Synthesis and preliminary biological studies of hemifluorinated bifunctional bolaamphiphiles designed for gene delivery

Séverine Denoyelle,[a] Ange Polidori,*[a] Mélanie Brunelle,[b] Pascal Y. Vuillaume,[b] Sylvette Laurent,[b] Yousef ElAzhary[b] and Bernard Pucci*[a]

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The multistep synthesis of a new series of dissymmetric hemifluorocarbon bolaamphiphiles designed for gene transport is described. The dissymmetric functionalization of diiodoperfluoroctane leads to bolaamphiphile molecules composed of a partially fluorocarbon core end-capped with a glycoside and an ammonium salt derived from histidine or lysine. Initial biological results indicate that one of the bolaamphiphile—end-capped with a lysine and a lactobionamide residue—induces a remarkably low cytotoxicity on COS-7 cells and, when self-assembled with DNA plasmid, generates a significant *in vitro* transfection efficiency without the addition of any fusogenic lipid.

Introduction

Applying drug controlled release technology to DNA delivery has become one of the major challenges of biomedical research.[1] For the purposes of gene therapy and DNA vaccines, oligonucleotides or DNA plasmids must be targeted at the nucleus of the cells where gene expression can take place. On the other hand, transfection efficiency depends, among other things, on the intake by the cells of the DNA–vector complex, the stability of the complex in the cytosol and its unpackaging. So far, viral vectors are the most efficient carriers in terms of transfection efficiency but their potential immunogenicity and oncogenicity seriously restrict their use for *in vivo* experiments.[1,2] On the other hand, synthetic delivery systems are safe and versatile when appropriately designed but remain obviously much less sophisticated and efficient than viruses. In this context, the electrostatically self-assembled complexes based on DNA and (poly)cationic lipids or synthetic surfactants have emerged as a credible alternative because of their capacity to transfect cells. However, complexes based on these types of cationic species are prone to serious limitations such as the low stability of the complexes in the serum and the cytotoxicity which both affect the level of gene delivery.[3] High cationic content[4,5] is the cause of the hepatic toxicity.[6] Other amphiphilic cationic species[7,8] such as gemini surfactants and bolaamphiphiles deserve particular attention for gene delivery because such species may also display a high level of functionality. These amphiphilic compounds are also capable of significant gene transfection especially when co-formulated with the presence of a helper fusogenic lipid that generally favours the fusion of the cationic amphiphiles with the endosomal membranes *via* a phase transition sensitive to the pH variations.[9]

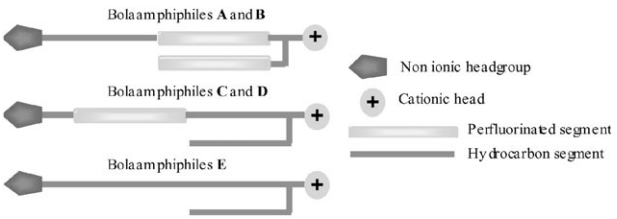


Fig. 1 Schematic representations of dissymmetric bolaamphiphiles.

Herein, we report the rational design, synthesis and the characterization of a new series of dissymmetric bolaamphiphiles.[10] The five novel bolaamphiphiles whose two different polar head groups are connected together *via* an apolar fluorinated or hydrocarbon segment are schematically depicted in Fig. 1.

In the following, we will also describe preliminary biological investigations. The biological data will show that bolaamphiphiles with an appropriate design can generate significant *in vitro* transfection efficiency without inclusion of helper lipid low cytotoxicity.

Results and discussion

Design and synthesis

In the present case, the designed bolaamphiphiles possess one or two apolar fragments connected with two polar heads. One of the two polar heads is a cationic ammonium head group derived from either lysine or histidine. This part of the molecule should be involved in the formation of bolaamphiphile–DNA complexes (bolaplexes) due to interactions with the phosphate groups of nucleic acids.

[a] *Laboratoire de chimie bioorganique et des systèmes moléculaires vectoriels, Faculté des sciences d'Avignon, 33 rue Louis Pasteur, F-84000 Avignon, France. E-mail: bernard.pucci@univ-avignon.fr; ange.polidori@univ-avignon.fr.; Fax: +33 490144449; Tel: +33 490144442*
[b] *Université de Montréal, Faculté de médecine vétérinaire, Institut de biotechnologie vétérinaire et alimentaire, 3200 rue Sicotte, Saint-Hyacinthe, Québec, Canada J2S 2M2. Tel: +1 450 773 8521*

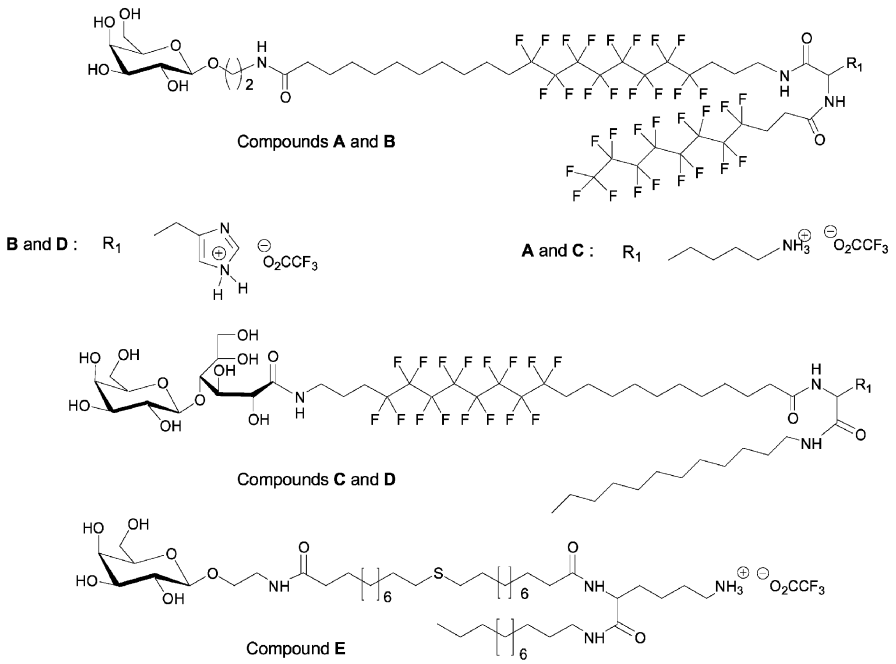


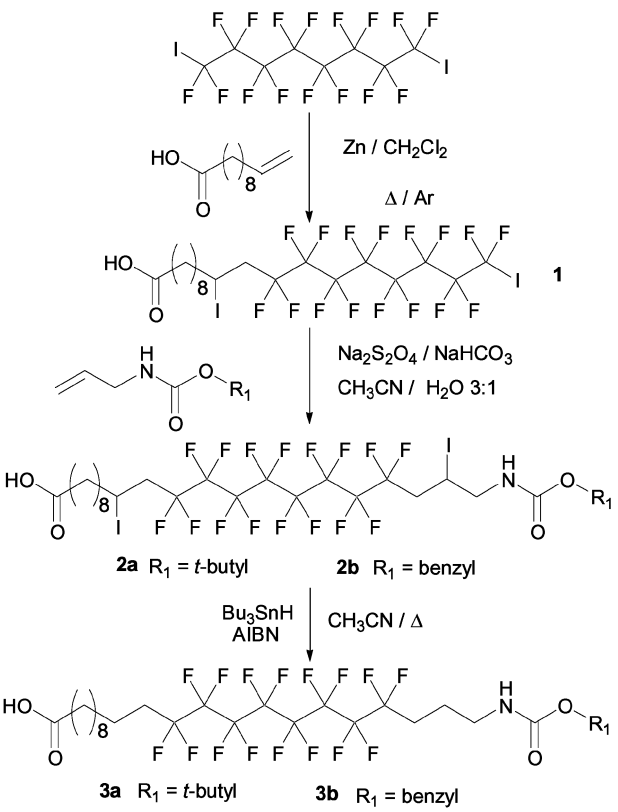
Fig. 2 Chemical structure of hybrid dissymmetric bolaamphiphiles **A–E**.

The other polar head group is neutral and derived from galactose or lactobionamide and is expected to provide the required hydrosolubility to the bolaplexes and avoid the formation of bulky polyaggregates.[11,12] By preventing the presence of electric charges at the outer surface of the bolaplexes, global electric neutrality may also reduce cytotoxicity.

The apolar segment links together end to end a hydrocarbon and a fluorocarbon segment and forms the hydrophobic core of the molecule. A second hydro or perfluorocarbon chain is grafted onto the main chain through a lysine or a histidine residue. The position of the perfluorocarbon segment within the main chain has been adjusted in order to provide a series of four different bolaamphiphiles (Fig. 2). The perfluorooctyl segments are located close to either the cationic part (**A** and **B**) or the sugar polar head (**C** and **D**) whereas the hydro or perfluorinated nature of the lateral chain is always the same as the facing hydrophobic segment of the main chain.

We also synthesized a fully hydrocarbon bolaamphiphile (**E**) (see Fig. 2) in order to evaluate the impact of the fluorinated segment on DNA complexation by hemifluorinated bolaamphiphiles and transfection.

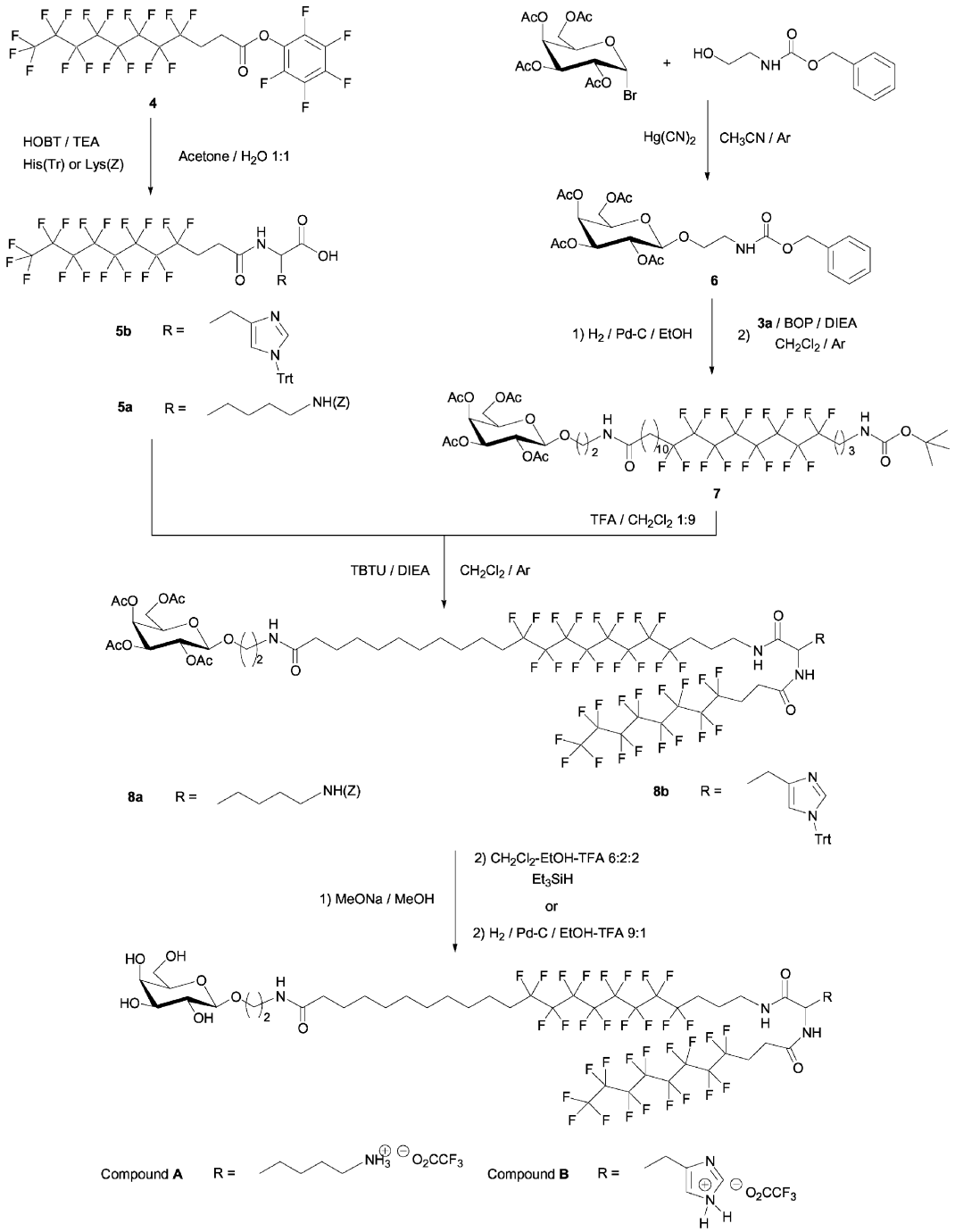
It is well known that fluorocarbon chains self-organize in water due to their high hydrophobicity[13] and usually lead to stable and highly tidy supramolecular systems. For the formation of the bolaplexes, the impact on their organization and stability should be notable. The stability enhancement of the packaging brought about by hydrophobic interactions between the fluorocarbon chains may avoid the use of polycationic polar heads (derived for instance from spermine) that generate irreversible complexation of the nucleic acid[14] and increase cytotoxicity of the carrier. The hydrophobic core may also favour the stacking of the molecules by increasing the cationic charge density around nucleic acids through hydrophobic interactions. Moreover, considering the strong tendency of the perfluorocarbon chains not to interact to a great extent with hydrocarbon chains,[13] a partial or full segregation of hydrocarbon and fluorocarbon surfactants in aqueous solution is expected, thus forming two kinds of micelles, one rich in hydrocarbon, the other in fluorocarbon surfactants.[15] In the designed hemifluorocarbon bolaamphiphiles, the presence of this central fluorocarbon segment



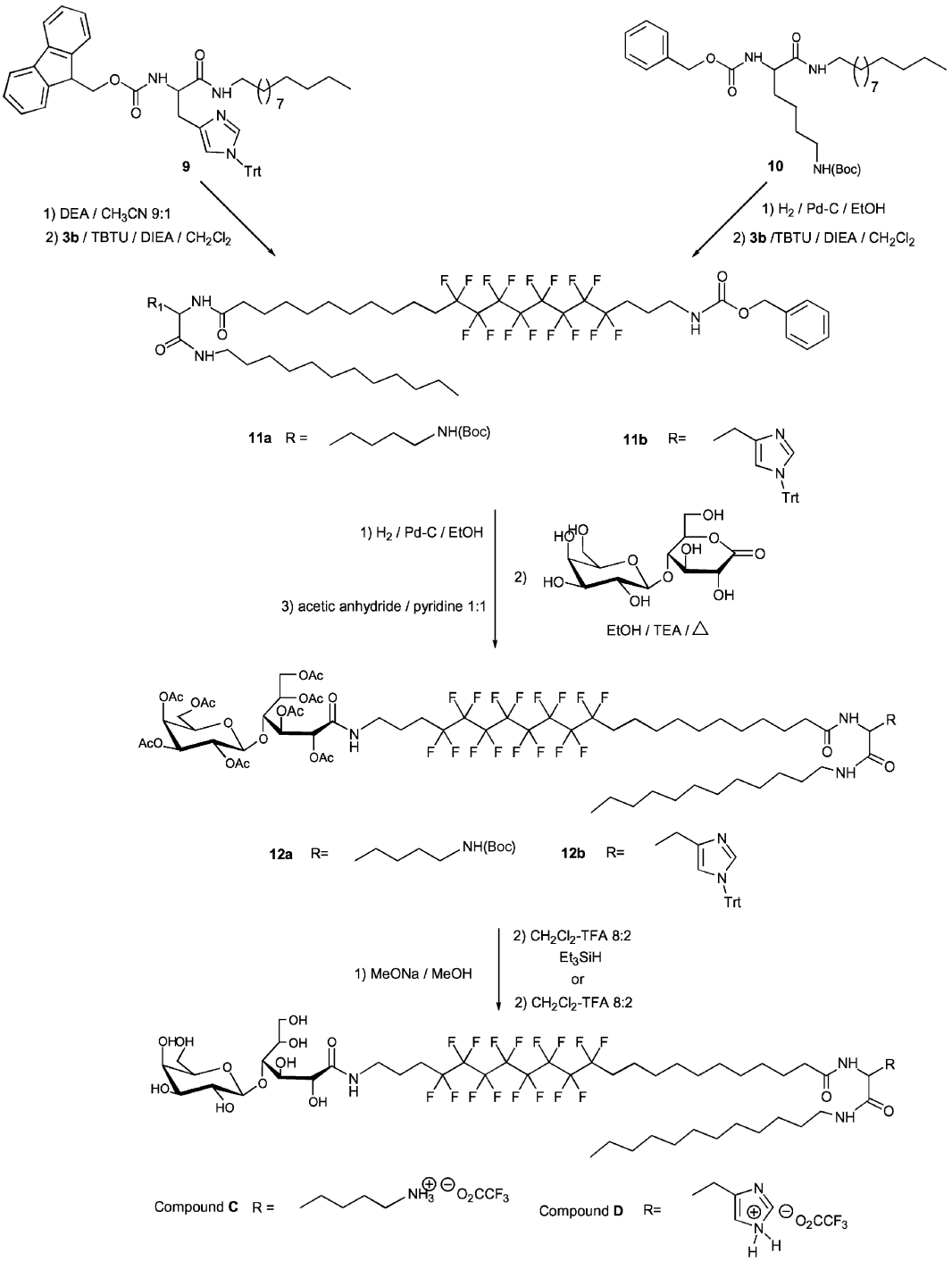
Scheme 1 Synthesis of hemifluorinated central segment.

should avoid the hydrophobic chain refolding. The hydrocarbon and fluorocarbon chain demixing should induce the formation of a monolayer exhibiting both polycationic and non-ionic polar surfaces. This possible dissymmetric organization should lead to one level of DNA complexation, restricting the size of the DNA–bolaamphiphile complex and favouring the global neutrality of its outer surface.

According to this chemical design, the central hydrofluorocarbon segment was synthesized from 1,8-diiodoperfluorooctane as starting material (Scheme 1). Following the methodology developed by Commeyras,[16] one molecule of undecenoic acid was grafted onto the perfluorocarbon chain by using zinc dust as radical initiator. This monofunctionalization provided the compound **1** in 70% yield. The chemical conditions used did not lead to the compound resulting from a double condensation. Thus, radical addition of Z-allylamine or Boc-allylamine on compound **1** was carried out in good conditions in the presence of sodium dithionite.[17] It has to be underlined that Huang's method allowed isolation of compounds **2a–b** in 65–80% yield, generally higher than those obtained by using Commeyras' procedure (40–60% yield). The diadduct so obtained was treated with tributyltin hydride in



Scheme 2 Synthetic pathway to bolaamphiphiles **A** and **B**.



Scheme 3 Synthetic pathway to bolaamphiphiles **C** and **D**.

the presence of AIBN to remove the iodine atoms and to give compounds **3a–b** in 60% yield.

Amphiphiles **A** and **B** were derived from compound **3a** as new starting material (Scheme 2) following a convergent synthetic pathway. In a first sequence, galactosylation of Z-ethanolamine following the Helferich procedure provided compound **6**.[18] After hydrogenolysis of the benzyloxycarbonyl group, the condensation of this glycosidic amine onto the hemifluorinated compound **3a** was performed in the presence of BOP as coupling reagent to provide compound **7**. Thus, treatment with TFA in methylene chloride led to the deprotected amine that was then grafted, in the presence of TBTU, onto the carboxylic function of histidine or (N^{ε}-Z)-lysine derivatives **5a–b** to give compounds **8a–b**. Compounds **5a–b** were obtained by grafting the pentafluorophenyl ester **4** of the 2H,2H,3H,3H-perfluoroundecanoic acid onto (N^{ε}-Z)-lysine or 2-amino-3-(*N*-tritylimidazolyl)propionic acid in an acetone–water mixture. After purification of the compounds **8a–b** by successive size exclusion chromatography and silica gel column chromatography, the sugar moieties were deacetylated by

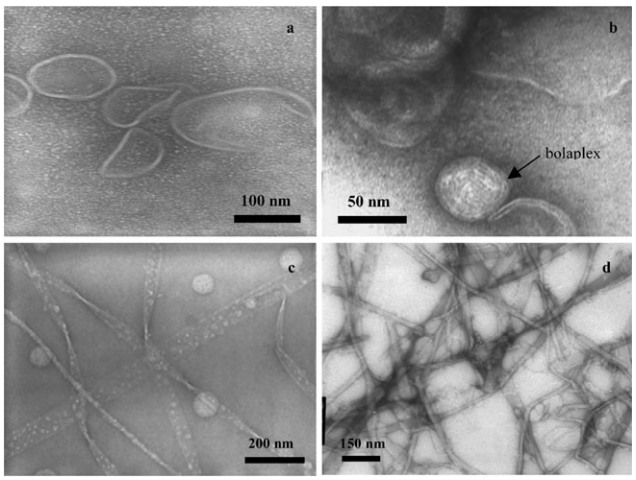


Fig. 3 Representative TEM images showing the morphology of (a) bolaamphiphile **C** (×150 K), (b) bolaplex **C** at $N/P = 5$ (×300 K), (c) bolaamphiphile **E** (×86 K), (d) bolaplex **E** at $N/P = 1.75$ (×86 K) (arrows indicate the bolaplex with its internal ordering).

transesterification in a MeONa–MeOH mixture. Then, the protective groups of amino acid moieties were removed either by hydrogenolysis in acidic medium (lysine derivative) or acid hydrolysis (histidine derivative) to provide compounds **A** and **B** which were purified by size exclusion chromatography (Sephadex LH20).

Compounds **C** and **D** were prepared from dodecylamine as starting material (Scheme 3). *Z*-(N^{ε}-Boc)-lysine and 2-Fmoc-amino-3-(*N*-tritylimidazolyl)propionic acid were coupled with dodecylamine in the presence of DCC–HOBT to give compounds **9** and **10**. After removal of the α-amino protective groups, **9** and **10** were coupled with compound **3b** in the presence of TBTU to give derivatives **11a** and **11b** in good yields (77–84%). The hydrogenolysis of the benzyloxycarbonyl group supported by their propylamine residue allowed their condensation with the lactobionolactone in boiling methanol. To carefully purify these derivatives through chromatography on silica gel column, their sugar residue was temporarily acetylated with an acetic anhydride–pyridine mixture to give compounds **12a** and **12b** in 58–68% yields (2 steps). Removal of the acetyl groups with sodium methylate and the amino acid protective groups with TFA finally afforded compounds **C** and **D**.

Compound **E** was prepared in 58% yield from mercaptoundecanoic acid as starting material (Scheme 4). Compound **14** was obtained following a substitution reaction of benzyl bromoundecanoate by mercaptoundecanoic acid in DMF with NaH as a strong base. Compound **6** was deprotected by hydrogenolysis and the amine obtained was then coupled with compound **14** in the presence of TBTU and DIEA to provide **15**, the median segment of compound **E**. The amino group of compound **10** was deprotected by hydrogenolysis, then grafted in the presence of TBTU onto compound **15** previously submitted to a catalytic hydrogenation in order to hydrolyse its acidic function. Removal of protecting groups with trifluoroacetic acid and sodium methylate provided finally compound **E** which was submitted to a last purification by size exclusion chromatography (LH20).

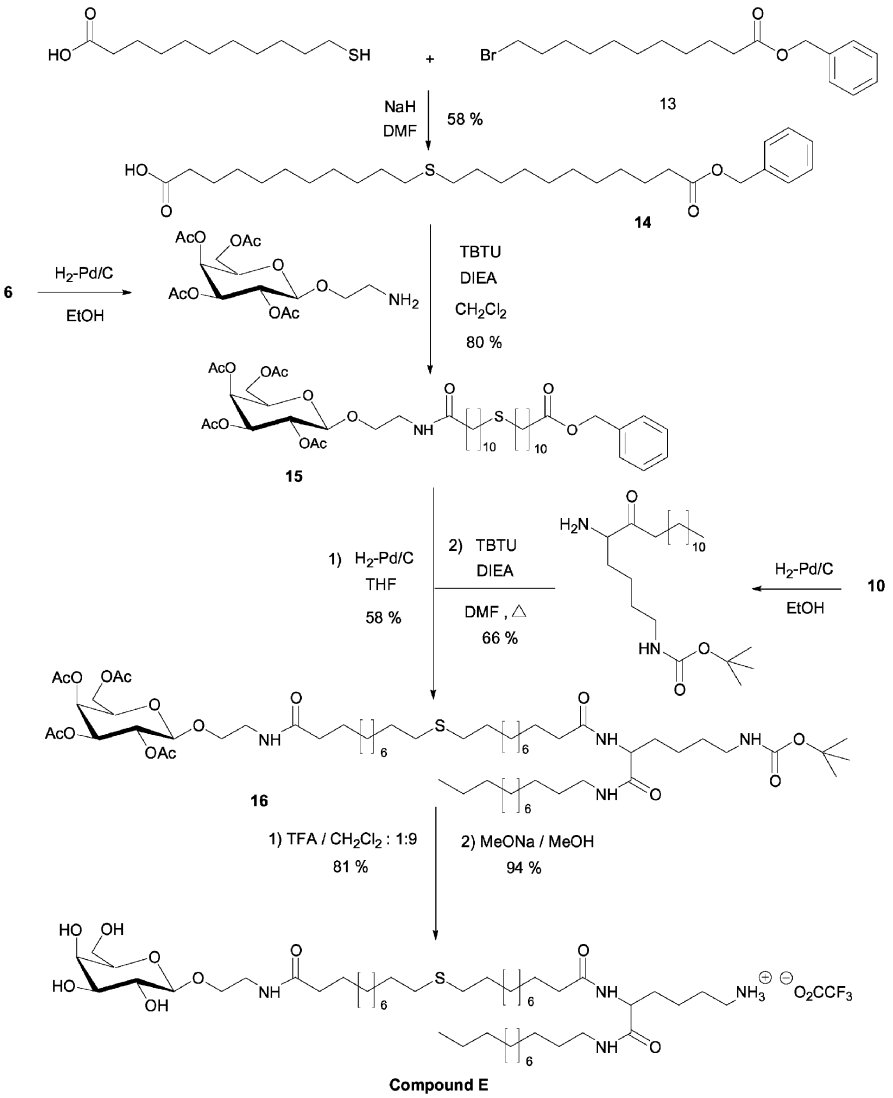
Aggregation behavior of bolaamphiphiles

When directly sonicated in water at a concentration of $\sim 4 \times 10^{-3}$ M, bolaamphiphiles **A–E** formed turbid suspensions. The poor stability of the suspensions prepared from bolaamphiphiles **A** and **B** [rapid sedimentation at room temperature (~15 min), detected by the naked eye] probably results from their greater fluorine content. In contrast, when compared to the other (**A**–**D**) bolaforms, bolaamphiphile **E** showed a better dispersibility and stability. TEM observation of bolaform **E** revealed the presence of vesicles (~85 nm) and fiber-like aggregates (Fig. 3c and 3d), such two-dimensional growth of the aggregates testifying to a rather good solubility. Nevertheless, it was not possible to rely on quasi-elastic light scattering measurement (QELS) data given the non spherical aspect of the objects. Sedimentation was also noticed for bolaamphiphile **D** but to a lesser extent compared with bolaamphiphiles **A** and **B**. Finally, bolaamphiphile **C** appeared much more stable than the other fluorinated compounds when dispersed in aqueous conditions. Its greater stability was evidenced by storage in a cold (4 °C) place for at least 12 h. As expected, these observations suggest that both the presence of lysine (much more hydrophilic than histidine) and lactobionamide residues confer a greater hydrophilic character on the bolaamphiphile **C** and, therefore, a greater stability on the suspensions than the other bolaamphiphiles.

In more dilute conditions ($\sim 10^{-6}$ M, concentration at which complexation is carried out), QELS performed on suspensions made from bolaamphiphile **C** indicated the absence of significant evolution of the particle size over a period of 1 h. The suspension was composed of a large proportion of particles with small size [238 nm (intensity), 95%; 115 nm (number), 100%] and also of a small fraction of large size [~5.4 μm (intensity), 5%] that indicated the occurrence of some aggregation. The bolaamphiphile **C** was examined by transmission electron microscopy (TEM) in the same (dilute) conditions. The observations revealed the presence of vesicles whose sizes were in the range 100–160 nm (Fig. 3a) Bolaamphiphile **C** also presented a better capacity for complexing DNA than the other bolaamphiphiles (**A**, **B**, **D**). For all the reasons mentioned above, bolaamphiphile **C** was used to demonstrate the transfection capacities of asymmetric fluorinated bolaamphiphiles without the addition of a helper lipid. A detailed comparison of the physico-chemical and biological properties of the bolaamphiphiles **A**–**D** is out of the scope of this paper and will be detailed elsewhere.[19]

Preliminary biological results

Bolaamphile–DNA complexation. The ability of bolaamphiphiles **A**–**E** to complex plasmid DNA was tested using agarose gel shift assay that allowed the separation of macromolecules on the basis of both charge and size. It must be stressed that all of the bolaamphiphiles were able to complex DNA due to the electrostatic interactions between the ammonium and the phosphate groups of the two oppositely charged partners (data not shown). The proportion of bolaamphiphiles required to immobilize DNA varies with their chemical structure; for instance bolaamphiphiles with histidine head groups appear less efficient in complexing DNA. This is not surprising given



Scheme 4 Synthetic pathway to bolaamphiphile **E**.

that a large proportion of the free amines of the imidazole groups is probably not protonated (pK_a is close to the physiological pH) under electrophoresis buffering conditions (see Experimental section).[20]

Gel mobility shift assays performed at various N/P [number of amine/number of phosphate] charge ratios for **C**–DNA bolaplexes are illustrated in Fig. 4a. In the left lane, naked DNA was used as a negative control. At an N/P ratio of 0.50 and 0.75 (lanes 2 and 3), the visible band can be reasonably associated with the free plasmid when compared with the negative control (lane 1). These formulations were also characterized by a negative ζ-potential (-21.4 ± 6.2 mV). At higher N/P ratios ($N/P > 1.0$), all of the bands disappeared, indicating the complete neutralization of DNA plasmid (lanes 4–6).

On the other hand, a complete DNA neutralization by the non fluorinated bolaamphiphile **E** was much more difficult to achieve. Indeed at similar ratios, *i.e.* at $N/P \approx 1.0$, bolaamphiphile **E** failed to retain DNA (Fig. 4b). Complete DNA retardation was only evidenced at higher ratios, namely in the N/P range 2.5–5.0. Contrasting with **C**–bolaplexes, a marked fluorescence was observed in the wells even when high amounts of bolaform **E** were used. This indicates that ethidium bromide can diffuse within the DNA strands. Therefore,

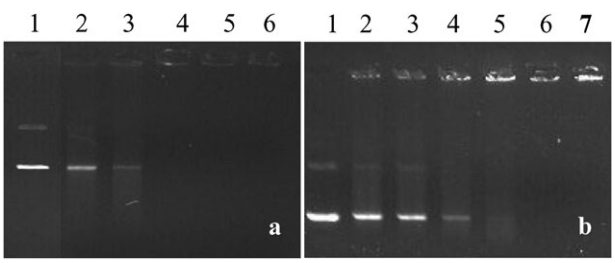


Fig. 4 Representative gel electrophoresis shift assays of naked DNA (lane 1), (**a**) **C**–bolaplexes at N/P ratios of 0.5, 0.75, 1, 1.5, 1.75; (lane 2–6) and (**b**) **E**–bolaplexes at N/P ratios of 0.75, 1, 1.5, 1.75, 2.5, 5 (lane 2–7).

bolaform **E** probably fails to efficiently compact DNA. The above comparison between the two bolaamphiphiles (**C** and **E**) would suggest that fluorine segments plays a major role in the mechanism of bolaplex formation, reducing the hydrophilic character of the conjugate and allowing for the increase of the driving force needed for DNA compaction.

Size and morphology of bolaplexes. Size is a crucial factor for particles internalization by non-specific endocytosis. It is well documented that internalization is efficient when particle size is less than 200 nm.[21,22] Therefore, the size of bolaplexes formed from bolaamphiphile **C** was investigated by QELS for different N/P ratios. For bolaplexes formed with an excess of bolaamphiphile **C** (*i.e.* for N/P ratios of 2.5 and 5) or with a stoichiometric ratio ($N/P = 1$) QELS revealed the presence of a bimodal distribution that consists in a fraction of small particle size averaging 225–300 nm (intensity) [130–250 nm (number), 100%] and a significant proportion of aggregates [0.7–1.2 μm (intensity), 27–59%]. For N/P ratios of 1.17 and 1.35, larger particles were observed with a mean diameter of ~835 nm (intensity, ~100%) [430 nm (number), 100%]. Such a noticeable increase in the size of the particles is generally related to the instability of electroneutral DNA–lipid lipoplexes.

The morphology of the particles has also an impact on the transfection efficiency,[23] in particular on the nuclear trafficking.[24] At a ratio N/P of 1.7, TEM observations indicated the presence of distinct and relatively spherical particles with a contrasted outline and a diameter of around 65–140 nm [see Fig. 3b]. These particles were assumed to correspond to bolaplexes. In fact, the propensity of **C**–bolaplexes to aggregate was also confirmed by TEM at other N/P ratios. At high N/P ratios ($N/P > 1.35$), a mixture of membrane debris and well-defined particles was also observed. A closer examination of Fig. 3b also revealed the internal lamellar ordering of the bolaplexes.

TEM examinations of **E**–bolaplexes (Fig. 3d) revealed, on a large range of ratios ($1 < N/P < 5$), the persistence of a fiber-like morphology, reminiscent of that observed for the uncomplexed bolaamphiphile **E**. DNA appeared to be aggregated according to a heterogeneous fashion onto the surface of the fibers, confirming the inefficient complexation process occurring between the non fluorinated bolaamphiphile and DNA.

Transfection and cytotoxicity. In order to evaluate the gene delivery potential of bolaamphiphile **C** and its hydrocarbonated analogous compound **E**, the *in vitro* cytotoxicity as well as the transfection efficiency of bolaamphiphiles **C** and **E**–pBudCE4.1LacZ–CAT based-bolaplexes were performed on COS-7 cell lines, as described in the Experimental section. Cell viability tests were carried out in the presence of bolaamphiphiles **C** or **E** and compared with those obtained from 25 kDa branched poly(ethylenimine) (PEI) which is known to be a very potent transfectant but with an acute cellular cytotoxicity (Fig. 5b). The LC_{50} of PEI was 9 μg mL^{-1} whereas at the same dose of bolaamphiphiles **C** and **E** (data not shown), the cell viability was ~89%. The profile in the form of a plateau of the cell viability as a function of the increasing weight of

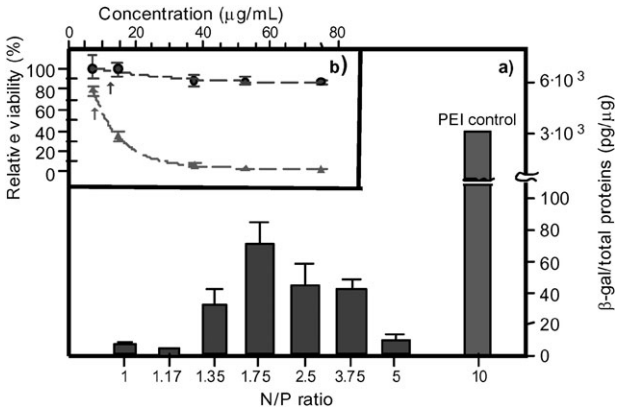


Fig. 5 (a) *In vitro* transfection data of **C**/pBudCE4.1LacZ/CAT bolaplexes and PEI control data. Standard deviation bars are shown. **(b)** Relative cell viability (%) as a function of bolaamphiphile **C** concentration (●). Arrows indicate the optimal ratios. Minima and maxima values are represented as bars. ▲: PEI control data.

bolaamphiphile testified to the notably low cytotoxicity for a high amount of bolaamphiphiles.

To estimate the transfection efficiency of bolaplexes formed from bolaamphiphile **C** or **E**, β-Gal protein (encoded by LacZ gene) expressed in COS-7 cells was quantified. The assays were performed in the absence of any helper lipid or co-formulated multifunctional (bola)amphiphile that commonly enhances *in vitro* transfection.[25] As illustrated on Fig. 5a, the transfection efficiency as a function of N/P ratios followed an asymmetric bell-shaped profile. The maximal level of transfection was observed at an N/P ratio of 1.75 but gene expression was still significant at higher N/P ratios (2.5 and 3.75). In fact, despite the fact that the transfection level was significantly lower than PEI (~45 times less efficient than PEI–DNA polyplexes), **C**–bolaplexes generated a significant transfection level, typically higher than three orders of magnitude than naked DNA. This result contrasted with the relatively low transfection efficiency generally obtained with (fluorinated) bolaamphiphiles when used alone, *i.e.* without the addition of any helper lipids[27f] or other functional (bola)amphiphile.[27d] A plausible reason to explain the relative difference measured between the PEI–polyplexes and the **C**–bolaplexes could be the ability of PEI–polyplexes to easily leave the vacuoles of lysosomes.[26] In the case of lipoplexes, efficient release in the cytoplasm would originate from a lamellar to a fusogenic inverted hexagonal phase in the acidic environment of the endosomal compartments.[9] TEM observations revealed the lamellar-like packing of the DNA–bolaamphiphile complexes but so far we have no evidence for such a phase transition. It is rather uncommon that such pH phase sensitive behaviour is an intrinsic property of a surfactant.[9] In fact, DNA–surfactant complexes generally appear to undergo the appropriate structural change when helper lipids are incorporated in the formulation.

In closing, it is worth noting that transfection experiments performed with the **E**–bolaplexes were characterized by the absence of any protein expression. The difference in the transfection efficiencies observed between bolaform **C** and **E** may be due in part to the inability of the non-fluorinated bolaform to bind and condense efficiently DNA. This last

result suggests that the partial fluorination of the hydrophobic core of these bolaamphiphiles seems to increase not only the self association and DNA complexation abilities of these compounds but also their DNA transfection efficiency.

Conclusion

The synthesis and the characterization of a new series of fluorinated asymmetric bolaamphiphiles, designed for gene delivery, were reported. We demonstrated that fluorinated bolaamphiphiles were capable of binding and condensing DNA in nanoparticles whose sizes were, according to TEM observations, in the range 65–150 nm. Preliminary biological data based on transfection and cytotoxicity assays indicated the strong potential of these bolaplexes as a DNA delivery system. Indeed bolaamphiphiles can present a low cytotoxicity and a significant *in vitro* transfection efficiency without the addition of helper lipids. In this context, post-functionalizations of bolaamphiphiles with a translocation peptide are currently under way with the aim of enhancing gene delivery through a co-formulation process.

Experimental

Abbreviations

AcOEt, ethyl acetate; AIBN, 2,2′-azobisisobutyronitrile; Ar, argon; Boc, *tert*-butoxycarbonyl; BOP, (benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate; DCC, dicyclohexylcarbodiimide; DCM, methylene dichloride; DIEA, diisopropylethylamine; cHex, cyclohexane; Fmoc, 9-fluorenylmethoxycarbonyl, His(Tr), 2-amino-3-(*N*-trityl-imidazolyl)propionic acid; HOBT, 1-hydroxybenzotriazole; PFP, pentafluorophenol, Pyr, pyridine; TBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Tr, trityl; Z, benzyloxycarbonyl; PBS, phosphate buffered saline; PEI, polyethylenimine; DMEM, Dulbecco's modified Eagle's medium; FBS, foetal bovine serum; BCA, bicinchonic acid; CMV, cytomegalovirus; QELS: quasi-elastic light scattering; TEM, transmission electron microscopy.

Materials and methods

All solvents were purchased from Acros Organics. DCM was distilled from P_2O_5 and THF from sodium. Other solvents were used without further purification. All chemicals were purchased from Sigma-Aldrich or Acros Organics and were used without further purification. Reactions were monitored by thin layer chromatography using Merck precoated $60F_{254}$ silica gel plates. Purifications were achieved by column chromatography over silica gel (Merck 60). Melting points were measured on an electrothermal apparatus and have not been corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer and processed using XWINNMR (Bruker). Chemical shifts are given in ppm relative to tetramethylsilane using the deuterium signal of the solvent as a heteronuclear reference for ^{1}H, ^{13}C and ^{19}F. Mass spectra were recorded on a APT *III* Plus Sciex apparatus. Elemental analyses were performed by the service central de microanalyses of the CNRS (Vernaison, France).

Sterile water (DNase free, molecular biology reagent; PBS, PEI (M_w 25 000 g mol^{-1}, branched), and ethidium bromide were obtained from Sigma-Aldrich (Oakville, ON). Cell culture plastics were purchased from Corning Costar (Corning, NY). Zeocin, pBudCE4.1/LacZ/CAT (8433 bp), *Escherichia coli* Top 10 chemically competent cells were from Invitrogen (Burlington, ON). Cell proliferation kit MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylpyrazolium)bromide)] assay and β-gal ELISA kit were purchased from Roche Diagnostics GmbH (Laval, PQ). DMEM and OPTI-MEM I reduced serum medium and FBS were purchased from GIBCO Invitrogen Corporation (Burlington, ON) and Medicorp (Montréal, PQ), respectively. Endotoxin-free Giga Kit was from QIAgen (Mississauga, ON). COS-7 cell line (Simian virus 40-transformed kidney cells of an African green monkey) was from American Type Culture Collection (ATCC) (Manassas, VA).

DNA preparation

pBudCE4.1/lacZ/CAT plasmid encoding β-galactosidase under the control of the CMV promoter was used. One Shot TOP10 chemically competent *Escherichia coli* grown in Luria Broth (LB) medium containing Zeocin (50 μg mL^{-1}) were transformed with the plasmid pBudCE4.1/lacZ/CAT. The plasmid was isolated and purified using the endotoxin-free Giga Kit and then dissolved in PBS (pH 7.3). The DNA concentration was measured by UV absorption at 260 nm, and the purity was confirmed with A_{260}/A_{280} and by 0.8% agarose gel electrophoresis [Tris–acetate–EDTA buffer (TAE, pH 8.0)]. DNA bands were visualized by UV illumination after coloration by ethidium bromide. DNA restriction analysis was used to confirm the nature of the plasmid. The DNA aliquots were stored at −20 °C prior to use.

Bolaamphiphiles and bolaplexes preparations

Bolaamphiphiles **A**–**E** were sonicated in H_2O for 2 h at 60 °C and pH was adjusted at 7 at a final concentration of 5 mg mL^{-1} ($\sim 4 \times 10^{-3}$ M). Only bolaamphiphiles **C** and **E** were found to be stable as observed by the naked eye (no sedimentation detected after a period at room temperature of at least 4 h). Bolaplexes were prepared in H_2O by directly mixing equal volumes of diluted bolaamphiphiles and DNA solution (20 μg mL^{-1} DNA). Final DNA concentration was 10 μg mL^{-1}.

Gel electrophoresis shift assay

Bolaamphiphile **C**–DNA or **E**–DNA complexes were formed at various nitrogen (*N*)/phosphate (*P*) ratios $> N/P$ of 0.5, 0.75, 1, 1.5, 1.75, 2.5 and 5]. 40 μL of freshly prepared bolaplex solutions (0.4 μg of DNA) were loaded with bromophenol blue in glycerol into 0.8% agarose gel in buffer TAE (pH 8.0) and electrophoresis performed at 90 V for 1 h. Gel stained with ethidium bromide solution (0.5 mg L^{-1}) was transilluminated in ultraviolet light to visualized the DNA and photographed.

Size distribution and zeta (ζ) potential measurement

Size distribution of bolaamphiphile **C** and **E** was obtained from quasi-elastic light scattering (QELS) using Zetasizer (Malvern, NanoZS ZEN3600). The instrument was equipped with a monochromatic coherent helium neon laser (633 nm) as a light source. The scattered light was recorded at an angle of 90°, and the analysis of the autocorrelation function was performed automatically to yield the diffusion coefficient, D_T, taking the values 1.33 and 25 °C for refractive index and temperature, respectively. Size distributions by intensity or number (see text for details) were given relative to the hydrodynamic diameter using a bimodal distribution. For bolaplexes, both size and ζ potential measurements were carried out at different N/P ratios with the disposable cell (folded capillary cell DTS 1060). ζ potential was calculated by using the Schmoluchowsky approximation.

Transmission electron microscopy (TEM)

Bolaamphiphile **C** and **E** and **C** or **E**–bolaplexes prepared at different N/P ratios were analyzed for their morphological characteristics. 10 μL of the sample was added onto a 150 mesh copper grid covered with Formvar. The excess of solution was gently dried with filter paper and the preparation was negatively stained with a droplet of 1% uranyl acetate (aqueous solution at a pH of 4.5) for 2 min. After removal of the stain the grid was air-dried. Samples were observed under transmission electron microscope Philips EM 410 operating at 80 kV.

Transfection protocol

COS-7 cells were used for transfection and cell viability tests. Cells (2.7×10^5 per well) were grown to 90% confluence 24 h after plating in six-well tissue culture plates using complete medium [90% (v/v) DMEM containing l-glutamine, 10% FBS] at 37 °C in a humidified atmosphere containing 5% CO_2 (v/v). Immediately before the initiation of β-galactosidase transfection, the medium was removed, the cells were washed twice with PBS, and 1 mL of OPTI-MEM I serum-free medium was added before the addition of the fresh bolaplex solution (500 μL, 5 μg of DNA per well). Serum-free transfection mixtures were incubated for 4 h, and replaced by complete medium without antibiotics for an additional 18 h. β-Galactosidase quantity was assayed using a commercially available kit (Roche). Results were expressed as pg of β-galactosidase per μg of total protein using the BCA assay (Pierce). Control experiments were performed with naked DNA plasmid (5 μg per well) and PEI/DNA polyplexes at weight ratios of 1.29 [equivalent to a N/P ratio of 10].[26] Experiments were performed in triplicate.

Cytotoxicity

Cytotoxicity of bolaamphiphiles was evaluated by measuring the viability of treated cells as a function of the concentration of bolaamphiphile (μg mL^{-1}). The viability of metabolically viable COS-7 cells was measured by using the MTT Cell Proliferation Assay kit, 24 h after incubation with the bolaamphiphile. Cells were grown in 96-well plates 24 h before at an initial seeding density of 1.9×10^4 cells per well in 100 μL of DMEM. Bolaamphiphiles were directly dissolved in OPTI-MEM I at different concentrations (μg mL^{-1}) [related to the transfection experiments]. Untreated cells were used as a positive control and PEI cells treated for comparison model. Cells were grown for 24 h in the presence of complexes and then immediately tested for metabolic activity. MTT reagent (10% v/v) was added to each well (final concentration 0.5 mg mL^{-1}). After 4 h of incubation at 37 °C, the purple insoluble salt was dissolved by adding 100 μL of solubilization solution. The plate was incubated in the dark at 37 °C for 24 h. Absorbance was measured at 550 nm using a reference wavelength of 650 nm. The results were expressed as a relative percentage of cell viability related to the control (untreated cells). Cell viability (%) = $(OD_{550(sample)}/OD_{550(negative\ control)}) \times 100$. Experiments were performed in triplicate.

Syntheses

10, 19-Diiodo-12, 12, 13,13,14,14,15,15,16,16,17,17,18,18,19, 19 hex adecafluorononadecanoic acid (1). Undecylenic acid (0.289 g, 1.53 mmol), 1,8-diiodoperfluorooctane (2 g, 3.06 mmol) and zinc dust (0.4 g) were dissolved in freshly distilled and degassed DCM (10 mL) under argon. The mixture was refluxed for 2 h. The mixture was diluted with DCM (20 mL) and filtered over Celite. The solvent was removed from the filtrate *in vacuo*. The crude product was purified by flash chromatography on silica gel (cHex–AcOEt 9 : 1) to yield 900 mg (1.07 mmol, 70%) of monoadduct intermediate **1** as a white solid. R_f: 0.5 (cHex–AcOEt 7 : 3), mp: 66–68 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.29–1.45 (10H, s, $CH_{2\ chain}$), 1,66 (2H, m, HO_2C-CH_2-CH_2), 1.80 (2H, m, CH_2-CH_2-CHI), 2.38 (2H, t, HO_2C-CH_2, J = 7.5 Hz), 2.85 (2H, m, CH_2-CF_2), 4.34 (1H, m, CHI). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.9 (HO_2C-CH_2-CH_2), 24.6 (CHI), 28.4–29.4 ($CH_{2\ chain}$), 34.0 (HO_2C-CH_2), 40.0 (CH_2-CHI), 41.9 (CH_2-CF_2), 106.9–117.9 (CF_2), 180.3 (CO). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −60 (2F, s, CF_2I), −111.0 to −115.3 (4F, m, CH_2-CF_2, CF_2-CF_2I), −120.8 to −123.5 (10F, m, 5 CF_2).

22-*N*-(*tert*-Butyloxycarbonylamino)-10, 21-diiodo-12, 12, 13, 13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanoic acid (2a). Compound **1** (2 g, 2.38 mmol) and Boc-allylamine (1.5 g, 9.55 mmol) were dissolved in 15 mL freshly distilled acetonitrile. Sodium dithionite (0.414 g, 2.38 mmol) and sodium hydrogencarbonate (0.4 g, 4.76 mmol) dissolved in 5 mL of distilled water were added to the mixture. After stirring for 16 h at room temperature, the mixture was acidified to pH = 3 with 2 M HCl. Acetonitrile was removed *in vacuo* and the mixture was extracted with ethyl acetate. The organic layers were washed with 1 M HCl then water and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (cHex–AcOEt 8 : 2) to yield 1.9 g (1.9 mmol, 80%) of compound **2a** as a white solid. R_f: 0.51 (cHex–AcOEt 6 : 4), mp: 93–95°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.27–1.40 (10H, s, $CH_{2\ chain}$), 1.47 (9H, s, $C(CH_3)_3$), 1.63 (2H, m, HO_2C-CH_2-CH_2), 1.79 (2H, m, CH_2-CH_2-CHI), 2.35 (2H, t, HO_2C-CH_2, J = 7.5 Hz), 2.83 (4H, m, 2 CH_2-CF_2), 3.58 (2H, m, CH_2-NH), 4.37 (2H, m, 2 CHI), 5.09 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 18.8 (CHI-CH_2-NH),

20.9 (HO_2C-CH_2-CH_2), 24.6 (CHI-CH_2-CF_2), 26.9–33.9 (CH_2 $_{chain}$, $C(CH_3)_3$), 33.9 (HO_2C-CH_2), 38.6 (CF_2-CH_2), 40.3 (CH_2-CHI), 41.7 (CH_2-CF_2), 49.0 (CH_2-NH), 81.1 ($C(CH_3)_3$), 106.1–121.9 (CF_2), 155.7 (NH-CO), 179.1 (CO_2H). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −112.2 to −114.1 (4F, m, 2 CH_2-CF_2), −120.8 to −123.5 (12F, m, 6 CF_2).

22-*N*-(*tert*-Butyloxycarbonylamino)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanoic acid (3a). Compound **2a** (1.85 g, 1.86 mmol) was dissolved in 20 mL of anhydrous and degassed acetonitrile with argon. The solution was refluxed and then Bu_3SnH (1.10 mL, 4.09 mmol) and AIBN (0.34 g, 2.04 mmol) dissolved in 2 mL of dry acetonitrile were added slowly *via* a syringe. The mixture was refluxed for 16 h under argon. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (cHex–AcOEt 8 : 2) to yield 830 mg (1.11 mmol, 60%) of compound **3a** as a white solid. R_f: 0.53 (cHex–AcOEt 6 : 4), mp: 99–100°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.23–1.39 (12H, m, CH_2 $_{chain}$), 1.47 (9H, s, $C(CH_3)_3$), 1.61 (4H, m, HO_2C-CH_2-CH_2, CH_2-CH_2-CF_2), 1.80 (2H, m, CH_2-CH_2-NH(Boc)), 2.15 (4H, m, 2 CH_2-CF_2), 2.35 (2H, t, HO_2C-CH_2, J = 7.5 Hz), 3.24 (2H, m, CH_2-NH), 4.67 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.1–21.3 (CH_2-CH_2-NH, HO_2C-CH_2-CH_2), 24.8–31.2 (CH_2 $_{chain}$, $C(CH_3)_3$, 2 CH_2-CF_2), 34.0 (HO_2C-CH_2), 39.6 (CH_2-NH), 79.6 ($C(CH_3)_3$), 106.5–122.4 (CF_2), 156 (NH-CO), 179.7 (CO_2H). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.27 (4F, s, 2 CH_2-CF_2), −121.86 to −123.59 (12F, m, 6 CF_2).

22-*N*-(Benzyloxycarbonylamino)-10, 21-diiodo-12, 12, 13, 13, 14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanoic acid (2b). The same procedure as used for compound **2a** was applied to **2b**. From compound **1** (2 g, 2.386 mmol), Z-allylamine (1.37 g, 7.158 mmol), sodium dithionite (0.415 g, 2.39 mmol) and sodium hydrogencarbonate (0.4 g, 4.77 mmol), 1.6 g (1.55 mmol, 65%) of compound **2b** was obtained as a white powder after purification by flash chromatography on silica gel (cHex–AcOEt 9 : 1), R_f: 0.32 (cHex–AcOEt 8 : 2), mp: 74–76 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.25–1.55 (10H, m, CH_2 $_{chain}$), 1.66 (2H, m, CH_2-CH_2-CO_2H), 1.82 (2H, m, CH_2-CH_2-CHI), 2.37 (2H, t, HO_2C-CH_2, J^3 = 7.5 Hz), 2.86 (4H, m, 2 CH_2-CF_2), 3.55 (1H, m, CHI), 3.66 (1H, m, CHI), 4.38 (2H, m, CHI-CH_2-NH), 5.16 (2H, s, CH_2-Φ), 7.27 (1H, s, NH), 5.39 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 18.4 (CHI-CH_2-NH), 20.9 (HO_2C-CH_2-CH_2), 24.6 (CHI-CH_2-CF_2), 28.4–29.5 (CH_{2chain}), 34.0 (HO_2C-CH_2), 38.7 (CF_2-CH_2), 40.3 (CH_2-CHI), 41.7 (CH_2-CF_2), 49.3 (CH_2-NH), 67.3 (CH_2-Φ), 106.3–121.8 (CF_2), 128.4 ($CH_{arom.}$), 146.2 ($CH_{arom.}$), 156.3 (NH-CO), 179.1 (CO_2H). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −111 to −115.1 (4F, m, 2 CH_2-CF_2), −121.7 (8F, s, 4 CF_2), −123.2 (4H, s, 2 CF_2).

22-*N*-(Benzyloxycarbonylamino)-12, 12, 13, 13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanoic acid (3b). Deiodination was carried out with the same procedure used for compound **3a**. From compound **2b** (1.5 g, 1.46 mmol), Bu_3SnH (863 µL 3.21 mmol) and AIBN (0.263 g 1.60 mmol), 610 mg (0.78 mmol, 54%) of compound **3b** was obtained as a white powder after purification by flash chromatography on silica gel (cHex–AcOEt 8 : 2) and recrystallization from heptane. R_f: 0.36 (cHex–AcOEt 6 : 4), mp: 97–98 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.32 (12H, m, CH_{2chain}), 1.63 (4H, m, CH_2-CH_2-CO_2H, CH_2-CH_2-CF_2), 1.86 (2H, m, CH_2-CH_2-NH), 2.07 (4H, m, 2 CH_2-CF_2), 2.35 (2H, t, HO_2C-CH_2, J^3 = 7.5 Hz), 3.31 (2H, t, CH_2-NH, J^3 = 6 Hz), 4.88 (1H, s, NH), 5.14 (2H, s, CH_2-Φ), 7.36 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.1–30.6 (CH_{2chain}, 2 CH_2-CF_2, CH_2-CH_2-NH(Z)), 34.0 (HO_2C-CH_2), 40.2 (CH_2-NH(Z)), 66.9 (CH_2-Φ), 106.5–123.1 (CF_2), 128.1–128.6 ($CH_{arom.}$), 136.1 ($C_{arom.}$), 156.9 (NH-CO-O), 179.4 (HO_2C). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.3 (4F, s, 2 CH_2-CF_2), −121.8 (8F, m, 4 CF_2), −123.5 (4F, s, 2 CF_2).

Pentafluorophenyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate (4). 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecanoic acid (3 g, 6.1 mmol) and pentafluorophenol (1.23 g, 6.7 mmol) were dissolved in 20 mL of freshly distilled DCM. The mixture was cooled to 0 °C and DCC (1.63 g, 7.9 mmol) was added. After stirring for 12 h at room temperature the solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (cHex–AcOEt 9 : 1) then recrystallized from AcOEt–Hexane to yield 3.9 g (5.92 mmol, 97%) of compound **4** as white crystals. R_f: 0.44 (cHex–AcOEt 7 : 3), mp: 48–50 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.55 (2H, m, CH_2-CF_2), 3.05 (2H, t, CH_2CO, J^3 = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 25.09 (CH_2-CO), 26.5 (CF_2-CH_2), 106.6–121.7 (CF_2), 136.0 (2 CF_{PFP}), 138.7 (CF_{PFP}), 143.1 (2 CF_{PFP}), 167.5 (CO). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −80.9 (3F, s, CF_3), −114.8 (2F, s, CF_2-CH_2), −121.8 to −123.5 (10F, m, 5 CF_2), −126.2 (2F, s, CF_3-CF_2), −152.8 (2F, s, 2 CF_{PFP}), −157.3 (1F, s, CF_{PFP}), −162.1 (2F, s, 2 CF_{PFP}).

***N*$^{\alpha}$-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecanoyl)-*N*$^{\varepsilon}$-(benzyloxycarbonyl)lysine (5a).** Lys(Z)OH (0.5 g 1.78 mmol) and HOBT (0.12 g, 0.89 mmol) were dissolved in 10 mL of acetone–distilled water (1 : 1). The solution was basified to pH = 8–9 with TEA. Compound **4** (1.29 g, 1.96 mmol) dissolved in 2 mL of acetone was added dropwise. After stirring for 12 h at room temperature the mixture was acidified to pH = 2 with 3 M HCl solution and the solvent removed *in vacuo*. The aqueous layer was extracted with ethyl acetate three times. The organic layer was washed with 1 M HCl solution and water, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (cHex–AcOEt 5 : 5 to cHex–AcOEt 3 : 7) to yield 834 mg (1.10 mmol, 62%) of **5a** as a white solid. R_f: 0.46 (AcOEt), mp: 112–114°C, $[\alpha]_D^{20}$: +3.94 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.31–1.52 (4H, m, CH_2-$(CH_2)_2$-CH_2), 1.83 (2H, m, CH-CH_2), 2.46–2.57 (4H, m, CH_2-CH_2- CF_2), 3.19 (2H, m, CH_2-NH(Z)), 4.57 (1H, m, CH-CH_2), 5.09 (2H, s, CH_2-Φ), 5.25 (1H, s, NH), 7.29 (5H, s, CH $_{arom.}$), 7.87 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 22.1–30.9 (CH_2-CH_2-CF_2, CH-$(CH_2)_3$), 40.1 (CH_2-NH(Z)), 52.4 (CH), 67.3 (CH_2-Φ), 106.5–122.2 (CF_2), 126.5–128.6 ($CH_{arom.}$), 138.6 ($C_{arom.}$), 151.8 (NH-CO-O), 169.5 (NH-CO-CH_2), 173.1 (HO_2C). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ

−80.7 (3F, s, CF_3), −114.6 (2F, s, CF_2-CH_2), −121.9 to −126.1 (12F, m, 6 CF_2).

***N*$^{\alpha}$-(4,4,5,5,6,6,7,7,8,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecanoyl)-*N*^{im}-(trityl)histidine (5b).** The procedure described for the synthesis of compound **5a** was applied to **5b**. From His(Trt)OH (0.640 g, 1.61 mmol), HOBT (0.109 g, 0,81 mmol) and compound **4** (1.165 g, 1.77 mmol) and after purification by flash chromatography on silica gel (AcOEt–cHex 9 : 1 to AcOEt–MeOH 9 : 1) and recrystallization from AcOEt–*n*-heptane 1.15 g of compound **5b** was obtained (1.32 mmol, 82%) as white crystals. R_f: 0.33 (AcOEt–MeOH 9 : 1), mp: 109–111 °C. $[\alpha]_D^{20}$: +14.03 (*c* 1, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 250 MHz, 45 °C): δ 2.34–2.51 (4H, m, CH_2-CH_2-CF_2), 2.88 (2H, m, CH_2-CH), 4.52 (1H, m, CH-CH_2), 6.9–7.4 (17H, m, $CH_{arom.}$, CH_{his}), 8.04 (1H, s, OH), 8.37 (1H, d, NH, J^3 = 8 Hz). ^{13}C NMR (DMSO-d_6, 62.86 MHz): δ 26.1–28.8 (CO-CH_2-CH_2-CF_2), 39.6 (CH-CH_2), 52.2 (CH-CH_2), 76.4 ($C(\Phi)_3$), 105.8–119.3 (CF_2, CF_3), 120.6 (N–CH=C_{his}), 128.8–130.1 ($CH_{arom.}$), 134 (C_{his}), 137.6 (N–C=N_{his}), 141.7 ($C_{arom.}$), 169.7 (NH-CO), 172.9 (CO-OH). ^{19}F NMR (DMSO-d_6, 235.19 MHz): δ −80.2 (3F, s, CF_3), −113.3 (2F, s, CH_2-CF_2), −121.4 to −122.9 (10F, m, 5 CF_2), −125.5 (2F, s, CF_2-CF_3).

***O*-Benzyl *N*-[2-((2,3,4,6-tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethyl]carbamate (6).** *O*-Benzyl-*N*-hydroxyethylcarbamate (4 g, 20.51 mmol), $Hg(CN)_2$ (7.77 g, 30.76 mmol) and molecular sieves (3 Å) (2 g) were stirred in 50 mL of anhydrous and degassed acetonitrile under argon. After stirring for 15 min, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (12.64 g, 30.76 mmol) was added and the reaction mixture was stirred for 1 d at room temperature. The resulting mixture was filtered and the solvent was removed from the filtrate *in vacuo*. The crude product was dissolved in ethyl acetate (100 mL) and the organic layer washed successively with 10% $NaHCO_3$ solution, 10% KI solution, 10% sodium thiosulfate solution. The solution was dried over sodium sulfate, concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel (cHex–AcOEt 6 : 4) to yield 6.78 g (12.91 mmol, 63%) of compound **6** as a white solid. R_f: 0.46 (cHex–AcOEt 4 : 6), mp: 46–48 °C. $[\alpha]_D^{20}$: +20.7 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.95–2.13 (12H, m, CH_3CO), 3.38 (2H, m, CH_2-NH), 3.89 (2H, t, O-CH_2, J^3 = 6 Hz), 4.11 (3H, m, $CH_{(5)}$, $CH_{2(6)}$), 4.45 (1H, d, $CH_{(1)}$, J^3 = 7,5 Hz), 4.96–5.49 (6H, m, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, CH_2-Φ, NH), 7.31 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.6 (CH_3CO), 61.3–70.6 (CH_2-Φ, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{(6)}$), 101.5 ($C_{1\beta}$) 128.3 ($CH_{arom.}$), 136.4 ($C_{arom.}$), 156.4 (CO-CH_2-Φ), 169.7–170.5 (CO-CH_3).

***N*-[2-((2,3,4,6-Tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethyl]-22-(*N*-*tert*-butyloxycarbonylamino)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (7).** Compound **6** (604 mg, 1.15 mmol) was dissolved in 10 mL of ethanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (69 mg, 60 mg $mmol^{-1}$) was added portionwise. The mixture was stirred under hydrogen pressure (8 bars) for 12 h at room temperature. The mixture was filtered over Celite and the solvent removed *in vacuo*. The crude product was dissolved in 5 mL of freshly distilled DCM. Compound **3a** (713 mg, 0.96 mmol) and BOP reagent (508 mg, 1.15 mmol) were added. The mixture was basified to pH = 8 with DIEA. After stirring for 12 h under argon, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (cHex–AcOEt 5 : 5 to cHex–AcOEt 2 : 8) to yield 514 mg (0.46 mmol, 48%) of compound **7** as a white solid. R_f: 0.6 (AcOEt), mp: 45–47 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.35 (12H, m, $CH_{2\ chain}$), 1.46 (9H, s, $C(CH_3)_3$), 1.61 (4H, m, NH-CO-CH_2-CH_2, CH_2-CH_2-CF_2), 1.76 (2H, m, CF_2-CH_2-CH_2-CH_2-NH(Boc)), 1.96–2.30 (18H, m, CH_3CO, 2 CH_2-CF_2, NH-CO-CH_2), 3.15 (2H, t, CH_2-NH(Boc), J^3 = 6.5 Hz), 3.37 (2H, m, CH_2NH), 3.70 (1H, m, OCH_2), 3.86 (1H, m, OCH_2), 4.15 (3H, m, $CH_{2(6)}$, $CH_{(5)}$), 4.68 (1H, d, $CH_{(1)}$, J = 7.25 Hz), 4.91–5.51 (4H, m, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 19.1–20.7 (CH_3-CO, CH_2-CH_2-NH(Boc), NH-CO-CH_2-CH_2), 25.6–29.1 ($CH_{2\ chain}$, 2 CH_2-CF_2, $C(CH_3)_3$, NH-CO-CH_2), 35.7 (CH_2-NH(Boc)), 38.9 (OCH_2-CH_2-NH), 61.2 ($CH_{2(6)}$), 67.4–71 (OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$), 78.7 ($C(CH_3)_3$), 100.8 ($C_{1\beta}$), 105.3–122.5 (CF_2), 157.1 (CO_{Boc}), 170.1–170.6 (CO-CH_3), 175.1 (NH-CO-CH_2). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −115.3 (4F, s, 2 CH_2-CF_2), −122.8 to −124.5 (12F, m, 6 CF_2).

***N*-[2-((2,3,4,6-Tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethyl]-22-[2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-6-(benzyloxycarbonylamino)hexanamido]-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (8a).** Compound **7** (200 mg, 0.179 mmol) was dissolved in 5 mL of TFA–CH_2Cl_2 2 : 8 mixture After stirring for 1 h the solvent was removed *in vacuo*. The crude product was dissolved in 10 mL of ethyl ether and the solvent removed *in vacuo*. The operation was repeated twice until total removal of TFA. The crude product was dissolved in 5 mL of freshly distilled DCM. Compound **5a** (162 mg, 0.215 mmol) and TBTU (75 mg, 0.233 mmol) were added. The mixture was basified to pH = 8–9 with DIEA. After stirring for 16 h under argon in boiling DCM (CH_2Cl_2), the solvent was removed *in vacuo*, the crude product was purified by flash chromatography on silica gel (AcOEt–cHex 8 : 2) and filtration by size exclusion chromatography using LH20 (MeOH–CH_2Cl_2 1 : 1) to yield 220 mg (0.12 mmol, 70%) of fully protected compound **8a** as a white solid. R_f: 0.46 (AcOEt), mp: 100–101 °C. $[\alpha]_D^{20}$: −4.17 (*c* 1, CH_2Cl_2), ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.21–1.72 (24H, m, $CH_{2\ chain}$, CH_2-CH_2-CH_2-NH(Z), CF_2-CH_2-CH_2-CH_2-NH, CH-CH_2), 1.90–2.11 (18H, m, CH_3CO, 2 CH_2-CF_2, NH-CO-CH_2), 2.39 (4H, m, C_8F_{17}-CH_2-CH_2), 2.97 (2H, m, CH_2-NH-(Z)), 3.17 (4H, m, CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH), 3.51 (1H, m, OCH_2), 3.64 (1H, m, OCH_2), 4.04 (3H, m, CH-CH_2, $CH_{2(6)}$), 4.18 (1H, m, $CH_{(5)}$), 4.82 (1H, d, $CH_{(1)}$, J^3 = 8 Hz), 4.90–5.00 (3H, m, $CH_{(2)}$, CH_2-Φ), 5.15 (1H, dd, $CH_{(3)}$, J^3 = 3.25 Hz, J^3 = 10.5 Hz), 5.26 (1H, m, $CH_{(4)}$), 7.25 (1H, m, NH), 7.29 (5H, s, $CH_{arom.}$), 7.78 (1H, m, NH), 7.99 (1H, m, NH), 8.25 (1H, m, NH-CH). ^{13}C NMR (DMSO-d_6, 62.86 MHz): δ 20.0–31.3 (CO-CH_3, $CH_{2\ chain}$, CF_2-CH_2-CH_2-CO, CH_2-CF_2, CF_2-$(CH_2)_2$-CH_2-NH, CH-CH_2-CH_2-CH_2), 35.7–41.0 (OCH_2-CH_2-NH, CF_2-$(CH_2)_2$-CH_2-NH, CH_2-NH(Z)), 54.2 (CH-CH_2), 61.7 ($CH_{2(6)}$), 65.5–

71.1 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, CH_2-Φ, OCH_2-CH_2), 100.5 ($C_{1\beta}$), 105.9–119.8 (CF_2, CF_3), 128.2–128.8 ($CH_{arom.}$), 137.7 ($C_{arom.}$), 156.5 (NH-CO-O), 169.6–172.8 (CO-CH_3, NH-CO-CH_2, NH-CO-CH, CH-NH-CO). ^{19}F NMR (DMSO-d_6, 235.19 MHz): δ −80.2 (3F, s, CF_3), −114.3 (6F, s, 3 CF_2), −121.8 to −123.4 (22F, m, 11 CF_2), −126 (2F, s, CF_2). m/z (FAB$^+$MS): [M + H$^+$] 1753, [M + Na$^+$] 1775.

***N*-[2-(β-D-Galactopyranosyloxy)ethyl]-22-[2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-6-(benzyloxycarbonylamino)hexanamido]-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (deacetylated compound 8a).** Compound **8a** (180 mg, 0.103 mmol) was dissolved in 10 mL of MeOH. A catalytic amount of sodium methylate was added. After stirring for 6 h, IRC50 ion exchange resin (1 g) was added. After 10 min the mixture was filtered. The solvent was removed *in vacuo* and the crude product purified by filtration by size exclusion chromatography using LH20 (MeOH) to yield 153 mg (0.096 mmol, 94%) of deacetylated compound **8a** as a white solid. R_f: 0.67 (AcOEt –MeOH–H_2O 7 : 2 : 1). ^{1}H NMR (CD_3OD, 250 MHz): δ 1.18–1.85 (24H, m, $CH_{2\ chain}$, CH_2-CH_2-CH_2-NH(Z), CF_2-CH_2-CH_2-CH_2-NH, CH-CH_2), 2.08–2.26 (6H, m, 2 CH_2-CF_2, NH-CO-CH_2), 2.46–2.64 (4H, m, C_8F_{17}-CH_2-CH_2), 3.11–3.97 (14H, m, CH_2-NH(Z), CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$), 4.26 (2H, m, $CH_{(1)}$, CH-CH_2), 5.09 (2H, s, CH_2-Φ), 7.33 (5H, s, $CH_{arom.}$). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 19.9–30.9 ($CH_{2\ chain}$, CF_2-CH_2-CH_2-CO, CH_2-CF_2, CF_2-CH_2-CH_2-CH_2-NH, CH-CH_2-CH_2-CH_2), 35.7–40.0 (OCH_2-CH_2-NH, CF_2-$(CH_2)_2$-CH_2-NH, CH_2-NH-(Z)), 54.1 (CH-CH_2), 61.1 ($CH_{2(6)}$), 65.9–73.3 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, CH_2-Φ, OCH_2-CH_2), 103.7 ($C_{1\beta}$), 104.5–123.6 (CF_2, CF_3), 127.3–128.1 ($CH_{arom.}$), 137 ($C_{arom.}$), 157.6 (NH-CO-O), 168.5–175.0 (NH-CO-CH_2, NH-CO-CH, CH-NH-CO). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −82.2 (3F, s, CF_3), −115.1 (6F, s, 3 CF_2), −122.6 to −124.3 (22F, m, 11 CF_2), −127.0 (2F, s, CF_2).

***N*-[2-(β-D-Galactopyranosyloxy)ethyl]-22-[2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-6-(ammonio)hexanamido]-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide trifluoroacetate (A).** Deacetylated compound **8a** (153 mg, 0.0966 mmol) was dissolved in 10 mL of methanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (20 mg, 200 mg mmol^{-1}) was added portionwise. TFA (22 mg, 0.193 mmol) was added and the mixture was stirred under hydrogen pressure (8 bar) for 48 h. The mixture was filtered over Celite and the solvent removed *in vacuo*. The crude product was dissolved in diethyl ether and the solvent removed *in vacuo*. The operation was repeated twice until total removal of TFA was achieved. The crude product was purified by filtration by size exclusion chromatography using LH20 (MeOH) to yield 142 mg (0.090 mmol, 94%) of final compound **A** as a white solid, mp (dec) > 123 °C. $[\alpha]_D^{20}$: −3.07 (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.35–1.86 (24H, m, $CH_{2\ chain}$, CH_2-CH_2-CH_2-NH_3^+, CF_2-CH_2-CH_2-CH_2-NH, CH-CH_2), 2.07–2.25 (6H, m, 2 CH_2-CF_2, NH-CO-CH_2), 2.44–2.67 (4H, m, C_8F_{17}-CH_2-CH_2), 2.90–3.96 (14H, m, CH_2-NH_3^+, CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$), 4.27–4.30 (2H, m, $CH_{(1)}$, CH-CH_2). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 22,4–30,7 ($CH_{2\ chain}$, CF_2-CH_2-CH_2-CO, CH_2-CF_2, CF_2-CH_2-CH_2-CH_2-NH, CH-CH_2-CH_2-CH_2), 35.7–42.0 (OCH_2-CH_2-NH, CF_2-$(CH_2)_2$-CH_2-NH, CH_2-NH_3^+), 53.7 (CH-CH_2), 61.1 ($CH_{2(6)}$), 68.2–75.3 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, OCH_2-CH_2), 103.7 ($C_{1\beta}$), 106.9–123.2 (CF_2, CF_3), 171.5–173.1–175.1 (3 NH-CO).^{19}F NMR (CD_3OD, 235.19 MHz): δ −76.8 (3F, s, CF_3-CO_2^-), −82.2 (3F, s, CF_3), −115.3 (6F, s, 3 CF_2), −122.6 to −124.3 (22F, m, 11 CF_2), −127 (2F, s, CF_2). m/z (FAB$^+$MS): [M$^+$] 1451 (without CF_3COO^-). Elemental analysis calculated for $C_{49}H_{60}F_{36}N_4O_{11} \cdot 2H_2O$: C: 36.76, H: 4.03, N: 3.50; found C: 37.19, H: 4.14, N: 3.72%.

***N*-[2-((2,3,4,6-Tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethyl]-22-[2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-3-(N^{im}-(trityl)imidazoyl)propanamido]-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (8b).** The same procedure as used for compound **8a** was applied to compound **8b**. From compound **7** (226 mg, 0.20 mmol), compound **5b** (209 mg, 0.24 mmol) and TBTU (83.5 mg, 0.26 mmol), 277 mg (0.15 mmol, 73%) of compound **8b** was obtained as a white powder after purification by flash chromatography on silica gel (AcOEt) and filtration by size exclusion chromatography using LH20 (MeOH–CH_2Cl_2 1 : 1). R_f: 0.7 (AcOEt–MeOH 9.5 : 0.5), mp: 72.7–74.5 °C. $[\alpha]_D^{20}$: +2.76 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz, 45 °C): δ 1.25–1.32 (12H, m, $CH_{2\ chain}$), 1.62 (4H, m, NH-CO-CH_2-CH_2, CH_2-CH_2-CF_2), 1.82 (2H, m, CF_2-CH_2-CH_2-CH_2-NH), 2.00–2.22 (18H, m, CH_3CO, 2 CH_2-CF_2, NH-CO-CH_2), 2.55 (4H, m, C_8F_{17}-CH_2-CH_2), 2.89 (1H, m, CH-CH_2), 3.05 (1H, m, CH-CH_2), 3.31 (2H, m, CF_2-$(CH_2)_2$-CH_2-NH), 3.50 (2H, m, OCH_2-CH_2-NH), 3.72 (1H, m, OCH_2-CH_2-NH), 3.92 (2H, m, OCH_2-CH_2-NH, $CH_{(5)}$), 4.16 (2H, d, $CH_{2(6)}$, J^3 = 6.75 Hz), 4.50 (1H, d, $CH_{(1)an}$, J^3 = 7.85 Hz), 4.60 (1H, td, CH-CH_2, J^3 = 5.15 Hz), 5.05 (1H, dd, $CH_{(2)}$, J^3 = 3.35 Hz, J^3 = 10.45 Hz), 5.21 (1H, dd, $CH_{(3)}$, J^3 = 2.55 Hz, J^3 = 10.4 Hz), 5.43 (1H, m, $CH_{(4)}$), 5.86 (1H, m, NH-CO-CH), 6.70 (1H, s, N-CH=C_{his}), 7.10–7.16 (6H, m, N-CH=N_{his}, $CH_{arom.}$), 7.29–7.38 (10H, m, $CH_{arom.}$), 7.61 (1H, d, CH-NH, J^3 = 6.25 Hz), 7.69 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.1–20.8 (CF_2-CH_2-CH_2-CH_2-NH, CH_2-CH_2-CF_2, CH_3CO), 25.7–30.9 ($CH_{2\ chain}$, NH-CO-CH_2-CH_2, 2 CH_2-CF_2, C_8F_{17}-CH_2-CH_2, CH-CH_2), 36.7 (NH-CO-CH_2), 38.5–39.1 (CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH), 53.5 (CH-CH_2), 61.3 ($CH_{2(6)}$), 67.0–70.8 (OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$), 75.5 ($C(\Phi)_3$), 101.5 ($C_{1\beta}$), 106.2–118.9 (CF_2, CF_3), 119.7 (N-CH=C_{his}), 128.1–129.7 ($CH_{arom.}$), 136.8 (N-CH=N_{his}), 138.2 (CH_2-C_{his}), 142.1 ($C_{arom.}$), 169.7–173.2 (CH_3CO, NH-CO-CH_2, NH-CO-CH, CH-NH-CO). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −80.7 (3F, s, CF_3), −114.2 to −114.6 (6F, m, CH_2-CF_2, CF_2), −121.9 to −123.5 (22F, m, CF_2), −126.1 (2F, s, CF_2-CF_3). m/z (FAB$^+$MS): [M + H$^+$] 1870, [M + Na$^+$] 1892.

***N*-[2-(β-D-Galactopyranosyloxy)ethyl]-22-[2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-3-(N^{im}-(trityl)imidazoyl)propanamido]-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (deacetylated**

compound 8b). The same procedure as used for the deacetylation of compound **8a** was applied to deacetylated compound **8b**. From compound **8a** (267 mg, 0.143 mmol), 228 mg of deacetylated compound **8b** (0.13 mmol, 94%) was obtained as a white powder after purification by size exclusion chromatography using LH20 (MeOH). R_f: 0.63 (AcOEt–MeOH–H_2O 7 : 2 : 1). ^{1}H NMR (CD_3OD, 250 MHz): δ 1.31–1.47 (12H, m, $CH_{2\ chain}$), 1.62 (4H, m, NH-CO-CH_2-CH_2, CH_2-CH_2-CF_2), 1.80 (2H, m, CF_2-CH_2-CH_2-CH_2-NH), 2.05–2.25 (6H, m, 2 CH_2-CF_2, NH-CO-CH_2), 2.39–2.49 (4H, m, C_8F_{17}-CH_2-CH_2), 2.84 (1H, dd, CH-CH_2), 2.92 (1H, dd, CH-CH_2), 3.21–3.89 (12H, m, CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$), 4.26 (1H, d, $CH_{(1)}$, J^3 = 6.85 Hz), 4.54 (1H, m, CH-CH_2), 6.76 (1H, s, N-CH=C_{his}), 7.12–7.16 (6H, m, N–CH=N_{his}, $CH_{arom.}$), 7.36–7.41 (10H, m, $CH_{arom.}$), 8.54 (3H, m, NH). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 19.9 (CF_2-CH_2-CH_2-CH_2-NH, CH_2-CH_2-CF_2), 25.6–30.4 ($CH_{2\ chain}$, NH-CO-CH_2-CH_2, 2 CH_2-CF_2, C_8F_{17}-CH_2-CH_2, CH-CH_2), 35.7 (NH-CO-CH_2), 37.9–39.2 (CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH), 53.9 (CH-CH_2), 61.1 ($CH_{2(6)}$), 68.3–75.5 (OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $C(\Phi)_3$), 103.7 ($C_{1\beta}$), 106.9–119.3 (CF_2, CF_3), 119.7 (N–CH=C_{his}), 127.9–129.5 ($CH_{arom.}$), 136.2 (N–CH=N_{his}), 138.1 (CH_2-C_{his}), 142.2 ($C_{arom.}$), 171–175 (NH-CO-CH_2, NH-CO-CH, CH-NH-CO). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −82.2 (3F, s, CF_3), −115.1 (6F, s, 3 CF_2), −122.5 to −124.3 (22F, m, 11 CF_2), −126.9 (2F, s, CF_2).

***N*-[2-(β-D-Galactopyranosyloxy)ethyl]-22-[2-(4, 4, 5,5,6,6,7,7, 8,8,9,9,10,10,11,11,11-heptadecafluoroundecanamido)-3-(imidazolio)propanamido]-12,12,13,13,14,14,15,15,16,16, 17,17,18,18, 19,19-hexadecafluorodocosanamide trifluoroacetate (B).** Deacetylated compound **6a** (213 mg, 0.125 mmol) was dissolved in 5 mL of ethanol. Et_3SiH (15.5 mg, 0.125 mmol) and 15 mL of DCM–TFA 8 : 2 were added to the mixture. After stirring for two days, ethanol and TFA were removed *in vacuo*. The crude product was dissolved in diethyl ether and the solvent removed *in vacuo*. The operation was repeated twice. 175 mg of final compound **B** (0.11 mmol, 89%) was obtained as a white powder after purification by filtration by size exclusion chromatography using LH20 (MeOH), mp (dec) > 145 °C. $[\alpha]_D^{20}$: +2.61 (*c* 1, CH_2Cl_2). ^{1}H NMR (CD_3OD, 250 MHz): δ 1.23 (12H, m, $CH_{2\ chain}$), 1.50 (4H, m, NH-CO-CH_2-CH_2, CH_2-CH_2-CF_2), 1.70 (2H, m, CF_2-CH_2-CH_2-CH_2-NH), 2.07–2.13 (6H, m, 2 CH_2-CF_2, NH-CO-CH_2), 2.39–2.46 (4H, m, C_8F_{17}-CH_2-CH_2), 2.89–3.85 (14H, m, CH-CH_2, CF_2-CH_2-CH_2-CH_2-NH, OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$), 4.17 (1H, d, $CH_{(1)}$), 4.52 (1H, m, CH-CH_2), 7.21 (1H, s, N–CH=C_{his}), 8.62 (1H, s, N–CH=N_{his}). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 19.9 (CF_2-CH_2-CH_2-CH_2-NH, CH_2-CH_2-CF_2), 25.6–39.1 ($CH_{2\ chain}$, NH-CO-CH_2-CH_2, 2 CH_2-CF_2, C_8F_{17}-CH_2-CH_2, CH-CH_2), 35.7 (NH-CO-CH_2), 38.0–39.2 (CF_2-$(CH_2)_2$-CH_2-NH, OCH_2-CH_2-NH), 52.8 (CH-CH_2), 61.1 ($CH_{2(6)}$), 68.2–75.4 (OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$), 103.7 ($C_{1\beta}$), 106.1–119.2 (CF_2), 117.9 (N–CH=C_{his}), 130.2 (N–CH=N_{his}), 133.8 (CH_2-C_{his}), 171.0–175.4 (NH-CO-CH_2, NH-CO-CH, CH-NH-CO). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −76.8 (3F, s, CF_3-CO_2^-), −82.3 (3F, s, CF_3), −115.4 to −115.8 (6F, s, CF_2), −122.8 to −124.6 (22F, m, CF_2), −127.2 (2F, s, CF_2). *m*/*z* (FAB^+MS): [M^+] 1460 (without CF_3COO^-). Elemental analysis calculated for $C_{49}H_{55}F_{36}N_5O_{11}$: C: 37.39, H: 3.50, N: 4.45; found C: 37.79, H: 3.74, N: 4.38%.

***N*-Dodecyl-[N^{α}-((9*H*-fluorenyl)methyloxycarbonyl)-N^{im}-(trityl)]histidinamide (9).** Fmoc-Hist(Trt)OH (3 g, 4.84 mmol), DCC (1.2 g, 5.81 mmol) and HOBT (0.785 g, 5.81 mmol) were dissolved in 30 mL of DCM freshly distilled and degassed under argon. After stirring for 15 min, dodecylamine (0.986 g, 5.33 mmol) was added and the mixture stirred for 2 d. The mixture was then filtered and the solvent removed from the filtrate *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 4 : 6) to yield 3.14 g (3.99 mmol, 82%) of compound **9** as a white solid. R_f: 0.35 (AcOEt–cHex 4 : 6), mp: 59–61 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.90 (3H, t, CH_3, J^3 = 6.86 Hz), 1.21–1.30 (20H, m, $CH_{2\ chain}$), 2.93 (1H, m, CH-$CH_{2\ his}$), 3.18–3.33 (3H, m, CH-$CH_{2\ his}$, CO-NH-CH_2), 4.11–4.33 (3H, m, CH-$CH_{2\ Fmoc}$), 4.65 (1H, m, CH-$CH_{2\ hist}$), 5.79 (2H, m, 2 NH), 6.72 (1H, s, N–CH=C_{his}), 7.04–7.78 (24H, m, $CH_{Trt.}$, $CH_{Fmoc.}$, N–CH=N_{his}). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.2 (CH_3), 22.7–31.9 ($CH_{2\ chain}$, CH-$CH_{2\ his}$), 39.8 (CO-NH-CH_2), 47.1 (CH-$CH_{2\ Fmoc}$), 55.0 (CH-$CH_{2\ his}$), 67.2 (CH-$CH_{2\ Fmoc}$), 76.3 ($C(\Phi)_3$), 119.1–129.6 (N–CH=C_{his}, $CH_{arom.(Trt)}$, $CH_{arom.\ (Fmoc)}$), 135.0–137.5 (N–CH=N_{his}, CH_2-C_{his}), 141.3–143.9 ($C_{arom.\ (Trt)}$, $C_{arom.\ (Fmoc)}$), 156.2 (O-CO-NH), 170.9 (CO-NH-CH_2).

***N*-Dodecyl-[N^{α}-(benzyloxycarbonyl)-N^{ε}-(*tert*-butyloxycarbonyl)]lysinamide (10).** Z-Lys(Boc)OH (1 g, 2.63 mmol), DCC (0.651 g 3.16 mmol) and HOBT (0.427 g, 3.16 mmol) were dissolved in 20 mL of freshly distilled DCM. After stirring for 15 min under argon, dodecylamine (0.532 g, 2.89 mmol) was added and the mixture was stirred for 2 d at room temperature. The mixture was filtered and the solvent removed from the filtrate *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 4 : 6) to yield 1.3 g (2.3 mmol, 90%) of compound **10** as a white solid. R_f: 0.49 (AcOEt–cHex 4 : 6), mp: 83–85 °C. $[\alpha]_D^{20}$: +2.77 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.90 (3H, t, CH_3, J^3 = 6.77 Hz), 1.14–1.37 (20H, m, $CH_{2\ chain}$, CH-CH_2-CH_2), 1.44 (9H, m, $C(CH_3)_3$), 1.59–1.91 (6H, m, 2 CH_2-CH_2-NH, CH_2-CH), 3.10 (2H, m, CO-NH-CH_2), 3.24 (2H, m, CH_2-NH(Boc)), 4.15 (1H, m, CH-CH_2), 4.65 (1H, s, NH), 5.12 (2H, s, CH_2-Φ), 5.55 (1H, s, NH), 6.19 (1H, s, NH), 7.31 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.1 (CH_3), 22.4–31.1 ($CH_{2\ chain}$, CH-CH_2-$(CH_2)_2$, $C(CH_3)_3$), 33.9 (CO-NH-CH_2), 39.6 (CH_2-NH(Boc)), 49.1 (CH-CH_2), 54.9 $C(CH_3)_3$), 67.0 (CH_2-Φ), 128.0–128.5 ($CH_{arom.}$), 132.2 ($C_{arom.}$), 156.2 (HN-CO-O), 171.5 (CH-CO-NH).

***N*-[1-(Dodecylcarbamoyl)-4-(*tert*-butyloxycarbonylamino)butyl] - 22 -(benzyloxycarbonylamino)-12,12,13,13,14,14,15,15,16, 16,17,17,18,18,19,19-hexadecafluorodocosanamide (11a).** Compound **10** (300 mg, 0.548 mmol) was dissolved in 10 mL of ethanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (33 mg, 60 mg $mmol^{-1}$) was added portionwise. The mixture was stirred under hydrogen pressure (8 bar) for 6 h at room temperature. The mixture was filtered over Celite and the solvent removed *in vacuo*. The crude

product was dissolved in 5 mL of freshly distilled DCM. Compound **3b** (327.8 mg, 0,422 mmol) and TBTU reagent (176 mg, 0.548 mmol) were added. The mixture was basified to a pH of 8 with DIEA. After stirring for 12 h under argon at room temperature, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (cHex–AcOEt 5 : 5 to cHex–AcOEt 5 : 5) to yield 415.3 mg (0.35 mmol, 84%) of compound **11a** as a white solid. R_f: 0.5 (AcOEt–cHex 5 : 5), mp: 90–91 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.89 (3H, t, CH_3, J^3 = 6.82 Hz), 1.17–1.35 (32H, m, CH_2 $_{chain}$, CH-CH_2-CH_2), 1.45 (9H, s, $C(CH_3)_3$), 1.51–1.70 (10H, m, 3 CH_2-CH_2-NH, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.82–2.24 (8H, m, CH-CH_2, 2 CH_2-CF_2, CH_2-CO-NH), 3.09 (2H, m, CH_2-NH-CO-CH), 3.18–3.32 (4H, m, CH_2-NH(Boc), (Z)NH-CH_2), 4.41 (1H, td, CH-CH_2, J^3 = 6.42 Hz, J^3 = 7.37 Hz), 4.71 (1H, s, NH), 5.00 (1H, s, NH), 5.12 (2H, s, CH_2-Φ), 6.43 (1H, d, NH-CH-CH_2, J^3 = 7.35 Hz), 6.60 (1H, s, NH), 7.35 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.0 (CH_3), 20.1–31.1 (CH_2 $_{chain}$, CH-CH_2-CH_2, $C(CH_3)_3$, 3 CH_2-CH_2-NH, CH_2-CH_2-CO-NH, 2 CH_2-CF_2), 36.6–40.2 (CH_2-NH-CO-CH, CH_2-NH(Boc), NH-CH_2-$(CH_2)_2$-CF_2), 52.3 (CH-CH_2), 66.9 (CH_2-Φ), 79.1 ($C(CH_3)_3$), 106.9–119.0 (CF_2), 128.1–128.6 ($CH_{arom.}$), 136.4 ($C_{arom.}$), 156.2 (NH-CO-O), 156.5 (NH-CO-O), 171.7 (CO-NH), 173.4 (CO-NH). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.1 to −114.3 (4F, d, 2 CH_2-CF_2), −121.8 (8F, m, 4 CF_2), −123.5 (4F, s, 2 CF_2).

***N*-[1-(Dodecylcarbamoyl)-2-(N^{im}-(trityl)imidazolyl)ethyl]-22-(benzyloxycarbonylamino)-12, 12, 13, 13, 14, 14, 15,15,16,16,17, 17,18,18,19,19-hexadecafluorodocosanamide (11b).** Compound **9** (607 mg, 0.772 mmol) was dissolved in 10 mL of a mixture of acetonitrile–DIEA 9 : 1. After stirring for 1 h at room temperature, the solvent was removed *in vacuo*. The crude product was dissolved in 5 mL of dry DCM under argon. Compound **3b** (400 mg, 0.515 mmol) and TBTU reagent (215 mg, 0.669 mmol) were added to the solution. The mixture was basified to pH = ~8–9 with few drops of DIEA and stirred for 12 h under argon at room temperature. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (AcOEt–cHex 3 : 7 to AcOEt–cHex 6 : 4) and filtration by size exclusion chromatography using LH20 (MeOH) to yield 525 mg (0.39 mmol, 77%) of compound **11b** as a white solid. R_f: 0.43 (AcOEt–cHex 5 : 5), mp: 87–88 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.89 (3H, t, CH_3, J^3 = 6.84 Hz), 1.20–1.50 (32H, m, CH_2 $_{chain}$), 1.53–1.62 (4H, m, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.82 (2H, m, NH-CH_2-CH_2-CH_2-CF_2), 1.87–2.23 (6H, m, 2 CH_2-CF_2, CH_2-CO-NH), 2.93 (2H, m, CH-CH_2), 3.17 (2H, m, CH_2-NH-CO), 3.26 (2H, m, NH-CH_2-$(CH_2)_2$-CF_2), 4.68 (1H, td, CH-CH_2, J^3 = 6.1 Hz, J^3 = 6.56 Hz), 5.08 (1H, s, NH), 5.10 (2H, s, CH_2-Φ), 6.68 (1H, s, C=CH-N_{hist}), 7.09–7.42 (23H, m, $CH_{arom.}$, N-CH=N_{his}, 2 NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.1 (CH_3), 20.1–31.9 (CH_2 $_{chain}$, 2 CH_2-CF_2, 2 NH-CH_2-CH_2, CH-CH_2), 36.6–42.0 (CH_2-CO-NH, 2 CH_2-NH-CO), 53.1 (CH-CH_2), 66.7 (CH_2-Φ), 75.6 ($C(Φ)_3$), 106.0–118.7 (CF_2), 119.0 (N-CH=C_{his}), 128.1–129.7 ($CH_{arom.}$), 136.7–137.9 (N-CH=N_{his}, CH_2-C_{his}), 142.1 ($C_{arom.}$), 156.6 (O-CO-NH), 171.1 –173.3 (CH_2-CO-NH, NH-CO-CH). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.0 to −114.3 (4F, d, 2 CH_2-CF_2), −121.7 (8F, m, 4 CF_2), −123.4 (4F, s, 2 CF_2).

***N*-[1-(Dodecylcarbamoyl)-4-(*tert*-butyloxycarbonylamino)butyl] - 22 - [(2, 3, 5, 6, 2′, 3′, 4′, 6′-octa-*O*-acetyl)lactobionamido]-12, 12, 13, 13, 14, 14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (12a).** Compound **11a** (375 mg, 0.320 mmol) was dissolved in 10 mL of ethanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (70 mg, 220 mg $mmol^{-1}$) was added portionwise. The mixture was stirred under hydrogen pressure (8 bar) for 48 h at room temperature. The mixture was filtered over Celite and the solvent removed *in vacuo* to obtain the amine. At the same time, lactobionic acid (168 mg, 4.705 mmol) was dissolved in 20 mL of a mixture of toluene–2-methoxyethanol 1 : 1. A few drops of TFA were added and the solvents were removed *in vacuo*. The operation was repeated twice and the crude product obtained was added to the previous amino compound. The mixture was dissolved in 20 mL of methanol under argon and basified at pH = 8–9 with few drops of TEA. The mixture was refluxed under argon for 12 h. The solvent was removed *in vacuo* and a mixture of acetic anhydride–pyridine 1 : 1 (20 mL) was added. The reaction was stirred for 12 h at room temperature. The mixture was poured into cooled 1 M HCl solution and the solution extracted with ethyl acetate. The organic layer was washed with saturated sodium hydrogencarbonate solution, then with brine. The organic layer was dried over sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 5 : 5 to AcOEt–cHex 8 : 2) to yield 370 mg (0.21 mmol, 67%) of fully protected compound **12a** as a white solid. R_f: 0.07 (AcOEt–cHex 5 : 5), mp: 83–84 °C. $[\alpha]_D^{20}$: +5.09 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.89 (3H, t, CH_3, J^3 = 6.85 Hz), 1.28–1.40 (32H, m, CH_2 $_{chain}$, CH-CH_2-CH_2), 1.45 (9H, s, $C(CH_3)_3$), 1.49–1.66 (10H, m, 3 CH_2-CH_2-NH, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.80–2.21 (32H, m, CH-CH_2, 8 CO-CH_3, 2 CH_2-CF_2, CH_2-CO-NH), 3.09–3.42 (6H, m, CH_2-NH-CO-CH, CH_2-NH(Boc), NH-CH_2-$(CH_2)_2$-CF_2), 3.93 (1H, m, $CH_{(5')}$), 4.06–4.39 (3H, m, $CH_{2(6')}$, $CH_{(6)}$), 4.31–4.39 (2H, m, CH-CH_2, $CH_{(4)}$), 4.47–4.63 (2H, m, $CH_{(6)}$, NH), 4.70 (1H, d, $CH_{(1')}$, J^3 = 7.80 Hz), 4.96–5.20 (3H, m, $CH_{(2')}$, $CH_{(3')}$, $CH_{(5)}$), 5.39 (1H, m, $CH_{(4')}$), 5.56–5.60 (2H, m, $CH_{(2)}$, $CH_{(3)}$), 6.20–6.33 (3H, m, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.0 (CH_3), 20.4–31.9 (CH_2 $_{chain}$, CH-CH_2-CH_2, $C(CH_3)_3$, 3 CH_2-CH_2-NH, CH_2-CH_2-CO-NH, 2 CH_2-CF_2, CO-CH_3), 36.6–39.6 (CH_2-NH-CO-CH, CH_2-NH(Boc), NH-CH_2-$(CH_2)_2$-CF_2), 52.9 (CH-CH_2), 60.9 ($CH_{2(6')}$), 61.8 ($CH_{2(6)}$), 66.9–71.6 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$), 77.4 ($CH_{(4)}$), 79.1 ($C(CH_3)_3$), 101.6 ($C_{1'\beta}$), 106.9–123.0 (CF_2), 156.1 (NH-CO-O), 167.4–173.2 (3 CO-NH, CO-CH_3). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.1 to −114.4 (4F, d, 2 CH_2-CF_2), −121.7 (8F, m, 4 CF_2), −123.4 (4F, s, 2 CF_2). *m*/*z* (FAB$^+$MS): [M + 2H$^+$] 1716.

***N*-[1-(Dodecylcarbamoyl)-4-(*tert*-butyloxycarbonylamino)butyl]-22-lactobionamido-12,12,13,13,14,14,15,15,16,16,17,17,18, 18,19,19-hexadecafluorodocosanamide (deacetylated compound 12a).** The same procedure as used for the deacetylation of compound **8a** was applied to compound **12a**. From compound **12a** (320 mg, 0.187 mmol), we obtained after purification by

filtration by size exclusion chromatography usingLH20 (MeOH), 237 mg of deacetylated compound **12a** (0.17 mmol, 92%). R_f: 0.72 (AcOEt–MeOH–H_2O 7 : 2 : 1). ^{1}H NMR (CD_3OD, 250 MHz): δ 0.92 (3H, t, CH_3, J^3 = 6.85 Hz), 1.32–1.38 (32H, m, CH_2 $_{chain}$, CH-CH_2-CH_2), 1.45 (9H, s, $C(CH_3)_3$), 1.49–1.62 (10H, m, 3 CH_2-CH_2-NH, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.86 (2H, m, CH-CH_2), 2.05–2.29 (6H, m, 2 CH_2-CF_2, CH_2-CO-NH), 3.04 (2H, td, CH_2-NH(Boc), 3.19 (2H, td, CH_2-NH-CO-CH), 3.33–4.93 (13H, m, NH-CH_2-$(CH_2)_2$-CF_2, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$, $CH_{2(6')}$, NH), 4.25–4.28 (2H, m, CH-CH_2, $CH_{(2)}$), 4.38 (1H, m, $CH_{(3)}$), 4.50 (1H, d, $CH_{(1')}$, J^3 = 7,23 Hz), 6.58 (1H, s, NH), 7.95–8.10 (2H, m, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 12.9 (CH_3), 20.1–31.7 (CH_2 $_{chain}$, CH-CH_2-CH_2, $C(CH_3)_3$, 3 CH_2-CH_2-NH, CH_2-CH_2-CO-NH, 2 CH_2-CF_2), 35.9–39.8 (CH_2-NH-CO-CH, CH_2-NH(Boc), NH-CH_2-$(CH_2)_2$-CF_2), 53.3 (CH-CH_2), 61.2 ($CH_{2(6')}$), 62.4 ($CH_{2(6)}$), 69.0–75.8 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$), 79.2 ($C(CH_3)_3$), 81.9 ($CH_{(4)}$), 104.4 ($C_{1'\beta}$), 106.9–122.8 (CF_2), 157.1 (NH-CO-O), 172.9, 174.1, 174.8 (3 CO-NH). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −115.2 (4F, s, 2 CH_2-CF_2), −122.7 (8F, m, 4 CF_2), −124.4 (4F, s, 2 CF_2).

***N*-[1-(Dodecylcarbamoyl)-4-(ammonio)butyl]-22-(lactobionamido)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide trifluoroacetate (C).** Deacetylated compound **12a** (200 mg, 0.145 mmol) was dissolved in 8 mL of DCM. 2 mL of TFA was added dropwise at room temperature. After stirring for 48 h, the solvents were removed *in vacuo*. The crude product was dissolved in diethyl ether and the solvent removed *in vacuo*. The operation was repeated twice. The crude product was purified by filtration by size exclusion chromatography using LH20 (MeOH) to yield 184 mg of final compound **C** (0.13 mmol, 91%) as a white powder, mp (dec) > 109 °C. $[\alpha]_D^{20}$: +1.06 (*c* 1, MeOH). ^{1}H NMR (CD_3OD, 250 MHz): δ 0.92 (3H, t, CH_3, J^3 = 6.84 Hz), 1.31–1.35 (32H, m, CH_2 $_{chain}$, CH-CH_2-CH_2), 1.46–1.73 (10H, m, 3 CH_2-CH_2-NH, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.83 (2H, m, CH-CH_2), 2.14–2.30 (6H, m, 2 CH_2-CF_2, CH_2-CO-NH), 2.94 (2H, t, CH_2-NH_3^+, J^3 = 7.60 Hz), 3.19–3.93 (1H, m, CH_2-NH-CO-CH, NH-CH_2-$(CH_2)_2$-CF_2, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$, $CH_{2(6')}$), 4.25–4.38 (3H, m, CH-CH_2, $CH_{(2)}$, $CH_{(3)}$), 4.51 (1H, d, $CH_{(1')}$, J^3 = 7.10 Hz). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 12.7 (CH_3), 29.9–31.7 (CH_2 $_{chain}$, CH-CH_2-CH_2, 3 CH_2-CH_2-NH, CH_2-CH_2-CO-NH, 2 CH_2-CF_2), 35.4–39.1 (CH_2-NH-CO-CH, CH_2-NH_3^+, NH-CH_2-$(CH_2)_2$-CF_2), 53.0 (CH-CH_2), 61.2 ($CH_{2(6')}$), 62.3 ($CH_{2(6)}$), 69.0–75.8 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$), 81.9 ($CH_{(4)}$), 104.4 ($C_{1'\beta}$), 106.8–122.9 (CF_2), 172.7, 174.1, 174.9 (3 CO-NH). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −76.8 (3F, s, ^-O_2C-CF_3), −115.3 (4F, s, 2 CH_2-CF_2), −122.7 (8F, m, 4 CF_2), −124.4 (4F, s, 2 CF_2). *m*/*z* (ESI-MS) $[M]^+$ = 1279.8 (without CF_3COO^-). Elemental analysis calculated for $C_{54}H_{87}F_{19}N_4O_{15} \cdot 1H_2O$: C: 45.96, H: 6.36, N: 3.97; found C: 45.97, H: 6.44, N: 4.20%.

***N*-[1-(Dodecylcarbamoyl)-2-(N^{im}-(trityl)imidazolyl)ethyl]-22-[(2, 3, 5,6,2′,3′,4′,6′-octa-*O*-acetyl)lactobionamido]-12,12,13,13, 14, 14, 15, 15, 16,16,17,17,18,18,19,19-hexadecafluorodocosanamide (12b).** The same procedure as used for compound **12a** was applied to compound **12b**. From compound **11b** (373 mg, 0.282 mmol) and lactobionic acid (150 mg, 0.410 mmol), after acetylation, the crude product was purified by flash chromatography on silica gel (AcOEt–cHex 7 : 3 to AcOEt) and filtration by size exclusion chromatography using LH20 (MeOH) to yield 296 mg (0.16 mmol, 58%) of compound **12b** as a white solid. R_f: 0.41 (AcOEt), mp: 80–82 °C. $[\alpha]_D^{20}$: +8.12 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.88 (3H, t, CH_3, J^3 = 6.8 Hz), 1.25–1.43 (32H, m, CH_2 $_{chain}$), 1.52–1.59 (4H, m, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.83 (2H, m, NH-CH_2-CH_2-CH_2-CF_2), 1.99–2.25 (30H, m, CO-CH_3, 2 CH_2-CF_2, CH_2-CO-NH), 2.91–3.8 (6H, m, CH-CH_2, CH_2-NH-CO, NH-CH_2-$(CH_2)_2$-CF_2), 3.93–4.33 (5H, m, $CH_{(4)}$, $CH_{(6)}$, $CH_{(5')}$, $CH_{2(6')}$), 4.53 (1H, dd, $CH_{(6)}$, J^2 = 2.25 Hz, J^3 = 12.15 Hz), 4.65 (1H, d, $CH_{(1')}$, J^3 = 7.85 Hz), 4.99–5.19 (4H, m, CH-CH_2, $CH_{(2')}$, $CH_{(3')}$, $CH_{(5)}$), 5.40 (1H, m, $CH_{(4')}$), 5.53–5.58 (2H, m, $CH_{(2)}$, $CH_{(3)}$), 6.43 (2H, m, NH), 6.78 (1H, s, C=CH-N_{his}), 7.24–7.44 (17H, m, $CH_{arom.}$, N–CH=$N_{his,}$ NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.1 (CH_3), 20.1–20.8 (CO-CH_3), 22.7–31.9 (CH_2 $_{chain}$, 2 CH_2-CF_2, 2 NH-CH_2-CH_2, CH-CH_2), 36.4–39.9 (CH_2-CO-NH, 2 CH_2-NH-CO), 53.3 (CH-CH_2), 60.9 ($CH_{2(6')}$), 61.8 ($CH_{2(6)}$), 66.8–71.6 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$), 76.5 ($C(\Phi)_3$), 78.8 ($CH_{(4)}$), 101.7 ($C_{1'\beta}$), 107.1–118.8 (CF_2), 120.7 (N–CH=C_{his}), 127.9–129.6 ($CH_{arom.}$), 132.7–134.5 (N–CH=N_{hist}, CH_2-C_{his}), 139.5 ($C_{arom.}$), 167.6–174.0 (3 NH-CO, CO-CH_3). ^{19}F NMR ($CDCl_3$, 235.19 MHz): δ −114.0 to −114.3 (4F, d, 2 CH_2-CF_2), −121.7 (8F, m, 4 CF_2), −123.4 (4F, s, 2 CF_2). *m*/*z* (FAB+): $[M + H]^+$ = 1866.

***N*-[1-(Dodecylcarbamoyl)-2-(N^{im}-(trityl)imidazolyl)ethyl]-22-(lactobionamido)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19, 19-hexadecafluorodocosanamide (deacetylated compound 12b).** The same procedure as used for the deacetylation of compound **8a** was applied to compound **12b**. From compound **12b** (250 mg, 0.134 mmol), we obtained after purification by filtration by size exclusion chromatography using LH20 (MeOH), 193 mg of deacetylated compound **12b** (0.126 mmol, 94%). R_f: 0.69 (AcOEt–MeOH–H_2O 7 : 2 : 1). ^{1}H NMR (CD_3OD, 250 MHz): δ 0.90 (3H, t, CH_3, J^3 = 6.74 Hz), 1.24–1.65 (36H, m, CH_2 $_{chain}$, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.86 (2H, m, NH-CH_2-CH_2-CH_2-CF_2), 2.02–2.24 (6H, m, 2 CH_2-CF_2, CH_2-CO-NH), 2.83–3.16 (4H, m, CH-CH_2, CH_2-NH-CO), 3.32–3.97 (12H, m, NH-CH_2-$(CH_2)_2$-CF_2, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$, $CH_{2(6')}$), 4.26 (1H, m, $CH_{(2)}$), 4.38 (1H, m, $CH_{(3)}$), 4.61 (1H, d, $CH_{(1')}$, J^3 = 7.3 Hz), 4.61 (4H, m, CH-CH_2), 6.76 (1H, s, C=CH-N_{his}), 7.10–7.39 (16H, m, $CH_{arom.}$, N–CH=$N_{his,}$ NH). ^{13}C NMR (CD_3OD, 62.86 MHz): δ 13.1 (CH_3), 19.9–7–31.7 (CH_2 $_{chain}$, 2 CH_2-CF_2, 2 NH-CH_2-CH_2, CH-CH_2), 35.6–39.1 (CH_2-CO-NH, 2 CH_2-NH-CO), 53.3 (CH-CH_2), 61.3 ($CH_{2(6')}$), 62.4 ($CH_{2(6)}$), 69.0–75.8 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$, $C(\Phi)_3$), 82.0 ($CH_{(4)}$), 104.4 ($C_{1'\beta}$), 106.5–118.8 (CF_2), 119.6 (N–CH=C_{his}), 127.3–129.5 ($CH_{arom.}$), 136.4–138.0 (N–CH=N_{his}, CH_2-C_{his}), 142.3 ($C_{arom.}$), 172.0–174.1–175.5 (3 NH-CO). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −114.8 (4F, s, 2 CH_2-CF_2), −122.4 (8F, m, 4 CF_2), −124.1 (4F, s, 2 CF_2).

***N*-[1-(Dodecylcarbamoyl)-2-(imidazolio)ethyl]-22-(lactobionamido)-12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-hexadecafluorodocosanamide trifluoroacetate (D).** Deacetylated compound **12b** (170 mg, 0.111 mmol) was dissolved in 5 mL of ethanol. 15 mL of a mixture of DCM–TFA 8 : 2 and Et_3SiH (13 mg, 0.11 mmol) were added to the solution. After stirring for 2 d at room temperature solvents were removed *in vacuo* and the crude product dissolved in diethyl ether. The solvent was removed *in vacuo* and the operation repeated twice. The crude product was purified by filtration by size exclusion chromatography using LH20 (MeOH) to yield 139 mg (0.099 mmol, 89%) of final compound **D** as a white solid, mp (dec) >101 °C. $[\alpha]_D^{20}$: +6.18 (*c* 1, MeOH). ^{1}H NMR (CD_3OD, 250 MHz): δ 0,90 (3H, t, CH_3, J^3 = 6.84 Hz), 1.29–1.59 (36H, m, $CH_{2\ chain}$, CF_2-CH_2-CH_2, CH_2-CH_2-CO-NH), 1.83 (2H, m, NH-CH_2-CH_2-CH_2-CF_2), 1.99–2.23 (6H, m, 2 CH_2-CF_2, CH_2-CO-NH), 2.96–3.91 (16H, m, CH-CH_2, CH_2-NH-CO, NH-CH_2-$(CH_2)_2$-CF_2, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$, $CH_{2(6')}$), 4.24–4.50 (3H, m, $CH_{(2)}$, $CH_{(3)}$, $CH_{(1')}$), 4.68 (4H, m, CH-CH_2,), 7.33 (1H, s, C=CH–N_{his}), 8.82 (1H, s, N–CH=N_{his}). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 13.0 (CH_3), 22.9–3–29.4 ($CH_{2\ chain}$, 2 CH_2-CF_2, 2 NH-CH_2-CH_2, CH-CH_2), 35.4–39.1 (CH_2-CO-NH, 2 CH_2-NH-CO), 52.1 (CH-CH_2), 61.2 ($CH_{2(6')}$), 62.4 ($CH_{2(6)}$), 69.0–75.8 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(5)}$, $CH_{(2')}$, $CH_{(3')}$, $CH_{(4')}$, $CH_{(5')}$), 82.3 ($CH_{(4)}$), 104.2 ($C_{1'\beta}$), 106.5–119.2 (CF_2), 116.5 (N–CH=C_{his}), 130.0 (N–CH=N_{his}), 133.6 (CH_2-C_{his}), 170.6–174.1–174.9 (3 NH-CO). ^{19}F NMR (CD_3OD, 235.19 MHz): δ −76.8 (3F, s, ^-O_2C-CF_3), −115.3 (4F, s, 2 CH_2-CF_2), −122.8 (8F, m, 4 CF_2), −124.4 (4F, s, 2 CF_2). *m*/*z* (ESI-MS): $[M]^+$ 1288.8 (without CF_3COO^-). Elemental analysis calculated for $C_{54}H_{82}F_{19}N_5O_{15}\cdot 3H_2O$: C: 44.54, H: 6.09, N: 4.81; found C: 44.58, H: 5.80, N: 4.77%.

Benzyl 11-bromoundecanoate (13). 11-Bromoundecanoic acid (3 g, 11.3 mmol) was dissolved in 10 mL of benzyl alcohol. When the solution was perfectly homogeneous, $SOCl_2$ (0.9 mL, 17.5 mmol) was added. After stirring for 16 h at room temperature, benzyl alcohol was removed by distillation under reduced pressure and the crude product was purified by flash chromatography on silica gel (cHex–AcOEt 8 : 2) to yield 3.2 g (9.04 mmol, 80%) of compound **13** as a translucent oil. R_f: 0.57 (cHex–AcOEt 5 : 5). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.32–1.45 (12H, m, $CH_{2\ chain}$), 1.68 (2H, m, CH_2-CH_2-CO), 1.88 (2H, q^t, CH_2-CH_2-Br, J^3 = 6.80 Hz), 2.39 (2H, t, CH_2-CO, J^3 = 7.58 Hz), 3.44 (2H, t, CH_2-Br, J^3 = 6.85 Hz), 5.16 (2H, s, CH_2-Φ), 7.40 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 24.9 (CH_2-CH_2-CO), 28.2–30.3 ($CH_{2\ chain}$), 32.8 (CH_2-CH_2-Br), 34.0–34.3 (CH_2-CO, CH_2-Br), 66.1 (CH_2-Φ), 126.9–128.5 ($CH_{arom.}$), 136.1 ($C_{arom.}$), 173.6 (CO).

Benzyl 22-carboxy-12-thiadocosanoate (14). Mercaptopropionoic acid (368 mg, 1.69 mmol) was dissolved in 10 mL of anhydrous and degassed DMF with argon. At the same time, NaH 60% (135 mg, 3.38 mmol) was rinsed with heptane, dried under reduced pressure during 10 min and added to the reaction mixture. Then, compound **13** (300 mg, 0.84 mmol) dissolved in 5 mL of DMF was added dropwise. After stirring for 4 h at room temperature, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 1 : 9) to yield 340 mg (0.487 mmol, 58%) of compound **14** as a white powder. R_f: 0.49 (AcOEt–cHex 3 : 7), 0.32 (AcOEt–cHex 2 : 8), mp: 78–79 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.30–1.45 (24H, m, $CH_{2\ chain}$), 1.53–1.65 (8H, m, HO_2C-CH_2-CH_2, CH_2-CH_2-CO, 2 CH_2-CH_2-S), 2.33–2.39 (4H, m, HO_2C-CH_2, CH_2-CO), 2.54 (4H, t, CH_2-S-CH_2, J^3 = 7.17 Hz), 5.13 (2H, s, CH_2-Φ), 7.33 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 24.7–25.0 (HO_2C-CH_2-CH_2, CH_2-CH_2-CO), 29.9–29.7 ($CH_{2\ chain}$), 32.2 (CH_2-CO), 34.1–34.3 (CH_2-S-CH_2, HO_2C-CH_2), 66.1 (CH_2-Φ), 128.2–128.5 ($CH_{arom.}$), 136.1 ($C_{arom.}$), 173.8 (CH_2-CO), 180.1 (HO_2C-CH_2).

Benzyl 22-[2-((2,3,4,6-tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethylcarbamoyl]-12-thiadocosanoate (15). Compound **6** (960 mg, 1.83 mmol) was dissolved in 10 mL of ethanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (109 mg, 60 mg $mmol^{-1}$) was added portionwise. The mixture was stirred under hydrogen pressure (8 bar) for 12 h at room temperature. The mixture was filtered over Celite and the solvent removed *in vacuo* to obtain the amine (**15′**) as a white powder. It was dissolved in 10 mL of DCM freshly distilled and degassed under argon. Then, compound **14** (750 mg, 1.52 mmol) and TBTU (587 mg, 1.83 mmol) were added to the reaction mixture. The pH was adjusted to 8 with DIEA. After stirring for 12 h at room temperature, 596 mg of amine was added again. After 12 h, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 4 : 6) to yield 1.05 g (1.22 mmol, 80%) of compound **15** as a translucent oil. R_f: 0.25 (AcOEt–cHex 5 : 5). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.28–1.44 (24H, m, $CH_{2\ chain}$), 1.52–1.63 (8H, m, NH-CO-CH_2-CH_2, CH_2-CH_2-CO, 2 CH_2-CH_2-S), 2.00–2.20 (14H, m, 4 CH_3CO, NH-CO-CH_2), 2.36 (2H, t, CH_2-CO, J^3 = 7.43 Hz), 2.50 (4H, t, CH_2-S-CH_2, J^3 = 7.22 Hz), 3.49 (2H, m, CH_2-NH-CO), 3.66 (1H, m, OCH_2), 3.93 (2H, m, OCH_2, $CH_{(5)}$), 4.05–4.18 (2H, m, $CH_{2(6)}$), 4.48 (1H, d, $CH_{(1)}$, J^3 = 7.83 Hz), 5.00–5.48 (5H, m, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, CH_2-Φ), 5.89 (1H, s, NH), 7.34 (5H, s, $CH_{arom.}$). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 20.6 (CH_3CO), 24.9–25.7 (NH-CO-CH_2-CH_2, CH_2-CH_2-CO), 28.9–29.7 ($CH_{2\ chain}$), 32.2 (CH_2-CO, NH-CO-CH_2), 34.3 (CH_2-S-CH_2), 39.1 (OCH_2-CH_2-NH), 61.3 ($CH_{2(6)}$), 65.9–70.8 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, CH_2-Φ, OCH_2-CH_2-NH), 101.4 ($C_{1\beta}$), 128.2–128.5 ($CH_{arom.}$), 136.1 ($C_{arom.}$), 169.6–170.4 (CH_3CO), 173.2–173.7 (NH-CO-CH_2, CH_2-CO-O).

***N*-[1-(dodecylcarbamoyl)-5-(*tert*-butyloxycarbonylamino)-pentyl]-22-[2-((2,3,4,6-tetra-*O*-acetyl)-β-D-galactopyranosyloxy)ethylcarbamoyl]-12-thiadocosanamide (16).** Compound **10** (220 mg, 0.40 mmol) was dissolved in 10 mL of ethanol. The solution was stirred and cooled at 0 °C and palladium on charcoal (24 mg, 60 mg $mmol^{-1}$) was added portionwise. The mixture was stirred under hydrogen pressure (8 bar) for 12 h at room temperature. The mixture was filtered over Celite and the solvent removed *in vacuo* to obtain the amine as a white powder. It was dissolved in 5 mL of anhydrous and degassed DMF under argon. 208 mg of amine **15′** (0,27 mmol, 1 eq) and 103 mg of TBTU (0.32 mmol, 1.2 eq) were added. The pH was

adjusted to 8 with DIEA. The mixture was refluxed for 16 h. Then, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (AcOEt–cHex 8 : 2) and filtered by size exclusion chromatography using LH20 (MeOH–CH_2Cl_2 1 : 1) to yield 207 mg (0.178 mmol, 66%) of fully protected compound **16** as a white solid. R_f: 0.38 (AcOEt), mp: 98–99 °C. $[\alpha]_D^{20}$: −5.79 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.88 (3H, t, CH_3, J^3 = 6.86 Hz), 1.25–1.37 (42 H, m, CH_2 chain, CH-CH_2-CH_2), 1.44 (9H, s, $C(CH_3)_3$), 1.47–1.67 (12H, s, NH-CO-CH_2-CH_2, CH_2-CH_2-CO-NH, 2 CH_2-CH_2-S, CH_2-CH_2-NH-CO-CH, CH_2-CH_2-NH(Boc)), 1.79 (2H, m, CH-CH_2), 1.99–2.16 (12H, m, CH_3CO), 2.19 (4H, m, NH-CO-CH_2, CH_2-CO-NH-CH), 2.49 (4H, t, CH_2-S-CH_2, J^3 = 7.23 Hz), 3.08 (2H, m, CH_2-NH(Boc)), 3.20 (2H, td, CH_2-NH-CO-CH, J^3 = 6.33 Hz), 3.46 (2H, m, OCH_2-CH_2-NH), 3.68 (1H, m, OCH_2), 3.91 (2H, m, OCH_2, $CH_{(5)}$), 4.14 (2H, m, $CH_{2(6)}$), 4.37 (1H, m, CH-CH_2), 4.47 (1H, d, $CH_{(1)}$, J^3 = 7.83 Hz), 4.62 (1H, m, NH), 5.02 (1H, dd, $CH_{(3)}$, J^3 = 3.38 Hz, J^3 = 10.46 Hz), 5.19 (1H, dd, $CH_{(2)}$, J^3 = 7.82 Hz, J^3 = 10.46 Hz), 5.40 (1H, m, $CH_{(4)}$), 5.87 (1H, s, NH), 6.23 (1H, m, NH), 6.33 (1H, m, NH). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.5 (CH_3), 20.6–29.7 (CH_3CO, CH_2 chain, CH-CH_2, $C(CH_3)_3$), 32.2 (NH-CO-CH_2), 35.5 (CH_2-S-CH_2), 36.6–36.7 (CH_2-CO-NH-CH, CH_2-NH-CO-CH), 39.06–39.58 (OCH_2-CH_2-NH-CO, CH_2-NH(Boc)), 52.8 (CH-CH_2), 61.3 ($CH_{2(6)}$), 67.0–70.7 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, OCH_2-CH_2-NH), 79.4 ($C(CH_3)_3$), 101.4 ($C_{1\beta}$), 169.7–173.4 (CH_3CO, NH-CO-CH_2, NH-CO-CH, CO_{Boc}). *m*/*z* (FAB$^+$MS): $[M + H^+]^+$ 1172.1, $[M + NH_4^+]^+$ 1189.2, $[M + Na^+]^+$ 1194.1, $[M + K^+]^+$ 1210.1.

***N*-[1-(dodecylcarbamoyl)-5-(ammonio)pentyl)]-22-[2-(β-D-galactopyranosyloxy)ethylcarbamoyl]-12-thiadocosanamide trifluoroacetate (E).** Compound **16** (150 mg, 0.128 mmol) was dissolved in 10 mL of MeOH freshly distilled and degassed under argon. A catalytic amount of sodium methylate was added. After stirring for 6 h, IRC50 ion exchange resin (1 g) was added. After 10 min the mixture was filtered. The solvent was removed *in vacuo* and the crude product purified by filtration by size exclusion chromatography using LH20 (MeOH) to yield 120 mg (0.196 mmol, 93%) of deacetylated compound. Then, it was dissolved in 9 mL DCM freshly distilled and degassed under argon. 1 mL of TFA was added dropwise to the reaction mixture. After stirring for 16 h at room temperature, the solvent was removed *in vacuo* and the product was filtered by size exclusion chromatography using LH20 (MeOH–CH_2Cl_2 1 : 1) to yield 95.5 mg (0.159 mmol, 81%) of final compound **E** as a white powder, mp (dec) > 88 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.80 (3H, t, CH_3, J^3 = 6.21 Hz), 1.19–1.35 (42 H, m, CH_2 chain, CH-CH_2-CH_2), 1.36–1.72 (14H, s, NH-CO-CH_2-CH_2, CH_2-CH_2-CO-NH, 2 CH_2-CH_2-S, CH_2-CH_2-NH-CO-CH, CH_2-CH_2-NH_3^+, CH-CH_2), 2.06–2.14 (4H, m, NH-CO-CH_2, CH_2-CO-NH-CH), 2.39 (4H, t, CH_2-S-CH_2, J^3 = 7.09 Hz), 2.79 (2H, m, CH_2-NH_3^+), 3.09 (2H, m, CH_2-NH-CO-CH), 3.19–3.85 (10H, m, OCH_2-CH_2-NH, $CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, $CH_{2(6)}$), 4.14 (1H, d, $CH_{(1)}$, J^3 = 7.07 Hz), 4.18 (1H, m, CH-CH_2). ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ 14.3 (CH_3), 22.4–29.4 (CH_2 chain, CH-CH_2), 31.7 (NH-CO-CH_2), 35.6–35.7 (CH_2-NH-CO-CH, CH_2-S-CH_2, CH_2-CO-NH-CH), 39.0–39.2 (OCH_2-CH_2-NH-CO, CH_2-NH_3^+), 53.0 (CH-CH_2), 61.1 ($CH_{2(6)}$), 68.3–75.3 ($CH_{(2)}$, $CH_{(3)}$, $CH_{(4)}$, $CH_{(5)}$, OCH_2-CH_2-NH), 105.2 ($C_{1\beta}$), 172.6 (OCH_2-CH_2-NH-CO), 178.7 (NH-CO-CH_2, NH-CO-CH). *m*/*z* (ESI-MS): $[M + H^+]^+$ 904.1 (without ^-O_2C-CF_3), $[M + H^+ + Na^+]^{2+}$ 927.0 (without ^-O_2C-CF_3).

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