# Synthesis of Bifunctional Hydroxamic Acids as Novel Ligands for the Hydrophilic Stabilization of Iron Oxide Nanoparticles

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**Abstract:** A general method for synthesizing bifunctional hydroxamic acids containing carboxylic acid or amino functionalities is reported. Various products from simple alkyl to complex dendrimer-like structures are described. Such molecules have recently been used in ligand-exchange reactions for the hydrophilic stabilization of originally oleic acid protected iron oxide nanoparticles.

**Key words:** protecting groups, hydroxamic acids, hydrogenation, ethers, alkylations

Hydroxamic acid derivatives possess a wide spectrum of biological activity[1] and are well known as chelating ligands for metal ions.[2] Extensive studies have shown that the bond strength between Fe(II)/Fe(III) ions and hydroxamic acids greatly exceeds that between carboxylic acids and iron ions because of the possibility of forming a five-membered chelating ring, instead of the four-membered rings or monodendate species formed in case of the carboxylic acid ligands.[3,4] This enhanced bond strength could also be observed with other isolated metal ions, such as Co(II), Ni(II), Cu(II), and Zn(II) as well as on metal surfaces and self-assembled monolayers.[2,3,5] As a consequence, hydroxamic acid derivatives are particularly suitable for functionalizing metal-containing complexes as well as metal-containing nanoparticles.[6] Moreover, the use of hydroxamic acid ligands with additional functional groups allows the introduction of new functional groups into the ligand sphere of nanoparticles and permits alteration of the solubility of nanoparticles in a controlled way. This is especially interesting for the transfer of iron oxide nanoparticles from nonpolar solvents into polar solvents.[7] Most applications of iron oxide nanoparticles, such as magnetic resonance tomography or hyperthermia treatment, require water-dispersible systems.[8–11] Such functionalization involves the necessity of synthesizing hydroxamic acid derivatives containing additional polar functional groups, such as carboxylic acids or amines. In spite of the potential applications of these compounds and the well-known synthesis routes for normal hydroxamic acids without additional functionalities,[1,12–14] the synthesis of bifunctional hydroxamic acids is often tedious because of the polarity and reactivity of the hydroxamic acid group. The size of the ligands is an important parameter for steric stabilization of nanoparticles, because bulky ligands often exhibit a considerably higher stability of the nanoparticle–ligand system.[15,16] Therefore, it is necessary to synthesize polar groups containing bulky hydroxamic acid ligands for the stabilization of nanoparticles as well as model compounds of smaller size.[6]

We describe in this work a general synthetic route for the preparation of alkanehydroxamic and arenecarbohydroxamic acids containing carboxylic **1**, **2**, and **3** or amino **4** end groups (Figure 1).

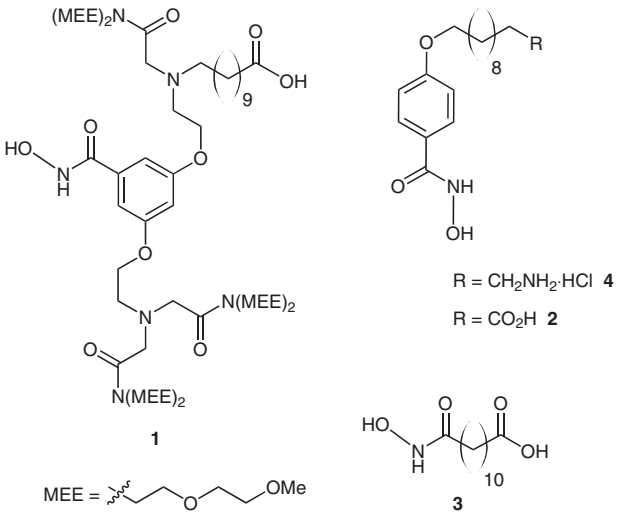


**Figure 1** Bifunctional hydroxamic acid compounds as novel ligands for iron oxide nanoparticles

The preparation of key intermediate compounds **6**, **8**, and **10** is shown in Scheme 1. Thus, 11-aminoundecanoic acid (**5**) was reduced by lithium aluminum hydride and the resulting primary alcohol was converted into the desired alkyl bromide using concentrated hydrobromic acid, as described by Niwa et al.[17] After the introduction of the Boc group, **6** was obtained in 5% overall yield. The benzyl-protected carboxylic acid **8** was prepared from 11-bromoundecanoic acid (**7**) in one step in 84% overall yield.[18]

Compound **10** was prepared from benzylamine (**9**) in three steps and in 49% overall yield. First, tosylated diethylene glycol monomethyl ether[19] was added to

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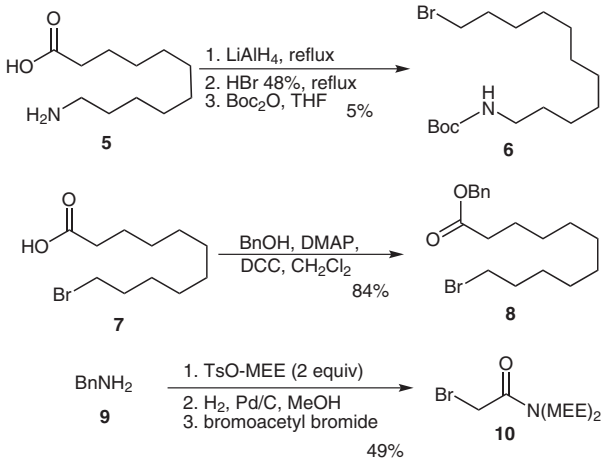
benzylamine in a nucleophilic substitution reaction. Subsequently, the benzyl group was removed by palladium-catalyzed hydrogenolysis reaction at 1 bar.[19] Finally, reaction of the resulting free amine and bromoacetyl bromide afforded **10**, containing two amine-bound 2-(2-methoxyethoxy)ethyl (MEE) groups.[6]

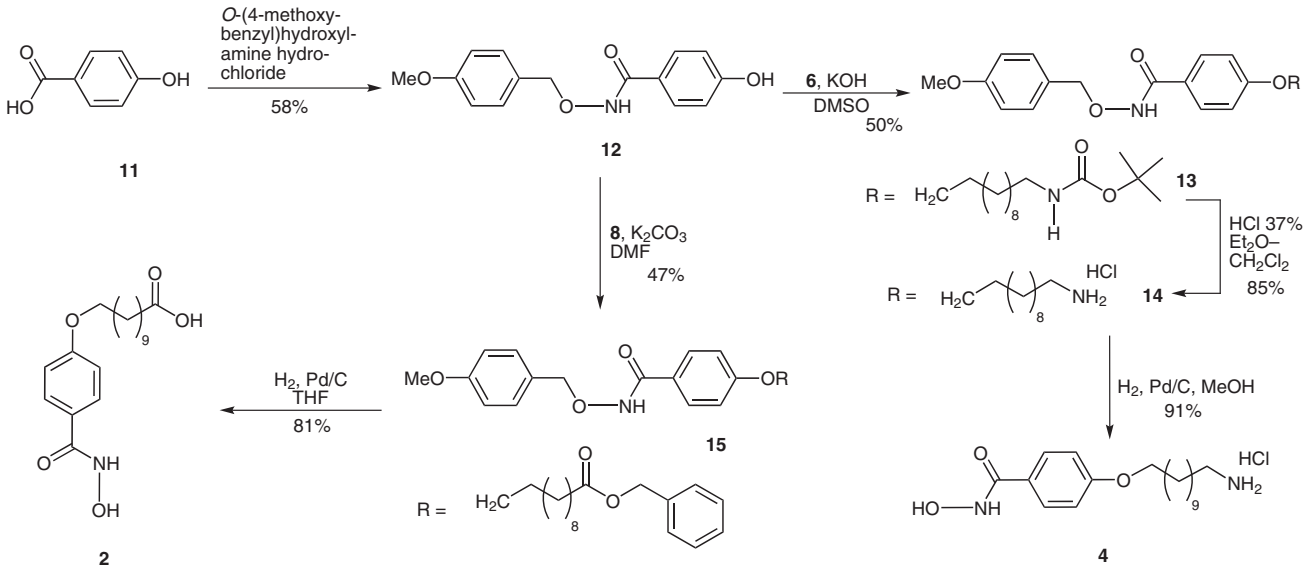



**Scheme 1** Synthesis of the key intermediate compounds **6**, **8**, and **10**

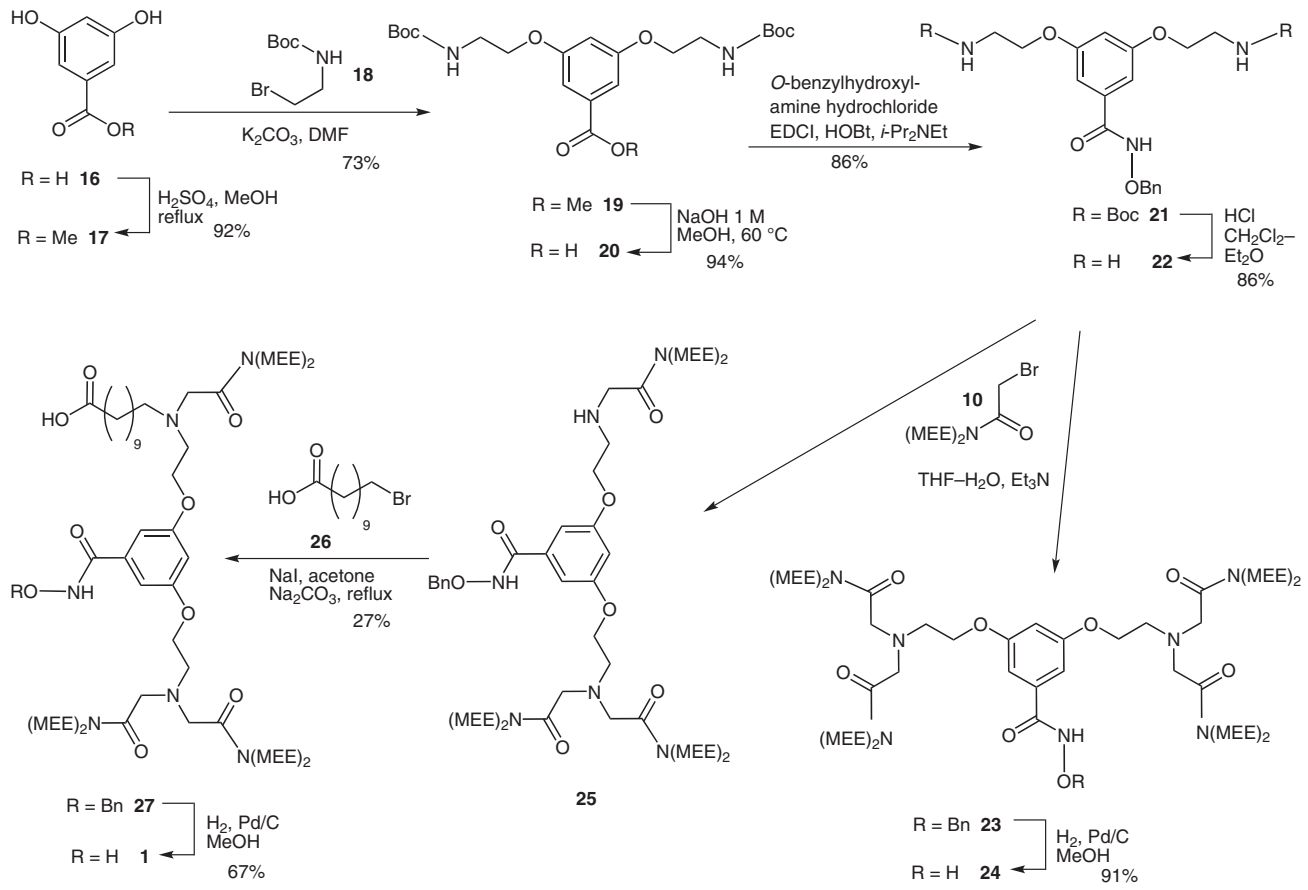
The long-chain carboxylic acid and amine containing benzenecarbohydroxamic acids **2** and **4** were prepared as shown in Scheme 2. Protection of 4-hydroxybenzoic acid (**11**) using *O*-(4-methoxybenzyl)hydroxylamine hydrochloride[20] gave **12** in 58% yield. This product can be further functionalized in different ways. For the preparation of amine **4**, an ether linkage between compound **12** and **6** was formed under highly basic conditions at pH >12.[21] After deprotecting of the amino group by hydrochloric acid at room temperature, the 4-methoxybenzyl group was removed by hydrogenation to give **4** in 22% overall yield starting from **11**. It should be pointed out that the 4-methoxybenzyl group was stable under acidic conditions and no cleavage was observed. In the same way, an ether linkage between **12** and **8** afforded product **15** in 47% yield. Both protecting groups in compound **15**, namely the benzyl group and the 4-methoxybenzyl group, could be removed in one step by hydrogenolysis at 1.5 bar in tetrahydrofuran. Thus, the desired hydroxamic acid **2** was obtained in 22% overall yield starting from **11**.

The preparation of the more complex dendron-like structures **1** and **24** is shown in Scheme 3.

3,5-Dihydroxybenzoic acid (**16**) was esterified[22] and alkylation with **18**[23] yielded monomer **19** (73%),[6,24,25] from which the methyl ester group was cleaved using sodium hydroxide in methanol to give acid **20** (94%). The hydroxamic acid protecting benzyl group was introduced with *O*-benzylhydroxylamine hydrochloride by using *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as carboxylic acid activating agents. Optimization of this process led to an improved procedure affording **21** in 86% yield by using dichloromethane as solvent and *N*,*N*-diisopropylethylamine instead of triethylamine. The diamine hydrochloride salt **22** was obtained from Boc cleavage. Both compounds **23** (14%) and **25** (27%) could be obtained in one step by using 3.2 equivalents of **10**. However, this method required a tedious purification process. In contrast, **23** could be synthesized from **22** in 56% yield, without formation of **25**, using excess **10** (5 equiv) and *N*,*N*-diisopropylethylamine instead of triethylamine. After subsequent hydrogenolysis of **23** the final product **24** was obtained in 91% yield. In order to obtain hydroxamic acid **1**, compound **25** was treated with **26** in acetone under refluxing conditions with sodium carbonate followed by palladium-catalyzed hydrogenolysis, which gave **1** in 67% yield. During the synthesis of **23** and **25**, also a product with two *N*,*N*-bis[2-(2-methoxyethoxy)ethyl]ethylamide groups could be isolated. This compound can also be used to prepare hydroxamic acid dendrons with two



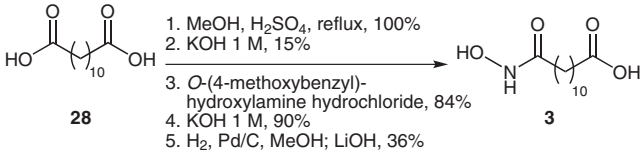

**Scheme 2** Synthesis of the carboxylic acid and amino containing arenecarbohydroxamic acids **2** and **4**




**Scheme 3** Synthesis of the dendritic hydroxamic acids **1** and **24**

carboxylic acid groups. In principle, dendritic hydroxamic acids with up to four carboxylic acid groups are conceivable starting from **22**.

Alternatively, the preparation of the hydroxamic acids **1** and **24** without using a benzyl-protected hydroxamic acid derivative was also attempted. In this case, after the introduction of **10**, we simply tried to convert the aryl methyl ester (in **19**) into the acid and subsequently to the hydroxamic acid group.[6] However, even under relatively mild basic ester cleavage conditions using dilute sodium or lithium hydroxide, the ester cleavage could only be performed in 25% yield. Moreover, after deprotection of the aryl ester, **24** could be synthesized only with 21% yield by using hydroxylamine directly. In addition, the poor solubility of the product and the presence of inseparable impurities impeded its purification. In the case of **1**, we were not able to prepare the final product without using the benzyl-protected hydroxamic acid.




**Scheme 4** Synthesis of the alkyl chain hydroxamic acid compound **3**

For comparing arenecarbohydroxamic and alkanehydroxamic acids and investigating the general accessibility of the described synthetic method for preparing carboxylic acid containing hydroxamic acids, **3** was prepared from dodecanedioic acid (**28**) in five steps (Scheme 4).

Compound **28** was first converted into the corresponding dimethyl ester under acidic conditions followed by partial cleavage of the resulted dimethyl ester under basic conditions. The free carboxylic acid group was activated by EDCI and coupled with *O*-(4-methoxybenzyl)hydroxylamine hydrochloride for the introduction of the protected hydroxamic acid group. Subsequently, the remaining ester group was hydrolyzed under basic conditions at 60 °C in 90% yield. During deprotection of the hydroxylamine group in the last step by a palladium-catalyzed hydrogenolysis reaction, a methyl ester group was generated, which could be cleaved by lithium hydroxide to give compound **3** in 40% yield. The formation of an ester can be avoided by performing the hydrogenolysis in tetrahydrofuran or dioxane.

In summary, we conclude that the two protecting groups *O*-benzylhydroxylamine and *O*-(4-methoxybenzyl)hydroxylamine can be used as suitable and easily removable groups for the protection of hydroxamic acids during the integration of new reactive functionalities into hydroxamic acid containing molecules.

In conclusion, various bifunctionalized arenecarbohydroxamic and alkanehydroxamic acids with free carboxylic acids and amino groups were prepared. These molecules are highly suitable to be used as ligands for the polar functionalization of iron oxide nanoparticles, since they are able to replace even strong binding long chain carboxylic acid ligands. This ligand exchange approach has already been used by Kim et al. for methylated triethylene glycol capped hydroxamic acid based dendron ligands.[6] However, the ligands used in ref. 6 do not contain reactive groups besides the hydroxamic acid group. Hence, their use for the electrostatic stabilization of nanoparticles is restricted. In contrast, the novel dendron ligands exhibit, in principle, an adjustable number of up to four carboxylic acid functionalities. In this way, even more polar ligands become available. In addition, the adjustable size of the different types of ligands presented in this work permits controlled steric stabilization of nanoparticles and clusters. We selected molecules from simple systems up to dendrimer-like structures to establish a universal approach of surface stabilization of nanoparticles as well as metal complexes. The graded electrostatic stabilization of iron oxide nanocrystals with these novel type of ligands and the characterization and properties of the obtained highly water-dispersible and biocompatible particles will be described in detail elsewhere.[11]

The chemicals were purchased from Sigma-Aldrich, Alfa Aesar, and ABCR and were used without purification. All solvents were purified by distillation before use and dried according to standard procedures where necessary. All reactions were carried out in a dry argon atmosphere unless otherwise mentioned. Melting points are determined by a Büchi 510 apparatus. NMR spectra were recorded on a Jeol ECX 400 (100.62 MHz for $^{13}C$, 400.13 MHz for $^{1}H$) spectrometer. Chemical shifts are referenced to the residual proton or carbon resonance of the deuterated solvent [$CHCl_3$ $\delta = 7.26$ ($^{1}H$) or $\delta = 77.00$ (proton decoupled $^{13}C$)]. The samples were characterized by ESI-TOF using an Agilent 6210 ESI-TOF, Agilent Technologies. The solvent flow rate was adjusted to 4 μL/min and the spray voltage was set to 4 kV. The drying gas flow rate was set to 15 psi (≈1 bar). All other parameters were adjusted for a maximum abundance of $[M + H]^+$, where M is the parent cation. Flash chromatography was carried out using silica gel (43–60 mesh) purchased from Fluka.

*tert*-Butyl *N*-(2-bromoacetyl)carbamate (**18**),[23] 2-(2-methoxyethoxy)ethyl 4-methylbenzenesulfonate TsO-MEE,[19] and *O*-(4-methoxybenzyl)hydroxylamine[20] were prepared according to known literature procedures.

### *tert*-Butyl *N*-(11-Bromoundecyl)carbamate (6)

11-Aminoundecanoic acid (**5**, 3.74 g, 18.6 mmol) was added in small portions to a stirred suspension of $LiAlH_4$ (1.06 g, 27.9 mmol) in anhyd THF (50 mL). The mixture was refluxed for 20 h, $CHCl_3$ was added, and the mixture was washed with sat. $NaHCO_3$. The organic phase was dried ($Na_2SO_4$), the solvent was removed, and the product was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 1:0 to 15:1) to afford 11-aminoundecan-1-ol (0.95 g, 27%) as a slightly yellowish solid. 11-Aminoundecan-1-ol (0.95 g, 5.0 mmol) was refluxed with concd HBr (48%, 15 mL) for 24 h. The mixture was cooled to 0 °C and the precipitate was filtered and purified by recrystallization (acetone) to give 11-bromoundecan-1-amine hydrobromide (0.33 g, 20%) as a brown solid.[17] A mixture of $Boc_2O$ (0.44 g, 2.0 mmol) in THF (2.5 mL) was added dropwise to a soln of 11-bromoundecan-1-amine hydrobromide (0.33 g, 1.0 mmol) and $Et_3N$ (0.5 mL) in THF–$H_2O$ (1:2, 7.5 mL) at 0 °C. The mixture was stirred at r.t. for 20 h, $Et_2O$ (50 mL) was added, and the product was washed with 0.5 M HCl (2 × 25 mL), $H_2O$ (25 mL), and brine (25 mL). The solvent was dried and evaporated and the product was purified by column chromatography (silica gel, hexane–EtOAc, 1:0.05 to 1:0.11) to afford **6** (0.3 g, 88%) as a colorless solid; mp 59–60 °C.

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 4.50$ (br, 1 H), 3.39 (t, $J = 6.8$ Hz, 2 H), 3.31–3.04 (m, 2 H), 1.87–1.80 (m, 2 H), 1.45–1.36 (m, 13 H), 1.29–1.20 (m, 12 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 155.9$ (s), 78.9 (s), 40.6 (t), 34.0 (t), 32.8 (t), 30.0 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 28.7 (t), 28.4 (q, 3 C), 28.1 (t), 26.8 (t).

### Benzyl 11-Bromoundecanoate (8)[18]

11-Bromoundecanoic acid (**7**, 5.0 g, 19 mmol) was mixed with anhyd $CH_2Cl_2$ (50 mL) under an argon atmosphere. Subsequently, BnOH (2.03 g, 1.74 mL, 19 mmol) and DMAP (0.59 g, 4.8 mmol) were added under stirring. To the stirred mixture a soln of DCC (4.65 g, 23 mmol) in a small amount of $CH_2Cl_2$ was added slowly. The reaction was left overnight and the product was filtered to remove the urea. The solvent was removed under reduced pressure and the product was purified by column chromatography ($CH_2Cl_2$) to afford **8** (5.63 g, 84%) as a colorless oil.[18]

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.29$ (m, 5 H), 5.11 (s, 2 H), 3.39 (t, $J = 6.8$ Hz, 2 H), 2.34 (t, $J = 7.5$ Hz, 2 H), 1.87–1.80 (m, 2 H), 1.67–1.60 (m, 2 H), 1.45–1.36 (m, 2 H), 1.34–1.23 (m, 10 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 173.5$ (s), 136.1 (s), 128.5 (d, 2 C), 128.1 (d, 3 C), 65.9 (t), 34.2 (t), 33.9 (t), 32.7 (t), 29.3 (t), 29.2 (t), 29.1 (t), 29.0 (t), 28.7 (t), 28.1 (t), 24.9 (t).

### 2-Bromo-*N*,*N*-bis[2-(2-methoxyethoxy)ethyl]acetamide (10)

$BnNH_2$ (**9**, 9.00 g, 89.0 mmol) and $K_2CO_3$ (35 g, 254 mmol) were dispersed in MeCN (85 mL). To this suspension was added dropwise a soln of TsO-MEE (50.7 g, 185 mmol) in MeCN (165 mL) at r.t. When the addition was complete, the mixture was refluxed at 90 °C for 48 h. The suspension was filtered and the residue was washed with $CHCl_3$. The solvent was evaporated, the crude product was dissolved in 5% HCl (100 mL), and the side products were extracted with $Et_2O$ (3 × 100 mL). Sat. $NaHCO_3$ soln was added to the acidic phase to change the pH value to 7–8. The product was extracted with $Et_2O$ (5 × 75 mL). The solvent was dried and removed at reduced pressure to yield *N*,*N*-bis[2-(2-methoxyethoxy)ethyl]benzylamine (26.7 g, 98%) as a yellowish oil.[19]

$^{1}H$ NMR (250 MHz, $CDCl_3$): $\delta = 7.32–7.20$ (m, 5 H), 3.69 (s, 2 H), 3.58–3.46 (m, 12 H), 3.35 (s, 6 H), 2.75 (t, $J = 6.4$ Hz, 4 H).

A mixture of *N*,*N*-bis[2-(2-methoxyethoxy)ethyl]benzylamine (39.8 g, 128 mmol), Pd/C (10%) (2.00 g), and MeOH (50 mL) was hydrogenated at r.t. at 1.5 bar $H_2$ pressure for 24 h. Subsequently, the mixture was centrifuged and filtered and the solvent was removed. The mixture was dissolved in sat. $NaHCO_3$ soln and extracted with $CHCl_3$ (5 ×). The combined organic fractions were dried and the solvent was removed. The product was purified by distillation to afford bis[2-(2-methoxyethoxy)ethyl]amine (22.5 g, 80%) as a colorless oil.[19]

$^{1}H$ NMR (250 MHz, $CDCl_3$): $\delta = 3.55–3.40$ (m, 12 H), 3.28 (s, 6 H), 2.72 (t, $J = 5.4$ Hz, 4 H), 1.68 (br s, 1 H).

Bromoacetyl bromide (41.4 g, 205 mmol) was added dropwise to a cooled soln (0 °C) of bis[2-(2-methoxyethoxy)ethyl]amine (22.4 g, 101 mmol) and $Et_3N$ (10.2 g, 101 mmol) in EtOAc (300 mL) over 90 min. When the addition was complete, the mixture was stirred at 0 °C for an additional 3 h and then at r.t. for 24 h. The reaction was quenched by the addition of sat. $NaHCO_3$ soln and the product was

washed with $H_2O$ (3 × 50 mL) and brine. The crude product was purified by column chromatography (silica gel, EtOAc–$CHCl_3$ to $CHCl_3$–EtOH, 5:0.2 to $CHCl_3$–EtOH, 5:0.6) to give **10** (21.6, 62%) as a yellowish oil; bp 138–140 °C/0.1 mbar.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.00 (s, 2 H), 3.63–3.58 (m, 6 H), 3.56–3.52 (m, 6 H), 3.48–3.44 (m, 4 H), 3.33 (s, 3 H), 3.22 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 167.7 (s), 71.7 (t), 71.6 (t), 70.6 (t), 70.3 (t), 68.9 (t), 68.7 (t), 58.9 (q), 58.8 (q), 49.9 (t), 46.7 (t), 27.1 (t).

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{24}{}^{79}BrNNaO_5$: 364.0736; found: 364.0744; *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{24}{}^{81}BrNNaO_5$: 366.0715; found: 366.0723.

Anal. Calcd for $C_{12}H_{24}BrNO_5$: C, 42.11; N, 4.09; H, 7.07. Found: C, 38.99; N, 3.78; H, 7.15.

**4-Hydroxy-*N*-(4-methoxybenzyloxy)benzamide (12)**

4-Hydroxybenzoic acid (**11**, 0.6 g, 4.34 mmol) was dissolved in anhyd DMF (10 mL) and the mixture was cooled to –10 °C. HOBt (0.76 g, 5.64 mmol), EDCI (1.08 g, 5.64 mmol), *O*-(4-methoxybenzyl)hydroxylamine hydrochloride (0.99 g, 5.21 mmol), *i*-$Pr_2NEt$ (3.75 mL, 21.7 mmol), and DMAP (0.01 g, 0.0868 mmol) were added at –10 °C with vigorous stirring and the mixture was stirred at r.t. for 20 h. When the reaction was complete, the mixture was neutralized with 1 M HCl, extracted with $CH_2Cl_2$, washed with brine, and dried ($Na_2SO_4$). The crude product was purified by column chromatography ($CH_2Cl_2$–MeOH, 50:1) to afford **12** (0.69 g, 58%) as a white powder; mp 129–132 °C.

$^1$H NMR (400 MHz, $CDCl_3$–$CD_3OD$): δ = 7.49 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 4.83 (s, 2 H), 3.73 (s, 3 H), 3.50 (br, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$–$CD_3OD$): δ = 166.7 (s), 160.5 (s), 159.8 (s), 130.9 (d, 2 C), 128.9 (d, 2 C), 127.5 (s), 122.6 (s), 115.2 (d, 2 C), 113.7 (d, 2 C), 77.7 (t), 55.1 (q).

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NNaO_4$: 296.0899; found: 296.0891.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; N, 5.13; H, 5.53. Found: C, 64.95; N, 6.07; H, 5.33.

***tert*-Butyl *N*-(11-{4-[(4-Methoxybenzyloxy)carbamoyl]phenoxy}undecyl)carbamate (13)**

To a soln of KOH (0.23 g, 4.1 mmol) in DMSO (4 mL) was added benzamide **12** (0.200 g, 0.732 mmol) and carbamate **6** (0.282 g, 0.805 mmol). The mixture was stirred for 2 h and quenched by addition of $H_2O$ (15 mL). The product was extracted with $CH_2Cl_2$ (3 × 25 mL) and EtOAc (2 × 25 mL). The combined organic fractions were washed with brine (2 × 25 mL) and dried and the solvents were removed at reduced pressure. Recrystallization (EtOAc) gave **13** (0.20 g, 50%) as a colorless solid; mp 107–108 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.12 (br s, 1 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 6.7 Hz, 2 H), 6.83 (d, *J* = 6.9 Hz, 2 H), 4.91 (s, 2 H), 4.57 (br, 1 H), 3.93 (t, *J* = 6.5 Hz, 2 H), 3.77 (s, 3 H), 3.09–3.22 (m, 2 H), 1.78–1.71 (m, 2 H), 1.41 (s, 9 H), 1.48–1.20 (m, 16 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.0 (s), 162.0 (s), 159.8 (s), 156.0 (s), 130.9 (d, 2 C), 128.9 (d, 2 C), 127.5 (s), 123.9 (s), 114.2 (d, 2 C), 113.8 (d, 2 C), 78.9 (s), 77.7 (t), 68.1 (t), 55.2 (q), 40.5 (t), 30.0 (t), 29.4 (t, 2 C), 29.3 (t), 29.2 (t, 2 C), 29.0 (t), 28.3 (t, 3 C), 26.7 (t), 25.8 (t).

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{46}N_2NaO_6$: 565.3254; found: 565.3234.

Anal. Calcd for $C_{31}H_{46}N_2O_6$: C, 68.61; N, 5.16; H, 8.54. Found: C, 68.55; N, 5.16; H, 8.71.

**4-(11-Aminoundecyloxy)-*N*-(4-methoxybenzyloxy)benzamide Hydrochloride (14)**

Concd HCl (37%, 0.4 mL) was added with stirring to a soln of carbamate **13** (65 mg, 0.12 mmol) in $Et_2O$–$CH_2Cl_2$ (1:1, 4 mL). The mixture was stirred at r.t. for a further 3 h. The solvent was removed at reduced pressure and the resulting solid was suspended in $Et_2O$ and filtered to afford **14** (49 mg, 85%) as a colorless solid; mp 166 °C (dec).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.67 (br s, 1 H), 8.07 (br s, 3 H), 7.76 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.6 Hz, 2 H), 4.86 (s, 2 H), 4.03 (t, *J* = 6.4 Hz, 2 H), 3.80 (s, 3 H), 2.81–2.70 (m, 2 H), 1.79–1.67 (m, 2 H), 1.63–1.53 (m, 2 H), 1.48–1.38 (m, 2 H), 1.38–1.23 (m, 12 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 164.5 (s), 161.8 (s), 159.8 (s), 131.2 (d, 2 C), 129.4 (d, 2 C), 128.5 (s), 124.8 (s), 114.6 (d, 2 C), 114.2 (d, 2 C), 77.1 (t), 68.2 (t), 55.6 (q), 39.2 (t), 29.5 (t), 29.4 (t), 29.36 (t), 29.28 (t), 29.1 (t, 2 C), 27.5 (t), 26.4 (t), 26.0 (t).

HRMS (+ESI): *m*/*z* [M – HCl + H]$^+$ calcd for $C_{26}H_{39}N_2O_4$: 443.2910; found: 443.2911.

HRMS (–ESI): *m*/*z* [M – H]$^-$ calcd for $C_{26}H_{38}{}^{35}ClN_2O_4$: 477.2520; found: 477.2516.

Anal. Calcd for $C_{26}H_{39}ClN_2O_4$: C, 65.19; N, 5.85; H, 8.21. Found: C, 64.26; N, 6.03; H, 8.29.

**4-(11-Aminoundecyloxy)benzenecarbohydroxamic Acid Hydrochloride (4)**

A mixture of benzamide hydrochloride **14** (40 mg, 83 μmol), MeOH (6 mL), $CHCl_3$ (3 mL), and Pd/C (20 mg) was hydrogenated for 3 h. When the reaction was complete, the catalyst was removed by centrifugation and the organic phases were combined and evaporated to dryness. The solid was washed with $CH_2Cl_2$ to give **4** (27 mg, 91%) as a white solid.

IR (KBr): 3294 (m), 2921 (m), 2841 (m), 2730 (w), 1647 (s), 1608 (s), 1566 (m), 1506 (s), 1392 (m), 1306 (s), 1254 (s), 1165 (s), 1018 (s), 900 (m), 847 (s), 754 (m), 652 (m), 544 cm$^{-1}$ (w).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.11 (br s, 1 H), 8.93 (br, 1 H), 7.76–7–94 (br, 3 H), 7.75 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 8.9 Hz, 2 H), 4.04 (t, *J* = 4.3 Hz, 2 H), 2.81–2.73 (m, 2 H), 1.76–1.71 (m, 2 H), 1.58–1.53 (m, 2 H), 1.45–1.25 (m, 14 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 164.9 (s), 161.8 (s), 129.5 (d, 2 C), 125.7 (d), 114.9 (d, 2 C), 68.5 (t), 39.7 (t), 29.9 (t), 29.8 (t), 29.73 (t), 29.66 (t), 29.47 (t), 29.44 (t), 27.9 (t), 26.7 (t), 26.4 (t).

HRMS (+ESI): *m*/*z* [M – HCl + H]$^+$ calcd for $C_{18}H_{31}N_2O_3$: 323.2335; found: 323.2352.

**Benzyl 11-{4-[(4-Methoxybenzyloxy)carbamoyl]phenoxy}undecanoate (15)**

Benzamide **12** (0.150 g, 0.549 mmol) and $K_2CO_3$ (0.390 mg, 2.86 mmol) were added to anhyd DMF (50 mL) and the mixture was heated to 80 °C under stirring for 1 h. Undecanoate **8** (0.298 g, 0.803 mmol) in anhyd DMF (5 mL) was added slowly and the mixture was stirred at 80 °C for 24 h. The precipitate was removed by hot filtration, $H_2O$ was added to the filtrate, and the product was extracted with EtOAc. Purification by column chromatography (hexane–EtOAc, 7:3 to 0:1) gave **15** (0.14 g, 47%) as a colorless solid; mp 106–107 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 1 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 7.39–7.27 (m, 7 H), 6.90–6.82 (m, 4 H), 5.09 (s, 2 H), 4.92 (s, 2 H), 3.94 (t, *J* = 6.5 Hz, 2 H), 3.16 (s, 3 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 1.80–1.71 (m, 2 H), 1.68–1.56 (m, 2 H), 1.50–1.37 (m, 2 H), 1.36–1.18 (m, 10 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 173.7 (s), 166.2 (s), 162.1 (s), 159.9 (s), 136.0 (s), 131.0 (d, 2 C), 128.8 (d, 2 C), 128.5 (d, 2 C),

128.1 (d, 3 C), 127.4 (s), 123.8 (s), 114.3 (d, 2 C), 113.8 (d, 2 C), 77.8 (t), 68.1 (t), 66.0 (t), 55.2 (q), 34.2 (t), 29.3 (t), 29.24 (t), 29.20 (t), 29.1 (t), 29.0 (t, 2 C), 25.9 (t), 24.8 (t).

HRMS (+ESI): *m/z* [M + Na]$^+$ calcd for $C_{33}H_{41}NNaO_6$: 570.2832; found: 570.2835.

Anal. Calcd for $C_{33}H_{41}NO_6$: C, 72.37; N, 2.56; H, 7.55. Found: C, 71.93; N, 2.62; H, 7.05.

**11-[4-(Hydroxycarbamoyl)phenoxy]undecanoic Acid (2)**

Pd/C (10%, 0.06 g) was added to a stirred soln of undecanoate **15** (70 mg, 0.13 mmol) in THF (5 mL) and the system was flushed with $H_2$. The mixture was stirred in a $H_2$ atmosphere for 72 h at 1.5 bar. The Pd/C was removed by centrifugation and the product was dissolved in THF and filtered through a syringe filter (PTFE, 0.2 μm). Removal of the solvent under reduced pressure gave **2** (35 mg, 81%) as a colorless solid; mp 135–137 °C.

IR (KBr): 3087 (m), 2923 (s), 2852 (s), 2770 (w), 1770 (w), 1693 (s), 1606 (s), 1577 (w), 1511 (w), 1427 (m), 1280 (m), 1253 (s), 1172 (m), 1014 (m), 946 (w), 854 (w), 777 (m), 642 cm$^{-1}$ (m).

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 12.25 (br, 1 H), 8.90 (br, 1 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 4.06 (t, *J* = 6.5 Hz, 2 H), 3.50 (br, 1 H), 2.22 (t, *J* = 7.3 Hz, 2 H), 1.78–1.71 (m, 2 H), 1.55–1.48 (m, 2 H), 1.47–1.41 (m, 2 H), 1.38–1.20 (m, 10 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 175.4 (s), 165.0 (s), 161.9 (s), 129.5 (d, 2 C), 125.7 (s), 115.0 (d, 2 C), 68.6 (t), 34.6 (t), 29.9 (t), 29.8 (t), 29.6 (t, 2 C), 29.5 (t, 2 C), 26.4 (t), 25.4 (t).

HRMS (+ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{27}NNaO_5$: 360.1787; found: 360.1747.

HRMS (–ESI): *m/z* [M – H]$^-$ calcd for $C_{18}H_{26}NO_5$: 336.1811; found: 336.1823; *m/z* [2 M – H]$^-$ calcd for $C_{36}H_{53}N_2O_{10}$: 673.3700; found: 673.3712.

Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; N, 4.15; H, 8.07. Found: C, 64.39; N, 4.08; H, 7.60.

**Methyl 3,5-Dihydroxybenzoate (17)[22]**

A soln of 3,5-dihydroxybenzoic acid (**16**, 30.0 g, 0.195 mol) and concd $H_2SO_4$ (1.5 mL) in MeOH (150 mL) was refluxed at 68 °C for 72 h. The solvent was removed under reduced pressure and the crude product was dissolved in EtOAc (150 mL) and washed with sat. $NaHCO_3$ (2 × 50 mL), $H_2O$ (50 mL), and brine (3 × 50 mL). The organic phase was dried ($Na_2SO_4$) and filtered. Removal of the solvent at reduced pressure gave **17** (30.0 g, 92%) as a slightly yellowish solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 2.3 Hz, 2 H), 6.46 (t, *J* = 2.3 Hz, 1 H), 3.85 (s, 3 H).

**Methyl 3,5-Bis[2-(*tert*-butoxycarbonylamino)ethoxy]benzoate (19)[25]**

A suspension of methyl 3,5-dihydroxybenzoate (**17**, 9.0 g, 54 mmol), *tert*-butyl *N*-(2-bromoacetyl)carbamate (**18**, 32.0 g, 143 mmol), and $K_2CO_3$ (40 g, 290 mmol) in anhyd DMF (100 mL) was stirred at r.t. for 48 h. The precipitate was removed by filtration through a glass filter frit and washed with EtOAc (3 × 80 mL). The combined organic fractions were carefully washed with $H_2O$ (5 × 75 mL) and brine (50 mL) and dried and the solvent was removed under reduced pressure. Purification by column chromatography ($CHCl_3$–EtOAc, 5:0.3 to 5:1.5 to $CHCl_3$–MeOH, 5:2) gave **19** (17.8 g, 73%) as a colorless solid.[25]

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 2.3 Hz, 2 H), 6.61 (t, *J* = 2.2 Hz, 1 H), 5.04 (br s, 2 H), 4.01 (t, *J* = 5.1 Hz, 4 H), 3.87 (s, 3 H), 3.54–3.48 (m, 4 H), 1.43 (s, 18 H).

**3,5-Bis[2-(*tert*-butoxycarbonylamino)ethoxy]benzoic Acid (20)**

A 1.0 M NaOH soln (18 mL) was added to a soln of benzoate **19** (3.00 g, 6.60 mmol) in MeOH (22 mL) and the resulting mixture was stirred at r.t. for 24 h and at 70 °C for 3 h. The solvent was removed and the product dissolved in $H_2O$ (10 mL) and washed with $Et_2O$. After acidification with concd HCl (37%) to pH 2, the product was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were washed with brine. The organic phase was dried ($Na_2SO_4$) and the solvent was removed to give **20** (2.7 g, 94%) as a colorless solid; mp 125–127 °C.

$^1$H NMR (400 MHz, $CDCl_3$–$CD_3OD$): δ = 7.08 (d, *J* = 2.3 Hz, 2 H), 6.54 (t, *J* = 2.1 Hz, 1 H), 3.93 (t, *J* = 5.1 Hz, 4 H), 3.41 (t, *J* = 6.4 Hz, 4 H), 1.35 (s, 18 H).

$^{13}$C NMR (100 MHz, $CDCl_3$–$CD_3OD$): δ = 168.8 (s), 159.3 (s, 2 C), 156.2 (s, 2 C), 133.0 (s), 108.0 (d, 2 C), 106.1 (d), 19.6 (s, 2 C), 67.1 (t, 2 C), 39.6 (t, 2 C), 18.1 (q, 6 C).

HRMS (+ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{32}N_2NaO_8$: 463.2056; found: 463.2062; *m/z* [2 M + Na]$^+$ calcd for $C_{42}H_{64}N_4NaO_{16}$: 903.4215; found: 903.4222.

Anal. Calcd for $C_{21}H_{32}N_2O_8$: C, 57.26; N, 6.36; H, 7.32. Found: C, 56.46; N, 6.28; H, 7.31.

***N*-(Benzyloxy)-3,5-bis[2-(*tert*-butoxycarbonylamino)ethoxy]benzamide (21)**

Benzoic acid **20** (3.00 g, 6.81 mmol) was dissolved in anhyd $CH_2Cl_2$ (50 mL) and cooled to 0 °C. HOBt (1.12 g, 8.44 mmol), EDCI (1.58 g, 8.15 mmol), *O*-benzylhydroxylamine hydrochloride (1.11 g, 6.95 mmol), and *i*-$Pr_2NEt$ (4 mL) were added to this soln and the mixture was stirred at r.t. for 24 h. $CH_2Cl_2$ (50 mL) was added and the mixture was washed with 1 M HCl and brine, and dried ($Na_2SO_4$). The crude product was purified by column chromatography ($CHCl_3$–MeOH, 5:0.5) to afford **21** (3.20 g, 86%) as a colorless foam.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.64 (br s, 1 H), 7.43–7.40 (m, 2 H), 7.36–7.31 (m, 3 H), 6.84–6.81 (m, 2 H), 6.47–6.44 (m, 1 H), 5.12 (br s, 2 H), 5.00 (s, 2 H), 3.91 (t, *J* = 5.1 Hz, 4 H), 3.45–3.41 (m, 4 H), 1.42 (s, 18 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 159.6 (s, 2 C), 155.9 (s, 2 C), 135.3 (s), 134.0 (s), 129.1 (d, 2 C), 128.6 (d), 128.5 (d, 2 C), 105.8 (d, 2 C), 104.9 (d), 79.6 (t), 78.2 (s, 2 C), 67.1 (t, 2 C), 39.7 (t, 2 C), 28.3 (q, 6 C). (The C=O from the hydroxamic acid group could not be observed.)

HRMS (+ESI): *m/z* [M + Na]$^+$ calcd for $C_{28}H_{39}N_3NaO_8$: 568.2635; found: 568.2653.

**3,5-Bis(2-aminoethoxy)-*N*-(benzyloxy)benzamide Dihydrochloride (22)**

Concd HCl (37%, 4.5 mL) was added to a soln of carbamate **21** (3.20 g, 5.87 mmol) in $Et_2O$–$CH_2Cl_2$ (1:1, 60 mL) and the mixture was stirred at r.t. for 3 h. The solvent was removed at reduced pressure and the product was washed with $Et_2O$ to give **22** (2.11 g, 86%) as a colorless solid; mp 210 °C (dec).

$^1$H NMR (400 MHz, $D_2O$): δ = 7.42–7.38 (m, 2 H), 7.37 (s, 1 H), 7.35–7.31 (m, 3 H), 4.89 (s, 2 H), 4.15 (t, *J* = 5.0 Hz, 4 H), 3.31 (t, *J* = 4.8 Hz, 4 H).

$^{13}$C NMR (100 MHz, $D_2O$): δ = 166.9 (s), 159.0 (s, 2 C), 134.6 (s), 133.1 (s), 130.1 (d, 2 C), 129.3 (d), 128.8 (d, 2 C), 106.5 (d, 2 C), 105.5 (d), 78.4 (d), 64.3 (t, 2 C), 38.9 (t, 2 C).

HRMS (+ESI): *m/z* [M – 2 HCl + H]$^+$ calcd for $C_{18}H_{24}N_3O_4$: 346.1767; found: 346.1773.

Anal. Calcd for $C_{18}H_{25}Cl_2N_3O_4$: C, 51.68; N, 10.05; H, 6.02. Found: C, 53.39; N, 9.24; H, 6.01.

**N-(Benzyloxy)-3,5-bis{2-[bis(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino]ethoxy}benzamide (23) and N-(Benzyloxy)-3-{2-[bis(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino]ethoxy}-5-{2-[(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino]ethoxy}benzamide (25)**

$Et_3N$ (6.4 mL, 46 mmol) and acetamide **10** (5.09 g, 14.85 mmol, 3.2 equiv) were added slowly to a suspension of benzamide dihydrochloride **22** (1.94 g, 4.64 mmol, 1 equiv) in THF–$H_2O$ (40 mL:7 mL), and the resulting mixture was stirred at r.t. for 24 h. The solvent was removed and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic fractions were washed with brine and dried ($Na_2SO_4$) and the solvent was removed at reduced pressure. The crude product was separated by column chromatography (silica gel, $CHCl_3$–MeOH, 5:0.1 to 5:2) to afford the tetrasubstituted product **23** (0.91 g, 14%), the trisubstituted product **25** (1.40 g, 27%), the disubstituted product (0.32 g, 8%) and mixtures of different di-, tri- and tetrasubstituted products (2.18 g, 42%). The mixtures of the different substituted and the disubstituted products were treated with excess acetamide **10** (4.5 equiv) using the same experimental procedure described above. The crude product (2.5 g) was purified by HPLC ($CH_2Cl_2$–MeOH, 91:9) to afford **23** (1.92 g, 37%) as a colorless oil.

**Tetrasubstituted product 23**

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.72 (br s, 1 H), 7.45–7.41 (m, 2 H), 7.34–7.27 (m, 3 H), 7.05 (d, *J* = 2.2 Hz, 2 H), 6.49 (t, *J* = 2.1 Hz, 1 H), 5.00 (s, 2 H), 4.11 (t, *J* = 5.8 Hz, 4 H), 3.68 (s, 8 H), 3.59–3.49 (m, 48 H), 3.45–3.42 (m, 16 H), 3.31 (s, 12 H), 3.28 (s, 12 H), 3.06 (t, *J* = 5.6 Hz, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.0 (s, 4 C), 165.0 (s), 159.7 (s, 2 C), 135.7 (s), 133.7 (s), 129.2 (d, 2 C), 128.3 (d), 128.2 (d, 2 C), 105.8 (d), 105.4 (d, 2 C), 77.9 (t), 71.8 (t, 4 C), 71.7 (t, 4 C), 70.4 (t, 4 C), 70.1 (t, 4 C), 69.2 (t, 4 C), 69.1 (t, 4 C), 66.8 (t, 2 C), 58.8 (q, 8 C), 56.3 (t, 4 C), 52.9 (t, 2 C), 48.0 (t, 4 C), 46.1 (t, 4 C).

HRMS (+ESI): *m/z* $[M + 2 H]^{2+}$ calcd for $C_{66}H_{117}N_7O_{24}$: 695.9075; found: 695.9078; *m/z* $[M + H + Na]^{2+}$ calcd for $C_{66}H_{116}N_7NaO_{24}$: 706.8985; found: 706.8987.

Anal. Calcd for $C_{66}H_{115}N_7O_{24}$: C, 57.00; N, 7.05; H, 8.34. Found: C, 55.88; N, 6.94; H, 8.40.

**Trisubstituted product 25**

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.41 (br s, 1 H), 7.44–7.42 (m, 2 H), 7.36–7.30 (m, 3 H), 7.06–7.03 (m, 1 H), 6.99–6.97 (m, 1 H), 6.54 (t, *J* = 2.2 Hz, 1 H), 5.01 (s, 2 H), 4.12 (t, *J* = 5.9 Hz, 2 H), 4.05 (t, *J* = 5.2 Hz, 2 H), 3.68 (s, 4 H), 3.60–3.42 (m, 50 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.32 (s, 6 H), 3.29 (s, 6 H), 3.05 (t, *J* = 5.9 Hz, 2 H), 2.95 (t, *J* = 5.2 Hz, 2 H), 2.38 (br s, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.3 (s), 171.2 (s), 171.0 (s), 165.2 (s), 160.0 (s), 159.8 (s), 135.8 (s), 133.8 (s), 129.4 (d, 2 C), 128.6 (d), 128.5 (d, 2 C), 106.3 (d), 106.2 (d), 105.3 (d), 78.0 (t), 71.8 (t, 3 C), 71.7 (t, 3 C), 70.5 (t), 70.4 (t, 2 C), 70.2 (t), 70.1 (t, 2 C), 69.2 (t, 2 C), 68.9 (t), 66.8 (t, 2 C), 58.9 (q, 6 C), 56.4 (t, 3 C), 56.3 (t), 55.5 (t, 2 C), 53.0 (t), 52.8 (t), 48.4 (t), 48.0 (t, 2 C), 46.3 (t), 46.1 (t, 2 C).

HRMS (+ESI): *m/z* $[M + H]^+$ calcd for $C_{54}H_{93}N_6O_{19}$: 1129.6495; found: 1129.6545.

Anal. Calcd for $C_{54}H_{92}N_6O_{19}$: C, 57.43; N, 7.44; H, 8.21. Found: C, 56.35; N, 6.78; H, 8.14.

**3,5-Bis{2-[bis(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino]ethoxy}benzenecarbohydroxamic Acid (24)**

Pd/C (10%, 0.1 g) was added to a stirred soln of benzamide **23** (0.70 g, 0.50 mmol) in MeOH (20 mL) and the system was flushed with $H_2$. The mixture was stirred in a $H_2$ atmosphere for 48 h at 1.5 bar. The Pd/C was removed by centrifugation and the product was dissolved in $CHCl_3$ (20 mL) and washed with $NaHCO_3$ (1 × 10 mL) and brine (1 × 10 mL). The solvent was removed to give **24** (0.59 g, 91%) as a slightly yellowish oil.

IR (film): 3246 (w), 2877 (s), 2821 (m), 2727 (w), 1651 (s), 1597 (m), 1456 (m), 1356 (m), 1304 (w), 1200 (m), 1115 (s), 1026 (m), 850 $cm^{-1}$ (m).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.42 (br s, 1 H), 7.14 (d, *J* = 2.1 Hz, 2 H), 6.48 (t, *J* = 2.1 Hz, 1 H), 4.13 (t, *J* = 6.0 Hz, 4 H), 3.69 (s, 8 H), 3.60–3.50 (m, 48 H), 3.48–3.43 (m, 16 H), 3.31 (s, 12 H), 3.30 (s, 12 H), 3.06 (t, *J* = 6.0 Hz, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.1 (s, 4 C), 164.0 (s), 159.8 (s, 2 C), 132.6 (s), 106.2 (d), 105.1 (d, 2 C), 71.8 (t, 4 C), 71.7 (t, 4 C), 70.5 (t, 4 C), 70.1 (t, 4 C), 69.3 (t, 4 C), 69.2 (t, 4 C), 66.9 (t, 2 C), 58.9 (q, 8 C), 56.3 (t, 4 C), 52.7 (t, 2 C), 48.1 (t, 4 C), 46.2 (t, 4 C).

HRMS (+ESI): *m/z* $[M + Na]^+$ calcd for $C_{59}H_{109}N_7NaO_{24}$: 1322.7422; found: 1322.7410; *m/z* $[M + H]^+$ calcd for $C_{59}H_{110}N_7O_{24}$: 1300.7602; found: 1300.7586; *m/z* $[M + 2 Na]^{2+}$ calcd for $C_{59}H_{109}N_7Na_2O_{24}$: 672.8660; found: 672.8648.

Anal. Calcd for $C_{59}H_{109}N_7O_{24}$: C, 54.49; N, 7.54; H, 8.45. Found: C, 53.77; N, 7.20; H, 8.59.

**11-({2-[3-(Benzyloxycarbamoyl)-5-{2-[bis(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxo-ethyl)amino]ethoxy}phenoxy]ethyl}(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino)undecanoic Acid (27)**

11-Bromoundecanoic acid (**26**, 0.56 g, 2.14 mmol), NaI (79.6 mg, 531 μmol), and $Na_2CO_3$ (225 mg, 2.14 mmol) were added to a soln of benzamide **25** (0.600 g, 531 μmol) in acetone (10 mL) and the resulting mixture was refluxed for 48 h. The solvent was removed and the precipitate was dissolved in $CHCl_3$ and washed with 1 M HCl and brine. The solvent was removed and the product was purified by column chromatography ($CHCl_3$–MeOH, 5:0.3 to 5:2.5) to afford **27** (185 mg, 27%) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.69 (br, 1 H), 7.45–7.39 (m, 2 H), 7.36–7.24 (m, 3 H), 7.06 (m, 2 H), 6.48 (s, 1 H), 5.00 (s, 2 H), 4.11–3.99 (m, 4 H), 3.67 (s, 6 H), 3.57–3.40 (m, 48 H), 3.29 (s, 9 H), 3.26 (s, 9 H), 3.05–2.87 (m, 4 H), 2.59 (m, 2 H), 2.24 (t, *J* = 7.4 Hz, 2 H), 1.60–1.50 (m, 2 H), 1.48–1.39 (m, 2 H), 1.28–1.18 (m, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 173.9 (s), 171.1 (s, 3 C), 165.1 (s), 159.7 (s, 2 C), 135.7 (s), 133.6 (s), 129.2 (d, 2 C), 128.4 (d), 128.3 (d, 2 C), 105.9 (d), 105.3 (d, 2 C), 77.9 (t), 71.8 (t, 3 C), 71.7 (t, 3 C), 70.4 (t, 3 C), 70.1 (t, 3 C), 69.2 (t, 6 C), 66.8 (t), 66.1 (t), 64.2 (t), 58.8 (q, 6 C), 56.3 (t, 3 C), 52.9 (t), 52.5 (t), 48.0 (t, 3 C), 46.1 (t, 3 C), 34.3 (t), 29.5 (t), 29.3 (t), 29.2 (t), 29.0 (t), 28.5 (t), 27.3 (t), 25.7 (t), 24.8 (t).

HRMS (+ESI): *m/z* $[M + 2 H]^{2+}$ calcd for $C_{65}H_{114}N_6O_{21}$: 657.4018; found: 657.4016.

**3-{2-[Bis(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)amino]ethoxy}-5-{2-[(2-{bis[2-(2-methoxyethoxy)ethyl]amino}-2-oxoethyl)(11-hydroxy-11-oxo-undecyl)amino]ethoxy}benzenecarbohydroxamic Acid (1)**

Undecanoic acid **27** (178 mg, 135 μmol) and Pd/C (25 mg) were dispersed in MeOH (6 mL) and hydrogenated for 72 h at 1.5 bar. The solvent was removed by centrifugation to give **1** (110 mg, 67%) **1** as a slightly yellowish oil.

IR (film): 3400 (w), 2931 (s), 2862 (m), 2725 (w), 1736 (w), 1654 (m), 1595 (m), 1456 (m), 1359 (w), 1105 (s), 849 $cm^{-1}$ (w).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.56 (br s, 1 H), 9.13 (br s, 1 H), 7.19 (s, 2 H), 6.64 (s, 1 H), 5.04–4.63 (m, 4 H), 4.48 (s, 6 H), 3.92–3.48 (m, 36 H), 3.48–3.40 (m, 14 H), 3.30 (s, 9 H), 3.27 (s, 3 H),

3.26 (s, 6 H), 3.22–3.01 (m, 4 H), 2.25 (t, *J* = 7.4 Hz, 2 H), 1.87–1.71 (m, 2 H), 1.60–1.47 (m, 2 H), 1.36–1.11 (m, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.3 (s), 173.9 (s), 165.3 (s, 3 C), 158.4 (s, 2 C), 133.3 (s), 106.1 (d), 106.6 (d, 2 C), 71.7 (t, 6 C), 70.2 + 70.0 (t, 6 C), 68.9 + 68.4 (t, 6 C), 64.2 (t), 63.5 (t), 58.9 + 58.8 + 58.6 (q, 6 C), 56.9 (t, 3 C), 55.7 (t), 55.1 (t), 53.1 (t), 48.6 + 48.4 + 46.5 + 46.2 (t, 6 C), 34.0 (t), 29.6 (t), 29.3 (t), 29.2 (t), 29.0 (t), 28.6 (t), 28.5 (t), 25.9 (t), 24.5 (t).

HRMS (+ESI): *m/z* [M + H]$^+$ calcd for $C_{58}H_{107}N_6O_{21}$: 1223.7489; found: 1223.7508; *m/z* [M + Na]$^+$ calcd for $C_{58}H_{106}N_6NaO_{21}$: 1245.7309; found: 1245.7324.

**11-(Hydroxycarbamoyl)undecanoic Acid (3)**

Dodecanedioic acid (**28**, 25.00 g, 108.55 mmol), MeOH (85 mL), and $H_2SO_4$ (2 mL) were refluxed for 24 h. The mixture was cooled to r.t. and the solvent was removed to give a colorless solid that was dissolved in $Et_2O$ and poured into ice $H_2O$ for extraction. The aqueous phase was washed with $Et_2O$ (3 ×). The organic phases were combined and washed with 10% $NaHCO_3$ soln and brine and dried ($Na_2SO_4$). Evaporation at reduced pressure gave dimethyl dodecanedioate (27.63 g, 100%) as a colorless powder.[26]

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 6 H), 2.26 (t, *J* = 7.5 Hz, 4 H), 1.62–1.51 (m, 4 H), 1.35–1.20 (m, 12 H).

KOH (6 g, 106.92 mmol) and MeOH (130 mL) were combined in a bottom flask. When the soln became fully clear, dimethyl dodecanedioate (27.63 g, 106.96 mmol) was added and the mixture was stirred for 4 h. Subsequently, the solvent was removed at reduced pressure at 40 °C. The resulting solid was dissolved in $Et_2O$ and the product was extracted with $H_2O$. The aqueous phase was acidified with concd HCl. Then the aqueous phase was extracted with $Et_2O$ (4 × 75 mL) and the combined organic phases were washed with brine and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to give a solid that was washed extensively with hexane. The washings were combined and evaporated to give dodecanedioic acid monomethyl ester (4.01 g, 15%) as a colorless powder.[26]

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.64 (br, 1 H), 3.65 (s, 3 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 2.28 (t, *J* = 7.5 Hz, 2 H), 1.64–1.54 (m, 4 H), 1.34–1.21 (m, 12 H).

Dodecanedioic acid monomethyl ester (0.20 g, 0.82 mmol) was dissolved in anhyd $CH_2Cl_2$ (6 mL) and cooled to –10 °C. HOBt (0.13 g, 0.98 mmol), EDCI (0.19 g, 0.98 mmol), *O*-(4-methoxybenzyl)hydroxylamine hydrochloride (0.19 g, 0.98 mmol), and *i*-$Pr_2NEt$ (0.47 mL) were added to this soln. The mixture was stirred at r.t. for 6 h and then it was extracted with $H_2O$, acidified with HCl to pH 2, washed with brine and dried ($Na_2SO_4$). The crude product was purified by column chromatography ($CH_2Cl_2$) to afford methyl 11-[(4-methoxybenzyloxy)carbamoyl]undecanoate (0.26 g, 84%) as a colorless powder; mp 70–72 °C.

$^1$H NMR (400 MHz, $CDCl_3$–$CD_3OD$): δ = 7.25 (d, *J* = 7.4 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 4.74 (s, 2 H), 3.74 (s, 3 H), 3.59 (s, 3 H), 2.97 (br, 1 H), 2.23 (t, *J* = 7.5 Hz, 2 H), 1.96 (t, *J* = 7.2 Hz, 2 H), 1.55–1.50 (m, 4 H), 1.31–1.19 (m, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$–$CD_3OD$): δ = 174.6 (s), 171.1 (s), 159.8 (s), 130.8 (d, 2 C), 127.5 (s), 113.7 (d, 2 C), 77.4 (t), 55.1 (q), 51.3 (q), 33.9 (t), 33.0 (t), 29.2 (t, 2 C), 29.03 (t), 28.99 (t, 2 C), 28.89 (t), 25.3 (t), 24.7 (t, C).

Methyl 11-[(4-methoxybenzyloxy)carbamoyl]undecanoate (1.69 g, 4.45 mmol), KOH (0.76 g, 13.57 mmol), and MeOH (47 mL) were stirred at 55 °C for 20 h. The solvents was evaporated and the mixture was extracted with EtOAc and washed with HCl soln and brine and dried ($Na_2SO_4$). The crude product was purified by column chromatography ($CH_2Cl_2$–MeOH, 20:1) to give 11-[(4-methoxybenzyloxy)carbamoyl]undecanoic acid (1.62 g, 90%); mp 99–102 °C.

$^1$H NMR (400 MHz, $CDCl_3$–$CD_3OD$): δ = 7.25 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.72 (s, 2 H), 3.74 (s, 3 H), 2.90 (br, 1 H), 2.21 (t, *J* = 7.4 Hz, 2 H), 1.95 (t, *J* = 7.2 Hz, 2 H), 1.54–1.50 (m, 4 H), 1.26–1.19 (m, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$–$CD_3OD$): δ = 176.8 (s), 171.5 (s), 159.9 (s), 131.0 (d, 2 C), 127.6 (s), 113.8 (d, 2 C), 77.6 (t), 55.3 (q), 34.1 (t), 33.1 (t), 29.3 (t, 2 C), 29.1 (t, 3 C), 29.0 (t), 25.4 (t), 24.9 (t).

11-[(4-Methoxybenzyloxy)carbamoyl]undecanoic acid (0.51 g, 1.40 mmol), anhyd MeOH (6 mL), $CHCl_3$ (3 mL), and Pd/C (50 mg) were hydrogenated for 1 h. When the reaction was complete, the catalyst was removed by centrifugation and the organic phases were combined and evaporated to dryness to give a white solid (0.34 g, 96%). The solid (0.25 g, 1.02 mmol) was dissolved in *i*-PrOH–$H_2O$ (2:1, 44 mL) and LiOH (0.3 g, 4.1 mmol, 56%) was added. The mixture was stirred for 20 h and then acidified with HCl soln to pH 3, extracted with EtOAc and dried ($Na_2SO_4$). The resulting solid was recrystallized ($CHCl_3$–MeOH) to afford **3** (90 mg, 38%) as a colorless solid; mp 102–105 °C.

IR (KBr): 3265 (w), 3070 (w), 2914 (s), 2848 (s), 2737 (w), 1700 (s), 1662 (s), 1620 (m), 1470 (s), 1425 (m), 1294 (m), 1215 (m), 1117 (m), 1078 (m), 1047 (m), 970 (m), 899 (m), 720 (m), 647 (m), 555 (m), 474 cm$^{-1}$ (m).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.22 (br, 1 H), 8.67 (br, 1 H), 3.39 (br, 1 H), 2.20 (t, *J* = 7.4 Hz, 2 H), 1.94 (t, *J* = 7.3 Hz, 2 H), 1.53–1.44 (m, 4 H), 1.30–1.20 (m, 12 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 175.5 (s), 170.1 (s), 34.6 (t), 33.2 (t), 29.8 (t, 2 C), 29.7 (t, 2 C), 29.52 (t), 29.50 (t), 26.1 (t), 25.4 (t).

HRMS (+ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{23}NNaO_4$: 268.1525; found: 268.1522.

Anal. Calcd for $C_{14}H_{27}NO_4$·HCl: C, 54.27; N, 4.52; H, 9.11. Found: C, 54.55; N, 5.11; H, 8.89.

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