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Conformationally-locked *N*-glycosides: exploiting long-range non-glycone interations in the design of pharmacological chaperones for Gaucher disease

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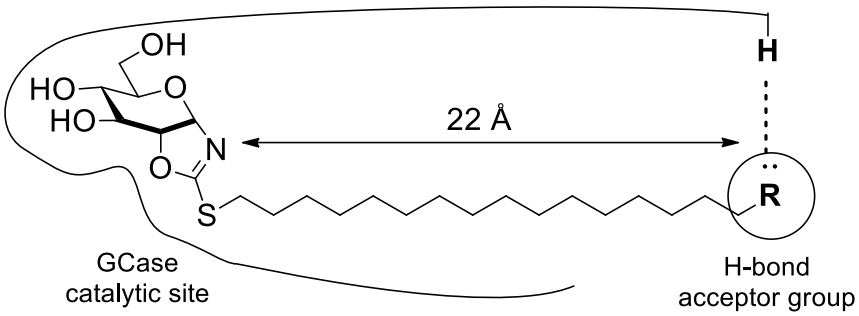


Abstract: Pyranoid-type glycomimetics having a *cis*-1,2-fused glucopyranose−2-alkylsulfanyl-1,3-oxazoline (PSO) structure exhibit an unprecedented specificity as inhibitors of mammalian β-glucosidase. Notably, their inhibitory potency against human β-glucocerebrosidase was found to be strongly dependent on the nature of aglycone-type moieties attached at the sulfur atom. In the particular case of ω-substituted hexadecyl chains, an amazing influence of the terminal group was observed. A comparative study on a series of PSO derivatives suggests that hydrogen bond acceptor functionalities, e.g. fluoro or methyloxycarbonyl, significantly stabilize the PSO:GCase complex. The S-(16-flurohexadecyl)-PSO glycomimetic turned out to be a more

potent GCase competitive inhibitor than ambroxol, a non glycomimetic drug currently in pilot trials as a pharmacological chaperone for Gaucher disease. Moreover, the inhibition constant increase by one order of magnitude when shifting from neutral (pH 7) to acidic (pH 5) media, a favorable characteristic for a chaperone candidate. Indeed, the fluoro-PSO derivative also proved superior to ambroxol in mutant GCase activity enhancement assays in N370S/N370S Gaucher fibroblasts. The results represent a proof of concept of the potential of exploiting long-range non-glycone interactions in glycosidase inhibitor/chaperone design.

Introduction

The search for compounds capable of modulating the activity of glycosidases, the enzymes that catalyze the hydrolysis of the glycosidic bond in polysaccharides and glycoconjugates, represents one of the more active research fields in glycobiology.[1] Glycosidase inhibitors are fundamental tools to interrogate biological processes involving biosynthesis, metabolism and recognition of carbohydrates[2] and bear strong potential for the development of drugs against associated pathologies,[3] including cancer,[4] diabetes,[5] infection,[6] ischemia[7] or neurodegenerative diseases.[8] On the other hand, compounds stabilizing the proper folding of trafficking-incompetent mutant glycosidases at the endoplasmid reticulum (ER), thereby rescuing them from degradation by the quality control system of the cell, show high promise as pharmacological chaperones for the treatment of lysosomal storage disorders[9] such as Gaucher,[10] Fabry[11] or G_{M1} gangliosidosis,[12] formally acting as effectors of the corresponding dysfunctional enzyme. Someway counterintuitively, the glycosidase inhibitory and chaperoning activities often coexist, the balance between them being a function of concentration and relative binding affinities at neutral (ER) and acidic pH (lysosome).[13]

With few exceptions,[14] most naturally occurring or de novo synthesized glycosidase inhibitors/chaperones are carbohydrate-like derivatives (glycomimetics) in which the acetal group characteristic of glycosides has been modified while preserving a hydroxylation pattern of stereochemical complementarity with the aglycone moiety of the putative glycosidase substrate. Yet, recent work has shown the importance of implementing non-glycone interactions to achieve glycosidase selectivity levels within isoenzymes compatible with clinical applications.[15] Most of the work in this sense has focused on nitrogen- (iminosugars,[16] sp^2-iminosugars,[17] azasugars[18]) and carbon-in-the-ring (carbasugars,[19] cyclitols[20]) carbohydrate mimics. Surprisingly, aglycon effects for glycomimetics keeping the pyranose core intact have been much less studied,[21] even though modifications at the glycosidic region has the potential to be compatible with molecular diversity-oriented strategies with a relatively low synthetic cost.[22]

In a previous report,[23] we developed a new family of pyranoid-type glycomimetics having a *cis*-1,2-fused glucopyranose−2-alkylsulfanyl-1,3-oxazoline structure (Glc-PSO, Figure 1) behaving as selective β-glucosidase inhibitors. PSO derivatives can be formally considered as conformationally locked *N*-glycosides, which warrant chemical and enzymatic stability. Their

fused six-membered—five-membered bicyclic skeleton, analogous to that of the potent *O*-(*N*-acetylglucosaminidase) inhibitors NAG-thiazoline, NButGT and thiamet-G (Figure 1),[24] imposes a skew-boat conformation to the pyranose ring, which has been found to impart glycosidase transition state mimic character.[25] Structure-chaperone activity relationship studies on fibroblasts from Gaucher disease patients evidenced a strong impact of the nature of exocyclic *S*-substituents of Glc-PSO glycomimetics on the mutant lysosomal β-glucosidase (β-glucocerebrosidase; GCase) effector abilities. Notably, the *S*-(16-hydroxyhexadecyl) derivative (Glc-PSO-HHD) was as efficient as the non-glycomimetic chaperone candidate ambroxol (ABX), currently in pilot trials in humans,[26] for the N370S homozygous mutation, the most prevalent for this lysosomal storage disorder. The possibility of hydrogen bonding involvement of the terminal hydroxyl group, once the pyranoid ring sits in the active site of the enzyme, with an amino acid residue located at an appropriate distance was advanced. To test this hypothesis, we have now expanded the PSO family with the preparation of a series of analogues keeping the hexadecyl chain in the aglycone but modifying the terminal group or the configuration of the core. The synthetic strategy and the evaluation of the new compounds as glycosidase inhibitors and chaperone candidates are reported.

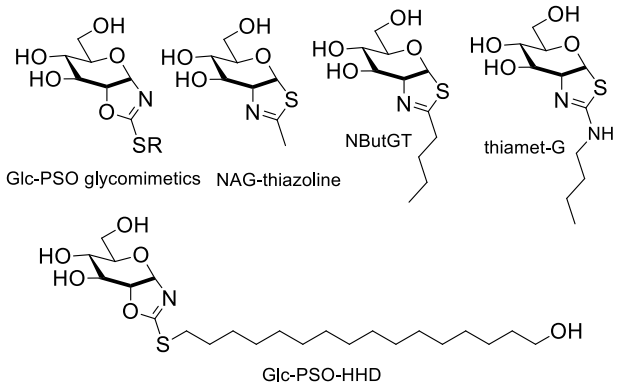
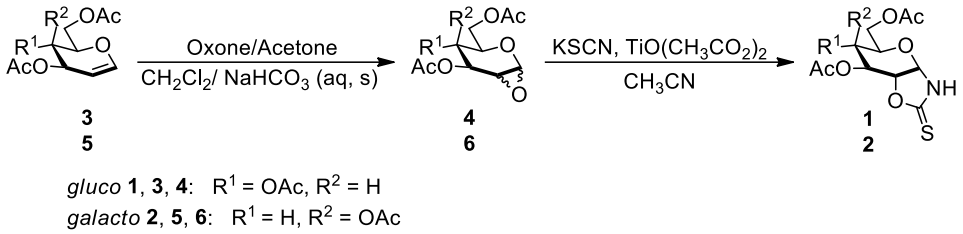


Figure 1.

Results

The preparation of PSO glycomimetics with a hydroxylation profile matching that of D-glucose and differing in the S-linked aglycon portion relies on the S-alkylation reaction of the pivotal 1,3-oxazolidine-2-thione glucopyranose intermediate **1**. Taking into consideration that the target enzyme GCase has been shown to exhibit low discriminating capabilities between active site-binding ligands differing in the configuration at C-4 for some glycomimetic families,[27] the corresponding D-galacto configured epimer **2** was also initially considered. The methodology used for the synthesis of **1** and **2** starts from tri-*O*-acetyl-D-glucal (**3**) or -D-galactal (**5**), respectively, and involved epoxidation of the double bond with *in situ* generated dimethyldioxirane. In the first case, the reaction afforded a mixture of the α-D-*gluco* and β-D-

manno tri-*O*-acetyl-1,2-anhydrosugars **4** (D-*gluco*/D-*manno* ratio 7:1) in 90 % yield.[28] Epoxidation of **5** provided instead exclusively the α-epoxide **6** (α-D-*galacto* configuration) in an almost quantitative yield.[28] Reaction of **4** and **6** with potassium thiocyanate and catalytic amounts of $TiO(CH_3CO_2)_2$ led to the requested thionocarbamates **1** and **2** in 87 and 79% yield, respectively (Scheme 1).[29]



Scheme 1. Synthesis of 1,3-oxazolidine-2-thione glycopyranose derivatives **1** and **2**.

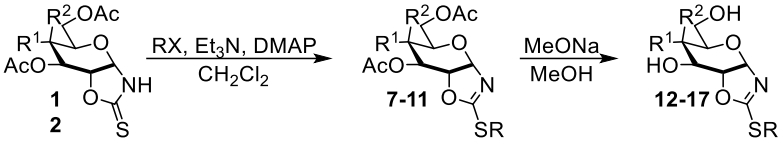
In view of the good GCase chaperon properties observed for the D-*gluco*-PSO derivative bearing an *S*-(ω-hydroxyhexadecyl) aglycon moiety Glc-PSO-HHD and the significant contribution of the terminal hydroxyl to this behaviour,[23] in this work we have chosen to examine the incorporation of a series of ω-substituted hexadecyl chains bearing different terminal groups, including ester, carboxylic acid, iodo and fluoro. These compounds were prepared using the corresponding distal iodo derivatitves as the alkylating agents. Methyl 16-iodohexadecanoate and 16-iodohexadecanoic acid were prepared from the corresponding commercially available 16-bromo derivatives by reaction with sodium iodide in acetone (see Supporting Information). Given the ambident character of the thionocarbamate functionality,[30] the reaction conditions for the alkylation step had to be carefully adjusted in order to warrant the alkylation reaction regioselectively at the sulfur atom. Thus, compound **1** was treated with a series of different alkyl iodides in dichloromethate in the presence of triethylamine and *N,N*-dimethylaminopyridine (DMAP) following the work by Rollin *et al*.[31] Indeed, all reactions carried out under these soft conditions afforded the expected acetyl-protected PSO derivatives **7**-**10** in 52-87 % yields (Table 1). Interestingly, reaction of **1** with 1,16-diiodohexadecane not only afforded the expected S-(16-iodohexadecyl)sulfanyl derivative **8**, but also the dialkylation product **9**, isolated in 32 % yield (Table 1, entry 2). We also prepared the corresponding D-*galacto*-PSO derivative **11**, bearing the S-(16-hydroxyhexadecyl) antenna, to test the effect of the configurational change on the inihibitory/chaperone properties.

The S-alkyl character of compounds **7-11** was confirmed by ^{13}C NMR spectroscopy: the chemical shift for the quaternary sp^2 carbon atom at position 2 in the five-membered heterocycle varied from roughly 190 ppm (-N-C=S in 1,3-oxazolidine-2-thiones **1** and **2**) to approximately 170 ppm (-N=C-SR in PSO derivatives **7**-**11**). This data is in accordance with analogous thionocarbamates already reported in the literature.[23]

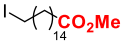
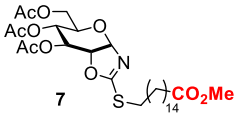
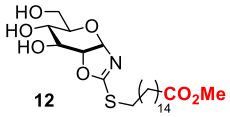
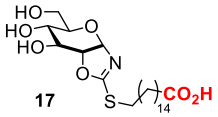
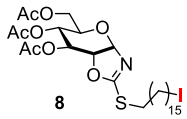
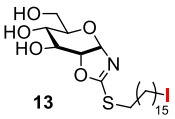
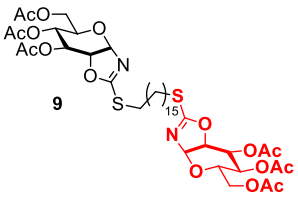
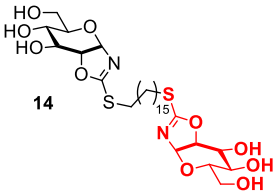
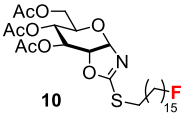
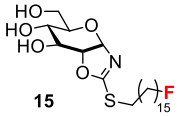
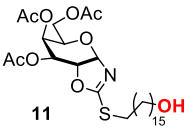
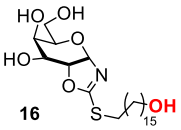
The target fully-unprotected PSOA-glycomimetics **12-16** were obtained in 81-100 % yield by final removal of the acetyl protecting groups using methanol under standard NaOMe-catalyzed

conditions. In order to obtain derivative **17**, precursor **7** was treated with a solution of sodium hydroxide in methanol under similar reactions conditions (Table 1, entry 2). The vicinal proton-proton coupling constants about the pyranose ring both for the acetylayed (**7**-**11**) and the unprotected (**12-17**) PSO derivatives were in agreement with a skew-boat conformation close to $^{0}S_{2}$ as previously observed for us[23] and others[32] in structurally related bicyclic cis-1,2-fused glucopyranose structures in solution.

Table 1. Synthesis of 2-*S*-alkylsulfanyl-1,3-oxazoline D-glycopyranose derivatives.



gluco **1, 7-10**: R^1 = OAc, R^2 = H; **12-15, 17**: R^1 = OH, R^2 = H
galacto **2, 11**: R^1 = H, R^2 = OAc; **16**: R^1 = H, R^2 = OH

			S-alkylation[a]		O-deprotection[b]	
Entry	**Starting M.**	**Alkyl Halide**	**Product**	**Yield (%)**	**Product**	**Yield (%)**
1	**1**		 **7**	52	 **12**	95
					 **17**	81
2	**1**		 **8**	64	 **13**	100
			 **9**	32	 **14**	94
3	**1**		 **10**	87	 **15**	70
4	**2**		 **11**	89	 **16**	90

[a] Carried out at rt during 24 h with 1.0 eq. substrate, 3.0 eq. alkyl halide, 3.0 eq. Et_3N and 2 mol% DMAP in CH_2Cl_2. [b] Carried out at rt during 12 h with 1.0 eq. of *S*-alkylated substrate and 5 mol% MeONa in MeOH. [c]

Biological evaluation

The new PSO derivatives **12**-**17** were first screened as inhibitors against a panel of commercial glycosidases including α-glucosidase (yeast), β-glucosidase (β-Glcase; almonds and bovine liver, cytosolic), α-mannosidase (Jack bean), β-mannosidase (*Helix pomatia*), trehalase (pig kidney), amyloglucosidase (*Aspergillus niger*), naringinase (β-glucosidase/α-L-rhamnosidase, *Penicillium decumbens*), α-galactosidase (green coffee beans), β-galactosidase (*E. coli*), and amyloglucosidase (*Aspergillus niger*). All compounds behaved as competitive inhibitors of the mammalian β-Glcase and exhibited total selectivity within the series of enzymes assayed; a unique signature of the PSO family whose molecular basis is still unknown. The corresponding inhibition constants (K_i) at the optimal pH of β-Glcase (7.3) ranged from 5.5 to 26.4 μM (Table 1), similar to that previously encountered for Glc-PSO-HHD (12 μM).[23] Interestingly, the inhibition potency decreased from 2 to 11-fold when moving from pH 7.3 to 5.5, suggesting that the neutral form of the compounds is the most active species.

Table 1. K_i Values (μM) against Bovine Liver (Cytosolic) β-Glucosidasea and IC50 Values (μM) against Human GCase for Compounds **12**-**17**

Enzyme	pH	**12**	**13**	**14**	**15**	**16**	**17**
β-Glcase (bovine liver)	7.3	26.4	19.3	11.8	11.1	5.5	22.6
β-Glcase (bovine liver)	5.5	45	98	139	66	62	61
GCase (*Homo sapiens*)	7.0	33	230	NI.	3.9	NI	420
GCase (*Homo sapiens*)	5.0	300	>1000	NI	27	NI	>1000

[a]Inhibition was competitive in all cases. No inhibition was observed for any of the compounds at 2 mM on almonds β-glucosidase, yeast α-glucosidase, jack bean α-mannosidase, *Helix pomatia* β-mannosidase, pig kidney trehalase, *Aspergillus niger* amyloglucosidase, *Penicillium decumbens* naringinase, green coffee α-galactosidase, *E. coli* β-galactosidase, or yeast isomaltase. [b]NI: no inhibition observed at 1 mM.

Inhibition of bovine liver β-glucosidase is often used as a preliminary parameter to select candidates as pharmacological chaperones for mutant human GCase associated with Gaucher disease. Yet, the predictive character of the data must be taken with care: although both enzymes are members of the GHA clan in the CAzY classification,[33] meaning that they share three-dimensional structural similarities, they belong to different glycosyl hydrolase families,

namely GH1 and GH30, with only limited sequence similarity.[33] Indeed, determination of the inhibition activity against human GCase (pH 7.0) revealed that the D-Gal-PSO representative **16** was inactive, whereas a strong influence of the terminal functional group at the hexadecyl aglycone chain was observed in the D-Glc-PSO series, the inhibitory potency decreasing in the sense F (**15**; IC_{50} 3.9 μM) > COOMe (**12**; IC_{50} 33 μM) > I (**13**; IC_{50} 230 μM) > COOH (**17**; IC_{50} 420 μM). The dimeric derivative **14** turned out to be inactive (Table 1). No inhibition of other lysosomal enzymes, such as α-glucosidase, α-galactosidase, β-galactosidase, and β-hexosaminidase, was observed, reproducing the selectivity pattern already found in commercial enzymes. Most interestingly an about one-order-of-magnitude decrease in the GCase inhibiton strength was also observed at pH 5 (Table 1; see also Figure 2 for the most active compounds **15** and **12**), a favorable feature for chaperone candidates.

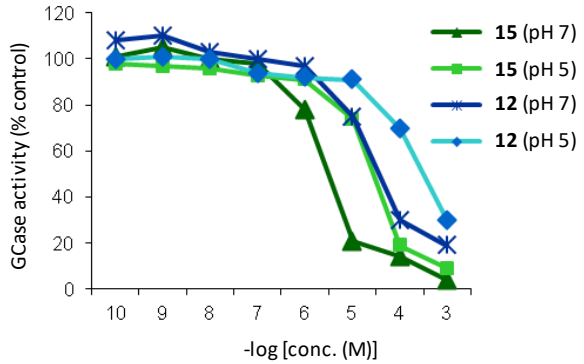


Figure 2. Effects of the PSO derivatives **15** and **12** on GCase activity in lysate from human normal fibroblasts as a function of pH. Enzyme activity in normal cell lysates was determined in the absence or presence of increasing concentrations of the chaperones. Each point represents the mean of triplicate determinations obtained in a single experiment. Values were expressed relative to the activity in the absence of compounds (100%). 4-Methylumbelliferyl β-D-glucopyranoside was used as substrate.

The dramatic effect of the ω-substituent in the hexadecyl chain on the ability of PSO derivatives to inhibit GCase, above two orders of magnitude when comparing the fluoro and the carboxylic acid groups, reinforces our initial hypothesis that PSO:GCase complexes might be stabilized by a long-range interaction involving this terminal group and an amino acid residue located at a maximum distance of 22 Å from the catalytic site (Figure 3). Comparing with Glc-PSO-HHD (IC_{50} 11.2 μM),[23] were the ω-substituent is OH, only the fluoro (**15**) and methoxycarbonyl (**12**) derivatives exhibit comparable binding affinities, much higher that the iodo (**13**) or carboxylic acid (**17**) partners. It is interesting to speculate that the terminal group is acting as hydrogen bond acceptor and that optimizing this long-range hydrogen bonding interaction may provide a general strategy for the design of potent and specific GCase inhibitors/chaperones. The IC_{50} value for **15** is even lower as compared to that encountered for the reference chaperone drug ambroxol against GCase in a similar assay (4.1 μM).[23]

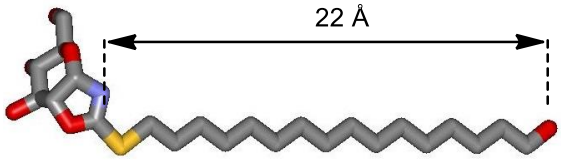


Figure 3. 3D Molecular model of Glc-PSO-HDD (carbons in grey, oxygens in red, nitrogen in light blue, sulfur in yellow; hydrogens have been omitted for the sake of clarity). The pyranose ring is in a $^{0}S_{2}$ coformation and the hexadecyl chain has been set to the more stable extended conformation. The distance between the anomeric nitrogen atom and the terminal substituent in the chain, which remains identical in all the new PSO derivatives prepared in this work, is indicated.

Compounds **12** and **15** were selected for further enzyme activity enhancement assays in healthy and Gaucher fibroblasts from patients having the N370S/N370S or the L444P/L444P mutations. The first one, the most common mutation among Gaucher patients, is located in the catalytic domain of the enzyme, while the second one is located in a noncatalytic domain. The cells were cultured for 5 days in the absence and in the presence of various concentrations of **12** or **15**, then lysed and the β-glucocerebrosidase activity determined using 4-methylumbelliferyl β-D-glucopyranoside as substrate.

In normal cells, **12** and **15** had no effect on GCase activity. In N370S/N370S Gaucher fibroblasts (Figure 4) compound **12** had only a marginal effect (12% activity increase at 30 μM concentration), whereas **15** up-regulated the activity of the mutant enzyme in a very significant manner (62% at 30 μM), actually more efficiently than the hydroxyl-bearing analogue Glc-PSO-HHD (55% at 90 μM). In a parallel assay, ABX led to a maximum activity enhancement of 33% at 10 nm,[23] with a decrease in the chaperone efficiency when moving to 30 μM, meaning that the inhibitory activity overcomes the chaperone effect. In the case of **15**, this situation occurred only a 60 μM, indicating a more favorable chaperone/ inhibitor balance. Neither **12** or **15** nor ABX or Glc-PSO-HHD were effective at increasing the activity in the case of the L444P/L444P mutant GCase, nor did they exhibit toxic effect on any of the normal or mutant cell lines assayed for 5 days of incubation.

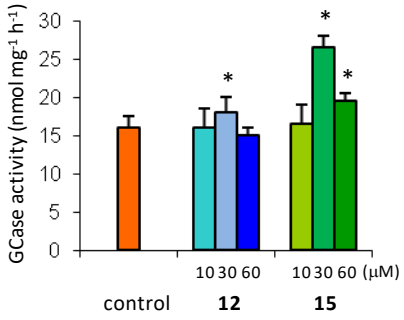


Figure 4. Effect of PSO glycomimetics **12** and **15** in GCase activity in N370S/N370S fibroblasts. Fibroblasts from patients were cultured in the absence or presence of the indicated concentrations of the chaperone for 96 h and the GCase activities in lysates were measured using 4-methylumbelliferyl β-D-glucopyranoside as substrate. Each bar represents the mean ± SEM of three determinations each done in triplicate. The asterisks indicate highly significant statistical difference ($p < 0.01$) from the values in the absence of the compound (t test).

The ensemble of results supports the potential of the PSO scaffold for the design of selective β-Glc inhibitors and active site-directed pharmacological chaperones for Gaucher disease. Although the observed activity enhancements do not surpass the values reported for the most efficient iminosugar-type chaperones,[34] they are in principle medically useful. Most importantly, they also provide a proof of concept that long-range non-glycone interactions can be advantageously exploited to endow a rigid pyranoid glycone moiety with high binding affinity and selectivity toward a given glycosidase and suggest a key structural element for the design of GCase chaperones. The current data also validate the synthetic methodology for the purpose of structure-activity relationship studies and pharmacological chaperone optimization.

Experimental section

General procedure for the preparation of the 1,2-anhydrosugars 4 and 6:[28] The corresponding glycal **3** or **5** (1.00 mmol) was dissolved in an ice bath cooled biphasic solution of CH_2Cl_2 (4 mL), acetone (0.4 mL) and saturated aqueous $NaHCO_3$ (6.5 mL). The mixture was vigorously stirred and a solution of Oxone® (1.23 g, 2.00 mmol) in H_2O (5 mL) was added dropwise over 15 min. The crude reaction was vigorously stirred at 0º C for 30 min and then allowed to warm to room temperature until complete consumption of the glycal (TLC monitoring). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford the 1,2-anhydro-pyranoses **4** (90 %, mixture D-*gluco*/D-*manno* 7:1) or **6** (98 %, only α-epoxide). The crude could not be purified due the inherent instability of 1,2-anhydrosugars.

General procedure for the synthesis of *cis*-1,2-fused 1,3-oxazolidine-2-thione precursors 1 and 2:[29] To a stirred solution of the crude 1,2-anhydro-sugar **4** or **6** (1.00 mmol) and KSCN (3.00 mmol) in dry CH_3CN (5 mL), finely powdered $TiO(CF_3COO)_2$ (0.02 mmol) was added under an Ar atmosphere, and the mixture was heated to boiling for appropriate time. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature, H_2O (10 mL) was added and the resultant mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (ethyl acetate/hexanes 2:1) gave the bycyclic derivatives **1** or **2** (87 % and 79 %, respectively).

General procedure for the S-alkylation of cis-1,2-fused D-glycopyranose—1,3-oxazolidine-2-thione derivatives: To a solution of the 1,3-oxazolidine-2-thione derivative (1.00 mmol) in CH_2Cl_2 (3.5 mL), the corresponding alkyl iodide (3.00 mmol), Et_3N (3.00 mmol) and TBD (0.2 mmol) were added followed by stirring at room temperature. After completion of the reaction, the mixture was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Chromatographic purification afforded the *S*-alkylated compounds in the yields shown.

General procedure for acetyl deprotection of cis-1,2-fused D-glycopyranose—2-alkylsulfanyl-1,3-oxazoline derivatives: Sodium methoxide (0.05 mmol) was added to a solution of protected 1,3-oxazoline carbohydrate (1.00 mmol) in methanol (20 mL), followed by stirring at room temperature. Upon completion of the reaction, the solvent was removed *in vacuo*, and the crude product was purified by flash chromatography on silica gel to afford the deprotected compounds in the yields shown.

Add here the description of the new compounds

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyranoside[1,2-d]-1,3-oxazolidine-2-thione (2). The title compound was prepared following the general procedure for the synthesis of *cis*-1,2-fused 1,3-oxazolidine-2-thione carbohydrate derivatives starting from **6** (810 mg, 2.81 mmol), KSCN (642 mg, 8.43 mmol), $TiO(CF_3COO)_2$ (16.6 mg, 0.06 mmol) in dry CH_3CN (14 mL). The reaction mixture was stirred under reflux for 2,5 h. Standard workup, followed by flash chromatography on silica gel (2:1 AcOEt/hexane), afforded **2** (776 mg, 79% yield) as a white solid. Data: R_f (4:1 AcOEt/hexane): 0.56. Mp: 52-55 ºC. $[\alpha]_D$ + 46.5 (*c* 1.38, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 3301, 2923, 2853, 1743, 1490, 1368, 1225, 1174, 1033. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.41 (bs, 1H, =NH); 5.75 (d, 1H, $J_{1,2}$= 6.0 Hz, H-1); 5.56 (pt, 1H, $J_{4,3}$ = 3.2 Hz, $J_{4,5}$= 3.6 Hz, H-4); 5.17 (dd, 1H, $J_{3,2}$= 6.6 Hz, $J_{3,4}$= 3.2 Hz, H-3); 4.85 (pt, 1H, $J_{2,1}$= 6.0 Hz, $J_{2,3}$= 6.6 Hz, H-2); 4.37 (ddd, $J_{4,5}$= 3.6 Hz, $J_{5,6}$= 7.4 Hz, $J_{5,6'}$ = 5.8 Hz, 1H, H-5); 4.25 (dd, $J_{6,5}$= 7.4 Hz, $J_{6,6'}$= 11.6 Hz, H-6); 3.99 (dd, $J_{6',5}$= 5.8 Hz, $J_{6',6}$= 11.6 Hz, H-6'); 2.11 (s, 3H, AcO); 2.08 (s, 3H, AcO); 2.05 (s, 3H, AcO). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 189.8 (C=S); 170.9, 169.9, 168.7 (C(O), AcO); 82.1 (C-1); 81.0 (C-2); 70.7 (C-3); 70.4 (C-5); 66.2 (C-4); 60.6 (C-6); 20.8, 20.7, 20.6 (CH_3, AcO). +TOF MS Calcd for $C_{29}H_{49}NO_9S$ *m/z* [M-Na]+: 610.3020, found: 610.3039.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranoside[1,2-d]-16-methoxycarbonylhexadecylsulfanyl-1,3-oxazoline (7). The title compound was prepared following the general procedure for the S-alkylation of *cis*-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **1** (41.3 mg, 0.12 mmol), methyl 16-iodo hexadecanoate (141.4 mg, 0.36 mmol), Et_3N (52 µL, 0.36 mmol), TBD (0.4 mg, 3 µmol) and CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at rt for 24 h. After standard workup, the crude was purified by flash chromatography (from 1:10 to 2:1 AcOEt/hexane) followed by recrystallization from AcOEt-Hexane to afford compound **7** (38.1 mg, 52% yield) as a white solid. Data: Rf (1:1 AcOEt/hexane): 0.74. Mp: 67-68 ºC. $[\alpha]_D$ + 44.8 (*c* 3.13, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 2917, 2851, 1734, 1602, 1372, 1218, 1110, 1045, 1034, 1012, 883. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.86 (d, 1H, $J_{1,2}$= 7.5 Hz, H-1); 5.18 (t, 1H, $J_{3,2}$= $J_{3,4}$= 4.1 Hz, H-3); 4.90 (dd, 1H, $J_{4,3}$= 4.1 Hz, $J_{4,5}$= 8.1 Hz, H-4); 4.50 (ddd, 1H, $J_{2,1}$= 7.5 Hz, $J_{2,3}$= 4.0 Hz, $J_{2,4}$= 0.8 Hz, H-2); 4.26 (dd, 1H, $J_{6,5}$= 5.5 Hz, $J_{6,6'}$= 12.2 Hz, H-6); 4.15 (dd, 1H, $J_{6',5}$= 3.1 Hz, $J_{6',6}$= 12.2 Hz, H-6'); 3.67 (ddd, $J_{5,4}$= 8.1 Hz, $J_{5,6}$= 5.5 Hz, $J_{5,6'}$ =3.1 Hz, 1H, H-5); 3.64 (s, 3H, MeO); 3.04 (t, 2H, *J*= 7.4 Hz, CH_2-S aliph); 2.28 (t, 2H, *J*= 7.8 Hz, CH_2-C(O) aliph); 2.10 (s, 3H, AcO); 2.06 (s, 3H, AcO); 2.05 (s, 3H, AcO); 1.69 (quint, 2H, *J*= 7.5 Hz, CH_2 aliph.); 1.59 (quint, 2H, *J*= 7.4 Hz, CH_2 aliph.); 1.38 (quint, 2H, *J*= 7.3 Hz, CH_2 aliph.); 1.35-1.22 (20H, CH_2 aliph.). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 174.6 (C=N); 171.2, 170.9, 169.8, 169.5 (C(O), AcO); 92.5 (C-1); 77.1 (C-2); 70.2 (C-3); 68.1 (C-4); 67.5 (C-5); 63.5 (C-6); 51.6 (MeO); 34.3 (CH_2-C(O)); 32.4 (CH_2-S); 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.3, 28.9, 25.1 (CH_2 aliph); 21.0, 21.0, 20.9 (CH_3, AcO). +TOF MS Calcd for $C_{30}H_{49}NO_{10}S$ *m/z* [M-Na]+: 638.2969, found: 638.2976.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranoside[1,2-d]-(16-iodohexadecyl)sulfanyl-1,3-oxazoline (8) and 1,16-Di(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranoside[1,2-d]-1,3-oxazolidine-2-thione)hexadecane (9). The title compounds were prepared following the general procedure for the S-alkylation of cis-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **1** (37.3 mg, 0.10 mmol), 1,16-diiodohexadecane (130 mg, 0.27 mmol), Et_3N (38 µL, 0.27 mmol), TBD (0.3 mg, 2 µmol) and CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 24 h. After standard workup, the crude was purified by flash chromatography (from 1:9 to 1:2 AcOEt/hexane) to afford **8** (48.4 mg, 64 % yield) as a colourless syrup and **9** (31.6 mg, 32 % yield) as an off-white syrup. Data for **8**: Rf (1:1 AcOEt/hexane): 0.78. $[\alpha]_D$ +41.9 (*c* 0.82, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 2922, 2852, 1745, 1592, 1461, 1367, 1222, 1147, 1110, 1038. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.89 (d, 1H, $J_{1,2}$= 7.4 Hz, H-1); 5.2 (pt, 1H, $J_{3,2}$= 3.8, $J_{3,4}$= 4.2 Hz, H-3); 4.93 (ddd, 1H, $J_{4,2}$= 0.8 Hz, $J_{4,3}$= 4.2 Hz, $J_{4,5}$= 8.8 Hz, H-4); 4.52 (ddd, 1H, $J_{2,1}$= 7.4 Hz, $J_{2,3}$= 3.8 Hz, $J_{2,4}$=0.8 Hz, H-2); 4.29 (dd, 1H, $J_{6,5}$= 5.2 Hz, $J_{6,6'}$=12.2 Hz, H-6); 4.18 (dd, 1H, $J_{6',5}$= 2.8 Hz, $J_{6',6}$=12.2 Hz, H-6'); 3.70 (m, 1H, H-5); 3.19 (t, 2H, J= 7.0 Hz, CH_2-I); 3.06 (t, 2H, J= 7.4 Hz, CH_2-S); 2.12 (s, 3H, AcO); 2.09 (s, 3H, AcO); 2.07 (s, 3H, AcO); 1.82 (quint, 2H, J= 7.2 Hz, CH_2 aliph); 1.72 (quint, 2H, J= 7.4 Hz, CH_2 aliph); 1.41-1.20 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 171.2 (C=N); 170.9, 169.8, 169.6 (C(O), AcO); 92.5 (C-1); 77.1 (C-2); 70.2 (C-

3); 68.0 (C-4); 67.4 (C-5); 63.5 (C-6); 32.4 (CH_2-S); 30.7, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 28.9, 28.8, 27.0 (CH_2 aliph); 21.1, 21.0, 21.0 (CH_3, AcO); 7.7 (CH_2-I).+TOF MS Calcd for $C_{29}H_{48}INO_8S$ *m/z* [M-Na]+: 720.2038, found: 720.2049. Data for **9**: Rf (1:1 AcOEt/hexane): 0.26. $[\alpha]_D$ +1.4 (*c* 3.98, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 3460, 2923, 2852, 1741, 1590, 1368, 1224, 1147, 1111, 1038, 752. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.88 (d, 2H, $J_{1,2}$= 7.4 Hz, 2x H-1); 5.2 (pt, 2H, $J_{3,2}$= 4.0, $J_{3,4}$= 4.2 Hz, 2x H-3); 4.93 (ddd, 2H, $J_{4,2}$= 0.8 Hz, $J_{4,3}$= 4.2 Hz, $J_{4,5}$= 8.8 Hz, 2x H-4); 4.52 (ddd, 2H, $J_{2,1}$= 7.4 Hz, $J_{2,3}$= 4.0 Hz, $J_{2,4}$=0.8 Hz, 2x H-2); 4.29 (dd, 2H, $J_{6,5}$= 5.4 Hz, $J_{6,6'}$=12.2 Hz, 2x H-6); 4.18 (dd, 2H, $J_{6',5}$= 2.8 Hz, $J_{6',6}$=12.2 Hz, 2x H-6'); 3.69 (m, 2H, 2x H-5); 3.06 (t, 4H, J= 7.4 Hz, 2x CH_2-S); 2.12 (s, 6H, 2x AcO); 2.09 (s, 6H, 2x AcO); 2.07 (s, 6H, 2x AcO); 1.72 (quint, 4H, J= 7.4 Hz, 2x CH_2 aliph); 1.43-1.20 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 172.1 (2x C=N); 170.9, 169.8, 169.5 (2x C(O), AcO); 92.5 (2x C-1); 77.1 (2x C-2); 70.2 (2x C-3); 68.0 (2x C-4); 67.4 (C-5); 63.5 (2x C-6); 32.4 (2x CH_2-S); 29.8, 29.8, 29.8, 29.7, 29.4, 29.3, 28.9 (2x CH_2 aliph); 21.0, 21.0, 21.0 (2x CH_3, AcO). +TOF MS Calcd for $C_{42}H_{64}N_2O_{16}S_2$ *m/z* [M-H]+: 939.3589, found: 939.3565.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranoside[1,2-d]-(16-fluorohexadecyl)sulfanyl-1,3-oxazoline (10). The title compound was prepared following the general procedure for the S-alkylation of cis-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **1** (50.7 mg, 0.15 mmol), 1-fluoro-16-iodohexadecane (138 mg, 0.37 mmol), Et_3N (52 µL, 0.37 mmol), TBD (0.4 mg, 0.03 mmol) and CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 24 h. After standard workup, the crude was purified by flash chromatography (from 1:9 to 1:1 AcOEt/hexane) to afford compound **10** (74.7 mg, 87 % yield) as an off-white solid. Data: Rf (1:1 AcOEt/hexane): 0.66. Mp: 51-52 ºC. $[\alpha]_D$ +41.8 (*c* 3.62, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 2918, 2850, 1742, 1600, 1464, 1371, 1213, 1141, 1109, 1049. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.88 (d, 1H, $J_{1,2}$= 7.4 Hz, H-1); 5.20 (pt, 1H, $J_{3,2}$= 3.8 Hz, $J_{3,4}$= 4.2 Hz, H-3); 4.92 (dd, 1H, $J_{4,3}$= 4.2 Hz, $J_{4,5}$= 8.8 Hz, H-4); 4.52 (dd, 1H, $J_{2,1}$= 7.4 Hz, $J_{2,3}$= 3.8 Hz, H-2); 4.44 (dt, 2H, J= 6.0 Hz, J_{HF}= 47.3, CH_2-F aliph); 4.29 (dd, 1H, $J_{6,5}$= 5.0 Hz, $J_{6,6'}$=12.0 Hz, H-6); 4.17 (dd, 1H, $J_{6',5}$= 2.8 Hz, $J_{6',6}$=12.0 Hz, H-6'); 3.69 (ddd, $J_{5,4}$= 8.8 Hz, $J_{5,6}$= 5.0 Hz, $J_{5,6'}$ =2.8 Hz, 1H, H-5); 3.06 (t, 2H, J= 7.4 Hz, CH_2-S aliph); 2.12 (s, 3H, AcO); 2.09 (s, 3H, AcO); 2.07 (s, 3H, AcO); 1.77-1.60 (4H, CH_2 aliph); 1.40-1.20 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 171.1 (C=N); 170.8, 169.8, 169.5 (C(O), AcO); 92.5 (C-1); 84.4 (d, J_{CF} = 164.6 Hz, CH_2-F); 77.1 (C-2); 70.2 (C-3); 68.0 (C-4); 67.4 (C-5); 63.5 (C-6); 32.4 (CH_2-S); 30.7, 30.5, 29.8, 29.8, 29.7, 29.7, 29.7, 29.7, 29.4, 29.3, 28.9, 25.3, 25.3 (CH_2 aliph); 21.0, 21.0, 20.9 (CH_3, AcO). ^{19}F NMR (376 MHz, $CDCl_3$) δ in ppm: -218.0 (tt, J_{FH}= 47.3 Hz, $J_{FH'}$= 24.8, CH_2-F Hz). +TOF MS Calcd for $C_{29}H_{48}FNO_8S$ *m/z* [M-Na]+: 612.2977, found: 612.2986.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyranoside[1,2-d]-(16-hydroxyhexadecyl)sulfanyl-1,3-oxazoline (11). The title compound was prepared following the general procedure for the S-alkylation of cis-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **2** (54.0 mg, 0.16 mmol), 16-iodohexadecanol (172 mg, 0.47 mmol),

Et_3N (66 µL, 0.47 mmol), TBD (0.4 mg, 0.03 mmol) and CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 24 h. After standard workup, the crude was purified by flash chromatography (from 1:10 to 1:3 AcOEt/hexane) to afford compound **11** (89 mg, 91 % yield) as a colourless syrup. Data: Rf (1:1 AcOEt/hexane): 0.46. Mp: 32-33 ºC. $[\alpha]_D$ +85.5 (*c* 2.50, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 3410, 2921, 2851, 1747, 1590, 1467, 1369, 1215, 1162, 1117, 1051, 753. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.85 (d, 1H, $J_{1,2}$= 7.1 Hz, H-1); 5.43 (pt, 1H, $J_{4,3}$= 3.0 Hz, $J_{4,5}$= 2.2 Hz, H-4); 4.96 (dd, 1H, $J_{3,2}$= 7.3 Hz, $J_{3,4}$= 3.0 Hz, H-3); 4.56 (pt, 1H, $J_{2,1}$= 7.1 Hz, $J_{2,3}$= 7.3 Hz, H-2); 4.22 (pdt, $J_{5,4}$= 2.2 Hz, $J_{5,6}$= 7.0 Hz, $J_{5,6'}$ = 6.6 Hz, 1H, H-5); 4.15 (dt, 1H, $J_{6',5}$= 6.6 Hz, $J_{6',6}$= 11.0 Hz, H-6'); 4.12 (dd, 1H, $J_{6,5}$= 7.0 Hz, $J_{6,6'}$=11.0 Hz, H-6'); 3.61 (t, 2H, J= 6.6 Hz, CH_2-OH aliph); 3.03 (m, 2H, CH_2-S aliph); 2.11 (s, 3H, AcO); 2.05 (s, 3H, AcO); 2.03 (s, 3H, AcO); 1.67 (quint, 2H, J= 7.4 Hz, CH_2 aliph); 1.61 (bs, 1H, OH); 1.54 (quint, 2H, J= 6.9 Hz, CH_2 aliph); 1.40-1.20 (26H, CH_2 aliph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 170.7 (C=N); 170.7, 170.2, 170.1 (C(O), AcO); 93.9 (C-1); 77.9 (C-2); 71.7 (C-3); 69.3 (C-5); 66.2 (C-4); 63.1 (CH_2-OH); 61.4 (C-6); 32.9 (CH_2 aliph); 32.4 (CH_2-S); 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.2, 28.8, 25.9 (CH_2 aliph); 20.9, 20.8, 20.8 (CH_3, AcO). +TOF MS Calcd for $C_{29}H_{49}NO_9S$ *m/z* [M-Na]+: 610.3020, found: 610.3039.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyranoside[1,2-d]-(16-hydroxyhexadecyl)sulfanyl-1,3-oxazoline (11). The title compound was prepared following the general procedure for the S-alkylation of cis-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **2** (54.0 mg, 0.16 mmol), 16-iodohexadecanol (172 mg, 0.47 mmol), Et_3N (66 µL, 0.47 mmol), TBD (0.4 mg, 0.03 mmol) and CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 24 h. After standard workup, the crude was purified by flash chromatography (from 1:10 to 1:3 AcOEt/hexane) to afford compound **11** (89 mg, 91 % yield) as a colourless syrup. Data: Rf (1:1 AcOEt/hexane): 0.46. Mp: 32-33 ºC. $[\alpha]_D$ +85.5 (*c* 2.50, $CHCl_3$). FT-IR (neat) υ in cm^{-1}: 3410, 2921, 2851, 1747, 1590, 1467, 1369, 1215, 1162, 1117, 1051, 753. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 5.85 (d, 1H, $J_{1,2}$= 7.1 Hz, H-1); 5.43 (pt, 1H, $J_{4,3}$= 3.0 Hz, $J_{4,5}$= 2.2 Hz, H-4); 4.96 (dd, 1H, $J_{3,2}$= 7.3 Hz, $J_{3,4}$= 3.0 Hz, H-3); 4.56 (pt, 1H, $J_{2,1}$= 7.1 Hz, $J_{2,3}$= 7.3 Hz, H-2); 4.22 (pdt, $J_{5,4}$= 2.2 Hz, $J_{5,6}$= 7.0 Hz, $J_{5,6'}$ = 6.6 Hz, 1H, H-5); 4.15 (dt, 1H, $J_{6',5}$= 6.6 Hz, $J_{6',6}$= 11.0 Hz, H-6'); 4.12 (dd, 1H, $J_{6,5}$= 7.0 Hz, $J_{6,6'}$=11.0 Hz, H-6'); 3.61 (t, 2H, J= 6.6 Hz, CH_2-OH aliph); 3.03 (m, 2H, CH_2-S aliph); 2.11 (s, 3H, AcO); 2.05 (s, 3H, AcO); 2.03 (s, 3H, AcO); 1.67 (quint, 2H, J= 7.4 Hz, CH_2 aliph); 1.61 (bs, 1H, OH); 1.54 (quint, 2H, J= 6.9 Hz, CH_2 aliph); 1.40-1.20 (26H, CH_2 aliph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 170.7 (C=N); 170.7, 170.2, 170.1 (C(O), AcO); 93.9 (C-1); 77.9 (C-2); 71.7 (C-3); 69.3 (C-5); 66.2 (C-4); 63.1 (CH_2-OH); 61.4 (C-6); 32.9 (CH_2 aliph); 32.4 (CH_2-S); 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.2, 28.8, 25.9 (CH_2 aliph); 20.9, 20.8, 20.8 (CH_3, AcO). +TOF MS Calcd for $C_{29}H_{49}NO_9S$ *m/z* [M-Na]+: 610.3020, found: 610.3039.

1,2-Dideoxy-α-D-glucopyranoside[1,2-d]-16-16-iodohexadecylsulfanyl-1,3-oxazoline (13). The title compound was prepared following the g**eneral procedure for acetyl deprotection of**

cis-1,2-fused D-glucopyranose—2-alkylsulfanyl-1,3-oxazoline derivatives starting from 8 (30.3 mg, 0.04 mmol), MeONa (0.2 mg, 3 μmol) and MeOH (1 mL). The reaction mixture was stirred at rt for 12 h. After standard workup, the crude was purified by flash chromatography (1:9 MeOH/CH_2Cl_2) to afford compound **13** (24.8 mg, 100% yield) as a white solid. Data: Rf (1:9 MeOH/CH_2Cl_2): 0.53. Mp: 64-66 ºC. $[\alpha]_D$ + 15.0 (*c* 1.35, CH_3OH). FT-IR (neat) υ in cm^{-1}: 3304, 2915, 2859, 1579, 1469, 1350, 1292, 1163, 1117, 1073, 964. ^1H NMR (400 MHz, 2:1 CD_3OD/ $CDCl_3$) δ in ppm: 5.78 (d, 1H, $J_{1,2}$= 7.0 Hz, H-1); 4.47 (dd, 1H, $J_{2,1}$= 7.0 Hz, $J_{2,3}$= 5.3 Hz, H-2); 3.78 (dd, 1H, $J_{6',5}$= 2.8 Hz, $J_{6',6}$=12.0 Hz, H-6'); 3.72 (dd, 1H, $J_{6',5}$= 5.2 Hz, $J_{6',6}$=12.0 Hz, H-6); 3.69 (dd, 1H, $J_{3,2}$= 5.3 Hz, $J_{3,4}$= 7.0, H-3); 3.47 (dd, 1H, $J_{4,3}$= 7.0 Hz, $J_{4,5}$= 8.8 Hz, H-4); 3.32 (m, 1H, H-5); 3.22 (t, 2H, J= 7.0 Hz, CH_2-I); 3.03 (t, 2H, J= 7.4 Hz, CH_2-S); 1.79 (quint, 2H, J= 7.2 Hz, CH_2 aliph); 1.71 (quint, 2H, J= 7.4 Hz, CH_2 aliph). 1.45-1.28 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, 2:1 CD_3OD/ $CDCl_3$) δ in ppm: 172.1 (C=N); 93.6 (C-1); 83.4 (C-2); 75.0 (C-5); 74.9 (C-3); 69.1 (C-4); 62.7 (C-6); 34.5 (CH_2 aliph); 32.4 (CH_2-S); 31.3, 30.6, 30.5, 30.5, 30.4, 30.0, 29.5, 29.4 (CH_2 aliph); 7.2 (CH_2-I). +TOF MS Calcd for $C_{23}H_{42}INO_5S$ *m/z* [M-Na]+: 594.1721, found: 594.1701.

1,16-Di(1,2-dideoxy-α-D-glucopyranoside[1,2-d]-1,3-oxazolidine-2-thione)hexadecane (14). The title compound was prepared following the g**eneral procedure for acetyl deprotection of cis-1,2-fused D-glucopyranose—2-alkylsulfanyl-1,3-oxazoline derivatives starting from 9** (31.6 mg, 0.03 mmol), MeONa (0.1 mg, 2 μmol) and MeOH (1 mL). The reaction mixture was stirred at rt for 12 h. After standard workup, the crude was purified by crystallization from MeOH to afford compound **14** (21.6 mg, 94% yield) as a white solid. Data: Rf (1:9 MeOH/CH_2Cl_2): 0.53. Mp: 125-126 ºC. $[\alpha]_D$ + 19.2 (*c* 3.10, 2:1 CH_3OH/$CHCl_3$). FT-IR (neat) υ in cm^{-1}: 3330, 2919, 2850, 1743, 1590, 1462, 1352, 1155, 1094, 997. ^1H NMR (400 MHz, 2:1 CD_3OD/ CD_3Cl) δ in ppm: 5.78 (d, 2H, $J_{1,2}$= 7.3 Hz, 2x H-1); 4.47 (dd, 2H, $J_{2,1}$= 7.3 Hz, $J_{2,3}$= 5.4 Hz, 2x H-2); 3.79 (dd, 2H, $J_{6',5}$= 3.2 Hz, $J_{6',6}$= 12.0 Hz, 2x H-6'); 3.78-3.71 (stack, 3H, 2x H-3 and 2x H-6); 3.52 (dd, 2H, $J_{4,3}$= 7.0 Hz, $J_{4,5}$= 9.0 Hz, 2x H-4); 3.35 (m, 2H, 2x H-5); 3.01 (td, 4H, J= 7.0 Hz, J'= 1.9 Hz, CH_2-S); 1.69 (quint, 4H, J= 7.5 Hz, 2x CH_2 aliph); 1.45-1.23 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, 2:1 CD_3OD/ CD_3Cl) δ in ppm: 172.2 (2x C=N); 93.5 (2x C-1); 83.0 (2x C-2); 74.8 (2x C-5); 74.4 (2x C-3); 68.9 (2x C-4); 62.4 (2x C-6); 32.4 (2x CH_2-S); 30.5, 30.5, 30.4, 30.4, 30.3, 30.0, 29.5 (2x CH_2 aliph). +TOF MS Calcd for $C_{30}H_{52}N_2O_{10}S_2$ *m/z* [M-Na]+: 687.2956, found: 687.2904.9.

1,2-Dideoxy-α-D-glucopyranoside[1,2-d]-16-fluorohexadecylsulfanyl-1,3-oxazoline (15). The title compound was prepared following the g**eneral procedure for acetyl deprotection of cis-1,2-fused D-glucopyranose—2-alkylsulfanyl-1,3-oxazoline derivatives starting from 10** (44.3 mg, 0.08 mmol), MeONa (0.2 mg, 5 μmol) and MeOH (1 mL). The reaction mixture was stirred at rt for 12 h. After standard workup, the crude was purified by flash chromatography (from 0:1 to 1:9 MeOH/CH_2Cl_2) to afford compound **15** (24.3 mg, 70% yield) as a white solid. Data: Rf (1:9 MeOH/CH_2Cl_2): 0.53. Mp: 72-73 ºC. $[\alpha]_D$ + 21.4 (*c* 2.25, 2:1 CH_3OH/$CHCl_3$). FT-IR

(neat) υ in cm^{-1}: 3327, 2915, 2850, 1579, 1469, 1162, 1115, 720. ^{1}H NMR (400 MHz, 2:1 $CD_3OD/CDCl_3$) δ in ppm: 5.76 (d, 1H, $J_{1,2}$= 7.2 Hz, H-1); 4.43 (dd, 1H, $J_{2,1}$= 7.2 Hz, $J_{2,3}$= 5.3 Hz, H-2); 4.39 (dt, 2H, J= 6.4 Hz, J_{HF}= 41.0, CH_2-F aliph); 3.78 (dd, 1H, $J_{6',5}$= 3.2 Hz, $J_{6',6}$=12.5 Hz, H-6'); 3.74 (dd, 1H, $J_{6,5}$= 4.6 Hz, $J_{6,6}$=12.4 Hz, H-6); 3.70 (dd, 1H, $J_{3,2}$= 5.3 Hz, $J_{3,4}$= 7.3, H-3); 3.49 (dd, 1H, $J_{4,3}$= 7.3 Hz, $J_{4,5}$= 9.2 Hz, H-4); 3.35 (ddd, 1H, $J_{5,4}$= 9.2 Hz, $J_{5,6}$= 4.6 Hz, $J_{5,6'}$= 3.2 Hz, H-5); 2.79 (m, 2H, CH_2-S); 1.715-1.57 (4H, CH_2 aliph); 1.40-1.20 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, 2:1 $CD_3OD/CDCl_3$) δ in ppm: 170.8 (C=N); 92.5 (C-1); 84.0 (d, J_{CF} = 163.0 Hz, CH_2-F); 82.1 (C-2); 73.8 (C-5); 73.6 (C-3); 67.9 (C-4); 61.5 (C-6); 31.5 (CH_2-S); 30.3, 30.1 29.4, 29.0, 28.9, 28.4, 24.9 (CH_2 aliph). ^{19}F NMR (376 MHz, $CDCl_3$) δ in ppm: -215.1 (tt, J_{FH}= 41.0 Hz, $J_{FH'}$= 24.8, CH_2-F Hz). +TOF MS Calcd for $C_{23}H_{42}FNO_5S$ *m/z* [M-Na]+: 486.2660, found: 486.2661.

1,2-Dideoxy-α-D-galactopyranoside[1,2-d]-(16-hydroxyhexadecyl)sulfanyl-1,3-oxazoline (16). The title compound was prepared following the general procedure for **acetyl deprotection of** cis-1,2-fused 1,3-oxazoline carbohydrate derivatives starting from **11** (45.2 mg, 0.08 mmol), MeONa (0.3 mg, 5 µmol) and MeOH (1 mL). The reaction mixture was stirred at rt for 20 h. After standard workup, the crude was purified by recrystallization from MeOH to afford compound **16** (31.9 mg, 90 % yield) as white crystals. Data: Rf (1:1 AcOEt/hexane): 0.00. Mp: 90-92 ºC. $[\alpha]_D$: +31.7 (*c* 2.73, CH_3OH/ $CHCl_3$ 2:1). FT-IR (neat) υ in cm^{-1}: 3487, 3299, 2919, 2851, 1744, 1590, 1468, 1374, 1300, 1161, 1119, 1057, 984. ^{1}H NMR (400 MHz, 1:2 $CD_3OD/CDCl_3$) δ in ppm: 5.60 (d, 1H, $J_{1,2}$= 7.0 Hz, H-1); 4.34 (pt, 1H, $J_{2,1}$= 7.0 Hz, $J_{2,3}$= 6.6 Hz, H-2); 3.75 (dd, 1H, $J_{4,3}$= 3.2 Hz, $J_{4,5}$= 2.0 Hz, H-4); 3.65-3.49 (stack, 3H, H-5, H-6, and H-6'); 3.47 (dd, 1H, $J_{3,2}$= 6.6 Hz, $J_{3,4}$= 3.2, H-3); 3.35 (t, 2H, J= 7.0 Hz, CH_2-OH aliph); 2.80 (m, 2H, CH_2-S aliph); 1.50 (quint, 2H, J= 7.6 Hz, CH_2 aliph); 1.33 (quint, 2H, J= 7.0 Hz, CH_2 aliph); 1.25-1.00 (24H, CH_2 aliph). ^{13}C NMR (100.6 MHz, 1:2 $CD_3OD/CDCl_3$) δ in ppm: 170.7 (C=N); 92.8 (C-1); 82.1 (C-2); 73.0 (C-5); 71.3 (C-3); 67.4 (C-4); 62.1 (CH_2-OH); 61.1 (C-6); 32.3 (CH_2-S); 31.5, 29.4, 29.4, 29.3, 29.3, 29.3, 29.0, 28.9, 28.4, 25.6 (CH_2 aliph). +TOF MS Calcd for $C_{23}H_{43}NO_6S$ *m/z* [M-Na]+: 484.2703, found: 484.2704.

1,2-Dideoxy-α-D-glucopyranoside[1,2-d]-16-carboxyhexadecylsulfanyl-1,3-oxazoline (17). The title compound was prepared following the g**eneral procedure for acetyl deprotection of cis-1,2-fused D-glucopyranose—2-alkylsulfanyl-1,3-oxazoline derivatives starting from 7** (31.3 mg, 0.05 mmol), NaOH (2.4 mg, 0.06 mmol) and MeOH (1 mL). The reaction mixture was stirred at rt for 12 h. After standard workup, the crude was purified by flash chromatography (5:95 MeOH/CH_2Cl_2) to afford compound **17** (19.6 mg, 81% yield) as a white solid. Data: Rf (1:9 MeOH/CH_2Cl_2): 0.94. Mp: 77-75 ºC. $[\alpha]_D$ + 44.3 (*c* 0.86, MeOH/$CHCl_3$ 2:1). FT-IR (neat) υ in cm^{-1}: 3320, 2918, 2849, 1736, 1579, 1468, 1379, 1229, 1161, 1030. ^{1}H NMR (400 MHz, CD_3OD) δ in ppm: 5.79 (d, 1H, $J_{1,2}$= 7.4 Hz, H-1); 4.48 (dd, 1H, $J_{2,1}$= 7.4 Hz, $J_{2,3}$= 5.2 Hz, H-2); 3.78 (dd, 1H, $J_{6',5}$= 2.8 Hz, $J_{6',6}$=12.0 Hz, H-6'); 3.73 (dd, 1H, $J_{6',5}$= 5.2 Hz, $J_{6',6}$=12.0 Hz, H-6); 3.71 (dd,

1H, $J_{3,2}$= 5.2 Hz, $J_{3,4}$= 6.8, H-3); 3.48 (dd, 1H, $J_{4,3}$= 6.8 Hz, $J_{4,5}$= 9.0 Hz, H-4); 3.30 (m, 1H, H-5); 3.03 (t, 2H, J= 7.6 Hz, CH_2-S); 2.31 (t, 2H, J= 7.4 Hz, CH_2-CO_2Me); 1.72 (quint, 2H, J= 7.4 Hz, CH_2 aliph); 1.59 (quint, 2H, J= 7.2 Hz, CH_2 aliph). 1.45-1.28 (stack, 22H, CH_2 aliph). ^{13}C NMR (100.6 MHz, CD_3OD) δ in ppm: 176.1 (C=O); 172.2 (C=N); 93.8 (C-1); 83.7 (C-2); 75.4 (C-5); 75.0 (C-3); 69.4 (C-4); 62.9 (C-6); 34.8 (CH_2-CO_2H); 32.4 (CH_2-S); 30.7, 30.7, 30.7, 30.6, 30.6, 30.4, 30.2, 30.2, 29.6, 26.0 (CH_2 aliph). +TOF MS Calcd for $C_{23}H_{41}NO_7S$ *m/z* [M-Na]+: 498.2496, found: 498.2509.

Supporting Information Available: General experimental methods, experimental procedure for the preparation of methyl 16-iodohexadecanoate and 16-iodohexadecanoic acid, protocol for determination of K_i values against commercial enzymes and representative Lineweaver-Burk and double reciprocal analysis plots against β-glucosidase, detailed description of methods for determination of IC_{50} values against GCase in lysates and chaperone activity in normal and Gaucher fibroblasts and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://xxxxxxxx.xxx

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