)$_2$NHCO-CH$_2$NHMe + H), 440/438/436/434 (Lys(Troc)NH(CH$_2$)$_2$-NHCOCH$_2$NHMe + H); *m/z* (electrospray) 833/832/831/830 (M − SarNH(CH$_2$)$_2$NH)$^{2+}$, 814/812/810/808 (GlyPheLeuGly-Lys(Troc)NH(CH$_2$)$_2$ NHCOCH$_2$ NHMe + H), 757/755/753/751 (PheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NHMe + H), 610/608/606/604 (LeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NHMe), 566/564/562/560 (M − TPPNHCOCH$_2$)$^{2+}$, 497/495/493/491 (GlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NHMe), 440/438/436/434 (Lys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$NHMe), 407.5/406.5/405.5/404.5 (GlyPheLeuGlyLys(Troc)NH(CH$_2$)$_2$NHCOCH$_2$-NHMe)$^{2+}$, 380/378/377/376 (PheLeuGlyLys(Troc)NH(CH$_2$)$_2$-NHCOCH$_2$NHMe)$^{2+}$.

SarGln((CH$_2$)$_5$COGlyNHTPP)GlyPheLeuGlyNH(CH$_2$)$_2$-NHCOCH$_2$NHMe·4HBr (78). From **70**: 100%, dark green glass: δ_H − 0.36 (2 H, br s) and − 0.01 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 0.86 (3 H, d, *J* 6.0, Leu Me), 0.90–0.93 (3 H, m, Leu Me), 1.23 (2 H, m, hexyl 3-H$_2$), 1.38 (2 H, qn, *J* 7.3, hexyl 2-H$_2$), 1.49 (3 H, m, hexyl 4-H$_2$ + Leu β-H), 1.58 (1 H, Leu β,γ-H$_2$), 1.80 (1 H, m, Gln β-H), 1.99 (1 H, m, Gln β-H), 2.12 (2 H, t, *J* 7.3, hexyl 5-H$_2$), 2.18 (2 H, m, Gln γ-H$_2$), 2.58 (3 H, t, *J* 5, NMe), 2.59 (3 H, t, *J* 5, NMe), 2.76 (1 H, m, Phe β-H), 2.92 (1 H, m, Gly-H), 2.99 (3 H, m, hexyl 1-H$_2$ + Gly′-H), 3.10 (1 H, m, Phe β-H), 3.18 (1 H, m, Gly′-H), 3.22 (4 H, br d, *J* 5, NCH$_2$CH$_2$N), 3.40 (2 H, m, Gly-H + Gly″-H), 3.58 (1 H, m, Gly″-H), 3.71 (3 H, m, Sar-H$_2$ + Leu α-H), 3.76 (2 H, m, Sar′-H$_2$), 4.10 (1 H, m, Phe α-H), 4.21 (1 H, m, Gln α-H), 7.25–7.35 (5 H, m, Phe Ph-H$_5$), 7.46 (1 H, br, NH), 7.53 (2 H, d, *J* 8.5, Ar 2,6-H$_2$), 7.9–8.2 (15 H, 3 × Ph 3,4,5-H$_3$ + Gly-NH + Gly′-NH + Gly″-NH + Phe NH + Gln α-NH + Gln γ-NH), 8.25 (1 H, br, Leu NH), 8.40–8.55 (10 H, m, 3 × Ph 2,6-H$_2$ + Ar 3,5-H$_2$ + *H*NCH$_2$CH$_2$N*H*), 8.65–8.80 (13 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + Ar-NH + 2 × N$^+$H$_2$); *m/z* 803 (M + H − TPPNHCOCH$_2$NH$_2$), 687 (TPPNHCOCH$_2$-NH$_2$ + H), 630 (TPPNH$_2$ + H).

SarGln((CH$_2$)$_5$COGlyNHTPP)NH(CH$_2$)$_2$NHCOCH$_2$-NHMe·4HBr (79). From **71**: 94%, dark green amorphous powder: mp > 300 °C: λ_{max} (MeOH + 1 drop Pr$^i_2$NEt) 404, 509, 546, 588, 646 nm; δ_H − 0.30 (2 H, br s) and − 0.26 (2 H, br s) (porphyrin 21,22,23,24-H$_4$), 1.34 (2 H, m, hexyl 3-H$_2$), 1.45 (1 H, m, hexyl 2-H$_2$), 1.58 (2 H, m, hexyl 4-H$_2$), 1.70–1.95 (2 H, m, Gln β-H$_2$), 2.12 (2 H, m, Gln γ-H$_2$), 2.25 (2 H, m, hexyl 5-H$_2$), 2.57 (6 H, t, *J* 5.3, 2 × NMe), 3.06 (2 H, m, hexyl 1-H$_2$), 3.18 (4 H, br, NCH$_2$CH$_2$N), 3.7–4.0 (6 H, m, 2 × Sar-H$_2$ + Gly-H$_2$), 4.24 (1 H, m, Gln α-H), 7.82 (11 H, m, 3 × Ph 3,4,5-H$_3$ + Ar 2,6-H$_2$), 8.00–8.35 (15 H, m, Ar 3,5-H$_2$ + 3 × Ph 2,6-H$_2$ + 5 × NH), 8.51 (1 H, br, NH), 8.6–8.9 (12 H, m, porphyrin 2,3,7,8,12,13,17,18-H$_8$ + 2 × N$^+$H$_2$); *m/z* 1113.5455 (M + H) (C$_{65}$H$_{69}$N$_{12}$O$_6$ requires 1113.5463).

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