Scientific paper

The Design, Synthesis, and Antioxidant Activity of Amphiphilic Oximes and Amidoximes

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Received: 13-12-2012

Abstract

New amphiphilic benzamidoxime, benzoxime, and aliphatic oxime derivatives of glycolipid mimetics were synthesized. The total antioxidant capacity of these amphiphilic derivatives was evaluated using DPPH assay. The observed antioxidant activity was the highest for benzamidoxime derivatives and glycolipid mimetics with two oxime functionalities, followed by benzoxime derivatives, glycolipid mimetics with one oxime group, and dimers of oxime. Due to their amphiphilic structure, which was a guidance for compound design and synthesis, these novel amphiphilic compounds can be proposed as potential antioxidants for tackling oxidative processes in two-phase systems, either biological (cell membranes) or artificial (emulsions).

Keywords: Amphiphilic molecules, amidoximes, oximes, glycolipid mimetics, antioxidant activity.

1. Introduction

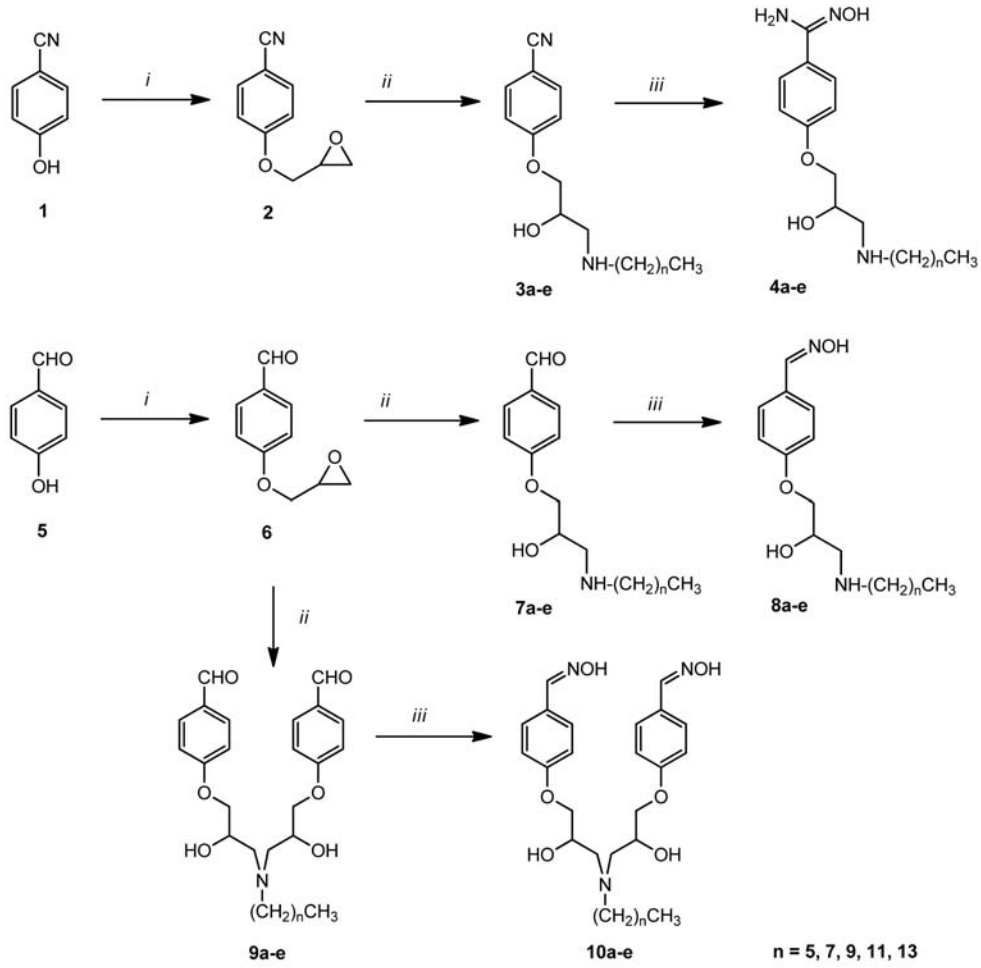
The stability of an active pharmaceutical ingredient (API) and/or final formulation is of the primary concern in the field of pharmaceutical formulation, with oxidation processes being one of the common contributors to instability problems. Various approaches can be used to eliminate or diminish the extent of oxidative degradation, the addition of antioxidants being one of them.[1] Antioxidants are molecules that prevent oxidation even in a low concentration and an antioxidant effect can be achieved through their ability to complex transition metal ions, catalyzing the breakdown of oxidizing species, or reacting directly with free radicals.[2] Antioxidants are used not only as excipients, but can also be used as APIs themselves. Namely, all living organisms require molecular oxygen for energy production, but as triplet oxygen is a biradical it is impossible to avoid secondary oxidations not involved in physiological metabolism. Free radicals, reactive oxygen species, and reactive nitrogen species are formed. These mediate oxidative stress, defined as an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. They are involved in many pathologies such as cancer, ischemia-reperfusion disorders, cardiovascular diseases, and neurodegenerative disorders (Parkinson's disease and Alzheimer's disease). The role of antioxidants in prophylaxis of these conditions, as well as in the aging process, emphasizes the importance of developing antioxidants as APIs.[3–5]

Antioxidant is any substance that delays, prevents or removes oxidative damage to a target molecule.[6] Most of them are reactive and therefore highly unstable compounds. Their consumption and loss of efficacy can usually be attributed to oxidation processes (and hydrolysis in some cases). An acknowledged approach for increasing their stability is incorporation into a suitable delivery system because stability can be influenced by the structural properties of the formulation. However, this is often insufficient to achieve adequate long-term stability.[7–8] Therefore a new approach for increasing the stability of ascorbyl palmitate (AP), an antioxidant, incorporated as API in microemulsions for preventing skin aging, was reported by our research group. The oxime molecule, 4-(tridecyloxy)benzaldehyde oxime (TDBO), was designed and synthesized based on structural similarity to AP, and its antioxidant activity was confirmed. Incorporation of the oxime molecule as a co-antioxidant resulted in increased AP stability in hydrophilic microemulsions and the effect was explained by higher local concentration of both molecules in the inner phase of the system and consequently better

protection of AP.[9] This led us to further investigation oriented towards designing and synthesizing antioxidants with an amphiphilic structure for incorporation into two-phase delivery systems; that is, regular emulsions, microemulsions, or lyotropic liquid crystals. The design strategy was oriented towards long linear molecules composed of lipophilic alkyl or acyl residue of varying length and polar moiety, bearing either the oxime or amidoxime group. The oxime group is often associated with its antioxidant activity, and therefore oxime compounds are of particular interest in a state of oxidative stress displaying free-radical scavenging and/or chelating properties. They have been used as cholinesterase reactivators following organophosphate-induced oxidative damage and have been studied as inhibitors of low-density lipoprotein oxidation and lipid peroxidation.[10–12] Amidoximes have been proven to exhibit numerous biological activities (anti-inflammatory, antiviral, etc.). For nicotinic amidoxime derivative behavior similar to antioxidants was confirmed, as ischemia-reperfusion-induced mitochondrial reactive oxygen species formation and oxidative cell damage was decreased due to inhibition of specific nuclear polymerase.[13]

Amphiphilic molecules are distinctive for their surfactant properties. Surfactant molecules find a wide range of uses in pharmaceutical preparation, but can also contribute to adverse reactions, skin irritation following dermal application being one of them.[14] Therefore the use of biocompatible and naturally occurring surfactants is a trend and a must in pharmacy, one important group of amphiphilic biomolecules being glycolipids.[15] Recently, we reported the synthesis of novel amphiphilic oximes of galactose and glucosamine.[16]

In this context, this work is a continuation of our previous study[9] and reports the design, synthesis, and characterization of a new set of amphiphilic oxime and amidoxime molecules and the evaluation for their antioxidant activity. The new group of compounds was designed to improve polarity by introducing a polar ethanolamine spacer between benzoxime or benzamidoxime functionality and the lipophilic hydrocarbon chain of TDBO. In the second part of our research we synthesized glycolipid mimetics in which the aromatic ring was replaced by a biologically acceptable monosaccharide D-galactose or D-glucose with one or two oxime functionalities.[16]



Scheme 1. Synthesis of amphiphilic benzamidoxime and benzoxime derivatives: *i.* epichlorhydrine, $NaOH/H_2O$, dioxane, r.t., 12 h *ii*. $Ca(OTf)_2$, $H_2N(CH_2)_nCH_3$ (n = 5, 7, 9, 11, 13), anhydrous dioxane, reflux, 6 h, *iii*. $NH_2OH \times HCl$, K_2CO_3, anhydrous ethanol, reflux, 12 h.

2. Results and Discussion

2. 1. Chemistry

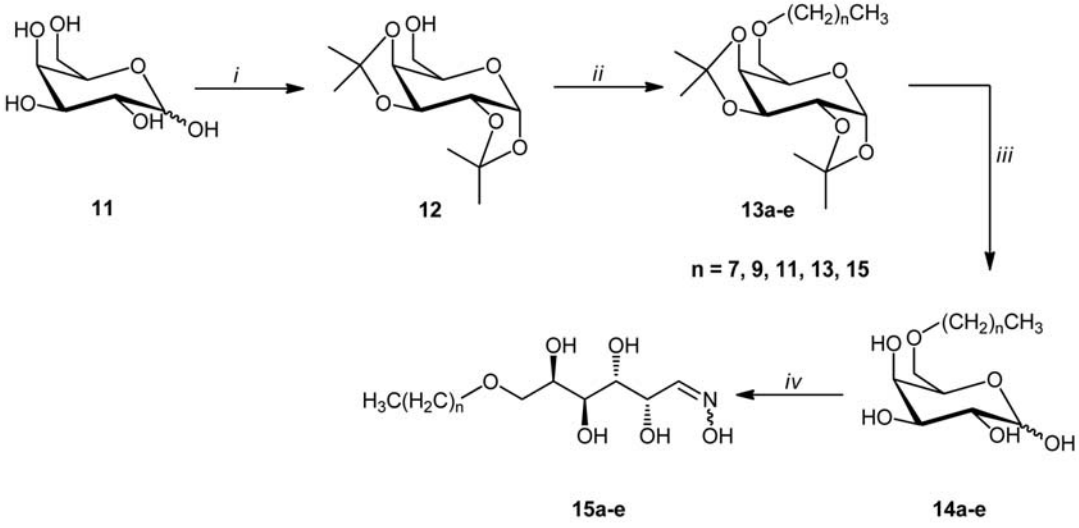
Based on our previous studies in the field of new antimicrobial drug design[17,18] and further docking studies, we came across several useful intermediates for the synthesis of amphiphilic compounds. The overall synthetic approach is outlined in Schemes 1, 2, and 3. The synthesis of benzamidoxime and benzoxime derivatives (Scheme 1) was started from 4-cyanophenol (**1**),[19] which was reacted with epichlorhydrine to yield compound **2**, followed by nucleophylic substitution at the less sterically hindered carbon with aliphatic amines with different length of alkyl chain to yield amphiphilic compounds **3a–e**. In the last step, nitrile functionality was transformed to amidoxime **4a–e** with hydroxylamine hydrochloride. Oximes **8a–e** were prepared in an analogous way, starting from 4-hydroxybenzaldehyde **(5)**. The reaction of epoxide with alkyl amines[20] in the latter case resulted in the formation of about 10% of tertiary amines **9a–e** that were also transformed to oximes **10a–e**.

The synthesis of glycolipid derivatives[21] is presented in Schemes 2 and 3 and described in detail in a recent paper.[16]

The HLB parameter is used to characterize the ratio between hydrophilic and lipophilic parts of the surfactant molecule and was calculated for all synthesized compounds with the results depicted in Table 1. As expected, among individual groups of compounds HLB values vary by changing the length of the aliphatic tail: the HLB value and thereby the hydrophilic character decreases with increasing length of the alkyl or acyl residue. The data obtained show that benzamidoxime and benzoxime derivatives are more hydrophilic compared to previously synthesized highly lipophilic glycolipid mimetic TDBO; this effect is the most notable for dimers of oxime (**10a–10e**).

2. 2. Evaluation of Aantioxidant Capacity of Amphiphilic Amidoxime, Oxime, and Glycolipid Derivatives

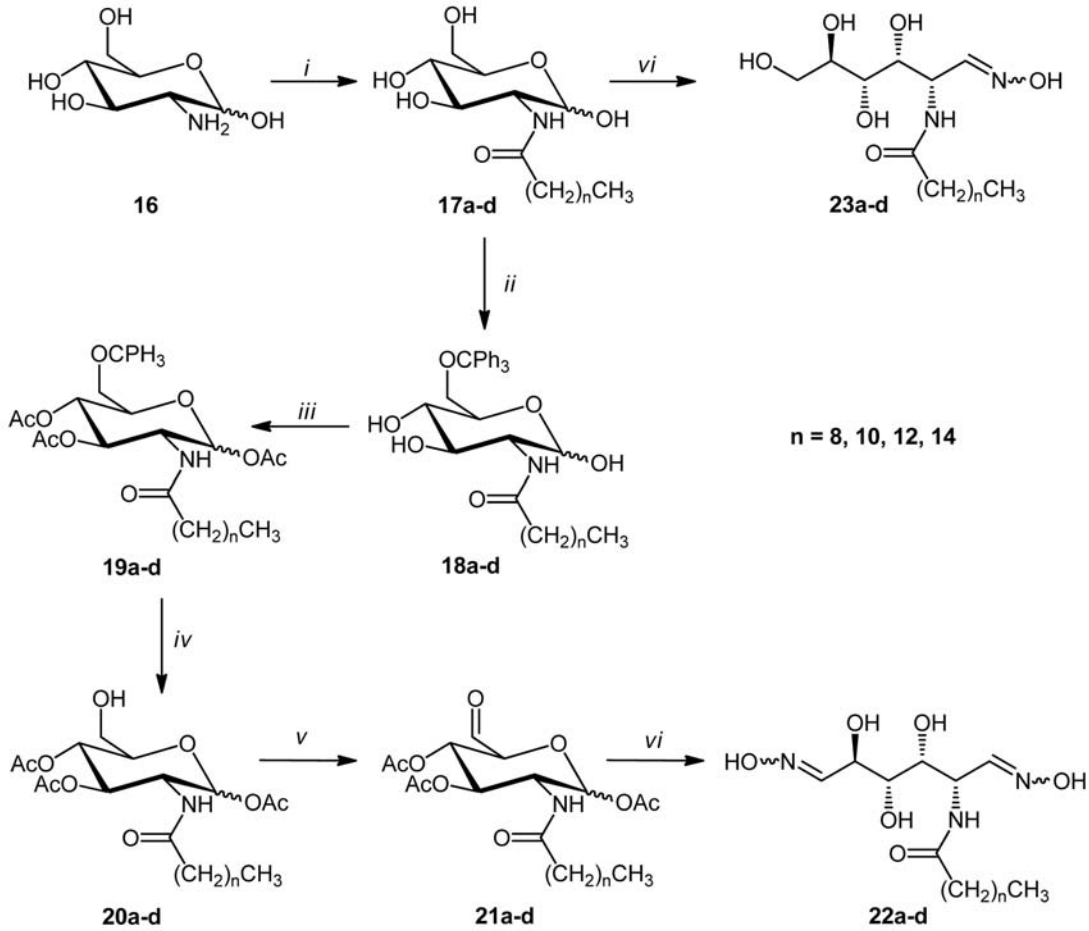
Total antioxidant capacity assay was used to determine the hierarchy of radical-scavenging abilities of potential antioxidants that work either through electron- or H-donating mechanisms. Accordingly, DPPH assay was used to assess the radical-scavenging ability of synthesized derivatives that can be divided among different groups regarding their structure; that is, benzamidoxime (**4a–e**), benzoxime (**8a–e**), benzoxime dimers (**10b, 10d**), galactose derivatives (**15a–e**), and glucosamine derivati-



Scheme 2: Synthesis of amphiphilic derivatives of galactose: *i.* acetone, $CuSO_4$ (2.4 equiv), H_2SO_4 (0.35 equiv), r. t., 24 h, then $Ba(OH)_2$ (0.35 equiv); *ii.* $CH_3(CH_2)_nBr$ (n = 7, 9, 11, 13, 15; 1.5 equiv), NaH (1.5 equiv), 15-Crown-5 (0.02 equiv), imidazole (0.01 equiv), 1,4-dioxane; *iii.* 75% TFA, H_2O, 0 °C → r. t., 1.5 h; *iv.* NH_2OH (5 equiv), pyridine, 40 °C, 48 h.

Table 1. HLB values of synthesized amphiphilic derivatives

HLB values														
benzamidoxime & benzoxime derivatives														
4a	**4b**	**4c**	**4d**	**4e**	**8a**	**8b**	**8c**	**8d**	**8e**	**10a**	**10b**	**10c**	**10d**	**10e**
14.50	13.29	12.27	11.39	10.64	14.21	12.98	11.94	11.05	10.29	16.51	15.61	14.80	14.08	13.42
derivatives of galactose & glucose														
	15a	**15b**	**15c**	**15d**	**15e**	**22a**	**22b**	**22c**	**22d**	**23a**	**23b**	**23c**	**23d**	
	12.63	11.58	10.68	9.92	9.26	12.96	12.03	11.22	10.51	12.68	11.73	10.91	10.20	



Scheme 3: Synthesis of amphiphilic derivatives of glucose: *i.* $CH_3(CH_2)_nCOCl$ (n = 8, 10, 12, 14; 1.1 equiv), $NaHCO_3$ (2 equiv), H_2O, 1,4-dioxane, r. t., 24 h; *ii.* Ph_3CCl (1.7 equiv), DMAP (0.05 equiv), pyridine, 75 °C, 2 h; *iii.* Ac_2O (6 equiv), pyridine, 0 °C → r. t., 12 h; *iv.* $FeCl_3$ (2 equiv), H_2O, CH_2Cl_2, r. t., 2 h; *v.* DMP (1.2 equiv), CH_2Cl_2, r. t., 1.5 h, then work-up with $Na_2S_2O_3$; *vi* NH_2OH (7 equiv), EtOH, 40 °C, 48 h.

ves with two (**22a–d**) or one (**23a–d**) oxime functionality.

It is evident for all tested benzamidoxime and benzoxime derivatives that their antioxidant activity correlates with concentration: the higher the concentration, the lower the amount of remaining DPPH• (DPPH• rem) and the higher the free radical–scavenging activity (Figure 1). The molecular structure of tested molecule had a great impact on its radical-scavenging ability against DPPH. Benzamidoxime derivatives (**4a–e**) demonstrate the highest antioxidant potential, followed by benzoxime derivatives (**8a–e**), and being the lowest for compounds with two oxime moieties (**10b, 10d**). Comparison of amidoxime with oxime group emphasizes additional amino group as an important factor that enhances antioxidant activity. In the same series, benzamidoxime derivatives **4a**-**e** exhibit similar antioxidant performance; **4b** being the most pronounced (it reacted rapidly with the DDPH radical, which was completely reduced in a reaction time of 4 minutes) with a chain of eight carbon atoms. Antioxidant activity decreases with either shortening or prolongation of the alkyl chain within this series. The same tendency was also observed for benzoxime derivatives **8a**-**e**. A proportional relationship of antioxidant properties and concentration was also noted for glycolipid mimetics, except for derivatives of galactose **15a**-**e**, which expressed no antioxidant activity. It should be mentioned that galactose derivatives **15a**-**e** were tested only at the lowest concentration, due to solubility limitations (Figure 2). Amphiphilic derivatives of glucose express significant differences in antioxidant properties, depending on whether they consist of two (**22a**-**d**) or only one oxime functionality (**23a**-**d**). The results agreed well with the expected activities because the compounds with two oxime groups (**22b–d**) showed higher antioxidant activity compared to compounds with only one oxime group (**23a–d**). Among compounds with two oxime groups, the highest scavenging activity was observed for **22c** with a long length of the aliphatic tail.

In addition, compared to TDBO, which was confirmed as an effective co-antioxidant in microemulsion systems in our previous published work, benzamidoximes and derivatives of glucose with two oxime functionalities

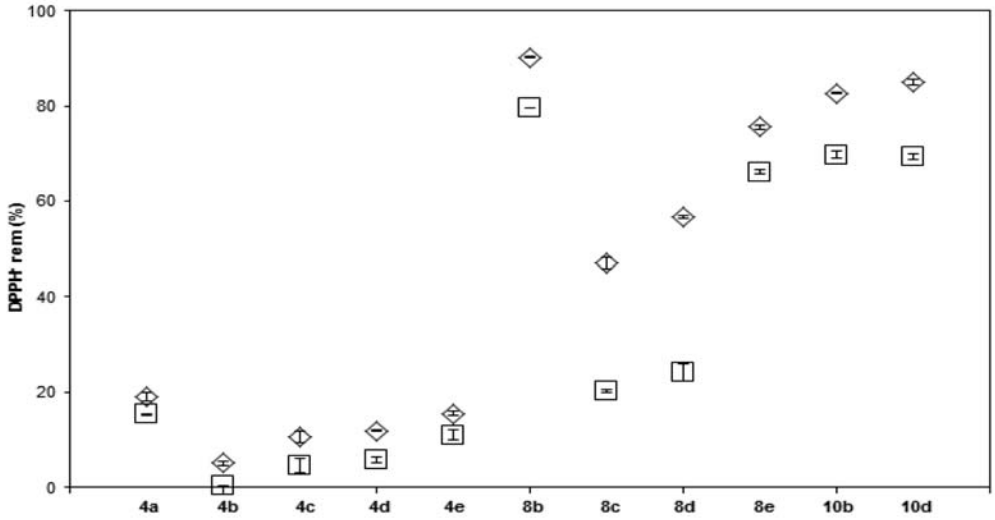


Figure 1. Free radical scavenging activity expressed as DPPH• rem of tested benzamidoxime and benzoxime derivatives at concentrations of 5 mM (◇) and 10 mM (□) after 30 min.

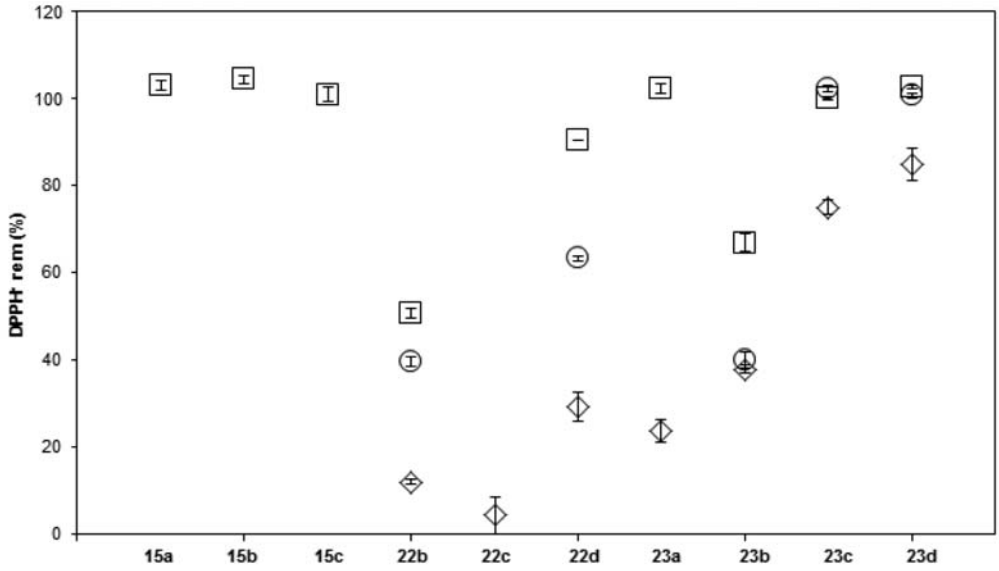


Figure 2. Free radical scavenging activity expressed as DPPH• rem of tested glycolipid derivatives at concentrations of 0.5 mM (□), 1 mM (○) and 5 mM (◇) after 30 min.

demonstrated superior antioxidant activity in the same concentration range.

3. Experimental

3. 1. General

Chemicals from Fluka and Sigma-Aldrich Chemical Co. were used without further purification. Anhydrous dioxane, dichloromethane and Et_3N were dried and purified by distillation over Na, K_2CO_3 and KOH, respectively. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel ($60F_{254}$) plates (0.25 mm). Column chromatography was performed on silica gel 60 (Merck, particle size 240–400 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX_{300} spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as internal standard. Chemical shifts were reported in ppm (δ) downfield from TMS. All the coupling constants (*J*) are in hertz. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer. Mass spectra were obtained with a VG-Analytical Autospec Q mass spectrometer with EI or FAB ionization (MS Centre, Jožef Stefan Institute, Ljubljana). All reported yields are yields of purified products.

3. 2. Synthesis of 4-(oxiran-2-ylmethoxy) benzonitrile (2)

To a solution of 4-hydroxybenzonitrile (6.00 g; 50.4 mmol) in 30 mL 2M NaOH, epichlorhydrin (4.68 g; 50.0 mmol) was added dropwise on ice-bath. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours. After the addition of dichloromethane (100 mL) the phases were separated. The organic phase was washed with 1M HCl (3 × 40 mL), water (40 mL) and brine (40mL), dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude product was further purified by column chromatography to yield white solid (MF: petroleter/ethyl acetate = 2:1). Yield 84%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.72 (m, 1H, CH_2), 2.85 (m, 1H, CH_2), 3.35 (m, 1H, CH), 3.93 (m, 1H, CH_2), 4.45 (m, 1H, CH_2), 7.12 (A_2X_2, J = 8.6 Hz, Δν = 201 Hz, 2H, Ar-H), 7.79 (A_2X_2, J = 8.6 Hz, Δν = 201 Hz, 2H, Ar-H)ppm. MS *m/z* (relative intensity): 175(M^+, 100). IR (KBr) ν 3609, 3006, 2224, 1605, 1509, 1300, 1259, 1175, 1026, 919, 841, 766 cm^{-1}. Anal. Calcd for $C_9H_{10}NO_2$: C 68.56, H 5.18, N 8.00. Found: C 68.61, H 5.23, N 7.79, mp 37–38 °C.

3. 3. Synthesis of 4-(oxiran-2-ylmethoxy) benzaldehyde (6)[19]

To a solution of 4-hydroxybenzaldehyde (6.10 g; 50.0 mmol) in 30 mL 2M NaOH, epichlorhydrin (4.68 g; 50.0 mmol) was added dropwise on ice-bath. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours. After the addition of dichloromethane (100 mL) the phases were separated. The organic phase was washed with 1M HCl (3 × 40 mL), water (40 mL) and brine (40mL), dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude product was further purified by column chromatography to yield white solid (MF: petrolether/ethyl acetate = 2:1). Yield 79%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.73 (m, 1H, CH_2), 2.87 (m, 1H, CH_2), 3.37 (m, 1H, CH), 3.96 (m, 1H, CH_2), 4.47 (m, 1H, CH_2), 7.16 (A_2X_2, J = 8.7 Hz, Δν = 214 Hz, 2H, Ar-H), 7.87 (A_2X_2, J = 8.7 Hz, Δν = 214 Hz, 2H, Ar-H), 9.88 (s, 1H, CHO) ppm. ^{13}C NMR (300 MHz, DMSO-d_6): 44.6, 50.3, 70.3, 115.9, 130.8, 132.7, 164.0, 192.2 ppm. MS *m/z* (relative intensity): 178(M^+, 100). IR (KBr) ν 3675, 3069, 1681, 1600, 1576, 1424, 1303, 1246, 1163, 1024, 911, 837 cm^{-1}, Anal. Calcd for $C_{10}H_{10}O_3$: C 67.41, H 5.66, N 0. Found: C 67.77, H 5.78, N 0; mp 32–34 °C.

3. 4. General procedure for the synthesis of 1-(alkylamino)-3-phenoxypropan-2-ols (3a-e, 7a-e)

The corresponding oxiran 4-(oxiran-2-ylmethoxy)benzonitrile (**2**) or 4-(oxiran-2-ylmethoxy)benzaldehyde (6) (8.50 mmol), $Ca(OTf)_2$ (1.45 g; 4.28 mmol) and alkylamine (13.0 mmol) were dissolved in anhydrous dioxane (50 mL). The reaction mixture was stirred at reflux for 6 hours, allowed to cool to room temperature and stirred overnight under argon atmosphere. The precipitate was filtered off and the filtrate was concentrated in vacuo. The crude product was further purified by column chromatography to yield white solid (MF: dichloromethane/methanol = 20:1). In case of aldehydes a small amount of tertiary amines as yellow viscous liquids (**9a-e**) were also isolated.

4-(2-hydroxy-3-(hexylamino)propoxy)benzonitrile (3a)

Yield 86%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 6.6 Hz, CH_3), 1.28 (m, 6H, CH_2), 1.52 (m, 2H, CH_2), 2.85 (m, 4H, CH_2), 3.57 (s, 1H, OH), 4.05 (m, 3H, CH, CH_2), 5.71 (s, 1H, NH), 7.14 (A_2X_2, J = 9.0 Hz, Δν = 180 Hz, 2H, Ar-H), 7.74 (A_2X_2, J = 9.0 Hz, Δν = 180 Hz, 2H, Ar-H) ppm. MS *m/z* (relative intensity): 277(M+H, 19), 114(100). IR (KBr) ν 3435, 3283, 2928, 2855, 2227, 1606, 1510, 1258, 1162, 1028, 943, 833 cm^{-1}, mp 65–68 °C.

4-(2-hydroxy-3-(octylamino)propoxy)benzonitrile (3b)

Yield 73%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 6.3 Hz, CH_3), 1.24 (m, 10H, CH_2), 1.51 (m, 2H, CH_2), 2.64 (m, 4H, CH_2), 3.39 (s, 1H, OH), 3.90 (m, 2H, CH_2), 4.07 (m, 1H, CH), 4.86 (s, 1H, NH), 7.09 (A_2X_2, J = 9.0 Hz, Δν = 204 Hz, 2H, Ar-H), 7.77 (A_2X_2, J = 9.0 Hz, Δν = 204 Hz, 2H, Ar-H) ppm. MS *m/z* (relative intensity): 305(M+H, 24), 142 (100). IR (KBr) ν 3484, 3288, 2927, 2855, 2227, 1606, 1511, 1258, 1162, 1026, 951, 833 cm^{-1}, mp 63–66 °C.

4-(2-hydroxy-3-(decylamino)propoxy)benzonitrile (3c)

Yield 77%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J=6.3 Hz, CH_3), 1.24 (m, 14H, CH_2), 1.47 (m, 2H, CH_2), 2.77 (m, 4H, CH_2), 3.48 (s, 1H, OH), 4.04 (m, 3H, CH, CH_2), 5.19 (s, 1H, NH), 7.12 (A_2X_2, J = 9.0 Hz, Δν = 204 Hz, 2H, Ar-H), 7.78 (A_2X_2, J = 9.0 Hz, Δν = 204 Hz, 2H, Ar-H) ppm. MS *m/z* (relative intensity): 333(M+H, 100). IR (KBr) ν 3482, 3159, 2922, 2852, 2226, 1606, 1510, 1258, 1162, 1117, 1038, 834 cm^{-1}, mp 63–66 °C.

4-(2-hydroxy-3-(dodecylamino)propoxy)benzonitrile (3d)

Yield 79%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 6.6 Hz, CH_3), 1.24 (m, 18H, CH_2), 1.48 (m, 2H, CH_2), 2.78 (m, 4H, CH_2), 3.50 (s, 1H, OH), 4.04 (m, 3H, CH, CH_2), 5.53 (s, 1H, NH), 7.12 (A_2X_2, J = 8.7 Hz, Δν = 192 Hz, 2H, Ar-H), 7.76 (A_2X_2, J = 8.7 Hz, Δν = 192 Hz, 2H, Ar-H) ppm. MS *m/z* (relative intensity): 361(M+H, 100). IR (KBr) ν 3445, 3288, 2920, 2852, 2227, 1606, 1511, 1258, 1161, 1026, 950, 834 cm^{-1}, mp 76–78 °C.

4-(2-hydroxy-3-(tetradecylamino)propoxy)benzonitrile (3e)

Yield 81%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 6.6 Hz, CH_3), 1.24 (m, 22H, CH_2), 1.50 (m, 2H,

CH_2), 2.82 (m, 4H, CH_2), 3.55 (s, 1H, OH), 4.04 (m, 3H, CH, CH_2), 5.73 (s, 1H, NH), 7.12 (A_2X_2, J = 8.7 Hz, Δν = 197 Hz, 2H, Ar-H), 7.77 (A_2X_2, J = 8.7 Hz, Δν = 197 Hz, 2H, Ar-H) ppm. MS *m/z* (relative intensity): 389(M+H, 100), HRMS: calcd for $C_{24}H_{41}N_2O_2$, 389.3168; found, 389.3170. IR (KBr) ν 3445, 3287, 2920, 2851, 2225, 1605, 1510, 1467, 1257, 1161, 1038, 833 cm^{-1}, mp 77–78 °C.

4-(3-(hexylamino)-2-hydroxypropoxy)benzaldehyde (7a)

Yield 43%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 1.29 (m, 6H, CH_2), 1.62 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 4.10 (d, 2H, J = 5.1 Hz, CH_2), 4.20 (m, 1H, CH), 5.91 (s, 1H, OH), 7.15 (A_2X_2, J = 9.0 Hz, Δν = 221 Hz, 2H, Ar-H), 7.89 (A_2X_2, J = 9.0 Hz, Δν = 221 Hz, 2H, Ar-H), 8.57 (s (broad), 1H, NH), 9.89 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 280(M+H, 21), 141(100). IR (KBr) ν 3479, 2957, 2860, 1685, 1606, 1582, 1509, 1249, 1161, 1039, 828 cm^{-1}, mp 78–82 °C.

4-(3-(octylamino)-2-hydroxypropoxy)benzaldehyde (7b)

Yield 34%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, 3H, J = 6.3 Hz, CH_3), 1.27 (m, 10H, CH_2), 1.64 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 3.16 (m, 2H, CH_2), 4.10 (d, 2H, J = 5.1 Hz, CH_2), 4.22 (m, 1H, CH), 5.91 (s, 1H, OH), 7.15 (A_2X_2, J = 9.0 Hz, Δν = 226 Hz, 2H, Ar-H), 7.90 (A_2X_2, J = 9.0 Hz, Δν = 226 Hz, 2H, Ar-H), 8.67 (s (broad), 1H, NH), 9.89 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 308(M+H, 100). HRMS: calcd for $C_{18}H_{30}NO_3$, 308.2226; found, 308.2226. IR (KBr) ν 3468, 2924, 2855, 1681, 1600, 1581, 1508, 1242, 1160, 1031, 829 cm^{-1}, mp 93–94 °C.

4-(3-(decylamino)-2-hydroxypropoxy)benzaldehyde (7c)

Yield 51%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.3 Hz, CH_3), 1.26 (m, 14H, CH_2), 1.64 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 4.11 (d, 2H, J = 5.1 Hz, CH_2), 4.24 (m, 1H, CH), 5.93 (s, 1H, OH), 7.16 (A_2X_2, J = 8.7 Hz, Δν = 217 Hz, 2H, Ar-H), 7.88 (A_2X_2, J = 8.7 Hz, Δν = 217 Hz, 2H, Ar-H), 8.57 (s (broad), 1H, NH), 9.89 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 336(M+H, 100). HRMS: calcd for $C_{20}H_{34}NO_3$, 336.2539; found, 336.2528. IR (KBr) ν 3413, 2921, 2852, 1681, 1601, 1582, 1508, 1245, 1159, 1038, 830 cm^{-1}, mp 100–103 °C.

4-(3-(dodecylamino)-2-hydroxypropoxy)benzaldehyde (7d)

Yield 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.6 Hz, CH_3), 1.25 (m, 18H, CH_2), 1.63 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 4.11 (d, 2H, J = 5.1 Hz, CH_2), 4.23 (m, 1H, CH), 5.92 (s, 1H, OH), 7.16 (A_2X_2, J = 9.0 Hz, Δν = 221 Hz, 2H, Ar-H), 7.88 (A_2X_2, J = 9.0 Hz, Δν = 221 Hz, 2H, Ar-H), 8.76 (s (broad), 1H, NH), 9.89 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 364(M+H, 100). HRMS: calcd for $C_{22}H_{38}NO_3$, 364.2852; found, 364.2845. IR (KBr) ν 3413, 2920, 2850, 1681, 1601, 1583, 1508, 1244, 1158, 1038, 832 cm^{-1}, mp 120–125 °C.

4-(3-(tetradecylamino)-2-hydroxypropoxy)benzaldehyde (7e)

Yield 17%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.3 Hz, CH_3), 1.25 (m, 22H, CH_2), 1.62 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 4.11 (d, 2H, J = 5.1 Hz, CH_2), 4.17 (m, 1H, CH), 5.93 (s, 1H, OH), 7.16 (A_2X_2, J = 8.7 Hz, Δν = 221 Hz, 2H, Ar-H), 7.90 (A_2X_2, J = 8.7 Hz, Δν = 221 Hz, 2H, Ar-H), 8.74 (s (broad), 1H, NH), 9.89 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 392(M+H, 100). HRMS: calcd for $C_{24}H_{42}NO_3$, 392.3165; found, 392.3163. IR (KBr) ν 3468, 2920, 2851, 1684, 1603, 1578, 1508, 1468, 1252, 1164, 1030, 832 cm^{-1}, mp 69–74 °C.

4,4'-(((hexylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (9a)

Yield 8%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77 (m, 3H, CH_3), 1.14 (m, 6H, CH_2), 1.32 (m, 2H, CH_2), 2.44 (m, 6H, CH_2), 4.00 (m, 6H, CH, CH_2), 4.93 (s, 2H, OH), 7.03 (A_2X_2, J = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.08 (A_2X_2, J = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H),), 7.79 (A_2X_2, J = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.82 (A_2X_2, J = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H), 9.85 (s, 2H, CHO)ppm. MS *m/z* (relative intensity): 458(M+H, 100). HRMS: calcd for $C_{26}H_{36}NO_6$, 458.2453; found 458.2448. IR (KBr) ν 3404, 2929, 2856, 1689, 1601, 1510, 1310, 1257, 1161, 1029, 832 cm^{-1}.

4,4'-(((octylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (9b)

Yield 16%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (m, 3H, CH_3), 1.11 (m, 10H, CH_2), 1.34 (m, 2H, CH_2), 2.43 (m, 6H, CH_2), 4.00 (m, 6H, CH, CH_2), 4.92 (s, 1H, OH), 4.94 (s, 1H, OH), 7.03 (A_2X_2, J = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.06 (A_2X_2, J = 8.7 Hz, Δν = 229 Hz, 2H, Ar-H),), 7.79 (A_2X_2, J = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.82 (A_2X_2, J = 8.7 Hz, Δν = 229 Hz, 2H, Ar-H), 9.83 (s, 2H, CHO), 9.85 (s, 2H, CHO) ppm. MS *m/z* (relative intensity) : 486(M+H, 100). HRMS: calcd for $C_{28}H_{40}NO_6$, 486.2856; found 486.2858. IR (KBr) ν 3410, 2926, 2854, 1686, 1601, 1509, 1312, 1259, 1161, 1029, 832 cm^{-1}.

4,4'-(((decylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (9c)

Yield 10%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (m, 3H, CH_3), 1.14 (m, 14H, CH_2), 1.31 (m, 2H, CH_2), 2.48 (m, 6H, CH_2), 4.02 (m, 6H, CH, CH_2), 4.93 (s, 2H, OH), 7.02 (A_2X_2, J = 8.7 Hz, Δν = 231 Hz, 2H, Ar-H), 7.08 (A_2X_2, J = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H),), 7.79 (A_2X_2, J = 8.7 Hz, Δν = 231 Hz, 2H, Ar-H), 7.82 (A_2X_2, J = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H), 9.83 (s, 2H, CHO), 9.85 (s, 2H, CHO) ppm. MS *m/z* (relative intensity):

514(M+H, 38), 77 (100). HRMS: calcd for $C_{30}H_{44}NO_6$, 514.3169; found, 514.3163. IR (KBr) ν 3412, 2925, 2853, 1690, 1601, 1510, 1311, 1257, 1161, 1030, 832 cm^{-1}.

4,4'-(((dodecylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (9d)

Yield 5%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, 3H, *J* = 6.3 Hz, CH_3), 1.16 (m, 18H, CH_2), 1.34 (m, 2H, CH_2), 2.43 (m, 6H, CH_2), 4.02 (m, 6H, CH, CH_2); 4.93 (s, 2H, OH), 7.03 (A_2X_2, *J* = 8.7 Hz, Δν = 205 Hz, 2H, Ar-H), 7.08 (A_2X_2, *J* = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H), 7.76 (A_2X_2, *J* = 8.7 Hz, Δν = 205 Hz, 2H, Ar-H), 7.82 (A_2X_2, *J* = 8.7 Hz, Δν = 223 Hz, 2H, Ar-H), 9.85 (s, 2H, CHO)ppm. MS *m/z* (relative intensity): 542(M+H, 100). HRMS: calcd for $C_{32}H_{48}NO_6$, 542.3482; found, 542.3485. IR (KBr) ν 3409, 2925, 2853, 1689, 1601, 1509, 1311, 1259, 1161, 1030, 832 cm^{-1}.

4,4'-(((tetradecylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (9e)

Yield 10%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, *J* = 6.3 Hz, CH_3), 1.19 (m, 22H, CH_2), 1.34 (m, 2H, CH_2), 2.48 (m, 6H, CH_2), 4.02 (m, 6H, CH, CH_2), 4.94 (s, 2H, OH), 7.03 (A_2X_2, *J* = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.07 (A_2X_2, *J* = 8.7 Hz, Δν = 225 Hz, 2H, Ar-H),), 7.79 (A_2X_2, *J* = 8.7 Hz, Δν = 228 Hz, 2H, Ar-H), 7.82 (A_2X_2, *J* = 8.7 Hz, Δν = 225 Hz, 2H, Ar-H), 9.83 (s, 1H, CHO), 9.85 (s, 1H, CHO) ppm. MS *m/z* (relative intensity): 570(M+H, 100). HRMS: calcd for $C_{34}H_{52}NO_6$, 570.3795; found, 570.3807. IR (KBr) ν 3382, 2924, 2853, 1689, 1601, 1509, 1311, 1259, 1160, 1030, 832 cm^{-1}.

3. 5. General Procedure for the Synthesis of Amidoximes (4a-e)

The corresponding 4-(3-(alkylamino)-2-hydroxypropoxy)benzonitrile (**3a-e**) (3.60 mmol), hydroxylamine hydrochloride (500 mg; 7.20 mmol) and potassium carbonate (1.00 g; 7.25 mmol) were suspended in anhydrous ethanol (50 mL). The reaction mixture was stirred at reflux for 12 hours. The precipitate was rapidly filtered off before cooling and the solvent was removed in vacuum. The crude product was recrystallized from ethanol to yield white solid.

4-(3-(hexylamino)-2-hydroxypropoxy)-N'-hydroxybenzimidamide (4a)

Yield 40%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, 3H, *J* = 6.3 Hz, CH_3), 1.30 (m, 6H, CH_2), 1.64 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.01 (m, 2H, CH_2), 3.99 (m, 2H, CH_2), 4.55 (m, 1H, CH), 5.72 (s, 1H, NH), 5.85 (s, 1H, OH), 6.95 (A_2X_2, *J* = 8.7 Hz, Δν = 198 Hz, 2H, Ar-H), 7.61 (A_2X_2, *J* = 8.7 Hz, Δν = 198 Hz, 2H, Ar-H), 8.68 (s, 2H, NH_2), 9.44 (s, 1H, NOH) ppm. MS *m/z* (relative intensity): 310(M+H, 17), 77 (100). HRMS: calcd for $C_{16}H_{28}N_3O_3$, 301.2131; found, 310.2130. IR (KBr) ν 3295, 2929, 2854, 1641, 1519, 1381, 1251, 1180, 1113, 1034, 916, 832 cm^{-1}, mp 173–178 °C.

4-(3-(octylamino)-2-hydroxypropoxy)-N'-hydroxybenzimidamide (4b)

Yield 57%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, 3H, *J* = 6.6 Hz, CH_3), 1.27 (m, 10H, CH_2), 1.64 (m, 2H, CH_2), 3.03 (m, 4H, CH_2), 3.99 (m, 2H, CH_2), 4.21 (m, 1H, CH), 5.73 (s, 1H, NH), 5.86 (s, 1H, OH), 6.95 (A_2X_2, *J* = 9.0 Hz, Δν = 198 Hz, 2H, Ar-H), 7.61 (A_2X_2, *J* = 9.0 Hz, Δν = 198 Hz, 2H, Ar-H), 8.75 (s, 2H, NH_2), 9.45 (s, 1H, NOH) ppm. MS *m/z* (relative intensity): 338(M+H, 24), 77 (100). HRMS: calcd for $C_{18}H_{32}N_3O_3$, 338.2444; found, 338.2436. IR (KBr) ν 3264, 2924, 2855, 1642, 1522, 1368, 1256, 1184, 1120, 940, 832 cm^{-1}, mp 176–180 °C.

4-(3-(decylamino)-2-hydroxypropoxy)-N'-hydroxybenzimidamide (4c)

Yield 40%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, *J* = 6.3 Hz, CH_3), 1.25 (m, 14H, CH_2), 1.64 (m, 2H, CH_2), 3.02 (m, 4H, CH_2), 3.99 (m, 2H, CH_2), 4.22 (m, 1H, CH), 5.72 (s, 1H, NH), 5.87 (s, 1H, OH), 6.94 (A_2X_2, *J* = 8.7 Hz, Δν = 201 Hz, 2H, Ar-H), 7.61 (A_2X_2, *J* = 8.7 Hz, Δν = 201 Hz, 2H, Ar-H), 8.84 (s, 2H, NH_2), 9.45 (s, 1H, NOH) ppm. MS *m/z* (relative intensity): 366(M+H, 11), 77 (100). IR (KBr) ν 3263, 2920, 2855, 1634, 1521, 1368, 1259, 1176, 1121, 1046, 926, 831 cm^{-1}. Anal. Calcd for $C_{20}H_{35}N_3O_3$: C 65.72, H 9.65, N 11.50. Found: C 65.91, H 9.68, N 11.21. mp 183–186 °C.

4-(3-(dodecylamino)-2-hydroxypropoxy)-N'-hydroxybenzimidamide (4d)

Yield 54%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, *J* = 6.6 Hz, CH_3), 1.25 (m, 18H, CH_2), 1.61 (m, 2H, CH_2), 3.02 (m, 4H, CH_2), 3.99 (m, 2H, CH_2), 4.18 (m, 1H, CH), 5.71 (s, 1H, NH), 5.82 (s, 1H, OH), 6.94 (A_2X_2, *J* = 8.7 Hz, Δν = 195 Hz, 2H, Ar-H), 7.59 (A_2X_2, *J* = 8.7 Hz, Δν = 195 Hz, 2H, Ar-H), 8.56 (s, 2H, NH_2), 9.44 (s, 1H, NOH) ppm. MS *m/z* (relative intensity): 394(M+H, 17), 77 (100). HRMS: calcd for $C_{22}H_{40}N_3O_3$, 394.3070; found, 394.3058. IR (KBr) ν 3343, 2922, 2850, 1651, 1522, 1378, 1255, 1181, 1121, 1043, 923, 830 cm^{-1}, mp 183–185 °C.

4-(3-(tetradecylamino)-2-hydroxypropoxy)-N'-hydroxybenzimidamide (4e)

Yield 67%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, *J* = 6.6 Hz, CH_3), 1.24 (m, 22H, CH_2), 1.64 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 3.99 (m, 2H, CH_2), 4.21 (m, 1H, CH), 5.72 (s, 1H, NH), 5.87 (s, 1H, OH), 6.96 (A_2X_2, *J* = 8.7 Hz, Δν = 196 Hz, 2H, Ar-H), 7.61 (A_2X_2, *J* = 8.7 Hz, Δν = 196 Hz, 2H, Ar-H), 8.81 (s, 2H, NH_2), 9.44 (s, 1H, NOH) ppm. MS *m/z* (relative intensity): 394(M+H, 3), 77 (100). IR (KBr) ν 3341, 2921, 2849, 1651, 1522, 1376, 1255, 1180, 1119, 1044, 830 cm^{-1}, Anal. Calcd for $C_{24}H_{43}N_3O_3$: C 68.73, H 10.28, N 9.97. Found: C 68.98, H 10.53, N 9.64, mp 186–189 °C.

3. 6. General Procedure for the Synthesis of Oximes (8a-e, 10a-e)

The corresponding aldehydes (**7a-e, 9a-e**) (1.15 mmol), hydroxylamine hydrochloride (100 mg; 1.44 mmol) and potassium carbonate (200 mg; 1.45 mmol) were suspended in anhydrous ethanol (10 mL). The reaction mixture was stirred at reflux for 12 hours. The precipitate was rapidly filtered off before cooling and the solvent was removed in vacuo. The crude product was further purified by column chromatography (MF: dichloromethane/methanol = 20 : 1).

4-(2-hydroxy-3-(hexylamino)propoxy)benzaldehyde oxime (8a)

Yield 56%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 1.28 (m, 6H, CH_2), 1.58 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.12 (m, 2H, CH_2), 3.99 (d, 2H, J = 5.4 Hz, CH_2), 4.12 (m, 1H, CH), 5.75 (s, 1H, OH), 6.99 (A_2X_2, J = 8.7 Hz, Δν = 162 Hz, 2H, Ar-H), 7.53 (A_2X_2, J = 8.7 Hz, Δν = 162 Hz, 2H, Ar-H), 8.07 (m, 1H, CH), 8.61 (s (broad), 1H, NH), 10.96 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 295(M+H, 70), 77 (100). HRMS: calcd for $C_{16}H_{27}N_2O_3$, 295.2022; found, 295.2030. IR (KBr) ν 3447, 2931, 2858, 1611, 1516, 1457, 1240, 1168, 1107, 1036, 965, 832 cm^{-1}, mp 79–83 °C.

4-(2-hydroxy-3-(octylamino)propoxy)benzaldehyde oxime (8b)

Yield 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, 3H, J = 6.3 Hz, CH_3), 1.27 (m, 10H, CH_2), 1.59 (m, 2H, CH_2), 2.78 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.99 (d, 2H, J = 5.1 Hz, CH_2), 4.12 (m, 1H, CH), 5.76 (s, 1H, OH), 6.99 (A_2X_2, J = 9.0 Hz, Δν = 163 Hz, 2H, Ar-H), 7.53 (A_2X_2, J = 9.0 Hz, Δν = 163 Hz, 2H, Ar-H), 8.07 (m, 1H, CH), 8.61 (s (broad), 1H, NH), 10.96 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 323(M+H, 100). HRMS: calcd for $C_{18}H_{31}N_2O_3$, 323.2335; found, 323.2328. IR (KBr) ν 3446, 2926, 2856, 1610, 1516, 1457, 1238, 1171, 1113, 1035, 965, 832 cm^{-1}, mp 81–84 °C.

4-(2-hydroxy-3-(decylamino)propoxy)benzaldehyde oxime (8c)

Yield 46%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.3 Hz, CH_3), 1.28 (m, 14H, CH_2), 1.63 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 4.00 (d, 2H, J = 5.1 Hz, CH_2), 4.21 (m, 1H, CH), 5.88 (s, 1H, OH), 6.99 (A_2X_2, J = 8.7 Hz, Δν = 165 Hz, 2H, Ar-H), 7.53 (A_2X_2, J = 8.7 Hz, Δν = 165 Hz, 2H, Ar-H), 8.07 (m, 1H, CH), 8.76 (s (broad), 1H, NH), 10.96 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 351(M+H, 100). HRMS: calcd for $C_{20}H_{35}N_2O_3$, 351.2648; found, 351.1647. IR (KBr) ν 3394, 2924, 2852, 1609, 1518, 1466, 1250, 1176, 1119, 1046, 939, 816 cm^{-1}, mp 83–86 °C.

4-(2-hydroxy-3-(dodecylamino)propoxy)benzaldehyde oxime (8d)

Yield 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.6 Hz, CH_3), 1.25 (m, 18H, CH_2), 1.63 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 4.00 (d, 2H, J = 5.4 Hz, CH_2), 4.19 (m, 1H, CH), 5.86 (s, 1H, OH), 6.99 (A_2X_2, J = 8.7 Hz, Δν = 162 Hz, 2H, Ar-H), 7.53 (A_2X_2, J = 8.7 Hz, Δν = 162 Hz, 2H, Ar-H), 8.07 (m, 1H, CH), 8.63 (s (broad), 1H, NH), 10.96 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 379(M+H, 100). HRMS: calcd for $C_{22}H_{39}N_2O_3$, 379.2961; found, 379.2956. IR (KBr) ν 3410, 2923, 2850, 1609, 1517, 1465, 1249, 1175, 1115, 1045, 939, 815 cm^{-1}, mp 84–88 °C.

4-(2-hydroxy-3-(tetradecylamino)propoxy)benzaldehyde oxime (8e)

Yield 55%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 6.3 Hz, CH_3), 1.24 (m, 22H, CH_2), 1.56 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 3.07 (m, 2H, CH_2), 3.98 (d, 2H, J = 4.8 Hz, CH_2), 4.08 (m, 1H, CH), 5.75 (s, 1H, OH), 6.98 (A_2X_2, J = 8.7 Hz, Δν = 165 Hz, 2H, Ar-H), 7.53 (A_2X_2, J = 8.7 Hz, Δν = 165 Hz, 2H, Ar-H), 8.07 (m, 1H, CH), 8.61 (s (broad), 1H, NH), 10.96 (s, 1H, CHO)ppm. MS *m/z* (relative intensity): 323(M+H, 100). HRMS: calcd for $C_{24}H_{43}N_2O_3$, 407.3274; found, 407.3264. IR (KBr) ν 3436, 2919, 2850, 1610, 1516, 1469, 1240, 1167, 1037, 966, 833 cm^{-1}, mp 83–87 °C.

4,4'-(((hexylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (10a)

Yield 48%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.78 (m, 3H, CH_3), 1.14 (m, 6H, CH_2), 1.34 (m, 2H, CH_2), 2.45 (m, 4H, CH_2), 2.63 (m, 2H, CH_2), 3.97 (m, 6H, CH, CH_2), 4.86 (s, 2H, OH), 6.89 (A_2X_2, J = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 6.92 (A_2X_2, J = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H),), 7.47 (A_2X_2, J = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 7.49 (A_2X_2, J = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H), 8.04 (s, 1H, CH), 8.05 (s, 1H, CH), 10.92 (s, 2H, NOH)ppm. MS *m/z* (relative intensity): 488(M+H, 100). HRMS: calcdfor $C_{26}H_{38}N_3O_6$, 488.2682; found, 488.2714. IR(KBr) ν 3307, 2928, 1606, 1514, 1458, 1302, 1249, 1173, 1035, 953, 830 cm^{-1}.

4,4'-(((octylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (10b)

Yield 53%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81 (m, 3H, CH_3), 1.18 (m, 10H, CH_2), 1.33 (m, 2H, CH_2), 2.45 (m, 4H, CH_2), 2.64 (m, 2H, CH_2), 3.94 (m, 6H, CH, CH_2), 4.85 (s, 2H, OH), 6.89 (A_2X_2, J = 8.7 Hz, Δν = 177 Hz, 4H, Ar-H), 7.47 (A_2X_2, J = 8.7 Hz, Δν = 177 Hz, 4H, Ar-H), 8.04 (s, 1H, CH), 8.05 (s, 1H, CH), 10.92 (s, 2H, NOH)ppm. MS *m/z* (relative intensity): 516(M+H, 60), 77(100). HRMS: calcd for $C_{28}H_{42}N_3O_6$, 516.3074; found, 516.3074. IR (KBr) ν 3308, 2926, 2854, 1607, 1514, 1458, 1303, 1250, 1173, 1037, 955, 830 cm^{-1}.

4,4'-(((decylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (10c)

Yield 47%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (t, 3H, *J* = 6.6 Hz, CH_3), 1.14 (m, 14H, CH_2), 1.33 (m, 2H, CH_2), 2.42 (m, 4H, CH_2), 2.65 (m, 2H, CH_2), 3.94 (m, 6H, CH, CH_2), 4.85 (s, 2H, OH), 6.89 (A_2X_2, *J* = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 6.91 (A_2X_2, *J* = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H),), 7.48 (A_2X_2, *J* = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 7.48 (A_2X_2, *J* = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H), 8.04 (s, 1H, CH), 8.05 (s, 1H, CH), 10.92 (s, 2H, NOH)ppm. MS *m/z* (relative intensity): 544(M+H, 15), 77 (100). HRMS: calcd for $C_{30}H_{46}N_3O_6$, 544.3389; found, 544.3387. IR(KBr) ν 3308, 2924, 2853, 1606, 1514, 1458, 1302, 1250, 1173, 1036, 830 cm^{-1}.

4,4'-(((dodecylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (10d)

Yield 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (m, 3H, CH_3), 1.17 (m, 18H, CH_2), 1.34 (m, 2H, CH_2), 2.38 (m, 4H, CH_2), 2.65 (m, 2H, CH_2), 3.93 (m, 6H, CH, CH_2), 4.86 (s, 2H, OH), 6.89 (A_2X_2, *J* = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 6.92 (A_2X_2, *J* = 8.7 Hz, Δν = 170 Hz, 2H, Ar-H),), 7.47 (A_2X_2, *J* = 8.7 Hz, Δν = 177 Hz, 2H, Ar-H), 7.48 (A_2X_2, *J* = 8.7 Hz, Δν = 170 Hz, 2H, Ar-H), 8.03 (s, 1H, CH), 8.04 (s, 1H, CH), 10.92 (s, 2H, NOH)ppm. MS *m/z* (relative intensity): 572(M+H, 100). HRMS: calcd for $C_{32}H_{50}N_3O_6$, 532.3700; found, 532.3690. IR (KBr) ν 3308, 2923, 2852, 1606, 1514, 1458, 1302, 1250, 1173, 1035, 954, 830 cm^{-1}.

4,4'-(((tetradecylazanediyl)bis(2-hydroxypropane-3,1-diyl))bis(oxy))dibenzaldehyde (10e)

Yield 63%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (m, 3H, CH_3), 1.18 (m, 22H, CH_2), 1.34 (m, 2H, CH_2), 2.41 (m, 4H, CH_2), 2.67 (m, 2H, CH_2), 3.93 (m, 6H, CH, CH_2), 4.85 (s, 2H, OH), 6.89 (A_2X_2, *J* = 8.7 Hz, Δν = 175 Hz, 2H, Ar-H), 6.92 (A_2X_2, *J* = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H),), 7.46 (A_2X_2, *J* = 8.7 Hz, Δν = 175 Hz, 2H, Ar-H), 7.48 (A_2X_2, *J* = 8.7 Hz, Δν = 172 Hz, 2H, Ar-H), 8.03 (s, 1H, CH), 8.04 (s, 1H, CH), 10.91 (s, 2H, NOH)ppm. MS *m/z* (relative intensity): 600(M+H, 100). HRMS: calcd for $C_{34}H_{54}N_3O_6$, 600.4013; found, 600.4017. IR (KBr) ν 3307, 2924, 2852, 1606, 1514, 1458, 1302, 1250, 1173, 1036, 954, 829 cm^{-1}.

3. 7. General Procedure for the Synthesis of Galactose Oximes[16]

1(*E*/*Z*)2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-(octyloxy)hexanal oxime (15a)[16]

1(*E*/*Z*)2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-(decyloxy)hexanal oxime (15b)

Yield 68%. A 80/20 mixture of (*E*)- and (*Z*)-oxime. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.86 (t, 3H, *J* = 6.9 Hz, -CH_2-C$\underline{H}_3$), 1.18–1.33 (m, 14H, -(C$\underline{H}_2$)$_7$-CH_3), 1.51–1.58 (m, 2H, -O-CH_2-C$\underline{H}_2$-$(CH_2)_7$-CH_3), 3.43–3.51 (m, 2H, -O-C$\underline{H}_2$-CH_2-$(CH_2)_7$-CH_3), 4.03–4.07 (m, 2H, -O-C$\underline{H}_2$CH(OH)-), 4.64–4.71 (m, 2H, 2 × C$\underline{H}$-OH), 4.95–5.01 (m, 1H, C$\underline{H}$-OH), 5.55 (dd, 1H, *J* = 1.6, 6.94 Hz, -C$\underline{H}$(OH)-CH=N-), 8.47 (d, 1H, *J* = 6.93, -C$\underline{H}$=N-), 12.88 (s, 1H, =N-O$\underline{H}$) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~6.36, ~7.71 and ~13.07 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 358 (MNa^+, 75), 336 (M+H, 100). IR (KBr) ν 3393, 3268, 2954, 2922, 2851, 2805, 2374, 2345, 1671, 1466, 1439, 1379, 1318, 1304, 1262, 1228, 1126, 1102, 1070, 1036, 1016, 996, 723 cm^{-1}, mp 171–173 °C.

1(*E*/*Z*)2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-(dodecyloxy)hexanal oxime (15c)

Yield 72%. A 81/19 mixture of (*E*)- and (*Z*)-oxime. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.87 (t, 3H, *J* = 6.72 Hz, -CH_2-C$\underline{H}_3$), 1.23–1.31 (m, 18H, -(C$\underline{H}_2$)$_9$-CH_3), 1.52–1.58 (m, 2H, -O-CH_2-C$\underline{H}_2$-$(CH_2)_9$-CH_3), 3.43–3.51 (m, 2H, -O-C$\underline{H}_2$-CH_2-$(CH_2)_9$-CH_3), 4.03–4.07 (m, 2H, -O-C$\underline{H}_2$CH(OH)-), 4.64–4.70 (m, 2H, 2 × C$\underline{H}$-OH), 4.96–5.01 (m, 1H, C$\underline{H}$-OH), 5.55 (dd, 1H, *J* = 1.6, 6.94 Hz, -C$\underline{H}$(OH)-CH=N-), 8.47 (d, 1H, *J* = 6.93, -C$\underline{H}$=N-), 12.87 (s, 1H, =N-O$\underline{H}$) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~6.36, ~7.71 and ~13.07 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 362 ($M-H^+$, 100). IR (KBr) ν 3394, 3272, 2953, 2922, 2850, 2366, 2345, 1667, 1490, 1465 1438, 1379, 1317, 1304, 1262, 1228, 1126, 1102, 1072, 1036, 1002, 987, 724 cm^{-1}, mp 165–167 °C.

1(*E*/*Z*)2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-(tetradecyloxy)hexanal oxime (15d)

Yield 71%. A 60/40 mixture of (*E*)- and (*Z*)-oxime. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.87 (t, 3H, *J* = 7.1 Hz, -CH_2-C$\underline{H}_3$), 1.22–1.30 (m, 22H, -(C$\underline{H}_2$)$_{11}$-CH_3), 1.53–1.60 (m, 2H, -O-CH_2-C$\underline{H}_2$-$(CH_2)_{11}$-CH_3), 3.45–3.55 (m, 2H, -O-C$\underline{H}_2$-CH_2-$(CH_2)_{11}$-CH_3), 4.05–4.09 (m, 2H, -O-C$\underline{H}_2$CH(OH)-), 4.65–4.73 (m, 2H, 2 × C$\underline{H}$-OH), 4.95–5.01 (m, 1H, C$\underline{H}$-OH), 5.66–5.74 (m, 1H, -C$\underline{H}$(OH)-CH=N-), 8.50 (d, 1H, *J* = 6.93, -C$\underline{H}$=N-), 12.90 (s, 1H, =N-O$\underline{H}$) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~6.39, ~7.73 and ~13.10 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 203 (100), 392 ($M+H^+$, 50). IR (KBr) ν 3394, 3272, 2953, 2922, 2849, 2362, 2344, 1670, 1491, 1464 1441, 1379, 1317, 1304, 1262, 1228, 1211, 1126, 1102, 1074, 1036, 1012, 997, 724 cm^{-1}, mp 172–174 °C.

1(*E*/*Z*)2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6-(hexadecyloxy)hexanal oxime (15e)

Yield 70%. A 59/41 mixture of (*E*)- and (*Z*)-oxime. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.87 (t, 3H, *J* = 6.72 Hz, -CH_2-C$\underline{H}_3$), 1.23–1.31 (m, 26H, -(C$\underline{H}_2$)$_{13}$

-CH_3), 1.52–1.58 (m, 2H, -O-CH_2-C$\underline{H}_2$-$(CH_2)_{13}$-CH_3), 3.43–3.51 (m, 2H, -O-C$\underline{H}_2$-CH_2-$(CH_2)_{13}$-CH_3), 4.04–4.08 (m, 2H, -O-C$\underline{H}_2$CH(OH)-), 4.64–4.69 (m, 2H, 2 × C$\underline{H}$-OH), 4.96–5.01 (m, 1H, C$\underline{H}$-OH), 5.58–5.70 (m, 1H, -C$\underline{H}$(OH)-CH=N-), 8.49 (d, 1H, *J* = 6.93, -C$\underline{H}$=N-), 12.89 (s, 1H, =N-O$\underline{H}$) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~6.38, ~7.72 and ~13.09 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 420 ($M+H^+$, 100). IR (KBr) ν 3395, 3273, 2952, 2921, 2849, 2369, 1670, 1491, 1464 1442, 1378, 1317, 1304, 1262, 1228, 1126, 1102, 1077, 1036, 999, 986, 935, 724 cm^{-1}, mp 152–154 °C.

3. 8. General Procedure for the Synthesis of Glucose Bisoximes Derivatives (22a-22d)[16]

N-((*E*/*Z*,2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,-trihydroxy-1,6-bis(hydroxyimino)hexan-2-yl)-decanamide (22a)

Yield 81%. A mixture of four isomers was formed (the predominant (*E*,*E*)-form in 58% yield) as a colourless viscous oil. ^{1}H NMR (pyridine-d_5, 300 MHz) predominant (*E*,*E*)-oxime: δ 0.79 (t, 3H, *J* = 6.5 Hz, -CH_2-C$\underline{H}_3$), 1.12–1.34 (m, 8H, -(C$\underline{H}_2$)$_4$-CH_3), 1.72–1.85 (m, 2H, -CO-CH_2-C$\underline{H}_2$-$(CH_2)_4$-CH_3), 2.43 (t, 2H, *J* = 7.75 Hz, -CO-C$\underline{H}_2$-CH_2-$(CH_2)_4$-CH_3), 3.62 (s, 1H, -OH), 4.60 (dd, 1H, *J* = 2.83, 7.86 Hz, HO-N=CH-CH(OH)-C$\underline{H}$(OH)-CH(OH)-CH(NH-)-CH=N-OH), 5.05 (dd, 1H, *J* = 2.65, 5.97 Hz, -C$\underline{H}$(OH)-CH(NH-)-CH=N-), 5.25–5.32 (m, 1H, HO-N=CH-C$\underline{H}$(OH)-), 5.83–5.89 (m, 1H, -C$\underline{H}$(NH-)-CH=N-), 8.29 (d, 1H, *J* = 7.2, -C$\underline{H}$=N-OH), 8.33 (d, 1H, *J* = 5.9, -C$\underline{H}$=N-OH), 8.81 (d, 1H, *J* = 8.0 Hz, -NH-CO), 11.62 (s, 1H, =N-O$\underline{H}$), 12.91 (s, 1H, =N-O$\underline{H}$) ppm. All hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~4.70, ~4.96, ~5.96, ~6.14, ~6.39, ~7.52, ~8.36, ~8.75, ~11.25 and ~11.4 ppm (corresponding to other oximes) are visible. MS *m/z* (relative intensity): 332 ($M-H^+$, 100); IR (KBr) ν 3242, 2926, 2855, 2360, 2343 1651, 1645, 1634, 1557, 1435, 1375, 1323, 1303, 1089, 1043, 987 cm^{-1}.

N-((*E*/*Z*,2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,-trihydroxy-1,6-bis(hydroxyimino)hexan-2-yl)-dodecanamide (22b)

Yield 84%. A mixture of four isomers was formed (the predominant (*E*,*E*)-form in 77% yield) as a white solid. ^{1}H NMR (pyridine-d_5, 300 MHz) predominant (*E*,*E*)-oxime: δ 0.87 (t, 3H, *J* = 6.6 Hz, -CH_2-C$\underline{H}_3$), 1.18–1.35 (m, 16H, -(C$\underline{H}_2$)$_8$-CH_3), 1.74–1.84 (m, 2H, -CO-CH_2-C$\underline{H}_2$-$(CH_2)_8$-CH_3), 2.44 (t, 2H, *J* = 7.5 Hz, -CO-C$\underline{H}_2$-CH_2-$(CH_2)_8$-CH_3), 4.60 (dd, 1H, *J* = 2.8, 7.6 Hz, HO-N=CH-CH(OH)-C$\underline{H}$(OH)-CH(OH)-CH(NH-)-CH=N-OH), 5.04 (dd, 1H, *J* = 2.8, 5.8 Hz, -C$\underline{H}$(OH)-CH(NH-)-CH=N-), 5.24–5.29 (m, 1H, HO-N=CH-C$\underline{H}$(OH)-), 5.83–5.89 (m, 1H, -C$\underline{H}$(NH-)-CH=N-), 8.29 (d, 1H, *J* = 7.3, -C$\underline{H}$=N-OH), 8.32 (d, 1H, *J* = 5.9, -C$\underline{H}$=N-OH), 8.78 (d, 1H, *J* = 8.0 Hz, -NH-CO), 12.89 (s, 1H, =N-O$\underline{H}$), 12.96 (s, 1H, =N-O$\underline{H}$) ppm. All hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~4.70, ~4.96, ~5.96, ~6.12, ~6.39, ~7.51, ~8.35, ~8.68, ~13.24 and ~13.40 ppm (corresponding to other oximes) are visible. MS *m/z* (relative intensity): 388 ($M-H^+$, 100); IR (KBr) ν 3286, 2915, 2849, 2365, 2345, 1655, 1618, 1560, 1465, 1376, 1324, 1294, 1251, 1221, 1197, 1144, 1090, 1065, 1047, 1016, 985 cm^{-1}, mp 158–159 °C.

N-((*E*/*Z*,2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,-trihydroxy-1,6-bis(hydroxyimino)hexan-2-yl)-tetradecanamide (22c)[16]

N-((*E*/*Z*,2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,-trihydroxy-1,6-bis(hydroxyimino)hexan-2-yl)-hexadecanamide (22d)

Yield 86%. A mixture of four isomers was formed (the predominant (*E*,*E*)-form in 87% yield) as a white solid. ^{1}H NMR (pyridine-d_5, 300 MHz) predominant (*E*,*E*)-oxime: δ 0.87 (t, 3H, *J* = 6.4 Hz, -CH_2-C$\underline{H}_3$), 1.18–1.35 (m, 24H, -(C$\underline{H}_2$)$_{12}$-CH_3), 1.74–1.83 (m, 2H, -CO-CH_2-C$\underline{H}_2$-$(CH_2)_{12}$-CH_3), 2.44 (t, 2H, *J* = 7.5 Hz, -CO-C$\underline{H}_2$-CH_2-$(CH_2)_{12}$-CH_3), 3.61 (s, 1H, -OH), 4.58 (dd, 1H, *J* = 2.5, 7.5 Hz, HO-N=CH-CH(OH)-C$\underline{H}$(OH)-CH(OH)-CH(NH-)-CH=N-OH), 5.03 (dd, 1H, *J* = 2.7, 5.8 Hz, -C$\underline{H}$(OH)-CH(NH-)-CH=N-), 5.23–5.30 (m, 1H, HO-N=CH-C$\underline{H}$(OH)-), 5.81–5.87 (m, 1H, -C$\underline{H}$(NH-)-CH=N-), 8.27 (d, 1H, *J* = 7.2, -C$\underline{H}$=N-OH), 8.31 (d, 1H, *J* = 5.8, -C$\underline{H}$=N-OH), 8.88 (d, 1H, *J* = 8.2 Hz, -NH-CO), 11.10 (bs, 1H, =N-O$\underline{H}$), 11.68 (s, 1H, =N-O$\underline{H}$) ppm. All hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~4.68, ~4.94, ~5.94, ~6.11, ~6.37, ~7.50, ~8.10, ~8.34, ~12.90 and ~13.33 ppm (corresponding to other oximes) are visible. MS *m/z* (relative intensity): 444 ($M-H^+$, 100); IR (KBr) ν 3422, 2917, 2849, 2369, 2345, 1654, 1560, 1458, 1376, 1294, 1229, 1090, 1046, 1018, 988 cm^{-1}, mp 100–101 °C.

3. 9. General Procedure for the Synthesis of Glucose Oximes Derivatives (23a-23d)[16]

N-((2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,6-tetrahydroxy-1-(hydroxyimino)hexan-2-yl)-decanamide (23a)

N-((2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,6-tetrahydroxy-1-(hydroxyimino)hexan-2-yl)-dodecanamide (23b)

Yield 65%. A 70/30 mixture of (*E*)- and (*Z*)-oxime as a white solid. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.86 (t, 3H, *J* = 6.62 Hz, -CH_2-C$\underline{H}_3$), 1.17–1.34 (m, 16H, -(C$\underline{H}_2$)$_8$-CH_3), 1.72–1.82 (m, 2H, -CO-CH_2-C$\underline{H}_2$-$(CH_2)_8$-CH_3), 2.42 (t, 2H, *J* = 7.55 Hz, -CO-C$\underline{H}_2$-CH_2-$(CH_2)_8$-CH_3), 4.28–4.33 (m, 1H, HO-CH_2-C$\underline{H}$(OH)-), 4.44–4.57 (m, 3H, HO-C$\underline{H}_2$-CH(OH)-C$\underline{H}$(OH)-CH(OH)-CH(NH-)-CH=N-), 5.02 (dd, 1H, *J* = 2.27, 5.91 Hz, -C$\underline{H}$(OH)-CH(NH-)-CH=N-), 5.76–5.82 (m, 1H, -C$\underline{H}$(NH-)-CH=N-), 8.28 (d, 1H, *J* = 6.01, -C$\underline{H}$=N-), 8.77 (d,

1H, *J* = 7.96 Hz, -NH-CO), 13.38 (bs, 1H, =N-OH) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~2.44, ~4.36, ~5.20, ~6.30, and ~7.46 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 399 ($M+Na^+$, 100), 377 (M+H, 39); HRMS: calcd for $C_{18}H_{37}N_2O_6$, 377.2652; found, 377.2633. IR (KBr) ν 3288, 2955, 2917, 2850, 1994, 1649, 1546, 1403, 1307, 1252, 1082, 1027, 932, 878 cm^{-1}, mp 115–117 °C.

***N*-((2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,6-tetrahydroxy-1-(hydroxyimino)hexan-2-yl)-tetradecanamide (23c)**

Yield 76%. A 70/30 mixture of (*E*)- and (*Z*)-oxime as a white solid. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.88 (t, 3H, *J* = 6.45 Hz, $-CH_2-CH_3$), 1.19–1.37 (m, 20H, $-(CH_2)_{10}-CH_3$), 1.76–1.85 (m, 2H, $-CO-CH_2-CH_2-(CH_2)_{10}-CH_3$), 2.42 (t, 2H, *J* = 7.55 Hz, $-CO-CH_2-CH_2-(CH_2)_{10}-CH_3$), 4.29–4.35 (m, 1H, $HO-CH_2-CH(OH)-$), 4.46–4.57 (m, 3H, $HO-CH_2-CH(OH)-CH(OH)-CH(OH)-CH(NH-)-CH=N-$), 5.03 (dd, 1H, *J* = 2.27, 5.85 Hz, $-CH(OH)-CH(NH-)-CH=N-$), 5.78–5.85 (m, 1H, $-CH(NH-)-CH=N-$), 8.30 (d, 1H, *J* = 5.98, $-CH=N-$), 8.76 (d, 1H, *J* = 8.40 Hz, -NH-CO), 12.92 (bs, 1H, =N-OH) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~2.54, ~4.36, ~5.22, ~6.33, and ~7.47 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 427 ($M+Na^+$, 100), 405 (M+H, 61); HRMS: calcd for $C_{20}H_{41}N_2O_6$, 405.2965; found, 405.2971. IR (KBr) ν 3292, 2955, 2918, 2850, 2346, 1701, 1648, 1543, 1467, 1406, 1308, 1284, 1260, 1238, 1216, 1082, 1027, 931, 877 cm^{-1}, mp 119–120 °C.

***N*-((2*S*,3*R*,4*S*,5*R*,*E*/*Z*)-3,4,5,6-tetrahydroxy-1-(hydroxyimino)hexan-2-yl)-hexadecanamide (23d)**

Yield 68%. A 70/30 mixture of (*E*)- and (*Z*)-oxime as a white solid. ^{1}H NMR (pyridine-d_5, 300 MHz) (*E*)-oxime: δ 0.88 (t, 3H, *J* = 6.41 Hz, $-CH_2-CH_3$), 1.20–1.35 (m, 24H, $-(CH_2)_{12}-CH_3$), 1.76–1.85 (m, 2H, $-CO-CH_2-CH_2-(CH_2)_{12}-CH_3$), 2.42 (t, 2H, *J* = 7.55 Hz, $-CO-CH_2-CH_2-(CH_2)_{12}-CH_3$), 4.28–4.34 (m, 1H, $HO-CH_2-CH(OH)-$), 4.45–4.63 (m, 3H, $HO-CH_2-CH(OH)-CH(OH)-CH(OH)-CH(NH-)-CH=N-$), 5.03 (dd, 1H, *J* = 2.29, 5.85 Hz, $-CH(OH)-CH(NH-)-CH=N-$), 5.77–5.84 (m, 1H, $-CH(NH-)-CH=N-$), 8.29 (d, 1H, *J* = 5.99, $-CH=N-$), 8.76 (d, 1H, *J* = 8.10 Hz, -NH-CO), 12.91 (bs, 1H, =N-OH) ppm. The hydroxyl groups are not visible due to exchange with residual water. Small resonances at ~2.43, ~4.39, ~5.23, ~6.33, ~7.47 and ~13.37 ppm (corresponding to the (*Z*)-oxime) are visible. MS *m/z* (relative intensity): 467 ($M+Cl^-$, 100), 431 ($M-H^+$, 20); HRMS: calcd for $C_{22}H_{43}N_2O_6$, 431.3121; found, 431.3104. IR (KBr) ν 3393, 3292, 3050, 2953, 2917, 2849, 2361, 2344, 2018, 1654, 1648, 1636, 1558, 1541, 1463, 1405, 1313, 1285, 1250, 1230, 1211, 1083, 1017, 935, 880 cm^{-1}, mp 162–163 °C.

3. 10. Calculation of HLB Values

The HLB (hydrophilic lipophilic balance) parameter was calculated according to Griffin's method[22] as follows: HLB = Mh / M × 20, where Mh correspond to the molecular mass of the hydrophilic part of the molecule and M to the molecular mass of the whole molecule. For all synthesized compounds, an aliphatic tail was considered as lipophilic part of the molecule.

3. 11. The DPPH· Assay

Total antioxidant capacity assay was performed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH•) method.[23] The radical scavenging activity was evaluated through the degree of $DPPH^·$ reduction, followed by monitoring the decrease in its absorbance at 516 nm during the reaction. Various concentrations of synthesized compounds (10 and 5 mM for benzamidoxime and benzoxime derivatives and 0.5, 1, and 5 mM for glycolipid derivatives) were prepared in methanol and each solution (1 mL) was added to 2 mL of methanolic DPPH• solution (0.063 mM). The absorbance was recorded (Hewlett Packard UV/VIS 8453 spectrophotometer (Germany)) every minute for a 30 min period. All measurements were performed in duplicate.

The remaining DPPH• concentration in the reaction medium was calculated from a calibration curve obtained with DPPH• at 516 nm. The percentage of remaining $DPPH^·$ ($DPPH^·$ rem) was calculated as follows: % DPPH• rem = $(A_f / A_0) \times 100$, where A_f is the absorbance of the DPPH• solution with the sample at the final state and A_0 is the absorbance of the $DPPH^·$ solution without the sample (2 mL of $DPPH^·$ solution plus 1 mL of methanol).

4. Conclusion

New amphiphilic benzamidoxime (**4a–e**) and benzoxime (**8a–e**; **10a–e**) derivatives were synthesized with more pronounced hydrophilic properties compared to previously synthesized oxime derivative TDBO. The antioxidant activity was estimated using DPPH assay. The radical-scavenging ability data obtained for synthesized amphiphilic compounds against DPPH radical can be correlated with their molecular structure: it is the highest in benzamidoxime series, followed by derivatives of glucose with two oxime functionalities and compounds constituting benzoxime series; it is lower when only one oxime group is introduced on glucose derivatives, and is the lowest for compounds with two oxime moieties and galactose derivatives. Glycolipid derivatives have the advantage of being synthesized from natural products, whereas all of these novel agents provide a value-added use for two-phase or lipid-based systems due to their amphiphilic character. Due to their notable antioxidant properties, especially amidoximes and glycolipid mimetics with two oxi-

me functionalities show great promise for use as antioxidants in topical formulations.

5. References

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Povzetek

Sintetizirali smo nove amfifilne spojine benzamidoksimskega in benzoksimskega tipa ter oksimske derivate glikolipidnih mimetikov z alkilno verigo. Celokupno antioksidativno kapaciteto amfifilnih derivatov smo ovrednotili z DPPH metodo. Benzamidoksimi in glikolipidni mimetiki z dvema oksimskima skupinama imajo najmočnejše antioksidativno delovanje, sledijo jim benzoksimski derivati, glikolipidni mimetiki z eno oksimsko skupino ter dimeri oksimov. Zaradi amfifilne strukture, ki je bila vodilo pri načrtovanju in sintezi, bi nove sintetizirane amfifilne spojine lahko uporabili kot potencialne antioksidante za omejitev oksidativnih procesov v dvofaznih sistemih, tako bioloških (celične membrane) kot umetnih (emulzije).